Curtin School of Population Health

Modelling the Effects of Fine Particulate Matter Air Pollution and Biothermal Stress on Birth Outcomes in Australia and Ghana

Sylvester Dodzi Nyadanu
0000-0002-6233-0262

This thesis is presented for the Degree of
Doctor of Philosophy
at
Curtin University

May 2023

Acknowledgement of Country

I acknowledge that Curtin University works across hundreds of traditional lands and custodial groups in Australia, and with First Nations people around the globe. I wish to pay my deepest respects to their ancestors and members of their communities, past, present, and to their emerging leaders. Curtin University's passion and commitment to work with all Australians and peoples from across the world, including our First Nations peoples, is reflective of the institutions' values and commitment to our roles as leaders in the Reconciliation space in Australia.

Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

This thesis contains both unpublished manuscripts and works that have been published in peer-reviewed journals. The detailed contributions and signed statements from all co-authors are presented in **Appendix M**. The permission to reproduce the published works from the publishers can be found in the **Appendix N**.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Human Research Ethics Committees of the Western Australia Department of Health (#2016/51), Curtin University (#HRE2020-0523), and Ghana Health Service (#GHS-ERC016/12/20).

Signature:

Date: 1[s] May 2023

Statement from Principal Supervisor

This thesis has been prepared by Sylvester Dodzi Nyadanu in accordance with the guidelines for a Doctor of Philosophy thesis by publication. I am recommending the thesis now be sent for examination.

Signature:

Date: 1st May 2023

Acknowledgement

First and foremost, I thank the Almighty God for the gift of life, strength, and support through my PhD journey.

I would like to express my profound gratitude to my amazing and supportive supervisors –Professor Gavin Pereira, Dr Gizachew A. Tessema, and Professor Ben Mullins. Your invaluable guidance, advice, mentorship, intellectual inputs, and continuous support throughout my PhD candidature were paramount for the successful completion of my PhD and future endeavours. Your critical revisions of my manuscripts and suggestions have helped me to significantly improve my research and organizational skills and research writing. A further special thanks to Professor Gavin Pereira for introducing me to Professor Michelle Bell and the international Perinatal Outcomes in the Pandemic (iPOP) team for collaboration. I thank Professor Bernard Kumi-Boateng, my Ghanaian collaborator who also contributed to the success of this thesis. Thanks to all co-authors for your inputs and suggestions to improve the quality of the papers presented in this thesis. I thank my thesis Chairperson, Dr. Jun Chih for your support, encouragement, and congratulation messages.

I would like to specially thank Curtin School of Population Health, Curtin University for the funding support through Curtin University International Postgraduate Research Scholarship (CIPRS) for making my PhD dream a reality.

I am thankful for the solidarity and support from the many PhD students at Curtin University. I acknowledge the support and interaction from the G Pereira's Epidemiology lab. This is an amazing team that am privilege to be part.

I would like to express special appreciation to Data Linkage Branch of the Department of Health, Western Australia and the Data Custodian for the Midwives Notification System, and the Centre for Health Information Management of the Ghana Health Service for providing the birth data to support my PhD project.

I thank Diana Blackwood, the Faculty of Health Sciences librarian of Curtin University for your expertise and technical support in developing the search strategy for my systematic reviews.

I would like to deeply express my gratitude to my lovely wife and children for all the supports. You are very important part of this success story.

Finally, I would like to express my sincerest gratitude to my parents abroad, other family members and close friends who have provided me with unlimited support and encouragement throughout.

Indeed, this work would not have been possible without the network of mentors, colleagues, family, and friends that I have met throughout my doctoral programme. Big thanks to all.

Abstract

Background and objectives

Air pollution and climate change are ubiquitous environmental exposures of leading global public health concerns. Extensive epidemiological studies have shown positive associations between maternal exposure to criteria air pollutants (particularly $PM_{2.5}$) and extreme ambient temperatures and the risks of birth outcomes. Yet, there were several limitations such as unknown critical susceptible periods, exposure-response associations did not account for both intensity and timing of past exposures, and the surrogate usage of ambient temperature instead of composite biothermal metrics. Also, there is insufficient evidence from developing settings or other areas within the same country. This thesis aimed to assess spatiotemporal $PM_{2.5}$ and biothermal stress (Universal Thermal Climate Index, UTCI) exposures and the risks of birth outcomes in Western Australia and Ghana using robust study designs and statistical modelling techniques to identify potential critical susceptible periods and vulnerable subpopulations.

Methods

Two comprehensive umbrella reviews were conducted to synthesise the current evidence on the associations between ambient air pollution and temperature and birth outcomes. These were followed by primary investigations that included a total of 414,771 singleton births obtained from the Midwives Notification System between 1st January 2000 to 31st December 2015 in Western Australia. The adverse birth outcomes assessed were stillbirth, spontaneous preterm birth (sPTB), the term small for gestational age (SGA), large for gestational age (LGA), and low birth weight (LBW). The births were linked to fine spatiotemporal monthly $PM_{2.5}$ concentrations and daily UTCI based on the maternal residential address as statistical area level 1 (SA1, second smallest geographical unit in Australia) at the time of birth delivery. Distributed lag linear and nonlinear models (DLNM) integrated with Cox proportional hazard regressions were performed to investigate maternal exposure to monthly $PM_{2.5}$, both weekly and monthly UTCI for three months preconception to birth, and the adjusted hazard of birth outcomes. Moreover, space-time-stratified case-crossover analysis of 15,576 singleton sPTB and 2835 singleton stillbirths and short-term exposure to daily UTCI in a week before birth at SA1 levels were examined using DLNM conditional quasi-Poisson regressions. Due to data availability, the Ghana study involved a district-level aggregated monthly 5,961,328 total births that included 90,532 stillbirths across all 260 local districts between 1st January 2012 and 31st December 2020 was obtained from Ghana Health Service. The district-level births were linked to monthly $PM_{2.5}$ and UTCI exposures and exposure-lag-response associations were investigated using within-space time-series design analyses with DLNM conditional quasi-Poisson regressions.

Results

$PM_{2.5}$ exposure: Results from the umbrella review indicated studies were mostly conducted in the United States and China. Air pollution associated with increased risks of birth outcomes and $PM_{2.5}$ showed more consistent positive associations than other pollutants. Entire pregnancy period exposures were more consistent than trimester-specific exposure averages with no clear susceptible periods based on trimester-specific effect estimates. From our primary investigations in Western Australia, $PM_{2.5}$ exposure mostly showed non-linear dose-response associations with birth outcomes. Critical susceptible exposure periods were found during the 3rd–7th gestational months for stillbirth and sPTB. Using 5 μg/m^3 (new international annual limit) as a reference, the strongest hazards at the 99th centile (10.7 μg/m^3) exposure were 1.10 (95% CI 1.02, 1.19) during the 7th gestational month for stillbirth and 1.04 (95% CI 1.01, 1.06) during the 5th gestational month for sPTB. For term fetal growth outcomes, higher hazards were found during the 2nd–6th gestational months but only term LBW showed critical susceptible periods. The strongest hazards were 1.01 (95% CI 1.00, 1.02) for term SGA for exposure above the median during the 4th gestational month, 1.03 (95% CI 1.00, 1.05) for term LGA for exposure at 99th $PM_{2.5}$ centile during 1st gestational month, and 1.03 (95% CI 1.01, 1.05) at 50th $PM_{2.5}$ centile during the 3rd gestational month for term LBW. Monthly preconception and late pregnancy exposures showed small 'protective effects' on birth outcomes. The ratio of hazard ratios indicated joint effects of $PM_{2.5}$ and biothermal stress exposures for all birth outcomes, except sPTB. The disproportionately affected subpopulations were births to mothers who were unmarried, non-Caucasian, multiparous, smoked during pregnancy, rural residents, and complicated pregnancies. For the Ghana cohort, $PM_{2.5}$ exposures above the 50th centile showed critical susceptible exposure periods during the 6th –7th months before birth (early pregnancy periods) and the strongest risk was 1.17 (95% CI 1.06, 1.28) at the 99th centile during the 6th month before birth, using 5 μg/m^3 as reference. The preconception period showed a small 'protective effect'.

Biothermal stress exposure: Despite the varied exposure metrics and windows for ambient temperature, the synthesised evidence in the umbrella review revealed that high temperatures in particular showed positive associations with PTB, stillbirth, and LBW for mostly short-term and very few long-term (entire pregnancy and trimester-average) effects. Our primary investigations in Western Australia found that short-term extreme biothermal stress exposures were associated with increased risks of stillbirth and sPTB. As compared to the median, long-term exposures at both lower (1st, 5th, 10th centiles) and higher (90th, 95th, 99th) UTCI centiles showed positive associations with the birth outcomes with identified potential critical susceptible periods. For example, the identified critical susceptible periods were found during the 23rd–42nd gestational weeks with the strongest hazard of 1.15 (95% CI 1.04, 1.29) in the 42nd week for stillbirth. Critical susceptible periods were 27th–36th gestational weeks with the strongest hazard of 1.12 (95% CI 1.09, 1.16) in the 36th weeks for sPTB at 1st centile (10.2˚C) as compared to median exposure (14.2˚C). For term fetal growth outcomes, the long-term UTCI effects were more obvious in monthly than weekly exposures as fetal growth is more observable within a month than a week. Positive associations were found during the 6th-10th gestational months for term SGA and LGA. The strongest hazards were 1.13 (95% CI 1.10, 1.17) for term SGA and 1.07 (95% CI 1.03, 1.11) for term LGA in 10th month at 1st centile. The strongest hazard of term LBW was 1.02 (95% CI 1.01, 1.04) during 3rd – 5th gestational months at 99th centile as compared to median exposure. Almost the same disproportionately affected subpopulations were identified as found for $PM_{2.5}$ exposure above. For the Ghana cohort, the relative risk of stillbirth ranged from 1.02 (95% CI 0.99, 1.05) to 1.18 (95% CI 1.02, 1.36) for the 90th centile (30.8 ˚C), relative to the median UTCI (28.8 ˚C). But exposure at the 99th centile (33.2 ˚C) offered a 'protective effect', 0.61 (95% CI 0.44, 0.86). The positive exposure-outcome association was stronger in rural than urban districts.

Conclusion

$PM_{2.5}$ and UTCI exposures independently and synergistically were associated with higher risks of birth outcomes and the magnitudes of the effect estimates were stronger for UTCI than $PM_{2.5}$ exposure. Despite slight variations in specific exposure-outcome association, we found that critical susceptible periods for the birth outcomes were early to mid-gestational periods for $PM_{2.5}$ exposure but mid to late gestational periods for the UTCI exposure. The potential critical exposure periods of increased susceptibility and vulnerable subpopulations identified could inform clinical and public health interventions and further investigations. As these pieces of knowledge are very important for clinical and public health interventions and understanding biological mechanisms with diagnostic and treatment potentials, further high-quality studies are required in these directions.

Publications included in this thesis

Peer-reviewed published articles

1. **Nyadanu SD**, Tessema GA, Mullins B, Kumi-Boateng B, Ofosu AA, Pereira G. 2023. Prenatal exposure to long-term heat stress and stillbirth in Ghana: a within-space time-series analysis. *Environ Res 222.* https://doi.org/10.1016/j.envres.2023.115385.
2. **Nyadanu SD**, Tessema GA, Mullins B, Pereira G. 2022. Prenatal acute thermophysiological stress and spontaneous preterm birth in Western Australia, 2000-2015: A space-time-stratified case-crossover analysis. *Int J Hyg Environ Health 245:114029*. https://doi.org/10.1016/j.ijheh.2022.114029.
3. **Nyadanu SD**, Tessema GA, Mullins B, Kumi-Boateng B, Ofosu AA, Pereira G. 2022. Ambient particulate matter air pollution and stillbirth in Ghana: A difference-in-differences approach. *Atmos. Pollut. Res*. 13(7). https://doi.org/10.1016/j.apr.2022.101471
4. **Nyadanu SD,** Dunne J, Tessema GA, Mullins B, Kumi-Boateng B, Bell ML, Duko B, Pereira G. 2022. Prenatal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of 36 systematic reviews and meta-analyses. *Environ. Pollut. 306*, 119465. https://doi.org/https://doi.org/10.1016/j.envpol.2022.119465.
5. **Nyadanu SD**, Tessema GA, Mullins B, Pereira G. 2022. Maternal acute thermophysiological stress and stillbirth in Western Australia, 2000-2015: A space-time-stratified case-crossover analysis. *Sci. Total Environ.*, 155750. https://doi.org/10.1016/j.scitotenv.2022.155750.
6. **Nyadanu SD**, Tessema GA, Mullins B, Kumi-Boateng B, Bell ML, Pereira G. 2020. Ambient air pollution, extreme temperatures, and birth outcomes: a protocol for an umbrella review, systematic review and meta-analysis. *Int. J. Environ. Res. Publ. Health* 17 (22). https://doi.org/10.3390/ijerph17228658.

Returned for revision

Nyadanu SD, Tessema GA, Mullins B, Chai K, Yitshak-Sade M, Pereira G. Maternal exposure to biothermal stress and birth weight for gestational age in Western Australia: a distributed lag non-linear model with time-to-event analysis to identify potential windows of susceptibility. *Environ. Health Perspect.* 2023

Peer-reviewed conference abstracts and presentations from this thesis

1. **Nyadanu SD**, Tessema GA, Mullins B, Pereira G. The association between acute thermophysiological stress and stillbirth by obstetric conditions. *Population Health Congress*. September 2022. Oral presentation.

2. **Nyadanu SD**, Tessema GA, Mullins B, Pereira G. Maternal exposure to acute thermophysiological stress and spontaneous preterm birth: a space-time-stratified case-crossover analysis in Western Australia, 2000-2015. *International Society for Environmental Epidemiology Asia and Western Pacific Chapter & International Society for Exposure Science Asia Chapter Joint Conference*. June 2022. Oral presentation.

3. **Nyadanu SD**, Tessema GA, Mullins B, Pereira G. Air pollution, climate change and birth outcomes in Western Australia: epidemiological evidence, challenges, and prospects. *The Royal Society of Western Australia*. June 2022. Oral presentation.

4. **Nyadanu SD**, Tessema GA, Dunne J, Mullins B, Duko B, Pereira G. Ambient air temperature and adverse birth outcomes: an umbrella review. *Australian Public Health Conference*. September 2021. Oral presentation.

5. **Nyadanu SD**, Tessema GA, Dunne J, Mullins B, Duko B, Pereira G. Ambient air pollution and adverse birth outcomes: a systematic synthesis of meta-analyses of epidemiological studies. *World Congress of Epidemiology*. September 2021. Oral presentation.

Int. J. Epidemiol. 50, Suppl_1, 2021. dyab168.496. https://doi.org/10.1093/ije/dyab168.496.

6. **Nyadanu SD**, Tessema GA, Mullins B, Pereira G. Long-term prenatal exposure to particulate matter air pollution and stillbirth in Ghana: a difference-in-differences approach. *Mark Liveris Seminar*. Curtin University. August 2021. Oral presentation.

Recognitions and awards from this thesis

1. Australasian Epidemiological Association (AEA) Student bursary award during the 2022 Population Health Congress at Adelaide, Australia. 22-23 September 2022.
Awarded to AEA student members who obtained highest peer-review scores for conference abstract.

2. International Society for Environmental Epidemiology Asia and Western Pacific Chapter & International Society for Exposure Science Asia Chapter Joint Conference. June 2022.
Young Investigator Award.

Authorship contribution statements

This thesis has been completed during my period of candidature for the degree of Doctor of Philosophy (Public Health) at the Curtin School of Population Health, Curtin University. The thesis contains six peer-reviewed publications and eight unpublished manuscripts in preparation. The ideas, study designs, formal analyses, development and writing up of all papers or sections in this thesis were the principal responsibility of myself, the candidate under the supervision of my thesis supervisors. The inclusion of co-authors reflects active collaboration with other researchers. The contribution of each co-author included in the publications, or each chapter of the thesis has been detailed and endorsed by co-authors in **Appendix M.**

My contributions in Chapters 3-11 that contain published works or unpublished manuscripts in preparation are described below:

Thesis Chapter	Publication title	Publication status	My contribution
3	1. Ambient air pollution, extreme temperatures, and birth outcomes: a protocol for an umbrella review, systematic review and meta-analysis 2. Prenatal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of 36 systematic reviews and meta-analyses	1. Published in *International Journal of Environmental Research and Public Health* 2. Published in *Environmental Pollution*	Conceptualised and led the development and registration of the original protocol. Led the writing of the full protocol. Developed the search strategy and conducted the database searches. Extracted and analysed the data. Wrote the original manuscript and responses to reviewer comments. Led the writing of the manuscript.
4	Long-term maternal exposure to ambient fine particulate matter and the risks of stillbirth and spontaneous preterm birth in Western Australia	In preparation for submission	Managed the project. Conceptualised and designed the methods. Acquired the exposure data. Conducted the data curation and performed the formal data analyses. Wrote the original manuscript. Led the writing of the manuscript.
5	Long-term maternal exposure to ambient fine particulate matter and the risks of adverse fetal growth in Western Australia	In preparation for submission	Managed the project. Conceptualised and designed the methods. Acquired the exposure data. Conducted the data curation and performed the formal data analyses. Wrote the original manuscript. Led the writing of the manuscript.
6	1. Ambient particulate matter air pollution and stillbirth in Ghana: A difference-in-differences approach 2. Long-term maternal exposure to ambient fine particulate matter and the risk of stillbirth in Ghana	1. Published in *Atmospheric Pollution Research* 2. In preparation for submission	Managed the project. Conceptualised and designed the methods. Acquired the exposure data. Conducted the data curation and performed the formal data analyses. Wrote the original manuscripts and responses to reviewer comments Led the writing of the manuscript.
7	Maternal exposure to ambient air temperature and adverse birth outcomes: An umbrella review of systematic reviews and meta-analyses.	In preparation for submission	Managed the project. Conceptualised and designed the methods. Acquired the exposure data. Conducted the data curation and performed the formal data analyses. Wrote the original manuscript. Led the writing of the manuscript.

8	1. Maternal acute thermophysiological stress and stillbirth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis 2. Prenatal acute thermophysiological stress and spontaneous preterm birth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis	1. Published in *Science of the Total Environment* 2. Published in *International Journal of Hygiene and Environmental Health*	Managed the project. Conceptualised and designed the methods. Acquired the exposure data. Conducted the data curation and performed the formal data analyses. Wrote the original manuscripts and responses to reviewer comments. Led the writing of the manuscripts.
9	Long-term maternal exposure to biothermal stress and the risks of stillbirth and spontaneous preterm birth in Western Australia	In preparation for submission	Managed the project. Conceptualised and designed the methods. Acquired the exposure data. Conducted the data curation and performed the formal data analyses. Wrote the original manuscript. Led the writing of the manuscript.
10	Maternal exposure to biothermal stress and birth weight for gestational age in Western Australia: a distributed lag non-linear model with time-to-event analysis to identify potential windows of susceptibility	Returned for revision in *Environmental Health Perspective*	Managed the project. Conceptualised and designed the methods. Acquired the exposure data. Conducted the data curation and performed the formal data analyses. Wrote the original manuscript. Led the writing of the manuscript.
11	Prenatal exposure to long-term heat stress and stillbirth in Ghana: a within-space time-series analysis	Published in *Environmental Research*	Managed the project. Conceptualised and designed the methods. Acquired the exposure data. Conducted the data curation and performed the formal data analyses. Wrote the original manuscript and responses to reviewer comments. Led the writing of the manuscript.

Table of contents

Acknowledgement of Country……………………………………………………….ii
Declaration……………………………………………………………………..iii
Statement from Principal Supervisor ……………………………………………..iv
Acknowledgement…………………………………………………………………v
Abstract……………………………………………………………………………vi
Publications included in this thesis………………………………………………..ix
Peer-reviewed conference abstracts and presentations from this thesis…………..x
Recognitions and awards from this thesis…………………………………………xi
Authorship contribution statements………………………………………………xii
Table of Contents…………………………………………………………….....xiv

List of Tables……………………………………………………………………..xix
List of Figures……………………………………………………………………xxii
List of Abbreviations……………………………………………………………..xxv

Part I. Preface……………………… ……………………………………………...1

Chapter 1. Introduction……………………………………………………………2

1.0 Preamble …………………………………………………….................2

1.2 Study hypothesis, aims and objectives………………………………………...7

1.3 Significance and public health implications………………………………..8

1.4 Structure of the thesis……………………………………………………………9

Chapter 2. Methodology overview……………………………………………12

2.0 Preamble ……………………………………………………………………..12

2.1 Ambient air pollution, temperature, and birth outcomes: An umbrella review of systematic reviews and meta-analyses……………………………………………………..12

2.2 Ambient particulate matter, biothermal stress, and birth outcomes:
Retrospective observational studies in Western Australia and Ghana..................12

Part II. Ambient air pollution and adverse birth outcome……………………17

Chapter 3. Maternal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of systematic reviews and meta-analyses ……………………………………………………………………18

3.0 Preamble…………………………………………………………………18

3.1 Abstract…………………………………………………….................18

3.2 Introduction………………………………………………………………19

3.3 Methods……………………………………………………………………...20

3.4 Results……………………………………………………………………….23

3.5 Discussion……………………………………………………………………53

3.6 Conclusion…………………………………………………………………65

Chapter 4. Long-term maternal exposure to ambient fine particulate matter and the risks of stillbirth and spontaneous preterm birth in Western Australia……………………………………………………………67

4.0 Preamble……………………………………………………………………67

4.1Abstract…………………………………………………………………...67

4.2 Introduction……………………………………………………………69

4.3 Methods……………………………………………………………………71

4.4 Results……………………………………………………………………76

4.5 Discussion………………………………………………………………..82

4.6 Conclusion………………………………………………………………..87

Chapter 5. Long-term maternal exposure to ambient fine particulate matter and the risks of adverse fetal growth in Western Australia.................88

5.0. Preamble………………………………………………………………88

5.1 Abstract……………………………………………………………………..88

5.2 Introduction………………………………………………………..…………..89

5.3 Methods……………………………………………………….……………91

5.4 Results…………………………………………………………….............93

5.5 Discussion……………………………………………………………….99

5.6 Conclusion……………………………………………………………………103

Chapter 6. Long-term maternal exposure to ambient fine particulate matter and the risk of stillbirth in Ghana……………………………………105

6.0 Preamble……………………………………………………………………..105

6.1 Abstract………………………………………………………………………105

6.2 Introduction…………………………………………………………………..107

6.3 Materials and Methods ……………………………………………...............108

6.4 Results………………………………………………………………………..113

6.5 Discussion……………………………………………………………………118

6.6 Conclusion……………………………………………………………………121

Part III. Biothermal stress and adverse birth outcomes………………………122

Chapter 7. Maternal exposure to ambient air temperature and adverse birth outcomes: An umbrella review of systematic reviews and meta-analyses………………………………………………………………123

7.0 Preamble……………………………………………………………………123

7.1 Abstract……………………………………………………………………..122

7.2 Introduction……………………………………………………………………125
7.3 Method…………………………………………………………………………126
7.4 Results…………………………………………………………………………126
7.5 Discussion……………………………………………………………………135
7.6 Conclusion……………………………………………………………………142
Chapter 8. Short-term maternal exposure to biothermal stress and the risks of stillbirth and spontaneous preterm birth in Western Australia…………….143
8.0 Preamble………………………………………………………………………143
8.1 Maternal acute thermophysiological stress and stillbirth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis……………….............143
8.1.1 Abstract………………………………………………………………………143
8.1.2 Introduction…………………………………………..………………145
8.1.3 Methods……………………………………………..………………..146
8.1.4 Results…………………………………………………………………..…150
8.1.5 Discussion……………………………………………………..............156
8.1.6 Conclusion……………………………………………………………………161
8.2 Prenatal acute thermophysiological stress and spontaneous preterm birth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis……………………………………………………………………………..163
8.2.1 Abstract…………………………………………………….............163
8.2.2 Introduction……………………………………………………………………164
8.2.3 Materials and Methods…………………………………………….............165
8.2.4 Results ………………………………………………………………………169
8.2.5. Discussion……………………………………………………………………173
8.2.6 Conclusion……………………………………………………………………177
Chapter 9. Long-term maternal exposure to biothermal stress and the risks of stillbirth and spontaneous preterm birth in Western Australia…………………..178
9.0 Preamble………………………………………………………………………178
9.1 Abstract……………………………………………………………………………..178
9.2 Introduction……………………………………………………...................179
9.3 Materials and Methods……………………………………………..................181
9.4 Results…………………………………………………………………………184
9.5 Discussion……………………………………………………………………..190

9.6 Conclusion…194
Chapter 10. Long-term maternal exposure to biothermal stress and the risks of adverse fetal growth in Western Australia…196
10.0 Preamble…196
10.1 Abstract…196
10.2 Introduction…198
10.3 Methods…200
10.4 Results…202
10.5 Discussion…207
10.6 Conclusion…211
Chapter 11. Long-term maternal exposure to biothermal stress and the risk of stillbirth in Ghana…212
Preamble 11.0…212
11.1 Abstract…212
11.2 Introduction…213
11.3 Methods…215
11.4 Results…219
11.5 Discussion…224
11.6 Conclusions…228
Part IV. General Discussion and Conclusions…229
Chapter 12. General Discussion and Conclusions…230
12.0 Preamble…230
12.1 Summary of main findings…230
12.2 Implications of this thesis…232
12.3 Strengths of this thesis…233
12.4 Limitations of this thesis…232
12.5 Recommendations…235
12.6 Conclusions…236
References…237
Appendices…281
Appendix A. Supplementary materials for Chapter 3…282
Appendix B. Supplementary materials for Chapter 4…438
Appendix C. Supplementary materials for Chapter 5…458
Appendix D. Supplementary materials for Chapter 6…481

Appendix E. Supplementary materials for Chapter 7..494
Appendix F. Supplementary materials for paper one of Chapter 8.......................................512
Appendix G. Supplementary materials for paper two of Chapter 8......................................515
Appendix H. Supplementary materials for Chapter 9..521
Appendix I. Supplementary materials for Chapter 10...539
Appendix J. Supplementary materials for Chapter 11..567
Appendix K. Ambient Air Pollution, Extreme Temperatures and Birth Outcomes: A Protocol for an Umbrella Review, Systematic Review and Meta-Analysis………………………………...573
Appendix L. Ambient particulate matter air pollution and stillbirth in Ghana: A difference-in-differences approach…………………………………………………………………….592
Appendix M. Authorship attribution statement …………………………………………....603
Appendix N. Copyright Information ……………………………………………………606
Appendix O. Ethical approvals 607
Appendix P. R codes for DLNM model for Cox model and quasi-Poisson regressions …...611
Appendix Q. References for supplementary materials……………………………………...617

List of Tables

Table 3.1 Characteristics of systematic reviews without meta-analysis, ordered from most recent to earliest publication……………………………..…………………………………..27

Table 3.2 Characteristics of systematic reviews with meta-analysis, ordered from recent to earliest……………………………………………………………………………………….31

Table 3.3 Association between birth weight and ambient air pollution…………………..41

Table 3.4 Association between low birth weight (LBW) and ambient air pollution……..44

Table 3.5 Association between PTB and ambient air pollution…………………………..48

Table 3.6 Association between stillbirth, spontaneous abortion (SAB) and ambient air pollution……………………………………………………………………………………..51

Table 4.1 Maternal characteristics of included singleton births in Western Australia, 2000-2015 (N= 414,771) ……………………………………………………………………………..77

Table 4.2 Descriptive statistics of the monthly environmental exposures for three months preconception through to birth delivery for included singleton births in Western Australia, 2000-2015 (N= 414,771) ………………………………………………….……………………..77

Table 4.3 Adjusted hazard ratios per 5 and 10 µg/m^3 $PM_{2.5}$ increments for stillbirth and sPTB for cumulative $PM_{2.5}$ exposures over three months preconception through to pregnancy and trimester-specific periods in Western Australia, 2000……………………………………………….81

Table 4.4 Interaction effects as the ratio of hazard ratios per 5 µg/m^3 $PM_{2.5}$ increment for stillbirth and sPTB for preconception to pregnancy cumulative $PM_{2.5}$ exposures in moderate and high UTCI exposure, using low UTCI as a reference in Western Australia, 2000-2015 ……………………..……………………………………………………………………….82

Table 5.1 Maternal characteristics of included singleton term births in Western Australia, 2000-2015 (N= 384,882)…………………………………………………………………94

Table 5.2. Descriptive statistics of the monthly environmental exposures for three months preconception through to birth delivery for included singleton term births in Western Australia, 2000-2015 (N= 384,882)……………………………………………………………………95

Table 5.3 Adjusted hazard ratios per 5 and 10 µg/m^3 $PM_{2.5}$ increments for adverse fetal growth for cumulative $PM_{2.5}$ exposures over three months preconception through to pregnancy and trimester-specific periods in Western Australia, 2000–2015. ……………………………………..98

Table 5.4 Interaction effects as the ratio of hazard ratios per 5 µg/m^3 $PM_{2.5}$ increment for adverse fetal growth for preconception to pregnancy cumulative $PM_{2.5}$ exposures in moderate and high UTCI exposure, using low UTCI as a reference in Western Australia, 2000-2015…………99

Table 6.1 Descriptive statistics of the births, environmental exposures, and sociodemographic factors across the 260 districts in Ghana, 2012–2020……………………………………………..114
Table 6.2 Monthly adjusted ratio of relative risk for the distributed lag linear association between $PM_{2.5}$ exposure at 5 and10 μg/m^3 increase and risk of stillbirth from the month of stillbirth in high as compared to low biothermal stress in Ghana, 2012–2020……….…………………………118
Table 7.1 Characteristics of the systematic reviews on ambient air temperature and adverse birth outcomes, ordered from current to earliest………………………………….………………129
Table 7.2 Summary of main findings in the systematic reviews on ambient air temperature and adverse birth outcomes…………………………………………………………………......132
Table 8.1.1The descriptive statistics of daily mean UTCI (°C), Western Australia, 2000-2015…………………………………………………………………………………………151
Table 8.1.2 Number of stillbirths by year, season, and fetal and maternal sociodemographic characteristics included in the study, Western Australia, 2000-2015 (N= 2,835)……………151
Table 8.1.3. The cumulative relative risks of stillbirth for different UTCI levels relative to median (13.9 °C), Western Australia, 2000-2015………………..……………………………………152
Table 8.1.4. The attributable risk of stillbirths per 10,000 births for exposure to 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015…………………………..153
Table 8.1.5 The cumulative relative risks of stillbirth stratified by fetal gestational age and sex for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015………………………………………………………………………….…………...153
Table 8.1.6. The cumulative relative risks of stillbirth stratified by maternal tobacco smoking status, marital status, race/ethnicity, and socioeconomic status for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015……………………………………………..155
Table 8.1.7 The cumulative relative risks of stillbirth stratified by maternal age for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015………….…156
Table 8.2.1 The number of spontaneous PTB by year, season, type, and fetal and maternal sociodemographic characteristics in Western Australia, 2000-2015 (N=15,576)……………..170
Table 8.2.2. The cumulative relative risks of spontaneous PTB for different UTCI percentiles relative to the median (13.8 °C) in Western Australia, 2000-2015……………………….....................171
Table 8.2.3 The estimated interaction effects as ratio of relative risks (RRRs) and 95% confidence intervals (95% CI) of spontaneous preterm birth, relative to the indicated reference subgroup for acute cumulative exposure (lag 0-6) to 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015 ………………………………………….……………………………………..172

Table 9.1 Maternal characteristics of included singleton births in Western Australia, 2000-2015 (N =415,271)…………………………………………………………………………………………185
Table 9.2 Descriptive statistics of the average UTCI (℃) during twelve weeks preconception through to gestational weeks at delivery exposure periods for included singleton births in Western Australia, 2000-2015 (N= 415,271)…………………………..…………………………………………....185
Table 9.3 The exposure-response association between maternal cumulative UTCI exposures over twelve weeks preconception through to pregnancy and trimester-specific periods as compared with median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB at various percentiles of the exposure in Western Australia, ……………………………………………………………………189
Table 10.1Maternal characteristics of included singleton term births in Western Australia, 2000-2015 (N= 385,337) …………………………………………………………….............................202
Table 10.2 Descriptive statistics of the average UTCI (℃) during twelve weeks preconception through to gestational weeks at delivery exposure periods for included singleton term births in Western Australia, 2000-2015 (N= 385,337)…………………………………………………...203
Table 10.3. The exposure-response association between maternal cumulative UTCI exposures over twelve weeks preconception through to pregnancy and trimester-specific periods with reference to the median 13.4 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various percentiles of the exposure in Western Australia, 2000–2015……………………………………206
Table 11.1 Descriptive statistics of the births, environmental exposures, and sociodemographic conditions across the 260 districts in Ghana, 2012–2020……………………………………….220
Table 11.2 The estimated cumulative relative risks (RRs) and 95% confidence intervals (95% CIs) of stillbirth at different percentiles of UTCI, relative to the median UTCI (28.8 °C) in Ghana, 2012-2020……………………………………………………………………………………………..222
Table 11.3 The cumulative monthly attributed risks (ARs) and 95% confidence intervals (95% CIs) per 10,000 births at 90th percentile of UTCI (30.8 °C), relative to median UTCI (28.8 °C) in Ghana, 2012-2020……………………………………………………………..........................222
Table 11.4 The ratio of relative risk (RRR) and 95% confidence intervals (95% CI) of stillbirth for comparing the risk between two subgroups at 90th percentile relative to the median UTCI in Ghana, 2012-2020. ……………………………………………………………….…………………223

List of Figures

Figure 1.1 Plausible biological mechanistic pathways of reproductive health outcomes: a conceptual framework of the shared pathoaetiological effects of physical and socio-economic environments on maternal biological factors resulting in adverse birth outcomes and pregnancy complications ……………………………………………………………………………………………………4

Figure 1.2 Flow chart showing the structure of the thesis………………………………….………9

Figure 3.1 Spatial distribution of 287 country-specific primary studies from 31 countries included in the 36 systematic reviews and meta-analyses on ambient air pollution and adverse birth outcomes ……………………………………………………………………………………………………24

Figure 3.2 Forest plot of the association between change in birth weight (BW) per 10µg/m^3 $PM_{2.5}$ increase at different pregnancy periods…………………………………………………………40

Figure 3.3 Forest plot of the association between preterm birth (PTB and fine particulate matter ($PM_{2.5}$) per 10µg/m^3 increment) during different pregnancy periods……………………….........47

Figure 4.1. Adjusted hazard ratios for the association between 10, 8, 5, and 3 µg/m^3 increase in $PM_{2.5}$ exposure and risks of stillbirth and sPTB, by month of gestation from three months preconception (-2 to 0) to birth (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015………………………………………………………………………….....................78

Figure 4.2. Adjusted hazard ratios of stillbirth and sPTB due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10 for stillbirth and 1 to 9 for sPTB) at different thresholds using 5µg/m^3 $PM_{2.5}$ as a reference in Western Australia, 2000–2015…........................80

Figure 5.1. Adjusted hazard ratios for the association between 10, 8, 5, and 3µg/m^3 increase in $PM_{2.5}$ exposure and risks of term adverse fetal growth, by month of gestation from three months preconception (-2 to 0) to birth (1 to 10) in Western Australia, 2000–2015. ……………………..96

Figure 5.2. Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5µg/m^3 $PM_{2.5}$ as a reference in Western Australia2000-2015……………………………………………………….97

Figure 6. 1 Average monthly variation of $PM_{2.5}$ exposure (µg/m^3) and stillbirth rate across the 260 districts in Ghana from January 2012 to December 2020………………………………………114

Figure 6.2 District-level spatial distribution of the overall average $PM_{2.5}$ exposure (µg/m^3) and incidence of stillbirth (per 1000 births) across the 260 districts in Ghana during 2012–2020 …………………………………………………………………………………………………115

Figure 6.3 Monthly adjusted relative risk for the distributed lag linear association between $PM_{2.5}$ exposure at 5,10, 20.5, and 23.3 µg/m^3 increase and risk of stillbirth from the month of stillbirth (lag

0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020……………………………………………………………………………………………116
Figure 6.4 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 μg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. ………………………………………..……………………………117
Figure 7.1. Distribution of 71 country-specific distinct primary studies from 28 countries (out of 78 total of which 7 were multi-country studies) included in the 9 systematic reviews………………131
Figure 8.1.1 Exposure-response curves of daily UTCI and cumulative relative risk of stillbirths, relative to median UTCI of 13.9 ºC on the event day and up to different preceding days……….152
Figure 8.2.1 Flow chart of the selection of the eligible spontaneous vaginal delivery preterm births included in this study, Western Australia, 2000-2015. Note, SA1; statistical area level ………………………………………………………………………………………..………..167
Figure 8.2.2 Exposure-response curves of daily UTCI and cumulative relative risk of spontaneous PTB at different lag structures using median UTCI of 13.8 ºC as reference. ………..…………………………………………..……………………………………..171
Figure 9.1 Adjusted hazard ratios of stillbirth and sPTB associated with weekly-specific UTCI over 12-week preconception (-11 to 0) through to gestational week at delivery (1 to 42 for stillbirth and 1 to 36 for sPTB) at different thresholds of UTCI using the median of 14.2 ˚C as a reference in Western Australia, 2000–2015. …………………..……………………..186
Figure 9.2 Adjusted hazard ratios of stillbirth and sPTB associated with monthly-specific UTCI over from three months preconception (-2 to 0) to birth (1 to 10 for stillbirth and 1 to 9 for sPTB) at different thresholds of UTCI using the median of 14.2 ˚C as a reference in Western Australia, 2000 – 2015 …………………………………………………………..……………………..187
Figure 10.1 Adjusted hazard ratios of term SGA, LGA, and LBW associated with weekly-specific UTCI over 12- week preconception (-11 to 0) through to gestational week at delivery (1 to 42) at different thresholds of UTCI using median of 14.2 ◦C as reference……………………………204
Figure 10.2. The exposure-response association between maternal monthly-specific UTCI exposures for three months preconception through to pregnancy with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW……………………………………………205
Figure 11.1 Geographical distribution of the overall average incidence of stillbirth (per 1000 births) and the UTCI (˚C) across the 260 districts in Ghana during 2012–2020. Mapping was based equal interval classification method in ArcGIS……………………………………………………..220

Figure 11.2 Average monthly variations of UTCI and stillbirth rate across the 260 districts in Ghana from January 2012 to December 2020…………………………………………….....................221
Figure 11.3 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 ^{o}C)………………………………………….………...221

List of Abbreviations

AIC	Akaike Information Criterion
AQG	Air Quality Guidelines
AODs	Aerosol Optical Depths
CASP	Critical Appraisal Skills Program
CHIM	Centre for Health Information Management
Cox PH	Cox Proportional Hazard
CI	Confidence Interval
DLM	Distributed Lag linear Model
DLNM	Distributed Lag Non-linear Model
DHS	Demographic and Health Survey
DHIMS2	District Health Information Management System version 2
GHS	Ghana Health Service
HSP	Heat Shock Proteins
HREC	Human Research Ethics Committees
HR	Hazard Ratios
JBI	Joanna Briggs Institute
LGA	Large for gestational age
LMICs	Low-to-middle-income countries
MNS	Midwives Notification System
$PM_{2.5}$	Particulate matter ≤ 2.5 µm in aerodynamic diameter
PET	Physiologically Equivalent Temperature
PTB	Preterm birth
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Relative Risk
RHR	Ratio of Hazard Ratios
RRR	Ratio of Relative Risk
SDG	Sustainable Development Goal
SA1	Statistical Area level 1
SES	Socioeconomic Status
SGA	Small for gestational age
sPTB	Spontaneous Preterm birth
SSA	Sub-Saharan Africa
USA	United States of America

UTCI	Universal Thermal Climate Index
WHO	World Health Organization

Part I

Preface

Chapter 1: Introduction

1.0 Preamble

This chapter includes important information such as the background and reasons for the study, the hypothesis being tested, the goals and objectives of the research, the significance of the study, and its potential impact on public health. Additionally, it outlines the structure of the thesis.

1.1 Background and rationales

1.1.1 Ambient air pollution, extreme temperatures, and birth outcomes

1.1.1.1 The burden and plausible biological mechanistic pathways

Air pollution and air pollution events transcend geographical and political boundaries and pose a global threat to public health.[1] Air pollution has moved from the fifth to the fourth global leading risk factor for mortality (causing one in every nine deaths) with case fatalities more than those from other well-known risk factors.[1,2] Air pollutants, either gaseous or particulates are derived from biogenic (caused naturally) and/or anthropogenic (caused by a human) activities. Anthropogenic activities such as the combustion of fossil fuels and biomass to generate energy for transportation (with cars estimated as the highest contributor), industrial and domestic uses, and suspended particles from construction activities are major sources of air pollution.[2,3] Minor sources include other human activities and several natural sources such as wildfires, desert dust, and volcanic eruption.[3] The air pollutants that are known to have harmful effects on human health include both gaseous pollutants such as nitrogen dioxide, carbon monoxide, ozone, and sulphur dioxide, as well as particulate matter (PM) with aerodynamic diameter ≤ 2.5 µm ($PM_{2.5}$) and ≤ 10 µm (PM_{10}).[2,4] These pollutants are considered as criteria air pollutants. In 2019, more than 90% of the global population, particularly low-to-middle income countries (LMICs) lived in heavily polluted areas with ambient $PM_{2.5}$ concentration exceeding the 2005 World Health Organization (WHO) air quality guideline (AQG) of 10 µg/m^3 annual average.[2,4] Although, air pollution in many countries, particularly in LMICs has not improved substantially, WHO has recently updated the AQGs to more stringent limits based on accumulating epidemiological evidence of increasing health burden associated with air pollution. For example, the annual average AQG for $PM_{2.5}$ is now 5 µg/m^3 to stimulate improved air quality and health benefits.[2] Among the criteria air pollutants, $PM_{2.5}$ has the highest penetration capacity which makes it easily inhaled deep into the lungs and entering the bloodstream to cause cardiovascular, cerebrovascular, respiratory, reproductive, and neurodevelopmental disorders, cancers, developmental morbidities, and related mortality.[2,3,5,6]

The formation and effects of air pollution are influenced by climate change,[2] which has been caused in large part by human activities.[7] These activities have contributed substantially to the increasing frequency, duration, and intensity of extreme weather events such as heatwaves, droughts, flooding, hurricanes, and wildfires.[7] These events have direct and indirect adverse impacts on human health and the ecological system, making it a matter of global public health concern.[7,8] Climate change, including extreme weather events, can have negative impacts on health similar to air pollution. These impacts include respiratory, cardiovascular, neurological diseases, infectious diseases, and premature mortality.[9]

Air pollution and extreme climate events are ubiquitous environmental exposures that affect everyone but some subpopulations such as socioeconomically disadvantaged persons, the aged, people with underlying chronic health conditions, young children, pregnant women and newborn babies are disproportionately vulnerable.[8,9] Given the long-term and intergenerational effects of air pollution and climate change, the impacts on pregnant women and unborn babies are particularly worrying.[10,11] Adverse birth outcomes such as preterm birth, low birth weight, stillbirth, and fetal growth restriction are critical markers of survivorship, health in early life and potential health later in the lifecourse.[12-14] Several recent epidemiological findings have indicated both ambient air pollution and extreme temperatures as risk factors for birth outcomes.[15,16] This is pathophysiologically plausible as explored through environmental epigenetics understanding of gene-environment interaction [17-19] and experimental investigations in animals.[20-22] The shared patho-aetiological process for adverse pregnancy outcomes is suggested to involve cumulative effects through synergistic interactions among maternal biologic factors, obstetric/health conditions, social factors, sociodemographic factors, behavioural risk factors, and physical environmental stressors (e.g., air pollutants and extreme temperatures) that induce placental modifications or mal-pathophysiologies.[23-25] The environmental stressors disrupt normal maternal physiology and thereby trigger pathophysiological responses, especially excess oxidative stress, immuno-inflammatory dysfunction, and metabolic alterations or damage to the functional biomolecules (lipids, proteins, DNA, RNA), irregular vascular constriction and dilation in both the mother and fetus (Figure 1.1).[17-22]

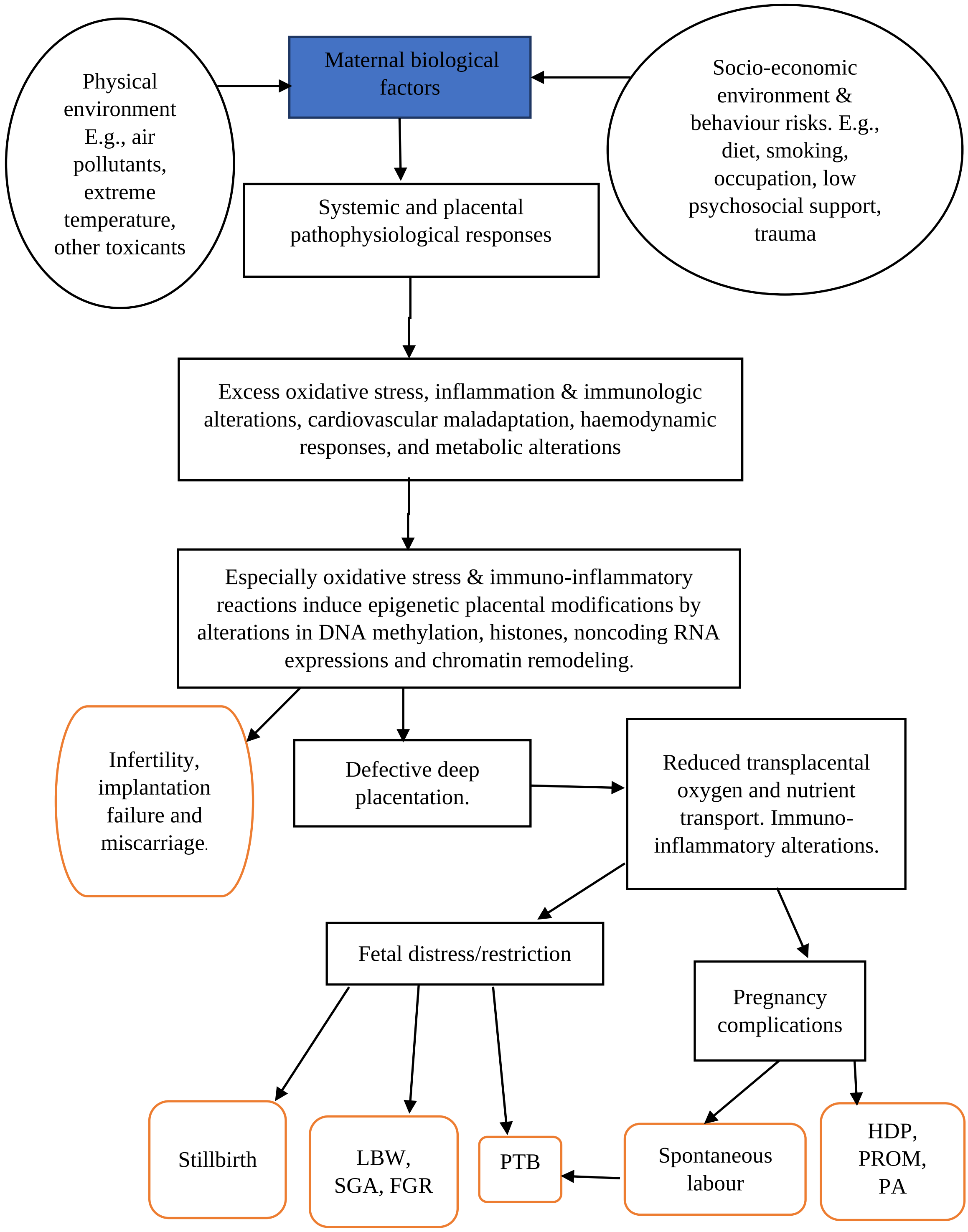

Figure 1.1: Plausible biological mechanistic pathways of reproductive health outcomes: a conceptual framework of the shared pathoaetiological effects of physical and socio-economic environments on maternal biological factors resulting in adverse birth outcomes and pregnancy complications. Note: LBW, low birth weight; SGA, small for gestational age; FGR, fetal growth restriction; PTB, preterm birth; PROM, prelabour rupture of membranes; PA, placental abruption; HDP, Hypertensive disorders of pregnancy.

1.1.2 Epidemiological evidence, methodological limitations, and gaps

$PM_{2.5}$ has received the most attention because of the complex and heterogeneous mixture of particulate matter, high inhalation capacity, high toxicity, and a better understanding of the potential biological and molecular pathways of the plausible causality of $PM_{2.5}$ on human health.[26,27]

Epidemiological findings from several systematic reviews with or without meta-analyses (SRMAs) have shown that maternal exposure to ambient air pollution, particularly $PM_{2.5}$ [15,28-34] and ambient temperature [11,16,35,36] exposure during pregnancy has a putative causal effect on various adverse birth outcomes. However, the SRMAs have varied scopes, quality, and conclusions. In situations like this, it is advisable to conduct a systematic summary of reviews, also known as an umbrella review. This type of review allows for a comprehensive and systematic evaluation of existing evidence, enabling researchers to compare and contrast different studies and synthesise findings in order to inform future research and policy decisions.[37,38] Umbrella reviews on the association between birth outcomes and other exposures such as periodontal disease [39] and antenatal depression [40] have been conducted but not for air pollution or temperature. One exception is a broad summary of meta-analyses which conducted a literature search in December 2011 [41] and included only one meta-analysis.[28] Moreover, in addition to residual confounding by individual predisposition which is difficult to rule out completely in observational studies, several other methodological limitations and gaps have been identified in the current primary studies that require further rigorous investigations to strengthen the evidence for timely and appropriate interventions.[42] Specific issues are, surrogate use of temperature instead of a biothermal metric, choice of statistical analysis of the exposure-response association, unknown critical susceptible exposure windows and lack of sufficient evidence from LMICs or from other areas within the same country. The geographical variability in the effects of exposure is also a concern because spatiotemporal variations in the exposures ($PM_{2.5}$ and temperature), population characteristics, and acclimatisation make it difficult to extend findings to other unstudied geodemographic settings.

The current variations in the exposure assessment techniques and geographically sparse measurement of pollutants make it challenging to synthesise the results because applying different exposure assessment methods on different study populations is highly likely to yield results of different effect sizes or directions. Modern advanced assessments of national [43,44] or global [45-47] $PM_{2.5}$ concentrations by combining aerosol optical depth (AOD) data from multiple satellites, simulations from chemical transport models, and ground monitoring measurements with an application of Geographically Weighted Regression techniques at the fine spatiotemporal resolutions are emerging to minimise the issue of exposure misclassification.[43] This provides a suitable approach for the estimation of environmental exposures, especially for LMICs and areas with sparse local ground-based measurements. For example, the few studies from Australia were mostly restricted to cities, predominantly in Brisbane [48] with only one on $PM_{2.5}$ in Perth, Western Australia.[49] This is partly due to the geographic sparsity of air quality monitoring. The global $PM_{2.5}$ concentrations at fine spatiotemporal resolutions [43-45] as applied in related studies [50-56] provide the opportunity for state-wide investigation in Western Australia to fill this gap. The identification of *in utero* critical susceptible exposure windows is one of the more commonly investigated objectives in the perinatal and environmental epidemiology literature. However, investigation of air pollution-birth outcome associations was commonly based on whole-pregnancy and separate models for trimester-average exposures.[15,57] For ambient temperature-birth outcome associations, studies mostly examined short-term or acute effects with varied exposure thresholds or definitions of heatwaves while few investigated the whole-pregnancy and trimester-specific effects.[11,16] It has been shown that trimester-specific effects give bias effect estimates, identify incorrect critical windows, and cannot identify other potential biologically fine temporal critical windows (e.g., days, weeks, months) that might not follow pre-defined clinical trimesters.[58] Time-varying environmental exposures have immediate, delayed (lagged), and cumulative effects which require a unified modelling framework to characterise both the exposure-response and lag-response associations to flexibly describe unbiased estimates and to identify fine temporal critical susceptible exposure windows.[58-60] To address exposure-lag-response association and cumulative effects of environmental exposures, distributed lag linear and non-linear model (DLNM) was proposed and implementable with the 'dlnm' R package recently developed.[58-60] This novel approach was applied to identify the potential critical susceptible exposure windows of the effects of ambient air pollution and temperature on birth outcomes in other countries such as the United States,[61-63] China,[64-71] Israel [72] and France.[73] High-quality methods such as this need to be investigated in other settings such as Australia and particularly high-risk LMICs (e.g., Ghana) to identify potential critical susceptible exposure windows of clinical relevance to guide public health interventions and policy.

Another important issue that is now receiving attention is the surrogate use of ambient temperature or apparent temperature (combination of temperature and relative humidity) as a thermal metric to assess the impact of heat and cold stress on health outcomes. Ambient temperature is easily available and forecasted but it is well known that air temperature alone cannot represent the ambient thermal environment which is a combination of air temperature, radiant temperature, humidity, and wind.[74,75] Also, thermal stress imposed on a person with a resultant physiological response (thermal strain) is a cumulative function of the total thermal environment, activity-based metabolic heat production, and thermophysiological or behavioural responses such as clothing.[74,76] Given technological and computational advancement, it is, therefore, recommended recently that human thermophysiological (biothermal) metrics rather than singular air temperature should be used in related epidemiological research, thermal-health warning systems, and policy decisions.[74-77] Comprehensive evaluation of several biothermal metrics identified four metrics as principally appropriate: Universal Thermal Climate Index, Perceived Temperature, (Modified) Physiologically

Equivalent Temperature, and rational Standard Effective Temperature.[76] Comparative studies indicated Universal Thermal Climate Index (UTCI) to be most suitable as it has relatively high climatic sensitivity and best simulates the thermal response of the human body.[78-80] Recent applications of UTCI in epidemiology, biomedical, weather forecasting, and thermal-health warning systems studies have been reviewed elsewhere.[81,82] Thus, there are methodological challenges in environmental and perinatal epidemiological studies [42] but emerging novel approaches are encouraging to strengthen the evidence.

The impact of air pollution on health, especially on vulnerable populations like pregnant women and unborn babies, is well-documented. However, it is important to note that the effects of air pollution and climate change-related health risks may vary across different regions due to varying levels of exposure and vulnerability. This is why it is crucial to conduct further scientific inquiries in regions that are most affected or vulnerable, particularly in LMICs like Ghana, which shares many exposures and health vulnerabilities experienced in LMICs in the African region. By studying the effects of air pollution and climate change-related health risks in Ghana, we can better understand how these issues impact vulnerable populations in LMICs. In contrast, Australia, as a high-income country, has unique attributes such as high temperatures and more prevalent bushfires, which may also pose health risks to vulnerable populations. Additionally, while Australia has relatively low city-wide average particulate matter air pollution emissions compared to other countries, it is still important to investigate how air pollution affects vulnerable populations in this context. Thus, by synthesising the available evidence and using birth cohorts in both Australia and Ghana, this thesis aims to provide a comprehensive understanding of the effects of air pollution and climate change-related health risks on vulnerable populations in different regions. By doing so, we can inform development of more targeted and effective strategies to mitigate the impact of air pollution and climate change on public health.

1.2 Study hypothesis, aims and objectives

We hypothesise that maternal exposures to fine particulate air pollution ($PM_{2.5}$) and biothermal stress will elevate the risk of birth outcomes substantially in high-exposure high-morbidity settings that are under-researched (Ghana) as well as in low-exposure low-morbidity settings (Australia), which will reveal that there is no safe lower limit of exposure. The primary aim of this project is to estimate the exposure-lag-response effects of spatiotemporal $PM_{2.5}$ and biothermal stress (measured with UTCI) on the following adverse birth outcomes: preterm birth (PTB), stillbirth, low birth weight (LBW), small for gestational age (SGA), and large for gestational age (LGA).

Specifically, this thesis aims

i. To employ systematic review of reviews (umbrella review) to synthesise the current evidence on the association between ambient air pollution and birth outcomes.

ii. To estimate the risks attributable to $PM_{2.5}$ on birth outcomes with identification of the potential critical susceptible exposure periods and the vulnerable subpopulations.

iii. To employ systematic review of reviews (umbrella review) to synthesise the current evidence on the association between ambient temperature and birth outcomes.

iv. To estimate the risks attributable to biothermal stress on birth outcomes with the identification of the potential critical susceptible exposure periods and the vulnerable subpopulations.

1.3 Significance and public health implications

The umbrella review will provide the first comprehensive evidence synthesis of the systematic reviews or meta-analyses on the environmental exposures (air pollution and extreme temperatures) and adverse birth outcomes to guide policy and further studies. This thesis will address some methodological limitations and gaps, contribute to, and strengthen the existing evidence on adverse birth outcomes associated with two important environmental exposures. Potential susceptible windows of the exposures will be identified to elucidate plausible biological mechanisms and to inform time points for intervention during maternal care. This study will also provide empirical evidence from low-exposure low-morbidity settings with high-quality data (Western Australia) and high-exposure high-morbidity settings with less or low-quality data where the effects are poorly understood (Ghana). The study's findings may provide insights into the exposure-response relationships in environmental and perinatal epidemiology at both high and low exposure levels. However, it is important to note that the study designs are different due to varying levels of data availability. Therefore, the thesis is not intended for direct comparison of findings from Australia and Ghana. Additionally, highlighting environmental health discrepancies within countries by identifying biologically susceptible and sociodemographically vulnerable subpopulations is crucial to prioritise public health interventions, targeted toxicological investigations, and a better understanding of aetiologic pathways. This is also the first study to use a modern biothermal metric (UTCI) rather than ambient temperature to examine the association and critical susceptible periods of bioclimatic conditions and birth outcomes. Thus, this thesis will provide useful information for the scientific community, healthcare providers such as public health officers and clinicians, policymakers, and pregnant women to protect fetal health.

1.4 Structure of the thesis

This thesis included both peer-reviewed published articles and unpublished manuscripts. The thesis has been structured into 12 chapters, divided into four parts as summarised in Figure 1.2.

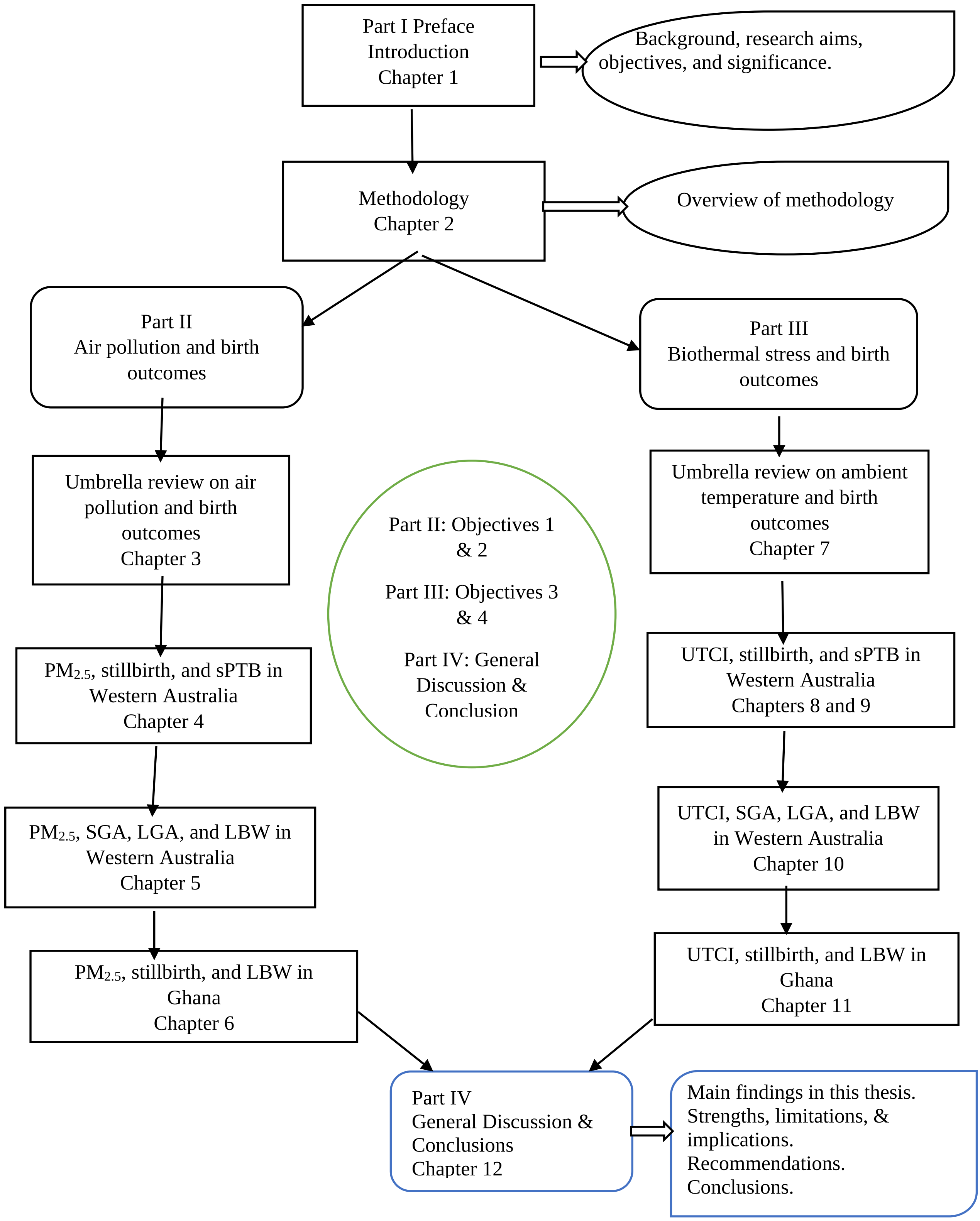

Figure 1.2 Flow chart showing the structure of the thesis.
Note: sPTB, spontaneous preterm birth; SGA/LGA, small and large for gestational age; LBW, low birth weight; $PM_{2.5}$, fine particulate matter; UTCI, Universal Thermal Climate Index

The Preface (Part I) is composed of Chapters 1 and 2 and provides an introduction and overview of the methodology employed in this thesis, respectively.

Chapter 1 introduces the background and rationale, study hypotheses, aims and specific objectives, significance, and public health implications, and ended with the structure of this thesis.

Chapter 2 provides a concise description of the overall methodology employed in this thesis which included the study designs, data sources, outcomes and exposure measures, statistical analyses, and ethical approvals.

Part II covers Chapters 3 to 6 on the association between air pollution and birth outcomes. Specially,

Chapter 3 provides umbrella review of systematic reviews and meta-analyses on ambient air pollution and adverse birth outcomes. The up-to-date epidemiological findings, gaps, and recommendations were presented.

Chapter 4 contains primary investigations of the long-term effects of maternal exposure to $PM_{2.5}$ and the risks of stillbirth and sPTB in Western Australia. Critical exposure periods of increased susceptibility and vulnerable subpopulations and joint effects with biothermal stress were examined in this chapter.

Chapter 5 contains primary investigations of the long-term effects of maternal $PM_{2.5}$ exposure on the risks of adverse fetal growth (SGA, LGA, and LBW) in Western Australia. The identification of susceptible exposure periods and vulnerable subpopulations and the joint effect of $PM_{2.5}$ with biothermal stress were also examined.

Chapter 6 contains a primary investigation of long-term maternal exposure to ambient $PM_{2.5}$ and the risks of stillbirth in Ghana. The identification of susceptible exposure periods and vulnerable subpopulations and the joint effect of $PM_{2.5}$ with biothermal stress were also examined.

Part III covers Chapters 7 to 11 on the association between ambient temperature or biothermal stress and birth outcomes. Specially,

Chapter 7 provides systematic umbrella review of systematic reviews and meta-analyses on ambient temperature and adverse birth outcomes. The up-to-date epidemiological findings, gaps, and recommendations were presented.

Chapter 8 contains primary investigations of maternal exposure to short-term biothermal stress and the risks of stillbirth and sPTB and the identification of vulnerable subpopulations in Western Australia.

Chapter 9 contains primary investigations of maternal exposure to long-term biothermal stress and the risks of stillbirth and PTB with the identification of susceptible exposure periods and vulnerable subpopulations in Western Australia.

Chapter 10 contains primary investigations of the long-term effects of biothermal stress exposure on the risks of adverse fetal growth (SGA, LGA, and LBW) with the identification of susceptible exposure periods and vulnerable subpopulations.

Chapter 11 contains a primary investigation of long-term maternal exposure to biothermal stress and the risks of stillbirth in Ghana with the identification of susceptible exposure periods and vulnerable subpopulations.

Part IV covers Chapter 12 concludes the thesis with general discussion and conclusions. Specifically, this chapter gives summary of the main findings, implications, strengths, limitations, recommendations, and conclusions.

References and appendices are presented at the end of this chapter.

Chapter 2: Methodology overview

2.0 Preamble

This chapter provides a concise summary of the overall methodology utilised in this thesis, covering the umbrella reviews of systematic reviews and meta-analyses, and retrospective observational studies conducted in Western Australia and Ghana on ambient particulate matter, biothermal stress, and birth outcomes. Successive chapters contain detailed descriptions of the methodology applied to investigate each specific objective outlined in chapter 1 of this thesis.

2.1 Ambient air pollution, temperature, and birth outcomes: An umbrella review of systematic reviews and meta-analyses

Objectives 1 and 3 were achieved by adopting an umbrella reviews approach to systematically synthesise the existing evidence in the systematic reviews and meta-analyses on ambient air pollution, ambient temperature, and adverse birth outcomes. Before the umbrella review, a comprehensive protocol was developed, registered prospectively in PROSPERO (CRD42020200387), and published as a peer-reviewed working document.[83] The umbrella reviews were conducted by following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [84] and the Joanna Briggs Institute (JBI) umbrella review guidelines.[37,85] Search terms and strategies were developed to conduct an advanced search in electronic databases such as PubMed, CINAHL, Scopus, Medline, Embase, the Web of Science Core Collection, systematic reviews repositories, grey literature databases, and internet search engines. References of included studies were also used as the data sources. The results were synthesised by adapting a semi-quantitative and narrative synthesis method as reported elsewhere.[86-89] The umbrella review was reported separately for ambient air pollution and temperature as detailed in Chapters 3 and 7, respectively.

2.2 Ambient particulate matter, biothermal stress, and birth outcomes: retrospective observational studies in Western Australia and Ghana

2.2.1 Study populations and settings

To address objectives 2 and 4, primary studies were conducted in Western Australia and Ghana. Western Australia is the largest state in Australia by area, covering 2.5 million km^2 with a population of 2.7 million in 2021.[90] This state has diverse climatic conditions, ranging from tropical north, temperate south-west, and arid or semi-arid in the other parts. There are generally four seasons –summer (hottest months December–February), Autumn (transition months March-May), winter (coldest months June–August), and spring (transition months September–November). In 2016, a total of 35,890 births at or greater than 20 completed weeks of gestation or more than 400 grams in weight were recorded in Western Australia. Of these, 0.7% were stillbirths and 6.5% were LBW (5.5% of LBW were among singleton births). PTB prevalence was 8.9% of which 7.3% were among singleton births and 2.2 % of PTB died during labour while 3.9% died before the onset of labour or at an unknown time.[91] Ghana is a Sub-Saharan Africa (SSA) country along the coast of West Africa. According to the 2021 census, Ghana's population was 30.8 million at a growth rate of 2.1% with a population density of 129 persons/km^2.[92] The country currently has 16 administrative regions which are further subdivided into 260 local districts. The local districts are the lowest level of policy implementations, including health services management. Due to the data availability, these 260 geographical local districts are the unit of analysis in the Ghana study. Ghana has a tropical and humid monsoon climate with two seasons – a dry winter season ("harmattan season") characterised by the Sahel dust (December-March) and a rainy summer season (April-November). Recent Ghana demographic or maternal health surveys reported that 2% of births ended in stillbirth [93] and 10% in LBW.[94] The state of global air report in 2019 indicated average $PM_{2.5}$ values of 8.6 μg/m^3 and 35.0 μg/m^3 in 2017 for Australia and Ghana, respectively.[95] The average yearly temperature of Australia is 23^{0}C and 30 ^{0}C for Ghana.

2.2.2 Study designs, birth data, and variables

Longitudinal retrospective birth cohort study designs were conducted at the individual-level in Western Australia and local district-level in Ghana using birth delivery registries. Electronic record in the form of a de-identified Midwives Notification System (MNS) was obtained from Western Australia Health Departments from 1st January 2000 to 31st December 2015 to define a birth cohort from conception to birth delivery (either live or stillborn). The MNS is a statutory routine data collection system that includes all births with ≥20 completed gestational weeks or ≥400 g birth weight if the gestational length is unknown.[96] The MNS contains sociodemographic and clinical information on both mother and baby, including maternal residential address as statistical area level 1 (SA1, second smallest geographical unit in Australia) at the time of birth delivery. This thesis included singleton births with SA1 addresses (n= 426,465). Further inclusion and exclusion criteria were applied depending on the specific study as detailed in each chapter.

Ghana is now piloting electronic birth or maternal and child health registry with individual-level details. Thus, as a common challenge in LMICs, particularly SSA countries, including Ghana, individual-level electronic maternal or birth registries are currently unavailable to conduct large population-based birth cohort studies.[97] However, Ghana Health Service (GHS) recently started using an integrated internet-based electronic District Health Information Management System (DHIMS2) to routinely aggregate monthly health reports as counts, including birth records from public and private health facilities. The records are collated by local district health directorates and remotely transferred into a centralised depository.[98,99] The monthly district-level stillbirth in Ghana from 1st January 2012 to 31st December 2020 were obtained from the Centre for Health Information and Management (CHIM) of GHS.

A birth from at ≥37 completed weeks of gestation is defined as term birth. The adverse birth outcomes considered for Western Australia were sPTB (<37 completed weeks of gestation with spontaneous onset of labour and vaginal delivery), stillbirth (fetal death at ≥ 20 completed weeks of gestation based on Australian definition[100]), and adverse fetal growth which included term LBW (birth weight <2,500 g), and term SGA and LGA (birth weight below the 10th and 90th centile, respectively for that gestational age and sex). The birth outcome included in the Ghana study was stillbirth (fetal death at ≥ 28 completed weeks of gestation based on the WHO classification [93,94,100]).

Covariates or potential confounding factors were selected *a priori* and included based on biological mechanism and epidemiological evidence in the literature[15,16,101] and data availability. For the Western Australian birth cohort, this included sex (male or female), year and season of conception, maternal age, race or ethnicity (Caucasian or non-Caucasian), marital status (married or unmarried), smoking during pregnancy (non-smoker or smoker), parity (nulliparous or multiparous), remoteness indicator (urban or rural) and area-level socioeconomic status (SES) derived by the Australian Bureau of Statistics as Relative Socio-economic Disadvantage.[102] The covariates included for Ghana were district-level percentages of sex (male and female) and maternal age at delivery (10–19, 20–34, and ≥35 years), SES, and population density.

2.2.3 Exposures and other socio-environmental data

The main exposures assessed in this thesis were $PM_{2.5}$ and UTCI. The annual average of $PM_{2.5}$ concentrations for both total mass and dust/sea-salt removed [46,47] and monthly total mass $PM_{2.5}$ concentrations [45] at grid cell resolution of 0.01º x 0.01º (~1km x 1 km) covering the global land surface were obtained freely from the Atmospheric Composition Analysis Group. The $PM_{2.5}$ estimates were derived by combining aerosol optical depth estimates from multiple satellite instruments, GEOS-Chem chemical transport model, and ground-based monitoring measurements of $PM_{2.5}$ to calibrate the global gridded $PM_{2.5}$ concentrations using geographically weighted regression with good performance.[45-47] The biothermal metric, UTCI is a composite bioclimatic metric that captures the total ambient thermal environmental condition (air temperature, wind speed, relative humidity, and radiation) and non-meteorological variables, and the thermal properties of clothing derived from the advanced Fiala multi-node model of human heat balance under reference conditions.[103-105] Daily or 24-h averages of the global gridded UTCI derived from ERA5 reanalysis at 0.25˚× 0.25˚spatial resolution (~27 km x 27 km) were obtained freely from the Climate Data Store of Copernicus Climate Change Service.[106]

The spatiotemporally resolved monthly $PM_{2.5}$ and daily UTCI datasets were obtained over the study periods and processed at SA1 for Western Australia and local districts of Ghana using ArcGIS software (version 10.8.1) and 'terra' R package. For the Western Australia birth cohort, exposures were assigned to each birth based on dates of birth and conception and SA1 maternal residential address. The annual average $PM_{2.5}$ concentrations with both total mass and dust/sea-salt removed [46,47] and other gridded datasets such as population,[107,108] and Gross Domestic Production [109] were additionally processed at the local districts in Ghana.

2.2.4 Statistical analyses

2.2.4.1 Analysis of Western Australia birth cohort

Preconception periods, especially 12 weeks or three months before pregnancy have been suggested as a critical window as this is the period for gametogenesis [110,111] and fetal and children's health outcomes were associated with maternal preconception environmental exposures.[112] To identify the critical susceptible exposure periods, DLNM was incorporated into Cox proportional hazard (Cox PH) regression to investigate long-term maternal exposure to monthly $PM_{2.5}$ exposure from three months preconception to birth to estimate monthly specific adjusted hazard of birth outcomes (stillbirth, sPTB, term SGA, LGA, and LBW) in Western Australia as reported in several previous studies.[61,65,67,69] Cumulative exposure models such as preconception, whole pregnancy, and trimesters were also reported. The adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Several stratified analyses by sociodemographic and biologic factors were also performed to identify the more vulnerable subpopulations. Details on model specifications, stratified and sensitivity analyses were described in Chapters 4 and 5. R statistical software (version 4.2.1) was used for all analyses and the package 'dlnm' was used to fit DLNM [59,60] before fitting the Cox PH regression with the package 'survival'.[113] Short-term effect of $PM_{2.5}$ was not conducted as only monthly $PM_{2.5}$ concentrations were assessed due to data availability.

For biothermal stress (UTCI) exposure, both short and long-term effects were investigated. Short-term or acute effects were investigated for birth outcomes with abrupt onset (that is stillbirth and sPTB) due to transient effect of the exposure.[114] Small area-level (SA1) aggregated analysis with a novel design known as a space-time-stratified case-crossover was conducted.[115] DLNM was combined with conditional quasi-Poisson regression to estimate the relative risk of stillbirth and sPTB attributable to UTCI exposure during the days of the last gestational week.[59,60,115-118] Using the median UTCI as a reference, the relative risks (RRs) and 95% confidence intervals (CIs) were estimated for the immediate (delivery day) and cumulative short-term (up to six preceding days) exposures to different thresholds of UTCI.[119-121] The analyses were performed using R package 'dlnm' to fit DLNM [59,60] before fitting a conditional quasi-Poisson regression with 'gnm' package.[122]

For long-term effects analyses to identify the critical susceptible UTCI exposure periods, DLNM Cox PH regression at individual level was performed as described briefly above for $PM_{2.5}$ exposure. Here, both weekly and monthly UTCI exposures from twelve weeks or three months preconception to birth and the adjusted hazard of birth outcomes (stillbirth, sPTB, term SGA, LGA, LBW) were investigated. Cumulative exposure models such as preconception, whole pregnancy, and trimesters, and stratified analyses were also reported. Details were described in Chapters 9 and 10.

2.2.4.2 Analyses of Ghana birth cohort

Within-space time-series analysis with DLNM combined with conditional quasi-Poisson regression was used to estimate the risks of stillbirth due to monthly UTCI and $PM_{2.5}$ exposures. Also, the annual $PM_{2.5}$ with source decompositions was used to estimate the risks associated with anthropogenic and natural sources of $PM_{2.5}$ exposure by applying a variant difference-in-differences design with conditional quasi-Poisson regression.[50,123,124] Details on model specifications, stratified and sensitivity analyses for UTCI and $PM_{2.5}$ exposures were described in Chapters 6 and 9, respectively. All statistical analyses were performed using the R statistical software (version 4.2.1) and main packages 'dlnm' and 'gnm' were used.

2.2.5 Ethical approval

Ethical approvals were obtained from the Human Research Ethics Committees of the Western Australia Department of Health (#2016/51), Curtin University (#HRE2020-0523), and Ghana Health Service (#GHS-ERC016/12/20). Participants informed consent was waived because of the implausibility of obtaining retrospective consent for de-identified routinely collected secondary data.

Part II
Ambient air pollution and adverse birth outcomes

Chapter 3: Maternal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of systematic reviews and meta-analyses

3.0 Preamble

This chapter provides an umbrella review that comprehensively synthesised the existing systematic reviews and meta-analyses of the epidemiological evidence on prenatal exposure to ambient air pollution and the risks of adverse birth outcomes globally with recommendations for practice, policy, and further studies. Before the conduct of the umbrella review, a general systematic review protocol was registered prospectively in a PROSPERO (CRD42020200387) and then developed into a peer-reviewed published article in the *International Journal of Environmental Research and Public Health*.[83] The umbrella review was presented in this chapter as it was published in *Environmental Pollution* with the title 'Prenatal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of 36 systematic reviews and meta-analyses'**.**[125]

3.1 Abstract

Multiple systematic reviews and meta-analyses linked prenatal exposure to ambient air pollutants to adverse birth outcomes with mixed findings, including results indicating positive, negative, and null associations across the pregnancy periods. The objective of this study was to systematically summarise systematic reviews and meta-analyses on air pollutants and birth outcomes to assess the overall epidemiological evidence. Systematic reviews with/without meta-analyses on the association between air pollutants (NO_2, CO, O_3, SO_2, $PM_{2.5}$, and PM_{10}) and birth outcomes (preterm birth; stillbirth; spontaneous abortion; birth weight; low birth weight, LBW; small-for-gestational-age) up to 30th March 2022 were included. We searched PubMed, CINAHL, Scopus, Medline, Embase, and the Web of Science Core Collection, systematic reviews repositories, grey literature databases, internet search engines, and references of included studies. The *consistency* in the directions of the effect estimates was classified as more consistent positive or negative, less consistent positive or negative, unclear, and consistently null. Next, the *confidence* in the direction was rated as either *convincing, probable, limited-suggestive, or limited non-conclusive* evidence. Final synthesis included 36 systematic reviews (21 with and 15 without meta-analyses) that contained 295 distinct primary studies. $PM_{2.5}$ showed more consistent positive associations than other pollutants. The positive exposure-outcome associations based on the entire pregnancy period were more consistent than trimester-specific exposure averages. For whole pregnancy exposure, a *more consistent positive association* was found for $PM_{2.5}$ and birth weight reductions, particulate matter and spontaneous abortion, and SO_2 and LBW. Other exposure-outcome associations mostly showed *less consistent positive associations* and few *unclear directions* of associations. Almost all

associations showed *probable evidence*. The available evidence indicates plausible causal effects of criteria air pollutants on birth outcomes. To strengthen the evidence, more high-quality studies are required, particularly from understudied settings, such as low-and-middle-income countries. However, the current evidence may warrant the adoption of the *precautionary principle*.

3.2 Introduction.

Increasing urbanisation and modernisation contribute to higher levels of environmental toxicants, among which air pollution is a significant contributor.[89,126] Globally, air pollution is ranked as the 5th leading risk factor for mortality. Air pollution causes one in every nine deaths worldwide from non-accidental mortality due to noncommunicable diseases such as lung cancer, chronic obstructive pulmonary disease, ischemic heart disease, stroke, and lower respiratory infections [126,127] with a high economic burden.[128] As a ubiquitous environmental risk factor, air pollution has impacts on everyone with no geopolitical boundaries. [126,127] Notably, there is early evidence that some subpopulations such as people with chronic diseases, children, older adults, and pregnant women and their children *in utero* are more susceptible to the health outcomes associated with air pollution exposure. [126,127,129] Air pollutants vary in chemical composition and physical characteristics and can have negative impacts on vulnerable groups differently and at multiple stages in the life course. [24,127,130] The general physiological changes associated with pregnancy (e.g., changes in the endocrine system, increased rates of inhalation and cardiac outputs) put pregnant women and the developing fetus at a potentially greater risk of air pollution exposure. This results in adverse pregnancy outcomes and elevated risk of morbidity from cardio-respiratory and neurodevelopmental disorders later in the life course.[126,127,129]

Many air pollutants have negative impacts on human health and the environment.[3] Commonly regulated markers of ambient air pollution, the criteria air pollutants are nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3), sulphur dioxide (SO_2), and particulate matter (PM) with aerodynamic diameter $\leq$ 2.5 µm ($PM_{2.5}$) and $\leq$10 µm (PM_{10}).[4] Prenatal exposure to the criteria ambient air pollutants (hereon *pollutants*) has been documented as a potentially modifiable risk factor for adverse birth outcomes.[127,128] For example, even at concentrations lower than the 2005 World Health Organization (WHO) guideline annual average of 10 µg/m^3, $PM_{2.5}$ has been found as a contributor to the risk of adverse birth outcomes.[4,24,127] There are multiple relevant biological mechanisms by which pollutants can influence birth outcomes.[24] Prenatal exposure to pollution initiates a sequence of pathophysiological responses, including oxidative stress, metabolic, cardiovascular, and immuno-inflammatory alterations.[19,24] These responses have the potential to disrupt normal fetal development, resulting in adverse birth outcomes.[19,24] The associations can be modified by climatic factors, infection, obstetric conditions, socio-economic status, nutrition, and psychosocial environment.[23,25,40]

Systematic reviews and meta-analyses (SRMAs) have the potential to improve upon precision, provide answers to unanswered questions, and settle conflicting findings in primary studies.[131] However, meta-analysis "also have the potential to mislead seriously, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered." [131] Several SRMAs have been conducted on the pollutants and birth outcomes with findings indicating greater risks, but also with inconsistent findings, including null association, and lower risks.[28-31,33,132,133] As the number of SRMAs increase with varied quality, scope, and conclusions, umbrella reviews are recommended to systematically compare, contrast, and synthesise the emerging evidence from the SRMAs to provide overall concise direction and strength of the observed associations.[37,38] Except for one related broad summary of meta-analyses [41] that included only one meta-analysis,[28] to our knowledge, no umbrella review has been conducted to systematically evaluate the exposure-outcome associations for ambient air pollution and adverse birth outcomes. This study aimed to provide an overall clear synthesis of the available epidemiological evidence through an umbrella review to evaluate if sufficient evidence is available to adopt the *precautionary principle*; protecting the health of pregnant women and their fetuses by minimising air pollution while scientific uncertainty is resolved.[134]

3.3 Methods

3.3.1 Umbrella review methodology

This umbrella review involved a critical evaluation of SRMAs on the association between criteria air pollutants and adverse birth outcomes. The review was based on a published protocol, [135] prospectively registered in PROSPERO (CRD42020200387), and followed reporting guidelines, including PRISMA statement [84,136] and JBI umbrella review guideline.[37,85]

3.3.2 Eligibility criteria

Eligibility criteria were defined according to the PECOS (Participants, Exposures, Comparators, Outcomes, and Study design) statement[137] as described in the published protocol.[135] Briefly, the 'Population' was pregnant women or *in utero* infants. 'Exposures' were the pollutants: NO_2, CO, O_3, SO_2, $PM_{2.5}$, and PM_{10}. 'Comparators' were pregnant women unexposed or exposed to lower levels of the exposures as compared to those with higher exposures. 'Outcomes' were the birth outcomes: preterm birth (PTB), pregnancy loss (spontaneous abortion or stillbirth), reduced birth weight, and fetal growth restriction (low birth weight, LBW; and small-for-gestational-age, SGA), and related outcomes such as very low birth weight. ‘Study’ designs were systematic reviews with or without meta-analyses that included quantitative human epidemiologic studies on the exposure-outcome associations of interest. Assisted reproductive technology studies were excluded. A review study was included if the review article specified inclusion or exclusion criteria, was based on the search of at least one electronic database and described the search strategy or protocol, reported results on the exposure-outcome association as the main objective, provided sufficient information on the included primary studies [138] and included no fewer than three primary studies for the exposure-outcome association.[139]

3.3.3 Data Sources

We conducted a systematic search in (i) six major bibliographic databases: PubMed, CINAHL, Scopus, Medline/Ovid, Embase/Ovid, and Web of Science Core Collection; (ii) systematic reviews repositories: Cochrane Database of Systematic Reviews, JBI Database of Systematic Reviews and Implementation Reports, and Epistemonikos (www.epistemonikos.org/); (iii) electronic grey literature databases: OpenGrey (http://www.opengrey.eu/) and WorldWideScience.org; (iv) Internet search engines: Google and Google Scholar in Incognito mode, screening the first 200 search results [140]; (v) the World Health Organization website; and (vi) manually searched references of the identified eligible studies.

3.3.4 Study selection and data extraction

Searches were restricted to the English language with no limitations on the date of publication. We developed comprehensive search terms with the relevant medical subject heading (MeSH) terms, keywords, and previous reviews’ search terms for advanced search in the databases (Table S1). An experienced librarian from the Faculty of Health Sciences, Curtin University was consulted to refine the search strategies. The literature search was conducted for the broader umbrella review described in the protocol.[135] The databases were searched on September 21, 2020, and with weekly alerts and updates up to 30th March 2022 using the same criteria. The titles and abstracts of all identified citations were imported into the *EndNote* library and duplicated records were excluded. Studies were first screened for relevant titles and abstracts. The full texts of potentially eligible studies were retrieved and assessed comprehensively per the eligibility criteria. The JBI SUMARI was used to aid the selection process at the full-text level.[141] Data were extracted from the selected studies with the data extraction tool [135] and was piloted by two investigators (SN and JD). Study selection and data extraction were conducted independently by two investigators (SN and JD) and any disagreements were resolved by discussion or with a third investigator (GT, BM, and GP). Authors were contacted for additional or unclear information where necessary.

3.3.5 Risk of bias assessment

Two authors independently assessed the risk of bias (SN and JD) of the included reviews and any disagreements were resolved by discussion or with a third investigator (BD). The JBI standardised critical appraisal tool [85] for review studies and the JBI SUMARI software [141] was used. The 11 items were checked as 'yes' (1), 'unclear' or 'no' (0). Item 9 was scored not applicable (NA) for reviews without meta-analyses. The 'yes' items were summed to total scores, which were categorised as 0-5, 6-8, and 9-11 and rated 'high', 'moderate', and 'low' risk of bias, respectively.

3.3.6 Data Synthesis

The general characteristics and scope of the included reviews were presented using tables and figures such as forest plots and a map with textual descriptions. To account for multiple inclusion of primary studies (overlaps) in the review articles, we constructed separate citation matrices for systematic reviews with and without meta-analyses for computing the overlaps according to Corrected Covered Area (CCA) algorithm; [138]

$$CCA = \frac{N-r}{rc-r},$$

where *N* is the sum of the number of included primary studies (the total number of times studies appeared in the reviews) in the umbrella review, *r* is the total number of distinct indexed primary studies and *c* is the number of reviews. The CCA score ≤ 5% implies slight, 6-10% moderate, 11-15% high, and >15% very high degrees of overlaps.[138] Overlap of primary studies across the reviews is unavoidable. However, higher overlap indicates that synthesised evidence in the umbrella review is based on different review studies that largely integrated the same primary studies. This could bias the results or decrease the confidence in the evidence as compared to low overlap.[138]

Systematic reviews without meta-analyses (hereon *systematic reviews*) were narratively synthesised. For systematic reviews with meta-analyses (hereon *meta-analyses*), we adapted the similar approaches described elsewhere [86-89] to provide overall epidemiological evidence. Specifically, the two updated grading scales [88] were adapted as described in our protocol.[135] Briefly, by considering the *consistency* in the direction and statistical significance of the meta-analyses results, each pollutant-outcome association was graded as demonstrating a *more consistent positive association* (++) in all results and without null in the confidence intervals, or a *less consistent positive association* (+) for which there was agreement in at least 75% of the results in the direction, otherwise a *mixed/unclear or contradictory direction (0)*. Similarly, lower risks were graded more (--) or less (-) *consistent negative associations*. Consistently *null association* in all meta-analyses was graded (00). Where only one meta-analysis was available for a particular pollutant-outcome association, the criteria were applied to the included primary studies in the meta-analysis while considering agreement in the direction of association in at least 80% of the included primary studies.[142] Next, informed by the benchmarks developed using Bradford Hills' guidelines for causation [143] as applied previously,[86-88] the *confidence* in the observed direction or plausible causation was rated as; i)'convincing evidence' (Ce), ii) 'probable evidence' (Pe), iii) 'limited-suggestive evidence' (Lse) and iv) 'limited, no conclusive evidence' (Lnce) by considering the level of strengths and weaknesses in the reported associations, including imprecision and heterogeneity in the meta-analyses results, and the number and quality/study designs of the pooled primary studies. Here, 'convincing evidence' of an observed direction or causality is that there is low heterogeneity and high precision in all pooled estimates and included at least two cohort studies of large sample sizes, and experimental studies.[88,135] Before the evidence synthesis, all effect estimates (odd ratios for dichotomous outcomes and beta coefficient for continuous outcomes) were standardised as an increase in exposure per 10 $\mu g/m^3$ for $PM_{2.5}$ and PM_{10}; 10 parts per billion (ppb) for NO_2, SO_2, and O_3; and 100 ppb for CO as described elsewhere [15] and applied in one of the included meta-analyses.[144]

3.3.7 Protocol Amendments

Few amendments were made to the published protocol.[135] We did not use the AMSTAR2 critical appraisal tool for the further assessment of the methodological quality. Given that AMSTAR2 was originally developed for randomised and non-randomised intervention studies,[145] modifying it within the context of environmental health studies may create discrepancies. Moreover, the JBI critical appraisal tool,[85] which was more general as compared to the AMSTAR2, captured the necessary items for assessing the risk of bias of the included systematic reviews or meta-analyses. Also, considering the small number of meta-analyses for each pollutant-outcome association for each pregnancy period, we applied at least 75% agreement of meta-analyses in each direction of association for grading the *less consistent associations* as reported previously [86-88] instead of the 80% stated in the protocol.[135] We, however, maintained the 80% agreement in the direction of association for the included primary studies in instances where only one meta-analysis was available.

3.4 Results

3.4.1 Systematic literature search results

The initial literature search in the electronic databases identified a total of 3,663 records, of which 1,513 were retrieved after deduplications. Title and abstract screening excluded 1,460 records. An additional six potentially eligible studies were identified from the other search sources. The full-text assessment included 59 studies and 34 were further excluded for other reasons, including retraction (n =1), non-English (n = 4), a summary of reviews or general literature reviews (n = 16), unrelated outcomes or pollutants (n = 4), and fewer than three or insufficient details on the included primary studies (n = 9). From the prospective literature search based on the weekly databases' alerts and updates using the same criteria after the initial search up to 30th March 2022, we added 11 additional reviews.[146-156] Thus, 36 systematic reviews, 15 (42%) without and 21 (58%) with meta-analyses were included in the final synthesis (Figure S3.1). The full lists of excluded studies after the full-text examination with reasons were provided (Table S3.2).

3.4.2 Characteristics of the included reviews

The detailed descriptions of the general characteristics of the included reviews were summarised (Tables 3.1 and 3.2 and Tables S3.3 and S3.4). The 36 SRMAs were published between January 2004 [29] and October 2021 [153,154] by authors from multiple countries (Figures S3.2 and S3.3). Most of the reviews (30 of 36, 83%) included primary studies from several countries, although some countries and regions of the world were more represented in the included studies than others. The other six reviews were restricted to the USA,[34,157,158] China,[159], Europe ,[147] and Australia.[152] The 36 SRMAs included a total of 295 distinct primary studies that included eight multi-country studies (including one each from 33 African countries [160] and three South Asian countries,[161] both based on Demographic Health Survey data) and 287 country-specific studies from 31 countries. The geographical distribution of the 287 country-specific primary studies was skewed towards studies from the USA, 113 (39%), and China, 44 (15%). South Asia and Africa each contributed only one study from India and Tanzania, respectively (Figure 3.1).

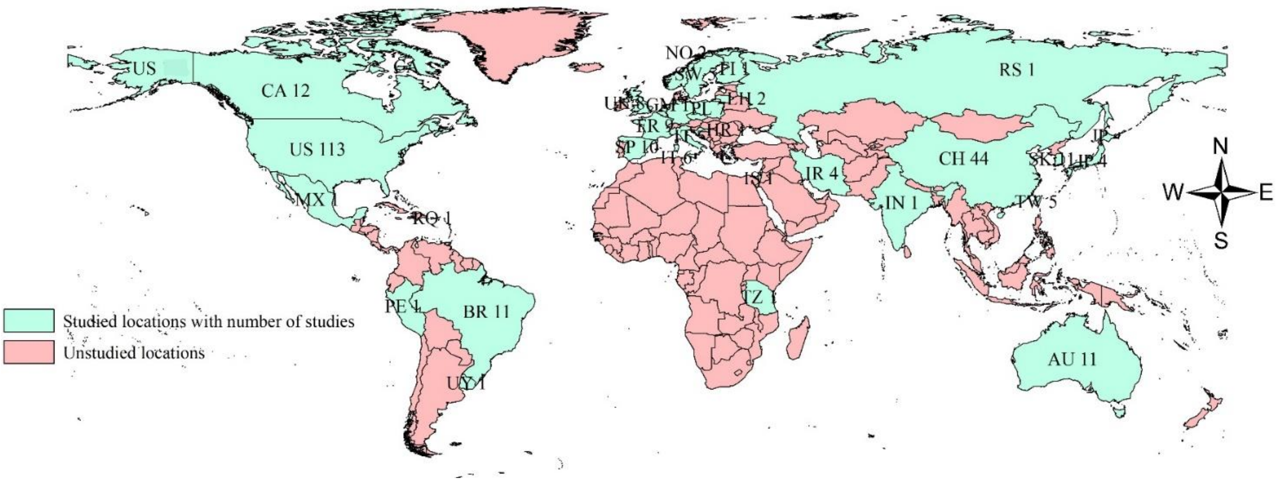

Figure 3.1 Spatial distribution of 287 country-specific primary studies from 31 countries included in the 36 systematic reviews and meta-analyses on ambient air pollution and adverse birth outcomes.

Note: Number of studies for US, United States (113); CA, Canada (12); ME, Mexico (1); RQ, Puerto Rico (1); PE, Peru (1); BR, Brazil (11); UY, Uruguay (1); TZ, Tanzania (1); AU, Australia (11); IN, India (1); CH, China (44); TW, Taiwan (5); JP, Japan (4); SK, South Korea (11); RS, Russia (1); IR, Iran (4); IS, Israel (1); IT, Italy (5); SP, Spain (10); FR, France (9); BE, Belgium (3); GM, Germany (1); CZ, Czech Republic (5); HR, Croatia (1); NL, Netherlands (4); UK, United Kingdom (8); PL, Poland (7); LH, Lithuania (2); SW, Sweden (5); FI, Finland (1); NO, Norway (2).

The included systematic reviews sourced literature from an average of four databases. Out of the 15 systematic reviews, three searched the literature in both English and Chinese languages [146,159,162] while the remaining were restricted to only English. The number of primary studies included in each systematic review ranged from three [153] to 82,[163] with an average of 27 primary studies. The 15 systematic reviews included a total of 211 unique primary studies with a moderate overlap of 6.8% (Table S3.5).

Most of the systematic reviews (n=13) investigated the association between $PM_{2.5}$ and LBW while only one review investigated the association between the pollutants with spontaneous abortion (SAB).[164] Study design classifications varied among reviews. The total sample sizes studied ranged from 146,271 births [165] to 41,793,876 births [157] with an average of 12,792,818 births. The reported average ranges of the concentrations for particulate matter were 1.1-71.9 $\mu g/m^3$ for $PM_{2.5}$ and 3.2-889.7 $\mu g/m^3$ for PM_{10}. The exposure levels of the gaseous pollutants reported (most likely for entire pregnancy periods, although specific pregnancy periods were not clearly stated) ranged from 9.4 - 117.9 $\mu g/m^3$ for NO_2, 3.8 - 308 $\mu g/m^3$ for SO_2, 33 - 91.4 $\mu g/m^3$ for O_3, and 0.5 -17.8 mg/m^3 for CO. The majority, 9/15 (60%) of the systematic reviews did not assess the risk of bias in the included primary studies. The majority, 9/15 (60%) of the systematic reviews explicitly stated having used systematic review guidelines, mostly PRISMA. Only one review had a protocol registered which is available at Open Science Foundation.[153] Two reviews, however, stated that a pre-specified review method was available but not registered or published prior to the conduct of the review [132,163] (Table 3.1). Other details were provided in Table S3.3.

The earliest meta-analysis, published in 2010 analysed the association between $PM_{2.5}$/PM_{10} and LBW and PTB.[28] The number of meta-analyses increased over time with 15 published between 2016-2021 (Figure S3.2) that investigated the various pollutants and birth outcomes. The majority, 14 of 21 (67%) meta-analyses (Table 3.2) were restricted to only $PM_{2.5}$/PM_{10}. Only one meta-analysis searched one electronic database (PubMed) [147] and the rest searched in two or more databases. Restriction to only English articles was typical but six meta-analyses included both English and Chinese.[32,33,154,166-168] The number of included primary studies per meta-analysis ranged from six to 62 with an average of 27. A total of 228 different primary studies were included with a moderate overlap of 7.6% (Table S3.5). The average number of births or pregnancies per meta-analysis was 12,149,542 births, ranging from 735,719 natural pregnancies [156] to 57,960,152 births.[148] There were few unreported sample sizes for some included primary studies.

Table 3.1 Characteristics of systematic reviews without meta-analysis, ordered from most recent to earliest publication

First author, date [number of authors, countries]	Exposure type and range or IQR	Outcome	Number of Databases, grey literature searched	Search date range and languages applied	No. of primary studies, study design, coverage	Publication year range	Total births	Risk of bias tool	Quality rating summary	Reporting guideline	Evidence of pre-specified review protocol
1. Edwards [153] 12/10/2021 [4; 3 UK and 1 Nepal]	$PM_{2.5}$, PM_{10}, NO_2, SO_2 Ranges: NA	LBW, SGA, PTB	Db =3 Grey =No	01/1989 - 10/2020. English	3 total: all cohort	2010-2019	663,255	Adapted the Navigation Guide tool	2 'probably low' and 1 'probably high'.	PRISMA	Open Science Foundation
2. Walter [152], 08/06/2021 [6; all Australia]	$PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3, CO. Ranges NA	LBW, BW, SGA, PTB	Db = 2 Grey = No	Inception - 01/07/2019. English	9 total: 8 cohort, 1 case-crossover. Australia	2006-2019	356382	NOS, Navigation Guide, and Mustafic's criteria	Moderate and high	PRISMA	No
3. Luo [146] 09/03/2021 [6; 5 China and 1 UK]	$PM_{2.5}$: 1.1-20.1 μg/m^3 PM_{10}: 3.3 - 39.2 μg/m^3 NO_2: 9.4 - 64.1 μg/m^3 NO: 2.7 - 39.5 ppb NO_x: 19.6 - 102.8 ppb	PTB, BW, LBW, SGA	Db= 6 Grey = No	Inception - 01/05/2019. English and Chinese.	39 total: 35 cohort, 4 case-control	2007-2019	10,533,974	NOS	7-9	No	No
4. Bekkar [34] 18/06/2020 [4; all USA]	$PM_{2.5}$:1.3 - 6.9 μg/m^3 O_3: 7.1 - 11.5 ppb	PTB, LBW, and SB	Db= 3 Grey =2	01/01/2007 - 30/04/2019. English	51 total: (43 retrospective cohort, 2 cross-sectional, 4 time series, 3 case-control. USA	2007-2019	30,731,001	No	No	Arskey O'Malley PRISMA	No
5. Heo [157] 12/11/2019 [3; All USA]	PM_{10}, $PM_{2.5}$ ($PM_{2.5-10}$, PM_1, $PM_{0.1}$) Ranges NA	PTB, LBW, SGA, and SB	Db=1 Grey = No	01/01/2000 - 07/07/2019. English	44 total: 35 case-control, 5 cohort, 1	1999-2019	41,793,876	No	No	STROBE, HEQAT, Cochran	No

					case-control/cohort, 2 time-series, 1 ecologic. USA					e.	
6. Yuan [162] 20/03/2019 [4; all China]	$PM_{2.5}$: 1.8 - 71.9 μg/m^3	BW, LBW, SGA, PTB	Db=1 Grey = No	01/2008 - 22/07/2017. English and Chinese.	42 total: 6 prospective, 35 retrospective cohort and 1 nested case-control. Global	2008-2017	33,419,565	No	No	No	No
7. Tsoli [163] 31/01/2019 [3; 2 Greece and 1 UK]	$PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, PM_1, TSP Ranges NA	TBW, TLBW	Db=2 Grey = No	Inception - 08/2018. English	82 total:: 73 cohort, 6 ecological, 2 case-control, 1 cross-sectional. Global.	1997-2018	39,056,189	No	No	No	No#
8. Grippo [164] 25/09/2018 [8; 3 USA and 5 China]	TSP, PM_{10}, $PM_{2.5}$, CO, SO_2, NO_2, O_3 Ranges NA	SAB (miscarriage) and SB	Db= 1 Grey = No	Inception - 03/2018. No language indicated	15 total: 3 each prospective cohort, retrospective cohort, and time-series, 4 case-control and 1 each cross-sectional and ecological. Global	1998-2018	4,432,632	No	No	No	No
9.	$PM_{2.5}$: 9.1 -	TLBW	Db=2	Inception –	6 total: 1	2013-2016	5,149,128	No	No	No	No

Westergaard [169] 06/04/2017 [4; 2 Denmark, 1 Netherlands, and 1 France]	32.4 µg/m^3 NO_2: 13.4 ppb (one study) SO_2: NA O_3: NA SPM: NA		Grey= No	21/08/2016. English	prospective, 4 retrospective and 1 nationwide longitudinal survey. Global.		births				
10. Jacobs [159] 01/02/2017 [9; 8 Australia and 1 USA]	$PM_{2.5}$: 61 µg/m^3 (one study) PM_{10}: 40 - 212 µg/m^3, NO_2: 24 - 61 µg/m^3, SO_2: 16 -102 µg/m^3 CO: 814 - 1730 µg/m^3 O_3: 61 µg/m^3 (one study)	BW, LBW, PTB, SB	Db= 5 Grey = No	1980 - 2015. English and Chinese	17 total: 2 prospective cohort, 4 retrospective cohort, 3 case-control, 1 case-crossover, 7 cross-sectional. China	1995-2015	505,734 births	Berman and Parker (2002) criteria	Stated but not reported	PRISMA	No
11. Shah [132] (26/11/2010) [2; both Canada]	PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, O_3, TSP. Ranges NA	LBW, PTB, SGA/IUGR, BW	Db=3 Grey = No	Inception - 15/10/2010. English	40 total: 30 cohorts, 4 case-control, 5 ecological Global.	1987-2011	7,476,326 births	Referred to their previous checklist	38/40 included studies had an overall moderate RoB, whereas 2 studies had a low RoB	MOOSE	No*
12. Bonzini [170] 09/2010 [6; All Italy]	$PM_{2.5}$: 5.1 - 25.4 µg/m^3 PM_{10}: 16.3 - 89.7 µg/m^3 NO_2: 10.4 - 117.9 µg/m^3 O_3: 33 - 91.4 µg/m^3 CO: 0.5-17.8 mg/m^3	PTB, LBW, SGA, BW	Db = 1 Grey = No	01/2004 - 12/2008. English.	18 total: 12 birth cohort, 1 matched case-control, 5 time-series.	2004-2008	1,987,093	No	No	No	No

13. Bosetti [171] 06/02/2010 [6; 5 Italy and 1 Spain]	$PM_{2.5}$: 5.3 - 21.9 μg/m^3 PM_{10}:3.2 - 889.7 μg/m^3 TSP: 68.5 - 375 μg/m^3	PTB, LBW, VLBW, SGA	Db= 1 Grey = No	1966 - 06/2009. English	30 total : 22 cross-sectional*, 4 time series, 3 case-control, 1 ecological Global	1995-2008	2,848,020	No	No	No	No
14. Ghosh [165] 09/05/2007 [4; all UK]	$PM_{2.5}$: 10.3 - 43.0 μg/m^3 PM_{10}: 31.5 - 85.9 μg/m^3 TSP: 5.93 μg/m^3 CO: 1.0 - 1.7 ppm SO_2: 3.8 -308 μg/m^3 NO_2: 12.1 - 43.5 ppb O_3: 18 - 27.23 ppb	BW, LBW, VLBW, PTB	Db=10 Grey = No	1966 -2005. English	5 total: 2 retrospective cohort, 1 prospective cohort, 2 case-control. Global	1997-2004	146,271	Developed a checklist from other guidelines	4 studies were rated 'fully meet the quality criteria' and 1 rated 'satisfactory'	Cochrane.	No
15. Glinianaia [29] 09/01/2004 [5; all UK]	TSP, $TSPSO_2$, PM_{10}, $PM_{2.5}$ Ranges NA	LBW, VLBW, IUGR, PTB, and SB	Db=12 Grey =3	01/01/1996 – 31/12/2001. English	11 total: 8 cohorts, 1 case-control, 1 time-series, 1 ecological Global	1997-2001	Not provided for primary studies	No	No	CRD's Guidance and the U.K. National Health Service Centre for Reviews and Dissemination	No

Note: NO_2, Nitrogen dioxide; NO_x, Nitrogen oxides; CO, Carbon monoxide; O_3, Ozone; SO_2, Sulphur dioxide; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤ 2.5μm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10μm; TSP, total suspended particles; SPM, suspended particulate matter; μg/m^3, micrograms per cubic meter; ppm, parts per million; ppb, parts per billion; NA, not available; IQR, interquartile range; PTB, preterm birth; BW, birth weight; LBW, low birth weight; TLBW, term low birth weight; VLBW, very low birth weight; SGA, small-for-gestational age; IUGR, intrauterine growth retardation; SB, stillbirth; SAB, spontaneous abortion; Db, database; NOS, Newcastle- Ottawa scale; USA, United States of America; UK, United Kingdom; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; MOOSE, The Strengthening the

Reporting of Observational Studies in Epidemiology; STROBE, Strengthening the reporting of observational studies in epidemiology; HEQAT, Health Evidence Quality Assessment Tool. Statement# "A review protocol reporting inclusion and exclusion criteria was available during the screening process to consolidate reviewers' judgement. The review protocol was not registered." Statements* "The methods adopted by our group for systematically reviewing birth outcomes of various determinants have been described previously and are briefly outlined below (Shahand Zao, 2009; McDonald et al., 2010). A decision was made a priori to systematically review these data rather than to perform meta-analyses, as heterogeneities were identified in previous reviews". *The cross-sectional used in this review included studies for birth cohorts classified in almost all reviews as retrospective cohort study design.

Table 3.2 Characteristics of systematic reviews with meta-analysis, ordered from recent to earliest.

First author, date [number of authors, countries]	**Exposure type and range or IQR**	**Outcome**	**Number of databases (Db) and grey literature searched**	**Search date range and languages applied**	**No. of primary studies and study designs, coverage**	**Publication year range**	**Total births**	**RoB tool**	**Quality rating summary**	**Reporting guidelines**	**Evidence of pre-specified review protocol**
1. Gong [154] 04/10/2021 [5; 4 China and 1 USA]	PM2.5: Range: 8.43 -66.09 μg/m^3	TBW (continuous outcome)	Db =6 Grey=No	Inception – 03/03/2021. English and Chinese.	31 total: all cohort.	2008-2021	24,824,520	NOS for quality assessment. GRADE handbook to grade certainty of evidence	22/31 studies had high NOS score (≥ 7; high quality) and 9 had medium scores. 'Very low' quality of the effect estimates in all meta-analysis due to high heterogeneity but moderate for the LUR-models subgroup.	PRISMA	No
2. *Zhu [156] 03/08/2021 [11; all China]	$PM_{2.5}$, PM_{10} Range: NA	SAB	Db=3 Grey=No	Inception – 01/02/2021. English	6 total: 3 cohort, 3 case-control	2014-2021	735,719 natural pregnancies (65,726 SABs)	NOS for quality assessment. GRADE	All studies were "high quality" (NOS score ≥ 7).	PRISMA	No

								pro app to grade the certainty of evidence	GRADE results of PM2.5 and PM10 were both "moderate"		
3. Ju [155] 09/07/2021 [7; all China]	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3. Ranges: NA	PTB (including subtypes: moderate, very, and extremely PTB). 2.8 – 11.76%	Db=2 Grey=No	Inception - 10/2020. English	60 total: all cohort	1995-2020	21, 872,454 (1,499, 479; 6.86% PTB)	NOS	Included only studies with a total score of 7–9 ('high quality')	No	No
4. Xie [151] 13/06/2021 [10; 9 China and 1 USA]	$PM_{2.5}$: 11.8 – 70.6 μg/m^3	Stillbirth	Db=4 Grey=No	Inception – 18/10/2020 . English	7 total: 6 cohorts and 1 case-control. Global	2012-2020	4,342,251	Navigation Guide RoB criteria	"Low" or "Probably low" risk of bias	PRISMA	PROSPERO
5. Rappazzo [150] 12/05/ 2021 [4; all USA]	O_3: 17 - 57 ppb	PTB	Db=2 Grey = 1	Inception - 31/01/2021 . English	20 total:17 cohort, 3 case-control Global	2005 - 2021	5,031,661	OHAT	One high, and 9 each ranked medium and low confidence overall	No	No
6. Zhang [149] 22/02/2021 [7; All China]	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3 Ranges: NA	SB	Db=4 Grey=No	Inception – 11/12/2020 . No language indicated	14 total: 3 prospective and 5 retrospective cohorts, 2 case-control, 3 case-crossover, 1 time series. Global	2007-2020	7,227,534	NOS and OHAT tools	"Most included studies showed "low" or "probably low" risk, and "were of high quality.	PRISMA	No
7. Uwak [148]	$PM_{2.5}$,	BW	Db=3	Inception	54 total: 43	2003-	57,960,152	Navigati	$PM_{2.5}$: 12/30	Navigati	PROSPERO

25/01/2021 [13, All USA]	PM_{10}, and $PM_{2.5-10}$ Ranges: NA		Grey=No	– 27/02/2020 . English	retrospective , 9 prospective cohorts, 2 cross-sectional. Global.	2020		on Guide RoB criteria as	studies were rated overall as “low” or “probably low”. PM_{10}: 10/29 studies were rated overall as “low” or “probably low” but high risk for all 5 studies on coarse PM.	on guide systematic review methodology	
8. Simonici [147] 03/11/2020 [4, All France]	$PM_{2.5}$, PM_{10}, NO_2 Ranges: NA	BW/LBW, PTB, SGA	Db=1 Grey=No	Inception – 01/04/2020 . English	30 total: 20 cohorts, 9 ecological time series, 1 spatial. Europe	2002-2019	3,466,265	Adapted from Croteau et al (2009) and Doi and Thalib (2008).	Minimum score was 0.806 out of 1.000	PRISMA	No
9. Thayamballi [158] 08/09/2020 [4; all USA]	$PM_{2.5}$: 1.0-7.6 µg/m^3 PM_{10}: 2.7 - 7.4 µg/m^3	BW, LBW/TLBW, PTB, SGA, Stillbirth	Db=4 Grey=No	Inception – 30/06/2018 . English	18 total. Unreported study design. USA	2007-2017	17,779,343	Unclear	Unclear	No	No
10. Li [144] 04/08/2020 [7, all China]	$PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, and O_3 Ranges NA	LBW	Db=2 Grey=No	Inception – 06/2020.English	54 total: all cohort Global	1997-2020	27,087,009	NOS	High qualities: scores 7-9.	No	No
11. Ji [32] 30/05/2017 [6; All China]	$PM_{2.5}$ and PM_{10} Ranges	TLBW	Db = 5 Grey = No	Inception – 06/03/2017 . English	14 total: all cohort	2004-2016	933,272	NOS	7 high quality and 7 moderate	PRISMA	No

	NA			and Chinese	Global				quality		
12. Liu [166] 15/06/2017 [7; all China]	$PM_{2.5}$: 5.1-70.8 μg/m^3	PTB	Db=5 Grey=No	No date indicated English and Chinese	11 total: 7 retrospective and 3 prospective cohorts, 1 nested case-control. Global	2007-2016	1,207,542	NOS	Average NOS score is 8	MOOSE	No
13. Li [167] 28/04/2017 [17; all China]	$PM_{2.5}$: 1.8 - 22.1 μg/m^3	TLBW, PTB	Db=4 Grey=No	12/2015 - 07/2016 in English and Chinese	24 total : 19 retrospective cohort, 1 prospective cohort, 2 case-control, 1 and 1 cross-sectional. Global	2006-2016	14,600,860	NOS and AHRQ	Mean score ranged 6 to 8	MOOSE	No
14. Zhang [133] 30/11/2016 [8; All China]	$PM_{2.5}$, PM_{10} Ranges: NA	SGA/IUGR, SGA, SB, SAB	Db=4 Grey=No	Inception - 31/12/2015 . English	17 studies: 14 retrospective cohort, 2 case-control, 1 cross-sectional. Global.	2005-2015	6,506,961	No	No	No	No
15. Siddika [172] 24/05/2016 [4; 3 Finland and 1 Ghana]	PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, O_3. Ranges: NA	SB	Db=3 Grey=No	Inception – 04/2015 "without any language restriction."	11 total :1 prospective cohort, 5 retrospective cohort, 1 case-control, 1 case-crossover, 1 daily time-series, 2 ecological. Global	1984-2015	4,467,963	NOS	Very high quality (3 studies), high quality (1 study).	No	No

16. Sun [168] 29/12/2015 [8, all China]	$PM_{2.5}$: 5.1-43.8 μg/m^3	LBW, BW	Db=5 Grey=No	Inception – 03/2015. English and Chinese	32 total: 4 prospective and 28 retrospective cohorts. Global	2004-2015	15,951,040	No	No	No	No
17. Sun [33] 18/11/2015 [7; 5 China and 2 Australia]	$PM_{2.5}$: 5.1-22.1 μg/m^3	PTB	Db=5 Grey=No	Inception – 12/2014. English and Chinese	19 total: 13 retrospective and 6 prospective cohort studies. Global	2005-2014	6,091,718	NOS	The average NOS quality score is 8	PRISMA	No
18. Lamichhane [30] 03/11/2015 [4; All Incheon, Korea]	$PM_{2.5}$: 5.1 -21.9 μg/m^3 PM_{10}: 3.0 - 142.1 μg/m^3	PTB, BW.	Db= 2 Grey = No	01/1980 - 04/2015. English	44 total: 40 cohort, 4 case-control. Global	2000-2015	11,502,353	Downs and Black checklists	"14 studies were rated as relatively high quality (score≥15) and 13 rated as relatively low quality (score <15)."	MOOSE	No
19. Zhu [173] 28/08/2014 [6, all China]	$PM_{2.5}$ Ranges: NA	BW, LBW, PTB, SGA, and stillbirth	Db= 3 Grey = 1	Inception – 01/03/2014. English	26 total: 25 cohort studies and 1 case-control. Global	2005-2014	10,719,453	No	No	No	No
20. Stieb [31] 21/06/2012 [4, all Canada]	$PM_{2.5}$: 1.8 - 44.2 μg/m^3 PM $_{10}$: 3.3 - 89.7 μg/m^3 NO_2: 6.2 - 36.6 ppb SO_2: 1.1 - 12.2 ppb CO: 0.5 - 4.6 ppm O_3:13.4 -	BW, LBW/VLBW (3.5 - 17.3%), PTB (3.3 - 10.3%), SGA/IUGR	Db = 8 Grey = No	01/01/1980 -01/2011 English	62 total: 54 cohort, 6 case-control, 2 ecological. Global	1987-2011	9,697,911	No	No	No	No

	34.1 ppb										
21. Sapkota [28] 23/11/2010 [5, all USA]	$PM_{2.5}$: 5.1 - 21.9 μg/m^3 PM_{10}: 11.8 - 71.1 μg/m^3	LBW/TLBW, PTB	Db= 2 Grey = No	Inception – 07/2009.No information on language	20 total: Unreported study designs. Global	2000-2009	3,134,406	No	No	No	No

*Zhu et al (2022) included 6 articles with 7 studies because one cohort study additionally reported separate results from case-crossover design.

Note: NO_2, Nitrogen dioxide; CO, Carbon monoxide; O_3, Ozone; SO_2, Sulphur dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5μm; $PM_{10,}$ particulate matter with aerodynamic diameter ≤ 10μm; μg/m^3, micrograms per cubic meter; ppm, parts per million; ppb, parts per billion; NA, not available; IQR, interquartile range; PTB, preterm birth; BW, birth weight; LBW, low birth weight; TLBW, term low birth weight; VLBW, very low birth weight; SGA, small-for-gestational age; IUGR, intrauterine growth retardation; SB, stillbirth; SAB, spontaneous abortion; Db, database; RoB, Risk of bias; USA, United States of America; UK, United Kingdom; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; MOOSE, The Strengthening the Reporting of Observational Studies in Epidemiology; NOS, Newcastle-Ottawa Scale; OHAT, Office of Health Assessment and Translation; AHRQ, Agency for Healthcare Research and Quality; PROSPERO, International prospective register of systematic reviews.

From 11/21 (52%) of the meta-analyses that provided the exposure levels for the included primary studies, the reported mean concentrations of pollutants in the primary studies (most likely for entire pregnancy periods, although specific pregnancy periods were not clearly stated) ranged from 1.8-70.8 $\mu g/m^3$ for $PM_{2.5}$, 3.0-142.1 $\mu g/m^3$ for PM_{10}, 6.2-36.6 ppb for NO_2, 1.1-12.2 ppb for SO_2, 13.4 - 57.0 ppb for O_3, and 0.5 - 4.6 ppm for CO.

Two meta-analyses provided the prevalence ranges of 3.5-17.3% for LBW [31] and 2.8-11.76% for PTB.[155] The majority, 15/21 (71%) of the meta-analyses reported the risk of bias in the included primary studies, which were mostly rated low. Two meta-analyses had registered their protocols *a priori*.[148,151] Effect estimates were often reported as odds ratios and most meta-analyses did not indicate if other effect estimate metrics were converted or not. The pooled odds ratios were often reported as per 10 $\mu g/m^3$ increment for particulate pollutants but the reference units for the gaseous pollutants differed greatly among meta-analyses (Table S3.4).

3.4.3 Risk of bias assessment

Out of the 10 maximum scorable points for systematic reviews using the JBI critical appraisal checklist, 12 systematic reviews scored 6-8 points (moderate risk of bias) and three reviews scored 9-10 points (low risk of bias). The major areas of weaknesses were limited sources of literature searched, searching a single electronic database (n = 5), lack of risk of bias assessment for included primary studies (n = 8), and critical appraisal (n = 12) or data extraction (n = 11) were not conducted independently by at least two authors (Figure S4). Out of the 11 scorable points for meta-analyses, 19 meta-analyses scored 9-11 points (low risk of bias) and two scored 6-8 points (moderate risk of bias). The main reasons for lower scores were failure to appraise and report the risk of bias in the included primary studies (n = 5) and lack of at least two independent authors appraising the risk of bias (n = 7) (Figure S5).

3.4.4 Major findings

The detailed results from the systematic reviews were summarised in the supplemental material (Table S3.3). Earlier global systematic reviews indicated that there were some associations between the pollutants and birth outcomes, particularly for $PM_{2.5}/PM_{10.}$ and SO_2 but concluded that the available findings were generally either of “no effect”, “very small”, or “inconclusive” to provide convincing epidemiological evidence.[29,132,170,171] Three recent global systematic reviews showed that particulate matter, especially $PM_{2.5,}$ had been consistently linked in many observational studies to a higher risk of birth outcomes at varied prenatal periods.[162-164] However, another recent systematic review restricted the inclusion to only primary studies that utilised the land-use regression model for exposure assessment that mainly investigated $PM_{2.5}$ and NO_2 [146] and concluded otherwise. That review found that prenatal $PM_{2.5}$ exposure increased the risk of reduced birth weight but with an unclear link with other birth outcomes investigated.[146] The authors also observed that although NO_2 consistently showed an increase in the risk of reduced fetal growth and development, its association with PTB was unclear and the associations of other pollutants with birth outcomes were found to be generally uncertain.[146] Similarly, another systematic review also found "insufficient or conflicting evidence" for an association of NO_2 and SO_2 with stillbirth and SAB.[164] However, a recent systematic review of the USA population indicated higher risks of PTB, LBW, and stillbirth following prenatal exposure to $PM_{2.5}$ and ozone and with heightened risk among infants of Black-American mothers.[34] A systematic review of studies from the Chinese population on the impacts of the six pollutants on birth weight, LBW, PTB, and stillbirth found only SO_2 to be consistently associated with LBW and PTB.[159] Another systematic review that included nine primary studies conducted in Australia also indicated that there was some evidence for PTB and intrauterine growth retardation (IUGR) but stated that the discrepancies in the results hindered overall firm conclusions.[152] A review on maternal relocation during pregnancy included three studies and found limited evidence of the influence of relocating into environments of different concentrations of pollutants on birth outcomes.[153]

Three systematic reviews [157,165,169] explored the associations between the pollutants and birth outcomes by maternal or neonatal underlying sociodemographic or obstetrical conditions. It was found that while females were at a higher risk of LBW, males were at a higher risk of PTB.[165] Furthermore, a higher risk of term LBW was observed for neonates whose mothers smoked tobacco during pregnancy, were under/overweight or obese, or had lower socio-economic status.[169] The third review that included studies from the USA population on exposure to particulate matter concluded "suggestive evidence" of higher risk of PTB and LBW in infants of Black-American mothers but "weak evidence" of higher risk for neonates of mothers with lower educational attainments.[157]

The most frequently pooled exposure-outcome association was $PM_{2.5}$ with LBW and PTB (n=7) during the entire pregnancy period. There was only one meta-analysis on the association between gaseous pollutants (O_3, SO_2, CO) and reduced birth weight [31] (Table 2). The meta-analyses reported the pooled effect estimates based on single-pollutant models and the effect metric for dichotomous birth outcomes were odd ratios (ORs) with random effect model. The pooled effect estimates showed inconsistencies in terms of direction and magnitude of effects, statistical significance, precisions, and heterogeneities but publication bias was often found to be absent based on Egger's or Begg's test with funnel plots (Table S4). By geographical regions (defined as Asia, North or South America, Europe, Oceania), although with varied magnitude of the effect estimates, positive associations between particulate matters and birth weight [148,154] and all pollutants and PTB [155] were found across all regions (Table S4). The direction of effect estimates, and consistency differed for each exposure-outcome association at different pregnancy periods, resulting in different gradings in the overall direction of the association. However, high heterogeneity, as high as 99%,[33,156,168] and imprecision were reported across almost all meta-analyses. Also, due to the nature of the exposure, no study included an experimental or randomised controlled trial (RCT). Consequently, the maximum possible confidence of the evidence according to the adopted classification was *probable evidence* (Pe). Thus, unless stated otherwise, the confidence of the evidence observed across exposure-outcome associations described below was *probable evidence.*

i) Birth weight reduction

$PM_{2.5}$: Six meta-analyses examined the association with exposure over the entire pregnancy period, and the overall results showed a *more consistent positive association*. The largest pooled effect estimate was -28 g (95% CI = -48, -7) per 10 µg/m^3 increase in exposure with heterogeneity of 94%, from 15 studies of 15,424,198 births.[148] For trimester-specific exposures, *less consistent positive associations* were observed for each trimester (Table 3.3, Figure 3.2).

PM_{10}: Entire pregnancy exposure from three meta-analyses [30,31,148] showed a *less consistent positive association* with birth weight reduction. The largest reported pooled effect estimate was -10 g (95% CI = -14, -7) per 10 µg/m^3 increase in exposure with 0% heterogeneity based on five cohort studies of 477,123 births that adjusted for prenatal tobacco smoking.[30] All trimester-specific results showed *less consistent positive associations* (Table 3.3, Figure S3.6).

NO_2: The overall evidence from the results of one global study[31] and one SRMA from Europe [147] was graded with a *less consistent positive association* for the entire pregnancy period, first and third trimesters. However, the second-trimester exposure showed an *unclear* or *contradictory direction* (Table 3.3 and Figure S3.7).

O_3: Only one meta-analysis[31] was conducted that found a positive association between exposure during the entire pregnancy period with high heterogeneity; the effect estimate was -5 g (95% CI = -16, 6; I^2 = 81%) per 10 ppb increase in exposure. This meta-analysis pooled four cohort studies where two of the cohort studies each reported positive and negative associations with the change in birth weight. Given that only one meta-analysis was identified, applying the grading criteria to the results of the included primary studies (available in the original meta-analysis) indicated *unclear or*

contradictory direction for the entire pregnancy period, first and third trimesters. However, the second-trimester exposure showed a *less consistent positive association* (Table 3.3).

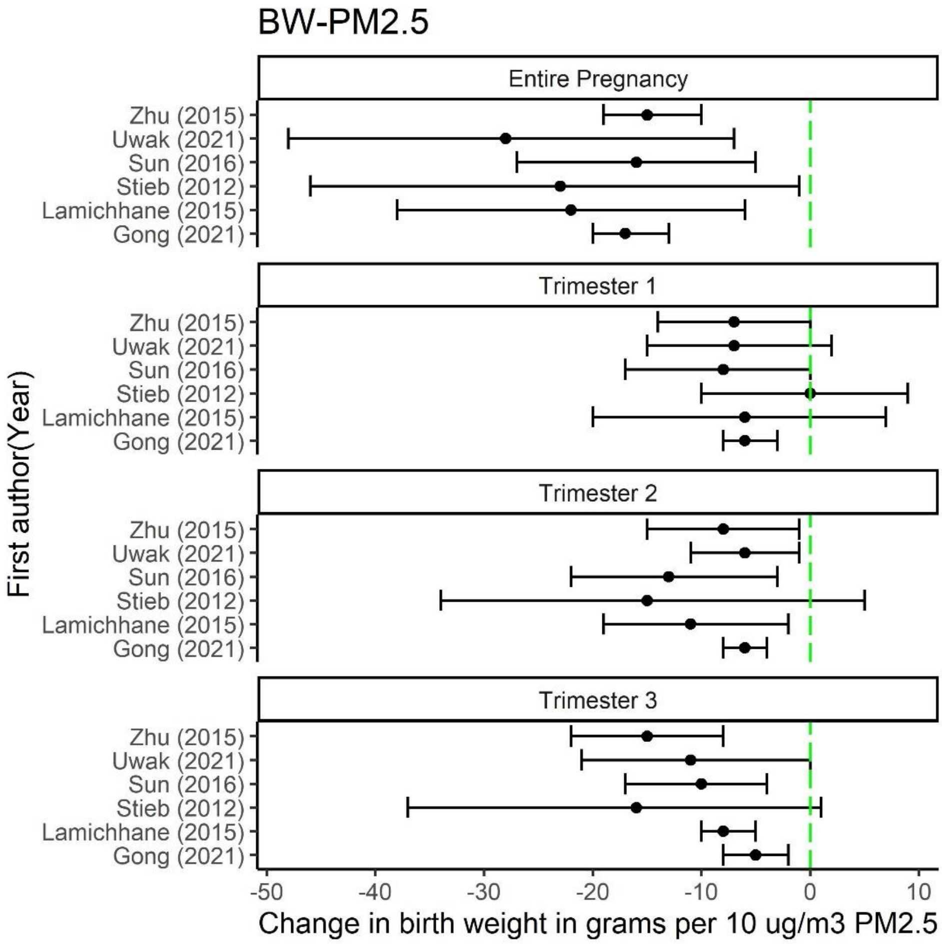

Figure 3.2 Forest plot of the association between change in birth weight (BW) per 10μg/m^3 $PM_{2.5}$ increase at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dashed line represents change in birth weight of 0 grams. Note: $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5μm.

SO_2: Only one meta-analysis was included that pooled three to six studies and found lower risks for the entire pregnancy period, second and third trimesters but higher risk for the first trimester.[31] In all pregnancy periods, the results of the included primary studies (available in the original meta-analysis) showed both higher and lower risks. Hence overall evidence was considered *unclear or contradictory direction* for each pregnancy period (Table 3.3).

CO: Only one meta-analysis pooled this exposure-outcome association for each pregnancy period based on four to eight cohort studies.[31] The pooled effect showed a 1 g decrease in birth weight for the entire pregnancy but no association for trimester-specific effects per 100 ppb increase in the exposure. However, less than 80% of the included primary studies reported both higher and lower risks for each pregnancy period. Hence the overall evidence was graded in *unclear or contradictory directions* for each pregnancy period (Table3.3).

$PM_{2.5}$ or PM_{10} by race/ethnicity: Two meta-analyses pooled the effect estimates by race or ethnicity for $PM_{2.5}$ and PM_{10} over the entire pregnancy exposure, dominated by studies conducted in the USA [148,158]. Applying the grading criteria, the overall evidence for $PM_{2.5}$ showed a *more consistent positive association* for White persons, a *less consistent positive association* for Hispanic persons and Black persons but an *unclear or contradictory direction* for Asian persons. The largest pooled effect estimate was -32 g (95% CI = -60, -4) per 10 µg/m^3 increase in exposure among the White population.[148] Only one meta-analysis pooled results for PM_{10} and birth weight association.[148] The overall evidence based on the results of the primary studies showed a *less consistent positive association* for White persons and *unclear or contradictory directions* for both Black and Hispanic persons (Table S3.6, Figure S3.8).

Table 3.3 Association between birth weight and ambient air pollution

Pollutant (incremental units)	**Exposure period**	**Meta-analysis First author (Year)**	**Change in birthweight (g) (95% CI)**	**I^2 (%)**	**Primary studies (n)**	**Total births (N)**	**Consistency, confidence**
$PM_{2.5}$ (10 µg/m^3)	Entire Pregnancy	Gong (2021) [154]	-17 (-20, -13)	96	26	23,926,140	++, Pe
		Uwak (2021)[148]	-28 (-48, -7)	94	15	15,424,198	
		Sun (2016)[168]	-16 (-27, -5)	99	17	7,857,127	
		Lamichhane (2015)[30]	-22 (-38, -6)	92	7	2,090,972	
		Zhu (2015)[173]	-15 (-19, -10)	87	12	7,388,985	
		Stieb (2012)[31]	-23 (-46, -1)	95	7	4,271,411	
	Trimester 1	Gong (2021) [154]	-6 (-8, -3)	91	13	6,707,042	+, Pe
		Uwak (2021) [148]	-7 (-15, 2)	87	11	3,547,223	
		Sun (2016) [168]	-8 (-17, 0)	90	11	NA	
		Lamichhane (2015) [30]	-6 (-20, 7)	88	5	1,261,503	
		Zhu (2015) [173]	-7 (-14, 0)	82	7	5,153,167	
		Stieb (2012) [31]	0 (-10, 9)	37	4	3,637,501	
	Trimester 2	Gong (2021) [154]	-6 (-8, -4)	85	13	6,707,042	+, Pe
		Uwak (2021) [148]	-6 (-11, -1)	68	11	3,547,223	
		Sun (2016) [168]	-13 (-22, -3)	92	10	NA	
		Lamichhane (2015) [30]	-11 (-19, -2)	82	4	1,257,650	
		Zhu (2015) [173]	-8 (-15, -1)	85	5	4,742,687	
		Stieb (2012) [31]	-15 (-34, 5)	75	4	3,634,129	
	Trimester 3	Gong (2021) [154]	-5 (-8, -2)	94	20	10,361,367	+, Pe

		Uwak (2021) [148]	-11 (-21, 0)	84	12	3,556,290	
		Sun (2016) [168]	-10 (-17, -4)	86	13	NA	
		Lamichhane (2015) [30]	-8 (-10, -5)	0	6	2,236,549	
		Zhu (2015) [173]	-15 (-22, -8)	86	7	5,153,167	
		Stieb (2012) [31]	-16 (-37, 1)	86	4	3,637,501	
PM_{10} (10 μg/m^3)	Entire Pregnancy	Uwak (2021) [148]	-9 (-17, 0)	84	8	2,679,928	+, Pe
		Lamichhane (2015) [30]	-10 (-14, -7)	0	5	477,123	
		Stieb (2012) [31]	-8 (-10, -7)	16	7	3,932,746	
	Trimester 1	Uwak (2021) [148]	3 (-3, 10)	14	6	757,843	+, Pe
		Lamichhane (2015) [30]	-1 (-5, 2)	0	4	507,286	
		Stieb (2012) [31]	-2 (-4, 1)	67	10	4,505,769	
	Trimester 2	Uwak (2021)	-3 (-8, 1)	0	6	757,843	+, Pe
		Lamichhane (2015) [30]	-7 (-14, 1)	68	4	507286	
		Stieb (2012) [31]	-2 (-4, 0)	41	10	4,505,769	
	Trimester 3	Uwak (2021) [148]	-7 (-11, -2)	0	7	766,910	+, Pe
		Lamichhane (2015) [30]	-5 (-8, -2)	0	5	913,913	
		Stieb (2012) [31]	-2 (-7, 3)	93	10	4,505,769	
CO (100 ppb)	Entire Pregnancy	Stieb (2012)[31]	-1 (-3, 1)	95	4	3,702,544	0, Pe
	Trimester 1	Stieb (2012) [31]	0 (-1, 0)	95	8	4,576,045	0, Pe
	Trimester 2	Stieb (2012) [31]	0 (0, 0)	0	7	4,299,282	0, Pe
	Trimester 3	Stieb (2012) [31]	0 (-1, 1)	91	7	4,299,282	0, Pe
NO_2 (10 ppb)	Entire Pregnancy	Simoncic (2020)[147]	-3 (-12, 7)	28	6	86,680	+, Pe
		Stieb (2012) [31]	-14 (-22, -6)	85	10	3,780,571	
	Trimester 1	Simoncic (2020)[147]	-27 (-56, 2)	36	4	3,435	+, Pe
		Stieb (2012) [31]	-2 (-10, 5)	90	11	4,259,729	
	Trimester 2	Simoncic (2020)[147]	-17 (-46, 13)	26	4	3,435	0, Pe
		Stieb (2012) [31]	0 (-1, 1)	0	9	3,979,113	
	Trimester 3	Simonici (2020)	-3 (-26, 19)	32	5	12,502	+, Pe
		Stieb (2012) [31]	-4 (-15, 7)	94	10	3,982,966	
O_3 (10 ppb)	Entire Pregnanc	Stieb (2012) [31]	-5 (-16, 6)	81	4	3,370,657	0, Pe

	y						
	Trimester 1	Stieb (2012) [31]	1 (-3, 5)	81	8	4,325,899	0, Pe
	Trimester 2	Stieb (2012) [31]	-5 (-9, -2)	77	8	4,325,899	+, Pe
	Trimester 3	Stieb (2012) [31]	-1 (-4, 1)	80	8	4,325,899	0, Pe
SO_2 (10 ppb)	Entire Pregnancy	Stieb (2012) [31]	15 (-15, 45)	80	3	3,718,863	0, Pe
	Trimester 1	Stieb (2012) [31]	-15 (-42, 12)	95	6	4,098,747	0, Pe
	Trimester 2	Stieb (2012) [31]	9 (-9, 28)	66	4	3,808,425	0, Pe
	Trimester 3	Stieb (2012) [31]	15 (-5, 35)	93	5	3,883,096	0, Pe

Note: NO_2, Nitrogen dioxide; CO, Carbon monoxide; O_3, Ozone; SO_2, Sulphur dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5µm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10µm; BW, birth weight; OR, odd ratio; CI, confidence intervals; ppb, parts per billion; NA, Not available; I^2, Heterogeneity; '++' represents more consistent positive association; '+' represents less consistent positive association; '0' represents contradictory/unclear direction; Pe, probable evidence of the observed direction of exposure effect.

ii) Low birth weight (LBW)

$PM_{2.5}$: Applying the grading criteria, the findings from seven meta-analyses based on 4 to 29 cohort studies for the entire pregnancy period were found to have a *less consistent positive association*. The largest pooled OR was 1.09 (95% CI =1.03, 1.15) per 10 µg/m^3 increase in exposure with high heterogeneity (I^2 = 93%) based on 19 cohort studies that included 10,405,729 births.[168] Considering four meta-analyses for each trimester, the overall evidence for each trimester showed a *less consistent positive association* (Table 3.4 and Figure S3.9).

PM_{10}: For the entire pregnancy period, four meta-analyses reported positive associations which included the null [28,32] and without the null [31,144] in the confidence intervals. The largest pooled effect estimate indicated a higher risk of 5% per 10 µg/m^3 increase in the exposure based on 23 cohort studies with 286,188 LBW cases, with OR of 1.05 (95% CI=1.03, 1.08; I^2= 70%).[144] The overall evidence was graded as a *less consistent positive association* for the entire pregnancy exposure. Regarding the trimester-specific risks, the overall evidence was *less consistent positive associations* for first and second trimesters but an *unclear or contradictory direction* for the third trimester (Table 3.4 and Figure S3.10).

CO: From the results of two meta-analyses,[31,144] the overall evidence of *less consistent positive association* was found for the entire pregnancy. The same pooled OR of 1.01 (95% CI=1.00, 1.01) per 100 ppb increase in exposure based on six and eight cohort studies with low to moderate heterogeneities were reported. The same two meta-analyses reported similar findings of *less consistent positive association* for the second trimester, but an *unclear or contradictory direction* for the first-trimester exposure and consistently *null association* for the third trimester (Table 3.4, Figure S3.11).

Table 3.4 Association between low birth weight (LBW) and ambient air pollution

Pollutant (incremental units)	**Exposure period**	**Meta-analysis**	**OR (95% CI)**	**I^2 (%)**	**Primary studies (n)**	**Total births (N)**	**Consistency, confidence**
$PM_{2.5}$ (10 μg/m^3)	Entire Pregnancy	*Li (2020)[144]	1.08 (1.04, 1.12)	86	29	536,218	+, Pe
		Ji (2017)[32]	1.04 (0.99, 1.09)	67	6	594,626	
		Li (2017)[167]	1.05 (0.98, 1.12)	85	4	8,226,866	
		Sun (2016) [168]	1.09 (1.03, 1.15)	93	19	10,405,729	
		Zhu (2015) [173]	1.05 (1.02, 1.07)	40	6	5,691,348	
		Stieb (2012) [31]	1.05 (0.99, 1.12)	86	5	4,160,105	
		Sapkota (2010)[28]	1.09 (0.90, 1.32)	57	4	831,042	
	Trimester 1	Li (2020) [144]	1.03 (0.97, 1.09)	95	19	NA	+, Pe
		Ji (2017) [32]	1.01 (0.98, 1.03)	0	3	436,799	
		Li (2017) [167]	1.00 (0.91, 1.11)	90	3	1,163,751	
		Sun (2016) [168]	1.03 (0.93, 1.13)	87	7	NA	
	Trimester 2	Li (2020) [144]	1.03 (0.98, 1.08)	92	20	NA	+, Pe
		Ji (2017) [32]	1.15 (0.96, 1.38)	66	3	436,799	
		Li (2017) [167]	1.00 (0.96, 1.03)	81	4	1,587,470	
		Sun (2016) [168]	1.04 (0.95, 1.13)	80	7	NA	
	Trimester 3	Li (2020) [144]	1.05 (1.01, 1.10)	92	20	NA	+, Pe
		Ji (2017) [32]	1.17 (0.94, 1.46)	79	3	436,799	
		Li (2017) [167]	1.03 (0.98, 1.09)	55	3	1,163,751	
		Sun (2016) [168]	1.23 (0.96, 1.59)	99	8	NA	
PM_{10} (10 μg/m^3)	Entire Pregnancy	Li (2020) [144]	1.05 (1.03, 1.08)	70	23	286,188	+, Pe
		Ji (2017) [32]	1.01 (0.96, 1.08)	68	9	326,518	
		Stieb (2012) [31]	1.05 (1.02, 1.07)	68	14	4,419,929	
		Sapkota (2010) [28]	1.02 (0.99, 1.05)	55	11	1,935,404	
	Trimester 1	Li (2020) [144]	1.02 (1.00, 1.05)	72	13	NA	+, Pe
		Ji (2017) [32]	1.06 (0.99, 1.12)	20	7	315,469	
		Stieb (2012) [31]	1.01 (0.97, 1.05)	42	7	1,153,736	
		Sapkota (2010) [28]	1.00 (0.97, 1.03)	NA	5	NA	
	Trimester 2	Li (2020) [144]	1.01 (1.01, 1.02)	28	13	NA	+, Pe
		Ji (2017) [32]	1.05 (0.99, 1.44)	23	6	313,955	
		Stieb (2012) [31]	1.01 (0.98, 1.04)	23	7	1,153,736	
	Trimester 3	Li (2020) [144]	1.00 (1.00, 1.01)	21	13	NA	0, Pe
		Ji (2017) [32]	1.06 (0.97, 1.15)	50	7	315,469	
		Stieb (2012) [31]	1.00 (0.98, 1.03)	13	7	1,153,736	

		Sapkota (2010) [28]	1.00 (0.99, 1.01)	NA	7	NA	
CO (100 ppb)	Entire Pregnancy	Li (2020) [144]	1.01 (1.00, 1.01)	53	8	112,239	+, Pe
		Stieb (2012) [31]	1.01 (1.00, 1.01)	38	6	4,543,308	
	Trimester 1	Li (2020) [144]	1.01 (1.00, 1.01)	12	5	NA	0, Pe
		Stieb (2012) [31]	1.00 (1.00, 1.01)	0	5	1,129,363	
	Trimester 2	Li (2020) [144]	1.01 (0.99, 1.02)	54	5	NA	+, Pe
		Stieb (2012) [31]	1.01 (1.00, 1.01)	0	4	900,278	
	Trimester 3	Li (2020) [144]	1.00 (0.98, 1.02)	68	5	NA	00, Pe
		Stieb (2012) [31]	1.00 (0.99, 1.01)	86	5	1,129,363	
NO_2 (10 ppb)	Entire Pregnancy	Li (2020) [144]	1.03 (1.01, 1.05)	90	23	509,997	+, Pe
		Stieb (2012) [31]	1.02 (1.00, 1.04)	78	7	4,211,351	
	Trimester 1	Li (2020) [144]	1.02 (1.01, 1.04)	11	12	NA	+, Pe
		Stieb (2012) [31]	1.01 (0.99, 1.03)	0	5	1043794	
	Trimester 2	Li (2020) [144]	1.01 (0.99, 1.04)	75	13	NA	+, Pe
		Stieb (2012) [31]	1.02 (1.00, 1.04)	0	4	814,709	
	Trimester 3	Li (2020) [144]	1.01 (0.97, 1.06)	78	13	NA	0, Pe
		Stieb (2012) [31]	0.99 (0.93, 1.05)	70	5	1,043,794	
O_3 (10 ppb)	Entire Pregnancy	Li (2020) [144]	1.05 (1.01, 1.09)	90	14	311,189	0, Pe
		Stieb (2012) [31]	1.00 (0.91, 1.12)	25	3	3,377,984	
	Trimester 1	Li (2020) [144]	1.00 (0.95, 1.05)	79	9	NA	0, Pe
		Stieb (2012) [31]	0.99 (0.95, 1.04)	0	5	1,002,748	
	Trimester 2	Li (2020) [144]	1.02 (0.95, 1.09)	87	8	NA	0, Pe
		Stieb (2012) [31]	0.97 (0.89, 1.07)	34	3	496,900	
	Trimester 3	Li (2020) [144]	1.09 (0.99, 1.20)	96	9	NA	+, Pe
		Stieb (2012) [31]	1.01 (0.92, 1.12)	76	5	1,002,748	
SO_2 (10 ppb)	Entire Pregnancy	Li (2020) [144]	1.12 (1.02, 1.24)	83	13	171,360	++, Pe
		Stieb (2012) [31]	1.06 (1.04, 1.10)	0	7	4,400,175	
	Trimester 1	Li (2020) [144]	1.05 (1.00, 1.12)	65	10	NA	+, Pe
		Stieb (2012) [31]	1.04 (0.98, 1.08)	58	5	889,204	
	Trimester 2	Li (2020) [144]	1.02 (0.99, 1.05)	20	10	NA	+, Pe
		Stieb (2012) [31]	1.02 (0.96, 1.08)	41	4	660,119	
	Trimester 3	Li (2020) [144]	0.98 (0.95, 1.01)	45	10	NA	-, Pe
		Stieb (2012) [31]	0.98 (0.94, 1.04)	59	6	963,875	

Note: NO_2, Nitrogen dioxide; CO, Carbon monoxide; O_3, Ozone; SO_2, Sulphur dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5µm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10µm; LBW, low birth weight; OR, odd ratio; CI, confidence intervals; pp, parts per billion; NA, Not available; I^2, Heterogeneity; '++' represents more consistent positive association; '+' represents less consistent positive association; '0' represents contradictory/unclear

direction; '-' represents less consistent negative association; Pe, probable evidence of the observed direction of exposure effect.
*Li (2020) reported number of LBW cases instead of total births for all exposures.

NO_2: Two meta-analyses reported on this exposure-outcome association.[31,144] The overall evidence for the entire pregnancy period, first and second trimesters were found to be *less consistent positive associations*. For the entire pregnancy exposure, the larger pooled OR was 1.03 (95% CI=1.01, 1.05) per 10 ppb increase in exposure with high heterogeneity (I^2 = 90%) based on 23 cohort studies of 509,997 LBW cases.[144] The third trimester showed an *unclear or contradictory direction* (Table 3.4, Figure S3.12).

O_3: The results of two meta-analyses[31,144] indicated overall evidence of *unclear or contradictory directions* for the entire pregnancy period, first and second trimesters while the third trimester showed a *less consistent positive association* (Table 3.4, Figure S3.13).

SO_2: Two meta-analyses were reported for each pregnancy period[31,144] and found a *more consistent positive association* across the entire pregnancy exposure period. The larger OR of LBW was 12% with high heterogeneity (I^2= 83%) based on 13 cohort studies of 171,360 LBW births with pooled OR of 1.12 (95% CI= 1.02, 1.24) per 10 ppb increase in exposure.[144] The results of both first and second trimesters showed *less consistent positive association*s while the third trimester was a *less consistent negative association* (Table 3.4, Figure S3.14).

iii) Small-for-gestational age (SGA)

$PM_{2.5}$: The two meta-analyses on the association between SGA and $PM_{2.5}$ considered the same primary studies.[133,173] We, therefore, considered the two pooled results as one. The entire pregnancy period result from six cohort studies on 1,515,887 births indicated positive association with pooled OR of 1.15 (95% CI= 1.10, 1.20; I^2= 0%) per 10 µg/m^3 increase in exposure. The overall evidence was graded as a *less consistent positive association* for the entire pregnancy period based on the results of the included primary studies. Similarly, applying the grading criteria to the results of the primary studies, we graded the overall evidence as *unclear or contradictory direction* for the first trimester and *less consistent positive associations* for both second and third trimesters (Table S3.7).

iv) Preterm birth (PTB)

$PM_{2.5}$: There were seven meta-analyses based on 4 to 31 cohort studies. The overall evidence for the entire pregnancy period was graded as a *less consistent positive association* and the largest pooled OR of PTB was 1.16 (95% CI=1.07,1.26; I^2=17%) per 10 µg/m^3 increase in the exposure based on four cohort studies conducted on 197,980 births.[31] The *unclear or contradictory direction* was observed for the first trimester. Both second and third trimesters, however, showed *a less*

consistent positive association. The largest pooled OR of PTB per 10 μg/m^3 increase in the exposure for second trimester was 1.09 (95% CI=0.82, 1.44; I^2 = 99%) based on five cohort studies conducted on 1,340,807 births and third trimester was 1.08 (95% CI= 0.99, 1.17; I^2 = 92%) based on nine cohort studies conducted on 2,208,883 births [33] (Table 3.5, Figure 3.3).

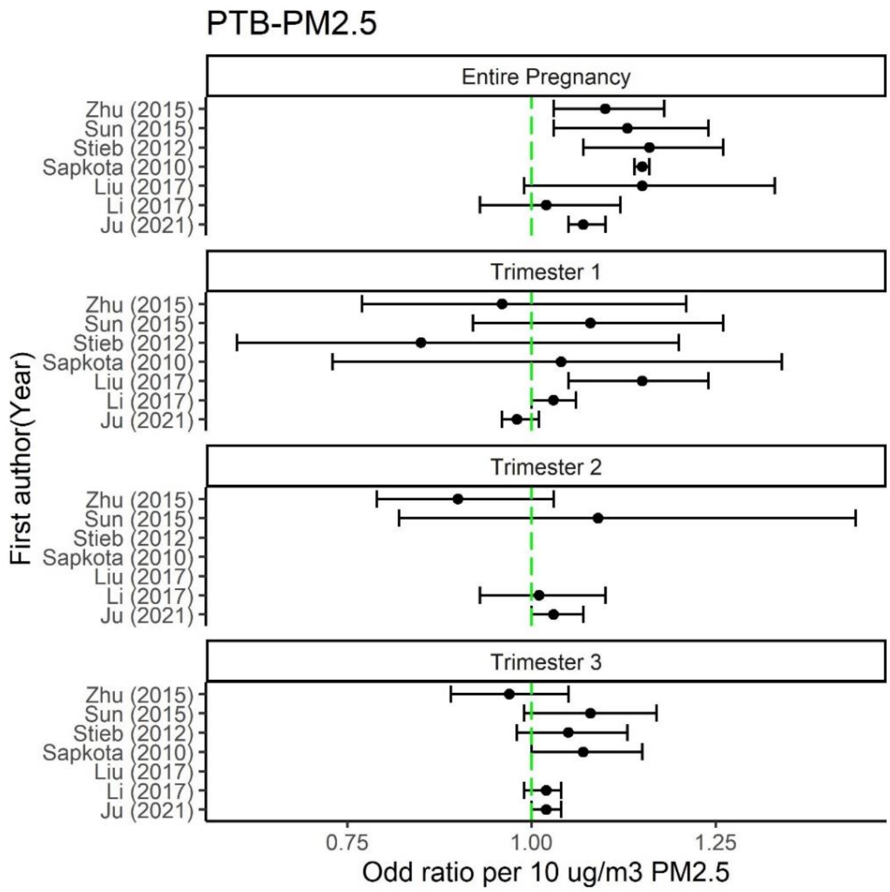

Figure 3.3 Forest plot of the association between preterm birth (PTB and fine particulate matter ($PM_{2.5}$) per 10μg/m^3 increment) during different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dashed line represents the reference for null association of 1. Note: $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5μm.

PM_{10}: From the reported pooled OR of three meta-analyses,[28,30,31] the overall evidence showed a *less consistent positive association* for the entire pregnancy period. The largest pooled OR indicated 24% increased odds of PTB per 10 μg/m^3 increase in the exposure with an OR of 1.24 (95% CI= 1.03, 1.45) with no heterogeneity (I^2 = 0%) based on two cohort studies of 9,294 births that adjusted for maternal tobacco smoking.[30] Regarding the trimester-specifics, we observed *less consistent negative associations* for both first and second trimesters but a *less consistent positive association* for the third trimester (Table 3.5 and Figure S3.15).

NO_2: Two global meta-analyses based on 20 primary studies [155] and six primary studies,[31] and one for the European region based on four studies [147] reported on this exposure-outcome association. The overall evidence was a *less consistent positive association* for the entire pregnancy period and the larger OR of PTB was 1.14 (95% CI= 0.81, 1.64) per 10 ppb increase in the exposure from four

cohort studies of 80,458 European births with moderate heterogeneity (I^2 = 72%).[147] From two meta-analyses for each trimester exposure period, the overall evidence was a *less consistent negative association* for the first trimester, *unclear or contradictory direction* for the second trimester, and a *less consistent positive association* for the third trimester (Table 3.5, Figure S3.16).

CO: From the findings of two meta-analyses,[31,155] both entire pregnancy and first trimester exposure periods showed *unclear or contradictory directions* while the third trimester consistently showed a *null association*. One meta-analysis[155] evaluated the second trimester and the results of the three included primary studies indicated an *unclear or contradictory direction* (Table 3.5, Figure S3.17).

O_3: Two meta-analyses were reported for the entire pregnancy, and second and third trimesters,[31,155] and three meta-analyses were reported for the first trimester.[31,150,155] The entire pregnancy and first and second trimesters showed *less consistent positive associations* while the third trimester was an *unclear or contradictory direction* (Table 3.5, Figure S3.18).

Table 3.5 Association between PTB and ambient air pollution

Pollutant (incremental units)	Exposure period	Meta-analysis	OR (95% CI)	I^2 (%)	Primary studies (n)	Total births (N)	Consistency, confidence
$PM_{2.5}$ (10 μg/m^3)	Entire Pregnancy	*Ju (2021)[155]	1.07 (1.05, 1.10)	89	31	1,007,827	+, Pe
		Liu (2017)[166]	1.15 (0.99, 1.33)	85	7	882,479	
		Li (2017) [167]	1.02 (0.93, 1.12)	97	6	4,098,419	
		Sun (2015)[33]	1.13 (1.03, 1.24)	91	13	3,089,186	
		Zhu (2015)[173]	1.10 (1.03, 1.18)	52	8	1,764,632	
		Stieb (2012)[31]	1.16 (1.07, 1.26)	17	4	197,980	
		Sapkota (2010)[28]	1.15 (1.14, 1.16)	0	6	517,760	
	Trimester 1	Ju (2021)[155]	0.98 (0.96, 1.01)	97	26	920,837	0, Pe
		Liu (2017) [166]	1.15 (1.05, 1.24)	33	9	1,041,382	
		Li (2017) [167]	1.03 (1.00, 1.06)	70	5	1,371,800	
		Sun (2015)[33]	1.08 (0.92, 1.26)	91	10	1,668,004	
		Zhu (2015)[173]	0.96 (0.77, 1.21)	87	6	743,647	
		Stieb (2012)[31]	0.85 (0.60, 1.20)	94	4	589,100	
		Sapkota (2010) [28]	1.04 (0.73, 1.34)	NA	4	NA	
	Trimester 2	Ju (2021) [155]	1.03 (1.00, 1.07)	97	23	880542	+, Pe
		Li (2017) [167]	1.01 (0.93, 1.10)	98	4	1,367,947	
		Sun (2015)[33]	1.09 (0.82, 1.44)	99	5	1,340,807	
		Zhu (2015)[173]	0.90 (0.79, 1.03)	0	3	598,606	
	Trimester 3	Ju (2021) [155]	1.02 (1.00, 1.04)	93	23	923,545	+, Pe
		Li (2017) [167]	1.02 (0.99, 1.04)	59	4	1,367,947	
		Sun (2015)[33]	1.08 (0.99, 1.17)	92	9	2,208,883	
		Zhu (2015)[173]	0.97 (0.89, 1.05)	31	6	1,240,212	

		Stieb (2012)[31]	1.05 (0.98, 1.13)	33	4	589,100	
		Sapkota (2010) [28]	1.07 (1.00, 1.15)	NA	3	NA	
PM_{10} (10 μg/m^3)	Entire Pregnancy	Ju (2021)[155]	1.03 (1.01, 1.06)	92	15	210,850	+, Pe
		Lamichhane (2015) [30]	1.24 (1.03, 1.45)	0	2	9,294	
		Stieb (2012)[31]	1.16 (0.98, 1.38)	17	3	98,774	
		Sapkota (2010)[28]	1.02 (0.99, 1.04)	73	8	1,047,489	
	Trimester 1	Ju (2021)[155]	0.97 (0.94, 1.00)	97	16	263,928	-, Pe
		Lamichhane (2015) [30]	0.99 (0.92, 1.07)	42	4	264,672	
		Stieb (2012)[31]	0.98 (0.93, 1.03)	85	6	1,043,954	
		Sapkota (2010)[28]	1.02 (0.97, 1.06)	NA	4	NA	
	Trimester 2	Ju (2021)[155]	0.99 (0.96, 1.03)	98	14	257,476	-, Pe
		Lamichhane (2015)[30]	0.97 (0.95, 0.99)	0	4	1,024,360	
		Stieb (2012)[31]	0.97 (0.95, 0.99)	0	3	794,396	
	Trimester 3	Ju (2021)[155]	1.01 (0.99, 1.02)	59	13	223,574	+, Pe
		Lamichhane (2015) [30]	0.97 (0.86, 1.08)	58	3	229,967	
		Stieb (2012)[31]	1.03 (1.01, 1.05)	20	6	1,043,954	
		Sapkota (2010) [28]	1.02 (1.01, 1.03)	NA	5	NA	
CO (100 ppb)	Entire Pregnancy	Ju (2021)[155]	1.04 (1.00, 1.08)	95	5	71,906	0, Pe
		Stieb (2012)[31]	1.00 (0.99, 1.02)	0	2	112,941	
	Trimester 1	Ju (2021)[155]	0.99 (0.96, 1.02)	95	3	70,680	0, Pe
		Stieb (2012)[31]	1.00 (0.99, 1.00)	92	5	911,850	
	Trimester 2	Ju (2021)[155]	1.04 (0.96, 1.12)	96	3	68,920	0, Pe
	Trimester 3	Ju (2021) [155]	1.00 (0.99, 1.02)	78	4	71,049	00, Pe
		Stieb (2012) [31]	1.00 (1.00, 1.01)	0	5	911,850	
O_3 (10 ppb)	Entire Pregnancy	Ju (2021)[155]	1.07 (1.04, 1.10)	86	11	243,295	+, Pe
		Stieb (2012)[31]	1.39 (0.62, 3.12)	89	2	98,449	
	Trimester 1	Ju (2021)[155]	1.07 (1.04, 1.10)	91	11	304,353	+, Pe
		Rappazzo (2021)[150]	1.06 (1.03, 1.10)	97	17	4,525,441	
		Stieb (2012)[31]	1.10 (0.95, 1.28)	90	4	799,840	
	Trimester 2	Ju (2021)[155]	1.04 (1.00, 1.08)	95	8	293,593	+, Pe
		Rappazzo (2021)[150]	1.05 (1.02, 1.08)	97	15	4,713,201	
	Trimester 3	Ju (2021)[155]	1.09 (1.03, 1.15)	96	8	201,663	0, Pe
		Stieb (2012)[31]	0.98 (0.93, 1.05)	44	4	799,840	
NO_2 (10 ppb)	Entire Pregnancy	Ju (2021)[155]	1.02 (0.98, 1.06)	88	20	343,203	+, Pe
		Simoncic (2020)[147]	1.14 (0.81, 1.64)	72	4	80,458	

		Stieb (2012)[31]	1.08 (0.91, 1.28)	53	5	162,815	
	Trimester 1	Ju (2021)[155]	0.94 (0.90, 0.99)	69	21	398,229	-, Pe
		Stieb (2012)[31]	0.93 (0.80, 1.08)	89	6	807,681	
	Trimester 2	Ju (2021)[155]	1.00 (0.94, 1.07)	95	18	390,413	0, Pe
		Stieb (2012)[31]	1.01 (0.88, 1.18)	22	2	422,703	
	Trimester 3	Ju (2021)[155]	1.14 (1.06, 1.21)	92	15	331,248	+, Pe
		Stieb (2012)[31]	1.03 (0.98, 1.09)	20	6	807,681	
SO_2 (10 ppb)	Entire Pregnancy	Ju (2021)[155]	1.19 (0.95, 1.50)	83	8	158,735	0, Pe
	Trimester 1	Ju (2021)[155]	0.95 (0.83, 1.09)	92	7	166,190	0, Pe
	Trimester 2	Ju (2021)[155]	0.99 (0.89, 1.10)	85	6	160,122	0, Pe
	Trimester 3	Ju (2021)[155]	0.97 (0.85, 1.10)	91	7	166,190	0, Pe

Note: NO_2, Nitrogen dioxide; CO, Carbon monoxide; O_3, Ozone; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5µm; PM_{10}, particulate matter with aerodynamic diameter ≤ 10µm; PTB, preterm birth; OR, odd ratio; CI, confidence intervals; pp, parts per billion; NA, Not available; I^2, Heterogeneity; '+' represents less consistent positive association; '0' represents contradictory/unclear direction; '-' represents less consistent negative association; Pe, probable evidence of the observed direction exposure effect; *Ju (2021) reported number of PTB cases instead of total births for all exposures.

v) Stillbirth

$PM_{2.5}$: The pooled OR from three meta-analyses [149,151,172] showed a *less consistent positive association* for the entire pregnancy period. The largest reported pooled OR was 1.15 (95% CI=1.07, 1.25) per 10 µg/m^3 increase in the exposure with high heterogeneity (I^2 = 75%) based on six primary studies of 3,222,578 births.[151] Trimester-specific exposures showed a *less consistent positive association* for the second trimester but *unclear or contradictory directions* for both the first and third trimesters (Table 3.6, Figure S3.19).

PM_{10}. This was reported in three meta-analyses [133,149,172] where two [133,172] published in the same year were duplicated (i.e., based on the same primary studies) and were considered as one result. The overall evidence for the entire pregnancy showed a *less consistent positive association* with a 1% higher risk per 10 µg/m^3 increase in the exposure based on either two or four cohort studies. Regarding the trimester-specific associations, both first and second trimesters showed *unclear or contradictory directions* while the third trimester was a *less consistent positive association* (Table 3.6, Figure S3.20).

NO_2: This was investigated in two meta-analyses based on three to six cohort studies.[149,172] The overall evidence for the entire pregnancy period and each of the three trimesters showed *less consistent positive associations*. The larger risk was 7% higher with OR of 1.07 (95% CI= 0.97, 1.18; I^2 = 80%) per 10 ppb increase in the exposure based on three primary studies of 3,847,818 births for the entire pregnancy.[172] The pooled effect estimates were roughly similar for the first and third trimesters based on three to six primary studies (Table 3.6, Figure S3.21).

SO_2: The results of two meta-analyses [149,172] for the entire pregnancy period, pooled from three and six primary studies, showed a *less consistent positive association*. The larger pooled OR was 1.08 (95% CI= 0.95, 1.22; I^2 = 20%) per 10 ppb increase in the exposure from three primary studies of 3,847,818 births [172]. Both first and second trimesters indicated *unclear or contradictory directions* of associations while the third trimester was *a less consistent positive association* (Table 3.6, Figure S3.22).

CO: This was examined in two meta-analyses.[149,172] The overall evidence across the entire pregnancy and the third trimester showed *unclear or contradictory directions* while both first and second trimesters consistently indicated *null association* based on three to six primary studies (Table 3.6, Figure S3.23).

O_3: Two meta-analyses pooled two to five primary studies for this exposure-outcome association.[149,172] The overall epidemiological evidence was graded in *unclear or contradictory directions* for the entire pregnancy period and each of the three trimesters (Table 3.6, Figure S24).

vi) Spontaneous abortion (SAB)

$PM_{2.5}$: One meta-analysis reported on this exposure-outcome association and found a pooled OR of 1.20 (95% CI=1.01, 1.40) based on five primary studies conducted on 69,507 natural pregnancies with high heterogeneity (I^2 = 99%).[156] Findings from the included primary studies showed a *more consistent positive association*.

PM_{10}: Pooled OR from two meta-analyses[133,156] indicated a *more consistent positive association.* The larger pooled OR for 10 µg/m^3 increment based on three primary studies (one each for cohort, case-control, and cross-sectional) on 515,932 total pregnancies during the first trimester found 34% higher odds of SAB, 1.34 (95% CI= 1.04, 1.72) with moderate heterogeneity (I^2 = 62.4%)[133] (Table 3.6). There were no meta-analyses for the gaseous pollutants.

Table 3.6 Association between stillbirth, spontaneous abortion (SAB) and ambient air pollution

Pollutant (incremental units)	Exposure period	Meta-analysis	OR (95% CI)	I^2 (%)	Primary studies (n)	Total births (N)	Consistency, confidence
$PM_{2.5}$ (10 µg/m^3)	Entire Pregnancy	Xie (2021)[151]	1.15 (1.07, 1.25)	75	6	3,222,578	+, Pe
		Zhang (2021)[174]	1.10 (1.07, 1.13)	62	7	4,647,479	
		Siddika (2016)[172]	1.05 (0.99, 1.12)	0	2	3,745,243	
	Trimester 1	Xie (2021)[151]	1.01 (0.90, 1.13)	87	6	3,892,183	0, Pe
		Zhang (2021)[174]	0.96 (0.83, 1.09)	89	7	5,078,391	
		Siddika (2016)[172]	1.11 (0.81, 1.51)	57	2	3,745,243	
	Trimester 2	Xie (2021) [151]	1.06 (0.98, 1.14)	80	5	3,762,441	+, Pe

		Zhang (2021)[174]	1.03 (0.94, 1.12)	82	6	4,855,016	
		Siddika (2016)[172]	1.10 (0.86, 1.42)	48	2	3,745,243	
	Trimester 3	Xie (2021) [151]	1.09 (1.01, 1.18)	79	4	3,180,667	0, Pe
		Zhang (2021)[174]	1.09 (1.01, 1.18)	75	5	4,273,242	
		Siddika (2016)[172]	1.00 (0.95, 1.05)	0	2	3,745,243	
PM_{10} (10 μg/m^3)	Entire Pregnancy	Zhang (2021)[174]	1.01 (0.96, 1.05)	17	4	1,88,661	+, Pe
		Siddika (2016)[172] and Zhang (2016)[175]*	1.01 (0.95, 1.09)	85	2	104,089	
	Trimester 1	Zhang (2021)[174]	0.94 (0.83, 1.04)	94	6	2,471,949	0, Pe
		Siddika (2016)[172] and Zhang (2016) [175]	1.00 (0.94, 1.06)	54	2	104089	
	Trimester 2	Zhang (2021)[174]	0.99 (0.92, 1.05)	77	5	2248574	0, Pe
		Siddika (2016)[172] and Zhang (2016) [175]	1.01 (0.91, 1.12)	81	2	104,089	
	Trimester 3	Zhang (2021)[174]	1.04 (0.97, 1.11)	89	4	1,666,800	+, Pe
		Siddika (2016)[172] and Zhang (2016)[175]	1.02 (0.92, 1.13)	91	2	104,089	
CO (100 ppb)	Entire Pregnancy	Zhang (2021)[174]	1.00 (1.00, 1.00)	53	6	5,657,393	0, Pe
		Siddika (2016)[172]	1.01 (1.00, 1.02)	21	3	3,847,818	
	Trimester 1	Zhang (2021)[174]	1.00 (1.00, 1.00)	52	6	5,657,393	00, Pe
		Siddika (2016)[172]	1.00 (0.99, 1.01)	32	3	3,847,818	
	Trimester 2	Zhang (2021)[174]	1.00 (1.00, 1.00)	38	5	5,434,118	00, Pe
		Siddika (2016)[172]	1.00 (0.99, 1.02)	64	3	3,847,818	
	Trimester 3	Zhang (2021)[174]	1.00 (1.00, 1.00)	70	5	5,434,118	0, Pe
		Siddika (2016)[172]	1.01 (0.99, 1.03)	80	3	3,847,818	
O_3 (10 ppb)	Entire Pregnancy	Zhang (2021)[174]	1.02 (0.95, 1.09)	64	6	5,259,297	0, Pe
		Siddika(2016) [172]	1.00 (0.97, 1.03)	20	2	3,128,844	
	Trimester 1	Zhang (2021)[174]	1.06 (1.00, 1.11)	74	6	5,482,705	0, Pe
		Siddika(2016) [172]	1.00 (0.98, 1.02)	0	2	3,128,844	
	Trimester 2	Zhang (2021)[174]	1.02 (0.97, 1.08)	74	5	5,259,330	0, Pe
		Siddika	0.99 (0.94, 1.04)	69	2	3,128,844	

		(2016)[172]					
	Trimester 3	Zhang (2021)[174]	0.96 (0.86, 1.06)	93	4	4,677,556	0, Pe
		Siddika (2016)[172]	1.01 (0.97, 1.06)	63	2	3,128,844	
SO_2 (10 ppb)	Entire Pregnancy	Zhang (2021)[174]	1.05 (0.96, 1.15)	7	6	5,657,493	+, Pe
		Siddika (2016)[172]	1.08 (0.95, 1.22)	20	3	3,847,818	
	Trimester 1	Zhang (2021)[174]	0.98 (0.83, 1.15)	73	6	5,657,493	0, Pe
		Siddika (2016)[172]	1.14 (0.88, 1.48)	81	3	3,847,818	
	Trimester 2	Zhang (2021)[174]	0.96 (0.80, 1.14)	73	5	5,434,118	0, Pe
		Siddika (2016)[172]	1.01 (0.93, 1.10)	0	3	3,847,818	
	Trimester 3	Zhang (2021)[174]	1.27 (0.98, 1.61)	89	5	5,434,118	+, Pe
		Siddika (2016)[172]	1.15 (0.85, 1.56)	82	3	3,847,818	
NO_2 (10 ppb)	Entire Pregnancy	Zhang (2021)[174]	1.05 (1.00, 1.11)	65	5	5,434,118	+, Pe
		Siddika (2016)[172]	1.07 (0.97, 1.18)	80	3	3,847,818	
	Trimester 1	Zhang (2021)[174]	1.01 (0.01, 1.06)	57	6	6,015,892	+, Pe
		Siddika (2016)[172]	1.04 (0.98, 1.09)	55	3	3,847,818	
	Trimester 2	Zhang (2021)[174]	0.99 (0.95, 1.04)	59	6	6,015,892	+, Pe
		Siddika (2016)[172]	1.01 (0.95, 1.07)	66	3	3,847,818	
	Trimester 3	Zhang (2021)[174]	1.04 (0.99, 1.10)	63	5	5,434,118	+, Pe
		Siddika (2016)[172]	1.02 (0.98, 1.05)	0	3	3,847,818	
SAB-$PM_{2.5}$ (10 µg/m^3)	Trimester 1 or within 180 days of gestation	Zhu (2021)[156]	1.20 (1.01, 1.40)	99	5	69,507	++, Pe
SAB-PM_{10} (10 µg/m^3)	Trimester 1 or within 180 days of gestation	Zhu (2021)[156]	1.09 (1.02, 1.15)	79	5	12,741	++, Pe
		Zhang (2016)[175]	1.34 (1.04, 1.72)	62	3	515,932	

*Two meta-analyses published in same year with complete duplicate and hence considered as one result. Note: NO_2, Nitrogen dioxide; CO, Carbon monoxide; O_3, Ozone; SO_2, Sulphur dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5µm; $PM_{10,}$ particulate matter with aerodynamic diameter ≤ 10µm; SAB, spontaneous abortion; OR, odd ratio; CI, confidence intervals; ppb, parts per billion; NA, Not available; I^2, Heterogeneity; '+' represents less consistent positive association; '0' represents contradictory/unclear direction; '-' represents less consistent negative; Pe, probable evidence of the observed direction of exposure effect.

3.5 Discussion

3.5.1 Characteristics and quality of the reviews

The 36 included reviews published from January 2004 [29] to October 2021 [153,154] organised their evidence from 295 distinct observational studies (published between 1984-2021) of varied study designs, included eight multi-country studies and 287 country-specific studies from 31 countries.

The included primary studies were dominated by studies from the USA (39%) and China (15%) and the limited or lack of studies from many regions, particularly in developing countries could introduce potential selection bias. This could impact the generalisability of the findings but may not necessarily change the overall epidemiological evidence. This is because subgroup analyses reported positive associations, particularly between the pollutants and birth weight and PTB across all geographical regions defined as South or North America, Europe, Asia, and Oceania.[148,155] For instance, subgroup analysis of 13 studies in the USA and four studies from "Other" countries indicated reduced birth weight by -19 (95% CI= -31, -6; I^2= 99%) and -2 (95% CI= -12, 9; I^2= 26%) per 10 µg/m^3 increment in $PM_{2.5}$ exposure during the entire pregnancy, respectively. Similarly, the authors reported pooled OR of LBW per 10 µg/m^3 increment in $PM_{2.5}$ exposure during the entire pregnancy as 1.08 (95% CI=1.02, 1.14; I^2= 94%) based on 14 studies in USA and 1.14 (95% CI=1.04, 1.25; I^2= 36%) based on five studies in "Other" countries, respectively.[168] Africa and South Asia each contributed only two studies to the evidence. Generally, regions with limited evidence that require particular attention from the academic and research community are Africa, Pacific Island, South Asia, Latin America, and the Caribbean. Some developed countries such as Germany, Russia, Finland, Israel, and Uruguay also contributed only one study each. Particulate matter was more studied than gaseous pollutants. The most extensively researched exposure-outcome associations were $PM_{2.5}$ with LBW and PTB while stillbirth, SGA, and SAB were less frequently studied for all criteria pollutants.

Comparatively, review guidelines were more closely adhered to in systematic reviews with meta-analyses than those without meta-analyses. A previous overview study also observed similar non-adherence to available review guidelines for environmental health studies.[41] The purpose of review guidelines is to aid consistency and systematic assessment, yet they have limitations and there is no consensus on the degree to which systematic reviews or meta-analyses should adhere to the available review guidelines. One key limitation is that such review guidelines were mainly designed for medical sciences (e.g., clinical trials) rather than environmental health sciences. Notable examples include the development and use of protocols, the approach to critical appraisal or risk of bias assessment of included studies, and methods for assessment of confidence in the body of evidence.[176] Another limitation is that the risk of bias assessment severely discounts work from rapidly developing areas of the world where the best available data are often of lower quality than that in more developed regions. An example of a review guideline for research synthesis in environmental health sciences is the Navigation Guide systematic review methodology.[137] This guideline was applied by one of the included studies [148] while three other included studies adopted its risk of bias assessment tool.[151-153] A standard guideline specifically designed for systematic reviews in toxicology and environmental health research (COSTER) is now available for the planning and conduct of systematic reviews or meta-analyses in the field.[176]

Many of the included review studies were conducted collaboratively by experts from different parts of the world, including investigators from non-English language countries, although few studies included non-English articles. For example, some (25%) of the reviews searched articles written in Chinese languages in addition to English. The focus on English articles could also contribute to why some countries such as Germany and Russia contributed only one study each to the current epidemiological evidence. This means that although excluding non-English articles is considered a systematic bias with minimal effects,[177,178] the inclusion of non-English studies, if resources allow, could contribute to further reducing selection bias and enhancing the generalisability of the findings.[179]

3.5.2 Overall summary of the epidemiologic evidence and implications

3.5.2.1 Summary of the overall epidemiologic evidence

There was little detected publication bias across meta-analyses via funnel plots and Egger or Begg tests. However, some authors have recently suggested that instead of investigating publication bias with the p-value-based tests that are underpowered due to their dependency on the number of studies included in the meta-analyses, non-p-value-based methods (e.g., Luis Furuya-Kanamori; LFK index) should be used.[180] Also, publication bias could be further reduced if "negative results" have an equal chance of publication, irrespective of p-values, effect sizes, and statistical significance.[181] Another critical issue is the barrier to publishing due to high article processing charges.[182] Rethinking the business model of the scientific publication to enhance "free-to-publish and free-to-access research" regardless of one's funding status or organisational affiliation has been suggested to promote the dissemination of evidence-based information for scientific and public health benefits.[182]

The overall epidemiologic findings differed largely depending on the pollutant, birth outcome, and pregnancy period. Specifically, $PM_{2.5}$ showed a *more consistent positive association* with reduced birth weight across the entire pregnancy exposure but *less consistent positive associations* for each trimester. Reduction in birth weight for trimester-specific exposure showed *less consistent positive associations* for $PM_{2.5}$, PM_{10}, and NO_2 during the first trimester, for $PM_{2.5}$, PM_{10}, and O_3 during the second trimester, and $PM_{2.5}$, PM_{10}, and NO_2 during the third trimester. For risk from exposure based on the whole pregnancy period, SO_2 showed a *more consistent positive association* with LBW but a *less consistent positive association* for the other criteria pollutants except O_3 which indicated *contradictory or unclear direction*. First-trimester exposure showed *less consistent positive associations* with the odds of LBW for all criteria pollutants except for CO and O_3 showing *contradictory or unclear directions*. For the second trimester, all criteria pollutants showed *less consistent positive associations* except for O_3 which showed *contradictory or unclear direction* with LBW. Except for $PM_{2.5}$ and O_3 found to be *less consistent positive associations*, other pollutants showed *contradictory or unclear directions* (PM_{10} and NO_2), no association (CO), and *less consistent negative association* (SO_2) with the odds of LBW during third-trimester exposure. Similar findings were observed in related overviews.[183,184] There were *less consistent positive associations* of PTB with exposure to $PM_{2.5}$, PM_{10}, O_3, and NO_2 during the whole pregnancy period, only O_3 for first-trimester exposure, O_3 and $PM_{2.5}$ for second-trimester exposure, $PM_{2.5}$, PM_{10}, and NO_2 for third-trimester exposure. For stillbirth, *less consistent positive associations* were observed for all criteria pollutants during the entire pregnancy period except for CO and O_3 which indicated *contradictory or unclear directions*. The trimester-specific exposure association with stillbirth showed *less consistent positive associations* for only NO_2 during the first trimester, for $PM_{2.5}$ and NO_2 during the second trimester but for three pollutants (PM_{10}, NO_2, and SO_2) during the third trimester. Only particulate matter pollutants were reported for SAB and both $PM_{2.5}$ and PM_{10} showed *more consistent positive associations*. For SGA, the pooled result was available for only $PM_{2.5}$ and with *less consistent positive association* for the entire pregnancy, second and third trimesters but the direction of association was *contradictory or unclear* for the first-trimester exposure. Reduction in birth weight among different races/ethnicity across the entire pregnancy period with $PM_{2.5}$ showed a *more consistent positive association* in White persons but *less consistent positive associations* in both Hispanic and Black/African-American persons. PM_{10} showed a *less consistent positive association* in White persons but *contradictory or unclear directions* in Hispanic and Black/African-American persons. The results indicate that different criteria pollutants may have different critical exposure windows of susceptibility for each birth outcome and are also likely to be heterogeneous across different levels of the population and maternal characteristics.

3.5.2.2 Exposure-outcome associations across pregnancy periods

Generally, there was more evidence for associations between adverse birth outcomes and exposure to particulate matter than gaseous pollutants. This could be attributable to more observational studies or higher toxicity of the particulate matter as compared to the gaseous pollutants.[3,185,186] This could also be due to greater measurement errors in the assessment of the gaseous as compared with the particulate matter pollutants. The overall epidemiologic evidence was largely stronger across the entire pregnancy than trimester-specific exposure averages. There are several possible explanations for this observation. Firstly, the tendency for pregnant women to be cautious of exposure to environmental stressors is high during early pregnancy (after pregnancy is recognised) but this consciousness decreases over time.[166] As a result, time exposed to outdoor pollutants might increase when approaching the date of delivery and would result in higher risks for the whole pregnancy period and third-trimester exposures being more observable than those for first and second trimester exposures. Secondly, the potential of exposure misclassification for trimester exposure assignments is likely to be higher than that for the entire pregnancy due to the uncertainties in defining the pregnancy period, especially using the last menstrual period with known imprecision by relying on maternal self-reporting.[187] Moreover, although pregnancy may be counted from the first day of the last menstrual period, conception begins two weeks later, and uncertainties regarding the start of pregnancy could bias estimates observed for first trimester exposures, not necessarily towards the null. Finally, regressing a birth outcome in separate models for each trimester using trimester-specific averaged exposures without adjusting for the other trimesters was found to bias the estimates with the identification of inaccurate susceptible windows because each susceptible window can potentially span multiple windows.[58] Exposures of air pollution across different trimesters can be highly correlated in some locations and not in others. Furthermore, the potential aetiology of the pollutant may not strictly follow the obstetrically defined trimester calendars.[58] Hence accurate measurement of the gestational period and a shorter temporal exploration (e.g., days or weeks) is required and the specific definition of pregnancy time should be defined e.g., obstetric versus embryonic weeks.[58,187] This could improve the identification of critical windows of susceptibility, help elucidate the biological mechanisms of specific stages of fetal development [58,188] and improve the ability to synthesise results of multiple studies. Additionally, a recent molecular epidemiologic study had indicated associations in pre-conception periods with a critical window spanning from 12 weeks before and 13 weeks into the gestational period for maternal $PM_{2.5}$ exposure and reduced birth weight.[189] There is therefore the need to include some pre-conception exposure periods to capture the full impacts of the pollutants on the birth outcomes when assessing chronic effects. Also, the available evidence was solely based on single-pollutant models which do not fully characterise the complex associations and interactions of multiple time-varying mixtures of the pollutants on birth outcomes.[190] There are emerging approaches to identify critical exposure windows and convoluted associations of multi-pollutants in exposure-lag-response associations such as the Bayesian kernel machine regression distributed lag model [190] or a regression tree-based model for mixtures of exposures.[191] Despite the advantages of assessing exposure mixtures, a recent review identified the potential for increasing the existing measurement errors and biases in environmental exposure mixture research.[192]

3.5.2.3 Heterogeneity and sources

Inevitably, heterogeneity is expected in SRMAs.[193] This was quantified with I^2 statistics in the included meta-analyses and found to be high across almost all meta-analyses with values as high as 99%.[33,168] Variability among the observational studies could be clinical heterogeneity (variability in characteristics of the participants, exposures, and outcomes) or methodological heterogeneity (variability in study designs, exposure assessment methods, and outcome definitions or assessments, risk of bias, and confounding adjustments).[131] These variabilities from either clinical or methodological heterogeneity consequently manifest in the non-random differences in the effect estimates from the different studies pooled in the meta-analyses.[131] The high heterogeneity indicated that the observational studies were estimating different quantities of the effects but do not necessarily imply that the true exposure effect estimate varies.[131] The major sources of heterogeneity acknowledged in the included SRMAs and related previous overviews [41,183,184] are differences in methodology and study designs, statistical analyses, sample size, population demographics, birth, and exposure data collections, including outcome definitions (especially stillbirth) and exposure assessment methods, adjusted confounding factors, geographical variability, and sources and chemical compositions of particulate matter. Where data permitted, the included SRMAs attempted to account for some of the sources of heterogeneity by restricting to cohort studies [144,155,166] or ‘low’ or ‘probably low’ risk of bias studies; [148] stratifying by adjustment for maternal tobacco smoking,[30] exposure assessment methods,[32,33,154,168] exposure dosage using WHO thresholds,[166] region; [148,154] and many other subgroup analyses, but the heterogeneity persisted in most instances. Gong *et al*, however, observed very low heterogeneity with the closest effect estimates to the overall estimates for subgroup analysis of studies that assessed exposure with land-use regression models among other exposure assessment methods.[154] This suggests the need for improved exposure assessment methods.[148,154] It is worth noting that subgroup analyses are observational by nature and non-randomised, hence findings from multiple subgroup analyses may also be difficult to interpret.[131] On the other hand, the high heterogeneity between studies could also be considered a strength to some extent as the epidemiological evidence on the ubiquitous air pollutants covers different levels of risks in different populations with diverse physical, biological, sociodemographic, and medical conditions, and genetic constitutions.[194]

In the absence of RCTs, prospective cohort studies in which participants are recruited with a detailed collection of confounding factors and personalised space-time-activity exposure assessment could address some of the challenges.[149,195] Population-based retrospective cohort designs provide the opportunity to recruit a large sample size to detect small effects at the population level. Therefore, improvement in the availability, coverage, and quality of routine perinatal data collections for retrospective cohort designs serves as a practical alternative because prospective cohort designs can be very costly in terms of funding and time, and infringement of privacy. Related SRMAs and overviews disclosed that maternal tobacco smoking,[196,197] illicit drug or alcohol intake,[198] pregnancy complications,[199] infections,[200,201] nutritional status,[202] and psychosocial conditions [40] are known risk factors for birth outcomes. These factors have potential modification and mediation effects but are rarely investigated in observational studies or SRMAs due to the dearth of information. Most of these and other important confounders could be collected by healthcare practitioners in the routine data as a collective effort towards a common goal of improving maternal and neonatal health, although other challenges would remain (e.g., the accuracy of maternal smoking data). One of the reviewed meta-analyses specifically found larger reductions in birth weight per 10 $\mu g/m^3$ increased in the particulate matter after adjusting for maternal tobacco smoking.[30] Thus, our observed overall epidemiological evidence is likely to be higher if relevant residual confounding, modifying, or mediating factors are adjusted. As reported previously, the 2008 Beijing Olympics ‘natural experiment’ due to air pollution reduction provided an opportunity to reduce residual confounding and exposure misclassification from which more convincing evidence of the higher risk of air pollution exposure on birth outcomes was found [203]. The recent COVID-19 pandemic also offered another unique opportunity for the ‘natural experiment’ at a larger scale for both national and international collaborative investigations.[204]

3.5.2.4 Combined associations and geodemographic variability

Other critical, yet unexplored areas are the synergistic associations of the pollutants with other closely related environmental stressors and the spatiotemporal exposure-outcome associations. The combined impacts of the criteria pollutants with related environmental exposures such as green vegetation and meteorological factors, especially extreme temperatures on birth outcomes [149] has been evidenced recently.[205] Also, despite the evolving spatiotemporal exposure assessments with modern advanced machine learning technology and integration of land-use regression models [146] and the distributed lagged effect modelling,[58,60] empirical incorporation of the spatiotemporal variations in the exposure-outcome analysis has not received expected attention in the current body of evidence. Warren and colleagues[206] recently demonstrated that ignoring spatial variation in the lagged effect of the parameters nullified the elevated association between $PM_{2.5}$ and term LBW in selected gestational weeks. This implies that spatiotemporal variations also need to be considered in future studies and this could include geographically weighted regression models as exemplified elsewhere,[207] an effective and efficient technique for targeted local public health interventions.

Another means of having a broader view of the spatial variability and relevant information on the sources and chemical compositions of the pollutants is by broadening the geodemographic coverage of the evidence. Geodemographically, the current evidence was heavily based on epidemiologic studies from the USA and China with limited studies from other developed countries. Paradoxically, the low-and-middle-income countries (LMICs) which are socio-demographically vulnerable and with invariably high exposure levels and high incidence of birth outcomes are missing in the current evidence. A global estimated PTB rate across 107 countries was recently estimated at 10.6% (14.84 million live PTB) and 81.1% (12. 0 million) of these PTB were from Sub-Saharan Africa (SSA) and Asia.[208] The LMICs also accounted for 98% of stillbirths, with three-quarters in SSA and South Asia [209]. Notably, these regions are experiencing increasingly high concentrations of the criteria pollutants above WHO Air Quality Guidelines (AQGs).[186] The SSA region is suffering from 10 to 20-fold higher levels than the 2005 AQGs [210] due to Saharan desert dust and biomass burning.[211] Thus, the LMICs are heavily polluted and have high burdens of birth outcomes but lacked related epidemiologic evidence, largely due to a lack of functional and reliable air quality monitoring data [135,211,212] and population-based health registries for the related high-quality epidemiologic investigations.[213] A new global attributable burden analysis estimated that over 5.9 million PTB and 2.8 million LBW infants could be attributable to $PM_{2.5}$ exposure during the entire pregnancy period in 2019 and the highest attributable burdens were estimated for SSA.[194] Those authors further suggested that these burdens could have been prevented if $PM_{2.5}$ was reduced to theoretical minimum risk exposure levels of 2.4 to 5.9 μg/m^3 in 2019.[194] It was also estimated that about a 78% reduction in the global LBW and PTB in 2019 could have been achieved by South Asia and SSA combined since they suffered the highest attributable burden.[194] Similar disproportionate elevated impacts of $PM_{2.5}$ on health outcomes in LMICs were reported in another recent global study.[185] All these findings indicate that our observed epidemiological evidence of mostly *less consistent positive associations* could be an underestimation in the absence of evidence in high-exposure, high-outcome, and most vulnerable settings. Therefore, despite the known challenges in conducting related studies in these under-resourced regions, a call for an innovative investigation to have a glimpse of the state of pollutants and birth outcomes in LMICs as illustrated by Xue *et al* [160,161] cannot be overemphasised.

3.5.3 Plausible biological pathways and interdisciplinary approach

A complex interaction of environmental, maternal, placental, and fetal factors regulating fetal growth and development [25,214] makes the pathoaetiology of the air pollutant-birth outcome associations very complex to be postulated in a single biological pathway.[24] Physiologically, suppressed maternal immunity, higher blood volume, greater metabolic rate, and the added nutritional requirements from the fetus among other factors increase maternal sensitivity and thus intensify the vulnerability of pregnant women and the developing fetuses to air pollutants.[169] As a very sensitive period of susceptibility, exposure to any harmful substance during fetal development can have both *in* and *ex utero* adverse effects at birth and later in the life course.[25,127 128]

The pollutants enter the mother's cardiovascular system by inhalation and reach the embryo or fetus by way of fetoplacental translocation.[24,127] Upon entry, the pollutants interact with the maternal biologic environment to generate excess oxidative free radicals and endocrine-disrupting chemicals.[19,215,216] These trigger a cascade of maternal biological and physiological processes, including alterations in immuno-inflammatory, cardiovascular, and respiratory systems, and induce placental modifications with negative impacts on fetal development and growth,[19,215,216] Recent molecular epidemiologic mechanisms also showed that oxidative stress, global DNA methylation, mitochondrial DNA content alteration, and endocrine perturbations that cause placental reprogramming are potential pathways for the induced adverse association of particulate matter and birth outcomes.[189,214,216] Generally, the associations are more profound in the particulate matter than the gaseous pollutants, resulting in comparatively higher risks in particulate matter.[3] Again, this could also be due to more studies on the particulate matter as compared to gaseous pollutants and greater measurement errors in gaseous pollutants. Of particular interest among the gaseous pollutants is CO with a well-documented mechanism where CO binds to the haemoglobin to be transported across the placenta and reduces the availability of oxygen to the fetus.[29,165] Environmental epigenetics also indicated that birth outcomes are phenotypic manifestations of environmentally induced epigenetic toxicity through environment-gene interactions.[19,215] The impacts are shared synergistic interactions among maternal biologic, psychosocial, sociodemographic, and behavioural risk factors, obstetric or health conditions, and pollutants.[23-25] There can also be interplay among the exposures on the birth outcomes where the impacts of $PM_{2.5}$ on birth weight and gestational age, could in turn make a considerable contribution to the LBW and PTB.[194]

While advances in epidemiological methodologies, statistical analyses, and environmental exposure science technology are key, interdisciplinary approaches could contribute to understanding the biological mechanisms and providing convincing evidence of causal inference.[217] This is largely due to the complexities of environmental health science [217] and the inability to conduct RCTs owing to ethical issues.[137] Stingone *et al* recently proposed an interdisciplinary framework for environmental health research that provides the opportunity to integrate epidemiology, clinical science, pathophysiology, toxicology, epigenetics, and bioinformatics (examples; genomics, proteomics, metabolomics),[217] and social and biophysical sciences.[218] As a result, causal inference on the associations between population-level environmental exposures and birth outcomes may be achievable [217,218] even from under-resourced settings. For instance, Wang and colleagues demonstrated how DNA methylation measurement in cord blood or bloodspot can be used to predict prenatal exposures to NO_2 and $PM_{2.5}$ in cohorts without explicitly measuring the exposures.[219] We, therefore, require not only well-designed longitudinal studies but possibly integrating the environmental exposomes with the different *omics* to ascertain the biological signatures of the *in utero* exposures for prevention, diagnosis, and treatment of birth outcomes.[214,217,218]

3.5.4 Strengths and limitations

This study is accorded with several strengths. To the best of our knowledge, this is the first umbrella review that comprehensively assessed, evaluated, and provided an overall global state of the epidemiological evidence on prenatal exposure to the six criteria air pollutants and birth outcomes, for which we assessed 36 systematic reviews and meta-analyses. We also developed a protocol registered in PROSPERO and elaborated it as a peer-reviewed article before the conduct of the review.[135] The literature search was comprehensive and conducted prospectively by activating database alerts which ensured regular updates of the results with new eligible studies. The review process followed standard guidelines. To depict the geographical variability of contributing countries or regions to the current epidemiological evidence, we mapped the locations with the number of the distinct primary studies included in the included reviews. The degree of overlap of the primary studies was also quantified with a validated index. We adapted a semi-quantitative objective approach to grade the overall direction of associations and the confidence for each pollutant-outcome association at differing pregnancy periods. We also summarised key themes that emerged from the included reviews' recommendations.

Some limitations are also associated with this study. The current epidemiological evidence is highly representative of two regions (the USA and China) and a few highly industrialised countries which may introduce selection bias and weaken the generalisation of the findings. However, this also indicated that evidence exists in both low-level (USA) and high-level (China) exposure settings.

The limited evidence from the most vulnerable regions such as Africa, South Asia, and other LMICs is a serious limitation that requires urgent attention. We included only reviews reported in English which could result in potential English-based publication bias. This is, however, expected to be very minimal, [177,178] particularly for an umbrella review. Multiple inclusion of primary studies is a known limitation of umbrella review but was estimated to be moderate in our study. All meta-analyses identified substantial heterogeneity of varied sources in the primary studies and there were no RCTs by default. Consequently, the available epidemiological evidence indicated *probable evidence* of causality for most of the pollutant-outcome associations. The grading approach might not be entirely objective, was limited to the number of studies, and consistency in direction of effect estimates and could not provide the overall magnitude of the effect estimates. We standardised the effect estimates across meta-analysis to compare results across studies. However, the implications of a given increment (e.g., 10 ppb O_3) can differ across the regions. For example, that increment may be a small increase relative to baseline conditions for some areas and a large increase for others. Similarly, caution would be used when comparing results for PM_{10} and $PM_{2.5}$ as a given increment (e.g., 10 μg/m^3) has a different relative meaning for these particle size fractions. The conclusions and recommendations evolving from this umbrella review should therefore be interpreted and applied within the context of the outlined strengths and limitations based on the available scientific evidence gathered from the 36 SRMAs.

3.5.5 Recommendations for research, practice, and policy

3.5.5.1 For primary studies

Further studies are required, particularly from LMICs and other developed countries that contributed a limited number of studies. Additional studies are also required on gaseous pollutants, small-for-gestational-age, stillbirth, and spontaneous abortion. More well-designed and standardised observational studies with high-quality data, harmonised outcome definitions, and spatiotemporal exposure assessments could minimise the high heterogeneity. This could highlight where such heterogeneity reflects the true underlying systems (e.g., different effects due to different sources of particulate matter and thereby different chemical composition) versus heterogeneity that is not a reflection of true variation. Given that RCTs are unethical in this field, prospective cohorts with personal time-activity trajectory exposure monitoring are gold-standard and should be pursued if funding and time allow. However, acknowledging the logistical and practical issues for large-scale prospective cohort design, liaising with healthcare providers to improve the quality and volume of the routine health data collection and emerging advancements in epidemiological methodologies and analyses will help strengthen the evidence. Even here, important limitations exist (e.g., the additional burden to health care providers, the accuracy of some variables such as maternal smoking). Considering the peculiar multifactorial nature and complexities in this field, a multisectoral approach is urgently needed. This, including extensive exploration of the *omics* technologies, will help illuminate the biological pathways but also has potential for diagnosis, prevention, and treatment.[217] More detailed recommendations for observational studies provided by the included reviews are available (Tables S3 and S4). Briefly, the review authors recommended more refined methodological designs, including prospective or large population-based retrospective cohort studies for chronic effects and time-series or case-crossover studies for short-term effects on acute events (e.g., PTB, stillbirth, and SAB) using high-quality data and individual level spatiotemporal exposure assessment. Further approaches to reduce residual and spatial confounders and account for residential mobility were suggested. More studies at finer temporal scales for identifying the critical susceptible periods and biological pathways, potential effect modifications, and chemical compositions of particulate matter were also recommended.

3.5.5.2 For Systematic reviews and meta-analyses

The increment in exposure used to present effect estimates needs to be unified across meta-analyses. For systematic reviews without meta-analyses, counting of findings for the specific statistical direction of association with median or range of the effect estimates as exemplified in one of the included reviews [34] together with graphical displays, such as forest plots, and a concise level of evidence as indicated in Heo *et al* [157] is recommended. This will be more helpful than the general 'narrative synthesis' which has been associated with serious weaknesses.[220] Rather than the narrative synthesis, we recommend a semi-quantitative approach for a more objective synthesis of the evidence as applied elsewhere.[142] This approach, however, should not be considered entirely objective. Future review authors may refer to the recently developed comprehensive guideline for synthesis without meta-analysis (SWiM) for systematic reviews examining quantitative effects.[220] The methodological quality of future systematic reviews or meta-analyses needs to be improved by better adherence to the standard review guidelines, particularly the new COSTER guideline.[176] Also, the availability of review protocol could contribute to reducing the duplication or near-duplication of review studies in addition to other advantages reported in the review guidelines.[84,136,176]

3.5.5.3 Policy action

The probable epidemiological evidence of cause-and-effect of prenatal exposure to the criteria air pollutants and birth outcomes warrants consideration of the *precautionary principle* which states that “*when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically*”.[134] The precautionary action to prevent harm may be particularly necessary for particulate matter and to some extent SO_2 and NO_2 which often showed consistent positive associations with adverse birth outcomes, despite the difficulty in establishing causality with certainty. Clinicians and public health workers have a unique opportunity to educate pregnant women or women of reproductive age and raise the awareness about the potential risk of exposure to air pollutants and some precautions to be taken such as minimising outdoor activities or using particulate filter masks in polluted areas and consider pollution levels when choosing residential locations. Environmental policy and legislation such as enforcing new WHO air quality guidelines,[2] increased investment into renewable energy sources, and transitioning towards “clean” fuels or new technologies to reduce or eliminate anthropogenic ambient air pollution may be helpful.[185,221] Although there is no safe level, reducing the pollutants could substantially improve perinatal health and save lives.[222]

3.6 Conclusion

The toxic effects of the criteria air pollutants on human health are well known for outcomes such as mortality and hospital admissions, with growing evidence for reproductive and neonatal health. We found five *more consistent positive associations* for entire pregnancy period exposure, including exposure to $PM_{2.5}$ and reduced birth weight (all populations and among White persons), both $PM_{2.5}$ and PM_{10} and SAB, and exposure to SO_2 and LBW. We observed several *less consistent positive associations* and few *contradictory or unclear directions* of association. We also found one each of *more* and *less consistent negative associations* and three instances where CO consistently showed no association. However, due to the high heterogeneity, imprecision, and absence of RCTs, the observed epidemiological pieces of evidence were classified as ‘*probable evidence*’, differing greatly among the pollutants, birth outcomes, and pregnancy periods. Particulate matter ($PM_{2.5}$ or PM_{10}), particularly $PM_{2.5}$ was most studied and found to show a higher risk than gaseous pollutants. Among the gaseous pollutants, NO_2 and SO_2 often showed more *consistent positive associations* than CO and O_3. The positive associations across the entire pregnancy period showed more consistency than the trimester-specific exposure averages. The supporting biological causal mechanisms are also currently limited, particularly for gaseous pollutants. The omics technologies and environmental epigenetics are, however, unfolding strong aetiological pathways for the particulate matter pollutants. Interdisciplinary research approaches and well-planned standardised epidemiological studies with broader geodemographic coverage, and biological mechanisms are recommended to strengthen the current evidence. This will contribute to providing evidence-based guidance or direction for mitigating the adverse associations of the pollutants on birth outcomes. In the interim, the current level of evidence and the large populations involved warrant the adoption of the *precautionary principle*. Health practitioners could play an active role in integrating and communicating the risks of prenatal air pollution exposure to women and policymakers.

Chapter 4. Long-term maternal exposure to ambient fine particulate matter and the risks of stillbirth and spontaneous preterm birth in Western Australia

4.0 Preamble

This chapter provides the results of a primary investigation for the association between maternal exposure to monthly fine particulate matter air pollution ($PM_{2.5}$) from three months before conception up to birth and the risks of stillbirth and spontaneous preterm birth in Western Australia. Potential critical exposure periods of increased susceptibility and vulnerable subpopulations were identified.

4.1 Abstract

Introduction: Few studies have investigated weekly or monthly exposure-lag-response associations between fine particulate matter ($PM_{2.5}$) and preterm birth, and there has been no known such study for stillbirth. Particularly, critical susceptible periods have not been investigated in Australia.

Objectives: To identify potential critical susceptible periods of the association between monthly $PM_{2.5}$ exposure and stillbirth and spontaneous preterm birth (sPTB) in Western Australia.

Methods: A total of 414,771 singleton births, of which 0.5% and 3.7% were stillbirth and sPTB respectively, between 1st January 2000 and 31st December 2015 in Western Australia were included. Births were linked to fine spatiotemporal monthly $PM_{2.5}$ concentrations. Distributed lag linear and nonlinear Cox proportional hazard models were performed to investigate maternal exposure to $PM_{2.5}$ for three months preconception to birth and the hazard of stillbirth and sPTB.

Results: The mean (standard deviation) monthly $PM_{2.5}$ exposure during the study period was 8.1 (1.0) $\mu g/m^3$. Maternal $PM_{2.5}$ exposure showed dose-response associations with stillbirth and sPTB with critical susceptible periods spanning the 3rd–7th gestational months. The strongest hazards for 5 $\mu g/m^3$ and 3 $\mu g/m^3$ $PM_{2.5}$ exposure increases were 1.12 (95% CI 1.05, 1.19) and 1.07 (95% CI 1.03, 1.11), respectively during 3rd gestational month for stillbirth and 1.04 (95% CI 1.02, 1.05) and 1.02 (95% CI 1.01, 1.03), respectively during 5th gestational month for sPTB. Monthly exposures outside the susceptible periods showed relatively small protective effects. Joint effects of $PM_{2.5}$ exposure and biothermal stress were found for stillbirth but not sPTB. Consistently higher-hazard subpopulations for both birth outcomes were male births, births to mothers aged 20-34 years, high socioeconomic status, and complicated pregnancy.

Conclusion: Monthly $PM_{2.5}$ exposure, even below the new international annual average of 5 $\mu g/m^3$ associated with higher hazards of stillbirth and sPTB. The identified exposure months of increased

susceptibility and vulnerable subpopulations could inform public health interventions, policy decisions, and future aetiological research.

4.2 Introduction

Preterm birth (PTB, born before 37 completed gestational weeks) is a leading cause of infant mortality and with immediate to long-term morbidities such as physical, cognitive, cardiorespiratory, metabolic, and neurodevelopmental disorders, and many other health problems.[223] This places a substantial burden on families, society, and the healthcare system. Closely linked to PTB is stillbirth which has long-lasting socioemotional, psychological, and economic impacts, particularly on the mother and the families. Stillbirth is defined by World Health Organization (WHO) as a baby born with no signs of life at or after 28 weeks of gestation.[224] Globally, the prevalence of live PTB was estimated as 10.6% (14.8 million) in 2014 [208] and stillbirth was 13.9 stillbirths per 1000 total births (2.0 million) in 2019.[224] The rates are usually highest in low-and middle-income countries but quite high in some high-income countries, including Australia.[100,225,226] In Australia, PTB increased slightly from 8.4% in 2010 to 8.7% in 2017.[226] Australia records over 2,000 stillbirths (fetal death after ≥20 weeks' completed gestation) annually which translates to at least six women experiencing this painful event daily.[225] Despite several well-known risk factors, the majority of PTB and stillbirth cases have unspecified or unexplained causes and unclear biological mechanisms for appropriate prevention strategies.[100,209,223,227] A better understanding of the causal pathways of stillbirth and PTB is indispensable for achieving the Sustainable Development Goal (SDG) 3.2 –reducing stillbirth or neonatal mortality to zero or fewer than 12 per 1,000 live births and under-5 mortality to lower than 25 per 1,000 live births in every country by 2030.[228,229]

Ambient air pollution, particularly particulate matter ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) is the biggest environmental exposure of global concern with serious health implications,[2,6] including the impacts on birth outcomes.[194,230] In the WHO Air quality guidelines (AQGs), the $PM_{2.5}$ annual average limit was reduced from 10 to 5 μg/m^3 to stimulate improved air quality for health benefits [2] towards the achievement of the SDG 3.9.[228] Pregnant women and developing fetuses are among the most vulnerable groups for the negative effects of air pollution.[2,125] Our umbrella review on the topic indicated that maternal exposure to ambient air pollution, especially $PM_{2.5}$ is a modifiable risk factor for birth outcomes such as PTB and stillbirth.[125] An attributable global burden analysis for 204 countries and territories estimated that 35.7% of all PTB infants were attributable to total $PM_{2.5}$ which is equivalent to nearly six million infants worldwide in 2019.[194]

$PM_{2.5}$ is a mixture of liquid and solid particles, especially heavy metals and toxic organic and inorganic components suspended in the atmosphere.[2,3] The toxic constituent components and the high penetration and inhalation potentials make $PM_{2.5}$ the most harmful among the six criteria air pollutants.[2,3] The high diffusion and respiration rates of pregnant women and the fetal metabolism put them at higher risk. $PM_{2.5}$ can directly or indirectly affect birth outcomes through placental oxidative stress, epigenetic changes, placental dysfunction, and decreasing transplacental transport of oxygen, nutrients, and metabolic wastes.[19,214,215,231] To identify *in utero* critical susceptible exposure periods for a better understanding of biological mechanisms and health interventions, previous epidemiological studies examined trimester-average exposures.[125] A recent simulation study revealed that the three-trimester-average exposures approach produces biased estimates with incorrect identification of susceptible exposure periods.[58] The findings from the umbrella review also showed contradictory or less consistent positive associations for trimester-specific average exposures with no clear susceptible exposure periods.[125] A novel methodology, distributed lag linear and non-linear model (DLM or DLNM) has been proposed to investigate unbiased estimates that account for both the intensity and timing of the past exposures and to flexibly identify finer critical susceptible periods shorter than a trimester.[58-60] This approach has been applied in several recent studies from the USA and mostly China on the associations between $PM_{2.5}$ and PTB [61,65,67,232] and adverse fetal growth.[68,69,233] In addition to the unknown related approach for stillbirth, this high-quality method has not been investigated in other settings such as Australia to identify potential critical susceptible exposure periods of clinical relevance to better understand the pathophysiological mechanisms and guide public health interventions and policy. Moreover, most of those previous studies assessed $PM_{2.5}$ exposure based on limited fixed-site ground monitoring stations, resulting in exposure misclassification.[67,125] There is also a dearth of information on the joint effect of air pollution and extreme temperature or thermal stress.[234] Limited epidemiologic evidence also suggested an association between maternal preconception exposure and health outcomes, [112] especially for three months before conception.[69,111]

The few studies from Australia on the topic were predominantly from the eastern region.[48,125] A recent systematic review of Australian observational studies found no study on stillbirth but included few studies on PTB and reduced fetal growth with heterogeneous findings to draw firm conclusions. Further research and identification of critical susceptible periods were suggested.[152] Effects in Western Australia have not been investigated, partly due to geographically sparse air monitoring stations. Modern advanced national or global $PM_{2.5}$ exposure assessments are becoming available by combining multiple satellite retrievals of aerosol optical depth, chemical transport models, and ground-based measurements.[43,45,47] Spatiotemporal $PM_{2.5}$ estimates based on local models in Australia [43] provide annual estimates, while the recent global spatiotemporal $PM_{2.5}$ models provide monthly estimates.[45] The monthly $PM_{2.5}$ estimates are a more relevant time scale for pregnancy exposures. These monthly $PM_{2.5}$ estimates have been used in several studies in the USA,[56] Germany,[235] China,[236-238] and Colombia.[54]

Given the above-outlined epidemiological gaps, this study aimed to investigate state-wide exposure-lag-response associations between monthly $PM_{2.5}$ exposure at maternal residence locations and the risks of stillbirth and spontaneous PTB (sPTB) in Western Australia. In addition to identifying potential critical periods of exposure susceptibility from three months of preconception to birth, the interaction effects of $PM_{2.5}$ with biothermal stress, and the more vulnerable subpopulations were also identified by performing several stratified analyses.

4.3 Methods

The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines were followed in the analysis and reporting of results.[239]

4.3.1 Study area, design, and population

Western Australia, the largest state by area in Australia covers 2.6 million km^2 with diverse climates and has a total population of 2.8 million.[90] We conducted a population-based retrospective cohort study from 1st January 2000 to 31st December 2015 in Western Australia using a de-identified Midwives Notification System (MNS). The MNS is a statutory routine data collection system that includes all births with ≥20 completed gestational weeks or ≥400 g fetal weight if the gestational length is unknown.[96] The MNS contains sociodemographic and clinical information on both mother and baby, including maternal residential address as statistical area level 1 (SA1) at the time of birth delivery. The second smallest geographical unit in Australia, SA1 has variable geographical size with a median of 19 hectares and an average population of 400 persons.[240] From a total of 474,835 births, we excluded births with missing SA1 (n=35,352), gestational age (n=1021), and sex (n=5). We also excluded multiple births (n=13,018), births with gestational age outside the range of 22-42 completed weeks (n =1,412), and births to mothers >50 years old (n = 7). To account for the potential fixed or truncated cohort bias, [101,241] we created a cohort defined by the date of conception and further excluded pregnancies with conception dates < 22 weeks before the beginning of the cohort (women who conceived before 31st July 1999, n= 7,310) and > 42 weeks before the cohort ended (women who conceived after 12th March 2015, n= 1,434).[68,101] Births with incompatible address or SA1 with missing $PM_{2.5}$ exposure were excluded (n=505). The final sample included in this study was 414,771 singleton births for the stillbirth cohort but 400,387 for the sPTB cohort as 14,384 induced or non-spontaneous PTB were excluded (Figure S4.1).

4.3.2 Outcomes assessment

The main outcomes of this study were stillbirth and sPTB. Stillbirth was defined as a baby born with no sign of life at or after ≥20 weeks' completed gestation according to Australian standard definition.[96,225] sPTB was defined as a baby born before 37 weeks' completed gestation with spontaneous onset of labour and vaginal delivery.[223] Gestational age was calculated from the perinatal records as the difference between the date of birth and the start of pregnancy based on the best available clinical estimates from ultrasonography or the last menstrual period if ultrasound was not available.

4.3.3 Covariates

The covariates, including sociodemographic and biological factors, and medical or clinical information on both mothers and neonates were selected *a priori* from the birth records as potential confounders based on biological and epidemiological evidence in the literature [61,65,67-69,232,233] and availability in the dataset. This included sex (male or female), year index variable for the year of conception (1999 =1 to 2015 =17), a season of conception (autumn, March-May; winter, June-August; spring, September-November; summer, December-February), maternal age as a continuous variable, race or ethnicity (Caucasian or non-Caucasian), marital status (married or unmarried), smoking during pregnancy (non-smoker or smoker), parity (nulliparous or multiparous), pregnancy complications (yes or no for gestational diabetes, preeclampsia, placental abruption, premature rupture of membrane, asthma, urinary tract infection, threatened miscarriage, and threatened preterm birth), and remoteness indicator (urban or rural). The area-level Index of Relative Socio-economic Disadvantage derived by the Australian Bureau of Statistics [102] was assigned to the maternal residence at the time of delivery and categorised into tertiles to define high, moderate, and low socioeconomic status (SES). Few births without smoking status (n=14), SES (n=22), and remoteness indicator (n=143) were assigned a separate category as "unknown".

4.3.4 Environmental exposures assessment

Environmental exposures assessed were $PM_{2.5}$ concentrations as the main exposure. Because of the sparsity of surface measurements in Australia, the newly produced monthly global satellite-based $PM_{2.5}$ estimates at a fine spatial resolution of 0.01° × 0.01° (~1 km × 1 km) were obtained freely from the Washington University Atmospheric Composition Analysis Group website as version V5.GL.01.[45] Detail descriptions of this dataset were provided elsewhere.[45-47] Briefly, the surface $PM_{2.5}$ estimates were produced based on a geophysical relationship between Aerosol Optical Depths (AODs) and $PM_{2.5}$. Daily AOD retrievals from multiple satellite products were fused with aerosol vertical profiles from the GEOS-Chem chemical transport model and transformed onto a regular 0.01° × 0.01° grid and averaged to monthly means. These estimates were then calibrated to ground-based monitored $PM_{2.5}$ measurements by applying a geographically weighted regression. Despite the fine-gridded resolution, it was indicated that the $PM_{2.5}$ gradients may not be resolved fully due to the influence of information sources at a coarser resolution.[45] The monthly global satellite-based $PM_{2.5}$ concentration was obtained between January 1999 and December 2015 over Australia and processed at the SA1 levels in Western Australia using R package 'terra' and ArcGIS 10.8.1 software.

Universal Thermal Climate Index (UTCI) was assessed as a confounder and for investigating interactive association. UTCI (˚C) is a composite biothermal metric that combines the total thermal environment (air temperature, radiant temperature, relative humidity, and wind speed) with human physiological characteristics. This describes a human thermophysiological condition based on the advanced Fiala's multi-node human physiology and thermal comfort model.[76,80,105] A global hourly gridded UTCI at 0.25° × 0.25° (~27 km x 27 at the equator) spatial resolution generated by Di Napoli *et al* were freely accessed at the European Copernicus Climate Data Store.[106] In this study, 24 h averages for daily gridded UTCI were obtained between 1st January 1999 and 31st December 2015 over Australia and processed at the SA1 levels in Western Australia using ArcGIS 10.8.1 software.

For each birth, both $PM_{2.5}$ and UTCI were assigned as monthly exposures from three months preconception [69,111,242] through to birth based on dates of conception and birth and SA1 of the maternal residential address to the earlier of birth and the 42nd gestational week, after which the birth contributed no exposure time.[69,232] The maximum number of exposure months was therefore 13 months. Trimester-average exposures (1-3, 4-6, and 7-birth delivery gestational months) and other cumulative exposures such as preconception to pregnancy, entire pregnancy (conception to birth), and preconception (average of three months before pregnancy) were also calculated for each birth.

4.3.5 Statistical analyses

4.3.5.1 Main and subgroup analyses

To flexibly capture the intensity of linear and non-linear and delayed effects of $PM_{2.5}$ exposure on the birth outcomes, DLNM was incorporated with Cox proportional hazard (Cox PH) models to explore the monthly exposure-lag-response associations between stillbirth and sPTB as reported previously.[61,65,67,232] Gestational age was used as the time axis for the exposure lag space. The modelling framework was formulated as

$$h_i(t|x, C) = h_0(t)\exp(\beta x_t + \mathcal{B}C)$$

where *h* is the hazard, *i* is the *i*th birth, *x* denotes the cross-basis matrix for individual-level monthly $PM_{2.5}$ exposure at month *t* and the lag dimensions, *C* denotes the set of covariates, $h_0(t)$ denotes the baseline birth outcome at month *t* (i.e., the hazard function for a birth whose exposures and covariates are all equal to 0), and β and $\mathcal{B}$ are coefficients of the exposure and covariates, respectively. The smooth cross-basis function was constructed with the R package 'dlnm' and entered the Cox PH model (fitted with R package 'survival') for simultaneous analysis of monthly exposure–lag-response associations [59,60] to identify critical susceptible exposure periods.[61,65,67,232] The maximum lag dimension (exposure period) was 13 months for stillbirth (3 months preconception up to 42 gestational weeks or 10 months) and 12 months for sPTB (3 months preconception up to 36 gestational weeks or 9 months). Technically, the exposure-lag-response modelling with a linear exposure-response relationship is known as a distributed lag linear model (DLM) while with a non-linear exposure-response relationship is distributed lag non-linear model (DLNM). For easy interpretation of the exposure-response association as a given unit increment (usually 10 μg/m^3 increment), previous studies reported DLM.[61,65,67,232] But several studies also reported a non-linear relationship between air pollution and health outcomes and employed the DLNM method.[243-248] Hence in this study, both DLM and DLNM were fitted and results were reported in the context of national and international AQGs as reported elsewhere.[243] For DLNM, both exposure-response and lag-response associations were modelled as natural cubic splines with several combinations of 2-7 degrees of freedom (*dfs*). For DLM, a linear exposure-response function was used, and natural cubic splines with varying 2-7 *df*s for lag space (lag-response association). Based on the lowest Akaike Information Criterion (AIC) comparisons, the following *dfs* were used for the final analyses: [59,60,249] 3 for both exposure and lag space (DLNM) and *5* for lag space (DLM) for stillbirth but 2 for exposure and 4 for lag space (DLNM) and *5* for lag space (DLM) for sPTB.

The proportional assumption of the Cox PH model was first checked with Schoenfeld residual test and time-by-covariate interaction terms were specified for covariates that violated the assumption.[61,250,251] Following,[243] the monthly hazard ratios (HRs) and the 95% confidence intervals (95% CIs) were estimated for both DLM and DLNM outputs for each birth outcome. For DLM results, HRs (95% CIs) were estimated by comparing a change in exposure levels to both previous and new annual WHO AQGs (10 and 5 μg/m^3),[2] the Australia AQG (8 μg/m^3),[252] and excess increase in Australia AQG over the new WHO AQG (that is 3 μg/m^3). For DLNM, the HRs (95%

CIs) were calculated at 1st, 5th, 10th, 50th, 90th, 95th, and 99th centiles of exposure, using the new WHO AQG of 5 μg/m³ (which was 0.5 centile of $PM_{2.5}$ exposure) as reference. Critical susceptible exposure periods were identified as those months in which the 95% CI excluded the null.

The cumulative effects of $PM_{2.5}$ exposure during preconception, the entire pregnancy, and each trimester were also evaluated using separate Cox PH models. Average exposures for the preconception and entire pregnancy periods were included together to minimise the bias in the estimates if separate models were used. Similarly, all three trimester-average exposures were included together in the model instead of separate models for each trimester.[58,72,101] For each cumulative exposure period, the *one-basis* function of the 'dlnm' R package was used to construct unlagged or standard linear exposure-outcome associations with Cox PH regression.[59,60,249] All the models were adjusted for the potential confounders described earlier. Maternal age [253,254] and cumulative UTCI [65,69,232] were modelled as a continuous variable using natural splines with 3 *df*. To avoid various biases and paradoxical results due to conditioning on an intermediate, pregnancy complications were not adjusted for in the model as they are mediators in the association between $PM_{2.5}$ exposure and birth outcomes.[255,256]

Several stratified analyses were performed to explore the potential for effect modification by infant sex (male, female), race or ethnicity (Caucasians, non-Caucasians), maternal age at delivery (20–34, ≤19 or ≥35 years), SES (high, moderate, low), remoteness (urban, rural), maternal smoking status (non-smoker, smoker), and parity (nulliparous, multiparous), and pregnancy complications (yes, no). Preconception to pregnancy cumulative exposure with the linear exposure-response association was performed to estimate HR (95% CI) at 5 μg/m³ increment in $PM_{2.5}$ exposure and results were presented graphically.

4.3.5.2 Interactive effects of $PM_{2.5}$ and UTCI on birth outcomes

The cumulative preconception up to birth UTCI exposure for each birth was categorised into tertiles to define high, moderate, and low UTCI categories. The linear exposure-response association was performed to estimate separate HR (95% CI) per 5 μg/m³ $PM_{2.5}$ exposure increment for each UTCI category. Altman and Bland test of interaction effects was performed to compare the hazards in moderate and high subgroups, using the low subgroup as a reference by estimating the ratio of hazard ratios (RHRs) and the corresponding 95% CIs.[257,258]

4.3.5.3 Sensitivity analyses

The stability of the main monthly exposure-lag-response results was examined by performing several sensitivity analyses. (i) the *dfs* in the natural cubic spline was increased by one for both

$PM_{2.5}$ exposure and lag period in the cross-basis function. (ii) maternal age was included as a categorical variable (≤19, 20-34, ≥35 years) instead of as a natural spline of the continuous covariate. (iii) seasonality was adjusted with the calendar month of conception (1 to 12) instead of four-season categories. (iv) *df* for UTCI was increased by one to four. (v) the model was adjusted for mother-specific clusters to account for repeated births by the same mother. (vi) the model was adjusted for local government area-specific clusters to account for potential spatial clustering and maternal mobility. The local government area is a subdivision of Western Australia. Sensitivity analyses were fitted from DLNM for stillbirth and DLM for sPTB based on the main model of the birth outcome with the lowest AIC.

All statistical analyses were performed using the statistical software R 4.2.1 (R Development Core Team 2020), and main R packages 'dlnm', 'splines', and 'survival' were used. We reported and interpreted the HRs (95% CI) without considering any 'statistically significant' threshold as recommended by the American Statistical Association [181].

4.4 Results

4.4.1 Characteristics of the study population and environmental exposures

This study included 414,771 singleton births, of which 1,922 (0.5%) were stillbirths and 15,499 (3.7%) were sPTB. Slightly more than half of the births were male (51.2%), and most of the births were from mothers who were 20-34 years old (75.4%), Caucasian (78.3%), married (87.3%), non-smokers (85.3%), multiparous (58.1%), and urban residents (61.9%). Births were almost equally distributed among the four seasons of conception (Table 4.1). The mean (standard deviation) and median (interquartile range) $PM_{2.5}$ exposure during the period from preconception to birth were equivalent, 8.1 (1.0) $\mu g/m^3$ and 8.1 (1.2) $\mu g/m^3$, respectively. This was equivalent to the Australian AQG for annual average $PM_{2.5}$ concentration of 8 $\mu g/m^3$ [252] which was below the former annual WHO AQG of 10 $\mu g/m^3$ but exceeded the new more stringent recommendation of 5 $\mu g/m^3$.[2] The specific average exposures for preconception, pregnancy and each trimester were similar to the full exposure period. The mean (standard deviation) and median (interquartile range) UTCI exposure were 14.5 (2.5) ˚C and 14.2 (1.2) ˚C, respectively, for the full exposure period and these were almost similar across specific cumulative exposure periods (Table 4.2). The distributions of the environmental exposures were almost the same for the sPTB birth cohort which included 400,387 births (Table S4.1).

Table 4.1 Maternal characteristics of included singleton births in Western Australia, 2000-2015 (N= 414,771)

Characteristics	n (%)	Characteristics	n (%)
Stillbirth		Smoked	
No	412,849 (99.5)	No	353751 (85.3)
Yes	1,922 (0.5)	Yes	61,006 (14.7)
PTB		Unknown	14 (0.0)
Term birth	384,888 (92.8)	Parity	
Non-spontaneous PTB	14,384 (3.5)	Nulliparity	173,714 (41.9)
sPTB	15,499 (3.7)	Multiparity	241,057 (58.1)
Sex		Remoteness indicator	
Male	212,313 (51.2)	Urban	256,704 (61.9)
Female	202,458 (48.8)	Rural	157,924 (38.1)
Maternal age (years)		Unknown	143 (0.0)
≤19	19,026 (4.6)	SES	
20–34	312,592 (75.4)	High	138,417 (33.4)
≥35	83,153 (20.0)	Moderate	138,209 (33.3)
Race/ethnicity		Low	138,123 (33.3)
Caucasian	324,890 (78.3)	Unknown	22 (0.0)
Non-Caucasian	89,881 (21.7)	Season	
Marital status		Autumn	100,781 (24.3)
Married	362,110 (87.3)	Winter	105,458 (25.4)
Unmarried	52,661 (12.7)	Spring	104,693 (25.2)
		Summer	103,839 (25.0)

Note: PTB, Preterm birth; sPTB, spontaneous preterm birth; SES, socioeconomic status

Table 4.2 Descriptive statistics of the monthly environmental exposures for three months preconception through to birth delivery for included singleton births in Western Australia, 2000-2015 (N= 414,771)

Exposure	Exposure period	Min	Mean ± SD	Median	P25	P75	IQR	Max
$PM_{2.5}$ (μg/m^3)	Preconception to pregnancy	3.6	8.1 ± 1.0	8.1	7.5	8.7	1.2	17.8
	Preconception	1.0	8.1 ± 1.5	7.9	7.3	8.7	1.4	27.6
	Pregnancy	2.9	8.1 ± 1.1	8.0	7.5	8.7	1.2	20.5
	1st Trimester	1.3	8.1 ± 1.5	7.9	7.3	8.7	1.4	27.6
	2nd Trimester	0.8	8.1 ± 1.5	7.9	7.3	8.7	1.4	27.6
	3rd Trimester	0.0	8.1 ± 1.6	7.9	7.3	8.7	1.4	26.4
UTCI (˚C)	Preconception to pregnancy	7.4	14.5 ± 2.5	14.2	13.6	14.8	1.2	30.9
	Preconception	1.6	14.4 ± 5.1	14.0	9.8	18.5	8.7	35.8
	Pregnancy	4.7	14.6 ± 2.8	14.2	12.9	15.6	2.7	34.1
	1st Trimester	1.6	14.5 ± 5.2	14.2	9.8	18.7	8.9	36.0
	2nd Trimester	1.7	14.6 ± 5.2	14.2	10.0	18.7	8.7	36.1
	3rd Trimester	-3.0	14.5 ± 5.2	14.0	9.9	18.5	8.6	35.8

Note: SD, standard deviation; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm; UTCI, Universal Thermal Climate Index; P25 and P75, 25th and 75th centiles; IQR, Interquartile range= P75-P25

4.4.2 Maternal $PM_{2.5}$ exposure and the hazards of stillbirth and sPTB

The DLM hazards of both stillbirth and sPTB showed a nearly inverted 'V'-shaped relationship with the $PM_{2.5}$ exposure at AQGs 10 μg/m^3, 8 μg/m^3, 5 μg/m^{3,} and 3 μg/m^3, using 0 μg/m^3 as a reference. The hazards of the birth outcomes decreased with the decreasing incremental exposures. For stillbirth, $PM_{2.5}$ exposures from preconception to two months into pregnancy and from five months to birth were associated with lower hazards of stillbirth. The lowest hazards at 10 μg/m^3 (former WHO AQG) and 5 μg/m^3 (new WHO AQG) increase in $PM_{2.5}$ exposure were 0.87 (95% CI 0.78, 0.96) and 0.93 (95% CI 0.88, 0.99), respectively, during the 7th gestational month.

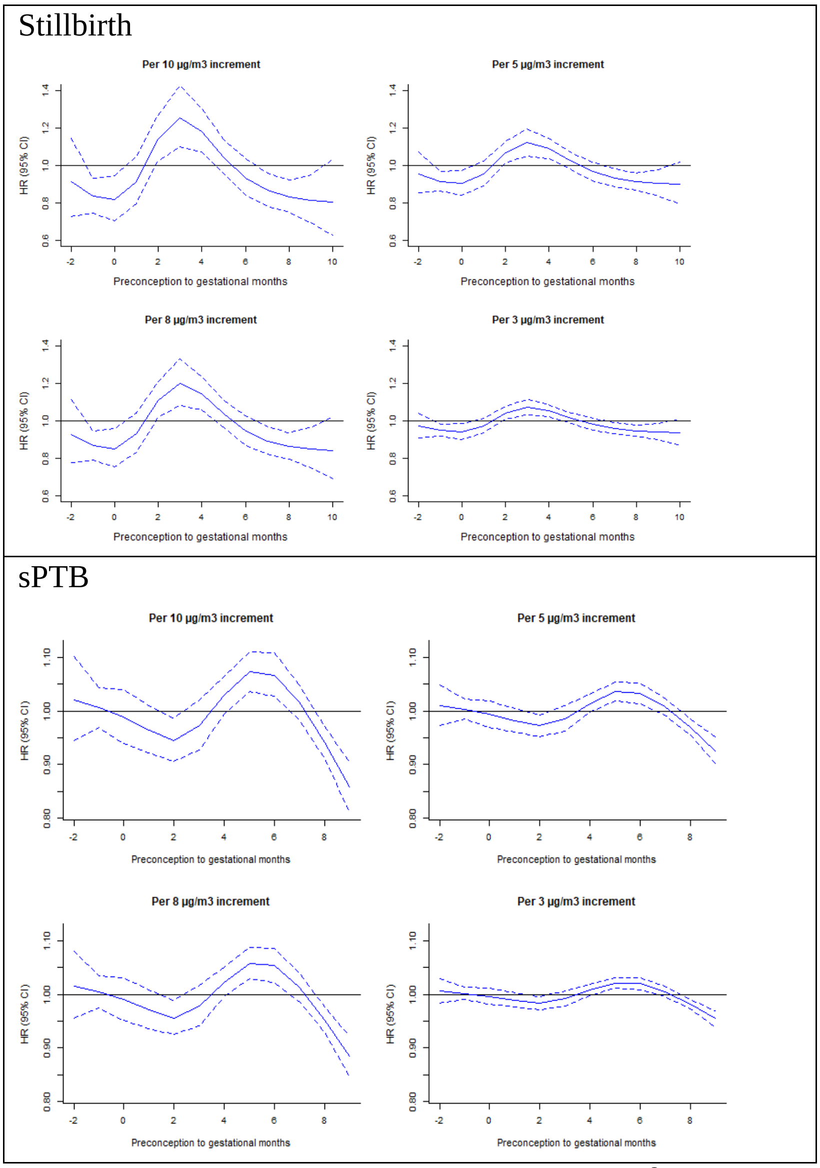

Figure 4.1. Adjusted hazard ratios for the association between 10, 8, 5, and 3 μg/m^3 increase in $PM_{2.5}$ exposure and risks of stillbirth and sPTB, by month of gestation from three months preconception (-2 to 0) to birth (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from DLM Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, year and season of conception, and ambient Universal Thermal Climate Index. Note: DLM, distributed lag model; HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm.

Between two and five months of pregnancy exposures were associated with higher hazards of stillbirth and the strongest hazards were found during the 3rd gestational month, 1.25 (95% CI 1.10, 1.43) and 1.12 (95% CI 1.05, 1.19) at 10 μg/m^3 and 5 μg/m^3 increase in $PM_{2.5}$ exposure, respectively. The excess $PM_{2.5}$ exposure increase in Australian AQG over the new WHO AQG (3 μg/m^3) also showed the strongest hazard of 1.07 (95% CI 1.03, 1.11) during the 3rd gestational month (Figure 4.1 and Table S4.2). The DLNM method which had better model performance than DLM based on the lowest AIC showed essentially no association at $PM_{2.5}$ exposures below the median but increasing hazards of stillbirth for exposures above the median as compared to the new WHO AQG annual average of 5 μg/m^3. The hazards of stillbirth were particularly higher at the 99th centile (10.7 μg/m^3) as compared to 5 μg/m^3 during the 4th –7th gestational months and most elevated during the 7th gestational month, 1.10 (95% CI 1.02, 1.19). The same exposure threshold showed the lowest hazard of 0.79 (95% CI 0.71, 0.88) during the 3rd preconception month (Figure 4.2 and Table S4.4).

For sPTB, DLM performed better than the DLNM method. From the DLM hazards of sPTB, the higher hazards were found just after the 4th –7th gestational months. The DLM estimates for exposure to WHO AQG increments of 10 μg/m^3 and 5 μg/m^3 $PM_{2.5}$ showed the strongest hazards of 1.07 (95% CI 1.04, 1.11) and 1.04 (95% CI 1.02, 1.05), respectively during the 5th gestational month. The linear effect estimates of increased $PM_{2.5}$ exposure in Australian AQG over the new WHO AQG (that is excess of 3 μg/m^3) also showed the strongest hazard of 1.02 (95% CI 1.01, 1.03) during the 5th gestational month. Exposures during preconception to early pregnancy and after seven months of pregnancy were associated with lower hazards of sPTB. The lowest hazards of sPTB at 10 μg/m^3 and 5 μg/m^3 increase in $PM_{2.5}$ exposure were 0.86 (95% CI 0.81, 0.90) and 0.93 (95% CI 0.90, 0.95), respectively, during the 9th gestational month (Figure 4.1 and Table S4.3). Using 5 μg/m^3 $PM_{2.5}$ exposure as a reference, the DLNM estimates showed hazards of sPTB at the 1st centile through to the 99th centile of $PM_{2.5}$ exposure which increased slightly with increasing dosage of the exposure, especially between the 4th–6th gestational months. The strongest hazard of sPTB was 1.04 (95% CI 1.01, 1.06) during the 5th gestational month for exposure to the 99th centile as compared to 5 μg/m^3. There were also lower hazards of sPTB during preconception to early months of pregnancy and after seven months of pregnancy. The lowest hazard of sPTB was 0.94 (95% CI 0.91, 0.97) at the 99th centile of $PM_{2.5}$ exposure as compared to 5 μg/m^3 (Figure 4.2 and Table S4.5).

Cumulative exposures during preconception showed lower hazards for stillbirth but no association with sPTB. Pregnancy exposure showed higher hazards for both birth outcomes which included the null in the confidence interval. At 5 µg/m^3 $PM_{2.5}$ exposure increment, trimester-average exposures showed higher hazard during the first trimester, 1.17 (95% CI 0.98, 1.39) for stillbirth and second trimester, 1.01 (95% CI 0.95, 1.07) for sPTB. The hazards were stronger for 10 µg/m^3 $PM_{2.5}$ exposure increment but also included the null in the confidence interval (Table 4.3).

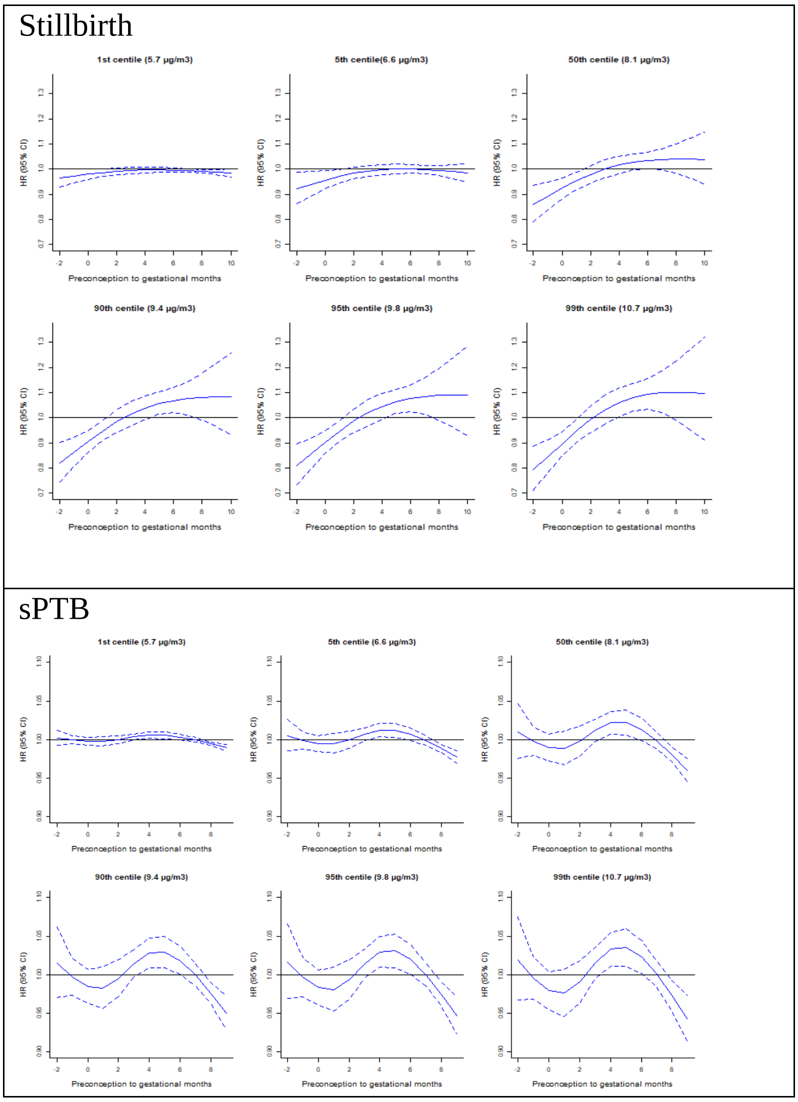

Figure 4.2. Adjusted hazard ratios of stillbirth and sPTB due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10 for stillbirth and 1 to 9 for sPTB) at different thresholds using 5µg/m^3 $PM_{2.5}$ as a reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from DLNM Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, year and season of conception, and Universal Thermal Climate Index. Note: DLNM, distributed lag non-linear model; HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 µm.

Table 4.3 Adjusted hazard ratios per 5 and 10 μg/m^3 $PM_{2.5}$ increments for stillbirth and sPTB for cumulative $PM_{2.5}$ exposures over three months preconception through to pregnancy and trimester-specific periods in Western Australia, 2000–2015.

Exposure period	$PM_{2.5}$ μg/m^3	Stillbirth HR (95% CI)	sPTB HR (95% CI)
Preconception to pregnancy	5	0.95 (0.75, 1.21)	0.99 (0.91, 1.08)
	10	0.91 (0.57, 1.46)	0.98 (0.82, 1.16)
Preconception	5	0.77 (0.64, 0.92)	1.00 (0.94, 1.06)
	10	0.59 (0.42, 0.85)	1.00 (0.89, 1.12)
Pregnancy	5	1.17 (0.95, 1.44)	1.06 (0.98, 115)
	10	1.37 (0.90, 2.08)	1.13 (0.96, 1.31)
First Trimester	5	1.17 (0.98, 1.39)	0.99 (0.93, 1.05)
	10	1.37 (0.96, 1.94)	0.98 (0.86, 1.10)
Second Trimester	5	0.97 (0.83, 1.14)	1.01 (0.95, 1.07)
	10	0.94 (0.69, 1.29)	1.02 (0.90, 1.15)
Third Trimester	5	0.98 (0.86, 1.11)	1.00 (0.96, 1.04)
	10	0.96 (0.75, 1.23)	1.00 (0.92, 1.09)

Note: HR, hazard ratios; CI, Confidence Intervals; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm; PTB, preterm birth. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year and season of conception, and Universal Thermal Climate Index exposure. sPTB, Spontaneous preterm birth.

4.4.3 Interaction and modification effects

The results showed an interactive association of higher hazards of stillbirth for 5 μg/m^3 $PM_{2.5}$ exposure increment in moderate UTCI exposure, 2.17 (95% CI 1.00, 4.72) and high UTC exposure, 1.56 (95% CI 0.88, 2.74) as compared to low UTCI exposure. There was no interactive association between $PM_{2.5}$ and UTCI exposures on the hazards of sPTB (Table 4.4).

Stratified analyses indicated effect modifications. Comparatively, the $PM_{2.5}$ exposure showed a higher hazard in male birth for both birth outcomes (Figure S4.2), higher in non-Caucasian for stillbirth but no racial or ethnicity differences for sPTB (Figure S4.3). For both birth outcomes, higher hazards were found in mothers aged 20-34 years old (Figure S4.4) and mothers that resided in high SES areas (Figure S4.5). A higher hazard of stillbirth was found for urban dwellers but no difference for a place of residence regarding sPTB hazard (Figure S4.6). Mothers who smoked were at higher hazard of stillbirth, but non-smokers showed a slightly higher hazard of sPTB (Figure S4.7). The association of $PM_{2.5}$ exposure with stillbirth showed a higher hazard in nulliparous women but no observable difference for sPTB (Figure S4.8). Mothers who married were at higher hazard of stillbirth but unmarried showed a slightly higher hazard of sPTB (Figure S4.9). Mothers who experienced complications during pregnancy were at higher hazard of both stillbirth and sPTB (Figure S4.10). The identified critical susceptible exposure periods for the subgroups were almost consistent with the main results.

Table 4.4 Interaction effects as the ratio of hazard ratios per 5 μg/m^3 $PM_{2.5}$ increment for stillbirth and sPTB for preconception to pregnancy cumulative $PM_{2.5}$ exposures in moderate and high UTCI exposure, using low UTCI as a reference in Western Australia, 2000-2015.

UTCI level	Stillbirth		sPTB	
	HR (95% CI)	RHR (95% CI)	HR (95% CI)	RHR (95% CI)
Low	0.63 (0.39, 1.00)	Reference	0.95 (0.80, 1.14)	Reference
Moderate	1.37 (0.74, 2.54)	2.17 (1.00, 4.72)	0.95 (0.79, 1.16)	1.00 (0.77, 1.30)
High	0.98 (0.72, 1.35)	1.56 (0.88, 2.74)	0.95 (0.85, 1.06)	1.00 (0.81, 1.23)

Note: HR, hazard ratios; CI, Confidence Intervals; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm; sPTB, Spontaneous preterm birth; UTCI, Universal Thermal Climate Index; RHR, ratio of hazard ratios.

4.4.4 Sensitivity

The sensitivity results did not show any substantial discrepancy from the results of the main analyses. Similar critical susceptible exposure periods were found for the sensitivity results (Figure S4.11-S4.16).

4.5 Discussion

4.5.1 Main findings

This was the first state-wide investigation of ambient $PM_{2.5}$ and the risks of stillbirth and sPTB in Western Australia and the first to employ exposure-lag-response methodology on this topic in Australia. The findings of this study showed that monthly ambient $PM_{2.5}$ exposure was associated with higher hazards of both stillbirth and sPTB even at exposure below the new WHO AQG of 5 μg/m^3 as shown in the DLM effect estimates for exposure to 3 μg/m^3, using 0 μg/m^3 $PM_{2.5}$ as a reference. This reaffirms the suggestion that there is currently no safe $PM_{2.5}$ exposure level, particularly for vulnerable populations such as pregnant women and their unborn babies.[2,222] Results of both DLM and DLNM indicated dose-response associations of the greater the $PM_{2.5}$ exposure the higher the hazards of stillbirth and sPTB. The identified critical susceptible exposure periods were the 3rd–7th and 4th–7th gestational months for stillbirth and sPTB, respectively. Exposures outside these critical susceptible periods which included preconception to early months of pregnancy and late pregnancy showed critical protective periods. But the magnitudes of the ‘protective effects’ in the protective periods were smaller that the hazard effects found in the susceptible periods. Average exposures during the first and second trimesters were associated with higher hazards of stillbirth and sPTB, respectively, but both included the null value in the 95% CIs. Interactive effects of $PM_{2.5}$ exposure and biothermal stress (UTCI) were observed for stillbirth, not sPTB. The interactive effect was more elevated for moderate than high UTCI exposure as compared to low UTCI exposure. There were biological and sociodemographic disproportionate effects of $PM_{2.5}$ exposure with slight variations between the two birth outcomes. Consistently higher-hazard subpopulations for both birth outcomes were male birth and births to mothers aged 20-34 years, high SES, and complicated pregnancy.

As demonstrated and recommended by Wilson et al,[58] few epidemiological studies have applied the DLM method to investigate monthly or weekly-specific associations between $PM_{2.5}$ exposure and PTB and reported somewhat consistent critical susceptible exposure periods.[61,65,67,232] The identified critical susceptible exposure periods were 20th–28th weeks (5th–7th months),[65] 17–24 weeks (4th–6th months),[61] 27–30 weeks (6th-7th months),[232] and 18th–27th weeks (4th–6th months).[67] These were consistent with the 4th–7th gestational months for sPTB in our study but with slightly higher magnitude than reported previously based on weekly-specific exposure assessment.[61,65,67,232] Put together, the findings suggest the 17th-30th gestational weeks (4th–7th months) as potential critical susceptible exposure periods for intervention and a better understanding of the biological mechanism. Related exploration of critical susceptible exposure period has not been reported in the literature on stillbirth for comparison. There is generally limited investigation of the association between air pollution and stillbirth as compared to other birth outcomes such as preterm birth and birth weight.[125] Trimester-specific odds of stillbirth per 10 μg/m³ $PM_{2.5}$ increase reported in the updated meta-analysis were 0.96 (95% CI: 0.83, 1.09) based on seven primary studies for the first trimester, 1.03 (95% CI: 0.94, 1.12) on six studies for the second trimester, and 1.09 (95% CI: 1.01, 1.18) on five studies during the third trimester.[259] Thus, second to third trimesters are potential susceptible periods which somewhat aligns with the finding in the present study with novel exposure-lag-response analysis which specifically found 3rd–7th gestational months as susceptible periods. As demonstrated in a simulation study, the traditional method of using separate models for each trimester-average exposure could produce biased estimates and identify incorrect susceptible exposure periods or identify critical periods which span multiple trimesters.[58] This could also be due to many contributing factors such as differences in population characteristics, exposure assessment methods, and definitions of stillbirth which varied largely among studies. Cumulative preconception exposure showed a small protective effect on stillbirth but did not show any association with sPTB. This was consistent with previous studies on $PM_{2.5}$ and PTB [260,261] but no known comparison study for stillbirth. A mouse experimental study also found no association between $PM_{2.5}$ exposure before implantation and PTB.[262] However, limited epidemiologic findings have reported the potential effects of preconception exposures on children's health.[112] This suggests further studies in this direction as this neglected period is being recognised as a critical period for intervention.[110,112] Moreover, our monthly effect estimates generally showed that preconception to early months of pregnancy and late pregnancy showed a small magnitude of critical protective periods for both birth outcomes. It could be that pregnant women are more likely to be cautious of environmental exposures (e.g., reduce outdoor activities) and often take other perinatal care precautions more serious during early and late stages of pregnancy, leading to lower risk during these periods.

4.5.2 Interactive association and modification effects

Given the independent effects of $PM_{2.5}$ and ambient temperature on birth outcomes through similar biological mechanisms,[16,125] the interactive effect of these exposures by trimesters on PTB has been found in a few previous studies.[234,263,264] However, an interactive effect for preconception to pregnancy cumulative exposure was observed for stillbirth but not for sPTB. More studies are required on the interactive effects of these environmental exposures. The interactive effects on stillbirth, particularly higher for moderate UTCI exposure than high UTCI exposure as compared to low UTCI exposure could be explained from behavioural perspective. Generally, outdoor activities are increased more during moderate than high or low biothermal stress conditions. This increases the exposure to ambient air pollution, resulting in higher hazards of stillbirth. Awareness and reduction in outdoor activities are suggested to minimise the interaction of air pollution and climate change.[234] Special attention should also be paid to vulnerable mothers such as those that conceived male babies, non-Caucasians, high SES, smokers, and those with any complicated pregnancy.[265,266] The higher hazards in the high SES subgroup as reported elsewhere [67] could be due to high exposure levels in the urban areas that are predominantly high SES areas. Moreover, the SES used in this study was area-level data which is less accurate as compared to individual-level data such as occupation and educational attainment. A review in the United States concluded that mothers with low educational levels are more vulnerable to the impacts of particulate matter on birth outcomes.[158]

4.5.3 Plausible pathophysiological mechanisms

The underlying pathophysiology of $PM_{2.5}$ exposure and birth outcomes are currently unclear but several epidemiological, toxicological, *in vivo* models and *omic*s studies have provided many plausible pathways regarding the effects of $PM_{2.5}$ exposure on the placenta at the cellular and molecular levels.[125] Briefly, *in utero* $PM_{2.5}$ generate excess oxidative free radicals such as reactive oxygen or nitrogen species as the primary response to particulate matter in humans and other variables that causes changes in the cellular composition of the placenta.[26,267] These induce a series of biological and physiological processes that alters inflammatory, immune, and cardiorespiratory responses.[26] These also impair the normal function of cells, can cause apoptosis, and modify the anatomy and physiology of the placental with negative effects on fetal development and growth. Placental dysfunction impairs the fetoplacental transport of nutrients, oxygen, and water which could result in stillbirth. The $PM_{2.5}$-mediated endocrine-disrupting properties, induced inflammations, and upregulation of pro-inflammatory cytokines and birth hormones such as oxytocin and prostaglandins initiate preterm labour that leads to sPTB.[267,268] Males are more sensitive to oxidative protein damage induced by air pollutants.[231,269] Other biological, health conditions, sociodemographic and lifestyle factors such as smoking, malnutrition, and infections were found to increase oxidative stress and endocrine disrupting potentials that further exacerbate $PM_{2.5}$-mediated toxicity on birth outcomes.[23,25,268] Molecular epidemiologic studies have also found that epigenetic modifications, mitochondrial DNA mutation, and global placental DNA methylation during early pregnancy together with oxidative stress and endocrine disrupting properties of $PM_{2.5}$ to reprogram the placenta and cause adverse birth outcomes.[19,189,231,270] Moreover, there is a reproductive toxicity effect of $PM_{2.5}$ exposure in males with a potential impact on birth outcomes.[231] More pathophysiological and biological studies have been suggested.[231,270]

4.5.4 Public health strategies and policies

A recent systematic review of the interventions to reduce ambient air pollution and the corresponding effects on health revealed that some interventions improved air quality and human health with little evidence of the harmful effects of the interventions.[271] This implies that, although there is no safe limit for air pollution, precautionary actions at personal, population, clinical, and governmental levels to further reduce exposure to $PM_{2.5}$ are necessary to save lives.[125,222] Personal-level actions, especially by pregnant women or women of reproductive age include reducing outdoor activities or using particulate matter filters in polluted areas. Governmental-level actions such as more stringent regulatory actions and climate governance, increasing investment to ensure access and affordable “green” or modern “clean” energy, and increasing the number and affordability of electric vehicles are necessary.[125,222,272,273] Active involvement of clinicians in raising awareness, education, and environmental advocacy for mitigation strategies has also been suggested.[10,274] These are particularly important as we get closer to 2030 with the target of achieving SDG 3.[228]

4.5.5 Strengths and limitations

This study has several strengths. (i) The space-time varying exposure assessments of both $PM_{2.5}$ and biothermal metric (UTCI) are major strengths that reduced exposure misclassification as compared to the conventional use of simple models or proximity to sparse monitoring stations that tend to be distant from where people reside. (ii) Application of DLNM integrated with Cox PH allowed for investigating monthly preconception to birth exposure-lag-response association in addition to the usual cumulative entire pregnancy and trimester-based periods. (iii) The few previous studies that used the DLNM approach applied only a linear exposure-lag-response approach.[61,65,67,232] But both linear and nonlinear exposure–lag-response functions were reported in this study and results were interpreted in the context of national and international air quality guidelines as reported elsewhere.[243] (iv) Given the limited research on the exposure-lag-response association for PTB and no known previous evidence on the exposure-lag-response association for stillbirth, the findings in this study have added important epidemiological evidence to the literature. (vii) The interactive effect of $PM_{2.5}$ and biothermal stress was investigated in this study which is hardly reported. (v) This was the first state-wide investigation on the topic in Western Australia. Also, this study was the first in Australia to investigate monthly critical susceptible exposure periods for the birth outcomes as previous Australian studies only investigated trimester-average exposure effects and did not include stillbirth,[152] a critical indicator in the SDG 3.[228]

Several limitations should also be considered in this study. (i) Both UTCI and $PM_{2.5}$ were assigned at a small-area (SA1) scale, a very fine spatial resolution to reduce exposure misclassification. But this has a reduced exposure variability compared to individual-level exposure and did not account for residential mobility during pregnancy. Regarding residential mobility, a recent review on maternal relocation[275] and simulation study [276] found no impact of residential mobility on the effect estimates. Furthermore, the sensitivity analysis that adjusted for local government area-specific clusters to account for potential spatial clustering and maternal mobility produced the same result with the same precision. However, the gold standard approach, although impracticable in large-scale studies is a personalised real-time-activity exposure measurement by using personal air monitors.[277,278] (ii) Previous studies that employed the DLNM technique mostly investigated weekly-specific effects [61,65,67,232] but monthly-specific effects were investigated in this study due to the availability of the $PM_{2.5}$ data. (iii) The performance of the $PM_{2.5}$ prediction model was high ($R^2 = 0.90–0.92$) and this included ground-based monitoring measurements from Australia.[45,47] Despite this, geographically sparse surface measurements in Australia could result in low model performance in some areas. It was also indicated that $PM_{2.5}$ gradients may not be fully resolved due to the influence of information sources at coarser resolution.[45] Together with the uncertainties in the estimated $PM_{2.5}$, these measurement errors may introduce some bias in the effect estimates, especially towards the null. However, several epidemiological studies have demonstrated the utility of this high spatiotemporally resolved dataset.[54,56,236-238] (iv) Effects of other pollutants were not investigated due to lack of data and this is consistent with the literature as previous primary studies, systematic reviews, and meta-analyses were based on a single-pollutant model.[125] Exposure measurement errors and biases can occur when analysing multiple environmental exposures [192] while results of single-pollutant models are more robust than multi-pollutant models.[174] However, future studies could benefit from the increasingly novel statistical methods for investigating environmental mixtures in epidemiology.[279] (v) Investigation of constituent components of $PM_{2.5}$ is important for policy regulation and public health intervention but was not included in this study due to a lack of data. vi) There is a potential live-birth bias as fetuses that were more susceptible to $PM_{2.5}$ exposure may have resulted in early pregnancy loss and were unobserved, resulting in an underestimation of the harmful effects.[101] Related studies on early pregnancy loss may be helpful. vii) As an inherent limitation in observational studies, residual confounding cannot be overruled. Although many factors were adjusted for in this study, several other important covariates or confounding factors were not included due to a lack of data. This includes maternal alcohol or illicit drug intake, educational level, nutritional status, employment, infection (e.g., seasonal influenza), maternal weight, height, physical activity during pregnancy, and indoor air pollution. Most of these factors, however, were partly controlled through SES and remoteness variables.

4.6 Conclusion

In this study, monthly $PM_{2.5}$ concentrations derived from a combination of satellite retrievals of aerosol optical depth, chemical transport models, and ground-based measurements were linked with births in Western Australia. The hazards of stillbirth and sPTB due to $PM_{2.5}$ exposure from three months of preconception to birth were investigated by applying an advanced statistical modelling technique. Monthly $PM_{2.5}$ exposure even below the new WHO AQG of 5 $\mu g/m^3$ was associated with higher hazards of stillbirth and sPTB. Identified exposure periods of increased susceptibility were the 3^{rd}–7^{th} gestational months. However, monthly exposures outside these critical periods (including preconception periods) showed relatively small magnitudes of protective effects. $PM_{2.5}$ and biothermal stress exposures interactively elevated the hazards of stillbirth but not sPTB. Disproportionate effects were consistently found for both birth outcomes for male birth and births to mothers aged 20-34 years, high SES, and complicated pregnancy. Together with previous studies,[61,65,67,232] the identified specific periods of increased susceptibility to $PM_{2.5}$ during pregnancy could inform public health interventions, policy decisions, and future aetiological research. Further high-quality studies to identify critical susceptible exposure periods, particularly for stillbirth are necessary from other geodemographic settings.

Chapter 5. Long-term maternal exposure to ambient fine particulate matter and the risks of adverse fetal growth in Western Australia

5.0. Preamble

This chapter provides a primary investigation of the association between maternal exposure to monthly fine particulate matter air pollution ($PM_{2.5}$) from three months before conception up to birth and the risks of term adverse fetal growth (small for gestational age, large for gestational age, and low birth weight) in Western Australia. Plausible critical exposure periods of increased susceptibility and vulnerable subpopulations were identified.

5.1 Abstract

Background: We have very limited epidemiologic evidence on weekly or monthly fine particulate matter ($PM_{2.5}$) exposure and adverse fetal growth to identify critical susceptible exposure periods.
Objectives: To identify critical susceptible exposure periods of monthly $PM_{2.5}$ and term small and large for gestational age (SGA and LGA), and term low birth weight (LBW).
Methods: This study included 384,882 singleton term births, including 9.8%, 9.9%, and 1.7% term SGA, LGA, and LBW, respectively, between 1st January 2000 and 31st December 2015 in Western Australia. Births were linked to spatiotemporal monthly $PM_{2.5}$ estimates. Distributed lag linear and non-linear Cox proportional hazard regression was performed to investigate monthly $PM_{2.5}$ exposure for three months preconception to birth and the adjusted hazards of each birth outcome.
Results: The mean (standard deviation) $PM_{2.5}$ exposure during the study period was 8.1 (1.0) µg/m^3. Generally, $PM_{2.5}$ exposure during early to mid-gestational months (1st–7th months) showed small positive associations. Using 5 µg/m^3 as a reference, the largest hazards were 1.01 (95% CI 1.00, 1.02) for term SGA for exposure above the median during the 4th gestational month, 1.03 (95% CI 1.00, 1.05) for term LGA for exposure at 99th $PM_{2.5}$ centile during 1st gestational month, and 1.03 (95% CI 1.01, 1.05) at 50th $PM_{2.5}$ centile during the 3rd gestational month for term LBW. Exposure during preconception months and late gestational months (8th–10th months) showed very small protective effects. The results also showed interactive effects of $PM_{2.5}$ and biothermal stress exposures on the birth outcomes. For all birth outcomes, consistently elevated hazards were found in non-Caucasian, unmarried, and mothers with any complicated pregnancy. Critical susceptible exposure periods were found in high socioeconomic status, rural, and smokers for term LBW.
Conclusion: Potential exposure periods of increased susceptibility required further investigations for evidence-based public health interventions, particularly for higher-risk subpopulations.

5.2 Introduction

Fetal growth indicators such as low birth weight (LBW, birth weight < 2500 g regardless of gestational age),[280] small for gestational age (SGA, < 10th centile of birth weight for gestational age and sex), and large for gestational age (LGA, > 90th centile of birth weight for gestational age and sex)[281] are important markers of fetal health, growth and development. These fetal growth outcomes are associated with childhood mortality, and many short- and long-term health outcomes, including stunting, childhood obesity, cardiometabolic and respiratory disorders, neurodevelopmental delay, and immunologic dysregulation.[12,282-284] The increasing fetal growth outcomes is a global public health concern. For example, a recent global systematic analysis estimated 14.6% worldwide prevalence of LBW in 2015 as compared with 17.5% in 2000, a 1.2% average annual reduction rate.[280] This means that to achieve the average annual relative reduction rate of 2.7% between 2012 and 2025 in the global nutrition target 3 (30% reduction of LBW), we need to double the progress made so far.[280,285]

Ambient air pollution, particularly particulate matter ≤ 2.5 µm in aerodynamic diameter ($PM_{2.5}$) has been recognised globally as a major environmental exposure with serious health-damaging effects,[2,6] including birth outcomes.[194,230] The toxic organic and inorganic constituent components, high diffusion, and inhalation capacity of $PM_{2.5}$ increase its relative pathogenicity.[2,3] The World Health Organization (WHO) has, therefore, recently updated the Air quality guidelines (AQGs) and recommended 5 $\mu g/m^3$ instead of 10 $\mu g/m^3$ as the annual average $PM_{2.5}$ concentration guideline towards improving health[2] and achieving Sustainable Development Goal (SDG) 3.[228] Several epidemiological evidence summarised in an umbrella review suggests that maternal exposure to $PM_{2.5}$ during entire pregnancy or trimesters associated with adverse fetal growth.[125] Pathophysiologically, $PM_{2.5}$ can directly or indirectly affect birth outcomes through placental oxidative stress, epigenetic changes, and placental dysfunction.[19,214,215,231] There are, however, several limitations in the current body of evidence regarding fetal growth. Epidemiological studies mostly examined $PM_{2.5}$ and preterm birth and LBW but few studies examined SGA as reported in the umbrella review.[125] Evidence on LGA is particularly scarce. Very few primary studies reported on the association between $PM_{2.5}$ and LGA and found lower risk during the first and third trimesters, and entire pregnancy[53,286] and higher risk during 1st–12th preconception weeks and the 1st–5th gestational weeks.[69] The umbrella review indicated less consistent positive associations with no clear critical susceptible $PM_{2.5}$ exposure period and as previous studies relied on trimester-average exposures.[125] A recent simulation study documented that estimates derived from trimester-average exposures are biased and wrongly identified critical susceptible exposure periods.[58] Also, biological pathways of the environmental exposures might not necessarily follow clinically defined trimesters. As such, critical susceptible exposure periods could span multiple trimesters or be shorter than the three-month intervals.[24,58] Shorter than trimester exposure periods such as weeks and months for long-term effects and using distributed lag models to obtain unbiased estimates was recommended for targeted intervention and a better understanding of biological mechanisms.[24,58] Furthermore, the effects of time-varying environmental exposures such as $PM_{2.5}$ are due to multiple exposures in the past (delayed or lagged effects) with different intensities.[59,60] This is described as exposure–lag–response association and can be characterised by distributed lag linear or non-linear models (DLM or DLNM).[59,60] Following the recommendation [58] and the development of the R package “dlnm”,[60] very few recent studies have applied DLM to estimate more accurate and weekly critical susceptible $PM_{2.5}$ exposure periods on adverse fetal growth – SGA,[62,69,287] LGA,[69] and LBW or term LBW.[67,232] Apart from one study from the United States,[62] other studies were conducted in China.[67,69,232,287] Because of differences in population characteristics and geochemical properties of $PM_{2.5}$, generalisation of the associations between $PM_{2.5}$ and birth outcomes between and within countries or regions and populations could be misleading. Another notable limitation is exposure misclassification as $PM_{2.5}$ exposure assessment in most of the previous studies was based on proximity to limited fixed-site ground monitoring stations.[67,125] This would have also excluded the more vulnerable rural populations as $PM_{2.5}$ monitors are often located in the cities, urban centres, and industrialised areas. There is also limited evidence regarding the joint effect of air pollution and extreme temperature or thermal stress.[287] Few epidemiologic studies also suggested preconception exposure, especially three months before conception,[69,111] as critical period that need further investigation.[112]

A recent systematic review of studies conducted on the Australian population included only three primary studies on $PM_{2.5}$ and adverse fetal growth (SGA, LGA, and LBW) which were from the eastern parts and were dissimilar to drawing firm conclusions.[152] Also, none of those studies applied a high-quality method such as DLM or DLNM methodology to obtain unbiased effect estimates and to identify critical susceptible exposure periods.[58-60] The review authors also suggested that further studies should investigate critical susceptible exposure periods.[152] Moreover, there is no known study on $PM_{2.5}$ and adverse fetal growth in Western Australia. The prevalence of LBW in Western Australia was 6.5% in 2016 [91] which was equivalent to the national prevalence of 6.7% in 2017.[288] Lack of state-wide epidemiological evidence in Western Australia may partly be due to geographically sparse air monitoring stations. This limitation has been circumvented in several related environmental epidemiological studies in the USA,[56,289] China,[236-238] Colombia,[54] Kenya,[55] and across six countries in East Africa [290] by using the recent global monthly $PM_{2.5}$ estimates. This estimate was derived by combining multiple satellite retrievals of aerosol optical depth, chemical transport models, and ground-based measurements at a fine spatial resolution of 0.01° × 0.01° (~1 km × 1 km).[45] To address the epidemiological gaps identified above, this study aimed to investigate state-wide monthly $PM_{2.5}$ exposure at maternal residences and the hazards of term SGA, LGA, and LBW in Western Australia. DLM and DLNM Cox proportional hazard models were conducted to identify potential critical periods of exposure susceptibility from three months of preconception to birth and interaction with biothermal stress. Biological and sociodemographic vulnerable subpopulations were also identified by performing several stratified analyses.

5.3 Methods

The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines were followed in the analysis and reporting of results.[239]

5.3.1 Study area, design, and population

The study area, design, and population have been described in the previous Chapter 4 section 4.3.1. The eligibility criteria, however, differed slightly. From a total of 474,835 births, we excluded births with missing SA1 (n=35,352), gestational age (n=1021), and sex (n=5). We also excluded multiple births (n=13,018), births with a questionable birth weight of <400g or >6000g (n = 858), [62,291] gestational age outside the range of 22-42 completed weeks (n = 768), and births to mothers >50 years old (n = 7). To account for the potential fixed or truncated cohort bias, [101,241] we created a cohort defined by the date of conception and further excluded pregnancies with conception dates < 22 weeks before the beginning of the cohort (women who conceived before 31st July 1999, n= 7,309) and > 42 weeks before the cohort ended (women who conceived after 12th March 2015, n= 1,433).[68,101] Births with incompatible address or SA1 with missing $PM_{2.5}$ exposure were excluded (n=505). Preterm births were also excluded (n= 29,677). The final sample included in this study was 384,882 singleton term births (Figure S5.1). Using term births enabled the estimation of the *direct effects* of the exposure on fetal growth independent of preterm birth.[255,292,293]

5.3.2 Outcomes assessment

Adverse fetal growth outcomes considered were term SGA, LGA, and LBW. Gestational age was calculated from the perinatal records as the difference between the date of birth and the start of pregnancy based on the best available clinical estimates from ultrasonography or the last menstrual period if ultrasound was not available. Term SGA and LGA were defined as births at ≥37 weeks' gestation with a birth weight below the 10th centile and more than the 90th centile, respectively, for sex-specific gestational age using the study population. Term LBW was defined as births with birth weight < 2500 g at ≥37 weeks' gestation.[280]

5.3.3 Covariates

The included covariates have been described in the previous Chapter 4 section 4.3.3.

5.3.4 Environmental exposures assessment

Environmental exposures assessed were $PM_{2.5}$ concentrations as the main exposure and Universal Thermal Climate Index (UTCI) as a confounder and for investigating interactive association. Details on the exposure data sources and monthly $PM_{2.5}$ and UTCI assignment for each birth from three months preconception to birth and cumulative exposures by trimesters, preconception, and entire pregnancy have been described in the previous Chapter 4 section 4.3.4.

5.3.5 Statistical analyses

The same statistical analyses at the individual level as described in the previous Chapter 4 section 4.3.5 was performed with only slight modifications regarding the cross-basis matrices. Briefly, DLM or DLNM Cox proportional hazard (Cox PH) regression using gestational age as the time axis for the exposure lag space was performed to explore the monthly $PM_{2.5}$ exposure-lag-response associations with adverse fetal growth outcomes as reported previously.[62,67,69,232,287] The maximum lag dimension was 13 months (3 months preconception up to 42 gestational weeks or 10 months). Cross-basis matrices were constructed with R package 'dlnm' and entered a standard Cox PH regression.[59,60] Previous studies assumed linear exposure-response association and fitted only DLM for easy interpretation of the exposure-response association as per exposure reference increment (usually 10 $\mu g/m^3$ increment).[62,67,69,232,287] However, both DLM and DLNM were fitted in this study and results were reported in the context of national and international air quality guidelines as reported elsewhere.[243] In the DLM method that used linear exposure-response function, the lag distribution of $PM_{2.5}$ (lag-response) was modelled with natural cubic splines. The optimal degree of freedoms (*dfs*) after testing 2-7 *dfs* based on the minimum Akaike Information Criterion (AIC) were 5 *df* for term LGA and 3 *df* for both term SGA and term LBW. In the DLNM method, both $PM_{2.5}$ exposure and lag space dimensions were modelled with natural cubic splines. The optimal *dfs* were 2 and 5 in $PM_{2.5}$ exposure and lag space dimensions, respectively, for term LGA and 2 and 3 in $PM_{2.5}$ exposure and lag space dimensions, respectively, for both term SGA and term LBW.

The estimations of monthly and cumulative adjusted hazard ratios (HRs) and the 95% confidence intervals (HRs, 95% CIs) in the context of WHO AQGs and Australian AQG, confounding adjustments, stratified, and interactive effects analyses described in the previous Chapter 4 section 4.3.5 were applied here. Critical susceptible exposure periods were identified as those months in which 95% CI excluded the null.

5.3.6 Sensitivity analyses

The stability of the main monthly exposure-lag-response results was examined by performing several sensitivity analyses. (i) the *dfs* in the natural cubic spline was increased by one for both $PM_{2.5}$ exposure and lag period in the cross-basis function. (ii) maternal age was included as a categorical variable (≤19, 20-34, ≥35 years) instead of as a natural spline of the continuous covariate. (iii) seasonality was adjusted with the season of conception (autumn, winter, spring, summer) instead of the month of conception (1 to 12). (iv) *df* for UTCI was increased by one to four. (v) the model was adjusted for mother-specific clusters to account for repeated births by the same mother. (vi) the model was adjusted for local government area-specific clusters to account for potential spatial clustering and maternal mobility. The local government area is a subdivision of the state in Australia. (vii) all eligible singleton births with 22-42 gestational weeks were analysed. Informed by lower AIC of the main models from DLM and DLNM, sensitivity analyses were fitted from DLNM.

All statistical analyses were performed using the statistical software R 4.2.1 (R Development Core Team 2020), and main R packages ‘dlnm’, ‘splines’, and ‘survival’ were used. We reported and interpreted the HRs (95% CI) without considering any ‘statistically significant’ threshold as recommended by the American Statistical Association.[181]

5.4 Results

4.4.1 Characteristics of the study population and environmental exposures

A total of 384,882 singleton term births were analysed which included 37,677 (9.8%) SGA, 38,184 (9.9%) LGA, and 6,441 (1.7%) LBW. Slightly above half of the births were male (51.0%), and the majority were from mothers who were 20-34 years old (75.6%), Caucasian (78.7%), married (87.7%), non-smokers (85.8%), multiparous (58.3%), and urban residents (61.9%). Births were distributed equally among the four seasons of conception (Table 5.1).

The mean (standard deviation) and median (interquartile range) of $PM_{2.5}$ exposure during preconception to birth were the same, 8.1 (1.0) $\mu g/m^3$ and 8.1 (1.2) $\mu g/m^3$, respectively. This was equivalent to the annual average of Australian AQG for $PM_{2.5}$ concentration of 8 μg/m^3 [252] which was lower than the former annual WHO AQG (10 μg/m^3) but exceeded the new recommended limit of 5 μg/m^3.[2] The specific average exposures for preconception, pregnancy and each trimester were almost the same as that of the full exposure period. The mean (standard deviation) and median (interquartile range) of UTCI exposure were 14.5 (2.5) ˚C and 14.2 (1.2) ˚C, respectively, for the full exposure period and these were almost the same as the specific cumulative exposure periods (Table 5.2).

Table 5.1 Maternal characteristics of included singleton term births in Western Australia, 2000-2015 (N= 384,882)

Characteristics	n (%)	Characteristics	n (%)
SGA		*Smoking status*	
No	347,205 (90.2)	No	330,211 (85.8)
Yes	37,677 (9.8)	Yes	54,664 (14.2)
LGA		Unknown	7 (0.0)
No	346,698 (90.1)	*Parity*	
Yes	38,184 (9.9)	Nulliparity	160,532 (41.7)
LBW		Multiparity	224,350 (58.3)
No	378,441 (98.3)	*Remoteness indicator*	
Yes	6,441 (1.7)	Urban	238,412 (61.9)
Infant sex		Rural	146,336 (38.0)
Male	196,153 (51.0)	Unknown	134 (0.0)
Female	188,729 (49.0)	*SES*	
Maternal age (years)		High	127,831 (33.2)
≤19	17,163 (4.5)	Moderate	128,246 (33.3)
20-34	291,102 (75.6)	Low	128,784 (33.5)
≥35	76,617 (19.9)	Unknown	21 (0.0)
Race/ethnicity		*Season of conception*	
Caucasian	302,965 (78.7)	Autumn	93,576 (24.3)
Non-Caucasian	81,917 (21.3)	Winter	97,867 (25.4)
Marital status		Spring	97,129 (25.2)
Married	337,379 (87.7)	Summer	96,310 (25.0)
Unmarried	47,503 (12.3)		

Note: SES, Socioeconomic status; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight

Table 5.2. Descriptive statistics of the monthly environmental exposures for three months preconception through to birth delivery for included singleton term births in Western Australia, 2000-2015 (N= 384,882)

Exposure	Exposure period	Min	Mean ± SD	P25	Median	P75	IQR	Max
$PM_{2.5}$ ($\mu g/m^3$)	Preconception to pregnancy	3.8	8.1 ±1.0	7.5	8.1	8.7	1.2	17.8
	Preconception	1.0	8.1 ± 1.5	7.3	7.9	8.7	1.4	27.6
	Pregnancy	2.9	8.1 ± 1.1	7.5	8.0	8.7	1.2	20.5
	1st Trimester	1.3	8.1 ± 1.5	7.3	7.9	8.7	1.4	27.6
	2nd Trimester	0.8	8.1 ± 1.5	7.3	7.9	8.7	1.4	27.6
	3rd Trimester	0.0	8.1 ± 1.5	7.3	7.9	8.7	1.4	26.4
UTCI (˚C)	Preconception to pregnancy	8.0	14.5 ± 2.5	13.6	14.2	14.8	1.2	30.2
	Preconception	1.6	14.4 ± 5.1	9.8	14.0	18.5	8.7	35.8
	Pregnancy	6.6	14.5 ± 2.8	12.9	14.2	15.5	2.6	32.7
	1st Trimester	1.6	14.5 ± 5.2	9.8	14.1	18.7	8.9	36.0
	2nd Trimester	1.7	14.6 ± 5.2	10.0	14.2	18.7	8.7	36.1
	3rd Trimester	1.5	14.5 ± 5.1	9.9	14.0	18.5	8.6	35.7

Note: SD, standard deviation; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm; UTCI, Universal Thermal Climate Index; P25 and P75, 25th and 75th centiles; IQR, Interquartile range= P75-P25

5.4.2 Maternal $PM_{2.5}$ exposure and the hazards of term adverse fetal growth

The DLNM method performed better than the DLM method for all adverse fetal growth outcomes based on the lowest AIC, but the results were generally consistent. The monthly exposure-lag-response associations from the DLM method showed very small higher hazards of SGA during 3rd–5th gestational months that included null in the confidence intervals for incremental exposures to 10 $\mu g/m^3$, 8 $\mu g/m^3$, 5 $\mu g/m^{3,}$ and 3 $\mu g/m^3$, using 0 $\mu g/m^3$ as a reference. Preconception months and 7th–10th gestational months showed very small lower hazards of term SGA (Figure 5.1, Table S5.2). Similarly, estimates from DLNM showed very small higher hazards of term SGA that increased marginally with the intensity of the $PM_{2.5}$ exposure with reference to 5 $\mu g/m^3$ during the 2nd–6th gestational months, all of which included null in the confidence intervals. $PM_{2.5}$ exposure above the median (90th to 99th centile) with reference to 5 $\mu g/m^3$ during the 4th gestational month was associated with term SGA, 1.01 (95% CI 1.00, 1.02). Preconception months and 7th–10th gestational months showed very small lower hazards or essentially no association and the lowest hazard was 0.98 (95% CI 0.96, 1.01) at the 99th centile during the 3rd preconception month (Figure 5.2, Table S5.3). Regarding cumulative exposures, only entire pregnancy exposure was associated with higher hazards of term SGA, 1.03 (95% CI 0.98, 1.09) for 5 $\mu g/m^3$ $PM_{2.5}$ increase or 1.06 (95% CI 0.95, 1.18) for 10 $\mu g/m^3$ $PM_{2.5}$ increase while preconception and trimester-specific estimates did not show any association (Table 5.3).

From the DLM method, exposures at the standard guidelines (10 $\mu g/m^3$, 8 $\mu g/m^3$, 5 $\mu g/m^{3,}$ and 3 $\mu g/m^3$) for monthly $PM_{2.5}$ exposures showed very small lower hazards of term LGA during the preconception period, very small higher hazards during the 1st gestational month and no association during the remaining gestational months (Figure 5.1, Table S5.4). DLNM method with better precision showed small lower hazards of term LGA during the third to second months preconception. But there were small higher hazards during the first preconception to first gestational months which increased slightly with $PM_{2.5}$ exposure intensity, and essentially no association thereafter for exposure at the various thresholds of $PM_{2.5}$ exposures as compared to 5 μg/m^3. The lowest and largest hazards of term LGA were 0.90 (95% CI 0.86, 0.94) during 2nd preconception month and 1.03 (95% CI 1.00, 1.05) during 1st gestational month, respectively, at the 99th centile (9.4 μg/m^3) as compared to 5 μg/m^3. (Figure 5.2, Table S5.5).

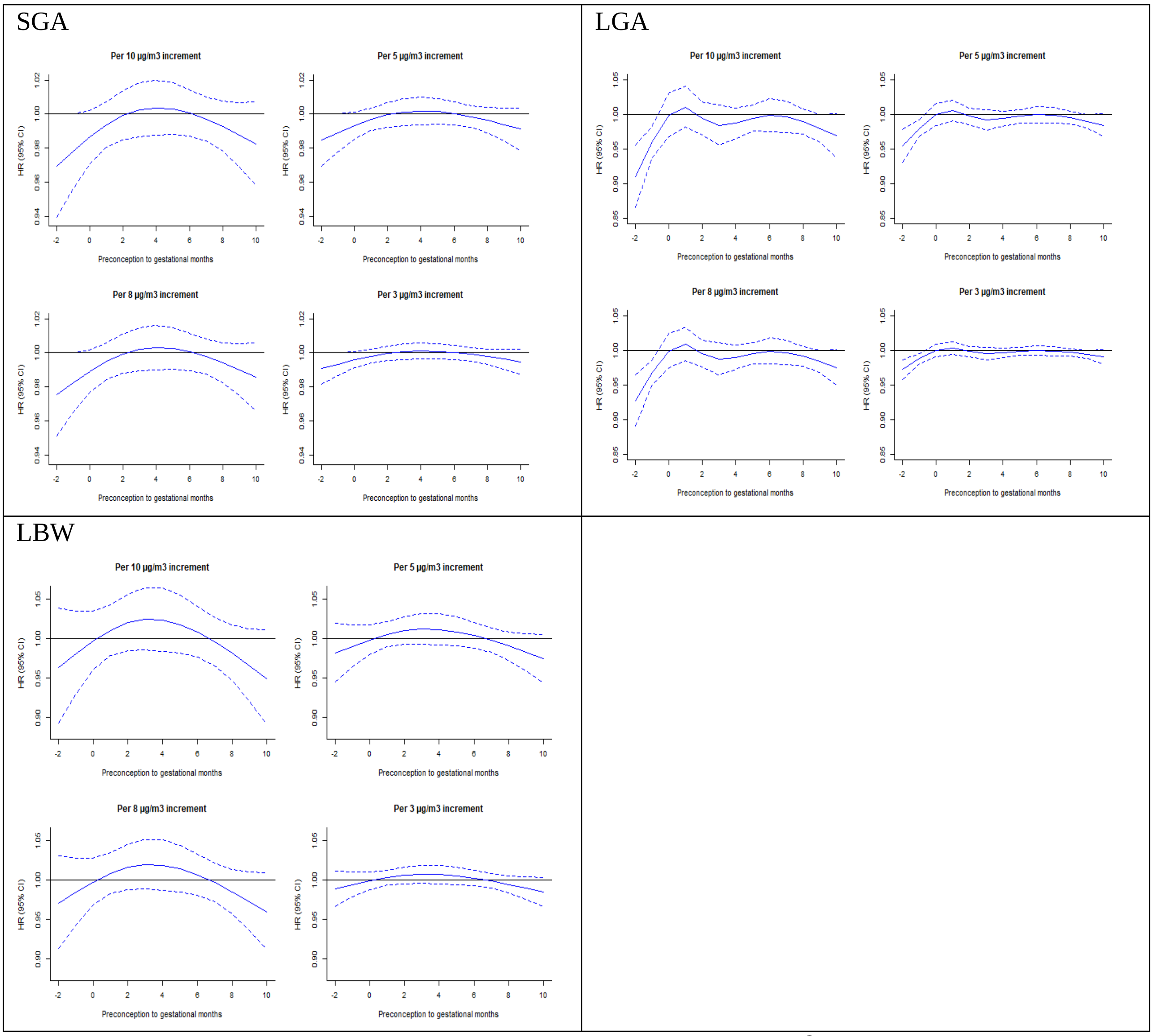

Figure 5.1. Adjusted hazard ratios for the association between 10, 8, 5, and 3μg/m^3 increase in $PM_{2.5}$ exposure and risks of term adverse fetal growth, by month of gestation from three months preconception (-2 to 0) to birth (1 to 10) in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, year and month of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm.

All cumulative exposures showed very small lower hazards or essentially no association with the term LGA (Table 5.3).

The hazards of the term LBW, as estimated from the DLM method, showed very small effects that included the null but increased slightly with increasing exposure at 3 μg/m^3, 5 μg/m^3, 8 μg/m^{3,} and 10 μg/m^3 as compared to no exposure (0 μg/m^3). The higher hazard of term LBW was found during the 1st–6th gestational months while exposure during preconception and 7th–10th gestational months showed a very small lower hazard (Figure 5.1, Table S5.6).

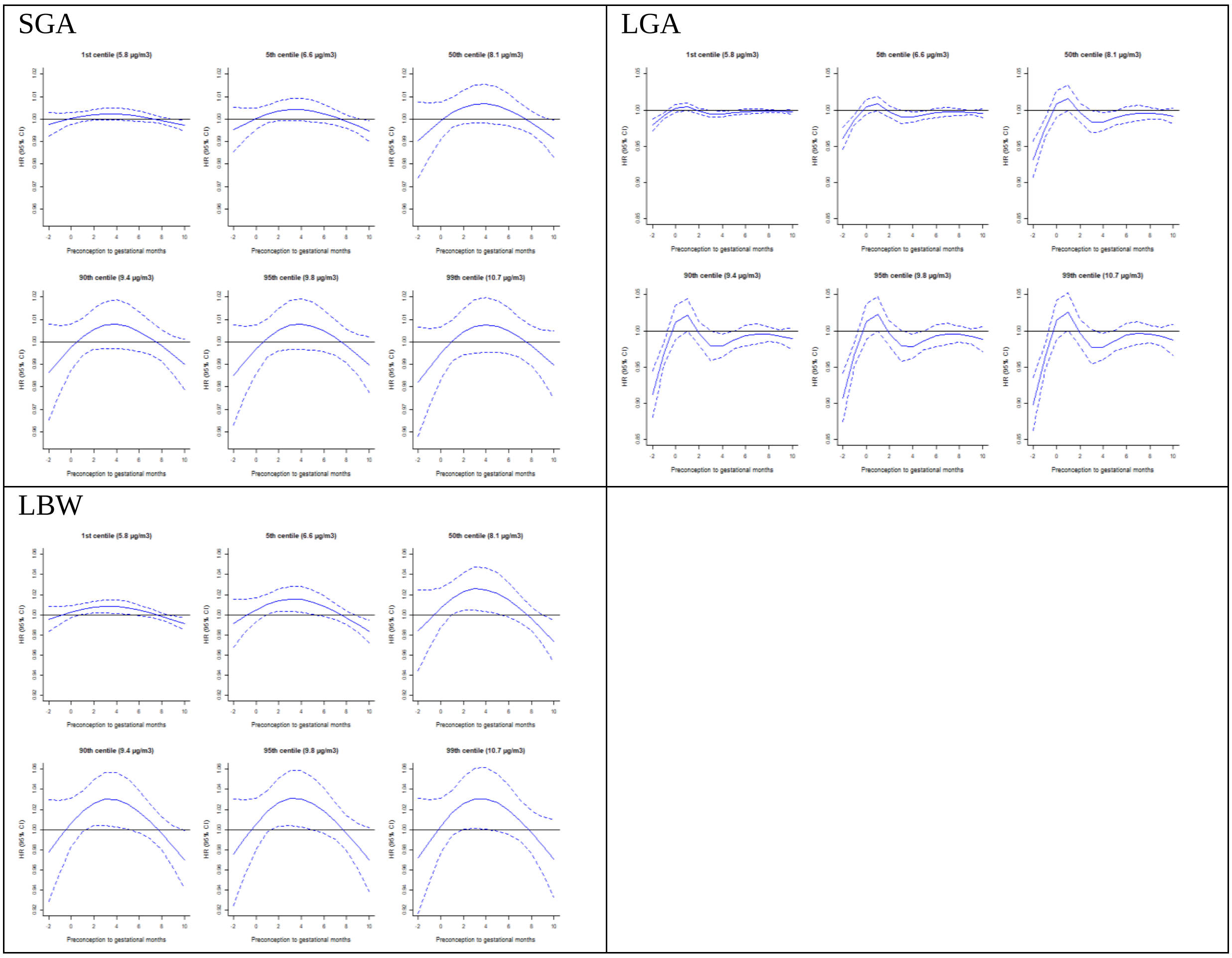

Figure 5.2. Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5μg/m^3 $PM_{2.5}$ as a reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

Similarly, the effect estimates from the DLNM method with better precision indicated higher hazards of term LBW which increased slightly with the intensity of $PM_{2.5}$ exposures as compared to 5 μg/m^3 during the 1st preconception–7th gestational months. The largest hazard of term LBW which showed a critical susceptible exposure period (that is, did not include null in the confidence intervals) was 1.03 (95% CI 1.01, 1.05) at 50th centile (8.1 μg/m^3) $PM_{2.5}$ exposure as compared to 5 μg/m^3 during the 3rd gestational month within 2nd–4th gestational months. The 3rd and 2nd preconception months and 8th–10th gestational months showed very small lower hazards and the lowest hazard of term LBW was 0.97 (0.95, 1.00) during the 10th gestational months at 50th centile exposure as compared to 5 μg/m^3 (Figure 5.2, Table S5.7).

All cumulative exposures showed higher hazards of term LBW, except the second trimester which showed essentially no association. For example, 5 μg/m^3 $PM_{2.5}$ exposure increment showed the same hazards for preconception and pregnancy, 1.08 (95% CI 0.95, 1.23) and the largest trimester-specific hazard was 1.02 (95% CI 0.93, 1.12) during the first trimester (Table 5.3).

Table 5.3 Adjusted hazard ratios per 5 and 10 μg/m^3 $PM_{2.5}$ increments for adverse fetal growth for cumulative $PM_{2.5}$ exposures over three months preconception through to pregnancy and trimester-specific periods in Western Australia, 2000–2015.

Exposure period	$PM_{2.5}$	SGA	LGA	LBW
Preconception to pregnancy	5	0.97 (0.91, 1.02)	0.90 (0.85, 0.95)	1.02 (0.89, 1.16)
	10	0.94 (0.84, 1.05)	0.81 (0.72, 0.91)	1.03 (0.79, 1.34)
Preconception	5	0.95 (0.92, 0.99)	0.92 (0.89, 0.96)	1.08 (0.95, 1.23)
	10	0.91 (0.84, 0.98)	0.85 (0.79, 0.92)	1.17 (0.91, 1.51)
Pregnancy	5	1.03 (0.98, 1.09)	0.99 (0.94, 1.04)	1.08 (0.95, 1.23)
	10	1.06 (0.95, 1.18)	0.98 (0.88, 1.09)	1.17 (0.91, 1.51)
1st Trimester	5	0.98 (0.95, 1.02)	0.95 (0.92, 0.99)	1.02 (0.93, 1.12)
	10	0.97 (0.89, 1.04)	0.91 (0.84, 0.98)	1.04 (0.86, 1.25)
2nd Trimester	5	1.00 (0.96, 1.04)	1.00 (0.96, 1.04)	0.99 (0.90, 1.09)
	10	1.00 (0.92, 1.08)	1.00 (0.92, 1.08)	0.97 (0.80, 1.18)
3rd Trimester	5	1.00 (0.96, 1.04)	0.97 (0.93, 1.01)	1.01 (0.93, 1.11)
	10	1.01 (0.93, 1.09)	0.94 (0.87, 1.02)	1.03 (0.86, 1.23)

Note: HR, hazard ratios; CI, Confidence Intervals; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year and month of conception, and Universal Thermal Climate Index exposure.

5.4.3 Interaction and modification effects

The ratio of hazard ratios estimation with the Altman and Bland test of interaction effects[257,258] indicated interactive associations between $PM_{2.5}$ and UTCI exposures on term adverse fetal growth for 5 μg/m^3 $PM_{2.5}$ exposure increment in moderate and high UTCI as compared to low UTCI exposure. Specifically, the interaction effect was more elevated in moderate UTCI exposure for the hazard of term SGA, 1.15 (95% CI 0.97, 1.36), high UTCI exposure for the hazard of term LGA, 1.14 (95% CI 0.99, 1.32) and moderate UTCI exposure for the hazard of term LBW, 1.31 (95% CI 0.86, 1.98) (Table 5.4).

Stratified analyses indicated comparatively elevated hazards of $PM_{2.5}$ exposure in female births for both term SGA and LBW but in male births for term LGA (Figure S5.2), non-Caucasians for all birth outcomes (Figure S5.3), and mothers aged 20–34 years for both term SGA and LBW but no obvious difference for term LGA (Figure S5.4). The estimated hazards were elevated in high SES for both term SGA and LBW with critical susceptible exposure periods during 1st–5th gestational

Table 5.4 Interaction effects as the ratio of hazard ratios per 5 μg/m^3 $PM_{2.5}$ increment for adverse fetal growth for preconception to pregnancy cumulative $PM_{2.5}$ exposures in moderate and high UTCI exposure, using low UTCI as a reference in Western Australia, 2000-2015.

	SGA		LGA		LBW	
UTCI level	HR (95% CI)	RHR	HR (95% CI)	RHR	HR (95% CI)	RHR
Low	0.92 (0.82, 1.04)	Reference	0.83 (0.74, 0.93)	Reference	0.85 (0.63, 1.14)	Reference
Moderate	1.06 (0.94, 1.19)	1.15 (0.97, 1.36)	0.90 (0.81, 1.01)	1.08 (0.93, 1.27)	1.11 (0.83, 1.49)	1.31 (0.86, 1.98)
High	0.94 (0.88, 1.02)	1.02 (0.89, 1.18)	0.95 (0.87, 1.03)	1.14 (0.99, 1.32)	1.01 (0.85, 1.20)	1.19 (0.84, 1.67)

Note: HR, hazard ratios; CI, Confidence Intervals; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight; UTCI, Universal Thermal Climate Index; RHR, ratio of hazard ratios.

months for term LBW, but in moderate SES for term LGA (Figure S5.5). For remoteness or place of residence (urban or rural), estimated hazards showed no obvious difference for term SGA but elevated in rural for both term LGA and LBW with particularly observable critical susceptible exposure periods during 1st–5th gestational months for term LBW (Figure S5.6). Maternal smoking status showed no obvious difference for term SGA, but the hazards were elevated in smokers with observable critical susceptible exposure periods of 1st and 3rd–5th gestational months for term LGA and LBW, respectively (Figure S5.7). The hazards were elevated in multiparous mothers for term SGA, but in nulliparous mothers for both term LGA and LBW (Figure S5.8). For all birth outcomes, hazards were elevated in unmarried mothers (Figure S5.9) and mothers with any complicated pregnancy (Figure S5.10).

5.4.4 Sensitivity

All sensitivity analyses described earlier showed almost similar results and critical susceptible exposure periods (where identified in the main results) as compared to the main analyses. This implies the robustness of the results under the model assumptions and conditions (Figure S4.11-S4.17).

5.5 Discussion

5.5.1 Main findings

This was the first investigation of the monthly exposure-lag-response association between ambient $PM_{2.5}$ and fetal growth outcomes in Australia. Monthly $PM_{2.5}$ exposure showed small dose-response associations with the term SGA, LGA, and LBW, especially from the DLNM method which was more precise than the DLM method. Although a critical susceptible $PM_{2.5}$ exposure period was not identified for term SGA and LGA, relatively small higher hazards were found during the 2nd–6th gestational months for SGA and the first month of preconception to the first gestational month for LGA. Exposures outside these periods showed very small protective effects. $PM_{2.5}$ exposure showed lower hazards of term LBW during parts of preconception and late gestational months but higher hazards during the 1st preconception–7th gestational months with a critical susceptible period during the 3rd gestational month. For cumulative exposures, including trimester-specific estimates, only entire pregnancy exposure was associated with higher hazards of term SGA and all cumulative exposures showed very small protective effects or essentially no association with term LGA. For term LBW, all but the second trimester showed higher hazards, and the largest trimester-specific hazard was found in the first trimester. Generally, $PM_{2.5}$ exposure during preconception months and 8th–10th gestational months showed small protective effects while exposure during 1st–7th gestational months showed small positive associations, especially for term LBW and SGA.

The results also showed interactive effects of $PM_{2.5}$ exposure and biothermal stress (UTCI) in either moderate or high UTCI exposures. There were biological and sociodemographic disparities that varied slightly among the birth outcomes, but consistently elevated hazards were found in mothers who were non-Caucasian, unmarried, and with any complicated pregnancy as compared to their counterparts for all birth outcomes. For term LBW, critical susceptible exposure periods were found in high SES, rural, and smokers.

In a search for critical susceptible exposure periods with unbiased effect estimates, few recent studies applied DLM to investigate weekly $PM_{2.5}$ exposure-lag-response association and the hazards of term SGA, LGA, and LBW [67,69,232,287] as recommended elsewhere.[58,59] Only two Chinese studies reported on $PM_{2.5}$ exposure and SGA. One study found critical susceptible exposure periods during the 1st–9th preconception weeks and 1st–2nd gestational weeks, with the largest hazard of 1.06 (95% CI 1.03, 1.09) for a 10 $\mu g/m^3$ increase during the 5th preconception week in Tianjin, China with a mean (standard deviation) of 71.4 (6.8) $\mu g/m^3$ $PM_{2.5}$ exposure.[69] The second study found extremely small odds or essentially no association from 16 counties of eight provinces in China where a mean (standard deviation) $PM_{2.5}$ exposure was 50.7 (25.7) $\mu g/m^3$.[287] The findings by Chen *et al* across the eight provinces in China [287] were somewhat consistent with the DLM results reported in the present study but DLNM results showed small higher hazards of term SGA during 2nd–6th gestational months. On the other hand, the higher hazards with critical susceptible exposure periods detected by Chen *et al* in Tianjin, China [69] could be due to the very high $PM_{2.5}$ exposure, differences in composition or sources of exposure, weekly exposure assessment, and population characteristics as compared to the results in the present study with monthly $PM_{2.5}$ exposure and low concentration. That same study was the only comparative study for LGA and the authors found critical susceptible exposure periods during 1^{st}–12^{th} preconception weeks and 1^{st}–5^{th} gestational weeks, with the largest hazard of 1.10 (95% CI 1.08, 1.12) in the 7^{th} preconception week per 10 μg/m^3 increment.[69] The findings were contrary to the present study with comparatively very low exposure levels where we found very small protective effects during preconception periods and most of the gestational months, except a very small positive association during the first gestational month per 10 μg/m^3 increase. This could be due to the reasons given earlier but more related studies from other geodemographic settings are required, given the very limited evidence on LGA. Another two Chinese studies reported weekly or monthly $PM_{2.5}$ exposure and term LBW.[67,232] Yuan *et al* found critical susceptible exposure periods of 39^{th}–42^{nd} gestational weeks (9^{th}–10^{th} months) with the largest hazard of 1.08 (95% CI 1.02, 1.14) for a 10 μg/m^3 increase in the 42^{nd} gestational week in Shanghai with an average of 49.3 (5.0) μg/m^3 $PM_{2.5}$ exposure.[232] The second study with an average of 94.5 (25.4) μg/m^3 $PM_{2.5}$ exposure in Henan found critical susceptible exposure periods during 4^{th}–5^{th} gestational months for LBW but not for term LBW which showed higher hazards in the same period that included null in the confidence intervals for a 10 μg/m^3 $PM_{2.5}$ increase.[67] This was closely consistent with the 1^{st}–6^{th} gestational months found in the present study in a low-exposure setting. Together with previous studies,[67,69,232,287] early up to the beginning of mid-gestational months mostly appear to be critical susceptible periods for fetal growth outcomes. Also, apart from Yuan *et al* that found critical susceptible periods during late gestational periods for LBW, previous studies found small protective effects of $PM_{2.5}$ exposure on SGA, LGA, and LBW during late gestational periods [67,69,287] as found in the present study. This could be because pregnant women would generally take perinatal care precautions more seriously during the late stages of pregnancy, which may include reducing outdoor activities, hence exposures, leading to a lower risk of fetal growth outcomes during these periods. Further studies are required. Early pregnancy periods (embryo implantation, vascularisation, and placentation) in particular, and late pregnancy periods with the fastest fetal development are likely sensitive periods.[294,295] Moreover, many biological processes, including the effects of air pollution on birth outcomes, exhibit feedback control and continuous predictors may behave non-linearly.[294] Thus, both DLM and DLNM should be considered in future studies rather than assuming linear $PM_{2.5}$ exposure-outcome association. This was further shown in a recent study that defined $PM_{2.5}$ wave as $PM_{2.5}$ concentration exceeding specified centiles for at least 2, 3, or 4 consecutive days and found that longer duration and higher thresholds of $PM_{2.5}$ concentration elevated the hazards of SGA and LGA.[296] Our study found small protective effects during preconception periods which could be due to exposure misclassification as the exposure was assessed based on a maternal residential address at the time of birth. However, findings from extremely polluted settings indicated that preconception $PM_{2.5}$ exposures were also associated with higher hazards of SGA and LGA.[69,296] This implies that preconception exposure periods, especially in high-$PM_{2.5}$ exposure settings could also be given public health attention by women of reproductive age and clinicians.[110,274] This is important in achieving Sustainable Development Goal 3[228] which requires society-wide approaches (see '4.5.4 Public health strategies and policies' section in the previous Chapter 4).

5.5.2 Interactive association and modification effects

Similar pathophysiological pathways of $PM_{2.5}$ and ambient temperature on birth outcomes[125,297] explain the elevated interactive effects of the two environmental exposures on the fetal growth outcomes found in this study and a few previous studies.[234,263,264] This has serious public health implications as climate change increases with direct and indirect impacts on human health and further elevation of the effects of air pollution.[7] With emerging experimental and epidemiologic evidence for climate change, air pollution, especially $PM_{2.5}$, and other environmental endocrine-disrupting chemicals in the pathophysiology of pregnancy or birth outcomes and across the life course, actionable prevention and mitigation strategies are urgently needed now.[10,125,274,298] Some subgroups of mothers such as those with any pregnancy complications,[266] unmarried, smoking during pregnancy,[197] residing in rural areas, and racial minority groups (non-Caucasians)[158] are disproportionately more vulnerable to environmental exposures. Most of these subpopulations often contribute the least to these environmental exposures but suffer the most and this recognised environmental injustice deserves consideration by governments and policymakers for targeted interventions.[273,298] Sexual dimorphic effect was not consistent across all birth outcomes because female births were at higher hazards for term SGA and LBW [67] but male birth for term LGA. This suggests that the sex differential effects of $PM_{2.5}$ on fetal growth may depend on the specific fetal growth outcome. The unexpected high hazards of adverse fetal growth in moderate or high SES as reported elsewhere [67] could be due to high vehicular movements and industrial activities in these areas as compared to low SES areas. However, nuanced SES indicators at the individual level such as education, employment status, or occupation should be collected in future studies to better understand the modification effect of SES. A systematic review and meta-analysis concluded that mothers with low educational levels are more vulnerable to the impacts of particulate matter on birth outcomes in the United States.[158]

5.5.3 Plausible pathophysiologic mechanism

The potential pathophysiological and biological mechanisms of $PM_{2.5}$ exposure on pregnancy and birth outcomes are not fully clarified. Yet several epidemiological, toxicological, *in vivo* models and *omic*s or epigenetic studies have provided many plausible pathways as summarised in the published umbrella review [125] presented in Chapter 3 and also in the previous Chapter 4 section 4.5.3. Briefly, the high diffusion and inhalation capacity of $PM_{2.5}$ leads to easy intake of ambient $PM_{2.5}$ into the respiratory system and subsequently transported into other systems, including translocation across the fetoplacental barrier. Reactive oxidising species in $PM_{2.5}$ induce systemic oxidative stress, immune-inflammatory and cardiovascular responses, and cellular and molecular processes that disrupt placental development and physiology. These cause hemodynamic alterations in the placenta which impair the fetoplacental transport of water, oxygen, and nutrients to the developing fetus with consequential intrauterine growth restrictions such as SGA and LBW.[26,125,267,294] Unlike SGA and LBW, biological mechanisms linking maternal $PM_{2.5}$ exposure to LGA are less studied. However, animal and clinical studies indicated that systemic oxidative stress and immune-inflammatory responses can cause maternal hyperglycaemia (high blood glucose) which is transportable to the developing fetus. This together with the extra insulin produced by the fetus increase adipose fat deposition and weight gain, resulting in an increased risk of LGA.[299-301]

5.5.4 Strengths and limitations

This study added to the very limited epidemiological evidence on maternal $PM_{2.5}$ exposure and the adverse fetal growth outcomes with the exploration of potential critical susceptible exposure periods and interactive effects with biothermal stress. All strengths and limitations described in previous Chapter 4 section 4.5.5 are applicable here.

5.6 Conclusion

Space-time varying $PM_{2.5}$ concentrations were linked with singleton term births in Western Australia to investigate the monthly exposure-lag-response associations between $PM_{2.5}$ exposure from three months of preconception to birth and the hazards of adverse fetal growth outcomes (SGA, LGA, and LBW). Generally, $PM_{2.5}$ exposure during preconception months and late (8^{th}–10^{th}) gestational months showed small protective effects while exposure during early to mid-gestational months (1^{st}–7^{th} months) showed small positive associations, especially for term LBW and SGA. There were negligible associations of trimester-average exposures with the term SGA and LGA, but LBW showed higher hazard with the largest hazard found in the first trimester. The results also showed interactive effects of $PM_{2.5}$ exposure and biothermal stress on birth outcomes. For all birth outcomes, consistently elevated hazards were found in non-Caucasian, unmarried, and mothers with any complicated pregnancy. Also, critical susceptible exposure periods were found in high SES, rural, and smokers for term LBW. Together with a few previous studies, all from China,[67,69,232,287] early pregnancy periods mostly appear to be sensitive exposure periods while late pregnancy periods may be protective periods. Further epidemiological and biological mechanism investigations from other geodemographic settings are required to optimise public health interventions.

Chapter 6. Long-term maternal exposure to ambient fine particulate matter and the risk of stillbirth in Ghana

6.0 Preamble

This chapter provides a primary investigation of the association between maternal exposure to monthly fine particulate matter air pollution ($PM_{2.5}$) and the risk of stillbirth in Ghana. Prior to the availability of monthly satellite-derived gridded $PM_{2.5}$ concentration,[45] annual $PM_{2.5}$ concentration [47] was used to assess three types of $PM_{2.5}$ exposure (all-sources, total mass; anthropogenic sources, total mass with dust/sea salts removed; and natural sources, total mass $PM_{2.5}$ minus anthropogenic $PM_{2.5}$). Applying difference-in-differences design with conditional quasi-Poisson regression analysis, small magnitudes of positive associations between long-term $PM_{2.5}$ exposure and stillbirth and with the same magnitude for both natural and anthropogenic $PM_{2.5}$ sources were found in Ghana. The results were published in *Atmospheric Pollution Research*.[302] To identify plausible critical susceptible exposure periods, the new monthly $PM_{2.5}$ concentration was used to investigate the monthly exposure-lag-response association between $PM_{2.5}$ exposure and stillbirth in this chapter. This knowledge is very important to guide the critical time for public health intervention and understanding biological mechanisms.

6.1 Abstract

Introduction*:* Few studies examined the association between long-term maternal exposure to fine particulate matter air pollution ($PM_{2.5}$) and stillbirth and fewer still from African countries. Also, critical susceptible periods are unknown. Hence, this study aimed to investigate monthly exposure-lag-response associations between $PM_{2.5}$ and stillbirth to identify potential critical susceptible periods in Ghana.

Methods: A total of 5,961,328 births of which 90,532 (1.5%) were stillbirths at all 260 local districts between 1st January 2012 and 31st December 2020 was obtained from Ghana Health Service and linked with monthly $PM_{2.5}$ concentration. A within-space time-series design was conducted and analysed with a distributed lag linear or non-linear conditional quasi-Poisson regression.

Results: The overall mean (standard deviation) $PM_{2.5}$ exposure was 30.0 (17.9) μg/m^3. From distributed lag linear method, $PM_{2.5}$ showed a very small positive association with stillbirth which increased slightly with the exposure dosage. For example, the adjusted risk of stillbirth for 10 μg/m^3 increased in $PM_{2.5}$ exposure during the 6th month before birth was 1.01 (95% CI 1.00, 1.02). The distributed lag non-linear method with better precision showed a higher risk of stillbirth with increasing $PM_{2.5}$ exposure thresholds for both individual and cumulative lag exposures, using 5 $\mu g/m^3$ or 10 $\mu g/m^3$ as reference. $PM_{2.5}$ exposures above the 50^{th} centile showed critical susceptible exposure periods during the 6^{th}-7^{th} months before birth. The most elevated risk of stillbirth was 1.17 (95% CI 1.06, 1.28) and 1.14 (95% CI 1.05, 1.24) for $PM_{2.5}$ exposure at the 99^{th} centile during 6^{th} month before birth with reference to 5 $\mu g/m^3$ and 10 $\mu g/m^3$, respectively. The risk was more elevated in urban areas that were densely populated than in rural areas.

Conclusions: There was a small dose-response association between monthly $PM_{2.5}$ exposure and stillbirth in Ghana. The early stage of pregnancy (embryogenesis period) is a potentially critical susceptible exposure period for public health intervention and further biological mechanisms.

6.2 Introduction

One of the neglected health outcomes yet with considerable long-lasting psychosocial and economic impacts on families is stillbirth (a fetal death of at ≥ 28 weeks' gestation or at least birth weight of 1000 g if the gestational length is unknown).[303] Stillbirth is preventable but the rate is still high globally at 13.9 stillbirths per 1000 total births in 2019 with wide variations from 22.8 stillbirths in West and Central Africa to 2.9 per 1000 total births in Europe.[224] Low-to-middle-income countries (LMICs) accounted for 84% of the total stillbirths in 2019.[303] With an estimated global annual rate of reduction in stillbirth rate of 2.3% from 2000 to 2019, achieving the Sustainable Development Goal 3.2 (SDG 3.2) or the Newborn Action Plan target of ≤ 12 stillbirths per 1000 total births by 2030 [209,228,229] is very difficult. This is especially concerning in most Sub-Saharan Africa (SSA) countries which have not recorded any reduction in the stillbirth rate since 2000, suggesting increased investment for accelerated improvement. [224]

As part of the strategies for future prevention of stillbirth, comprehensive understanding, identification, and integration of non-traditional modifiable risk factors such as climate change and improved air quality has been recommended.[125,274,298] The accumulating epidemiological evidence is suggesting air pollution, especially fine particulate matter at ≤ 2.5 µm ($PM_{2.5}$) as a plausible risk factor for stillbirth.[125] The health and clinical impacts of air pollution and climate change are now being recognised by clinicians [274,298,304] as biological or pathophysiological mechanisms are being elucidated.[26,231,270,305] $PM_{2.5}$ is a complex mixture of toxic inorganic or heavy metals (e.g., Cadmium) and organic components, including polycyclic aromatic hydrocarbons.[3,270] The proposed underlying biological mechanisms whereby $PM_{2.5}$ causes adverse birth outcomes, including stillbirth are inducing intracellular oxidative stress, mutagenicity or genotoxicity, apoptosis, inflammatory responses, and disruption of the reproductive endocrine system.[26,231,270,305] In recognition of this and the documented evidence of the burden associated with air pollution, the World Health Organization (WHO) has recently updated Air Quality Guidelines (AQGs) and further recommended an annual $PM_{2.5}$ average of 5 µg/m^3 instead of 10 µg/m^3.[2] Although Africa or SSA countries are hotspot areas for both stillbirth [224] and $PM_{2.5}$ concentration,[186] the few current epidemiological evidence connecting $PM_{2.5}$ with stillbirths were mostly from high-income countries.[125] Little is known on this topic in Africa or SSA due to the challenges of collecting air quality data [211,306] and electronic maternal and child health registries for large-scale related population-based cohort investigations in LMICs, particularly in SSA.[97,125] To close this epidemiological gap in Africa, a recent study used the global satellite-based $PM_{2.5}$ estimates and stillbirths identified from the Demographic and Health Surveys (DHS) in 33 African countries and reported a positive association between entire pregnancy $PM_{2.5}$ exposure and the odds of stillbirths.[160] Those authors in another study combined the satellite-based $PM_{2.5}$ estimates and stillbirths identified from DHS in 54 LMICs which included SSA countries and results from previous meta-analyses to estimate that 0.83 million stillbirths in 2015 were attributable to $PM_{2.5}$ exposure above the 10 $\mu g/m^3$ reference level in 137 countries.[307] In addition to the need for country-specific related studies for locally and contextually tailored public health intervention, the previous studies in Africa relied on self-report stillbirth from survey data.[160,307] Underreporting and misreporting and other inherent bias, especially for pregnancy outcomes in the DHS due to stigma, psychosocial and socio-cultural beliefs have been documented.[308,309] Thus clinically determined stillbirth may help minimise the issues related with self-report stillbirth from survey data.

It is commonly known that environmental exposures often show protracted time-varying effects where the health effect measured at a time is the outcome of multiple exposure events at varying intensities in the past.[59,60] Thus, to obtain unbiased effect estimates or predictions and to better understand the pathophysiological processes linking environmental exposures to health outcomes, bi-dimensional associations that simultaneously describe both intensity (exposure-response) and timing of past exposures (lag-response) have been recommended.[58-60] This novel approach, known as distributed lag linear or non-linear models (DLM or DLNM) [59,60] has been applied to describe associations between $PM_{2.5}$ exposure and birth outcomes and to identify critical susceptible periods at fine temporal scales in several recent studies.[61,62,65,67-69,232,233] However, this high-quality methodology has not been applied to investigate the association between $PM_{2.5}$ and stillbirth in Africa, including Ghana. According to the 2021 World Air Quality Report, Ghana's population-weighted $PM_{2.5}$ concentration was 25.9 $\mu g/m^3$ in 2021, ranking Ghana as the 30th and 6th most polluted country globally and in Africa, respectively.[310] The country also has a high stillbirth prevalence of 2% based on the 2017 Ghana Maternal Health Surveys (GMHS) [93] with spatial variations, ranging from 2.1% to 3.2%.[311-313]

To fill in the research gaps outlined above, a spatiotemporal monthly $PM_{2.5}$ estimate [45] was linked to the clinically diagnosed stillbirths at local district levels obtained from Ghana Health Service to examine the distributed exposure-lag-response association between maternal long-term $PM_{2.5}$ exposure and stillbirth in Ghana.

6.3 Materials and Methods

This study was conducted according to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines.[239]

6.3.1 Study design, area, and population

A within-space time-series DLM and DLNM modelling study design was implemented. Some previous studies applied time-series DLNM analysis [59,60] to investigate exposure-lag-response associations between ambient air pollution or temperature and birth outcomes using aggregated time series data at a place, mostly for short-term effects.[119-121,245,246,314] To identify critical susceptible exposure periods, a few studies have also applied the time-series design with DLNM to investigate the long-term effects of maternal exposure to air pollution on low birth weight,[244] congenital heart disease,[247,315] and orofacial clefts.[248] Given the space-time varying dataset, the previously applied time-series design was extended to include spatial variations in the analysis, resulting in a variant of time-series termed within-space time-series DLM and DLNM. Specifically, variations within districts nested within regions were self-matched to control by design for spatially varying measured and unmeasured known and unknown confounders. This is a quasi-experimental design similar to randomised controlled trial where repeated measure is taken on the same participant (here local district) over the study period. The seasonal and long-term trends and potential temporal autocorrelation, under or over-dispersion were also controlled.[59,60]

Ghana is a coastal Sub-Saharan West African country with 30.8 million population at a growth rate of 2.1% and a population density of 129 persons/km^2 according to the 2021 census.[92] The country is administratively organised into non-overlapping 16 regions and further subdivided into 260 local districts with an average population size per district of 118,130 persons.[92] The local district is the lowest level for policy implementations and was the geographical unit of analysis in this study as the birth data were available as monthly counts at the district level. The country has a tropical and humid climate with two seasons characterised by the dry dusty winter or harmattan season (December-March) and the wet rainy summer season (April-November). The average temperature in the southern belt is 25°C to 27°C and 29°C to 31°C in the northern belt [316] where it can rise to 40°C.[317]

6.3.2 Birth data

Ghana just like most LMICs or SSA countries does not currently have nationwide individual-level electronic birth records.[97] However, the Centre for Health Information Management (CHIM) of the Ghana Health Service (GHS) recently started monthly collation of health information from public and private health facilities at district levels across the country and transfer to a centralised depository using the District Health Information Management System version 2 (DHIMS2).[99] These data are collated by district health directorates. District-level monthly stillbirths – defined as fetal death in pregnancies that lasted for at least seven months were obtained from the CHIM of GHS across the 260 districts from 1st January 2012 to 31st December 2020.

6.3.3 Environmental exposures assessment

The newly produced monthly $PM_{2.5}$ concentration was the main exposure assessed in this study. Monthly global satellite-based $PM_{2.5}$ estimates at a fine spatial resolution of 0.01° × 0.01° (~1 km × 1 km) were freely accessed from the Washington University Atmospheric Composition Analysis Group website as version V5.GL.01.[45] Detail descriptions of this dataset were provided elsewhere[45-47] and described briefly in the previous Chapter 4 section 4.3.4. The data was produced by combining multiple satellite retrievals of aerosol optical depth, chemical transport models, and ground-based measurements. Despite the high model performance of the $PM_{2.5}$ prediction (R^2 = 0.90–0.92),[45,47] the prediction could differ across or within countries and may be low in some areas, particularly in SSA countries such as Ghana with very limited ground-based monitoring measurements. In Ghana, ground-based measurements were predominantly in the Greater Accra region where the capital city is located.[318] With R package 'terra' and ArcGIS 10.8.1 software and using district centroids, a zonal statistics technique was applied to process monthly $PM_{2.5}$ concentrations for each district between 1st January 2011 and 31st December 2020. Data for 2011 were included to allow for a delayed (lagged) exposure period before the first observation in January 2012. Because of geographically sparse air monitoring stations, the global spatiotemporal $PM_{2.5}$ estimates [45,47] have been used in several epidemiological studies even in high-income countries such as the USA,[56,289] Australia,[50] China,[236-238] Colombia,[54] Kenya,[55] and across multiple LMICs.[160,161,290,307,319]

A biothermal metric, Universal Thermal Climate Index (UTCI) was also assessed as a confounder and for interaction effect analysis. UTCI (˚C) is a composite climate metric that combines the total thermal environment (air temperature, radiant temperature, relative humidity, and wind speed) with human physiological characteristics as detailed elsewhere.[104-106] A daily average of gridded UTCI at 0.25° spatial grid (~27 km at the equator), was freely accessed at the European Copernicus Climate Data Store [106] across Ghana. Monthly district-level UTCI was processed as described for $PM_{2.5}$ above.

6.3.4 Other sociodemographic covariates

District-specific values were extracted with ArcGIS software (version 10.8.1) for other annual global gridded datasets and used as covariates. This included ambient population (24 h average population modelling that included potential activity space of people throughout the day and night rather than merely a residential area) between 2012 and 2019 at approximately 1 km × 1 km.[107] Total Gross Domestic Production (Purchasing Power Parity), (hereon GDP) in constant 2011 international United States dollars at a spatial resolution of 5 arc-min (approximately 10 km at the equator) was also obtained for 2010-2015.[109] For each covariate, linear interpolation was performed with the R package 'imputeTS'[320] to extrapolate to 2020 to use data between 2012 and 2020 for the analysis. The ambient population was divided by the district area to obtain the population density. Overall means were also computed to dichotomise the districts into low (≤median) or high (>median) subgroups for each covariate.

Global Positioning System coordinates for all the 900 survey clusters in 2017 GMHS [93] was obtained. The number of households using biomass fuel or unclean cooking fuel (wood, charcoal, dung, kerosene, crop residues, shrubs, and coal) [321,322] for all survey clusters was organised.[93] Inverse distance weighting geostatistical interpolation was applied within ArcGIS to generate a continuous raster of the number of households using polluted cooking fuel for the entire study area. District-specific values were extracted and dichotomised as described earlier.

6.3.5 Statistical analyses

6.3.5.1 Main and subgroup analyses

To describe both linear and non-linear exposure-lag-response associations, DLM and DLNM were combined with conditional quasi-Poisson regression to simultaneously investigate the immediate, delayed, and cumulative effects of $PM_{2.5}$ exposure on stillbirth.[59,60] The model was specified as

$$\log\left[\mathrm{E}\left(\mathrm{Y}_{\mathrm{t,i,s}}\right)\right] = \alpha + \mathrm{cb}(PM_{2.5}) + \mathrm{cb}(\mathrm{UTCI}) + \mathrm{Month} + \mathrm{ns}(\mathrm{time}, \mathrm{df}) + \mathrm{cov},$$

$$\mathrm{offset} = \log(\mathrm{total\ birth})$$

where $Y_{t,s}$ is the observed number of stillbirths in month t for a year i at district s; α is the intercept; $cb(PM_{2.5})$ is the *cross-basis* matrix of the $PM_{2.5}$ exposure to define the exposure–lag–response association using the R package 'dlnm'.[60] The maximum lag period was set at 9 months to capture preconception periods or gestational ages that might extend to the 10th month. That is, monthly exposure was analysed retrospectively from the month of the stillbirth (lag 0) to nine previous months (lag 9 and lag 0-9). Previous studies often assumed a linear relationship between $PM_{2.5}$ and birth outcomes by employing the DLM method for direct interpretation of the results as per exposure reference increment (usually 10 μg/m^3).[61,65,67,232] However, the non-linear relationship of air pollution with health outcomes is also reported in many studies by employing the DLNM method.[243-248,315] Therefore, following Mork *et al*, [243] both DLM and DLNM methods were implemented to define the cross-basis matrix of $PM_{2.5}$ exposure. In the DLM method, a linear function was specified for $PM_{2.5}$ exposure and a non-linear relationship for the lag space with natural cubic splines to construct the *cb($PM_{2.5}$)*. In the DLNM method, both $PM_{2.5}$ exposure and lag space dimensions were specified as non-linear relationships with natural cubic splines. Equally spaced spline knots were placed at the log scale of lags. Several combinations of 2–7 degrees of freedom (*df*) were checked and the optimum 7 *df* was chosen based on the smallest Akaike information criterion (AIC).[59,60] UTCI exposure was adjusted by specifying natural cubic splines in both the UTCI exposure and the lag dimensions as cross-basis matrix, *cb (UTCI)*. The *month* is the month factor variable (1, 2, 3, ….., 12) to control for annual seasonality. The *ns (time, df)* is a natural spline of time in a continuous number of months over the study period with 36 *df* (4 per year based on the lowest AIC) to control for long-term temporal trends over the study period. The *cov* is the other covariates as percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20–34, and ≥ 35 years), and natural splines with 2 *df* to flexibly model the continuous variables GDP and population density. *Stratum is a* conditioning factor to define variations in the same district in the same region which was entered through the “eliminate” function to fit conditional quasi-Poisson regression using the R package “gnm”.[122] For DLM results, the Relative Risks (RRs) and 95% Confidence Intervals (CIs) were estimated at both previous (now interim target 4) and new annual WHO AQGs of 10 and 5 $\mu g/m^3$ $PM_{2.5}$ exposure,[2] using 0 $\mu g/m^3$ as reference for the usual interpretation of RR (95% CI) as per 10 $\mu g/m^3$ and 5 $\mu g/m^3$ increment, respectively. For DLNM, the RRs (95% CIs) were estimated at the 1^{st}, 5^{th}, 10^{th}, 50^{th}, 90^{th}, 95^{th}, and 99^{th} centiles of $PM_{2.5}$ exposure, using the new WHO AQG of 5 $\mu g/m^3$ as a reference in the main results. The RRs (95% CIs) were obtained directly by the *crosspred* function in the R package ‘dlnm’.[60] Months in which 95% CI excluded the null were identified as critical susceptible exposure periods.

Modification effects by sociodemographic disparities were examined by stratified analyses for the dichotomised (low and high) subgroups for population density, GDP, and household air pollution, and the results were presented graphically.

6.3.5.2 Interactive effects of $PM_{2.5}$ and UTCI on stillbirth

The linear exposure-response association was performed to estimate separate RR (95% CI) per 5 $\mu g/m^3$ $PM_{2.5}$ exposure increment for each UTCI category. Altman and Bland test of interaction effects was then performed to compare the risk in high subgroups, using the low subgroup as a reference by estimating the ratio of relative risks (RRRs) and the corresponding 95% CIs.[257,258]

6.3.5.3 Sensitivity analyses

A series of sensitivity analyses were performed to ascertain the stability of the main results. (i) The *df* for the cross-basis matrix of UTCI was increased from 3 to 4 *df* for both dimensions. (ii) The *df* for the cross-basis matrix of $PM_{2.5}$ was decreased from 7 to 6 *df* for both exposure and lag space dimensions. (iii) The *ns* (*time*, *df*) was replaced with a year index factor variable (1, 2, 3, …, 9) to control for long-term trends as inter-annual variability. (iv) Month of birth was replaced by the season (winter and summer) of birth. (v) The month factor was excluded to maintain only ns (time, *df*) as previous studies considered this to have accounted for both seasonal and long-term trends.[119,120,244,314] (vi) GDP and population density were entered as linear instead of non-linear variables. (vii) *df* in ns (time, *df*) was changed from 36 (4 per year) to 45 (5 per year). (viii) UTCI exposure was not adjusted for. (ix) Because the earliest final gestational age of stillbirth was 28 weeks, the maximum lag was changed to seven months (that is, eight pregnancy months). Sensitivity analyses were fitted from DLNM as it performed better than the DLM based on lower AIC. Results were presented graphically using the reference of 5 ug/m^3.

All statistical analyses were performed utilising R statistical software (version 4.1.1)[323]. Following the recent recommendation by the American Statistical Association, results were interpreted without considering statistical significance.[181]

6.4 Results

6.4.1 *Characteristics of the study population, exposure, and covariates*

A total of 5,961,328 births of which 90,532 (1.5%) were stillbirths with an overall district-level monthly mean (standard deviation) of 212.3 (345.6) births were included in this study. There were slightly more male births (51%) than female births and were mostly by mothers aged 20-34 years (72%). The overall mean (standard deviation) of the $PM_{2.5}$ and UTCI exposures was 30.0 (17.9) µg/m^3 and 28.5 (2.0 ˚C), respectively. The overall mean (standard deviation) of household air pollution, GDP, and population density was 582 (555) households, 281.8 (778.6) per million US dollars, and 1225 (4114) persons per km^2, respectively (Table 6.1). On a monthly scale, both $PM_{2.5}$ concentration and incidence of stillbirth decreased over the study period (Figure 6.1).

Spatially, $PM_{2.5}$ concentration was very high in the northern part, ranging from 30.7–43.6 µg/m^3 as compared to the southern part with about 21.9–30.6 µg/m^3. Only a few districts had a relatively high incidence of stillbirths ranged 19.3–48.1 stillbirths per 1000 births (Figure 6.2).

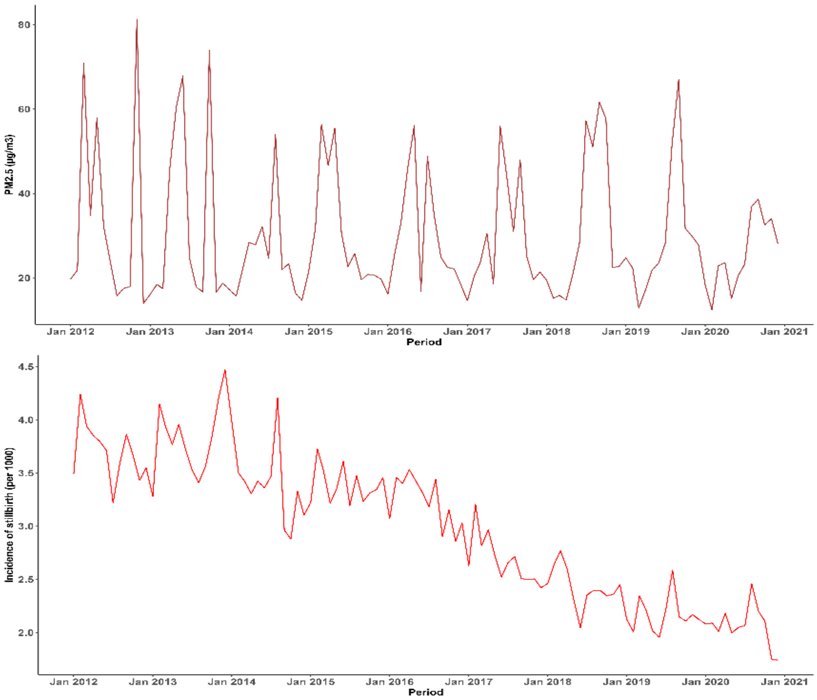

Figure 6. 1 Average monthly variation of $PM_{2.5}$ exposure ($\mu g/m^3$) and stillbirth rate across the 260 districts in Ghana from January 2012 to December 2020.

Table 6.1 Descriptive statistics of the births, environmental exposures, and sociodemographic factors across the 260 districts in Ghana, 2012–2020.

Variables	Mean	SD	Median	Min	P25	P75	Max	IQR
Births (N = 5,961,328)	212.3	345.6	162.0	1.0	86.0	266.0	45929.0	180
Stillbirths (N = 90,532)	3.2	5.4	2.0	0.0	0.0	4.0	111.0	4.0
Male (%)	50.9	5.7	50.9	0.0	47.9	53.8	100.0	5.9
Female (%)	49.0	5.7	49.1	0.0	46.1	52.1	100.0	6.0
Teen:10–19 years (%)	13.0	5.7	13.0	0.0	9.4	16.4	65.3	7.0
Young adult: 20–34 years (%)	72.1	6.3	72.2	0.0	68.5	75.9	96.4	7.4
Adult: ≥35 years (%) (%)	14.0	4.5	13.9	0.0	11.2	16.7	77.6	5.5
$PM_{2.5}$ ($\mu g/m^3$)	30.0	17.9	23.3	5.0	17.5	38.0	132.4	20.5
UTCI (˚C)	28.5	2.0	28.8	19.6	27.2	29.9	35.2	2.7
HAP	581.6	555.2	437.5	9.0	225.8	688.8	3862.0	463
GDP (per million US dollars)	281.8	778.6	50.5	0.8	24.8	106.8	5132.5	82
Population density (persons/km^2)	1224.9	4113.8	141.8	7.7	77.8	318.2	39070.4	240.4

Note. SD, standard deviation; UTCI, Universal Thermal Climate Index; P25 and P75, 25th and 75th percentiles; *IQR, Interquartile range = P75–P25; HAP, Household air population; GDP, Gross Domestic Production; US, United States; $PM_{2.5}$; fine particulate matter at aerodynamic diameter ≤2.5 µm.

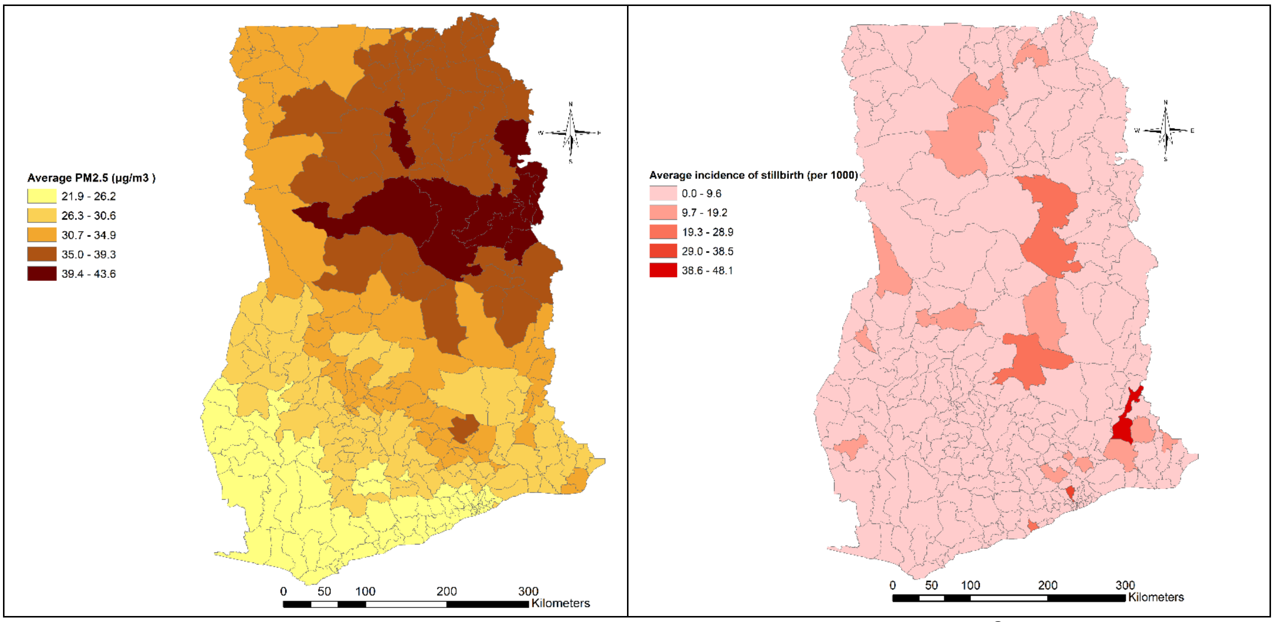

Figure 6.2 District-level spatial distribution of the overall average $PM_{2.5}$ exposure (μg/m^3) and incidence of stillbirth (per 1000 births) across the 260 districts in Ghana during 2012–2020. Map was constructed based on the equal interval classification method in ArcGIS (version 10.8.1) with a base map obtained from https://data.humdata.org/dataset/ghana-administrative-boundaries.

6.4.2 Association between monthly $PM_{2.5}$ exposure and stillbirth

The DLNM performed better than the DLM method based on the minimisation of AIC. From the DLM method with 0 μg/m^3 as a reference, $PM_{2.5}$ exposure at new annual WHO AQG (5 μg/m^3), new interim target four (10 μg/m^3), and study-specific interquartile range (20.5 μg/m^3) and median (23.3 μg/m^3) showed a very small positive association with stillbirth which increased slightly with the exposure dosage, but all effect estimates included null in the confidence interval. The risk of stillbirth was most elevated during the 6th month and lowered marginally or essentially no association during the 8th month before birth. For example, the adjusted risks of stillbirth for 10 μg/m^3 and interquartile range increased in $PM_{2.5}$ exposure during 6th month before birth were 1.01 (95% CI 1.00, 1.02) and 1.02 (95% CI 1.00, 1.03), respectively, and during 8th month before birth was 0.99 (95% CI 0.98, 1.00) and 0.99 (95% CI 0.97, 1.01), respectively (Figure 6.3 and Table S6.1). Although with slightly higher risk, cumulative RRs from cumulative exposure-lag-response associations also showed similar patterns and with lower precision (Figure S6.1, Table S6.2). DLNM method with better precision than DLM showed a higher risk of stillbirth with increasing $PM_{2.5}$ exposure thresholds for both individual and cumulative lag exposures, using either reference of 5 μg/m^3 (Figure 6.4, Table S6.3, Table S6.4) or 10 μg/m^3 (Figure 6.4, Table S6.5, Table S6.6, Figure S6.2). Critical susceptible periods were found for exposures above 50th $PM_{2.5}$ exposure centile during the 6th–7th months before birth. $PM_{2.5}$ exposure at the 99th centile during 6th month before birth showed the most elevated risk of 1.17 (95% CI 1.06, 1.28) and 1.14 (95% CI 1.05, 1.24) with reference to 5 μg/m^3 and 10 μg/m^3, respectively.

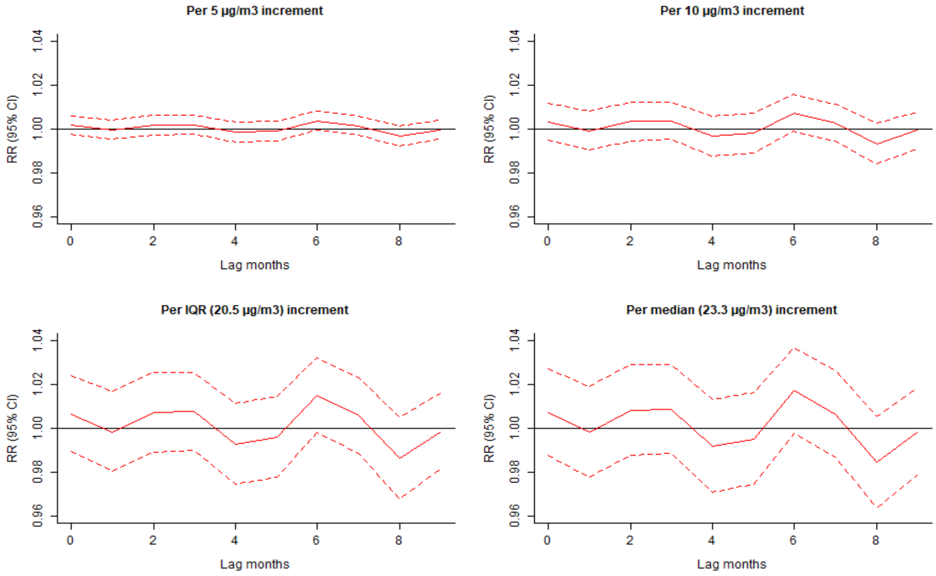

Figure 6.3 Monthly adjusted relative risk for the distributed lag linear association between $PM_{2.5}$ exposure at 5,10, 20.5, and 23.3 μg/m^3 increase and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Models were fitted from DLM conditional quasi-Poisson regression models with adjustment for the month of birth, natural splines of a continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLM, Distributed Lag linear Model; RR, Relative Risk; CI, confidential interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

The same 99th centile of $PM_{2.5}$ exposure showed a small 'protective effect' during the 8th month before birth, 0.85 (95% CI 0.76, 0.95) and 0.84 (95% CI 0.76, 0.92) with reference to 5 µg/m^3 and 10 µg/m^3, respectively (Figure 6.4, Table S6.3 and Table S6.5). Cumulative lag exposures showed similar patterns with greater magnitudes of the risk estimates but were less precise and included null in the confidence intervals (Figure S6.2, Table S6.6, and Table S6.4).

Results of modification effects by stratified analyses (low and high subgroups) of districts showed that the risk was more elevated in areas with high population density (Figure S6.3), with no difference for low or high GDP (Figure S6.4), and areas with low household air pollution (Figure S6.5).

The ratio of relative risk from the Altman and Bland test of interaction effects indicated no observable interaction effects between $PM_{2.5}$ and biothermal exposures on stillbirth (Table 6.2). Although with comparatively lower precision, the results of the sensitivity analyses under varying model assumptions and conditions were mostly consistent with that of the main analysis (Figures S6.6–S6.14).

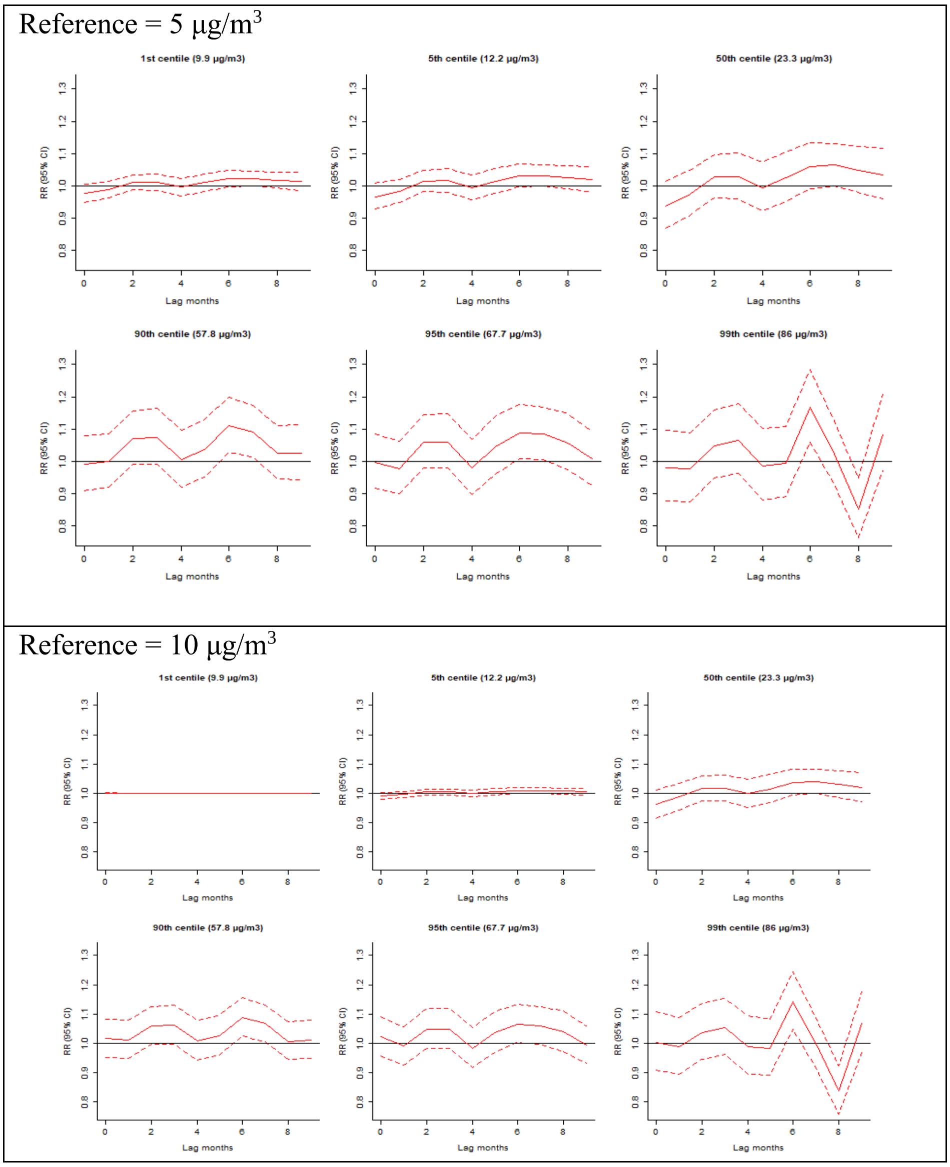

Figure 6.4 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 µg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for the month of birth, natural splines of a continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

Table 6.2 Monthly adjusted ratio of relative risk for the distributed lag linear association between $PM_{2.5}$ exposure at 5 and10 μg/m^3 increase and risk of stillbirth from the month of stillbirth in high as compared to low biothermal stress in Ghana, 2012–2020

Lag month	5 μg/m^3 $PM_{2.5}$ High vs Low UTCI RRR (95% CI)	10 μg/m^3 $PM_{2.5}$ High vs Low UTCI RRR (95% CI)
0	0.99 (0.98, 1.00)	0.98 (0.96, 1.00)
1	0.99 (0.98, 1.00)	0.98 (0.96, 1.00)
2	0.99 (0.99, 1.00)	0.99 (0.97, 1.01)
3	1.00 (0.99, 1.00)	0.99 (0.98, 1.01)
4	1.00 (0.99, 1.01)	0.99 (0.98, 1.01)
5	1.00 (0.99, 1.01)	0.99 (0.98, 1.01)
6	0.99 (0.98, 0.99)	0.97 (0.96, 0.99)
7	0.99 (0.98, 0.99)	0.97 (0.96, 0.99)
8	0.99 (0.98, 1.00)	0.99 (0.97, 1.01)
9	1.00 (0.99, 1.00)	0.99 (0.97, 1.01)

Note: RRR, Ratio of Relative Risk; CI, confidential interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm; UTCI, Universal Thermal Climate Index

6.5 Discussion

6.5.1Main findings

Nearly six million births with 1.5% clinically determined stillbirths linked with district-level monthly $PM_{2.5}$ exposure over nine years were analysed with a within-space time-series distributed lag linear and non-linear conditional quasi-Poisson regression. The overall district-level monthly mean $PM_{2.5}$ concentration was 30.0 μg/m^3 which varied spatially across the local districts in Ghana, ranging from 21.9–43.6 μg/m^3. This implies that as compared to the annual WHO AQGs of 5 μg/m^3, Ghana was on average six times polluted on monthly basis. This is consistent with the World Air Quality Report, ranking Ghana as the 6th most polluted country in Africa with a population-weighted $PM_{2.5}$ concentration of 25.9 μg/m^3 in 2021.[310] A recent large-scale $PM_{2.5}$ measurement campaign using low-cost and low-power devices at 146 distinct locations in Accra, the capital city of Ghana between April 2019 and June 2020 also reported that mean annual $PM_{2.5}$ concentrations across the fixed sites ranged from 26 μg/m^3 at a peri-urban site to 43 μg/m^3 at more socioeconomically active urban areas.[324] Another recent $PM_{2.5}$ measurement campaign for 36 weeks in four areas within Tema, the industrial area of the Greater Accra Region found mean weekly baseline and actual $PM_{2.5}$ concentration of 38.9 μg/m^3 and 38.1 μg/m^3, respectively, exceeding weekly $PM_{2.5}$ limit of 35 μg/m^3 in Ghana.[325] These results further confirm the high $PM_{2.5}$ concentrations in Ghana and provided some reliability in the monthly satellite-derived $PM_{2.5}$ estimates used in this present study as the $PM_{2.5}$ concentrations were generally similar.

Both DLM and DLNM methods indicated a small dose-response association (mostly included null in the confidence interval) between $PM_{2.5}$ exposure and stillbirth in Ghana, especially for individual or cumulative exposures during the 6th-7th months before birth. Using either 5 μg/m^3 or 10 μg/m^3 as references, the DLNM method with better model performance than the DLM revealed critical susceptible exposure periods for exposures above 50th $PM_{2.5}$ exposure centile during 6th-7th months before birth and was most elevated at 99th centile during 6th month before birth. At the same 99th $PM_{2.5}$ exposure centile, a small 'protective effect' during the potential preconception period (that is 8th month before the month of stillbirth) was observed.

The findings in this study have public health significance as this is among a few studies in the literature and the first study in Africa to estimate the time-varying effect of $PM_{2.5}$ exposure on stillbirth, providing additional critical evidence on this important but neglected public health issue.[303,326] The recent umbrella review indicated very limited studies on $PM_{2.5}$ exposure and stillbirth as compared to other birth outcomes and all the few studies were almost from high-income countries.[125] Although the study design and exposure period analysed were not comparable, one study on this topic in SSA that linked $PM_{2.5}$ to 68 survey datasets across 33 African countries also reported higher odds of stillbirth for the whole pregnancy exposure,1.09 (95% CI: 1.05, 1.14) per 10 $\mu g/m^3$ $PM_{2.5}$ increase.[160]

The updated systematic review and meta-analysis of seven primary studies found odds of stillbirth per 10 $\mu g/m^3$ $PM_{2.5}$ increase of 1.10 (95% CI: 1.07, 1.13) for entire pregnancy exposure. Trimester-specific odds of stillbirth per 10 $\mu g/m^3$ $PM_{2.5}$ increase were 0.96 (95% CI: 0.83, 1.09) based on seven studies, 1.03 (95% CI: 0.94, 1.12) based on six studies, and 1.09 (95% CI: 1.01, 1.18) based on five studies during first, second, and third trimesters, respectively.[259] These findings[160,259] have been compared in the previous preliminary published study that examined total mass and by the source (natural and anthropogenic).[302] But there is no known comparable study that examined the exposure-lag-response association for $PM_{2.5}$ and stillbirth as reported for other birth outcomes for identifying potential critical susceptible exposure periods.[61,62,65,67-69,232,233] The present finding, therefore, provided additional epidemiological evidence that, like other birth outcomes, there are potential critical susceptible $PM_{2.5}$ exposure periods for stillbirth. This could be the early stage of pregnancy such as the 6th–7th month before the month of stillbirth. This finding was also consistent with individual-level cohort analysis in Western Australia where the identified critical susceptible $PM_{2.5}$ exposure periods on stillbirth were the 3rd–7th gestational months as reported in Chapter 4 of this thesis. The small 'protective effect' found, particularly at the 99th $PM_{2.5}$ exposure centile during the 8th month before birth (a potential preconception period) may be due to exposure misclassification as mothers are most likely to be in different districts or regions during that time. Small births within the 99th $PM_{2.5}$ exposure centile could also be a factor. Given the significance of critical susceptible exposure periods for public health intervention and understanding biological mechanisms, further studies in this direction are required, especially from LMICs.

Stratified analyses showed no difference in $PM_{2.5}$ exposure association with stillbirth by low/high GDP but districts with high population density and low household air pollution which could define as urban districts were at higher risk as compared to those in low levels (most likely rural districts). Urban areas are densely populated and have high industrial activities and vehicular movements that contribute more to $PM_{2.5}$ exposure with an associated more elevated risk of stillbirth as compared to rural areas with lower industrial activities and traffic. $PM_{2.5}$ campaign measurement of within-city variations in the capital city Accra found higher $PM_{2.5}$ concentration in densely populated neighbourhoods in the commercial business sites with high road traffic in the urban centres which peaked at traffic rush hours than in peri-urban areas with lower industrial, commercial, and road-traffic. [324]

No observable interaction effects between $PM_{2.5}$ and biothermal exposures on stillbirth were found in this study according to the ratio of relative risk from the Altman and Bland test of interaction effects.[257,258] The interactive effect of these environmental exposures was expected due to the independent effects of $PM_{2.5}$ and ambient temperature on birth outcomes through similar biological mechanisms.[16,125] Few studies found the interaction effects of $PM_{2.5}$ exposure and ambient temperature by trimesters on preterm.[234,263,264] Further related studies on stillbirth are required.

6.5.2 Plausible pathophysiologic mechanisms

The pathophysiologic mechanisms of $PM_{2.5}$ exposure have not been finalised, but toxicological evidence based on *in vivo, in vitro,* and clinical studies suggested that oxidative stress, endocrine and inflammatory responses, and placental genomic alterations caused by $PM_{2.5}$ disrupt fetoplacental transport of nutrients, oxygen, and water which lead to stillbirth. [125,231,270,305] The observed potential critical susceptible exposure during the early stage of pregnancy could be explained by $PM_{2.5}$-induced DNA methylation and mitochondrial DNA content alteration.[231,270] Findings based on *in vivo* studies found that $PM_{2.5}$ exposure in early pregnancy (embryogenesis period) changed global placental DNA methylation. This interfered with placental growth and physiology and affects late fetal survival. It was also shown that $PM_{2.5}$ may induce apoptosis in granulocytes and oocytes which affect the female reproductive system.[270] Due to the different sources and complex physicochemical properties of $PM_{2.5}$ components with substantial geographical and temporal variations,[2] it is difficult to conclude definitively.[270] It is also unclear if $PM_{2.5}$ only acts as a carrier or interacts with the toxic substances on its surface to damage human health.[270] Further biological and pathophysiological studies on $PM_{2.5}$ and adverse birth outcomes will be helpful.

6.5.3 Strengths and limitations

The strengths and limitations are almost the same as what was described in previous Chapter 4 section 4.5.5. Few specific additions or modifications were presented here. To the best of our knowledge, this was the first investigation of monthly critical susceptible $PM_{2.5}$ exposure periods for stillbirth in Africa as the previous study only investigated whole pregnancy-average exposure effects.[160] The district-level temporal and spatial confounding factors and maternal mobility within districts in the same region were controlled by the novel design. Unlike previous studies, household or indoor air pollution was included in this study. Although the longitudinal aggregated design implemented here is closely related to the individual-level model, its statistical power may not be sufficient as compared to high-quality individual-level longitudinal studies if data is available. Only annual instead of monthly data on the population density and GDP were available.

6.6 Conclusion

A quasi-experimental design of within-space time-series distributed lag linear and non-linear modelling of nearly 6 million births linked with monthly satellite-derived $PM_{2.5}$ estimates indicated small dose-response associations between $PM_{2.5}$ exposure and stillbirth in Ghana. The potential critical susceptible period was the early stage of pregnancy (embryogenesis period) when $PM_{2.5}$ causes global placental DNA methylation and mitochondrial DNA content alterations which interfered with placental growth and physiology, leading to stillbirth.[231,270] The risk was more elevated in urban areas that were densely populated with potentially high industrial activities and traffic emissions as compared to rural areas. Together with previous studies,[125,326] the findings in this study suggest that the improvement of air quality may contribute to achieving SDG 3.2 and the Newborn Action Plan target.[209,228,229]

Part III
Biothermal stress and adverse birth outcomes

Chapter 7. Maternal exposure to ambient air temperature and adverse birth outcomes: An umbrella review of systematic reviews and meta-analyses

7.0 Preamble

This chapter provides an umbrella review that comprehensively synthesised the existing systematic reviews and meta-analyses of the epidemiological evidence on maternal exposure to ambient air temperature and the risks of adverse birth outcomes globally with recommendations for practice, policy, and further studies. The protocol of this umbrella review was registered prospectively in a PROSPERO (CRD42020200387) and later peer-reviewed and published in the *International Journal of Environmental Research and Public Health.*[83]

7.1 Abstract

Background: Multiple systematic reviews on prenatal ambient temperature and adverse birth outcomes exist, but the overall epidemiological evidence and the appropriate metric for thermal stress remain unclear. An umbrella review was performed to summarise and appraise the evidence with recommendations.

Methods: Systematic reviews and meta-analyses on the associations between ambient temperature and birth outcomes (preterm birth, stillbirth, birth weight, low birth weight, and small-for-gestational-age) up to February 4, 2023, were synthesised according to a published protocol. Databases PubMed, CINAHL, Scopus, MEDLINE/Ovid, EMBASE/Ovid, Web of Science Core Collection, systematic reviews repositories, electronic grey literature, and references were searched.

Results: A total of nine systematic reviews, including one meta-analysis were included. This comprised 78 observational studies that employed multiple temperature assessments. All systematic reviews indicated that maternal exposure to particularly high temperatures during late gestation are contributing to increased risks of preterm birth, stillbirth, and low birth weight. From the included meta-analysis, the odds ratios (OR) for high versus low temperatures were 1.14 (95% CI 1.11, 1.16; I^2= 88.2%) for preterm birth based on nine primary studies and 3.39 (95% CI 2.33, 4.96; I^2= 27.8%) for stillbirth based on two primary studies for whole pregnancy or trimester-average exposures. Exposures up to four weeks before delivery was 1.01 (95% CI 1.01, 1.02; I^2= 89.8 %) for preterm birth based on 21 studies and 1.24 (95% CI 1.12, 1.36; I^2= 53.1%) for stillbirth based on four studies. The median OR of low birth weight was 1.09 (interquartile range 1.04 to 1.47) based on eight primary studies. Overall, there was *probable* evidence of causation. No study assessed biothermal metrics for thermal stress.

Conclusions: Prenatal exposure to ambient temperatures, particularly high temperatures was associated with adverse birth outcomes. Future studies would benefit from the incorporation of biothermal metrics into exposure assessment.

7.2 Introduction

Birth outcomes such as preterm birth (PTB, birth before 37 weeks of completed gestation) and low birth weight (LBW, birth weight ≤ 2,500 g) are regarded as important markers of maternal and fetal health and are associated with mortality, stunting, and the onset of chronic conditions later in the life course.[208,280] The rate of these birth outcomes and stillbirth (a baby born with no signs of life at or after 28 weeks of gestation), which is regarded as a sensitive marker of the quality of prenatal care are high globally.[224] Systematic reviews and modelling estimated a global rate of 10.6% (14.8 million) live PTB in 2014,[208] 14.6% (20.5 million) livebirths with LBW in 2015,[280] and 13.9 stillbirths per 1000 total births (2.0 million) in 2019.[224] Besides the common risk factors, accelerating climate change and associated events such as extreme temperatures could be contributing factors to these high rates of birth outcomes.[274,327] The potential direct and indirect impacts of climate change on human health with disproportionate impacts on vulnerable populations such as pregnant women, developing fetuses, and children is a global public health concern.[7,274,327]

As a result of severe climate change, extreme weather events such as heat and cold waves, droughts, and storms are on the rise globally and are expected to increase in intensity, duration, and frequency in the coming decades.[7] This has serious implications for population health, health system, and reproductive health.[327] The role of thermal conditions as a putative modifiable risk factor in the pathophysiology of adverse birth outcomes cannot be underestimated.[10] Pathophysiologically, prenatal exposure to extreme temperatures disrupts maternal thermal homeostasis and causes oxidative stress and inflammation among other biological processes with the potential endpoint of adverse birth outcomes.[297] One of the earliest epidemiologic studies linking ambient temperature to birth outcomes was conducted by Lajinian *et al* on the association between heat-humidity index (combination of temperature and relative humidity) and PTB from March 1993 to March 1994 using municipal hospital cohort data in Brooklyn, USA.[328] Many observational studies have been conducted since then and summarised in multiple systematic reviews of varied scope and quality.[35,139,329,330] As the number of systematic reviews has also increased, researchers, healthcare practitioners, and policymakers may find it difficult to keep abreast of evolving findings and recommendations.[37] Past systematic reviews also examined single or few birth outcomes and the overall picture of the exposure-birth outcome associations from multiple systematic reviews, accuracy, reliability, and thermophysiological relevance of the varied temperature metrics being used to assess the thermal environmental exposure remain unclear.[74] Following the recommendations by Joanna Briggs Institute (JBI) for evidence synthesis,[37,85] an umbrella review was conducted to systematically collect, appraise, and summarise evidence from the available systematic reviews or meta-analyses to produce a high-quality tertiary-level of evidence to guide policy and future studies. An umbrella review has been conducted for other risk factors of birth outcomes such as periodontal disease [39] and antenatal depression.[40] But we are not aware of any umbrella review to date on the effect of prenatal ambient heat or cold stress, and extreme temperature exposure, on the risk of adverse birth outcomes.[39,40]

This study aimed to conduct the first systematic umbrella review to evaluate, map, and summarise the accumulated epidemiologic evidence from existing systematic reviews with or without meta-analysis, to identify research gaps, and common challenges, and provide recommendations for future studies and policies on this topic.

7.3 Method

Apart from the ambient temperature rather than ambient air pollution considered here as the exposure of interest, all methodological procedures were the same as reported in Chapter 3 for the published umbrella review on the association between criteria air pollutants and adverse birth outcomes.[125] The keywords or search terms used for the exposure were temperature, weather, heat, cold, climate, heatwave, coldwave, and thermal stress. The literature search was conducted for the broader umbrella review on ambient air pollution, temperature, and birth outcomes described in the prospectively registered PROSPERO protocol (CRD42020200387) and published as a peer-reviewed article.[83] The databases were searched on September 21, 2020, and with weekly alerts and updates up to February 4, 2023, using the same criteria. Eligibility criteria, data extraction, risk of bias assessment, and data synthesis were followed as described in Chapter 3 above.[125] Due to the considerable heterogeneities in the temperature metrics, exposure periods, and lag variables analysed, systematic reviews without meta-analyses (hereon *systematic reviews*) were always reported. The systematic reviews were synthesised narratively.

7.4 Results

7.4.1 Systematic literature search results

A total of 3,663 records were initially identified, of which 1,513 were retrieved for a title and abstract screening after deduplication. One potentially eligible additional study was identified from the other search sources. Title and abstract screening excluded 1,502 unrelated records and 12 studies were assessed fully for eligibility. After the full-text assessment, eight studies were eligible, and four studies were excluded due to unrelated outcomes (n=1) and general literature reviews (n=3). The prospective literature search based on the weekly databases' alerts and updates using the same criteria after the initial search up to February 4, 2023, retrieved five related studies. One of those studies was included [331] and the remaining four were excluded as they were general literature or scoping reviews with no review method (n=1) and no details on the included primary studies (n =3). Finally, this umbrella review included nine systematic review studies (eight without and one with a meta-analysis). The study selection flow chart and full lists of excluded studies after the full-text examination with reasons were provided in Figure S7.1 and Table S7.1, respectively.

7.4.2 Characteristics of the included systematic reviews

The general characteristics of the included systematic reviews were summarised in Table 7.1 and Table S7.2. The nine systematic reviews (eight without and one with meta-analysis) were published between February 2011[35] and March 2021[331] by 37 review authors from eight countries with the highest number of systematic review authors, 13 (35%) from Australia. All systematic reviews included primary studies across the globe, but one review included only primary studies from the USA.[34] The nine systematic reviews included a total of 78 distinct primary studies (71 country-specific studies from 28 countries and seven multi-country studies). There was a high degree of primary study overlap estimated at 19% based on Pieper's Corrected Covered Area algorithm.[138] The spatial distribution of the 71 country-specific primary studies indicated high representations in a few countries such as the USA, 19 (27%), Australia, 7 (10%), and 6 (8%) each in China and Spain. Africa contributed only two studies that included a study from Ghana and Uganda, and South Asia contributed only one study from Bangladesh (Figure 7.1). The nine systematic reviews were conducted by sourcing literature from an average of four databases. Except for the only systematic review with meta-analysis that included primary studies in multiple languages (Chinese, English, German, or Italian),[16] all systematic reviews were restricted to only articles in the English language. Included primary studies in the systematic reviews ranged from five primary studies [332] to 67 primary studies [16] with an average of 22 primary studies. Although study design classifications varied slightly among reviews, included primary studies were predominantly time-series for short-term analysis with few case-crossover designs and long-term effects retrospective cohorts.[16] Sample sizes included in the systematic reviews ranged from 674,655 births [329] to 65,860,570 births [16] with an average of 24,563,542 births. Systematic reviews often examined three outcomes (stillbirth, PTB, and LBW) but some reviews examined only stillbirth [331] or PTB.[329] The rates of the birth outcomes reported in the primary studies ranged from 1.1-30.5% for LBW, 2.6-9.3% for PTB, and 2.5-9.6 stillbirths per 1000 births.[16] All systematic reviews observed high variations across the primary studies in the ambient temperature exposure metrics, exposure periods, and threshold or intensity of exposure assessment which was mainly derived from ground-based meteorological stations. Exposure assessments involved different temperature metrics such as mean, minimum, maximum, standard deviation, and diurnal temperatures, and apparent temperature (a combination of temperature and relative humidity or dew point). Multiple exposure periods assessed mostly involved short-term exposures such as individual days in the week before delivery, a week before delivery, up to 4 weeks before delivery, and up to three months before delivery, and few long-term exposures as entire pregnancy period or by trimesters. Exposure thresholds varied as 1st, 5th, 10th, 25th, 75th, 85th, 90th, 95th, 98th, and 99th centiles of the temperature metric, using median or mean as reference. Few studies also used the tertile, quartile, and quintile of the temperature. Temperatures at the 1st or 5th centiles and 90th to 99th centiles were mostly considered as *cold (low temperature)* and *heat (high temperature)*, respectively, as compared with the reference temperature. Few studies included 75th and 85th into the heat (high temperature) category and few studies further analysed 75th to 90th as moderate temperature. Some primary studies included in the systematic reviews used the duration of the exposure, by threshold temperature, or a combination therein to define cold or heat waves. The majority, 5/9 (56%) of the systematic reviews did not assess the risk of bias of the included primary studies. The remaining four reviews used Critical Appraisal Skills Program (CASP) appraisal tool [329-331] or the Joanna Briggs Institute (JBI) appraisal checklist [16] and reported moderate or high qualities of the included primary studies. The majority, 5/9 (56%) of the systematic reviews did not indicate any review guideline that was followed, two used the Arskey O'Malley methodologic framework and PRISMA guidelines,[34,36] while two only indicated that PRISMA flow chart was used to present the selection of eligible primary studies.[16,331] Only two systematic reviews had a protocol registered which is available at PROSPERO registry [16,331] and the remaining reviews provided no evidence of publicly accessible pre-specified review methods prior to the conduct of the review.

The results of the risk of bias of the systematic reviews included in this umbrella review according to the JBI critical appraisal checklist indicated an overall moderate risk of bias across all nine systematic reviews. Specifically, this included a low risk of bias in two systematic review studies (9/10 score point [331] and 9/11 score point [16] and a moderate risk of bias (7-8 out of 10 score points) in the remaining seven studies. The major areas of weaknesses were the failure to appraise and report the risk of bias in the included primary studies (n = 5), and that critical appraisal (n = 9) or data extraction (n = 6) were not conducted by at least two independent authors (Figure S7.2).

Table 7.1 Characteristics of the systematic reviews on ambient air temperature and adverse birth outcomes, ordered from current to earliest.

First author, date [number of authors, countries]	**Outcome(s) and range**	**Databases (Db) and grey literature searched**	**Search date range and languages applied**	**No. of eligible primary studies, study designs, coverage**	**Publication year range of included studies**	**Total sample size of included studies**	**RoB tool used**	**Author's quality rating summary of included primary studies**	**Review guidelines used**	**Evidence of pre-specified review method (e.g. registered or/and published protocol)**
Sexton[331] 26/03/2021 [6; all Australia]	Stillbirth: 1.4-26.3 per 1000 births.	Db=6 Grey=No	2000-January 20, 2021	12 total=9 retrospective cohorts, 3 case-crossover. Global	2012-2020	3,461,823	CASP appraisal tool	From 4-14, out of a maximum of 14 points, generally high.	No[b]	PROSPERO
Chersich[16] 04/11/2020 [11; 5 South Africa, 2 Australia, 1 Germany, 2 Ireland,1 Lodon/UK]	LBW: 1.1-30.5%, BW, PTB:2.6-9.3%, Stillbirth: 2.5-9.6 per 1000 births	Db=4 Grey=No	Inception - September 2019. Chinese, English, German, or Italian	67 total: 57 time series, 8 case-crossover, 1 time series with case-crossover, 1 case-control. Global	1997-2019	65,860,570 births (and unreported in 8 studies).	JBI appraisal checklist	High quality for 33/47 (70%) for PTB, were 14/28 (50%) of 28 for BW, and 7/8 (87.5%) for stillbirths	No[b]	PROSPERO
Bekkar[34] 18/06/2020 [4, all USA]	PTB, LBW, and Stillbirth	Db=3 Grey=2	1st January 2007 - 30th April 2019. English	7 total: 5 case-crossover, 1 retrospective cohort, 1 cross-sectional. USA	2010-2018	2,832,263 births (3 studies reported only cases of PTB or Stillbirths; 37,442)	No	No	Arskey O'Malley framework and PRISMA	No
Kuehn[36] 29/07/2017 [2; both USA]	PTB, reduced BW, LBW, Stillbirth, early term birth	Db = 2 Grey = No	Inception - January 2017. English	26 total: study designs were not provided. Global	2002-2017	6,964,917 births (not reported in 3 studies	No[c]	No	PRISMA	No

Zhang[330] 09/03/2017 [3, All China]	PTB, BW/LB, Stillbirth.	Db=4 Grey=1	Inception - November 2016. English.	36 total: 17 ecological of which 12 were time series and 19 retrospective cohort of which 4 were case-crossover and 5 time-to-event studies. Global	1997-2017	42,453,906 births (and unreported for 9 studies)	CASP appraisal tool	Scores ranged from 7-12 out of a total of 12 possible points.	No	No
Poursafa[332] 04/2015 [3, all Iran]	LBW, PTB	Db=4 Grey=No	Inception- June 2014. English	5 total: 1 ecologic time-series and unreported for 4 studies. Global	2010-2013	4,125,025 births (and unreported for multi-country study)	No	No	No	No
Beltran[139] 20/12/2013 [3, all USA]	PTB, mean gestational length, BW, LBW, SGA	Db= 2 Grey= No	1st January 1990 -1st November 2013. English	24 total: 18 retrospective cohort, 3 time-series, 3 ecological. Global	1997-2013	56,045,324 births (not reported in 3 studies)	No	No	No	No
Carolan-Olah[329] 12/03/2013 [2; both Australia]	PTB	Db = 5 Grey = No	1992- May 2012 No search language indicated.	7 total: 5 retrospective cohort, 1 case-crossover, 1 ecological. Global	1997-2012	674,655 births for 6 studies (7th study reported PTB=3,97 2)	CASP appraisal tool	Quality scores varied from 7 to 12, out of a total of 12 possible points	No	No
Strand[35] 18/02/2011 [3, all Australia]	PTB, BW	Db=3 Grey=No	After 1985 in English No date indicated.	13 total:11 retrospective cohort, 2 ecological. Global	1997-2010	38,653,392 births (not reported in 3 studies)	No	No	No	No

[a]The review indicated 70 studies but location-specific results in a study were not counted as separate studies. [b]Only stated that PRISMA flow chart was used to present the selection of eligible primary studies. [c]Stated specific domains but no report on the risk of bias. Note: PTB, preterm birth; BW, Birth weight; LBW, low birth weight; VLBW; Very low birth weight; SGA, Small for gestational age; CASP, Critical Appraisal Skills Programme; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; JBI, Joanna Briggs Institute.

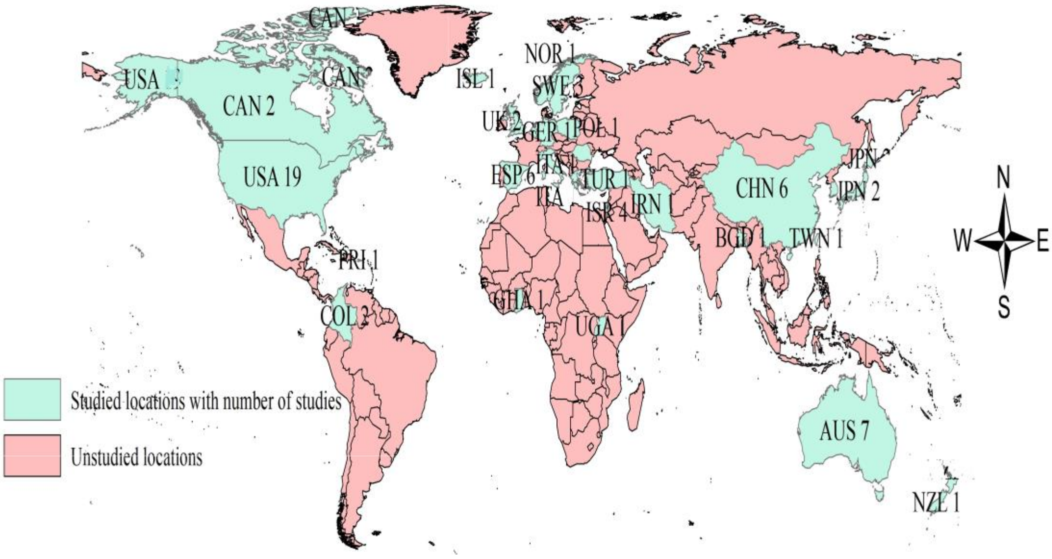

Figure 7.1. Distribution of 71 country-specific distinct primary studies from 28 countries (out of 78 total of which 7 were multi-country studies) included in the 9 systematic reviews. Note: Country (number of studies) for USA, United States of America (19); CAN, Canada (2); PRI, Puerto Rico (1), COL, Colombia (2); AUS, Australia (7); NZL, New Zealand (1), CHN, China (6); TWN, Taiwan (1); KOR, South Korea (1); JPN, Japan (2); BGD, Bangladesh (1); ISR, Israel (4); IRN, Iran (1); TUR, Turkey (1); ROU, Romania (1); GRC, Greece (1), ITA, Italy (1); ESP, Spain (6); BEL, Belgium (1), NLD, Netherland (1); GER, Germany (1), UK, United Kingdom (2); POL, Poland (1); SWE, Sweden (3); NOR, Norway (1), ISL, Iceland (1); UGA, Uganda (1); GHA, Ghana (1).

7.4.3 Summary of major findings from the systematic reviews

Almost all systematic reviews found that maternal exposure to high ambient temperatures was associated with higher risks of birth outcomes, particularly for PTB and stillbirth during late pregnancy. In most instances, more than 60% of the included primary studies reported 'significant' positive associations despite marked variations in exposure metrics, window periods, and thresholds examined (Table 7.2). Overall conclusions by all systematic review authors alluded that exposure to high ambient temperature or heat is a possible risk factor for birth outcomes such as PTB, stillbirth, LBW, and reduced birth weight. Some, however, further stated that the current evidence is limited and the results should be interpreted with care due to the considerable differences and uncertainties in exposure sources, metrics and assessment methods, and differing definitions of outcomes.[329-331] Limited investigation and evidence were also reported for a positive association of low temperature or cold but weaker than that of high temperature or heat exposure.[34,330] Due to the high differences in exposure metrics, assessment, and exposure windows reported in primary studies, only one out of the nine systematic reviews conducted a meta-analysis with few primary studies by reclassifying temperature exposures into four groups.[16] Considering high versus low temperatures for long-term exposures (whole pregnancy or trimester), a random effect pooled odds ratios (OR) were 1.14 (95%

CI 1.11, 1.16; I^2= 88.2%) for PTB based on nine primary studies with 4,327,821 births and 3.39 (95% CI 2.33, 4.96; I^2= 27.8%) for stillbirth based on two primary studies with 512,726 births.

Table 7.2 Summary of main findings in the systematic reviews on ambient air temperature and adverse birth outcomes

First author	Summary of main findings
Sexton (2021)[331]	**Stillbirth** 12 studies: 3,461,823 births or pregnancies Despite the variety of statistical and methodological approaches for exposure assessments, exposure windows, and data linkage, all studies reported associations of increased risk of stillbirth with ambient temperature exposures throughout pregnancy, particularly in late pregnancy. Overall, the risk of stillbirth was observed to increase below 15 ˚C and above 23.4 ˚C, where the highest risk is above 29.4 ˚C.
Chersich (2020)[16]	**PTB** *High vs low temperatures* (at whole pregnancy or trimester) 9 studies: 4,327,821 births. RE pooled OR = 1.14 (95% CI 1.11, 1.16), I^2= 88.2% *Heatwaves vs non-heatwaves days* 6 studies:1,211,581 births with unreported size for one time series study RE pooled OR = 1.11 (95% CI 1.10, 1.23), I^2= 44.7% *High vs low temperature (periods ≤ 4 weeks)* 21 studies with 29 results as 3 studies had more than one site-specific result: 40,940,531 births with unreported births for 3 studies). RE pooled OR = 1.01 (95% CI 1.01, 1.02), I^2= 89.8 % *Odds per 1 degree Celsius of increase in temperature.* 6 studies with 7 results as one study included two site-specific results: 736,719 births with unreported births for one study). RE pooled OR = 1.05 (95% CI 1.03, 1.07), I^2= 87.7% **Stillbirth** *High vs low temperature exposure (last week of pregnancy)* 4 studies: 2,138,017 births. RE pooled OR = 1.24 (95% CI 1.12, 1.36), I^2= 53.1% *Exposure in whole pregnancy or trimester* 2 studies: 512,726 births). RE pooled OR = 3.39 (95% CI 2.33, 4.96), I^2= 27.8% *OR per degree increase in temperature* 3 studies: 232,594 births RE pooled OR = 1.04 (95% CI 1.01, 1.08), I^2= 81.3% **LBW and Birth weight** No meta-analysis was done. 28 studies: 45,191,630 births with unreported births in 2 studies. Out of 16 studies for LBW, 10 (63%) reported increased risk at higher temperatures, only 1 reported the contrary, and 5 had null findings. The median OR of LBW was 1.09 (interquartile range 1.04 to 1.47) based on 8 studies. Out of 19 studies for BW, 12 (63%) found reduction in birth weight at higher temperatures, including 2 studies where the direction of the effect varied by trimester, 3 studies found non-significant increased risk, and 4 found weight increased at higher temperatures (protective effect).
Bekkar (2020)[34]	*Heat exposure for entire pregnancy period.* **PTB** 5 studies: 0.8 million births 4/5 (80%) studies found significant increased risk, median (range) of 15.8 (9.0 to 22.0) of heat exposure. **LBW** 3 studies: 2.7 million births All studies (100%) found significant increased risk, median (range) of 31.0 (13.0 to 49.0) of heat exposure. One study also reported increased risk in extreme cold. **Stillbirth** 2 studies: 0.2 million births Both studies found significant increased risk of heat exposure. Median (range) was not reported.

Kuehn (2017)[36]	**PTB** 17 studies: 4,591,684 births. 15/17 studies (88%) found significant increased risk of heat exposure (8 of these studies were for entire pregnancy period and the rest for varied periods such as 1 week, 3 weeks, 4 weeks, 3 months prior to delivery). Remaining 2 studies found no significant effect (one each for entire pregnancy and 1 week prior to delivery). One study also found protective effect for entire pregnancy. **Early term birth** 6 studies:1,744,211 births. 5/6 studies (83%) found increased risk of excess heat exposure (2/5 were for entire pregnancy and 2 studies for 1 week prior to deliver, and another for 4 weeks prior to delivery. The 6th study found no association for entire pregnancy. **LBW** 5 studies: 1,133,067 births. All for entire pregnancy exposure. 3/5 studies (60%) found significant increased risk of heat exposure and the remaining 2 studies found no significant risk. **Birth weight** 7 studies: 2,621,806 births + unreported in a global study on 125 populations. All 7 studies reported on full gestation. 6/7 (85%) studies found a significant reduction in birth weight. The 7th study found no significant risk. **Stillbirth** 3 studies: 115,527 births + one unreported study. 2/3 studies (one for 4 weeks prior to delivery and the other entire pregnancy) found increasing rates of stillbirth with increasing ambient temperatures. The 3rd found no significant risk for the entire pregnancy.
Zhang (2017)[330]	**PTB** 24 studies: 4,500,885 births with unreported births for 6 studies 14/24 (58%) studies consistently found a significant increased risk for high ambient air temperature exposure during pregnancy. 4 studies found cold-related or both extreme cold and heat increased risks. 2 studies found a significant protective effect of high temperatures. 4 studies found no association. One study also reported higher risk in younger women, Blacks and Asians. **LBW/BW** 14 studies: 38,906,745 births with unreported in 4 studies 8/14 (57%) studies found significant increased risk of high temperature on BW reduction. 2 studies found lower temperature decreasing BW (high temp is protective) 3 studies found no association (no effect) 1 study found non-significant increased risk of both cold and heat effects on LBW. **Stillbirth** 4 studies: 414,132 births All 4 studies found significant increased risk with high temperature. 1 study also reported and found greater risk in the mothers that were younger and less educated, and male fetuses.
Poursafa (2015)[332]	**PTB** 2 studies; one found significant high risk and 1 found weak evidence of association. Another cohort study estimated a 5-day reduction in average gestational age at delivery after an unusually high heat-humidity index on the day before delivery. **VLBW/Birth weight** 1 study each reported. Relatively colder temperatures increased the risk of VLBW. The results of a global study from 60 countries suggested that 'BW will decrease by 0.44-1.05% per each °C increase in temperature under projected climate change".
Beltran (2013)[139]	**PTB** 9 studies: 8,913,266 births 6/9 (67%) studies reported positive associations. Another study on PTB and heat waves reported increased risk of PTB by 13% to 100% depending on the heat wave definition. Other studies focussed on the week and the few days preceding birth, first month or trimester and found no association. **Mean gestational age**

	3 cohort studies: 536,431 births. 2/3 studies reported an inverse association between mean gestational age or length and average temperature. **Birth weight/SGA** 13 studies for BW and 1 study for SGA**:** 47,403,110 births with unreported birth for 2 global studies) 3/13 (23%) studies found an inverse association between heat stress index and mean birth weight. 2 studies found significant increase in mean birth weight per 1 °C increase in the mean daily maximum temperature during the second trimester but another reported no effect of temperature "peaks" and "troughs" during any trimester on term birth weight. 3 other studies found an inverse association between mean temperature in the month of birth with birthweight. 2 studies found a higher number of days of extreme temperatures within each trimester associated with lower mean birth weight. 3 studies found no association with the term LBW for any trimester, association with very LBW of colder temperatures during summer, and increase odds of SGA with average temperature in another study.
Carolan-Olah (2013)[329]	**PTB** 7 studies: 674,655 singleton births for 6 studies (7th study reported PTB=3,972) All but two of the included studies (71%) found that high ambient temperature was associated with an increased risk of PTB. Higher rates of preterm birth were linked to high ambient temperature among different subgroups; younger mothers, and among Black and Asian mothers but did not reach statistical significance.
Strand (2011)[35]	**PTB** 3 cohort studies: 541,249 plus unreported size in one study. One study found a non-significant rate of PTB in the hottest and coldest weeks of summer and winter. One study found significant increased risk and the other found no association. Another cohort study reported no association with gestational age. **Birth weight** 8 studies: 38,088,372 births and 2 studies with unreported births. 2 studies were reported for 1st trimester, and both found a significant reduction in birth weight. 4 studies were reported for 2nd trimester where 1 each found a significant reduction and increase (protective effect) in birth weight and 2 found a non-significant protective effect. 2 studies reported for 3rd trimester and found a significant reduction in birth weight in one and a non-significant protective effect in the other. 2 studies both found a significant reduction in birth weight. One study reported and found a significant reduction in birth weight for birth month mean temperature.

Note: PTB, preterm birth; BW, birth weight; LBW, low birth weight; VLBW, very low birth weight; SGA, Small for gestational age; RE, random effect; OR, odds ratio, CI, Confidence Interval.

For high as compared to low temperature for short-term exposure periods ≤4 weeks before delivery, the OR was 1.01 (95% CI 1.01, 1.02; I^2= 89.8 %) for PTB based on 21 studies with over 41 million births and 1.24 (95% CI 1.12, 1.36; I^2= 53.1%) for stillbirth based on four studies with 2,138,017 births. The OR per 1˚C increase in temperature was 1.05 (95% CI 1.03, 1.07; I^2= 87.7%) for PTB based on six primary studies with over 736,719 births and 1.04 (95% CI 1.01, 1.08, I^2= 81.3%) for stillbirth based on three primary studies with 232,594 births.[16] However, given the relatively high diversities in the methodology, magnitude, and direction of effect estimates, the authors did not conduct any meta-analysis for LBW or change in birth weight. From 28 studies of over 45 million births, 10 out of 16 studies (63%) that reported on LBW found increased risk at higher temperatures, but the remaining found the contrary or no association. The median OR of LBW was 1.09 (interquartile range 1.04 to 1.47) based on eight primary studies. Out of 19 studies that examined birth weight, 12 (63%) found a reduction in birth weight at higher temperatures, including two studies where the direction of the effect varied by trimester, three studies found 'non-significant' increased risk, and four found birth weight increased at higher temperatures (protective effect).[16] As the results from the single meta-analysis showed high heterogeneity in the primary studies (as indicated by the I^2 statistic) and no randomised controlled trials by default, the observed consistent positive exposure-outcome associations were graded as *probable evidence* of causality.[83,86-88,125]

All systematic reviews identified common limitations in the primary studies and offered some recommendations to improve the epidemiological evidence in future studies. These were spatiotemporal and standardised assessment of temperature exposure, more sophisticated study designs of high quality with standardised statistical analysis, long-term effects analysis to identify critical susceptible periods, identification of sociodemographically vulnerable subpopulations, investigating cold-related effects, individual participant data meta-analysis, and exploring biological mechanisms and intervention studies (Table S7.2).

7.5 Discussion

7.5.1 Characteristics of the reviews and main findings

This umbrella review of nine systematic reviews, including one meta-analysis, included 78 distinct primary studies reporting epidemiological evidence on the association between ambient temperature exposure during pregnancy and adverse birth outcomes. The most-studied outcomes were PTB, stillbirth, and LBW. Short-term exposure was most frequently investigated. Despite substantial variations in methodological approaches in the exposure metrics assessments, windows, and thresholds, and statistical analyses across the primary studies, all systematic reviews concluded that maternal exposure to high (and in a few instances low) ambient temperatures during pregnancy was associated with increased risks of birth outcomes. The positive associations were mostly consistent for PTB and stillbirth, particularly at high-temperature exposures during the late pregnancy periods. The high methodological differences across the primary studies have been identified as major limitations with recommendations for further studies with high-quality exposure assessment and standardised analytical approach to strengthen the evidence. On the other hand, this could be regarded as a compelling case that irrespective of the approach employed, maternal exposure to extreme temperatures were consistently associated with higher risks of adverse birth outcomes, particularly PTB and stillbirth.

The included primary studies were dominated by studies from high-income countries such as the USA, Australia, China, and Spain while developing regions such as Africa and South Asia were under-represented with only two and one study, respectively. This may affect the generalisability due to known substantial geodemographic variations in climatic factors, mitigation and adaptation strategies, and population characteristics. However, given the high rates of birth outcomes in LMICs,[208,224,280] lack of mitigation and adaptation resources, and poor healthcare systems among other peculiar indirect effects in LMICs (for example, infection, food security), the effect of climate change is more likely to be heightened in these regions.[16,274,333] Lack of exposure data and individual-level electronic health records are major drawbacks for large-scale population-based longitudinal studies in LMICs.[97] Demographic health survey (DHS) datasets are the main related population-based data in LMICs, despite their known inherent limitations, particularly for reporting adverse pregnancy outcomes.[308,309] Three recent studies linked fine spatiotemporal climate data to the DHS dataset and provided related epidemiological evidence in LMICs.[334-336] The findings indicated that long-term exposure to high temperature increased the risks of induced or spontaneous abortion, LBW, and stillbirth across 15 African countries [334] and macrosomia across 14 African countries.[336] The third study examined short-term exposure to higher maximum temperatures and smaller diurnal temperature ranges during the last gestational week across 14 LMICs (9 African and 5 non-African countries) and also reported increased risks of PTB and stillbirth.[335]

Building the capacity to facilitate availability and access to population-based electronic data of high scientific quality in LMICs is critically important.[97,337] Considering the influence of population characteristics, thermal mitigation strategies, and acclimatisation, more robust high-quality studies have been suggested from diversified sociodemographic and climatic settings to further build stronger epidemiological evidence for urgent climate change governance and public health interventions.[330,331,333] This also means that the credibility of systematic reviews and meta-analysis needs to be improved by adhering to standard review guidelines such as PRISMA[84] or the new environmental health-specific guideline for conducting systematic reviews in toxicology and environmental health research (COSTER).[176] Notable areas of concern to be addressed in future systematic reviews and meta-analyses as recommended in both PRISMA [84] and COSTER [176] clear information on review protocol such as not available publicly prior to the conduct of the review, registration or publication of review protocol, or any form of availability for public access. Also, critical appraisal, or risk of bias assessment of included primary studies, and methods for assessment of confidence in the body of evidence need improvement.[84,176] Making protocols available could also minimise duplication, which resulted in high overlaps of primary studies as observed in this umbrella review.

When considered together, the evidence summarised from the included systematic reviews and meta-analysis, and the conclusion from recent systematic scoping reviews [11,337-339] indicates that maternal exposure to elevated temperatures is a *potential* risk factor for pregnancy outcomes.

7.5.2 Plausible pathophysiological mechanisms

Despite the recognition that maternal exposure to particularly extreme heat is associated with adverse birth outcomes, the underlying pathophysiological mechanisms remain unclear.[297] However, several experimental and clinical observational studies have identified plausible pathways. [21,22,297,340-343] Pregnancy induces numerous anatomical and physiological changes in women such as a change in surface area-to-mass ratio, weight gain, high basal metabolic rate, higher-fat deposits that retain heat, reduced systemic vascular resistance, and heat generated by the fetus' metabolism.[297,333] With these conditions, extreme thermal exposure easily disrupts normal thermoregulation and makes it difficult for pregnant women to maintain normothermia.[297,333] This increases thermal strain, especially heat strain, and causes hyperthermia. Hyperthermia or hypothermia can cause oxidative stress, affect placental growth and physiology, including a reduction in placental blood flow, and trigger central neuroendocrine and inflammatory systems to release prostaglandins, oxytocins, cytokines, adrenalin, and other inflammatory factors.[22,297,340] A chronic reduction in uteroplacental blood flow reduces the transfer of water, oxygen, and nutrients to the fetus and the removal of toxic substances from the fetus.[21,297,341] These together with apoptosis and disruption of normal processes of embryogenesis and organogenesis caused by oxidative stress affect fetal health, growth, and development which can result in fetal growth restriction, LBW, and stillbirth.[342] The release by neuroendocrine and inflammatory systems, especially prostaglandins and oxytocin secretion could initiate premature labour, resulting in spontaneous PTB.[128,344,345] Heat stress can also cause dehydration which could affect blood volume and uteroplacental blood flow.[346] Upregulated production of heat-shock proteins (HSPs) with associated increased production of inflammatory factors and effects on placental leading to birth outcomes have also been documented in the literature.[341,343] The HSPs, especially HSP 60, 70, 90, and 100 in reproduction and other pathologies have been also reported as potential clinical biomarkers for diagnostic and therapeutic interventions.[343,347-349] Fetal core temperature is dependent on fetoplacental temperature gradients and to a lesser extent heat dissipation through the amniotic fluid and uterine wall which determines another plausible pathway of stillbirth as a direct effect of the fetal heat-shock response.[22,297]

7.5.3 Recommendations for research, practice, and policy

7.5.3.1 For primary, systematic reviews and meta-analyses studies

Because establishing more robust evidence is required to design and implement thermal-health interventions,[333] methodological limitations regarding study designs, multiple temperature metrics, choice of exposure windows and threshold need to be addressed to strengthen the evidence. In addition to using spatiotemporally resolved temperature data to improve exposure assessment, novel, and robust statistical modelling approaches such as distributed lag linear and non-linear models to account for both intensity and timing of past exposures to flexibly model linear or nonlinear exposure-lag-response association is recommendable.[58-60] This approach has been applied in several recent studies to investigate both short-term [119-121,314] and long-term effects [62,63,256] of temperature to identify finer temporal susceptible exposure periods such as days, weeks, or months instead of the trimester-average exposures. A simulation study has demonstrated that trimester-specific effect estimates are biased and wrongly identified susceptible periods which could even span multiple trimesters.[58] Also, there are limited investigations for other serious birth outcomes which are now being investigated in a few recent studies such as small for gestational age [63,242,292] and macrosomia [336] but none for large for gestational age. These birth outcomes are gaining more attention in air pollution epidemiology.[53,68,286,296] Investigations on these less-studied birth outcomes, as well as cold-related effects, are required. Recent literature has also indicated that preconception periods, especially up to twelve weeks before pregnancy [111] are critical susceptible periods of environmental exposures [112,350,351] and critical periods to prevent pregnancy outcomes.[110] This requires attention in future studies. Further studies are also needed to better understand the pathophysiological processes that underpin maternal exposure to thermal stress and pregnancy outcomes.[297] Developing novel methods to quantify the health impact and economic value of climate change on pregnancy outcomes will also be helpful [337] as reported for air pollution and birth outcomes in Spain.[352]

Another important issue raised in the recent literature is that to design cost-effective and effective adaptation or mitigation strategic action plans for thermal vulnerability, it is critical to first build a quality body of evidence with appropriate thermal metrics.[74,75] The ambient thermal environment is a combination of air temperature, relative humidity, solar radiation or radiant temperature, and air speed, and this cannot be represented adequately by temperature alone.[74,76] As the human body does not have sensors to "feel" individual meteorological parameters such as temperature, the impact of thermal exposure on humans is a function of the total thermal environment and human thermophysiological responses.[75,76] It is thus recognised that rather than temperature, composite biothermal or thermophysiological metrics that integrate the total thermal environment with human physiology (metabolic heat production), and behaviour will become the usual exposure metrics as the necessary meteorological data and computational techniques become available.[74,76,353] Four out of several thermophysiological or biothermal (hereon biothermal) metrics have been evaluated comprehensively and found appropriate for thermal-related epidemiological studies, biometeorological forecasting and warning systems, and many human biometeorological applications. These are Universal Thermal Climate Index (UTCI), Physiologically Equivalent Temperature (PET) or updated PET (modified PET, mPET), Perceived Temperature, and rational Standard Effective Temperature (SET).[76] Although with different reference conditions, these biothermal metrics are computable with the same combined climatic variables stated above using RayMan and SkyHelios Model software [354] or with R packages 'ClimInd' for UTCI, [355] and 'comf' for SET,[356] and a python package 'pythermalcomfort' for UTCI and SET,[357] being extended for all thermal metrics (https://pythermalcomfort.readthedocs.io/en/latest/index.html). Another useful resource is the recent global gridded UTCI dataset at 0.25°×0.25° spatial resolution (~31 km at the equator) at an hourly scale, spanning from 1979 to the present. [106] This dataset can be accessed freely from the Copernicus Climate Change Data Store (https://doi.org/10.24381/cds.553b7518). Future studies could benefit from this dataset. Comparison studies have shown that UTCI derived from the advanced Fiala multi-node model based on contemporary science,[103-105] is currently the most suitable biothermal metric.[78,79,358] But few recent comparison studies no substantial difference or little improvement in the updated PET (mPET) and UTCI, depending on the climatic conditions.[359,360] Thus, UTCI and mPET based on the principle of the human body-energy-balance model of heat transfer inside the human body, thermophysiological model, clothing model, and human-environmental interaction are outstandingly suitable state-of-the-art biothermal metrics.[76,361] Therefore, to make thermal-related findings thermophysiologically relevant and comparable, the application of UTCI is now gaining popularity in epidemiological and medical research as reviewed elsewhere [81] and in other different fields.[82] However, none of the primary studies in the systematic reviews included in this umbrella review used any of the biothermal metrics. For environ-perinatal epidemiology, two recent studies have used the biothermal metrics PET [121] and UTCI [119] which were computed with RayMan software.[362] With the increasing availability of meteorological data and open-access computational packages, future studies could consider biothermal metrics to increase the robustness, comparability, and physiological relevance of the findings.[74,76,80]

The methodological and reporting qualities of future systematic reviews and meta-analyses need to be improved by adhering to standard review guidelines, especially the new environmental health-specific guideline, COSTER.[176] Notable areas that require improvement include providing data on the prevalence of outcomes and the average of the exposure in each included primary study, an explicit statement on prior review protocol (and accessibility), risk of bias assessment of included primary studies, and assessment of confidence in the body of evidence.[84,176]

7.5.3.2 Climate change-resilient strategies at the population, health system, and policy

As both climate change and air pollution continue to increase globally, [2,7] and given that climate change also increases the concentration of air pollutants, their joint effects may further affect reproductive health outcomes either directly or indirectly.[2,274,337] Therefore, taking society-wide urgent actions to address the impacts of climate change as recommended in *Sustainable Development Goal (SDG) 13* is needed now more than ever.[228,327] This is particularly important for vulnerable groups such as pregnant women and unborn babies where the impacts can be immediate through to adulthood and future generations.[7,363] Some climate change adaptation and mitigation strategies to consider are behavioural changes (examples, reduced outdoor activities during extreme climate events, hydration during hot climates, seeking shade or cool areas, wearing appropriate thermal-resilient clothing), thermal-resilient health system, changes to the built environment (examples, use of air conditioning or fans with water spraying device, improved natural ventilation, thermal-resilient building materials, green infrastructure), and the necessary structural and policy interventions.[333,364] As climate change is expected to increase in the coming years,[7] building climate change-resilient health systems should be given urgent action to prevent many of the associated health risks.[327] Preparing health systems for climate change should include the development of comprehensive and appropriate thermal-health guidelines that integrate climate change with the traditional non-climatic factors in managing maternal and child health.[272,327,363] *Greening* strategies to cool the environment,[364,365] awareness creation, education, and climate change advocacy roles by clinicians are also needed.[274,298] These are essential in achieving SDG 3 regarding improvement in maternal and child health.[228] The increasing climate change and associated health outcomes, including pregnancy outcomes as reported in this umbrella review and related reviews [11,337-339] also support SDG 7 for transitioning to affordable, clean or non-fossil-based fuel, and renewable energy sources such as geothermal, solar, wave, wind and other green or clean energy technologies.[228,272,366] Causes of climate change are anthropogenic, especially through greenhouse emissions with well-recognised health impacts.[7,363] Thus, albeit the *probable evidence* of thermal stress-birth outcome effect, consideration of the precautionary principle is necessary to achieving the related "by 2030" agenda for SDGs 3, 7, and 13.[228] Application of the precautionary principle means that "*when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically*" to protect the public health, environment, and future generation.[134]

7.5.4 Strengths and limitations

To the best of our knowledge, this is the first umbrella review that systematically and comprehensively assessed, evaluated, and provided an overall summary of the epidemiological evidence linking ambient temperature to birth outcomes. The review process followed standard review guidelines. A review protocol was registered in PROSPERO and developed into a published peer-reviewed article [83] before the conduct of this umbrella review. The literature search was comprehensive and conducted prospectively by activating database alerts based on the same criteria to ensure regular updates of the results with new eligible studies. The geographical variability of countries or regions that contributed primary epidemiological evidence to the current literature was shown geo-visually. The degree of overlap of the primary studies was also quantified with a validated index. Key themes and gaps were identified with clear recommendations for future studies, pregnant women, clinicians, public health officers, and policymakers.

Some limitations also exist in this umbrella review. The generalisability of the finding is limited as the current epidemiological evidence is highly representative of a few developed countries. The limited evidence from the most vulnerable regions, LMICs due to data challenges is a serious limitation that requires urgent attention. However, recent analyses of survey datasets indicated consistent results of increased risk of birth outcomes for high-temperature exposure in LMICs.[334-336] The substantial differences in exposure metrics, exposure assessments, exposure periods, and thresholds make the results incomparable. The only systematic review that conducted a meta-analysis by regrouping the effect estimates broadly still had obvious heterogeneity such as combining effect estimates of exposures over a trimester or entire pregnancy for long-term effects and exposure period <4 weeks for short-term effects.[16] The current epidemiological evidence was rated as *probable evidence* of causality. We note that this is an outcome of, and not a limitation of the study, and should not delay any precautionary measures by pregnant women, healthcare providers, and policymakers to protect maternal and fetal health. Another limitation of this umbrella review was that all findings were based on surrogate use of ambient temperature rather than biothermal metric. There is also a potential for publication bias due to English-language restriction, but the impact is expected to be negligible as reported elsewhere.[177,178] A known limitation of umbrella reviews is the multiple inclusion of primary studies. This was estimated to be high for this umbrella review.

7.6 Conclusion

Up-to-date epidemiological studies connecting extreme temperatures to birth outcomes were summarised, and challenges and gaps in the field were highlighted with detailed recommendations for further studies and precautionary measures. Numerous exposure metrics and windows for ambient temperature were reported in primary studies that mostly focused on the association with PTB, stillbirth, and LBW, making results incomparable. Overall, the current epidemiologic evidence, predominantly from a few developed countries indicated *probable evidence* of causation due to high heterogeneity and the absence of randomised controlled trials. To strengthen the evidence, more high-quality studies, including the use of biothermal metrics and investigation of critical susceptible exposure periods are required, particularly from geodemographically susceptible settings. However, given the observed positive temperature-birth outcome associations summarised here and the recognised increasing climate change,[7] a society-wide precautionary measures to minimise the potentially devastating associated risks of climate change on maternal and fetal health is needed as advised in the SDGs 3, 7, and 13.[228]

Chapter 8. Short-term maternal exposure to biothermal stress and the risks of stillbirth and spontaneous preterm birth in Western Australia

8.0 Preamble

This chapter provides primary investigations of the short-term (acute) maternal exposure to biothermal (thermophysiological) stress, measured with Universal Thermal Climate Index (UTCI) and the risks of stillbirth and spontaneous preterm birth in Western Australia. The chapter is made of two articles as they were published in the peer-reviewed journals with the titles 'Maternal acute thermophysiological stress and stillbirth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis' in *Science of the Total Environment* [367] and 'Prenatal acute thermophysiological stress and spontaneous preterm birth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis' in *International Journal of Hygiene and Environmental Health*.[368]

8.1 Maternal acute thermophysiological stress and stillbirth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis

8.1.1 Abstract

Background: The extreme thermal environment driven by climate change disrupts thermoregulation in pregnant women and may threaten the survival of the developing fetus.

Objectives: To investigate the acute effect of maternal exposure to thermophysiological stress (measured with Universal Thermal Climate Index, UTCI) on the risk of stillbirth and modification of this effect by sociodemographic disparities.

Methods: We conducted a space-time-stratified case-crossover analysis of daily UTCI and 2,835 singleton stillbirths between 1st January 2000 and 31st December 2015 across multiple small areas in Western Australia. Distributed lag non-linear models were combined with conditional quasi-Poisson regression to investigate the effects of the UTCI exposure from the preceding 6 days to the day of stillbirth. We also explored effect modification by fetal and maternal sociodemographic factors.

Results: The median UTCI was 13.9 ^{o}C (representing no thermal stress) while the 1st and 99th percentiles were 0.7 ^{o}C (slight cold stress) and 31.7 ^{o}C (moderate heat stress), respectively. Relative to median UTCI, we found positive associations between acute maternal cold and heat stresses and higher risks of stillbirth, increasing with the intensity and duration of the thermal stress episodes. The cumulative risk from the preceding 6 days to the day of stillbirth was stronger in the 99th

percentile (RR= 1.19, 95% CI: 1.17, 1.21) than the 1st percentile (RR= 1.14, 95% CI: 1.12, 1.15), relative to the median UTCI. The risks were disproportionately higher in term and male stillborn fetuses, smoking, unmarried, ≤19 years old, non-Caucasian, and low socioeconomic status mothers.

Discussion: Acute maternal exposure to both cold and heat stresses may contribute to the risk of stillbirth and be exacerbated by sociodemographic disparities. The findings suggest public health attention, especially for the identified higher-risk groups. Future studies should consider the use of a human thermophysiological index, rather than surrogates such as ambient temperature.

8.1.2 Introduction

With nearly two million stillbirths occurring annually worldwide, stillbirth causes substantial psychosocial burdens for families and economic burdens for countries.[303] Several risk factors have been associated with stillbirth, but a high proportion of the causes of stillbirth remain unexplained.[100,209] The biological mechanisms of stillbirth are also yet to be established. A better understanding of the causal pathways is indispensable towards the global goal of reducing stillbirth to zero or fewer than 12 per 1000 live births in every country by 2030.[100,303]

The increasing climate change events such as extreme temperatures have potentially disproportionate impacts on health outcomes of vulnerable populations such as pregnant women and developing fetuses.[369,370] Pathophysiologic evidence from animal studies indicated that maternal exposure to extreme temperatures (heat or cold stress) disrupts thermoregulation, causes hyper- or hypothermia and oxidative stress that affect placental and fetal physiology, leading to adverse pregnancy outcomes.[22,371]

Recent epidemiologic studies are showing a strong association between maternal exposure to heat and cold stress and the higher risk of stillbirth with multiple temperature metrics.[16,331] However, defining heat or cold stress from ambient temperature with or without relative humidity [74,331] has been reported as an oversimplification of the net heat load of human exposure.[74] This approach does not account for the heat balance between the actual thermal environment and human physiological and behavioural responses.[74,77] Also, the exposure assessments were mostly derived from ground-based meteorological monitors that are distant from where people reside.[77,331] Consequently, the findings may be unrealistic with high uncertainty which impedes timely and cost-effective decision-making.[74,369] The multiple temperature metrics also hinder the objective comparison of findings across studies.[80,81] Some recent studies have recommended exposure assessment with human thermophysiological indices at high spatiotemporal resolution.[74,76,77] Four principal thermophysiological indices that have been recommended to date include Universal Thermal Climate Index (UTCI), Physiological Equivalent Temperature (PET), Perceived Temperature, and rational Standard Effective Temperature (SET).[76] Among these indices, UTCI best represents specific climatic conditions at a location and is most sensitive to changes in ambient thermal stimuli as similar to the human body.[78,79] There are growing applications of UTCI.[82] However, a recent systematic review reported the underutilisation of UTCI in thermal stress-related studies in epidemiology and medical sciences, despite the prognostic potential of UTCI to support climate change-related public health and clinical interventions. UTCI was utilised in only a few studies on mortality and cardiovascular diseases.[81] So far, only one known study on pregnancy outcomes used

UTCI and calculated UTCI with meteorological parameters from one synoptic station,[119] which would have introduced increasing exposure misclassification with distance from the station.

Stillbirth remains a major public health concern in high-income countries (HICs), including Australia.[100,225] Compared with other HICs, Australia's late-gestation (> 28 weeks) stillbirth rate in 2015 was 2.7 per 1,000 births which was found to be 30% higher than other best-performing HICs such as Iceland and Denmark.[100,225] Annually, Australia records over 2,000 stillbirths which translates to at least six women experiencing this traumatic event daily.[225] About 40% of Australia's stillbirths occurring in late gestation were unexplained.[225] Given severe climate change events in Australia,[370] maternal exposure to heat or cold stress during late gestation may explain some fraction of the unexplained causes of stillbirths. Three previous Australian studies, all from Brisbane, Queensland found a positive association between extreme ambient temperatures and stillbirth. However, there were some inconsistencies: higher risk in both low and high temperatures in the second trimester,[372] higher risk in early than late pregnancy exposure to a heatwave in warm months,[373] and higher risk in the last four weeks of gestation.[253] Also, none of these studies examined the acute effect of the exposure leading up to the day of fetal death as reported in other HICs through a time-stratified case-crossover design.[374-376] Furthermore, due to the geoclimatic variations, acclimatisation, and mitigation strategies, even findings at specific geographic locations within the same country cannot necessarily be generalised to different climatic and sociodemographic conditions. Therefore, geoclimatic-specific studies that reflect local-level variation can be more beneficial.[331]

We aimed to address the above limitations by using a spatiotemporally resolved UTCI rather than ambient air temperature to investigate the associations between maternal exposure to acute heat and cold stresses and stillbirth in Western Australia (WA). This study hypothesised that maternal exposure to both heat and cold thermophysiological stress on and up to 6 days before stillbirth was associated with a higher risk of stillbirth, and that such associations were further higher among sociodemographically susceptible groups.

8.1.3 Methods

This study was reported following the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines.[239]

8.1.3.1 Study design

We conducted a space-time-stratified case-crossover design.[115] A case-crossover design is a case-only self-matched approach in which a case serves as its control and therefore eliminates within-person time-invariant confounders such as sociodemographic factors.[114,377] Time-varying confounders are also controlled by a referent selection strategy that matches a series of ‘control or referent times’ to the ‘case or index time’.[378] Furthermore, the time-stratified self-matching can be implemented at multiple small-area levels for assigning the exposure at a fine spatiotemporal scale to reduce exposure misclassification.[116,118,379] We used a time-stratified case-crossover design at a small area level to control for seasonal and long-term trends by matching case and control days within a day of the week, month, and a year within the same small area in the study location.[115,116,118] A maximum lag of 21 days was used to eliminate the potential displacement of acute effect or the ‘mortality displacement’, defined as the reduction in the risk at longer lags which cancel out the higher risk associated with the acute exposure effect.[380,381]

8.1.3.2 Study population and case identification

WA is the largest state in Australia, covering 2.6 million km², with a total population of 2.7 million and diversified climatic zones.[90] This study used a retrospective birth cohort of all births in WA between 1st January 2000 to 31st December 2015, selected from the Midwives Notification System. The Midwives Notification System is a statutory health data collection of all births with at least 20 weeks’ of completed final gestation or at least 400 g birth weight if the gestational length is unknown.[96] The system contains individual-level information for mothers and children along with the maternal residential address at the time of delivery at statistical area level 1 (SA1). SA1s are the second smallest geographical unit defined in Australia.[240] A total of 474,835 births occurred during the study period. We sequentially excluded the births with missing SA1 (n = 35,352), multiple births (n = 13,026), and live births (n = 423,611). Given that we considered a maximum of 21 lag days, we excluded births less than 21 days before the end of the study period to allow sufficient follow-up time (n = 11). The final sample consisted of 2,835 singleton stillbirths in 2,041 SA1, representing 6.0 per 1,000 births in this study. Stillbirth was defined as neonates born with no sign of life at or after ≥ 20 weeks’ completed gestation.[225,253,372,373] We also defined subgroups based on the following information: fetal sex (male or female), gestational age (preterm if < 37 weeks’ gestation or term birth), maternal age at birth delivery (≤ 19, 20–34, and ≥ 35 years), tobacco smoking status (non-smoker or smoker), and race or ethnicity (Caucasians and non-Caucasians). We also categorised birth into three seasons: summer (December-February), winter (June-August), and the transition period (remaining months). Similarly, the year of birth was trisected (2000-2004, 2005-2009, 2010-2015). The Index of Relative Socio-economic Disadvantage at a Statistical Local Area level derived by the Australian Bureau of Statistics[102] was assigned to the maternal residence at the time of birth and categorised into quintiles as described previously.[382] We grouped quintiles 1st and 2nd as high and 3rd-5th as low socioeconomic status (SES) groups.

A known limitation in stillbirth data is the unknown time of fetal death.[374] The date of stillbirth delivery is pathologically different from the time of fetal death due to the wide window period between the last evidence of fetal life and the first evidence of fetal death.[383] The average delay time between fetal death and delivery has been reported as 48 hours with a median of fewer than 24 hours based on histologic evaluation.[384,385] In HICs, 5.5–18.4% of stillbirths occur during labour (intrapartum) with the majority occurring before the onset of labour (antepartum).[209] The antepartum stillbirth rate in Australia is 82.7%.[386] Therefore, as commonly reported in previous studies, we defined the day of stillbirth (case day) by deducting 2 days from the date of stillbirth delivery to correct for the estimated 48 hours average of death-to-delivery delay.[374,376,384]

8.1.3.3 The UTCI exposure

The UTCI is an isothermal equivalent air temperature (°C) that describes both atmospheric heat exchange conditions (stress) and human physiological responses (strain) based on thermophysiological and heat exchange theories.[80,103] UTCI was derived from the advanced Fiala multi-node model of human thermoregulation.[80,104] We obtained the UTCI from the ERA5-HEAT (Human thermal comforT) dataset, a novel dataset derived by Di Napoli *et al* from the ERA5 reanalysis.[106] The ERA5 reanalysis is a climate dataset that combines global climate model data with quality-controlled historical in situ and satellite observations across the world to provide a global complete and consistent description of multiple climate variables.[387] The ERA5 dataset was created by the European Centre for Medium-Range Weather Forecasts (ECMWF) at an hourly level from 1979 to date at $0.25^{\circ} \times 0.25^{\circ}$ (27 km x 27 km) spatial resolution. The ERA5-HEAT dataset took inputs from the following ERA5 variables: 2 metres above ground level for both air temperature and dew point temperature (relative humidity), wind speed at 10 metres above ground level, solar radiation, and thermal radiation at the surface of the Earth.[106] As a thermophysiological stress index, UTCI calculation requires the mean radiant temperature (MRT) as an input variable. The MRT describes the heat load experienced by a person in an outdoor environment and irradiated by solar and thermal radiation given an environment, posture, and thermal properties of clothing.[388,389] MRT was calculated from the ECMWF numerical weather prediction model radiation outputs that accounted for changes in the Sun's position to generate global gridded MRT (Di Napoli et al 2020). The gridded UTCI was then computed by an automated operational procedure via a six-order polynomial equation from four gridded stacks: MRT and ERA5-retrieved air temperature, relative humidity, and wind speed.[104,106] Further description of the gridded UTCI dataset is available elsewhere.[106] We obtained the daily gridded UTCI at 0.25° × 0.25° spatial resolution of the 24-hour averages between 1st January 2000 to 31st December 2015 across Australia and extracted the UTCI at the SA1 levels in WA using ArcGIS software (version 10.8.1).

8.1.3.4 Statistical analysis

8.1.3.4.1 Main and subgroup analyses

We combined distributed lag non-linear model (DLNM) with conditional quasi-Poisson regression to simultaneously investigate the immediate and cumulative lagged effects of the time-varying UTCI exposure on stillbirth.[60,116,118,119] The non-linear exposure–lag–response association was defined through the cross-basis term [59,60] of the UTCI predictor using natural cubic splines in both dimensions of the UTCI predictor and the lags with a maximum of 21 lag days. Spline knots were set at equally spaced values on the log scale of lags.[59,60] The selection of the degrees of freedom (number of knots) for UTCI predictor and lag days was based on the minimisation of the Akaike information criterion (AIC) among different combinations.[59,60] Accordingly, we selected 2 and 3 degrees of freedom for the predictor and lags, respectively. The modelling framework was specified as follows:

$$\log\left[E\left(Y_{t,s}\right)\right] = \alpha + cb(UTCI) + holiday, eliminate = factor\ (stratum)$$

where α is the intercept; $Y_{t,s}$ is the observed number of daily stillbirths at day *t* in spatial location *s* (SA1); *cb* is the cross-basis function to model the non-linear exposure-lag-association of daily UTCI, and *holiday* is a binary indicator variable for public holidays. The factor variable *stratum* defined the same days of the week in the same month of the same year at the same SA1. We conditioned on the *stratum* through the "eliminate" function in "gnm" package to include adjusted factors that are required in the model but are not of direct interest.[116,122] This also substantially improved the computational efficiency of the modelling even where there were many factor levels.[116,122] This modelling framework has been applied recently,[118,379] and the methodology has been previously described elsewhere.[59,116] The median UTCI was used as a reference to estimate the relative risks (RRs) and 95% confidence intervals (CIs) at the cold (1st and 5th percentiles), mild (25th and 75th percentiles), and heat stress (95th and 99th percentiles). We presented the results for the immediate effects of exposure on the day of fetal death (lag 0) and cumulative effects from day 0 up to preceding day N (lag 0-N) for the first six preceding days.[119,121,374-376] We also reported lag 0-13 and lag 0-21, representing exposure up to the second- and third-weeks preceding stillbirth respectively.[119,121] We reported cumulative effects rather than individual lag days to avoid potential spurious findings due to collinearity associated with single-lag results in distributed lag models.[380,390]

We also calculated the attributed risk (AR) as the number of excess stillbirths per 10,000 births that could be attributable to cold and heat stress exposures:[351]

$$AR = I_u\,(RR - 1)$$

where I_u is the background rate. This was taken as the study-specific incidence rate and calculated as from the eligible stillbirths and the total birth over the study period (0.6%). RR is the estimated RR (95% CI) for immediate (lag 0) and cumulative (lag 0-6) cold and heat stress exposures, relative to the median UTCI.

Subgroup analyses were conducted to investigate the potential modification effects of the fetal and maternal sociodemographic factors described earlier. Missing fetal sex (n = 6), gestational age (n = 29), and tobacco smoking status (n = 16) records were excluded from subgroup analyses. We reported the RR (95% CI) for the 1st and 99th percentiles, relative to the median UTCI.

8.1.3.4.2 Sensitivity analyses

We also performed several sensitivity analyses to ascertain the robustness of the main analysis to choices of the model assumptions. We changed the degrees of freedom to 3 for both UTCI predictor and lags; and then to 3 for the predictor with 4 for lags. Also, we changed the reference median UTCI to mean UTCI; and then to the average of the standard *no thermal stress* range which is 17.5 ^{o}C.[103,106] Due to discrepancies in the event day definition, we redefined the stillbirth date as a day death-to-delivery delay [375] and then day of stillbirth delivery [119,121] and reanalysed the data.

All analyses were performed with R software (version 4.1.1) and the packages 'dlnm' [60] and 'gnm' [122] were used to fit DLNM and conditional quasi-Poisson regression, respectively. Following the recent recommendations of the American Statistical Association, we reported and interpreted the RR (95% CI) without considering the 'statistically significant' threshold.[181]

8.1.4 Results

8.1.4.1 The UTCI exposure and birth cohort characteristics

The standard UTCI ranges were originally categorised into 10 thermal stresses levels corresponding to specific human physiological responses to the actual thermal environment.[103,106] Across the study period, the mean (± standard deviation) and median UTCI (interquartile range) were 14.6 ^{o}C (± 6.8 ^{o}C) and 13.9 ^{o}C (9.4 ^{o}C), respectively, both falling within the *no thermal stress* range of 9 ^{o}C to 26 ^{o}C. The 1st (0.7 ^{o}C) and the 99th (31.7 ^{o}C) percentiles were within *slight cold stress* and *moderate heat stress* levels, respectively. The largest mean UTCI was observed in summer (20.6 ± 5.4 ^{o}C), 2010-2015 (15.2 ± 6.8 ^{o}C) which also lied within the *no thermal stress* range (Table 8.1.1).

Table 8.1.1The descriptive statistics of daily mean UTCI (ºC), Western Australia, 2000-2015.

Variable	Subgroup	Min	Mean ± SD	P1	P25	Median	P75	P99	Max
	All	-15.4	14.6 ± 6.8	0.7	9.7	13.9	19.1	31.7	41.9
Season	Winter	-12.4	8.5 ±4.1	-1.3	5.9	8.5	10.9	20.9	31.9
	Transition	-15.4	14.6 ± 5.8	1.5	10.9	14.1	18.0	30.8	40.2
	Summer	-0.6	20.6 ± 5.4	9.6	16.6	20.3	24.3	33.7	41.9
Year	2000-2004	-11.0	14.2 ± 6.7	0.5	9.4	13.5	18.7	31.2	41.9
	2005-2009	-15.4	14.1 ± 6.9	0.2	9.3	13.4	18.6	31.7	40.3
	2010-2015	-10.2	15.2 ± 6.8	1.5	10.3	14.6	19.8	32.0	41

Note: SD, standard deviation; P1, P25, P75, and P99 are 1st, 25th, 75th, and 99th percentiles respectively; UTCI, Universal Thermal Climate Index in degree Celsius.

Out of the total of 2,835 singleton stillbirths included in this study, 41.4% occurred during 2010-2015 and over half (51.4%) in the transition seasons. Slightly above half were males (52.1%), and the majority were preterm stillborn (80.8%). Most of the pregnant women did not smoke (78.4%), were married (83.5%), were aged between 20–34 years (71.1%), and Caucasians (69.6%). More than three-fifth of the births were to women who resided in high SES areas (64.3%) (Table 8.1.2).

Table 8.1.2 Number of stillbirths by year, season, and fetal and maternal sociodemographic characteristics included in the study, Western Australia, 2000-2015 (N= 2,835).

Variable	**Characteristics**	**n (%)**
Year	2000-2004	780 (27.5)
	2005-2009	880 (31.0)
	2010-2015	1,175 (41.4)
Season	Transition	1,456 (51.4)
	Winter	682 (24.0)
	Summer	697 (24.6)
Sex*	Male	1,476 (52.1)
	Female	1,353 (47.7)
	Unknown	6 (0.2)
Gestational age (weeks)*	Term (≥ 37)	514 (18.1)
	Preterm (< 37)	2,292 (80.8)
	Unknown	29 (1.0)
Smoking status during pregnancy*	Non-smoker	2,223 (78.4)
	Smoker	596 (21.0)
	Unknown	16 (0.6)
Marital status	Married/de facto married	2,370 (83.5)
	Unmarried#	465 (16.1)
Maternal age at delivery (years)	Teenagers (≤19)	180 (6.3)
	Young adults (20–34)	2,015 (71.1)
	Older adults (≥35)	640 (22.6)
Maternal race/ethnicity	Caucasian	1,974 (69.6)
	Non- Caucasian	861 (30.4)
Residential area's socioeconomic disadvantage status	Low	1,011 (35.7)
	High	1,824 (64.3)

#Never married/separated/divorced/widowed/unknown. *The missing records were excluded from subgroup analyses.

8.1.4.2 Thermophysiological stress and stillbirth

The exposure-response association on the day of fetal death (lag 0) and the cumulative effects showed U-shaped curves, indicating that both cold and heat thermal stresses were associated positively with the risk of stillbirth (Figure). Relative to the median UTCI (no thermal stress), the positive associations increased with the intensity and duration of the thermal stress episodes. The risks were stronger at the cold stress (1st and 5th percentiles) and heat stress (95th and 99th percentiles) than the 'mild' thermal stress (25th and 75th percentiles), increasing with cumulative exposures. Relative to no thermal stress (median UTCI), the risk of stillbirth for exposure to cold stress (1st percentile) and heat stress (99th percentile) were very similar on the day of stillbirth up to two preceding days and then the same at 8% higher risk on the cumulative three days (RR=1.08, 95% CI: 1.07, 1.09).

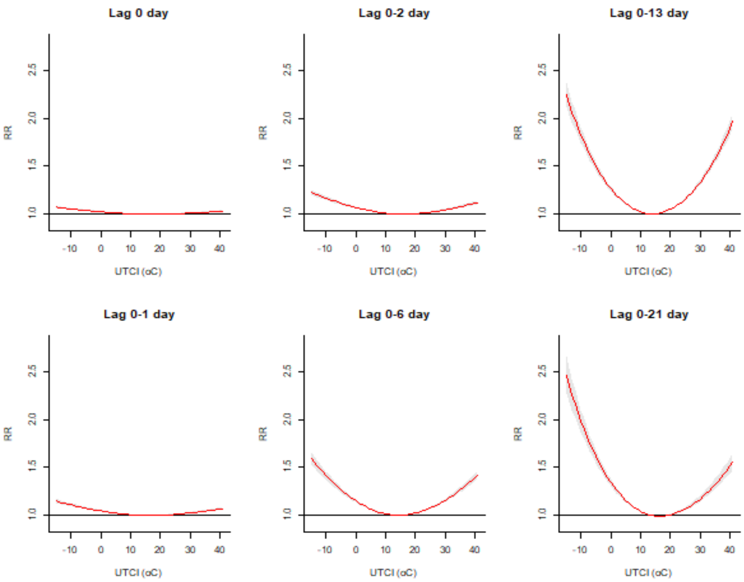

Figure 8.1.1 Exposure-response curves of daily UTCI and cumulative relative risk of stillbirths, relative to median UTCI of 13.9 ºC on the event day and up to different preceding days. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals (CIs). Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Thereafter, the cumulative risks were stronger in the heat than cold stress. The cumulative risk from the 6 preceding days to the day of stillbirth was higher by 14% in the 1st percentile (RR= 1.14, 95% CI: 1.12, 1.15) but higher by 19% in the 99th percentile (RR= 1.19, 95% CI: 1.17, 1.21) as compared to the risks at the median UTCI.

Table 8.1.3. The cumulative relative risks of stillbirth for different UTCI levels relative to median (13.9 °C), Western Australia, 2000-2015

Lag days	1st (0.7 ºC) RR (95% CI)	5th (4.2 ºC) RR (95% CI)	25th (9.7 ºC) RR (95% CI)	75th (19.1 ºC) RR (95% CI)	95th (26.7 ºC) RR (95% CI)	99th (31.7 ºC) RR (95% CI)
0	1.02 (1.02, 1.03)	1.01 (1.01, 1.02)	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)	1.01 (1.00, 1.01)	1.01 (1.01, 1.02)
0-1	1.04 (1.04, 1.05)	1.03 (1.02, 1.03)	1.01 (1.01, 1.01)	1.00 (1.00, 1.00)	1.01 (1.01, 1.02)	1.03 (1.02, 1.04)
0-2	1.06 (1.05, 1.07)	1.04 (1.03, 1.04)	1.01 (1.01, 1.01)	1.00 (1.00, 1.00)	1.03 (1.02, 1.03)	1.05 (1.04, 1.06)
0-3	1.08 (1.07, 1.09)	1.05 (1.04, 1.06)	1.01 (1.01, 1.02)	1.00 (1.00, 1.01)	1.04 (1.03, 1.05)	1.08 (1.07, 1.09)
0-4	1.10 (1.09, 1.11)	1.06 (1.05, 1.07)	1.01 (1.01, 1.02)	1.01 (1.00, 1.01)	1.06 (1.05, 1.07)	1.12 (1.10, 1.13)
0-5	1.12 (1.11, 1.13)	1.07 (1.06, 1.08)	1.02 (1.01, 1.02)	1.01 (1.01, 1.01)	1.08 (1.07, 1.09)	1.15 (1.13, 1.17)
0-6	1.14 (1.12, 1.15)	1.08 (1.07, 1.09)	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)	1.10 (1.09, 1.11)	1.19 (1.17, 1.21)
0-13	1.24 (1.22, 1.26)	1.13 (1.12, 1.14)	1.03 (1.02, 1.03)	1.03 (1.03, 1.04)	1.21 (1.19, 1.22)	1.41 (1.38, 1.44)
0-21	1.31 (1.28, 1.35)	1.18 (1.17, 1.20)	1.05 (1.04, 1.06)	1.00 (0.99, 1.00)	1.10 (1.08, 1.12)	1.22 (1.18, 1.25)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

There was also an indication of long-term effects as observed in the higher risk in relatively prolonged cumulative lag days (0-13 and 0-21) (Table 8.1.3). Compared to the median UTCI, acute cumulative exposures for days 0 to 6 of cold and heat stress were approximately attributed to 8

(95% CI: 7, 9) and 11 (95% CI: 10, 12) excess stillbirths per 10,000 births, respectively, using our study-specific background incidence as reference (Table 8.1.4). Both heat and cold stresses indicated lower risks during winter but higher risks during summer and transition seasons. The cumulative effect for days 0 to 6 of heat stress was 124% higher during the transition (RR = 2.24, 95% CI: 2.19, 2.30) and 21% higher during summer (RR = 1.21, 95% CI: 1.18, 1.25), relative to season-specific median UTCI (Table S8.1.1). The risks were relatively elevated in the earliest year 2000-2004 (Figure S8.1.1).

Table 8.1.4. The attributable risk of stillbirths per 10,000 births for exposure to 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015

Lag days	1st percentile (0.7 °C) AR (95% CI)	99th percentile (31.7 °C) AR (95% CI)
0	1 (1, 1)	1 (0, 1)
0-6	8 (7, 9)	11 (10, 12)
0-13	14 (13, 16)	24 (22, 26)
0-21	19 (17, 21)	13 (11, 15)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; AR, attributable risk

8.1.4.3 Thermophysiological stress and stillbirth by fetal factors

The immediate and cumulative effects by gestational age showed a higher risk in the term than preterm stillbirths.

Table 8.1.5 The cumulative relative risks of stillbirth stratified by fetal gestational age and sex for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015.

Fetal variable	Lag days	1st percentile (0.7 °C) RR (95% CI)		99th percentile (31.7 °C) RR (95% CI)	
Gestational age		Term	Preterm	Term	Preterm
	0	1.03 (1.03, 1.03)	1.03 (1.02, 1.03)	1.07 (1.07, 1.08)	1.00 (1.00, 1.01)
	0-1	1.07 (1.06, 1.08)	1.05 (1.05, 1.06)	1.16 (1.15, 1.17)	1.01 (1.01, 1.02)
	0-2	1.12 (1.11, 1.13)	1.07 (1.06, 1.08)	1.26 (1.25, 1.28)	1.03 (1.02, 1.04)
	0-3	1.19 (1.18, 1.20)	1.09 (1.08, 1.10)	1.39 (1.38, 1.41)	1.04 (1.03, 1.06)
	0-4	1.26 (1.25, 1.28)	1.10 (1.09, 1.11)	1.54 (1.52, 1.56)	1.06 (1.05, 1.08)
	0-5	1.35 (1.33, 1.37)	1.11 (1.10, 1.12)	1.71 (1.69, 1.74)	1.09 (1.07, 1.10)
	0-6	1.45 (1.43, 1.47)	1.12 (1.10, 1.13)	1.91 (1.88, 1.94)	1.11 (1.10, 1.13)
	0-13	2.39 (2.35, 2.44)	1.12 (1.10, 1.14)	3.58 (3.50, 3.66)	1.25 (1.22, 1.27)
	0-21	3.32 (3.24, 3.40)	1.14 (1.11, 1.17)	3.81 (3.69, 3.94)	1.10 (1.07, 1.13)
Fetal sex		Male	Female	Male	Female
	0	1.07 (1.06, 1.07)	0.98 (0.98, 0.98)	1.06 (1.06, 1.07)	0.96 (0.96, 0.96)
	0-1	1.12 (1.11, 1.13)	0.97 (0.97, 0.98)	1.13 (1.12, 1.14)	0.93 (0.93, 0.94)
	0-2	1.16 (1.16, 1.17)	0.97 (0.97, 0.98)	1.21 (1.20, 1.22)	0.91 (0.90, 0.92)
	0-3	1.20 (1.19, 1.21)	0.98 (0.97, 0.99)	1.29 (1.28, 1.31)	0.90 (0.89, 0.91)
	0-4	1.22 (1.21, 1.23)	1.00 (0.99, 1.01)	1.38 (1.36, 1.40)	0.90 (0.89, 0.91)
	0-5	1.23 (1.22, 1.25)	1.03 (1.02, 1.04)	1.46 (1.44, 1.49)	0.90 (0.89, 0.91)
	0-6	1.24 (1.22, 1.25)	1.06 (1.05, 1.07)	1.55 (1.53, 1.57)	0.91 (0.90, 0.92)
	0-13	1.16 (1.14, 1.18)	1.38 (1.36, 1.41)	1.82 (1.78, 1.86)	1.12 (1.10, 1.15)
	0-21	1.15 (1.12, 1.18)	1.61 (1.57, 1.65)	0.98 (0.96, 1.01)	1.70 (1.65, 1.75)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Relative to the median UTCI, the risks were higher in heat stress (99th percentile) than cold stress (1st percentile) for term stillbirth but higher in cold than heat stress for preterm stillbirths. Consistent with the main findings, all the risks were higher with increasing cumulative exposure to either cold or heat thermal stress. For example, the cumulative risk for cumulative exposure in the 6 days preceding stillbirth to the 1st and 99th percentiles, relative to the median UTCI were higher by 45% (RR=1.45, 95% CI: 1.43, 1.47) and 91% (RR=1.91, 95% CI:1.88, 1.94) for term and 12% (RR=1.12, 95% CI: 1.10, 1.13) and 11% (RR=1.11, 95% CI:1.10, 1.13) for preterm stillbirths. While female fetuses were almost unaffected, male fetuses were more susceptible to both cold and heat stresses. The risks were elevated with more cumulative days of exposure and were higher in the 99th percentile than the 1st percentile, relative to the median UTCI (Table 8.1.5).

8.1.4.4 Thermophysiological stress and stillbirth by maternal sociodemographic factors

Relative to the median UTCI, there was no observable short-term effect of exposure to thermal stress among pregnant women who did not smoke during pregnancy. Conversely, both cold and heat stresses showed higher risks of stillbirth in pregnant women who smoked, increasing with duration of exposure and stronger for cold than heat stress. For example, for cumulative 0 to 6 days exposure, the risks were 142% higher in the 1st percentile (RR= 2.42, 95% CI= 2.39, 2.45) and 81% higher in the 99th percentile (RR= 1.81, 95% CI: 1.78, 1.83), relative to median UTCI among those women that smoked during pregnancy. Unmarried pregnant women experienced a higher risk of stillbirth from cold and heat stresses as compared to those identified as married and the risk was stronger in the 99th percentile than 1st percentile, relative to the median UTCI. Regarding races or ethnicity, Caucasians experienced essentially no impact for cold stress but for heat stress, example 8% higher risk (RR=1.08, 95% CI: 1.06, 1.09) for cumulative exposure in the 6 days preceding stillbirth. Relative to median UTCI during the same exposure period, non-Caucasians experienced more elevated risks of 92% higher (RR= 1.92, 95% CI: 1.90, 1.95) and 44% higher (RR=1.44, 95% CI: 1.42, 1.46) for cold and heat stresses, respectively. The immediate effect and cumulative effects for the first five preceding days were more elevated in the high than low SES women for both 1st and 99th percentiles, relative to the median UTCI. However, periods of exposure (from 6 days upward) showed more elevated risk in low than high SES groups (Table 8.1.6).

Women aged ≥ 35 years experienced no or small lower risk from exposure to cold or heat stress, but adverse associations were observed in the other subgroups and more elevated in adolescents (≤19 years) than young adults (20–34 years). Relative to the median UTCI, the risk was stronger in the

99th than 1st percentile for lag 0 to lag 0-4 but became stronger in the 1st than 99th percentiles for longer periods of exposure (Table 8.1.7).

Table 8.1.6. The cumulative relative risks of stillbirth stratified by maternal tobacco smoking status, marital status, race/ethnicity, and socioeconomic status for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015.

Maternal variable	Lag days	1st percentile (0.7 °C) RR (95% CI)		99th percentile (31.7 °C) RR (95% CI)	
Smoking status		Non-smoker	Smoker	Non-smoker	Smoker
	0	0.98 (0.98,0.990	1.17 (1.17, 1.18)	0.94 (0.93, 0.94)	1.22 (1.21, 1.22)
	0-1	0.97 (0.97, 0.98)	1.36 (1.35, 1.37)	0.90 (0.89, 0.90)	1.42 (1.41, 1.43)
	0-2	0.96 (0.95, 0.97)	1.56 (1.55, 1.57)	0.88 (0.87, 0.89)	1.58 (1.57, 1.60)
	0-3	0.95 (0.94, 0.96)	1.77 (1.75, 1.78)	0.88 (0.87, 0.89)	1.71 (1.69, 1.73)
	0-4	0.95 (0.94, 0.96)	1.98 (1.96, 2.00)	0.89 (0.88, 0.91)	1.79 (1.77, 1.81)
	0-5	0.94 (0.93, 0.95)	2.20 (2.17, 2.22)	0.92 (0.91, 0.93)	1.82 (1.79, 1.84)
	0-6	0.94 (0.93, 0.95)	2.42 (2.39, 2.45)	0.96 (0.94, 0.97)	1.81 (1.78, 1.83)
	0-13	0.91 (0.90, 0.93)	4.22 (4.14, 4.30)	1.35 (1.32, 1.38)	1.25 (1.22, 1.27)
	0-21	0.82 (0.80, 0.84)	7.68 (7.49, 7.87)	1.33 (1.29, 1.37)	0.91 (0.89, 0.94)
Marital status		Married/de facto	Unmarried	Married/de facto	Unmarried
	0	1.01 (1.01, 1.02)	1.08 (1.08, 1.08)	0.97 (0.97, 0.97)	1.25 (1.24, 1.25)
	0-1	1.02 (1.02, 1.03)	1.19 (1.18, 1.19)	0.95 (0.95, 0.96)	1.49 (1.48, 1.50)
	0-2	1.03 (1.02, 1.04)	1.32 (1.31, 1.33)	0.95 (0.94, 0.96)	1.72 (1.70, 1.73)
	0-3	1.03 (1.02, 1.04)	1.49 (1.48, 1.51)	0.96 (0.95, 0.98)	1.91 (1.89, 1.93)
	0-4	1.03 (1.02, 1.04)	1.70 (1.69, 1.72)	0.99 (0.97, 1.00)	2.05 (2.02, 2.07)
	0-5	1.02 (1.01, 1.04)	1.96 (1.94, 1.98)	1.01 (1.00, 1.03)	2.14 (2.11, 2.17)
	0-6	1.02 (1.00, 1.03)	2.27 (2.24, 2.30)	1.05 (1.04, 1.07)	2.18 (2.15, 2.21)
	0-13	0.94 (0.92, 0.95)	6.35 (6.23, 6.47)	1.36 (1.33, 1.39)	1.65 (1.62, 1.69)
	0-21	0.88 (0.86, 0.90)	14.04 (13.68,14.41)	1.26 (1.28, 1.30)	1.03 (1.00, 1.06)
		Caucasians	Non-Caucasians	Caucasians	Non-Caucasians
Race or ethnicity	0	0.99 (0.99, 0.99)	1.10 (1.10, 1.10)	0.98 (0.97, 0.98)	1.09 (1.09, 1.10)
	0-1	0.98 (0.98, 0.99)	1.21 (1.20, 1.22)	0.97 (0.96, 0.98)	1.18 (1.17, 1.18)
	0-2	0.97 (0.96, 0.98)	1.33 (1.32, 1.34)	0.97 (0.96, 0.98)	1.25 (1.24, 1.26)
	0-3	0.96 (0.95, 0.97)	1.46 (1.45, 1.47)	0.99 (0.97, 1.00)	1.32 (1.30, 1.33)
	0-4	0.95 (0.94, 0.96)	1.60 (1.58, 1.62)	1.01 (1.00, 1.02)	1.37 (1.35, 1.39)
	0-5	0.93 (0.92, 0.94)	1.75 (1.73, 1.78)	1.04 (1.03, 1.06)	1.41 (1.39, 1.43)
	0-6	0.92 (0.91, 0.93)	1.92 (1.90, 1.95)	1.08 (1.06, 1.09)	1.44 (1.42, 1.46)
	0-13	0.81 (0.79, 0.82)	3.50 (3.44, 3.57)	1.36 (1.33, 1.39)	1.42 (1.40, 1.45)
	0-21	0.67 (0.65, 0.69)	6.47 (6.31, 6.63)	1.19 (1.15, 1.23)	1.19 (1.16, 1.22)
Area-level SES		Low	High	Low	High
	0	1.04 (1.03, 1.04)	1.01 (1.01, 1.01)	1.07 (1.07, 1.07)	0.97 (0.97, 0.98)
	0-1	1.07 (1.06, 1.07)	1.02 (1.02, 1.03)	1.13 (1.12, 1.13)	0.97 (0.96, 0.97)
	0-2	1.09 (1.08, 1.10)	1.04 (1.03, 1.05)	1.16 (1.15, 1.17)	0.98 (0.97, 0.99)
	0-3	1.11 (1.10, 1.12)	1.06 (1.05, 1.07)	1.19 (1.17, 1.20)	1.02 (1.00, 1.03)
	0-4	1.12 (1.11, 1.13)	1.08 (1.07, 1.09)	1.19 (1.18, 1.21)	1.07 (1.05, 1.08)
	0-5	1.13 (1.11, 1.14)	1.11 (1.10, 1.12)	1.19 (1.17, 1.21)	1.13 (1.11, 1.15)
	0-6	1.13 (1.12, 1.14)	1.14 (1.12, 1.15)	1.18 (1.16, 1.19)	1.20 (1.19, 1.22)
	0-13	1.09 (1.07, 1.11)	1.35 (1.33, 1.38)	1.02 (1.00, 1.04)	1.79 (1.75, 1.83)
	0-21	1.06 (1.03, 1.08)	1.48 (1.45, 1.52)	1.14 (1.11, 1.17)	1.31 (1.27, 1.35)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; SES, Socioeconomic status

Table 8.1.7 The cumulative relative risks of stillbirth stratified by maternal age for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015.

Lag days	1st percentile (0.7 °C) RR (95% CI)			99th percentile (31.7 °C) RR (95% CI)		
	≤19	20-34	≥35	≤19	20-34	≥35
0	1.11 (1.10, 1.11)	1.02 (1.01, 1.02)	1.00 (1.00, 1.00)	1.22 (1.21, 1.22)	1.07 (1.07, 1.08)	0.76 (0.76, 0.77)
0-1	1.23 (1.22, 1.24)	1.03 (1.03, 1.04)	0.99 (0.99, 1.00)	1.43 (1.42, 1.44)	1.14 (1.14, 1.15)	0.62 (0.61, 0.62)
0-2	1.37 (1.36, 1.38)	1.05 (1.04, 1.06)	0.98 (0.98, 0.99)	1.61 (1.59, 1.62)	1.22 (1.21, 1.23)	0.52 (0.51, 0.52)
0-3	1.54 (1.53, 1.56)	1.07 (1.06, 1.08)	0.97 (0.96, 0.98)	1.75 (1.73, 1.77)	1.30 (1.28, 1.31)	0.46 (0.45, 0.46)
0-4	1.74 (1.72, 1.75)	1.08 (1.07, 1.10)	0.95 (0.94, 0.96)	1.85 (1.83, 1.88)	1.38 (1.36, 1.39)	0.42 (0.41, 0.42)
0-5	1.95 (1.93, 1.98)	1.10 (1.09, 1.12)	0.93 (0.92, 0.94)	1.92 (1.89, 1.94)	1.45 (1.43, 1.47)	0.40 (0.39, 0.40)
0-6	2.20 (2.17, 2.23)	1.12 (1.11, 1.14)	0.91 (0.90, 0.92)	1.95 (1.92, 1.97)	1.53 (1.51, 1.55)	0.38 (0.38, 0.39)
0-13	4.25 (4.17, 4.33)	1.25 (1.23, 1.28)	0.77 (0.76, 0.79)	1.87 (1.83, 1.91)	1.88 (1.84, 1.92)	0.41 (0.40, 0.42)
0-21	4.60 (4.49, 4.72)	1.34 (1.31, 1.37)	0.73 (0.71, 0.75)	3.26 (3.17, 3.35)	1.58 (1.53, 1.62)	0.30 (0.29, 0.31)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

8.1.4.5 Sensitivity analyses

Results were generally similar to that of the main analyses after changing the degrees of freedom for defining the cross-basis matrices (Table S8.1.2). Similarly, the main results showed no substantial difference when either daily mean UTCI or average of the standard no thermal stress range was used as the reference UTCI (Table S8.1.3). However, redefining the case day (day of stillbirth) as a day preceding the delivery day showed no association for the immediate and most of the shorter durations of exposure, particularly for the 1st percentile relative to the median UTCI. The results showed lower risk when the delivery day was used as the case day (Table S8.1.4).

8.1.5 Discussion

8.1.5.1 Main findings

Both mean and median UTCI were within the standard no thermal stress ranges. The 1st and 99th percentiles of UTCI were within slight cold stress and moderate heat stress ranges, respectively.[103,106] Relative to the median UTCI, we found positive associations between both immediate and short-term cumulative exposures to various thermal stress conditions and the risk of stillbirth in WA. The risks were particularly elevated in both the 1st percentile (cold stress) and the 99th percentile (heat stress). The risks were higher by the intensity and duration of the thermal stress episodes and were comparatively stronger in heat than in cold stress. We also observed higher risks in cumulative exposures from 13 and 21 days until stillbirth, suggesting that longer thermal stress also played a role and should be considered in future studies.[253]

Our findings were consistent with previous studies that evaluated acute exposure to extreme temperatures and the risk of stillbirth.[374-376] For instance, studies from the USA reported a percentage change of 10.4% (95% CI: 4.4, 16.8) [376] and 39% higher odds (OR= 1.39, 95% CI: 1.15, 1.69) [375] of stillbirth per 10 °F increase in mean apparent temperature for cumulative average exposure of lag days 2 to 6 before the day of delivery during the warm season. Basu *et al* further reported for the cold season and found no association.[376] Our results showed positive associations in both cold and heat stresses that increased with intensity and duration of exposure but were stronger in the heat than cold stress. Considering the exposure, the more comparable studies were two time-series analyses, both in Iran that also used UTCI [119] and Physiological Equivalent Temperature (PET).[121] However, in addition to the design, these studies varied from ours as the UTCI and PET were derived with meteorological factors from one synoptic meteorological station and used the delivery day as the event day (day of stillbirth). Khodadadi *et al* found a higher risk of stillbirth that included the null at 99th percentile (46.4 °C) and lower risk at 1st percentile (11.6°C), relative to median UTCI (17.5 °C, no thermal stress) for acute exposures.[119] Compared to median PET (defined as no thermal stress), the risk of stillbirth with high PET (99th percentile) was most elevated at lag 0 but weaker at cumulative lag days and the low PET (1st percentile) showed lower risks.[121] From our sensitivity analysis that considered delivery day as the day of stillbirth, we found small lower risks in both 99th and 1st percentiles, relative to the median UTCI. However, it has been documented extensively in the literature that there is a death-to-delivery delay for which reason the time of death in stillborn fetuses will be highly inaccurate if taken as the time of stillbirth delivery.[383-385] Consistent with our main findings, Li *et al* concluded that maternal exposure to both low and high ambient temperatures showed higher risks of preterm birth and stillbirth in Brisbane, Australia.[372] This also means that depending on the population characteristics, climatic conditions, adaptation strategies, and the level of outdoor activities during either cold or heat stress, the lower risks could be observed. The difference between our results and few previous studies, may be justified by the strength of the study design and analysis,[114,115] the UTCI, and spatiotemporal exposure assessment[74,76,77] in addition to the climatic and maternal behavioural characteristics described earlier. Furthermore, compared with other thermal indexes, including PET, the UTCI has been shown to be most appropriate and best represents specific climatic conditions at any geographical location, is very sensitive to changes in ambient thermal stimuli just as the human body, and can express even slight differences in the intensity of the thermal stimuli.[78,80] A recent review therefore recommended UTCI for future thermal-related studies and early warning systems.[82] We found that the most elevated risks were during the transition seasons and earliest year 2000-2004. During the study period there may have been continuous improvements in antenatal care services; housing conditions, which included the use of air conditioners and other mitigation strategies; and acclimatisation. These may have contributed to the lower risks in the later years as compared to the early years. However, with increasing severity of climate change and noticeable impacts on health outcomes,[369,370] risks may be expected to be higher in the most recent years. Furthermore, by the standard UTCI range, our estimated risks were for *slight cold stress* and *moderate heat stress,* relative to *no thermal stress.*[103,106] It is therefore more plausible to observe stronger risks and higher number of excess stillbirths in other study areas where the 1st and 99th percentiles of UTCI are in greater thermal stress ranges. Our result also indicated that sudden adaptation during transition periods for acute exposure might be difficult, leading to relatively elevated risk in this season. It is also plausible that pregnant women reduced exposure levels by cautiously reducing outdoor activities or increasing the use of cooling and heating systems during winter and summer as compared with the transition season.

The finding was also consistent with the recent meta-analysis of four studies that found 24% higher odds (OR =1.24, 95% CI: 1.12, 1.36) of stillbirth during high versus low ambient temperatures with exposure period less than one week.[16] Thus, pregnant women and particularly at late gestational periods may not be able to immediately adapt or thermoregulate the acute exposure to thermal stresses, potentially elevating the risk of stillbirth.[16,374]

8.1.5.2 Potential effect modification by fetal factors

Consistent with the previous finding, our results indicated a comparatively stronger risk of stillbirth in male than in female fetuses.[376] This is explainable as sex-specific maternal–placental–fetal interaction through the mechanisms of genetic, epigenetic, and hormonal effects.[391,392] The response to environmental exposures is favoured by natural selection *in utero.*[391,392] Compared to the female fetus, the male fetus has faster fetal development and metabolic rates that result in potentially higher allostatic load, which can be increased in the presence of environmental stressors.[392,393] Therefore, when pregnant women are exposed to environmental stressors, the biological system could easily abort less resilient male fetuses than female fetuses to enhance survivability and liveability.[392] A systematic review and meta-analysis found an elevated risk of stillbirth in males by about 10%.[393]

Regarding gestational age, we found a stronger risk in term stillborn than preterm stillborn fetuses which is consistent with findings in Quebec, Canada.[374] Conversely, a study in Brisbane, Australia found that increasing temperature associated with a higher risk of stillbirth for preterm but observed no association for term stillborn.[253] This study, however, analysed the association of mean temperature in the last four weeks [253] which represents chronic exposure rather than the acute exposure assessment applied in our study, and others.[121,374-376] Given the ubiquity of the thermal environment, extremes in maternal thermal exposure may occur throughout the pregnancy period which puts term stillbirths at longer exposure than the preterm stillbirths. Preterm stillbirths, however, have other major competing risk factors such as malformations, chromosomal abnormalities, and congenital infections [393] that may far exceed the impact of acute thermal stress, which thereby remains concealed. Pregnant women at term need to be more cautious and warrant closer monitoring during thermal stress episodes.[374]

8.1.5.3 Potential effect modification by maternal sociodemographic factors

Some subpopulations of pregnant women such as smokers, unmarried, adolescents, and non-Caucasians were more susceptible to the acute effect of cold or heat stress. Residing in high SES areas showed a stronger risk from case day up to the previous 5 days after which the risk became stronger in low SES areas. Apart from smoking status which showed elevated risk in cold than heat stress, the observed risks were more elevated in the heat stress for all other examined sociodemographic factors. Smoking during pregnancy, which is more likely to be intensified and hazardous in cold conditions,[394] has been well-documented as a contributor to pregnancy outcomes, including stillbirth.[197] This could also be due to more complex interactions with age, race, and SES where the risks may be further elevated in young, non-Caucasian, unmarried and low SES mothers who are more vulnerable to smoking and at higher risk of stillbirth. Further investigation is necessary to evaluate the magnitude of such interactions. There is a tendency for reduced risky behaviours and outdoor activities among married individuals and older adults, resulting in lower risks in these subgroups as compared to their counterparts.[376] Additionally, married women may also benefit from economic and psychosocial support from their partners which reduce economic and psychosocial stress, thereby also reducing their risk of stillbirth as compared to the unmarried women. For racial or ethnicity disparities, genetic and socioeconomic vulnerabilities, structural or systemic racism, low level of antenatal care utilisation, and indulgence in more risky behaviours (e.g., smoking, illicit drug or alcohol intake) were reported previously to have contributed to the added risk of stillbirth in the non-Caucasians in high-income countries.[265,375,376] Generally, climate change-related factors such as thermal stress interact with these maternal factors to exacerbate the impacts on health outcomes.[395] Several other modifiable risk factors, and maternal infections such as syphilis, hepatitis,[209] and seasonal influenza with a peak during cold weather [396] also contribute to the higher risk of stillbirth. With the projection of more severe extreme climatic events, more investment in research and appropriate thermal stress risk management actions are required to prevent preventable climate change-related adverse health outcomes, especially among the vulnerable subpopulations.[16,395] These may include thermal mitigation strategies such as hydration, *greening* the environment (particularly planting of shade or canopy cover trees), providing public shade structures, increasing affordability of cooling and heating technologies and other biophysical solutions, and heat warning systems.

8.1.5.4 Biological mechanisms

Evidence regarding biological pathways by which the ambient thermal environment can lead to stillbirth is accumulating. Findings from *in vivo* studies have indicated that heat or cold stress could cause hyper- or hypothermia and oxidative stress that affect placental and fetal physiology, and fetoplacental exchange of materials, leading to adverse pregnancy outcomes.[22,371] Human thermophysiological responses to thermal stress involve energy balance and metabolism to maintain the core body temperature within a narrow range on either side of 37°C.[103,344] Thermal stress disrupts the maternal thermoregulatory mechanism, alters the *in utero* thermal environment, and causes hyperthermia or hypothermia with negative impacts on the mother and fetus.[22,397] Such thermal stress and the associated thermophysiological responses can induce cellular and biochemical catalytic processes, leading to oxidative damage, cell death, and other pathophysiological responses that lead to adverse pregnancy outcomes, including stillbirth.[342,344,398] Thermal vulnerability is also exacerbated by women's risk profiles involving maternal age, sweating capacity, cardiovascular function, respiration rate, subcutaneous fat, pH, and nutritional status[342] and worsened by poor maternal low sociodemographic status. Moreover, decreased surface area to body mass ratio during pregnancy reduces the ability of the body to dissipate heat to the external environment through sweating.[399] Maternal weight gain, fetal growth, and fetal metabolic activity further increase the maternal basal metabolic rate and heat stress..[393,399] These increase at the late gestational period, peaking at term, and higher in male than female fetuses.[374,393] There is also impairment of placental development and function by maternal hyperthermia and severity depends on the gestational period.[371] Another pathway is related to dehydration from increased maternal urination and sweating which could result in a low volume of blood water. Consequently, the uterine and placental blood flow reduces and affects the transport of heat, oxygen, and nutrients to the developing fetus, a precursor to fetal death. Furthermore, as a heat dissipation mechanism, asymptomatic thermal stress can theoretically increase the shunting of blood volume to the periphery, alter placental and umbilical blood perfusion, and thereby reduce the fetoplacental exchange of heat and materials.[22,342] Maternal heat or cold stress can also induce a 'thermal shock' response in the developing fetus.[22] Rapid cell division makes the fetus sensitive to the fetal thermal environment which is largely regulated by the mother, leading to fetal vulnerability to maternal thermal stress.[342]

8.1.5.3.5 Strengths and Limitations

This study has several strengths. One major strength was the space-time-stratified case-crossover design and the analytical framework. These enabled us to significantly minimise time-invariant and known and unknown confounding factors. Unlike previous studies that used temperature or apparent temperature, we used a more robust, and physiologically relevant thermophysiological index, the UTCI with spatiotemporal variability.[74,77,80,82] We also examined many maternal sociodemographic effect modifiers. Furthermore, this was the first study to our knowledge that specifically investigated the acute effect of thermal stress in a few days preceding delivery and the risk of stillbirth in Australia.

We also acknowledged some limitations in this study. First, a known limitation of all stillbirth data is the lack of accurate information on the time of stillbirth and so estimated this with 48 hours (2 days) delay as mostly reported in the literature based on a histologic report.[384,385] There are presently no reliable imaging techniques for the accurate estimation of the fetal or stillbirth time of death.[383] Second, we did not have information on indoor thermal conditions or the use of air conditioning systems. Third, our exposure assessment did not account for time-location-activity patterns of pregnant women and the change of residential address during pregnancy. However, the potential exposure misclassification from activity patterns would be expected to bias the estimated effects towards the null.[375] For residential mobility, we least expect this to result in minimal misclassification given that we analysed associations in short-term periods shortly before delivery.[375] Moreover, previous studies on associations between air pollutants and pregnancy outcomes found no clear evidence of the influence of maternal residential mobility during pregnancy.[275] Fourth, we did not have sufficient data to separately analyse intrapartum and antepartum stillbirths. Finally, we cannot exclude the possibility of the existence of influential effect modifiers that were not included in this study. We did not have data to adjust for any air pollutants, but this was not considered as a limitation.[374] The adjustment of an air pollutant (an intermediate but not a confounder) in estimating the total effect of temperature or thermal stress on health outcomes has been discouraged and considered conceptually inappropriate.[400,401] Moreover, some previous studies examined this and reported no change in the results after the adjustment of air pollutants.[253,372,375,376]

8.1.6 Conclusion

Relative to the median UTCI (no thermal stress), we observed higher risks of stillbirth for acute maternal exposures to thermal stresses. Risk increased with the intensity and duration of the thermal stress episodes and was particularly elevated for both cold stress (1^{st} percentile) and heat stress (99^{th} percentile). The impact of heat stress was stronger than cold stress. Acute exposures to cold or heat stress up to 6 preceding days, relative to no thermal stress were attributed to about 8 to 11 additional stillbirths per 10,000 births. We also found the most elevated risks during the transition period between summer and winter, and 2000-2004. The risks were disproportionately higher in term and male stillborn fetuses, smoking, unmarried, ≤19 years old, non-Caucasians, and low socioeconomic status mothers. Given the increasing frequency of climate change events, which include thermal extremes, healthcare practitioners and policymakers may want to consider thermal mitigation and adaptation strategies and improve resources for pregnant women, especially the identified higher-risk groups. This may contribute to preventing a proportion of stillbirths as well as have co-benefits in reducing other associated morbidities of pregnancy. Future studies may consider the use of a human thermophysiological index, such as UTCI, as a more thermophysiologically relevant exposure.[74,82]

8.2 Prenatal acute thermophysiological stress and spontaneous preterm birth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis

8.2.1 Abstract

Introduction: Epidemiologic evidence on acute heat and cold stress and preterm birth (PTB) is inconsistent and based on ambient temperature rather than a thermophysiological index. The aim of this study was to use a spatiotemporal thermophysiological index (Universal Thermal Climate Index, UTCI) to investigate prenatal acute heat and cold stress exposures and spontaneous PTB.

Methods: We conducted a space-time-stratified case-crossover analysis of 15,576 singleton live births with spontaneous PTB between 1st January 2000 and 31st December 2015 in Western Australia. The association between UTCI and spontaneous PTB was examined with distributed lag nonlinear models and conditional quasi-Poisson regression. Relative to the median UTCI, there was negligible evidence for associations at the lower range of exposures (1st to 25th percentiles).

Results: We found positive associations in the 95th and 99th percentiles, which increased with increasing days of heat stress in the first week of delivery. The relative risk (RR) and 95% confidence interval (CI) for the immediate (delivery day) and cumulative short-term (up to six preceding days) exposures to heat stress (99th percentile, 31.2 °C) relative to no thermal stress (median UTCI, 13.8 ^{o}C) were 1.01 (95% CI: 1.01, 1.02) and 1.05 (95% CI: 1.04, 1.06), respectively. Elevated effect estimates for heat stress were observed for the transition season, the year 2005-2009, male infants, women who smoked, unmarried, ≤ 19 years old, non-Caucasians, and high socioeconomic status. Effect estimates for cold stress (1st percentile, 0.7 °C) were highest in the transition season, during 2005-2009, and for married, non-Caucasian, and high socioeconomic status women.

Conclusions: Acute heat stress was associated with an elevated risk of spontaneous PTB with sociodemographic vulnerability. Cold stress was associated with risk in a few vulnerable subgroups. Awareness and mitigation strategies such as hydration, reducing outdoor activities, and affordable heating and cooling systems may be beneficial. Further studies with the UTCI are required.

8.2.2 Introduction

Preterm birth (PTB) – birth before 37 completed weeks of gestation remains the leading cause of child mortality and long-term health morbidity, and is accompanied by sizeable economic burdens.[223] Analysis across 107 countries estimated a global rise in PTB from 9.8% in 2000 to 10.6% in 2014, an equivalent of 15 million live PTB.[402] In Australia, the rate increased slightly from 8.4% in 2010 to 8.7% in 2017.[226] Most PTB cases are spontaneous, and the causes are multifactorial and heterogeneous.[223,227] Despite the several well-known risk factors, the majority of PTB have unspecified causes and unclear biological mechanisms for appropriate prevention strategies.[223,227] For instance, an individual participant meta-analysis of 4.1 million singleton births in five high-income countries reported that the aetiology of about 65% of PTB could not be explained with a range of commonly reported risk factors.[403] Recommendations included investigation of biological mechanisms and non-conventional risk factors.[223,403] such as environmental exposures.

Climate change continues to increase heat or cold extremes across the globe with potential impacts on health outcomes.[7] Emerging observational studies have indicated that prenatal exposure to extreme ambient temperatures (heat or cold stress) may contribute to the pathophysiology of PTB.[16] The hypothesised biological pathway is that thermal stress disrupts maternal thermoregulatory capacity and stimulates excessive immune-inflammatory activities prematurely, initiating labour and thereby leading to PTB.[341,345] However, the findings are disparate and have suggested both extreme heat and cold stress as risk factors.[372,404,405] heat stress as a risk factor but 'protective' effect or no association with cold stress,[406] and cold stress as a risk factor but 'protective' effect or no association for heat stress.[120,407,408] These differences may be attributed to heterogeneity in the study designs, geographic location, population characteristics, acclimatisation, adaptation, exposure assessment, and varied temperature metrics.[16,120]

Most importantly, the existing literature is limited to the surrogate use of ambient temperature for heat or cold stress instead of the human thermophysiological index.[74,80] The results have been criticised as unrealistic and physiologically less relevant for a better understanding of the associated health effects for appropriate interventions.[74,76,80] Four appropriate human thermophysiological indices were recently recommended.[76] These included the Universal Thermal Climate Index (UTCI) which was reported in comprehensive comparative studies to be most suitable as it has high climatic sensitivity and best captures thermal stimuli similar to that of the human body, making it more thermophysiologically appropriate for medical and preventive medicine.[76,78-80] UTCI is a potential universal tool for monitoring the impacts of climate change on humans but it is underutilised in epidemiology and medical sciences until recently.[81] Several recent studies are now using the UTCI in heatwave warning systems and medical or epidemiological fields as reviewed elsewhere.[81,82] Only one recent study has used UTCI derived with meteorological parameters from one synoptic meteorological station and investigated the association with preterm labour, [119] but no study has investigated PTB.

Here, we used spatiotemporal UTCI and conducted a space-time-stratified case-crossover analysis of the association between prenatal exposure to thermophysiological stress and spontaneous PTB in Western Australia over 16 years. We estimated the overall effects and the influence of sociodemographic vulnerabilities.

8.2.3 Materials and Methods

Our analysis and reporting of results were informed by the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines.[239]

8.2.3.1 Study design and setting

A space-time-stratified case-crossover design was conducted.[115] This is similar to the classic time-stratified case-crossover design, a case-only self-matched approach that compares the exposure at the time of the event ('case or hazard time') with related non-event periods ('control or referent times').[114,377] The classic time-stratified case-crossover design is applied for time-series data where all individuals have a shared area-level exposure.[114-116] However, the availability of space-time varying environmental exposure assessment led to the extension of this design into the so-called space-time-stratified case-crossover to accommodate the analysis of multiple space-time series datasets.[115,117] The design has been applied previously for investigating acute effects.[117,118,367,379,409] Specifically, we matched the case and control times by a day of the week in the same calendar month and year within the same small spatial unit in the study location.[115,117,367] Thus, by design, the time-stratified case-crossover accounted for both measured and unmeasured individual-level characteristics and co-exposures that are short-term or time-invariant and controlled for long-term and seasonal trends.[114,115] The extension to space-time-stratified case-crossover further allowed for the analysis of multi-location time-series data, minimised exposure measurement bias and spatial confounding.[115,118,367]

This study was conducted for births between 1st January 2000 and 31st December 2015 in Western Australia. Western Australia is the largest state in Australia by area and covers 2.5 million km² areas with a population of 2.7 million as of 31 March 2021.[90] The state has diverse climatic conditions, ranging from temperate in the south-west, tropical in the north, and arid or semi-arid in the other parts.

8.2.3.2 Study population and case definition

We obtained de-identified data on births collected by the Midwives Notification System from the Western Australia Department of Health data linkage unit. The Midwives Notification System is a population-wide registry of all births with at least 20 weeks of gestation or at least a birth weight of 400 g if the gestational length is unknown.[96] The data contained maternal and neonatal information. Maternal residential address at the time of delivery was available as the statistical area level 1(SA1), the second smallest geographical unit in Australia. This study included 4,504 SA1s where eligible births were located. A total of 474,835 births were screened for eligibility. We included only singleton live births with spontaneous onset of labour and vaginal delivery at 20-36 weeks of gestation that had an SA1. The gestational age was estimated as the best clinical estimate from the perinatal records as the difference between the date of birth and start of pregnancy based on ultrasonography or the last menstrual period if ultrasound was not available. To eliminate the potential displacement of short-term effects by the reductions in the risk at longer periods, we considered a maximum lag of 21 days.[119,367,380,381] For this reason, we further excluded births within the first 20 days of the study period. Our final analytic sample included 15,576 spontaneous PTB (Figure 8.2.1).

We extracted the available sociodemographic information to derive subgroups. Infant-related subgroups were based on sex (male or female) and gestational age (20-27, 28-31, and 32-36 weeks).[410] We further obtained the extreme ends of the PTB as periviable birth (20-26 weeks, the range of viability) [411] and late PTB (34-36 weeks).[410] Maternal-related subgroups were age at birth delivery (≤ 19, 20–34, and ≥ 35 years),[373,412] tobacco smoking status (non-smoker or smoker), marital status (married or unmarried), and race or ethnicity (Caucasian or non-Caucasian). We also categorised the season of birth into three (summer, December-February; winter, June-August; and transition, the remaining months that form autumn and spring) and year (2000-2004, 2005-2009, 2010-2015). The Index of Relative Socio-economic Disadvantage at a geographic area derived by the Australian Bureau of Statistics [102] was assigned to the maternal residence at the time of birth and categorised into quintiles in a previous study,[382] We derived two socioeconomic status (SES) subgroups from the quintiles as high (1st and 2nd quintiles) and low (3rd-5th quintiles) SES.[367]

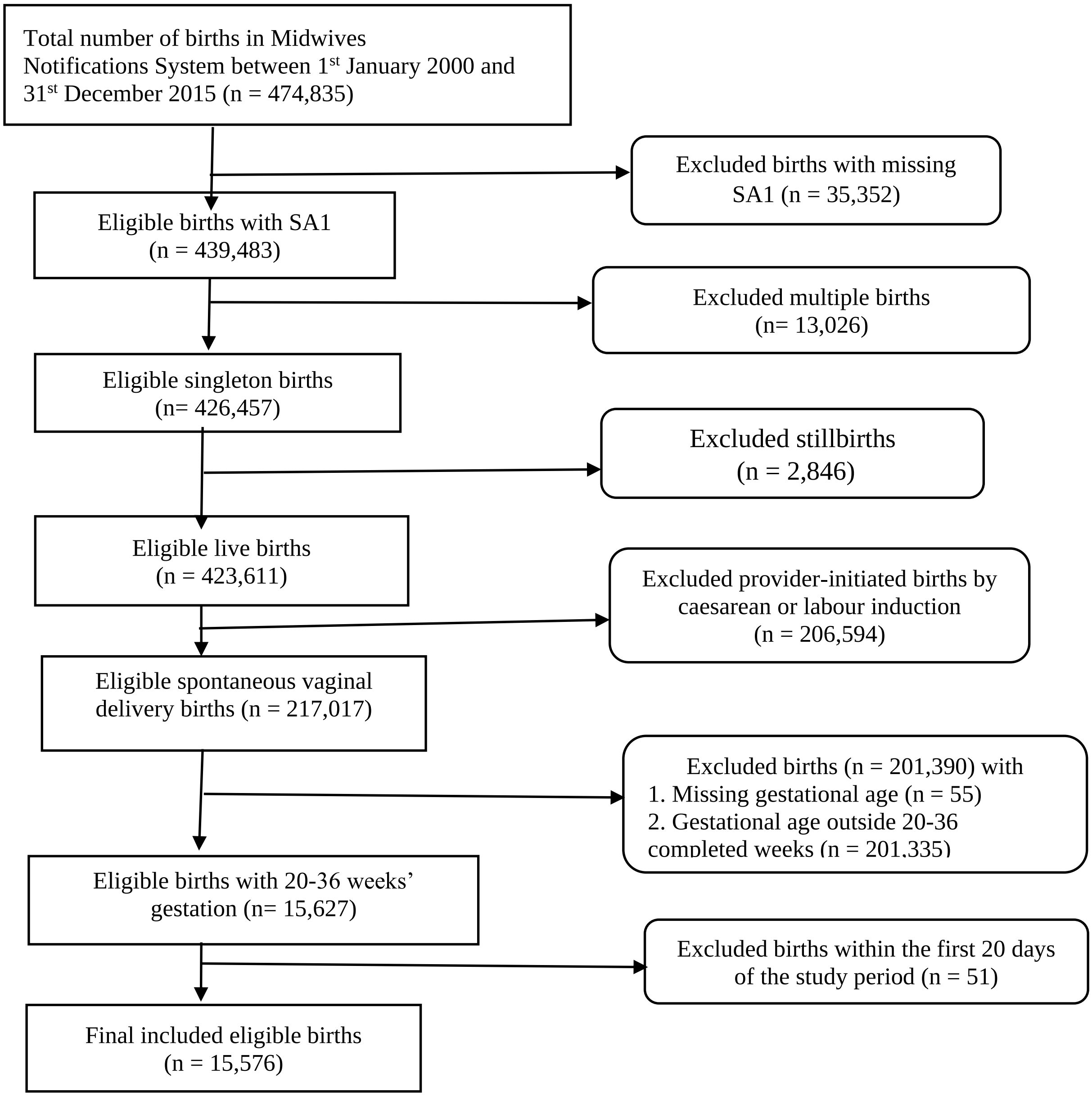

Figure 8.2.1 Flow chart of the selection of the eligible spontaneous vaginal delivery preterm births included in this study, Western Australia, 2000-2015. Note, SA1; statistical area level 1.

8.2.3.3 Spatiotemporal Universal Thermal Climate Index exposure assessment

The UTCI is an equivalent air temperature (^{o}C) that assesses the ambient thermal environment and accounts for heat transfer and exchange, both within the body and between the body surface and the ambient air layer.[80,103] UTCI is computed through a six-order polynomial equation with four input variables: air temperature and dew point temperature or relative humidity at 2 m above ground level, wind speed at 10 m above ground level, and mean radiant temperature.[103,104,106] The mean radiant temperature is a measure of thermal-related comfort and includes non-meteorological variables such as metabolic rate and the thermal properties of clothing.[80,103,104] We used the open-access UTCI dataset recently derived from the ERA5 reanalysis.[106] ERA5 is the 5th historical global gridded climate dataset of several climate variables produced by the European Centre for Medium-

Range Weather Forecasts by merging the global climate model, measurements made near the Earth's surface at land stations, and satellite observations.[387] A novel global dataset, ERA5-HEAT (Human thErmAl comforT) which contains the UTCI was produced from the ERA5 reanalysis climate dataset at a spatial resolution of 0.25° × 0.25° at an hourly level from 1979 to the present.[106] Details on UTCI calculation and assumptions were described elsewhere.[103,104,106] We accessed the daily gridded UTCI of the 24-hour averages from 1st January 2000 to 31st December 2015 across Australia. UTCI values were extracted at the SA1 level in Western Australia using ArcGIS software (version 10.8.1). UTCI has been used in several medical and epidemiologic studies.[81]

8.2.3.4 Statistical analyses

8.2.3.4.1 Main and subgroup analyses

The analytical dataset was an SA1-level time-series of daily counts of spontaneous PTB and the corresponding daily UTCI exposures. To simultaneously investigate the immediate and cumulative risks, we combined a distributed lag non-linear model (DLNM) with conditional quasi-Poisson regression.[60,116] With the cross-basis term, the non-linear exposure–lag–response association was defined through natural cubic splines in both dimensions of the UTCI predictor and the lag days with 21 maximum lag days.[60,119,367] Spline knots were set at equally spaced values on the log scale of lags.[60] The selection of the optimum degrees of freedom (*df*) for UTCI predictor and lag days was based on the smallest Akaike Information Criterion.[60] This process resulted in 2 and 3 *df* for the UTCI predictor and lags being selected, respectively. The model specification was given as

$$\log\left[\mathrm{E}\left(\mathrm{Y}_{\mathrm{t,s}}\right)\right] = \alpha + \mathrm{cb(UTCI)} + \mathrm{holiday}, \mathrm{eliminate} = \mathrm{factor}\ (stratum) \qquad (1)$$

where α is the intercept; $Y_{t,s}$ is the observed number of spontaneous PTB at day *t* in spatial unit *s* (SA1); *cb* is the cross-basis function, the *holiday* is a binary indicator variable for public holidays, and *stratum* (introduced through the "eliminate" function in "gnm" package [122] was the conditional factor that defined the same day of the same week in the same calendar month of the same year at the same SA1.This analytical framework had been applied previously.[115,117,118,367,379,409]

With reference to the median UTCI, we estimated the relative risks (RRs) and 95% confidence intervals (CIs) at the 1st, 5th, 25th, 75th, 95th, and 99th percentiles of UTCI. Following previous reports, [119,120,413] we reported the RR (95% CI) for only the immediate effects of exposure on the day of PTB (lag 0) and cumulative effects from event day 0 up to the preceding day N (lag 0-N). The results of the individual lag days in distributed lag models could be biased by temporal collinearity or autocorrelation with potential erroneous findings,[380,390] Additionally, labour could last more than one day, or the pregnant woman may not be admitted until a day following the thermal stress exposure [376]. The acute immediate and cumulative effects up to the first six preceding days were reported. We also reported results for 0-13 and 0-21 lag days, representing second and third weeks, respectively as "long-term" exposures.[119,367]

Potential effect modifications were investigated by performing subgroup analyses for each of the subgroups described earlier. The RRs (95% CIs) for the 1st and 99th percentiles, relative to the median UTCI were reported. Furthermore, the respective reference subgroups were used to compare the two RRs (95% CIs) for each subgroup by estimating the ratio of relative risks (RRRs) and the corresponding 95% CIs for both 1st and 99th percentiles of UTCI exposure for lag 0-6 for each subgroup with the Altman and Bland test of interaction effects.[257,258]

We also estimated the attributed risk (AR) as the number of excesses per 10,000 singletons spontaneous PTB that could be attributable to immediate (lag 0) and cumulative (lag 0-6) heat stress exposure, relative to the median UTCI by following Ha *et al* [351] as

$$AR = I_u (RR - 1) \quad (2)$$

where I_u is the background rate which was defined as the study-specific incidence rate and calculated from the eligible spontaneous vaginal delivery births (7.2%). This was also equivalent to the average of 2009-2015 state-wide singleton PTB incidence reported elsewhere.[414]

8.2.3.4.2 Sensitivity analyses

The robustness of the main analysis was checked by performing several sensitivity analyses for varying model conditions or assumptions. The *dfs* were changed to 3 for both UTCI predictor and lags and then to 3 for UTCI predictor and 4 for lags dimensions. Two separate reference values (the mean UTCI and the average of the standard 'no thermal stress' range, 17.5 °C) were also used. All analyses were performed with R statistical software (version 4.1.1).[323] The DLNM was fitted with the "dlnm" package [60] and the conditional quasi-Poisson regression with the "gnm" package.[122] We reported and interpreted the RR (95% CI) contextually without a 'statistical significance' threshold as recommended by the American Statistical Association.[181]

8.2.4 Results

8.2.4.1 Exposure and cohort characteristics

The standard UTCI has 10 thermophysiological stress categories where 9 to 26 °C is considered as *no thermal stress*, and values below and above this range are varied intensities of *cold thermal stress* and *heat thermal stress*, respectively.[103,106] The mean UTCI (standard deviation) and median (interquartile range) across the entire study period were 14.5 °C (6.7 °C) and 13.8 °C (9.2 °C), respectively and both were within the standard *no thermal stress* category. The 1st percentile (0.7 ^{o}C) and the 99th percentile (31.2 ^{o}C) were within the *slight cold stress* and *moderate heat stress* categories, respectively.[103,106] The UTCI distribution varied slightly among subgroups and the largest records were in summer (20.5 ± 5.3 ^{o}C) and 2010-2015 (15.1 ± 6.8 ^{o}C) (Table S8.2.1). Spontaneous PTB was fairly distributed across the seasons with half observed during the six months of transition season and approximately 25% each during the three months, each of winter and summer. The prevalence of spontaneous PTB increased across the years. Most of the births were to women who had moderate PTB (86.6%), had male babies (56.2%), were non-smokers (75.8%), married (81.6%), aged 20-34 years (73.7%), Caucasian (71.6%), and low socioeconomic status, SES (64.7%) (Table 8.2.1).

Table 8.2.1 The number of spontaneous PTB by year, season, type, and fetal and maternal sociodemographic characteristics in Western Australia, 2000-2015 (N=15,576).

Variable	**Characteristics**	**n (%)**
Year	2000-2004	4,162 (26.7)
	2005-2009	5,101 (32.7)
	2010-2015	6,313 (40.5)
Season	Transition	7,793 (50.0)
	Winter	3,963 (25.4)
	Summer	3,820 (24.5)
PTB type	Extremely PTB (20-27 weeks)	889 (5.7)
	Very PTB (28-31 weeks)	1,194 (7.7)
	Moderate PTB (32-36 weeks)	13,493 (86.6)
PTB type at extreme ends	Periviable birth (20-26 weeks)	709 (4.6)
	Late PTB (34-36 weeks)	11,905 (76.4)
Fetal sex	Male	8,752 (56.2)
	Female	6,824 (43.8)
Prenatal smoking	Non-smoker	11,805 (75.8)
	Smoker	3,771 (24.2)
Marital status	Married/de facto	12,710 (81.6)
	Unmarried*	2,866 (18.4)
Delivery age (years)	≤19	1,196 (7.7)
	20–34	11,476 (73.7)
	≥35	2,904 (18.6)
Race/ethnicity	Caucasian	11,155 (71.6)
	Non-Caucasian	4,421 (28.4)
Socioeconomic status	High	5,506 (35.3)
	Low	10,070 (64.7)

*Never married/separated/divorced/widowed/unknown. PTB, preterm birth

8.2.4.2 Thermophysiological stress and risk of spontaneous PTB

The exposure-lag-response association for the short-term cumulative effects within a week showed changes from lower to greater risks across the exposures, relative to the median UTCI. The magnitude of effects began to decrease for exposures from the second week before birth (Figure 8.2.2). Relative to the median UTCI, there was negligible change in the risk in the 1st to 25th percentiles for all exposure periods. However, strong positive associations were found in the 95th and 99th percentiles (heat stress) which increased with increasing cumulative heat stress episodes for the first week but were lower afterward. Specifically, for 99th percentile relative to median UTCI, immediate (lag 0 day) and cumulative acute exposure (lag 0-6 day) risks were 1% (RR= 1.01, 95% CI: 1.01, 1.02) and 5% (RR= 1.05, 95% CI: 1.04, 1.06) greater, respectively (Table 8.2.2).

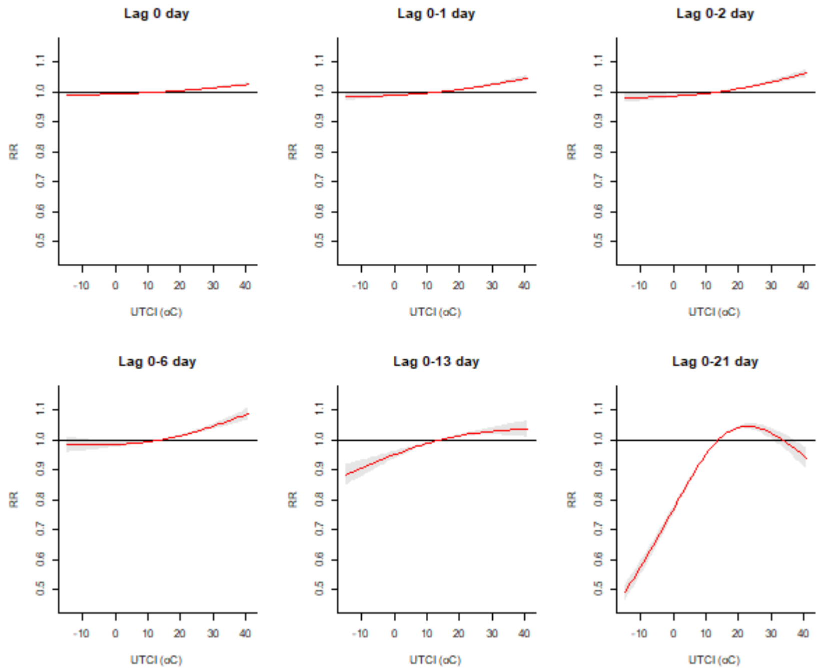

Figure 8.2.2 Exposure-response curves of daily UTCI and cumulative relative risk of spontaneous PTB at different lag structures using median UTCI of 13.8 ºC as reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals. Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Compared to no thermal stress, attributable risks indicated excesses of 11(95% CI: 9, 13) and 36 (95% CI: 29, 43) per 10,000 liveborn singletons with spontaneous PTB due to immediate (lag 0) and cumulative acute (lag 0-6) heat stress (99th percentile of UTCI) exposures, respectively. The attributable risk was not estimated for cold stress as it showed no association.

Table 8.2.2. The cumulative relative risks of spontaneous PTB for different UTCI percentiles relative to the median (13.8 °C) in Western Australia, 2000-2015.

Lag days	1st (0.7 °C) RR (95% CI)	5th (4.2 °C) RR (95% CI)	25th (9.7 °C) RR (95% CI)	75th (18.9 °C) RR (95% CI)	95th (26.4 °C) RR (95% CI)	99th (31.2 °C) RR (95% CI)
0	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.01 (1.01, 1.01)	1.01 (1.01, 1.02)
0-1	0.99 (0.99, 0.99	0.99 (0.99, 0.99)	1.00 (0.99, 1.00)	1.01 (1.01, 1.01)	1.02 (1.02, 1.02)	1.03 (1.02, 1.03)
0-2	0.99 (0.98, 0.99)	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.02 (1.02, 1.03)	1.04 (1.03, 1.04)
0-3	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.03 (1.02, 1.03)	1.04 (1.04, 1.05)
0-4	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.03 (1.03, 1.04)	1.05 (1.04, 1.06)
0-5	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.03 (1.03, 1.04)	1.05 (1.04, 1.06)
0-6	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.03 (1.03, 1.04)	1.05 (1.04, 1.06)
0-13	0.95 (0.94, 0.96)	0.97 (0.96, 0.98)	0.99 (0.98, 0.99)	1.01 (1.01, 1.02)	1.02 (1.02, 1.03)	1.03 (1.02, 1.04)
0-21	0.78 (0.77, 0.80)	0.85 (0.84, 0.86)	0.95 (0.94, 0.95)	1.04 (1.03, 1.04)	1.04 (1.03, 1.05)	1.02 (1.00, 1.04)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

8.2.4.3 Thermophysiological stress and risk of spontaneous PTB in subgroups

Both cold and heat stress showed the most elevated risk during transition season for both immediate and cumulative acute effects but either lower or small positive associations during winter and summer (Table S8.2.2a and Table S8.2.2b). Cumulative acute exposure to both 1st and 99th percentiles relative to median UTCI showed lower effects during both winter and summer as compared to the transition season. This was as low as 18% lower effect in summer as compared to the transition season, for exposure to 99th percentile relative to median UTCI (RRR= 0.82, 95% CI: 0.80, 0.83) (Table 8.2.3). The risk was most elevated for the middle year 2005-2009 (Figure S8.2.1).

Relative to median UTCI (no thermal stress), cold stress (1st percentile of UTCI) showed essentially no association for both extreme and moderate PTB but strong positive associations for very PTB while heat stress (99th percentile of UTCI) showed no association for very PTB but strong positive associations for both extremely PTB and moderate PTB (Table S8.3). Cumulative acute exposure (lag 0-6) showed 6% lower effect of cold stress exposure (RRR=0.94, 95% CI: 0.93, 0.95) and a 50% higher effect of heat stress exposure (RRR=1.50, 95% CI:1.47, 1.52) for extremely PTB as compared to moderate PTB. Conversely, cumulative acute exposure showed 35% higher effect of cold stress exposure (RRR=1.35, 95% CI:1.34, 1.36) but 5% lower effect of heat stress exposure (RRR=0.95, 95% CI: 0.94, 0.96) in very PTB as compared to moderate PTB (Table 8.2.3). The impact of the thermal stress was strong in the periviable births but essentially had no association with late PTB (Figure S8.2.2).

Table 8.2.3 The estimated interaction effects as ratio of relative risks (RRRs) and 95% confidence intervals (95% CI) of spontaneous preterm birth, relative to the indicated reference subgroup for acute cumulative exposure (lag 0-6) to 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015.

Subgroup	1st percentile of UTCI RRR (95% CI)	99th percentile of UTCI RRR (95% CI)
Winter (ref Transition)	0.83 (0.81, 0.85)	0.87 (0.85, 0.89)
Summer (ref Transition)	0.90 (0.89, 0.92)	0.82 (0.80, 0.83)
Extremely PTB (ref Moderate PTB)	0.94 (0.93, 0.95)	1.50 (1.47, 1.52)
Very PTB (ref Moderate PTB)	1.35 (1.34, 1.36)	0.95 (0.94, 0.96)
Male (ref Female)	1.02 (1.01, 1.03)	1.15 (1.14, 1.17)
Smoker (ref Non-smoker)	0.91 (0.90, 0.92)	1.19 (1.17, 1.21)
Unmarried (ref Married)	0.57 (0.57, 0.58)	1.23 (1.21, 1.24)
non-Caucasian (ref Caucasian)	1.10 (1.09, 1.12)	1.07 (1.05, 1.08)
Low (ref High) SES	0.94 (0.93, 0.95)	0.89 (0.85, 0.94)
≤ 19 (ref 20-34) years	0.80 (0.79, 0.81)	1.46 (1.44, 1.47)
≥ 35 (ref 20-34) years	0.87 (0.87, 0.88)	1.01 (1.00, 1.02)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth; SES, Socioeconomic status.

Relative to no thermal stress, both thermal stress exposures, particularly heat stress showed sociodemographic disparities (Table S8.2.3-S8.2.5). Specifically, cumulative acute exposure (lag 0-6) showed 15% higher effect of heat stress in males as compared to female infants (RRR=1.15, 95%

CI: 1.14, 1.17). As compared to non-smokers, mothers who smoked during pregnancy showed 19% higher effect for cumulative acute exposure to heat stress (RRR=1.19, 95% CI: 1.17, 1.21). Cumulative acute exposure to heat stress showed 23% higher effect among unmarried as compared to married mothers (RRR=1.23, 95% CI: 1.21, 1.24). Non-Caucasians experienced higher effect as compared to Caucasians and this was particularly stronger for cold stress exposure at 10 % higher (RRR=1.10, 95% CI: 1.09, 1.12) than heat stress exposure at 7% higher (RRR=1.07, 95% CI: 1.05, 1.08). Cumulative acute exposures to both cold and heat stress showed a small lower effect among mothers in low SES as compared to high SES residential areas. Compared to mothers aged 20-34 years old, cumulative acute exposure to heat stress showed 46% higher effect among mothers aged ≤ 19 years old (RRR=1.46, 95% CI: 1.44, 1.47) and 1% higher effect among mothers aged ≥ 35 years old (RRR=1.01, 95% CI: 1.00, 1.02) (Table 8.2.3).

The results of the sensitivity analyses for varying modelling assumptions and conditions were similar to the main results (Tables S8.2.6 and S8.2.7).

8.2.5. Discussion

8.2.5.1 Thermophysiological stress and risk of spontaneous PTB

Relative to the median UTCI (no thermal stress), we found no association with exposures to the first to 25th percentiles but strong positive associations were observed for the 95th and 99th percentiles for immediate and cumulative acute effects. The risk increased with increasing duration of heat stress exposure episodes and was strongest during transition seasons (spring and autumn) and 2005-2009. Assuming causality, attributable risk indicated that heat stress (99th percentiles) exposure relative to no thermal stress on the event day and cumulatively up to six preceding days could account for 11 (95% CI: 9, 13) and 36 (95% CI: 29, 43) excess cases per 10,000 spontaneous PTB, respectively.

Given that we used a human thermophysiological index as recently recommended [74,76] and applied elsewhere,[81,82] our findings are unique as compared to the previous findings that were based on ambient air temperature metrics.[16] Previous studies considered extremes of high and low-temperature thresholds (1st or 5th and 99th or 95th percentiles as compared to median) as heat and cold stress. Our findings were consistent with a study in Belgium and the USA that also found a greater risk for acute heat stress but a small lower risk or essentially no association for cold stress based on ambient temperature metrics.[404,406] For example, the USA study of 32 million singleton births reported an RRs (95% CI) for PTB of 1.03 (95% CI: 1.02, 1.04) and 0.99 (95% CI: 0.98, 0.99) over the previous four days for heat and cold stress, respectively, relative to the median ambient temperature.[406] Furthermore, the only available meta-analysis that pooled 21 studies found

1% greater odds of PTB (OR= 1.01, 95% CI: 1.01, 1.02) during high versus low-temperature exposure periods of < 4 weeks which increased to 5% (OR=1.05, 95% CI: 1.04, 1.05) after excluding two studies (outliers).[16] There were, however, a few contradictory findings. Two time-series analyses on the Chinese population found greater risks for cold stress but a small lower risk or no association for heat stress in Shenzhen and Xuzhou.[120,407] Another Chinese study found a greater risk for both heat and cold stress for the immediate effect but no association for short-term cumulative effects in Guangzhou.[415] Vicedo-Cabrera *et al* found a greater risk for moderate heat but inconsistent associations for extreme cold and heat during the last one to four gestational weeks in Stockholm, Sweden.[416] Specific to Australia, three previous studies examined the acute effect of ambient temperature on preterm birth.[314,405,412] Matthew *et al* found a greater risk of PTB that ranged from 2% up to 8.3% for 90th, 95th, and 99th percentiles of minimum and maximum summer temperatures relative to the median temperature on the day of delivery and up to 21 preceding days in Alice Springs, Central Australia.[405] Wang *et al* analysed warm-season births in Brisbane, Queensland, and found the greatest hazard ratio of 2.00 (95% CI: 1.37, 2.91) for their highest heat stress, defined as a daily maximum temperature over the 98th percentile for four consecutive days in the last gestational week.[412] The third study was conducted across New South Wales state with spatiotemporal exposure assessment and time-series analysis that reported the risk of spontaneous PTB at the 95th percentile of daily mean temperature (25℃) relative to the median (17℃). The results showed 3% greater risk (RR=1.03, 95% CI: 1.01, 1.05) on day 0 (day of initial exposure, defined as one day before the event) and 16% greater risk (RR= 1.16, 95% CI: 1.08, 1.25) for the cumulative effect of exposure up to seven preceding days.[314] Our results were similar, although, the cumulative effect estimate was greater than that of our study. This could be due to the one-day-delay exposure assessment, differences in population characteristics and climates, study design, and the use of ambient temperature. Given the geographical variability in climatic conditions and the influence of acclimatisation, adaptation, and mitigation strategies, even within a country or region, generalising location-specific findings to other parts is difficult and if necessary, should be done cautiously.[331,416] However, it is expected that there might be greater risks of PTB for heat stress than cold stress due to more severe heat stress episodes than cold stress across most regions in the world as the climate change crisis progresses.[7] Also, there could be better acclimatisation or easier adaptation to cold than heat stress.[406]

8.2.5.2 Thermophysiological stress and risk of spontaneous PTB in subgroups

We found attenuation of risk in our latest period, similar to findings reported in Brisbane, Australia.[372] This may be attributed to thermal adaptation through acclimatisation or increasing mitigation responses such as the use of air conditioning,[417] improved climate-specific clothing, thermal stress-resilient housing infrastructure, and improved healthcare system over the years.[364,372,406] However, our observed elevated risk in the transition season as compared to other seasons could imply that pregnant women may not be able to quickly thermo-adapt when transitioning from high to low thermal stress or vice versa. It could also mean that pregnant women took more behavioural precautions such as reduced outdoor activities or increased use of heating or cooling systems during summer or winter seasons as compared with the transition season.

We observed lower risks of heat stress with increasing gestational age which was consistent with the previous findings [404,415,418] and indicates a plausible causal link between prenatal heat stress and the shortening of gestational age.[253,417] Basu *et al*, however, observed the strongest risk for near-term PTB in California, USA.[413] We also observed that cold stress showed strong positive associations with very PTB but not for other types of PTB. A cold season analysis in California, USA, however, indicated the strongest odds of mean apparent temperature for near-term PTB.[418] Among the reasons stated earlier, the analytical design, exposure metrics, and climatic conditions could explain the differences. This requires further studies from other locations with a thermophysiological index. We found a stronger impact of heat stress in male neonates as compared with the female neonates similar to the largest cohort study conducted in the USA[406] but others reported otherwise.[404,413,418] However, it has been recognised extensively in the literature that male neonates are more vulnerable to pregnancy outcomes and the influence of environmental exposures.[391] As reported in a few previous studies, the comparatively higher-risk women for heat stress were women who smoked, unmarried, teenagers, and non-Caucasians.[405,413,419] These vulnerabilities are attributed to the level of outdoor activities, risky behaviours and lifestyle, poor antenatal care utilisation, resources for mitigation strategies, hereditary, and systemic racism.[265,274,364,405,413,419] Surprisingly, we observed a stronger risk of thermal stress for women that resided in the high SES areas but lower risk or no association for those in low SES areas. We used area-level SES as a proxy for individual SES which is known to produce misclassification bias to some extent.[412] However, there are possible reasons for this finding. Women with low SES are more likely to be exposed to outdoor working conditions over long periods and lack cooling or heating systems at home.[364] Consequently, they are more likely to acclimatise to thermal stress as compared to women with high SES, resulting in the observed elevated risk in the high than low SES groups. Better individual-level indicators for SES such as occupation and further investigations are required. Given that climate change impacts are exacerbated by maternal sociodemographic and lifestyle factors, a better understanding and identification of higher-risk subpopulations is crucial for prioritised intervention.[274,395]

Public health interventions and mitigation strategies may be required, particularly for the most vulnerable women. Examples include raising awareness and educating women to sufficiently hydrate and decrease outdoor activities during hot days, *greening* the environment to improve shade, provision of public shade structures, provision of affordable heating and cooling systems, and thermal stress warning systems that account for the human thermophysiology.[274,364,367]

8.2.5.3 Biological mechanisms

Several animal studies and clinical evidence have provided strong support for the pathophysiology of prenatal thermal stress exposure and PTB. Generally, any factor or exposure that initiates the breakdown of feto-maternal immune tolerance and excessive or premature activation of the inflammatory pathways causes uterine contractility, cervical ripening, and rupture of membranes which results in PTB.[345,420] Heat or cold stress induces molecular and biochemical catalytic processes that cause oxidative damage, apoptosis, deregulate inflammatory production and abnormally high intracellular expression of heat shock proteins in the serum. These affect placental physiology and fetal development (particularly higher in sociodemographically vulnerable women) and cause implantation failure and feto-maternal complications such as pregnancy outcomes, including spontaneous PTB. [341,343-345,420] Heat stress also causes dehydration which reduces uterine blood flow and increases secretion of the pituitary antidiuretic hormone, prostaglandin, and oxytocin. These affect fetoplacental transport and induce spontaneous labour.[346]

8.2.5.4 Strengths and limitations

Our study has several strengths. The novel study design and the modelling framework accounted for and substantially minimised both time-invariant and time-varying known and unknown confounding factors in the short-term periods, temporal autocorrelation, and spatial confounding.[60,115,116,367] The space-time varying assessment of the UTCI exposure at the individual's residential microenvironment reduced exposure misclassification as compared to using ground-based monitoring stations that may be distant from the participants.[77] To the best of our knowledge, this is the first study that used the available most suitable contemporary human thermophysiological index (UTCI) at a spatiotemporal resolution to examine the association between heat or cold stress and spontaneous PTB. This makes the findings more robust and physiologically relevant by combining knowledge from climate science, physiology, and epidemiology.[74,76,80,81] This was also the first study on this topic in Western Australia.

This study has some limitations, including our inability to account for indoor thermal environments (e.g., use of heating or cooling systems) and prenatal activity-time patterns. A prospective cohort with personalised activity-time exposure assessment using portable thermal sensors and indoor thermal environment assessments may help minimise some of these limitations. Given the space-time varying exposure assessment and acute exposure analysis, we expect any remaining exposure misclassification to be minimal and non-differential which would have rather attenuated the observed effect estimates towards the null.[406] We also lacked information on other relevant sociodemographic factors such as maternal occupation, education, illicit drug or alcohol use, and nutrition. As the primary aim in the present study was to investigate short-term associations between thermal stress and spontaneous PTB, future studies should investigate long-term effect across the entire pregnancy periods with the extended DLNM to identify other potential critical windows of susceptibility.

8.2.6 Conclusion

We find that prenatal exposure to acute heat but not cold stress relative to no thermal stress elevated the risk of spontaneous PTB. However, both heat and cold stresses elevated the risk in the more vulnerable subpopulations. Given the expected increasing events of climate change extremes in the coming years [7] and the potential impacts on birth outcomes, we call on the public health officers, antenatal care providers, and obstetricians to help communicate the potential risk to pregnant women.[274] The provision of thermal adaptation or mitigation strategies and resources may help reduce the risk of spontaneous PTB, particularly for higher-risk pregnant women. In addition to an improved healthcare system, an appropriate climate change policy is required. Several comparative studies had indicated the suitability and relevance of thermophysiological metrics as compared to ambient temperature for medical and preventive medicine given that thermophysiological metrics capture the total thermal environment and human thermophysiological responses.[76,78,79,358] Future studies should consider human thermophysiological indices such as UTCI which is now gaining high application in scientific research and recommendations among clinicians, epidemiologists, and specialists in public health and thermal stress management.[74,76,77,81,82]

Chapter 9. Long-term maternal exposure to biothermal stress and the risks of stillbirth and spontaneous preterm birth in Western Australia

9.0 Preamble

This chapter provides a primary investigation of the association between maternal exposure to biothermal stress from preconception to birth and the risks of stillbirth and spontaneous preterm birth in Western Australia. Critical exposure periods of increased susceptibility and vulnerable subpopulations were identified.

9.1 Abstract

Introduction: Very few studies investigated the long-term effects of temperature on stillbirth and preterm birth to identify susceptible periods. Also, temperature rather than a biothermal metric was used. This study aimed to investigate the long-term association between biothermal stress (Universal Thermal Climate Index, UTCI) and stillbirth and spontaneous preterm birth (sPTB).
Methods: A total of 415,271 singleton births which included 0.5% stillbirth and 3.7% sPTB between 1st January 2000 and 31st December 2015 were linked to spatiotemporal UTCI in Western Australia. Distributed lag non-linear Cox regression was used to investigate maternal UTCI exposure from twelve weeks preconception to birth and the adjusted hazard of stillbirth and sPTB.
Results: As compared to median exposure (14.2 ˚C), both lower and higher exposures were associated with higher hazards of stillbirth and sPTB. Critical susceptible periods were found at 1st centile exposures during gestational weeks 23 to 42 with the strongest hazard of 1.15 (95% CI 1.04, 1.29) in the 42nd week for stillbirth and during weeks 27 to 36 with the strongest hazard of 1.12 (95% CI 1.09, 1.16) in the 36th weeks for sPTB. The same critical susceptible periods during 18 to 26 weeks were found with the hazard of 1.03 (95% CI 1.01, 1.05) at 90th centile exposure for stillbirth and 1.03 (95% CI 1.02, 1.05) at 99th centile exposure for sPTB. Exposure at the 99th centile additionally showed very small protective effects on sPTB during weeks 33 to 36. Monthly or cumulative preconception exposure especially at the 1st centile showed positive associations with both stillbirth and sPTB. Only nulliparity showed increased vulnerability in both stillbirth and sPTB.
Conclusions: Both lower and higher biothermal stress exposures were associated with higher hazards of stillbirth and sPTB. More investigations on the long-term effects of biothermal stress to raise awareness and advocate for appropriate mitigation actions during critical susceptible exposure periods.

9.2 Introduction

Preterm birth (PTB, born before 37 gestational weeks) and stillbirth (born with no signs of life at or after 28 weeks of gestation) are global public health concerns with health, psychological and economic burden implications.[208,224] There was an estimated 10.6% (14.8 million) of live PTBs in 2014 [208] and 13.9 stillbirths per 1000 total births (2.0 million stillbirths) in 2015.[224] In Australia, the rate of PTB increased slightly from 8.4% in 2010 to 8.7% in 2017.[226] Annually, Australia experiences over 2,000 stillbirths, which translate to at least six women experiencing this traumatic event daily.[225] Despite several well-known risk factors, the majority of the cases of PTB and stillbirth have unspecified or unexplained causes and unclear biological mechanisms for appropriate prevention strategies.[100,209,223,227] Scientific search for non-traditional risk factors like modifiable environmental exposures such as indoor and outdoor air pollution,[125,421] other chemicals [422,423] and recently climatic factors [11,338,339] are emerging and has been recognised by clinicians.[274,298] This is critically important as we strive towards attaining the Sustainable Development Goal (SDG) 3 of ensuring healthy lives and well-being for all at all ages.[228,229]

Anthropogenic-induced climate extremes have disproportionate immediate and long-term impacts on vulnerable populations such as pregnant women and developing fetuses.[7,424] Maternal exposure to extreme ambient temperatures (heat or cold stress) may contribute to the pathophysiology of PTB and stillbirth. The hypothesised pathophysiological pathways are that thermal stress disrupts maternal thermoregulatory capacity and causes hypo- or hyperthermia and oxidative stress. These affect placental and fetal physiology and initiate several pathophysiological processes that lead to adverse birth outcomes such as PTB and stillbirth.[22,297,341,345,371] However, critical susceptible exposure periods are not yet known and are very important to elucidate pathophysiological mechanisms and public health interventions. Previous studies mostly investigated the short-term effect and a few investigated trimester-average exposure effects.[16,331] Such approaches cannot identify fine pathophysiologically sensitive periods that do not necessarily align with pre-defined three-month intervals or may span across trimesters.[58] To better understand the underlying pathophysiological mechanisms of environmental exposures, distributed lag linear and non-linear modelling (DLM or DLNM), which accounts for both the intensity and timing of past environmental exposures has been recommended.[58-60] Ambient temperature often shows a non-linear relationship with birth outcomes and several recent studies applied DLNM and found that maternal acute (short-term) exposure to high or low temperatures during the late weeks of pregnancy was associated with higher risks of PTB [120,245,256,314,405,407,425] and stillbirth.[119,121,246] This statistical modelling approach can be used to identify weekly or monthly critical susceptible exposure periods of birth outcomes and has been adopted in several studies of air pollution.[61,65,67,69,232] However, to the best of our knowledge, there have only been two known such long-term effect studies on ambient temperature and PTB [256,426] and none for stillbirth.

Also, most of the previous studies assessed ambient temperature based on proximity to one or a few monitoring stations.[16,331] In addition to exposure misclassification, this approach would exclude the more vulnerable populations in rural areas because monitoring stations are mostly in or near urban or city centres.[256,331]

The lack of high-quality meteorological station data and computational challenges to characterise appropriate thermophysiological or biothermal (hereon biothermal) metrics has led to the surrogate use of readily available ambient temperature measurements in related epidemiological and thermal-health warning studies and forecasts.[74-76,353] Human thermophysiology is a complex process that cannot be described adequately by only temperature or apparent temperature.[74-76] To make the findings thermophysiologically relevant, it is therefore expected that biothermal metrics will become the usual exposure metric as meteorological data and computational technologies become available.[74-76] This is now possible with free access to gridded meteorological data and computational packages as detailed earlier in Chapter 7. Biothermal metrics integrate the actual thermal environment (a combination of the air temperature, solar radiation, relative humidity, and wind speed) and human physiological and insulation properties of clothing.[74,77] A comprehensive evaluation of several biothermal metrics recommended four metrics as principally appropriate for epidemiological and biometeorological research.[76] Of these, the Universal Thermal Climate Index (UTCI), the currently most advanced biothermal metric has been reported in several comparative studies to be most suitable with high climatic sensitivity and similar thermal stimuli as that of the human body.[76,78,79,358] Although underutilised in perinatal epidemiology, UTCI has been used and recommended in several medical, epidemiological, thermal-health warning systems, and forecasting.[81,82] In addition to a previous study that investigated short-term maternal exposure to UTCI and preterm labour and stillbirth,[119] our previous studies also presented findings on short-term exposure to UTCI and the risks of stillbirth [367] and spontaneous preterm birth (sPTB).[368] However, the long-term assessment of UTCI to identify critical susceptible exposure periods of these birth outcomes has not been reported in the literature.

To address the aforementioned limitations, this study aimed to use spatiotemporal UTCI to assess biothermal exposure at the maternal residential address. DLNM Cox proportional hazards (Cox PH) regression was performed to evaluate the non-linear time-varying associations between biothermal stress and the hazards of stillbirth and sPTB in Western Australia. Critical susceptible exposure periods and vulnerable subpopulations were identified.

9.3 Materials and Methods

The analysis and reporting of results were informed by the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines.[239]

9.3.1 Study area, design, and population

A population-based retrospective cohort study was conducted using de-identified Midwives Notification System (MNS) records between 1st January 2000 to 31st December 2015 in Western Australia. The MNS is a statutory routine data collection system that includes all births with ≥20 completed gestational weeks or ≥400 g fetal weight if the gestational length is unknown.[96] The MNS contains sociodemographic and clinical information on both mother and baby, including maternal residential address as statistical area level 1 (SA1) at the time of birth delivery. The SA1 is the second smallest geographical unit in Australia and has variable geographic size with a median of 19 hectares and an average population of 400 individuals.[240] The details of the study population and eligibility criteria have been described in the previous Chapter 4 section 4.3.1. The final sample included in this study was 415,271 singleton births with 22 to 42 weeks of gestation for the stillbirth cohort but 400,867 for the spontaneous PTB (sPTB) cohort as 14,404 induced PTB were excluded in the main analysis (Figure S9.1).

9.3.2 Outcome assessment and covariates

The birth outcomes (stillbirth and sPTB) and covariates were described in previous Chapter 4 sections 4.3.2 and 4.3.3, respectively.

9.3.3 *Spatiotemporal Universal Thermal Climate Index exposure assessment*

The UTCI is an equivalent air temperature (°C) that integrates the total ambient thermal environment (combination of air temperature, relative humidity, wind speed, and mean radiant temperature), metabolic rate, and clothing insulation.[80,103] Details on UTCI were provided elsewhere [103,104,106] and summarised in the previous Chapter 8 as published articles.[367,368] The recent UTCI dataset at a spatial resolution of 0.25° × 0.25° (~ 31 km at the equator) derived from the ERA5 reanalysis was obtained from the Copernicus Climate Data Store.[106] The daily gridded UTCI of the 24-hour averages from 1st January 1999 to 31st December 2015 across Australia were obtained. Daily UTCI was processed at the SA1 level in Western Australia using ArcGIS software (version 10.8.1).

Exposure was assigned at the individual level. That is, for each birth, daily UTCI exposure was assigned from 12 weeks preconception [69,111,242] through to birth based on dates of conception and birth and SA1 of the maternal residential address. Weekly (7-day average) exposures were calculated from 12 weeks preconception (-11 to 0 weeks) to the earlier of birth and the 42nd gestational week, after which the birth contributed no exposure time.[69,232] Monthly exposure from three months of preconception to birth was also calculated. Cumulative exposures such as the trimester-specific UTCI averages (1-13, 14-26, and 27-birth delivery gestational weeks), preconception to birth, entire pregnancy (conception to birth), and preconception (average of 12 weeks before pregnancy) were also calculated.

9.3.4 Statistical analyses

9.3.4 Main and subgroup analyses

DLNM Cox PH regression with gestational age as the time variable and dichotomised birth outcome status as the outcome was performed to estimate the weekly-specific effects of UTCI exposure from 12 weeks preconception through to birth on the hazards of sPTB and stillbirth.[61,65,67,69,232,256,426] The DLNM Cox PH regression was specified according to the formula:

$$h_i(t|x, C) = h_0(t)\exp(\beta x_t + \mathcal{B}C)$$

where *h* is the hazard, *i* is the *i*th birth, *x* denotes the cross-basis matrix for weekly UTCI exposure at week *t* and the lag dimension, *C* denotes the set of covariates, β and $\mathcal{B}$ are coefficients of the exposure and covariates, respectively, and $h_0(t)$ denotes the baseline birth outcome hazard at week *t* (i.e., the hazard function for a birth whose exposures and covariates are all equal to 0). The cross-basis matrix was constructed with a *crossbasis* function to define the exposure–lag–response association using the R package 'dlnm' [59,60] to identify potential critical susceptible exposure windows.[61,65,67,69,232,256,426] To flexibly describe any non-linear and delayed effects of the UTCI, both exposure-response and lag-response associations were modelled as natural cubic splines with several combinations of 2 to 7 degrees of freedom (*df*). The linear relationship of the exposure-response function was also tested. The maximum exposure period (lag period) was set at 54 weeks for stillbirth (12 weeks preconception up to 42 gestational weeks) and 48 weeks for sPTB (12 weeks preconception up to 36 gestational weeks). All spline knots were equally spaced values of the UTCI and the lag period. Based on the lowest Akaike Information Criterion (AIC) comparisons, the optimal *df* of UTCI exposure and lag period used for the final analyses were 7 and 5, respectively, for stillbirth, and 7 and 6, respectively, for sPTB.[59,60,249] The cross-basis matrix was entered into the model to perform a standard Cox PH regression using the R package 'survival'.[113] The Schoenfeld residual test was first performed to check the assumptions of the Cox PH model and time-by-covariate interaction terms were specified for covariates that violated the proportional hazards assumption.[61,250,251] The fitted model was used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of the UTCI at the 'extreme'(1st, 99th centiles), 'severe' (5th, 95th centiles), and 'moderate' (10th, 90th centiles) about median (50th centile) UTCI as reference using the *crosspred* function in the R package 'dlnm'.[59,60,249] Exposure periods in which 95% CIs did not include the null were identified as critical susceptible exposure periods.[61,65,67,69,232,256,426] Monthly-specific associations were also examined and 7 and 3 *df* were used for exposure and lag period, respectively for stillbirth and 7 and 4 *df* for exposure and lag period for sPTB were used in constructing the cross-basis matrices based on the lowest AIC.

Furthermore, cumulative effects of the UTCI exposure during preconception to birth, preconception, entire pregnancy, and trimester-average exposures were evaluated using separate standard Cox PH models without the cross-basis function of the exposure. As recommended, average exposures for the preconception and entire pregnancy periods were included together and so were all three-trimester exposures included together to minimise the bias in the estimates if separate models were used.[58,101] To estimate the non-linear effect of each cumulative exposure, a *onebasis* function of the R package 'dlnm' was used to construct unlagged exposure-outcome associations using natural splines with the following *df* based on lowest AIC [59,60,249]: 2 for preconception and entire pregnancy and 5 for the three trimester-average exposures for stillbirth, and 3 for preconception and entire pregnancy and 2 for the three trimester-average exposures for sPTB.

All the models were adjusted for the potential confounders. This included sex (male or female), year index (1999 =1 to 2015 =17) and season (summer, autumn, winter, spring) of conception, maternal age, race or ethnicity (Caucasian or non-Caucasian), marital status (married or unmarried), smoking during pregnancy (non-smoker or smoker), parity (nulliparous or multiparous) and remoteness indicator (urban or rural). The area-level Index of Relative Socio-economic Disadvantage derived by the Australian Bureau of Statistics [102] was assigned to the maternal residence at the time of delivery and categorised into tertiles to define high, moderate, and low socioeconomic status (SES). The few births without smoking status (n=14), SES (n=22), and remoteness indicator (n=143) were assigned separate categories as 'unknown'. Maternal age was modelled as a continuous variable using natural splines with 3 *df.* [253,254]

To explore the potential effect modification, we conducted stratified analyses by infant sex, race or ethnicity, maternal age at delivery (≤19, 20–34, and ≥35 years), SES, remoteness, maternal smoking status, marital status, parity, and pregnancy complications (yes or no). These analyses used preconception to birth cumulative exposure.

9.3.5 Sensitivity analyses

Several sensitivity analyses were performed to ascertain the credibility of the weekly-specific results. (i) Mean rather than median UTCI was used as the reference.[426] (ii) The *df* in the natural cubic spline was increased by one for both exposure and lag period in constructing the cross-basis matrices. (iii) Maternal age was included as a categorical variable (≤19, 20-34, ≥35 years) instead of as a natural spline of the continuous covariate. (iv) Seasonality was adjusted with calendar month index (1 to 12) instead of four-season categories. (v) Mother-specific cluster was included to account for repeated births by the same mother. (vi) Local government area-specific cluster was included to account for potential spatial clustering and maternal mobility. The local government area is a geographical subdivision of the state. (vii) The birth cohort was restricted to only live singleton births (N= 413,348 births) and PTB (6.9%) instead of sPTB was investigated as reported in the two previous studies.[256,426]

All statistical analyses were performed using the statistical software R 4.2.1 (R Development Core Team 2020), and main R packages ‘dlnm’, ‘spline’, and ‘survival’ were used. We reported and interpreted the HRs (95% CIs) without considering any ‘statistically significant’ threshold as recommended by the American Statistical Association.[181]

9.4 Results

9.4.1 Characteristics of the study population and biothermal stress exposure

This study included 415,271 singleton births, of which 1,923 (0.5%), 15,524 (3.7%), and 14,404 (3.5%) were stillbirth, sPTB, and non-sPTB, respectively. A little above half of the births were male (51.2%), and the majority were born to mothers who were 20-34 years old (75.3%), Caucasian (78.3%), married (87.3%), multiparous (58.1%), non-smokers (85.3%), and urban residents (61.9%). Births were almost equally distributed among the four seasons of conception (Table 9.1).

The average UTCI exposure over the full exposure period has approximately equal mean (14.5 ± 2.5˚C) and median (14.2˚C), ranging from 7.3 ˚C to 31.2˚C. The specific average exposures for preconception, pregnancy, and each trimester were similar to the overall preconception-to-birth exposures (Table 9.2). The UTCI distribution was almost the same as the 400,867 singleton birth for sPTB cohorts that excluded induced PTB (Table S9.1).

Table 9.1 Maternal characteristics of included singleton births in Western Australia, 2000-2015 (N =415,271)

Characteristics	N (%)	Characteristics	N (%)
Stillbirth		*Smoking status*	
No	413,348 (99.5)	No	354,235 (85.3)
Yes	1,923 (0.5)	Yes	61,022 (14.7)
PTB status		Unknown	14 (0.0)
Term	385,343 (92.8)	*Remoteness*	
non-PTB	14,404 (3.5)	Urban	257,158 (61.9)
sPTB	15,524 (3.7)	Rural	157,970 (38.0)
Sex		Unknown	143 (0.0)
Male	212,562 (51.2)	*SES*	
Female	202,709 (48.8)	High	138,417 (33.3)
Maternal age (years)		Moderate	138,416 (33.3)
≤19	19,033 (4.6)	Low	138,416 (33.3)
20–34	312,880 (75.3)	Unknown	22 (0.0)
≥35	83,358 (20.1)	*Season of conception*	
Race		Autumn	100,889 (24.3)
Caucasian	325,340 (78.3)	Winter	105,588 (25.4)
Non-Caucasian	89,931 (21.7)	Spring	104,824 (25.2)
Marital status		Summer	103,970 (25.0)
Married	362,575 (87.3)		
Unmarried	52,696 (12.7)		
Parity			
Nulliparity	173,932 (41.9)		
Multiparty	241,339 (58.1)		

Note: sPTB, spontaneous preterm birth; non-sPTB; Induced or non-spontaneous PTB; SES, socioeconomic status.

Table 9.2 Descriptive statistics of the average UTCI (°C) during twelve weeks preconception through to gestational weeks at delivery exposure periods for included singleton births in Western Australia, 2000-2015 (N= 415,271)

Exposure periods	Min	Mean ± SD	Median	P1	P5	P10	IQR	P90	P95	P99	Max
Preconception to pregnancy	7.3	14.5 ± 2.5	14.2	10.2	11.9	12.8	1.2	15.4	17.4	26.1	31.2
Preconception	1.4	14.4 ± 5.2	14.0	5.8	7.6	8.2	8.8	20.9	22.0	29.5	35.8
Pregnancy	4.9	14.6 ± 2.9	14.2	9.6	11.3	11.9	2.9	16.7	18.3	26.7	34.1
1st Trimester	1.7	14.6 ± 5.2	14.2	5.9	7.7	8.3	8.8	20.9	22.0	29.6	36.0
2nd Trimester	1.6	14.6 ± 5.2	14.2	6.1	7.8	8.5	8.7	20.9	22.0	29.8	36.1
3rd Trimester	-1.1	14.5 ± 5.2	14.0	5.6	7.7	8.3	8.7	20.8	22.0	29.7	35.7

Note: UTCI, Universal Thermal Climate Index; SD, standard deviation; P1 to P99, first to 99th centiles; IQR, interquartile range= P75-P25

9.4.2 Biothermal stress exposures and the hazards of Stillbirth and sPTB

Maternal exposure to various thresholds of weekly UTCI exposure with reference to median UTCI (14.2˚C) showed positive associations with both stillbirth and sPTB (Figure 9.1, Tables S9.2 and S9.3). The HR for exposures at 1st (10.2˚C) to 90th (15.4 ˚C) centiles of UTCI showed critical susceptible exposure periods. Lower exposures (1st to 10th centiles of UTCI), especially at the 1st centile showed critical susceptible exposure periods during the 23rd to 42nd gestational week which increased towards birth. The strongest hazard of stillbirth was 1.15 (95% CI 1.04, 1.29) during the 42nd gestational week. Higher exposure thresholds also showed positive associations which decreased in magnitude toward birth. Exposure at the 90th centile showed critical susceptible exposure periods during the 18th to 26th gestational weeks with a 1.03 (95% CI 1.01, 1.05) hazard of stillbirth. Weekly preconception exposure above 1st centile showed positive associations but no critical susceptible exposure period (Figure 9.1, Table S9.2).

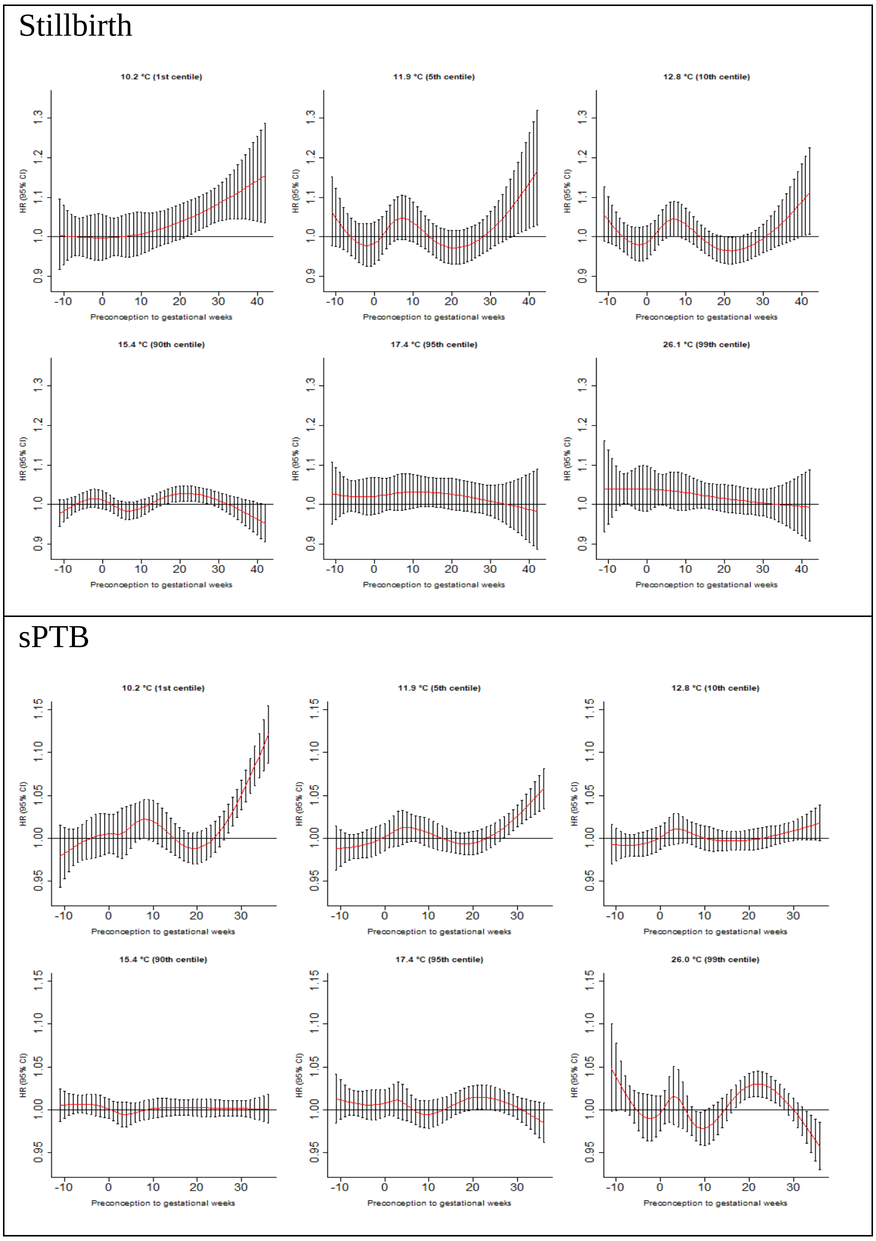

Figure 9.1 Adjusted hazard ratios of stillbirth and sPTB associated with weekly-specific UTCI over 12-week preconception (-11 to 0) through to gestational week at delivery (1 to 42 for stillbirth and 1 to 36 for sPTB) at different thresholds of UTCI using the median of 14.2 ˚C as a reference in Western Australia, 2000–2015. Solid horizontal red lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

Although with slightly higher magnitude and wider confidence intervals, monthly UTCI exposure showed almost similar patterns as weekly UTCI exposure. The strongest hazard of stillbirth was 1.25 (95% CI 1.02, 1.55) during the 10th gestational month at 1st centile exposure as compared with the median UTCI month (Figure 9.2, Table S9.4). Cumulative exposures, especially at lower thresholds showed positive associations with stillbirth. For each cumulative preconception and entire pregnancy period, exposure at 1st centile as compared with the median showed the strongest hazards of 1.28 (95% CI 1.07. 1.52) for the preconception period and 1.33 (95% CI 1.13, 1.55) for entire pregnancy period. Trimester-specific exposures showed critical susceptible exposure periods for the first and third trimesters, especially at 1st centile of UTCI which was stronger but less precise in the first trimester, 1.58 (95% 1.18, 2.11) than the third trimester, 1.33 (95% CI 1.04, 1.72). Cumulative exposures at high thresholds generally showed very small lower or essentially no hazard of stillbirth (Table 9.3, Figures S9.2 and S9.3).

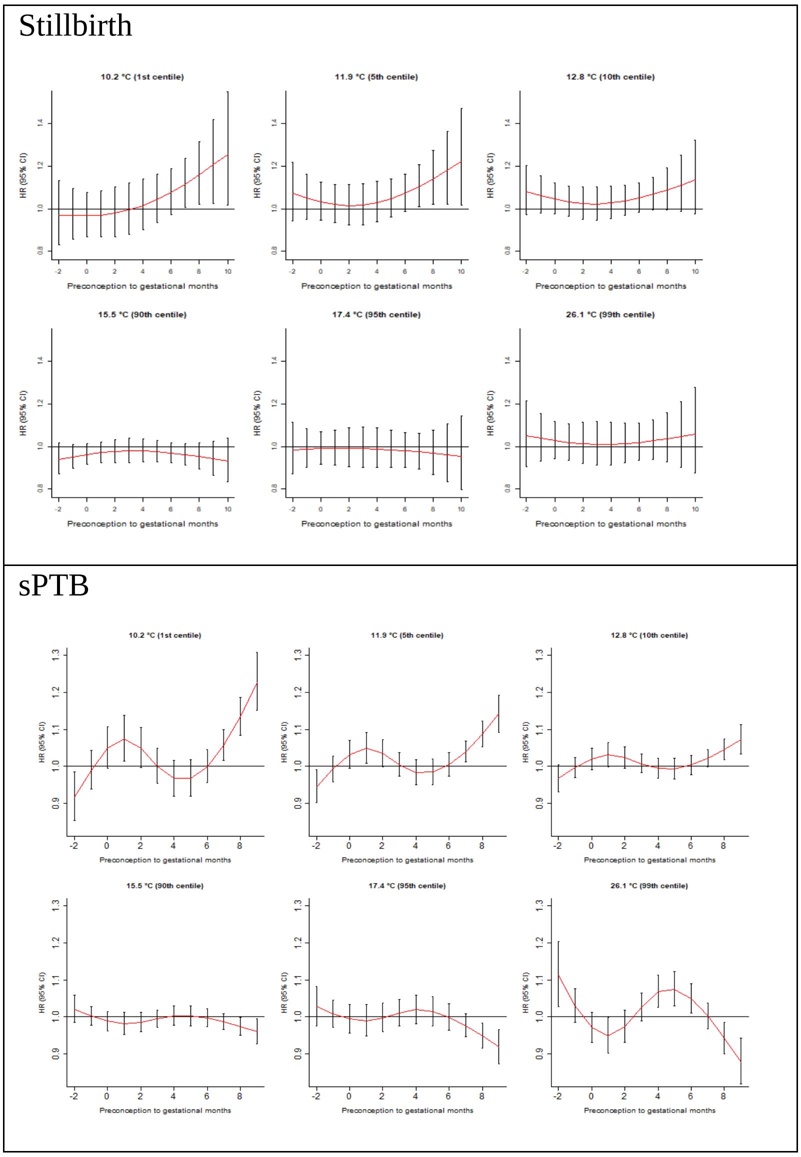

Figure 9.2 Adjusted hazard ratios of stillbirth and sPTB associated with monthly-specific UTCI over from three months preconception (-2 to 0) to birth (1 to 10 for stillbirth and 1 to 9 for sPTB) at different thresholds of UTCI using the median of 14.2 ˚C as a reference in Western Australia, 2000–2015. Solid horizontal red lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

For sPTB, the critical susceptible exposure periods were found for lower exposures (1st and 5th centiles) during the 27th to 36th gestational weeks, increasing with gestation with the strongest hazard of 1.12 (95% CI 1.09, 1.16) in the 36th gestational week at the 1st centile and for higher exposures (95th and 99th centiles) during the 18th to 26th gestational weeks with the strongest hazard of 1.03 (95% CI 1.02, 1.05) during the 21st to 23rd gestational weeks at the 99th centile. UTCI exposure at the 99th centile additionally showed very small critical protective exposure periods towards the end of pregnancy (33rd to 36th gestational weeks) with the lowest hazard of 0.96 (95% CI 0.93, 0.99) in the 36th gestational week. Weekly preconception exposure showed positive associations at higher exposures but no critical susceptible period (Figure 9.1, Table S9.3). Monthly UTCI exposure showed almost similar patterns as weekly UTCI exposure. In addition to increasing critical susceptible periods during late pregnancy (7th to 9th gestational months), lower exposure thresholds also showed small critical protection in the 3rd preconception month. Higher exposures, particularly at the 99th centile showed critical susceptibility in the 3rd preconception month and during the 4th to 6th gestational months but critical protection during the 8th to 9th gestational months. As compared to the median UTCI, the monthly hazard was strongest at 1st centile exposure, 1.23 (95% CI 1.15, 1.31), and lowest at 99th centile exposure, 0.88 (95% CI 0.82, 0.94), and both occurred in the 9th gestational month (Figure 9.2, Table S9.5). As compared to median UTCI, cumulative exposures at lower thresholds showed positive associations with sPTB. Higher threshold exposures showed negative associations, mostly with null in the confidence intervals. For each cumulative preconception and entire pregnancy period, exposure at 1st centile as compared to median UTCI showed the strongest hazard of 1.10 (95% CI 1.01. 1.20) for the preconception and 1.22 (95% CI 1.13, 1.32) for the entire pregnancy. For trimester-specific exposures, critical susceptible exposure periods were found at lower exposures in the first and third trimesters. Higher exposures showed critical susceptible exposure periods in the second trimester but small critical protection in the third trimester. Specifically, exposure at the 99th centile as compared to the median UTCI showed the strongest hazards of 1.31 (95% CI 1.13, 1.52) in the second trimester and the lowest hazard of 0.86 (95% CI 0.77, 0.97) in the third trimester (Table 9.3, Figures S9.2 and S9.3).

Stratified analyses indicated effect modifications, mostly showing critical susceptible exposure at lower exposure levels as compared with the median exposure. Comparatively, the UTCI exposure showed a higher hazard in male birth for stillbirth but female for sPTB (Figure S9.4) and higher in Caucasian for stillbirth but non-Caucasian for sPTB (Figure S9.5). The hazard was higher in births whose mothers were 20-34 years old for stillbirth but no difference for sPTB (Figure S9.6), and no difference in area-level SES for stillbirth but protective in high SES for sPTB (Figure S9.7). A higher hazard of stillbirth was found in rural areas but critical protection in urban areas for sPTB hazard at higher exposure levels (Figure S9.8). Mothers who did not smoke during pregnancy were at a higher hazard of stillbirth, but smokers showed a higher hazard of sPTB (Figure S9.9).

Table 9.3 The exposure-response association between maternal cumulative UTCI exposures over twelve weeks preconception through to pregnancy and trimester-specific periods as compared with median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB at various percentiles of the exposure in Western Australia, 2000–2015.

Exposure period	UTCI centile	Stillbirth HR (95% CI)	sPTB HR (95% CI)
Preconception to pregnancy	P1	1.28 (1.07, 1.52)	1.07 (0.98, 1.17)
	P5	1.14 (1.04, 1.25)	1.05 (1.01, 1.09)
	P10	1.08 (1.02, 1.13)	1.03 (1.01, 1.06)
	P90	0.95 (0.92, 0.98)	0.97 (0.95, 0.99)
	P95	0.90 (0.83, 0.96)	0.94 (0.89, 0.99)
	P99	0.91 (0.72, 1.15)	0.97 (0.89, 1.05)
Preconception	P1	1.28 (1.03, 1.60)	1.10 (1.01, 1.20)
	P5	1.20 (1.02, 1.41)	1.06 (1.00, 1.13)
	P10	1.17 (1.01, 1.35)	1.05 (1.00, 1.11)
	P90	0.98 (0.88, 1.10)	0.99 (0.93, 1.04)
	P95	1.00 (0.88, 1.13)	0.98 (0.92, 1.04)
	P99	1.16 (0.85, 1.59)	0.93 (0.83, 1.05)
Pregnancy	P1	1.33 (1.13, 1.55)	1.22 (1.13, 1.32)
	P5	1.18 (1.08, 1.29)	1.09 (1.05, 1.13)
	P10	1.13 (1.06, 1.21)	1.06 (1.03, 1.09)
	P90	0.91 (0.87, 0.96)	1.01 (0.97, 1.04)
	P95	0.88 (0.81, 0.95)	1.01 (0.96, 1.07)
	P99	0.91 (0.68, 1.21)	1.08 (0.97, 1.20)
First trimester	P1	1.58 (1.18, 2.11)	1.15 (1.06, 1.26)
	P5	1.30 (1.02, 1.65)	1.11 (1.04, 1.19)
	P10	1.24 (0.98, 1.56)	1.10 (1.04, 1.16)
	P90	1.02 (0.83, 1.24)	0.94 (0.90, 0.99)
	P95	1.03 (0.82, 1.29)	0.94 (0.89, 0.99)
	P99	0.97 (0.66, 1.42)	0.93 (0.83, 1.05)
Second trimester	P1	1.08 (0.81, 1.43)	0.97 (0.90, 1.05)
	P5	1.15 (0.92, 1.45)	0.97 (0.92, 1.03)
	P10	1.16 (0.93, 1.44)	0.97 (0.93, 1.02)
	P90	1.06 (0.86, 1.32)	1.09 (1.04, 1.15)
	P95	1.05 (0.83, 1.33)	1.11 (1.04, 1.18)
	P99	0.91 (0.59, 1.42)	1.31 (1.13, 1.52)
Third trimester	P1	1.33 (1.04, 1.72)	1.22 (1.12, 1.32)
	P5	1.02 (0.81, 1.29)	1.16 (1.09, 1.23)
	P10	0.99 (0.79, 1.23)	1.14 (1.08, 1.20)
	P90	0.86 (0.70, 1.05)	0.91 (0.88, 0.95)
	P95	0.89 (0.71, 1.11)	0.90 (0.86, 0.95)
	P99	1.17 (0.81, 1.70)	0.86 (0.77, 0.97)

Note: The model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, and year and season of conception. P1-P99, first to 99th centile of UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth.

The hazard of stillbirth was higher in married mothers for stillbirth, but unmarried mothers showed a higher hazard of sPTB (Figure S9.10). Nulliparous mothers showed a higher hazard of both stillbirth and sPTB (Figure S9.11). Mothers with complicated pregnancies were at higher hazard of stillbirth while those with uncomplicated pregnancies showed protection effects for sPTB (Figure S9.12).

9.4.3 Sensitivity

The sensitivity analyses did not change substantially, suggesting the stability of the results under varying modelling conditions and assumptions. The identified critical susceptible or protective exposure periods were consistent with the main results (Figure S9.13-S9.18).

9.5 Discussion

9.5.1 Main findings

Both lower (1^{st} to 10 the centile) and higher (90^{th} to 99^{th} centile) exposures as compared to median exposure showed positive associations with stillbirth and sPTB. Particularly, the 1^{st} centile exposure showed critical susceptible exposure periods during late pregnancy at 23^{rd} to 42^{nd} gestational weeks for stillbirth and 27^{th} to 36^{th} gestational weeks for sPTB. Critical susceptible exposure periods were also found during the 18^{th} to 26^{th} gestational weeks at the 90^{th} centile for stillbirth and at the 99^{th} centile of exposure for sPTB. Exposure at the 99^{th} centile additionally showed critical protection periods during the 33^{rd} to 36^{th} gestational weeks with a small magnitude of hazard of sPTB. The results of monthly UTCI exposure were consistent with that of weekly exposure. However, the 99^{th} centile exposure additionally showed increased susceptibility in 3^{rd} preconception month for sPTB. For each cumulative preconception and pregnancy exposure, the 1^{st} centile as compared to median exposure particularly showed higher hazards of both stillbirth and sPTB. Lower exposures, especially at 1^{st} centile as compared to median exposure indicated higher hazards in the first and third trimesters for both stillbirth and sPTB and the 99^{th} centile indicated small protection in the third trimester for sPTB. The effect estimates from the trimester-average exposures were less precise and varied slightly in some instances from that of the weekly exposures. This supports the recommendation from simulation studies to use more appropriate statistical approaches such as DLM or DLNM with fine temporal exposure periods because it is plausible that trimester-average exposures are less sensitive to the specific gestational time window of susceptibility.[58,59] Results showed disparities by sociodemographic or biological factors which varied for each birth outcome, except nulliparity which consistently showed vulnerability in both stillbirth and sPTB.

Although not fully comparable due to exposure assessment in particular, two recent studies employed DLNM Cox PH regression to investigate weekly critical susceptible exposure periods of ambient temperature exposure and the hazard of PTB.[256,426] The first study analysed 4,101 live singleton births, of which 5.7% were PTB in Guangzhou, China with weekly mean ambient temperature from conception up to birth with an overall mean temperature of 23.0 °C.[426] With the mean temperature as a reference, a higher hazard of PTB was found for temperature exposure at the 95th centile during the 4th to 8th, and 22nd to 27th gestational weeks with the strongest hazard of 1.83 (95% CI 1.27, 2.62) during the 24th gestational weeks. Exposure at the 5th centile as compared with mean temperature was associated with lower hazards of PTB with a critical protective period found during the 2nd to 10th and 20th to 26th gestational weeks; with the lowest hazard of 0.43 (95% CI 0.26, 0.72) observed for the 4th gestational week. The findings that higher exposures associated with a higher hazard of PTB, and lower exposures associated with a lower hazard of PTB, both during early gestational weeks (first trimester) and the mid-gestational weeks (second trimester) by Liu *et al* was somewhat contradictory to the findings of our study. In our study, both higher and lower exposures were associated with higher hazards of sPTB during late gestational weeks (third trimester) for lower exposure and mid-gestational weeks (second trimester) for higher exposure. The higher but not lower exposures, especially at the 99th centile additionally showed a small magnitude of protection periods in the third trimester. The second study examined the association between mean temperature with an average of 11.8 ˚C among 5,347 live singleton births with 4.3% PTB during the 26 weeks following conception and 30 days before birth in France.[256] At the 1st centile as compared with the median of mean temperature, the identified critical susceptible exposure periods of PTB were early pregnancy weeks (4th to 9th gestational weeks) and 10 to 4 days before delivery.[256] On the contrary, our study found late pregnancy weeks (27th to 36th gestational weeks) for sPTB at 1st centile as compared with the median UTCI. However, the observed short-term effect reported by Hough *et al* fell within the critical susceptible periods reported here and our findings on the short-term effect of UTCI on sPTB [368] and previous studies.[16] Hough *et al* did not find a critical susceptible period of PTB for exposure at high mean temperature but identified critical susceptible periods at the 95th and 99th centiles exposure when minimum or maximum temperatures were used as exposure metrics instead of mean temperature.[256] In addition to differences in outcome definitions and exposure metrics, differences in population characteristics, including genetic factors and lifestyle, adaptation or acclimatisation, and mitigation strategies could account for the different critical susceptible or protection periods. Rather than PTB in general as reported in the previous studies[256,426] the high-quality birth data enabled the investigation of non-induced PTB or sPTB in this study. The sensitivity analysis, however, showed consistent results of sPTB (singleton live or stillborn births with spontaneous onset of labour) with PTB that included only live singleton births with both induced and spontaneous PTB. Given that restricting the analysis to only live births could lead to biased results under certain conditions (live-birth bias),[101] future studies should include all eligible births irrespective of stillbirth status. However, bias from pregnancy loss more generally cannot be resolved completely unless data on all pregnancy loss is available at all stages of pregnancy, or, data on all common causes of pregnancy loss and the outcome of interest are available, which is infeasible.[101]

There is no known related study for stillbirth, but the results also indicated late gestational weeks for lower exposure and mid-gestational weeks for higher exposure as potential periods of increased susceptibility. These findings merit further investigation with clinical and policy implications for improved birth outcomes, given the potential impacts of climate change on birth outcomes with immediate and long-term effects.[10,274,298,424] While further studies are required for both birth outcomes, the findings in this study together with recent studies from different settings that have employed DLNM for short-term effect investigation for PTB or sPTB [120,245,314,368,404-407,425] and stillbirth [119,121,246,367] indicated that mid to late gestational periods are potential critical susceptible exposure periods for both stillbirth and PTB.

An unexpected but interesting finding was the ‘protective effect’ of the higher exposures toward the end of pregnancy, particularly at 99th centile exposure for sPTB. Mothers may have reduced exposure to higher exposure, particularly in late pregnancy as they were more likely to stay indoors and used air conditioning, especially in urban areas with high usage of air conditioning.[364] Staying indoors may also reduce exposure to ambient air pollution. These could potentially explain the observed critical protective exposure periods during late pregnancy at higher exposure mainly in urban areas. Further studies are required. Weekly preconception exposure did not show any critical susceptible periods but monthly or cumulative preconception exposure at a lower 1st centile as compared to median exposure associated with higher hazards of both stillbirth and sPTB. Two Chinese studies also reported on preconception exposures and found that three preconception months of exposure were associated with higher and lower odds of PTB for higher and lower exposures, respectively,[427] and exposures to both higher and lower temperatures within three or longer preconception weeks associated with a higher risk of PTB.[428] Further exploration is required for this neglected critical period for intervention [110] which is now gaining more attention in air pollution and perinatal epidemiology.[112] This is a crucial period of gametogenesis which can be affected by environmental exposures, leading to long-term effects.[110,112,427,428] Lower exposure levels as compared with the median exposure showed elevated risk in some sociodemographically or biologically vulnerable subpopulations depending on the birth outcomes as only nulliparity showed increased vulnerability in both stillbirth and sPTB. Generally, effect estimates were stronger and prolonged at lower than higher exposures which could be due to prolonged outdoor activities at lower than higher exposure thresholds.

Several climate change-resilient strategies at the population, health system, and climate governance policy levels have been discussed in Chapter 7 section 7.5.3.2.

9.5.2 Plausible pathophysiological mechanisms

The plausible pathophysiological mechanisms have been described in the previous chapters 7 and 8 above. A wealth of evidence from *in vivo*, *in vitro*, and human observational studies support cold or heat-induced adverse birth outcomes (elevated in biologically and sociodemographically vulnerable mothers) such as stillbirth and sPTB.[22,342,343,345,429-431] Briefly, biothermal stress can cause hypo- or hyperthermia which induces a series of biological and biochemical processes such as oxidative stress, apoptosis, and abnormal intracellular heat shock proteins (HSP), especially HSP 60 and 70, and neuroendocrine and inflammatory responses. As a result, placental growth and physiology are affected. This impairs implantation, embryogenesis, organogenesis, and fetoplacental transport of water, nutrients, and oxygen, and removal of fetal toxic waste substances, leading to fetal death or stillbirth. Also, the abnormal increase in neuroendocrine and inflammatory activities, especially high secretion of pituitary antidiuretic hormone, prostaglandin, and oxytocin induces labour prematurely, leading to spontaneous preterm delivery.

9.5.3 Strengths and limitations

This study has several strengths. This is the first known study to use the thermophysiologically relevant biothermal metric (UTCI) and long-term exposure assessment at a spatially and temporally resolved grid. The space-time varying exposure assessment reduces exposure misclassification as compared to the conventional use of simple models or proximity to sparse monitoring stations [16,331] that tend to be distant from where people reside and could exclude some vulnerable groups.[256,367,368] Application of DLNM Cox PH regression is a further strength as it accounted for both intensity and timing of past exposures to obtain unbiased hazards of the birth outcomes and to investigate fine and more reliable susceptible exposure periods such as gestational weeks and months [58-60] as compared to the usual trimester-based periods. Given the limited long-term effect of ambient temperature on PTB with this novel methodology,[256,426] no known related previous evidence on stillbirth, and the use of the biothermal stress exposure metric, the findings reported here provided very important epidemiological evidence for intervention strategies and understanding pathophysiological mechanisms. Compared to the two comparative studies,[256,426] the included cohort in this study was the largest and with detailed information to distinguish between induced and sPTB.

Several study limitations are also acknowledged. Despite the strength of being able to investigate effects at a small-area (SA1) scale, very fine spatial resolution can potentially also introduce misclassification due to the lack of information on exposures in nearby areas such as parks, shopping centres, and other local-level community centres that people access daily. As residential mobility among mothers is a well-established phenomenon, it is potentially less accurate to assess exposure at very fine spatial resolution targeted to the exact place of residence. Previous studies on ambient air pollution and pregnancy outcomes found that maternal residential mobility during pregnancy has no clear influence on the effect estimates.[275] This could explain why the same results were obtained after the local government area-specific cluster was included to account for potential spatial clustering and maternal mobility. Personalised activity-real-time exposure assessment remains the gold standard,[77] but is not feasible for large-scale studies. Possible non-differential exposure misclassification due to residential mobility, inability to incorporate daily activity patterns, time spent outdoors or indoors, and use of air conditioning could have biased the observed results. Even though comparative result with ambient temperature was not reported in this study, several evaluative and comparative studies have concluded that UTCI serves as a more useful biothermal metric to estimate and predict the risk of health outcomes.[78,79,353,358,359,432-434] As used in medical and other epidemiological areas,[81] future studies should consider UTCI. Data was not available on other covariates or potential confounding factors such as maternal alcohol or illicit drug intake, nutritional status, infection (e.g., seasonal influenza), maternal weight, and physical activity during pregnancy. Most of these factors, however, were partly controlled through SES and remoteness variables. Other factors such as education, employment, and height are less likely to be associated with UTCI and therefore are not expected to confound results.

9.6 Conclusion

This study investigated non-linear time-varying associations between biothermal stress (UTCI) from preconception to birth and the adjusted hazards of stillbirth and sPTB by applying DLNM Cox PH regression. As compared to median exposure, both lower and higher thresholds of the exposure were associated with higher hazards of stillbirth and sPTB. Mid to late gestational weeks such as weeks 23 to birth for stillbirth and 27 to birth for sPTB were potential critical susceptible exposure periods, especially stronger at lower than higher exposures. Higher exposure additionally offered a small ‘protective effect’ for sPTB towards the end of pregnancy. Weekly preconception exposure did not show a clear association, but monthly or cumulative preconception at lower thresholds of the exposure as compared to median exposure indicated positive associations with both stillbirth and sPTB. Apart from nulliparity showing increased vulnerability in both stillbirth and sPTB, vulnerable subpopulations varied between the birth outcomes. Together with the previous studies,[16,331] the long-term biothermal stress exposure associated with stillbirth and sPTB. The identified potential susceptible periods of mid to late gestational periods require further investigation and public health attention.

Chapter 10. Long-term maternal exposure to biothermal stress and the risks of adverse fetal growth in Western Australia

10.0 Preamble

This chapter provides a primary investigation of the association between maternal exposure to biothermal stress (Universal Thermal Climate Index) from preconception to birth and the risks of adverse fetal growth in Western Australia. Critical exposure periods of increased susceptibility and vulnerable subpopulations were identified. Part of this chapter is under review at *Environmental Health Perspective* with the title 'Maternal exposure to biothermal stress and birth weight for gestational age in Western Australia: a distributed lag non-linear model with time-to-event analysis to identify potential windows of susceptibility'.

10.1 Abstract

Background: There is very limited evidence on the potential critical susceptible periods of ambient temperature on fetal growth. Also, previous studies used temperature rather than biothermal metrics such as Universal Thermal Climate Index (UTCI). This study aimed to identify critical susceptible periods of UTCI exposure and the hazards of small for gestational age (SGA), large for gestational age (LGA), and low birth weight (LBW) using a robust statistical modelling approach.

Methods: We linked 385,337 singleton term births between 1st January 2000 and 31st December 2015 in Western Australia to spatiotemporal daily UTCI. Distributed lag linear and non-linear Cox regressions were used to investigate maternal exposure to UTCI from twelve weeks preconception to birth and the adjusted hazards of term SGA, LGA, and LBW.

Results: Relative to the median exposure, weekly-specific exposures showed small positive associations toward the end of pregnancy. The association was more obvious for monthly-specific exposures with critical susceptible periods from the 6th to 10th gestational months the strongest hazards of 1.13 (95% CI 1.10, 1.17) for term SGA, 1.07 (95% CI 1.03, 1.11) for term LGA in 10th gestational months at 1st UTCI centile and 1.02 (95% CI 1.01, 1.04) for term LBW in 3rd to 5th gestational months at 99th UTCI centile. Cumulative preconceptional exposure indicated small positive associations for only LGA at higher exposures. Entire pregnancy and trimester-specific average exposures showed strong positive associations at higher exposures relative to the median exposure. The strongest trimester-specific hazard was found in the second trimester for term SGA and the first trimester for term LGA and LBW. Male births, mothers who were non-Caucasians, 20-34 years old, smokers, and rural residents were most vulnerable.

Conclusions: As changes in fetal growth may not be obvious within short intervals, monthly rather than weekly exposure could better detect critical susceptible periods of biothermal stress on fetal

growth. The identified potential critical susceptible periods and vulnerable subpopulations could inform public health interventions and further investigations.

10.2 Introduction

Low birth weight (LBW), small for gestational age (SGA), and large for gestational age (LGA) are adverse fetal growth outcomes of public health concern.[280,281] LBW is defined as birth weight < 2500 g regardless of gestational age [280] while SGA and LGA are defined as birth weight less than 10th and more than 90th centiles, respectively, with reference to population-based birth weight at the same gestational age and sex.[281] These birth outcomes are commonly associated with perinatal mortality and various chronic morbidities from birth to adulthood such as stunting in childhood, neurodevelopmental delay, cardiometabolic disorders, and immunologic dysregulation.[12,280,282-284] The common risk factors of the birth outcomes include fetal factors (e.g., genetic diseases, male fetus), uteroplacental factors (e.g., structural placental factors, reduced blood flow, placental abruption), and maternal factors or conditions (e.g., race/ethnicity, malnutrition, substance use or abuse such as smoking and alcohol, maternal age, infections, excess gestational weight gain, parity).[280,281] Preventable or modifiable environmental exposures such as outdoor or indoor air pollution,[125,421] other chemicals, [422,423] and recently climatic factors are environmental risk factors of adverse fetal growth of increasing interest.[11,63]

The increasing severity of climate change [7] is being recognised as a serious threat to reproductive health.[274,435] Pathophysiologically, thermal stress exposures increase dehydration and induce oxidative stress and systemic inflammatory responses.[22,297,371] These affect both placental and fetal physiology, and fetoplacental transport of nutrients and oxygen, leading to adverse reproductive and fetal health outcomes.[22,297,371] Several recent observational studies reported on maternal exposure to ambient temperature and pregnancy outcomes such as pregnancy complications,[11,338] preterm birth, stillbirth, and low birth weight as reported in the umbrella review above (Chapter 7). However, there is limited related research on ambient temperature and SGA [63,292,436] and no related study for LGA as revealed in the umbrella review. Abnormal fetal growth includes both undergrowth (SGA) and overgrowth (LGA) and LGA was also implicated with many health outcomes throughout the life course.[281,437-439] LGA is now receiving greater attention in air pollution epidemiology [53,69,286] which requires corresponding investigation for climate change for actionable intervention.

As fetal development is a critical period of increased vulnerability to environmental exposures, the timing of exposure and critical exposure thresholds are clinically important to determine the specific nature of the dose-response relationship to develop prevention strategies.[297] Previous studies as reviewed in Chapter 7 investigated trimester-average exposures which could not detect fine temporal critical periods of increased susceptibility.[58] Also, regressing the outcome on each of the three trimester-average exposures without accounting for delayed (lagged) effects increases the potential to yield biased estimates and identify incorrect critical susceptible periods.[58] Distributed lag linear or non-linear models (DLNMs) were proposed to produce more accurate estimates and for flexible identification of fine temporal critical susceptible periods.[58-60] The DLNM methodology captures both the intensity and timing of past exposures by simultaneously describing the shape of the relationship along both exposure-response and lag-response dimensions.[59,60] Few recent studies employed DLNM to investigate weekly or monthly ambient temperature and change in term birth weight. [62,63,72,73,440] But for commonly used indicators of maternal health status and fetal growth outcomes, only one study on the topic applied this high-quality method for SGA[63] and LBW[70], and no known related study for LGA. The application of robust statistical modelling techniques such as DLNM to identify critical susceptible exposure periods is very important for public health interventions. This could contribute to achieving SDG 3.[228]

Some previous studies used heat index that included temperature and dew point [63] or temperature, vapour pressure, and air velocity [425] and recommended that future thermal-health studies should utilise proper thermal metrics that are more physiologically relevant rather than the usual surrogate thermal metrics such as minimum, maximum, mean, and standard deviation temperatures.[63,425] Although, the heat index is also limited in capturing human thermophysiological stress,[76] this recommendation reinforces several recent calls to researchers and policymakers to shift from surrogate usage of ambient temperature to modern thermophysiologically relevant metrics.[74-77] It is well known that the human body does not selectively perceive and respond to an individual climatic factor and that human thermophysiology is not a function of only air temperature.[75] Thermal stress is the net product of the combined thermal environment (air temperature, radiant temperature, humidity, and wind), activity (metabolic heat production), and clothing property which elicits the resultant physiological response (heat strain).[74] Thus, rather than only considering singular air temperature, it has been suggested that the estimation of thermal-health outcomes should be based on thermophysiological metrics (hereon, biothermal metrics) that account for human physiological heat responses.[74-76] Several comparative [78,79,358,441] and evaluative [76] studies have been conducted and four biothermal metrics were recommended recently as appropriate for thermal-health studies and warning systems.[76] Among them, Universal Thermal Climate Index (UTCI) was reported as most suitable as it best simulates the thermal response of the human body and has relatively high climatic sensitivity.[78-80,104] Recent applications of UTCI in thermal-health warning systems, operational weather forecasting, medical, and epidemiologic fields have been reviewed elsewhere.[81,82] So far, two studies have applied UTCI in perinatal epidemiology [119,442] but none for SGA and LGA.

Understanding the potential impacts of climate change on the risks of adverse fetal growth with biothermal metrics and the application of robust epidemiological methods is very important to identify critical susceptible periods and more vulnerable subpopulations to develop preventive strategies. To address the stated limitations, we used space-time varying UTCI from preconception periods [110,111] to birth and applied DLNM combined with Cox proportional hazard (Cox PH) regression [59,60,69] to examine the maternal exposure to average weekly, monthly, and cumulative UTCI and the hazards of term LBW, SGA and LGA. We identified potential critical periods of susceptibility and sociodemographically vulnerable subpopulations**.**

10.3 Methods

10.3.1 Study area, design, and population

A population-based retrospective cohort study was performed from 1st January 2000 to 31st December 2015 in Western Australia using a de-identified Midwives Notification System that contains sociodemographic and clinical information on both mother and baby. The details of the study population and eligibility criteria have been described in the previous Chapter 5 section 5.3.1. The final sample included in this study was 385,337 singleton term births (Figure 10.1).

10.3.2 Outcomes assessment and covariates

The fetal growth outcomes (term LBW, SGA, and LGA) and the same covariates have been described in the previous Chapter 5 section 5.3.

10.3.3 Exposure assessment

Biothermal stress was assessed using 24 h averages for daily gridded UTCI from the Copernicus Climate Data Store [106] as described in the previous Chapter 9 section 9.3.3. Weekly, monthly, and cumulative (preconception, pregnancy, trimester-specific averages) UTCI exposure was assigned to each birth from 12 weeks before conception (-11 to 0 weeks) to the earlier of birth and the 42nd gestational week, after which the birth contributed no exposure time.[69,232]

10.3.4 Statistical analyses

10.3.4.1 Main and subgroup analyses

To identify potential critical susceptible exposure periods, we applied DLNMs with Cox PH regression [61,69,232,426] to estimate weekly and monthly specific time-varying UTCI exposure and the hazard of term SGA, LGA, and LBW using gestational age in weeks as the underlying time scale as described in the previous Chapters 4, 5, and 9. Here the maximum lag for weekly exposure was 54 weeks. Both UTCI exposure and lagged exposure periods were modelled with natural cubic splines. The linear exposure-response relationship was also checked. The optimal exposure-response relationship and degree of freedom (*df*) were selected after testing several combinations of 2-7 *df* based on the minimum Akaike Information Criterion (AIC).[59,60] Thus, the *df* selected to build the cross-basis matrices using the *cross-basis* function of the 'dlnm' R package [59,60,249] were 6 and 3 for non-linear weekly exposure and exposure periods, respectively, for term SGA and LGA. For the term LBW, linear weekly exposure and 3 *df* for the exposure period were modelled. Similarly, monthly exposure-outcome associations were also examined for each fetal growth outcome over three months of preconception up to birth (13 months; -2 to 10 months). The HRs (95% CIs) of the UTCI exposures at the 1st, 5th, 10th, 90th, 95th, and 99th centiles were estimated, using median UTCI as the reference.

Furthermore, cumulative effects of the UTCI during preconception, entire pregnancy, and each trimester-average exposures were also evaluated with separate standard Cox PH models using a *one-basis* function of the 'dlnm' R package by constructing unlagged exposure-outcome associations and the *df* for non-linear relationship selected based on lowest AIC.[59,60,249] The final *df* selected were 5 for preconception and entire pregnancy and 2 for the three trimester-average exposures for SGA, and 2 for all cumulative exposures for LGA. All cumulative exposures for term LBW were modelled linearly. All the models were adjusted for the potential confounders described in the previous chapters. To explore the potential for effect modification, we conducted stratified analyses for the same subgroups described earlier in Chapters 4, 5, and 9. These analyses used preconception to pregnancy cumulative exposure.

10.3.4.2 Sensitivity analyses

Several sensitivity analyses were performed to ascertain the credibility of the weekly-specific results as described in previous Chapter 5 section 5.3.6.

All statistical analyses were performed using the statistical software R 4.2.1 (R Development Core Team 2020), and main R packages 'dlnm' and 'survival' were used. We reported and interpreted the HRs (95% CI) without considering any 'statistically significant' threshold as recommended by the American Statistical Association.[181]

10.4 Results

10.4.1Characteristics of the study population and biothermal stress exposure

This study included 385,337 singleton term births, of which 37,705 (9.8%) were SGA, 38,223 (9.9%) were LGA, and 6,444 (1.7%) were LBW. Slightly more than half of the births were

Table 10.1 Maternal characteristics of included singleton term births in Western Australia, 2000-2015 (N= 385,337)

Characteristics	n (%)	Characteristics	n (%)
SGA		*Smoking status*	
No	347,632 (90.2)	No	330,651 (85.8)
Yes	37,705 (9.8)	Yes	54,679 (14.2)
LGA		Unknown	7 (0.0)
No	347,114 (90.1)	*Parity*	
Yes	38,223 (9.9)	Nulliparity	160,731 (41.7)
LBW		Multiparity	224,606 (58.3)
No	378,893 (98.3)	*Remoteness indicator*	
Yes	6,444 (1.7)	Urban	238,826 (62.0)
Infant sex		Rural	146,377 (38.0)
Male	196,384 (51.0)	Unknown	134 (0.0)
Female	188,953 (49.0)	*SES*	
Maternal age (years)		High	127,831 (33.2)
≤19	17,170 (4.5)	Moderate	128,439 (33.3)
20-34	291,366 (75.6)	Low	129,046 (33.5)
≥35	76,801 (19.9)	Unknown	21 (0.0)
Race/ethnicity		*Season of conception*	
Caucasian	303,375 (78.7)	Autumn	93,678 (24.3)
Non-Caucasian	81,962 (21.3)	Winter	97,982 (25.4)
Marital status		Spring	97,250 (25.2)
Married	337,801 (87.7)	Summer	96,427 (25.0)
Unmarried	47,536 (12.3)		

Note: SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight; SES, socioeconomic status.

male (51.0%), and the majority were born to mothers who were Caucasian (78.7%), married (87.7%), non-smokers (85.8%), multiparous (58.3%), and urban residents (62.0%). Mothers were almost equally distributed among the four seasons of conception (Table 10.1).

The exposure to UTCI (biothermal stress) over the full exposure period ranged from 8.1˚C to 30.0˚C with an approximately equal mean (14.5 ± 2.5˚C) and median (14.2˚C). The UTCI distributions for the exposure periods tended to be within the range of 9-26˚C, consistent with the standard categories of *no thermal stress.*[103] The specific average exposures for preconception, pregnancy, and each trimester were similar to the overall preconception to birth exposures (Table 10.2).

Table 10.2 Descriptive statistics of the average UTCI (°C) during twelve weeks preconception through to gestational weeks at delivery exposure periods for included singleton term births in Western Australia, 2000-2015 (N= 385,337)

Exposure periods	Min	Mean ± SD	Median	P1	P5	P10	IQR	P90	P95	P99	Max
Preconception to pregnancy	8.1	14.5 ± 2.5	14.2	10.3	11.9	12.8	1.2	15.4	17.3	26.0	30.0
Preconception	1.4	14.4 ± 5.2	14.0	5.8	7.6	8.2	8.8	20.8	22.0	29.4	35.8
Pregnancy	6.6	14.5 ± 2.8	14.2	9.7	11.3	11.9	2.9	16.7	18.0	26.7	32.7
1st Trimester	1.7	14.5 ± 5.2	14.2	5.9	7.7	8.3	8.9	20.9	22.0	29.6	36.0
2nd Trimester	1.6	14.6 ± 5.1	14.2	6.1	7.8	8.5	8.7	20.9	22.0	29.8	36.1
3rd Trimester	1.7	14.5 ± 5.1	14.1	6.1	7.7	8.4	8.7	20.8	21.9	29.6	35.6

Note: UTCI, Universal Thermal Climate Index; SD, standard deviation; P1-99, 1st-99th centiles; IQR, interquartile range= P75-P25

10.4.2 Biothermal stress exposures and the hazards of term adverse fetal growth

Compared to the median UTCI (14.2 ˚C), exposure to various centiles of weekly UTCI mostly showed negative with the hazard of term SGA until the 10th gestational week after which the hazard increased slightly through to birth, especially for 1st (10.3˚C) and 95th (17.3˚C) centiles of exposure. The stronger positive associations were found towards the end of pregnancy (34th–42nd gestational weeks) and the strongest hazard was 1.02 (95% CI 1.01, 1.04) during the 42nd gestational week at the 1st centile exposure (Figure 10.1, Table S10.1). As compared to the median exposure, weekly UTCI exposure showed very small positive associations with the hazard of the term LGA (Figure 10.1). The strongest hazard of term LGA was 1.01 (95% CI 1.00, 1.02) during the 36th–42nd gestational weeks at the 95th centile as compared to the median UTCI (Figure 10.1, Table S10.2). As compared to the median UTCI, exposures at the 1st to 10th centiles showed negative associations while exposures at the 90th to 99th centiles showed very small positive associations with the hazard of the term LBW. The strongest hazard of term LBW was 1.01 (95% CI 1.00, 1.01) during the 10th–33rd gestational weeks at the 99th centile as compared to median UTCI (Figure 10.1, Table S10.3).

Monthly UTCI exposure showed similar patterns with more obvious critical susceptible periods from the 6th–10th gestational months, especially at the 1st to 10th UTCI centile as compared to median UTCI for term SGA and LGA. As compared to median UTCI, the strongest hazards were 1.13 (95% CI 1.10, 1.17) for term SGA and 1.07 (95% CI 1.03, 1.11) for term LGA in 10th gestational months at 1st centile and 1.02 (95% CI 1.01, 1.04) for term LBW in 3rd to 5th gestational months at 99th UTCI centile (Figure 10.2, Tables S10.4, S10.5, S10.6).

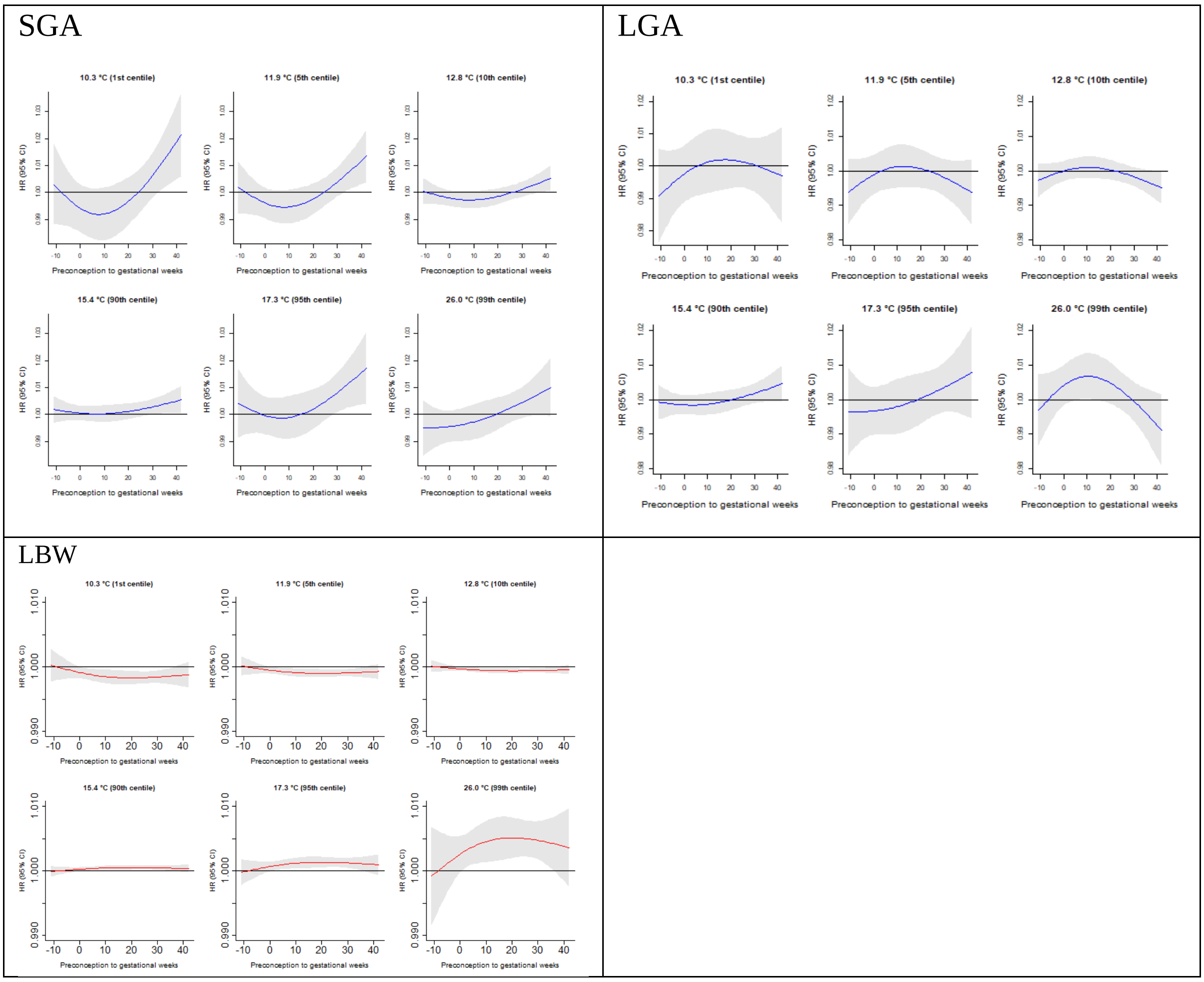

Figure 10.1 Adjusted hazard ratios of term SGA, LGA, and LBW associated with weekly-specific UTCI over 12-week preconception (-11 to 0) through to gestational week at delivery (1 to 42) at different thresholds of UTCI using the median of 14.2 ◦C as reference. Solid blue lines represent point estimates, and the whiskers represent 95% confidence intervals. All models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

Cumulative exposures from preconception through to birth showed small negative associations with the hazard of term SGA at the 1st to 10th and 95th UTCI centiles but a positive association at the 99th centile as compared to the median exposure. Preconception exposure showed very small negative associations. Entire pregnancy exposure showed positive associations at higher exposure levels (90th to 99th centiles) for term SGA and the strongest hazard was 1.11 (95% CI 1.04, 1.18) at the 99th centile as compared to median exposure (Table 10.3, Figure S10.2). Trimester-average exposures showed the strongest hazard of term SGA, 1.03 (95% CI 1.01, 1.05) during the second trimester for exposure to the 90th centile as compared to the median exposure (Table 10.3, Figure S10.3). The strongest hazard of term LGA for cumulative exposures during preconception through to birth was 1.03 (95% CI 1.01, 1.05) at the 95th centile. The strongest hazard of term LGA was 1.03 (95% CI 0.95, 1.11) for each preconception and entire pregnancy average exposure to the 99th centile as compared to the median exposure (Table 10.3, Figure S10.2). Trimester-specific average exposures showed the strongest hazard of LGA, 1.10 (95% CI 1.03, 1.18) during the first trimester at the 99th centile as compared to the median exposure (Table 10.3, Figure S10.3).

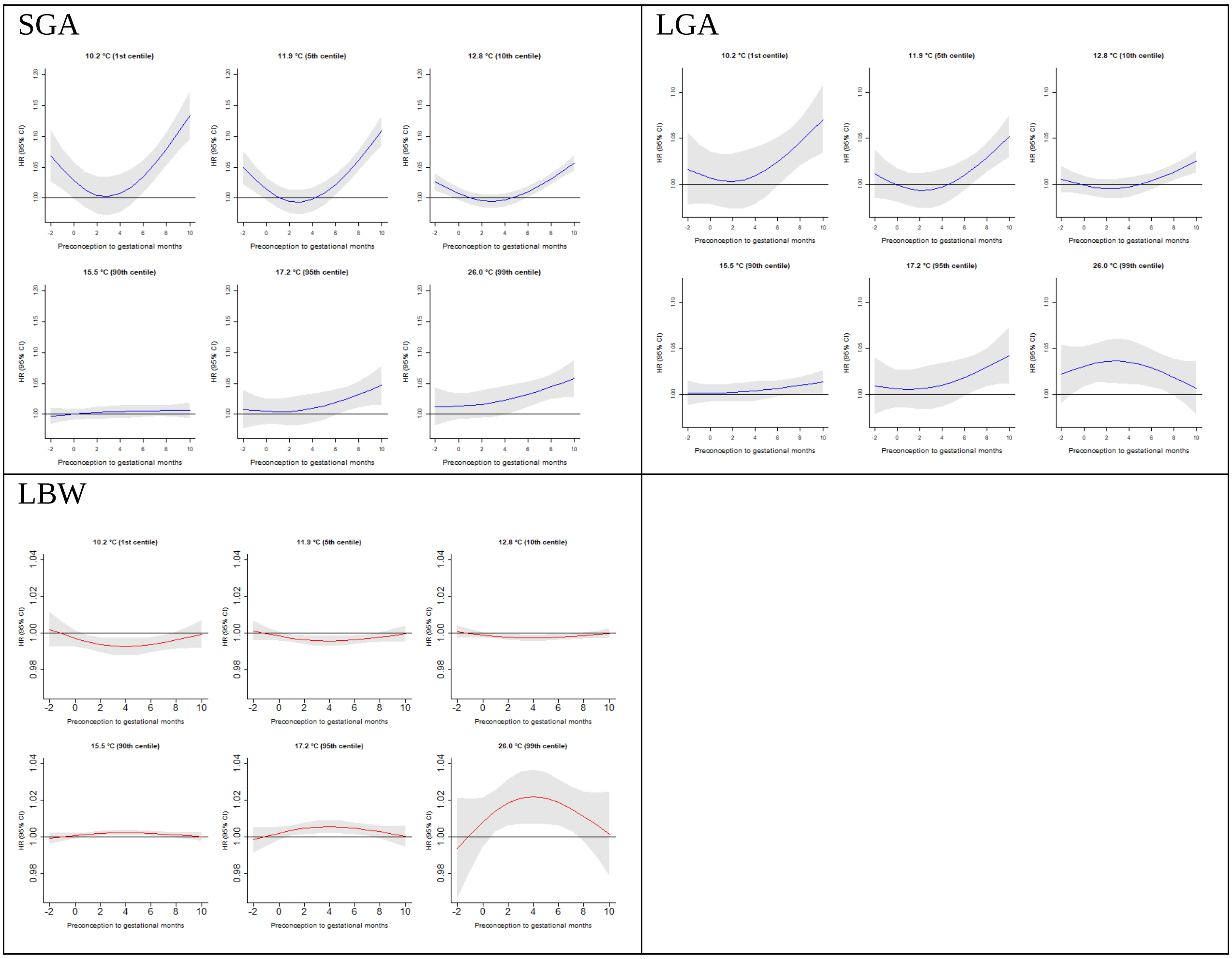

Figure 10.2. The exposure-response association between maternal monthly-specific UTCI exposures for three months preconception through to pregnancy with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

Cumulative exposures from preconception through to birth showed small negative associations with the hazard of term LBW at the 1st to 10th centiles but positive associations at the 90th to 99th centile as compared to the median exposure and the strongest hazard was 1.21 (95% CI 1.09, 1.33) at 99th centile. Preconception exposure showed no association with the term LBW. The entire pregnancy exposure showed positive associations and the strongest hazard of term LBW was 1.22 (95% CI 1.10, 1.35) at the 99th centile as compared to median exposure (Table 10.3, Figure S10.2). Trimester-specific average exposures showed the strongest hazard of term LBW, 1.10 (95% CI 1.01, 1.21) during the first trimester for exposure to the 99th centile as compared to the median exposure (Table 10.3, Figure S10.3).

Table 10.3. The exposure-response association between maternal cumulative UTCI exposures over twelve weeks preconception through to pregnancy and trimester-specific periods with reference to the median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various percentiles of the exposure in Western Australia, 2000–2015.

Exposure period	UTCI centile	SGA HR (95 % CI)	LGA HR (95 % CI)	LBW HR (95 % CI)
Preconception to pregnancy	P1	0.96 (0.90, 1.01)	0.94 (0.89, 0.98)	0.94 (0.91, 0.97)
	P5	0.97 (0.93, 1.01)	0.97 (0.94, 0.99)	0.96 (0.95, 0.98)
	P10	0.97 (0.94, 1.00)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)
	P90	1.01 (0.99, 1.03)	1.01 (1.01, 1.02)	1.02 (1.01, 1.03)
	P95	0.98 (0.93, 1.02)	1.03 (1.01, 1.05)	1.05 (1.02, 1.08)
	P99	1.07 (1.01, 1.12)	1.04 (0.98, 1.11)	1.21 (1.09, 1.33)
Preconception	P1	1.01 (0.96, 1.06)	0.94 (0.91, 0.98)	1.00 (0.95, 1.05)
	P5	0.99 (0.96, 1.03)	0.96 (0.93, 0.99)	1.00 (0.96, 1.04)
	P10	0.99 (0.96, 1.03)	0.96 (0.94, 0.99)	1.00 (0.97, 1.04)
	P90	0.98 (0.95, 1.02)	1.02 (1.00, 1.05)	1.00 (0.96, 1.04)
	P95	0.98 (0.94, 1.02)	1.02 (1.00, 1.05)	1.00 (0.96, 1.05)
	P99	0.98 (0.91, 1.05)	1.03 (0.95, 1.11)	1.00 (0.91, 1.09)
Pregnancy	P1	0.96 (0.91, 1.02)	0.97 (0.92, 1.01)	0.93 (0.90, 0.97)
	P5	0.99 (0.95, 1.03)	0.98 (0.95, 1.01)	0.96 (0.93, 0.98)
	P10	0.99 (0.96, 1.03)	0.98 (0.96, 1.01)	0.96 (0.95, 0.98)
	P90	1.03 (1.00, 1.06)	1.01 (1.00, 1.03)	1.04 (1.02, 1.06)
	P95	1.03 (0.99, 1.07)	1.02 (1.00, 1.04)	1.06 (1.03, 1.10)
	P99	1.11 (1.04, 1.18)	1.03 (0.95, 1.11)	1.22 (1.10, 1.35)
First Trimester	P1	1.00 (0.95, 1.05)	0.94 (0.89, 1.00)	0.95 (0.90, 1.00)
	P5	1.00 (0.96, 1.04)	0.95 (0.91, 0.99)	0.96 (0.92, 1.00)
	P10	1.00 (0.97, 1.03)	0.96 (0.92, 0.99)	0.96 (0.93, 1.00)
	P90	1.00 (0.98, 1.02)	1.05 (1.02, 1.07)	1.04 (1.00, 1.09)
	P95	1.00 (0.98, 1.02)	1.05 (1.03, 1.08)	1.05 (1.00, 1.10)
	P99	1.00 (0.94, 1.06)	1.10 (1.03, 1.18)	1.10 (1.01, 1.21)
Second Trimester	P1	0.98 (0.94, 1.02)	1.02 (0.98, 1.07)	0.97 (0.91, 1.04)
	P5	0.98 (0.95, 1.02)	1.02 (0.98, 1.05)	0.98 (0.93, 1.03)
	P10	0.99 (0.96, 1.01)	1.01 (0.99, 1.04)	0.98 (0.94, 1.03)
	P90	1.03 (1.01, 1.05)	0.99 (0.97, 1.02)	1.02 (0.97, 1.08)
	P95	1.03 (1.01, 1.06)	0.99 (0.96, 1.02)	1.03 (0.97, 1.10)
	P99	1.08 (1.00, 1.17)	0.99 (0.91, 1.08)	1.06 (0.93, 1.20)
Third Trimester	P1	0.99 (0.94, 1.05)	0.98 (0.92, 1.04)	0.95 (0.9, 1.00)
	P5	0.99 (0.95, 1.04)	0.98 (0.94, 1.03)	0.96 (0.92, 1.00)
	P10	0.99 (0.96, 1.03)	0.99 (0.95, 1.02)	0.96 (0.93, 1.00)
	P90	1.01 (0.99, 1.03)	1.01 (0.98, 1.03)	1.04 (1.00, 1.09)
	P95	1.01 (0.99, 1.04)	1.01 (0.98, 1.04)	1.05 (1.00, 1.11)
	P99	1.03 (0.97, 1.10)	1.01 (0.94, 1.09)	1.10 (0.99, 1.23)

Note: The model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; P1-99, 1st-99th centiles; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age.

Disproportionately higher hazards of adverse fetal growth were found in some vulnerable subpopulations, particularly for term SGA and LBW. The hazard was more elevated for male than female births (Figure S10.4) and mothers that were non-Caucasian (Figure S10.5), 20-34 years old

(Figure S10.6), resided in high or low SES areas (Figure S10.7), rural areas (Figure S10.8), and smokers (Figure S10.9). Parity did not show any difference for term SGA, but a higher hazard of term LGA and LBW was observed in multiparous mothers (Figure S10.10).

10.4.3 Sensitivity analyses

The results did not change substantially after altering modelling conditions such as estimating the hazards with mean rather median exposure as reference (Figure S10.11), varying the *dfs* for exposure and exposure period in the DLNM (Figure S10.12), adjusting for maternal age (Figure S10.13) and season of conception (Figure S10.14) as categorical variables. The inclusion of a mother-specific cluster to account for repeated births by the same mother (Figure S10.15), and a local government area-specific cluster to account for potential spatial clustering and maternal mobility (Figure S10.16) also produced consistent results. Finally, the inclusion of all eligible births with 22-42 gestational weeks also yielded similar results (Figure S10.17).

10.5 Discussion

10.5.1 Associations between biothermal stress and the hazards of adverse fetal growth

This is the first study to the best of our knowledge using a biothermal stress metric (UTCI) to evaluate weekly and monthly-specific preconception to birth associations with the hazards of adverse fetal growth. Overall, weekly-specific biothermal stress exposures showed small positive associations with fetal growth outcomes with critical susceptible periods during late gestational weeks, especially for term SGA. Monthly-specific exposures showed more obvious critical susceptible periods at lower exposure thresholds during the 6^{th}–10^{th} gestational months for term SGA and LGA, particularly elevated at 1^{st} centile exposure as compared to median exposure. For term LBW, the strongest hazard or critical susceptible periods was found during the 3^{rd}–5^{th} gestational months at the 99^{th} centile as compared with the median exposure. The cumulative preconception exposure showed positive associations for LGA at higher thresholds of the exposure. Entire pregnancy and trimester-average exposures showed relatively strong positive associations at higher thresholds of the exposure (90^{th} to 99^{th} centiles) as compared with the median exposure. The trimester-average exposures showed the strongest hazards during the second trimester for term SGA and the first trimester for term LGA and LBW. The identified higher-risk subpopulations were male births, and births by mothers who were non-Caucasian, 20-34 years old, smokers, and rural area residents. Births by mothers in high SES areas were at a higher hazard of term SGA and LBW while low SES mothers were at a higher hazard of term LGA.

Our umbrella review presented in Chapter 7 indicated that, although with some inconsistent findings, several studies reported positive associations between cumulative ambient temperature exposure (entire pregnancy or trimester-average) and SGA and LBW but no known related evidence for LGA. Only two recent studies applied DLNM to investigate weekly mean temperature and mean heat index (temperature and dew point) and the odds of term SGA on 4,442 term births in Boston, United States,[63] and weekly mean temperature and humidity exposures and the odds of term LBW on 6,202 singleton term births in Jinan City, China.[70] Carlson *et al* found no obvious association of either mean temperature or mean heat index with the odds of SGA for a 5 ˚C increase in mean weekly-specific exposures.[63] This is contrary to the finding in our study where critical susceptible periods were found towards the end of pregnancy (34th–42nd gestational weeks) which was most elevated at the 1st centile exposure as compared to median exposure. Du *et al* found 1st–6th gestational weeks as critical susceptible periods for low humidity but no critical susceptible period for both low (5th centile, 11.8 ˚C) and high (95th centile, 20.2 ˚C) levels of ambient temperature as compared to median temperature (15.6 ˚C) at each gestational week and the odds of term LBW.[70] We found a very small magnitude of the higher hazard of term LBW at higher exposures (90th to 99th centile) as compared to the median exposure, especially during early to mid-pregnancy. The differences in our findings from the previous studies [63,70] could be due to the variations in geodemographic characteristics, mitigation strategies, acclimatisation and particularly using temperature or simple heat index instead of composite biothermal metrics. Using biothermal metrics, particularly UTCI has been reported to characterise the thermal-health outcomes more adequately than temperature or simple heat indexes.[76,78,79,358,441] Du *et al* also concluded that the effect of temperature on the odds of term LBW seemed to be more cumulative than weekly-specific exposure.[70] This explained why we found more obvious critical susceptible periods for monthly than weekly UTCI exposures for all the fetal growth outcomes. Thus, as changes in fetal growth may not be obvious within short intervals, monthly rather than weekly exposure assessment could better detect susceptible critical periods of thermal stress on fetal growth. Also, large proportions of SGA or LGA cases may be constitutionally small or large which is not related to any underlying pathologic condition[242,443] or requires a very sensitive biothermal metric such as UTCI to detect the thermal-health association.[74,78] Further investigations using more sensitive and thermophysiologically relevant biothermal metrics such as UTCI [76,78,79,358,441] will be helpful. Also, using lower cut-offs such as the 5th or 3rd centile (95th or 97th centile) has been suggested to identify higher at-risk groups for SGA or LGA.[242,444]

We reported the effect estimates from the trimester-average exposures as the usual approach for identifying critical susceptible periods. Our results were similar to that of a large cohort study that found that high temperature was associated with higher odds of term SGA during both the second and third trimesters and that low temperature showed no association with the odds of term SGA.[292] However, there were other discrepant findings such as no associations with cumulative exposures by trimesters,[63,242] and high temperature associated with lower odds of term SGA during the first trimester and higher odds of term SGA during the third trimester.[436] For term LBW, we found higher hazards at higher exposure thresholds with the strongest hazard of term LBW in the first trimester. This was consistent with a recent study that consistently found the strongest odds of term LBW in the first trimester for multiple extreme heat events defined by intensities and durations of ambient temperature.[445] Again there were other discrepant findings such as strongest odds of term LBW in the third trimester for low temperature,[436] and positive associations in both second and third trimesters for both high and low temperatures but strongest odds of term LBW in the third trimester for high temperature as compared to mild temperature.[242] Such discrepancies may be due to geographical differences in thermal or temperature distributions even within the same setting, acclimatisation, adaptation or mitigation strategies, differences in study design, characteristics of the study population, exposure assessment method, and exposure thresholds. Moreover, our findings from both weekly and monthly-specific exposures indicated late gestation periods (late second trimester to third trimester) as critical susceptible periods for adverse fetal growth outcome which differed from our findings from trimester-average exposures where the second trimester for term SGA and first trimester for both term LGA and LBW were identified as critical susceptible periods. This difference has been demonstrated elsewhere and indicated that the analyses of trimester-average exposures could result in biased estimates and incorrect critical susceptible periods.[58] This is the reason why the DLNM method that accounts for both intensity and timing of past exposures to accurately identify critical susceptible periods has been recommended.[58,59] Our findings also showed that while preconception exposure showed essentially no association with the term SGA and LBW as reported previously,[242] it showed small positive associations with LGA at high exposure levels. As there is no known previous evidence for LGA, our findings are novel, suggesting the need for further related studies on LGA to contribute to the evidence base, which has also been proposed for studies on air pollution exposure.[53,69,286] Given the very limited evidence on weekly or monthly-specific thermal exposures and adverse fetal growth,[63,70] more high-quality studies with robust statistical modelling such as DLNM and using biothermal metrics such as UTCI are required.

The differences in the sensitivity to exposures, degree of climate extremes, population characteristics such as sociodemographic and underlying health conditions, acclimatisation, and adaptation or mitigation measures determine the vulnerability of the population to biothermal stress exposures.[436,442] These could explain the high risks of adverse fetal growth in vulnerable subpopulations such as male births, and births by mothers that were non-Caucasians, smokers, and rural area residents. Male fetuses have low plasma anti-inflammatory capacity to counteract the inflammatory responses due to thermal stress-induced oxidative stress.[446] Female fetuses also respond to reduced maternal nutrition and moderation in placental physiology and better response to higher levels of reactive oxygen species and maternal glucocorticoids than males which may reduce the risk of adverse fetal growth in female births as compared to male births.[447] Higher risks in non-Caucasians and rural area residents may be explained by existing underlying factors such as hereditary, high-risk behaviours and lifestyle (e.g., smoking, alcohol, and illicit drug intake), underutilisation of antenatal care services, lack of mitigation strategies (e.g., use of heating or cooling systems), and higher involvement in outdoor activities.[364] Racial/ethnic reproductive health inequalities have also been attributed to systemic discrimination, and residential and housing segregation.[265]

Society-wide public health interventions and climate change-resilient strategies were described in detail earlier in Chapter 7 section 7.5.3.2. These measures are critically important to ensure that the health outcomes at birth are not affected by the changing climate with serious health implications.[10,274,448]

10.5.2 Plausible pathophysiological mechanisms

The biological mechanisms of maternal exposure to thermal or biothermal stress and fetal growth have not been completely elucidated. However, *in vivo* studies provide convincing plausible pathophysiological pathways, particularly for fetal growth restriction resulting in SGA and LBW. The general physiological changes during pregnancy and fetal metabolic activities increase the thermal vulnerability of pregnant women which affects their thermoregulatory capacity.[367,399] Exposure to extreme thermal environments increases thermal strain during pregnancy, causing hypo- or hyperthermia. This can induce oxidative stress, heat or cold shock, and inflammatory responses, and reduce the uterine blood flow which affects placental growth and cause placental dysfunction as demonstrated in experimental animal studies.[21,22,449] Consequently, both passive and active maternal-to-fetal transport of oxygen and nutrients is affected and has been observed to be profound at mid to late pregnancy periods.[371] These cause fetal hypoxemia and hypoglycaemia which slow fetal growth and alter their metabolic and endocrine activities, resulting in abnormal fetal growth.[21,297,371] It was also found that maternal inflammation at the mid-gestational period impairs myoblast (stem cell) function, increases protein catabolism and reduces skeletal muscle growth near term.[449] Moreover, fetal growth restriction in ewes was found to be an adaptative mechanism at the expense of normal fetal growth and development to hyperthermia-induced placental insufficiency to preserve the placental transport capacity of oxygen and nutrients.[21]

As compared to SGA and LBW, biological mechanisms linking environmental exposures such as biothermal stress to LGA are not well-understood. The plausible causal pathways are the known processes by which oxidative stress and inflammation cause high blood glucose or hyperglycaemia which can be transported to the developing fetus. The fetus produces extra insulin which together with the extra glucose or fetal hyperglycaemia can lead to increased fetal growth and fat deposition, resulting in an increased risk of LGA.[300,301]

10.5.3 Strengths and limitations

The strengths and limitations described earlier in Chapter 9 section 9.5.3 are applicable here.

10.6 Conclusion

Compared to the median UTCI exposure, the results showed that both weekly and monthly-specific exposures were associated with adverse fetal growth. But there were very clear monthly-specific critical susceptible periods of term SGA and LGA during the 6th–10th gestational months and 3rd-5th gestational months for term LBW at extreme exposures as compared to median exposure. Cumulative preconception exposure showed no association with the hazard of the term SGA and LBW, but an association was found for the hazard of the term LGA at high exposure levels. Entire pregnancy and trimester-specific average exposures showed relatively strong positive associations at higher exposure levels as compared with the median exposure. The strongest elevation in hazards was found during the second trimester for term SGA and the first trimester for term LGA and LBW. We also found disproportionately elevated hazards for some vulnerable subpopulations such as male births, and births by mothers who were non-Caucasians, 20-34 years, smokers, and rural area residents. The identified potential critical susceptible periods and vulnerable subpopulations could inform public health interventions and further investigations. Further studies should take advantage of the leveraged technological advancements for the application of biothermal metrics such as UTCI rather than the singular use of ambient temperature.[74-76,81]

Chapter 11. Long-term maternal exposure to biothermal stress and the risk of stillbirth in Ghana

Preamble 11.0

This chapter provides primary investigations of the long-term maternal exposure to biothermal stress, measured with the Universal Thermal Climate Index (UTCI) and the risks of stillbirth as published in a peer-reviewed journal *Environmental Research* with the title 'Prenatal exposure to long-term heat stress and stillbirth in Ghana: a within-space time-series analysis'.[450]

11.1 Abstract

Introduction: Few studies examined the association between prenatal long-term ambient temperature exposure and stillbirth and fewer still from developing countries. Rather than ambient temperature, we used a human thermophysiological index, Universal Thermal Climate Index (UTCI) to investigate the role of long-term heat stress exposure on stillbirth in Ghana.

Methods: District-level monthly UTCI was linked with 90,532 stillbirths of 5,961,328 births across all 260 local districts between 1st January 2012 and 31st December 2020. A within-space time-series design was applied with distributed lag nonlinear models and conditional quasi-Poisson regression.

Results: The mean (28.5 ± 2.1 ºC) and median UTCI (28.8 ºC) indicated *moderate heat stress.* The Relative Risks (RRs) and 95% Confidence Intervals (CIs) for exposure to lower-moderate heat (1st to 25th percentiles of UTCI) and strong heat (99th percentile) stresses showed lower risks, relative to the median UTCI. The higher-moderate heat stress exposures (75th and 90th percentiles) showed greater risks which increased with the duration of heat stress exposures and were stronger in the 90th percentile. The risk ranged from 2% (RR=1.02, 95% CI 0.99, 1.05) to 18% (RR= 1.18, 95% CI 1.02, 1.36) for the 90th percentile, relative to the median UTCI. Assuming causality, 19 (95% CI 3, 37) and 27 (95% CI 3, 54) excess stillbirths per 10,000 births were attributable to long-term exposure to the 90th percentile relative to median UTCI for the past six and nine months, respectively. Districts with low population density, low gross domestic product, and low air pollution which collectively defined rural districts were at higher risk as compared to those in the high level (urban districts).

Discussion: Maternal exposure to long-term heat stress was associated with a greater risk of stillbirth. Climate change-resilient interventional measures to reduce maternal exposure to heat stress, particularly in rural areas may help lower the risk of stillbirth.

11.2 Introduction

A fetal death of at least 28 weeks' gestation or at least 1,000 g birth weight, if the gestational length is unknown, is defined by World Health Organization (WHO) as stillbirth.[303] Between 2000 and 2019, the world recorded 48 million stillbirths and 84% of these were from low-and-middle-income countries (LMICs) with Sub-Saharan Africa (SSA) as the highest contributor.[303] The human-induced climate change crisis,[7] particularly extreme ambient temperatures and air pollution are adding to the usual risk factors of stillbirth.[125,274]

Establishing causality with certainty is challenging, yet many coherent biological pathways explain the plausible impacts of extreme ambient temperatures on stillbirth. These include the impacts of hyperthermia, dehydration, thermally-induced oxidative stress on placental growth and physiology, and maternal-fetal transport of materials such as nutrients, water, oxygen, and the removal of fetal metabolic wastes.[22,343,451] A recent systematic review that included 12 studies from seven countries found an association between extreme ambient temperatures and stillbirth.[331] The review included only one study from the most vulnerable settings, LMICs which was based on a cross-sectional analysis of the 2007 Ghana Maternal Health Survey (GMHS) at larger geographic units [452] with notable exposure misclassification due to varying temperatures at different locations across the country. A recent cross-sectional retrospective study in 14 LMICs also linked gridded daily temperature to a demographic health survey and reported acute or short-term effects of ambient temperature on stillbirth and preterm birth.[335] However, there is currently no study from an LMIC that has applied a longitudinal design, and no study from this region that has ascertained stillbirth by clinical diagnosis and investigated chronic or long-term effects of the exposure. Moreover, given the wide differences in thermal variability, adaptation and mitigation strategies, a geodemographic-specific assessment of the impact of thermal stress on stillbirth will be more relevant for contextually and targeted interventions.[331]

The ambient thermal environment is a combination of the air temperature, solar radiation, relative humidity, and the air velocity.[74,76] Thus, using only ambient temperature as a surrogate of thermal stress cannot be considered as adequate characterisation of human thermal exposure.[74,75] However, thermal stress-related epidemiologic studies, in general, use ambient temperature rather than a human thermophysiological index. This limitation has been raised recently with a recommendation for a change to the human thermophysiological indices to improve the reliability, robustness, comparability, and physiological relevance of the findings.[74,76] The human body only feels the impact of all climatic factors collectively as human physiologic systems do not have specific sensors to detect and differentially respond to a single climatic factor such as air temperature.[75] The thermal stress imposed on a person is a result of the total thermal environment together with activity or metabolic heat production and behaviours such as clothing worn.[74,76] The use of air temperature metrics in measuring relationships between thermal stress and health outcomes is partly due to lack of access to the necessary meteorological data and computational complexities to characterise the total thermal environment to produce more valid thermal-health outcomes and projections.[74,76,353] It is, therefore, expected that thermophysiological indices instead of air temperature will become the thermal indices of preference as the necessary climatic variables and operational procedures for easy computation are becoming increasingly available.[74,76,77,353] Four of several thermophysiological indices were evaluated to be appropriate [76] and Universal Thermal Climate Index (UTCI) was proven most suitable.[78,79,358] Regardless of climate zone, seasons, and personal characteristics, UTCI has a prognostic potential to describe the actual thermal environment and human thermophysiological response in different climates.[78,79,81] UTCI is useful to examine both the impacts of the ambient thermal environment (heat or cold stress) on health outcomes and as thermal stress warning systems to support public health interventions and climate governance.[81,82]

Using a single ambient temperature or apparent temperature (temperature and relative humidity) or inappropriate thermal metric to predict related health outcomes can result in less realistic projections for either under or overspending on the limited resources of the health system.[74,76] For instance, among three thermal metrics (Apparent Temperature, Net Effective Temperature, and UTCI) assessed in Spain and Portugal, the relative risk of cardiovascular morbidity was lowest with UTCI.[434] This was explained by the fact that UTCI, which also integrates the individual's physiological characteristics while taking into account the thermal environmental influences, may smooth out any overestimations present in the other two indices.[434] Analysis of daily mortality data from 21 cities across nine European countries found a strong correlation between the results of the UTCI and air temperature for heat stress but larger differences between the results of UTCI and air temperature for cold stress due to the role of wind in the definition of UTCI.[353] Another study examined daily minimum and maximum temperatures and UTCI and concluded that UTCI serves as a more useful tool to predict the risk of mortality.[433] A recent systematic review revealed that UTCI is now gaining attention among epidemiologists, clinicians, and public health professionals.[81] While a few studies have utilised UTCI to investigate mortality, emergency department visits, and cardiovascular diseases,[81] only three studies have so far reported UTCI in perinatal epidemiology.[119,367,368] Further epidemiologic studies with UTCI had been recommended,[81], particularly from LMICs, including Ghana where related evidence is currently limited.

Environmental exposures often show effects that are delayed (lagged) in time which requires accounting for the time structure of the effect in assessing the exposure–response relationship.[60] A modelling framework known as Distributed Lag Nonlinear Model (DLNM) was developed to flexibly describe the potential nonlinear exposure-response relationship together with the lagged effects, defined as exposure-lag-response associations.[59,60] Some previous studies employed this robust novel methodology by combining the DLNM with time-series to investigate exposure-lag-response associations.[119,120,314] Based on these contexts, we aimed to link fine spatiotemporal UTCI to the clinically diagnosed stillbirths at small area levels and implemented a within-space time-series DLNM to examine the exposure-lag-response association between prenatal exposure to long-term heat stress and stillbirth in Ghana.

11.3 Methods

The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines was followed in reporting the results.[239]

11.3.1 Study design

A previously applied DLNM time-series design [119,120,314] was extended to include spatial variation, resulting in a within-space time-series DLNM analysis. Specifically, we matched the variations within districts nested within regions to control by design for measured and unmeasured known and unknown, spatially varying confounders. The seasonal and long-term trends, potential temporal autocorrelation, and overdispersion were also controlled.

11.3.2 Study population and birth data

Ghana is a coastal SSA country in West Africa and located at 8° 00' N and 2° 00' W. Ghana's population from the 2021 census was 30.8 million at a growth rate of 2.1% with a population density of 129 persons/km^2.[92] As a tropical humid monsoon climatic region, Ghana has a dry winter characterised by dust (harmattan) and rainy summer seasons. The average temperature is 26.1 °C in the southern and 28.9 °C in the northern and could rise above 40 °C in the north-eastern parts of the country. About 2.3% of pregnancies end up in stillbirths [93] but the prevalence varies geographically from 2.1 to 3.2%.[311-313]

Ghana is organised into 16 geopolitical regions which are subdivided into 260 non-overlapping local districts. From the recent 2021 census, the average population size per district was 118,130 persons.[92] The local district is the lowest level of health service management and policy implementation. As a common challenge in most LMICs or SSA countries, including Ghana, nationwide individual-level electronic birth records are currently unavailable.[97] Previous studies in LMICs, therefore, used population-based surveys to investigate the association between heat stress and stillbirth, [335,452] despite the inherent limitations of the survey datasets, especially for reporting pregnancy and adverse pregnancy outcomes such as stillbirth.[308,309] Recently in Ghana, however, district health directorates collate health information from public and private health facilities monthly and transfer the data remotely to the Centre for Health Information Management (CHIM) of the Ghana Health Service (GHS) using the District Health Information Management System (DHIS2).[99] We obtained district-level monthly stillbirths – defined as fetal death in pregnancies that lasted for at least seven months - from the CHIM of GHS across the 260 districts from 1st January 2012 to 31st December 2020.

11.3.3 Universal Thermal Climate Index exposure and other covariates

The primary exposure, UTCI is an isothermal equivalent air temperature (˚C) of the reference condition causing the same human physiological response to the actual thermal environmental condition (combination of air temperature, wind speed, relative humidity, and radiation).[80,103,104] For interpretation and application of UTCI across the different climatic zones and human physiological responses, non-meteorological variables, and the thermal properties of clothing (insulation, vapour resistance, air permeability) are critical and included in defining the reference conditions. The reference conditions are 4 km/h walking speed, 2.3 MET ($\simeq$135 W m^{-2}) rate of metabolic heat production, wind speed of 0.5 m/s at 10 m above the ground level, mean radiant temperature equal to air temperature (that is no additional thermal radiation), and relative humidity of 50% (with vapour pressure capped at 20 hPa for air temperature above 29°C).[104] UTCI is derived from the advanced Fiala multi-node model of human heat balance that fully accounts for heat transfer and exchange.[80,103] We used the UTCI from the global hourly gridded historical dataset of human thermal comfort indices derived from ERA5 reanalysis (ERA5-HEAT, Human thErmAl comforT).[106] ERA5 dataset is the fifth global climate reanalysis produced by the European Centre for Medium-Range Weather Forecasts.[387] The UTCI calculation involved two major steps. First, the solar and thermal radiation fluxes at the surface of the Earth were extracted from ERA5 with numerical weather prediction models and used to calculate the mean radiant temperature (MRT).[389] Second, the MRT, and ERA5-retrieved 2 m above ground level for both air temperature and relative humidity and wind speed at 10 m above ground level were used as inputs into a six-order polynomial equation to derive the global gridded UTCI (except for Antarctica) for each hour on regular latitude-longitude grids at $0.25^{\circ} \times 0.25^{\circ}$ spatial resolution from 1979 to present.[106] Further details on the operational procedures for deriving the UTCI were described elsewhere [104,106]. We obtained 24-hour averages of the gridded UTCI over Ghana between 1st January 2011 and 31st December 2020 and processed them with ArcGIS software (version 10.8.1). Data for 2011 were included to allow for a lag period before the first observation in January 2012. District-level monthly mean UTCI was calculated.

We also obtained the following annual global gridded datasets as covariates: between 2012 and 2019 at approximately 1 km × 1 km spatial resolution for fine particulate matter air pollution ($PM_{2.5}$) estimates version V4.GL.03 [47] and ambient population (24 h average population modelling that fully exploited the potential activity space of people throughout the day and night rather than merely a residential area).[107] Between 2010 and 2015 at a spatial resolution of 5 arc-min (approximately 10 km at the equator) for total Gross Domestic Production (Purchasing Power Parity) (hereon GDP) in constant 2011 international United States dollars were also obtained.[109] District-specific values were extracted with ArcGIS software (version 10.8.1). For each covariate, linear interpolation was performed using the 'imputeTS' package [320] to extrapolate to 2020. Data between 2012 and 2020 were used for the analysis. The ambient population was divided by the district area to obtain the population density. Overall means were also computed to dichotomise the districts into low (≤ median) or high (> median) subgroups for each covariate.

11.3.4 Statistical analysis

11.3.4.1 Main analyses

The DLNM was combined with conditional quasi-Poisson regression for simultaneous investigation of the immediate, delayed, and cumulative effects of UTCI on stillbirth.[59,60] The model was specified as

$$\log\left[E\left(Y_{t,i,s}\right)\right] = \alpha + cb(UTCI) + Month + ns(time, df) + cov, offset = \log(total\ birth) \qquad (1)$$

where $Y_{t,s}$ is the observed number of stillbirths in month t for a year i at district s; α is the intercept; *cb* is the cross-basis function to define the nonlinear exposure–lag–response association using the 'dlnm' R package.[60] The *cb* was specified through natural cubic splines in both the UTCI predictor and the lag dimensions with the maximum lag of 9 months to capture preconception periods or gestational ages that might extend to the 10th month. Equally spaced spline knots were placed at the log scale of lags. The choice of optimum degrees of freedom (*df*) was informed by the minimisation of the Akaike information criterion (AIC).[59,60] Several combinations of 2 to 5 *df* were investigated following the previous studies [119,120,314,335] and practical recommendations.[453] Finally, 5 and 3 *dfs* were selected to model the exposure-response and lag-response associations, respectively. The

Month is the month factor variable (1, 2, 3, ….., 12) to control for annual seasonality. The *ns (time, df)* is a natural spline of time in a continuous number of months over the study period with 36 *df* (4 per year based on the lowest AIC) to control for long-term temporal trends. The *cov* is the covariates as percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), and natural splines with 2 *df* to flexibly model the continuous variables GDP and population density. To control for unobserved and unmeasured spatially varying confounding effects, we fitted the conditional quasi-Poisson regression using the "gnm" R package by including a conditional factor *stratum*, indicating the variation in the same district in the same region through the "eliminate" function.[122] We estimated the Relative Risks (RRs) and 95% Confidence Intervals (CIs) at the 1st, 10th, 25th, 75th, 90th, and 99th percentiles, relative to median UTCI. Because of the potential temporal collinearity or autocorrelation in individual lag effect estimates which could lead to spurious findings,[390] we reported immediate (lag 0) and cumulative effects (lag 0-N, where N= 1, 2,…., 9 months) as the main results.[119,120,376]

We also calculated the number of excess stillbirths per 10,000 births attributable to heat stress by estimating the Attributed Risk (AR) following [351] as

$$AR = I_u \,(RR - 1) \quad (2)$$

Two measures for I_u (the background incidence of stillbirth) were used: our study-specific incidence (1.5%) and the prevalence rate from the GMHS 2017 (2.3%).[93] We used the RR (95% CI) for the UTCI threshold (which was the 90th percentile from the main analysis) that showed the most consistent higher risks across the exposure periods to estimate the AR.

Stratified analyses for the dichotomised subgroups for seasons (wet summer or rainy season: April-November and dry winter or harmattan season: December-March), population density, GDP, and air pollution) were also performed using the UTCI threshold at the 90th percentile. For stratification analysis by season, we excluded the factor month to avoid over-adjustment. The estimated risks between the subgroups were compared by performing the Altman and Bland test of interaction.[257,258]

11.3.4.2 Sensitivity analyses

A series of sensitivity analyses were performed to ascertain the robustness of the main results. We included GDP and population density as linear terms. $PM_{2.5}$ (a mediator) was not included in the main analysis for estimating the *total effect* (overall effect) of thermal stress because temperature contributes to the formation of particulate matter as recommended [400,454]. But $PM_{2.5}$ was included to ascertain the *direct effect* of UTCI in which any variation in the $PM_{2.5}$ mediator was eliminated [454,455] by including the annual $PM_{2.5}$ as natural splines with 2 *df*. The reference UTCI was changed to 26 °C (upper value for *no thermal stress* range) [103] which was the closest to our median UTCI. Because the earliest final gestational age of stillbirth was 28 weeks, the maximum lag was changed to seven months. The *dfs* were changed to 4 and 3 for the predictor and lag space dimensions, respectively. We replaced the *ns (time, df)* with a year index factor variable (1, 2, 3, …, 9) to control for long-term trends as inter-annual variability. We also excluded the month factor and included only *ns (time, df)* as previous acute effect studies on daily exposure-lag-association considered this to have accounted for both seasonal and long-term trends.[119,120,314]

All statistical analyses were performed utilising R statistical software (version 4.1.1).[323] Results were interpreted in the context of human thermophysiology without considering statistical significance as recommended by the American Statistical Association.[181]

11.4 Results

11.4.1 Characteristics of the birth cohorts, exposure, and covariates

The cohort consisted of 5,961,328 births of which 90,532 (1.5%) were stillbirths. Slightly above half of the births were male (mean = 51%) and the majority (mean=72%) were born by young adults (20–34 years). The overall mean (28.5 ± 2.1 °C) and median UTCI (28.8 °C), as well as that of specific subgroups, indicated *moderate heat stress*. From the minimum to the 10th percentile of UTCI were in the *no thermal stress* range. UTCI above the median fell within the *moderate heat stress* range, except in the 99th percentile which indicated *strong heat stress* (Table 11.1 and Table S11.1) according to the standard ten categories of UTCI that range from extreme cold stress to extreme heat stress.[103] The overall average (mean ± standard deviation) for GDP was 281.8 ± 778.6 per million US dollars for population density of 1225 ± 4114 persons per km^2 with $PM_{2.5}$ concentration of 59.7 ± 9.2 μg/m^3 (Table 11.1).

The geographical distribution revealed that most of the districts had an average of fewer than 10 stillbirths per 1000 births. Almost all districts were exposed to UTCI of 27.6 ˚C to 30.2 ˚C which is within the moderate heat stress threshold (Figure 11.1). Both UTCI and stillbirth varied temporally in somewhat similar patterns over the study period (Figure 11.2).

Table 11.1 Descriptive statistics of the births, environmental exposures, and sociodemographic conditions across the 260 districts in Ghana, 2012–2020.

Variables	Mean	SD	Median	Min	P25	P75	Max	IQR*
Births (N=5,961,328)	212.3	345.6	162.0	1.0	86.0	266.0	45929.0	180.0
Stillbirths (N=90,532)	3.2	5.4	2.0	0.0	0.0	4.0	111.0	4.0
Male (%)	50.9	5.7	50.9	0.0	47.9	53.8	100.0	5.9
Female (%)	49.0	5.7	49.1	0.0	46.1	52.1	100.0	6.0
Teen:10-19 years (%)	13.0	5.7	13.0	0.0	9.4	16.4	65.3	7.0
Young adult: 20-34 years (%)	72.1	6.3	72.2	0.0	68.5	75.9	96.4	7.4
Adult: ≥ 35 years (%)	14.0	4.5	13.9	0.0	11.2	16.7	77.6	5.5
UTCI (˚C)	28.5	2.0	28.8	19.6	27.2	29.9	35.2	2.7
$PM_{2.5}$ (µg/m^3)	59.7	9.2	59.6	38.4	52.8	67.8	81.4	15.0
GDP (per million US dollars)	281.8	778.6	50.5	0.8	24.8	106.8	5132.5	82.0
Population density (persons/km^2)	1224.9	4113.8	141.5	8.0	78.0	318.0	39070.0	240.0

Note. SD, standard deviation; UTCI, Universal Thermal Climate Index; P25 and P75, 25th and 75th percentiles; *IQR, Interquartile range = P75–P25; GDP, Gross Domestic Production (Purchasing Power Parity); US, United States; $PM_{2.5}$; fine particulate matter at aerodynamic diameter ≤ 2.5 µm.

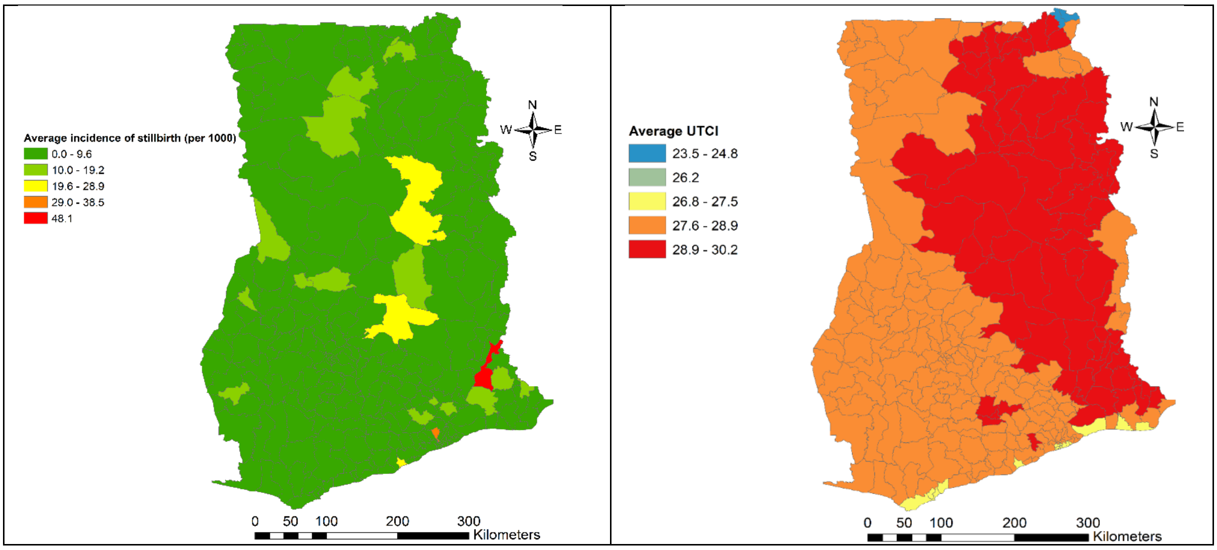

Figure 11.1 Geographical distribution of the overall average incidence of stillbirth (per 1000 births) and the UTCI (˚C) across the 260 districts in Ghana during 2012–2020. Mapping was based equal interval classification method in ArcGIS. Note: UTCI, Universal Thermal Climate Index. The base map was obtained from https://data.humdata.org/dataset/ghana-administrative-boundaries.

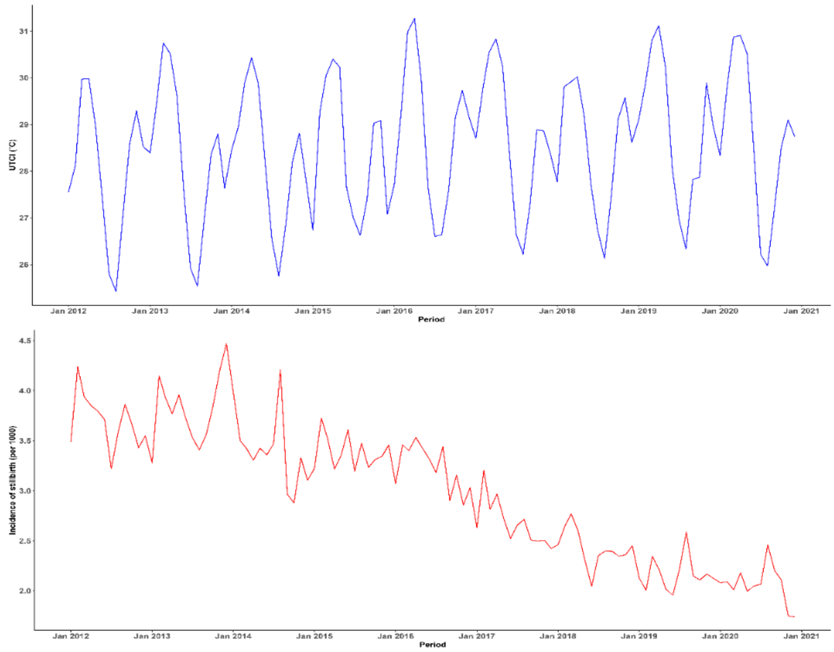

Figure 11.2 Average monthly variations of UTCI and stillbirth rate across the 260 districts in Ghana from January 2012 to December 2020.

11.4.2 Thermophysiological stress exposures and risk of stillbirth

The unadjusted (that is included only UTCI exposure) cumulative effect of UTCI on stillbirth indicated a rise-and-fall pattern (Figure S11.1). Similar patterns were found for adjusted (that is additionally included confounding factors) cumulative exposure-lag-response associations with better precision than unadjusted effect estimates. Compared to the monthly median UTCI, we found lower risks of stillbirth at both ends of UTCI distribution but higher risk within 29 ^{o}C to 32 ^{o}C (Figure 11.3).

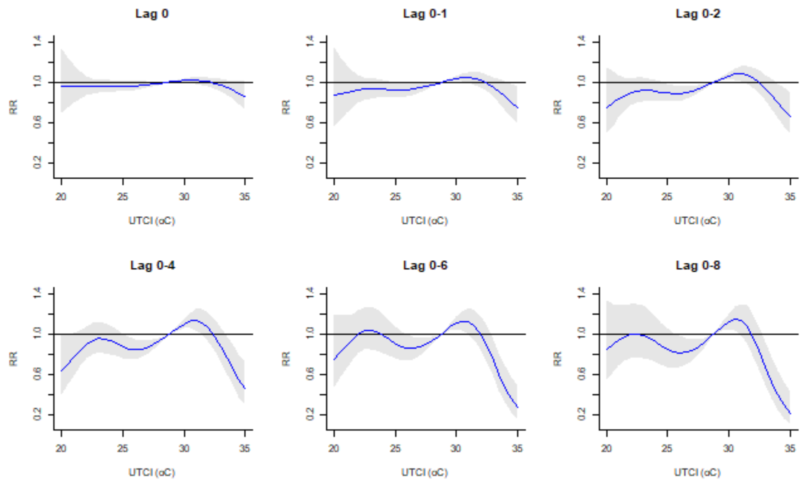

Figure 11.3 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 ^{o}C).

The range from no thermal stress up to lower levels of moderate heat stress thresholds (1st to below the 75th percentile of UTCI) showed lower risks of stillbirth as compared to the median thermal stress. The higher-moderate heat stress exposure levels (that is the 75th to 90th percentiles of UTCI), relative to median thermal stress showed higher risks and increased with the duration of heat exposure episodes from the month of birth up to the past nine months. These ranged from 1% (RR= 1.01, 95% CI 1.00, 1.03) to 14% (RR= 1.14, 95% CI 1.06, 1.22) for the 75th percentile (29.9 ^{o}C) and 2% (RR=1.02, 95% CI 0.99, 1.05) to 18% (RR= 1.18, 95% CI 1.02, 1.36) for the 90th percentile (30.8 ^{o}C), relative to the median UTCI (28.8 ^{o}C). However, the relative risk began to decrease at the 95th percentile and became almost 'protective' at the 99th percentile (strong heat stress, 33.2 ^{o}C) relative to the median UTCI (Table 11.2).

Table 11.2 The estimated cumulative relative risks (RRs) and 95% confidence intervals (95% CIs) of stillbirth at different percentiles of UTCI, relative to the median UTCI (28.8 °C) in Ghana, 2012-2020.

Lag month	1st (23.0 ^{o}C)	10th (25.8 ^{o}C)	25th (27.2 ^{o}C)	75th (29.9 ^{o}C)	90th (30.8 ^{o}C)	95th (31.6 ^{o}C)	99th (33.2 ^{o}C)
0	0.96 (0.89, 1.03)	0.96 (0.92, 1.01)	0.98 (0.95, 1.00)	1.01 (1.00, 1.03)	1.02 (0.99, 1.05)	1.01 (0.97, 1.05)	0.96 (0.90, 1.02)
0-1	0.93 (0.84, 1.04)	0.92 (0.86, 0.99)	0.95 (0.91, 0.99)	1.03 (1.01, 1.06)	1.05 (1.00, 1.10)	1.04 (0.97, 1.11)	0.93 (0.83, 1.04)
0-2	0.92 (0.81, 1.04)	0.88 (0.81, 0.96)	0.92 (0.87, 0.96)	1.06 (1.03, 1.09)	1.08 (1.02, 1.15)	1.07 (0.98, 1.16)	0.91 (0.79, 1.06)
0-3	0.93 (0.81, 1.07)	0.86 (0.77, 0.95)	0.89 (0.84, 0.94)	1.08 (1.04, 1.12)	1.11 (1.04, 1.20	1.09 (0.99, 1.21)	0.88 (0.74, 1.06)
0-4	0.96 (0.82, 1.12)	0.84 (0.75, 0.95)	0.88 (0.82, 0.94)	1.10 (1.05, 1.14)	1.13 (1.04, 1.23)	1.10 (0.98, 1.24)	0.83 (0.67, 1.02)
0-5	1.00 (0.84, 1.19)	0.85 (0.74, 0.97)	0.87 (0.81, 0.94)	1.10 (1.05, 1.15)	1.13 (1.04, 1.24)	1.09 (0.95, 1.24)	0.75 (0.59, 0.95)
0-6	1.04 (0.85, 1.27)	0.86 (0.73, 1.00)	0.88 (0.80, 0.96)	1.10 (1.05, 1.16)	1.13 (1.02, 1.25)	1.06 (0.92, 1.23)	0.67 (0.51, 0.88)
0-7	1.04 (0.82, 1.31)	0.85 (0.71, 1.02)	0.87 (0.79, 0.96)	1.10 (1.04, 1.16)	1.12 (1.00, 1.26)	1.04 (0.89, 1.23)	0.62 (0.46, 0.84)
0-8	0.99 (0.76, 1.28)	0.81 (0.66, 0.99)	0.85 (0.76, 0.95)	1.11 (1.05, 1.19)	1.14 (1.00, 1.29)	1.06 (0.88, 1.27)	0.61 (0.44, 0.86)
0-9	0.88 (0.65, 1.18)	0.74 (0.59, 0.92)	0.81 (0.71, 0.91)	1.14 (1.06, 1.22)	1.18 (1.02, 1.36)	1.10 (0.89, 1.36)	0.65 (0.45, 0.94)

Although with lower magnitudes of effects, almost similar patterns were observed for the adjusted individual lag effects. The most elevated risk of 3% higher (RR= 1.03, 95% CI 1.01, 1.05) was consistently found for the first to third months before the month of stillbirth delivery (third trimester) for the 90th percentile, relative to the median UTCI (Table S11.2). There were 19 (95% CI 3, 37) excess stillbirths per 10,000 births attributable to long-term heat stress exposure at the 90th percentile, relative to the median UTCI for the past six months and 27 (95% CI 3, 54) for the past nine months based on 1.5% baseline rate of stillbirth (Table 11.3).

Table 11.3 The cumulative monthly attributed risks (ARs) and 95% confidence intervals (95% CIs) per 10,000 births at the 90th percentile of UTCI (30.8 °C), relative to median UTCI (28.8 °C) in Ghana, 2012-2020.

Lag months	AR (95% CI)*	AR (95% CI)**
0	2.8 (-1.5, 7.2)	4.3 (-2.4, 11.1)
0-1	7.0 (-0.1, 14.5)	10.8 (-0.1, 22.2)
0-2	12.3 (3.0, 22.1)	18.8 (4.6, 33.8)
0-3	17.1 (5.8, 29.3)	26.3 (8.9, 45.0)
0-4	20.0 (6.7, 34.4)	30.6 (10.3, 52.7)
0-5	20.2 (5.4, 36.3)	31.0 (8.3, 55.7)
0-6	18.9 (2.7, 36.9)	29.0 (4.1, 56.6)
0-7	18.5 (0.4, 38.8)	28.4 (0.6, 59.4)
0-8	20.8 (0.5, 43.9)	31.9 (0.7, 67.3)
0-9	26.8 (3.2, 54.2)	41.2 (4.9, 83.1)

*Calculated using study-specific background incidence rate (1.5%)
**Calculated using background prevalence rate from Ghana Maternal Health Survey 2017 (2.3 %)

11.4.3 Thermophysiological stress and risk of stillbirth by subgroups

Relative to the season-specific median UTCI, the risk was slightly greater in winter than in summer (Table S11.2). Comparing the risk between the two seasons indicated that the risk in the month of stillbirth (lag 0) and up to eight preceding months (lag 0-8) were 4% (RRR=1.04, 95% CI 0.95, 1.14) and 11% (RRR =1.11, 95% CI 0.72, 1.69) greater, respectively, in winter as compared to summer exposure at the 90th percentile relative to the median UTCI (Table 11.4). The stratification analyses also showed slightly greater risk in districts with low population density, low GDP, and low $PM_{2.5}$ concentration than the risks in the high subgroup categories (Table S11.3). The comparative test of interaction showed that the risks in low as compared to high population density areas for exposure to the 90th percentile relative to median UTCI increased from the month of stillbirth at 4% (RRR=1.04, 95% CI 0.97, 1.11) to the nine months preceding the month of stillbirth at 29% (RRR=1.29, 95% CI 0.93, 1.79). A similar observation was found in low relative to high GDP areas at 2% (RRR=1.02, 95% CI 0.95, 1.09) in the month of stillbirth to 63% (RRR=1.63, 95% CI 1.16, 2.28) in up to nine preceding months. Low relative to high $PM_{2.5}$ concentrations also indicated the same pattern, but the greatest risk was found in the six preceding months (RRR=1.21, 95% CI, 0.95, 1.55). However, all except GDP included the null in the confidence intervals (Table 11.4).

Table 11.4 The ratio of relative risk (RRR) and 95% confidence intervals (95% CI) of stillbirth for comparing the risk between two subgroups at the 90th percentile relative to the median UTCI in Ghana, 2012-2020.

Lag month	Season	Population density	GDP	$PM_{2.5}$
	Winter vs summer	Low vs High	Low vs High	Low vs High
0	1.04 (0.95, 1.14)	1.04 (0.97, 1.11)	1.02 (0.95, 1.09)	0.96 (0.89, 1.03)
0-1	1.04 (0.90, 1.19)	1.07 (0.96, 1.19)	1.07 (0.96, 1.19)	0.98 (0.88, 1.10)
0-2	1.02 (0.86, 1.21)	1.10 (0.97, 1.26)	1.13 (0.99, 1.29)	1.04 (0.90, 1.19)
0-6	1.00 (0.70, 1.43)	1.16 (0.92, 1.45)	1.41 (1.11, 1.79)	1.21 (0.95, 1.55)
0-7	1.04 (0.70, 1.55)	1.17 (0.91, 1.52)	1.47 (1.13, 1.92)	1.19 (0.92, 1.55)
0-8	1.11 (0.72, 1.69)	1.22 (0.92, 1.62)	1.55 (1.15, 2.09)	1.16 (0.86, 1.56)
0-9	1.19 (0.76, 1.88)	1.29 (0.93, 1.79)	1.63 (1.16, 2.28)	1.11 (0.79, 1.56)

11.4.4 Sensitivity analyses

Adjustment for annual $PM_{2.5}$ had a negligible influence on the effect estimates (Figure S11.2). The results of all sensitivity analyses under varying modelling conditions or assumptions were consistent with the results from the main analysis but with comparatively lower precision (Figure S11.3 to S11.9).

11.5 Discussion

11.5.1 Thermophysiological stress and risk of stillbirth

Using 6 million births in Ghana with monthly district-level clinically determined stillbirths (1.5%), we investigated the immediate, delayed, and cumulative effects of heat stress on stillbirths. We found that long-term exposure to moderate heat stress showed a higher risk of stillbirth. Our findings also suggested possible effects of heat stress during the preconception period as shown in lag 0-9 and lag 9 months (that is from the last 9 months before the month of stillbirth). The risk was slightly greater during the dry and dusty winter season (harmattan) than during the wet rainy summer season.

Our findings, based on the use of a UTCI to describe the impact of thermophysiological stress, were unique as compared to previous findings based on ambient temperature metrics.[331] Our findings were consistent with a few of the 12 previous studies included in a recent systematic review that reported an association between long-term ambient temperature exposures and stillbirth.[331] The magnitudes of the effect estimates were, however, incomparable across studies as each study used different temperature metrics and thresholds. For instance, Ha *et al* [351] reported 3.71 times higher odds of stillbirth (OR= 3.71, 95% CI: 3.07, 4.47) for exposure to heat (> 90^{th} percentile) as compared to mild (10^{th}–90^{th} percentile) mean temperatures in the United States. Wang *et al* [373] combined the 90^{th} and 95^{th} percentiles of maximum temperatures over two, three, and four days for six heatwave definitions in Brisbane, Australia. The authors found the most elevated hazard ratio of 1.52 (HR=1.52, 95% CI 1.11, 2.09) in the 8^{th} gestational month for their greatest heatwave definition. Other studies compared minimum-prevalence temperatures to estimate the risks at given thresholds.[372,456] The previous studies included in the systematic review were from temperate and subtropical regions and reported higher relative risks for both heat and cold temperatures across the pregnancy period.[331] We reported only heat stress because our study area is tropical with UTCI ranging from no thermal stress to strong heat stress on the standard scale.[103,106] There was only one previous study on long-term effects from SSA country, which was also conducted in Ghana. This study found 12% higher odds of miscarriage or stillbirth per degree increase in annual mean wet-bulb globe temperature (OR= 1.12, 95% CI 0.90, 1.39) after adjusting for maternal age but the association diminished (OR= 1.00, 95% CI 0.80, 1.25) after additional adjustment for gravidity.[452] This may be because high gravidity is a marker of recurrent pregnancy loss. Our findings showed stronger magnitude of effects, which may be due to differences in the study designs. The previous study was a cross-sectional analysis of maternal self-reported outcomes from a survey dataset, considered pregnancy loss with miscarriage and stillbirth together as one outcome, and assessed exposure at relatively larger geographic units (i.e., regions) with notable exposure misclassification. Moreover, the potential for spatial confounding effects was not accounted for in their analysis.

The individual month exposure-response associations did not show a higher risk at the early stages of pregnancy which was consistent with findings reported in the United States [351] but contrary to those from a study in Brisbane, Australia that found higher effects of heat exposure in early as compared to late pregnancy.[373] Differences in exposure assessment and outcome definition, acclimatisation, and behavioural interventions by pregnant women in the context of climatic conditions could account for these contrasting findings. However, considering the transient nature of the heat exposure and abrupt stillbirth outcome, the risk is more likely to be stronger in late pregnancy. This is partly due to the fact that the late pregnancy period has more advanced physiological changes with greater difficulty for maternal thermoregulation as compared to the early pregnancy period.[399] Contrary to Ha *et al*,[351] we also found possible higher effects of stillbirth in preconception periods, a crucial period for gametogenesis and placental development where the negative impacts from environmental stressors such as heat stress can be profound.[110] For the thresholds in the no thermal stress or lower-moderate heat stress ranges as compared to the median UTCI (also moderate heat stress), acclimatisation could have explained the observed lack of association or "protective" effects at these thresholds. We also observed a lower or "protective" effect at the 99th percentile (strong heat stress) as compared to the median UTCI (moderate heat stress). While this could be due to small births within the 99th UTCI percentile range, this observation also suggests that pregnant women are more likely to adopt behavioural or coping interventions such as minimising outdoor activities, drinking water, using water or ice to cool down during the unbearable strong heat stress episodes as compared to moderate heat stress.[457] The dryness of the environment and associated dust blown by the strong wind from the Sahel desert during harmattan, especially stronger in the northern part may explain the observed greater risk in the dry winter season as compared to the rainy summer season.

11.5.2 Modifying effects of population density, socioeconomic status, and air pollution

We observed that districts with low population density, low GDP, and comparatively low air pollution which could collectively be defined as rural districts were at higher risk as compared to those in the high level (most likely urban districts). Compared to urban areas, rural areas are sociodemographically more vulnerable to many other underlying major risk factors such as infection, malnutrition, anaemia, poor sanitation, and lack of access to quality antenatal care.[303] Moreover, rural residents, including pregnant women predominantly engage in small-scale subsistence farming. This would expose them to heat stress during farming activities, nutritional depletion from temperature-related effects on crop production, and indirect effects from other climate change-related extreme events.[274,334,457] Thus, the association of climate change with higher risks of stillbirth may be direct through heat stress or indirect,[274] but heat stress comparatively has more direct biological impacts.[334] Furthermore, pregnant women in rural settings often travel long distances and may have to walk through unfavourable climatic conditions to access a distant healthcare service. For example, a study conducted in the second most urbanised and developed region of Ghana (Ashanti region) revealed that members of some rural districts in the region had to travel long distances as far as 39 km to access the nearest health facility.[458] Urban resident women are also more likely to adopt better heat stress mitigation strategies such as use of cooling facilities (air conditioner and fan) and better housing conditions than their rural counterparts. The greater effect estimates for those from rural settings are roughly the same as known harmful hazards such as the effects of smoking on stillbirth.[197]

11.5.3 Plausible pathophysiologic pathways

Plausible pathophysiologic pathways have been established by several experimental and clinical observational studies. Pregnancy results in higher-fat deposits, high basal metabolic rate, and reduced systemic vascular resistance which increases thermal susceptibility.[22,399] As a result, heat stress can cause hyperthermia and in turn, causes the death of proliferating cells or apoptosis and disruption of normal processes of embryogenesis and organogenesis. These can result in heat-induced structural and functional defects in the central neuroendocrine and inflammatory systems, and placental development and physiology.[22,342] The fetoplacental exchange of materials such as oxygen, water, nutrients, and the removal of fetal toxic waste materials is decreased. Consequently, fetal health, growth, and development are affected where fetal death or stillbirth is the endpoint.[342] Experimental studies identified excess reactive oxygen species and high concentrations of serum heat shock proteins in the heat-induced impacts on biological processes that elevate the risks of pregnancy complications and birth outcomes.[22,343,451] Also, increased dehydration due to increased sweating and urination, and heat dissipation that reduces uterine blood flow decreases fetoplacental transport of essential materials.[22,342] Given that the maternal thermoregulatory capacity determines the *in utero* thermal environment and that of the developing fetus,[342] a direct effect of the heat-shock response in the developing fetus is also a plausible pathway.[22] At lower temperatures, protective responses in reduced concentrations of heat shock proteins have also been reported.[22] This could explain why we observed “protective effects” in the ranges of no thermal stress up to lower-moderate heat stress, relative to higher-moderate heat stress.

11.5.4 Public health and climate governance strategies and policies

The increasing pace of anthropogenic-induced climate change and its disproportionate impacts on vulnerable subpopulations, particularly pregnant women in sociodemographically deprived settings require that climate change should be integrated with the known non-climatic factors in managing birth outcomes.[7,274] Together with actionable evidence from the previous findings,[331] public health and environmental or climate governance policies and education for attitudinal change are required to save the environment and save lives. These include increased awareness and response to climate change crisis, reduce outdoor activities during thermal stress episodes, protecting and managing the ecological environment (e.g., greening the environment), increase access to essential thermal mitigation and adaptation resources, increasing investments in biotechnological solutions, and transitioning to clean and renewable energy sources such as wind, wave, solar, and geothermal.[272,366] These measures and building climate change-resilient health systems will contribute substantially to reducing the climate change crisis and associated impacts on health outcomes and health costs.[327] More geodemographic-specific studies that use a thermophysiological index such as UTCI are required to monitor the impacts of the ongoing climate change crisis on birth outcomes to help design appropriate mitigation and adaptation strategies suitable for the climatic and sociodemographic conditions of a given setting.[74,81,331]

11.5.5 Strengths and limitations

This study has several strengths. Our study is among the few studies that evaluated the long-term effects of heat stress on stillbirth.[331] Our study controls for temporal and spatial confounding by design. Rather than investigate ambient temperature, a practice that has been debated recently,[74,76] we used the relatively suitable recommended contemporary human thermophysiological metric, the UTCI [74,76,78,79] as reported elsewhere.[81,119,367,368] As the results were interpreted within the context of standard thermophysiological stress, the comparability and physiological relevance of the findings are enhanced.[80,81] To the best of our knowledge, this is the first study in the SSA region to examine the long-term effect of heat stress on stillbirth with clinically diagnosed stillbirth data. Given, similar geodemographic, socioeconomic, and climatic conditions in SSA, our findings could be generalised particularly in neighbouring West African countries.

We also note several limitations of our study. We did not account for indoor thermal conditions, daily activity patterns, and maternal migration during pregnancy which could lead to exposure misclassifications. However, the impact of maternal migration is expected to be negligible because of the within-district-region conditioning approach used in this study. It is also less likely for a pregnant woman to travel into another district in another region during pregnancy as compared to migration into another district in the same region that we controlled for by design. Any related residual effect would be non-differential, biasing the estimates towards the null. We only have annual instead of monthly data on the population density, GDP, and ambient air pollution. Although minimised by design, the ability to include more clinical factors, especially infection would also be helpful. Finally, our findings were based on an aggregated longitudinal dataset which is less well-powered than individual-level analysis. Nonetheless, the novel methodology may be applied in other SSA countries that currently do not have maternal and child electronic health registries for large-scale individual-level longitudinal cohort investigations.[97] Moreover, our approach is similar to individual-level cohort studies that assigned exposures at group levels, which is the common practice.[331] Previous studies have also demonstrated the methodological strengths of this approach in short-term effects analyses.[119,120,314]

11.6 Conclusions

Our findings suggest that long-term exposure to moderate heat stress during pregnancy elevated the risk of stillbirth in Ghana as reported in many studies from developed countries.[331] Pregnant women in deprived socioeconomic areas or rural districts were more susceptible than those in urban districts. Heat stress exposure during the preconception period also showed potential risk. Taken together, we recommend increased awareness and precautionary or preventive measures among pregnant women, women of reproductive age, healthcare providers, and policymakers to lessen maternal exposure to heat stress, particularly in rural areas. This is critical given that severe climate change events are projected to increase in intensity, frequency, and duration in the coming years globally.[7] Implementing heat warning systems with a human thermophysiological index may be beneficial. Well-designed individual-level cohort studies with spatiotemporal UTCI exposure and more studies from developing and SSA countries are required to confirm our results to facilitate appropriate evidence-based thermal adaptation and mitigation strategies and climate governance policies.

Part IV

General Discussion and Conclusions

Chapter 12. General Discussion and Conclusions

12.0 Preamble

This chapter provides a brief general discussion and conclusion of the thesis which included a summary of the main findings, implications of the findings, strengths, limitations, recommendations, and concluding comments.

12.1 Summary of main findings

This thesis aimed to examine the ambient $PM_{2.5}$ and biothermal stress exposures and the risks of adverse birth outcomes in a high-income country (Australia) and a low-income country (Ghana).

The umbrella review (Objective 1, Chapter 3) involved an up-to-date comprehensive systematic review of reviews to synthesise the current evidence on the association between ambient air pollution and birth outcomes. A total of 36 systematic reviews (21 with and 15 without meta-analyses) were included, and these contained 295 distinct primary studies, mostly from the United States and China. The results from the umbrella review indicated the most consistent positive associations for $PM_{2.5}$ compared to other criteria air pollutants and for whole pregnancy exposure compared to trimester-specific exposures.[125] This could be due to relatively high exposure and less exposure misclassification for the whole pregnancy period as compared to trimester-specific average exposure periods. This could also be due to bias if trimesters do not reflect the biologically relevant averaging period (three months) or reflect the biologically relevant times in pregnancy most susceptible to exposure.[58,125] A simulation study demonstrated that effect estimates from trimester-specific average exposures are biased and inaccurately identified susceptible periods which may even potentially span multiple trimesters.[58] More high-quality studies, including understudied settings, application of novel statistical modelling approaches that account for both intensity and timing of past exposures to obtain unbiased estimates, and critical susceptible periods finer than trimester-specific estimates have been recommended by other researchers.[58,59,125]

Informed by the findings of the umbrella review and other recommendations,[58,59,125] effects of maternal $PM_{2.5}$ exposure on birth outcomes were estimated with the identification of the potential critical susceptible periods and the identification of vulnerable subpopulations in Western Australia and Ghana (objective 2, Chapters 4 to 6). To obtain more accurate effect estimates and to identify critical susceptible exposure periods shorter than the predefined trimester periods, a novel robust statistical modelling approach, DLNM that simultaneously accounted for both the intensity and timing of past exposures was applied.[58-60] Exposure to $PM_{2.5}$ was assessed at the monthly level from three months preconception to birth and adjusted hazards of the birth outcomes (stillbirth, sPTB, SGA, LGA, and LBW) were estimated with an individual-level model for Western Australia. Due to data limitations, $PM_{2.5}$ effects were estimated for stillbirth only and at the small area levels (local districts) in Ghana.

Generally, the results indicated positive associations of monthly $PM_{2.5}$ exposure with stillbirth and sPTB, most notably in the 3^{rd}–7^{th} gestational months. Even exposure below the new international annual average of 5 $\mu g/m^3$ was associated with higher hazards of stillbirth and sPTB in Western Australia. Perturbed fetal growth (SGA, LGA, LBW) at term had small associations with exposure during the 2^{nd}– 6^{th} gestational months. Critical susceptible exposure periods were found for only term LBW in the 2^{nd}–4^{th} gestational months. Preconception exposure mostly showed small magnitudes of negative associations ('protective effects'). There were also joint effects of $PM_{2.5}$ and biothermal stress exposures on the birth outcomes, except sPTB. The identified vulnerable subpopulations with a comparatively elevated risk of exposure-response association were mostly mothers who were non-Caucasian, unmarried, smoked during pregnancy, rural residents, and with complicated pregnancies.

Objective 3 (Chapter 7) involved the second up-to-date comprehensive umbrella review to synthesise the current evidence on the association between ambient air temperature and birth outcomes. As of February 4, 2023, a total of 9 systematic reviews (8 without and one with meta-analysis) were included which contained 78 distinct primary studies, mostly from the United States and a few other developed countries. Numerous exposure metrics (mostly based on proximity to monitoring stations), thresholds, and durations for ambient temperature were reported. Findings from all 9 systematic reviews mostly included PTB, stillbirth, and LBW and revealed that maternal exposure to particularly high temperatures increased the risks of adverse birth outcomes. However, critical susceptible periods were unknown as previous studies mostly examined short-term effects and few trimester-specific effects. Moreover, the existing evidence was based on ambient temperature rather than biothermal metrics that include all climatic factors and human thermophysiological processes.[74,76]

Rather than ambient temperature, objective 4 (Chapters 8 to 11) was, therefore, conducted to use spatiotemporal biothermal metric UTCI [103,104,106] as applied in other medical and epidemiological areas,[81] thermal-health warning systems, and forecasting.[82] UTCI is the modern and currently most advanced biothermal metric which was reported to suitably represents bioclimatic conditions well and very sensitive to changes in ambient thermal stimuli like the human body.[76,78,79,358] A robust statistical modelling approach, the DLNM [59,60] was combined with conditional quasi-Poisson and Cox proportional hazard regressions to investigate both short and long-term effects of biothermal stress and the risks of birth outcomes. Critical susceptible exposure periods and vulnerable groups were identified.

The results of the short-term effects showed that both cold and heat biothermal stress were associated with stillbirth and sPTB. The identified sociodemographically vulnerable subpopulations were male fetuses, births to mothers who smoked during pregnancy, unmarried, ≤19 years old, non-Caucasians, and low socioeconomic status mothers.[367,368] For the long-term effects, lower (1st to 10th centiles) and higher (90th to 99th centiles) exposures as compared with the median showed higher hazards of adverse birth outcomes with critical susceptible periods during mid to late gestational periods. Specifically, the identified potential critical susceptible periods were 23rd to 42nd gestational weeks (strongest in the 10th gestational month) for stillbirth and 27th to 36th gestational weeks (strongest in the 9th gestational month) for sPTB. As changes in fetal growth may not be obvious within short intervals, monthly rather than weekly exposure showed obvious critical susceptible periods for term SGA, LGA, and LBW. The identified critical susceptible periods for term SGA and LGA were in the 6th–10th gestational months, and strongest in the 10th gestational month but 3rd–5th gestational months for term LBW at 99th centile as compared to median exposure. For the Ghana cohort, the relative risk of stillbirth ranged from 1.02 (95% CI 0.99, 1.05) to 1.18 (95% CI 1.02, 1.36) for the 90th centile (30.8 ˚C), relative to the median UTCI (28.8 ˚C) but exposure at the 99th centile (33.2 ˚C) showed a 'protective effect'. The positive exposure-outcome association was stronger in rural than urban districts in Ghana.

12.2 Implications of this thesis

This thesis makes significant contributions to the existing knowledge on the association between birth outcomes and environmental exposures such as air pollution and climate change as measured with the biothermal metric UTCI. The findings in this thesis together with previous epidemiological evidence suggest that environmental exposures such as air pollution and climate change-related events are potential risk factors for birth outcomes in both developed and developing countries. These have serious health implications for pregnant women or women of reproductive age, clinicians, and policymakers. Given that it is unethical to conduct randomised controlled trials in environmental health to establish causality with certainty, human observational studies are the 'gold standard' of the evidence base.[137] Several *in vivo, in vitro, omic*s or epigenetic studies, toxicological or biological mechanistic studies have also demonstrated that *in utero* exposure to air pollution (especially $PM_{2.5}$) and extreme temperatures cause oxidative stress, apoptosis, placental DNA methylation, endocrine-disrupting properties, immune-inflammatory and epigenetic alterations, leading to birth outcomes.[21,26,270,297,305,343,371,430,449,451,459] Thus, the available body of evidence synthesised in the umbrella reviews and the primary investigations presented in this thesis suggest plausible causal effects of air pollutants, particularly $PM_{2.5}$ and climate change on birth outcomes. These findings may warrant the adoption of the *precautionary principle* [134] by taking interventions to address the increasing climate change and air pollution to improve reproductive health outcomes and long-term health conditions of children.[10,274,339] Clinicians are also recognising climate change and air pollution as putative risk factors for health outcomes [128,274,298] as the ongoing impacts of effects can be observable throughout the life course.[7,363] This recognition by clinicians and other health professionals is a step in the right direction as they could play active roles to educate and advise pregnant women or women at reproductive age and policymakers, act as advocates, and get involved in related research for developing and implementing prevention and mitigation strategies or policies, especially for the most vulnerable groups. Taking society-wide urgent precautionary actions at the individual, population, institutional, health system, and policy levels as detailed in Chapters 3 and 7 are necessary to address the impacts of these ubiquitous environmental exposures.[10,125,460] These will contribute to achieving SDGs 3.2, 3.9, 6.3, and 13 [228] and beyond. Critical susceptible exposure periods varied slightly, depending on the exposure ($PM_{2.5}$ and UTCI), intensity, and the specific birth outcome. However, the results generally indicated that potential critical susceptible exposure periods of the birth outcomes were early to mid-gestational periods for $PM_{2.5}$ exposure but mid to late gestational periods for UTCI exposure. While these findings could guide the time points for public health interventions, more related high-quality investigations in this direction and biological mechanisms are required. Specifically, the application of the novel statistical modelling framework,[58,59] study designs, and the use of biothermal metrics derive from human thermophysiological model such as UTCI, PET or mPET [74,76,361] have methodological implications for future research. Knowledge of the critical susceptible exposure periods could facilitate the potential prevention, diagnosis, and treatment of environmental exposure-induced birth outcomes through environmental exposomes with the different epigenetic biomarkers or *omics*.[217,218] The results also showed the plausibility of some level of mitigation, especially during late pregnancy and extreme biothermal stress where pregnant women reduce outdoor activities or adopt thermal mitigation strategies.[457]

12.3 Strengths of this thesis

This thesis addressed several epidemiological limitations and gaps in the literature.

i) To the best of our knowledge, the two umbrella reviews presented in Chapters 3 and 7 were the first systematic review of reviews on the topics and provided comprehensive syntheses on the current evidence, directions for future studies, prevention strategies, and policies.

ii) The space-time varying $PM_{2.5}$ and UTCI exposure assessments reduced exposure misclassification as compared to the conventional use of proximity to sparse monitoring stations. This also avoided the exclusion of some more vulnerable subpopulations such as rural residents as monitoring stations are often located in urban or city centres.

iii) Rather than the usual surrogate usage of ambient temperature, a composite biothermal metric (UTCI) that includes all climatic factors and human thermoregulation indicators was used. This makes the findings thermophysiologically more relevant as UTCI combines knowledge from climate science, physiology, and epidemiology.[74,76,80]

iv) The robust novel statistical modelling technique, DLNM allowed for the investigation of fine temporal scales (daily, weekly, and monthly) and accounted for both the intensity and timing of past exposures in addition to the usual trimester-based periods. The novel study designs such as difference-in-differences, space-time-stratified case-crossover, within-space time-series, and time-to-event designs are additional strengths of this thesis.

v) Given the very limited and in some instances no known related previous studies on critical susceptible exposure periods, the findings in this thesis have added new and important epidemiological evidence for further studies and public health interventions.

vi) This was the first state-wide investigation on the topics in Western Australia. Also, this study was the first in Australia to investigate weekly or monthly critical susceptible exposure periods for birth outcomes.

vii) The investigation in Ghana, to the best of our knowledge, is the first study in the SSA region to examine the long-term exposure-lag-response associations of monthly $PM_{2.5}$ and biothermal stress exposures and stillbirth in SSA. Thus, given similar geodemographic, socioeconomic, and climatic conditions in SSA, our findings in Ghana could be generalised particularly in neighbouring West African countries.

12.4 Limitations of this thesis

Several limitations were also acknowledged in this thesis.

i) As a known limitation in the field, we were unable to account for indoor thermal conditions, daily activity patterns, mitigation strategies, and maternal residential mobility during pregnancy which could lead to exposure misclassifications. These measurement errors may introduce some bias in the effect estimates. Regarding residential mobility, a recent review on maternal relocation [275] and simulation study [276] found that residential mobility has no obvious impacts on the effect estimates. Also, our sensitivity analysis that adjusted for local government area-specific clusters to account for potential spatial clustering and maternal mobility showed no change in the effect estimates.

ii) We did not have data to include other important covariates such as maternal alcohol or illicit drug intake, educational level, nutritional status, employment, infection (e.g., seasonal influenza, malaria), maternal weight, height, indoor air pollution, and physical activity during pregnancy. Most of these factors, however, were partly controlled through either SES or by design. Also, sensitivity analyses that adjusted for within-mother and local government area-specific clusters did not influence the effect estimates.

iii) We did not have data to investigate the effects of other pollutants, a limitation shared with others in the literature, as the main results of previous primary studies and meta-analyses were based on single-pollutant models.

iv) Investigation of constituent components of $PM_{2.5}$ is important for policy regulation and public health intervention but was not included in this thesis due to a lack of data.

v) As only monthly $PM_{2.5}$ was available, short-term, and weekly exposure effects were not investigated as was the case for UTCI.

vi) There is a potential live-birth bias as fetuses that were more susceptible to $PM_{2.5}$ and UTCI exposures may have resulted in early pregnancy losses which were unobserved,[101] resulting in underestimation of the effects.

vii) Because of data availability, only stillbirth at the local district level was investigated for Ghana. Although quasi-experimental designs were conducted, the results from aggregated longitudinal dataset may be less well-powered than individual-level analysis. Therefore, given the high air pollution, tropical climatic setting, high incidence of stillbirth, and other known related issues such as under-resourced healthcare system, nutrition, and infections, the epidemiologic evidence is expected to be stronger in future studies if high-quality individual-level longitudinal cohort studies are conducted in Ghana.

12.5 Recommendations

Comprehensive recommendations for future research, and mitigation or adaptation strategies at the individual population, health system, governmental and policy levels were provided in the two umbrella reviews presented in Chapters 3 and 7. Briefly, a society-wide approach is required to save the climate and improve air quality for healthy birth outcomes. The identified $PM_{2.5}$ and UTCI exposure periods of increased susceptibility and vulnerable subpopulations could inform targeted clinical and public health interventions, policy decisions, and future studies. Specifically, further high-quality studies, including environmental exposome [461] for long-term effects with robust statistical modelling approaches to identify critical susceptible exposure periods, including preconception periods and use of biothermal metrics are required from different geodemographic settings, including more studies from LMICs. Further biological mechanism studies to better understand the exposure-outcome associations and susceptible periods are also required to optimise clinical and public health interventions. Investigation of multi-pollutants, especially mixtures of chemical and non-chemical exposures or environmental exposome [461] to identify critical susceptible periods will be helpful with increasing appropriate statistical methods.[192,279,462]

12.6 Conclusions

Several experimental and human observational studies linked maternal exposure to criteria air pollutants (particularly $PM_{2.5}$) and ambient temperatures to birth outcomes. However, methodological limitations and research gaps exist, such as lack of spatiotemporal exposure assessment, unknown critical susceptible periods, exposure-outcome analyses did not account for both intensity and timing of past exposures, and current evidence was mostly from a few developed countries with a lack of sufficient evidence from LMICs or from other areas within the same country. Also, climate change-related studies used only ambient temperature instead of biothermal metrics which include all climatic factors and human thermophysiology. To address these issues, this thesis assessed spatiotemporal $PM_{2.5}$ and biothermal stress (UTCI) exposures and the risks of birth outcomes in Western Australia and Ghana. Robust study designs and statistical modelling techniques were implemented to identify potential critical susceptible periods and vulnerable subpopulations. $PM_{2.5}$ and UTCI exposures independently and synergistically were associated with adverse birth outcomes and the magnitudes of the effect estimates were stronger for UTCI than $PM_{2.5}$ exposure. Despite slight variations, we found that critical susceptible exposure periods for the adverse birth outcomes were early to mid-gestational periods for $PM_{2.5}$ exposure but mid to late gestational periods for the UTCI exposure. As this knowledge is very important to guide the time points for public health interventions, understanding biological mechanisms, and building prevention, diagnosis, and treatment epigenetic biomarkers for these environmental exposures, further studies are required in these directions. The disproportionately affected subpopulations– births to mothers who were unmarried, non-Caucasian, multiparous, smoked during pregnancy, rural residents, and with complicated pregnancies – may benefit from targeted interventions and policies.

References

1. World Health Organization (WHO). Ambient air pollution: a global assessment of exposure and burden of disease. Geneva, Switzerland: World Health Organization; 2016. https://apps.who.int/iris/handle/10665/250141. Accessed October 21, 2019.

2. World Health Organization (WHO). WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva, Switzerland: World Health Organization 2021. https://apps.who.int/iris/handle/10665/345329. Accessed October 20, 2021.

3. Manisalidis I, Stavropoulou E, Stavropoulos A, Bezirtzoglou E. Environmental and Health Impacts of Air Pollution: A Review. *Front Public Health* 2020; 8(14. https://doi.org/10.3389/fpubh.2020.00014.

4. World Health Organization (WHO). WHO Air quality guidelines for particulate matter, ozone, nitrogen
dioxide and sulfur dioxide: global update 2005 : summary of risk assessment. Geneva, Switzerland: World Health Organization; 2006. http://apps.who.int/iris/bitstream/handle/10665/69477/WHO_SDE_PHE_OEH_06.02_eng.pdf?sequence=1 Accessed April 7, 2021.

5. Zhang L, Wilson JP, Zhao N, Zhang W, Wu Y. The dynamics of cardiovascular and respiratory deaths attributed to long-term PM2.5 exposures in global megacities. *Sci Total Environ* 2022; 842:156951. https://doi.org/10.1016/j.scitotenv.2022.156951.

6. Sang S, Chu C, Zhang T, Chen H, Yang X. The global burden of disease attributable to ambient fine particulate matter in 204 countries and territories, 1990–2019: A systematic analysis of the Global Burden of Disease Study 2019. *Ecotoxicol Environ Saf* 2022; 238:113588. https://doi.org/https://doi.org/10.1016/j.ecoenv.2022.113588.

7. Intergovernmental Panel on Climate Change (IPCC). Summary for Policymakers. In: Climate Change 2021: The Physical Science Basis. Contribution of Working Group I to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change In Press. Geneva, Switzerland: World Meteorological Organization; 2021. https://www.ipcc.ch/report/ar6/wg1/downloads/report/IPCC_AR6_WGI_SPM_final.pdf. Accessed December 13, 2021.

8. Chambers J. Global and cross-country analysis of exposure of vulnerable populations to heatwaves from 1980 to 2018. *Climatic Change* 2020; 163(1):539-558. https://doi.org/10.1007/s10584-020-02884-2.

9. Rocque RJ, Beaudoin C, Ndjaboue R, Cameron L, Poirier-Bergeron L, Poulin-Rheault RA, et al. Health effects of climate change: an overview of systematic reviews. *BMJ Open* 2021; 11(6):e046333. https://doi.org/10.1136/bmjopen-2020-046333.
10. Giudice LC. Environmental impact on reproductive health and risk mitigating strategies. *Curr Opin Obstet Gynecol* 2021; 33(4):343-349. https://doi.org/10.1097/gco.0000000000000722.
11. Dalugoda Y, Kuppa J, Phung H, Rutherford S, Phung D. Effect of Elevated Ambient Temperature on Maternal, Foetal, and Neonatal Outcomes: A Scoping Review. *Int J Environ Res Public Health* 2022; 19(3. https://doi.org/10.3390/ijerph19031771.
12. Sacchi C, Marino C, Nosarti C, Vieno A, Visentin S, Simonelli A. Association of Intrauterine Growth Restriction and Small for Gestational Age Status With Childhood Cognitive Outcomes: A Systematic Review and Meta-analysis. *JAMA Pediatr* 2020; 174(8):772-781. https://doi.org/10.1001/jamapediatrics.2020.1097.
13. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. *BMC Med* 2016; 14(1):147. https://doi.org/10.1186/s12916-016-0692-5.
14. Crump C. An overview of adult health outcomes after preterm birth. *Early Hum Dev* 2020; 150:105187. https://doi.org/10.1016/j.earlhumdev.2020.105187.
15. Klepac P, Locatelli I, Korosec S, Kunzli N, Kukec A. Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges. *Environ Res* 2018; 167:144-159. https://doi.org/10.1016/j.envres.2018.07.008.
16. Chersich MF, Pham MD, Areal A, Haghighi MM, Manyuchi A, Swift CP, et al. Associations between high temperatures in pregnancy and risk of preterm birth, low birth weight, and stillbirths: systematic review and meta-analysis. *BMJ* 2020; 371:m3811. https://doi.org/10.1136/bmj.m3811.
17. Marczylo EL, Jacobs MN, Gant TW. Environmentally induced epigenetic toxicity: potential public health concerns. *Crit Rev Toxicol* 2016; 46(8):676-700. https://doi.org/10.1080/10408444.2016.1175417.
18. Lin V, Baccarelli A, Burris H. Epigenetics—a potential mediator between air pollution and preterm birth. *Environ Epigenet* 2016; 2:dvv008. https://doi.org/10.1093/eep/dvv008.
19. Saenen ND, Martens DS, Neven KY, Alfano R, Bové H, Janssen BG, et al. Air pollution-induced placental alterations: an interplay of oxidative stress, epigenetics, and the aging phenotype? *Clin Epigenetics* 2019; 11(1):124. https://doi.org/10.1186/s13148-019-0688-z.
20. Cadaret CN, Posont RJ, Beede KA, Riley HE, Loy JD, Yates DT. Maternal inflammation at midgestation impairs subsequent fetal myoblast function and skeletal muscle growth in rats,

resulting in intrauterine growth restriction at term1. *Trans Anim Sci* 2019; 3(2):867-876. https://doi.org/10.1093/tas/txz037.
21. Limesand SW, Camacho LE, Kelly AC, Antolic AT. Impact of thermal stress on placental function and fetal physiology. *Anim Reprod* 2018; 15(Suppl 1):886-898. https://doi.org/10.21451/1984-3143-ar2018-0056.
22. Edwards MJ, Saunders RD, Shiota K. Effects of heat on embryos and foetuses. *Int J Hyperth* 2003; 19(3):295-324. https://doi.org/10.1080/0265673021000039628.
23. Kannan S, Misra DP, Dvonch JT, Krishnakumar A. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. *Environ Health Perspect* 2006; 114(11):1636-1642. https://doi.org/10.1289/ehp.9081.
24. Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, et al. Meeting report: atmospheric pollution and human reproduction. *Environ Health Perspect* 2008; 116(6):791-798. https://doi.org/10.1289/ehp.11074.
25. Erickson AC, Arbour L. The Shared Pathoetiological Effects of Particulate Air Pollution and the Social Environment on Fetal-Placental Development. *J Environ Public Health* 2014; 2014:901017. https://doi.org/10.1155/2014/901017.
26. Thangavel P, Park D, Lee YC. Recent Insights into Particulate Matter (PM(2.5))-Mediated Toxicity in Humans: An Overview. *Int J Environ Res Public Health* 2022; 19(12. https://doi.org/10.3390/ijerph19127511.
27. Kelly FJ, Fussell JC. Toxicity of airborne particles-established evidence, knowledge gaps and emerging areas of importance. *Philos Trans A Math Phys Eng Sci* 2020; 378(2183):20190322. https://doi.org/10.1098/rsta.2019.0322.
28. Sapkota A, Chelikowsky AP, Nachman KE, Cohen AJ, Ritz B. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. *Air Quality, Atmosphere & Health* 2010; 5(4):369-381. https://doi.org/10.1007/s11869-010-0106-3.
29. Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. *Epidemiol* 2004; 15(1):36-45. https://doi.org/10.1097/01.ede.0000101023.41844.ac.
30. Lamichhane DK, Leem JH, Lee JY, Kim HC. A meta-analysis of exposure to particulate matter and adverse birth outcomes. *Environ Health Toxicol* 2015; 30:e2015011. https://doi.org/10.5620/eht.e2015011.

31. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res* 2012; 117:100-111. https://doi.org/10.1016/j.envres.2012.05.007.
32. Ji Y, Song F, Xu B, Zhu Y, Lu C, Xia Y. Association between exposure to particulate matter during pregnancy and birthweight: a systematic review and a meta-analysis of birth cohort studies. *J Biomed Res* 2017. https://doi.org/10.7555/JBR.31.20170038.
33. Sun X, Luo X, Zhao C, Chung Ng RW, Lim CE, Zhang B, et al. The association between fine particulate matter exposure during pregnancy and preterm birth: a meta-analysis. *BMC Pregnancy Childbirth* 2015; 15:300. https://doi.org/10.1186/s12884-015-0738-2.
34. Bekkar B, Pacheco S, Basu R, DeNicola N. Association of Air Pollution and Heat Exposure With Preterm Birth, Low Birth Weight, and Stillbirth in the US: A Systematic Review. *JAMA Network Open* 2020; 3(6):e208243-e208243. https://doi.org/10.1001/jamanetworkopen.2020.8243.
35. Strand LB, Barnett AG, Tong S. The influence of season and ambient temperature on birth outcomes: a review of the epidemiological literature. *Environ Res* 2011; 111(3):451-462. https://doi.org/10.1016/j.envres.2011.01.023.
36. Kuehn L, McCormick S. Heat Exposure and Maternal Health in the Face of Climate Change. *Int J Environ Res Public Health* 2017; 14(8. https://doi.org/10.3390/ijerph14080853.
37. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc* 2015; 13(3):132-140. https://doi.org/10.1097/xeb.0000000000000055.
38. Hartling L, Chisholm A, Thomson D, Dryden DM. A descriptive analysis of overviews of reviews published between 2000 and 2011. *PLoS One* 2012; 7(11):e49667. https://doi.org/10.1371/journal.pone.0049667.
39. Lavigne SE, Forrest JL. An umbrella review of systematic reviews of the evidence of a causal relationship between periodontal disease and adverse pregnancy outcomes: A position paper from the Canadian Dental Hygienists Association. *Can J Dent Hyg* 2020; 54(2):92-100. https://pubmed.ncbi.nlm.nih.gov/33240369 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7668275/.
40. Dadi AF, Miller ER, Bisetegn TA, Mwanri L. Global burden of antenatal depression and its association with adverse birth outcomes: an umbrella review. *BMC Public Health* 2020; 20(1):173. https://doi.org/10.1186/s12889-020-8293-9.

41. Nieuwenhuijsen MJ, Dadvand P, Grellier J, Martinez D, Vrijheid M. Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies. *Environ Health* 2013; 12:6. https://doi.org/10.1186/1476-069X-12-6.
42. Woodruff TJ, Parker JD, Darrow LA, Slama R, Bell ML, Choi H, et al. Methodological issues in studies of air pollution and reproductive health. *Environ Res* 2009; 109(3):311-320. https://doi.org/10.1016/j.envres.2008.12.012.
43. Knibbs LD, van Donkelaar A, Martin RV, Bechle MJ, Brauer M, Cohen DD, et al. Satellite-Based Land-Use Regression for Continental-Scale Long-Term Ambient PM(2.5) Exposure Assessment in Australia. *Environ Sci Technol* 2018; 52(21):12445-12455. https://doi.org/10.1021/acs.est.8b02328.
44. Wei J, Li Z, Lyapustin A, Sun L, Peng Y, Xue W, et al. Reconstructing 1-km-resolution high-quality PM2.5 data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. *Remote Sens Environ* 2021; 252:112136. https://doi.org/10.1016/j.rse.2020.112136.
45. van Donkelaar A, Hammer MS, Bindle L, Brauer M, Brook JR, Garay MJ, et al. Monthly Global Estimates of Fine Particulate Matter and Their Uncertainty. *Environ Sci Technol* 2021; 55(22):15287-15300. https://doi.org/10.1021/acs.est.1c05309.
46. van Donkelaar A, Martin RV, Brauer M, Hsu NC, Kahn RA, Levy RC, et al. Global Estimates of Fine Particulate Matter using a Combined Geophysical-Statistical Method with Information from Satellites, Models, and Monitors. *Environ Sci Technol* 2016; 50(7):3762-3772. https://doi.org/10.1021/acs.est.5b05833.
47. Hammer MS, van Donkelaar A, Li C, Lyapustin A, Sayer AM, Hsu NC, et al. Global Estimates and Long-Term Trends of Fine Particulate Matter Concentrations (1998–2018). *Environ Sci Technol* 2020; 54(13):7879-7890. https://doi.org/10.1021/acs.est.0c01764.
48. Walter CM, Schneider-Futschik EK, Lansbury NL, Sly PD, Head BW, Knibbs LD. The health impacts of ambient air pollution in Australia: a systematic literature review. *Intern Med J* 2021; 51(10):1567-1579. https://doi.org/10.1111/imj.15415.
49. Pereira G, Bell ML, Belanger K, de Klerk N. Fine particulate matter and risk of preterm birth and pre-labor rupture of membranes in Perth, Western Australia 1997-2007: a longitudinal study. *Environ Int* 2014; 73:143-149. https://doi.org/10.1016/j.envint.2014.07.014.
50. Yu W, Guo Y, Shi L, Li S. The association between long-term exposure to low-level PM2.5 and mortality in the state of Queensland, Australia: A modelling study with the difference-in-differences approach. *PLOS Med* 2020; 17(6):e1003141. https://doi.org/10.1371/journal.pmed.1003141.

51. Han C, Xu R, Gao CX, Yu W, Zhang Y, Han K, et al. Socioeconomic disparity in the association between long-term exposure to PM2.5 and mortality in 2640 Chinese counties. *Environ Int* 2021; 146:106241. https://doi.org/10.1016/j.envint.2020.106241.

52. He Y, Jiang Y, Yang Y, Xu J, Zhang Y, Wang Q, et al. Composition of fine particulate matter and risk of preterm birth: A nationwide birth cohort study in 336 Chinese cities. *J Hazard Mater* 2022; 425:127645. https://doi.org/10.1016/j.jhazmat.2021.127645.

53. Melody S, Wills K, Knibbs LD, Ford J, Venn A, Johnston F. Adverse birth outcomes in Victoria, Australia in association with maternal exposure to low levels of ambient air pollution. *Environ Res* 2020; 188:109784. https://doi.org/10.1016/j.envres.2020.109784.

54. Rodriguez-Villamizar LA, Belalcazar-Ceron LC, Castillo MP, Sanchez ER, Herrera V, Agudelo-Castañeda DM. Avoidable mortality due to long-term exposure to PM(2.5) in Colombia 2014-2019. *Environ Health* 2022; 21(1):137. https://doi.org/10.1186/s12940-022-00947-8.

55. Larson PS, Espira L, Glenn BE, Larson MC, Crowe CS, Jang S, et al. Long-Term PM(2.5) Exposure Is Associated with Symptoms of Acute Respiratory Infections among Children under Five Years of Age in Kenya, 2014. *Int J Environ Res Public Health* 2022; 19(5. https://doi.org/10.3390/ijerph19052525.

56. Cheeseman MJ, Ford B, Anenberg SC, Cooper MJ, Fischer EV, Hammer MS, et al. Disparities in Air Pollutants Across Racial, Ethnic, and Poverty Groups at US Public Schools. *Geohealth* 2022; 6(12):e2022GH000672. https://doi.org/10.1029/2022gh000672.

57. Ju L, Hua L, Xu H, Li C, Sun S, Zhang Q, et al. Maternal atmospheric particulate matter exposure and risk of adverse pregnancy outcomes: A meta-analysis of cohort studies. *Environ Pollut* 2023; 317:120704. https://doi.org/10.1016/j.envpol.2022.120704.

58. Wilson A, Chiu YM, Hsu HL, Wright RO, Wright RJ, Coull BA. Potential for Bias When Estimating Critical Windows for Air Pollution in Children's Health. *Am J Epidemiol* 2017; 186(11):1281-1289. https://doi.org/10.1093/aje/kwx184.

59. Gasparrini A. Modeling exposure–lag–response associations with distributed lag non-linear models. *Stat Med* 2014; 33(5):881-899. https://doi.org/10.1002/sim.5963.

60. Gasparrini A, Armstrong B, Kenward MG. Distributed lag non-linear models. *Stat Med* 2010; 29(21):2224-2234. https://doi.org/10.1002/sim.3940.

61. Sheridan P, Ilango S, Bruckner TA, Wang Q, Basu R, Benmarhnia T. Ambient Fine Particulate Matter and Preterm Birth in California: Identification of Critical Exposure Windows. *Am J Epidemiol* 2019; 188(9):1608-1615. https://doi.org/10.1093/aje/kwz120.

62. Yitshak-Sade M, Kloog I, Schwartz JD, Novack V, Erez O, Just AC. The effect of prenatal temperature and PM2.5 exposure on birthweight: Weekly windows of exposure throughout the pregnancy. *Environ Int* 2021; 155:106588. https://doi.org/10.1016/j.envint.2021.106588.
63. Carlson JM, Zanobetti A, Ettinger de Cuba S, Poblacion AP, Fabian PM, Carnes F, et al. Critical windows of susceptibility for the effects of prenatal exposure to heat and heat variability on gestational growth. *Environ Res* 2022):114607. https://doi.org/10.1016/j.envres.2022.114607.
64. Liu Y, Xu J, Chen D, Sun P, Ma X. The association between air pollution and preterm birth and low birth weight in Guangdong, China. *BMC Public Health* 2019; 19(1):3. https://doi.org/10.1186/s12889-018-6307-7.
65. Wang Q, Benmarhnia T, Zhang H, Knibbs LD, Sheridan P, Li C, et al. Identifying windows of susceptibility for maternal exposure to ambient air pollution and preterm birth. *Environ Int* 2018; 121(Pt 1):317-324. https://doi.org/10.1016/j.envint.2018.09.021.
66. Wu H, Jiang B, Zhu P, Geng X, Liu Z, Cui L, et al. Associations between maternal weekly air pollutant exposures and low birth weight: a distributed lag non-linear model. *Environ Res Lett* 2018; 13(2. https://doi.org/10.1088/1748-9326/aaa346.
67. Zhang H, Zhang X, Zhang H, Luo H, Feng Y, Wang J, et al. Assessing the effect of fine particulate matter on adverse birth outcomes in Huai River Basin, Henan, China, 2013–2018. *Environ Pollut* 2022; 306:119357. https://doi.org/10.1016/j.envpol.2022.119357.
68. Shang L, Yang L, Yang W, Xie G, Wang R, Sun L, et al. Prenatal exposure to air pollution and the risk of macrosomia: Identifying windows of susceptibility. *Sci Total Environ* 2022; 818:151775. https://doi.org/10.1016/j.scitotenv.2021.151775.
69. Chen J, Li PH, Fan H, Li C, Zhang Y, Ju D, et al. Weekly-specific ambient fine particular matter exposures before and during pregnancy were associated with risks of small for gestational age and large for gestational age: results from Project ELEFANT. *Int J Epidemiol* 2022; 51(1):202-212. https://doi.org/10.1093/ije/dyab166.
70. Du S, Bai S, Zhao X, Lin S, Zhai Y, Wang Z, et al. The effect and its critical window for ambient temperature and humidity in pregnancy on term low birth weight. *Environ Sci Pollut Res Int* 2022; 29(36):54531-54542. https://doi.org/10.1007/s11356-022-19512-4.
71. Xu R, Li Z, Qian N, Qian Y, Wang Z, Peng J, et al. Air pollution exposure and the risk of macrosomia: Identifying specific susceptible months. *Sci Total Environ* 2023; 859(Pt 1):160203. https://doi.org/10.1016/j.scitotenv.2022.160203.
72. Basagaña X, Michael Y, Lensky IM, Rubin L, Grotto I, Vadislavsky E, et al. Low and High Ambient Temperatures during Pregnancy and Birth Weight among 624,940 Singleton Term Births

in Israel (2010-2014): An Investigation of Potential Windows of Susceptibility. *Environ Health Perspect* 2021; 129(10):107001. https://doi.org/doi:10.1289/EHP8117.
73. Jakpor O, Chevrier C, Kloog I, Benmerad M, Giorgis-Allemand L, Cordier S, et al. Term birthweight and critical windows of prenatal exposure to average meteorological conditions and meteorological variability. *Environ Int* 2020; 142:105847. https://doi.org/10.1016/j.envint.2020.105847.
74. Vanos JK, Baldwin JW, Jay O, Ebi KL. Simplicity lacks robustness when projecting heat-health outcomes in a changing climate. *Nat Commun* 2020; 11(1):6079. https://doi.org/10.1038/s41467-020-19994-1.
75. Matzarakis A. Comments about Urban Bioclimate Aspects for Consideration in Urban Climate and Planning Issues in the Era of Climate Change. *Atmosphere* 2021; 12(5):546. https://www.mdpi.com/2073-4433/12/5/546.
76. Staiger H, Laschewski G, Matzarakis A. Selection of Appropriate Thermal Indices for Applications in Human Biometeorological Studies. *Atmosphere* 2019; 10(1):18. https://www.mdpi.com/2073-4433/10/1/18.
77. Nazarian N, Lee JKW. Personal assessment of urban heat exposure: a systematic review. *Environ Res Lett* 2021; 16(3):033005. https://doi.org/10.1088/1748-9326/abd350.
78. Blazejczyk K, Epstein Y, Jendritzky G, Staiger H, Tinz B. Comparison of UTCI to selected thermal indices. *Int J Biometeorol* 2012; 56(3):515-535. https://doi.org/10.1007/s00484-011-0453-2.
79. Bröde P, Błazejczyk K, Fiala D, Havenith G, Holmér I, Jendritzky G, et al. The Universal Thermal Climate Index UTCI compared to ergonomics standards for assessing the thermal environment. *Ind Health* 2013; 51(1):16-24. https://doi.org/10.2486/indhealth.2012-0098.
80. Jendritzky G, de Dear R, Havenith G. UTCI--why another thermal index? *Int J Biometeorol* 2012; 56(3):421-428. https://doi.org/10.1007/s00484-011-0513-7.
81. Romaszko J, Dragańska E, Jalali R, Cymes I, Glińska-Lewczuk K. Universal Climate Thermal Index as a prognostic tool in medical science in the context of climate change: A systematic review. *Sci Total Environ* 2022; 828:154492. https://doi.org/10.1016/j.scitotenv.2022.154492.
82. Krüger EL. Literature Review on UTCI Applications. In: Krüger EL, ed. Applications of the Universal Thermal Climate Index UTCI in Biometeorology: Latest Developments and Case Studies. Cham: Springer International Publishing;2021:23-65. https://doi.org/10.1007/978-3-030-76716-7_3.
83. Nyadanu SD, Tessema GA, Mullins B, Kumi-Boateng B, Bell ML, Pereira G. Ambient Air Pollution, Extreme Temperatures and Birth Outcomes: A Protocol for an Umbrella Review,

Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2020; 17(22):8658. https://www.mdpi.com/1660-4601/17/22/8658.
84. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372:n71. https://doi.org/10.1136/bmj.n71.
85. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Chapter 10: Umbrella Reviews. In: JBI Manual for Evidence Synthesis. In: Aromataris E, Munn Z, eds. Australia The Joanna Briggs Institute; 2020: https://synthesismanual.jbi.global. https://doi.org/10.46658/JBIMES-20-11 Accessed May 21, 2020.
86. Sleddens EF, Kroeze W, Kohl LF, Bolten LM, Velema E, Kaspers P, et al. Correlates of dietary behavior in adults: an umbrella review. *Nutr Rev* 2015; 73(8):477-499. https://doi.org/10.1093/nutrit/nuv007.
87. Sleddens EF, Kroeze W, Kohl LF, Bolten LM, Velema E, Kaspers PJ, et al. Determinants of dietary behavior among youth: an umbrella review. *Int J Behav Nutr Phys Act* 2015; 12:7. https://doi.org/10.1186/s12966-015-0164-x.
88. O'Donoghue G, Kennedy A, Puggina A, Aleksovska K, Buck C, Burns C, et al. Socio-economic determinants of physical activity across the life course: A "DEterminants of DIet and Physical ACtivity" (DEDIPAC) umbrella literature review. *PLoS One* 2018; 13(1):e0190737. https://doi.org/10.1371/journal.pone.0190737.
89. Rojas-Rueda D, Morales-Zamora E, Alsufyani WA, Herbst CH, AlBalawi SM, Alsukait R, et al. Environmental Risk Factors and Health: An Umbrella Review of Meta-Analyses. *Int J Environ Res Public Health* 2021; 18(2):704. https://www.mdpi.com/1660-4601/18/2/704.
90. Australian Bureau of Statistics (ABS). National, state and territory population ABS, Australia; 2021. https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/latest-release. Accessed October 19, 2021.
91. Hutchinson MJ, A; Bonner, D. Western Australia's Mothers and Babies, 2016: 34th Annual Report of the Western Australian Midwives' Notification System Western Australia: Department of Health; 2021. https://ww2.health.wa.gov.au/~/media/Corp/Documents/Reports-and-publications/Perinatal-infant-and-maternal/WA-Mothers-Babies-2016.pdf. Accessed February 1, 2023.
92. Ghana Statistical Service (GSS). Ghana 2021 Population and Housing Census: General Report; Population of Regions and Districts Vol 3A. Accra, Ghana: GSS; 2021. https://census2021.statsghana.gov.gh/gssmain/fileUpload/reportthemelist/2021%20PHC%20Genera

l%20Report%20Vol%203A_Population%20of%20Regions%20and%20Districts_181121.pdf. Accessed February 7, 2022.
93. Ghana Statistical Service (GSS), Ghana Health Service (GHS), and ICF International. Ghana Maternal Health Survey 2017. Accra, Ghana: GSS, GHS, and ICF; 2018. https://dhsprogram.com/pubs/pdf/FR340/FR340.pdf. Accessed August 11, 2020.
94. Ghana Statistical Service (GSS), Ghana Health Service (GHS). Ghana Demographic and Health Survey 2014. Rockville, Maryland, USA: GSS, GHS, and ICF International; 2015. http://dhsprogram.com/pubs/pdf/FR307/FR307.pdf. Accessed August 11, 2020.
95. Health Effects Institute (HEI). State of Global Air 2019. Special Report on Global exposure to air pollution and its disease burden. Boston, USA:HEI; 2019. https://www.stateofglobalair.org/sites/default/files/soga_2019_report.pdf. Accessed November 27, 2019.
96. Government of Western Australia. Midwives Notification System .Maternal and Child Health Unit, Department of Health. Vol 2021. Western Australia: Department of Health; 2021. https://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System. Accessed November 8, 2021.
97. Froen JF, Myhre SL, Frost MJ, Chou D, Mehl G, Say L, et al. eRegistries: Electronic registries for maternal and child health. *BMC Pregnancy Childbirth* 2016; 16:11. https://doi.org/10.1186/s12884-016-0801-7.
98. World Health Organization (WHO), Alliance for Health P, Systems R. Primary health care systems (primasys): case study from Ghana: abridged version. Geneva, Switzerland: WHO; 2017. https://apps.who.int/iris/handle/10665/341168. Accessed July 19, 2021.
99. Ghana Health Service (GHS), Centre for Health and Information Management (CHIM) of the Policy Planning, Monitoring, and Evaluation Division (PPMED) of the GHS in collaboration with the System for Health The Health Sector in Ghana: Facts and Figures. Accra, Ghana: GHS; 2018. https://open.africa/dataset/4176f749-cfa8-4e32-9418-86cef78f9db6/resource/0bcf9b54-3e35-4543-95cd-fd4de953edff/download/factsfigures_2018.pdf. Accessed July 19, 2021.
100. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. *Lancet* 2016; 387(10019):691-702. https://doi.org/10.1016/s0140-6736(15)01020-x.
101. Neophytou AM, Kioumourtzoglou MA, Goin DE, Darwin KC, Casey JA. Educational note: addressing special cases of bias that frequently occur in perinatal epidemiology. *Int J Epidemiol* 2021; 50(1):337-345. https://doi.org/10.1093/ije/dyaa252.

102. Australian Bureau of Statistics (ABS). Socio-Economic Indexes for Areas (SEIFA). Canberra, Australia: Bureau of Statistics; 2018. https://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa. Accessed October 20, 2021.

103. Blazejczyk K, Jendritzky G, Bröde P, Fiala D, Havenith G, Epstein Y, et al. An introduction to the Universal Thermal Climate Index (UTCI). *Geogr Pol* 2013; 86:5-10. https://doi.org/10.7163/GPol.2013.1.

104. Bröde P, Fiala D, Błażejczyk K, Holmér I, Jendritzky G, Kampmann B, et al. Deriving the operational procedure for the Universal Thermal Climate Index (UTCI). *Int J Biometeorol* 2012; 56(3):481-494. https://doi.org/10.1007/s00484-011-0454-1.

105. Fiala D, Havenith G, Bröde P, Kampmann B, Jendritzky G. UTCI-Fiala multi-node model of human heat transfer and temperature regulation. *Int J Biometeorol* 2012; 56(3):429-441. https://doi.org/10.1007/s00484-011-0424-7.

106. Di Napoli C, Barnard C, Prudhomme C, Cloke HL, Pappenberger F. ERA5-HEAT: A global gridded historical dataset of human thermal comfort indices from climate reanalysis. *Geosci Data J* 2021; 8(1):2-10. https://doi.org/10.1002/gdj3.102.

107. Rose AN, McKee JJ, Sims KM, Bright EA, Reith AE, Urban ML. LandScan 2019. 2019 ed. Oak Ridge, TN: Oak Ridge National Laboratory; 2020. https://landscan.ornl.gov/. Accessed September 4, 2021.

108. Center for International Earth Science Information Network (CIESIN). Documentation for the Gridded Population of the World, Version 4 (GPWv4), Revision 11 Data Sets. Palisades NY: NASA Socioeconomic Data and Applications Center (SEDAC). Columbia University 2018. https://doi.org/10.7927/H45Q4T5F. Accessed June 24, 2021.

109. Kummu M, Taka M, Guillaume JHA. Gridded global datasets for Gross Domestic Product and Human Development Index over 1990-2015. *Sci Data* 2018; 5:180004. https://doi.org/10.1038/sdata.2018.4.

110. Keikha M, Jahanfar S, Hemati Z. A neglected critical time to prevent maternal and offspring's adverse outcomes: The preconception period. *Int J Reprod Biomed* 2022; 20(1):65-67. https://doi.org/10.18502/ijrm.v20i1.10237.

111. Nachman RM, Mao G, Zhang X, Hong X, Chen Z, Soria CS, et al. Intrauterine Inflammation and Maternal Exposure to Ambient $PM_{2.5}$ during Preconception and Specific Periods of Pregnancy: The Boston Birth Cohort. *Environ Health Perspect* 2016; 124(10):1608-1615. https://doi.org/doi:10.1289/EHP243.

112. Blanc N, Liao J, Gilliland F, Zhang J, Berhane K, Huang G, et al. A systematic review of evidence for maternal preconception exposure to outdoor air pollution on Children's health. *Environ Pollut* 2023; 318:120850. https://doi.org/https://doi.org/10.1016/j.envpol.2022.120850.
113. Therneau T. A package for survival analysis in R. 2022. https://cran.r-project.org/web/packages/survival/vignettes/survival.pdf. (Accessed June 24, 2022).
114. Mostofsky E, Coull BA, Mittleman MA. Analysis of Observational Self-matched Data to Examine Acute Triggers of Outcome Events with Abrupt Onset. *Epidemiol* 2018; 29(6):804-816. https://doi.org/10.1097/ede.0000000000000904.
115. Wu Y, Li S, Guo Y. Space-Time-Stratified Case-Crossover Design in Environmental Epidemiology Study. *Health Data Sci* 2021; 2021:9870798. https://doi.org/10.34133/2021/9870798.
116. Armstrong BG, Gasparrini A, Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. *BMC Med Res Methodol* 2014; 14:122. https://doi.org/10.1186/1471-2288-14-122.
117. Ragettli MS, Vicedo-Cabrera AM, Schindler C, Röösli M. Exploring the association between heat and mortality in Switzerland between 1995 and 2013. *Environ Res* 2017; 158:703-709. https://doi.org/10.1016/j.envres.2017.07.021.
118. Vicedo-Cabrera AM, Goldfarb DS, Kopp RE, Song L, Tasian GE. Sex differences in the temperature dependence of kidney stone presentations: a population-based aggregated case-crossover study. *Urolithiasis* 2020; 48(1):37-46. https://doi.org/10.1007/s00240-019-01129-x.
119. Khodadadi N, Dastoorpoor M, Khanjani N, Ghasemi A. Universal Thermal Climate Index (UTCI) and adverse pregnancy outcomes in Ahvaz, Iran. *Reprod Health* 2022; 19(1):33. https://doi.org/10.1186/s12978-022-01344-7.
120. Cheng P, Peng L, Hao J, Li S, Zhang C, Dou L, et al. Short-term effects of ambient temperature on preterm birth: a time-series analysis in Xuzhou, China. *Environ Sci Pollut Res Int* 2021; 28(10):12406-12413. https://doi.org/10.1007/s11356-020-11201-4.
121. Dastoorpoor M, Khanjani N, Khodadadi N. Association between Physiological Equivalent Temperature (PET) with adverse pregnancy outcomes in Ahvaz, southwest of Iran. *BMC Pregnancy Childbirth* 2021; 21(1):415. https://doi.org/10.1186/s12884-021-03876-5.
122. Turner H, Firth D. Generalized nonlinear models in R: An overview of the gnm package. version 1.1-1. 2020. https://cran.r-project.org/web/packages/gnm/vignettes/gnmOverview.pdf. Accessed May 2, 2021.

123. Wang Y, Kloog I, Coull BA, Kosheleva A, Zanobetti A, Schwartz JD. Estimating Causal Effects of Long-Term PM2.5 Exposure on Mortality in New Jersey. *Environ Health Perspect* 2016; 124(8):1182-1188. https://doi.org/10.1289/ehp.1409671.
124. Leogrande S, Alessandrini ER, Stafoggia M, Morabito A, Nocioni A, Ancona C, et al. Industrial air pollution and mortality in the Taranto area, Southern Italy: A difference-in-differences approach. *Environ Int* 2019; 132:105030. https://doi.org/10.1016/j.envint.2019.105030.
125. Nyadanu SD, Dunne J, Tessema GA, Mullins B, Kumi-Boateng B, Lee Bell M, et al. Prenatal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of 36 systematic reviews and meta-analyses. *Environ Pollut* 2022; 306:119465. https://doi.org/10.1016/j.envpol.2022.119465.
126. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci* 2018; 115(38):9592-9597. https://doi.org/10.1073/pnas.1803222115.
127. World Health Organization (WHO). Air pollution and child health: prescribing clean air: summary. Geneva, Switzerland: WHO; 2018. https://apps.who.int/iris/handle/10665/275545. Accessed April 7, 2021.
128. Di Renzo GC, Conry JA, Blake J, DeFrancesco MS, DeNicola N, Martin JN, Jr., et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int J Gynaecol Obstet* 2015; 131(3):219-225. https://doi.org/10.1016/j.ijgo.2015.09.002.
129. Mannucci PM, Franchini M. Health Effects of Ambient Air Pollution in Developing Countries. *Int J Environ Res Public Health* 2017; 14(9):1048. https://doi.org/10.3390/ijerph14091048.
130. Pereira G, Bell ML, Lee HJ, Koutrakis P, Belanger K. Sources of fine particulate matter and risk of preterm birth in Connecticut, 2000-2006: a longitudinal study. *Environ Health Perspect* 2014; 122(10):1117-1122. https://doi.org/10.1289/ehp.1307741.
131. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Analysing data and undertaking meta-analyses In: Deeks JJ, Higgins JPT, Altman DG, eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane;2021.
132. Shah PS, Balkhair T, Knowledge Synthesis Group on Determinants of Preterm LBW. Air pollution and birth outcomes: a systematic review. *Environ Int* 2011; 37(2):498-516. https://doi.org/10.1016/j.envint.2010.10.009.
133. Zhang K, Lu Y, Zhao H, Guo J, Gehendra M, Qiu H, et al. Association between atmospheric particulate matter and adverse pregnancy outcomes in the populationInt J Clin Exp Med. *Int J Clin Exp Med* 2016; 9(11):20594-20604.

134. Martuzzi M, Tickner JA. The precautionary principle: protecting public health, the environment and the future of our children. Copenhagen, Denmark: WHO Regional Office for Europe; 2004. https://www.euro.who.int/__data/assets/pdf_file/0003/91173/E83079.pdf. Accesed May 19, 2021.
135. Nyadanu SD, Tessema GA, Mullins B, Kumi-Boateng B, Bell ML, Pereira G. Ambient Air Pollution, Extreme Temperatures and Birth Outcomes: A Protocol for an Umbrella Review, Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2020; 17(22. https://doi.org/10.3390/ijerph17228658.
136. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Med* 2009; 6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097.
137. Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environ Health Perspect* 2014; 122(10):1007-1014. https://doi.org/10.1289/ehp.1307175.
138. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol* 2014; 67(4):368-375. https://doi.org/10.1016/j.jclinepi.2013.11.007.
139. Beltran AJ, Wu J, Laurent O. Associations of meteorology with adverse pregnancy outcomes: a systematic review of preeclampsia, preterm birth and birth weight. *Int J Environ Res Public Health* 2013; 11(1):91-172. https://doi.org/10.3390/ijerph110100091.
140. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Systematic Reviews* 2017; 6(1):245. https://doi.org/10.1186/s13643-017-0644-y.
141. Munn Z, Aromataris E, Tufanaru C, Stern C, Porritt K, Farrow J, et al. The development of software to support multiple systematic review types: the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). *JBI Evidence Implementation* 2019; 17(1. https://journals.lww.com/ijebh/Fulltext/2019/03000/The_development_of_software_to_support_multiple.5.aspx.
142. Zeiher J, Ombrellaro KJ, Perumal N, Keil T, Mensink GBM, Finger JD. Correlates and Determinants of Cardiorespiratory Fitness in Adults: a Systematic Review. *Sports Medicine - Open* 2019; 5(1):39. https://doi.org/10.1186/s40798-019-0211-2.
143. Hill AB. The environment and disease: association or causation? *J R Soc Med* 2015; 108(1):32-37. https://doi.org/10.1177/0141076814562718.

144. Li C, Yang M, Zhu Z, Sun S, Zhang Q, Cao J, et al. Maternal exposure to air pollution and the risk of low birth weight: A meta-analysis of cohort studies. *Environ Res* 2020; 190:109970. https://doi.org/10.1016/j.envres.2020.109970.
145. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358:j4008. https://doi.org/10.1136/bmj.j4008.
146. Luo D, Kuang T, Chen Y-X, Huang Y-H, Zhang H, Xia Y-Y. Air pollution and pregnancy outcomes based on exposure evaluation using a land use regression model: A systematic review. *Taiwanese Journal of Obstetrics and Gynecology* 2021; 60(2):193-215. https://doi.org/10.1016/j.tjog.2021.01.004.
147. Simoncic V, Enaux C, Deguen S, Kihal-Talantikite W. Adverse Birth Outcomes Related to NO2 and PM Exposure: European Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2020; 17(21. https://doi.org/10.3390/ijerph17218116.
148. Uwak I, Olson N, Fuentes A, Moriarty M, Pulczinski J, Lam J, et al. Application of the navigation guide systematic review methodology to evaluate prenatal exposure to particulate matter air pollution and infant birth weight. *Environ Int* 2021; 148:106378. https://doi.org/10.1016/j.envint.2021.106378.
149. Zhang H, Zhang X, Wang Q, Xu Y, Feng Y, Yu Z, et al. Ambient air pollution and stillbirth: An updated systematic review and meta-analysis of epidemiological studies. *Environ Pollut* 2021; 278:116752. https://doi.org/10.1016/j.envpol.2021.116752.
150. Rappazzo KM, Nichols JL, Rice RB, Luben TJ. Ozone exposure during early pregnancy and preterm birth: A systematic review and meta-analysis. *Environ Res* 2021; 198:111317. https://doi.org/10.1016/j.envres.2021.111317.
151. Xie G, Sun L, Yang W, Wang R, Shang L, Yang L, et al. Maternal exposure to PM2.5 was linked to elevated risk of stillbirth. *Chemosphere* 2021; 283:131169. https://doi.org/10.1016/j.chemosphere.2021.131169.
152. Walter CM, Schneider-Futschik EK, Hall NL, Sly PD, Head BW, Knibbs LD. The health impacts of ambient air pollution in Australia: A systematic literature review. *Intern Med J* 2021. https://doi.org/10.1111/imj.15415.
153. Edwards L, Wilkinson P, Rutter G, Milojevic A. Health effects in people relocating between environments of differing ambient air pollution concentrations: A literature review. *Environ Pollut* 2022; 292:118314. https://doi.org/10.1016/j.envpol.2021.118314.

154. Gong C, Wang J, Bai Z, Rich DQ, Zhang Y. Maternal exposure to ambient PM2.5 and term birth weight: A systematic review and meta-analysis of effect estimates. *Sci Total Environ* 2022; 807:150744. https://doi.org/10.1016/j.scitotenv.2021.150744.
155. Ju L, Li C, Yang M, Sun S, Zhang Q, Cao J, et al. Maternal air pollution exposure increases the risk of preterm birth: Evidence from the meta-analysis of cohort studies. *Environ Res* 2021; 202:111654. https://doi.org/10.1016/j.envres.2021.111654.
156. Zhu W, Zheng H, Liu J, Cai J, Wang G, Li Y, et al. The correlation between chronic exposure to particulate matter and spontaneous abortion: A meta-analysis. *Chemosphere* 2022; 286:131802. https://doi.org/10.1016/j.chemosphere.2021.131802.
157. Heo S, Fong KC, Bell ML. Risk of particulate matter on birth outcomes in relation to maternal socio-economic factors: a systematic review. *Environ Res Lett* 2019; 14(12. https://doi.org/10.1088/1748-9326/ab4cd0.
158. Thayamballi N, Habiba S, Laribi O, Ebisu K. Impact of Maternal Demographic and Socioeconomic Factors on the Association Between Particulate Matter and Adverse Birth Outcomes: a Systematic Review and Meta-analysis. *Journal of Racial and Ethnic Health Disparities* 2020. https://doi.org/10.1007/s40615-020-00835-2.
159. Jacobs M, Zhang G, Chen S, Mullins B, Bell M, Jin L, et al. The association between ambient air pollution and selected adverse pregnancy outcomes in China: A systematic review. *Sci Total Environ* 2017; 579:1179-1192. https://doi.org/10.1016/j.scitotenv.2016.11.100.
160. Xue T, Zhu T, Geng G, Zhang Q. Association between pregnancy loss and ambient PM2·5 using survey data in Africa: a longitudinal case-control study, 1998-2016. *Lancet Planet Health* 2019; 3 5:e219-ee225. https://doi.org/10.1016/S2542-5196(19)30047-6.
161. Xue T, Guan T, Geng G, Zhang Q, Zhao Y, Zhu T. Estimation of pregnancy losses attributable to exposure to ambient fine particles in south Asia: an epidemiological case-control study. *Lancet Planet Health* 2021; 5(1):e15-e24. https://doi.org/10.1016/S2542-5196(20)30268-0.
162. Yuan L, Zhang Y, Gao Y, Tian Y. Maternal fine particulate matter (PM2.5) exposure and adverse birth outcomes: an updated systematic review based on cohort studies. *Environ Sci Pollut Res Int* 2019; 26(14):13963-13983. https://doi.org/10.1007/s11356-019-04644-x.
163. Tsoli S, Ploubidis GB, Kalantzi O-I. Particulate air pollution and birth weight: A systematic literature review. *Atmos Pollut Res* 2019; 10(4):1084-1122. https://doi.org/10.1016/j.apr.2019.01.016.
164. Grippo A, Zhang J, Chu L, Guo Y, Qiao L, Zhang J, et al. Air pollution exposure during pregnancy and spontaneous abortion and stillbirth. *Rev Environ Health* 2018; 33(3):247-264. https://doi.org/10.1515/reveh-2017-0033.

165. Ghosh R, Rankin J, Pless-Mulloli T, Glinianaia S. Does the effect of air pollution on pregnancy outcomes differ by gender? A systematic review. *Environ Res* 2007; 105(3):400-408. https://doi.org/10.1016/j.envres.2007.03.009.
166. Liu C, Sun J, Liu Y, Liang H, Wang M, Wang C, et al. Different exposure levels of fine particulate matter and preterm birth: a meta-analysis based on cohort studies. *Environ Sci Pollut Res Int* 2017; 24(22):17976-17984. https://doi.org/10.1007/s11356-017-9363-0.
167. Li X, Huang S, Jiao A, Yang X, Yun J, Wang Y, et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis. *Environ Pollut* 2017; 227:596-605. https://doi.org/10.1016/j.envpol.2017.03.055.
168. Sun X, Luo X, Zhao C, Zhang B, Tao J, Yang Z, et al. The associations between birth weight and exposure to fine particulate matter (PM2.5) and its chemical constituents during pregnancy: A meta-analysis. *Environ Pollut* 2016; 211:38-47. https://doi.org/10.1016/j.envpol.2015.12.022.
169. Westergaard N, Gehring U, Slama R, Pedersen M. Ambient air pollution and low birth weight - are some women more vulnerable than others? *Environ Int* 2017; 104:146-154. https://doi.org/10.1016/j.envint.2017.03.026.
170. Bonzini M, Carugno M, Grillo P, Mensi C, Bertazzi PA, Pesatori AC. Impact of ambient air pollution on birth outcomes: systematic review of the current evidences. *Med Lav* 2010; 101(5):341-363. Published 2010/11/26.
171. Bosetti C, Nieuwenhuijsen MJ, Gallus S, Cipriani S, La Vecchia C, Parazzini F. Ambient particulate matter and preterm birth or birth weight: a review of the literature. *Arch Toxicol* 2010; 84(6):447-460. https://doi.org/10.1007/s00204-010-0514-z.
172. Siddika N, Balogun HA, Amegah AK, Jaakkola JJ. Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence. *Occup Environ Med* 2016; 73(9):573-581. https://doi.org/10.1136/oemed-2015-103086.
173. Zhu X, Liu Y, Chen Y, Yao C, Che Z, Cao J. Maternal exposure to fine particulate matter (PM2.5) and pregnancy outcomes: a meta-analysis. *Environ Sci Pollut Res Int* 2015; 22(5):3383-3396. https://doi.org/10.1007/s11356-014-3458-7.
174. Zhang H, Zhang X, Wang Q, Xu Y, Feng Y, Yu Z, et al. Ambient air pollution and stillbirth: An updated systematic review and meta-analysis of epidemiological studies. *Environ Pollut* 2021; 278:116752. https://doi.org/10.1016/j.envpol.2021.116752.
175. Zhang K, Lu Y, Zhao H, Guo J, Gehendra M, Qiu H, et al. Association between atmospheric particulate matter and adverse pregnancy outcomes in the population. *Int J Clin Exp Med* 2016; 9(11):20594-20604.

176. Whaley P, Aiassa E, Beausoleil C, Beronius A, Bilotta G, Boobis A, et al. Recommendations for the conduct of systematic reviews in toxicology and environmental health research (COSTER). *Environ Int* 2020; 143:105926. https://doi.org/10.1016/j.envint.2020.105926.
177. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care* 2012; 28(2):138-144. https://doi.org/10.1017/s0266462312000086.
178. Dobrescu AI, Nussbaumer-Streit B, Klerings I, Wagner G, Persad E, Sommer I, et al. Restricting evidence syntheses of interventions to English-language publications is a viable methodological shortcut for most medical topics: a systematic review. *J Clin Epidemiol* 2021; 137:209-217. https://doi.org/10.1016/j.jclinepi.2021.04.012.
179. Jackson JL, Kuriyama A. How Often Do Systematic Reviews Exclude Articles Not Published in English? *J Gen Intern Med* 2019; 34(8):1388-1389. https://doi.org/10.1007/s11606-019-04976-x.
180. Furuya-Kanamori L, Xu C, Lin L, Doan T, Chu H, Thalib L, et al. P value–driven methods were underpowered to detect publication bias: analysis of Cochrane review meta-analyses. *J Clin Epidemiol* 2020; 118:86-92. https://doi.org/10.1016/j.jclinepi.2019.11.011.
181. Wasserstein RL, Schirm AL, Lazar NA. Moving to a World Beyond “p < 0.05”. *Am Stat* 2019; 73(sup1):1-19. https://doi.org/10.1080/00031305.2019.1583913.
182. Vervoort D, Ma X, Bookholane H. Equitable Open Access Publishing: Changing the Financial Power Dynamics in Academia. *Global Health: Science and Practice* 2021. https://doi.org/10.9745/GHSP-D-21-00145.
183. Steinle S, Johnston HJ, Loh M, Mueller W, Vardoulakis S, Tantrakarnapa K, et al. In Utero Exposure to Particulate Air Pollution during Pregnancy: Impact on Birth Weight and Health through the Life Course. *Int J Environ Res Public Health* 2020; 17(23):8948. https://www.mdpi.com/1660-4601/17/23/8948.
184. Lee JT. Review of epidemiological studies on air pollution and health effects in children. *Clin Exp Pediatr* 2021; 64(1):3-11. https://doi.org/10.3345/cep.2019.00843.
185. Han C, Xu R, Zhang Y, Yu W, Zhang Z, Morawska L, et al. Air pollution control efficacy and health impacts: A global observational study from 2000 to 2016. *Environ Pollut* 2021; 287:117211. https://doi.org/10.1016/j.envpol.2021.117211.
186. Shaddick G, Thomas ML, Mudu P, Ruggeri G, Gumy S. Half the world’s population are exposed to increasing air pollution. *NPJ Clim Atmos Sci* 2020; 3(1):23. https://doi.org/10.1038/s41612-020-0124-2.

187. Quinn JA, Munoz FM, Gonik B, Frau L, Cutland C, Mallett-Moore T, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine* 2016; 34(49):6047-6056. https://doi.org/10.1016/j.vaccine.2016.03.045.
188. Warren JL, Kong W, Luben TJ, Chang HH. Critical window variable selection: estimating the impact of air pollution on very preterm birth. *Biostatistics* 2020; 21(4):790-806. https://doi.org/10.1093/biostatistics/kxz006.
189. Deyssenroth MA, Rosa MJ, Eliot MN, Kelsey KT, Kloog I, Schwartz JD, et al. Placental gene networks at the interface between maternal PM2.5 exposure early in gestation and reduced infant birthweight. *Environ Res* 2021; 199:111342. https://doi.org/10.1016/j.envres.2021.111342.
190. Wilson A, Hsu H-HL, Mathilda Chiu Y-H, Wright RO, Wright RJ, Coull BA. Kernel Machine and Distributed Lag Models for Assessing Windows of Susceptibility to Environmental Mixtures in Children's Health Studies. 2019:arXiv:1904.12417. https://ui.adsabs.harvard.edu/abs/2019arXiv190412417W. Accessed April 01, 2019.
191. Mork D, Wilson A. Estimating perinatal critical windows of susceptibility to environmental mixtures via structured Bayesian regression tree pairs. *Biometrics* 2021; https://doi.org/10.1111/biom.13568.
192. Tanner E, Lee A, Colicino E. Environmental mixtures and children's health: identifying appropriate statistical approaches. *Curr Opin Pediatr* 2020; 32(2):315-320. https://doi.org/10.1097/MOP.0000000000000877.
193. Higgins JPT. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol* 2008; 37(5):1158-1160. https://doi.org/10.1093/ije/dyn204.
194. Ghosh R, Causey K, Burkart K, Wozniak S, Cohen A, Brauer M. Ambient and household PM2.5 pollution and adverse perinatal outcomes: A meta-regression and analysis of attributable global burden for 204 countries and territories. *PLOS Med* 2021; 18(9):e1003718. https://doi.org/10.1371/journal.pmed.1003718.
195. Steinle S, Reis S, Sabel CE. Quantifying human exposure to air pollution—Moving from static monitoring to spatio-temporally resolved personal exposure assessment. *Sci Total Environ* 2013; 443:184-193. https://doi.org/10.1016/j.scitotenv.2012.10.098.
196. Stock SJ, Bauld L. Maternal smoking and preterm birth: An unresolved health challenge. *PLoS Med* 2020; 17(9):e1003386. https://doi.org/10.1371/journal.pmed.1003386.
197. Gould GS, Havard A, Lim LL, The Psanz Smoking In Pregnancy Expert G, Kumar R. Exposure to Tobacco, Environmental Tobacco Smoke and Nicotine in Pregnancy: A Pragmatic Overview of Reviews of Maternal and Child Outcomes, Effectiveness of Interventions and Barriers

and Facilitators to Quitting. *Int J Environ Res Public Health* 2020; 17(6. https://doi.org/10.3390/ijerph17062034.
198. Patra J, Bakker R, Irving H, Jaddoe VW, Malini S, Rehm J. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)-a systematic review and meta-analyses. *BJOG* 2011; 118(12):1411-1421. https://doi.org/10.1111/j.1471-0528.2011.03050.x.
199. Liu L, Ma Y, Wang N, Lin W, Liu Y, Wen D. Maternal body mass index and risk of neonatal adverse outcomes in China: a systematic review and meta-analysis. *BMC Pregnancy Childbirth* 2019; 19(1):105. https://doi.org/10.1186/s12884-019-2249-z.
200. Niyibizi J, Zanré N, Mayrand MH, Trottier H. Association Between Maternal Human Papillomavirus Infection and Adverse Pregnancy Outcomes: Systematic Review and Meta-Analysis. *J Infect Dis* 2020; 221(12):1925-1937. https://doi.org/10.1093/infdis/jiaa054.
201. Thompson JM, Eick SM, Dailey C, Dale AP, Mehta M, Nair A, et al. Relationship Between Pregnancy-Associated Malaria and Adverse Pregnancy Outcomes: a Systematic Review and Meta-Analysis. *J Trop Pediatr* 2019; 66(3):327-338. https://doi.org/10.1093/tropej/fmz068.
202. Young MF, Ramakrishnan U. Maternal Undernutrition before and during Pregnancy and Offspring Health and Development. *Ann Nutr Metab* 2020; 76(suppl 3)(3):41-53. https://doi.org/10.1159/000510595.
203. Rich DQ, Liu K, Zhang J, Thurston SW, Stevens TP, Pan Y, et al. Differences in Birth Weight Associated with the 2008 Beijing Olympics Air Pollution Reduction: Results from a Natural Experiment. *Environ Health Perspect* 2015; 123(9):880-887. https://doi.org/10.1289/ehp.1408795.
204. Stock S, Zoega H, Brockway M, Mulholland R, Miller J, Been J, et al. The international Perinatal Outcomes in the Pandemic (iPOP) study: protocol [version 1; peer review: 1 approved]. *Wellcome Open Res* 2021; 6(21. https://doi.org/10.12688/wellcomeopenres.16507.1.
205. Sun Y, Ilango SD, Schwarz L, Wang Q, Chen J-C, Lawrence JM, et al. Examining the joint effects of heatwaves, air pollution, and green space on the risk of preterm birth in California. *Environ Res Lett* 2020; 15(10):104099. https://doi.org/10.1088/1748-9326/abb8a3.
206. Warren J, Luben T, Chang HH. A spatially varying distributed lag model with application to an air pollution and term low birth weight study. *Journal of the Royal Statistical Society Series C, Applied statistics* 2020; 69 3:681-696.
207. Tu J, Tu W, Tedders SH. Spatial variations in the associations of term birth weight with ambient air pollution in Georgia, USA. *Environ Int* 2016; 92-93:146-156. https://doi.org/10.1016/j.envint.2016.04.005.

208. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *The Lancet Global health* 2019; 7(1):e37-e46. https://doi.org/10.1016/S2214-109X(18)30451-0.
209. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016; 387(10018):587-603. https://doi.org/10.1016/S0140-6736(15)00837-5.
210. Katoto P, Byamungu L, Brand AS, Mokaya J, Strijdom H, Goswami N, et al. Ambient air pollution and health in Sub-Saharan Africa: Current evidence, perspectives and a call to action. *Environ Res* 2019; 173:174-188. https://doi.org/10.1016/j.envres.2019.03.029.
211. Agbo KE, Walgraeve C, Eze JI, Ugwoke PE, Ukoha PO, Van Langenhove H. A review on ambient and indoor air pollution status in Africa. *Atmos Pollut Res* 2021; 12(2):243-260. https://doi.org/10.1016/j.apr.2020.11.006.
212. Amegah AK. Proliferation of low-cost sensors. What prospects for air pollution epidemiologic research in Sub-Saharan Africa? *Environ Pollut* 2018; 241:1132-1137. https://doi.org/10.1016/j.envpol.2018.06.044.
213. Frøen JF, Myhre SL, Frost MJ, Chou D, Mehl G, Say L, et al. eRegistries: Electronic registries for maternal and child health. *BMC Pregnancy and Childbirth* 2016; 16(1):11. https://doi.org/10.1186/s12884-016-0801-7.
214. Street ME, Bernasconi S. Endocrine-Disrupting Chemicals in Human Fetal Growth. *Int J Mol Sci* 2020; 21(4. https://doi.org/10.3390/ijms21041430.
215. Marczylo EL, Jacobs MN, Gant TW. Environmentally induced epigenetic toxicity: potential public health concerns. *Crit Rev Toxicol* 2016; 46(8):676-700. https://doi.org/10.1080/10408444.2016.1175417.
216. Li Z, Tang Y, Song X, Lazar L, Li Z, Zhao J. Impact of ambient PM2.5 on adverse birth outcome and potential molecular mechanism. *Ecotoxicol Environ Saf* 2019; 169:248-254. https://doi.org/10.1016/j.ecoenv.2018.10.109.
217. Stingone JA, Triantafillou S, Larsen A, Kitt JP, Shaw GM, Marsillach J. Interdisciplinary data science to advance environmental health research and improve birth outcomes. *Environ Res* 2021; 197:111019. https://doi.org/10.1016/j.envres.2021.111019.
218. Eisenhauer E, Williams KC, Margeson K, Paczuski S, Hano MC, Mulvaney K. Advancing translational research in environmental science: The role and impact of social sciences. *Environ Sci Policy* 2021; 120:165-172. https://doi.org/10.1016/j.envsci.2021.03.010.

219. Wang Y, Perera F, Guo J, Riley KW, Durham T, Ross Z, et al. A methodological pipeline to generate an epigenetic marker of prenatal exposure to air pollution indicators. *Epigenetics* 2021):1-9. https://doi.org/10.1080/15592294.2021.1872926.
220. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020; 368:l6890. https://doi.org/10.1136/bmj.l6890.
221. Pereira G, Bell ML, Honda Y, Lee J-T, Morawska L, Jalaludin B. Energy transitions, air quality and health. *Environ Res Lett* 2021; 16:020202. https://doi.org/10.1088/1748-9326/abdaea.
222. Pereira G. Cut particulate air pollution, save lives. *BMJ* 2021; 375:n2561. https://doi.org/10.1136/bmj.n2561.
223. Vogel JP, Chawanpaiboon S, Moller A-B, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. *Best Pract Res Clin Obstet Gynaecol* 2018; 52:3-12. https://doi.org/10.1016/j.bpobgyn.2018.04.003.
224. Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. *Lancet* 2021; 398(10302):772-785. https://doi.org/10.1016/S0140-6736(21)01112-0.
225. Flenady VJ, Middleton P, Wallace EM, Morris J, Gordon A, Boyle FM, et al. Stillbirth in Australia 1: The road to now: Two decades of stillbirth research and advocacy in Australia. *Women and Birth* 2020; 33(6):506-513. https://doi.org/10.1016/j.wombi.2020.09.005.
226. Morris J, Brown K, Newnham J. The Australian Preterm Birth Prevention Alliance. *Aust N Z J Obstet Gynaecol* 2020; 60(3):321-323. https://doi.org/10.1111/ajo.13171.
227. Cobo T, Kacerovsky M, Jacobsson B. Risk factors for spontaneous preterm delivery. *Int J Gynaecol Obstet* 2020; 150(1):17-23. https://doi.org/10.1002/ijgo.13184.
228. United Nations. Global indicator framework for the Sustainable Development Goals and targets of the 2030 Agenda for Sustainable Development 2022. https://unstats.un.org/sdgs/indicators/Global%20Indicator%20Framework%20after%202022%20refinement_Eng.pdfFebruary. Accessed February 10, 2023.
229. de Bernis L, Kinney MV, Stones W, Ten Hoope-Bender P, Vivio D, Leisher SH, et al. Stillbirths: ending preventable deaths by 2030. *Lancet* 2016; 387(10019):703-716. https://doi.org/10.1016/s0140-6736(15)00954-x.
230. Liu X-X, Fan S-J, Luo Y-N, Hu L-X, Li C-C, Zhang Y-D, et al. Global, regional, and national burden of preterm birth attributable to ambient and household PM2.5 from 1990 to 2019: Worsening or improving? *Sci Total Environ* 2023):161975. https://doi.org/10.1016/j.scitotenv.2023.161975.

231. Li Z, Tang Y, Song X, Lazar L, Li Z, Zhao J. Impact of ambient PM(2.5) on adverse birth outcome and potential molecular mechanism. *Ecotoxicol Environ Saf* 2019; 169:248-254. https://doi.org/10.1016/j.ecoenv.2018.10.109.

232. Yuan L, Zhang Y, Wang W, Chen R, Liu Y, Liu C, et al. Critical windows for maternal fine particulate matter exposure and adverse birth outcomes: The Shanghai birth cohort study. *Chemosphere* 2020; 240:124904. https://doi.org/10.1016/j.chemosphere.2019.124904.

233. Wu H, Jiang B, Zhu P, Geng X, Liu Z, Cui L, et al. Associations between maternal weekly air pollutant exposures and low birth weight: a distributed lag non-linear model. *Environ Res Lett* 2018; 13(2):024023. https://doi.org/10.1088/1748-9326/aaa346.

234. Zhang H, Zhang X, Feng D, Gao Z, Gong Y, Zhang J, et al. Interaction effects of night-time temperature and PM2.5 on preterm birth in Huai River Basin, China. *Environ Int* 2023; 171:107729. https://doi.org/10.1016/j.envint.2023.107729.

235. Sogno P, Kuenzer C, Bachofer F, Traidl-Hoffmann C. Earth observation for exposome mapping of Germany: analyzing environmental factors relevant to non-communicable diseases. *Int J Appl Earth Obs Geoinf* 2022; 114:103084. https://doi.org/10.1016/j.jag.2022.103084.

236. Wensu Z, Wen C, Fenfen Z, Wenjuan W, Li L. The Association Between Long-Term Exposure to Particulate Matter and Incidence of Hypertension Among Chinese Elderly: A Retrospective Cohort Study. *Front Cardiovas Med* 2022; 8(https://doi.org/10.3389/fcvm.2021.784800.

237. Wu B, Yan T, Elahi E. The impact of environmental pollution on labor supply: empirical evidence from China. *Environ Sci Pollut Res Int* 2022. https://doi.org/10.1007/s11356-022-23720-3.

238. Xie G, Yue J, Yang W, Yang L, Xu M, Sun L, et al. Effects of PM(2.5) and its constituents on hemoglobin during the third trimester in pregnant women. *Environ Sci Pollut Res Int* 2022; 29(23):35193-35203. https://doi.org/10.1007/s11356-022-18693-2.

239. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* 2015; 12(10):e1001885. https://doi.org/10.1371/journal.pmed.1001885.

240. Australian Bureau of Statistcs (ABS). Australian Statistical Geography Standard (ASGS): Volume 1 - Main Structure and Greater Capital City Statistical Areas 1270.0.55.001 ed. 2011. https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1270.0.55.001July%202011?OpenDocument#Publications. Accessed October 19, 2021.

241. Strand LB, Barnett AG, Tong S. Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes. *BMC Med Res Methodol* 2011; 11(1):49. https://doi.org/10.1186/1471-2288-11-49.

242. Ha S, Zhu Y, Liu D, Sherman S, Mendola P. Ambient temperature and air quality in relation to small for gestational age and term low birthweight. *Environ Res* 2017; 155:394-400. https://doi.org/10.1016/j.envres.2017.02.021.

243. Mork D, Braun D, Zanobetti A. Time-lagged relationships between a decade of air pollution exposure and first hospitalization with Alzheimer's disease and related dementias. *Environ Int* 2023; 171:107694. https://doi.org/10.1016/j.envint.2022.107694.

244. Hao J, Peng L, Cheng P, Li S, Zhang C, Fu W, et al. A time series analysis of ambient air pollution and low birth weight in Xuzhou, China. *Int J Environ Health Res* 2022; 32(6):1238-1247. https://doi.org/10.1080/09603123.2020.1867828.

245. Ranjbaran M, Mohammadi R, Yaseri M, Kamari M, Yazdani K. Ambient temperature and air pollution, and the risk of preterm birth in Tehran, Iran: a time series study. *J Matern-Fetal Neonatal Med* 2022; 35(4):726-737. https://doi.org/10.1080/14767058.2020.1731458.

246. Ranjbaran M, Mohammadi R, Yaseri M, Kamari M, Habibelahi A, Yazdani K. Effect of ambient air pollution and temperature on the risk of stillbirth: a distributed lag nonlinear time series analysis. *J Environ Health Sci Eng* 2020; 18(2):1289-1299. https://doi.org/10.1007/s40201-020-00547-z.

247. Zhang W, Yang Y, Liu Y, Zhou L, Yang Y, Pan L, et al. Associations between congenital heart disease and air pollutants at different gestational weeks: a time-series analysis. *Environ Geochem Health* 2022. https://doi.org/10.1007/s10653-022-01315-8.

248. Liu Y, Zhou L, Zhang W, Yang Y, Yang Y, Pan L, et al. Time series analysis on association between ambient air pollutants and orofacial clefts during pregnancy in Lanzhou, China. *Environ Sci Pollut Res* 2022; 29(48):72898-72907. https://doi.org/10.1007/s11356-022-19855-y.

249. Gasparrini A. Extensions of the dlnm package. 2021. https://cran.r-project.org/web/packages/dlnm/vignettes/dlnmExtended.pdf (Accessed May 25, 2022).

250. Cox DR. Regression Models and Life-Tables. In: Kotz S, Johnson NL, eds. Breakthroughs in Statistics: Methodology and Distribution. New York, NY: Springer New York;1992:527-541. https://doi.org/10.1007/978-1-4612-4380-9_37.

251. Balan TA, Putter H. A tutorial on frailty models. *Stat Methods Med Res* 2020; 29(11):3424-3454. https://doi.org/10.1177/0962280220921889.

252. Government of Australia. Particulate matter (PM10 and PM2.5). Australia. https://www.dcceew.gov.au/environment/protection/npi/substances/fact-sheets/particulate-matter-pm10-and-pm25. Accessed February 20, 2023.
253. Strand LB, Barnett AG, Tong S. Maternal Exposure to Ambient Temperature and the Risks of Preterm Birth and Stillbirth in Brisbane, Australia. *Am J Epidemiol* 2011; 175(2):99-107. https://doi.org/10.1093/aje/kwr404.
254. Hviid A, Laksafoss A, Hedley P, Lausten-Thomsen U, Hjalgrim H, Christiansen M, et al. Assessment of Seasonality and Extremely Preterm Birth in Denmark. *JAMA Netw Open* 2022; 5(2):e2145800. https://doi.org/10.1001/jamanetworkopen.2021.45800.
255. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiol* 2012; 23(1):1-9. https://doi.org/10.1097/EDE.0b013e31823aca5d.
256. Hough I, Rolland M, Guilbert A, Seyve E, Heude B, Slama R, et al. Early delivery following chronic and acute ambient temperature exposure: a comprehensive survival approach. *Int J Epidemiol* 2022):dyac190. https://doi.org/10.1093/ije/dyac190.
257. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ (Clinical research ed)* 2003; 326(7382):219-219. https://doi.org/10.1136/bmj.326.7382.219.
258. Hutchon DJR. Calculations for comparing two estimated relative risks. . http://www.hutchon.net/CompareRR.htm. Published 2005. Updated 23 April 2015 08:47:27. Accessed January 10, 2022, 2022.
259. Zhang H, Zhang X, Wang Q, Xu Y, Feng Y, Yu Z, et al. Ambient air pollution and stillbirth: An updated systematic review and meta-analysis of epidemiological studies. *Environ Pollut* 2021; 278:116752. https://doi.org/10.1016/j.envpol.2021.116752.
260. Mendola P, Wallace M, Hwang BS, Liu D, Robledo C, Männistö T, et al. Preterm birth and air pollution: Critical windows of exposure for women with asthma. *J Allergy Clin Immunol* 2016; 138(2):432-440.e435. https://doi.org/10.1016/j.jaci.2015.12.1309.
261. Williams AD, Kanner J, Grantz KL, Ouidir M, Sheehy S, Sherman S, et al. Air pollution exposure and risk of adverse obstetric and neonatal outcomes among women with type 1 diabetes. *Environ Res* 2021; 197:111152. https://doi.org/10.1016/j.envres.2021.111152.
262. Blum JL, Chen L-C, Zelikoff JT. Exposure to Ambient Particulate Matter during Specific Gestational Periods Produces Adverse Obstetric Consequences in Mice. *Environ Health Perspect* 2017; 125(7):077020. https://doi.org/doi:10.1289/EHP1029.
263. Kwag Y, Kim MH, Ye S, Oh J, Yim G, Kim YJ, et al. The Combined Effects of Fine Particulate Matter and Temperature on Preterm Birth in Seoul, 2010-2016. *Int J Environ Res Public Health* 2021; 18(4. https://doi.org/10.3390/ijerph18041463.

264. Kwag Y, Kim M-h, Oh J, Shah S, Ye S, Ha E-H. Effect of heat waves and fine particulate matter on preterm births in Korea from 2010 to 2016. *Environ Int* 2021; 147:106239. https://doi.org/10.1016/j.envint.2020.106239.
265. Alson JG, Robinson WR, Pittman L, Doll KM. Incorporating Measures of Structural Racism into Population Studies of Reproductive Health in the United States: A Narrative Review. *Health Equity* 2021; 5(1):49-58. https://doi.org/10.1089/heq.2020.0081.
266. Bai W, Li Y, Niu Y, Ding Y, Yu X, Zhu B, et al. Association between ambient air pollution and pregnancy complications: A systematic review and meta-analysis of cohort studies. *Environ Res* 2020; 185:109471. https://doi.org/10.1016/j.envres.2020.109471.
267. Tosevska A, Ghosh S, Ganguly A, Cappelletti M, Kallapur SG, Pellegrini M, et al. Integrated analysis of an in vivo model of intra-nasal exposure to instilled air pollutants reveals cell-type specific responses in the placenta. *Sci Rep* 2022; 12(1):8438. https://doi.org/10.1038/s41598-022-12340-z.
268. Padmanabhan V, Song W, Puttabyatappa M. Praegnatio Perturbatio—Impact of Endocrine-Disrupting Chemicals. *Endocr Rev* 2021; 42(3):295-353. https://doi.org/10.1210/endrev/bnaa035.
269. Zhu L, Lu Y, Cheng F, Zhang L, Yusan A, Alifu X, et al. Association between atmospheric pollutant levels and oxidative stress in pregnant women and newborns in Urumqi. *BMC Public Health* 2023; 23(1):330. https://doi.org/10.1186/s12889-023-15222-9.
270. Wang L, Luo D, Liu X, Zhu J, Wang F, Li B, et al. Effects of PM2.5 exposure on reproductive system and its mechanisms. *Chemosphere* 2021; 264:128436. https://doi.org/10.1016/j.chemosphere.2020.128436.
271. Burns J, Boogaard H, Polus S, Pfadenhauer LM, Rohwer AC, van Erp AM, et al. Interventions to reduce ambient air pollution and their effects on health: An abridged Cochrane systematic review. *Environ Int* 2020; 135:105400. https://doi.org/10.1016/j.envint.2019.105400.
272. Zhao Q, Yu P, Mahendran R, Huang W, Gao Y, Yang Z, et al. Global climate change and human health: pathways and possible solutions. *Eco-Environ Health* 2022. https://doi.org/10.1016/j.eehl.2022.04.004.
273. Zhang Y, Smith SJ, Bell M, Mueller A, Eckelman M, Wylie S, et al. Pollution inequality 50 years after the Clean Air Act: the need for hyperlocal data and action. *Environ Res Lett* 2021; 16(7):071001. https://doi.org/10.1088/1748-9326/ac09b1.
274. Giudice LC, Llamas-Clark EF, DeNicola N, Pandipati S, Zlatnik MG, Decena DCD, et al. Climate change, women's health, and the role of obstetricians and gynecologists in leadership. *Int J Gynaecol Obstet* 2021; 155(3):345-356. https://doi.org/10.1002/ijgo.13958.

275. Edwards L, Wilkinson P, Rutter G, Milojevic A. Health effects in people relocating between environments of differing ambient air pollution concentrations: A literature review. *Environ Pollut* 2022; 292(Pt A):118314. https://doi.org/10.1016/j.envpol.2021.118314.
276. Warren JL, Son JY, Pereira G, Leaderer BP, Bell ML. Investigating the Impact of Maternal Residential Mobility on Identifying Critical Windows of Susceptibility to Ambient Air Pollution During Pregnancy. *Am J Epidemiol* 2018; 187(5):992-1000. https://doi.org/10.1093/aje/kwx335.
277. Ghassabian A, Afanasyeva Y, Yu K, Gordon T, Liu M, Trasande L, et al. Characterisation of personalised air pollution exposure in pregnant women participating in a birth cohort study. *Paediatr Perinat Epidemiol* 2023. https://doi.org/10.1111/ppe.12960.
278. Ha S, Nobles C, Kanner J, Sherman S, Cho S-H, Perkins N, et al. Air Pollution Exposure Monitoring among Pregnant Women with and without Asthma. *Int J Environ Res Public Health* 2020; 17(13):4888. https://www.mdpi.com/1660-4601/17/13/4888.
279. Joubert BR, Kioumourtzoglou M-A, Chamberlain T, Chen HY, Gennings C, Turyk ME, et al. Powering Research through Innovative Methods for Mixtures in Epidemiology (PRIME) Program: Novel and Expanded Statistical Methods. *Int J Environ Res Public Health* 2022; 19(3):1378. https://www.mdpi.com/1660-4601/19/3/1378.
280. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health* 2019; 7(7):e849-e860. https://doi.org/10.1016/S2214-109X(18)30565-5.
281. Nordman H, Jääskeläinen J, Voutilainen R. Birth Size as a Determinant of Cardiometabolic Risk Factors in Children. *Horm Res Paediatr* 2020; 93(3):144-153. https://doi.org/10.1159/000509932.
282. Levine TA, Grunau RE, McAuliffe FM, Pinnamaneni R, Foran A, Alderdice FA. Early Childhood Neurodevelopment After Intrauterine Growth Restriction: A Systematic Review. *Pediatrics* 2015; 135(1):126-141. https://doi.org/10.1542/peds.2014-1143.
283. Castro Conde JR, González Campo C, González González NL, Reyes Millán B, González Barrios D, Jiménez Sosa A, et al. Assessment of neonatal EEG background and neurodevelopment in full-term small for their gestational age infants. *Pediatr Res* 2019; 88:91 - 99.
284. Stevenson NJ, Lai MM, Starkman HE, Colditz PB, Wixey JA. Electroencephalographic studies in growth-restricted and small-for-gestational-age neonates. *Pediatr Res* 2022. https://doi.org/10.1038/s41390-022-01992-2.
285. World Health Organization (WHO). Global Nutrition Monitoring Framework: operational guidance for tracking progress in meeting targets for 2025. Geneva, Switzerland: WHO; 2017. https://apps.who.int/iris/handle/10665/259904. Accessed February 25, 2023.

286. Wang Q, Benmarhnia T, Li C, Knibbs LD, Bao J, Ren M, et al. Seasonal analyses of the association between prenatal ambient air pollution exposure and birth weight for gestational age in Guangzhou, China. *Sci Total Environ* 2019; 649:526-534. https://doi.org/10.1016/j.scitotenv.2018.08.303.

287. Chen X, Chen S, Zhu Z, Luo J, Wang H, Wulayin M, et al. Identifying the critical windows and joint effects of temperature and PM2.5 exposure on small for gestational age. *Environ Int* 2023; 173:107832. https://doi.org/10.1016/j.envint.2023.107832.

288. Australian Institute of Health and Welfare (AIHW). Australia's children. Cat. no. CWS 69. Canberra, Australia: Department of Health, AIHW; 2020. https://www.aihw.gov.au/getmedia/6af928d6-692e-4449-b915-cf2ca946982f/aihw-cws-69-print-report.pdf.aspx?inline=true. Accessed February 26, 2023.

289. Boing AF, deSouza P, Boing AC, Kim R, Subramanian SV. Air Pollution, Socioeconomic Status, and Age-Specific Mortality Risk in the United States. *JAMA Netw Open* 2022; 5(5):e2213540. https://doi.org/10.1001/jamanetworkopen.2022.13540.

290. Clarke K, Rivas AC, Milletich S, Sabo-Attwood T, Coker ES. Prenatal Exposure to Ambient PM(2.5) and Early Childhood Growth Impairment Risk in East Africa. *Toxics* 2022; 10(11. https://doi.org/10.3390/toxics10110705.

291. Joseph FA, Hyett JA, Schluter PJ, McLennan A, Gordon A, Chambers GM, et al. New Australian birthweight centiles. *Medical Journal of Australia* 2020; 213(2):79-85. https://doi.org/10.5694/mja2.50676.

292. Sun S, Spangler KR, Weinberger KR, Yanosky JD, Braun JM, Wellenius GA. Ambient Temperature and Markers of Fetal Growth: A Retrospective Observational Study of 29 Million U.S. Singleton Births. *Environ Health Perspect* 2019; 127(6):67005. https://doi.org/10.1289/ehp4648.

293. Pereira G, Blair E, Lawrence D. Validation of a model for optimal birth weight: a prospective study using serial ultrasounds. *BMC Pediatr* 2012; 12:73. https://doi.org/10.1186/1471-2431-12-73.

294. Proietti E, Roosli M, Frey U, Latzin P. Air pollution during pregnancy and neonatal outcome: a review. *J Aerosol Med Pulm Drug Deliv* 2013; 26(1):9-23. https://doi.org/10.1089/jamp.2011.0932.

295. Chen W-J, Rector AM, Guxens M, Iniguez C, Swartz MD, Symanski E, et al. Susceptible windows of exposure to fine particulate matter and fetal growth trajectories in the Spanish INMA (INfancia y Medio Ambiente) birth cohort. *Environ Res* 2023; 216:114628. https://doi.org/10.1016/j.envres.2022.114628.

296. Chen J, Wu S, Fang J, Liu Z, Shang X, Guo X, et al. Association of exposure to fine particulate matter wave over the preconception and pregnancy periods with adverse birth outcomes: Results from the project ELEFANT. *Environ Res* 2022; 205:112473. https://doi.org/10.1016/j.envres.2021.112473.
297. Samuels L, Nakstad B, Roos N, Bonell A, Chersich M, Havenith G, et al. Physiological mechanisms of the impact of heat during pregnancy and the clinical implications: review of the evidence from an expert group meeting. *Int J Biometeorol* 2022. https://doi.org/10.1007/s00484-022-02301-6.
298. Ryan Crowley SM, David Hilden. Environmental Health: A Position Paper From the American College of Physicians. *Ann Intern Med* 2022; 175(11):1591-1593. https://doi.org/10.7326/m22-1864 %m 36279541.
299. Della Guardia L, Wang L. Fine particulate matter induces adipose tissue expansion and weight gain: Pathophysiology. *Obes Rev*; n/a(n/a):e13552. https://doi.org/10.1111/obr.13552.
300. Geurtsen ML, van Soest EEL, Voerman E, Steegers EAP, Jaddoe VWV, Gaillard R. High maternal early-pregnancy blood glucose levels are associated with altered fetal growth and increased risk of adverse birth outcomes. *Diabetologia* 2019; 62(10):1880-1890. https://doi.org/10.1007/s00125-019-4957-3.
301. Zou J-j, Wei Q, Shi Y-y, Wang K, Zhang Y-h, Shi H-j. Longitudinal Associations Between Maternal Glucose Levels and Ultrasonographic Fetal Biometrics in a Shanghai Cohort. *JAMA Network Open* 2022; 5(4):e226407-e226407. https://doi.org/10.1001/jamanetworkopen.2022.6407.
302. Nyadanu SD, Tessema GA, Mullins B, Kumi-Boateng B, Ofosu AA, Pereira G. Ambient particulate matter air pollution and stillbirth in Ghana: A difference-in-differences approach. *Atmos Pollut Res* 2022; 13(7):101471. https://doi.org/10.1016/j.apr.2022.101471.
303. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). A Neglected Tragedy: The global burden of stillbirths. New York, USA: United Nations Children's Fund (UNICEF); 2020. https://data.unicef.org/wp-content/uploads/2020/10/UN-IGME-2020-Stillbirth-Report-updated.pdf. Accessed July 16, 2021.
304. Keswani A, Akselrod H, Anenberg SC. Health and Clinical Impacts of Air Pollution and Linkages with Climate Change. *NEJM Evidence* 2022; 1(7):EVIDra2200068. https://doi.org/doi:10.1056/EVIDra2200068.
305. Feng S, Gao D, Liao F, Zhou F, Wang X. The health effects of ambient PM2.5 and potential mechanisms. *Ecotoxicol Environ Saf* 2016; 128:67-74. https://doi.org/10.1016/j.ecoenv.2016.01.030.

306. Mustapha A, Amegah AK, Coker ES. Harmonization of Epidemiologic Research Methods to Address the Environmental and Social Determinants of Urban Slum Health Challenges in Sub-Saharan Africa. *Int J Environ Res Public Health* 2022; 19(18):11273. https://www.mdpi.com/1660-4601/19/18/11273.
307. Xue T, Tong M, Li J, Wang R, Guan T, Li J, et al. Estimation of stillbirths attributable to ambient fine particles in 137 countries. *Nat Commun* 2022; 13(1):6950. https://doi.org/10.1038/s41467-022-34250-4.
308. Kwesiga D, Tawiah C, Imam MA, Tesega AK, Nareeba T, Enuameh YAK, et al. Barriers and enablers to reporting pregnancy and adverse pregnancy outcomes in population-based surveys: EN-INDEPTH study. *Popul Health Metr* 2021; 19(1):15. https://doi.org/10.1186/s12963-020-00228-x.
309. McClure EM. Enhancing routine surveillance to improve stillbirth data. *Lancet Glob Health* 2020; 8(4):e464-e465. https://doi.org/10.1016/S2214-109X(20)30082-6.
310. IQAir. *2021 World Air Quality Report: Region and City PM2.5 Ranking. https://www.iqair.com/world-most-polluted-cities/world-air-quality-report-2021-en.pdf. Accessed on March 9, 2021*. 2021.
311. Nonterah EA, Agorinya IA, Kanmiki EW, Kagura J, Tamimu M, Ayamba EY, et al. Trends and risk factors associated with stillbirths: A case study of the Navrongo War Memorial Hospital in Northern Ghana. *PLoS One* 2020; 15(2):e0229013. https://doi.org/10.1371/journal.pone.0229013.
312. Agbozo F, Abubakari A, Der J, Jahn A. Prevalence of low birth weight, macrosomia and stillbirth and their relationship to associated maternal risk factors in Hohoe Municipality, Ghana. *Midwifery* 2016; 40:200-206. https://doi.org/10.1016/j.midw.2016.06.016.
313. Ha YP, Hurt LS, Tawiah-Agyemang C, Kirkwood BR, Edmond KM. Effect of socioeconomic deprivation and health service utilisation on antepartum and intrapartum stillbirth: population cohort study from rural Ghana. *PLoS One* 2012; 7(7):e39050-e39050. https://doi.org/10.1371/journal.pone.0039050.
314. Jegasothy E, Randall DA, Ford JB, Nippita TA, Morgan GG. Maternal factors and risk of spontaneous preterm birth due to high ambient temperatures in New South Wales, Australia. *Paediatr Perinat Epidemiol* 2022; 36(1):4-12. https://doi.org/10.1111/ppe.12822.
315. Zhang Q, Sun S, Sui X, Ding L, Yang M, Li C, et al. Associations between weekly air pollution exposure and congenital heart disease. *Sci Total Environ* 2021; 757:143821. https://doi.org/10.1016/j.scitotenv.2020.143821.
316. Oduro C, Shuoben B, Ayugi B, Beibei L, Babaousmail H, Sarfo I, et al. Observed and Coupled Model Intercomparison Project 6 multimodel simulated changes in near-surface temperature

properties over Ghana during the 20th century. *Int J Climatol* 2022; 42(7):3681-3701. https://doi.org/https://doi.org/10.1002/joc.7439.
317. Abbam T, Johnson FA, Dash J, Padmadas SS. Spatiotemporal Variations in Rainfall and Temperature in Ghana Over the Twentieth Century, 1900–2014. *Earth Space Sci* 2018; 5(4):120-132. https://doi.org/10.1002/2017EA000327.
318. World Health Organization (WHO), Mudu P. Ambient air pollution and health in Accra, Ghana. Geneva: WHO; 2021. https://apps.who.int/iris/handle/10665/340678.
319. Bachwenkizi J, Liu C, Meng X, Zhang L, Wang W, van Donkelaar A, et al. Maternal exposure to fine particulate matter and preterm birth and low birth weight in Africa. *Environ Int* 2022; 160:107053. https://doi.org/10.1016/j.envint.2021.107053.
320. Moritz S, Bartz-Beielstein, T. imputeTS: Time Series Missing Value Imputation in R. *R J* 2017; 9(1):207-218. https://doi.org/Doi: 10.32614/RJ-2017-009.
321. Bickton FM, Ndeketa L, Sibande GT, Nkeramahame J, Payesa C, Milanzi EB. Household air pollution and under-five mortality in sub-Saharan Africa: an analysis of 14 demographic and health surveys. *Environ Health Prev Med* 2020; 25(1):67. https://doi.org/10.1186/s12199-020-00902-4.
322. Weber E, Adu-Bonsaffoh K, Vermeulen R, Klipstein-Grobusch K, Grobbee DE, Browne JL, et al. Household fuel use and adverse pregnancy outcomes in a Ghanaian cohort study. *Reprod Health* 2020; 17(1):29. https://doi.org/10.1186/s12978-020-0878-3.
323. R. Core Team. R (version 4.1.1): A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2021. https://www.R-project.org/.
324. Alli AS, Clark SN, Hughes A, Nimo J, Bedford-Moses J, Baah S, et al. Spatial-temporal patterns of ambient fine particulate matter (PM(2.5)) and black carbon (BC) pollution in Accra. *Environ Res Lett* 2021; 16(7):074013. https://doi.org/10.1088/1748-9326/ac074a.
325. Sarpong SA, Donkoh RF, Konnuba JK-s, Ohene-Agyei C, Lee Y. Analysis of PM2.5, PM10, and Total Suspended Particle Exposure in the Tema Metropolitan Area of Ghana. *Atmosphere* 2021; 12(6):700. https://www.mdpi.com/2073-4433/12/6/700.
326. Tong M, Li P, Wang M, Sun Y, Han Y, Liu H, et al. Time-varying association between fetal death and gestational exposure to ambient fine particles: a nationwide epidemiological study of 49 million fetuses in the contiguous US from 1989 to 2004. *Int J Epidemiol* 2022; 51(6):1984-1999. https://doi.org/10.1093/ije/dyac103.
327. Ebi KL, Vanos J, Baldwin JW, Bell JE, Hondula DM, Errett NA, et al. Extreme Weather and Climate Change: Population Health and Health System Implications. *Annu Rev Public Health* 2021; 42(1):293-315. https://doi.org/10.1146/annurev-publhealth-012420-105026.

328. Lajinian S, Hudson S, Applewhite L, Feldman J, Minkoff HL. An association between the heat-humidity index and preterm labor and delivery: a preliminary analysis. *Am J Public Health* 1997; 87(7):1205-1207. https://doi.org/10.2105/ajph.87.7.1205.

329. Carolan-Olah M, Frankowska D. High environmental temperature and preterm birth: a review of the evidence. *Midwifery* 2014; 30(1):50-59. https://doi.org/10.1016/j.midw.2013.01.011.

330. Zhang Y, Yu C, Wang L. Temperature exposure during pregnancy and birth outcomes: An updated systematic review of epidemiological evidence. *Environ Pollut* 2017; 225:700-712. https://doi.org/10.1016/j.envpol.2017.02.066.

331. Sexton J, Andrews C, Carruthers S, Kumar S, Flenady V, Lieske S. Systematic review of ambient temperature exposure during pregnancy and stillbirth: Methods and evidence. *Environ Res* 2021; 197:111037. https://doi.org/10.1016/j.envres.2021.111037.

332. Poursafa P, Keikha M, Kelishadi R. Systematic review on adverse birth outcomes of climate change. *J Res Med Sci* 2015; 20(4):397-402. Published 2015/06/26.

333. Chersich MF, Scorgie F, Luchters S. Increasing global temperatures threaten gains in maternal and newborn health in Africa: a review of impacts and an adaptation framework. *Int J Gynaecol Obstet* 2022. https://doi.org/10.1002/ijgo.14381.

334. Davenport F, Dorélien A, Grace K. Investigating the linkages between pregnancy outcomes and climate in sub-Saharan Africa. *Popul Environ* 2020; 41(4):397-421. https://doi.org/10.1007/s11111-020-00342-w.

335. McElroy S, Ilango S, Dimitrova A, Gershunov A, Benmarhnia T. Extreme heat, preterm birth, and stillbirth: A global analysis across 14 lower-middle income countries. *Environ Int* 2022; 158:106902. https://doi.org/10.1016/j.envint.2021.106902.

336. Li G, Hu W, Lu H, Liu J, Li X, He J, et al. Maternal exposure to extreme high-temperature, particulate air pollution and macrosomia in 14 countries of Africa. *Pediatr Obes* 2023):e13004. https://doi.org/10.1111/ijpo.13004.

337. Ha S. The Changing Climate and Pregnancy Health. *Curr Environ Health Rep* 2022. https://doi.org/10.1007/s40572-022-00345-9.

338. Syed S, O'Sullivan TL, Phillips KP. Extreme Heat and Pregnancy Outcomes: A Scoping Review of the Epidemiological Evidence. *Int J Environ Res Public Health* 2022; 19(4. https://doi.org/10.3390/ijerph19042412.

339. Segal TR, Giudice LC. Systematic review of climate change effects on reproductive health. *Fertil Steril* 2022; 118(2):215-223. https://doi.org/10.1016/j.fertnstert.2022.06.005.

340. Edwards MJ. Review: Hyperthermia and fever during pregnancy. *Birth Defects Res Part A: Clin Mol Teratol* 2006; 76(7):507-516. https://doi.org/10.1002/bdra.20277.

341. Jee B, Dhar R, Singh S, Karmakar S. Heat Shock Proteins and Their Role in Pregnancy: Redefining the Function of "Old Rum in a New Bottle". *Front Cell Dev Biol* 2021; 9(1057. https://doi.org/10.3389/fcell.2021.648463.
342. Ziskin MC, Morrissey J. Thermal thresholds for teratogenicity, reproduction, and development. *Int J Hyperth* 2011; 27(4):374-387. https://doi.org/10.3109/02656736.2011.553769.
343. Berestoviy VO, Mahmood A, Venckivska IB, Ginzburg VG, Sokol IV, Berestoviy OO, et al. The overview and role of heat shock proteins (HSP) especially HSP 60 and 70 in reproduction and other pathologies (a literature review). *Med Perspekt* 2021; 26(1):54-62. https://doi.org/10.26641/2307-0404.2021.1.227733.
344. Collier RJ, Renquist BJ, Xiao Y. A 100-Year Review: Stress physiology including heat stress. *J Dairy Sci* 2017; 100(12):10367-10380. https://doi.org/10.3168/jds.2017-13676.
345. Green ES, Arck PC. Pathogenesis of preterm birth: bidirectional inflammation in mother and fetus. *Semin Immunopathol* 2020; 42(4):413-429. https://doi.org/10.1007/s00281-020-00807-y.
346. Stan C, Boulvain M, Hirsbrunner-Amagbaly P, Pfister R. Hydration for treatment of preterm labour. *Cochrane Database Syst Rev* 2002; Art. No:CD003096. https://doi.org/10.1002/14651858.CD003096.
347. Dubey A, Prajapati KS, Swamy M, Pachauri V. Heat shock proteins: a therapeutic target worth to consider. *Vet World* 2015; 8(1):46-51. https://doi.org/10.14202/vetworld.2015.46-51.
348. Hu C, Yang J, Qi Z, Wu H, Wang B, Zou F, et al. Heat shock proteins: Biological functions, pathological roles, and therapeutic opportunities. *MedComm (2020)* 2022; 3(3):e161. https://doi.org/10.1002/mco2.161.
349. Edkins AL, Price JT, Pockley AG, Blatch GL. Heat shock proteins as modulators and therapeutic targets of chronic disease: an integrated perspective. *Philosophical Transactions of the Royal Society B: Biological Sciences* 2018; 373(1738):20160521. https://doi.org/doi:10.1098/rstb.2016.0521.
350. Xiong T, Chen P, Mu Y, Li X, Di B, Li J, et al. Association between ambient temperature and hypertensive disorders in pregnancy in China. *Nat Commun* 2020; 11(1):2925. https://doi.org/10.1038/s41467-020-16775-8.
351. Ha S, Liu D, Zhu Y, Soo Kim S, Sherman S, Grantz KL, et al. Ambient Temperature and Stillbirth: A Multi-Center Retrospective Cohort Study. *Environ Health Perspect* 2017; 125(6):067011. https://doi.org/10.1289/ehp945.
352. Canto MV, Guxens M, García-Altés A, López MJ, Marí-Dell'Olmo M, García-Pérez J, et al. Air Pollution and Birth Outcomes: Health Impact and Economic Value Assessment in Spain. *Int J Environ Res Public Health* 2023; 20(3):2290. https://www.mdpi.com/1660-4601/20/3/2290.

353. Urban A, Di Napoli C, Cloke HL, Kyselý J, Pappenberger F, Sera F, et al. Evaluation of the ERA5 reanalysis-based Universal Thermal Climate Index on mortality data in Europe. *Environ Res* 2021; 198:111227. https://doi.org/10.1016/j.envres.2021.111227.
354. Matzarakis A, Gangwisch M, Fröhlich D. RayMan and SkyHelios Model. In: Palme M, Salvati A, eds. Urban Microclimate Modelling for Comfort and Energy Studies. Cham: Springer International Publishing;2021:339-361. https://doi.org/10.1007/978-3-030-65421-4_16.
355. Reig-Gracia F, Vicente-Serrano, S.M , Dominguez-Castro F, Bedia-Jiménez J. Package 'ClimInd'. 2022. https://cran.r-project.org/web/packages/ClimInd/ClimInd.pdf. Accessed February 9, 2023.
356. Schweiker M. comf: An R Package for Thermal Comfort Studies. *R J* 2016; 8(2):341-351. https://doi.org/10.32614/RJ-2016-050.
357. Tartarini F, Schiavon S. pythermalcomfort: A Python package for thermal comfort research. *SoftwareX* 2020; 12:100578. https://doi.org/10.1016/j.softx.2020.100578.
358. Kampmann B, Bröde P, Fiala D. Physiological responses to temperature and humidity compared to the assessment by UTCI, WGBT and PHS. *Int J Biometeorol* 2012; 56(3):505-513. https://doi.org/10.1007/s00484-011-0410-0.
359. Pecelj M, Matzarakis A, Vujadinović M, Radovanović M, Vagić N, Đurić D, et al. Temporal Analysis of Urban-Suburban PET, mPET and UTCI Indices in Belgrade (Serbia). *Atmosphere* 2021; 12(7):916. https://www.mdpi.com/2073-4433/12/7/916.
360. Chen Y-C, Matzarakis A. Modified physiologically equivalent temperature—basics and applications for western European climate. *Theoretical and Applied Climatology* 2018; 132(3):1275-1289. https://doi.org/10.1007/s00704-017-2158-x.
361. Chen Y-C, Chen W-N, Chou CC-K, Matzarakis A. Concepts and New Implements for Modified Physiologically Equivalent Temperature. *Atmosphere* 2020; 11(7):694. https://www.mdpi.com/2073-4433/11/7/694.
362. Lee H, Mayer H. Validation of the mean radiant temperature simulated by the RayMan software in urban environments. *Int J Biometeorol* 2016; 60(11):1775-1785. https://doi.org/10.1007/s00484-016-1166-3.
363. Romanello M, Di Napoli C, Drummond P, Green C, Kennard H, Lampard P, et al. The 2022 report of the Lancet Countdown on health and climate change: health at the mercy of fossil fuels. *Lancet* 2022; 400(10363):1619-1654. https://doi.org/10.1016/S0140-6736(22)01540-9.
364. Adnan MSG, Dewan A, Botje D, Shahid S, Hassan QK. Vulnerability of Australia to heatwaves: A systematic review on influencing factors, impacts, and mitigation options. *Environ Res* 2022; 213:113703. https://doi.org/10.1016/j.envres.2022.113703.

365. Sadeghi M, Chaston T, Hanigan I, de Dear R, Santamouris M, Jalaludin B, et al. The health benefits of greening strategies to cool urban environments – A heat health impact method. *Build Environ* 2022; 207:108546. https://doi.org/10.1016/j.buildenv.2021.108546.
366. Pereira G, Bell ML, Honda Y, Lee J-T, Morawska L, Jalaludin B. Energy transitions, air quality and health. *Environ Res Lett* 2021; 16(2):020202. https://doi.org/10.1088/1748-9326/abdaea.
367. Nyadanu SD, Tessema GA, Mullins B, Pereira G. Maternal acute thermophysiological stress and stillbirth in Western Australia, 2000-2015: A space-time-stratified case-crossover analysis. *Sci Total Environ* 2022):155750. https://doi.org/10.1016/j.scitotenv.2022.155750.
368. Nyadanu SD, Tessema GA, Mullins B, Pereira G. Prenatal acute thermophysiological stress and spontaneous preterm birth in Western Australia, 2000-2015: A space-time-stratified case-crossover analysis. *Int J Hyg Environ Health* 2022; 245:114029. https://doi.org/10.1016/j.ijheh.2022.114029.
369. Lee V, Zermoglio F, Kristie L, Ebi KL. Heat waves and human health: emerging evidence and experience to inform risk management in a warming world. Chemonics International Inc. 1717 H Street NW Washington, DC 20006: United States Agency for International Development (USAID), Adaptation Thought Leadership and Assessments (ATLAS); 2019. https://www.climatelinks.org/sites/default/files/asset/document/2019_USAID-ATLAS_Heat-Waves-and-Human-Health.pdf. Accessed 9 September 2021. Accessed September 9, 2021.
370. Hughes L, Hanna E, Fenwick J. The Silent Killer: Climate Change and the Health Impacts of Extreme Heat Australia: Climate Council of Australia Ltd; 2016. https://www.climatecouncil.org.au/uploads/b6cd8665c633434e8d02910eee3ca87c.pdf. Accessed September 9, 2021.
371. van Wettere WHEJ, Kind KL, Gatford KL, Swinbourne AM, Leu ST, Hayman PT, et al. Review of the impact of heat stress on reproductive performance of sheep. *J Anim Sci Biotechnol* 2021; 12(1):26. https://doi.org/10.1186/s40104-020-00537-z.
372. Li S, Chen G, Jaakkola JJK, Williams G, Guo Y. Temporal change in the impacts of ambient temperature on preterm birth and stillbirth: Brisbane, 1994-2013. *Sci Total Environ* 2018; 634:579-585. https://doi.org/10.1016/j.scitotenv.2018.03.385.
373. Wang J, Tong S, Williams G, Pan X. Exposure to Heat Wave During Pregnancy and Adverse Birth Outcomes: An Exploration of Susceptible Windows. *Epidemiol* 2019; 30 Suppl 1:S115-s121. https://doi.org/10.1097/ede.0000000000000995.

374. Auger N, Fraser WD, Smargiassi A, Bilodeau-Bertrand M, Kosatsky T. Elevated outdoor temperatures and risk of stillbirth. *Int J Epidemiol* 2017; 46(1):200-208. https://doi.org/10.1093/ije/dyw077.
375. Rammah A, Whitworth KW, Han I, Chan W, Hess JW, Symanski E. Temperature, placental abruption and stillbirth. *Environ Int* 2019; 131:105067. https://doi.org/10.1016/j.envint.2019.105067.
376. Basu R, Sarovar V, Malig BJ. Association Between High Ambient Temperature and Risk of Stillbirth in California. *Am J Epidemiol* 2016; 183(10):894-901. https://doi.org/10.1093/aje/kwv295.
377. Maclure M. The Case-Crossover Design: A Method for Studying Transient Effects on the Risk of Acute Events. *Am J Epidemiol* 2017; 185(11):1174-1183. https://doi.org/10.1093/aje/kwx105.
378. Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiol* 2005; 16(6):717-726. https://doi.org/10.1097/01.ede.0000181315.18836.9d.
379. Lu P, Xia G, Zhao Q, Xu R, Li S, Guo Y. Temporal trends of the association between ambient temperature and hospitalisations for cardiovascular diseases in Queensland, Australia from 1995 to 2016: A time-stratified case-crossover study. *PLOS Med* 2020; 17(7):e1003176. https://doi.org/10.1371/journal.pmed.1003176.
380. Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B. Time series regression studies in environmental epidemiology. *Int J Epidemiol* 2013; 42(4):1187-1195. https://doi.org/10.1093/ije/dyt092.
381. Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, Schwartz J, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015; 386(9991):369-375. https://doi.org/10.1016/S0140-6736(14)62114-0.
382. Gebremedhin AT, Regan AK, Ball S, Betrán AP, Foo D, Gissler M, et al. Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study. *Ann Epidemiol* 2019; 39:33-38.e33. https://doi.org/10.1016/j.annepidem.2019.09.004.
383. Paternoster M, Perrino M, Travaglino A, Raffone A, Saccone G, Zullo F, et al. Parameters for estimating the time of death at perinatal autopsy of stillborn fetuses: a systematic review. *Int J Legal Med* 2019; 133(2):483-489. https://doi.org/10.1007/s00414-019-01999-1.
384. Gardosi J, Mul T, Mongelli M, Fagan D. Analysis of birthweight and gestational age in antepartum stillbirths. *BJOG* 1998; 105(5):524-530. https://doi.org/10.1111/j.1471-0528.1998.tb10153.x.

385. Genest DR, Singer DB. Estimating the time of death in stillborn fetuses: III. External fetal examination; a study of 86 stillborns. *Obstet Gynecol* 1992; 80(4):593-600.
386. Australian Institute of Health Welfare (AIHW). Stillbirths and neonatal deaths. Canberra: Department of Health, AIHW; 2021. https://www.aihw.gov.au/reports/mothers-babies/stillbirths-and-neonatal-deaths. Accessed February 17, 2022.
387. Hersbach H, Bell B, Berrisford P, Hirahara S, Horányi A, Muñoz-Sabater J, et al. The ERA5 global reanalysis. *Q J R Meteorol Soc* 2020; 146(730):1999-2049. https://doi.org/https://doi.org/10.1002/qj.3803.
388. Tredre BE. ASSESSMENT OF MEAN RADIANT TEMPERATURE IN INDOOR ENVIRONMENTS. *Br J Ind Med* 1965; 22(1):58-66. https://doi.org/10.1136/oem.22.1.58.
389. Di Napoli C, Hogan RJ, Pappenberger F. Mean radiant temperature from global-scale numerical weather prediction models. *Int J Biometeorol* 2020; 64(7):1233-1245. https://doi.org/10.1007/s00484-020-01900-5.
390. Basagaña X, Barrera-Gómez J. Reflection on modern methods: visualizing the effects of collinearity in distributed lag models. *Int J Epidemiol* 2021. https://doi.org/10.1093/ije/dyab179.
391. Al-Qaraghouli M, Fang YMV. Effect of Fetal Sex on Maternal and Obstetric Outcomes. *Front Pediatr* 2017; 5(144. https://doi.org/10.3389/fped.2017.00144.
392. Catalano R, Bruckner T, Smith KR. Ambient temperature predicts sex ratios and male longevity. *Proc Natl Acad Sci U S A* 2008; 105(6):2244-2247. https://doi.org/10.1073/pnas.0710711104.
393. Mondal D, Galloway TS, Bailey TC, Mathews F. Elevated risk of stillbirth in males: systematic review and meta-analysis of more than 30 million births. *BMC Med* 2014; 12:220. https://doi.org/10.1186/s12916-014-0220-4.
394. Arku RE, Adamkiewicz G, Vallarino J, Spengler JD, Levy DE. Seasonal variability in environmental tobacco smoke exposure in public housing developments. *Indoor Air* 2015; 25(1):13-20. https://doi.org/10.1111/ina.12121.
395. Ebi KL, Capon A, Berry P, Broderick C, de Dear R, Havenith G, et al. Hot weather and heat extremes: health risks. *Lancet* 2021; 398(10301):698-708. https://doi.org/10.1016/S0140-6736(21)01208-3.
396. Wang R, Yan W, Du M, Tao L, Liu J. The effect of influenza virus infection on pregnancy outcomes: A systematic review and meta-analysis of cohort studies. *Int J Infect Dis* 2021; 105:567-578. https://doi.org/10.1016/j.ijid.2021.02.095.
397. Hansen PJ. Effects of heat stress on mammalian reproduction. *Philos Trans R Soc Lond B Biol Sci* 2009; 364(1534):3341-3350. https://doi.org/10.1098/rstb.2009.0131.

398. Xu B, Lian S, Guo JR, Wang JF, Zhang LP, Li SZ, et al. Activation of the MAPK signaling pathway induces upregulation of pro-apoptotic proteins in the hippocampi of cold stressed adolescent mice. *Neurosci Lett* 2019; 699:97-102. https://doi.org/10.1016/j.neulet.2018.12.028.
399. Wells JC, Cole TJ. Birth weight and environmental heat load: a between-population analysis. *Am J Phys Anthropol* 2002; 119(3):276-282. https://doi.org/10.1002/ajpa.10137.
400. Buckley JP, Samet JM, Richardson DB. Commentary: Does air pollution confound studies of temperature? *Epidemiol* 2014; 25(2):242-245. https://doi.org/10.1097/ede.0000000000000051.
401. Reid CE, Snowden JM, Kontgis C, Tager IB. The role of ambient ozone in epidemiologic studies of heat-related mortality. *Environ Health Perspect* 2012; 120(12):1627-1630. https://doi.org/10.1289/ehp.1205251.
402. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019; 7(1):e37-e46. https://doi.org/10.1016/S2214-109X(18)30451-0.
403. Ferrero DM, Larson J, Jacobsson B, Di Renzo GC, Norman JE, Martin JN, Jr., et al. Cross-Country Individual Participant Analysis of 4.1 Million Singleton Births in 5 Countries with Very High Human Development Index Confirms Known Associations but Provides No Biologic Explanation for 2/3 of All Preterm Births. *PLoS One* 2016; 11(9):e0162506. https://doi.org/10.1371/journal.pone.0162506.
404. Cox B, Vicedo-Cabrera AM, Gasparrini A, Roels HA, Martens E, Vangronsveld J, et al. Ambient temperature as a trigger of preterm delivery in a temperate climate. *J Epidemiol Community Health* 2016; 70(12):1191. https://doi.org/10.1136/jech-2015-206384.
405. Mathew S, Mathur D, Chang AB, McDonald E, Singh GR, Nur D, et al. Examining the Effects of Ambient Temperature on Pre-Term Birth in Central Australia. *Int J Environ Res Public Health* 2017; 14(2. https://doi.org/10.3390/ijerph14020147.
406. Sun S, Weinberger KR, Spangler KR, Eliot MN, Braun JM, Wellenius GA. Ambient temperature and preterm birth: A retrospective study of 32 million US singleton births. *Environ Int* 2019; 126:7-13. https://doi.org/10.1016/j.envint.2019.02.023.
407. Liang Z, Lin Y, Ma Y, Zhang L, Zhang X, Li L, et al. The association between ambient temperature and preterm birth in Shenzhen, China: a distributed lag non-linear time series analysis. *Environ Health* 2016; 15(1):84. https://doi.org/10.1186/s12940-016-0166-4.
408. Yu X, Feric Z, Cordero JF, Meeker JD, Alshawabkeh A. Potential influence of temperature and precipitation on preterm birth rate in Puerto Rico. *Sci Rep* 2018; 8(1):16106. https://doi.org/10.1038/s41598-018-34179-z.

409. Lu P, Xia G, Zhao Q, Green D, Lim Y-H, Li S, et al. Attributable risks of hospitalizations for urologic diseases due to heat exposure in Queensland, Australia, 1995–2016. *Int J Epidemiol* 2021; 51(1):144-154. https://doi.org/10.1093/ije/dyab189.
410. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born Too Soon: The global epidemiology of 15 million preterm births. *Reprod Health* 2013; 10(1):S2. https://doi.org/10.1186/1742-4755-10-S1-S2.
411. Catalano R, Bruckner T, Avalos LA, Stewart H, Karasek D, Kariv S, et al. Understanding periviable birth: A microeconomic alternative to the dysregulation narrative. *Soc Sci Med* 2019; 233:281-284. https://doi.org/10.1016/j.socscimed.2017.12.014.
412. Wang J, Williams G, Guo Y, Pan X, Tong S. Maternal exposure to heatwave and preterm birth in Brisbane, Australia. *BJOG* 2013; 120(13):1631-1641. https://doi.org/10.1111/1471-0528.12397.
413. Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. *Am J Epidemiol* 2010; 172(10):1108-1117. https://doi.org/10.1093/aje/kwq170.
414. Newnham JP, White SW, Meharry S, Lee H-S, Pedretti MK, Arrese CA, et al. Reducing preterm birth by a statewide multifaceted program: an implementation study. *Am J Obstet Gynecol* 2017; 216(5):434-442. https://doi.org/10.1016/j.ajog.2016.11.1037.
415. He J-R, Liu Y, Xia X-Y, Ma W-J, Lin H-L, Kan H-D, et al. Ambient Temperature and the Risk of Preterm Birth in Guangzhou, China (2001-2011). *Environ Health Perspect* 2016; 124(7):1100-1106. https://doi.org/10.1289/ehp.1509778.
416. Vicedo-Cabrera AM, Olsson D, Forsberg B. Exposure to seasonal temperatures during the last month of gestation and the risk of preterm birth in Stockholm. *Int J Environ Res Public Health* 2015; 12(4):3962-3978. https://doi.org/10.3390/ijerph120403962.
417. Barreca A, Schaller J. The impact of high ambient temperatures on delivery timing and gestational lengths. *Nat Clim Chang* 2020; 10(1):77-82. https://doi.org/10.1038/s41558-019-0632-4.
418. Avalos LA, Chen H, Li DK, Basu R. The impact of high apparent temperature on spontaneous preterm delivery: a case-crossover study. *Environ Health* 2017; 16(1):5. https://doi.org/10.1186/s12940-017-0209-5.
419. Vilcins D, Baker P, Jagals P, Sly PD. The Association of Ambient Temperature with Extremely Preterm Births. *Matern Child Health J* 2021; 25(10):1638-1645. https://doi.org/10.1007/s10995-021-03203-6.
420. Di Renzo GC, Tosto V, Giardina I. The biological basis and prevention of preterm birth. *Best Pract Res Clin Obstet Gynaecol* 2018; 52:13-22. https://doi.org/10.1016/j.bpobgyn.2018.01.022.

421. Younger A, Alkon A, Harknett K, Jean Louis R, Thompson LM. Adverse birth outcomes associated with household air pollution from unclean cooking fuels in low- and middle-income countries: A systematic review. *Environ Res* 2022; 204(Pt C):112274. https://doi.org/10.1016/j.envres.2021.112274.
422. Kamai EM, McElrath TF, Ferguson KK. Fetal growth in environmental epidemiology: mechanisms, limitations, and a review of associations with biomarkers of non-persistent chemical exposures during pregnancy. *Environ Health* 2019; 18(1):43. https://doi.org/10.1186/s12940-019-0480-8.
423. Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. *PLoS One* 2017; 12(7):e0176331. https://doi.org/10.1371/journal.pone.0176331.
424. Roos N, Kovats S, Hajat S, Filippi V, Chersich M, Luchters S, et al. Maternal and newborn health risks of climate change: A call for awareness and global action. *Acta Obstet Gynecol Scand* 2021; 100(4):566-570. https://doi.org/10.1111/aogs.14124.
425. Mohammadi D, Naghshineh E, Sarsangi A, Zare Sakhvidi MJ. Environmental extreme temperature and daily preterm birth in Sabzevar, Iran: a time-series analysis. *Environ Health Prev Med* 2019; 24(1):5. https://doi.org/10.1186/s12199-018-0760-x.
426. Liu X, Xiao J, Sun X, Chen Q, Yao Z, Feng B, et al. Associations of maternal ambient temperature exposures during pregnancy with the risk of preterm birth and the effect modification of birth order during the new baby boom: A birth cohort study in Guangzhou, China. *Int J Hyg Environ Health* 2020; 225:113481. https://doi.org/10.1016/j.ijheh.2020.113481.
427. Guo T, Wang Y, Zhang H, Zhang Y, Zhao J, Wang Y, et al. The association between ambient temperature and the risk of preterm birth in China. *Sci Total Environ* 2018; 613-614:439-446. https://doi.org/10.1016/j.scitotenv.2017.09.104.
428. Zhou G, Yang M, Chai J, Sun R, Zhang J, Huang H, et al. Preconception ambient temperature and preterm birth: a time-series study in rural Henan, China. *Environ Sci Pollut Res* 2021; 28(8):9407-9416. https://doi.org/10.1007/s11356-020-11457-w.
429. Lian S, Guo J, Wang L, Li W, Wang J, Ji H, et al. Impact of prenatal cold stress on placental physiology, inflammatory response, and apoptosis in rats. *Oncotarget* 2017; 8(70):115304-115314. https://doi.org/10.18632/oncotarget.23257.
430. Huusko JM, Tiensuu H, Haapalainen AM, Pasanen A, Tissarinen P, Karjalainen MK, et al. Integrative genetic, genomic and transcriptomic analysis of heat shock protein and nuclear hormone

receptor gene associations with spontaneous preterm birth. *Sci Rep* 2021; 11(1):17115. https://doi.org/10.1038/s41598-021-96374-9.
431. Zhao W, Liu F, Marth CD, Green MP, Le HH, Leury BJ, et al. Maternal Heat Stress Alters Expression of Genes Associated with Nutrient Transport Activity and Metabolism in Female Placentae from Mid-Gestating Pigs. *Int J Mol Sci* 2021; 22(8. https://doi.org/10.3390/ijms22084147.
432. Urban A, Kyselý J. Comparison of UTCI with Other Thermal Indices in the Assessment of Heat and Cold Effects on Cardiovascular Mortality in the Czech Republic. *Int J Environ Res Public Health* 2014; 11(1):952-967. https://www.mdpi.com/1660-4601/11/1/952.
433. Romaszko J, Cymes I, Dragańska E, Kuchta R, Glińska-Lewczuk K. Mortality among the homeless: Causes and meteorological relationships. *PLoS One* 2017; 12(12):e0189938. https://doi.org/10.1371/journal.pone.0189938.
434. Santurtún A, Almendra R, Fdez-Arroyabe P, Sanchez-Lorenzo A, Royé D, Zarrabeitia MT, et al. Predictive value of three thermal comfort indices in low temperatures on cardiovascular morbidity in the Iberian peninsula. *Sci Total Environ* 2020; 729:138969. https://doi.org/10.1016/j.scitotenv.2020.138969.
435. Giudice LC. A Clarion Warning About Pregnancy Outcomes and the Climate Crisis. *JAMA Netw Open* 2020; 3(6):e208811. https://doi.org/10.1001/jamanetworkopen.2020.8811.
436. Kloog I, Novack L, Erez O, Just AC, Raz R. Associations between ambient air temperature, low birth weight and small for gestational age in term neonates in southern Israel. *Environ Health* 2018; 17(1):76. https://doi.org/10.1186/s12940-018-0420-z.
437. Hong YH, Lee JE. Large for Gestational Age and Obesity-Related Comorbidities. *J Obes Metab Syndr* 2021; 30(2):124-131. https://doi.org/10.7570/jomes20130.
438. Chen S, Yang L, Pu F, Lin H, Wang B, Liu J, et al. High Birth Weight Increases the Risk for Bone Tumor: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2015; 12(9):11178-11195. https://doi.org/10.3390/ijerph120911178.
439. Johnsson IW, Haglund B, Ahlsson F, Gustafsson J. A high birth weight is associated with increased risk of type 2 diabetes and obesity. *Pediatr Obes* 2015; 10(2):77-83. https://doi.org/10.1111/ijpo.230.
440. Bakhtsiyarava M, Ortigoza A, Sánchez BN, Braverman-Bronstein A, Kephart JL, Rodríguez López S, et al. Ambient temperature and term birthweight in Latin American cities. *Environ Int* 2022; 167:107412. https://doi.org/10.1016/j.envint.2022.107412.
441. Zare S, Hasheminejad N, Shirvan HE, Hemmatjo R, Sarebanzadeh K, Ahmadi S. Comparing Universal Thermal Climate Index (UTCI) with selected thermal indices/environmental parameters

during 12 months of the year. *Weather and Climate Extremes* 2018; 19:49-57. https://doi.org/10.1016/j.wace.2018.01.004.
442. Bonell A, Sonko B, Badjie J, Samateh T, Saidy T, Sosseh F, et al. Environmental heat stress on maternal physiology and fetal blood flow in pregnant subsistence farmers in The Gambia, west Africa: an observational cohort study. *Lancet Planet Health* 2022; 6(12):e968-e976. https://doi.org/10.1016/S2542-5196(22)00242-X.
443. ACOG. Fetal Growth Restriction: ACOG Practice Bulletin, Number 227. *Obstet Gynecol* 2021; 137(2):e16-e28. https://doi.org/10.1097/aog.0000000000004251.
444. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. *Am J Obstet Gynecol* 2012; 207(4):318.e311-316. https://doi.org/10.1016/j.ajog.2012.06.039.
445. Lawrence WR, Soim A, Zhang W, Lin Z, Lu Y, Lipton EA, et al. A population-based case–control study of the association between weather-related extreme heat events and low birthweight. *J Dev Orig Health Dis* 2021; 12(2):335-342. https://doi.org/10.1017/S2040174420000392.
446. Ramiro-Cortijo D, de la Calle M, Böger R, Hannemann J, Lüneburg N, López-Giménez MR, et al. Male fetal sex is associated with low maternal plasma anti-inflammatory cytokine profile in the first trimester of healthy pregnancies. *Cytokine* 2020; 136:155290. https://doi.org/10.1016/j.cyto.2020.155290.
447. Phuthong S, Reyes-Hernández CG, Rodríguez-Rodríguez P, Ramiro-Cortijo D, Gil-Ortega M, González-Blázquez R, et al. Sex Differences in Placental Protein Expression and Efficiency in a Rat Model of Fetal Programming Induced by Maternal Undernutrition. *Int J Mol Sci* 2021; 22(1):237. https://www.mdpi.com/1422-0067/22/1/237.
448. Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Belesova K, Boykoff M, et al. The 2019 report of The Lancet Countdown on health and climate change: ensuring that the health of a child born today is not defined by a changing climate. *Lancet* 2019; 394(10211):1836-1878. https://doi.org/10.1016/S0140-6736(19)32596-6.
449. Cadaret CN, Posont RJ, Beede KA, Riley HE, Loy JD, Yates DT. Maternal inflammation at midgestation impairs subsequent fetal myoblast function and skeletal muscle growth in rats, resulting in intrauterine growth restriction at term. *Transl Anim Sci* 2019; 3(2):txz037. https://doi.org/10.1093/tas/txz037.
450. Nyadanu SD, Tessema GA, Mullins B, Kumi-Boateng B, Ofosu AA, Pereira G. Prenatal exposure to long-term heat stress and stillbirth in Ghana: A within-space time-series analysis. *Environ Res* 2023; 222:115385. https://doi.org/10.1016/j.envres.2023.115385.

451. Ayinzat F, Ek B, D O, Jo A. Oxidative stress and its effects on reproductive performance in thermally-stressed ewes. *Int J Vet Sci Anim Husb* 2021; 6(4): 9-17. https://doi.org/10.22271/veterinary.2021.v6.i4a.361.
452. Asamoah B, Kjellstrom T, Östergren PO. Is ambient heat exposure levels associated with miscarriage or stillbirths in hot regions? A cross-sectional study using survey data from the Ghana Maternal Health Survey 2007. *Int J Biometeorol* 2018; 62(3):319-330. https://doi.org/10.1007/s00484-017-1402-5.
453. Perperoglou A, Sauerbrei W, Abrahamowicz M, Schmid M. A review of spline function procedures in R. *BMC Med Res Methodol* 2019; 19(1):46. https://doi.org/10.1186/s12874-019-0666-3.
454. Gronlund CJ, Yang AJ, Conlon KC, Bergmans RS, Le HQ, Batterman SA, et al. Time series analysis of total and direct associations between high temperatures and preterm births in Detroit, Michigan. *BMJ Open* 2020; 10(2):e032476. https://doi.org/10.1136/bmjopen-2019-032476.
455. Igelström E, Craig P, Lewsey J, Lynch J, Pearce A, Katikireddi SV. Causal inference and effect estimation using observational data. *J Epidemiol Community Health* 2022; 76(11):960. https://doi.org/10.1136/jech-2022-219267.
456. Weng YH, Yang CY, Chiu YW. Adverse neonatal outcomes in relation to ambient temperatures at birth: A nationwide survey in Taiwan. *Arch Environ Occup Health* 2018; 73(1):48-55. https://doi.org/10.1080/19338244.2017.1299084.
457. Spencer S, Samateh T, Wabnitz K, Mayhew S, Allen H, Bonell A. The Challenges of Working in the Heat Whilst Pregnant: Insights From Gambian Women Farmers in the Face of Climate Change. *Front Public Health* 2022; 10(https://doi.org/10.3389/fpubh.2022.785254.
458. Ashiagbor G, Ofori-Asenso R, Forkuo EK, Agyei-Frimpong S. Measures of geographic accessibility to health care in the Ashanti Region of Ghana. *Sci Afr* 2020; 9:e00453. https://doi.org/10.1016/j.sciaf.2020.e00453.
459. Lian S, Li W, Wang D, Xu B, Guo X, Yang H, et al. Effects of prenatal cold stress on maternal serum metabolomics in rats. *Life Sci* 2020; 246:117432. https://doi.org/10.1016/j.lfs.2020.117432.
460. Ebi KL, Boyer C, Ogden N, Paz S, Berry P, Campbell-Lendrum D, et al. Burning embers: synthesis of the health risks of climate change. *Environ Res Lett* 2021; 16(4):044042. https://doi.org/10.1088/1748-9326/abeadd.
461. Wei X, Huang Z, Jiang L, Li Y, Zhang X, Leng Y, et al. Charting the landscape of the environmental exposome. *iMeta* 2022; 1(4):e50. https://doi.org/10.1002/imt2.50.
462. McGee G, Wilson A, Webster TF, Coull BA. Bayesian multiple index models for environmental mixtures. *Biometrics* 2023; 79(1):462-474. https://doi.org/10.1111/biom.13569.

Every reasonable effort has been made to acknowledge the owners of copyright material. I would be pleased to hear from any copyright owner who has been omitted or incorrectly acknowledged.

Appendices

Appendix A: Supplementary materials for Chapter 3.

Table S3.1 Search strategy for each databases
I. PubMed

Set #	Advanced search within the title and abstract with the function ‘Title/Abstract’
1	"air pollut*"[Title/Abstract] OR "particulate matter*"[Title/Abstract] OR "carbon monoxide"[Title/Abstract] OR "sulfur dioxide"[Title/Abstract] OR "sulphur dioxide"[Title/Abstract] OR "nitrogen dioxide"[Title/Abstract] OR "nitrogen oxides"[Title/Abstract] OR "nitric oxide"[Title/Abstract] OR ozone[Title/Abstract] OR "gaseous pollut*"[Title/Abstract] OR "fine partic*"[Title/Abstract] OR "air qualit*"[Title/Abstract] OR "total suspended partic*"[Title/Abstract] OR "PM10"[Title/Abstract] OR "PM2.5"[Title/Abstract] OR "NO2"[Title/Abstract] OR "SO2"[Title/Abstract] OR "NOx"[Title/Abstract] OR "CO"[Title/Abstract] OR "O3"[Title/Abstract] OR "TSP"[Title/Abstract] OR "temperature*"[Title/Abstract] OR weather [Title/Abstract] OR heat*[Title/Abstract] OR cold*[Title/Abstract] OR climat*[Title/Abstract] OR "heat wave*"[Title/Abstract] OR heatwave*[Title/Abstract] OR "cold wave*"[Title/Abstract] OR coldwave*[Title/Abstract] OR "thermal stress"[Title/Abstract] ; Filters: English
2	"Pregnancy Outcome*"[Title/Abstract] OR "Birth Outcome*"[Title/Abstract] OR "Perinatal Outcome*"[Title/Abstract] OR "Obstetric Outcome*"[Title/Abstract] OR "Fetal Outcome*"[Title/Abstract] OR "Foetal Outcome*"[Title/Abstract] OR "Spontaneous Abortion"[Title/Abstract] OR "Premature Birth"[Title/Abstract] OR "Preterm Birth"[Title/Abstract] OR "Preterm Delivery"[Title/Abstract] OR "Premature Labo*"[Title/Abstract] OR Stillbirth[Title/Abstract] OR "Still birth"[Title/Abstract] OR "Fetal Death"[Title/Abstract] OR "Foetal Death"[Title/Abstract] OR "Pregnancy Loss"[Title/Abstract] OR Miscarriage[Title/Abstract] OR "Perinatal Death"[Title/Abstract] OR "Birth Weight"[Title/Abstract] OR "Birthweight"[Title/Abstract] OR "Fetal Weight"[Title/Abstract] OR "Foetal Weight"[Title/Abstract] OR "Fetal Growth"[Title/Abstract] OR "Foetal Growth"[Title/Abstract] OR "Gestational Age"[Title/Abstract] OR "Small-for-gestational age"[Title/Abstract] OR "intra-uterine growth retardation*"[Title/Abstract] OR "intrauterine growth retardation*"[Title/Abstract] OR "intrauterine growth restriction*"[Title/Abstract] OR "intra-uterine growth restriction*"[Title/Abstract] OR "PTB"[Title/Abstract] OR "PTD"[Title/Abstract] OR "LBW"[Title/Abstract] OR "TLBW"[Title/Abstract] OR "SGA"[Title/Abstract] OR "FGR"[Title/Abstract] OR "IUGR"[Title/Abstract] ; Filters-English
3	#1 AND #2
4	Review [Title/Abstract] OR "meta-analysis"[Title/Abstract]
5	#3 AND #4
6	#5 Filters applied, *English*, *Humans*

II. CINAHL

Search ID	Advanced search in the title and abstract with the function 'TI OR AB'
S1	TI ("air pollut*" OR "particulate matter*" OR "carbon monoxide" OR "sulfur dioxide" OR "sulphur dioxide" OR "nitrogen dioxide" OR "nitrogen oxides" OR "nitric oxide" OR ozone OR "gaseous pollut*" OR "fine partic*" OR "air qualit*" OR "total suspended partic*" OR "PM10" OR "PM2.5" OR "NO2" OR "SO2" OR "NOx" OR "CO" OR "O3" OR "TSP" OR "temperature*" OR weather OR heat* OR cold* OR climat* OR "heat wave*" OR heatwave* OR "cold wave*" OR coldwave* OR "thermal stress") OR AB ("air pollut*" OR "particulate matter*" OR "carbon monoxide" OR "sulfur dioxide" OR "sulphur dioxide" OR "nitrogen dioxide" OR "nitrogen oxides" OR "nitric oxide" OR ozone OR "gaseous pollut*" OR "fine partic*" OR "air qualit*" OR "total suspended partic*" OR "PM10" OR "PM2.5" OR "NO2" OR "SO2" OR "NOx" OR "CO" OR "O3" OR "TSP" OR "temperature*" OR weather OR heat* OR cold* OR climat* OR "heat wave*" OR heatwave* OR "cold wave*" OR coldwave* OR "thermal stress") ; Expanders - Apply equivalent subjects; Search modes - Boolean/Phrase
S2	TI ("Pregnancy Outcome*" OR "Birth Outcome*" OR "Perinatal Outcome*" OR "Obstetric Outcome*" OR "F#etal Outcome*" OR "Spontaneous Abortion" OR "Premature Birth" OR "Preterm Birth" OR "Preterm Delivery" OR "Premature Labo*" OR Stillbirth OR "Still birth" OR "F#etal Death" OR "Pregnancy Loss" OR Miscarriage OR "Perinatal Death" OR "Birth Weight" OR "Birthweight" OR "F#etal Weight" OR "F#etal Growth" OR "Gestational Age" OR "Small-for-gestational age" OR "intra-uterine growth retardation*" OR "intrauterine growth retardation*" OR "intrauterine growth restriction*" OR "intra-uterine growth restriction*" OR "PTB" OR "PTD" OR "LBW" OR "TLBW" OR "SGA" OR "FGR" OR "IUGR") OR AB ("Pregnancy Outcome*" OR "Birth Outcome*" OR "Perinatal Outcome*" OR "Obstetric Outcome*" OR "F#etal Outcome*" OR "Spontaneous Abortion" OR "Premature Birth" OR "Preterm Birth" OR "Preterm Delivery" OR "Premature Labo*" OR Stillbirth OR "Still birth" OR "F#etal Death" OR "Pregnancy Loss" OR Miscarriage OR "Perinatal Death" OR "Birth Weight" OR "Birthweight" OR "F#etal Weight" OR "F#etal Growth" OR "Gestational Age" OR "Small-for-gestational age" OR "intra-uterine growth retardation*" OR "intrauterine growth retardation*" OR "intrauterine growth restriction*" OR "intra-uterine growth restriction*" OR "PTB" OR "PTD" OR "LBW" OR "TLBW" OR "SGA" OR "FGR" OR "IUGR") ; Expanders – Apply equivalent subjects, Search modes – Boolean/Phrase
S3	S1 AND S2 Expanders – Apply equivalent subjects, Search modes – Boolean/Phrase
S4	TI ("review" OR "meta-analysis") OR AB ("review" OR "meta-analysis") Expanders – Apply equivalent subjects; Search modes – Boolean/Phrase
S5	S3 AND S4; Limiters – English Language; Human Expanders – Apply equivalent subjects; Search modes – Boolean/Phrase

III. Scopus

#	Advanced search in the title and abstract with the function ‘TITLE-ABS’
1	TITLE-ABS (“air pollut*” OR “particulate matter*” OR “carbon monoxide” OR “sulfur dioxide” OR “sulphur dioxide” OR “nitrogen dioxide” OR “nitrogen oxides” OR “nitric oxide” OR ozone OR “gaseous pollut*” OR “fine partic*” OR “air qualit*” OR “total suspended partic*” OR “PM10” OR “PM2.5” OR “NO2” OR “SO2” OR “NOx” OR “CO” OR “O3” OR “TSP” OR “temperature*” OR weather OR heat* OR cold* O R climat* OR “heat wave*” OR heatwave* OR “cold wave*” OR coldwave* OR “thermal stress”)
2	TITLE-ABS (“Pregnancy Outcome*” OR “Birth Outcome*” OR “Perinatal Outcome*” OR “Obstetric Outcome*” OR “F*etal Outcome*” OR “Spontaneous Abortion” OR “Premature Birth” OR “Preterm Birth” OR “Preterm Delivery” OR “Premature Labo*” OR Stillbirth OR “Still birth” OR “F*etal Death” OR “Pregnancy Loss” OR Miscarriage OR “Perinatal Death” OR “Birth Weight” OR “Birthweight” OR “F*etal Weight” OR “F*etal Growth” OR “Gestational Age” OR “Small-for-gestational age” OR “intra-uterine growth retardation*” OR “intrauterine growth retardation*” OR “intrauterine growth restriction*” OR “intra-uterine growth restriction*” OR “PTB” OR “PTD” OR “LBW” OR “TLBW” OR “SGA” OR “FGR” OR “IUGR”)
3	#1 AND # 2
4	TITLE-ABS (“review OR “meta-analysis”)
5	#3 AND #4 **AND** (LIMIT-TO (LANGUAGE,"English")) AND (LIMIT-TO (SRCTYPE,"j") OR LIMIT-TO (SRCTYPE,"d") OR LIMIT-TO (SRCTYPE,"Undefined")) AND (LIMIT-TO (DOCTYPE,"ar") OR LIMIT-TO (DOCTYPE,"Undefined"))

IV. MEDLINE (Ovid) and
V. EMBASE (Ovid)

#	Advanced search within the title and abstract with the function ‘.ti,ab’
1	("air pollut*" or "particulate matter*" or "carbon monoxide" or "sulfur dioxide" or "sulphur dioxide" or "nitrogen dioxide" or "nitrogen oxides" or "nitric oxide" or ozone or "gaseous pollut*" or "fine partic*" or "air qualit*" or "total suspended partic*" or "PM10" or "PM2.5" or "NO2" or "SO2" or "NOx" or "CO" or "O3" or "TSP" or "temperature*" or weather or heat* or cold* or "climat*" or "heat wave*" or heatwave* or "cold wave*" or coldwave* or "thermal stress").ti,ab
2	limit #1 to (english language and humans)
3	("Pregnancy Outcome*" or "Birth Outcome*" or "Perinatal Outcome*" or "Obstetric Outcome*" or "F?etal Outcome*" or "Spontaneous Abortion" or "Premature Birth" or "Preterm Birth" or "Preterm Delivery" or "Premature Labo*" or Stillbirth or "Still birth" or "F?etal Death" or "Pregnancy Loss" or Miscarriage or "Perinatal Death" or "Birth Weight" or "Birthweight" or "F?etal Weight" or "F?etal Growth" or "Gestational Age" or "Small-for-gestational age" or "intra-uterine growth retardation*" or "intrauterine growth retardation*" or "intrauterine growth restriction*" or "intra-uterine growth restriction*" or "PTB" or "PTD" or "LBW" or "TLBW" or "SGA" or "FGR" or "IUGR").ti,ab
4	limit #3 to (english language and humans)
5	#2 AND #4
6	("review" or "meta-analysis").ti,ab.
7	limit #6 to (english language and humans)
8	#5 AND #7

VI. Web of Science Core Collection

#	Advanced search within the title, abstract and keywords with the function 'TS'
1	(TS=("air pollut*" OR "particulate matter*" OR "carbon monoxide" OR "sulfur dioxide" OR "sulphur dioxide" OR "nitrogen dioxide" OR "nitrogen oxides" OR "nitric oxide" OR ozone OR "gaseous pollut*" OR "fine partic*" OR "air qualit*" OR "total suspended partic*" OR "PM10" OR "PM2.5" OR "NO2" OR "SO2" OR "NOx" OR "CO" OR "O3" OR "TSP" OR "temperature*" OR weather OR heat* OR cold* OR climat* OR "heat wave*" OR heatwave* OR "cold wave*" OR coldwave* OR "thermal stress")) ; *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
2	(TS=("Pregnancy Outcome*" OR "Birth Outcome*" OR "Perinatal Outcome*" OR "Obstetric Outcome*" OR "F$etal Outcome*" OR "Spontaneous Abortion" OR "Premature Birth" OR "Preterm Birth" OR "Preterm Delivery" OR "Premature Labo*" OR Stillbirth OR "Still birth" OR "F$etal Death" OR "Pregnancy Loss" OR Miscarriage OR "Perinatal Death" OR "Birth Weight" OR "Birthweight" OR "F$etal Weight" OR "F$etal Growth" OR "Gestational Age" OR "Small-for-gestational age" OR "intra-uterine growth retardation*" OR "intrauterine growth retardation*" OR "intrauterine growth restriction*" OR "intra-uterine growth restriction*" OR "PTB" OR "PTD" OR "LBW" OR "TLBW" OR "SGA" OR "FGR" OR "IUGR")) ; *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
3	(#1 AND #2); *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
4	(TS=("systematic review" OR "meta-analysis")) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*
5	#3 AND #4 *AND* **LANGUAGE:** (English) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*

VII. Cochrane Database of Systematic Reviews

#	Advanced search within the title, abstract and keywords with the function 'Title Abstract Keyword'
1	("air pollut*" OR "particulate matter*" OR "carbon monoxide" OR "sulfur dioxide" OR "sulphur dioxide" OR "nitrogen dioxide" OR "nitrogen oxides" OR "nitric oxide" OR ozone OR "gaseous pollut*" OR "fine partic*" OR "air qualit*" OR "total suspended partic*" OR "PM10" OR "PM2.5" OR "NO2" OR "SO2" OR "NOx" OR "CO" OR "O3" OR "TSP" OR "temperature*" OR weather OR heat* OR cold* OR climat* OR "heat wave*" OR heatwave* OR "cold wave*" OR coldwave* OR "thermal stress") in Title Abstract Keyword - (Word variations have been searched)
2	("Pregnancy Outcome*" OR "Birth Outcome*" OR "Perinatal Outcome*" OR "Obstetric Outcome*" OR "Fetal Outcome*" OR "Foetal Outcome*" OR "Spontaneous Abortion" OR "Premature Birth" OR "Preterm Birth" OR "Preterm Delivery" OR "Premature Labo*" OR Stillbirth OR "Still birth" OR "Fetal Death" OR "Pregnancy Loss" OR Miscarriage OR "Perinatal Death" OR "Birth Weight" OR "Birthweight" OR "Fetal Weight" OR "Foetal Weight" OR "Fetal Growth" OR "Foetal Growth" OR "Gestational Age" OR "Small-for-gestational age" OR "intra-uterine growth retardation*" OR "intrauterine growth retardation*" OR "intrauterine growth restriction*" OR "intra-uterine growth restriction*" OR "PTB" OR "PTD" OR "LBW" OR "TLBW" OR "SGA" OR "FGR" OR "IUGR") in Title Abstract Keyword - (Word variations have been searched)
3	1 AND 2 in Title Abstract Keyword - in Cochrane Reviews (Word variations have been searched)

VIII. Joanna Briggs Institute EBP Database (Ovid)

#	Advanced search within the title and abstract with the function '.ti,ab.'
1	("air pollut*" or "particulate matter*" or "carbon monoxide" or "sulfur dioxide" or "sulphur dioxide" or "nitrogen dioxide" or "nitrogen oxides" or "nitric oxide" or ozone or "gaseous pollut*" or "fine partic*" or "air qualit*" or "total suspended partic*" or "PM10" or "PM2.5" or "NO2" or "SO2" or "NOx" or "CO" or "O3" or "TSP" or "temperature*" or weather or heat* or cold* or "climat*" or "heat wave*" or heatwave* or "cold wave*" or coldwave* or "thermal stress").ti,ab
2	("Pregnancy Outcome*" or "Birth Outcome*" or "Perinatal Outcome*" or "Obstetric Outcome*" or "F?etal Outcome*" or "Spontaneous Abortion" or "Premature Birth" or "Preterm Birth" or "Preterm Delivery" or "Premature Labo*" or Stillbirth or "Still birth" or "F?etal Death" or "Pregnancy Loss" or Miscarriage or "Perinatal Death" or "Birth Weight" or "Birthweight" or "F?etal Weight" or "F?etal Growth" or "Gestational Age" or "Small-for-gestational age" or "intra-uterine growth retardation*" or "intrauterine growth retardation*" or "intrauterine growth restriction*" or "intra-uterine growth restriction*" or "PTB" or "PTD" or "LBW" or "TLBW" or "SGA" or "FGR" or "IUGR").ti,ab.
3	#1 AND #2

IX. Epistemonikos Database (www.epistemonikos.org/)

#	Advanced search within the title and abstract with the function 'Title/Abstract'
1	Title/Abstract ("air pollut*" OR "particulate matter*" OR "carbon monoxide" OR "sulfur dioxide" OR "sulphur dioxide" OR "nitrogen dioxide" OR "nitrogen oxides" OR "nitric oxide" OR ozone OR "gaseous pollut*" OR "fine partic*" OR "air qualit*" OR "total suspended partic*" OR "PM10" OR "PM2.5" OR "NO2" OR "SO2" OR "NOx" OR "CO" OR "O3" OR "TSP" OR "temperature*" OR weather OR heat* OR cold* OR climat* OR "heat wave*" OR heatwave* OR "cold wave*" OR coldwave* OR "thermal stress")
2	Title/Abstract ("Pregnancy Outcome*" OR "Birth Outcome*" OR "Perinatal Outcome*" OR "Obstetric Outcome*" OR "Fetal Outcome*" OR "Foetal Outcome*" OR "Spontaneous Abortion" OR "Premature Birth" OR "Preterm Birth" OR "Preterm Delivery" OR "Premature Labo*" OR Stillbirth OR "Still birth" OR "Fetal Death" OR "Foetal Death" OR "Pregnancy Loss" OR Miscarriage OR "Perinatal Death" OR "Birth Weight" OR "Birthweight" OR "Fetal Weight" OR "Foetal Weight" OR "Fetal Growth" OR "Foetal Growth" OR "Gestational Age" OR "Small-for-gestational age" OR "intra-uterine growth retardation*" OR "intrauterine growth retardation*" OR "intrauterine growth restriction*" OR "intra-uterine growth restriction*" OR "PTB" OR "PTD" OR "LBW" OR "TLBW" OR "SGA" OR "FGR" OR "IUGR")
3	#1 AND #2; Publication type: systematic review

X. Grey literature sources and search strategy

Grey literature	Search straetgy
i. Google Scholar (first 200 hits) 21/10/2020	“air quality”|“air pollution”|“particulate matter”|“gaseous pollutants”|“total suspended particle”|“carbon monoxide”|“sulfur dioxide”|“sulphur dioxide”|“nitrogen dioxide”|“nitrogen oxides”|“nitricoxide”|ozone|temperature|weather|heat|cold|“climate change”|heatwave|coldwave|“thermal stress”|PM10|PM2.5|NO2|SO2|NOx|CO|O3|TSP AND (“Pregnancy outcomes”|“Birth Outcomes”|“Perinatal Outcomes”|“Obstetric Outcomes”|“Fetal Outcomes”|“Foetal Outcomes”|“Spontaneous Abortion”|“Premature Birth”|“Preterm Birth”|“Preterm Delivery”|“Premature Labor”|“spontaneous labour”|Stillbirth|“Still birth”|“Fetal Death”|“Foetal Death”|“Pregnancy Loss”|Miscarriage|“Perinatal Death”|“Birth Weight”|Birthweight|“Fetal Weight”|“Foetal Weight”|“Fetal Growth”|“Foetal Growth”|“Gestational Age”|“Small-for-gestational age”|“intra-uterine growth retardation”|“intrauterine growth retardation”|“intrauterine growth restriction”|“intra-uterine growth restriction”|PTB|PTD|LBW|TLBW|SGA|FGR|IUGR AND review|meta-analysis
ii. Google.com (screened first 200 hits where available) 21-22/10/2020	The following phrases were used: 1. systematic review and meta-analysis of air pollution and pregnancy and birth outcomes 2. systematic review and meta-analysis of air pollution and preterm birth 3. systematic review and meta-analysis of air pollution and low birth weight 4. systematic review and meta-analysis of air pollution and pregnancy loss, still birth, spontaneous abortion and miscarriage 5. systematic review and meta-analysis of air pollution and small for gestational age 6. systematic review and meta-analysis of climate change, temperature, heat and cold waves and pregnancy and birth outcomes 7. systematic review and meta-analysis of climate change, temperature, heat and cold waves and low birth weight 8. systematic review and meta-analysis of climate change, temperature, heat and cold waves and pregnancy loss, still birth, spontaneous abortion and miscarriage
iii. OpenGrey 24/10/2020	(“air pollut*” OR “particulate matter*” OR “carbon monoxide” OR “sulfur dioxide” OR “sulphur dioxide” OR “nitrogen dioxide” OR “nitrogen oxides” OR “nitric oxide” OR ozone OR “gaseous pollut*” OR “fine partic*” OR “air qualit*” OR “total suspended partic*” OR “PM10” OR “PM2.5” OR “NO2” OR “SO2” OR “NOx” OR “CO” OR “O3” OR “TSP” OR “temperature*” OR weather* OR heat* OR cold* OR “climat*” OR “heat wave*” OR heatwave* OR “cold wave*” OR coldwave* OR “thermal stress”) AND (“Pregnancy Outcome*” OR “Birth Outcome*” OR “Perinatal Outcome*” OR “Obstetric Outcome*” OR “F?etal Outcome*” OR “Spontaneous Abortion” OR “Premature Birth” OR “Preterm Birth” OR “Preterm Delivery” OR “Premature Labo*” OR Stillbirth OR “Still birth” OR “F?etal Death” OR “Pregnancy Loss” OR “Miscarriage” OR “Perinatal Death” OR “Birth Weight” OR “Birthweight” OR “F?etal Weight” OR “F?etal Growth” OR “Gestational Age” OR “Small-for-gestational age” OR “intra-uterine growth retardation*” OR “intrauterine growth retardation*” OR “intrauterine growth restriction*” OR “intra-uterine growth restriction*” OR “PTB” OR “PTD” OR “LBW” OR “TLBW” OR “SGA” OR “FGR” OR “IUGR”) AND (review OR meta-analysis)
iv. WorldWideScience.org 24/10/2020	Title: (“air pollut*” OR “particulate matter*” OR “carbon monoxide” OR “sulfur dioxide” OR “sulphur dioxide” OR “nitrogen dioxide” OR “nitrogen oxides” OR “nitric oxide” OR ozone OR “gaseous pollut*” OR “fine partic*” OR “air qualit*” OR “total suspended partic*” OR “PM10” OR “PM2.5” OR “NO2” OR “SO2” OR “NOx” OR “CO” OR “O3” OR “TSP” OR temperature* OR weather* OR heat* OR cold* OR climat* OR “heat wave*” OR heatwave* OR “cold wave*” OR coldwave* OR “thermal stress”) AND (“Pregnancy Outcome*” OR “Birth Outcome*” OR “Perinatal Outcome*” OR “Obstetric

	Outcome*" OR "F*etal Outcome*" OR "Spontaneous Abortion" OR "Premature Birth" OR "Preterm Birth" OR "Preterm Delivery" OR "Premature Labo*" OR Stillbirth OR "Still birth" OR "F*etal Death" OR "Pregnancy Loss" OR "Miscarriage" OR "Perinatal Death" OR "Birth Weight" OR "Birthweight" OR "F*etal Weight" OR "F*etal Growth" OR "Gestational Age" OR "Small-for-gestational age" OR "intra-uterine growth retardation*" OR "intrauterine growth retardation*" OR "intrauterine growth restriction*" OR "intra-uterine growth restriction*" OR "PTB" OR "PTD" OR "LBW" OR "TLBW" OR "SGA" OR "FGR" OR "IUGR") AND (review OR meta-analysis); Filters; English language
v. World Health Organisation Global Health Medicus databases 24/10/2020	'Title, abstract, subject' search (tw:(air pollut* OR particulate matter* OR "carbon monoxide" OR "sulfur dioxide" OR "sulphur dioxide" OR "nitrogen dioxide" OR "nitrogen oxides" OR "nitric oxide" OR ozone OR gaseous pollut* OR fine partic* OR air qualit* OR total suspended partic* OR "PM10" OR "PM2.5" OR "NO2" OR "SO2" OR "NOx" OR "CO" OR "O3" OR "TSP" OR temperature* OR weather* OR heat* OR cold* OR climat* OR heat wave* OR heatwave* OR cold wave* OR coldwave* OR "thermal stress")) AND (tw:(Pregnancy Outcome* OR "Birth Outcome* OR Perinatal Outcome* OR Obstetric Outcome* OR F*etal Outcome* OR "Spontaneous Abortion" OR "Premature Birth" OR "Preterm Birth" OR "Preterm Delivery" OR Premature Labo* OR Stillbirth OR "Still birth" OR F*etal Death OR "Pregnancy Loss" OR "Miscarriage" OR "Perinatal Death" OR "Birth Weight" OR "Birthweight" OR F*etal Weight OR F*etal Growth OR "Gestational Age" OR "Small-for-gestational age" OR "intra-uterine growth retardation* OR intrauterine growth retardation* OR intrauterine growth restriction* OR intra-uterine growth restriction* OR "PTB" OR "PTD" OR "LBW" OR "TLBW" OR "SGA" OR "FGR" OR "IUGR")) AND (tw:(review OR meta-analysis))

Table S3.2 Lists of articles excluded after full-text screening stage with reasons per pre-specified eligibility criteria.

S/N	Article excluded	Reason(s)
1	Zhu et al, 2017	Full text in Chinese language
2	Feng et al 2017	Full text in Chinese language
3	de Toledo et al 2011	Full text in Portuguese language
4	Guo et al 2019	Retracted (Doi: 10.1631/jzus.B18r0122)
5	Nieuwenhuijsen et al, 2013	Summary of meta-analysis
6	Vrijheid et al 2016	A broad summary of the literature on systematic reviews and/or meta-analyses published between 2010 to 2015
7	Backes et al 2013	General literature review (not systematic review). No method section, no in/exclusion criteria, no specification of search terms and database searched.
8	Deepak et al 2016	General literature review (not systematic review). No method section, no in/exclusion criteria, no specification of search terms and database searched.
9	Heinrich et al 2007	General literature review (not systematic review). No method section, no in/exclusion criteria, no specification of search terms and databases searched.
10	Huang et al 2019	Unrelated outcomes of interest
11	Kloog 2019	General literature review (not systematic review). No method section, no in/exclusion criteria, no specification of search terms and database searched.
12	Koranteng et al 2007	Included only one related primary study
13	Lai 2013	Insufficient related studies of interest and lack required details on included studies.
14	Li et al 2019	General literature review, not systematic review
15	Maisonet et al 2004	Very scanty method without any clearly specified search strategy with search terms used for the literature search apart from the indication “We identified articles through Medline searches, bibliographies of individual articles, and reviews of scientific journals from 1966 through December 2001.”
16	Melody et al, 2019	Not exposure measurement of interest
17	Morakinyo et al 2016	Not outcomes of interest
18	Nandasena et al 2010	Not outcomes of interest
19	Proietti et al 2013	General literature review, not systematic review.
20	Stillerman et al 2008	General literature review, not a systematic review
21	Tan et al 2017	General literature review, not a systematic review
22	Triche et al 2007	General literature review, not a systematic review
23	Wang et al 2007	General literature review, not a systematic review
24	Windham et al 2008	General literature review, not a systematic review
25	Zheng et al 2016	General literature review, not a systematic review
26	Klepac et al, 2018	Study-specific details of the included studies (e.g., study design, sample size, effect estimates, location etc.) were not provided.

27	Ma et al 2020	Exposure-outcome of interest was not primary focus of the review but included 4 studies without any details on the included studies.
28	Srám et al 2005	Lack some of the required key details on the included primary studies: participants/sample size and the effect estimate (but provided effect estimates for only significant increased risks while providing 'NE, no effect' without the effect estimates for other results).
29	Vieira et al 2015	Exposure-outcome of interest was not the primary outcome of but included few related studies without required details on the included primary studies.
30	Khader et al 2016	Included 3 primary studies but lack exposure-outcome effect estimates for each listed criteria air pollutant.
31	Porpora et al, 2019	Included less than 3 primary studies on the exposure-outcome and with no details on included studies.
32	Lee et al 2020	General literature review (not systematic review) and summarised existing meta-analyse
33	Yu et al 2016	Full text in Chinese language
34	Polichetti et al 2013	General literature review with no in/exclusion criteria. Also, provided only yes/no for exposure-outcome association without any other results, information or details on the included primary studies.
35*	Steinle et al 2020	Overview of meta-analysis on particulate matter, birth weight and health through the life course
36	Gómez-Roig et al 2021	General literature review, not a systematic review
37	Ekland et al 2021	No details on included studies as systematic review and meta-analysis was not the main objective
38	Eeden et al 2021	General literature review, not a systematic review
39	Pereira, 2022	No systematic literature search, was a re-analysis of some studies included in Ju et al (2021).
40	Whaibeh et al 2022	General literature review, not a systematic review

*35-40 were from the prospective literature search and the updates.

Table S3.3 Additional information on systematic reviews without meta-analysis, ordered from recent to earliest.

First author, date [number of authors, countries]	**Exposure(s)**	**Outcome(s)**	**Summary of results**	**Researchers' recommendations**	**Researchers' stated strengths and limitations**
1. Edwards [1] 12/10/2021 [4; 3 UK and 1 Nepal]	$PM_{2.5}$, PM_{10}, NO_2, SO_2 Ranges: NA	LBW, SGA, PTB	'No clear evidence of difference in the air pollution-pregnancy outcome relationship of those who did and did not move during pregnancy'. 'Three studies of relocation during pregnancy provided limited evidence to conclude an effect of relocation-related change in exposure on pregnancy outcome.'	'There would be value in expanding air pollution research that capitalizes on the advantages of relocation studies, but attention is needed to improve potential bias and confounder control in studies examining the effects of short-term relocations to environments of different air pollution levels.'	Strength This is the first literature review of the health effects of people who relocate from one environment to another of differing air pollution levels. Limitations 'Ambient pollutant levels were reported for the patients' entire pregnancies but pollutant levels before and after relocation were not explicitly reported in these studies.' 'The literature of relocation studies for studying the health effects of air pollution effects remains limited and very heterogenous in design and quality.'
2. Walter, 2021[2] 08/06/2021 [6; all Australia]	PM2.5,PM10,NO2,SO2,O3,CO	LBW, BW, SGA, PTB	'While some evidence indicated adverse birth outcomes, such as pre-term birth, and reduced intra-uterine growth, overall the birth outcomes were heterogeneous and it was not possible to draw firm conclusions.'	'There are apparent differences in the magnitude and range of health impacts across different pollutant sources, which may be beneficial in formulating preventative strategies aimed at reducing the health burden of outdoor air pollution in Australia.' 'Further research is required to characterise better the range of neo-natal	**Strength** 'The screening of each database, study selection and quality assessment of studies was independently undertaken by two authors'. 'All included studies controlled for some potential confounders'. **Limitations**

				impacts and identify specific exposure windows of heightened risk within the pregnancy.'	'Over two thirds of the studies included in this review used fixed site monitors, and noted the limitations in capturing spatial variability of population exposure.' 'The included studies ranged in design and size, with one quarter being cohort design and of modest size by international comparison. The exclusion of proxy exposure measurements and subjective health measurements, such as questionnaires, resulted in the omission of several otherwise well conducted studies that were relevant to the remit of our review.'
3. Luo [3] 09/03/2021 [6; 5 China, 1 UK]	$PM_{2.5}$, PM_{10}, NO_2, NO_x,	PTB, BW, LBW, SGA	**Note:** Specific exposure-outcome with exposure periods not done for this review because the review article reported only key results of the included studies. Indicated below are key findings highlighted in the review. **PTB-NO_2** "A total of 16 studies explored the relationship between NO_2 and PTB. Only five studies obtained statistically significant results, and the rest studies did not find a significant association between prenatal exposure to NO_2 and PTB. Overall, the results are inconclusive." **SGA-NO_2** "Twelve studies explored the relationship between NO2 exposure and SGA. Only four studies found statistical significance results. No significant association between NO_2	From conclusion: "It is recommended that future studies should apply LUR models for individual exposure evaluation in China to better characterize the relationship between air pollution and adverse pregnancy outcomes." From abstract: "In addition, further research is required given that a lot of the associations looked at in the review were inconclusive"	Not reported

			exposure and SGA was found in the rest studies. It is apparent that conclusions are inconsistent.” **LBW/BW-NO_2** “Twenty-four studies explored the relationship between NO_2 and birth weight.” Four studies “found that NO_2 exposure during pregnancy was associated with reduced birth weight (β range from -5.2 to - 43.6 g). Three studies found increased risk of term LBW. “However, two studies found exposure to NO_2 was associated with increased birth weight. “No substantive effects of NO_2 exposure on birth weight were evident in the rest of the studies. Overall, there is considerable heterogeneity in the effects of NO_2 exposure on birth weight, and therefore, results are inconclusive. “ **PTB-PM2.5** “Among seven studies investigating the link between PM2.5 and PTB, only one study showed a statistically significant result. Overall, PM2.5 exposure during pregnancy is not associated with PTB.” **SGA-PM2.5** “Six studies investigated the relationship between PM2.5 exposure during pregnancy and SGA, out of which three studies found that PM2.5 exposure was associated with an increased risk of SGA.” In the other three studies, no significant association between PM2.5 and SGA was found. Results on association between exposure to PM2.5 during pregnancy and SGA were not consistent.” **BW/LBW-PM2.5** **“**Seventeen studies explored the relationship between PM2.5		

			and birth weight. Eight of the 17 studies found that PM2.5 exposure during pregnancy was associated with reduced birth weight.**”** **“**In addition, four studies concluded that PM2.5 exposure increased the risk of TLBW.” **“**The rest of studies did not reach statistically significant conclusions. In general, the results show that PM2.5 exposure during pregnancy is associated with a decrease in birth weight**”** **BW-NOx :** “Six studies investigated the effect of NOx exposure on birth weight, however results were inconsistent.” **“**The inconsistency of results shows that the relationship between NOx and birth weight is not well established. The effect of exposure to NOx on other pregnancy outcomes has been studied. Given the limited number of studies and mixed results, it is impossible to reach conclusions regarding the relationship between NOx exposure and adverse pregnancy outcomes.**”**		
4. Bekkar [4] 18/06/2020 [4, all USA]	$PM_{2.5}$, O_3	PTB, LBW, and SB	**PTB** **PM2.5**: (24 studies; 18 cohorts, 2 each time series, case-control and cross-sectional; 9,286,285 births). 16 reports on the whole pregnancy: 12 found significant increased risks, 3 non-significant increased risk and 1 with no association. 7 reports on 1st trimester; 5 found significant increased risks, 1 non-significant increased risk and 1 with no association. 8 reports on 2nd trimester; 6 found significant increased risks, 1 non-significant increased risk and 1 with no association. 6 reports on 3rd trimester; 2 found significant increased risks, 2 non-significant increased risk, 1 non-significant decreased risk, and 1 with no association. **O3:** (6 studies; 4 cohorts, 1each for case-control and cross-sectional; 1,868,257 births) 4 reports on the whole pregnancy period; 3 were significant increased risks and 1 no association. 2 reports on 2nd trimester; 1 each found significant increased risk and no association.	The medical community at large and women’s health clinicians in particular should take note of the emerging data and become facile in both communicating these risks with patients and integrating them into plans for care. Moreover, physicians can adopt a more active role as patient advocates to educate elected officials entrusted with public policy and insist on effective action to stop the climate crisis.	**Strengths:** The considerable sample size and the wide geographic range that includes every region of the US domestic population; focus on the US population makes the findings particularly relevant to pregnant women and health care clinicians in the US; the merit of tabulating the overall preponderance of observations from varying studies examining the same outcomes where pooled analysis across studies is not feasible. Limitations: this review covers only observational studies with

			2 reports on 3rd trimester; 1 each found significant increased risk and no association. 1 report on 3rd trimester with no association. Varied weekly and week ranges of exposure periods reported with significant increased risks in early and late gestational weeks. **LBW** **PM2.5:** (17 studies; 15 cohorts and 1 each cross-sectional and case control; 11,729,145 births). 14 reports for entire pregnancy: 10 found significant increased risks and 4 non-significant increased risk. 4 for 1st trimester: 1 found significant increased risks and 3 non-significant increased risk 5 for 2nd trimester: 3 found significant increased risks and 2 non-significant increased risk 5 for 3rd trimester: 3 found significant increased risks and 2 non-significant increased risk **O3**: 8 studies (7 cohorts and 1 cross-sectional; 3,703,824 births). The cross-sectional study (222,259 births) examined and found significant increased risk of VLBW during birth month. 5 studies for whole pregnancy: 3 found significant increased risks and 2 non-significant increased risk 2 for 1st trimester: both found non-significant increased risk 3 for 2nd trimester: 2 found non-significant increased risk and 1 found significant decreased risk (protective effect). 1 for 3rd trimester and found non-significant increased risk **BW reduction** **PM2.5**: 12 studies (11 cohorts, 1 time series; 7,339,714 births). 11 studies for entire pregnancy: 8 found significant increased risks and 3 non-significant increased risk 3 for 1st trimester: all found significant increased risks. 3 for 2nd trimester: all found significant increased risks. 4 for 3rd trimester: all found significant increased risks. **O3**; 4 cohort studies (4,463,021 births). 3 studies for entire pregnancy: all found significant increased risks.		heterogeneous sources of air pollution and heat exposure as well as diverse methods of measurement; different study designs may complicate direct comparison of the data even within a single study; limited number of studies on stillbirth.

			SGA (and FGR) **PM2.5**: 3 cohort studies (479, 889 births) of which one of them (122,203 births from Utah) examined FGR separately in addition to SGA. 1 study (122,203 births) reported for entire pregnancy and found non-significant for SGA and significant increased risks for FGR. 2 studies for 1st trimester: both found non-significant increased risks for SGA and 1 found significant increased risk for FGR. 1 study for 2nd trimester; found non-significant decreased risk for SGA and increased risk for FGR. 1 study for 3rd trimesters: significant for SGA but insignificant (for FGR) increased risks. **O3**: 4 cohort studies (644,794 births) of which one of them (122,203 births from Utah) examined FGR separately in addition to SGA. One study reported and found significant decreased risk (protective effect) for SGA and FGR for entire pregnancy. 1 study reported for entire pregnancy and found significant decreased risk (protective effect) for both SGA and FGR. 2 for 1st trimester for SGA with non-significant increased and decreased risks. The only study for FGR found significant decreased risk. 1 study for 2nd trimester; non-significant decreased risk for SGA and significant decreased risk for FGR. 3 for 3rd trimester; 2 significant increased and 1 significant decreased risk for SGA. The only study for FGR found significant decreased risk. Three months pre-conception pollutant exposures were reported for one study (122,203 births from Utah, USA) found with significant increased risks for SGA/FGR. **Stillbirth** **PM2.5**: (5 studies; 4 cohorts and 1 nested case-control; 5,014,874 births). 4 reported for entire pregnancy; 1 found significant increased risk and 3 found non-significant increased risk. 1 reported for 1st, 2nd, and 3rd trimester with non-significant increased risk for 1st and 2nd , and significant increased risk for 3rd.		

			I study reported and found non-significant risk for 2 days before delivery. **O3**: 3 studies (2 cohorts and one nested case-control; 4,410,761 births). 2 reported for entire pregnancy; 1 each found significant and non-significant increased risks. 1 reported and found significant increased risk for 3rd trimester. 1 also found significant increased risk for the week before delivery. 'Specifically, significant PM2.5 and/or ozone association with PTB in 19/24 (79%) studies (all of these studies included PM2.5 and 7 also included ozone), from birth per study of mean (standard deviation) as 318 960 (393 272) with total births of 7.3 million; increased risk of median (range)% of 11.5 (2.0-19.0) for 11 studies on PM2.5. Significant ozone-PTB association in 2/4 (50%) studies for an increased risk from 3% to 9.6%; each measured the association by IQR, from 7.1 to 11.53 parts per billion (ppb) PM2.5 and/or ozone association with LBW was significant in 25/29 (86%) studies (all studies except 1 included PM2.5; 11 analyzed ozone in which 10 combined with PM2.5), from birth per study of mean (standard deviation) as 661 205 (878 074) with total births of 18.5 million, median (range) of 10.8 (2.0-36.0) for 8 studies on PM2.5 and 5/8 (62%) studies detected association of IQR increases which ranged from 2.0 to 6.9 μg/m3. Three studies found association between ozone and LBW. PM2.5 and/or ozone association with SB was significant in 4/5 (80%) studies from birth per study of 1 020 975 (1 176 174) with total births of 5.1 million, median (range)% of 14.5 (6.0-23.0) for PM2.5.'		
5. Heo [5] 12/11/2019 [3; All USA]	PM_{10}, $PM_{2.5}$ ($PM_{2.5-10}$, PM_1, $PM_{0.1}$)	PTB, LBW, SGA, and SB	**Effects modification by race/ethnicity**: **PM-LBW**: Among 14 studies that focused on LBW and maternal race/ethnicity, 9 studies reported statistically significant risks with higher risk for infants of African American/black mothers compared to others. Two other studies found that risks for PM exposure (separately by	We suggest that more studies are required to understand potential effect modification of the risk of SGA and stillbirth due to maternal exposure to PM during pregnancy. Future studies are also needed for	**Limitations** Limitations of our study include the small number of relevant studies and geographically limited estimates for effect modification of the relationship between air

			racial/ethnic subgroups) were non- significant but higher in African American/ blacks. ***Suggestive evidence*** *that PM exposure risks for LBW are higher in infants of African-American/black mothers than in other racial/ethnical groups.* **PM-PTB** (18 studies): Among 17 studies based on PTB and race/ethnicity, 5 studies found statistically significant risks of PM exposure, with estimated risks generally higher for African American/blacks, whereas 1 study showed significant and higher risk for infants of white mothers. 5 other studies presented different magnitude of the risks but not statistically significant to clearly state the evidence of effect modification. The other 6 studies reported no significant evidence of effect modification of PTB by race/ethnicity. ***Suggestive evidence*** *that PM exposure risks for PTB are higher in infants of African-American/black mothers than in other racial/ethnical groups*. **PM-SGA (8 studies):** among the 8 studies based on SGA and race/ethnicity, 2 studies reported significant and higher risks in African American/blacks, whereas 2 studies showed insignificant risk differences in the relationship between PM and SGA for racial/ethnical subpopulations and 4 studies found no evidence of effect modification by race/ ethnicity. *We concluded that there existed* ***no current evidence*** *of effect modification by race/ethnicity for SGA*. **PM-Stillbirth (3 studies):** ***No evidence*** *was found for the effect modification by race/ethnicity for stillbirth,* although our conclusion is hindered by the small number of studies, while 1 study reported higher risks in white mothers for the relationship between PM and stillbirth with 2 other studies reporting no significant effect modification. **Effects modification by maternal educational attainment** **PM-LBW (6 studies):** 2 studies reported significantly higher PM risks in infants of mothers with less education, 1 study reported significantly higher PM risks in mothers with higher education, and 3 studies reported no difference in the PM risk by maternal education level. *Overall,* ***weak***	other socio-economic factors that can potentially play a role as effect modifiers such as income, job categories, occupation status, and access to prenatal care. Lastly, additional efforts to understand the interplay of race/ ethnicity and SES on vulnerability of birth outcomes to air pollution are needed to provide information for identifying vulnerable communities and populations and planning preventive measures.	pollution exposure and birth outcomes. Due to the small number of studies, it was not feasible to conduct a quantitative risk summarization; instead we provide a narrative summary of the evidence of effect modification based on the identified studies and our study should be interpreted in this context. **Strengths** A strength of this study is that we critically highlight research gaps for the evidence of effect modification by various maternal risk factors covering race/ ethnicity and SES. The differences in the PM-adverse birth outcome relationships among subpopulations found in our review imply environmental injustice and provide important information relevant to decision-making for identifying and protecting vulnerable subpopulation.

			evidence of higher PM risk *for infants of mothers with less/high education existed for LBW*. **PM-PTB (8 studies):** 2 studies found that infants of mothers with less education had higher PM risk, whereas 6 studies did not find such evidence. *Overall,* ***weak evidence of higher PM risk*** *for infants of mothers with less/high education existed for PTB*. **PM-SGA (5 studies):** One study reported statistically significant results for the effect modification of PM risk for SGA by maternal education, whereas the 4 studies conducted in California did not find significant effect modification. *We concluded that there was* ***no evidence of higher risk*** *of SGA from PM exposure in mothers with less education*. **PM-SB (3 studies**): One study showed a tendency of higher risk by lower education level but the results were not statistically significant. Significant effect modification by maternal education was not found in the other 2 studies. Thus, *we concluded that there existed* ***no effect modification*** *by maternal education on the relationship between PM exposure and stillbirth*. **Effects modification by maternal income** **PM-LBW (4 studies):** ***No evidence*** was found for effect modification as the studies reported no differences in PM risks by income level. **PM-PTB (7 studies):** ***No evidence*** was found for effect modification as the studies reported no differences in PM risks by income level. **PM-SGA (2 studies):** We concluded that there is ***no evidence*** of effect modification was concluded for SGA, which may relate to the small number of studies. **Effects modification by maternal occupation or un/employed during pregnancy** **PM-PTB (2 studies):** One study examined the relationship between PTB and PM exposure as modified by mothers' occupation, reporting higher risks in infants of farmers than other workers. The other study did not find risk differences between mothers who were employed and those who were unemployed during pregnancy. *We concluded* ***no evidence*** *of effect modification by occupation for the examined birth outcomes.*		

			Effect modification by area-level integrated socioeconomic status (SES) levels. **PM-LBW (2 studies):** The 2 studies focusing on LBW reported significantly higher risks in regions with lower SES level. In conclusion, there existed ***no evidence*** for effect modification by area-level integrated SES levels for PM risk of LBW. **PM-PTB (3 studies):** In the 3 studies for PTB, the differences in the association between PM exposure and PTB were not statistically significant or the risk differences were not based on statistically comparable risk measurements. In conclusion, there existed ***no evidence*** for effect modification by area-level integrated SES levels for PM risk of PTB.		
6. Yuan [6] 20/03/2019 [4, all China]	$PM_{2.5}$	BW, LBW, SGA, PTB	**PM2.5 and BW** (22 studies: 4 prospective and 18 retrospective cohort; 12,723,279 births). 23 results on entire pregnancy (one study reported twice for different exposure levels); 14 found significant increased risk of reduction in BW, 4 found non-significant increased risk in BW reduction, 2 found significant decreased risk in BW (protective effect), 3 found non-significant decreased risk (protective effect). 7 studies reported for 1st trimester; 5 found significant increased risk and 2 found non-significant increased risk in BW reduction. 7 studies reported for 2nd trimester; 4 found significant increased risk and 2 found non-significant increased risk in BW reduction, and 1 found no association. 14 results from 12 studies reported for 3rd trimester; 6 found significant increased risk, 6 found non-significant increased risk in BW reduction, and 2 found non-significant decreased risk (protective effect). 2 studies reported for last month and both found increased risk which was significant in one and non-significant in the other. **PM2.5 and LBW/TLBW** (20 studies: 2 prospective and 18 retrospective cohorts; 24,577,804 births)	Relevant measures should be taken to reduce the exposure level of susceptible population and raise their awareness of health risks associated with PM2.5 exposure. Efforts should be made to implement more stringent air quality principles and improve ambient air quality.	**Strengths** Provide another subjective point of view to present varied effects of maternal exposure on multiple adverse outcomes through this comprehensive summary; the evaluations included were fully adjusted instead of extraction to get similar covariates to ensure the quality of meta-analysis and reduce heterogeneity among different studies. Besides, we also exhibit estimations based on different exposure assessment, including traditional fixed monitoring data, remote sensing, and satellite data were also obtained from the literature.

			22 findings from 20 studies reported for entire pregnancy; 6 found significant increased risk, 8 found non-significant increased risk, 1 found significant decreased risk (protective effect), 4 found non- significant decreased risk (protective effect), and 3 found no association. 9 studies reported for 1st trimester; 2 found significant increased risk, 4 found non-significant increased risk, 2 found non-significant decreased risk (protective effect), and 1 found no association. 10 studies reported for 2nd trimester; 3 found significant increased risk, 4 found non-significant decreased risk, and 3 found no association. 10 studies reported for 3rd trimester; 2 found significant increased risk, 4 found non-significant increased risk, 2 found significant decreased risk (protective effect), and 1 found no association. **PM2.5 and PTB** (18 studies: 1 prospective cohort, 16 retrospective cohort, 1 nested case-control; 10,593,350 births) 18 studies reported for entire pregnancy; 9 found significant increased risk, 2 found non-significant increased risk, 1 found significant decreased risk (protective), 5 found non-significant decreased risk, and 1 found no association. 11 studies reported for 1st trimester; 3 found significant increased risk, 1 found non-significant increased risk, 3 found non-significant decreased risk, and 4 found no association. 11 studies reported for 2nd trimester; 4 found significant increased risk, 1 found non-significant increased risk, 4 found non-significant decreased risk, and 2 found no association 11 studies reported for 3rd trimester; 3 found significant increased risk, 1 found non-significant increased risk, 6 found non-significant decreased risk, and 1 found no association 2 studies reported on last month where one found non-significant decreased risk and the other found no association.		

			One study reported and found non-significant decreased risk for the last three months. **PM2.5 and SGA** (9 studies: 1 prospective and 8 retrospective cohorts; 5,562,394 births) 9 studies reported for entire pregnancy; 5 found significant increased risk, 2 found non-significant increased risk, 1 found significant decreased risk, and 1 found non-significant decreased risk. 6 studies reported for 1st trimester; 2 found significant increased risk, 2 found non-significant increased risk, 1 found significant decreased risk, and 1 found non-significant decreased risk. 6 studies reported for 2nd trimester; 3 found significant increased risk, 2 found non-significant increased risk, and 1 found significant decreased risk. 6 studies reported for 3rd trimester; 3 found significant increased risk, 1 found non-significant increased risk, and 2 found significant decreased risk.		
7. Tsoli [7] 31/01/2019 [3, 2 Greece, 1 London, UK]	$PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, PM_1, TSP	TBW, TLBW	**PM2.5 and TBW change** 34 studies (31 cohort studies and 3 ecological;13,879,044 births with unreported for one study) 26 studies reported with 32 findings (site-specific results reported for some studies) for *entire pregnancy*: 15 found significant increased risk, 7 found non-significant increased risk, 5 found significant decreased risk (protective effect), 6 found non-significant decreased risk. 13 studies reported for *1st trimester*: 5 found significant increased risk, 2 found non-significant increased risk, 2 found significant decreased risk (protective effect), 4 found non-significant decreased risk. 14 studies reported for *2nd trimester*: 8 found significant increased risk, 2 found non-significant increased risk, 1 found significant decreased risk (protective effect), 2 found non-significant decreased risk, and 1 found no association. 17 studies reported for *3rd trimester*: 6 found significant increased risk, 6 found non-significant increased risk, 2 found significant decreased risk (protective effect), and 3 found non-significant decreased risk.	"These findings underline the need for protective measures for exposure of pregnant women to particulate pollution. Future research needs to focus on understanding which chemical constituents and sources of PM are responsible for TLBWT and by which mechanisms, expanding our knowledge of the critical time windows of exposure, study characteristics that are responsible for differences in results, consider maternal occupational exposure, outdoor activities or indoor air exposure, and elucidating the biological pathways that	**Limitations** 'Our search was restricted to English-only language publications and grey literature was not searched for eligible studies. Also, the review adopted a structured and independent screening process. The screening of the references of relevant reviews on the topic did not indicate additional papers for inclusion, thus we believe that all relevant publications were captured. In this review, results are presented using only single-pollutant models of PM.'

			One study reported and found no association in first month, 2 reported for last month with 1 significant and 1 non-significant increased risks, and another for last trimester found significant increased risk. **PM2.5 and TLBW change** 32 studies (29 cohort, 1 nested case-control, and 2 ecologic; 25,081,472 births) 49 findings (site-specific results reported for some studies) for *entire pregnancy*: 16 found significant increased risk, 15 found non-significant increased risk, 2 found significant decreased risk (protective effect), 15 found non-significant decreased risk. 15 studies reported (site-specific results reported for some studies) for *1st trimester*: 3 found significant increased risk, 4 found non-significant increased risk, 2 found significant decreased risk (protective effect), 5 found non-significant decreased risk, and 1 found no association. 16 studies reported (site-specific results reported for some studies) for *2nd trimester*: 1 found significant increased risk, 9 found non-significant increased risk, 1 found significant decreased risk (protective effect), 4 found non-significant decreased risk, and 1 found no association. 16 studies reported (site-specific results reported for some studies) for *3rd trimester*: 2 found significant increased risk, 6 found non-significant increased risk, 1 found significant decreased risk (protective effect), 6 found non-significant decreased risk, and 1 found no association. One study reported and found significant increased risk for 3rd month, another found non-significant decreased during preconception. One study reported monthly and found non-significant increased risk for almost all months. "The range of estimated change in BWT (in grams) was −0.51 (−1.58, 0.56) (Kumar, 2012) up to −3.1 (-5.1, −1.1) (Gehring et al., 2014) per 1 μg/m3 increase in PM2.5, −7 (−17.0, 2.0) (Pedersen et al., 2013) up to −16.0 (−29.0, −3.0) (Pedersen et al., 2015) per 5 μg/m3 increase in PM2.5 and −18.4 (SE 4.1) (Savitz et al., 2014) up to 11.00 (−3.0, 25.0) (Hannam et al., 2014) per 10 μg/m3 increase in PM2.5. An even more extreme reduction of BWT in	underline the associations between maternal exposure, particulate air pollution and neonatal health. Future studies also need to take into consideration potential effect modification by characteristics of the built environment, such as proximity to traffic and green spaces. Establishing similar guidelines among studies, as the ones described in ICAPPO (Woodruff et al., 2010), could be achieved through interdisciplinary collaborations that will expand our understanding and eliminate the differences employed among studies."	**Strengths** 'To the best of our knowledge, this is the first systematic literature review summarizing all the available scientific literature on this topic up to October 2018, which can be used as valuable guide tool for future studies'

			grams was recorded compared with the previous, −48.4 (SE 7.1) (Hannam et al., 2014). **NB**: Review authors omitted results for some studies and only indicated 'TBWT results also available in the primary paper' , 'TLBWT results also available in the primary paper' or '…… results are also graphically available, "…results are also available for the different exposure metrics'. We considered only results included in the review article. **PM10 and TBW change** 26 studies (24 cohort, 1 cross-sectional, and 1 ecologic; 5,894,513 births with unreported for one study) 18 results for *entire pregnancy*: 3 found significant increased risk, 13 found non-significant increased risk, 1 found significant decreased risk (protective effect), and 1 with no association. 13 studies for *1st trimester*: 3 found significant increased risk, 5 found non-significant increased risk, 1 found significant decreased risk (protective effect), 3 found non-significant decreased risk, and 1 with no association. 13 studies for *2nd trimester*: 3 found significant increased risk, 5 found non-significant increased risk, 5 found non-significant decreased risk. 16 studies for *3rd trimester*: 3 found significant increased risk, 7 found non-significant increased risk, 1 found non-significant decreased risk. First month, last month, last two months, and last trimester were also reported in 5 studies but none found significant in/decreased risk. "The range of estimated effects for LBWT (OR (95% CI)) was 1.01 (0.95, 1.08) (Brauer et al., 2008) up to 1.07 (1.01, 1.14) (Dibben and Clemens, 2015) per 1 μg/m3 increase in PM10 and 0.90 (0.60, 1.35) (Capobussi et al., 2016) up to 1.44 (0.62, 3.36) (Parker et al., 2011) per 10 μg/m3 increase in PM10. The range of estimated change in BWT (in grams) was −10.0 (−14.2, −5.7) (Gehring et al., 2014) up to 0.52 (0.19, 0.85) (Yang et al., 2003) per 1 μg/m3 increase in PM10 and -30.3 (−36.4, −24.2) (Parker et al., 2011) up to 47.0 (−10.5, 104.6) (Parker et al., 2011) per 10 μg/m3 increase in PM10"		

			NB: Review authors omitted results for some studies and only indicated 'TBWT results also available in the primary paper', 'TLBWT results also available in the primary paper' or '…. graphically available in original paper', "…results are also available per trimester'. We considered only results included in the review article. **PM10 and TLBW change** 31 studies (27 cohort, 1 case-control, and 2 ecologic, 1 cross-sectional; 8,327,332 births) 29 findings (site-specific results reported for some studies) for *entire pregnancy*: 9 found significant increased risk, 13 found non-significant increased risk, 2 found significant decreased risk (protective effect), 4 found non-significant decreased risk, and 1 found no association. 11 studies for *1st trimester*: 1 found significant increased risk, 5 found non-significant increased risk, 1 found significant decreased risk (protective effect), 3 found non-significant decreased risk, and 1 found no association. 11 studies for *2nd trimester*: 8 found non-significant increased risk, and 3 found non-significant decreased risk. 13 studies for *3rd t trimester*: 2 found significant increased risk, 6 found non-significant increased risk, 4 found non-significant decreased risk, and 1 found no association. 1 finding each for preconception, last month and last 2 month with no significant in/decreased risk. **NB**: Review authors omitted results for some studies and only indicated 'TBWT results also available in the primary paper', 'TLBWT results also available in the primary paper' or '…. graphically available in original paper', "…results are also available per trimester'. We considered only results included in the review article. **PM2.5-10 and TBW:** 5 studies (4 cohort and 1 ecologic; 12,829,812 births) 5 studies (1 all regions' results) reported for entire pregnancy: 4 found significant and 1 non-significant increased risks. 2 reported for 1st trimester; 1 each found significant and non-significant increased risks.		

			2 reported for 2nd trimester and both found significant increased risk. 3 reported for 3rd trimester; 2 found significant and 1 non-significant increased risks. 1 reported and found non-significant increased risk for 1st month. **PM2.5-10 and TLBW**: 3 studies (2 cohort, 1 ecologic; 4,405,320 births) All reported for entire pregnancy; 2 found non-significant increased risk and 1 found no association. "The range of estimated change for TBWT (in grams) was −12.7 (−18.0, −7.5) (Parker and Woodruff, 2008) −9.4 (-12.8, −6.0) (MorelloFrosch et al., 2010) per 10 µg/m3 increase (95% CI) in PM2.5-10. The range of effects for TLBWT (OR (95% CI) was 0.88 (0.79, 0.98) (Kingsley et al., 2017) up to 1.17 (0.95, 1.39) (Pedersen et al., 2013) for black carbon and 0.99 (0.96, 1.02) (Morello-Frosch et al., 2010) up to 1.04 (0.99, 1.09) (Parker and Woodruff, 2008) for PM2.5-10." **Chemical components of PM** 11 studies for PM2.5, 2 studies each for PM10 and PM0.1 investigated effects of specific chemical constituents. 'Different chemical components of PM such as elemental carbon, nickel, zinc, potassium, iron and copper were associated with reductions in TBWT or increased risk of TLBWT.' **TSP and TBW/TLBW** 2 cohort studies; 351,434 TBW: 1 reported and found significant increased risk for 3rd trimester. TLBW: 1 reported and found non-significant increased risk for 1st trimester; 2 reported for 3rd trimester where 1 each found significant in/decreased risks. Others: PM0.1 (2 studies), PM1 (1 study) and PM7 (1 study).		
8. Grippo [8] 25/09/2018	TSP, PM_{10}, $PM_{2.5}$, CO,	SAB (miscarriage) and SB	**SAB or miscarriage** **PM10**; Reported in 4 studies; 3 studies (1 prospective cohort for entire pregnancy, time-series study for	More evidence is needed.	**Limitations** The various definitions make it difficult to

[8; 3 USA, 5 China]	SO_2, NO_2, O_3		cumulative lag0-14 days, and a case-control for < 14 weeks of gestation) found non-significant increased risk. Third study, a time-series, found significant increased risk within 180 days of gestation. **PM2.5**; Reported in a prospective cohort that found significant increased risk. **CO**; Reported in 3 studies; a case-control study found significant increased risk for <14 weeks of gestation, no association in a prospective cohort study for entire pregnancy, and non-significant decreased risk in time-series for cumulative lag0-14 days. **NO**; Reported in a time-series study that found no association for cumulative lag0-14 days. **NO2**; Reported in 4 studies; case-control study found significant increased risk for <14 weeks of gestation, 2 studies (a prospective cohort for entire pregnancy, time-series study for cumulative lag0-14 days) found non-significant increased risk. The forth study, a time-series, found non-significant decreased risk within 180 days of gestation. **SO2**; Reported in 3 studies; a case-control study found significant increased risk for within 14 weeks of gestation, 2 studies (a prospective cohort for entire pregnancy and a time-series for cumulative lag0-14 days) found non-significant increased risk. **O3**; Reported in 4 studies; 3 studies (a prospective cohort for entire pregnancy, case-control for <14 weeks of gestation, and a time-series study for within 180 days of gestation) found significant increased risk. The forth study, a case-control study for cumulative lag0-14 days case-control study found no association. **TSP**; Reported in a case-control study that found significant increased risk within 14 weeks of gestation. **Stillbirth (SB)** *NB*: Included 2 time-series studies that **did not** examined entire or trimester periods; one examined cumulative lag0-14 days and found non-significant decreased risk for all included pollutants (PM10, SO2, NO, O3) but no association for NO2, the other examined daily rate ratio per increase on concurrent day and found significant		compare the results across the studies. Considering that women could be exposed to pollutants for only a short period during third trimester; at least some stillbirths occurring during this period could be attributed to an acute exposure to these pollutants. Findings from studies on the associations between third trimester exposure to pollutants and stillbirths should be interpreted with caution because of the lack of specificity in quantifying the exposure period before the occurrence of stillbirth outcome. Many of the studies used air monitoring station data to represent individual air pollution exposure, without taking into account indoor air pollution and mobility of human activity. This limitation could result in misclassification bias. Many papers in this review reported results relating to various combinations of pollutants. Multiple pollutant models were used, and caution should be used when interpreting this data.

			increased risk for PM10 but no significant association for other included pollutants (CO, NO2, SO2, O3) **PM10**; (6 studies; 2 each for prospective cohort and time series, and 1 each for retrospective cohort, and case-control). 2 studies reported for entire pregnancy period (> 20 or >23 or >28 gestational weeks); 1 each found non-significant increased and decreased risk. One study reported and found non-significant decreased risk in 1st trimester. One study reported and found non-significant increased risk in 2nd trimester. Two studies reported and both found significant increased risk in 3rd trimester. One study found generally no association. **PM2.5**; (7 studies; 3 retrospective cohort and 1 each for prospective cohort, and cross-sectional and 2 case-control). 5 studies reported for entire pregnancy period (>20 or >23 or >28 gestational weeks); 2 studies found significant increased risk and 3 found non-significant increased risk. One study reported and found non-significant decreased risk in the 1st and 2nd trimester. 4 studies reported for 3rd trimester and 2 each found significant and non-significant increased risk. One study found generally no association. **CO** (7 studies; 2 each for retrospective cohort and time-series, 1 each for prospective cohort, case-control, and cross-sectional). 3 studies reported for entire pregnancy period (or > 20 or >23 or >28 gestational weeks); 1 study found significant and 2 found non-significant increased risks. 3 studies reported for 3rd trimester; 1 study found significant increased risk and 2 studies found non-significant increased risk. 2 studies reported no association. **NO2** (8 studies; 2 each for retrospective cohort and time-series, 1 each for prospective cohort, case-control, cross-sectional, and ecological).		

			4 studies reported for entire pregnancy period (>20 or >23 or >28 gestational weeks); 2 studies found significant and 1 found increased risk, and 1 each found non-significant increased and decreased risk. 3 studies reported for 3rd trimester; 1 study found significant increased risk and 2 found non-significant increased risk. 1 study reported no association. **SO2**(8 studies; 2 each for retrospective cohort and time-series, 1 each for prospective cohort, case-control, cross-sectional, and ecological). 4 studies reported for entire pregnancy period (>20 or >23 or >28 gestational weeks); 3 studies found non-significant increased risk, and 1 found non-significant decreased risk. 3 studies reported for 3rd trimester; 2 found significant increased risk and 1 found non-significant decreased risk. 1 study reported no association. **O3**(6 studies; 2 each for retrospective cohort and time-series, 1 each for prospective cohort and case-control). 3 studies reported for entire pregnancy period (>20 or >23 or >28 gestational weeks); 1 each found significant increased, non-significant increased, and non-significant decreased risks. 1 study reported for 1st trimester and found significant increased risk. 1 study reported for 3rd trimester and found significant increased risk. 1 study reported no association. **TSP;**1 ecological reported and found non-significant decreased risk.		
9. Westergaard [9] 06/04/2017 [4; 2 Denmark, 1 Netherlands, 1 France]	$PM_{2.5}$, SPM, SO_2,NO_2, O_3	TLBW	**Effect modification of TLBW by smoking** **PM2.5**: a prospective cohort study of 74,178 births in 12 European countries; significant increased risk in both smokers (with higher OR) and non-smokers **SPM**: a nationwide population-based longitudinal survey in Japan of 44,109 births; non-significant decreased risk (protective effect) in smokers and significant increased risk in non-smokers. **SO2**: 1 study (44,109 births in the Japanese study); significant increased risk in both smokers (with higher OR) and non-smokers.	'The limited evidence precludes for definitive conclusions and further studies are recommended'	'This commentary is not a complete review of all potential effect modifiers' The limited evidence precludes for definitive conclusions.

			NO2: 1 study (44,109 births in the Japanese study); non-significant decreased risk in smokers and significant increased risk in non-smokers. **O3**: 1 study (44,109 births in the Japanese study); non-significant decreased risk in smokers and non-significant increased risk in non-smokers. However, none of the interactions for smoking status reached statistical significance, p>0.05. (**NB**: review authors mistakenly exchanged the smoker/non-smoker CIs for NO2 and O3 as in the primary study, Yorifuji et al, 2015) **Effect modification of TLBW by maternal obesity.** **PM2.5;** 2 studies (retrospective and prospective cohorts; 1,035,123 births)**.** Higher OR in obese women compared to normal weight women in both studies. Also, significant decreased risk among underweights in the retrospective study but non-significant increased risk in the prospective study. **NO2 and O3:** 1 Californian retrospective cohort study (960,945 births); showed a marginally increased risk of TLBW for the obese mothers (BMI> 35 kg/m2) as compared with those of normal weight (BMI 20–24.9 kg/m2), non-significant increased (O3) and decreased (NO2) risks for underweight women with underweight (BMI ≤19 kg/m2) compared to normal weight women (BMI 20–24.9 kg/m2) **Effect modification by socioeconomic status (SES: education and income in 4 studies)** **PM2.5:** 3 studies (1prospective and 2 retrospective cohorts) In 2/3 studies (988,780 births), women with low education had significantly higher OR compared with women with high education. The third, a retrospective study (297,043 births) found non-significant difference between women with less or more than high school. **O3:** a retrospective study (297,043 births) found significant increased risk in both women with less or more than high school (but with greater risk for > high school) **NO2:** A retrospective study (2,402,545 births) from Canada found non-significant decreased risk for women in the third tertile of the lowest income.		

			Effect modification of maternal asthma One retrospective study (362,800 births) from Canada reported for PM2.5,NO2 and O3; found no significant difference between women with and without asthma. Decreased risk for PM2.5 and NO2 but significant increased risk in non-asthmatic and non-significant increased risk for asthmatic women.'		
10. Jacobs [10] 01/02/2017 [9; 8 Australia, 1 USA]	NO_2, SO_2, CO, PM_{10}, $PM_{2.5}$, O_3	BW, LBW, PTB, SB	**BW** **NO2** (3 studies); One study (cross-sectional) examined monthly association and found all non-significant increased risk in almost all months. The other 2 studies (both cross-sectional and) reported entire/trimester-specific (7 scenarios). One study reported entire pregnancy and found significant protective effect. 2 reported for 1st trimester and found significant and non-significant increased risks. 2 reported for 2nd trimester and both found significant increased risks. 2 reported 3rd trimester and significant increased risk and significant protective effect. **PM10** (3 studies); 1 retrospective cohort and 2 cross-sectional reported 11 entire/trimester-specific scenarios. 2 reported entire pregnancy and both found significant increased risk. 3 reported 1st trimester and 2 found significant increased risk and one found non-significant increased risk. 3 reported on 3rd trimester and one found non-significant increased risk while 2 found significant protective effect. **PM2.5**: One study (cross-sectional) examined monthly and found non-significant increased risk in all months. **SO2** (3 studies); 1 prospective cohort and 2 cross-sectional. One study (cross-sectional) examined monthly and found mixed of non-significant increased risks in and protective effects and with significant increased risk in the 8th month. The other cross-sectional study reported on the entire, 1st and 2nd trimesters and found significant increased risk for both entire and 1st and non-significant increased risk for 2nd.	Further studies are needed to clarify associations for other outcomes and pollutants, particularly CO, PM2.5 and O3, for which there were relatively few studies.	**Strengths** An advantage of this study was that by including peer reviewed articles written in Chinese, we were able to include 14 additional studies on the topic that would not have been included had the review been limited to English language articles.

			2 reported on 3rd trimester where the prospective cohort found significant increased risk and the cross-sectional found non-significant protective effect. **CO:** One study (cross-sectional) examined monthly and found non-significant increased risk in almost all months and with significant increased risk in the 8th month. **LBW** **NO2**: 3 studies. A cross-sectional study reported and found no association for entire pregnancy. A retrospective cohort reported and found non-significant decreased risk for 1st trimester. 2 studies reported for 3rd trimester and one found significant decreased risk or protective effect (case-control study) and the non-significant decreased risk in the other (retrospective cohort). The retrospective cohort also reported non-significant decreased risk in 1st, 2nd, and 3rd months. **PM10**; 5 studies. One study (cross-sectional) reported for entire pregnancy and found non-significant increased risk. A retrospective cohort reported and found non-significant decreased risk for 1st trimester. 2 studies reported for 3rd trimester one found significant decreased risk or protective effect (case-control study) and the non-significant decreased risk in the other (retrospective cohort). Another retrospective study reported various monthly for VLBW and found non-significant decreased risk in most cases and a significant decreased risk or protective association for 7-9th months. **SO2**: 5 studies. One study (a cross-sectional) reported for entire pregnancy and found non-significant increased risk. 2 studies reported for 2nd trimester and found significant (case-control study) and non-significant (retrospective cohort) increased risks. 2 studies reported for 3rd trimester and one found significant increased risk (prospective cohort) but non-significant decreased risks in the other (retrospective cohort). Another retrospective study reported various monthly for LBW/VLBW and found mixed associations but with no statistical significance. **PTB**		

			PM10: 8 studies; 2 each for retrospective cohort and case-control, 4 cross-sectional. 4 studies reported for entire pregnancy and one found significant increased risk and the other 3 found non-significant increased risk. 3 reported for 1^{st} trimester where one found non-significant decreased risk and 2 found no association. 2 reported for 2^{nd} trimester with non-significant increased risk in one and decreased risk in the other. 3 reported for 3^{rd} trimester where 2 found non-significant increased risk and one found non-significant decreased risk. Several varied timeframes were examined in some studies and significant increased risk was found once for each of the following; 3 months before conception, 8 weeks, 2^{nd} months, 3^{rd} months, 4-6^{th} months, 7-9^{th} months, 2^{nd} month before delivery. One case-control study (8969 births; 677 cases, 8292 controls), further classified the PTB as moderate PTB (32–36 weeks) or very PTB (<32 weeks) and then further as either medically indicated or spontaneous. For the sub-outcome medically-indicated PTB, significant increased odds were found for the entire pregnancy and 1^{st} trimester. For very PTB, significant associations were observed in the last 4, 6, 8 weeks before delivery. **NO2**: 7 studies; 1 retrospective, 2 case-control, 4 cross-sectional. 3 reported on entire pregnancy and one found significant increased risk and the 2 found no association. 2 reported on 1^{st} trimester and both found non-significant decreased risk. 2 reported on 2^{nd} trimester and both found decreased risk where one is significant. 3 reported for 3^{rd} trimester and one found significant increased risk and 2 found non-significant decreased risk. Varied other timeframes were reported and one study found significant increased risk in 8th week before delivery. **SO2**: 7 studies; 2 each for retrospective cohort and case-control, 3 cross-sectional.		

			3 studies reported for entire pregnancy and all found significant increased risk. One reported for 1st trimester and found non-significant increased risk. 2 reported for 2nd trimester and both found non-significant increased risk. Varied other timeframes were reported a significant increased risk was reported once for each of the following: 3rd month, 1 month before delivery, 8th month before delivery. **O3**: One cross-sectional study reported for change in number of events in the 4,6, 8 weeks before delivery and found significant risk for 4 and 8weeks before delivery. **Stillbirth** Reported by one case-control study of 102,575 births (9325 cases, 93,250 controls). **CO**: no association for the entire pregnancy and all trimesters. **NO2**: no association for 1st trimester and non-significant decreased risk for the entire pregnancy, 2nd, and 3rd trimesters. **O3**: no association for 1st trimester and non-significant decreased risk for the entire pregnancy, 2nd, and 3rd trimesters. **PM10**: non-significant increased risk for 1st trimester and non-significant decreased risk for the entire pregnancy, 2nd, and 3rd trimesters. **SO2**: Non-significant increased risk for the entire pregnancy and 1st trimester but no association for the 2nd and 3rd trimesters. Stillbirth was further reported by term and preterm births, and also several other timeframes with mixed findings. Significant decreased risk was found in 2nd trimester for **O3** and **PM10** among term births, significant increased risk for **SO2** in 1st trimester, and 1st, 2nd, and 3rd months among PTB stillbirth.		
11. Shah [11] (26/11/2010) [2; both Canada]	PM_{10}, $PM_{2.5}$, NO_2, SO_2, CO, O_3, TSP	LBW, PTB, SGA/IUGR, BW	**LBW** **PM2.5;** 4 studies (3 cohort and 1 case-control; 3,971,602 births, 1 cohort had crude OR). 2 cohort studies reported on entire pregnancy where one found significant increased risk and the other found non-significant increased risk. 1 study several exposure levels	*Implications for practice* The results of this systematic review reinforce the need for action to be taken to reduce exposure to environmental pollutants, especially during	**Strengths** 'This is the first review to assess associations of birth outcomes using an exhaustive method that targets individual

			for first month, last 2 weeks, and total gestation and found significant increased risks for 8 out of 9 scenarios. Another cohort reported average exposure during pregnancy for 3 different exposure levels and found non-significant decreased risk for all. **PM10:** 12 studies (9 cohort, 3 ecological; 5,074,520 births; 2 studies had crude OR) 5 studies reported for entire pregnancy; 3 found non-significant increased risk (including 1 crude OR), 1 found non-significant decreased risk and 1 found no association. 5 studies reported for 1st trimester; 1 found significant increased risk, 3 found non-significant increased risk (including 1 crude OR), and 1 found non-significant decreased risk. 5 studies reported for 2nd trimester; 1 found significant increased risk, 3 found non-significant increased risk (including 1 crude OR), and 1 found non-significant decreased risk. 6 studies reported for 3rd trimester; 2 found non-significant increased risk, 3 found non-significant decreased risk, and 1 found no association (crude OR). One study reported city-specific average exposure during pregnancy for 7 cities in Korea and found significant increased risk for 2 cities and non-significant increased risk for remaining cities. Another study reported average exposure during pregnancy for three different exposure levels and found non-significant decreased risk for two and significant decreased risk for the relatively highest exposure. **SO2**: 14 studies; 8 cohort, 2 case-control, 4 ecological studies; 5,379,951 births and unreported for 1 ecological study (3 cohort studies, 749,700 births included reported crude ORs). 5 studies reported for entire pregnancy where one each found significant and non-significant increased risk, 1 found no association, and 2 found non-significant decreased risk.	pregnancy. Clinicians should therefore encourage their pregnant patients to pay attention to local air quality index information and adjust their activities where a risk is identified. Regional, national and international efforts are needed to reduce air pollution, not only to improve birth outcomes, but also other health outcomes. Individual action by pregnant women, such as limiting time spent outside when the outdoor pollution level is higher, and reducing infiltration of outdoor pollution to indoor areas is needed.' *'Implications for research* The body of research needs to expand to augment our understanding of the biological mechanisms underlying the impact of various air pollutants, as well as the interactions between them. Key areas where research is needed to improve our understanding of the strength and magnitude of the association between air pollution and birth outcomes include (Slama et al., 2008): an improved method of detecting exposure at a large population level, development of an objective	pollutants. Large number of studies, assessment of risk of biases in the included studies, and qualitative and quantitative analyses of exposure-outcome relationships are strengths of this review. **Limitations** We restricted our searches to English language publications. We did not include gray literature, abstracts, and proceedings, as the quality of such studies, particularly for the observational association type of studies, could not be assessed adequately.

			5 reported for 1st trimester where 1 found significant increased risk, 2 each found non-significant increased and decreased risks. 5 reported for 2nd trimester where 1 found significant increased risk, 3 found non-significant increased risk and 1 found non-significant decreased risk. 4 reported for 3rd trimester where 2 each found non-significant increased and decrease risks. Other exposure periods included during last month or trimester with different exposure levels with 2 finding significant increased risk and mixed finding in others, including non-significant increased/decreased risks. One case-control study (345 births) reported on VLBW and found significant increased risk. **NO2**: 11 studies; 9 cohort and 2 ecological; 5,228,442 births (one included cohort study with 388,105 births was a crude OR). 4 studies reported for entire pregnancy where 2 found significant increased risk, 1 each found non-significant increased and decreased risks. 4 reported for 1st trimester where 1 found significant increased risk and 2 each found non-significant increased and decreased risks. 5 studies reported for 2nd trimester where 1 found significant increased risk, and 2 each found non-significant increased and decreased risks. 4 studies reported for 3rd trimester where 2 each found non-significant increased and decreased risks. Other exposure periods include non-significant decreased risks for both 1st and last months reported in a cohort study (229,085 births). **NO**: 3 studies; 2 ecologic and 1 cohort; 165,470 births with unreported births in one ecologic (the included cohort had crude OR). A study reported on entire, 1st, 2nd and 3rd trimester and exposure above average at delivery; all found non-significant decreased risk in each instance. **CO**: 13 studies (9 cohorts, 2 case-control and 2 ecological studies; 5,367,034 births; one cohort study had crude OR).	measure to assess duration and intensity of exposure of individuals, inclusion of entire populations or performance of carefully designed nested studies, complete assessment of outcomes throughout pregnancy, identification of considerations necessary to avoid residual confounding, and adjustment for residential mobility.’	

			4 studies reported for entire pregnancy and 2 found non-significant increased risk and another 2 (including 1 crude OR) found non-significant decreased risk. 4 studies reported for 1st trimester and 1 (crude OR) found significant increased risk while 3 found non-significant increased risk. 3 studies reported for 2nd trimester and 1 (crude OR) found significant increased risk while 2 found non-significant increased risk. 4 studies reported for 3rd trimester and 1 found significant increased risk, 2 found non-significant increased risk and one (crude OR) found significant decreased risk. Other exposure periods included 1st month, last 3 months, last month, during last trimester, total gestational exposure with several exposure categories; mixed findings, predominantly non-significant increased and decreased risk. **O3**: 7 studies (5 cohort and 2 ecological; 4,445,775 births) 2 studies reported for entire pregnancy and both found non-significant increased risk. 3 studies reported for 1st trimester where 1 found non-significant increased risk and 2 found non-significant decreased risk. 2 studies reported for 2nd trimester finding non-significant increased risk in one and decreased risk in the other. 3 studies reported for 3rd trimester where 1 found non-significant increased risk and 2 found non-significant decreased risk. A cohort study reported for 1st and last months and found non-significant increased risk for both exposure periods. **TSP**: 3 studies (2 cohort and 1 ecological; 351434 births with unreported birth for the ecological study). 1 study reported and found significant increased risk for entire pregnancy. 2 studies reported for 1st trimester; 1 found significant increased risk and the other found non-significant increased risk. 1 study reported and found non-significant increased risk for 2nd trimester.		

			2 studies reported for 3^{rd} trimester; 1 found non-significant increased risk and the other found non-significant decreased risk. **BW (reduction)** **PM2.5:** 4 cohort studies; 3,929,272 births. 1 study reported and found significant increased risk for entire pregnancy 1 study reported and found significant increased risk for 1^{st} trimester. 1 study reported and found non-significant increased risk for 2^{nd} trimester. 1 study reported and found significant increased risk for 3^{rd} trimester. A prospective study reported and find significant increased risk for 2 days in second trimester. Another study reported for three exposure levels for average exposure during pregnancy and found significant increased risk for one and non-significant increased risk for the other two exposure dosage **PM10**: 4cohort studies; 393,2001 births. 2 studies reported for entire pregnancy; 1found significant increased risk and the other found non-significant increased risk. 1 study reported and found significant increased risk for 1^{st} trimester. 1 study reported and found non-significant increased risk for 2^{nd} trimester. 1 study reported and found non-significant increased risk for 3^{rd} trimester. Another study reported for three exposure levels for average exposure during pregnancy and found significant increased risk for one and non-significant increased risk for the other two exposure dosage **NO2**: 7 cohort studies; 3941118 births. 5 studies reported for entire pregnancy; 1 found significant increased risk, 2 each found non-significant increased and decreased risks. 3 studies reported for 1^{st} trimester; 2 found non-significant increased risk, 1 found non-significant decreased risk.		

			3 studies reported for 2nd trimester; 1 found non-significant increased risk, 2 found non-significant decreased risk. 3 studies reported for 3rd trimester; 1 found significant increased risk, 2 found non-significant decreased risk. **SO_2**: 4 cohort studies; 3,917,781 births. 1 study reported and found non-significant increased risk for entire pregnancy. 2 studies reported for 1st trimester; 1 found non-significant increased risk and the other found non-significant decreased risk. 2 studies reported for 2nd trimester; 1 found non-significant increased risk and the other found non-significant decreased risk. 2 studies reported for 3rd trimester; 1 found non-significant increased risk and the other found non-significant decreased risk. 1 study reported and significant increased risk for the first 2 months. **CO**: 3 cohort studies; 3,906,772 2 studies reported for entire pregnancy; 1 found non-significant increased risk and the other found non-significant decreased risk. 1 reported and found non-significant increased risk for 1st trimester. 1 reported and found significant creased risk for 2nd trimester. decreased risk. 1 reported and found significant increased risk for 3rd trimester. **O_3**: 2 cohort studies; 3,548,268 births. The first study (3,091 births) reported and found significant increased risk for entire pregnancy. The second study (3,545,177 births) reported for trimester-specific and found significant increased risk for 1st, 2nd, and 3rd trimesters. **PTB** **$PM_{2.5}$:** 1 case-control; 2,543 births. Reported 1st trimester for two different exposure level and significant and non-significant increased risks.		

			SO2: 5 studies; 4 cohort and 1 ecological studies; 5,97,922 births (2 included studies, a cohort and ecologic; 165,470 births reported crude ORs) 1 study each reported for each trimester and found significant increased risk for each trimester. A study each also reported and found nonsignificant decreased risk for 1st month, significant increased risk for last month and significant increased risk for at delivery. **PM10:** 2 cohort studies 285,515 births. 1 study (187,997 births) reported for entire pregnancy and found non-significant increased risk. The second study (97,518 births) reported and found non-significant increased risk for first month of pregnancy and significant increased risk for 6 weeks prior to delivery. **NO2**: 6 studies; 4 cohort and 1 each for case-control and ecological; 370,985 births (the included ecologic study with 126,752 births had crude OR). 3 studies reported for entire pregnancy where 2 found non-significant increased risk and 1 found non-significant decreased risk. 4 studies reported for 1st trimester where 2 found significant increased risk and 1 each found non-significant increased and decreased risks. 4 studies reported for 2nd trimester where 1 found significant increased risk, 2 found non-significant increased risk, and 1 found non-significant decreased risk. 4 studies reported for 3rd trimester where 3 found non-significant increased risk and 1 found non-significant decreased risk. One cohort study (229,085 births) reported for 1st and last months and found non-significant increased risk for both exposure periods. **NO**: 2 studies; a cohort and an ecologic; 165,470 births (both reported crude OR). The cohort study reported on 1st, finding significant increased risk, 2nd for non-significant increased risk, and 3rd trimester for significant increased risk. The ecological study reported for exposure above average at delivery and found non-significant increased risk. **CO**: 3 studies (2 cohort and 1 case-control; 329,146 births)		

			1 case-control (2,543 births) reported for and found non-significant decreased risk on entire pregnancy and non-significant increased risk for 1st trimester. The 2 cohort studies reported for 6weeks before delivery, first month, and last month with both non-significant increased/decreased risk, and a significant increased risk in last month. **O3**: 2 studies (1 each for case-control and cohort; 231,628 births). The cohort study (229,085 births) reported for first and last months and found non-significant decreased risk for both periods. The case-control study (2,543 births) reported different exposure categorised during 1st trimester finding both increased and decreased non-significant risks. **TSP**: 1 ecological study (unreported sample size) Significant increased risk for 1st trimester. Non-significant increased risk for 2nd trimester. Significant increased risk for 3rd trimester. **SGA** **PM2.5:** 4 studies (all cohort; 183475 births). A cohort study (138,056 births) reported on and non-significant decreased risk for1st trimester, significant increased risk for 2nd, and non-significant decreased risk for 3rd trimester. Others reported for over duration of pregnancy or average exposure and for several exposure level categories and found significant risk for 2 scenarios and no/decreased risk for the rest. **PM10:** 6 cohort studies; 175,116 births. 2 studies reported for entire pregnancy; 1 found significant increased risk and the other found non-significant increased risk (crude OR). 1 study reported and found no association for 1st trimester. 1 study reported and found significant increased risk for 2nd trimester. 1 study reported and found no association for 3rd trimester. 2 studies reported on and both found significant increased risk for first month of pregnancy.		

			Another study reported for average exposure during pregnancy for three levels of exposure categories and found no association for relatively lowest level and non-significant decreased risk for the other two higher levels. **SO2**; 1 cohort study with 229,085 births. Reported for first month and found significant increased risk but no association for last month. **NO2**: 6 studies; all cohort studies; 404,008 (2 included studies; 3,876 births were unadjusted ORs, one each for entire and 2nd trimester). 2 studies reported for entire pregnancy and found non-significant increased and decreased risk. 2 studies reported for 1st trimester where one found no association and non-significant decreased risk in the other. 3 studies reported for 2nd trimester where one found no association and non-significant increased and decreased risk in the other two. 3 studies reported for 3rd trimester where one found non-significant increased risk and 2 found non-significant decreased risk. One study reported average exposure during pregnancy and found no association and non-significant decreased risk in two exposure levels. One cohort study (229,085 births) reported for first month and found significant increased risk but non-significant decreased risk for last month. **CO**; 4 studies (all cohort; 388,479 births; 1 had crude OR) 2 reported for entire pregnancy where 1 found non-significant increased risk and the other (crude OR) found no association. A study (138,056 births cohort) reported on and found non-significant decreased risk for both 1st and 2nd trimesters, and non-significant increased risk for 3rd trimester. Another study reported for 1st month with significant increased risk and non-significant decreased risk for last month. **O3**: 3 studies (all cohort; 370,232 births; 1 had crude OR). 2 studies reported on 1st trimester and both found no association.		

			2 studies reported for 2nd trimester and both found non-significant increased risk. 2 studies reported for 3rd trimester and both found no association. The third study reported for 1st and last months and found non-significant decreased risk for both periods.'		
12. Bonzini [12] 09/2010 [6, All Italy]	PM_{10}, CO, NO_2, O_3, $PM_{2.5}$	PTB, LBW, SGA, BW	**PTB (8 studies)** **PM10 (6 studies):** odds ratios for 14 pregnancy period-specific exposures standardized to an increase of 10 µg/m3 PM10 and 8/14 cases showed a significant increase in PTB risk with odds ratios ranging from 1.014 to 1.364. (**NB**: only 2 cases actually found significant association, both in 1st trimester where CI didn't include 1). Two of the eight (25%) studies reported statistically significant increases in PTB in the first trimester of pregnancy (13% for 52,113 births cohort study and 36% for 28,200 births time series study). **CO (5 studies)** 14 period-specific odds ratios (ORs) standardized for an increase of 1 mg/m3 in exposure was estimated and results from most of the cases were associated with an increased risk of approximately 1.0, with the exception of data from Leem et al. (South Korea), which produced a two-fold increased risk in the first trimester and 78% increased risk in the third trimester. Results from two studies (Wilhelm et al. and Ritz et al.) showed significant but smaller (ORs=1.178 and 1.333, respectively) increases in PTB in the first trimester in Californian women. (**Note**; 9/14 with 4/9 significant; 3 in 1st trimester from 3 cohort studies of 225,391births; 1 in 3rd trimester from a 52,113 births cohort study) **NO2 (4 studies)** The effect of NO2 The 4 studies gave 9 period-specific ORs and adjusted ORs for an increased exposure to 10 µg/m3 showed mild, yet statistically significant increases in risk of PTB in the first (2 cohort studies of 118,908 births) and third (1 cohort study of 52,113 births) trimesters. .	'There is a need for large collaborative studies to validate the results, through comparison of different exposure assessment methods. These studies need to take time activity-patterns, maternal characteristics and behaviour, and spatial confounders into account. Studies of prospective cohorts, with the use of biomarkers of exposure might be particularly forthcoming. Meanwhile, because of the extreme susceptibility of the fetus and the impact of perinatal adverse events on adult health, it may be prudent to continue to try and reduce exposure of pregnant women to air pollution throughout the world.'	Not stated for the review But general statements on studies. 'In the absence of an a priori clear hypothesis it's also difficult to establish critical time windows of exposure for each outcome The variability across studies could reflect important differences in study design. Exposure assessment method is a crucial issue.'

			O3 (3 studies) The 3 studies gave estimations of 7 period-specific ORs that ranged from 0.974 to 1.177 per an increase of 10 µg/m3. Two Australian studies (Hansen et al and Jalaludin et al) reported statistically significant increases for exposure during the first trimester respectively as 1.177 and 1.072. No significant increases in PTB risk were found associated with exposure in the second or third trimester of pregnancy. Two time series studies found significant association in 1st trimester, from 152,040 Australian births **PM2.5 (4 studies**) 10 period-specific ORs (5 of them >1.00) based on the 4 studies, standardized to an increase of 1 µg/m3 exposure and only 1/4 (25%) study reported significant risk of PTB in the first trimester. The case-control study showed a significant increase of risk during the first month of pregnancy, and the last two weeks of pregnancy, as well as the entire pregnancy, but did not provide trimester-specific risk estimates. (NB: 9 period-specific ORs; 1 significant association in 2nd week, 1st month and whole pregnancy by 1 matched case-control study of 42,692 births; 1st trimester by 1 cohort study of 667,795 births) **Term LBW** **PM10** (7 studies) The 7 studies gave a total of 17 period-specific ORs. 11/17 (65%) showed non-significant increased risks ranging from point estimates1.037 to 1.480, and two found borderline significant (one each for 1st in 74,284 births and 3rd trimesters in 136,134 births, both are cohort studies). One study reported no association consistently across each trimester. **CO** (5 cohort studies) 11 period-specific ORs No clear association in all studies except 1 cohort study of 136,134 births that found a significant 35% increase in risk for the 3rd trimester **NO2** (4 studies + 1 same study data)		

			10 period-specific ORs. 4 cases showed association but 2 were significant for the entire pregnancy period from 2 cohort studies of 428,753 births **O3** (3 studies) 9 period-specific ORs. 3 associated marginally but none showed significantly increased ORs **PM2.5** (2 studies) Both studies studied entire pregnancy and 1(358,504 births cohort study) showed a small but statistically significant adverse exposure-related effect (OR=1.024;1.010 - 1.039) **SGA** **PM10 (4 studies)** 9 period-specific ORs 3 with increased ORs but none was significant **CO** (3 cohort studies) produced 9 period-specific ORs. One cohort study (386,202 births) showed statistically significant increased risks with exposure in each trimester (1.153 in the first trimester to 1.128 in the second trimester). Another 1 scenario found non-significant. **NO2** (3 cohort studies) 9 period-specific ORs. 5 associated with increased risk but 3 were significant (in each trimester from one cohort study of 386,202 births) **O3** (3 cohort studies) 8 period-specific ORs 1 showed non-significant increased risk in 1^{st} trimester, 4 showed a decreased risk (2 in 3^{rd} and 1 each in 1^{st} and 2^{nd} trimesters), the rest no association. **PM2.5** (3 cohort studies) 9 trimester-specific ORs 6 showed significant increased risk; 1 in 1^{st} (cohort study of 386,202 births) 3 in 2^{nd} (542,505 births of cohort studies) and 2 in 3^{rd} trimesters (404,449 births) **BW** **PM10** (6 studies) 19 period-specific risk estimates. 14/19 risk estimates showed an association between exposure and lower birth weights (<25 g) when exposures were aligned to an increase of 10 µg/m3. The 6/14 had		

			different levels of exposure (17 to 60 µg/m3), and all showed statistically significant decreases in birth weight (1 for whole preg in 358,504 births cohort, 1st trimester in 2 time series studies for 206,077 births, 2nd trimester and last month for 1 cohort of 138,056 births, 3rd trimester for 2 birth cohort studies of 362,405 births. One cohort study of 1,514 births found significant increase of birth weight in 1st trimester. No consistency across studies was evident with regard to the period of pregnancy in which the effects were found. **CO** (5 studies) 18 period-specific estimates; 10 showing a decrease in birth weight). Significant adverse effects were observed in the 1st trimester in 3 cases (a time series of 179,460 births, 2 cohort studies of 362,405 births); both whole preg and 3rd trimester in a cohort study of 358,504 births. Significant in last month was found in a cohort study of 138,056 births. **NO2** (5 studies) 15 period-specific estimates, of which 10 suggested a decrease in birth weight but significant in 3 cases (1st and 3rd trimesters in a 138,056 births cohort study, whole preg in a 358,504 births cohort study). **O3** (4 studies) 14 period specific estimates. 4 showed statistically significant in-verse relationship between exposure and birth weight (2 in 2nd trimester from 2 cohort studies of 141,957 births, 1 each in 3rd trimester and whole preg period from 3,901births cohort study). Others showed non-significant adverse association. **PM2.5** (3 cohort studies) 11 period-specific estimates, most of the estimates showed small but statistically significant decreases in BW for increasing levels of exposure in each trimester and also in the entire pregnancy (1 in whole preg from 18,247 cohort births, 2 in 1st trimester from 376,751 cohort births, 2 in 2nd trimester from 156,303 cohort births, 2 in 3rd trimester from 376,751 cohort births), and a last month from 138,056 cohort births.		

13. Bosetti [13] 06/02/2010 [6; 5 Italy, 1 Spain]	TSP, PM_{10}, $PM_{2.5}$	PTB, LBW, VLBW, SGA	**PTB** **TSP** (2 studies)-a time series and cross-sectional; 103,518 births. Significant for whole pregnancy period for the time series study. Associated for all trimesters but significant for 1st trimester for the cross-sectional study. **PM10** (9 studies)-3 time series and 6 cross-sectional;480,159 births and unreported for 2 studies. 5 studies examined 1st trimester and 2 found significant RR, 1 each non-significant increase and decrease RR and 1 no association. One found significant increased RR in first month and one found non-significant RR in whole preg. Only one reported 2nd trimester with no association. 3 reported 3rd trimester with non-significant increase RR. 3 reported last 6 week with one significant risk. **PM2.5** (4 studies)-all cross-sectional; 210,459 births and unreported in one study 2 out of 4 found significant for risk for 1st trimester. One found significant association for whole pregnancy. One each studied last 6 and 2 weeks and last 2 week was significant. No report on 3rd trimester. **LBW** 17 studies (2 case-control, 1 ecological, 14 cross-sectional) **TSP** (5 studies)- 3 cross-sectional, 1 case-control (for VLBW) and 1 ecological; 459,952 births excluding unreported births for the ecological study. 1 reported nonsignificant increased risk for LBW in whole preg the one case-control was significant for VLBW. 2 reported for 1st trimester and both showed significant increased risk. Only one reported for 2nd trimester and was significant risk. 3 reported for 3rd trimester and 2 showed significant risk. **PM10** (12 studies)- 11 cross-sectional on LBW and 1 case-control on VLBW; 1,259,186 births with one unreported size.	Further and better studies are needed to clarify whether there is a real effect of PM on these adverse pregnancy outcomes. The studies should include: better assessment of exposure using, for example geographic information system techniques, such as land use regression or air dispersion models, which take mobility into account; better information on confounders and analyze potential residual confounding; and measurement of biomarkers of exposure or personal exposure monitoring in order to validate exposure estimates. Other studies focused on better outcomes, such as ultrasound measurements during birth, may also help understand the effect of air pollution on adverse pregnancy outcomes.	NB: No statement on the limitations and strengths of the review. But highlighted the limitations of the included primary studies (and summarised this in the conclusion and recommendations)

			4 reported non-significant risk for whole preg 6 reported 1st trimester where 4 showed non-significant risk, 1 no association and 1 decreased risk. 6 reported for 2nd trimester where 2 showed significant risk, 3 non-significant risk and 1 decreased risk. 7 reported 3rd trimester with none significant, 3 each non-significant increase and decrease risks, and one no association. **PM2.5** (3 studies)- all cross-sectional; 429,769 births. 2 reported whole preg where one showed significant increase risk and the other found decreased risk. One reported prevalence ratio which was significant in 3rd trimester. **SGA** **PM10** (3 studies)- all cross-sectional; 234,922 births. One did not report RR. One reported on whole preg and found non-significant RR. The other one reported no association prevalence ratio for 1st and 3rd trimesters but significant for 2nd trimester. **PM2.5** (3 studies)-all cross-sectional; 226,552 births. One reported on whole preg and found non-significant RR. 2 reported on 1st trimester where one found significant increased risk and the other found a decreased risk. Both found significant risk for 2nd trimester. One found significant risk for 3rd trimester and the other decreased risk.		
14. Ghosh [14] 09/05/2007 [4, UK]	TSP, PM_{10}, $PM_{2.5}$, CO, SO_2, NO_2, O_3	BW, LBW, VLBW, PTB	**LBW (3 studies)** A case-control study (36,305 births in USA) that examined gender differential with males as reference reported significant excess risk in females for LBW compared to males for exposures PM10, CO, O3. One cohort study in China (74671 births) reported higher but insignificant risk each for exposures SO2 and TSP in females. **VLBW** Another case-control (345 births in USA) also reported insignificant excess risk in females for combined TSPSO2 exposure. **BW (1 study)** A study from Poland, a prospective cohort of 362 births reported a significantly lower mean in females (212.80 g) for PM2.5	'Further investigation to ascertain interaction is required in high-powered datasets across different populations.'	'The interactive effects of air pollution, pregnancy outcomes and gender should be considered in light of known limitations such as exposure misclassification, bias and confounding. Studies that reported a gender based estimate were those that reported a positive association between air pollution and adverse pregnancy outcomes. None

			PTB NB: None examined exposure-outcome association with empirical measurement of the exposures. The review authors (Ghost et al, 2007) estimated unadjusted (except 2 adjusted) gender-specific effects between air pollutant and birth outcomes based on additional information from primary authors (4 studies); one study for each association. **LBW-SO2;** excess significant adjusted OR in males but insignificant in females. **LBW-TSP**; excess significant adjusted OR in males but insignificant in females. **LBW-PM10**; excess but insignificant unadjusted OR in both but higher in males than females. **LBW-NO2**; excess significant unadjusted OR in males but insignificant in females. **LBW-CO**; excess but insignificant unadjusted OR in both but lower in males than females. **LBW-O3**; reduced insignificant unadjusted OR in both but higher in males than females. **VLBW-TSPSO2**; excess but insignificant unadjusted OR in both but higher in males than females. **BW-PM2.5**; no evidence of significant difference between genders, unadjusted. **PTB-PM10**; excess but insignificant unadjusted OR in both but higher in males than females. **PTB-CO**; excess significant unadjusted OR in males but insignificant in females. **PTB-O3**; reduced significant unadjusted OR in both but lower in males than females. **PTB-NO2**; excess significant unadjusted OR in both but higher in males than females.		of the studies that reported negative associations explored gender effects. Thus publication bias may be relevant here.'
15. Glinianaia [15] 09/01/2004 [5, UK]	TSP, $TSPSO_2$, PM_{10}, $PM_{2.5}$	LBW, VLBW, IUGR, PTB, and SB	**LBW/BW** **TSP** (3 cohort studies); 6 trimester-specific cases; increased non-significant risk for 2 studies in 1st, 1 in 2nd and 2 in 3rd trimesters of LBW. One found significant increased risk in 3rd trimester for LBW. 3 studies also reported significant reduction in mean BW (2 in 1st and 1 in 3rd trimesters).	'Future research is needed to clarify whether there is a small adverse effect of particulate air pollution on fetal health. Further ecologic studies are unlikely to add to the evidence. A time-series approach could be justified	**Limitations** 'Publication bias, and the exclusion of papers not published in English, could have decreased the number of results available for review. Most papers reported the results relating

			One ecological study with unadjusted OR also found increased non-significant OR of LBW. **PM10** (1 cohort); found decreased non-significant OR of LBW in each of the trimesters. **VLBW** Reported by one case-control study that found increased significant risk for TSPSO2. **IUGR** **TSP;** 1 cohort study found non-significant decreased OR in the 1st trimester and no association in other trimesters. **PM10**: 2 cohort studies each found significant increased adjusted OR in 1st month **PM2.5**; 1 cohort study found significant increased OR in 1st month. **PTB** **TSP**; 1 cohort study reported and found increased OR which was significant in 1st trimester but non-significant in 2nd and 3rd trimesters. Another cohort study found increased risk for 7-day lag and significant reduction in mean gestational age. **PM10**; 1 cohort reported and found increased risk which was non-significant in the 1st month but significant in 6 weeks before birth. **Stillbirth** **TSP**: Reported by an ecologic study with annual mean and found decreased non-significant adjusted rate. **PM10**: reported by one time-series study and found non-significant increased adjusted rate ratio of daily intrauterine deaths.	if the study examines the potential effect of short-term changes in air pollutant levels on acute events (eg, preterm birth, stillbirth), but it would not be useful when examining birthweight as an outcome variable. More refined methodologic designs are needed such as large population-based cohort or case-control studies using individual fetal outcome and covariate data and high-quality exposure data. Studies are more likely to find evidence for a small effect if they involve settings with wide variation of air pollution levels.’	to various combinations of pollutant, exposure period, and outcome. The findings should be interpreted with caution in these circumstances because of the increased likelihood of a positive finding occurring by chance. All relevant comparisons should be reported, whatever the findings. Misclassification of exposure, which biases effect estimates toward the null. Studies exploring the health effects of PM are complex to summarize because the definitions and measurement techniques have varied over time. Differences in PM level, size, and composition could have affected the strength of association between PM and fetal growth in the different geographic settings. Most semi-individual studies in this review chose to control for key confounding factors (ie, gestational age, maternal age, infant sex) at an individual level. However, adjustments were made less often for other important individual risk factors such as smoking,

					socioeconomic status, and environmental exposures, including other air pollutants (eg, SO2,NO2)’

Note: NO_2, Nitrogen dioxide; NO_x, Nitrogen oxides; CO, Carbon monoxide; O3, Ozone; SO_2, Sulphur dioxide; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤ 2.5μm; PM_{10}, particulate matter at aerodynamic diameter ≤ 10μm; TSP, total suspended particles; SPM, suspended particulate matter; PTB, preterm birth; BW, birth weight; LBW, low birth weight; TLBW, term low birth weight; VLBW, very low birth weight; SGA, small-for-gestational age; IUGR, intrauterine growth retardation; FGR, foetal growth restriction; SB, stillbirth; SAB, spontaneous abortion; TBWT, term birth weight; OR, odd ratio; CI, confidence interval; SES. Socioeconomic status; BMI, body mass index.

Table S3.4 Results and additional information on systematic reviews with meta-analysis, ordered from recent to earliest.

First author, date [number of authors, countries]	Exposure(s)	Outcome(s)	Main meta-analysis results and publication bias	Subgroups/Sensitivity	Researchers' recommendations	Researchers' stated strengths and limitations
1. Gong [16] 04/10/2021 [5; 4 China, 1 USA]	$PM_{2.5}$	TBW (continuous outcome)	**Change in TBW per 10 µg/m³** **Entire pregnancy** 26 cohort studies; 23,926,140 births RE model pooled beta= -16.54 (-20.07, -13.02) I^2= 95.6% 'No evidence of significant publication bias for any of the meta-analyses based on the Begg's test. However, a potential publication bias was observed in the overall meta-analyses during the entire pregnancy and the third trimester based on the Egger's test. There was no evidence of significant publication bias for the LUR-models subgroup based on the Begg's and Egger's test ($p > 0.05$)'.	**Change in TBW per 10µg/m³** **By trimester**, *1st trimester* 13 cohort studies; 6,707,042 births RE model pooled beta= -5.81 (-8.39, -3.23) I^2= 91.3% *2nd trimester* 13 cohort studies; 6,707,042 births RE model pooled beta= -6.17 (-8.46, -3.87) I^2= 85.4% *3rd trimester* 20 cohort studies; 10,361,367 births RE model pooled beta= -5.02 (-8.22, -1.82) I^2= 93.7% **Entire pregnancy by** exposure assessment methods. *Aerosol Optical depth-based method* 6 cohort studies; 2,163,255 births RE model pooled beta= -41.58 (-65.50, -17.67) I^2= 95.6% *From monitoring stations* 10 cohort studies; 12,792,286 births RE model pooled beta= -11.53 (-17.11, -5.947) I^2= 97.3% *Interpolation or dispersion models* 5 cohort studies; 5,888,150 births	'More studies based on LUR models in this area are needed to verify our observation' 'With regard to exposure prediction, further improvements in the temporal resolution of LUR predictions could allow an assessment as to whether very short-term (e.g., even hourly) peak maternal exposures are more critical than steady long-term exposures in affecting birth outcomes. Improvements in the GIS database would likely improve performance of LUR models in generating fine-scale spatial predictions.' 'Enhancements to	**Strengths** 'This is the first systematic review and meta-analysis of effects of PM2.5 on TBW.' **Limitations** 'The subgroup analyses included relatively few studies and needs more future studies to verify the findings. Second, the susceptible exposure time window has not yet been clarified.' 'Third, the I2 statistic, like other metrics, suffers from statistical power problems (Ioannidis, 2008).' 'Fourth, studies on non-linear concentration-response relationship were excluded because the results could not be inferred to relevant linear dose-response effect estimate and could not be pooled into the meta-analysis'.

				RE model pooled beta= -10.78 (-17.55, -4.01) I^2= 86.6% *LUR models* 5 cohort studies; 3,082,449 births RE model pooled beta= -16.77 (-22.51, -11.03) I^2= 18.3% **1st trimester by exposure assessment methods** *Aerosol Optical depth-based method* 5 cohort studies; 818581 births RE model pooled beta= -9.39 (-19.21, 0.44) I^2= 78.7% *From monitoring stations* 6 cohort studies; 3,194,424 births RE model pooled beta= -7.20 (-11.00, -3.41) I^2= 95.4% *Interpolation or Hierarchical Bayesian models* 4 cohort studies; 2,875,930 births RE model pooled beta= 2.00 (-6.39, -10.39) I^2= 92.8% *LUR models* 3 cohort studies; 3,012,531 births RE model pooled beta= -7.82 (-10.68, -4.97) I^2= 0.0% **2nd trimester by exposure assessment methods.** *Aerosol Optical depth-based method* 5 cohort studies; 818581 births RE model pooled beta= -13.38 (-30.38, 3.63) I^2= 89.5% *From monitoring stations* 6 cohort studies; 3,194,424 births	LUR models using spatio-temporal models that incorporate geostatistical smoothing (Keller et al., 2015), or that integrate other exposure predictions from satellite data or chemical transport models with LUR models (Lv et al., 2016; Friberg et al., 2016), may further reduce exposure measurement error and bias, as could use of biomarkers of exposure in pregnant women.' Application of models for generating exposure predictions for other pollutants may provide important insights into the components of the air pollutant mixture that are more toxic in producing adverse birth outcomes. 'More accurate exposure	

				RE model pooled beta= -3.54 (-5.11, -1.96) I^2= 68.8% *Interpolation or Hierarchical Bayesian models* 4 cohort studies; 2,875,930 births RE model pooled beta= -3.32 (-5.96, -0.69) I^2= 6.6% *LUR models* 3 cohort studies; 3,012,531 births RE model pooled beta= -13.48 (-16.36, -10.61) I^2= 85.4% **3rd trimester by exposure assessment methods** *Aerosol Optical depth-based method* 6 cohort studies; 875,214 births RE model pooled beta= -8.78 (-13.17, -4.40) I^2= 33.6% *From monitoring stations* 6 cohort studies; 3,590,147 births RE model pooled beta= -2.44 (-6.66, -1.79) I^2= 96.3% *Interpolation or Hierarchical Bayesian models* 4 cohort studies; 2,875,930 births RE model pooled beta= 2.57 (-2.08, 7.21) I^2= 48.8% *LUR models* 4 cohort studies; 3,020,076 births RE model pooled beta= -14.94 (-17.87, -12.01) I^2= 0.0% **Entire pregnancy by $PM_{2.5}$ concentration levels.** *Mean $PM_{2.5}$ exposure < 10 µg/m^3* 6 cohort studies; 3,868,577 births	assessment methods that incorporate indoor and outdoor pollutant exposures according to the time-activity pattern of pregnant women need to be developed.' 'Relatively standardized covariates are needed to be adjusted to increase the comparability among studies.' More studies based on the distributed lag model (DLM) or a distributed lag non-linear model (DLNM) need to be conducted to provide more precise susceptible exposure windows.'	

				RE model pooled beta= -15.58 (-25.38, -5.79) I^2= 60.8% *Mean $PM_{2.5}$ exposure* > 10 μg/m^3 20 cohort studies; 20,057,563 births RE model pooled beta= -16.58 (-20.35, -12.81) I^2= 96.3% **Entire pregnancy by region** *Asia* 6 cohort studies; 3,033,587 births. RE model pooled beta= -6.37 (-11.20, -1.53) I^2= 77.9% *Europe* 3 cohort studies; 598,061 births. RE model pooled beta= -28.39 (-57.83, 1.04) I^2= 78.3% *North America* 17 cohort studies; 20,294,492 births. RE model pooled beta= -19.12 (-23.62, -14.62) I^2= 95.8% **Change in TBW per IQR μg/m^3** *Entire pregnancy* 21 cohort studies; 19,634,754 births. RE model pooled beta= -8.16 (-10.79, -5.54) I^2= 94.3% **Leave-one-out sensitivity analyses** For the overall meta-analysis and subgroup meta-analyses based on exposure assessment methods during the entire pregnancy there was 'no meaningful impact on the pooled effect estimates or significance except for the interpolation/dispersion models subgroup.'		
2. Zhu [17] 03/08/2021 [11; all China]	$PM_{2.5}$, PM_{10}	SAB	**SAB:** *$PM_{2.5}$ per 10 μg/m^3*	**Leave-one-out sensitivity analysis** No substantial change	'Reducing pollution emissions should	**Strengths** **'**The first systematic review and meta-

			5 studies: (2 cohort, 2 case-control, 1 case crossover); 69,507 SABs RE model pooled RR= 1.20 (1.01, 1.40) I^2= 98.6% *PM_{10} per 10 µg/m^3* 5 studies: (2 cohort, 1 case-control, 1 case-crossover, 1 cross-sectional); 12,741 SABs RE model pooled RR= 1.09 (1.02, 1.15) I^2= 78.6%. Egger's regression and Begg's test; No publication bias for $PM_{2.5}$-SAB but PM_{10}-SAB showed possible publication bias.		be listed as a vital public health strategy to prevent pregnancy complications and improve human reproductive health worldwide.' "Extra studies are warranted to investigate their specific dose-response effects and detailed molecular mechanisms or pathways, and explore the constituent-specific (e.g., the organic compounds, toxic metals) effects of particulate matter exposure on reproductive events. Furthermore, the association underlying ambient particulate matter and SAB risks with the synergistic effects of other factors (e.g., physical, genetic, immunological, meteorological factors) still needs	analysis of epidemiological evidence regarding the effects of ambient PM2.5 on TBW**'.** **Limitations** Results were based on the study-specific effect estimates only. Results included only 'single-pollutant model and failed to evaluate the latent interactions among different pollutants.' 'The small number of the included studies precluded our ability to conduct subgroup analyses and explore extensively other potential sources of heterogeneity, and this present meta-analysis could not make further estimates of the exact dose- response relationship between PM2.5 or PM10 exposure levels and risks of SAB for insufficient information.'

					to be fully discussed and elucidated.'	
3. Ju [18] 09/07/2021 [7; all China]	$PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3. Ranges: NA	PTB (including subtypes: moderate, very, and extremely PTB).	**PTB:** **Entire pregnancy** *$PM_{2.5}$ per 10 μg/m^3* 31 cohort studies: 1,007,827 PTBs RE model pooled RR= 1.070 (1.046, 1.095) I^2= 88.9% *PM_{10} per 10 μg/m^3* 15 cohort studies: 210,850PTBs RE model pooled RR= 1.034 (1.009, 1.059) I^2= 91.6 % *NO_2 per 10 μg/m^3* 20 cohort studies: 343,203 PTBs RE model pooled RR= 1.010 (0.990, 1.030) I^2= 88.3% *SO_2 per 10 μg/m^3* 8 cohort studies: 158,735 PTBs RE model pooled RR= 1.072 (0.978, 1.175) I^2= 92.7% *O_3 per 10 μg/m^3* 11 cohort studies: 243,295 PTBs RE model pooled RR= 1.032 (1.018, 1.047) I^2= 86.3%	**PTB** **$PM_{2.5}$ per 10 μg/m^3** *1st trimester* 26 cohort studies: 920,837 PTBs RE model pooled RR= 0.982 (0.957, 1.007) I^2= 96.5% *2nd trimester* 23 cohort studies: 880,542 PTBs RE model pooled RR= 1.034 (1.001, 1.069) I^2=97.0 % *3rd trimester* 23 cohort studies: 923,545 PTBs RE model pooled RR= 1.018 (0.999, 1.037) I^2=93.2% *Last month* 5 cohort studies: RE model pooled RR= 0.997 (0.976, 1.018) I^2=0.0 % **PM_{10} per 10 μg/m^3** *1st trimester* 16 cohort studies: 263,928 PTBs RE model pooled RR=0.970 (0.937, 1.003) I^2= 97.4% *2nd trimester* 14 cohort studies: 257,476 PTBs RE model pooled RR=0.993 (0.960, 1.028) I^2= 97.8% *3rd trimester* 13 cohort studies: 223,574 PTBs RE model pooled RR=1.007 (0.992, 1.022)	'The results are not stable, there are few relevant literatures, and further investigation is needed, for CO and SO_2. The components of PM2.5 and PM10 should be evaluated in future studies to improve the comparability between studies. 'In addition, although the heterogeneity was reduced to some extent by analytical method, it was still high in most cases in this study. Therefore, it is necessary to further study the sensitive Windows of different air pollutants and their relationship with PTBs.' 'More longitudinal studies and experimental studies to further investigate the causes and	**Strengths** 'This meta-analysis covered a great number of high-quality cohort studies reporting associations between four different types of PTB and seven contaminants, and further sensitivity and subgroup analyses were performed to explore sources of heterogeneity and possible exposure-response relationships'. **Limitations** 'High degree of heterogeneity was found between included studies and among different subgroups.' "It is impossible to further explore the causes of the country-differences without sufficient data from original studies.' 'There was publication bias in exposure to O3 during a specific gestation period of PTB, PM2.5 during a specific gestation period of PTB and very PTB, and PM10

			Egger's and Begg's tests and the funnel plot did not show obvious publication bias. However, 'there was publication bias in exposure to O3 during a specific gestation period of PTB, PM2.5 during a specific gestation period of PTB and very PTB, and PM10 during a specific gestation period of PTB, very PTB and extremely PTB.' 'The trim and fill method, publication bias had little effect' but 'results of PM10 exposure to very PTB and O3 exposure to PTB during pregnancy showed that publication bias had a significant effect.'	I^2= 58.7% *Last month* 3 cohort studies RE model pooled RR=0.987 (0.935, 1.042) I^2= 61.1% **NO_2 per 10 µg/m^3** *1st trimester* 21 cohort studies: 398,229 PTBs RE model pooled RR=0.972 (0.950, 0.994) I^2= 86.9% *2nd trimester* 18 cohort studies: 390,413 PTBs RE model pooled RR=1.002 (0.970, 1.034) I^2= 94.9% *3rd trimester* 15 cohort studies: 331,248 PTBs RE model pooled RR=1.066 (1.031, 1.102) I^2= 91.5% *Last month* 6 cohort studies RE model pooled RR= 1.033 (0.981, 1.087) I^2= 75.8% **SO_2 per 10 µg/m^3** *1st trimester* 7 cohort studies: 166,190 PTBs RE model pooled RR=0.980 (0.930, 1.034) I^2= 91.5% *2nd trimester* 6 cohort studies: 160,122 PTBs RE model pooled RR=0.995 (0.954, 1.037) I^2= 84.8% *3rd trimester* 7 cohort studies: 166,190 PTBs	underlying mechanisms'.	during a specific gestation period of PTB, very PTB and extremely PTB.' 'This paper only studies the relationship between a single pollutant and PTBs, but does not discuss the interaction between multiple pollutants.'

				RE model pooled RR=0.988 (0.939, 1.040) I^2= 90.5% *Last month* 2 cohort studies RE model pooled RR= 1.057 (0.997, 1.121) I^2= 0.0% **O_3 per 10 μg/m^3** *1st trimester* 11 cohort studies: 304,353 PTBs RE model pooled RR=1.035 (1.020, 1.051) I^2= 91.0% *2nd trimester* 8 cohort studies: 293,593 PTBs RE model pooled RR=1.020 (1.001, 1.040) I^2= 94.9% *3rd trimester* 8 cohort studies: 201,663 PTBs RE model pooled RR=1.043 (1.014, 1.072) I^2= 95.5% *Last month* 3 cohort studies RE model pooled RR= 0.994 (0.959, 1.030) I^2= 75.4% **CO per 100 μg/m^3** *1st trimester* 3 cohort studies: 70,680 PTBs RE model pooled RR=0.991 (0.966, 1.017) I^2= 94.7% *2nd trimester* 3 cohort studies: 68,920 PTBs RE model pooled RR=1.031 (0.965, 1.101) I^2= 96.2% *3rd trimester*		

				4 cohort studies: 71,049 PTBs RE model pooled RR=1.002 (0.988, 1.017) I^2= 78.1% *Last month* 2 cohort studies RE model pooled RR= 1.002 (0.992, 1.012) I^2= 79.3% **NO_x per 20 µg/m^3** *1st trimester* 5 cohort studies: 61,828 PTBs RE model pooled RR=1.001 (0.959, 1.044) I^2= 80.4% *2nd trimester* 4 cohort studies: 59,728 PTBs RE model pooled RR=0.991 (0.948, 1.036) I^2= 85.6% *3rd trimester* 2 cohort studies: 26,016 PTBs RE model pooled RR=1.031 (0.996, 1.068) I^2= 6.2% *Last month* 1 cohort study RR = 0.960 (0.930, 1.000) **By region for entire pregnancy** *$PM_{2.5}$ per 10 µg/m^3* Asian (8 cohort studies), RR = 1.061 (1.039, 1.084); North America (16 cohort studies), RR= 1.071 (1.012, 1.134); Oceania (2 cohort studies), RR= 1.400 (1.199, 1.634); European (4 cohort studies), RR= 1.071 (0.859, 1.335); South American (1 cohort study), RR= 0.978 (0.941, 1.017) *PM_{10} per 10 µg/m^3* Asian (6 cohort studies), RR= 1.049 (1.014, 1.085); North America (4 cohort		

				studies), RR= 1.088 (1.005, 1.177); European (5 cohort studies), RR= 0.988 (0.939, 1.040) *NO_2 per 10 µg/m^3* Asian (7 cohort studies), RR= 1.103 (1.009, 1.206); North America (3 cohort studies), RR= 1.010 (0.968, 1.054); Oceania (2 cohort studies), RR= 1.085 (0.734, 1.605); European (8 cohort studies), RR= 1.003 (0.980, 1.028) *SO_2 per 10 µg/m^3* Asian (5 cohort studies), RR=1.009 (0.896, 1.136); North American (2 cohort) 0.982 (0.893, 1.080); Oceania (1 cohort) 2.737 (2.076, 3.609). *O_3 per 10 µg/m^3* Asian (4 cohort studies), RR= 1.071 (1.039, 1.103); North American (4 cohort studies), RR= 1.018 (1.004, 1.032); Oceania (1 cohort study), RR= 1.494 (1.190, 1.876); European (2 cohort studies), RR= 1.010 (1.006, 1.014) *CO per 100 µg/m^3* Asian (2 cohort studies), RR= 1.087 (0.976, 1.211); American (2 cohort studies), RR= 1.004 (0.979, 1.028); European (1 cohort study), RR= 0.898 (0.765, 1.054) *NO_x per 20 µg/m^3* European (2 cohort studies), RR= 0.985 (0.919, 1.056) **Note**: There were trimester-specific results with very small number of studies per region. **By unit of increase for entire pregnancy** *$PM_{2.5}$:* per IQR µg/m^3 (19 cohort studies), RR= 1.074 (1.013, 1.139);		

				per 10 μg/m^3 (8 cohort studies), RR= 1.054 (1.026, 1.082); per 5 μg/m^3 (3 cohort studies), RR= 1.007 (0.889, 1.140); per 1 μg/m^3 (2 cohort studies) 1.551 (1.038, 2.317) *PM_{10}:* per IQR μg/m^3 (7 cohort studies), RR= 1.024 (0.984, 1.064); per 10 μg/m^3 (4 cohort studies), RR=1.033 (0.985, 1.084); per 5 μg/m^3 (2 cohort studies), RR= 1.205 (0.864, 1.679); per 1 μg/m^3 (3 cohort studies), RR= 0.999 (0.942, 1.059); per SD μg/m^3 (1 cohort study), RR= 2.913 (0.801, 10.594) *NO_2:* Per IQR (11 cohort studies), RR= 1.010 (0.990, 1.029); Per 10 μg/m^3 (6 cohort studies), RR= 1.058 (0.982, 1.140); Per 3 μg/m3 (1 cohort study) 0.935 (0.888, 0.984); Per 1 μg/m3 (3 cohort studies), RR= 1.000 (0.982, 1.019); Per 5 ppb (1 cohort study), RR=0.936 (0.744, 1.177) *SO_2:* Per IQR (4 cohort studies), RR= 1.140 (0.987, 1.318); Per 10 μg/m3 (2 cohort studies), RR= 1.121 (0.848, 1.482); Per 3 μg/m3 (1		

				cohort study), RR= 0.903 (0.858, 0.950); Per 1 µg/m3 (1 cohort study), RR= 6.727 (1.103, 41.019) *O_3*: Per IQR (8 cohort studies), RR= 1.013 (1.005, 1.022); Per 10 µg/m3 (2 cohort studies), RR= 1.077 (1.013, 1.146); Per 1 µg/m3 (2 cohort studies), RR= 1.010 (1.006, 1.014); Per 10 ppb (1 cohort study), RR= 1.080 (1.062, 1.114). *CO*: Per IQR (3 cohort studies), RR= 1.001 (0.976, 1.026); Per 100 µg/m3 (2 cohort studies), RR= 1.087 (0.976, 1.211). NO_x Per IQR (1 cohort study), RR= 0.960 (0.921, 1.001); Per 20 µg/m3 (1 cohort study), RR= 1.034 (0.945, 1.131) **Note**: There were trimester-specific results with small number of studies per unit of increase. **By effect estimate for entire pregnancy** *$PM_{2.5}$ per 10* µg/m^3 OR (21 cohort studies), 1.061 (1.005, 1.121); HR (7 cohort studies) 1.073 (1.043, 1.103); RR (3 cohort studies) 1.086 (1.022, 1.153). *PM_{10} per 10* µg/m^3 OR (10 cohort studies), 1.055 (1.012, 1.100); HR (4 cohort studies), 1.001 (0.968, 1.036); RR (1 cohort study), 1.085 (1.051, 1.120). *NO_2 per 10* µg/m^3 OR (13 cohort studies), 1.024 (0.991, 1.059); HR (5 cohort studies), 0.998 (0.973, 1.023);		

				RR (2 cohort studies), 1.222 (0.674, 2.214). *SO_2 per 10* µg/m^3 OR (5 cohort studies), 0.995 (0.909, 1.089); HR (3 cohort studies), 1.357 (0.805, 2.287); *O_3 per 10* µg/m^3 OR (6 cohort studies), 1.031 (1.013, 1.050); HR (5 cohort studies), 1.037 (1.010, 1.065). CO *per 100* µg/m^3 OR (5 cohort studies), 1.034 (1.000, 1.069). *NO_x per 20* µg/m^3 OR (n = 2), 0.985 (0.919, 1.056). **Note**: There were trimester-specific results with small number of studies per effect estimate **Moderate PTB** *$PM_{2.5}$ per 10* µg/m^3 Entire pregnancy (8 cohort studies). RR=1.076 (1.039, 1.115) I^2= 61.3% 1st trimester (3 cohort studies) RR= 0.999 (0.986, 1.012) I^2= 0.0% 2nd trimester (3 cohort studies) RR=1.047 (1.034, 1.061) I^2= 36.2% 3rd trimester (3 cohort studies) RR=1.008 (0.967, 1.051) I^2= 80.9% *PM_{10} per 10* µg/m^3 Entire pregnancy (10 cohort studies) RR=1.081 (1.051, 1.111) I^2= 70.8% 1st trimester (3 cohort studies) RR= 1.012 (0.930, 1.100)		

				I^2= 93.0% 2nd trimester (3 cohort studies) RR=1.045 (1.009, 1.082) I^2= 62.1% 3rd trimester (3 cohort studies) RR=1.018 (0.955, 1.085) I^2= 89.2% *NO_2 per 10* μg/m^3 Entire pregnancy (9 cohort studies) RR=1.066 (1.034, 1.099) I^2= 81.8% 1st trimester (1 cohort study) RR= 0.896 (0.841, 0.955) 2nd trimester (1 cohort study) RR=1.153 (1.063, 1.251) 3rd trimester (1 cohort study) RR=1.010 (0.973, 1.048) *SO_2 per 10* μg/m^3 Entire pregnancy (2 cohort studies) RR=0.859 (0.805, 0.915) I^2= 45.2% 1st trimester (1 cohort study) RR=1.081 (0.820, 1.423) 2nd trimester (1 cohort study) RR=0.935 (0.785, 1.116) 3rd trimester (1 cohort study) RR=0.958 (0.841, 1.091) *O_3 per 10* μg/m^3 Entire pregnancy (6 cohort studies) RR=1.081 (1.060, 1.103) I^2= 60.3% 1st trimester (1 cohort study) RR=1.009 (0.989, 1.029) 2nd trimester (1 cohort study) RR=1.011 (0.981, 1.042) 3rd trimester (1 cohort study) RR=1.015 (0.998, 1.032) *O_3 per 100* μg/m^3 Entire pregnancy (3 cohort studies) RR=0.992 (0.966, 1.019) I^2= 87.0%		

				Very PTB *$PM_{2.5}$ per 10* μg/m^3 Entire pregnancy (9 cohort studies). RR=1.169 (1.120, 1.221) I^2= 79.6% 1st trimester (6 cohort studies) RR=1.090 (1.042, 1.141) I^2= 92.7% 2nd trimester (6 cohort studies) RR=1.151 (1.084, 1.223) I^2= 96.3% 3rd trimester (6 cohort studies) RR= 1.046 (0.981, 1.115) I^2= 96.5% *PM_{10} per 10* μg/m^3 Entire pregnancy (9 cohort studies). RR= 1.133 (1.061, 1.210) I^2= 82.3% 1st trimester (4 cohort studies) RR=1.061 (1.006, 1.119) I^2= 72.8% 2nd trimester (4 cohort studies) RR=1.022 (1.013, 1.032) I^2= 24.2% 3rd trimester (4 cohort studies) RR=1.053 (0.988, 1.121 I^2= 87.3% *NO_2 per 10* μg/m^3 Entire pregnancy (8 cohort studies). RR= 1.194 (1.111, 1.283) I^2= 77.0% 1st trimester (1 cohort study). RR= 0.939 (0.780, 1.131) 2nd trimester (1 cohort study) RR=1.370 (1.165, 1.612) 3rd trimester (1 cohort study) RR=1.109 (1.070, 1.149) *SO_2 per 10* μg/m^3 Entire pregnancy (1 cohort study). RR= 0.774 (0.374, 1.602)		

				1st trimester (1 cohort study) RR=0.928 (0.477, 1.805) 2nd trimester (1 cohort study) RR= 0.869 (0.652, 1.160) 3rd trimester (1 cohort study) RR= 0.960 (0.776, 1.187) *O_3 per 10* µg/m^3 Entire pregnancy (6 cohort studies). RR=1.119 (1.076, 1.164) I^2= 66.3% 1st trimester (2 cohort studies). RR=0.989 (0.892, 1.096) I^2= 83.8% 2nd trimester (2 cohort studies). RR=1.025 (0.974, 1.078) I^2=61.2% 3rd trimester (2 cohort studies) RR=0.993 (0.970, 1.017) I^2=0.0% *CO per 100* µg/m^3 Entire pregnancy (1 cohort study). RR= 0.991 (0.965, 1.017) **Extremely PTB** *$PM_{2.5}$ per 10* µg/m^3 Entire pregnancy (3 cohort studies). RR= 1.129 (1.019, 1.250) I^2= 78.0% 1st trimester (1 cohort study) RR= 1.140 (1.110, 1.180) 2nd trimester (1 cohort study) RR= 1.090 (1.060, 1.130) 3rd trimester (1 cohort study) RR= 1.000 (0.960, 1.040) *PM_{10} per 10* µg/m^3 Entire pregnancy (5 cohort studies). RR= 1.253 (1.133, 1.385) I^2= 88.8% 1st trimester (1 cohort study) RR= 1.090 (1.070, 1.120) 2nd trimester (1 cohort study) RR= 1.030 (1.010, 1.050)			

				3rd trimester (1 cohort study) RR= 0.990 (0.960, 1.020) *NO_2 per 10* µg/m^3 Entire pregnancy (4 cohort studies). RR= 1.228 (1.037, 1.454) I^2= 88.0% *O_3 per 10* µg/m^3 Entire pregnancy (2 cohort studies). RR=1.259 (1.084, 1.463) I^2= 75.9% *CO per 100* µg/m^3 Entire pregnancy (2 cohort studies). RR= 0.930 (0.847, 1.022) I^2= 86.9% **Note**: As reported in overall PTB, there were subgroup results for the PTB subtypes but with very limited studies, predominantly 1 or 2 studies per subgroup (by study region, increment unit and study effect estimation model). **Leave-one-out sensitivity analysis** No substantial change.		
4. Xie [19] 13/06/2021 [10; 9 China, 1 USA]	$PM_{2.5}$	Stillbirth	**Stillbirth per 10 µg/m^3 PM2.5** ***Entire pregnancy*** 6 studies: 5 cohort and 1 case-control; 3,222,578 births. RE pooled OR; 1.15(1.07,1.25) I^2= 74.7% (high) with p= 0.001 No publication bias reported by Egger's test	**1st trimester** 6 cohort studies; 3,892,183 births. 1.01(0.90,1.13) I^2= 87.0%(high) with P<0.001 **2nd trimester** 5 cohort studies; 3,762,441 births 1.06 (0.98,1.14) I^2= 80.1%(high) with P<0.001 **3rd trimester** 4 cohort studies; 3,180,667 births 1.09 (1.01,1.18) I^2= 78.9%(high) with p=0.003	'Studies should use exposure assessment models (land use model, dispersion model, etc.) or satellite remote sensing technology to estimate individual exposure level, adopt identical outcome definition, and adjusted more comprehensive confounding factors.' 'Further pathophysiological	**Strengths** 'Included recently published studies, and included more studies and population, which enhanced the reliability of the results.' Second, a new risk of bias assessment instrument was applied to assess the risk of bias of the included studies. Compared with other tools, it was more suitable for the observational air pollution epidemiological

					researches and high quality population studies were still warranted'. 'It was beneficial to carry out corresponding measures to reduce the stillbirth rate, so as to mitigate the social and economic burdens caused by stillbirth.'	studies on pregnant outcomes. Third, cumulative meta-analysis was conducted to reveal the effects of medical condition on the association between maternal exposure to PM2.5 and stillbirth.' **Limitations** ' First, most of the included studies appointed the concentration of PM2.5 of nearby monitoring stations to pregnant women, which might lead to potential exposure bias.' We just pooled the estimates of the single-pollutant model, failing to pool the multiple-pollutant model for few studies reported the results of it. There were high heterogeneity among the included studies'.
5. Rappazzo [20] 12/05/ 2021 [4; all USA]	O_3	PTB	**Note**: The main analysis was the 1st and 2nd trimesters for O_3-PTB effect estimates for 10 ppb increases. **1st trimester** **(**17 studies: 14 cohort and 3 case-control; 4,525,441 births) RE pooled OR; 1.06 (1.03, 1.10) I^2= 97% (high)	**1st trimester** **Leave-one-out sensitivity analyses** Indicated that no single study had a substantial influence on the pooled estimate. **Continent-specific** Australia; 1.15 (1.09, 1.22) with I^2= 0.24% (low) Asia; 1.03 (1.01, 1.04) with I^2= 84.58% (high)	'Further exploration in studies of ozone and PTB could address uncertainties, particularly with more complete consideration of other PTB risk factors, such as	**Strengths** The incorporation of an evaluation of study quality to our methods. 'Inclusion of a larger number of studies compared to previous meta-analyses'. 'Able to focus on specific time windows within pregnancy, and

			p <0.0001 with a prediction interval of 0.95–1.19. **2^{nd} trimester** (15 studies: 12 cohort and 3 case-control; 4,713,201 births) RE pooled OR; 1.05 (1.02, 1.08) with a prediction interval of 0.95–1.16. I^2= 97% (high) with p <0.001. **Overall confidence of evidence** Moderate **Publication bias** **1^{st} trimester** funnel plot and Egger's test (p<0.001) indicated the presence of potential publication bias but a rank correlation test did not (p = 0.2). Trim-and-fill analyses estimated three missing studies and resulted in a pooled odds ratio 1.04 (1.00, 1.08) **2^{nd} trimester** Funnel plot appeared balanced, the Egger's test (p<0.01) indicated evidence for potential publication bias but trim-and-fill analysis estimated no missing studies and rank correlation testing was non-statistically significant (p=0.55).	Europe; 1.14 (1.08, 1.20) with I^2= 60.39% (moderate) North America; 1.01 (1.00, 1.02) with I^2= 3.74% (moderate). **Meta-regression** Indicated that a some of the variability in 1st trimester was explained by continent of study, **2^{nd} trimester** Leave-one-out sensitivity analyses, indicated no single study had a substantial influence on the pooled estimate. **Meta-regression** No factors explained the observed heterogeneity in associations during the 2nd trimester.	socioeconomic status, and race/racism.'	perform several sensitivity analyses (e.g., trim and fill, leave one out, sub-group analyses) to examine robustness of the pooled effect estimates.' **Limitations** **"** The ability of the study quality analysis to identify specific influential components of the study quality scores is likely limited due to the large number of covariates adjusted for and other variability in the study designs and statistical analyses.**"** Study quality analysis did not directly consider statistical power. ' The inability to account for potential co-pollutant confounding is a limitation in the meta-analysis.' ' Information about the concentration-response relationship for ozone exposure and preterm birth is unavailable and an additional limitation.' 'Short-term ozone exposures may act on birth outcomes through

						different mechanistic pathways than long-term exposures, and thus were not included in this review.' No clear biological mechanism. 'Pooling estimates based on different averaging times likely contributes additional heterogeneity compared to analyses based on a consistent averaging time, and we did not adjust for effect measure in the meta-analysis'.
6. Zhang [21] 22/02/2021 [7; All China]	PM2.5, PM10, SO2, NO2, CO, O3	Stillbirth	**Stillbirth with:** **PM2.5 per 10 µg/m3 increase** *Entire pregnancy* 7 studies (4 retrospective and 2 prospective cohorts and 1 case-control; 4,647,479 births) Pooled OR = 1.103 (1.074 to 1.131) I^2= 62.1%--moderate with p=0.015 **PM10 per 10 µg/m3 increase for** *Entire pregnancy* 4 studies (1 retrospective and 2 prospective cohorts and 1 case-control; 1,888,661 births) Pooled OR = 1.005 (0.961 to 1.049) I^2= 16.8%--low with p=0.307 **SO2 per 10 µg/m3 increase for e***ntire pregnancy*	**Stillbirth per 10 µg/m3 increase in PM2.5 by** ***trimester*** *1st trimester* 7 studies (5 retrospective and 2 prospective cohorts; 5,078,391 births) Pooled OR = 0.962 (0.833 to 1.090) I^2= 88.7%--high with p=0.000 *2nd trimester* 6 studies (4 retrospective and 2prospective cohorts; 4,855,016 births) Pooled OR = 1.028 (0.939 to 1.116) I^2= 82.4%--high with p=0.000 *3rd trimester* 5 studies (3 retrospective and 2 prospective cohorts; 4,273,242 births) Pooled OR = 1.094 (1.008 to 1.180) I^2= 74.8%--moderate	'Prospective cohort studies, collecting maternal lifestyles and other exposures (e.g., green space) which may confound the air pollution-stillbirth relationship, with better study design and personal exposure strategies, are warranted in the future, especially in developing countries with severe air pollution. Furthermore, biological	**Strengths** "Our study used a large sample size and estimated a wide range of air pollutants, including airborne PM and gaseous pollutants. Second, we evaluated the quality and risk of bias of the included studies according to the widely accepted NOS and OHAT tools;all included studies were of high quality; with scores ranging from 7 to 8 for the NOS scale and from 3 to 5 for Mustafic's adapted scale (Mustafic et al., 2012)(Table S3), which makes our

			6 studies (3 retrospective and 2 prospective cohorts and 1 case-control; 5,657,493 births) Pooled OR = 1.020 (0.985 to 1.055) I^2= 7.3%--low with p=0.369 **NO2 per 10 µg/m3 increase for e***ntire pregnancy* 5 studies (2 retrospective and 2 prospective cohorts and 1 case-control; 5434118 births) Pooled OR = 1.026 (0.9996 to 1.057) I^2= 65.2%--low with p=0.022 **CO per 10 µg/m3 increase for e***ntire pregnancy* 6 studies (3 retrospective and 2 prospective cohorts and 1 case-control; 5,657,393 births) Pooled OR = 1.0007 (0.9991 to 1.0022) I^2= 52.8%--moderate with p=0.060 **O3 per 10 µg/m3 increase for e***ntire pregnancy* 6 studies (2 retrospective and 2 prospective cohorts, 1 case-control, and 1 case-crossover; 5,259,297 births) Pooled OR = 1.008 (0.974 to 1.043) I^2= 63.8%--moderate with p=0.017 **Publication bias** "Egger's tests were used to assess for publication bias for each pollutant during the short- and long-term exposure,	with p=0.003 **Stillbirth per 10 µg/m3 increase in PM10 by *trimester*** *1st trimester* 6 studies (2 retrospective and 3 prospective cohorts, and 1 case-control; 2,471,949 births) Pooled OR = 0.936 (0.830 to 1.042) I^2= 94.0%--high with p=0.000 **2nd** *trimester* 5 studies (1 retrospective and 3 prospective cohorts, and 1 case-control; 2,248,574 births) Pooled OR = 0.985 (0.916 to 1.053) I^2= 77.0%--high with p=0.002. **3rd** *trimester* 4 studies (3 prospective cohorts, and 1 case-control; 1,666,800 births) Pooled OR = 1.040 (0.970 to 1.110) I^2= 89.2%--high with p=0.000 **Stillbirth per 10 µg/m3 increase in SO2 by *trimester*** *1st trimester* 6 studies (3 retrospective and 2 prospective cohorts, and 1 case-control; 5,657,493 births) Pooled OR = 0.994 (0.933 to 1.055) I^2= 73.1%--moderate with p=0.002 *2nd trimester*	mechanistic studies remain needed to clarify the potential pathways underlying the air pollution-stillbirth association countries. Research and aggressive policy interventions, such as developing clean energy aiming at reducing fossil fuel consumption to lower air pollutants emissions, should be on the top list of the world leaders' agenda not only for the health of contemporary but also for future generations, which can help improve intergenerational inequity.'	findings reliable and valuable for public health professionals and policy makers. Third, we performed a meta-analysis of the effect estimates of long-term exposure by trimesters and found critical exposure windows for PM2.5, CO, and O3 exposure, which may help provide effective preventive measures for decreasing the risk of stillbirth, such as target policy interventions aimed at reducing the emission of PM2.5, CO, and O3.' **Limitations** 'First, the number of studies included is limited. Second, most of the included studies were performed in developed countries or areas with low levels of air pollution, which is not enough to represent the global population. Third, a possible correlation was observed among various air pollutants. Several studies have analyzed the correlation between

			and no substantial bias was detected."	5 studies (2 retrospective and 2 prospective cohorts, and 1 case-control; 5,434,118 births) Pooled OR = 0.984 (0.918 to 1.050) I^2= 73.2%--moderate with p=0.005 *3rd trimester* 5 studies (2 retrospective and 2 prospective cohorts, and 1 case-control; 5,434,118 births) Pooled OR = 1.095 (0.993 to 1.197) I^2= 88.9%--moderate with p=0.000 **Stillbirth per 10 µg/m3 increase in NO2 b*y trimester*** *1st trimester* 6 studies (3 retrospective and 2 prospective cohorts, and 1 case-control; 6,015,892 births) Pooled OR = 1.004 (0.980 to 1.029) I^2= 56.7%--moderate with p=0.041 *2nd trimester* 6 studies (3 retrospective and 2 prospective cohorts, and 1 case-control; 6,015,892 births) Pooled OR = 0.997 (0.972 to 1.022) I^2= 59.2%--moderate with p=0.032 *3rd trimester* 5 studies (2 retrospective and 2 prospective cohorts, and 1 case-control; 5,434,118 births) Pooled OR = 1.022 (0.995 to 1.050) I^2= 62.7%--moderate with p=0.030		different air pollutants and used the multipollutant model, while others did not. Therefore, some of the reported associations may be spurious. Due to the limited number of included studies, we did not consider the correlation between different air pollutants when conducting the meta-analysis. Fourth, we did not conduct a subgroup analysis to explore the source of heterogeneity due to the small number of studies included. High heterogeneity was observed concerning the air pollution-stillbirth association in some period; hence, we used random effect models to combine the effects. However, as typical limitations of random model, statistical errors may be underrated and overconfident conclusions can be yielded.'

				Stillbirth per 10 µg/m3 increase in CO by *trimester* *1st trimester* 6 studies (3 retrospective and 2 prospective cohorts and 1 case-control; 5,657,393 births) Pooled OR = 1.0000 (0.9985 to 1.0014) I^2= 52.1%--moderate with p=0.064 *2nd trimester* 5 studies (2 retrospective and 2 prospective cohorts and 1 case-control; 5,434,118 births) Pooled OR = 1.0004 (0.9992 to 1.0015) I^2= 38.2%--moderate with p=0.166 *3rd trimester* 5 studies (2 retrospective and 2 prospective cohorts and 1 case-control; 5,434,118 births) Pooled OR = 1.0009 (1.0001 to 1.0017) I^2= 70.3%--moderate with p=0.009 **Stillbirth per 10 µg/m3 increase in O3 by *trimester*** *1st trimester* 6 studies (3 retrospective and 2 prospective cohorts and 1 case-control; 5,482,705 births) Pooled OR = 1.028 (1.001 to 1.055) I^2= 73.5%--moderate with p=0.002 *2nd trimester* 5 studies (2 retrospective and 2 prospective cohorts and 1 case-control; 5,259,330 births) Pooled OR = 1.012 (0.986 to 1.038) I^2= 74.1%--moderate with p=0.004 *3rd trimester* 4 studies (1 retrospective and 2 prospective cohorts and 1 case-control; 4,677,556 births) Pooled OR = 0.978 (0.927 to 1.029)		

				I^2= 93.3%--moderate with p=0.000 **Short-term exposure of PM2.5 and stillbirth** *0 day* (event day) 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.000 (0.997 to 1.003) I^2= 0.0%--No with p=0.513 *1 day* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.997 (0.994 to 1.001) I^2= 0.0%--No with p=0.953 *2 days* 3 studies (one each retrospective, time series, and case-crossover; 261,175 births and unreported for the case-crossover study) Pooled OR = 1.001 (0.999 to 1.004) I^2= 0.0%--No with p=0.723 *3 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.001 (0.999 to 1.004) I^2= 45.7%--low with p=0.175 *4 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.999 (0.996 to 1.003) I^2= 0.0%--No with p=0.450 *5 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.999 (0.996 to 1.002) I^2= 0.0%--No with p=0.8343 **6** *days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.023 (0.947 to 1.098) I^2= 64.9%--No with p=0.091		

				Short-term exposure of PM10 and stillbirth *0 day* (event day) 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.000 (0.998 to 1.001) I^2= 0.0%--No with p=0.681 *1 day* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.999 (0.998 to 1.001) I^2= 12.4%--Low with p=0.285 *2 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.999 (0.998 to 1.001) I^2= 45.2%--Low with p=0.177 *3 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.018 (0.966 to 1.070) I^2= 64.1%--Low with p=0.095 *4 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.000 (0.998 to 1.002) I^2= 0.0%--Low with p=0.644 *5 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.999 (0.997 to 1.001) I^2= 0.0%--Low with p=0.404 *6 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.999 (0.997 to 1.001) I^2= 0.0%--Low with p=0.365 **Short-term exposure of SO2 and stillbirth**		

				0 day (event day) 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.998 (0.990 to 1.006) I^2= 0.0%--No with p=0.838 *1 day* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.000 (0.992 to 1.008) I^2= 0.0%--No with p=1.000 *2 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.026 (0.976 to 1.076) I^2= 60.1%--Low with p=0.081 *3 days* 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 1.002 (0.994 to 1.010) I^2= 0.0%--No with p=0.610 *4 days* 3 studies (1 each retrospective cohort, time series and case-crossover; 261,175 births) with unreported for the case-crossover study Pooled OR = 1.003 (0.995 to 1.011) I^2= 47.6%--Low with p=0.148 **Short-term exposure of NO2 and stillbirth** *2 days* 2 studies (1 case-crossover with unreported birth and 1 time series with 37,800 births) Pooled OR = 1.004 (0.994 to 1.014) I^2= 0.0%--No with p=0.424 *4 days* 2 studies (1 case-crossover with unreported birth and 1 time series with 37,800 births) Pooled OR = 1.003 (0.996 to 1.009) I^2= 0.0%--No with p=0.445		

				Short-term exposure of CO and stillbirth *0 day (event day)* 2 studies (1 retrospective cohort and 1 time series with 261,175 births) Pooled OR = 0.9991 (0.9965 to 1.0017) I^2= 0.0%--No with p=0.524 *1 day* 2 studies (1 retrospective cohort and 1 time series with 261,175 births) Pooled OR = 0.9891 (0.9605 to 1.0177) I^2= 73.4%--moderate with p=0.053 *2 days* 3 studies (1 each retrospective cohort, time series and case-crossover: 261,175 births with unreported for the case-crossover study) Pooled OR = 0.9998 (0.9963 to 1.0033) I^2= 69.2%--moderate with p=0.039 *3 days* 2 studies (1 each retrospective cohort and time series: 261,175 births) Pooled OR = 0.9976 (0.9948 to 1.0003) I^2= 29.1%--Low with p=0.235 *4 days* 2 studies (1 each retrospective cohort and time series: 261,175 births) Pooled OR = 1.0003 (0.9999 to 1.0008) I^2= 0.0%--No with p=0.574 *5 days* 2 studies (1 each retrospective cohort and time series: 261,175 births) Pooled OR = 0.9993 (0.9966 to 1.0019) I^2= 0.0%--No with p=0.639 *6 days* 2 studies (1 each retrospective cohort and time series: 261,175 births) Pooled OR = 1.0002 (0.9978 to 1.0026) I^2= 0.0%--No with p=0.461		

				Short-term exposure of O3 and stillbirth *0 day* (event day) 2 studies (1 retrospective and 1 time series; 261,175 births) Pooled OR = 0.999 (0.997 to 1.002) I^2= 45.8%--moderate with p=0.174 *1 day* 3 studies (1 each retrospective cohort, time series, and case-crossover; 619,541 births) Pooled OR = 0.999 (0.996 to 1.002) I^2= 0.0%--No with p=0.466 *2 day*s 3 studies (1 each retrospective cohort, time series, and case-crossover; 619,541 births) Pooled OR = 1.011 (0.982 to 1.039) I^2=53.5 %--moderate with p=0.116 *3 day*s 3 studies (1 each retrospective cohort, time series, and case-crossover; 619,541 births) Pooled OR = 1.013 (0.987 to 1.040) I^2=50.1 %--moderate with p=0.136 *4 day*s 4 studies (1 each retrospective cohort and time series, and 2 case-crossover; 619,541 births and unreported for one study) Pooled OR = 1.002 (1.001 to 1.004) I^2=32.7 %--moderate with p=0.216 *5 day*s 3 studies (1 each retrospective cohort, time series, and case-crossover; 619,541 births) Pooled OR = 1.020 (0.976 to 1.064) I^2=77.5 %--moderate with p=0.012		

				*6 day*s 3 studies (1 each retrospective cohort, time series, and case-crossover; 619,541 births) Pooled OR = 1.010 (0.971 to 1.049) I^2=74.2 %--moderate with p=0.021 **Leave-out sensitivity analyses** Pooled estimates of long-term NO2 exposure and stillbirth were influenced by the findings of Hwang et al.'s study." Other sensitivity analyses did not substantially change the pooled estimates of long-term PM2.5, PM10, SO2, CO, and O3 exposure on the incidence of stillbirth.' For short-term exposure, "Sensitivity analyses showed that the pooled estimates of lag day 2 for CO exposure and stillbirth were influenced by the findings of Mendola et al.'s study" with no changes in pooled estimates for PM2.5,SO2, and O3 exposures.		
7. Uwak [22] 25/01/2021 [13, All USA]	PM2.5, PM10, and PM2.5-10	BW	***IA. Only 'low' or 'probably low' RoB studies for PM2.5 and PM10. But PM2.5-10 has only 'high' or probably high' RoB studies****.* **BW change per 10 µg/m3 increase in PM2.5** *Entire pregnancy* 15 studies (13 retrospective and 2 prospective cohorts;15,424,198 births) RE pooled beta = −27.55 (-48.45 to −6.65) FE pooled beta =-15.58 (-16.07 to -15.09) I^2= 94%--high with p<0.01	***IB. Only 'low' or 'probably low' RoB studies for PM2.5 and PM10.*** ***But PM2.5-10 has only 'high' or probably high' RoB studies.*** **BW change per 10 µg/m3 increase in PM2.5** ***By trimester*** *1st trimester* 11 retrospective cohort studies; 3,547,223 births) RE pooled beta = −6.50 (-15.07 to 2.07) FE pooled beta =-4.97 (-6.38 to -3.56) I^2= 87%--high with p<0.01 *2nd trimester*	'Public health interventions to address infant birth weight suppression from PM may have a substantial impact on infant health, especially those at high risk for exposure. Future research and implementation strategies are recommended to help optimize interventions and policies to	**Limitations** 'Reliance on expert evaluation in the process used for the risk of bias, quality and strength ratings. However, this limitation was overcome by creating a diverse team of experts from relevant fields to participate in this process The rating of the quality of evidence across studies was dependent on the available data. For instance, PM10 and

			BW change per 10 µg/m3 increase in PM10 *Entire pregnancy* 8 studies (5 retrospective and 3 prospective cohorts; 2,679,928 births) RE pooled beta = −8.65 (-16.83 to −0.48) FE pooled beta =-7.34 (-9.46 to -5.23) I^2= 84%--high with p<0.01 **BW change per 10 µg/m3 increase in PM2.5-10 (coarse PM)** *Entire pregnancy* 5 studies (4 retrospective and 1 prospective cohorts; 12,829,812 births) RE pooled beta = −8.81 (-10.32 to −7.31) FE pooled beta =-8.61 (-9.41 to -7.81) I^2= 0%--No with p=0.54 ***IIA. All studies despite RoB rating*** **BW change per 10 µg/m3 increase in PM2.5** *Entire pregnancy* 28 studies (25 retrospective and 3 prospective cohorts; 44,516,228 births) RE pooled beta = −23.47 (-44.25 to −2.69) FE pooled beta =-13.49 (-13.94 to -13.04) I^2= 98%--high	11 retrospective cohort studies; 3,547,223 births) RE pooled beta = −5.69 (-10.58 to -0.79) FE pooled beta =-5.22 (-6.70 to -3.73) I^2= 68%--moderate with p<0.01 *3rd trimester* 12 studies (11 retrospective and 1 prospective cohort; 3,556,290 births) RE pooled beta = −10.67 (-20.91 to -0.43) FE pooled beta =-5.09 (-6.61 to -3.57) I^2= 84%--high with p<0.01 **BW change per 10 µg/m3 increase in PM10** ***By trimester*** *1st trimester* 6 studies (3 each retrospective and prospective cohorts; 757,843 births) RE pooled beta = 3.22 (-3.13 to 9.58) FE pooled beta =3.54 (-0.55 to 7.63) I^2= 14%--low with p=0.32 *2nd trimester* 6 studies (3 each retrospective and prospective cohorts; 757,843 births) RE pooled beta = -3.37 (-8.22 to 1.48) FE pooled beta =-3.37 (-7.96 to 1.23) I^2= 0%--No with p=0.66	mitigate infant health effects.’	PM2.5 are typically reported separately, but also likely occur in combination. Thus, models that consider multi-pollutant exposures may better represent gestational PM exposure. Most studies fail to consider secondary/co-exposures like ultrafine particulate matter, gas phase pollutants, or heat, which can also affect birth weight. Analyses did not include enough studies to evaluate weekly exposure. There is also the potential for additional unmeasured confounding.’ **Strengths** ‘By publishing a pre-specified protocol and employing two independent reviewers for each study, our analysis includes a degree of transparency and robustness that is absent when using less structured approaches. A major strength of our study is the transparency and thoroughness

			with $p<0.01$ **BW change per 10 μg/m3 increase in PM10** *Entire pregnancy* 21 studies (15 retrospective and 6 prospective cohorts; 10,200,344 births) RE pooled beta = −5.20 (-10.95 to 0.55) FE pooled beta =-3.62 (-4.32 to -2.92) I^2= 95%--high with $p<0.01$ **Publication bias** **PM2.5, PM10:** Begg's and Egger's tests: No evidence of publication bias (all p-values >0.05) was found as assessed using funnel plots and tests for asymmetry. **PM2.5-10:** Insufficient studies for publication test. **Quality of body of evidence according to Navigation guide methods** *PM2.5-BW* reduction (results from **'**low' or 'probably low' RoB studies) 1st trim: very low Entire pregnancy, 2nd and 3rd trimesters: low *PM10-BW* (results from **'**low' or 'probably low' RoB studies)**:** 1st and 2nd trimesters: low	*3rd trimester* 7 studies (3 retrospective and 4 prospective cohorts; 766,910 births) RE pooled beta = -6.57(-10.66 to -2.48) FE pooled beta =-5.74 (-9.68 to -1.80) I^2= 0%--No with $p=0.68$ **BW change per 10 μg/m3 increase in PM2.5-10** ***By trimester*** *1st trimester* 3 retrospective cohorts; 12,349,007 births) RE pooled beta = -2.70 (-3.90 to -1.49) FE pooled beta =-2.70 (-3.48 to -1.91) I^2= 0%--No with $p=0.62$ *2nd trimester* 3 retrospective cohorts; 12,349,007 births) RE pooled beta = -2.90 (-10.04 to 4.23) FE pooled beta =-2.80 (-3.64 to -1.96) I^2= 70%--moderate with $p=0.03$ *3rd trimester* 4 retrospective cohorts; 12,755,634 births) RE pooled beta = -4.93 (-10.82 to 0.96) FE pooled beta =-3.72 (-4.50 to -2.94)		of the Navigation Guide systematic review process, which incorporates the GRADE system for assessing the quality of synthesized human evidence in environmental health research in the absence of randomized clinical trials.'

			3rd trimester and entire pregnancy: moderate *PM2.5-10/BW* 1st, 2nd, and 3rd trimesters: very low Entire pregnancy: low **Strength of evidence of adverse effect** *PM2.5-BW reduction:* "inadequate evidence" for all exposure windows. *PM10-BW reduction* 1st and 2nd trimesters: "inadequate evidence" 3rd trim and entire pregnancy: "limited evidence" *PM2.5-10/BW reduction:* "inadequate evidence" for all exposure windows.	I^2= 76%--high with p<0.01 **IIB. All studies despite RoB rating** **BW change per 10 µg/m3 increase in PM2.5** ***By trimester*** *1st trimester* 18 retrospective cohorts; 28,587,814 births) RE pooled beta = -5.43 (-10.28 to -0.59) FE pooled beta =-3.75 (-4.53 to -2.97) I^2= 87%--high with p<0.01 *2nd trimester* 18 retrospective cohorts; 28,869,530 births) RE pooled beta = -5.65 (-9.27 to -2.03) FE pooled beta =-3.67 (-4.49 to -2.84) I^2= 84%--high with p<0.01 *3rd trimester* 20 studies (19 retrospective and 1 prospective cohorts; 29,003,508 births) RE pooled beta = -7.52 (-13.54 to -1.51) FE pooled beta =-1.37 (-2.20 to -0.54) I^2= 92%--high with p<0.01 **BW change per 10 µg/m3 increase in PM10** ***By trimester*** *1st trimester*		

				21 (15 retrospective, 5 prospective cohorts, 1 cross-sectional; 5,822,040 births) RE pooled beta = -3.02 (-6.18 to 0.14) FE pooled beta =-2.98 (-3.68 to -2.29) I^2= 88%--high with p<0.01 *2^{nd} trimester* 21 (15 retrospective, 5 prospective cohorts, 1 cross-sectional; 5,822,040 births) RE pooled beta = -3.48 (-6.23 to -0.73) FE pooled beta = -1.66 (-2.34 to -0.98) I^2= 88%--high with p<0.01 *3rd trimester* 24 (16 retrospective, 6 prospective cohorts, 2 cross-sectional; 6,259,325 births) RE pooled beta = -2.08 (-5.01 to -0.85) FE pooled beta = -1.27 (-1.95 to -0.59) I^2= 90%--high with p<0.01 **BW change per 10 µg/m3 increase in PM2.5 for entire pregnancy (all studies regardless of RoB) by *ethnicity*** *White* 7 studies (6 retrospective and 1 prospective cohorts;8,893,539 births) RE pooled beta = -32.00 (-60.03 to -3.98) FE pooled beta		

				=-7.74 (-8.71 to -6.78) I^2= 95%--high with p<0.01 *Black* 5 retrospective studies; 8,867,779 births. RE pooled beta = -27.10 (-81.57 to 27.37) FE pooled beta = -11.18 (-12.48 to -9.88) I^2= 93%--high with p<0.01 *Hispanic* 5 retrospective cohort studies; 8,525,968 births. RE pooled beta = -0.63 (-23.16 to 21.89) FE pooled beta = -6.88 (-7.67 to -6.09) I^2= 85%--high with p<0.01 **BW change per 10 µg/m3 increase in PM10 for entire pregnancy (all studies regardless of RoB) by *ethnicity*** *White* 4 studies (3 retrospective and 1 prospective cohorts; 5,461,652 births) RE pooled beta = -9.89 (-11.71 to -8.06) FE pooled beta = -9.89 (-11.11 to -8.66) I^2= 0%--No with p=0.47 *Black* 3 retrospective cohort studies ; 5,452,585 births) RE pooled beta =		

				3.47 (-64.74 to 71.67) FE pooled beta = -11.60 (-13.95 to -9.25) I^2= 97%--high with p<0.01 *Hispanic* 2 retrospective cohort studies; 5,094,081 births) RE pooled beta = -0.13 (-73.70 to 73.45) FE pooled beta = -4.96 (-6.12 to -3.80) I^2= 96%--high with p<0.01 **BW change per 10 µg/m3 increase in PM2.5 for entire pregnancy (all studies regardless of RoB)** ***By spatial scale of exposure assessment*** *Small ((*<5km proximity to monitor*)* 9 studies (6 retrospective and 3 prospective cohorts; 5,122,282 births) RE pooled beta = -20.3 (-34.87 to -5.18) FE pooled beta = -12.64 (-15.53 to –9.74) I^2= 83%--high with p<0.01 *Medium (*census tract, zip code, postal code, nearest monitor, <10 km and >/=5km) 9 retrospective cohort studies; 15,898,061 births) RE pooled beta = -45.07 (−113.16 to 23.02) FE pooled beta = -15.30 (-15.79 to –14.82) I^2= 98%--high with p<0.01		

				Large ((at the city or county level or >/= 10 km*)* 12 studies retrospective cohort studies; 27,441,062 births) RE pooled beta = -9.69 (-24.98 to -5.60) FE pooled beta = -6.35 (-7.30 to –5.40) I^2= 97%--high with p<0.01 **NB**: Trimester specific results for spatial scales were also reported to explore heterogeneity and most had high heterogeneity. **BW change per 10 µg/m3 increase in PM10 for entire pregnancy (all studies regardless of RoB)** ***By spatial scale of exposure assessment*** *Small* 10 studies (4 retrospective and 6 prospective cohorts; 4,193,340 births) RE pooled beta = -10.23 (-17.96 to -2.51) FE pooled beta = -4.56 (-5.50 to –3.61) I^2= 96%--high with p<0.01 *Medium* 6 retrospective cohorts; 3,172,207 births) RE pooled beta = -0.43 (-17.88 to 17.03) FE pooled beta = -3.29 (-5.10 to –1.48) I^2= 96%--high with p<0.01 *Large*		

				8 studies (7 retrospective and 1 prospective cohort studies; 6,781,000 births). RE pooled beta = -4.25 (-10.53 to 2.04) FE pooled beta = -6.11 (-6.69 to –5.54) I^2= 94%--high with p<0.01 **NB**: Trimester specific results for spatial scales were also reported to explore heterogeneity and most had high heterogeneity. **BW change per 10 µg/m3 increase in PM2.5 for entire pregnancy (all studies regardless of RoB)** ***By geographical settings*** *America* 20 retrospective cohort studies: 41,547,647 births) RE pooled beta = -27.36 (-56.98 to 2.26) FE pooled beta = -14.05 (-14.52 to –13.59) I^2= 98%--high with p<0.01 *Asia* 5 retrospective cohort studies: 2,884,855 births) RE pooled beta = -6.47 (-15.34 to 2.39) FE pooled beta = -5.09 (-6.87 to –3.30) I^2= 69%--moderate with p=0.01 *Europe* 3 prospective cohort studies: 83,726 births)		

				RE pooled beta = -17.35 (-26.54 to -8.17) FE pooled beta = -17.35 (-29.74 to –4.97) I^2= 0%-No with p=0.89 **NB**: Trimester specific results for geographical settings were also reported to explore heterogeneity and all had high heterogeneity. **BW change per 10 µg/m3 increase in PM10 for entire pregnancy (all studies regardless of RoB)** ***By geographical settings*** *America* 8 retrospective cohort studies: 6,718,959 births) RE pooled beta = -2.18 (-14.88 to 10.52) FE pooled beta = -4.69 (-5.83 to –3.54) I^2= 96%--high with p<0.01 *Europe* 8 studies (3 retrospective and 5 prospective cohort: 708,168 births) RE pooled beta = -14.55 (-23.52 to -5.58) FE pooled beta = -14.93 (-17.13 to –12.73) I^2= 89%--high with p<0.01 *Asia* 5 studies (4 retrospective and 1 prospective cohort: 2,773,217 births) RE pooled beta = -2.07 (-6.90 to 2.76)		

				FE pooled beta = -0.67 (-1.63 to 0.30) I^2= 88%--high with p<0.01 **NB**: Trimester specific results for geographical settings were also reported to explore heterogeneity and some had high heterogeneity. **Leave-one-out sensitivity analyses**. **PM2.5**: No significant difference but for the second trimester, heterogeneity is explained by a single study (Hyder et al. 2014) with a large effect size Omitting this study reduced I^2 from 68% to 40% and reduced the meta-estimate from − 5.69 g (−10.58, −0.79) to − 3.81 g (−7.88, 0.25)'. **PM10**: No significant difference instance but for the entire pregnancy, heterogeneity was explained largely by a single study (Geer et al. 2012) that reported a positive association, whereas all the other studies consistently showed an inverse association. Omitting this study reduced the I^2 from 84% to 0%, and changed the meta-estimate from − 8.65 g (−16.83 to −0.48) to − 11.22 g (−13.17 to −9.26). PM2.5-10: Heterogeneity was explained in 2nd and 3rd trimester by omitting single study but no difference for 1st trimester and entire pregnancy.		
8. Simonici [23] 03/11/2020 [4, All France]	PM2.5, PM10, NO2	BW/LBW, PTB, SGA	**PTB with** **PM2.5**: 2 cohort studies (74,061 births). 2 studies for whole pregnancy; no association in one and non-significant increased risk in the other.	**BW reduction per 10 µg/m3 increase in NO2** *1st trimester* 4 cohort studies; 3,435 births. FE pooled beta = -13.63 (-28.03 to 0.77) I^2= 35.8%-- low	'Our meta-analysis results provide pooled-risk for 5 combinations of air pollutant and birth weight and	**Limitations** 'The features of the studies described above—such as study population, study design, sample size,

			1 study (71493 births) reported for both 1st and 2nd trimesters and found non-significant decreased risk for both trimesters. **PM10**: 2 cohort studies (74,061 births) 2 for whole pregnancy; both found non-significant decreased risk. 1 study (71, 493 births) reported on both 1st and 2nd trimesters and found non-significant decreased risk for both trimesters. **NO2**: 4 cohort studies (80,458 births) examined whole pregnancy or trimester specific exposure periods. 4 reported for whole pregnancy; 1 found significant increased risk, 1 found non-significant increased risk, and 2 found non-significant decreased risk. 3 reported for 1st trimester; 1 each found significant increased risk, non-significant increased risk, and non-significant decreased risk. 3 reported for 2nd trimester; 2 found non-significant increased risk, and 1 found non-significant decreased risk. 2 reported for 3rd trimester; both found non-significant increased risk. **LBW** **NO2**: 3 cohort studies (84,604 births) examined whole	with p=0.197 *2nd trimester* 4 cohort studies; 3,435 births. FE pooled beta = -8.35 (-23.04 to 6.34) I^2= 25.8%- low with p=0.257 *3rd trimester* 5 cohort studies; 12,502 births. FE pooled beta = -1.73 (-12.83 to 9.36) I^2= 31.5%- low with p=0.212 **Leave-one-out sensitivity** The effect estimates of each 10 µg/m3 increase in NO2 exposure during the entire pregnancy on birth weight showed no significant change by removing one single study, suggesting that the combined results were relatively stable and reliable. This is except for the sensitivity analysis of the association between birth weight and NO2 exposure during the third trimester of pregnancy, where the omission of the study of Clemente et al. (2016) induced a reverse of the association that was hitherto negative; however, the result was still not statistically significant (beta = 2.5, 95% CI = (−9.18, 14.30)). Small variations were visible, and while point combined estimates were rather similar, the precision level of the confidence interval decreased.	PTB, which may provide a coherent exposure–response function for environmental health risk assessments in European countries.’	the classification and definition of infant death, exposure assessment, difference between interquartile (IQR) used to assess the increase of exposure and confounding factors—could all, independently or in combination, affect the quality of each study itself and, also, their comparison in our systematic review. Some factors may overestimate while other one may underestimate the risk of birth outcome. Additionally the search could suffer from study selection biases. Non-English publications of relevant articles may have been ignored. Furthermore, we cannot exclude the possibility that our systematic review could be impacted by publication bias. Indeed, unpublished results (including grey literature and results not statistically significant, which are not available) may influence our meta-

			pregnancy or trimester-specific. 3 reported for whole pregnancy; all found significant increased risk. 2 for 1st trimester: 1 each found non-significant increased and decreased risks. 2 for 2nd trimester: 1 each found non-significant increased and decreased risks. 2 for 3rd trimester: both found non-significant increased risks. **PM2.5**: 2 cohort studies (80616 births). The 2 for whole pregnancy; 1 found significant increased and the other non-significant increased risks. 1 study (6,438 births) reported for all trimesters and found non-significant increased risk for 1st and 2nd but two-fold significant increased risk for 3rd trimester (2.00; CI: 1.10 to 3.62) **PM10**: 2 cohort studies (80616 births) 2 for whole pregnancy; both found non-significant increased risks. 1 study (6438 births) for all trimesters and found no association, non-significant increased and significant increased risks for 1st, 2nd, 3rd trimesters respectively.			analysis findings towards the statistical significance of the risk estimates.’

			SGA **NO2**: 2 cohort studies (1,291 births) examined both whole pregnancy and trimester-specific periods 2 for whole pregnancy; 1 each found non-significant increased and decreased risks. 2 for 1st trimester: 1 each found non-significant increased and decreased risks. 2 for 2nd trimester: 1 each found significant increased and non-significant decreased risks. 2 for 3rd trimester: 1 each found non-significant increased and decreased risks. Other several different indicators for daily exposures as lag days, weeks and months were also evaluated in some studies with diverse findings. "Among studies focusing on the 1st trimester of exposure the risk of adverse birth outcomes ranges from 0.78 to 1.67 with confidence interval range from 0.53 to 2.18. For the 2nd trimester of exposure results (OR) range from 0.83 to 1.67 with a confidence interval range from 0.58 to 2.98. For the 3rd trimester of exposure results (OR) range from 0.88 to 2.00 with a confidence interval range from 0.62 to 3.62. These inconsistent results illustrate			

			the lack of uniformity in the methods employed, difference between cross section, variability of variable's definition, and the lack of studies, particularly in Europe". 'Overall, the results reveal that the risk of adverse outcomes including: PTB, LBW, SGA was not found to be significantly associated with any of the pollutants. As for the other windows of exposure (each pregnancy trimester), results are very heterogeneous and there appears to be no clear trend regardless of the model used. For NO2 exposure results (OR) range from 0.81 to 1.28 with a confidence interval range from 0.91 to 1.74. For PM10 exposure results (OR) range from 0.97 to 1.46 with a confidence interval range from 0.74 to 2.24. And for PM2.5 exposures, results (OR) range from 0.92 to 1.98 with a confidence interval range from 0.72 to 4.19.'			
9. Thayamballi [24] 08/09/2020 [4; all USA]	PM2.5, PM10 (and PM0.1)	BW, LBW/TLBW, PTB, SGA, Stillbirth	**Race/Ethnicity and PM2.5** **LBW**:2 studies (2,011,275 births) in California and found the most adverse effects among Blacks while the least were among Asians. **BW:** 7 studies with varied findings; 3 studies (4,954,011	**BW per 10µg/m3 of PM2.5 for race/ethnicity during entire pregnancy period** **Whites;** 5 retrospective cohort studies (6,484,085 births). Pooled effect = -15.7(-21.4 to -10.1) I^2= 68%-moderate with p= 0.01	'For future studies, researchers are encouraged to conduct and present this type of effect modification analysis. More	**Limitations** "There are some inconsistencies across studies in terms of the definition of variables and selection of exposure windows'. 'The small number of studies limits our

			births) identified Blacks as the most vulnerable. Another study (40,662 births) examined exposure during 3rd trimester and found Hispanics to be most vulnerable, followed by Blacks and then Whites. Another study (1,548,904) for entire pregnancy exposure found Whites to be most vulnerable, no association for Blacks and protective effects for Asians. Furthermore, 2 studies in California (339,674 births) found no strong influence of racial/ethnical effect modifications. **PTB**: 3 studies with varied results; higher risks in Blacks and Asians (231,637 births), Blacks and Hispanics (271,204), and no significant difference between Blacks and non-Blacks (3,389,450 births). **SGA**: Only one study in New Jersey (350,107 births) and found increased risk among the Blacks but not significance among the Hispanics and Whites. **Stillbirth**: Only one study in California (3,026,269 births) and found no support for effect modification. **Race/Ethnicity and PM10** **BW:** 4 studies; no significant difference between the Blacks and Whites in one study (358,504 Connecticut and Massachusetts births), Blacks	**Hispanics:** 5 retrospective cohort studies (6,484,085 births). Pooled effect = -9.3 (-15.8 to -2.7) I^2= 92%-high with P< 0.01 **Blacks:** 4 retrospective cohort studies (6,467,392 births). Pooled effect = -21.9 (-32.0 to -11.7) I^2= 73%-moderate with P= 0.01 **Asians: 3** retrospective cohort studies (4,918,488 births). Pooled effect = -5.8 (-20.7 to 9.0) I^2= 95%-high with P< 0.01 **NB:** “Meta-analysis was conducted if three or more studies were available, which was only the case for race/ethnicity modification on the PM2.5-BW relationship in all race subgroups.”	investigation is particularly expected for PTB, stillbirth, and birth defect outcomes, in order to draw more definitive conclusions about vulnerable subpopulations. Furthermore, other maternal factors, such as household income or medical health coverage, should also be considered as effect modifiers. Sociodemographic status and SES are a complicated measurement and difficult to capture by a single variable; therefore, investigating it from multiple angles is critical to understanding all implications. Characterizing vulnerable subpopulations and quantifying their vulnerabilities are essential for addressing environmental justice since it can ultimately help	ability to make conclusive statements.’ ‘Meta-analysis for race/ethnicity modification on PM2.5-PTB, and PM10-PTB, and educational modification on PM2.5-BW, PM2.5-PTB, and PM10-PTB were not conducted because numerical results of effect modifications were not reported in some of the papers and could not be obtained from the authors.’ ‘Some of the studies included in this review were conducted in the same area, California. Therefore, our findings may be skewed toward California, which would limit its generalization to other parts of the U.S.’ **Strengths** ‘This is a comprehensive review of the literature that encompasses three types of PMs and various types of birth outcomes. To date, only two systematic reviews have been performed on this topic [22, 23], but none

			most vulnerable, followed by Whites, Hispanics, and Asians (3,545,177 Californian births), Hispanics most vulnerable and Blacks less vulnerable during the 3rd trimester exposure (406,627 Atlanta births), and Whites most vulnerable while protective effects in Blacks and Hispanics (1,548,904 Texas births). **PTB:** 2 studies; non-Blacks were more vulnerable in full-gestational exposure (3,389,450 Georgian births), no influence of race/ethnicity in last month exposure (164,905 births in Detroit, Michigan) **SGA**: One study for last month pregnancy exposure (164,905 births in Detroit, Michigan) and found higher non-significant risk among Blacks than Whites. **Maternal Education and PM2.5** **LBW:** 3 studies in California; 2 studies (2,011,275 births) found higher adverse risk among mothers with less than high school for full-gestational exposure. The 3rd study (72,632 births) had non-convergent model for high school but reported no modification for other educational levels. **BW**: 2 studies (1,373,311 Californian births) and found		regulatory agencies allocate resources and design policy interventions for communities that need it the most.’	conducted a meta-analysis.’ ‘Limiting our study area to the U.S. enables us to better investigate the effect modification by maternal factors, which are unique to each country.’ ‘By attempting to perform a meta-analysis on the variables described above, this study revealed a major issue regarding the inconsistency of variable definitions and enlightens the need for a more consistent variable definition.

			more risk of reduced BW among mothers with less than high school/college education. **PTB**: 2 studies with mixed findings; higher risk among mothers with higher education (college/advanced degree graduates) compared to those with less than high school (231,637 Californian births) and opposite (i.e., higher risk in less than high school educated mothers) in a Georgia study (3,389,450 births) but weak evidence of effect modification in both studies. **Stillbirth**: Only one study (3,026,269 Californian births) and found increased risk among mothers with higher education. **Maternal Education and PM10** **PTB**: 2 studies and found no influence of effect modification; similar effects for with or more or less than high school (3389450 Georgian births), protective effect for mothers with less than 12 years education but not different from others (164,905 Michigan births). **SGA**: Only one study (164,905 births) in Detroit, Michigan and found non-significant increased risk among mothers with less than 12 years of education.			

			Publication bias Not reported			
10. Li [25] 04/08/2020 [7, all China]	PM2.5, PM10, NO2, SO2, CO, and O3	LBW	**LBW per 10μg/m3 of PM2.5** ***Entire pregnancy*** (29 cohort studies: 536,218 LBW births and unreported for one study). Pooled RR = 1.081 (95% CI: 1.043 to 1.120) I^2=86.0% - high, p=0.000, $\chi 2$ =199.55 **LBW per 10μg/m3 of PM10** ***Entire pregnancy*** (23 cohort studies [**but** actually 17 studies because Seo et al 2010 for 7 cities in Korea was repeated 7 times for city-specific results]: 286,188 LBW births and unreported for one study). Pooled RR =1.05 (95% CI: 1.03 to 1.08), I^2=% 70.3- moderate, p=0.000, $\chi 2$ =74.08 **NB**: RE for entire pregnancy and 1st trimester while FE for 2nd and 3rd trimester. **LBW per 10ppb of NO2** ***Overall risk for entire pregnancy*** (23 cohort studies; 509,997 LBW births). Pooled RR = 1.030 (1.008 to 1.053), I^2=% 89.5-high, p <0.001, $\chi 2$ = 209.32	***LBW per 10μg/m3 of PM2.5*** ***By trimester*** *1st trimester* (19 studies) RR =1.031(0.972 to 1.093) I^2=95.1% - high, p<0.001, $\chi 2$ = 364.48 2nd *trimester* (20 studies) RR =1.031(0.982 to 1.08) I^2=91.5%- high, p<0.001, $\chi 2$ = 223.43 *3rd trimester* (20 studies) RR = 1.053 (1.010 to 1.097) I^2= 92.0%- high, p<0.001, $\chi 2$ = 237.35 **By the study region for entire pregnancy** *American countries* (18 studies) RR= 1.070 (1.019 to 1.124) *Asian countries* (7 studies) RR=1.044 (0.991 to 1.101) *European countries* (4 studies) RR=1.376 (1.187 to 1.594) ***By unit of increase of PM2.5 for entire pregnancy*** *Per 10 μg/m3 increase* (8 studies) RR=1.071 (1.025 to 1.119) *Per IQR* (15 studies) RR=1.037 (0.994 to 1.081) *Per 5 μg/m3* (3 studies) RR= 1.194 (0.919 to 1.551); *Per 1 μg/m3* (3 studies) RR= 1.211 (0.925 to 1.586). **By effect estimate model for entire pregnancy** *OR* (25 studies) RR=1.078 (1.039 to 1.119) *HR* (2 studies) RR=1.483 (1.149, 1.916) *RR* (2 studies) RR=1.050(0.904 to 1.220) **By the reporting of detailed birth weights (Yes/No) for entire pregnancy**	**NB**: No specific section on this. But from the conclusion. 'The exposure of SO2 or O3 was not significantly associated with increased LBW risk in none of the trimesters, despite the significant effects of the exposure during the entire pregnancy, which need to be further investigated.'	**Limitations** High degree of heterogeneity between the included studies were found in the study, as well as in various subgroups. Most of the exposure data were from the environmental protection agencies, which reflected the average concentration of air pollutants over a period of time, without considering the adverse effects of extreme environmental pollution. Almost all mothers and infants information was from public records, such as birth certificates, which limited the ability to control other important confounding factors. Only the relationship between single pollutant and LBW was investigated in this meta-analysis, while the interactions between multiple pollutants were not explored, due to the inherent limitations of meta-analysis. **Strengths**

			Note: RE was used for the entire pregnancy and 2nd and 3rd trimesters while FE for 1st trimester. **LBW per 100ppb of CO *for entire pregnancy*** (8 cohort studies; 112,239 LBW births) Pooled RR = 1.007 (1.001 to 1.014), I^2= 53.1% -moderate, p= 0.037, $\chi2$ = 14.92 **Note**: RE was used for the entire pregnancy and 2nd and 3rd trimesters while FE for 1st trimester. **LBW per 10ppb of SO2 *for entire pregnancy*** (13 cohort studies); 171,360 LBW births Pooled RR =1.12 (1.02 to 1.24) I^2=82.9%-high, p=0.000 $\chi2$ = 70.34 **Note**: Random effect was used for the entire pregnancy and 1st trimester but fixed effect for 2nd and 3rd trimester. **LBW per 10ppb of O3 *for entire pregnancy (overall risk)*** (14 cohort studies; 311,189 LBW births) Pooled RR = 1.045 (1.005 to 1.086), I^2= 90.3%-high, p <0.001,	*Yes* (16 studies) RR=1.066(1.029 to 1.105) *No* (13 studies) RR=1.103(1.029 to 1.182). ***Others trimesters*** Trimester-specific stratified analyses about the association of PM2.5- LBW in studies reporting the detailed birth weights, per 10 μg/m3 increase, and effect estimate model of OR and HR showed significant effects in the third trimester. **Leave-one-out sensitivity analyses** No significantly change after studies were sequentially excluded one by one. **LBW per 10μg/m3 of PM10** ***By trimester*** *1st trimester* (13 studies) RR = 1.022(0.998 to 1.047), I^2=71.5% -moderate, p<0.001, $\chi2$ = 42.06 *2nd trimester* (13 studies) RR = 1.011 (1.005 to 1.017), I^2=28.2% -low, p=0.161, $\chi2$ = 16.72 *3rd trimester* (13 studies) RR = 1.003 (0.995 to 1.011), I^2=20.6% -low, p=0.236, $\chi2$ = 15.10 **By the study region for entire pregnancy** *American countries* (6 studies) RR= 1.018 (0.971 to 1.067) *Asian countries* (14 studies) RR= 1.050 (1.023 to 1.077) *European countries* (3 studies) RR= 1.105 (1.074 to 1.137) ***By unit of increase of PM10 for entire pregnancy*** *Per 10 μg/m3 increase* (5 studies) RR= 1.072 (0.998 to 1.151) *Per IQR* (17 studies)		This meta-analysis covered a large number of high-quality cohort studies and performed various stratified analyses, which demonstrated the relationship between LBW and common air pollutants

			$\chi2$ = 134.57 **N**: Random effect was used for the entire pregnancy and all trimesters. **Publication bias** **PM2.5** The funnel plot showed no evident publication bias, which was confirmed by the Egger' test (P > 0.05). **PM10** Significant publication bias was suggested in the entire pregnancy (P=0.031) but not the three trimesters (P > 0.05) **NO2** Significant publication bias were suggested in the entire pregnancy (P=0.004) but not the three trimesters (P > 0.05). **CO** The funnel plot indicated no publication bias, which was confirmed by the Egger's test (P=0.05) **SO2** The funnel plot suggested no publication bias, which was confirmed by the Egger's test (P > 0.05) **O3** The funnel plot suggested no evident publication bias, which was confirmed by the Egger's test (P > 0.05)	RR= 1.047 (1.022 to 1.072) *Per 1 μg/m3* (1 study) RR= 1.172 (0.855 to 1.606) **By effect estimate model for entire pregnancy** *OR* (21 studies) RR= 1.043 (1.021 to 1.066) *HR* (2 studies) RR= 1.063 (0.983 to 1.148) **By the reporting of detailed birth weights (Yes/No) for entire pregnancy** *Yes* (7 studies) RR= 1.016 (0.985 to 1.048) *No* (16 studies) RR= 1.078 (1.044 to 1.113) **Other trimesters for the subgroups** Trimester-specific stratified analysis in studies not reporting the detailed birth weights, per IQR increase, and in Asian countries showed significant effects in the second trimester. However, all such stratifications showed no significant effects in the first trimester or third trimester. **Leave-one-out sensitivity analyses** No significantly change after studies were omitted one after the other. **LBW per 10ppb of NO2** ***By trimester*** *1st trimester* (12 studies) RR = 1.022(1.009 to 1.035), I^2=10.6% - low, p= 0.243 $\chi2$ = 12.30 *2nd trimester* (13 studies) RR = 1.013 (0.988 to 1.038), I^2=74.9% - moderate, p<0.001, $\chi2$ =47.79 *3rd trimester* (13 studies) RR = 1.012 (0.969 to 1.058), I^2=78.1% - high, p<0.001, $\chi2$ =54.84 **By the study region for entire pregnancy**		

				American countries (10 studies) RR= 1.009 (0.985 to 1.034) *Asian countries* (7 studies) RR= 1.040 (0.997 to 1.084) *European countries* (6 studies) RR= 1.115 (1.026 to 1.212) ***By unit of increase of NO2 for entire pregnancy*** *Per 10 μg/m3 increase* (6 studies) RR= 1.115 (1.026 to 1.212) *Per IQR* (13 studies) RR= 1.009 (0.989 to 1.030) *Per 1 pphm* (1 study) RR= 1.040 (1.030 to 1.050) *Per 1ppb (1 study)* RR= 1.051 (0.961 to 1.149) *Per 10ppb (2 studies)* RR= 1.024 (0.977 to 1.075) **By effect estimate model for entire pregnancy** *OR* (21 studies) RR= 1.020 (0.999 to 1.042) *HR* (2 studies) RR= 1.331 (0.919 to 1.929 **By the reporting of detailed birth weights (Yes/No) for entire pregnancy** *Yes* (8 studies) RR= 1.023 (0.986 to 1.060) *No* (15 studies) RR= 1.035 (1.007 to 1.064) **Other trimesters for the subgroups** Trimester-specific stratified analysis in studies not reporting the detailed birth weights, per IQR increase, effect estimate model of OR, and at Asian countries showed significant effects in the first trimester. However, all such stratifications showed no significant effects in the second trimester or third trimester. **Leave-one-out sensitivity analyses**		

				No significantly change after studies were omitted one by one, showing consistent with overall findings. **LBW per 100ppb of CO** ***By trimester*** *1st trimester* (5 studies) RR = 1.008 (1.004 to 1.012), I^2=11.6% - low, p= 0.339 $\chi 2$ = 4.53 *2nd trimester* (5 studies) RR = 1.005 (0.990 to 1.020) I^2= 54.2% - moderate, p= 0.068, $\chi 2$ = 8.73 *3rd trimester* (5 studies) RR =1.000 (0.984 to 1.016), I^2= 67.4% - moderate, p= 0.016, $\chi 2$ =12.26 **By the study region for entire pregnancy** *American countries* (3 studies) RR 1.006 (1.000 to 1.011) *Asian countries* (2 studies) RR= 1.045 (0.963 to 1.133) *European countries* (3 studies) RR= 1.006 (0.986 to 1.133) ***By unit of increase of CO for entire pregnancy*** *Per 100 μg/m3 increase* (1 study) RR= 1.023 (0.951 to 1.100) *Per IQR* (5 studies) RR= 1.005 (0.991 to 1.019) *Per 1 pphm* (1 study) RR= *Per 1ppm (1 study)* RR= 1.006 (1.003 to 1.009) *Per 1mg/m3 (1 study)* RR= 1.017 (1.003 to 1.032) **By effect estimate model for entire pregnancy** *OR* (8 studies) RR= 1.007 (1.001 to 1.014)		

				By the reporting of detailed birth weights (Yes/No) for entire pregnancy *Yes* (4 studies) RR= 1.003 (0.995 to 1.011) *No* (4 studies) RR= 1.018 (1.001 to 1.036) **Other trimesters for the subgroups** Trimester-specific stratified analysis in studies not reporting the detailed birth weights, per IQR increase, per 1 mg/m3 increase, Asian countries and at European countries showed significant effects in the first trimester but no significant effects in the 2^{nd} or 3^{rd} trimesters. **Leave-one-out sensitivity analyses** Results were not significantly altered after the studies were omitted one by one. **LBW per 10ppb of SO2** ***By trimester*** *1^{st} trimester* (10 studies) RR = 1.054 (0.996 to 1.116), I^2=64.9% - moderate, p= 0.002 $\chi2$ = 25.61 *2^{nd} trimester* (10 studies) RR = 1.022 (0.994 to 1.052), I^2= 19.6% - low, p= 0.263, $\chi2$ = 11.19 *3^{rd} trimester* (10 studies) RR =0.981 (0.952 to 1.010), I^2= 44.5% - low, p=0.063, $\chi2$ =12.26 **By the study region for entire pregnancy** *American countries* (4 studies) RR= 1.653 (0.982 to 2.783) *Asian countries* (7 studies) RR= 1.049 (0.968 to 1.138) *European countries* (2 studies) RR= 1.108 (0.691 to 1.775)		

				By unit of increase of SO2 for entire pregnancy *Per 100 μg/m3 increase* (1 study) RR= 1.028 (1.016 to 1.041) *Per IQR* (7 studies) RR= 1.338 (1.048 to 1.709 *Per 1 ppb* (2 studies) RR= 1.102 (0.938 to 1.293) *Per 10oppb (1 study)* RR= 0.730 (0.438 to 1.216) *Per 1μg/m3 (2 studies)* RR= 1.108 (0.691 to 1.775)) **By effect estimate model for entire pregnancy** *OR* (12 studies) RR= 1.082 (1.007 to 1.164) *HR* (1 study) RR= 13.951 (6.078 to 32.024) **By the reporting of detailed birth weights (Yes/No) for entire pregnancy** *Yes* (4 studies) RR= 1.028 (1.016 to 1.041) *No* (9 studies) RR= 1.251 (1.012 to 1.545) **Other trimesters for the subgroups** Trimester-specific stratified analysis in studies per IQR increase and at Asian countries showed significant effects in the 2nd trimester. All other such stratifications showed no significant effects in the 1st or 2nd trimesters. **Leave-one-out sensitivity analysis** No significant change, indicating that the results were in consistent with before excluding each study. **LBW per 10ppb of O3** ***By trimester*** *1st trimester* (9 studies) RR = 0.996 (0.947 to 1.046), I^2=78.5% -high, p<0.001 $\chi 2$ = 37.24		

				2^{nd} trimester (8 studies) RR = 1.015 (0.948 to 1.087), I^2= 87.4% - high, p<0.001, $\chi2$ = 55.36 *3^{rd} trimester* (9 studies) RR =1.093 (0.992 to 1.204), I^2= 95.8% - high, p=0.063, $\chi2$ <0.001 **By the study region for entire pregnancy** *American countries* (10 studies) RR= 1.057 (1.013, 1.103) *Asian countries* (3 studies) RR= 1.051 (0.930 to 1.189) *European countries* (1 study) RR= 0.923 (0.859 to 0.992) ***By unit of increase of O3 for entire pregnancy*** *Per 10 μg/m3 increase* (1 study) RR= 0.923 (0.859 to 0.992) *Per IQR* (9 studies) RR= 1.066 (1.006 to 1.131) *Per 10ppb (1 study)* RR= 1.060 (0.942, 1.193) *Per 5ppb* (1 study) 1.173 (1.100 to 1.250) *Per 1 ppb* (1 study) RR= 1.038 (0.973 to 1.108) *Per pphm (1 study)* RR= 0.980 (0.965 to 0.995) **By effect estimate model for entire pregnancy** *OR* (13 studies) RR= 1.024 (0.991 to 1.059) *HR* (1 study) RR= 2.200 (1.751 to 2.765) **By the reporting of detailed birth weights (Yes/No) for entire pregnancy** *Yes* (5 studies) RR= 1.055 (0.987 to 1.127 *No* (9 studies) RR= 1.050 (0.988 to 1.117 **Other trimesters for the subgroups**		

				Trimester-specific stratified analysis in studies per 10 ppb increase and effect estimate model of HR in the 1st trimester, effect estimate model of HR in the 2nd trimester, reporting the detailed birth weights and at Asian countries in the 3rd trimester showed significant effects. **Leave-one-out sensitivity analyses** These indicated that the results were in consistent with before excluding each study. ***NB***: Unable to determine the sample sizes since forest plots were not provided to identify the specify studies.		
11. Ji [26] 30/05/2017 [6; All China]	PM2.5 and PM10	TLBW	***Entire pregnancy*** **LBW-PM2.5 per 10 μg/m³:** *Entire pregnancy* 6 cohort studies; 594,626 births OR= 1.04 (0.99,1.09); I^2= 67.4% (moderate) with p = 0.009 **LBW-PM10 per 10 μg/m³**: *Entire pregnancy* *(*9 cohort studies; 326,518 births*)* OR = 1.01 (0.96,1.08); I^2= 67.5% (moderate) with p = 0.002 ***Publication bias*** According to Egger's tests, except for the P-value (P = 0.025) of PM2.5 exposure in the 3rd trimester, no significant publication bias for the two pollutants can be seen.	***LBW risk By trimester*** **PM2.5 per 10 μg/m³** (3 cohort studies; 436,799 births for each trimester) *1st trimester* OR= 1.01 (0.98,1.03) I^2= 0.0% (low) p = 0.825 *2nd trimester:* 1.15 (0.96, 1.38) I^2= 65.8% (moderate) p = 0.054 *3rd trimester*: OR=1.17(0.94, 1.46) I^2= 79.4% (high) p = 0.008 **PM10** *1st trimester* (7 cohort studies; 315,469 births): OR= 1.06 (0.99,1.12); I^2= 20.3% (low) p = 0.275 *2nd trimester* (6 cohort studies; 313,955 births): OR= 1.05 (0.99, 1.44) I^2= 23.2% (low)	Further studies are warranted to examine the origins of heterogeneity as more meaningful studies are conducted in the future.	**Strength** The in-depth evaluation of the evidence from birth cohorts is one of the main strengths of this review. **Limitations** 'Although less heterogeneity in some subgroups, high or moderate heterogeneities appeared in many of the subgroup analyses. These findings illustrated that the heterogeneity may also be affected by other factors. The socioeconomic status were not investigated due to the limitation in quantity of relevant studies.'

				p = 0.260 *3rd trimester* (7 cohort studies; 315,469 births): OR= 1.06 (0.97, 1.15). I^2= 50.1% (low) p = 0.061 Other subgroups included study sample size, published year, study area, and exposure assessment method. **PM2.5 exposure with study sample size:** *Below 10,000* (OR = 1.20, 95% CI: 1.101-1.299, I^2 =0.0%, P = 0.554), *Above 10,000* (OR = 1.02, 95% CI: 1.00-1.042, I2=56.5% **Published year**: *Before to 2010* (OR = 1.03, 95% CI: 0.991-1.071, I2= 0.0%, P = 0.730), *After* 2010 (OR = 1.034, 95% CI: 1.007-1.061, I2= 61.8%, P = 0.001) **PM10 with study sample:** *Below 10,000* (OR = 1.08, 95% CI 1.00-1.15, I2 = 45.8%, P = 0.027), *Above 10,000* (OR = 1.02, 95% CI: 0.98-1.06, I2 = 54.3%, P = 0.008), **Published year** *before to 2010* (OR = 1.028, 95% CI: 0.99-1.067, I2 = 13.5%, P = 0.302), *After 2010* (OR = 1.047, 95% CI: 0.988-1.11, I2 = 68.1%, P< 0.001), **Study location at** *Europe and America* (OR = 1.05, 95% CI: 1.01-1.09, I2 = 54.2%, P = 0.003), at Asia (OR = 0.98, 95% CI: 0.90-1.07, I2 = 48.6%, P = 0.041), ***exposure measurement methods*** with *monitor* (OR = 1.03, 95% CI: 0.99-1.08, I2 = 32.7%, P = 0.079),		

				with model (OR = 1.05, 95% CI: 0.99-1.11, I2 = 70.3%, P = 0.001). Also collected articles which used *birth data directly from the national birth registry or hospital-birth records to explore the connection between PM exposure during pregnancy and LBW*: The pooled the estimate of PM10 for the entire pregnancy (OR = 1.07, 95%:1.02, 1.11) was larger than other trimesters, although no statistical significance of the three estimates can be obtained. Found that heterogeneity was lowest for the 3rd trimester and the highest for the 1st trimester.		
12. Liu [27] 15/06/2017 [7; all China]	PM2.5	PTB	**PTB per 10µg/m3 of PM2.5 for entire pregnancy** (7 studies; 5 retrospective and 2 prospective cohorts); 882,479 births. RE model OR= 1.15 (95% CI = 0.99 to 1.33) with p=0.07, I^2 =85%-high with p<0.00001, $\chi2$ =40.53 **PTB per 10µg/m3 of PM2.5 *for 1st trimester*r** (9 studies; 6 retrospective and 2 prospective cohorts and 1 nested case-control); 1,041,382 births. RE model OR= 1.15 (1.05 to 1.24) with p=0.001, I^2 =33%-moderate with p=0.15, $\chi2$ =11.92 **Publication bias**	**PTB per 10µg/m3 of PM2.5 for *entire pregnancy* by exposure level based on WHO IT-3** *high-level (≥15 µg/m3) exposure* (3 studies; 1 retrospective and 2 prospective cohorts); 303,326 births. FE model OR= 1.06 (1.04 to 1.08) with p<0.001, I^2 =0%-No with p=0.41, $\chi2$ =1.76 *low-level (<15 µg/m3) exposure* (4 studies; 3 retrospective and 1 prospective cohorts); 579,153 births. RE model OR= 1.31 (1.06 to 1.63) with p=0.01, I^2 =47%-moderate with p=0.13, $\chi2$ =5.68 **PTB per 10µg/m3 of PM2.5 for *1st trimester* by exposure level based on WHO IT-3** *high-level (≥15 µg/m3) exposure* (4 studies; 2 retrospective and 1 prospective cohorts, 1 nested case-control); 300,436 births. RE model	More prospected studies with clear exposure levels are still warranted in future.	**Strength** The studies included in this meta-analysis all employed cohort study design or nested case-control study design, which might prominently decrease heterogeneity between studies **Limitations** The results showed that although study designs, exposure levels, and main confounders partially explained the heterogeneity, moderate heterogeneities were still found in three of our analyses. Limited number of studies restricted us from conducting sensitivity

			The shape of the funnel plots seemed unsymmetrical in high-level exposure group in the entire pregnancy, indicating the existence of publication bias. Beyond that, we did not find any statistically significant publication bias in other groups	OR= 1.11 (0.94 to 1.32) with p=0.21, I^2 =38%-moderate with p=0.18, χ2 =4.83 *low-level (<15 µg/m3) exposure* (5 studies; 4 retrospective and 1 prospective cohorts); 740,946 births. RE model OR= 1.17 (1.04 to 1.30) with p=0.007, I^2 =44%-moderate with p=0.13, χ2 =7.09 **sensitivity analysis** 'Since no significant heterogeneities were observed in these four meta-analyses and no group of study number is more than 5, sensitivity analysis is inappropriate for this meta-analysis'.		analysis and subgroup meta-analyses between studies based on different geographic areas and PM2.5 constituents. The restriction of languages (only studies published in English or Chinese were selected), and the exclusion of studies, results of which could not be transformed into OR and 95% CI, could be partly attributable to the publication bias.
13. Li [28] 28/04/2017 [17; all China]	PM2.5	TLBW, PTB	**TLBW per 10µg/m3 of PM2.5 for entire pregnancy** (4 studies: 3 retrospective cohort and 1 cross-sectional); 8,226,866 births RE model; OR= 1.05 (0.98 to 1.12) with p=0.14 I^2 = 85%-high with p= 0.0001 **TLBW per IQR increases in PM2.5 for entire pregnancy** (7 studies: all retrospective cohort); 4,148,642 births FE model; OR= 1.03 (1.02 to 1.03) with p <0.00001 I^2= 22%-low with p= 0.26 **PTB per 10µg/m3 of PM2.5 for entire pregnancy** (6 studies; 3 retrospective cohort, 2 case-control, 1 cross-sectional); 4,098,419 births	**By trimester** **TLBW:** *1st trimester exposure (IQR)*- 3 retrospective cohort studies; 1,163,751 births OR= 1.00 (0.91 to 1.11) with p= 0.92 I^2 =90%- high with p <0.0001 *2nd trimester exposure (IQR)- 4 retrospective cohort studies*; 1,587,470 births. OR= 1.00 (0.96 to 1.03) with p=0.83 I^2 =81%- high with p= 0.001, *3rd trimester exposure (IQR)*-3 retrospective cohort studies; 1,163,751 births. OR= 1.03 (0.98 to 1.09) with p=0.28 I^2 =55%- moderate with p= 0.11, **PTB:** *1st trimester exposure (IQR)-5* studies (4 retrospective and 1 prospective cohorts; 1,371,800 births. OR= 1.03 (1.00 to 1.06) with p= 0.07 I^2 =70 moderate with p=0.009	'Future studies should employ individual direct exposure measurements to obtain more precise and accurate data.' 'More comprehensive and detailed birth records would help scientists control for such confounding variables.'	**Strengths** 'Our meta-analysis included all exposure models, including monitoring of network data, remote sensing data, or both, and we were inclined to choose exposure-estimate model, which used satellite data as exposure source.' **Limitations** 'The selection of study population, adjusted factors, air pollution data, and exposure estimation model varied among studies, and this is likely a source of heterogeneity.

			OR= 1.02 (0.93 to 1.12) with p=0.68 I^2 =97 %-high with p<0.00001 **PTB per IQR of PM2.5 for entire pregnancy** (8 studies; 7 retrospective cohort and 1 prospective cohort); 1,692,797 births OR= 1.03 (1.01 to 1.05) with p= 0.0002 I^2 = 63%-high, p= 0.008 **Publication bias** "We evaluated the possibility of a publication bias in the 23 studies, and the funnel plot illustrated a symmetrical distribution of the points, suggesting a lack of publication bias; furthermore, no publication bias was found by either Begg's test and Egger's test" P for Begg's test= 0.734	*2nd trimester exposure (IQR)-4* retrospective studies; 1,367,947 births. OR= 1.01 (0.93 to 1.10) with p= 0.83 I^2 =98- high with p<0.00001 *3rd trimester exposure (IQR)-4* retrospective studies; 1,367,947 births. OR= 1.02 (0.99 to 1.04) with p= 0.16 I^2 =59%- moderate with p=0.06		Furthermore, all of the studies' exposure estimation models used outdoor air pollution levels to calculate personal exposure. However, indoor air pollution varies and is vital to our discussion. Study region, the study design, and exposure assessment method could be sources of heterogeneity, we did not analyze them in this review owing to the restricted number of studies. Another variable is the fact that all of the included studies used different adjusting variables. Some vital variables, like smoking, were not included in the adjusted model. Due to our exclusion criteria, the number of included studies was limited. Furthermore, we only considered single pollutant models, because there was high heterogeneity between included studies in a subgroup analyses. Finally, a better understanding of the concentration-response association between air

						pollution and adverse birth outcome would be extremely valuable. We found there to be no publication bias based on an Egger's test, or a Begg's test. Nevertheless, owing to the limited sample size, we note that our study results should be interpreted with caution.'
14. Zhang [29] 30/11/2016 [8; All China]	PM2.5, PM10	SGA/IUGR, SGA, Stillbirth, SAB	**Stillbirth per 10µg/m3 of PM2.5 for entire pregnancy and trimesters** 4 studies **NB**: We excluded these meta-analytical results because results from a study (Pearce et al 2009) on black smoke levels, considered to be approximately equivalent to PM_4 were included to estimate the pooled OR. **Stillbirth per 10 µg/m3 of PM10 for entire pregnancy** 1 case-control study; 102,575 births OR = 0.98 (0.95 to 1.02) I^2= -- with p= -- **SGA per 10µg/m3 of PM2.5 for entire pregnancy** 6 retrospective cohort studies (1,515,887 births) RE pooled OR = 1.15 (1.10 to 1.20) I^2= 0.0%- No	**Stillbirth per 10µg/m3 of PM10 by trimester** *1st trimester* 2 studies (1 retrospective cohort and 1 case-control; 104,089 births) RE pooled OR = 1.00 (0.94 to 1.06) I^2= 54.1%- moderate p= 0.140 *2nd trimester* 2 studies (1 retrospective cohort and 1 case-control; 104,089 births) RE pooled OR = 1.00 (0.90 to 1.12) I^2= 81.1%- high p= 0.021 *3rd trimester* 2 studies (1 retrospective cohort and 1 case-control; 104,089 births) RE pooled OR = 1.02 (0.92 to 1.13) I^2= 90.9%- high p= 0.001 **SGA per 10µg/m3 of PM2.5 by trimester** *1st trimester* 6 retrospective cohort studies; 1,740,763 births RE pooled OR = 1.07 (1.05 to 1.10) I^2= 5.0%- low	More researches on such subjects are still needed.	**Limitations** 'First, we found different degrees of heterogeneity across PM, which could be partly explained by differences in population demography, sample size, exposure assessment, compounds of particulate matters, etc. Secondly, we only described the impact of single pollutants without taking combined effects of multipollutants into account. Third, in this study, the term of intrauterine growth retardation (IUGR) was treated as the same as SGA, for most articles defined them in the same way. Finally, a limited

			p= 0.877 **SGA per 10μg/m3 of PM10** **NB**: 'However, none article revealed the relationship between PM10 and SGA, and that was why we did not perform meta-analysis between them' **SAB per 10μg/m3 of PM2.5** **NB**: 'No article revealing the risk of PM2.5 on SAB was found' **Publication bias** 'With all the value of P>0.05 in Egger's test, no publication bias was found in all analysis'	p= 0.385 *2nd trimester* 5 retrospective cohort studies; 1,706,058 births RE pooled OR = 1.06 (1.02 to 1.10) I^2= 58.1%- moderate p= 0.049 *3rd trimester* 5 retrospective cohort studies; 1,706,058 births RE pooled OR = 1.06 (1.04 to 1.08) I^2= 13.4%- low p= 0.329 **SAB per 10μg/m3 of PM10 for 1st trimester** 3 studies (1 retrospective cohort, 1 case-control, and 1 cross-sectional; 515,932 births). RE pooled OR = 1.34 (1.04 to 1.72) I^2= 62.4%- moderate p= 0.070 **Sensitivity analysis** 'After removing each article sequentially, statistically steady results were obtained, suggesting our results of meta-analysis were robust.'		number of literatures were included in our final analysis.'
15. Siddika [30] 24/05/2016 [4; 3 Finland, 1 Ghana]	PM 10, PM2.5, NO2, SO2, CO, O3.	Stillbirth	NB: 4/11 studies were meta-analysed and the remaining synthesised narratively. **Stillbirth for entire-pregnancy period of exposure;** **PM2.5 per 4 μg/m3** (2 studies, both retrospective cohort, ranked high quality; 3,745,243 births): RE = 1.021 (0.996 to 1.046), FE = 1.021 (0.996 to 1.046) χ^2 = 0.18 p-value = 0.669 I^2 = 00.0%(No)	*By trimesters* **SO2** 1st *trimester* RE=1.040 (0.962 to 1.125) FE=0.997 (0.975 to 1.020) χ^2 = 10.34 p-value = 0.006 I^2 = 80.7% (high) *2nd trimester* RE = 1.003 (0.977 to 1.030) FE = 1.003 (0.977 to 1.030) χ^2 = 1.79 p-value =0.408 I^2 = 0.0% (No) *3rd trimester*	'Pregnant women should be aware of the potential adverse effects of ambient air pollution, although the prevention against exposure to air pollutants generally requires more action by the government than by the individual. The healthcare	**Strengths** 'We included all the studies identified in an extensive systematic search, so missing of important epidemiological studies is less likely to have happened.' **Limitations** 'Even though our review contains eight more studies and much more information than

			PM10 per 10 μg/m3 (2 studies, each prospective cohort and case-control, both ranked high-quality studies; 104,089 births): RE = 1.014 (0.948 to 1.085), FE = 1.012 (0.986 to 1.039) χ^2 = 6.67 p-value = 0.010 I^2 =85.0% (high) **SO2 per 3 ppb increase** (3 studies; 2 retrospective cohort, 1 case-control, all 3 studies ranked very high quality =3,847,818 births), RE =1.022 (0.984 to 1.062), FE=1.019 (0.989 to 1.049) χ^2 =2.49 p-value = 0.288 I^2=19.6% (low) **NO2 per 10ppb** (same 3 studies as in SO2) RE= 1.066 (0.965 to 1.178), FE = 1.049 (1.012 to 1.088) χ^2 = 9.78 p-value = 0.008 I^2 =79.6% (high) **CO per 0.4ppm** (same 3 studies as in SO2) RE = 1.025 (0.985 to 1.066), FE = 1.022 (0.995 to 1.050) χ^2 = 2.52 p-value = 0.284 I^2 = 20.5%(low) **O3 per10 ppb** (2 studies; one each for case-control and retrospective cohort, both ranked high	RE = 1.042 (0.951 to 1.142) FE = 0.996 (0.967 to 1.026) χ^2 = 11.26 p-value =0.004 I^2 = 82.2% (high) **NO2** 1^{st} *trimester* RE= 1.035 (0.983 to 1.089) FE= 1.025 (0.996 to 1.054) χ^2 = 4.43 p-value =0.109 I^2 = 54.8% (high) *2^{nd} trimester* RE =1.007 (0.948 to 1.071) FE =1.005 (0.977 to 1.034) χ^2 = 5.83 p-value =0.054 I^2 =65.7% (high) *3^{rd} trimester* RE = 1.015 (0.980 to 1.051) FE =1.015 (0.980 to 1.051) χ^2 = 1.88 p-value =0.391 I^2 =0.0% (No) **CO** 1^{st} *trimester* RE=1.011 (0.967 to 1.057) FE=1.002 (0.983 to 1.022) χ^2 = 2.92 p-value =0.232 I^2 =31.6% (moderate) *2^{nd} trimester* RE =1.015 (0.948 to 1.087) FE =1.002 (0.979 to 1.025) χ^2 = 5.60 p-value =0.061 I^2 =64.3%(high) *3^{rd} trimester* RE = 1.052 (0.973 to 1.138) FE =1.014 (0.992 to 1.038) χ^2 = 10.19	sector can create awareness and engage other sectors contributing to ambient air pollution (such as the housing sector, transportation sector, industries and the energy sector), to develop and implement policies such as control of vehicular emissions, fuel quality improvement and control of industrial waste emission, to reduce the risk of air pollutants. Future studies should integrate the use of personal monitoring methods and also consider the activity of mothers, change in residence, air exchange, mother's occupation and outdoor activities of the mothers. The pregnant women should	the previous reviews, we found a very limited number of estimates for each of the pollutants, and only five studies made attempts to adjust for other air pollutants when presenting effect estimates of each air pollutant. Therefore, we could not include all of the studies in the meta-analyses, and the reliability on the summary effect estimate's is further compromised.'

			quality; 3,128,844 births); RE = 1.002 (0.971 to 1.034) FE = 1.005 (0.982 to 1.029) χ^2 = 1.24 p-value = 0.265 I^2 = 19.6%(low) **Publication bias** It was assessed by funnel plots, Begg's and Egger's tests results; 'There was no indication of publication bias present, although these results should be interpreted with caution because they were based on two or three study-specific effect estimates only' **Narrative synthesis** **SO2**; one each of case-crossover, time-series, and ecological studies found significant association with SB. A cross-sectional study and another ecological study found no significant association. **NO2**; significant association in case-crossover, time-series with various lag days, ecological. **NO**; Two studies that investigated this found no association. **NOx**; one study investigated this and found no association. **CO**; The findings of CO exposure with stillbirth were less consistent **PM2.5**;	p-value =0.006 I^2 =80.4%(high) **PM10** 1st *trimester* RE=0.998 (0.936 to 1.064) FE=1.015 (0.991 to 1.039) χ^2 = 2.18 p-value =0.140 I^2 =54.1%(high) *2nd trimester* RE =1.005 (0.905 to 1.116) FE =0.968 (0.944 to 0.993) χ^2 = 5.31 p-value =0.021 I^2 =81.2%(high) *3rd trimester* RE = 1.021 (0.919 to 1.134 FE =0.995 (0.968 to 1.022) χ^2 = 10.96 p-value = 0.001 I^2 =90.9%(high) **PM2.5** 1st *trimester* RE=1.042 (0.920 to 1.180) FE= 1.002 (0.982 to 1.022) χ^2 = 2.35 p-value =0.126 I^2 =57.4%(high) *2nd trimester* RE =1.040 (0.940 to 1.152) FE =1.011 (0.996 to 1.026) χ^2 = 1.92 p-value =0.166 I^2=47.9% (moderate) *3rd trimester* RE = 1.00 (0.981 to 1.020) FE =1.00 (0.981 to 1.020) χ^2 = 0.23 p-value =0.631 I^2 =0.0% (No) **O3**	also be monitored if possible from the first month of pregnancy in order to ascertain the exact period of the effect.'	

			One time series found no significant association, one retrospective study found significant association only in the 3rd trimester. **O3**; The time series study found no association	1^{st} *trimester* RE=1.001 (0.983 to 1.020) FE=1.001 (0.983 to 1.020) χ^2 = 0.13 p-value =0.714 I^2 =0.0% (No) *2^{nd} trimester* RE =0.991 (0.944 to 1.040) FE =1.004 (0.985 to 1.022) χ^2 = 3.18 p-value =0.074 I^2 =68.6%(high) *3^{rd} trimester* RE = 1.012 (0.966 to 1.060) FE =1.025 (1.006 to 1.043) χ^2 = 2.72 p-value =0.099 I^2 =63.2%(high)		
16. Sun [31] 29/12/2015 [8, all China]	PM2.5 and chemical constituents	LBW, BW	**BW per 10μg/m3 of PM2.5 for entire pregnancy** 17 studies (1 prospective and 16 retrospective cohorts; 7,857,127 births) Pooled β= -15.9 (95% CI = -26.8 to -5.0) I^2 =98.5%-high with p <0.001 **LBW per 10μg/m3 of PM2.5 for entire pregnancy** 19 studies (2 prospective and 17 retrospective cohorts; 10,405,729 births) Pooled OR= 1.090 (95% CI = 1.032 to 1.150) I^2 =92.6%-high with p <0.001 **Publication bias** 'The results of Egger's tests showed that there was no significant publication bias in	**Note**: Forest plots were not presented to enable us determine the study designs and sample sizes for the subgroup analyses. **BW per 10μg/m3 of PM2.5 by:** ***Trimesters*** *1^{st} trimester* 11 studies Pooled β= -8.3 (-17.0 to 0.4) I^2 =89.8%-high with p <0.001 *2^{nd} trimester* 10 studies Pooled β= -12.6 (-21.7 to -3.1) I^2 =92.2%-high with p <0.001 *3^{rd} trimester* 13 studies Pooled β= -10.0 (-16.6 to -3.5) I^2 =85.8%-high with p <0.001	'More studies in counties other than the USA are needed, especially in middle- or low-income counties with heavier air pollution. Further meta-analyses are necessary to explore the sources of heterogeneity as more original studies are conducted in the future. It is crucial to reduce the ambient PM2.5 pollution and reduce maternal PM2.5 exposure	**Limitations** 'High or moderate heterogeneities in most of the subgroup meta-analyses, although less heterogeneity was found in some subgroups. These findings indicate that the heterogeneity among the included studies may also have been affected by other factors, such as socioeconomic status, that we did not consider in this study due to the limited number of relevant studies.'

			most of the meta-analyses **except** for the BW-PM2.5 exposure analysis during the 2nd trimester and the LBW-PM2.5 analyses during the entire pregnancy as well as in the 3rd trimester.'	***For entire pregnancy by study design*** *Prospective cohort* 2 studies Pooled β= -11.6 (-28.7 to 5.3) I^2 =0.0%-No with P=0.454 *Retrospective cohort* 15 studies Pooled β= -16.7(-28.7 to -4.8) I^2 =98.8%-high with p <0.001 ***For entire pregnancy by exposure assessment method*** *Individual level* 4 studies Pooled β= -15.7 (-42.1 to 10.6) I^2 =87.4%-high with p <0.001 *Semi-individual level* 8 studies Pooled β= -15.2 (-20.7 to -9.7) I^2 =76.3%-high with p =0.001 *Regional level* 6 studies Pooled β= -17.3 (-43.4 to 8.8) I^2 =97.7%-high with p <0.001 ***For entire pregnancy by country*** *USA* 13 studies Pooled β= -18.8 (-31.4 to -6.3) I^2 =99.0%-high with p <0.001 *Others* 4 studies Pooled β= -1.8 (-12.2 to 8.7)	during pregnancy to improve birth outcomes.'	

				I^2 =26.2%-low with p=0.401 **LBW per 10µg/m3 of PM2.5 by:** ***Trimesters*** *1st trimester* 7 studies Pooled OR= 1.026 (0.93 to 1.130) I^2 =86.9%-high with p <0.001 *2nd trimester* 7 studies Pooled OR= 1.035 (0.952 to 1.125) I^2 =79.8%-high with p <0.001 *3rd trimester* 8 studies Pooled OR= 1.233 (0.960 to 1.585) I^2 =98.7%-high with p <0.001 ***For entire pregnancy by* study design** *Prospective* 3 studies Pooled OR= 1.359 (1.102 to 1.676) I^2 =0.1%-low with p =0.269 *Retrospective* 16 studies Pooled OR= 1.078 (1.022 to 1.137) I^2 =93.1%-high with P<0.001 ***For entire pregnancy by* exposure *assessment method*** *Individual level* 2 studies Pooled OR= 1.431 (1.149 to 1.783) I^2 =0.0%-No with p =0.570 *Semi-individual level* 10 studies		

				Pooled OR= 1.008 (0.999 to 1.016) I^2 =40.5%-low with p =0.093 *Regional level* 8 studies Pooled OR= 1.145 (1.061 to 1.235) I^2 =73.6%-moderate with p<0.001 ***For entire pregnancy by* country** *USA* 14 studies Pooled OR= 1.079 (1.018 to 1.143) I^2 =94.3%-high with P<0.001 *Others* 5 studies Pooled OR= 1.141 (1.044 to 1.247) I^2 =36.1%-low with P=0.140 **Other subgroups** *Leave-out sensitivity analyses* Exclusion of single studies that had the largest and smallest effect size with regard to the significance of the estimated associations had no effect except one study where exclusion of the study with the smallest effect size resulted in significant pooled effect of BW during first trimester. Also, to test the influence of 3 studies that considered preterm low birth weight (PLBW), exclusion of these studies found did not change the pooled estimate significantly *Meta-regression* The results of meta-regression analysis of showed similar modification effect patterns of the study characteristics, but none of the tests was statistically significant for BW-PM2.5 association but results of the meta-regression		

				analyses of PM2.5 exposure on LBW was significantly impacted by the exposure assessment methods used (OR= 0.13, 95% CI: 0.06, 0.20) *PM2.5 chemical constituents* (7 studies in all; specifically, 2 to 4 studies for each and majority were 2 studies). Birth weight was negatively associated significantly with zinc, nickel, titanium, vanadium, organic carbon (OC), nitrate (NO^-_3); -all from 2 studies, and elemental carbon (EC) from 3 studies. For example, a 10 ng/m3 increase in Zn exposure was associated with a 7.5 g (95% CI: 5.0, 10.0) decrease in birth weight (from 2 studies). Similarly, the LBW risk was positively associated with potassium (3 studies), zinc (3 studies), nickel (4 studies), titanium (4 studies), elemental carbon (4 studies), silicon (3 studies), sulfur (2 studies) and ammonium ion (2 studies) levels. For instance, a 10 ng/m3 increase in Ti exposure was related to a 15.9% (95% CI: 0.7, 33.3) increase in the risk of LBW.		
17. Sun [32] 18/11/2015 [7; 5 China, 2 Australia]	PM2.5	PTB	**PTB per 10µg/m3 of PM2.5 for entire pregnancy** 13 studies (4 prospective, 9 retrospective cohort; 3,089,186 births Pooled OR= 1.13 (95% CI = 1.03 to 1.24) I^2 =91.4%-high with p <0.001 **Publication bias** Did not find any statistically significant publication bias in any of the meta-analyses	**PTB per 10µg/m3 of PM2.5 *for trimester*** *1st trimester* 10 studies (5 prospective and 5 retrospective cohorts; 1,668,004 births Pooled OR= 1.08 (0.92 to 1.26) I^2 =91.3%-high, with p<0.001 *2nd trimester* 5 studies (2 prospective and 3 retrospective cohorts; 1,340,807 births Pooled OR= 1.09 (0.82 to 1.44) I^2 =98.7%-high, with p<0.001 *3rd trimester*	"These results are important for policy makers and public health practitioners worldwide. More studies are needed in the future to explore which gestational windows are more susceptible to air pollution.	**Limitations** 'High heterogeneity between included studies. Heterogeneity across the included studies may also have been affected by other factors that we did not consider in this study, such as socioeconomic status and chemical constituents of PM2.5, due to the limited

				9 studies (1 prospective and 8 retrospective cohorts; 2,208,883 births Pooled OR= 1.08 (0.99 to 1.17) I^2 =92.1%-high, with p<0.001 **PTB per 10µg/m3 of PM2.5 for *1st month of gestation*** 3 retrospective cohort studies; 342,423 births Pooled OR= 1.10 (0.92 to 1.30) I^2 =91.0%-high, with p<0.001 **PTB per 10µg/m3 of PM2.5 for *one month before birth*** 6 retrospective cohort studies; 3,556,199 births. Pooled OR= 1.01 (0.86 to 1.19) I^2 =96.8%-high, with p<0.001 **PTB per 10µg/m3 of PM2.5 by exposure assessment methods** *Assessed exposure at individual level* 3 studies (1 prospective and 2 retrospective cohort studies; 350,652 births Pooled OR= 1.11 (0.89 to 1.37) I^2 =61.3%-moderate, with p = 0.085 **NB**: Considered individual-level exposure as assessed using complicated dispersion models based on traffic, meteorology, roadway geometry, vehicle emission, air quality monitoring, and land use databases to estimate each subject's daily PM2.5 exposure level with high accuracy. *Assessed exposure at semi-individual level*	More studies in countries other than the USA are needed, especially in middle or low income countries with higher levels of air pollution. More studies are needed in the future, especially studies assessing PM2.5 exposure at the individual level. Studies on the association between PM2.5 components and sources and preterm birth are still limited, and more studies are needed in the future. Improving the data quality of public records is one way to improve related studies. Future longitudinal studies that collect more detailed information at the individual level would be beneficial. Further studies are needed to explore the sources of heterogeneity in the future."	quantity of related studies.' **Strengths** No specific statement.

				9 studies (3 prospective and 6 retrospective cohort studies; 2,353,605 births. Pooled OR= 1.14 (0.97 to 1.35) I^2 =93.0%-high, with p<0.001 **NB**: Semi-individual exposure was estimated using the daily PM2.5 concentration from the monitoring station nearest to the individual's residence. *Assessed exposure at regional level* 4 retrospective cohort studies; 1,722,203 births. Pooled OR= 1.07 (0.94 to 1.23) I^2 =92.8%-high, with p<0.001 NB: Regional-level exposure was calculated using the average PM2.5 concentration in a region or a grid with low resolution. This method did not consider the variation in PM2.5 concentration within a region, and assumed that all subjects in this region had the same PM2.5 exposure concentration. **PTB per 10µg/m3 of PM2.5 by study design** *Retrospective cohort* 9 studies: 2,921,829 births. Pooled OR= 1.10 (1.01 to 1.21) I^2 =93.3%-high, with <0.001 *Prospective cohort* 4 studies: 167,357 births. Pooled OR= 1.42 (0.99 to 2.03) I^2 =39.5%-low, with p=0.201 **PTB per 10µg/m3 of PM2.5 by study setting/country** *USA* 8 studies (1 prospective and 7 retrospective cohort studies; 2,525,004 births.		

				Pooled OR= 1.16 (1.04 to 1.29) I^2 =90.6%-high, with p <0.001 *Other countries* 5 studies (3 prospective and 2 retrospective cohort studies; 564,182 births. Pooled OR= 0.98 (0.95 to 1.01) I^2 =0.1%-low, with p=0.095. **Other subgroup analyses** Several meta regression analyses employed to further evaluate the impacts of study characteristics on the associations between PM2.5 exposure and preterm birth risks found similar results. **Leave-one-out sensitivity analyses** In the meta-analysis that included studies assessing PM2.5 exposure at the semi-individual level, the estimate became significant after excluding a single study with the smallest effect size. All others after excluding a single study with the largest effect size, the smallest effect size, the largest standard error, or the smallest standard error did not yield any significant change.		
18. Lamichhane [33] 03/11/2015 [4; All Incheon, Korea]	PM2.5, PM10	PTB, change in BW.	**Change in BW (g) per 10µg/m3 of PM2.5** ***Entire pregnancy*** ---- combined studies. (8 cohort studies; 5,493,944 births). Pooled ES = -13.88 g (95% CI, -15.70 to -12.06 g) I^2=47.5% moderate, p=0.064 ***Studies that adjusted for smoking*** *Entire pregnancy*	***By trimester*** **Change in BW (g) per 10µg/m3 of PM2.5** *1st trimester* (6 cohort studies; 4,565,337 births). pooled ES = -8.03(-14.54 to -1.53) with I^2=85.1% -high, p=0.000 *2nd trimester* (5 cohort studies; 4,561,484 births). pooled ES = -7.90 (-13.70 to	'Future large cohort studies with sufficient data and detailed information on timing of smoking during pregnancy and other potential confounding factors as well as reliable exposure data are required for a better	**Strengths** 'One advantage of this review is that we appraised all individual studies included in the outcome specific analysis according to a structured and validated checklist, helping us to present quality assessment of methodological rigor

			(7 cohort studies; 2,090,972 births). pooled ES = -22.17 (-37.93 to -6.41) with I^2 =92.3% - high, p=0.000 (**NB**: Authors noted that meta-analysis for smoking-unadjusted was not conducted due to insufficient number of studies) **Change in BW (g) per 10µg/m3 of PM10** **(NB:** Separated by adjusted and unadjusted for smoking) **Studies that adjusted for smoking:** ***Entire pregnancy*** (5 cohort studies; 477,123 births). Pooled ES = - 10.31g (95% CI, - 13.57 to -7.05 g) I^2=0.0% low, p=0.947 **Studies that did not adjust for smoking:** ***Entire pregnancy*** (3 cohort studies; 3,788,093 births). Pooled ES = - 8.17g (95% CI, - 10.99 to -5.36g) I^2=35.2% low, p=0.214 **PTB per 10µg/m3 of PM2.5** **NB**: Ha et al (49) in the review article examined *PM10-PTB* and was described as such by the authors in Table 1 but Ha et al (2004;	-2.09) with I^2=88.0% -high, p=0.000 *3rd trimester* (7 cohort studies; 5,540,383 births). pooled ES = -6.04 (-7.69 to -4.39) with I^2 =14.6% - low p=0.318 ***Studies that adjusted for smoking*** *1st trimester* (5 cohort studies; 1,261,503 births). pooled ES = -6.20 (-19.51 to 7.12) with I^2 =87.8% - high p=0.000 *2nd trimester* (4 cohort studies; 1,257,650 births). pooled ES = -10.57 (-18.95 to -2.20) with I^2 =82.0% - high p=0.001 *3rd trimester* (6 cohort studies; 2,236,549 births). pooled ES = -7.60 (-9.84 to -5.36) with I^2 =0.0% - low p=0.819 **Change in BW (g) per 10µg/m3 of PM10** **(NB:** Separated by adjusted and unadjusted for smoking; by low/high quality studies). ***Studies that adjusted for smoking:*** *1st trimester* (4 cohort studies; 507,286 births). Pooled ES = -1.43 (-4.77 to1.92)	understanding of the association between PM and the risk of adverse birth outcomes.' 'Considering the ubiquitous nature of particulate air pollution [72]. exposure, variation in effects by exposure period, especially time periods shorter than trimester and sources of heterogeneity between studies and centers should be further explored. Our findings have substantial public health implications as reduced BW, although relatively small, is a risk factor for numerous adverse health effects early in life.'	of studies in a more organized and standardized way. The included studies allowed us to explore possible exposure-response relationship according to a critical exposure period, which offers another advantage of this meta-analysis.' **Limitations** "Although we realized that the countries where studies were conducted and the study design might also be sources of heterogeneity, they were not analyzed in the review due to the limited number of studies conducted in different countries. Though we recognized that several sensitivity analyses were conducted in relation to race or other factors, stratified analyses were not performed based on these categories due to the limited number of studies, particularly when divided by exposure period. We also aware that the use of effect estimates

			referenced wrongly in Table 1 and Figure S2 as '2014' but correctly referenced in reference list) was mistakenly included in estimating all the pooled ORs for *PM2.5-PTB* association. We therefore excluded the pooled ORs for the PM2.5-PTB association. The corresponding author was contacted twice but we did not receive any reply. **Adjusted for smoking;** **PTB per 10µg/m3 of PM10** ***Entire pregnancy*** (2 studies: 1 each cohort and case-control; 9,294 births). Pooled OR = 1.24 (95% CI, 1.03 to1.45) I^2=0.0% -No, p=0.960 **Publication bias** "Did not detect a statistically significant publication bias based on the Egger's test (p=0.181 for PM10; p=0.241 for PM2.5) or by using contour-enhanced funnel plot. The funnel plot revealed that studies were missing in areas of higher statistical significance, suggesting that asymmetry may be more likely to be due to factors other than publication bias, such as variable study quality."	I^2=0.0% -low, p=0.964 *2nd trimester* (4 cohort studies; 507,286 births). Pooled ES = -6.50 (-13.85 to 0.85) I^2=68.2% -moderate, p=0.024 *3rd trimester* (5 cohort studies; 913,913 births). Pooled ES = -5.11 (-8.32 to -1.89) I^2=0.0% -low, p=0.704 ***Studies that did not adjust for smoking:*** *1st trimester* (6 cohort studies; 3,836,556 births). Pooled ES = -3.31 (-6.45 to -0.18), I^2=81.1%-high, p=0.000 *2nd trimester* (6 cohort studies; 3,836,556 births). Pooled ES = -1.24 (-1.99 to -0.50), I^2=0.00% -low, p=0.603 *3rd trimester* (7 cohort studies; 40,149,12 births). Pooled ES = 1.36 (-4.90 to 7.63), I^2=94.1%-high, p=0.000 ***For relatively better-quality studies*** (NB: either un/adjusted smoking) *Entire pregnancy* (5 cohort studies; 630,250 births). Pooled ES = -10.59 (-13.24 to -7.94), I^2=0.0% -low, p=0.939. *1st trimester* (5 cohort studies; 686,746 births). Pooled ES = -2.16 (-5.40 to 1.09), I^2=0.0% No, p=0.500 *2nd trimester*		based on associations with ambient levels of pollutants as a surrogate for personal exposure levels may have resulted some exposure misclassification. Other limitation includes the fact that none of the included studies provided the precise information on the timing of smoking during pregnancy."

				(5 cohort studies; 686,746 births). Pooled ES = -5.95 (-12.19 to 0.29), I^2=57.8% - moderate, p=0.050 *3rd trimester* (6 cohort studies; 865102 births). Pooled ES = -5.23 (-10.35 to -0.12), I^2=49.5% - moderate, p=0.078 ***For relatively low-quality studies*** *Entire pregnancy* (4 cohort studies; 4,904,584 births). Pooled ES = -2.86 (-12.35 to 6.64), I^2=89.9% -high, p=0.000 *1st trimester* (5 cohort studies; 3,657,096 births). Pooled ES = -2.82 (-5.96 to 0.32), I^2=83.2% -high, p=0.000 *2nd trimester* (5 cohort studies; 3,657,096 births). Pooled ES = -1.24 (-1.98 to -0.49), I^2=0.0% -low, p=0.485 *3rd trimester* (6 cohort studies; 4,063,723 births). Pooled ES = 0.90 (-5.50 to 7.29), I^2=94.6% -high, p=0.000 **PTB per 10µg/m3 of PM10 (either un/adjusted for smoking)** *1st trimester* (8 cohort studies; 1,308,263 births). Pooled OR= 0.98 (0.94 to 1.03), I^2=72.6% -high p=0.001 *2nd trimester* (4 cohort studies; 1024360 births).		

				Pooled OR= 0.97 (0.95 to 0.99), I^2=0.0% -No p=0.601 *3rd trimester* (7 cohort studies; 1,273,558 births). Pooled OR= 1.03 (1.01 to 1.05), I^2=27.1% -low p=0.221 **PTB per 10µg/m3 of PM10 (*Studies that adjusted for smoking)*** *1st trimester* (4 cohort studies; 264,672 births). Pooled OR = 0.99 (0.92 to 1.07), I^2=41.6% -moderate, p=0.162 *2nd trimester* (1 cohort study; 8,969 births). OR = 1.10 (0.65 to 1.56), I^2=NA p=NA *3rd trimester* (3 cohort studies; 229,967 births). Pooled OR =0.97 (0.86 to 1.08), I^2=57.9% -moderate, p=0.093 **PTB per 10µg/m3 of PM10 (*Studies that did not adjusted for smoking)*** *Entire pregnancy* (1 cohort study; 28,200 births). OR = 1.19 (95% CI, 0.80 to 1.58) I^2=NA, p=NA *1st trimester* (4 cohort studies; 1,043,591 births). Pooled OR =0.98 (0.91 to 1.05), I^2=74.4% -moderate, p=0.008 *2nd trimester* (3 cohort studies; 1,015,391 births) Pooled OR =0.97(0.95 to 0.99), I^2=0.0% -moderate, p=0.466 *3rd trimester* (4 cohort studies; 1,043,591births) Pooled OR =1.04(1.02 to 1.06), I^2=0.0% -moderate, p=0.449		

				PTB per 10µg/m3 of PM10 by study quality ***For relatively better-quality studies*** *Entire pregnancy* (1 case-control; 325births) OR =1.24 (1.02 to 1.46), I^2=NA, p=NA *Overall risk* (6studies; 5 cohort and 1 case-control; 1,269,905 births) Pooled OR = 1.00 (0.97 to 1.02), I^2=77.6% -high p=0.000 *1st trimester* (5 cohort studies; 1,269,580 births) Pooled OR =0.98 (0.94 to 1.02), I^2=73.0% -moderate, p=0.005 *2nd trimester* (2 cohort studies; 1,013,877 births) Pooled OR =0.97 (0.94 to 0.99), I^2=0.0% -No, p=0.394 *3rd trimester* (4 cohort studies; 1,234,875 births). Pooled OR =1.03(1.00 to 1.06), I^2=57.2% -moderate, p=0.072 ***For relatively low-quality studies*** *Entire pregnancy* (2 cohort studies; 37,169 births). Pooled OR =1.20 (0.85 to 1.54), I^2=57.2% -moderate, p=0.072 *Overall risk* (4 cohort studies; 420,783 births). Pooled OR =1.00 (0.98 to 1.02), I^2=41.6% -low, p=0.057 *1st trimester* (4 cohort studies; 420,783 births). Pooled OR =1.01 (0.91 to 1.11), I^2=71.1% -moderate, p=0.015 *2nd trimester* (3 cohort studies; 392,583 births). Pooled OR =1.00 (0.98 to 1.01), I^2=0.0% -low, p=0.891		

				3rd trimester (4 cohort studies; 420,783 births). Pooled OR =1.02 (1.00 to 1.04), I^2=0.0% -low, p=0.566 ***3rd trimester or entire pregnancy by smoking status*** *Smoking adjusted* (4 studies: 3 cohort and 1 case-control; 230,292 births). Pooled OR =1.01 (0.90 to 1.13), I^2=64.4% -moderate, p=0.038 *Smoking unadjusted* (5 cohort studies; 1,557,554 births). Pooled OR =1.03 (1.01 to 1.05), I^2=33.3% -low, p=0.200 *Overall risk* (9 studies; 8 cohort and 1 case-control;1,655,983 births); 1.03 (1.01 to 1.05), I^2=44.6% -low, p=0.071 **Sensitivity Analyses** "With some noted exception, overall, we observed that meta-analysis estimates were stable, excluding a particular study did not change the summary point estimates much.		
19. Zhu [34] 28/08/2014 [6, all China]	PM2.5	BW, LBW, PTB, SGA, and stillbirth	**BW reduction per 10μg/m3 of PM2.5 for entire pregnancy** 12 cohort studies; 7,388,985 births) RE pooled ES = -14.58 (-19.31 to -9.86) I^2= 86.8%- high p= 0.000 **LBW per 10μg/m3 of PM2.5 for entire pregnancy** 6 cohort studies; 5,691,348 births)	**BW reduction per 10μg/m3 of PM2.5 for by trimester** *1st trimester* 7 cohort studies; 5,153,167 births. RE pooled ES = -6.63 (-13.65 to -0.39) I^2= 82.1%- high p= 0.000 *2nd trimester* 5 cohort studies; 4,742,687 births. RE pooled ES = -8.00(-14.52 to -1.48) I^2= 84.6%- high p= 0.000 *3rd trimester* 7 cohort studies; 5,153,167 births.	Extract from the discussion or conclusion: Socioeconomic status should be consistently adjusted in the future and other factors. Further explore the difference in effects by different exposure periods with consistency	**Limitations** 'We found a high or moderate degree of heterogeneity across some gestational exposure periods. We had not conceived the studies with other exposure periods (weeks and months, etc.) for the limited quantity of related studies.

			FE pooled OR = 1.05 (1.02 to 1.07) I^2= 39.7%- low p= 0.141 **PTB per 10µg/m3 of PM2.5 for entire pregnancy** 8 cohort studies; 1,764,632 births) RE pooled OR = 1.10 (1.03 to 1.18) I^2= 52.0%- moderate p= 0.042 **SGA per 10µg/m3 of PM2.5 for entire pregnancy** 6 cohort studies; 1,515,887 births. RE pooled OR = 1.15 (1.10 to 1.20) I^2= 0.0%- No p= 0.877 **Stillbirth per 10µg/m3 of PM2.5 for entire pregnancy** 1 cohort study by Faiz et al., 2012 (343,077 births in New Jersey, USA) OR= 1.18 (0.69 to 2.04) **Publication bias** No evidence of publication bias based on Begg's funnel plot and Egger's test, p>0.05	RE pooled ES = -14.91 (-21.73 to -8.09) I^2= 86.3%- high p= 0.000 **PTB per 10µg/m3 of PM2.5 by trimester** *1st trimester* 6 cohort studies; 743,647 births. RE pooled OR = 0.96 (0.77 to 1.21) I^2= 87.2%- high p= 0.000 *2nd trimester* 3 cohort studies; 598,606 births. RE pooled OR = 0.90 (0.79 to 1.03) I^2= 0.0%- No p= 0.700 *3rd trimester* 6 cohort studies; 1,240,212 births. RE pooled OR = 0.97 (0.89 to 1.05) I^2= 31.4%- low p= 0.200 **SGA per 10µg/m3 of PM2.5 for by trimester** *1st trimester* 6 cohort studies; 1,740,763 births. RE pooled OR = 1.07 (1.05 to 1.10) I^2= 5.0%- low p= 0.385 *2nd trimester* 5 cohort studies; 1,706,058 births. RE pooled OR = 1.06 (1.02 to 1.10) I^2= 58.1%- moderate p= 0.049 *3rd trimester* 5 cohort studies; 1,706,058 births. RE pooled OR = 1.06 (1.04 to 1.08) I^2= 13.4%- low p= 0.329 **Stillbirth per 10µg/m3 of PM2.5 by trimester**	of study design methods, exposure assessment, and adjustment for factors. Further research studies are needed to evaluate pathophysiological mechanisms by considering alternative exposure metrics. Review of pooled effects of chemical constituents might be doable in near future. A lot of studies on different trimesters are also needed to explore the sensitive exposure window of the risk of SGA. Pregnant women need to take effective measures to reduce PM2.5 exposure.	Our study was also confined to effect estimates on constituent of PM2.5'

				1st trimester 1 cohort study by Faiz et al., 2012 (343,077 births in New Jersey, USA OR= 1.42 (0.90 to 2.20) *2nd trimester* 1 cohort study by Faiz et al., 2012 (343,077 births in New Jersey, USA OR= 1.39 (0.90 to 2.12) *3rd trimester* 1 cohort study by Faiz et al., 2012 (343,077 births in New Jersey, USA OR= 1.21 (0.55 to 2.66) **Sensitivity analysis** 'After removing each study sequentially, statistically similar results were obtained, indicating the stability of our meta-analysis.' **Meta-regression** Of the characteristics of the studies we evaluated, only meta-regression for study design method and exposure assessment showed significant heterogeneity between studies in the reported PM2.5-PTB associations. However, the sources of heterogeneity in the change of birth weight could partly be explained by adjusted or unadjusted of socioeconomic status because meta-regression for this showed significant heterogeneity		
20. Stieb [35] 21/06/2012 [4, all Canada]	PM 10, PM2.5, NO2, SO2, CO, O3.	BW/LBW/VLBW, PTB, SGA/IUGR	**BW:** **BW per 10μg/m3 of PM2.5 for entire pregnancy** (7 cohort studies; 4,271,411 births) Pooled ES= -23.44 (95% CI = -45.50 to -1.38) I^2 =94.7%-high with p=0.000 **BW per 20μg/m3 of PM10 for entire pregnancy**	**Trimester-specific** ***BW:*** ***BW per 10μg/m3 of PM2.5 for*** *1st trimester* (4 cohort studies; 3,637,501 births) Pooled ES= -0.30 (-9.85 to 9.25) I^2 =37.3%-low with p=0.188 *2nd trimester* (4 cohort studies; 3,634,129 births) Pooled ES= -14.66 (-34.01 to 4.70) I^2 =74.5%-moderate with p=0.008	Variation in effects by exposure period and sources of heterogeneity between studies/centers should be further explored, potentially in coordinated multi-center analyses.	**NB**: No specific section but extracts from the discussion. **Strengths** Included 'increased number of studies (62 compared to 9–41 in previous reviews).' 'Evaluated effects by gestational period, estimated continuous

			(7 cohort studies; 3,932,746 births) Pooled ES= -16.77 (95% CI = -20.23 to -13.31) I^2 =15.9%-low with p=0.308. **BW per 1ppm of CO for entire pregnancy** (4 cohort studies; 3,702,544 births) Pooled ES= -11.40 (95% CI = -29.70 to 6.90) I^2 =95.4%-high with p=0.000 **BW per 20ppb of NO2 for entire pregnancy** (10 studies: 9 cohort and 1 ecologic; 3,780,571 births) Pooled ES= -28.13 (95% CI = -44.81 to -11.45) I^2 =84.7%-high with p=0.000 **BW per 20ppb of O3 for entire pregnancy** (4 cohort studies: 3,370,657 births) Pooled ES= -10.01 (95% CI = -32.39 to 12.37) I^2 =80.9%-high with p=0.001 **BW per 5ppb of SO2 for entire pregnancy** (3 studies: 2 cohort and 1 ecologic; 3,718,863 births) Pooled ES= 7.30 (95% CI = -7.69 to 22.29) I^2 =79.5%-high with p=0.008 **LBW:** **LBW per 10µg/m3 of PM2.5 for entire pregnancy**	*3rd trimester* (4 cohort studies; 3,637,501 births) Pooled ES= -16.05 (-37.43 to 1.34) I^2 =85.6%-low with p=0.000 ***BW per 20µg/m3 of PM10 f*or** *1st trimester* (10 cohort studies; 4,505,769 births.) Pooled ES= -3.92 (-8.97 to 1.13) I^2 =67.2%-moderate with p=0.001 *2nd trimester* (10 cohort studies; 4,505,769 births.) Pooled ES= -3.40 (-7.22 to 0.43) I^2 =41.2%-moderate with p=0.083 *3rd trimester* (10 cohort studies; 4,505,769 births.) Pooled ES= -4.20 (-14.27 to 5.86) I^2 =93.3%-high with p=0.000 **BW per 1ppm of CO** **for** *1st trimester* (8 cohort studies; 4,576,045 births) Pooled ES= -1.47 (-7.84 to 4.90) I^2 =94.5%-high with p=0.000 *2nd trimester* (7 cohort studies; 4,299,282 births) Pooled ES= 1.71 (0.76 to 2.67) I^2 =0.0%-No with p=0.445 ***3rd** trimester* (7 cohort studies; 4,299,282 births) Pooled ES= -0.90 (-7.85 to 6.04) I^2 =91.1%-high with p=0.000 **BW per 20ppb of NO2 for** *1st trimester* (11 cohort studies; 4,259,729 births) Pooled ES= -4.18 (-19.18 to 10.82) I^2 =90.0%-high with p=0.000 *2nd trimester* (9 cohort studies; 3,979,113 births)	Future research priorities also include consideration of alternative exposure metrics and evaluation of critical exposure windows and pathophysiological mechanisms.	effects from categorical exposures, quantified heterogeneity and conducted meta-regression to examine the influence of certain study characteristics on effect sizes, as well as conducting numerous sensitivity analyses, for instance in relation to alternative methods of exposure classification.' **Limitations** Evidence of publication bias based on funnel plot asymmetry for PM10 and ozone and low birth weight despite obtaining additional unpublished results from study authors when possible. A high degree of heterogeneity for some exposure periods.

			(6 studies: 5 cohort and 1 case-control; 4,160,105 births). Pooled OR= 1.05 (95% CI = 0.99 to1.12) I^2 =85.5%-high with p=0.000 **LBW per 20µg/m3 of PM10 for entire pregnancy** (14 cohort studies, one study with 7 city-specific estimates counted 7 times; 4,419,929 births) Pooled OR= 1.10 (95% CI = 1.05 to1.15) I^2 =68.4%-moderate with p=0.000 **LBW per 1ppm of CO for entire pregnancy** (6 cohort studies; 4,543,308 births) Pooled OR= 1.07 (95% CI = 1.02 to1.12) I^2 =38.2%-low with p=0.152 **LBW per 20ppb of NO2 for entire pregnancy** (10 studies; 7 cohort, 1 case-control, 1 ecological study with two results; 4,211,351 births) Pooled OR= 1.05 (95% CI = 1.00 to1.09) I^2 =78.4%-high with p=0.000 **LBW per 20ppb of O3 for entire pregnancy** (3 cohort studies; 3,377,984 births)	Pooled ES= 0.85 (-1.27 to 2.97) I^2 =0.0%-No with p=0.741 *3rd trimester* (10 cohort studies; 3,982,966 births) Pooled ES= -7.89 (-29.04 to 13.25) I^2 =93.5%-high with p=0.000 **BW per 20ppb of O3 for** *1st trimester* (8 cohort studies: 4,325,899 births) Pooled ES= 2.29 (-5.09 to 9.67) I^2 =80.6%-high with p=0.000 *2nd trimester* (8 cohort studies: 4,325,899 births) Pooled ES= -10.95 (-18.75 to -3.14) I^2 =77.2%-high with p=0.000 *3rd trimester* (8 cohort studies: 4,325,899 births) Pooled ES= -2.79 (-7.22 to 1.64) I^2 =80.0%-high with p=0.000. **BW per 5ppb of SO2 for** *1st trimester* (6 cohort studies; 4,098,747 births) Pooled ES= -7.57 (-21.09 to 5.95) I^2 =95.0%-high with p=0.000 *2nd trimester* (4 cohort studies; 3,808,425 births) Pooled ES= 4.64 (-4.59 to 13.87) I^2 =65.6%-moderate with p=0.033 *3rd trimester* (5 cohort studies; 3,883,096 births) Pooled ES= 7.61 (-2.38 to 17.59) I^2 =93.1%-high with p=0.000 **LBW:** **LBW per 10µg/m3 of PM2.5 for** Trimester-specifics were not available. **LBW per 20µg/m3 of PM10** **for** *1st trimester*		

			Pooled OR= 1.01 (95% CI = 0.82 to1.25) I^2 =24.9%-low with p=0.264 **LBW per 5ppb of SO2 for entire pregnancy** (7 studies; 4 cohort, 2 ecological with two results from one of the ecological; 4,400,175 births) Pooled OR= 1.03 (95% CI = 1.02 to1.05) I^2 =0.0%-No with p=0.434 **PTB:** **PTB per 10µg/m3 of PM2.5 for entire pregnancy** (4 studies; 3 cohort and 1 case-control; 197,980 births) Pooled OR= 1.16 (95% CI = 1.07 to1.26) I^2 =17.0%-low with p=0.306 **PTB per 20µg/m3 of PM10 for entire pregnancy** (3 studies; 2 cohort and 1 case-control; 98,774 births) Pooled OR= 1.35 (95% CI = 0.97 to1.90) I^2 =16.9%-low with p=0.300 **PTB per 1ppm of CO for entire pregnancy** (2 studies; 1 cohort and I case-control; 112,941 births) Pooled OR= 1.05 (95% CI = 0.95 to1.17) I^2 =0.0%-No with p=0.589 **PTB per 20ppb of NO2 for entire pregnancy**	(7 cohort studies; 1,153,736 births) Pooled OR= 1.03 (0.95 to1.11) I^2 =41.6%-low with p=0.114 *2nd trimester* (7 cohort studies; 1,153,736 births) Pooled OR= 1.02 (0.96 to1.09) I^2 =22.6%-low with p=0.256 *3rd trimester* (7 cohort studies; 1,153,736 births) Pooled OR= 1.01 (0.97 to1.06) I^2 =12.8%-low with p=0.332 **LBW per 1ppm of CO for** *1st trimester* (5 cohort studies; 1,129,363 births) Pooled OR= 1.05 (1.01 to1.09) I^2 =0.0%-No with p=0.644 *2nd trimester* (4 cohort studies; 900,278 births) Pooled OR= 1.07 (1.03 to1.12) I^2 =0.0%-No with p=0.666 *3rd trimester* (5 cohort studies; 1,129,363 births) Pooled OR= 1.01 (0.90 to1.14) I^2 =86.3%-high with p=0.000 **LBW per 20ppb of NO2 for** *1st trimester* (5 cohort studies; 1,043,794 births) Pooled OR= 1.03 (0.99 to1.06) I^2 =0.0%-No with p=0.905 *2nd trimester* (4 cohort studies; 814,709 births) Pooled OR= 1.04 (1.01 to1.08) I^2 =0.0%-No with p=0.863 *3rd trimester* (5 cohort studies; 1,043,794 births) Pooled OR= 0.98 (0.87 to1.10) I^2 =69.7%-moderate with p=0.010 **LBW per 20ppb of O3 for** *1st trimester* (5 cohort studies; 1,002,748 births) Pooled OR= 0.99 (0.91 to1.08)		

			(5 studies; 4 cohort and 1 ecological; 162,815 births) Pooled OR= 1.16 (95% CI = 0.83 to1.63) I^2 =53.3%-moderate with p=0.073 **PTB per 20ppb of O3 for entire pregnancy** (2 cohort studies; 98,449 births) Pooled OR= 1.92 (95% CI = 0.38 to 9.76) I^2 =88.5%-high with p=0.003 **PTB per 5ppb of SO2** NB: No pooled estimates due to 2 or fewer estimates as stated by authors. **Publication bias** 'There was evidence of funnel plot asymmetry, indicative of publication bias, in the case of PM10 and ozone and LBW, for which there was a greater than expected number of positive than negative effect sizes among small, imprecise studies with larger standard errors. The Begg's test p-value was 0.04 for PM10 and the p-value on Egger's bias coefficient was 0.03 for ozone.'	I^2 =0.0%- No with p=0.817 *2nd trimester* (3 cohort studies; 496,900 births) Pooled OR= 0.95 (0.79 to1.15) I^2 =33.5%-low with p=0.222 *3rd trimester* (5 cohort studies; 1,002,748 births) Pooled OR= 1.03 (0.84 to1.26) I^2 =75.6%-high with p=0.003 **LBW per 5ppb of SO2 for** *1st trimester* (5 cohort studies; 889,204 births) Pooled OR= 1.02 (0.99 to1.04) I^2 =58.3%-moderate with p=0.048 *2nd trimester* (4 cohort studies; 660,119 births) Pooled OR= 1.01 (0.98 to1.04) I^2 =40.6%-low with p=0.168 *3rd trimester* (6 cohort studies; 963,875 births) Pooled OR= 0.99 (0.97 to1.02) I^2 =59.3%-moderate with p=0.031 **PTB**: **PTB per 10µg/m3 of PM2.5 for** *1st trimester* (4 studies; 3 cohort and 1 case-control 589,100 births) Pooled OR= 0.85 (0.60 to1.20) I^2 =94.4%-high with p=0.000 *2nd trimester* (1 cohort study; 418,715 births) OR= 0.66 (0.57 to 0.77) I^2 = NA, p= NA *3rd trimester* (4 studies; 3 cohort and 1 case-control 589,100 births) Pooled OR= 1.05 (0.98 to1.13)		

				I^2 =33.2%-low with p=0.213 **PTB per 20μg/m3 of PM10** **for** *1st trimester* (6 cohort studies; 1,043,954 births) Pooled OR= 0.97 (0.87 to1.07) I^2 =85.3%-high with p=0.000 *2nd trimester* (3 cohort studies; 794,396 births) Pooled OR= 0.95 (0.91 to 0.99) I^2 =0.0%-No with p=0.461 *3rd trimester* (6 cohort studies; 1,043,954 births) Pooled OR= 1.06 (1.03 to 1.11) I^2 =20.1%-low with p=0.282 **PTB per 1ppm of CO for** *1st trimester* (5 studies; 4 cohort and 1 case-control; 911,850 births) Pooled OR= 0.96 (0.88 to1.05) I^2 =92.4%-high with p=0.000 *2nd trimester* (1 cohort study: 418,715 births) OR= 1.03 (0.99 to1.07) I^2 =NA, p=NA *3rd trimester* (5 studies; 4 cohort and 1 case-control; 911,850 births) Pooled OR= 1.04 (1.02 to1.06) I^2 =0.0%-No with p=0.569 **PTB per 20ppb of NO2 for** *1st trimester* (6 cohort studies; 807,681 births) Pooled OR= 0.87 (0.64 to1.17) I^2 =89.1%-high with p=0.000 *2nd trimester* (2 cohort studies; 422,703 births) Pooled OR= 1.03 (0.77 to1.39) I^2 =21.6%-low with p=0.259 *3rd trimester*		

				(6 cohort studies; 807,681 births) Pooled OR= 1.06 (0.96 to1.18) I^2 =19.5%-low with p=0.286 **PTB per 20ppb of O3 for** *1st trimester* (4 cohort studies; 799,840 births) Pooled OR= 1.22 (0.91 to 1.64) I^2 =89.8%-high with p=0.000 *2nd trimester* (1 cohort study; 418,715 births) OR= 0.94 (0.88 to 1.00) I^2 =NA, p=NA *3rd trimester* (4 cohort studies; 799,840 births) Pooled OR= 0.97 (0.86 to 1.10) I^2 =44.2%-low with p=0.146 **Sensitivity analyses** Pooled estimates were generally insensitive to the inclusion of additional results based on term IUGR and SGA at term to studies of LBW. Pooled estimates were not sensitive to differences between actual and estimated odds ratios (using ratios and relative risks from one study (Wilhelm and Ritz, 2005) Assessed the validity of deriving effect estimates expressed in relation to continuous pollutant concentrations from those based on discrete exposure categories and the results were not sensitive to inclusion of these additional values. Substituted effect estimates based on refined exposure classification in the place of base estimates; results were not sensitive to these substitutions. Conducted meta-regression of estimates of change in birth weight against explanatory variables for control for smoking, alcohol consumption, education, socioeconomic status, as well		

				as mean pollutant concentration and whether studies were restricted to singleton or term pregnancies. Analyses were confined to birth weight effects based on entire pregnancy exposure for PM10, PM2.5 and NO2 due to sufficient number of effect (n=7, 8 and 10, respectively). Only term pregnancy was consistently associated with reduction of effect size for the three pollutants. Control for socioeconomic status was associated with reduced effect size in studies of PM10 only.		
21. Sapkota [36] 23/11/2010 [5, all USA]	PM2.5, PM10	LBW/TLBW, PTB	**LBW per 10µg/m3 of PM2.5 for entire pregnancy** (4 studies; 831,042 births.) OR= 1.09 (95% CI = 0.90 to 1.32) I^2 =57.4%-moderate with p=0.071 **LBW per 10µg/m3 of PM10 for entire pregnancy** (11 studies; 1,935,404 births). OR= 1.02 (95% CI = 0.99 to 1.05) I^2 =54.5%-moderate with p=0.015 **PTB per 10µg/m3 of PM2.5 for entire pregnancy** (6 studies; 517,760 births) OR= 1.15 (1.14 to 1.16) I^2 =0.1%-low with p=0.416 **PTB per 10µg/m3 of PM10 for entire pregnancy** (8 studies; 1,047,489 births) OR= 1.02 (0.99 to 1.04) I^2 =73.0%-high with p=0.001	***By trimester*** **LBW per 10µg/m3 of PM2.5** NA due to insufficient study **LBW per 10µg/m3 of PM10** *1st trimester* (5 studies) OR=1.00 (0.97 to 1.03) *3rd trimester* (7 studies) OR=1.00 (0.99 to 1.01) **PTB per 10µg/m3 of PM2.5** *1st trimester* (4 studies) OR=1.04 (0.73 to 1.34) *3rd trimester* (3 studies) OR=1.07 (1.00 to 1.15) **PTB per 10µg/m3 of PM10** *1st trimester* (4 studies) OR=1.02 (0.97 to 1.06) *3rd trimester* (5 studies) OR=1.02 (1.01 to 1.03)	'Studies may need to assess outcome misclassification of gestational age and exposure at different developmental stages by matching or stratifying on gestational age and assessing exposures during specific gestational windows (such as <25, 25–30, 30–35, and 35–37 weeks). Future studies need to also pay more attention to the likely multifactorial nature of these adverse birth events.	**Strength** 'First to present results from a systematic review of the literature and meta-analysis of studies published to date providing quantitative estimates of association between exposure to PM (PM10 and PM2.5) and two major adverse birth outcomes: LBW and PTB.' **Limitations** 'While our meta-analysis further increased the statistical power to estimate even small increases in risk, this increased precision does, however, not exclude the possibility of greater residual confounding bias not reflected in our standard measures of

			NB: Stated in method as RE and FE but no indication which was used for each in the forest plot or the tables. **Publication bias** 'There was no significant publication bias for both outcomes according to both tests (p>0.05 for both Begg's and Egger's test for bias).'	**NB**: I^2 not provided here. Forest plot unavailable to determine sample size. **Leave-one-out sensitivity analyses** Removing a particular study did not change the summary point estimates much with some noted exceptions. For PM10 exposure and LBW, removing the study by Maisonet et al. (2001) results in a statistically significant increase in risk. Likewise, for PM10 and PTB, when Ritz et al. (2000) was removed, the observed association was no longer formally statistically significant.	Future epidemiological studies of air pollution and birth outcomes should consider mixture of chemical substances and geographical locations. It would be desirable to consider additional studies conducted in the low-resource countries in which levels of particulate pollution are much higher than those in the currently available studies when quantifying the burden of disease related to particles and adverse birth outcome worldwide. However, such studies would require resources in routine air monitoring and health and risk factor surveillance that likely may not be available in low-resource countries for some	uncertainty (CI) since birth record studies are typically limited to routinely recorded information and limits our ability to control for confounding by maternal or fetal risk factors.'

					time to come. Yet, this should not preclude inferences concerning health effects and implementing policies that may help to alleviate these important public health problems	

Note: NO_2, Nitrogen dioxide; CO, Carbon monoxide; O_3, Ozone; SO_2, Sulphur dioxide; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤ 2.5μm; PM_{10}, particulate matter at aerodynamic diameter ≤ 10μm; PTB, preterm birth; BW, birth weight; LBW, low birth weight; TLBW, term low birth weight; VLBW, very low birth weight; SGA, small-for-gestational age; IUGR, intrauterine growth retardation; SB, stillbirth; SAB, spontaneous abortion; Db, database; USA, United States of America; UK, United Kingdom; NOS, Newcastle-Ottawa Scale; OHAT, Office of Health Assessment and Translation; AHRQ, Agency for Healthcare Research and Quality; OR, odd ratio; CI, confidence interval; I^2, heterogeneity; FE, fixed effect; RE, random effect; RoB, risk of bias; IQR, interquartile range.

Table S3.5 Overlaps in the systematic reviews using Corrected Covered Area (CCA)

Review category	Number of times studies appeared in reviews (N)	Number of indexed primary studies (r)	Number of reviews (c)	CCA (%)	Overlap degree
SR	412	211	15	6.8	Moderate
SRMA	575	228	21	7.6	Moderate

Note: SR, systematic reviews without meta-analyses; SRMAs, systematic reviews with meta-analyses

$$CCA = \frac{N-r}{rc-r},$$

where N is the sum of the number of included primary studies (the total number of times studies appeared in the reviews) in the umbrella review, r is the total number of indexed primary studies c is the number of reviews. CCA score ≤ 5% implies slight overlap of primary studies, 6-10% moderate, 11-15% high and >15% very high degrees of overlaps [37]

Table S3.6 Association between birth weight and particulate matters by race/ethnicity during the entire pregnancy period

Pollutant (incremental units)	**Exposure period**	**Meta-analysis**	**Change in birthweight (g) (95% CI)**	**I^2 (%)**	**Primary studies (n)**	**Total births (N)**	**Consistency, confidence**
$PM_{2.5}$ (10 μg/m^3)	Whites	Uwak (2021)	-32 (-60, -4)	95	7	8,893,539	++, Pe
		Thayamballi (2020)	-16 (-21, -10)	68	5	6,484,085	
	Hispanics	Uwak (2021)	-1 (-23, 22)	85	5	8,525,968	+, Pe
		Thayamballi (2020)	-9 (-16, -3)	92	5	6,484,085	
	Blacks	Uwak (2021)	-27 (-82, 27)	93	5	8,867,779	+, Pe
		Thayamballi (2020)	-22 (-32, -12)	73	4	6,467,392	
	Asians	Thayamballi (2020)	-6 (-21, 9)	95	3	4,918,488	0, Pe
PM_{10} (10 μg/m^3)	Whites	Uwak (2021)	-10 (-12, -8)	0	4	5,461,652	+, Pe
	Blacks	Uwak (2021)	3 (-65, 72)	97	3	5,452,585	0, Pe
	Hispanics	Uwak (2021)	0 (-74, 73)	96	2	5,094,081	0, Pe

Note: CI, Confidence interval; I^2, Heterogeneity; Beta represents change in birth weight in grams; '++' represents significant positive association ; '0' represents contradictory/unclear direction; Pe, probable evidence.

Table S3.7 Association between small-for-gestational age (SGA) and ambient air pollution

Pollutant (incremental units)	Exposure period	Meta-analysis	OR (95% CI)	I^2 (%)	Primary studies (n)	Total births (N)	Consistency, confidence
$PM_{2.5}$ (10 µg/m^3	Entire Pregnancy	Zhang (2016) and Zhu (2015)*	1.15 (1.10, 1.20)	0	6	1,515,887	+, Pe
	Trimester 1	Zhang (2016) and Zhu (2015)	1.07 (1.05, 1.10)	5	6	1,740,763	0, Pe
	Trimester 2	Zhang (2016) and Zhu (2015)	1.06 (1.02, 1.10)	58	5	1,706,058	+, Pe
	Trimester 3	Zhang (2016) and Zhu (2015)	1.06 (1.04, 1.08)	13	5	1,706,058	+, Pe

* Complete duplicated meta-analyses and hence considered as one. Note: OR, odd ratio; CI, confidence intervals; I^2, Heterogeneity; '+' represents less consistent positive association; '0' represents contradictory/unclear direction; Pe, probable evidence.

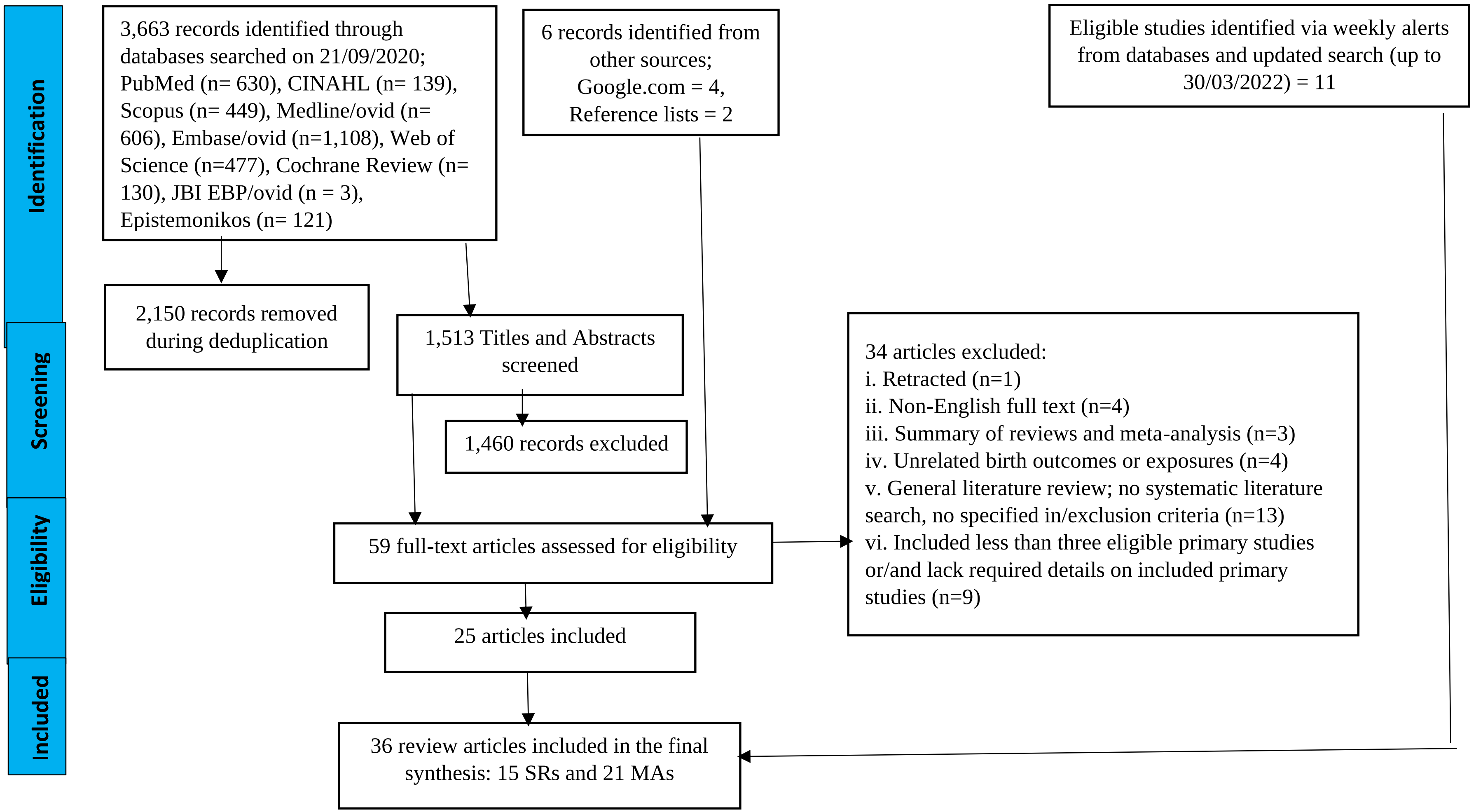

Figure S3.1 PRISMA flow chart showing the systematic literature search and processes involved in selecting the eligible studies for the umbrella review.
Note: PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; SRs, systematic reviews; MAs, meta-analyses

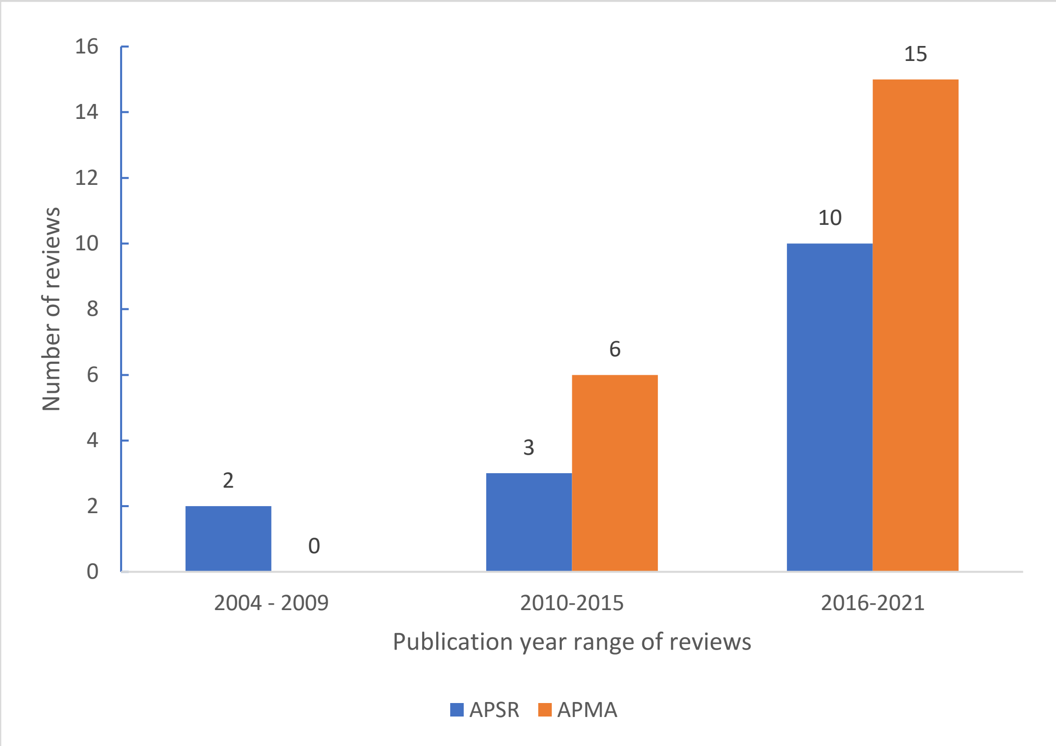

Figure S3.2 The number of systematic reviews on birth outcomes and air pollution without meta-analysis (APSR) and with meta-analysis (APMA) in five-year intervals.

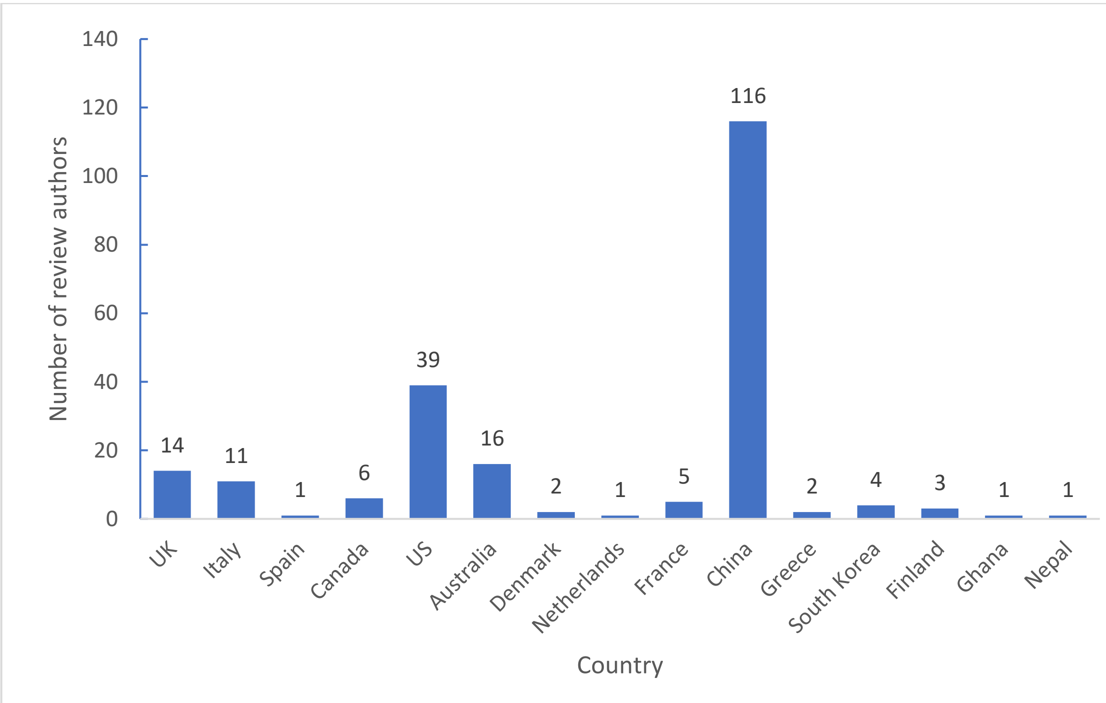

Figure S3.3 Country of affiliation and the number of reviews authors. A total of 222 authors were counted on the 36 included reviews. Note: Where there were multiple countries of affiliation for a review author on a given review paper, only the first affiliated country was considered, and review authors were counted per review without consideration to an author appearing in more than one review studies. UK, United Kingdom; US, United States.

First author, Year	1. Is the review question clearly and explicitly stated?	2. Were the inclusion criteria appropriate for the review question?	3. Was the search strategy appropriate?	4. Were the sources and resources used to search for studies adequate?[a]	5. Were the criteria for appraising studies appropriate?[b]	6. Was critical appraisal conducted by two or more reviewers independently?	7. Were there methods to minimize errors in data extraction?[c]	8. Were the methods used to combine studies appropriate?	9. Was the likelihood of publication bias assessed?	10. Were recommendations for policy and/or practice supported by the reported data?	11. Were the specific directives for new research appropriate?	Score (max=10)	Overall RoB
Edwards, 2021	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	10	L
Walter, 2021	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	Y	9	L
Luo, 2021	Y	Y	Y	Y	Y	N	N	Y	NA	Y	Y	8	M
Bekkar, 2020	Y	Y	Y	Y	N	N	N	Y	NA	Y	Y	7	M
Heo, 2019	Y	Y	Y	N	U	N	Y	Y	NA	Y	Y	7	M
Yuan, 2019	Y	Y	Y	N	N	N	N	Y	NA	Y	Y	6	M
Tsoli, 2019	Y	Y	Y	Y	N	N	N	Y	NA	Y	Y	7	M
Grippo, 2018	Y	Y	Y	N	N	N	N	Y	NA	Y	Y	6	M
Westergaard, 2017	Y	Y	Y	Y	N	N	N	Y	NA	Y	Y	7	M
Jacobs, 2017	Y	Y	Y	Y	U	N	N	Y	NA	Y	Y	7	M
Shah, 2011	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	10	L
Bonzini,2010	Y	Y	Y	N	N	N	N	Y	NA	Y	Y	6	M
Bosetti, 2010	Y	Y	Y	N	N	N	N	Y	NA	Y	Y	6	M
Ghosh, 2007	Y	Y	Y	Y	U	N	N	Y	NA	Y	Y	7	M

Glinianaia, 2004	Y	Y	Y	Y	N	N	Y	Y	NA	Y	Y	8	M
Y	15	15	15	10	4	3	4	15		15	15	**Average score = 7.4**	Average overall RoB
U	0	0	0	0	3	0	0	0		0	0		M
N	0	0	0	5	8	12	11	0		0	0		

Figure S3.4 Summary of the risk of bias (RoB) assessment with Joanna Briggs Institute (JBI) critical appraisal checklist of the systematic reviews without meta-analysis for ambient air pollution and birth outcomes. (https://jbi-global-wiki.refined.site/space/MANUAL/3283910853/Appendix+10.1+JBI+Critical+Appraisal+Checklist+for+Systematic+reviews+and+Research+Syntheses)

[a]'Yes' if at least two electronic databases were searched

[b]'Yes' if standardised tools were used and results reported for each study, 'Unclear' if stated as done but results were not reported for each study.

[c]'Yes' if data extraction was performed by at least two reviewers independently

Yes (Y)	
Unclear(U)	
No (N)	
Not applicable (NA)	
High (H)	
Moderate (M)	
Low (L)	

First author, Year	1. Is the review question clearly and explicitly stated?	2. Were the inclusion criteria appropriate for the review question?	3. Was the search strategy appropriate?	4. Were the sources and resources used to search for studies adequate?[a]	5. Were the criteria for appraising studies appropriate?[b]	6. Was critical appraisal conducted by two or more reviewers independently?	7. Were there methods to minimize errors in data extraction?[c]	8. Were the methods used to combine studies appropriate?	9. Was the likelihood of publication bias assessed?	10. Were recommendations for policy and/or practice supported by the reported data?	11. Were the specific directives for new research appropriate?	Score (max=11)	Overall RoB
Gong, 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Zhu, 2021	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	10	L
Ju, 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Xie, 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Rappazzo, 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Zhang, 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Uwak,2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Simonici, 2020	Y	Y	Y	N	Y	N	Y	Y	N	Y	Y	8	M
Thayamballi, 2020	Y	Y	Y	Y	U	Y	N	Y	N	Y	Y	8	M
Li, 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Ji, 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Liu, 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Li, 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Zhang, 2016	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9	L
Siddika, 2016	Y	Y	Y	Y	U	N	Y	Y	Y	Y	Y	9	L
Sun, 2016	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9	L
Sun, 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L
Lamichhane, 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	L

Zhu, 2015	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9	L
Stieb, 2012	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9	L
Sapkota, 2010	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	9	L
Y	21	21	21	20	14	13	20	21	19	21`	21	**Average score = 10.1**	Average overall RoB
U	0	0	0	0	2	0	0	0	0	0	0		
N	0	0	0	1	5	8	1	0	2	0	0		

Figure S3.5 Summary of the risk of bias (RoB) assessment with Joanna Briggs Institute (JBI) critical appraisal checklist of the systematic reviews with meta-analysis for ambient air pollution and birth outcomes. (https://jbi-global-wiki.refined.site/space/MANUAL/3283910853/Appendix+10.1+JBI+Critical+Appraisal+Checklist+for+Systematic+reviews+and+Research+Syntheses)

[a]'Yes' if at least two electronic databases were searched

[b]'Yes' if standardised tools were used and results reported for each study, 'Unclear' if stated as done but results were not reported for each study.

[c]'Yes' if data extraction was performed by at least two reviewers independently

Yes (Y)	
Unclear(U)	
No (N)	
Not applicable (NA)	
High (H)	
Moderate (M)	
Low (L)	

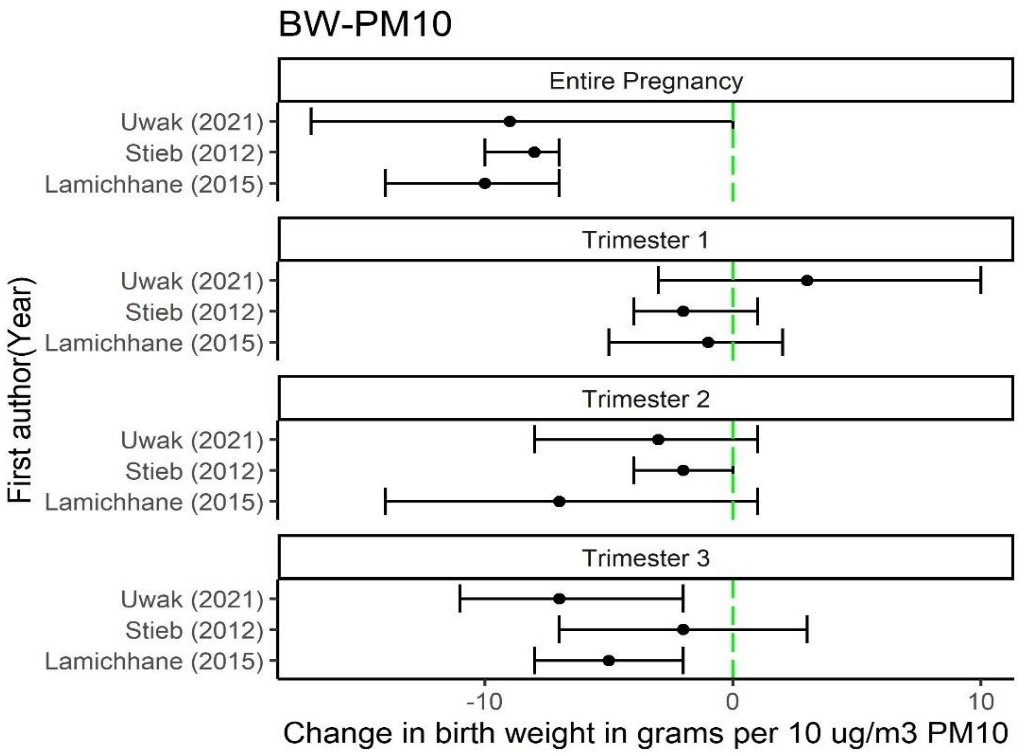

Figure S3.6 Association between change in birth weight (BW) in grams per 10µg/m^3 PM_{10} increase at different pregnancy periods. Solid points represent point estimates of the individual meta-analysis studies, and the whiskers represent 95% confidence intervals (CIs). The green dotted vertical line represents the reference for no change in birth weight of 0. Note: PM_{10}, particulate matter at aerodynamic diameter ≤ 10µm.

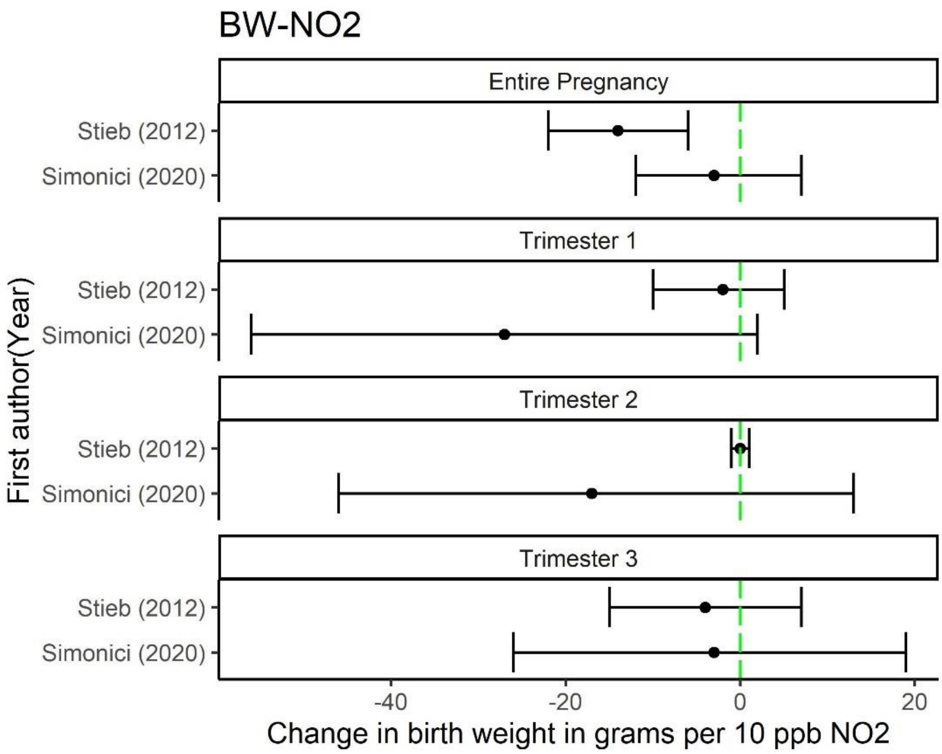

Figure S3.7 Forest plot of the association between change in birth weight (BW) in grams and Nitrogen dioxide (NO_2) per 10 parts per billion (ppb) increment in NO_2 at different pregnancy periods. Solid points represent point estimates of the meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for no change in birth weight of 0.

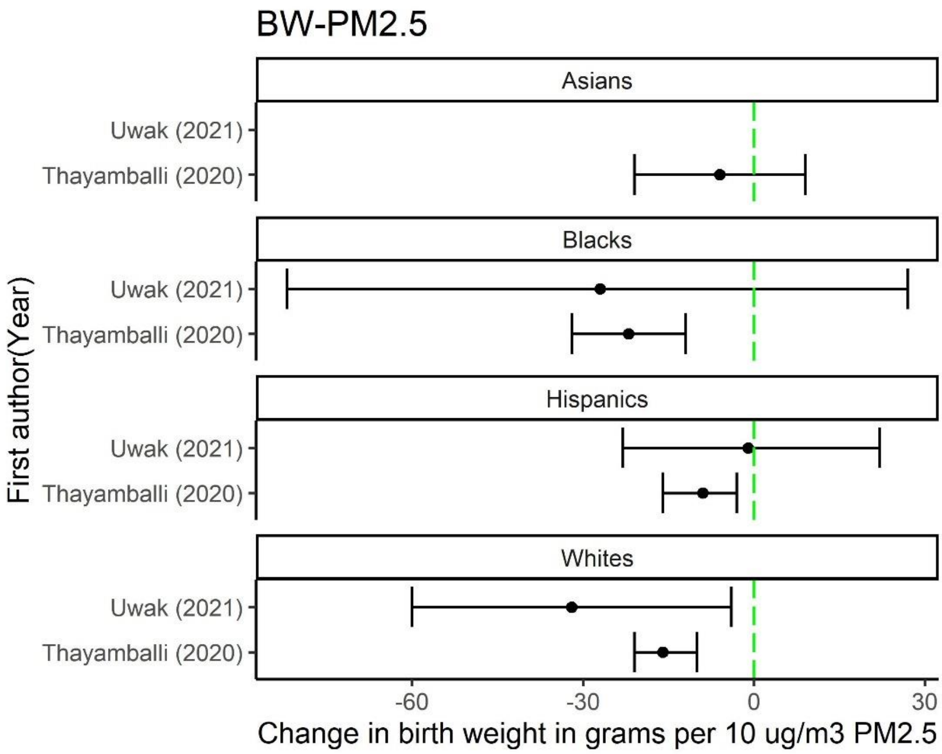

Figure S3.8 Forest plot of the association between $PM_{2.5}$ increase per 10µg/m^3 and change in birth weight in grams (BW) across entire pregnancy period by race/ethnicity. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for no change in birth weight of 0. Note: $PM_{2.5}$, particulate matter at aerodynamic diameter ≤ 2.5µm.

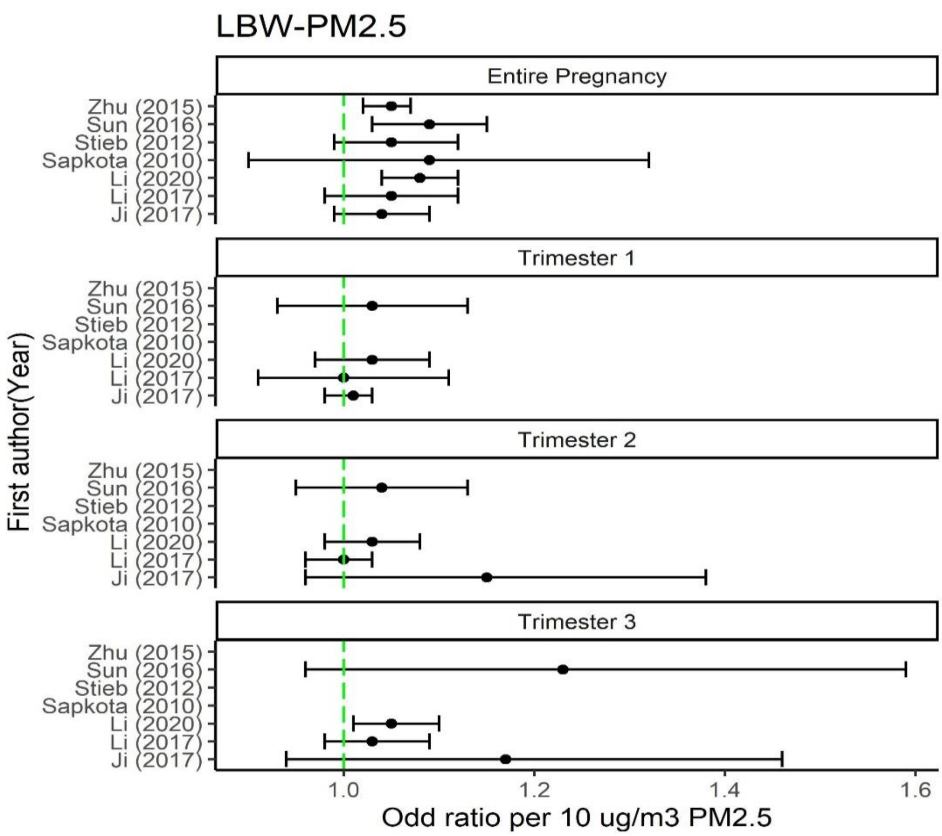

Figure S3.9 Forest plot of the association between low birth weight (LBW) per 10µg/m^3 $PM_{2.5}$ increase at different pregnancy periods) at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dashed line represents the reference for null association of 1. Note: $PM_{2.5}$, particulate matter with aerodynamic diameter ≤ 2.5µm.

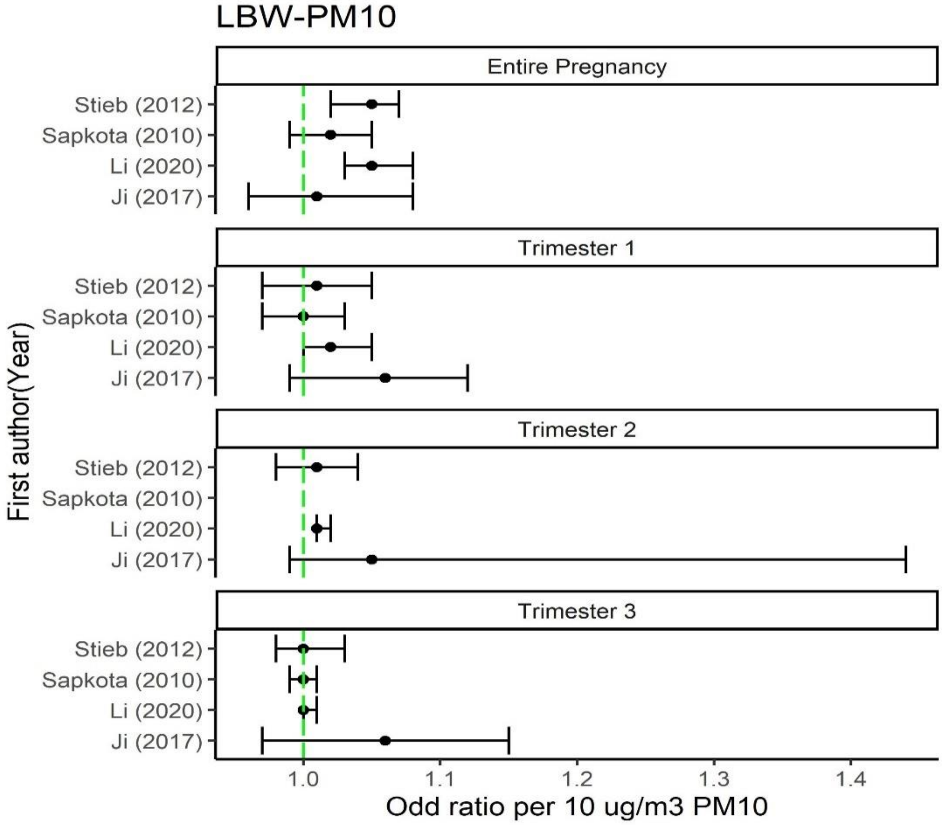

Figure S3.10 Forest plot of the association between low birth weight (LBW) per 10µg/m^3 PM_{10} increase at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1. Note: PM_{10}, particulate matter at aerodynamic diameter ≤ 10μm.

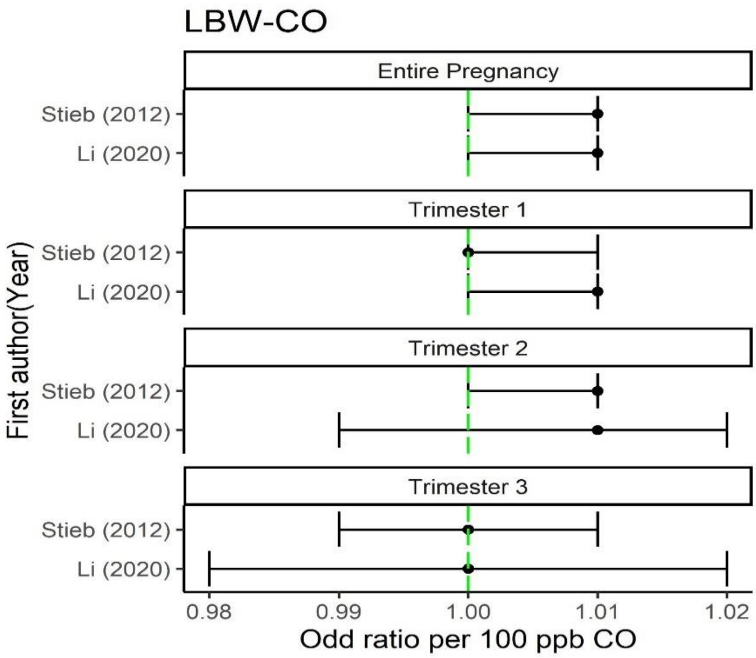

Figure S3.11 Forest plot of the association between low birth weight (LBW) and carbon monoxide (CO) per 100 parts per billion (ppb) increment in CO at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

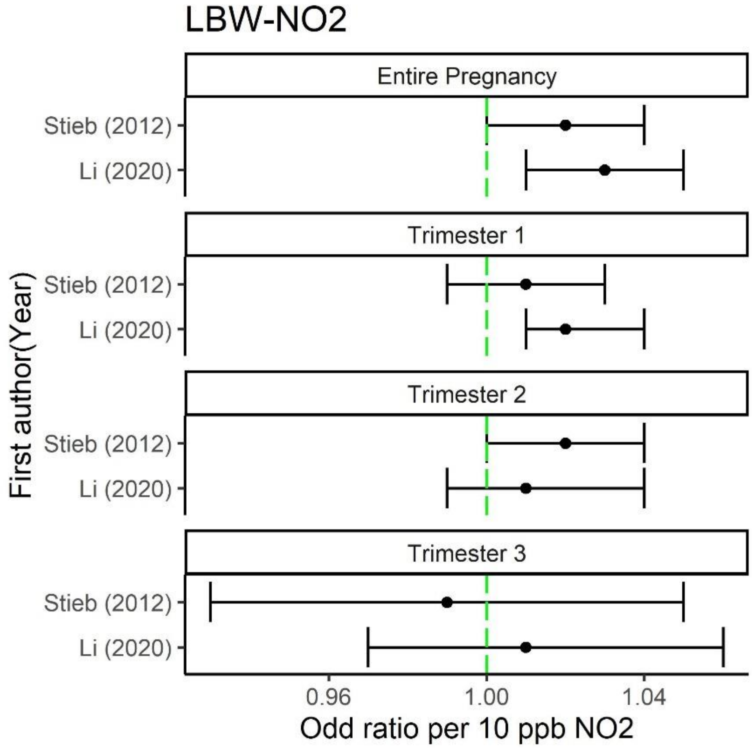

Figure S3.12 Forest plot of the association between low birth weight (LBW) and Nitrogen dioxide (NO_2) per 20 parts per billion (ppb) increment in NO_2 at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

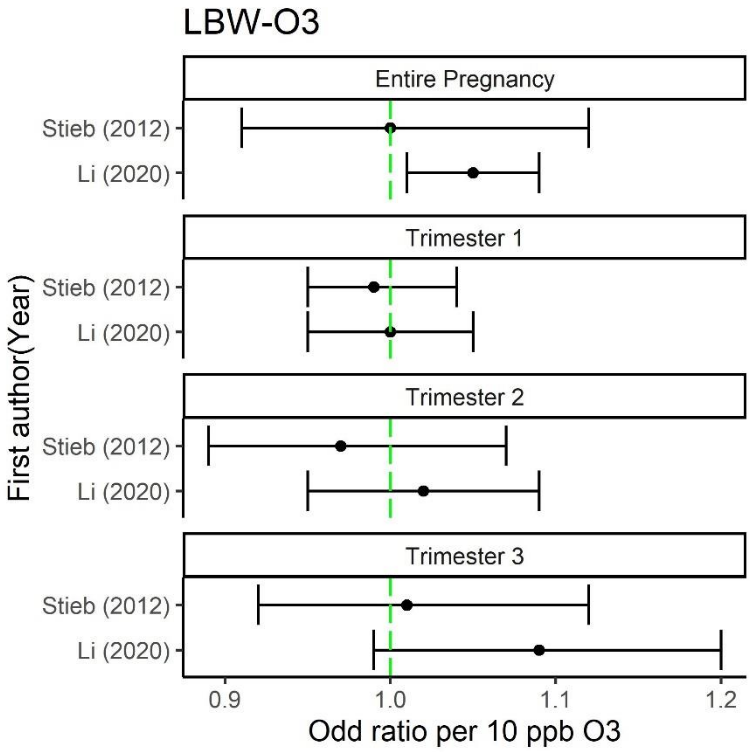

Figure S3.13 Forest plot of the association between low birth weight (LBW) and Ozone (O_3) per 10 parts per billion (ppb) increment in O_3 at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

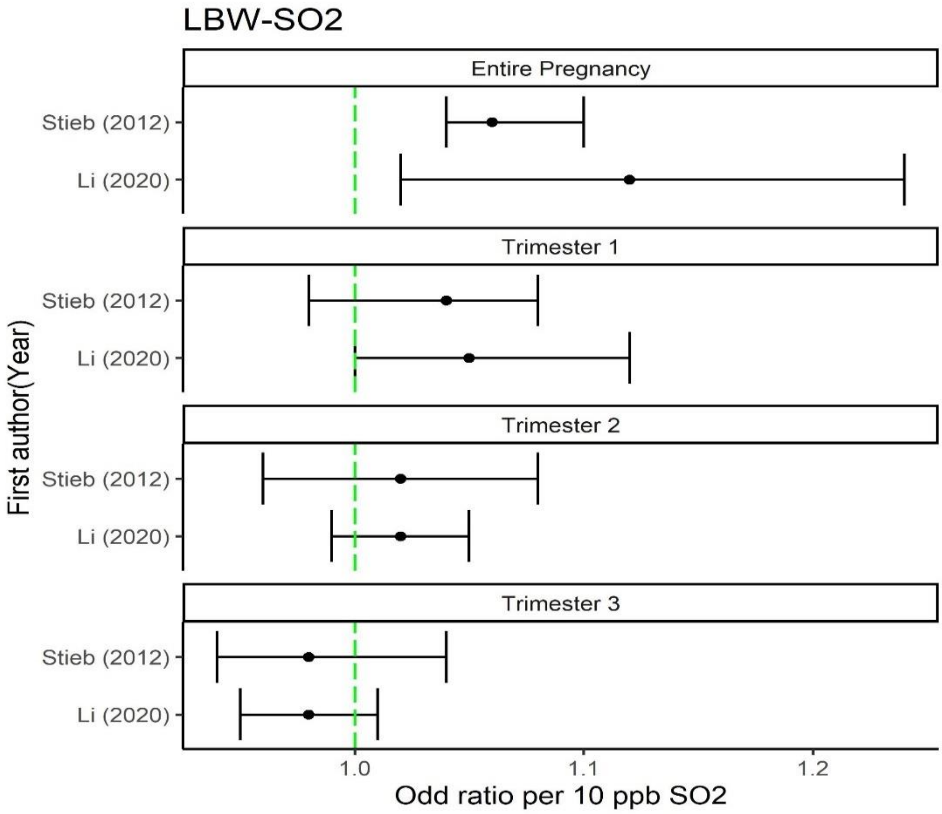

Figure S3.14 Forest plot of the association between low birth weight (LBW) and Sulphur dioxide (SO_2) per 10 parts per billion (ppb) increment in SO_2 at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

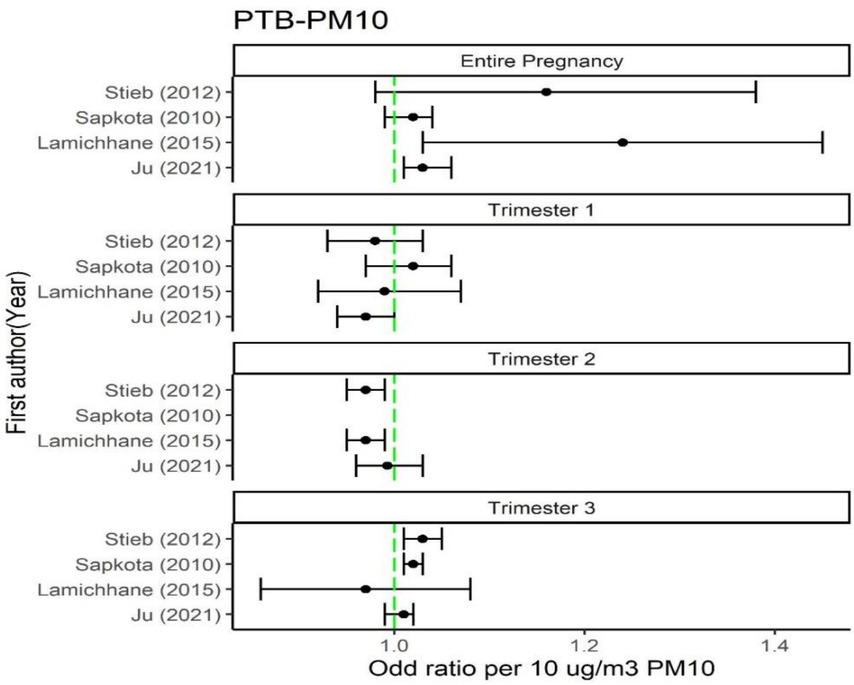

Figure S3.15 Forest plot of the association between preterm birth (PTB) per $10\mu g/m^3$ PM_{10} increase at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents null association of 1. Note: PM_{10}, particulate matter at aerodynamic diameter $\leq 10\mu m$.

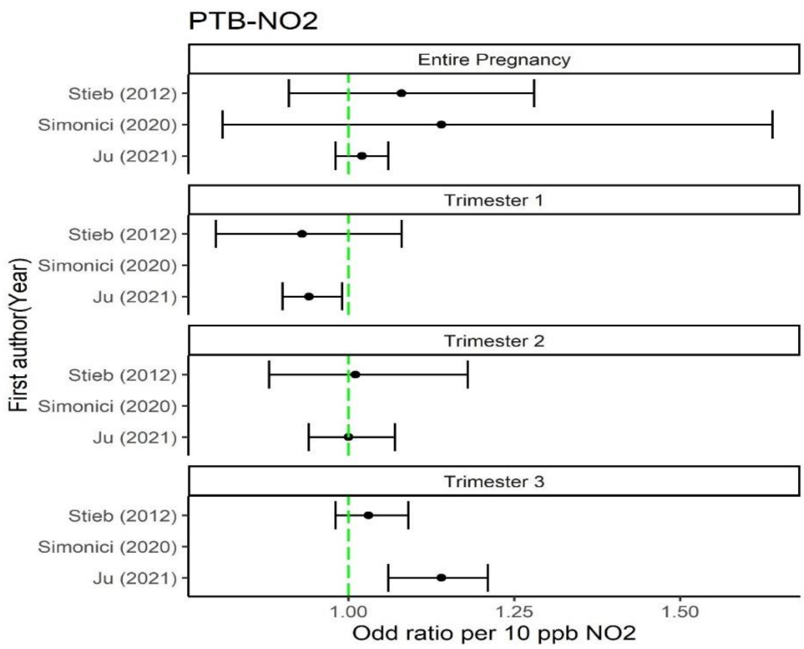

Figure S3.16 Forest plot of the association between preterm birth (PTB) and Nitrogen dioxide (NO_2) per 10 parts per billion (ppb) increment in NO_2 at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

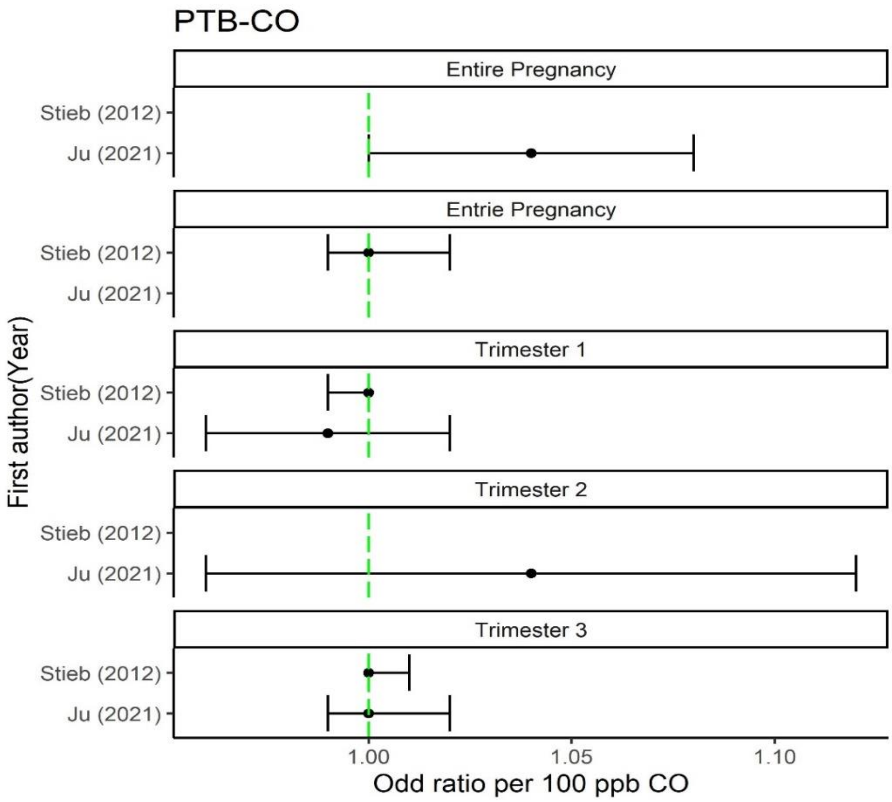

Figure S3.17 Forest plot of the association between preterm birth (PTB) and carbon monoxide (CO) per 100 parts per billion (ppb) increment in CO at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

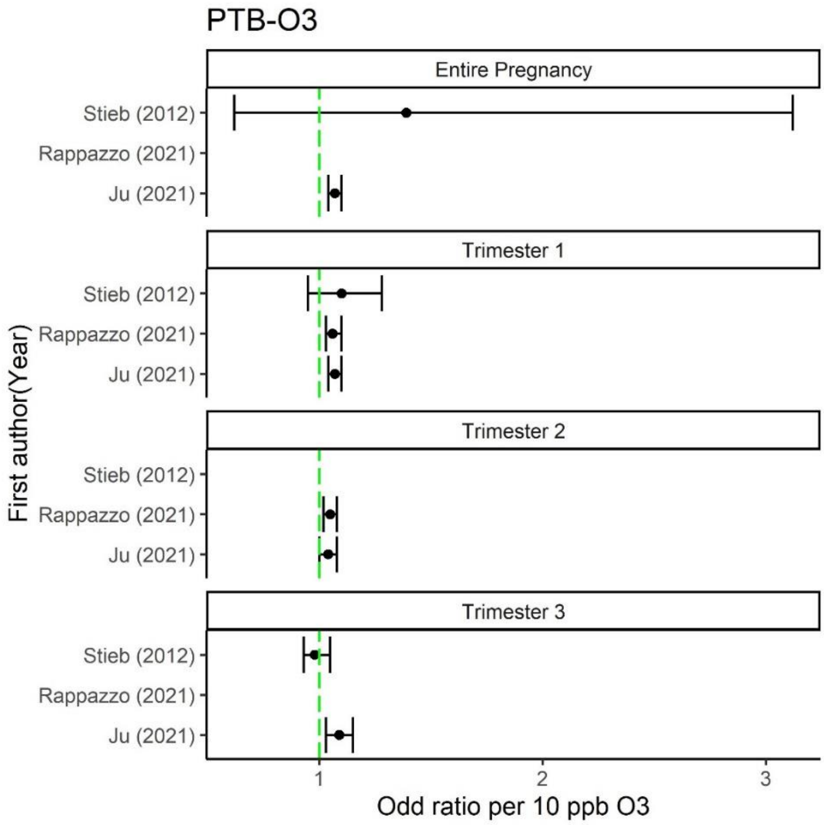

Figure S3.18 Forest plot of the association between preterm birth (PTB) and Ozone (O_3) per 10 parts per billion (ppb) increment in O_3 at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

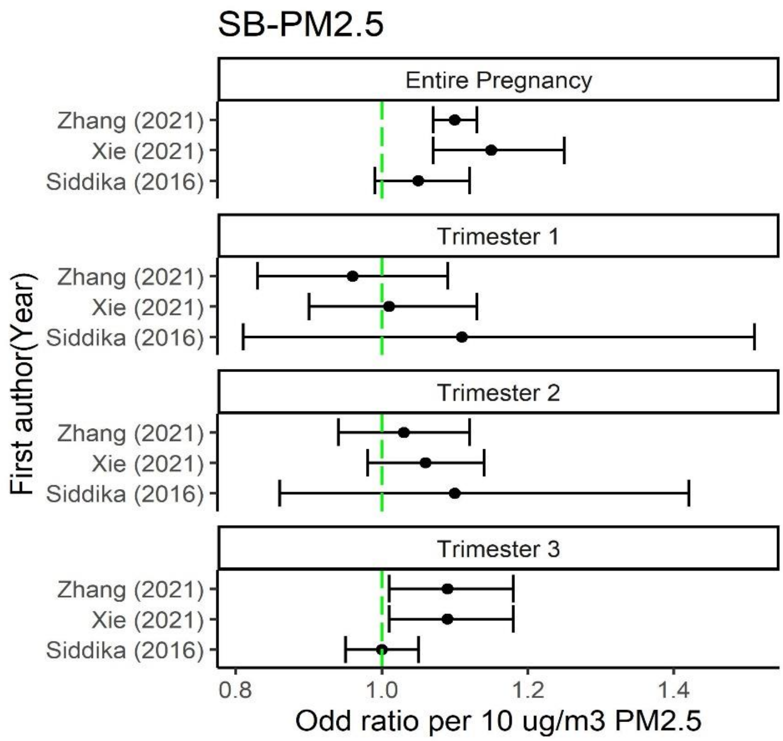

Figure S3.19 Forest plot of the association between stillbirth (SB) and fine particulate matter ($PM_{2.5}$) per $10\mu g/m^3$ increment) during different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1. Note: $PM_{2.5}$, particulate matter at aerodynamic diameter $\leq 2.5\mu m$.

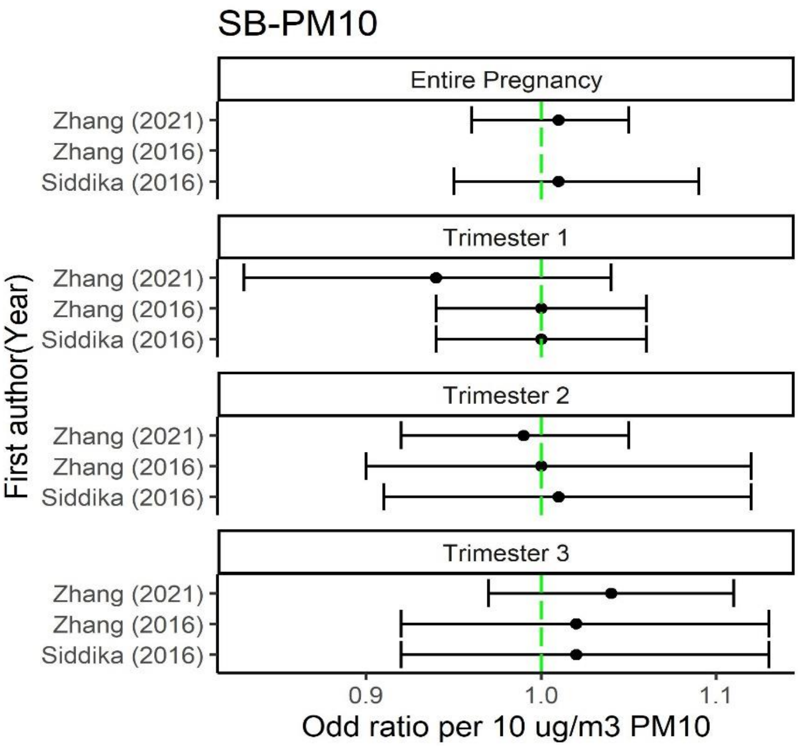

Figure S3.20 Forest plot of the association between stillbirth (SB) and fine particulate matter (PM_{10}) per 10µg/m^3 increment) during different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1. Note: PM_{10}, particulate matter at aerodynamic diameter ≤10µm.

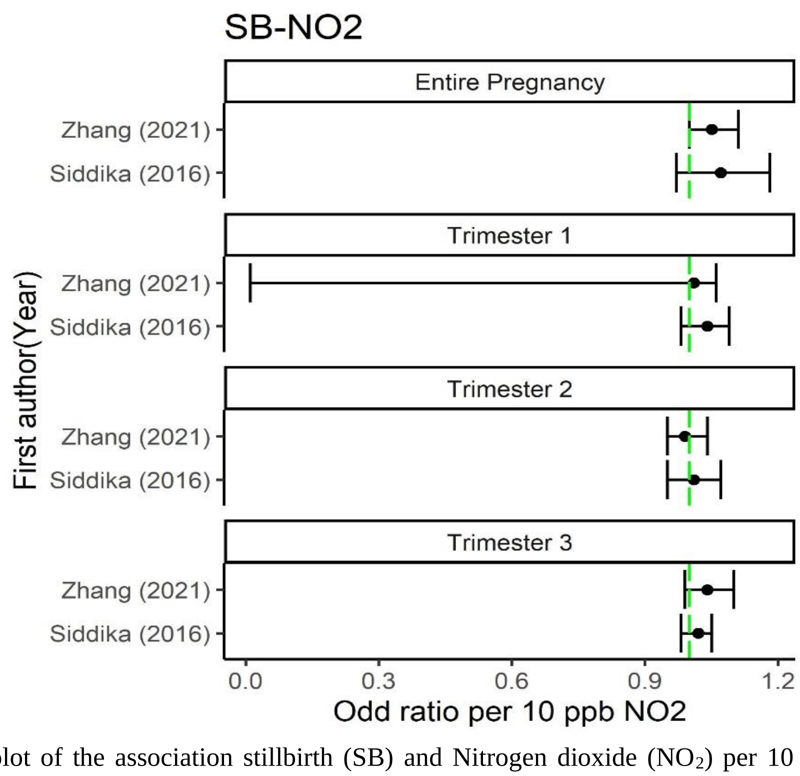

Figure S3.21 Forest plot of the association stillbirth (SB) and Nitrogen dioxide (NO_2) per 10 parts per billion (ppb) increment in NO_2 at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

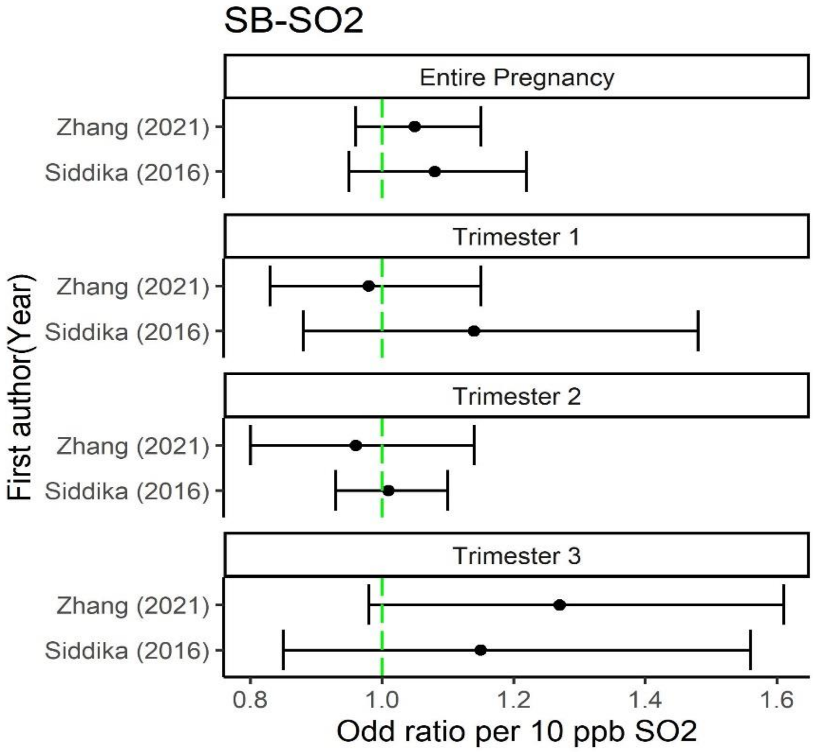

Figure S3.22 Forest plot of the association between stillbirth (SB) and Sulphur dioxide (SO_2) per 10 parts per billion (ppb) increment in SO_2 at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

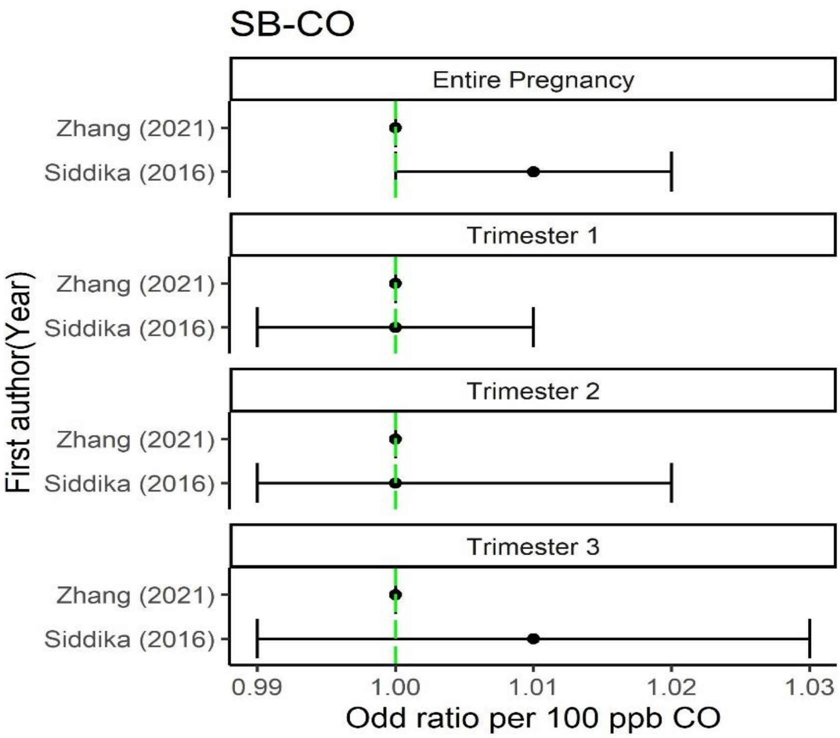

Figure S3.23 Forest plot of the association between stillbirth (SB) and carbon monoxide (CO) per 100 parts per billion (ppb) increment in CO at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

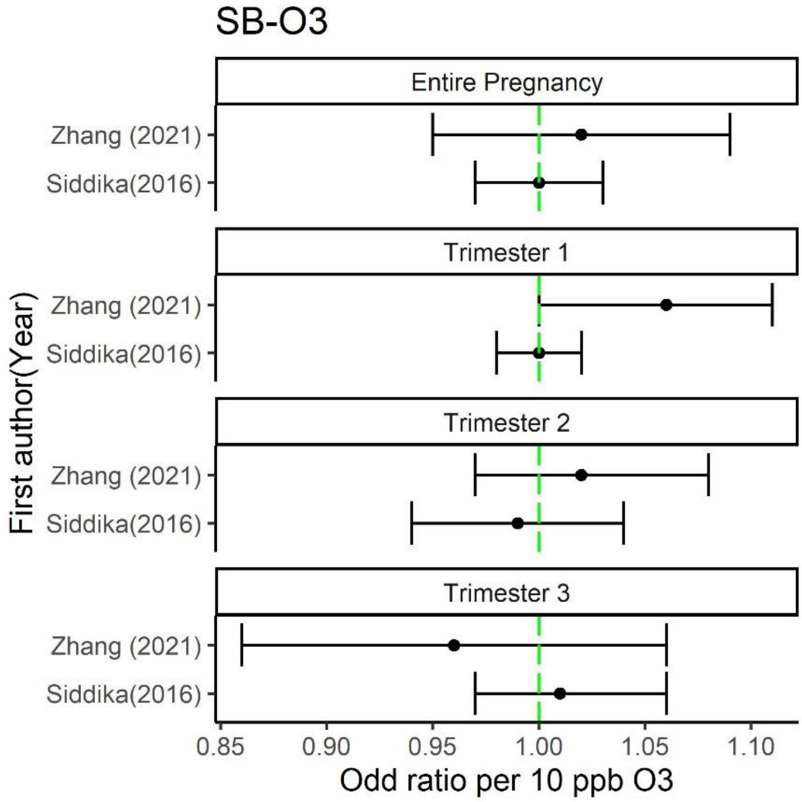

Figure S3.24 Forest plot of the association between stillbirth (SB) and ozone (O_3) per 10 parts per billion (ppb) increment in O_3 at different pregnancy periods. Solid points represent point estimates of the individual meta-analyses results, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

Appendix B: Supplementary materials for Chapter 4

Table S4.1. Descriptive statistics of the monthly environmental exposures for three months preconception through to birth delivery for included singleton spontaneous births in Western Australia, 2000-2015 (N= 400,867)

Exposure	Exposure period	Min	Mean ± SD	Median	P25	P75	IQR	Max
$PM_{2.5}$ (μg/m^3)	Preconception to pregnancy	3.8	8.1 ± 1.0	8.1	7.5	8.7	1.2	17.8
	Preconception	1.0	8.1 ± 1.5	7.9	7.3	8.7	1.4	27.6
	Pregnancy	2.9	8.1 ± 1.1	8.0	7.5	8.7	1.2	20.5
	1st Trimester	1.3	8.1 ± 1.5	7.9	7.3	8.7	1.4	27.6
	2nd Trimester	0.8	8.1 ± 1.5	7.9	7.3	8.7	1.4	27.6
	3rd Trimester	0.0	8.1 ± 1.6	7.9	7.3	8.7	1.4	26.4
UTCI (˚C)	Preconception to pregnancy	7.8	14.5 ± 2.5	14.2	13.6	14.8	1.2	30.9
	Preconception	1.6	14.4 ± 5.1	14.0	9.8	18.5	8.7	35.8
	Pregnancy	5.8	14.6 ± 2.8	14.2	12.9	15.6	2.7	34.1
	1st Trimester	1.6	14.5 ± 5.2	14.2	9.8	18.7	8.9	36.0
	2nd Trimester	1.7	14.6 ± 5.2	14.2	10.0	18.7	8.7	36.1
	3rd Trimester	-0.5	14.5 ± 5.1	14.0	9.9	18.5	8.6	35.7

Note: SD, standard deviation; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm; UTCI, Universal Thermal Climate Index; P25 and P75, 25th and 75th centiles; IQR, Interquartile range= P75-P25

Table S4.2. Adjusted hazard ratios for the association between 3, 5, 8, and 10 μg/m^3 increase in $PM_{2.5}$ exposure and risks of stillbirth by month of gestation from three months preconception (-2 to 0) to birth (1 to 10) in Western Australia, 2000–2015.

Month	3 μg/m^3 $PM_{2.5}$			5 μg/m^3 $PM_{2.5}$			8 μg/m^3 $PM_{2.5}$			10 μg/m^3 $PM_{2.5}$		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.972	0.908	1.041	0.954	0.851	1.068	0.927	0.773	1.112	0.910	0.725	1.142
-1	0.947	0.915	0.979	0.913	0.863	0.965	0.864	0.790	0.944	0.833	0.745	0.931
0	0.940	0.900	0.983	0.903	0.839	0.971	0.849	0.754	0.955	0.815	0.703	0.944
1	0.972	0.932	1.014	0.954	0.890	1.023	0.928	0.830	1.037	0.910	0.792	1.046
2	1.040	1.006	1.074	1.067	1.011	1.126	1.109	1.017	1.209	1.138	1.022	1.268
3	1.070	1.029	1.112	1.119	1.049	1.194	1.197	1.079	1.329	1.253	1.100	1.426
4	1.051	1.021	1.083	1.087	1.035	1.142	1.143	1.056	1.236	1.181	1.071	1.303
5	1.012	0.986	1.039	1.020	0.977	1.066	1.033	0.963	1.107	1.041	0.954	1.136
6	0.978	0.948	1.010	0.964	0.915	1.017	0.944	0.867	1.027	0.930	0.837	1.033
7	0.957	0.929	0.987	0.930	0.884	0.978	0.890	0.821	0.965	0.865	0.782	0.957
8	0.945	0.917	0.975	0.911	0.865	0.959	0.861	0.793	0.935	0.829	0.748	0.919
9	0.939	0.896	0.985	0.901	0.833	0.974	0.846	0.746	0.959	0.812	0.694	0.949
10	0.936	0.869	1.008	0.896	0.791	1.014	0.838	0.688	1.022	0.802	0.626	1.028

Note: HR, hazard ratio; LCI, lower confidential interval; UCI, upper confidential interval. Model was fitted from distributed lag Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and Universal Thermal Climate Index.

Table S4.3. Adjusted hazard ratios for the association between 3, 5, 8, and 10 μg/m^3 increase in $PM_{2.5}$ exposure and risks of sPTB by month of gestation from three months preconception (-2 to 0) to birth (1 to 9) in Western Australia, 2000–2015.

Month	3 μg/m^3 $PM_{2.5}$			5 μg/m^3 $PM_{2.5}$			8 μg/m^3 $PM_{2.5}$			10 μg/m^3 $PM_{2.5}$		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	1.006	0.983	1.029	1.010	0.972	1.049	1.016	0.956	1.080	1.020	0.945	1.101
-1	1.002	0.991	1.013	1.003	0.984	1.022	1.005	0.975	1.035	1.006	0.969	1.044
0	0.996	0.981	1.012	0.994	0.969	1.020	0.991	0.951	1.032	0.988	0.939	1.040
1	0.989	0.976	1.003	0.982	0.960	1.005	0.971	0.937	1.007	0.964	0.921	1.009
2	0.983	0.971	0.996	0.972	0.952	0.993	0.956	0.925	0.989	0.946	0.907	0.986
3	0.992	0.977	1.006	0.986	0.963	1.010	0.978	0.941	1.016	0.972	0.927	1.020
4	1.009	0.998	1.019	1.014	0.997	1.031	1.023	0.996	1.051	1.029	0.995	1.064
5	1.021	1.011	1.032	1.036	1.018	1.054	1.058	1.029	1.087	1.073	1.037	1.111
6	1.020	1.008	1.032	1.033	1.013	1.053	1.053	1.021	1.086	1.067	1.027	1.109
7	1.005	0.995	1.015	1.008	0.992	1.024	1.013	0.987	1.039	1.016	0.984	1.049
8	0.982	0.972	0.991	0.970	0.955	0.985	0.952	0.928	0.976	0.940	0.911	0.971
9	0.955	0.940	0.970	0.926	0.902	0.951	0.884	0.848	0.923	0.858	0.813	0.904

Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval. Model was fitted from distributed lag Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness (urban/rural), socioeconomic status, and year and season of conception, and Universal Thermal Climate Index. sPTB, spontaneous preterm birth.

Table S4.4. Adjusted hazard ratios of stillbirth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different exposure thresholds using 5μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015.

Month	P1			P5			P50			P90			P95			P99		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.965	0.93	1.002	0.923	0.862	0.988	0.86	0.791	0.936	0.820	0.745	0.902	0.81	0.733	0.895	0.793	0.711	0.884
-1	0.973	0.945	1.001	0.940	0.892	0.99	0.892	0.838	0.949	0.862	0.806	0.923	0.855	0.797	0.918	0.844	0.783	0.910
0	0.98	0.959	1.001	0.956	0.920	0.994	0.924	0.883	0.966	0.905	0.863	0.95	0.902	0.858	0.947	0.897	0.851	0.945
1	0.986	0.971	1.002	0.971	0.944	0.999	0.953	0.919	0.988	0.947	0.908	0.987	0.946	0.906	0.988	0.948	0.904	0.994
2	0.991	0.979	1.004	0.983	0.960	1.007	0.980	0.946	1.014	0.984	0.94	1.029	0.986	0.94	1.035	0.994	0.942	1.048
3	0.994	0.983	1.006	0.992	0.970	1.015	1.001	0.966	1.037	1.015	0.968	1.064	1.019	0.969	1.072	1.031	0.974	1.091
4	0.996	0.985	1.007	0.998	0.976	1.019	1.017	0.983	1.051	1.039	0.993	1.087	1.045	0.996	1.097	1.060	1.004	1.119
5	0.996	0.987	1.006	1.000	0.981	1.019	1.028	0.996	1.060	1.056	1.013	1.102	1.064	1.017	1.113	1.080	1.026	1.136
6	0.995	0.987	1.004	1.000	0.983	1.017	1.035	1.002	1.069	1.069	1.021	1.119	1.077	1.025	1.131	1.092	1.033	1.155
7	0.994	0.986	1.001	0.998	0.981	1.015	1.039	0.997	1.082	1.076	1.013	1.144	1.085	1.016	1.159	1.099	1.019	1.185
8	0.991	0.983	0.999	0.995	0.974	1.016	1.040	0.983	1.100	1.081	0.992	1.178	1.089	0.992	1.196	1.101	0.990	1.225
9	0.988	0.977	0.999	0.990	0.962	1.019	1.040	0.963	1.122	1.083	0.964	1.217	1.091	0.961	1.238	1.100	0.952	1.272
10	0.985	0.970	1.000	0.985	0.948	1.023	1.038	0.941	1.146	1.084	0.933	1.259	1.091	0.927	1.284	1.097	0.911	1.323

Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval; P1-P99, 1^{st} to 99^{th} centiles of $PM_{2.5}$. Model was fitted from distributed lag non-linear Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness (urban/rural), socioeconomic status, and year and season of conception, and Universal Thermal Climate Index.

Table S4.5. Adjusted hazard ratios of sPTB due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 9) at different exposure thresholds using 5μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015.

Month	P1			P5			P50			P90			P95			P99		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	1.005	0.985	1.026	1.007	0.982	1.032	1.010	0.975	1.047	1.015	0.970	1.062	1.016	0.969	1.066	1.020	0.967	1.075
-1	0.999	0.988	1.010	0.999	0.985	1.013	0.998	0.979	1.017	0.997	0.973	1.021	0.997	0.972	1.022	0.996	0.969	1.024
0	0.995	0.985	1.005	0.994	0.981	1.006	0.990	0.973	1.007	0.985	0.963	1.006	0.983	0.961	1.006	0.979	0.955	1.004
1	0.995	0.982	1.007	0.993	0.978	1.009	0.989	0.967	1.011	0.983	0.956	1.010	0.981	0.953	1.010	0.976	0.946	1.007
2	1.000	0.989	1.011	0.999	0.986	1.013	0.998	0.979	1.017	0.995	0.971	1.019	0.994	0.969	1.019	0.991	0.964	1.019
3	1.007	0.999	1.015	1.009	0.998	1.019	1.012	0.998	1.026	1.014	0.996	1.032	1.014	0.996	1.033	1.015	0.995	1.035
4	1.012	1.004	1.021	1.015	1.004	1.025	1.022	1.007	1.037	1.028	1.009	1.047	1.030	1.010	1.050	1.033	1.011	1.055
5	1.012	1.003	1.021	1.015	1.003	1.026	1.022	1.006	1.038	1.029	1.008	1.050	1.031	1.009	1.053	1.035	1.011	1.059
6	1.007	0.999	1.015	1.009	0.999	1.019	1.013	0.999	1.028	1.018	1.000	1.037	1.020	1.001	1.039	1.023	1.002	1.045
7	0.999	0.993	1.005	0.999	0.991	1.006	0.999	0.988	1.010	1.000	0.986	1.014	1.000	0.985	1.015	1.001	0.985	1.018
8	0.989	0.983	0.994	0.986	0.980	0.993	0.981	0.971	0.990	0.976	0.962	0.990	0.975	0.959	0.991	0.973	0.954	0.993
9	0.977	0.969	0.985	0.972	0.963	0.982	0.961	0.946	0.976	0.950	0.929	0.972	0.947	0.924	0.972	0.943	0.913	0.973

Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval; P1-P99, 1st to 99th centiles of $PM_{2.5}$. Model was fitted from distributed lag non-linear Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness (urban/rural), socioeconomic status, and year and season of conception, and Universal Thermal Climate Index. sPTB, spontaneous preterm birth.

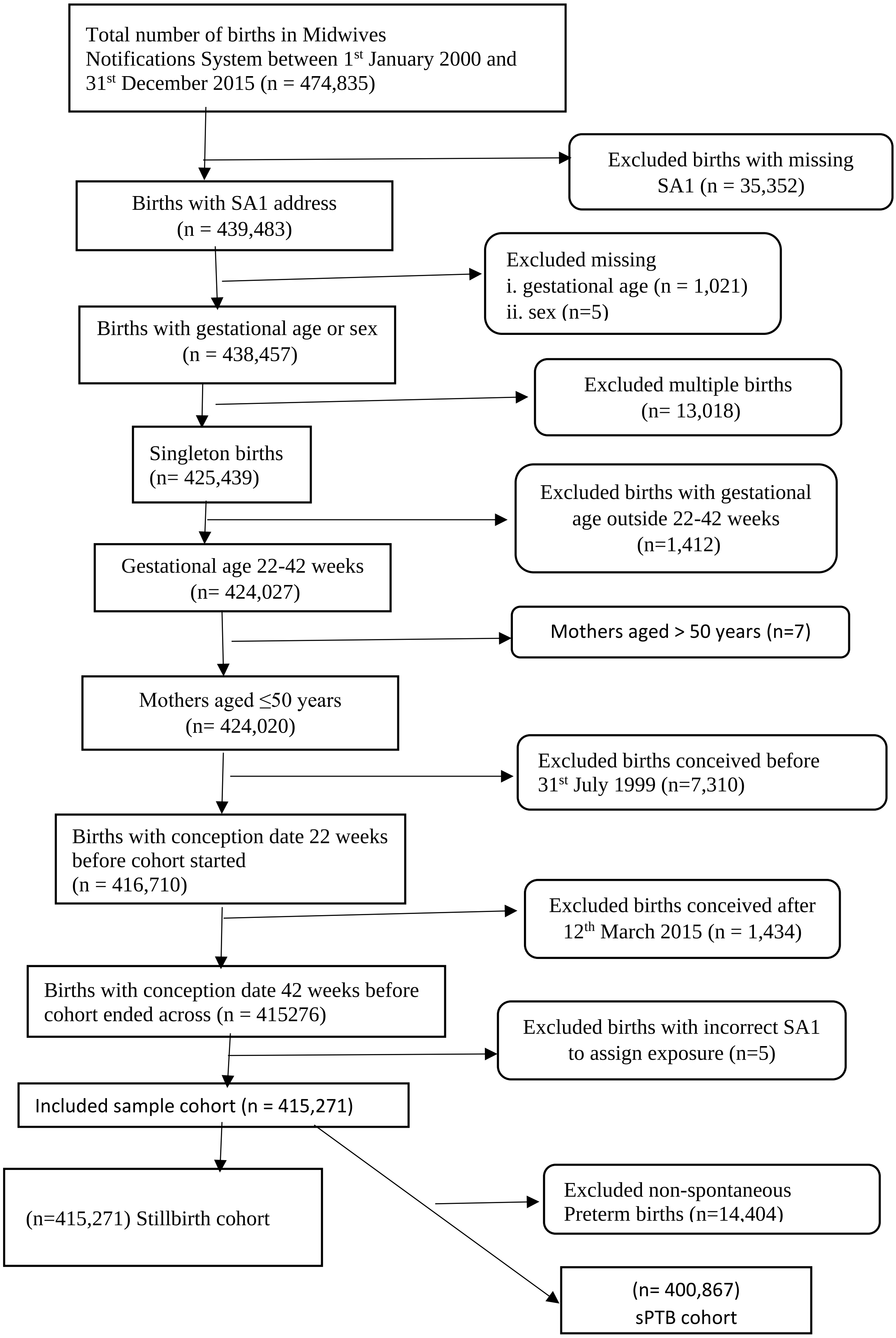

Figure S4.1. Flow chart for selecting the eligible births included in this study, Western Australia, 2000-2015. Note: SA1, statistical area level 1; sPTB, Spontaneous preterm birth.

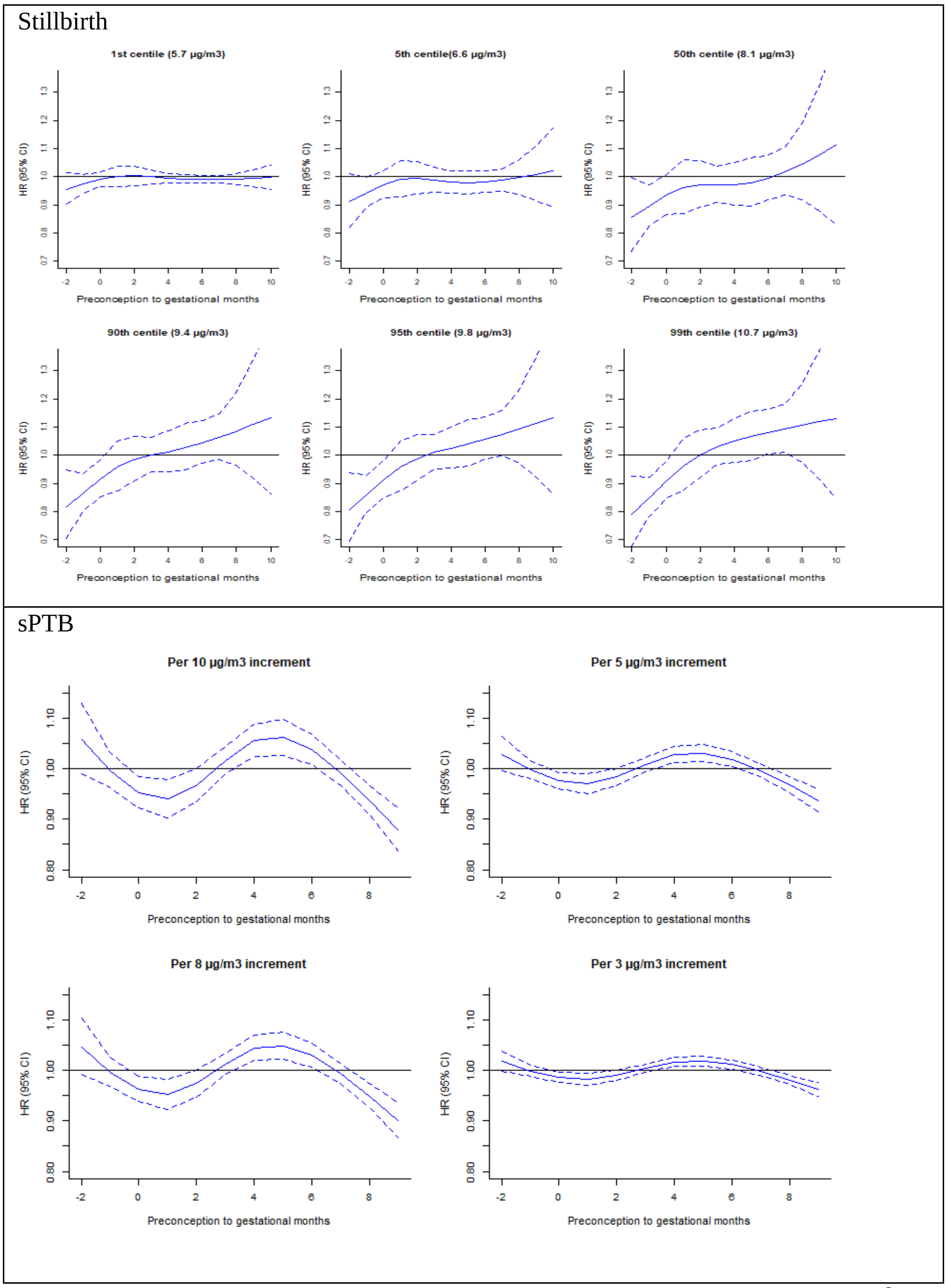

Figure S4.2. Adjusted hazard ratios of stillbirth at different $PM_{2.5}$ exposure thresholds using 5µg/m^3 $PM_{2.5}$ as reference (fitted from DLNM Cox PH model) and sPTB for 10, 8, 5 and 3µg/m^3 increase in $PM_{2.5}$ exposure (fitted from DLM Cox PH model) over three months preconception (-2 to 0) to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015. DLNM was constructed with natural splines of 4 *df* for both exposure and lag dimensions. DLM was constructed with linear function for exposure and natural splines of 4 *df* for lag dimension. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth. DLNM, distributed lag non-linear model; DLM, distributed lag model; df, degree of freedom; Cox PH, Cox proportional hazards.

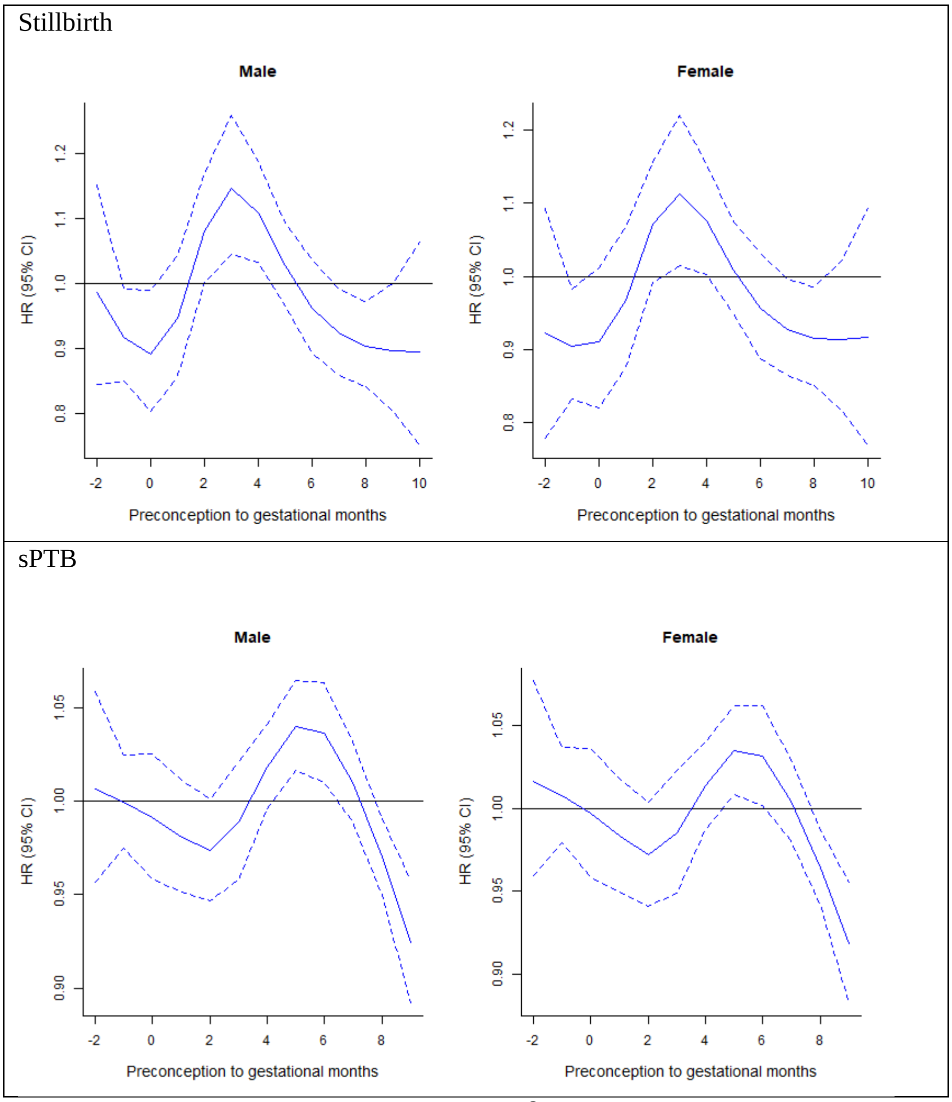

Figure S4.3 Adjusted hazard ratios stillbirth and sPTB per 5 μg/m^3 $PM_{2.5}$ increments for cumulative $PM_{2.5}$ exposures over three months preconception (-2 to 0) through to pregnancy(1 to 10 for stillbirth and 1 to 9 for sPTB) by sex in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 μm.

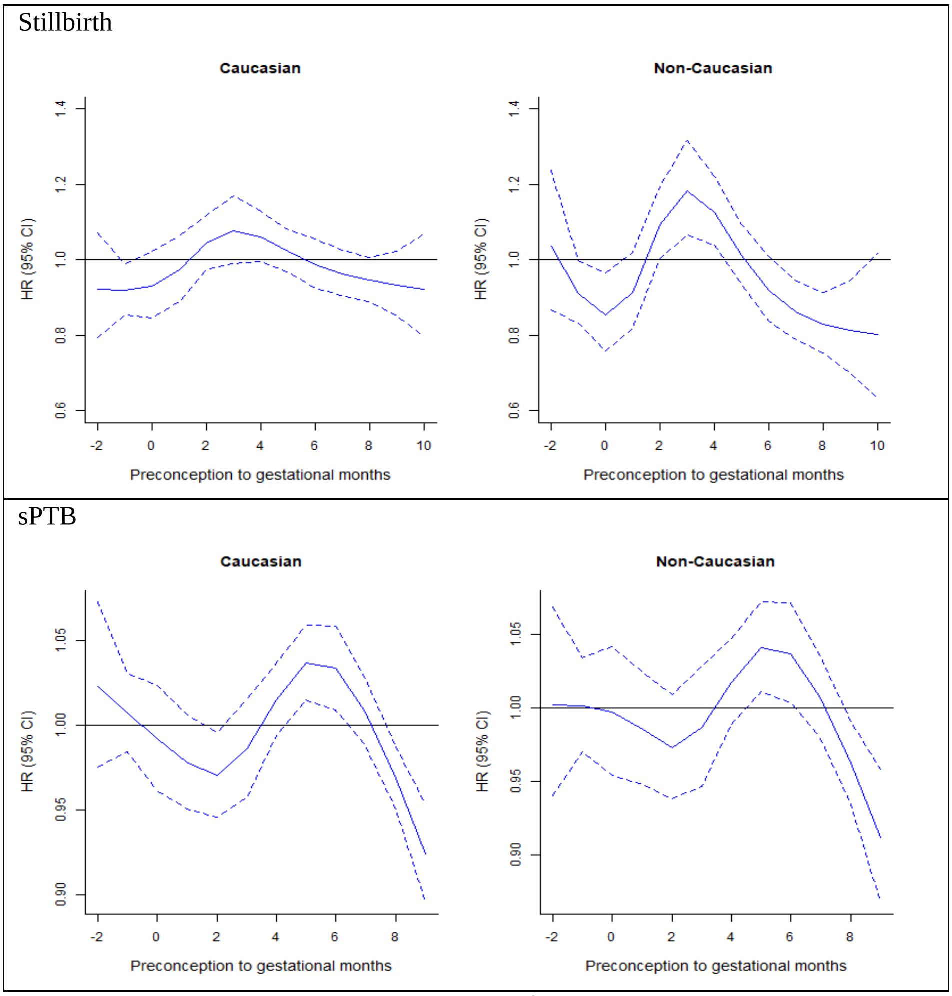

Figure S4.4 Adjusted hazard ratios stillbirth and sPTB per 5 µg/m^3 $PM_{2.5}$ increments for cumulative $PM_{2.5}$ exposures over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) by race or ethnicity in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for maternal age, sex, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 µm.

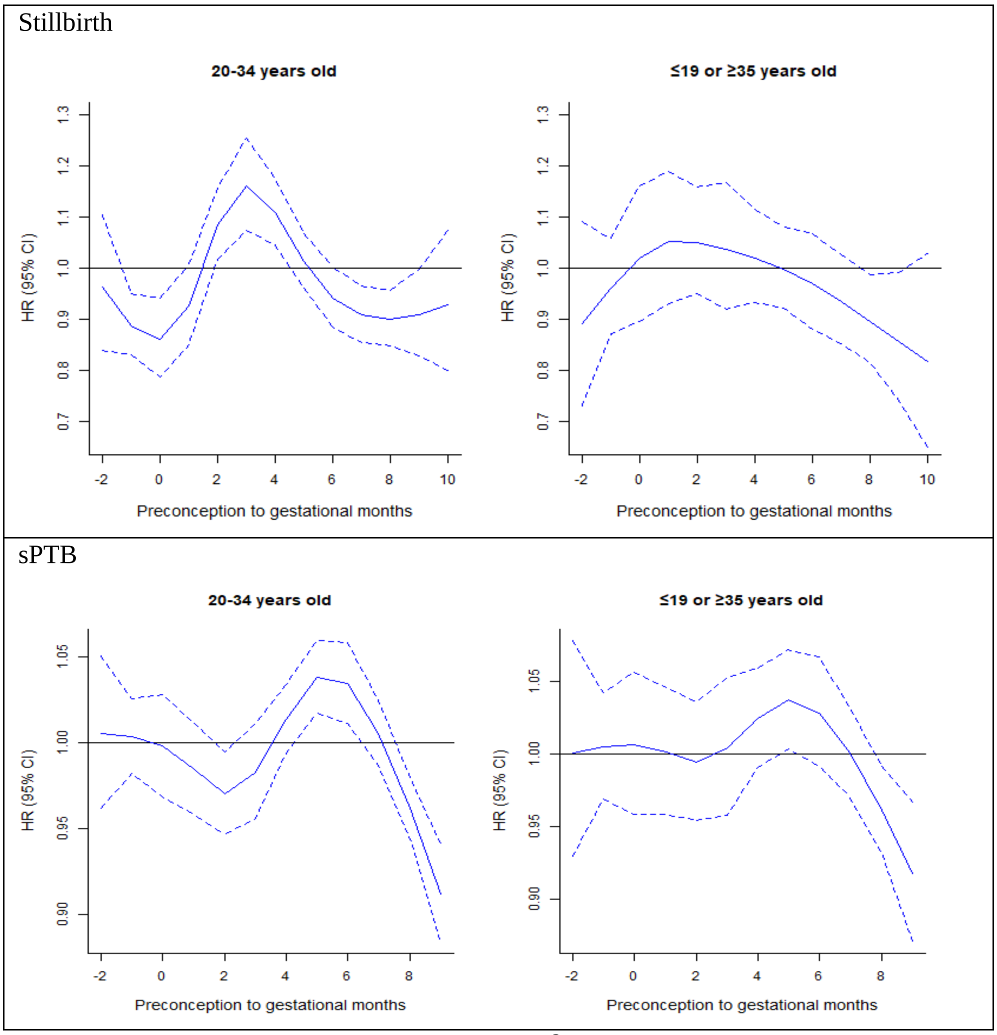

Figure S4.5 Adjusted hazard ratios stillbirth and sPTB per 5 µg/m^3 $PM_{2.5}$ increments for cumulative $PM_{2.5}$ exposures over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) by maternal age in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for race or ethnicity, sex, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 µm.

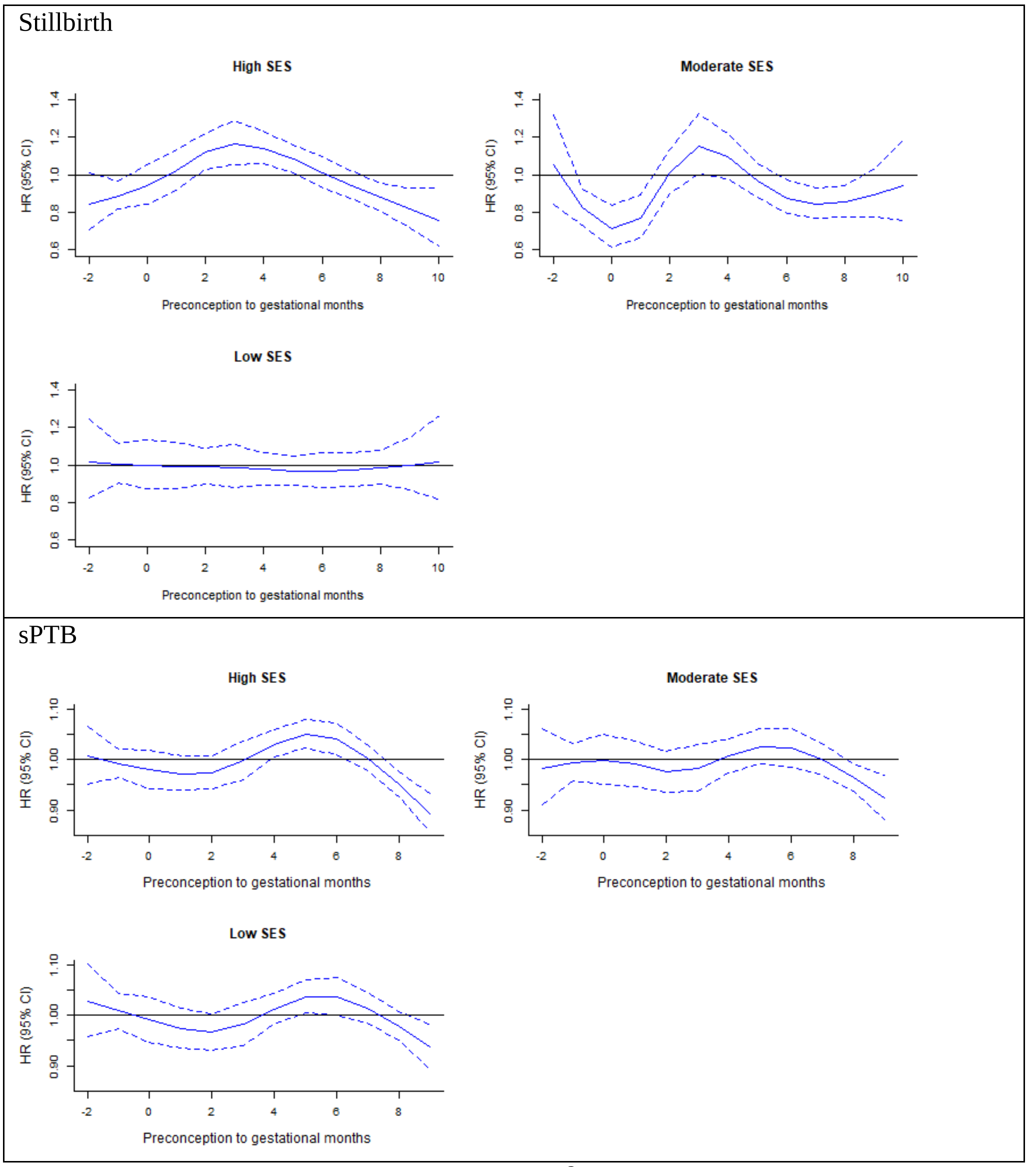

Figure S4.6 Adjusted hazard ratios stillbirth and sPTB per 5 µg/m^3 $PM_{2.5}$ increments for cumulative $PM_{2.5}$ exposures over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) by socioeconomic status in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for race or ethnicity, sex, marital status, smoking status, parity, remoteness, maternal age, and year and season of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 µm.

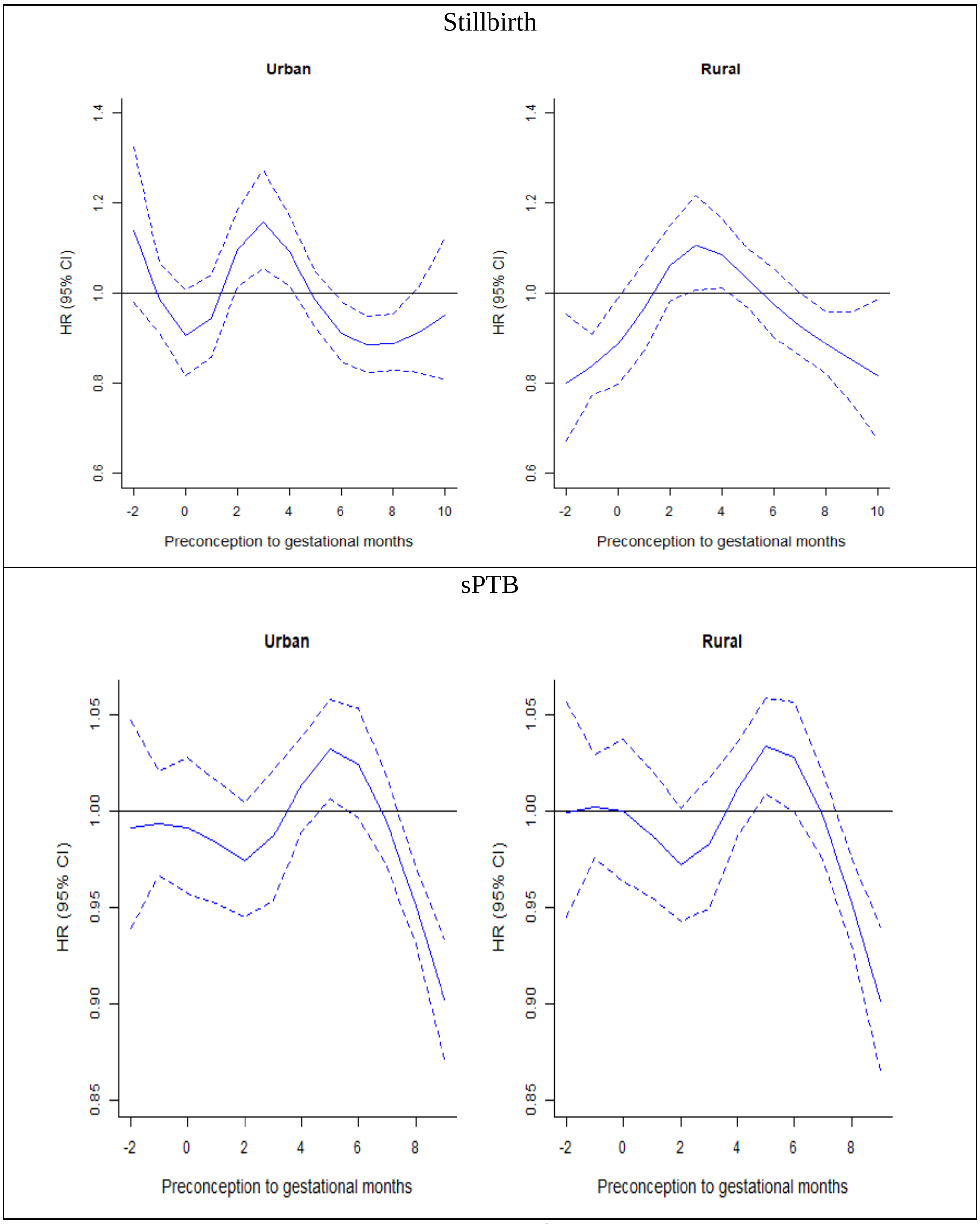

Figure S4.7 Adjusted hazard ratios stillbirth and sPTB per 5 µg/m^3 $PM_{2.5}$ increments for cumulative $PM_{2.5}$ exposures over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) by remoteness in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for race or ethnicity, sex, marital status, smoking status, parity, socioeconomic status, maternal age, and year and season of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 µm.

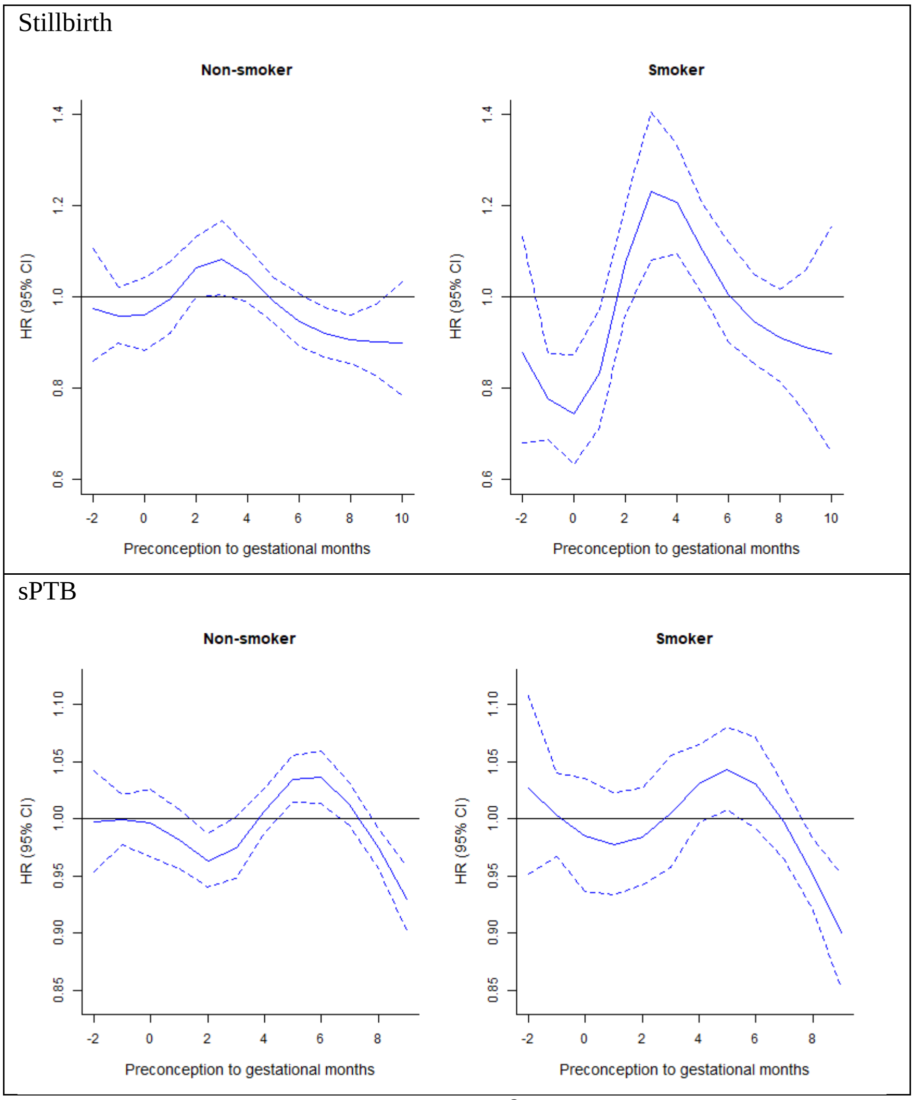

Figure S4.8 Adjusted hazard ratios stillbirth and sPTB per 5 µg/m³ $PM_{2.5}$ increments for cumulative $PM_{2.5}$ exposures over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) by smoking status in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for race or ethnicity, sex, marital status, remoteness, parity, socioeconomic status, maternal age, and year and season of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 µm.

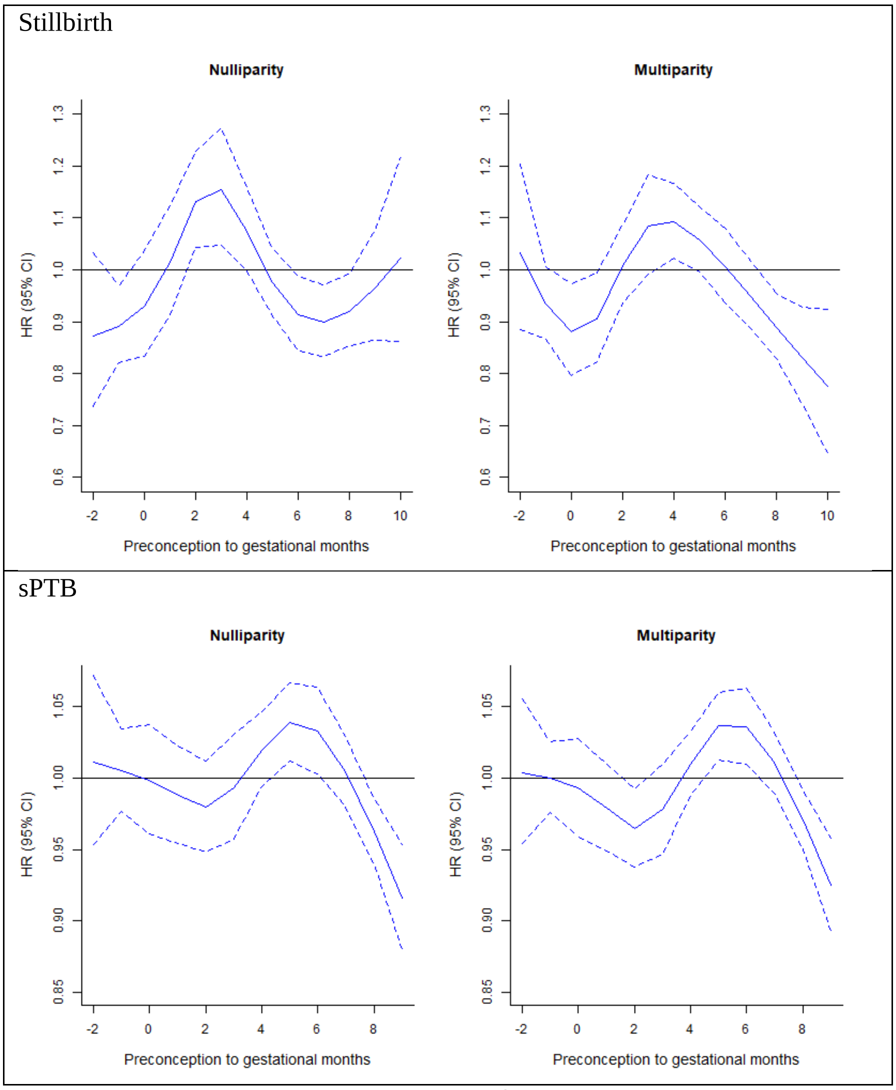

Figure S4.9 Adjusted hazard ratios stillbirth and sPTB per 5 µg/m³ $PM_{2.5}$ increments for cumulative $PM_{2.5}$ exposures over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) by parity in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for race or ethnicity, sex, marital status, remoteness, smoking status, socioeconomic status, maternal age, and year and season of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 µm.

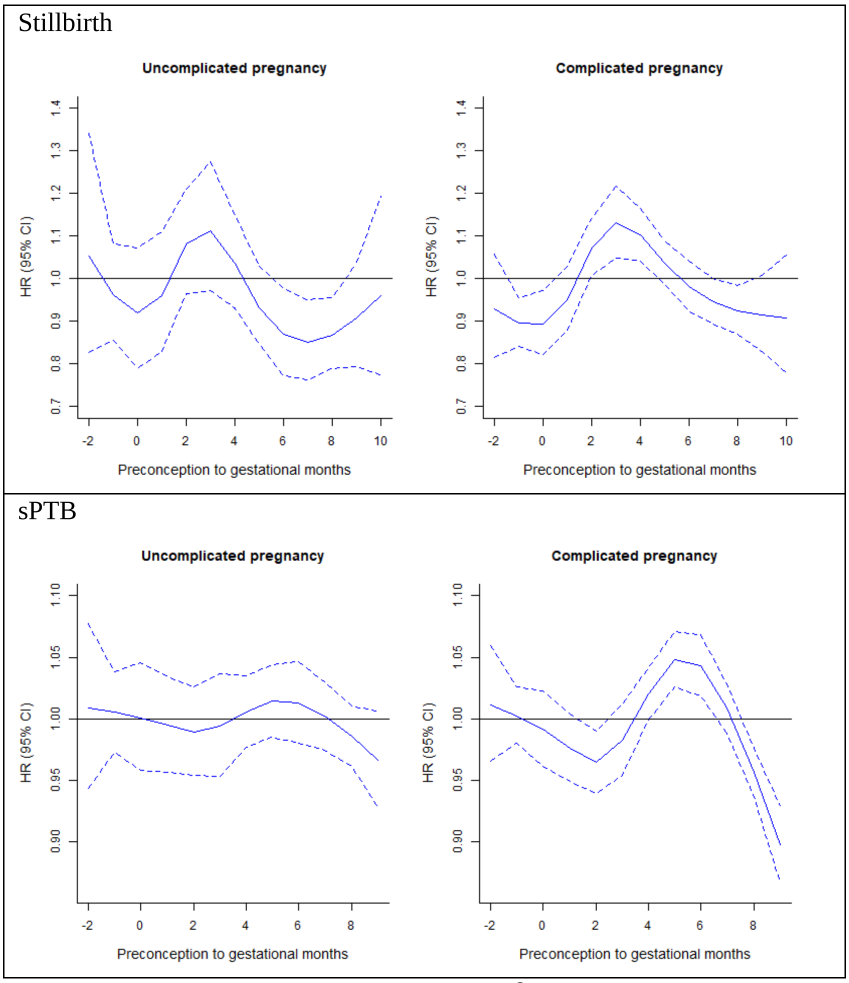

Figure S4.10 Adjusted hazard ratios stillbirth and sPTB per 5 µg/m[3] $PM_{2.5}$ increments for cumulative $PM_{2.5}$ exposures over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) by pregnancy complication status in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for race or ethnicity, sex, marital status, remoteness, smoking status, parity, socioeconomic status, maternal age, and year and season of conception, and ambient Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤2.5 µm.

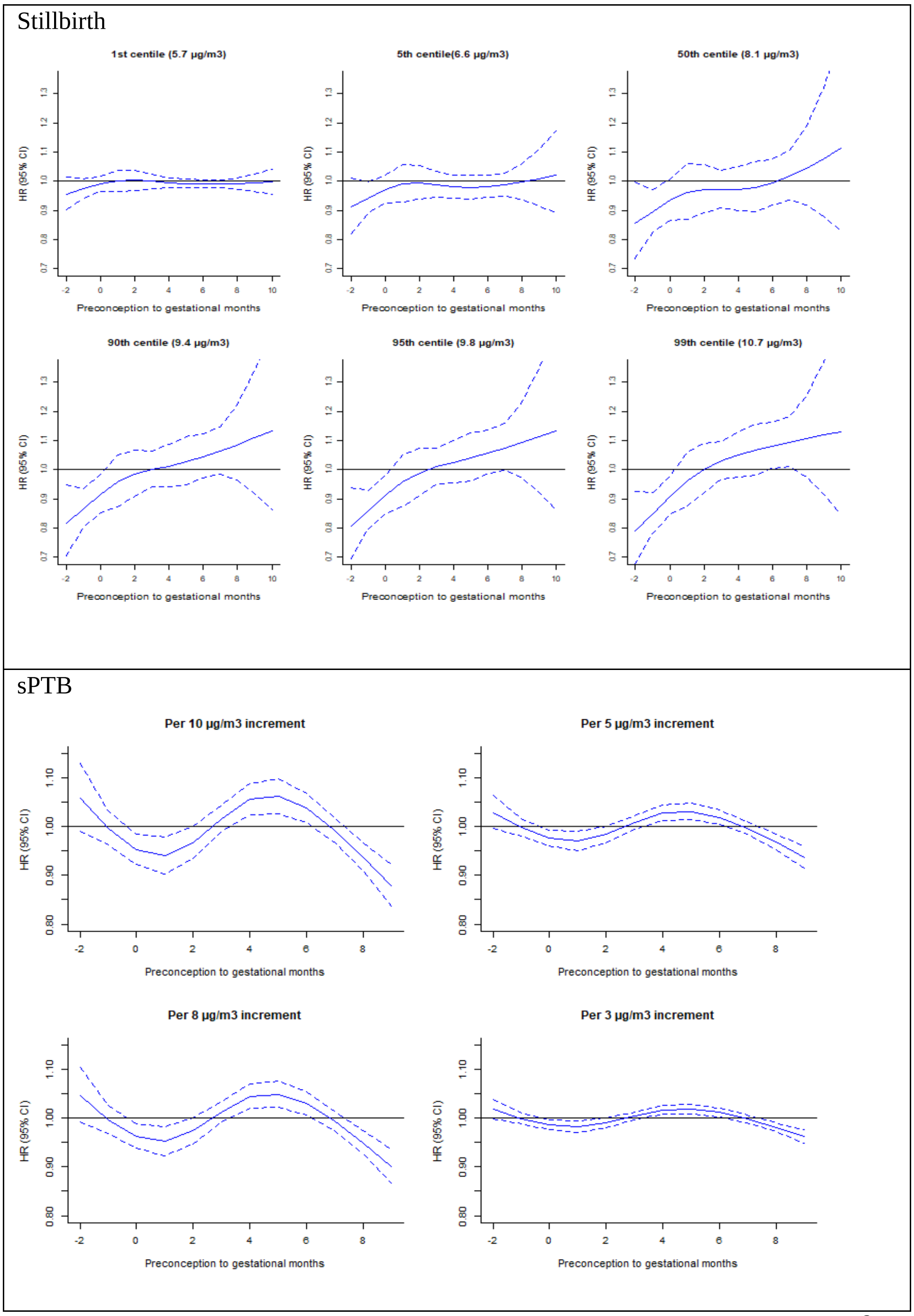

Figure S4.11 Adjusted hazard ratios of stillbirth at different $PM_{2.5}$ exposure thresholds using 5μg/m^3 $PM_{2.5}$ as reference (fitted from DLNM Cox PH model) and sPTB for 10, 8, 5 and 3μg/m^3 increase in $PM_{2.5}$ exposure (fitted from DLM Cox PH model) over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015. The *df* of natural cubic spline were varied by one as 4 *df* for both exposure and lag dimensions for stillbirth and 4 *df* for lag dimension for sPTB. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth. DLNM, distributed lag non-linear model; DLM, distributed lag model; df, degree of freedom; Cox PH, Cox proportional hazards.

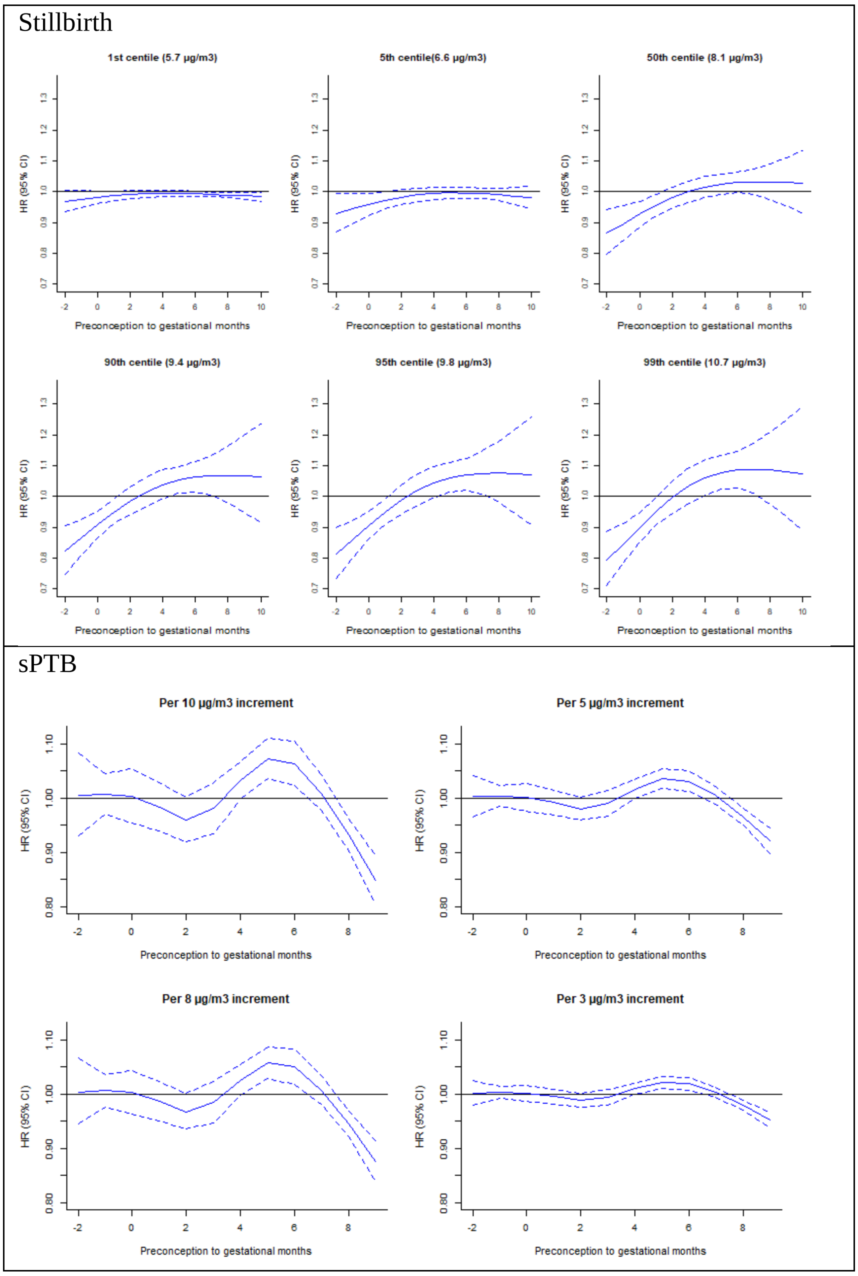

Figure S4.12 Adjusted hazard ratios of stillbirth at different $PM_{2.5}$ exposure thresholds using $5\mu g/m^3$ $PM_{2.5}$ as reference (fitted from DLNM Cox PH model) and sPTB for 10, 8, 5 and $3\mu g/m^3$ increase in $PM_{2.5}$ exposure (fitted from DLM Cox PH model) over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015. Models adjusted for maternal age as categories (≤19, 20-34, ≥35 years) instead of as a natural spline of the continuous variable. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth. DLNM, distributed lag non-linear model; DLM, distributed lag model; df, degree of freedom; Cox PH, Cox proportional hazards.

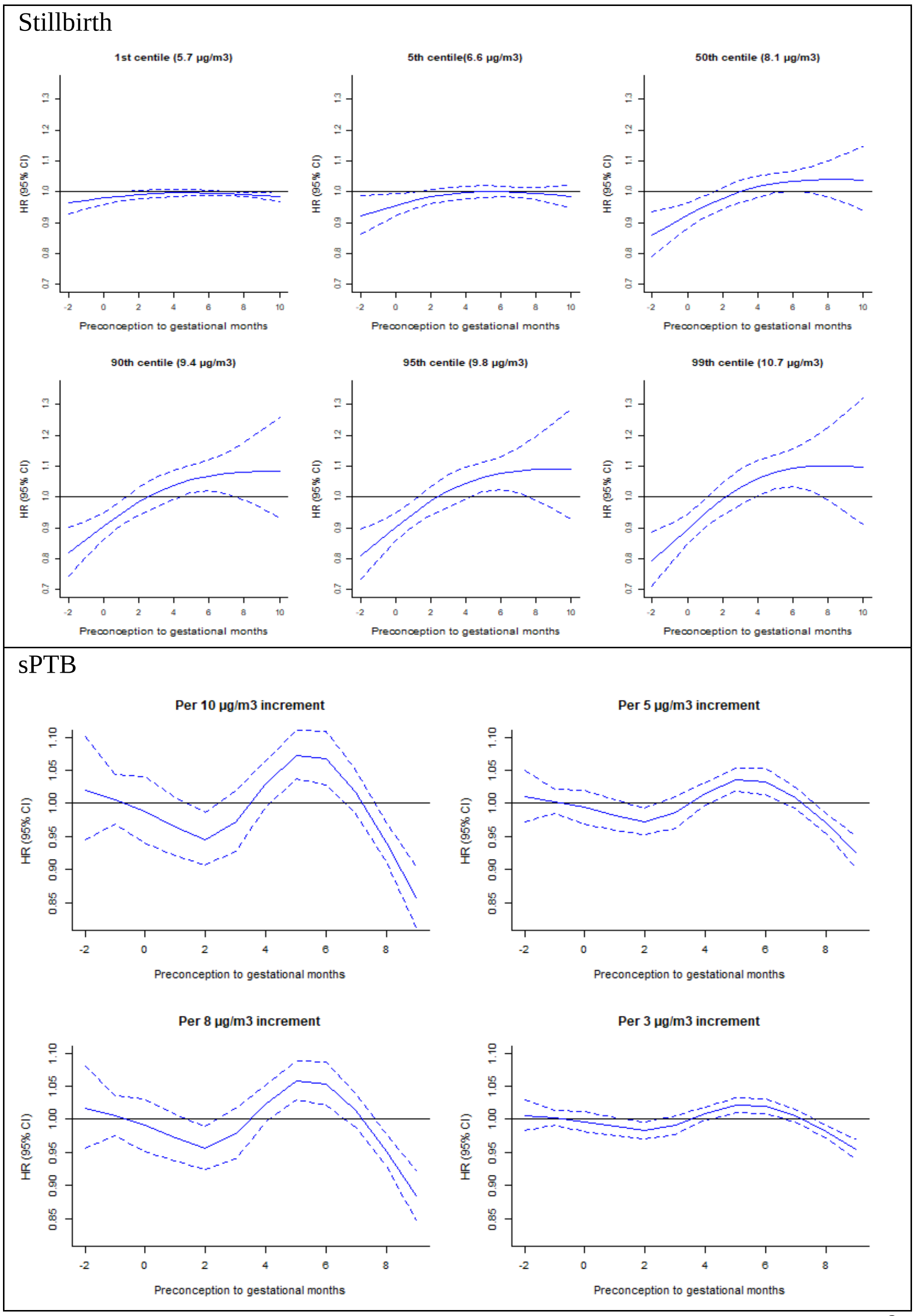

Figure S4.13 Adjusted hazard ratios of stillbirth at different $PM_{2.5}$ exposure thresholds using 5μg/m^3 $PM_{2.5}$ as reference (fitted from DLNM Cox PH model) and sPTB for 10, 8, 5 and 3μg/m^3 increase in $PM_{2.5}$ exposure (fitted from DLM Cox PH model) over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015. Models adjusted for month of conception instead of season of conception. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth. DLNM, distributed lag non-linear model; DLM, distributed lag model; *df*, degree of freedom; Cox PH, Cox proportional hazards.

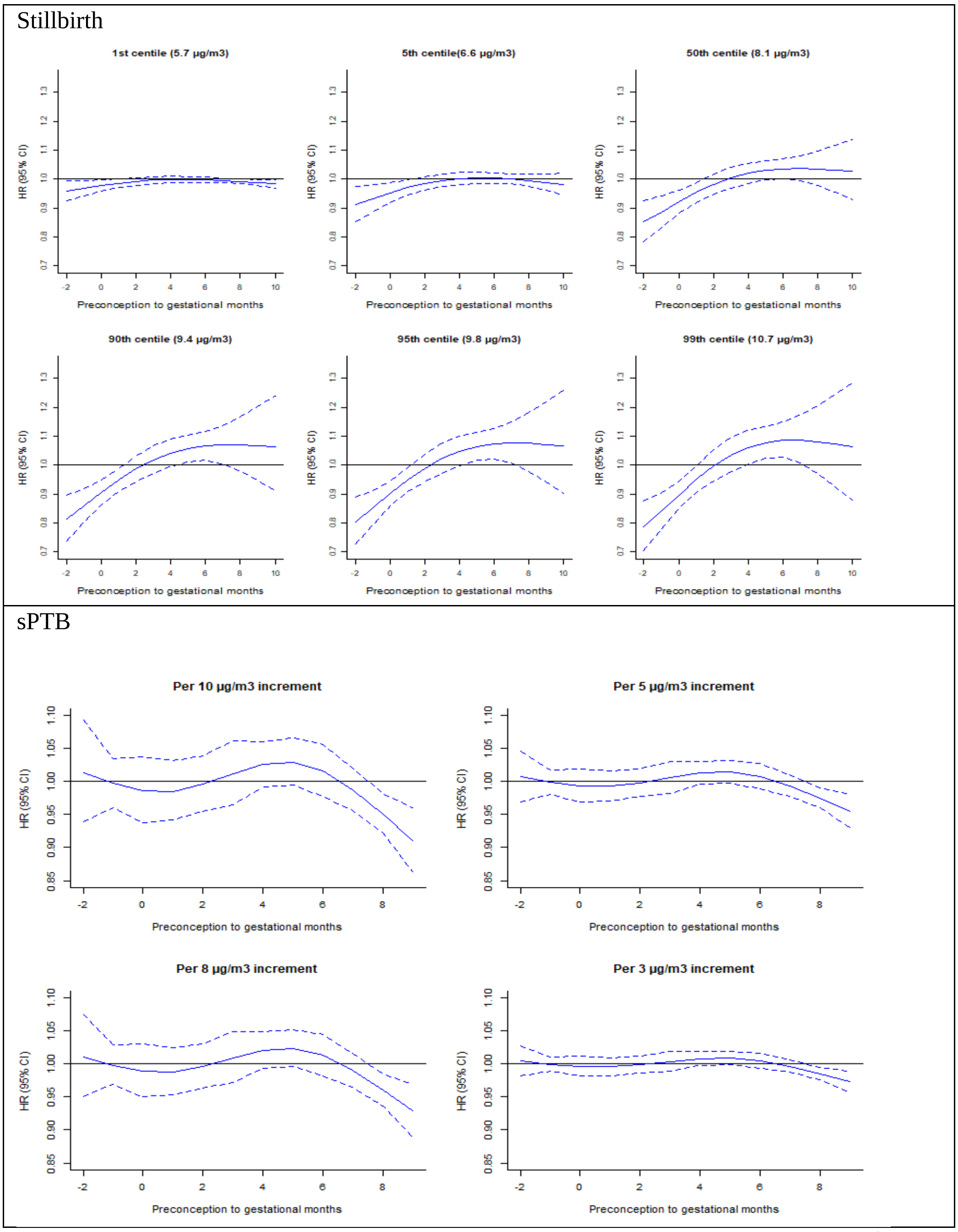

Figure S4.14 Adjusted hazard ratios of stillbirth at different $PM_{2.5}$ exposure thresholds using 5μg/m^3 $PM_{2.5}$ as reference (fitted from DLNM Cox PH model) and sPTB for 10, 8, 5 and 3μg/m^3 increase in $PM_{2.5}$ exposure (fitted from DLM Cox PH model) over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015. Models adjusted for Universal Thermal Climate Index with 4 instead of 3*df*. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth. DLNM, distributed lag non-linear model; DLM, distributed lag model; df, degree of freedom; Cox PH, Cox proportional hazards.

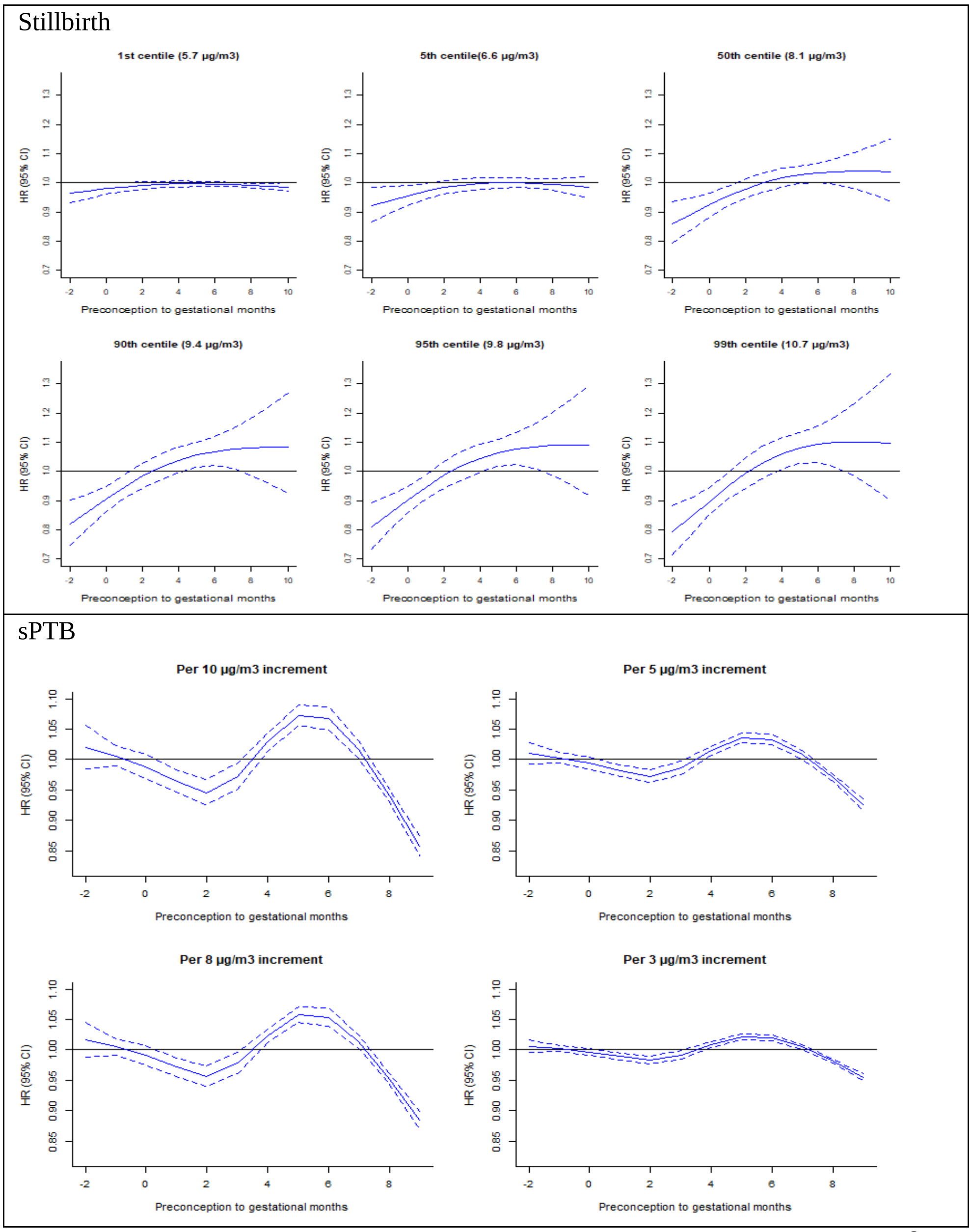

Figure S4.15 Adjusted hazard ratios of stillbirth at different $PM_{2.5}$ exposure thresholds using 5μg/m^3 $PM_{2.5}$ as reference (fitted from DLNM Cox PH model) and sPTB for 10, 8, 5 and 3μg/m^3 increase in $PM_{2.5}$ exposure (fitted from DLM Cox PH model) over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015. Model adjusted for mother-specific clusters to account for repeated births by the same mother. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, Universal Thermal Climate Index, and mother-specific clusters. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth. DLNM, distributed lag non-linear model; DLM, distributed lag model; df, degree of freedom; Cox PH, Cox proportional hazards.

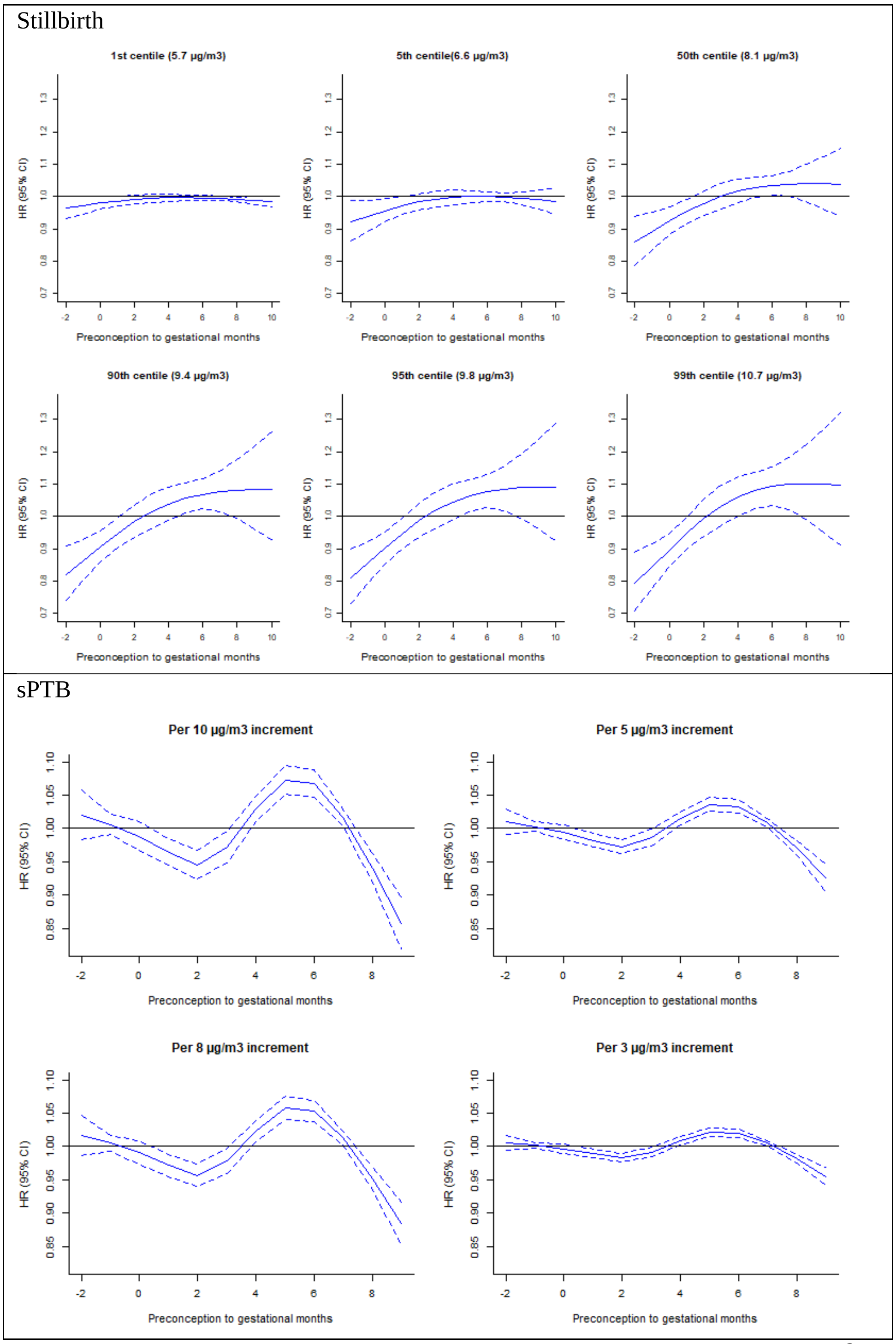

Figure S4.16 Adjusted hazard ratios of stillbirth at different $PM_{2.5}$ exposure thresholds using 5µg/m^3 $PM_{2.5}$ as reference (fitted from DLNM Cox PH model) and sPTB for 10, 8, 5 and 3µg/m^3 increase in $PM_{2.5}$ exposure (fitted from DLM Cox PH model) over three months preconception (-2 to 0) through to pregnancy (1 to 10 for stillbirth and 1 to 9 for sPTB) in Western Australia, 2000–2015. Model adjusted for local government area-specific clusters to account for spatial clustering and maternal mobility. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, Universal Thermal Climate Index, and mother-specific clusters. Note: HR, hazard ratio; CI, confidential interval; sPTB, spontaneous preterm birth. DLNM, distributed lag non-linear model; DLM, distributed lag model; df, degree of freedom; Cox PH, Cox proportional hazards.

Appendix C: Supplementary materials for Chapter 5

Table S5.2 Adjusted hazard ratios for the association between 3, 5, 8, and 10 μg/m³ increase in $PM_{2.5}$ exposure and risks of term small for gestational age by month of gestation from three months preconception (-2 to 0) to birth (1 to 10) in Western Australia, 2000–2015.

Month	3 μg/m³ $PM_{2.5}$			5 μg/m³ $PM_{2.5}$			8 μg/m³ $PM_{2.5}$			10 μg/m³ $PM_{2.5}$		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.991	0.982	1.000	0.985	0.969	1.000	0.976	0.951	1.000	0.969	0.940	1.000
-1	0.993	0.987	1.000	0.989	0.978	1.000	0.983	0.965	1.000	0.978	0.957	1.000
0	0.996	0.991	1.001	0.993	0.985	1.001	0.989	0.977	1.002	0.987	0.971	1.002
1	0.998	0.994	1.002	0.997	0.990	1.004	0.995	0.984	1.006	0.994	0.981	1.007
2	1.000	0.995	1.004	1.000	0.992	1.007	0.999	0.988	1.011	0.999	0.985	1.014
3	1.001	0.996	1.006	1.001	0.993	1.009	1.002	0.989	1.015	1.003	0.987	1.019
4	1.001	0.996	1.006	1.002	0.994	1.010	1.003	0.990	1.016	1.004	0.988	1.020
5	1.001	0.996	1.005	1.001	0.994	1.009	1.002	0.990	1.015	1.003	0.988	1.018
6	1.000	0.996	1.004	1.000	0.994	1.007	1.001	0.990	1.011	1.001	0.987	1.014
7	0.999	0.995	1.003	0.999	0.992	1.005	0.998	0.987	1.008	0.997	0.984	1.010
8	0.998	0.993	1.002	0.996	0.989	1.004	0.994	0.982	1.006	0.993	0.978	1.007
9	0.996	0.991	1.002	0.994	0.984	1.003	0.990	0.975	1.005	0.988	0.969	1.007
10	0.995	0.987	1.002	0.991	0.979	1.004	0.986	0.966	1.006	0.982	0.958	1.007

Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval. $PM_{2.5}$, particulate matter at aerodynamic diameter ≤ 2.5 μm. Model was fitted from distributed lag Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness (urban/rural), socioeconomic status, and year and month of conception, and Universal Thermal Climate Index.

Table S5.3 Adjusted hazard ratios of term small for gestational age due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different exposure thresholds using 5μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015.

Month	P1			P5			P50			P90			P95			P99		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.998	0.992	1.003	0.995	0.985	1.005	0.991	0.974	1.008	0.986	0.965	1.008	0.985	0.963	1.008	0.982	0.958	1.007
-1	0.999	0.995	1.003	0.998	0.991	1.005	0.995	0.983	1.007	0.992	0.977	1.007	0.991	0.975	1.007	0.989	0.972	1.006
0	1.000	0.998	1.003	1.000	0.995	1.005	0.999	0.991	1.008	0.998	0.987	1.008	0.997	0.986	1.008	0.995	0.984	1.007
1	1.001	0.999	1.003	1.002	0.998	1.006	1.003	0.996	1.009	1.002	0.994	1.010	1.002	0.993	1.010	1.000	0.991	1.010
2	1.002	1.000	1.004	1.004	0.999	1.008	1.005	0.998	1.013	1.006	0.997	1.015	1.005	0.996	1.015	1.005	0.994	1.015
3	1.002	1.000	1.005	1.004	0.999	1.009	1.007	0.998	1.015	1.007	0.997	1.018	1.007	0.997	1.018	1.007	0.995	1.019
4	1.002	1.000	1.005	1.004	0.999	1.009	1.007	0.998	1.016	1.008	0.997	1.019	1.008	0.997	1.019	1.008	0.995	1.020
5	1.002	0.999	1.005	1.004	0.999	1.008	1.006	0.998	1.014	1.007	0.997	1.017	1.007	0.996	1.018	1.007	0.995	1.018
6	1.001	0.999	1.004	1.002	0.998	1.007	1.004	0.997	1.011	1.005	0.996	1.014	1.005	0.996	1.014	1.005	0.995	1.015
7	1.000	0.999	1.002	1.001	0.997	1.004	1.001	0.996	1.007	1.002	0.994	1.009	1.002	0.994	1.010	1.002	0.993	1.011
8	0.999	0.998	1.001	0.999	0.996	1.002	0.998	0.993	1.004	0.998	0.991	1.005	0.998	0.991	1.006	0.998	0.989	1.007
9	0.998	0.997	1.000	0.997	0.994	1.000	0.995	0.989	1.001	0.994	0.986	1.003	0.994	0.985	1.003	0.994	0.983	1.005
10	0.997	0.995	1.000	0.995	0.990	0.999	0.991	0.983	1.000	0.990	0.979	1.001	0.990	0.978	1.002	0.990	0.975	1.005

Table S5.4 Adjusted hazard ratios for the association between 3, 5, 8, and 10 μg/m^3 increase in $PM_{2.5}$ exposure and risks of term large for gestational age by month of gestation from three months preconception (-2 to 0) to birth (1 to 10) in Western Australia, 2000–2015.

Month	3 μg/m^3 $PM_{2.5}$			5 μg/m^3 $PM_{2.5}$			8 μg/m^3 $PM_{2.5}$			10 μg/m^3 $PM_{2.5}$		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.972	0.958	0.986	0.954	0.930	0.977	0.927	0.891	0.964	0.909	0.865	0.955
-1	0.988	0.981	0.995	0.980	0.968	0.991	0.967	0.949	0.986	0.959	0.937	0.982
0	1.000	0.990	1.009	0.999	0.984	1.015	0.999	0.974	1.024	0.998	0.968	1.030
1	1.003	0.994	1.012	1.005	0.990	1.020	1.008	0.985	1.032	1.010	0.981	1.041
2	0.998	0.991	1.005	0.997	0.985	1.009	0.995	0.976	1.015	0.994	0.970	1.018
3	0.995	0.986	1.004	0.992	0.977	1.007	0.987	0.964	1.011	0.984	0.955	1.013
4	0.996	0.989	1.003	0.993	0.982	1.005	0.989	0.972	1.007	0.987	0.965	1.009
5	0.998	0.992	1.004	0.997	0.988	1.007	0.995	0.980	1.011	0.994	0.975	1.013
6	0.999	0.992	1.006	0.999	0.987	1.011	0.998	0.980	1.017	0.998	0.975	1.022
7	0.999	0.992	1.005	0.998	0.987	1.009	0.997	0.979	1.015	0.996	0.974	1.018
8	0.997	0.991	1.002	0.995	0.986	1.003	0.991	0.977	1.006	0.989	0.971	1.007
9	0.994	0.988	1.000	0.990	0.980	1.000	0.983	0.968	0.999	0.979	0.960	0.999
10	0.990	0.981	1.000	0.984	0.968	1.001	0.975	0.949	1.001	0.968	0.937	1.001

Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval. $PM_{2.5}$, particulate matter at aerodynamic diameter ≤ 2.5 μm. Model was fitted from distributed lag Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness (urban/rural), socioeconomic status, and year and month of conception, and Universal Thermal Climate Index.

Table S5.5 Adjusted hazard ratios of term large for gestational age due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different exposure thresholds using 5µg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015.
Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval; P1-P99, 1st to 99th centiles of $PM_{2.5}$; $PM_{2.5}$, particulate matter at aerodynamic

Month	P1			P5			P50			P90			P95			P99		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.979	0.972	0.987	0.961	0.946	0.976	0.931	0.907	0.957	0.912	0.881	0.944	0.907	0.874	0.941	0.898	0.862	0.935
-1	0.993	0.989	0.997	0.986	0.979	0.993	0.976	0.963	0.988	0.969	0.953	0.985	0.967	0.951	0.984	0.964	0.946	0.982
0	1.002	0.997	1.008	1.005	0.994	1.015	1.009	0.991	1.027	1.012	0.989	1.035	1.013	0.988	1.037	1.015	0.988	1.042
1	1.004	0.999	1.010	1.009	0.999	1.019	1.016	0.999	1.034	1.021	0.999	1.044	1.023	1.000	1.047	1.026	1.000	1.052
2	0.999	0.995	1.003	0.998	0.990	1.006	0.997	0.984	1.010	0.996	0.980	1.013	0.996	0.979	1.014	0.997	0.978	1.016
3	0.995	0.990	1.000	0.990	0.981	1.000	0.984	0.968	1.000	0.980	0.959	1.00	0.979	0.957	1.001	0.977	0.954	1.001
4	0.995	0.991	0.999	0.990	0.983	0.998	0.983	0.971	0.996	0.979	0.964	0.996	0.979	0.962	0.996	0.978	0.959	0.996
5	0.996	0.993	0.999	0.993	0.988	0.999	0.989	0.979	0.999	0.987	0.975	0.999	0.987	0.974	1.000	0.986	0.973	1.001
6	0.998	0.994	1.001	0.996	0.990	1.003	0.994	0.983	1.005	0.993	0.979	1.008	0.993	0.979	1.008	0.994	0.978	1.011
7	0.998	0.995	1.002	0.997	0.991	1.004	0.996	0.985	1.007	0.996	0.982	1.010	0.996	0.982	1.010	0.997	0.981	1.013
8	0.999	0.996	1.001	0.997	0.993	1.002	0.996	0.988	1.004	0.995	0.985	1.006	0.995	0.984	1.006	0.996	0.983	1.008
9	0.998	0.996	1.000	0.997	0.993	1.000	0.994	0.988	1.000	0.993	0.984	1.002	0.992	0.982	1.003	0.992	0.979	1.005
10	0.998	0.995	1.001	0.995	0.990	1.001	0.992	0.981	1.003	0.989	0.974	1.005	0.989	0.971	1.006	0.987	0.966	1.009

diameter ≤ 2.5 µm. Model was fitted from distributed lag non-linear Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness (urban/rural), socioeconomic status, and year and month of conception, and Universal Thermal Climate Index.

.

Table S5.6 Adjusted hazard ratios for the association between 3, 5, 8, and 10 μg/m^3 increase in $PM_{2.5}$ exposure and risks of term low birth weight by month of gestation from three months preconception (-2 to 0) to birth (1 to 10) in Western Australia, 2000–2015.

Month	3 μg/m^3 $PM_{2.5}$			5 μg/m^3 $PM_{2.5}$			8 μg/m^3 $PM_{2.5}$			10 μg/m^3 $PM_{2.5}$		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.989	0.967	1.011	0.981	0.945	1.019	0.970	0.914	1.031	0.963	0.893	1.039
-1	0.994	0.978	1.010	0.990	0.964	1.017	0.984	0.943	1.028	0.981	0.929	1.035
0	0.999	0.988	1.010	0.998	0.980	1.017	0.998	0.968	1.028	0.997	0.960	1.035
1	1.003	0.994	1.013	1.005	0.989	1.021	1.009	0.983	1.035	1.011	0.979	1.043
2	1.006	0.996	1.017	1.010	0.993	1.028	1.016	0.988	1.045	1.020	0.985	1.057
3	1.007	0.996	1.019	1.012	0.993	1.032	1.020	0.989	1.052	1.025	0.986	1.065
4	1.007	0.995	1.019	1.012	0.992	1.032	1.019	0.987	1.051	1.023	0.984	1.064
5	1.005	0.994	1.016	1.009	0.991	1.027	1.014	0.985	1.044	1.018	0.981	1.055
6	1.002	0.993	1.012	1.004	0.988	1.020	1.007	0.981	1.033	1.008	0.976	1.041
7	0.999	0.990	1.008	0.998	0.983	1.013	0.997	0.972	1.021	0.996	0.966	1.027
8	0.994	0.984	1.005	0.991	0.973	1.009	0.985	0.957	1.014	0.981	0.947	1.017
9	0.990	0.976	1.004	0.983	0.960	1.006	0.972	0.936	1.010	0.966	0.921	1.013
10	0.985	0.966	1.003	0.974	0.944	1.006	0.959	0.912	1.009	0.949	0.891	1.012

Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval. $PM_{2.5}$, particulate matter at aerodynamic diameter ≤ 2.5 μm. Model was fitted from distributed lag Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness (urban/rural), socioeconomic status, and year and month of conception, and Universal Thermal Climate Index.

Table S5.7 Adjusted hazard ratios of term low birth weight due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different exposure thresholds using 5 μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015.

Month	P1			P5			P50			P90			P95			P99		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.996	0.983	1.008	0.991	0.968	1.015	0.984	0.944	1.025	0.978	0.929	1.029	0.976	0.925	1.03	0.972	0.916	1.031
-1	0.999	0.991	1.008	0.998	0.982	1.015	0.996	0.968	1.025	0.992	0.957	1.029	0.991	0.955	1.029	0.988	0.949	1.029
0	1.003	0.997	1.009	1.005	0.993	1.017	1.007	0.988	1.027	1.006	0.982	1.031	1.006	0.981	1.031	1.004	0.977	1.031
1	1.006	1.001	1.011	1.010	1.001	1.020	1.016	1.000	1.033	1.018	0.998	1.038	1.018	0.997	1.039	1.017	0.994	1.039
2	1.008	1.002	1.013	1.014	1.003	1.025	1.023	1.005	1.042	1.026	1.004	1.049	1.027	1.003	1.051	1.026	1.001	1.052
3	1.008	1.002	1.015	1.016	1.003	1.028	1.026	1.005	1.047	1.030	1.004	1.057	1.031	1.004	1.059	1.031	1.001	1.061
4	1.008	1.001	1.015	1.015	1.002	1.028	1.025	1.003	1.047	1.030	1.003	1.057	1.030	1.002	1.059	1.031	1.000	1.062
5	1.007	1.000	1.013	1.013	1.001	1.025	1.021	1.001	1.041	1.025	1.000	1.051	1.026	1.000	1.053	1.027	0.999	1.055
6	1.005	0.999	1.010	1.009	0.999	1.019	1.014	0.998	1.032	1.018	0.997	1.039	1.018	0.996	1.041	1.019	0.995	1.044
7	1.002	0.998	1.006	1.003	0.995	1.011	1.006	0.993	1.019	1.008	0.991	1.025	1.008	0.990	1.026	1.009	0.989	1.030
8	0.998	0.995	1.002	0.997	0.990	1.004	0.996	0.984	1.008	0.996	0.980	1.012	0.996	0.979	1.014	0.997	0.976	1.019
9	0.995	0.991	0.999	0.990	0.982	0.999	0.985	0.970	1.000	0.983	0.963	1.004	0.983	0.961	1.006	0.984	0.957	1.013
10	0.991	0.985	0.997	0.983	0.972	0.995	0.974	0.953	0.995	0.970	0.942	0.999	0.970	0.939	1.002	0.971	0.933	1.010

Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval; P1-P99, 1st to 99th centiles of $PM_{2.5}$; $PM_{2.5}$, particulate matter at aerodynamic diameter ≤ 2.5 μm. Model was fitted from distributed lag non-linear Cox proportional hazards model with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness (urban/rural), socioeconomic status, and year and month of conception, and Universal Thermal Climate Index.

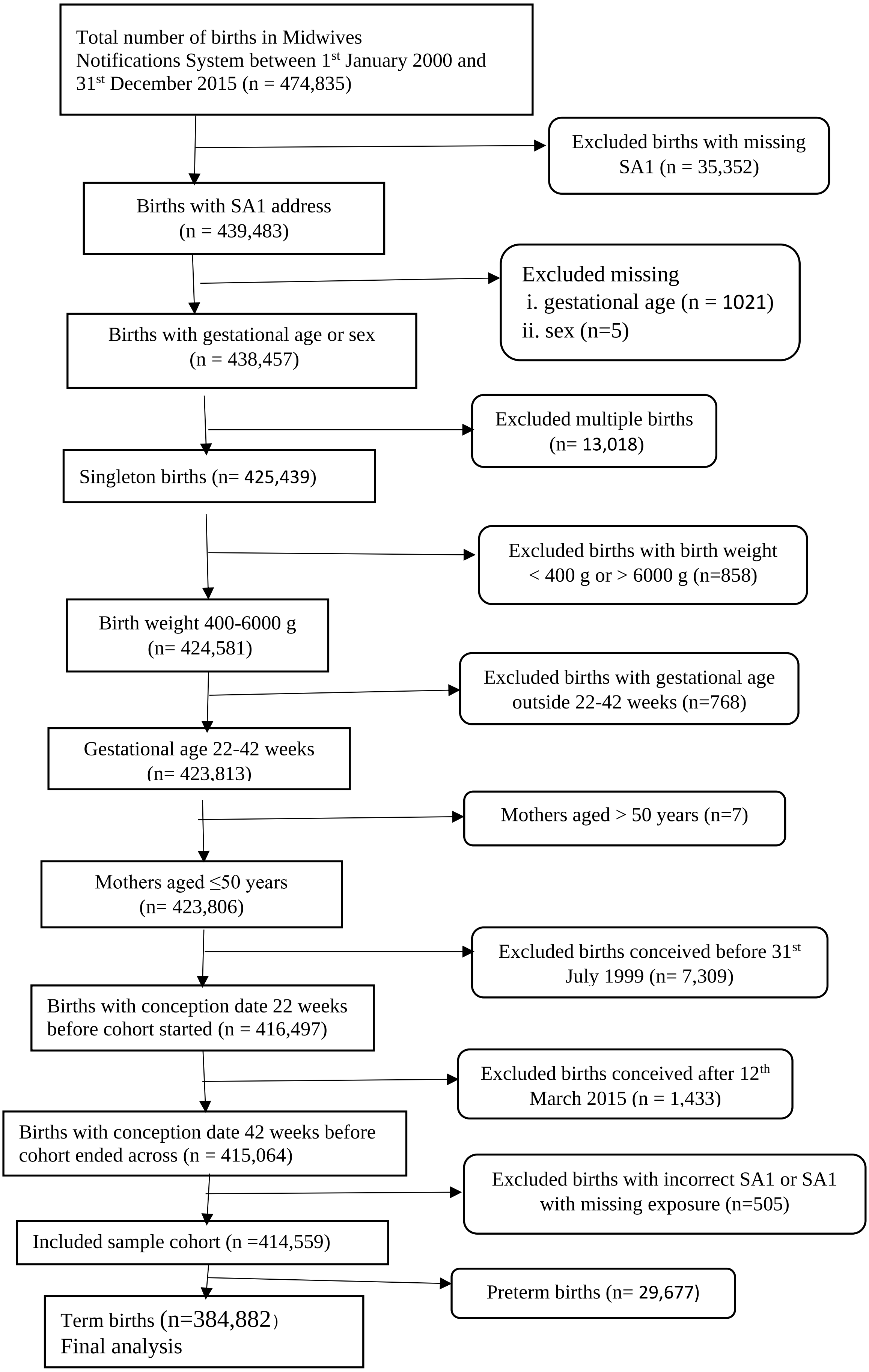

Figure S5.1. Flow chart for selecting the eligible births included in this study, Western Australia, 2000-2015. Note: SA1, statistical area level 1.

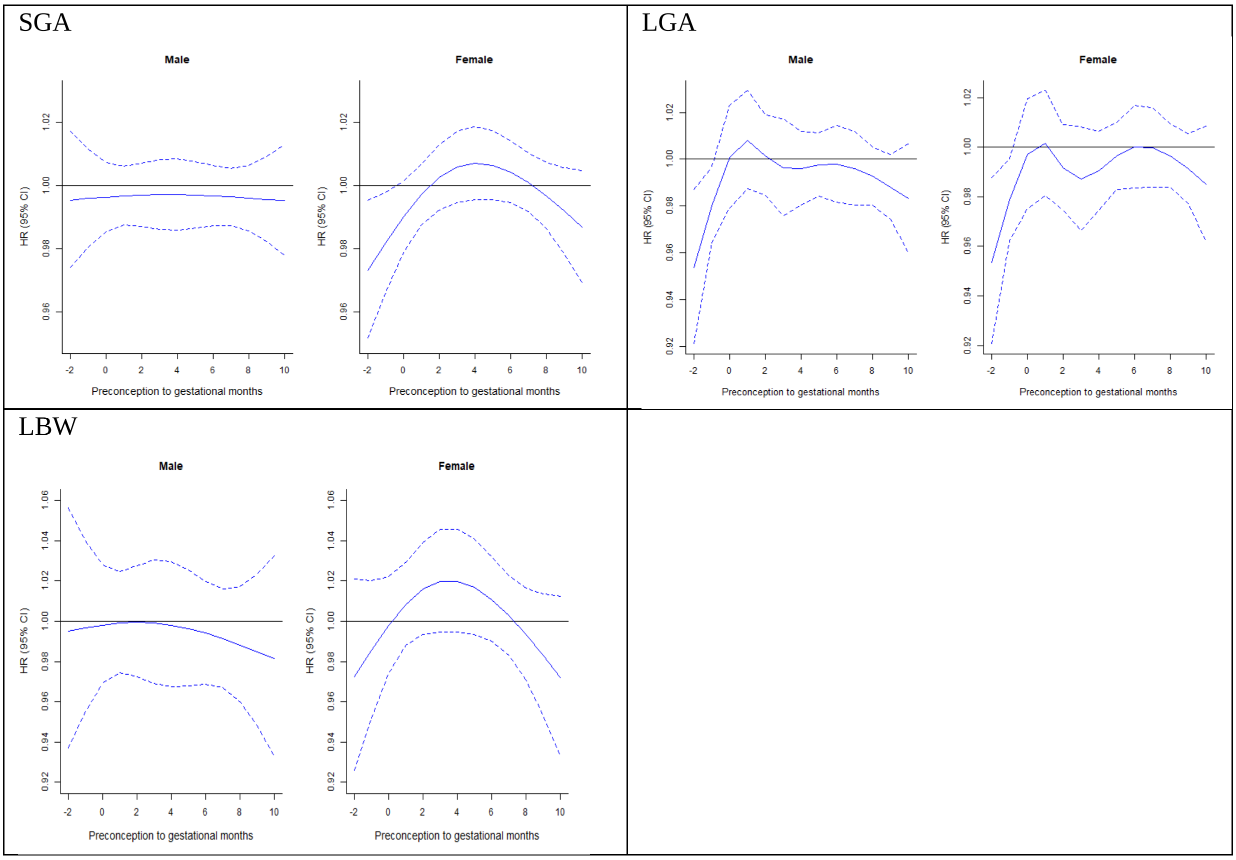

Figure S5.2 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 μg/m^3 increment in $PM_{2.5}$ exposure by sex in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

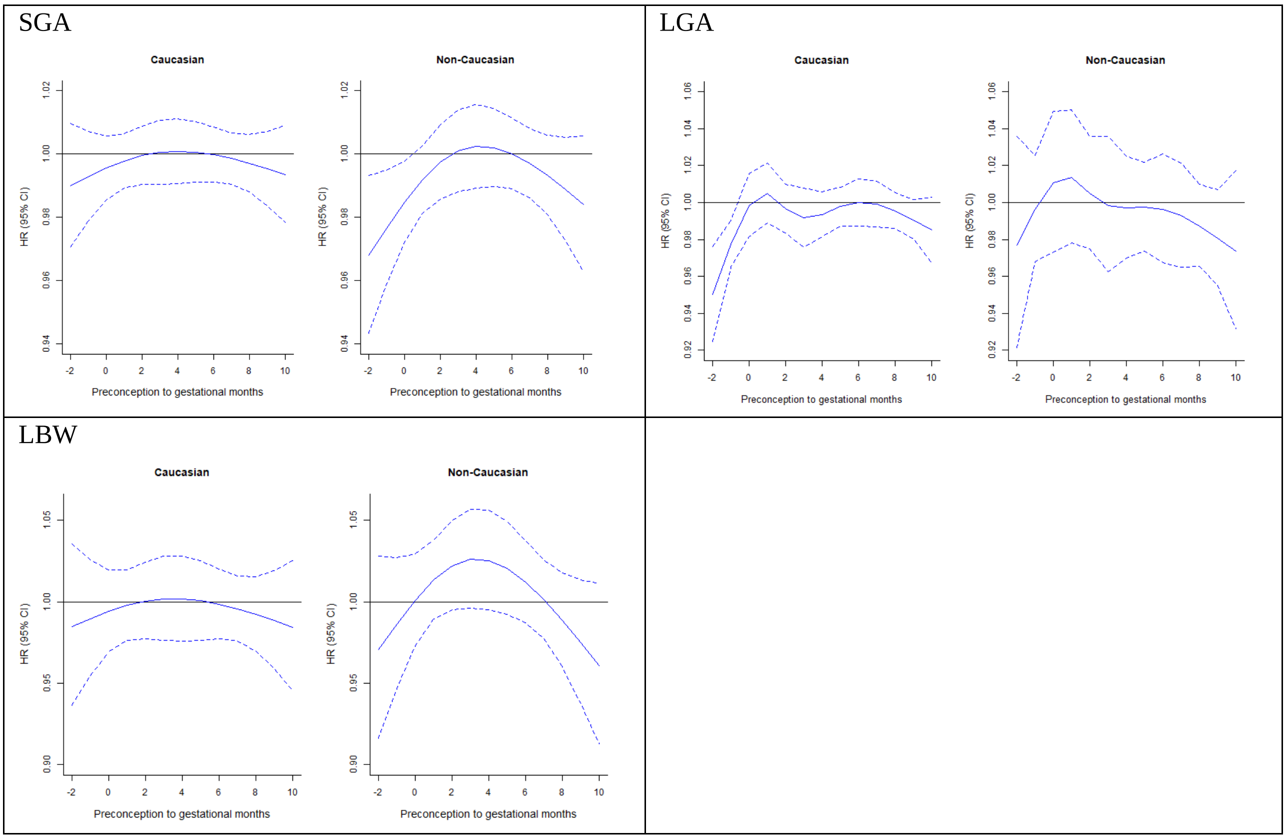

Figure S5.3 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 µg/m^3 increment in $PM_{2.5}$ exposure by race or ethnicity in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

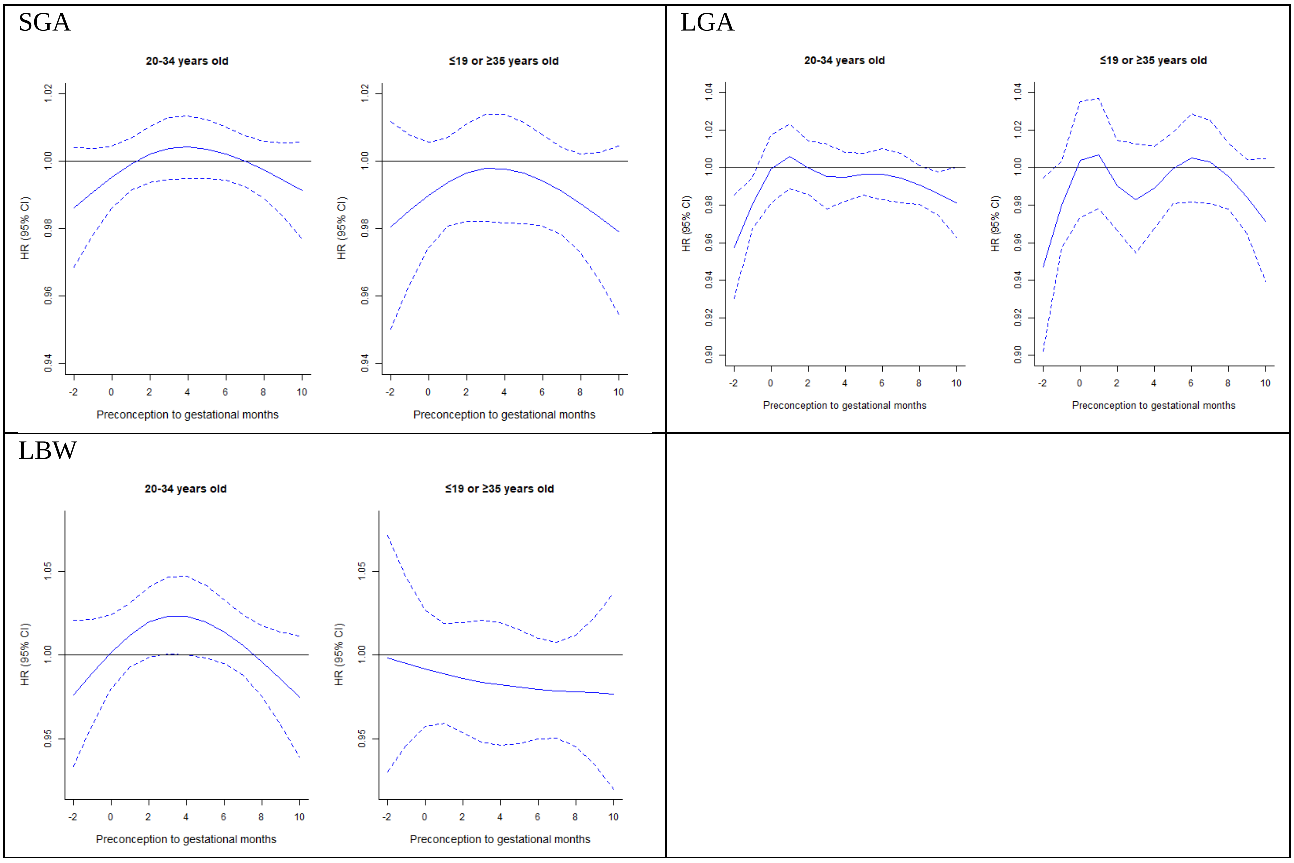

Figure S5.4 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 μg/m^3 increment in $PM_{2.5}$ exposure by maternal age in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

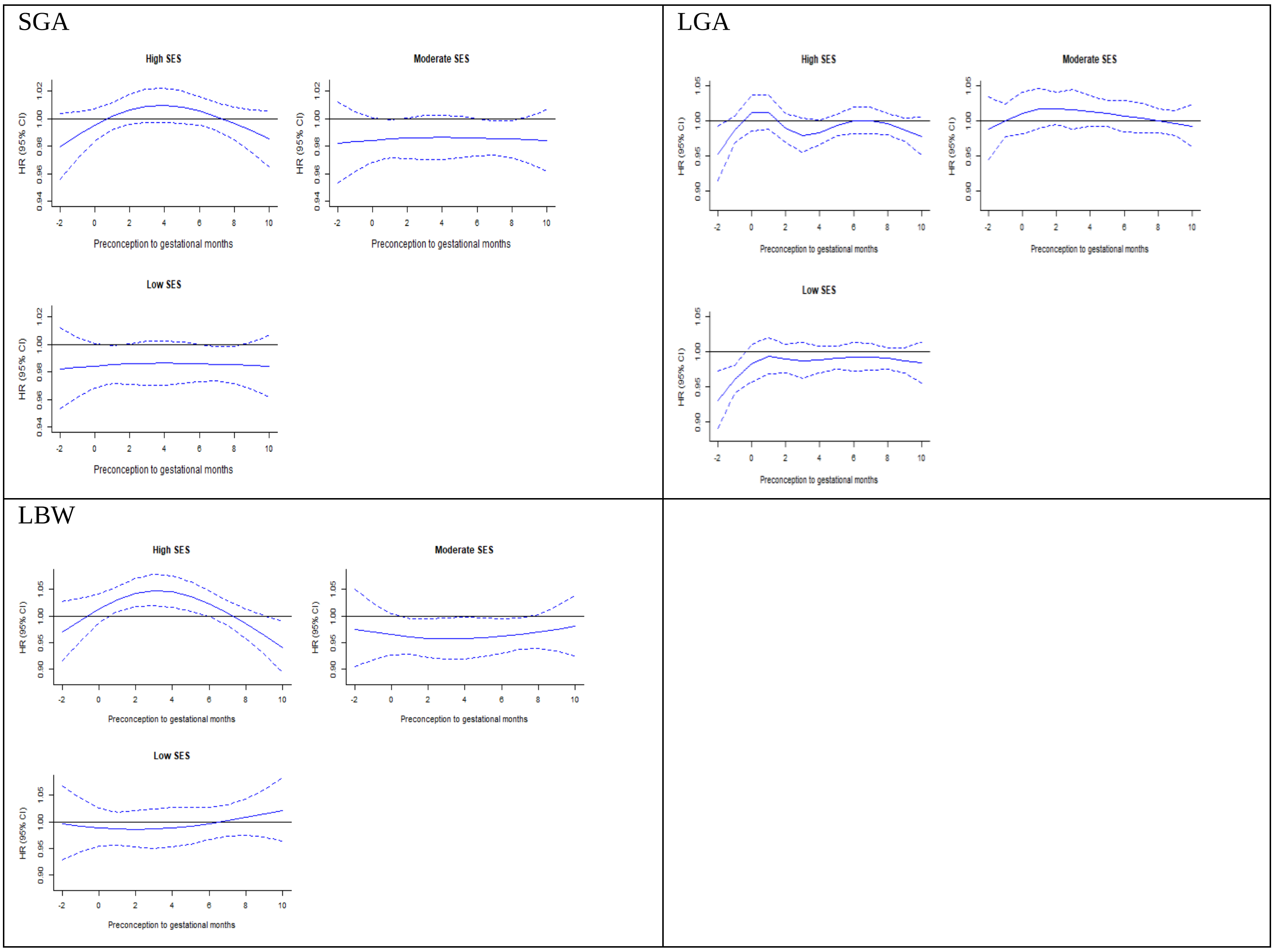

Figure S5.5 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 µg/m^3 increment in $PM_{2.5}$ exposure by socioeconomic status (SES) in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

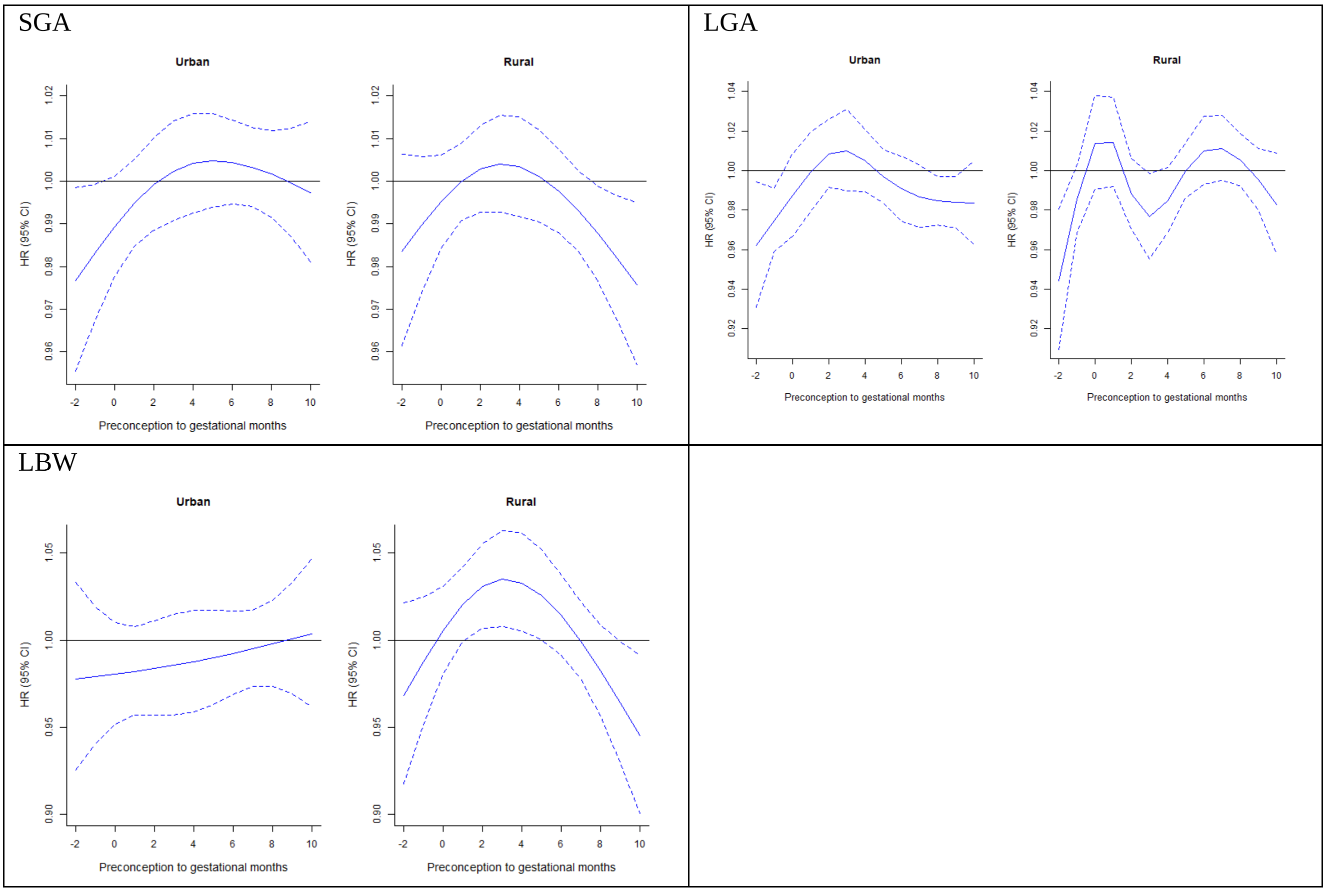

Figure S5.6 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 μg/m^3 increment in $PM_{2.5}$ exposure by remoteness in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, socioeconomic status and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

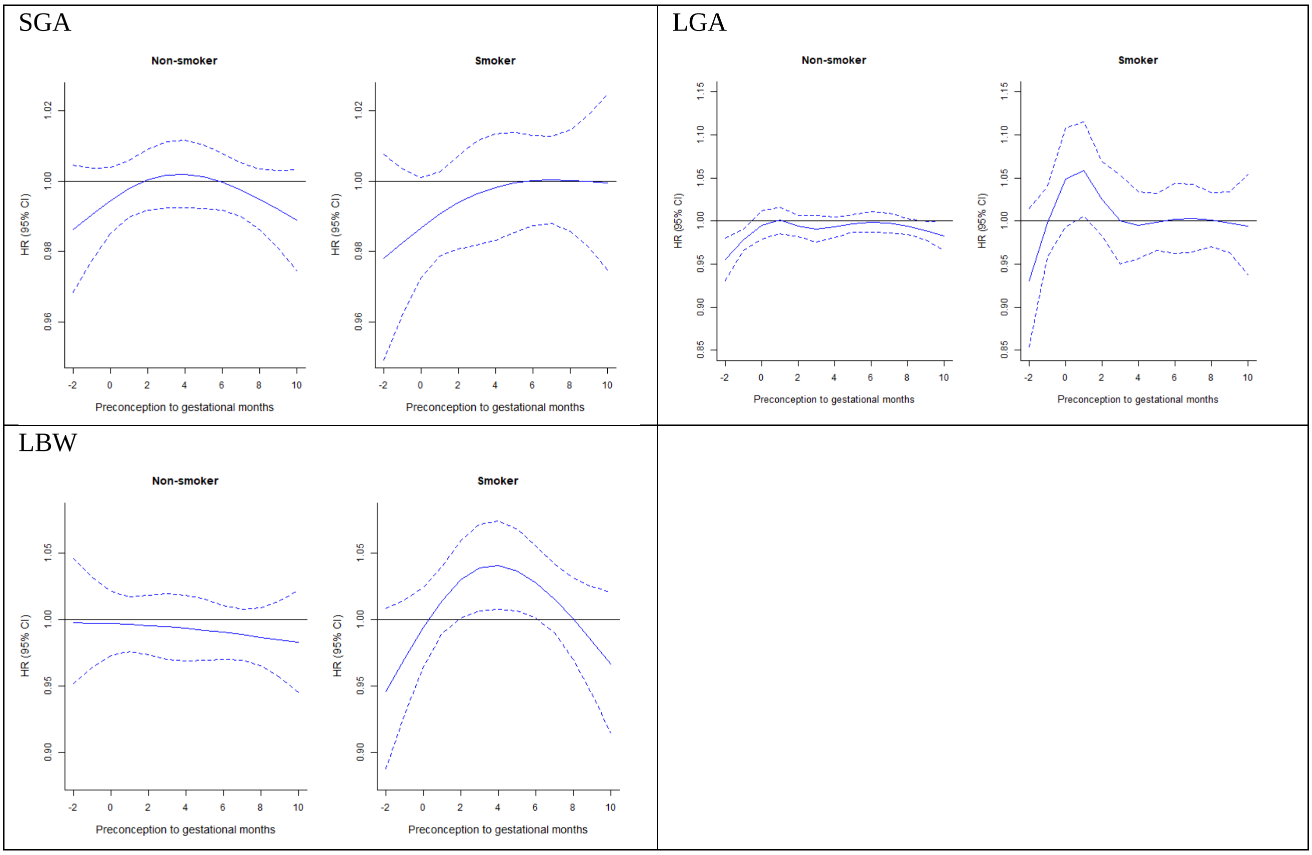

Figure S5.7 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 μg/m^3 increment in $PM_{2.5}$ exposure by maternal smoking status in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, remoteness (urban/rural), parity, socioeconomic status and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

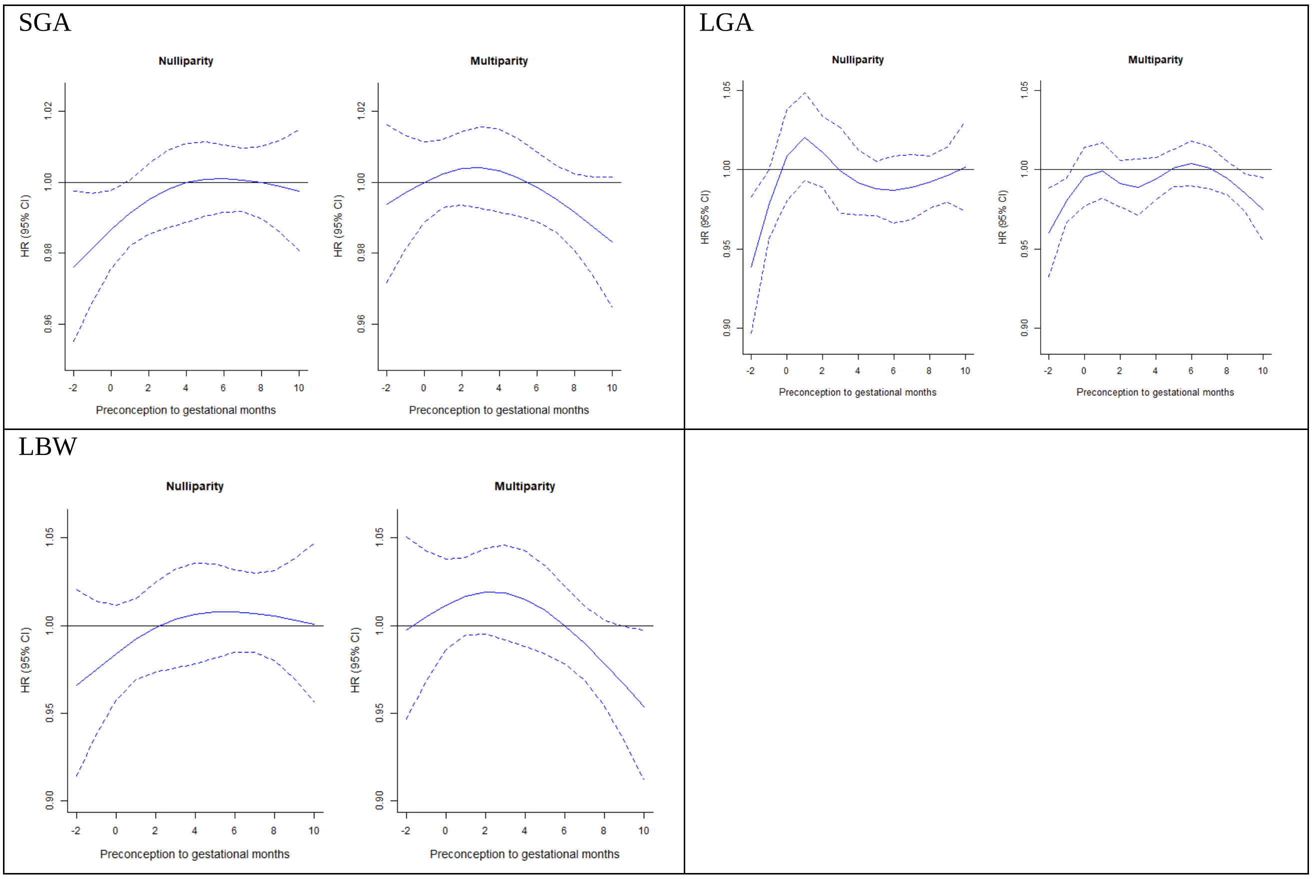

Figure S5.8 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 μg/m^3 increment in $PM_{2.5}$ exposure by parity in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, remoteness (urban/rural), smoking status, socioeconomic status and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

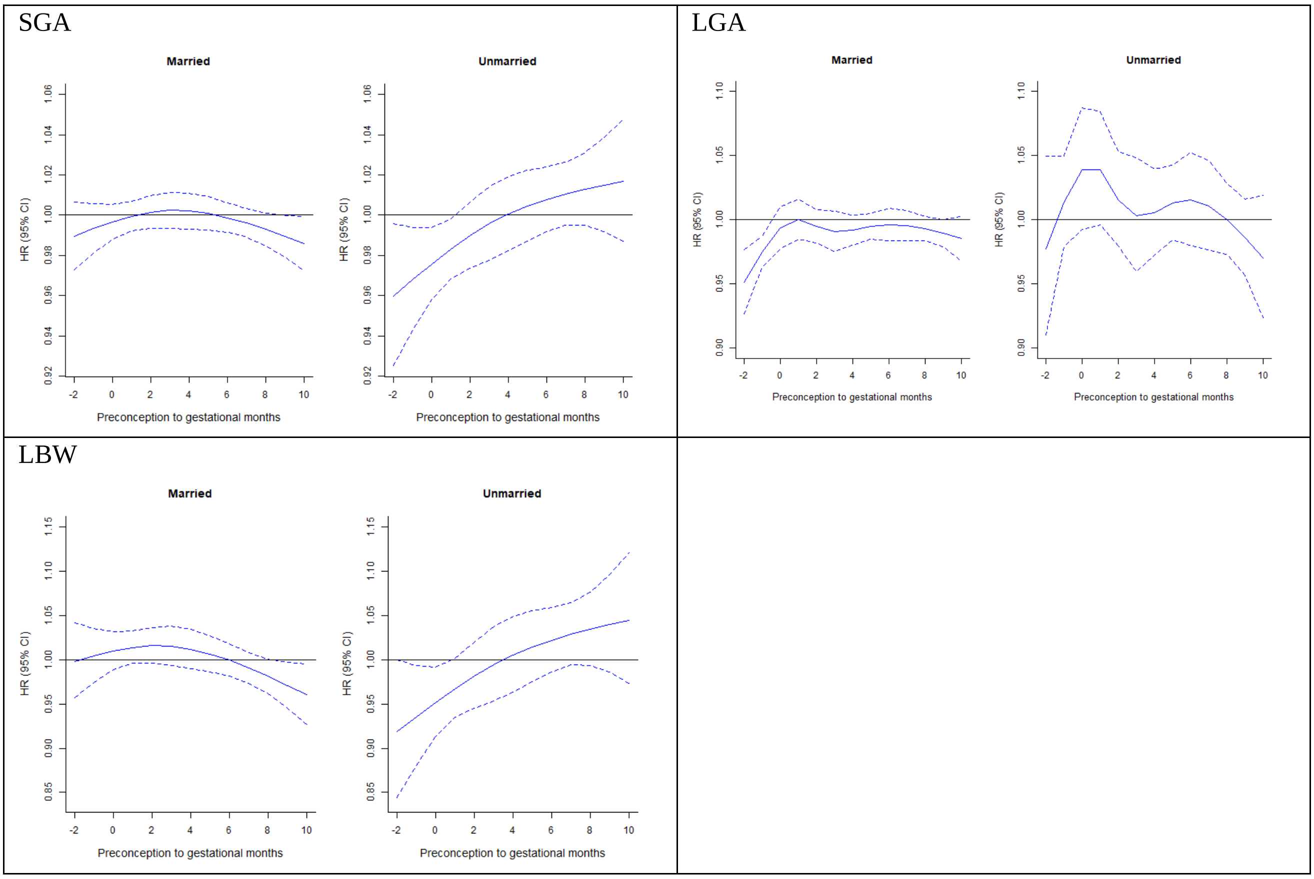

Figure S5.9 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 μg/m^3 increment in $PM_{2.5}$ exposure by marital status in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, remoteness (urban/rural), smoking status, parity, socioeconomic status and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

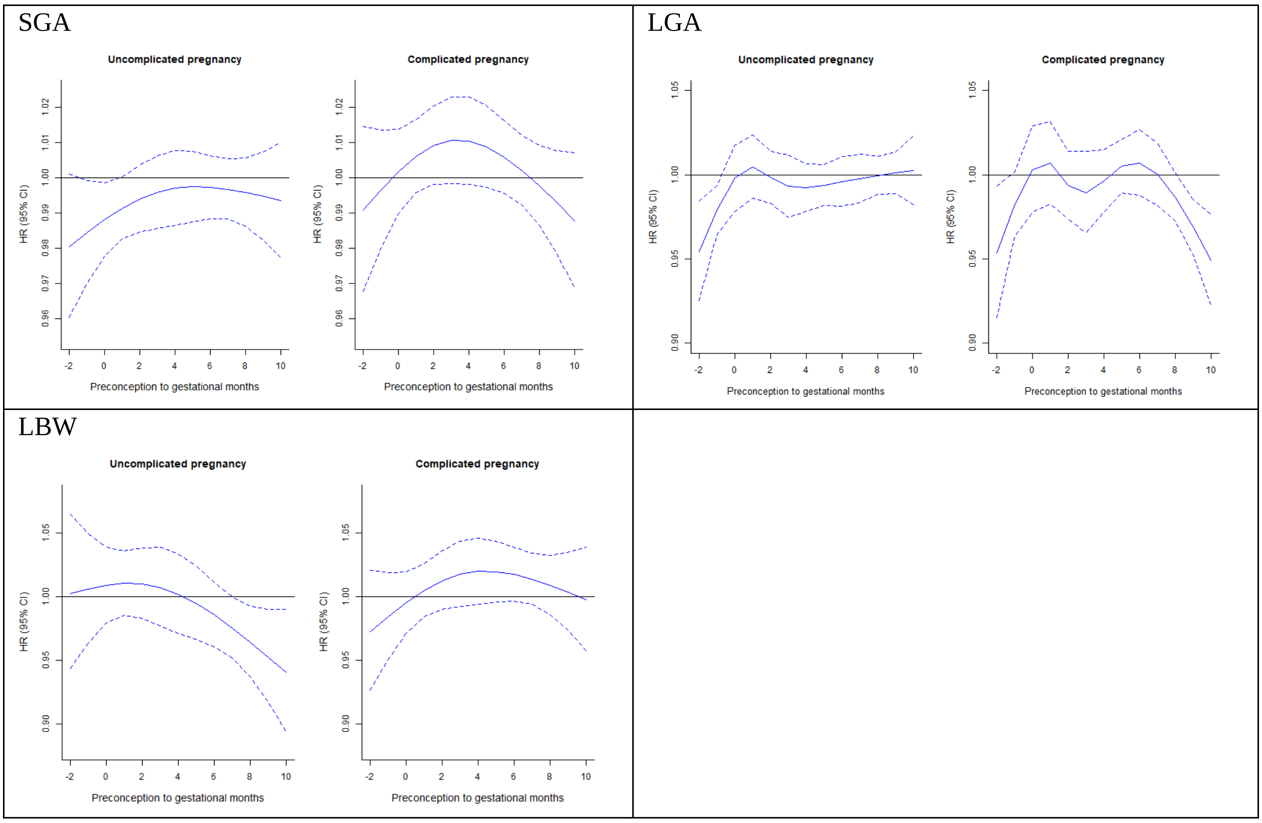

Figure S5.10 Adjusted hazard ratios of term adverse fetal growth outcomes due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at 5 μg/m^3 increment in $PM_{2.5}$ exposure by pregnancy complications in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Models were fitted from distributed lag Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, remoteness (urban/rural), parity, smoking status, socioeconomic status and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

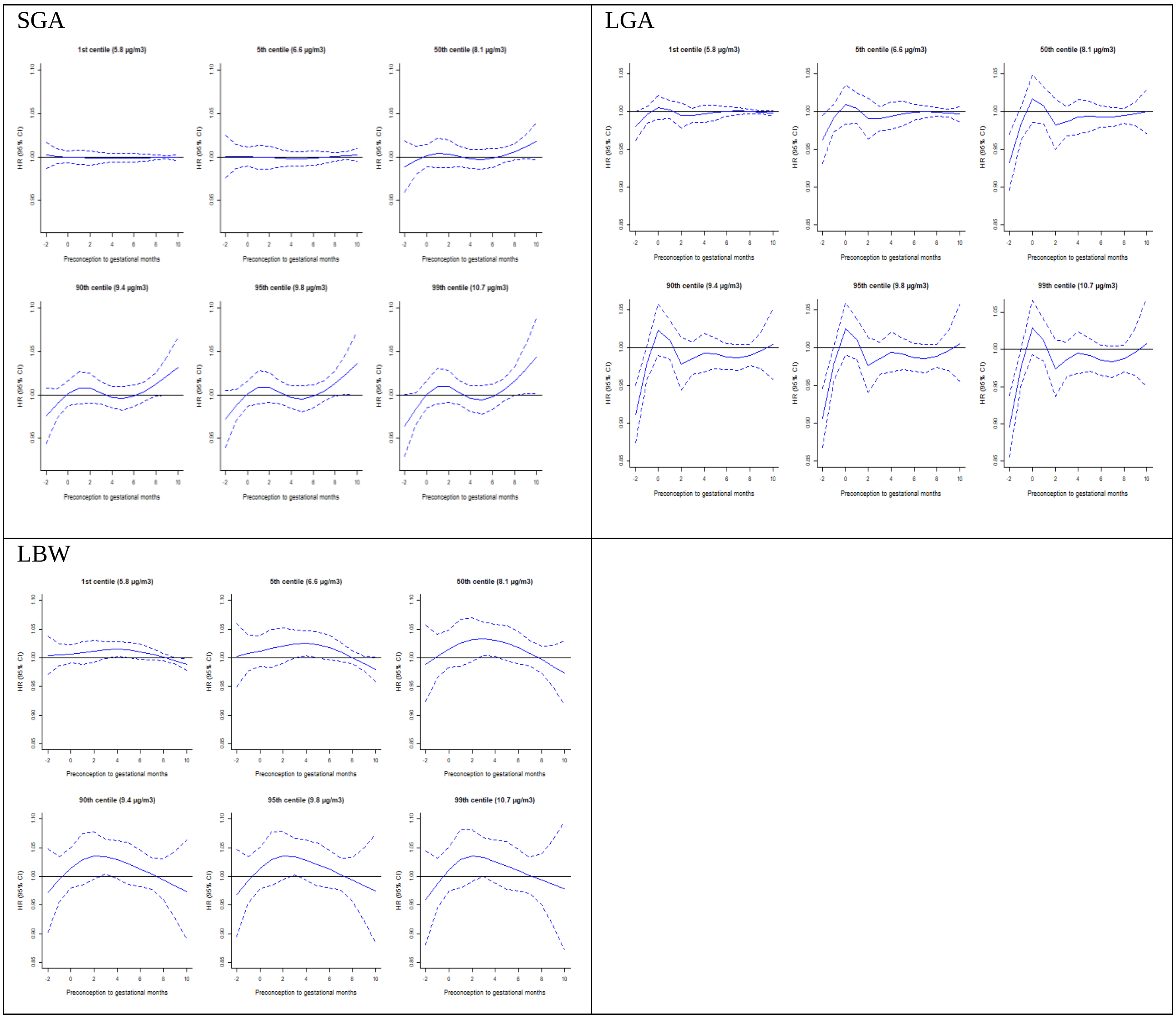

Figure S5.11 Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. DLNM was constructed with natural splines with one increase in the degree of freedoms used in the main analyses for both exposure and lag dimensions. Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight. DLNM, distributed lag non-linear model.

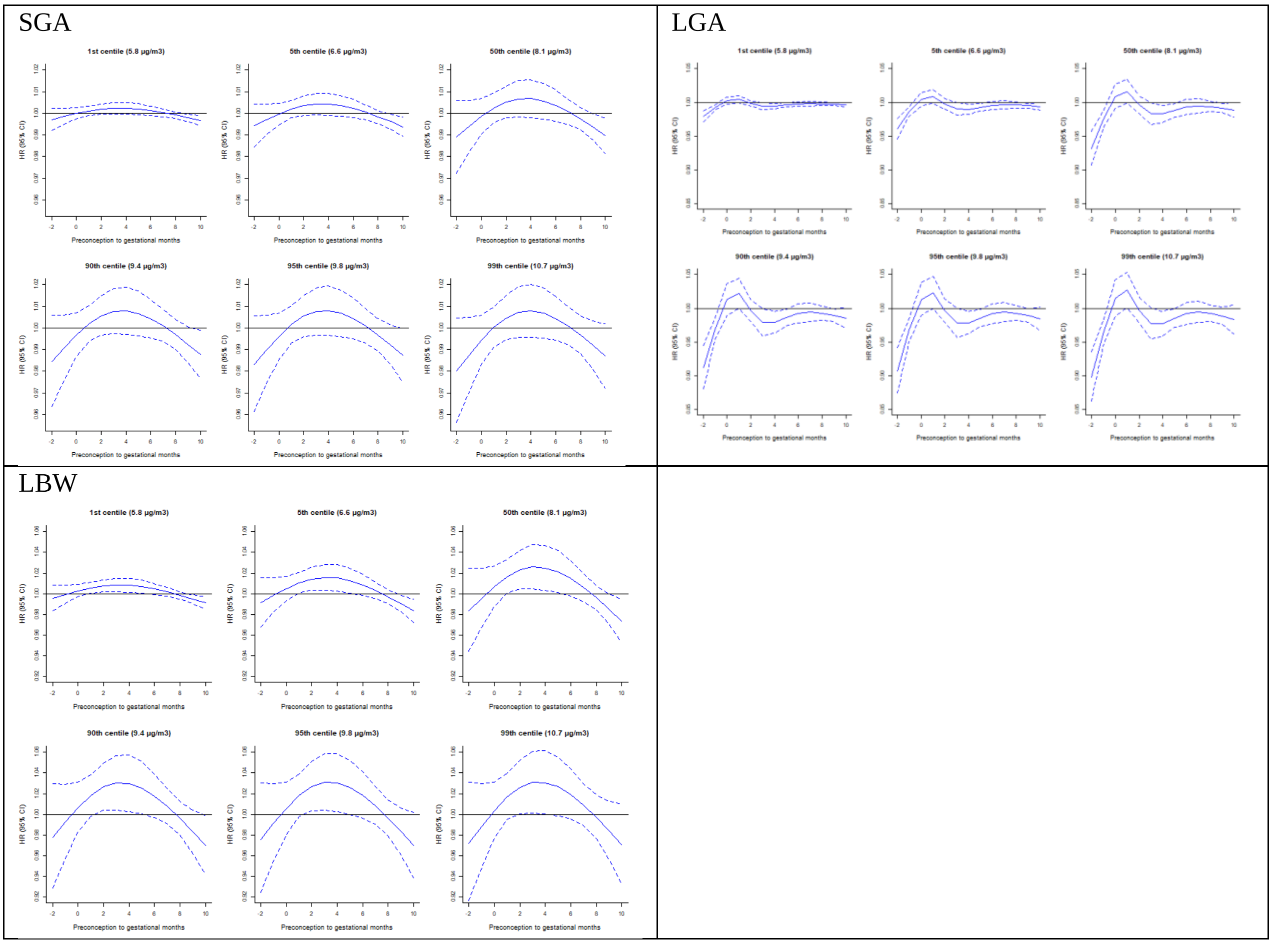

Figure S5.12 Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Categorical maternal age was used instead of natural spline of continuous variable.

Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

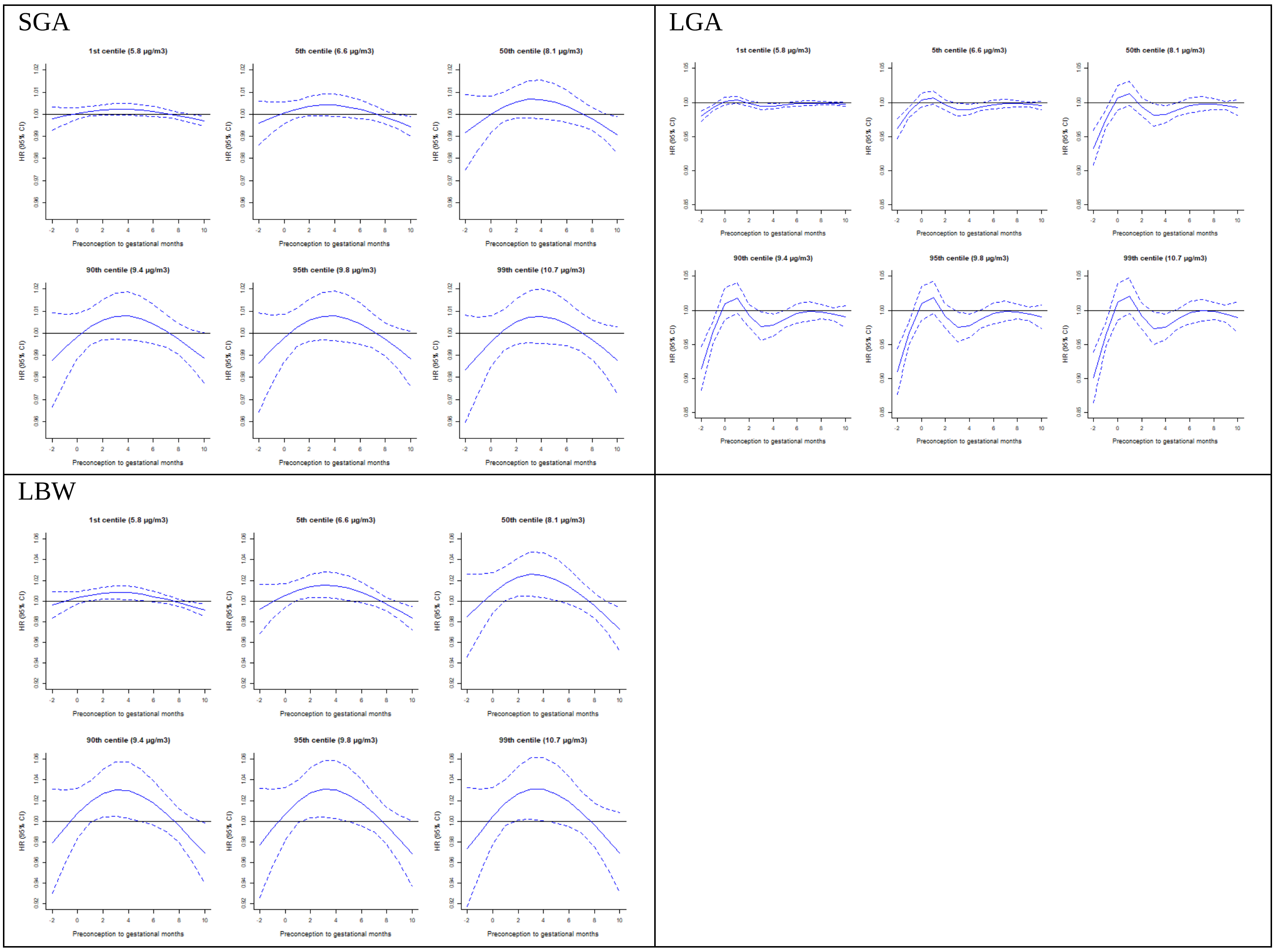

Figure S5.13 Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Adjusted for season of conception (autumn, winter, spring, summer) instead of month of conception (1 to 12). Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

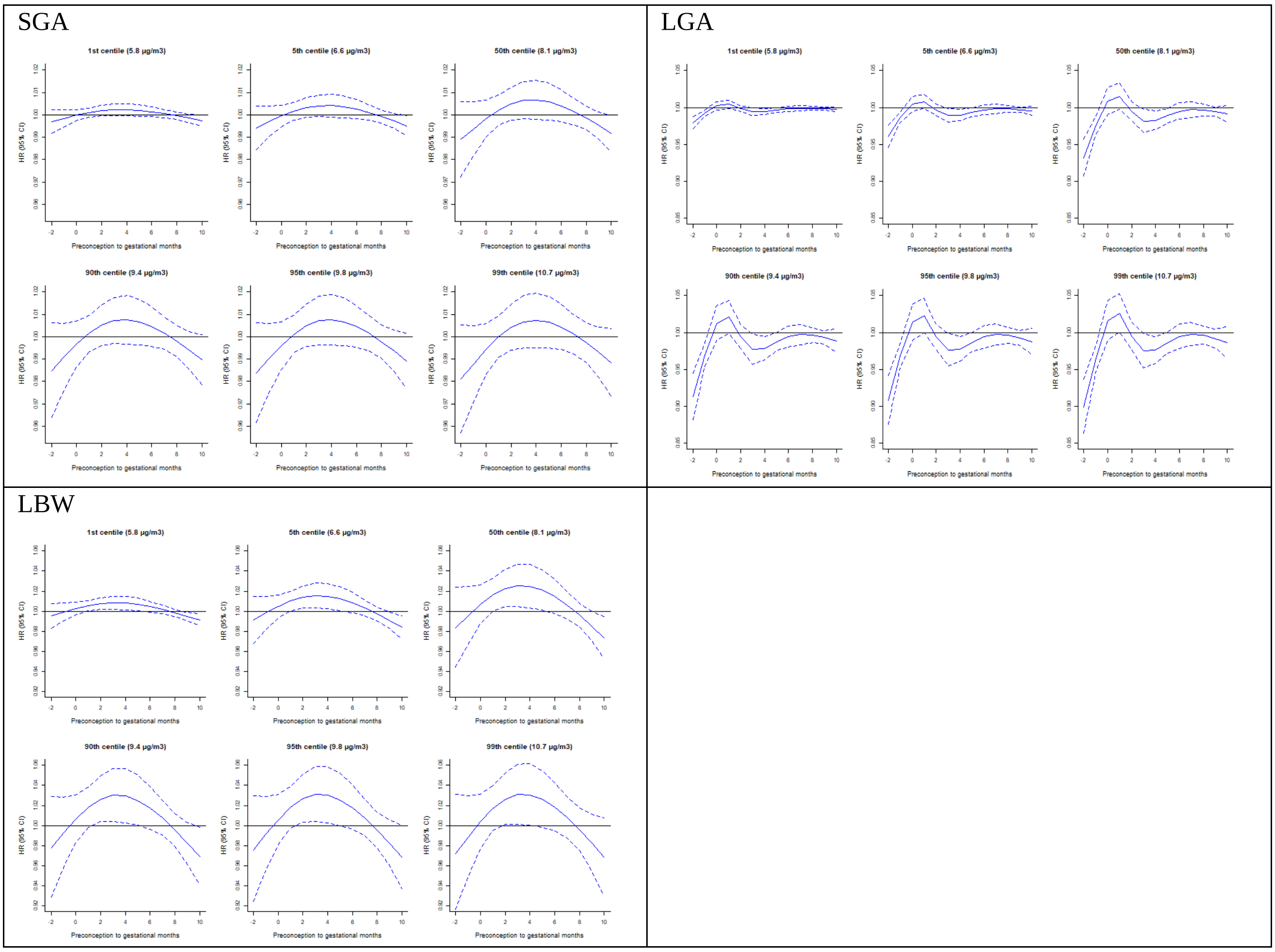

Figure S5.14 Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. The degree of freedom for natural spline of UTCI was increased by one to four. Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

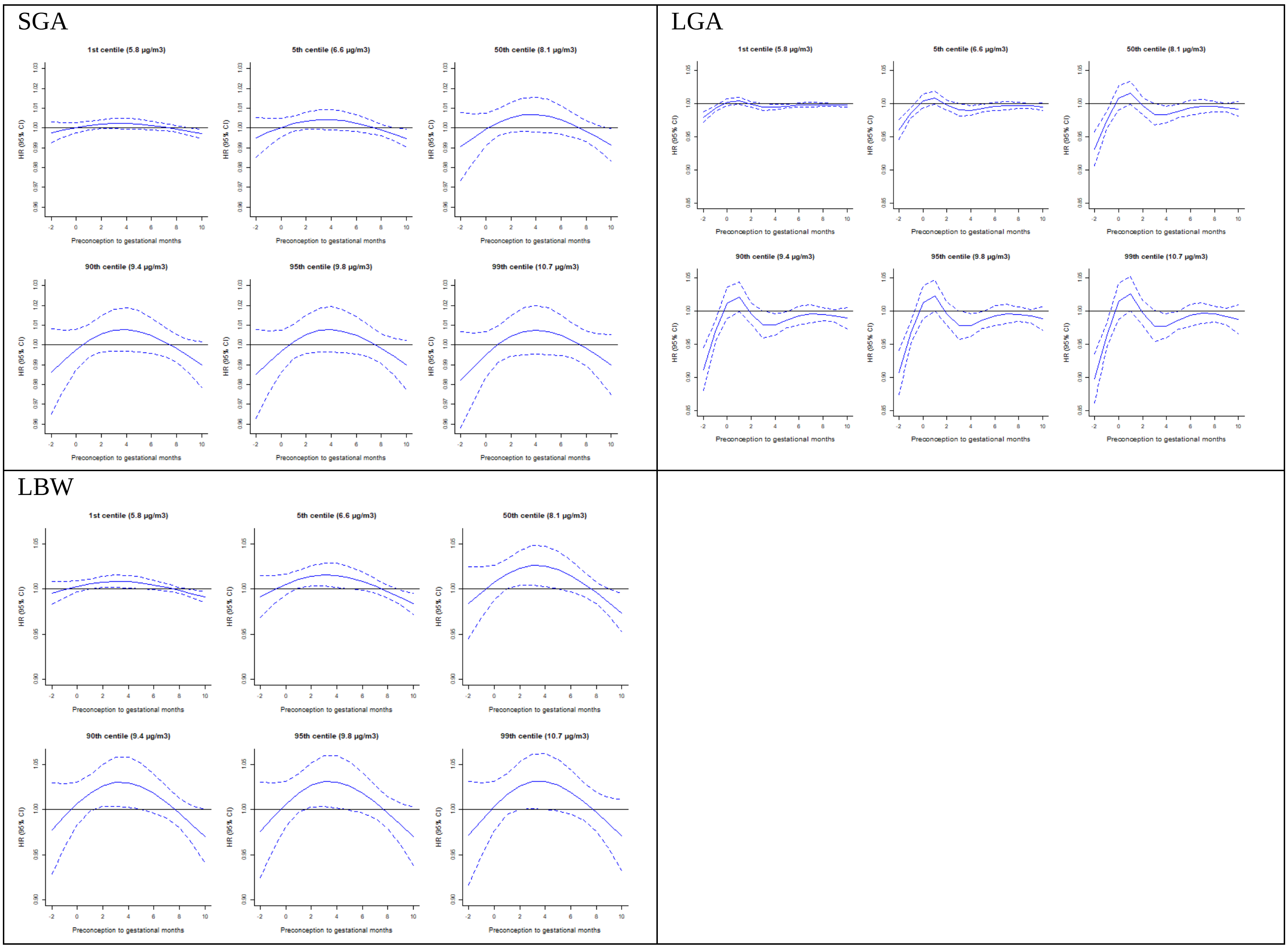

Figure S5.15 Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5µg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Model adjusted for mother-specific clusters to account for repeated births by the same mother. Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

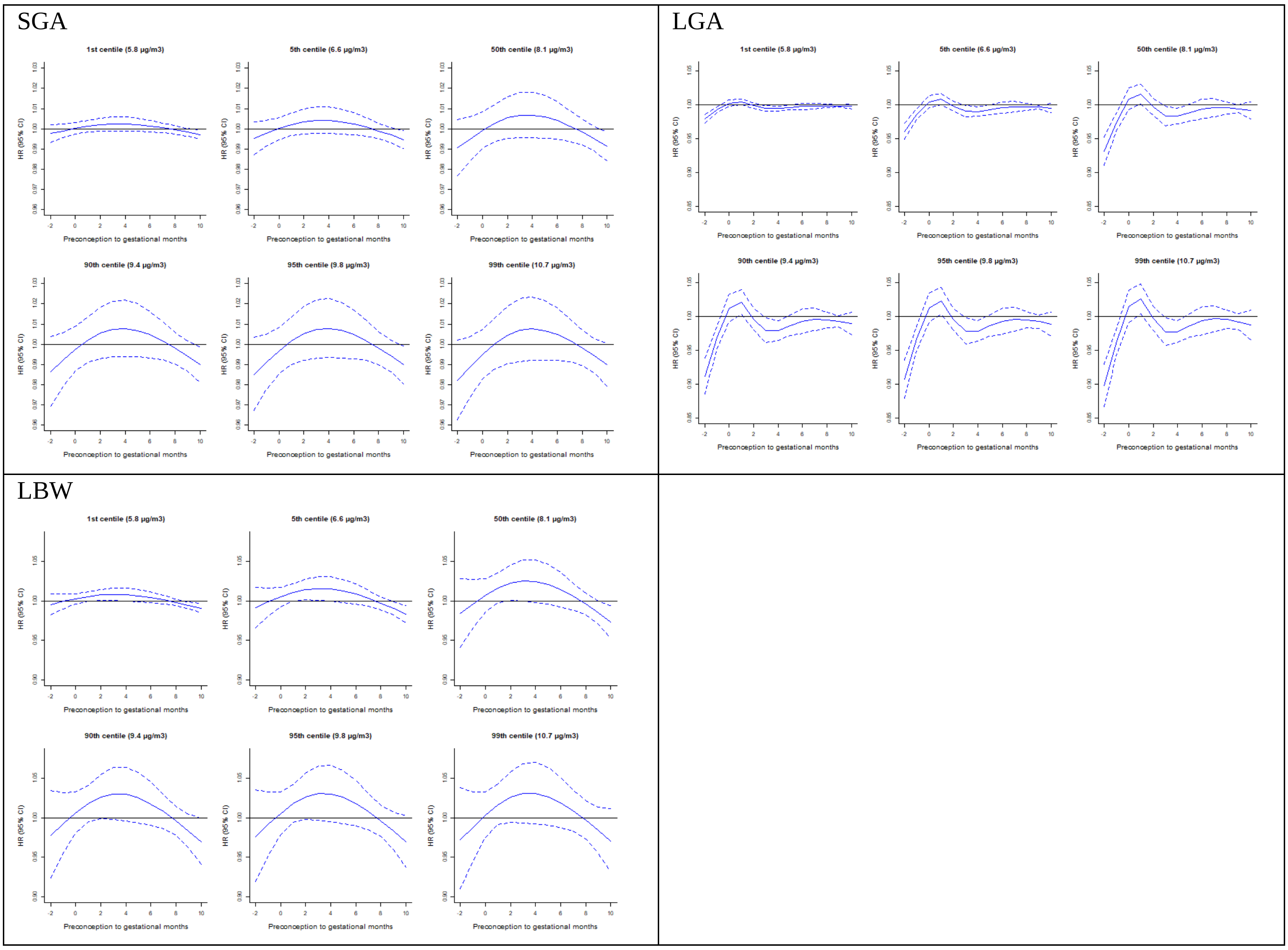

Figure S5.16 Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5µg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. Model was adjusted for local government area-specific clusters to account for potential spatial clustering and maternal mobility. Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

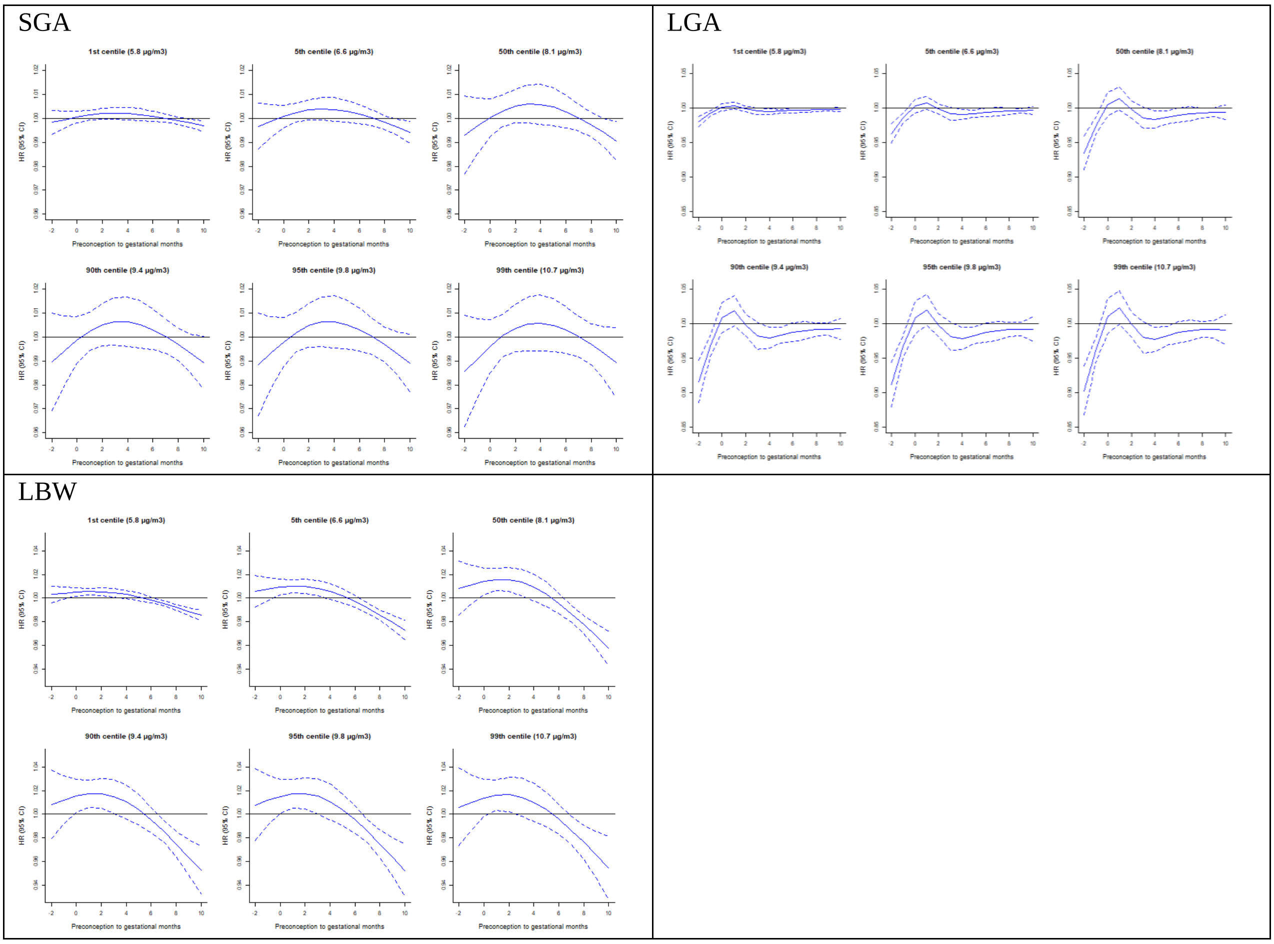

Figure S5.17 Adjusted hazard ratios of term adverse fetal growth due to monthly $PM_{2.5}$ exposure from three months preconception (-2 to 0) to birth (1 to 10) at different thresholds using 5μg/m^3 $PM_{2.5}$ as reference in Western Australia, 2000–2015. Solid blue lines represent HRs, and the broken lines represent 95% CIs. All eligible singleton births with 22-42 gestational weeks were analysed instead only of term births. Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception, and Universal Thermal Climate Index. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

Appendix D: Supplementary materials for Chapter 6

Table S6.1 Monthly adjusted relative risk for the distributed lag linear association between $PM_{2.5}$ exposure at 5,10, 20.5, and 23.3 μg/m^3 increase and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020.

Lag month	5 μg/m^3 $PM_{2.5}$			10 μg/m^3 $PM_{2.5}$			20.5 μg/m^3 $PM_{2.5}$			23.3 μg/m^3 $PM_{2.5}$		
	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
0	1.002	0.997	1.006	1.003	0.995	1.012	1.006	0.989	1.024	1.007	0.988	1.027
1	1.000	0.995	1.004	0.999	0.99	1.008	0.998	0.980	1.016	0.998	0.977	1.019
2	1.002	0.997	1.006	1.003	0.995	1.012	1.007	0.989	1.025	1.008	0.987	1.029
3	1.002	0.998	1.006	1.004	0.995	1.012	1.007	0.990	1.025	1.008	0.988	1.029
4	0.998	0.994	1.003	0.996	0.987	1.006	0.993	0.974	1.011	0.992	0.971	1.013
5	0.999	0.994	1.003	0.998	0.989	1.007	0.996	0.977	1.014	0.995	0.974	1.016
6	1.004	0.999	1.008	1.007	0.999	1.016	1.015	0.998	1.032	1.017	0.998	1.037
7	1.001	0.997	1.006	1.003	0.994	1.011	1.005	0.988	1.023	1.006	0.987	1.026
8	0.997	0.992	1.001	0.993	0.984	1.002	0.986	0.968	1.005	0.984	0.963	1.005
9	1.000	0.995	1.004	0.999	0.991	1.008	0.998	0.981	1.016	0.998	0.978	1.018

Note: The $PM_{2.5}$ exposure increments were the World Health Organization air quality guidelines (5 and 10 μg/m^3), interquartile range (20.5 μg/m^3), and median $PM_{2.5}$ exposure. Models were fitted from DLM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLM, Distributed Lag Model; RR, Relative Risk; CI, confidential interval; LCI and UCI, 95% lower and upper confidence intervals; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm.

Table S6.2 Cumulative monthly adjusted relative risk for the distributed lag linear association between $PM_{2.5}$ exposure at 5,10, 20.5, and 23.3 μg/m^3 increase and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 0-9) across 260 local districts in Ghana, 2012–2020.

Lag month	5 μg/m^3			10 μg/m^3			20.5 μg/m^3			23.3 μg/m^3		
	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
0	1.002	0.997	1.006	1.003	0.995	1.012	1.006	0.989	1.024	1.007	0.988	1.027
0-1	1.001	0.994	1.008	1.002	0.988	1.017	1.004	0.975	1.034	1.005	0.972	1.039
0-2	1.003	0.992	1.013	1.006	0.985	1.026	1.011	0.970	1.055	1.013	0.966	1.063
0-3	1.005	0.992	1.018	1.009	0.983	1.036	1.019	0.966	1.075	1.021	0.961	1.085
0-4	1.003	0.988	1.018	1.006	0.975	1.037	1.011	0.950	1.076	1.013	0.944	1.087
0-5	1.002	0.985	1.019	1.003	0.969	1.038	1.007	0.938	1.080	1.008	0.930	1.092
0-6	1.005	0.986	1.025	1.011	0.973	1.050	1.022	0.945	1.106	1.025	0.937	1.121
0-7	1.007	0.985	1.028	1.013	0.971	1.057	1.027	0.942	1.121	1.031	0.934	1.139
0-8	1.003	0.980	1.027	1.006	0.961	1.054	1.013	0.921	1.115	1.015	0.910	1.131
0-9	1.003	0.978	1.028	1.005	0.956	1.057	1.011	0.913	1.120	1.013	0.901	1.138

Note: The $PM_{2.5}$ exposure increments were the World Health Organization air quality guidelines (5 and 10 μg/m^3), interquartile range (20.5 μg/m^3), and median $PM_{2.5}$ exposure. Models were fitted from DLM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLM, Distributed Lag Model; RR, Relative Risk; CI, confidential interval; LCI and UCI, 95% Lower and Upper Confidence Intervals; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm.

Table S6.3 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds with reference to 5 µg/m^3 and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020.

Lag month	P1 (9.9 µg/m^3)			P5 (12.2 µg/m^3)			P50 (23.3 µg/m^3)			P90 (57.8 µg/m^3)			P95 (67.7 µg/m^3)			P99 (86 µg/m^3)		
	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
0	0.977	0.949	1.005	0.967	0.928	1.007	0.938	0.868	1.015	0.991	0.910	1.080	0.997	0.916	1.086	0.980	0.876	1.095
1	0.988	0.963	1.014	0.983	0.948	1.020	0.975	0.908	1.047	0.999	0.920	1.085	0.978	0.900	1.063	0.975	0.874	1.088
2	1.010	0.987	1.034	1.015	0.981	1.049	1.027	0.963	1.095	1.069	0.990	1.155	1.059	0.979	1.146	1.047	0.947	1.158
3	1.011	0.986	1.036	1.016	0.981	1.052	1.028	0.960	1.101	1.074	0.992	1.163	1.060	0.979	1.148	1.066	0.963	1.180
4	0.996	0.969	1.024	0.994	0.956	1.034	0.994	0.921	1.072	1.005	0.920	1.097	0.979	0.897	1.068	0.985	0.880	1.102
5	1.010	0.984	1.038	1.015	0.977	1.054	1.025	0.952	1.104	1.036	0.951	1.129	1.046	0.961	1.139	0.994	0.892	1.107
6	1.022	0.997	1.047	1.031	0.996	1.067	1.060	0.991	1.133	1.111	1.029	1.200	1.088	1.008	1.175	1.166	1.060	1.283
7	1.022	0.999	1.045	1.032	0.999	1.065	1.064	1.000	1.131	1.090	1.013	1.173	1.084	1.006	1.167	1.021	0.928	1.123
8	1.018	0.993	1.043	1.025	0.990	1.062	1.049	0.980	1.122	1.025	0.946	1.110	1.057	0.975	1.147	0.851	0.763	0.949
9	1.013	0.986	1.041	1.019	0.979	1.060	1.034	0.958	1.116	1.025	0.943	1.114	1.007	0.926	1.094	1.082	0.971	1.206

Note: Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; LCI and UCI, 95% Lower and Upper Confidence Intervals; P1-P99, 1st -99th centiles; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

Table S6.4 Cumulative monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds with reference to 5 μg/m^3 and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 0- 9) across 260 local districts in Ghana, 2012–2020.

Lag month	P1 (9.9 μg/m^3)			P5 (12.2 μg/m^3)			P50 (23.3 μg/m^3)			P90 (57.8 μg/m^3)			P95 (67.7 μg/m^3)			P99 (86 μg/m^3)		
	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
0	0.977	0.949	1.005	0.967	0.928	1.007	0.938	0.868	1.015	0.991	0.910	1.080	0.997	0.916	1.086	0.98	0.876	1.095
0-1	0.965	0.926	1.005	0.950	0.896	1.008	0.915	0.816	1.025	0.990	0.868	1.130	0.975	0.854	1.114	0.955	0.807	1.132
0-2	0.975	0.924	1.028	0.964	0.893	1.041	0.939	0.808	1.092	1.059	0.885	1.267	1.033	0.861	1.240	1.000	0.798	1.255
0-3	0.985	0.922	1.054	0.979	0.89	1.078	0.965	0.798	1.167	1.138	0.907	1.426	1.096	0.870	1.379	1.066	0.807	1.409
0-4	0.982	0.907	1.063	0.974	0.869	1.092	0.960	0.765	1.204	1.143	0.873	1.496	1.072	0.817	1.407	1.050	0.760	1.450
0-5	0.992	0.906	1.085	0.988	0.868	1.125	0.984	0.759	1.275	1.184	0.870	1.612	1.122	0.823	1.530	1.043	0.726	1.499
0-6	1.013	0.917	1.120	1.019	0.883	1.177	1.042	0.781	1.391	1.316	0.933	1.857	1.221	0.864	1.725	1.217	0.813	1.819
0-7	1.035	0.928	1.155	1.051	0.899	1.230	1.108	0.808	1.520	1.435	0.985	2.090	1.323	0.906	1.931	1.242	0.798	1.935
0-8	1.054	0.937	1.184	1.078	0.911	1.276	1.162	0.828	1.631	1.470	0.982	2.201	1.399	0.930	2.103	1.057	0.652	1.714
0-9	1.068	0.942	1.209	1.098	0.918	1.314	1.202	0.837	1.725	1.507	0.981	2.314	1.408	0.913	2.173	1.144	0.683	1.917

Note: Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; LCI and UCI, 95% Lower and Upper Confidence Intervals; P1-P99, 1st -99th centiles; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm.

Table S6.5 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds with reference to 10 μg/m^3 and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 0- 9) across 260 local districts in Ghana, 2012–2020.

Lag month	P1 (9.9 μg/m^3)			P5 (12.2 μg/m^3)			P50 (23.3 μg/m^3)			P90 (57.8 μg/m^3)			P95 (67.7 μg/m^3)			P99 (86 μg/m^3)		
	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
0	1.000	1.000	1.001	0.990	1.002	0.979	0.961	0.914	1.01	1.016	0.952	1.083	1.022	0.957	1.091	1.004	0.909	1.107
1	1.000	1.000	1.001	0.995	1.006	0.985	0.987	0.943	1.033	1.011	0.949	1.078	0.990	0.927	1.058	0.987	0.895	1.089
2	1.000	0.999	1.000	1.004	1.014	0.995	1.016	0.975	1.059	1.058	0.995	1.125	1.049	0.984	1.118	1.036	0.947	1.135
3	1.000	0.999	1.000	1.004	1.015	0.994	1.017	0.973	1.062	1.062	0.998	1.131	1.049	0.983	1.118	1.054	0.962	1.154
4	1.000	1.000	1.001	0.999	1.010	0.987	0.998	0.951	1.048	1.009	0.942	1.080	0.983	0.917	1.053	0.989	0.894	1.093
5	1.000	0.999	1.000	1.004	1.015	0.993	1.014	0.967	1.064	1.025	0.959	1.097	1.035	0.967	1.109	0.983	0.893	1.083
6	1.000	0.999	1.000	1.009	1.019	0.999	1.037	0.993	1.082	1.087	1.024	1.155	1.065	1.001	1.132	1.141	1.048	1.243
7	1.000	0.999	1.000	1.009	1.018	1.000	1.040	1.000	1.082	1.067	1.006	1.131	1.060	0.998	1.126	0.999	0.917	1.089
8	1.000	0.999	1.000	1.007	1.018	0.997	1.030	0.986	1.075	1.006	0.945	1.072	1.039	0.972	1.109	0.836	0.757	0.923
9	1.000	0.999	1.000	1.005	1.017	0.994	1.020	0.972	1.071	1.011	0.949	1.078	0.993	0.931	1.060	1.068	0.969	1.176

Note: Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; LCI and UCI, 95% Lower and Upper Confidence Intervals; P1-P99, 1st -99th centiles; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm.

Table S6.6 Cumulative monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds with reference to 10 $\mu g/m^3$ and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 0-9) across 260 local districts in Ghana, 2012–2020.

Lag month	P1 (9.9 $\mu g/m^3$)			P5 (12.2 $\mu g/m^3$)			P50 (23.3 $\mu g/m^3$)			P90 (57.8 $\mu g/m^3$)			P95 (67.7 $\mu g/m^3$)			P99 (86 $\mu g/m^3$)		
	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
0	1.000	1.000	1.001	0.990	0.979	1.002	0.961	0.914	1.010	1.016	0.952	1.083	1.022	0.957	1.091	1.004	0.909	1.107
0-1	1.001	1.000	1.001	0.986	0.969	1.002	0.949	0.882	1.020	1.027	0.928	1.137	1.012	0.910	1.124	0.991	0.852	1.153
0-2	1.000	0.999	1.002	0.99	0.968	1.012	0.964	0.875	1.062	1.087	0.944	1.252	1.061	0.915	1.230	1.027	0.838	1.258
0-3	1.000	0.999	1.002	0.994	0.967	1.022	0.980	0.867	1.108	1.155	0.966	1.381	1.112	0.922	1.341	1.082	0.844	1.388
0-4	1.000	0.999	1.002	0.993	0.960	1.026	0.978	0.844	1.133	1.165	0.941	1.441	1.093	0.877	1.362	1.070	0.803	1.425
0-5	1.000	0.998	1.002	0.997	0.960	1.035	0.992	0.838	1.175	1.194	0.935	1.525	1.132	0.880	1.455	1.052	0.763	1.450
0-6	1.000	0.998	1.002	1.006	0.964	1.049	1.028	0.851	1.242	1.299	0.988	1.706	1.205	0.910	1.594	1.200	0.842	1.713
0-7	0.999	0.997	1.001	1.015	0.969	1.062	1.070	0.870	1.315	1.385	1.028	1.866	1.277	0.939	1.736	1.199	0.811	1.774
0-8	0.999	0.997	1.001	1.022	0.973	1.074	1.102	0.883	1.375	1.394	1.012	1.921	1.326	0.951	1.849	1.002	0.653	1.539
0-9	0.999	0.996	1.001	1.028	0.975	1.083	1.124	0.888	1.424	1.410	1.003	1.981	1.317	0.925	1.875	1.070	0.677	1.692

Note: Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; LCI and UCI, 95% Lower and Upper Confidence Intervals; P1-P99, 1^{st} -99^{th} centiles; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

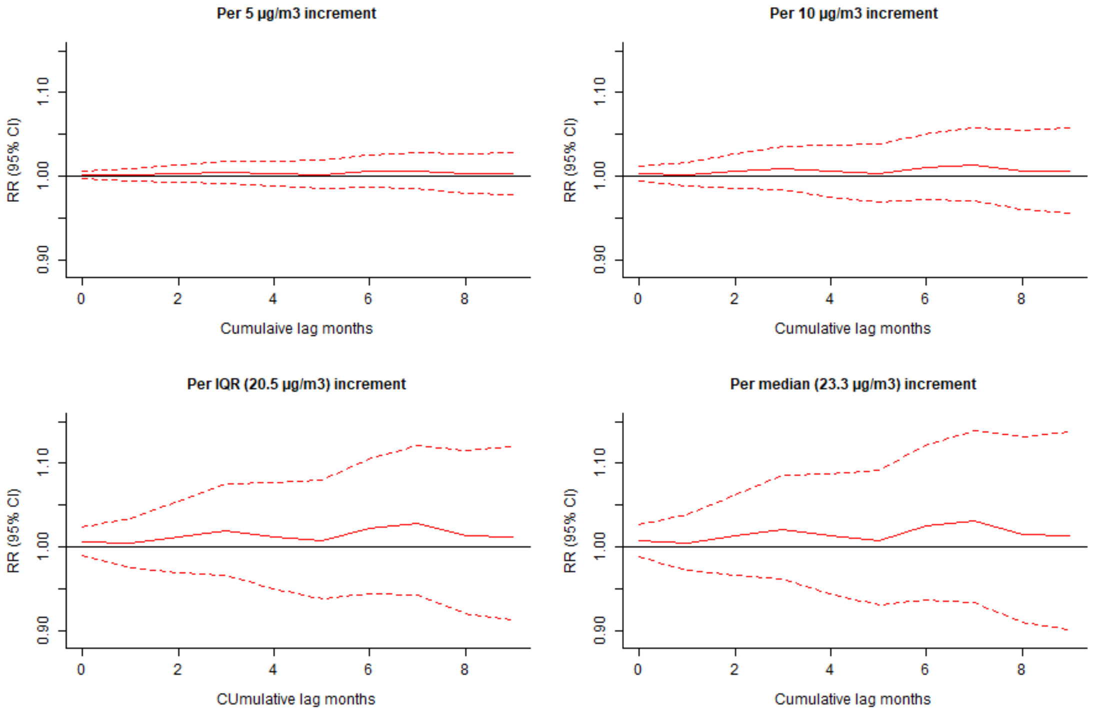

Figure S6.1 Cumulative monthly adjusted relative risks for the distributed lag linear association between $PM_{2.5}$ exposure at 5,10, 20.5, and 23.3 µg/m^3 increase and risks of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 0-9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Models were fitted from DLM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLM, Distributed Lag Model; RR, Relative Risk; CI, confidential interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

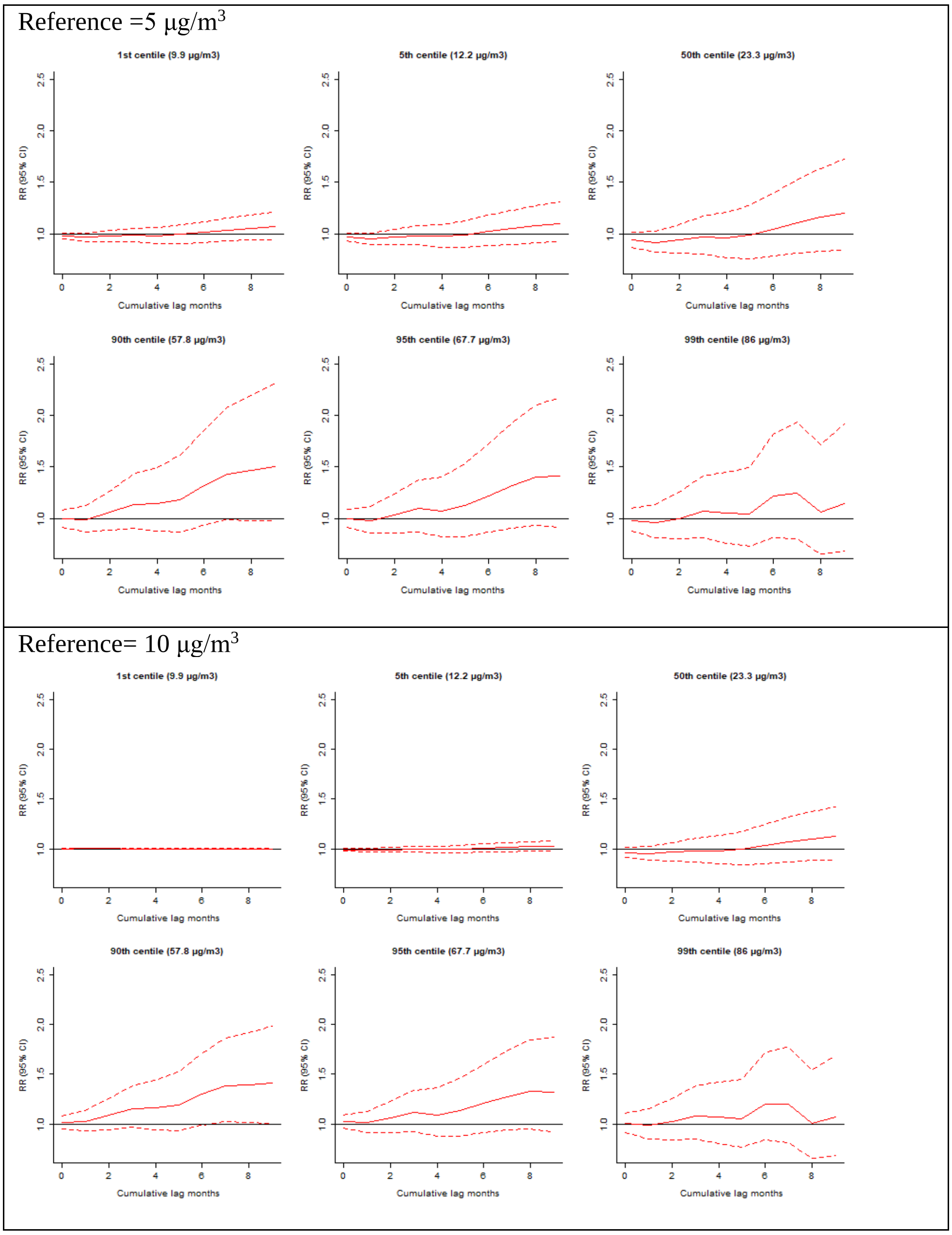

Figure S6.2 Cumulative monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 µg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 0-9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

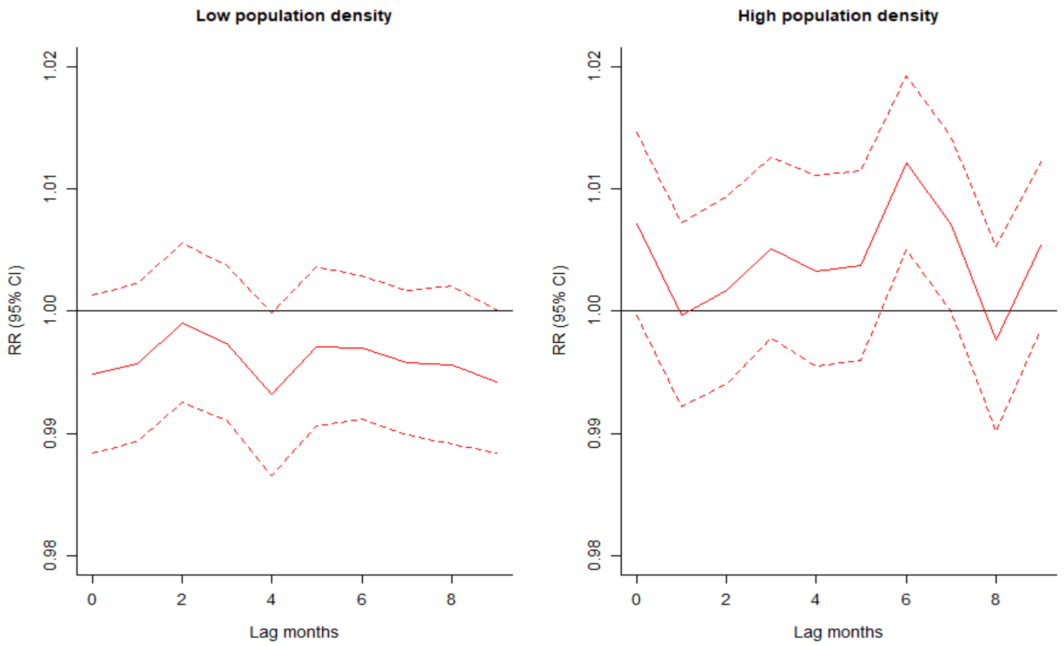

Figure S6.3 Monthly adjusted relative risks for the distributed lag linear association between $PM_{2.5}$ exposure at 5 μg/m^3 increase and risks of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) by low/high population density across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Models were fitted from DLM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, and Gross Domestic Product. Note: DLM, Distributed Lag Model; RR, Relative Risk; CI, confidential interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm.

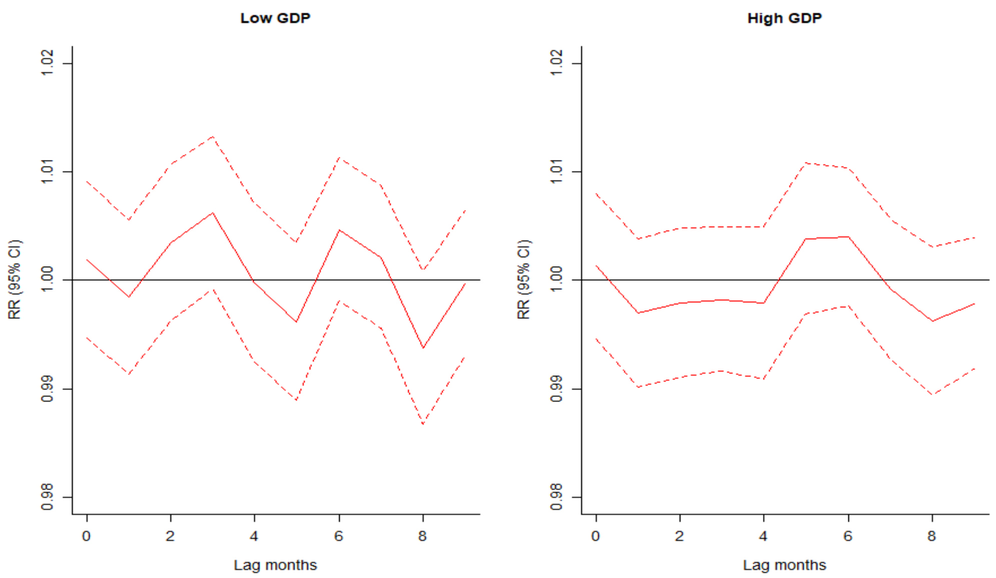

Figure S6.4 Monthly adjusted relative risks for the distributed lag linear association between $PM_{2.5}$ exposure at 5 μg/m^3 increase and risks of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) by low/high GDP across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Models were fitted from DLM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, and population density. Note: DLM, Distributed Lag Model; RR, Relative Risk; CI, confidential interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm; GDP, Gross Domestic Product.

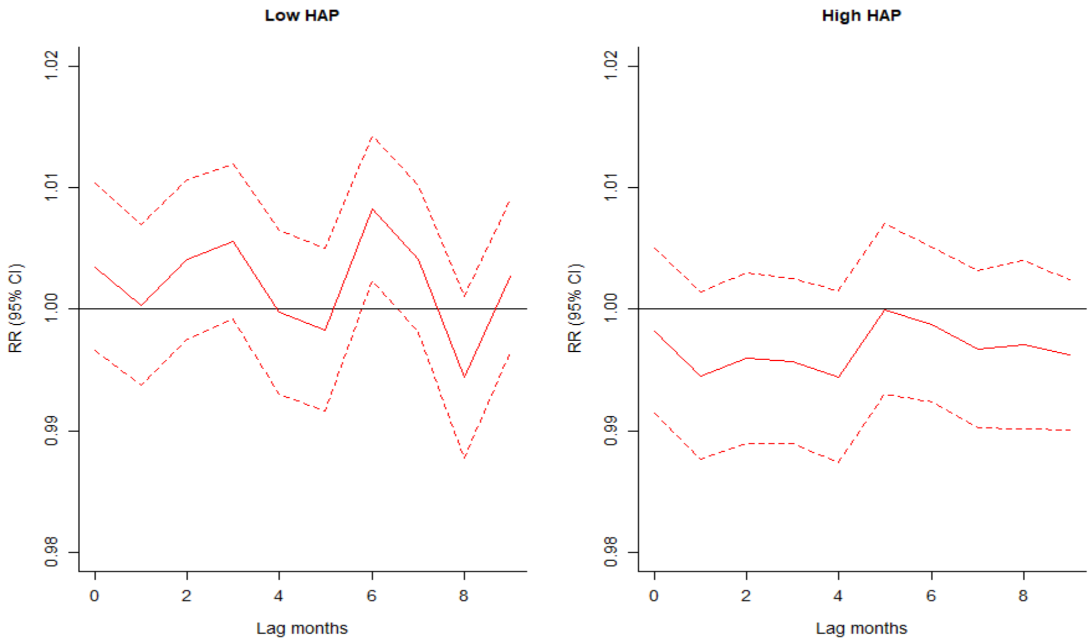

Figure S6.5 Monthly adjusted relative risks for the distributed lag linear association between $PM_{2.5}$ exposure at 5 μg/m^3 increase and risks of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) by low/high HAP across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Models were fitted from DLM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), and Gross Domestic Product, and population density. Note: DLM, Distributed Lag Model; RR, Relative Risk; CI, confidential interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm; HAP, household or indoor air pollution.

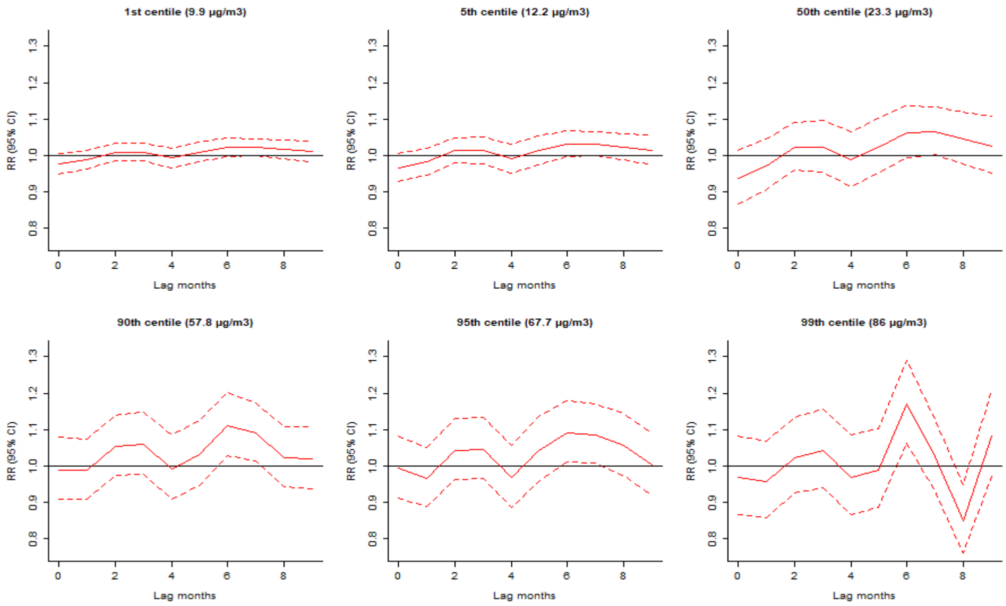

Figure S6.6 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 μg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. The *degree of freedoms* for cross-basis matrix of UTCI were increased by one as 4 for both dimensions. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm.

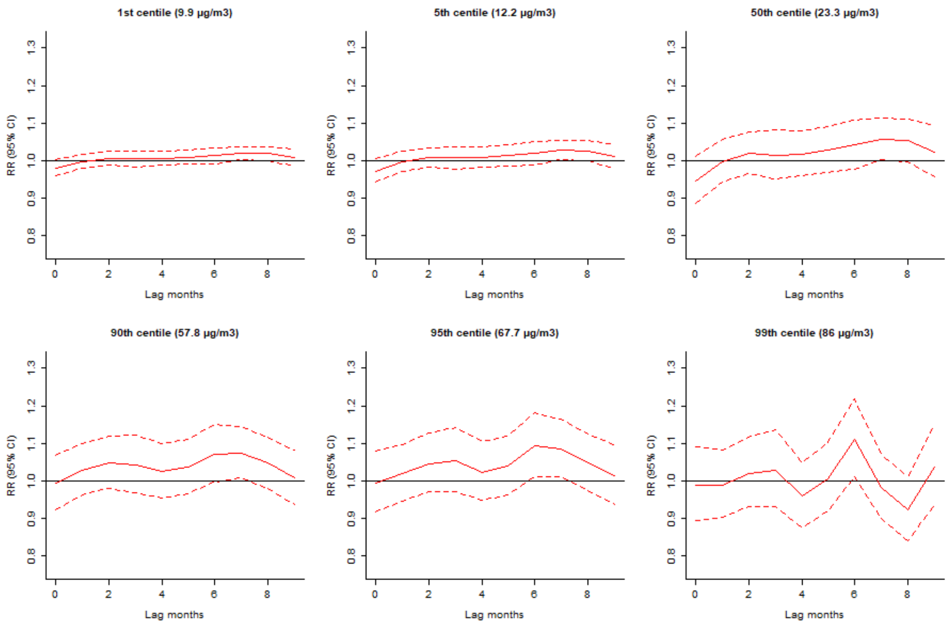

Figure S6.7 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 μg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. The *degree of freedoms* for cross-basis matrix of $PM_{2.5}$ were decreased by one as 6 for both dimensions. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

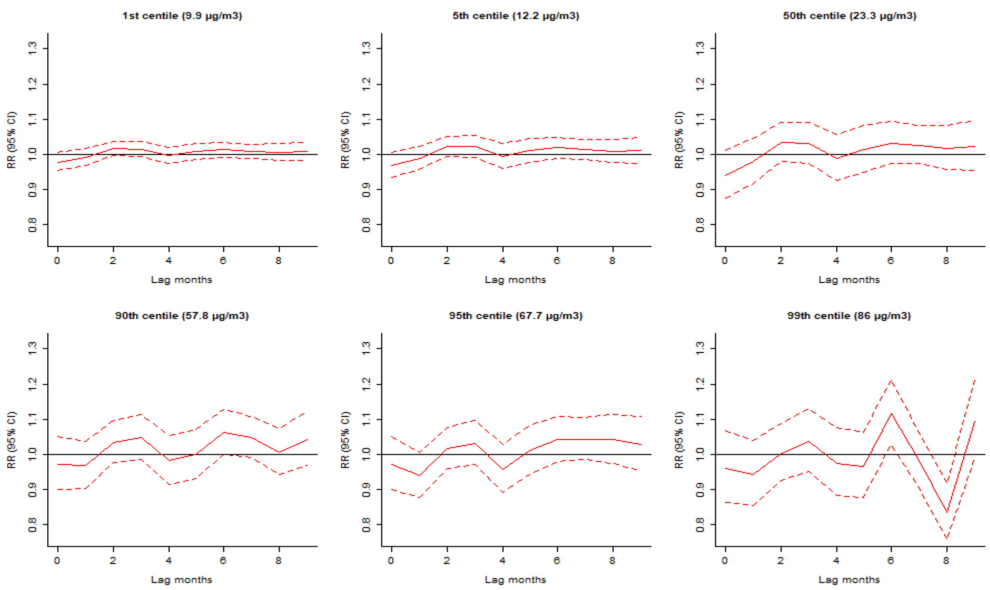

Figure S6.8 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 μg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. The natural splines of continuous number of months over the study period was replaced with a year index factor variable to control for long-term trends as inter-annual variability. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, year index factor, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

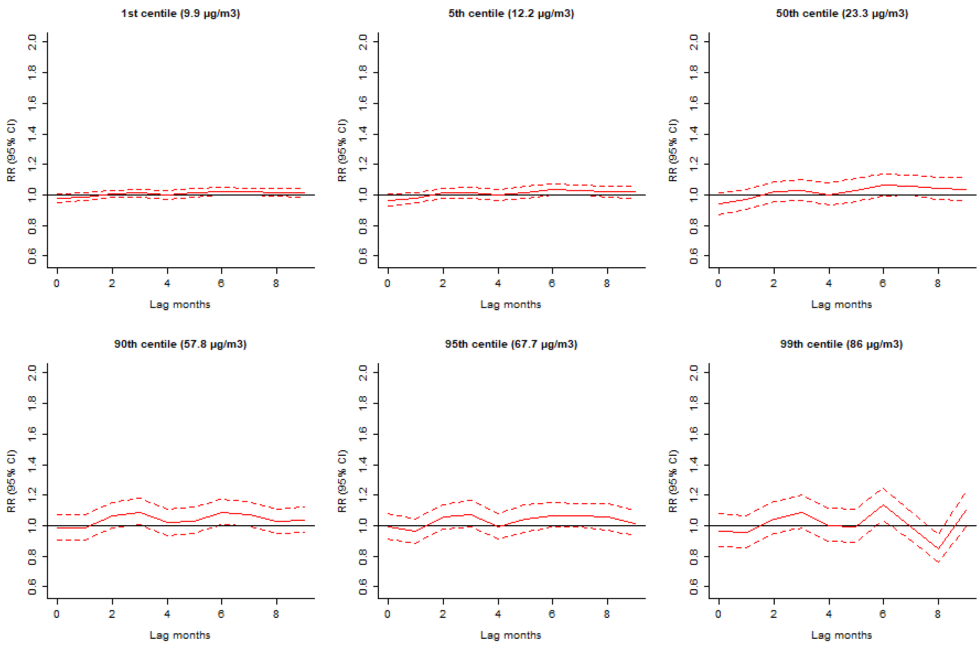

Figure S6.9 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 μg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Month of birth was replaced by season of birth. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for season of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

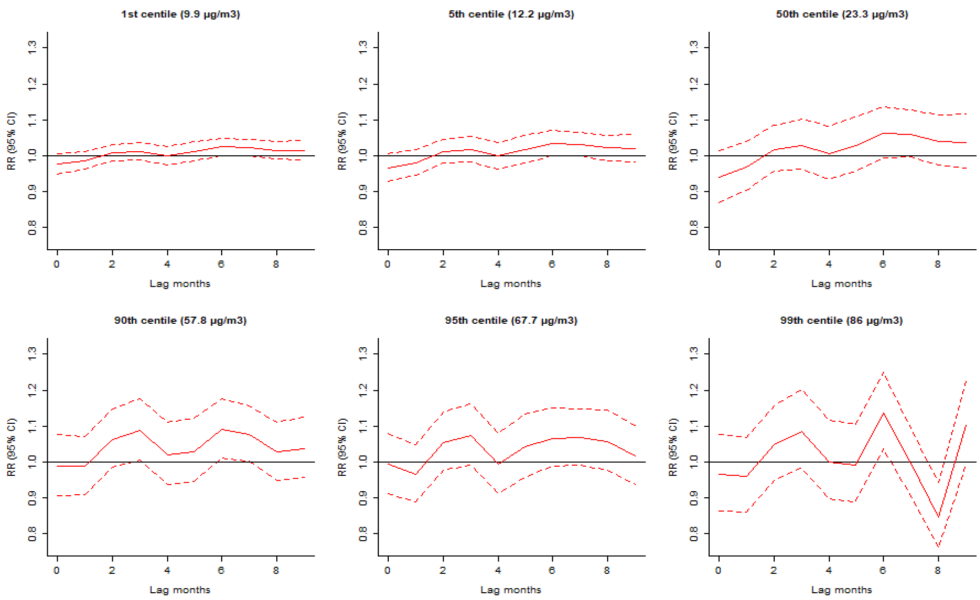

Figure S6.10 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 μg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. Month of birth was excluded. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

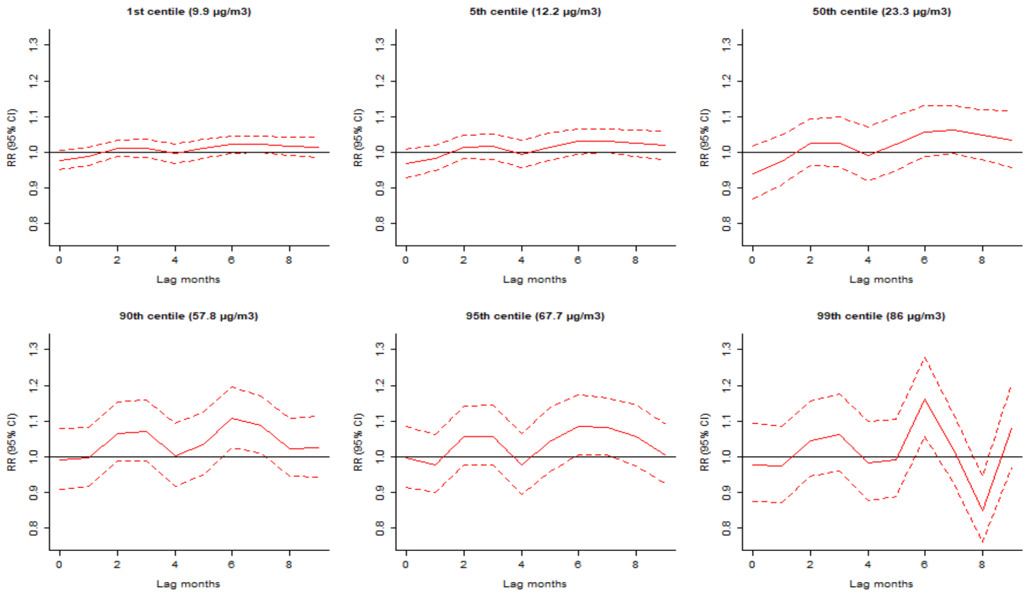

Figure S6.11 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 μg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. GDP and population density were entered as linear instead of natural splines for non-linearity. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm.

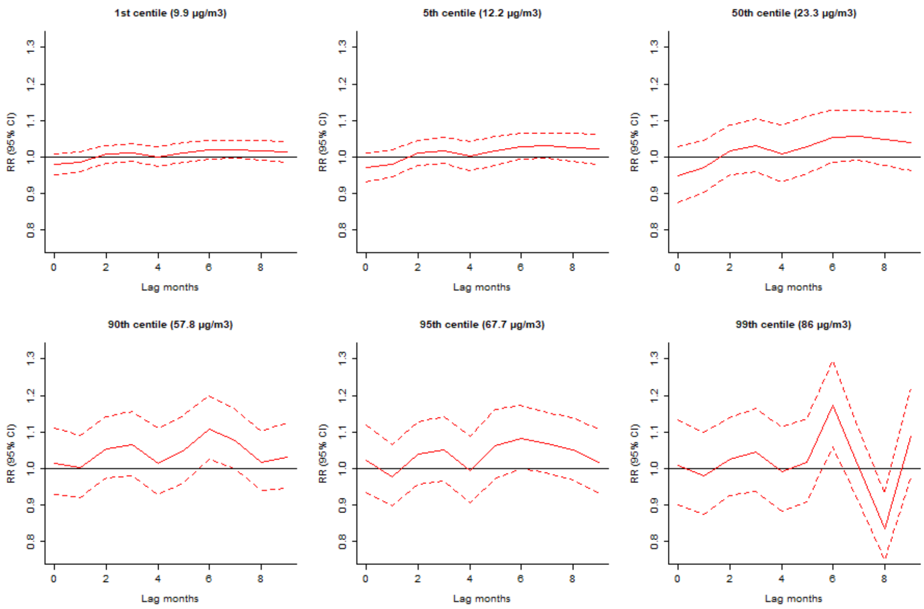

Figure S6.12 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 μg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. The degree of freedom for natural splines of continuous number of months over the study period was increased 5 per year instead of 4 per year. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 μm.

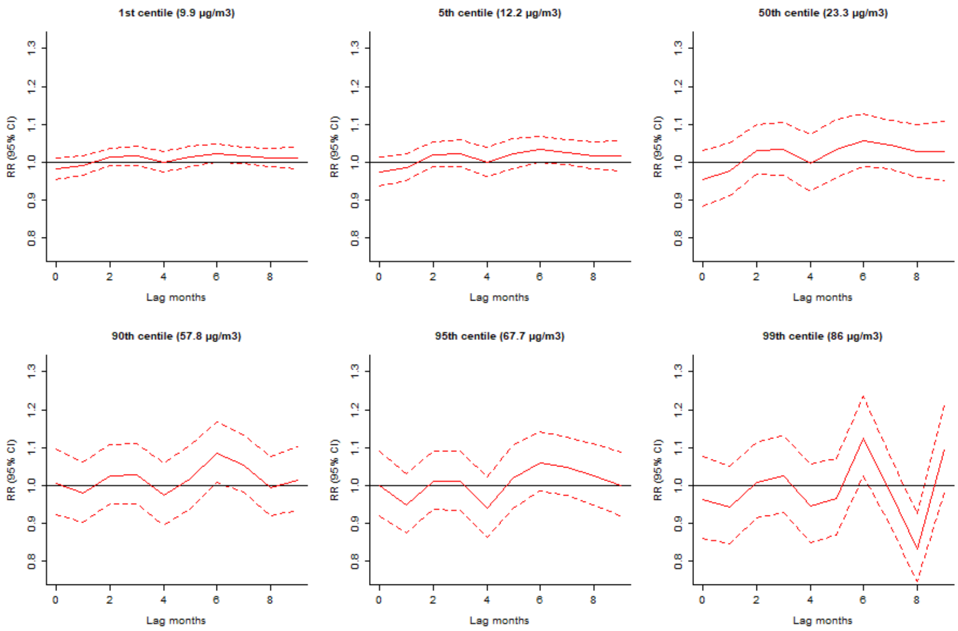

Figure S6.13 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 µg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. The Universal Thermal Climate Index was not adjusted for. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

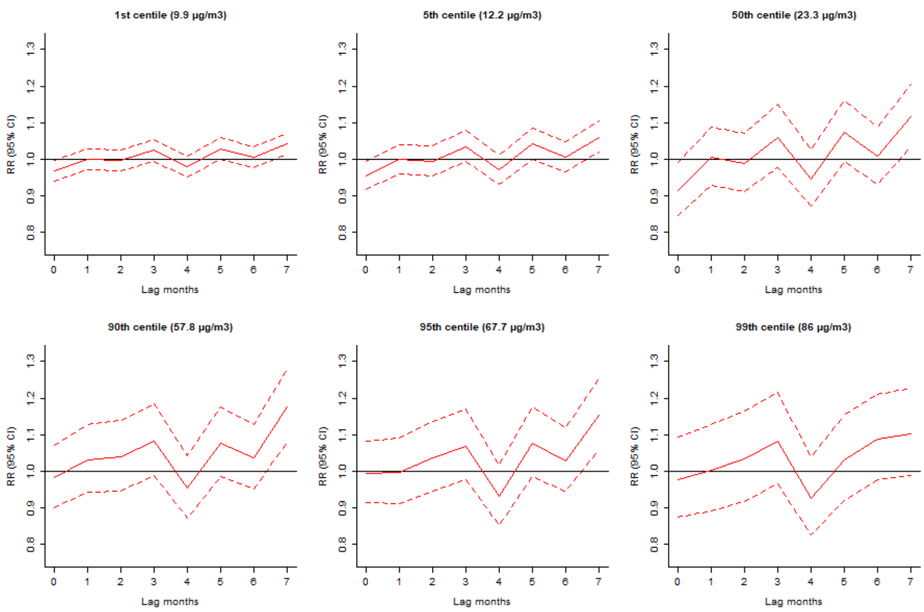

Figure S6.14 Monthly adjusted relative risk for the distributed lag non-linear association between $PM_{2.5}$ exposure at different $PM_{2.5}$ thresholds using 5 and 10 µg/m^3 as references and risk of stillbirth from the month of stillbirth (lag 0) to the past nine months of exposure (lag 9) across 260 local districts in Ghana, 2012–2020. Solid red lines represent RRs, and the broken lines represent 95% CIs. The maximum lag period was set to seven instead of nine. Models were fitted from DLNM conditional quasi-Poisson regression models with adjustment for month of birth, natural splines of continuous number of months over the study period, Universal Thermal Climate Index, percentages of fetal sex (male and female) and maternal age at delivery (10-19, 20-34, and ≥ 35 years), household air pollution, Gross Domestic Product, and population density. Note: DLNM, Distributed Lag Non-linear Model; RR, Relative Risk; CI, Confidential Interval; $PM_{2.5}$, Particulate Matter at aerodynamic diameter ≤2.5 µm.

Appendix E. Supplementary materials for Chapter 7

Table S7.1 Articles excluded after full-text assessment with reasons.

	Excluded review after full-text assessment	Reasons for exclusion
1	Anderko et al 2020	General literature review (not systematic review), no method section with specification of in/exclusion criteria, no specification of search terms and database searched, and clear reporting on the findings with details on included primary studies.
2	Arbuthnott et al 2017	General literature review (not systematic review). No clearly specified search strategy with key search terms in a database, either in the text or/and the additional file.
3	Martiello and Giacchi, 2010	Unrelated outcome of interest
4	Kloog 2019	General literature review (not systematic review). No method section, no in/exclusion criteria, no specification of search terms and database searched.
5	Segal et al 2022	General literature review (not systematic review). No method section, no in/exclusion criteria, no specification of search terms and database searched.
	Ha, 2022	General literature review (not systematic review). No method section, no in/exclusion criteria, no specification of search terms and database searched.
6	Chersich et al 222	General literature review (not systematic review). No method section, no in/exclusion criteria, no specification of search terms and database searched.
7	Dalugoda et al 2022	Scoping review with no details or data on the individual included primary studies.
8	Syed et al 2022	Scoping review with no details or data on the individual included primary studies.

Table S7.2. Additional information on systematic reviews on ambient air temperature and adverse birth outcomes, ordered from recent to earliest.

First author, date [number of authors, countries]	Birth outcomes	Summary of results	Researchers' recommendations	Researchers' stated strengths and limitations	Key findings/conclusion in abstract
i. Sexton[38] Sexton, 26/03/2021 [6; all Australia]	SB	12 studies: 3,461,823 births or pregnancies. Despite using a variety of statistical and methodological approaches for exposure assessments, exposure windows, and data linkage, all studies reported associations of increased risk of stillbirth with ambient temperature exposures throughout pregnancy, particularly in late pregnancy. Overall, risk of stillbirth was observed to increase below 15 ◦C and above 23.4 ˚C, where highest risk is above 29.4 ˚C.	Lifestyle factors, pre-existing and pregnancy-related health conditions, and other environmental indicators for quality of life should be considered in future studies. Ambient temperature exposure and other environmental exposures should be further investigated and considered for risk modelling and risk management during pregnancy as a strategy to reduce stillbirth. In the context of temperature exposure, the roles of other socioeconomic, lifestyle, and clinical factors should be further evaluated. To fully understand the effects of maternal exposure to ambient temperatures, future studies should focus on biological mechanisms and contributing factors in addition to improving measurement of ambient temperature exposure.	**Limitations** The studies included in the review are potentially vulnerable to publication and reporting bias. Study results are further limited by a lack of meta-analysis to estimate effective size ambient temperature exposure and stillbirth or variation of effects assessment to quantify the variability of results. The studies included in this review are heterogenous: High variability in model selection and statistical methods was observed. Lastly, no study considered important potential confounders such as maternal pregnancy conditions, sleep position during pregnancy (Gordon et al., 2015), personal movement patterns, home environment, variation in type of ambient temperature exposure, or food	All studies reported associations of increased risk of stillbirth with ambient temperature exposures throughout pregnancy, particularly in late pregnancy. One study estimates 17–19% (PAR) of stillbirths are potentially attributable to chronic exposure to hot and cold ambient temperatures during pregnancy. Overall, risk of stillbirth was observed to increase below 15 ◦C and above 23.4 ◦C, where highest risk is above 29.4 ◦C. Exposure to hot and cold temperatures during pregnancy may increase the risk of stillbirth, although a clear causative mechanism remains unknown. Despite lack of causal evidence, existing evidence across diverse settings observed similar effects of increased risk of stillbirth using a variety of statistical and methodological approaches for exposure assessments, exposure windows, and data linkage. Managing exposure to ambient temperatures during pregnancy could potentially decrease risk of

				access indicators in any statistical model.	stillbirth, particularly among women in low-resource settings where access to safe antenatal and obstetric care is challenging.
ii. Chersich [39] 04/11/2020 [11; 5 South Africa, 2 Australia, 1 Germany, 2 Ireland,1 Lodon/UK]	PTB, LBW, BW, SB	**Meta-analysis** **PTB** *high vrs low temperatures (at whole pregnancy or trimester)* 9 studies (8 time series and 1 time series with case-crossover; 4,327,821 births). RE pooled OR = 1.14 (1.11 to 1.16) I^2= 88.2%-high P=0.000 *Heatwaves vrs non-heatwaves days* 6 studies (5 time series and 1 case-crossover study; 1,211,581 births with unreported size for one time series study). RE pooled OR = 1.11 (1.10 to 1.23) I^2= 44.7%- low p= 0.11 *Odds per 1 degree increased in temp* 6 studies with 7 results as one study included two site-specific results (4 time series, 1 case-crossover and 1 time series with case-crossover; 736,719 births with unreported size for one case-crossover study). RE pooled OR = 1.05 (1.03 to 1.07) I^2= 87.7%- high p= 0.000 *high vrs low temp (periods ≤4weeks)* 21 studies with 29 results as 3 studies had more than one site-specific result (4 time series, 1 case-crossover and 1 time series with case-crossover; 40,940,531 births with unreported size for 3 studie). RE pooled OR = 1.01 (1.01 to 1.02) I^2= 89.8 %- high	'The review highlights the need for research to identify and study interventions to reduce problems due to heat among pregnant women. Standardising temperature metrics, lag durations, and subpopulation analyses in future studies would enable direct comparison between studies, identification of windows of vulnerability, and more robust estimates of overall size of associations. Standardisation could also reduce selective reporting of significant findings. Few studies examined whether temperature effects varied across subpopulations— critical evidence that would inform the targeting of specific groups of pregnant women. Many of these limitations could be overcome by an individual participant data meta-analysis that combined raw data from	**Strengths** The review included more studies than previous reviews and covered three outcomes, allowing comparisons among these outcomes and a more comprehensive assessment of heat sensitivity in pregnancy. **Limitations** Differences in the ways that temperature and lag measures were used meant that we had to develop decision rules for classifying temperature metrics and other variables. about a third of studies were of low quality, limiting analysis. Moreover, publication bias, multiple testing, and selective reporting of positive associations (eg, at different lag times) might have been common, as with all observational research.	In random effects meta-analysis, odds of a preterm birth rose 1.05-fold (95% confidence interval 1.03 to 1.07) per 1°C increase in temperature and 1.16-fold (1.10 to 1.23) during heatwaves. Higher temperature was associated with reduced birth weight in 18 of 28 studies, with considerable statistical heterogeneity. Eight studies on stillbirths all showed associations between temperature and stillbirth, with stillbirths increasing 1.05-fold (1.01 to 1.08) per 1°C rise in temperature. Associations between temperature and outcomes were largest among women in lower socioeconomic groups and at age extremes. Although summary effect sizes are relatively small, heat exposures are common and the outcomes are important determinants of population health. Linkages between socioeconomic status and study outcomes suggest that risks might be largest in low and middle income countries. Temperature rises with

		p= ---- **BW/LBW** **NB**: " No meta-analysis was done on any of the outcomes for birth weight given the marked variation in magnitude and direction of effect. We also did not present a summary measure of changes in birth weight for each degree increase in temperature given the high levels of methodological diversity between these studies" **SB** *Exposure in last week of pregnancy* 4 studies (1 time series, 3 case-crossover; 2,138,017 births). RE pooled OR = 1.24 (1.12 to 1.36) I^2= 53.1%- moderate with p= 0.094 *Exposure in whole pregnancy or trimester* 2 studies (a time series and times series with case-crossover; 512,726 births). RE pooled OR = 3.39 (2.33 to 4.96) I^2= 27.8%- low with p= 0.239 *per degree increase in temp* 3 studies (2 case-crossover and 1 time series with case-crossover; 232,594 births). RE pooled OR = 1.04 (1.01 to 1.08) I^2= 81.3%-high p= 0.005 **Sensitivity** An analysis that excluded a study in Shenzhen, China that reported a protective effect of high temperatures,46 reduced the heterogeneity, but the overall estimate was similar. **Publication bias** No test **<u>Narrative synthesis</u>**	several studies in a single analysis. The application of data science methodologies, such as machine learning, could also offer new opportunities to advance knowledge on this topic, and the association of heat exposure with health more generally. Importantly, potential confounding by air pollution could occur, and future reviews need to explicitly examine this problem. Future reviews might consider stratifying analyses by use of air conditioning, for example.		global warming could have major implications for child health.

		PTB and Temp/heat The median preterm birth rate of the included studies was 5.6% (interquartile range 5.0 to 7.9; range 2.6 to 15.5. Out of 47 studies on PTB (41 time series, 5 case-crossover, 1 for both studies; 56,324,738 births with unreported size for 6 studies), 40 studies documented an association between high temperatures and PTB. The median odds ratio for preterm birth after exposure to high temperatures over short periods (<4 weeks) was 1.07 (interquartile range 1.05 to 1.16) Positive associations were detected in all lag windows, including five with heat exposure in the month of conception and one for preconception. 5 studies from LMICs found increased risk in the 1st and 2nd trimester, and 3 studies for in the last week of pregnancy. In EU and Central Asian regions; only one found increased risk in 1st trimester, 8 studies in last week (most at lag0 to 3 days to birth). In North America, only 2 studies noted associations in the 1st or 2nd trimester while 6 studies noted for last week of pregnancy. **No association**: 6 studies reported no association, 3 of which were of low quality. One study (in Brisbane, Australia) reported and found no association between heat exposure and gestation length but detected association in a dichotomised outcome as PTB. One study in Shenzhen, China (1,040,638 births with PTB=58,411) reported protective effect and another in northern California (PTB=14,466 births) found lowest effect sizes in the areas that had the highest use of air conditioning. 5 studies found high risk of PTB with diurnal fluctuations or/and high night time temperature. **Age group**: Stratified by age group in 11 studies, 7 studies found higher risks in young women (under			

		25 years) in 2 studies found for older women (above 35 years). **SES**: 6 studies reported and found higher risk in low socioeconomic groups. **Race/ethnicity**: Higher risk in black or Hispanic than the whites (4 studies in USA), in indigenous coastal women than non-indigenous women (a study in Australia) **Neonate's sex**: Out of 9 studies, 6 found higher risk in females than males. **Maternal medical condition**: 3 studies reported and found higher risk in women with chronic conditions such as diabetes, depression. **Change over time**: Only one study in Brisbane, Australia reported and found lower hazard ratio in 2013 than 1994 for the same temp exposure. **LBW/BW** 28 studies (26 time series, 1 case-control and 1 time series with case-crossover; 45,191,630 births with unreported in 2 studies). 18 of 28 studies which assessed birth weight found an association. The median rate of LBW weights in the included studies was 3.0% (interquartile range 1.8 to 6.4). Out of 16 studies for LBW, 10 reported increased risk at higher temperatures, only 1 reported the contrary, and 5 had null findings. The median of the observed effect estimates of high temperatures on odds of LBW was 1.09 (interquartile range 1.04 to 1.47). For BW as continuous variable and temp, out of 19 studies, 12 found reduction in BW at higher temperatures, including 2 studies where the direction of effect varied by trimester, 3 studies found non-significant increased risk, and 4 found weight increased at higher temperatures (protective effect). Effects of temp on BW reduction was generally small, mostly less than 10g per change in degree or under 20g for high vrs low temperature.			

		Small changes in BW in LMICs (2 studies). For studies showing significant association, reduced BW is higher in women with less/equal to 22 or above 40 years. **SB** 8 studies (4 time series, 3 case-crossover and 1 for both; 3,029,746 births). The median stillbirth rate was 6.2 per 1000 births (interquartile range 4.4 to 6.4) All 8 included studies found an increase in stillbirths at higher temperatures and most pronounced in the last week or month of pregnancy. None of the 8 studies were done in LMICs. One study each reported and found higher risk in term than preterm stillbirths, higher risk in black and Hispanic than white women, in younger women, in male fetuses, and reduction over time. Only one study reported and found similar association between singleton and multiple pregnancies.			
iii. Bekkar[4] 18/06/2020 [4, all USA]	PTB, LBW, SB	**PTB** 5 studies; 1 cross-sectional, 4 case-crossover (697,352 births from the 2 studies, 87613 PTB cases from the other 3 studies). Myriad exposure periods and metric were explored even in a single study such as few days/weeks before birth, few/last month, entire pregnancy in 2 studies. Heat-PTB association was significant in 4/5 (80%) studies from birth per study of mean (standard deviation) as 192 625 (207 995) with total births of 0.8 million, increased risk median (range) of 15.8 (9.0-22.0). **LBW** 3 studies; a study each for cohort, case-crossover, and cross-sectional (2,750,460 births) The 3 studies reported for entire pregnancy; 2 found significant increased risk and 1 found non-significant increased risk with high temperature/heat. One study additionally reported significant increased risk with cold temp for 2nd	'The medical community at large and women's health clinicians in particular should take note of the emerging data and become facile in both communicating these risks with patients and integrating them into plans for care. Moreover, physicians can adopt a more active role as patient advocates to educate elected officials entrusted with public policy and insist on effective action to stop the climate crisis.'	**Strengths:** the considerable sample size and the wide geographic range that includes every region of the US domestic population; focus on the US population makes the findings particularly relevant to pregnant women and health care clinicians in the US; the merit of tabulating the overall preponderance of observations from varying studies examining the same outcomes where	

		and 3rd trimesters. One study also reported significant reduction in BW in 3rd trimester. **SB** 2 case-crossover studies; 223,375 births in a cohort with case-crossover design and 8,510 stillbirth cases in a time-stratified case-crossover. Both studies reported significant increased risk of heat for entire pregnancy or week before birth. **Subgroups** Significant race/ethnic disparity in 2/4 (50%) studies with higher risk among black mothers in 2 studies and Asian mothers in one study. Heat with LBW; increased risk of high temperature in 3rd trimester in each study (3/3, 100%), one study also reported increased risk of extreme cold in 2nd and 3rd trimester, significant race/ethnic disparity in 1/3 (33%) studies. Heat with SB; significant risk in minority racial/ethnic group in 2/2 (100%) studies.		pooled analysis across studies is not feasible. Limitations: this review covers only observational studies with heterogeneous sources of air pollution and heat exposure as well as diverse methods of measurement; different study designs may complicate direct comparison of the data even within a single study; limited number of studies on stillbirth.	
iv. Kuehn[40] 29/07/2017 [2; both USA]	PTB, ETB, LBW, BW, SB	**PTB** 17 studies; 4,591,684 births. Heat was significantly correlated with increased risk or rate of preterm birth in 15/17 studies (8 of these are for full gestation/entire pregnancy period and the rest for varied periods such as 1 week, 3 weeks, 4 weeks, 3 months prior to delivery); 2/17 studies found no significant effect (one each for full gestation and 1 week prior to delivery). A protective effect for full gestation was also found in one study of 1,040,638 births from Shenzhen, China. **Early term birth** 6 studies; 1,744,211 births. 5/6 six studies found excess heat exposure correlated with increased risk of early term birth (2/5 are for full gestation and 2 studies for 1 week prior to deliver, and another 4 weeks prior to delivery). The 6th study from NY, USA (514,104 births) found no association for full gestation. **LBW**	When considering the exaggerated impacts of heat, pregnant women must also be included as an at-risk class. Vulnerability and warnings should be specified to local context.	**Limitations** We only included articles that are written in English. Several studies report effect modification by socioeconomic factors, such as race, income, and profession, these factors are not included in analysis universally in the data sets. There is a widespread lack of information regarding home air conditioning access, or other resources that serve as mitigating factors in heat exposure. This review of the literature is not a meta-	

		5 studies; 1,133,067 births. All for full gestational exposure. 3/5 studies found significant correlations of increased heat exposure and LBW, and the remaining 2 studies found no significant risk. **Reduced BW** 7 studies; 2,621,806 births + unreported in Global study on 125 populations. All 7 studies reported on full gestation. 6/7 studies found significant negative correlations with birth weight at delivery. The 7th study from Sweden (13,657 births) found no significant risk. **SB** 3 studies; 115,527 births + one unreported by a study from Japan. 2/3 studies (one for 4 weeks prior to delivery and the other full gestation exposure) found increasing rates of stillbirth with increasing ambient temperatures. The 3rd study from Sweden (13,657 births) found no significant risk for full gestation exposure period.		analysis, and therefore cannot draw further statistical significance of heat impacts on birth outcomes beyond the findings of the original studies. **Strengths** Not stated specifically	
v. Zhang[41] 09/03/2017 [3, All China]	PTB/GA, LBW/BW, SB	**PTB/GA** (24 studies: 12 retrospective cohort 12 ecologic, mostly time series/case-crossover; 4,500,885 births with unreported for 6 studies) Despite the existence of great heterogeneity in terms of design, aims, temperature metrics, exposure periods, and statistical approach, 14 studies consistently found significant association between high ambient air temperature exposure during pregnancy and the occurrence of PTB in different climatic zones. Also, 4 studies found cold-related or both extreme cold and heat increased risks in PTB. 2 studies found significant protective effect of high temperatures on PTB occurrence. 4 studies found no association. One study also reported higher risk in the younger women, Blacks and Asians. **BW/LBW**	'More related studies are needed worldwide and should be conducted in more diversified climate zones, so as to further ascertain the association between temperature and birth outcomes. Future studies should focus on more sophisticated study designs with large samples, to produce more high-grade evidence based on scientific effect evaluation of extreme temperatures on birth outcomes. More accurate temperature exposure during pregnancy should	**Limitations** Great inconsistencies of included studies limited our ability to perform a meta-analysis for quantitative consolidation of the results.	

		(14 studies: 7 retrospective cohorts and 7 ecological which are mostly time series; 38,906,745 births with unreported in 4 studies) 8 studies found significant increased risk of high temperature on BW reduction. 2 studies with sample sizes of 3333 and 447,499 singleton live births each found lower temperature decreasing BW. weight (high temp is protective) 3 studies found no association (no effect) 1 study found non-significant increased risk of both cold and heat effects on LBW. Same gender effect reported in one study and racial disparity in another study. **SB** (4 studies; 3 retrospective cohort and 1 ecological time-series; 414,132 births) All the 4 studies found significant increased risk of stillbirth with high temperature. 1 study also reported and found greater risk in the mothers that were younger and less educated, and male foetuses.	be estimated and assigned to individual women using the satellite remote sensing and GIS technologies (e.g., land use regression). Efforts should be made to find out the exposure windows if there exist vulnerable periods, which could make the estimated effects comparable between studies using the same exposure periods. Also, the nonlinear temperature impact and cold-related effect on birth outcomes should be taken into account. Additionally, more investigations should be conducted aiming at exploring the potential individual-level modifiers in the effects of temperature exposure on birth outcomes. These continuous efforts and further findings would have important implications for decision-making of public intervention strategies to reduce the burden of adverse birth outcomes due to prenatal temperature exposure.		

vi. Poursafa[42] 04/2015 [3, all Iran]	PTB, VLBW/BW	**PTB**: Reported in 2 studies and one found significant high risk and 1 found weak evidence of association. Another cohort study estimated a 5-day reduction in average gestational age at delivery after an unusually high heat-humidity index on the day before delivery. **VLBW/BW**: 1 study each reported. Relatively colder temperatures increased the risk of VLBW. The results from the global study from 60 countries suggested that 'BW will decrease by 0.44-1.05% per each °C increase in temperature under projected climate change". **Note**: We did not consider results without empirical assessment of temperature.	'Increasing number of studies related to weather and temperature changes highlights the importance of these changes in human health especially on mothers and infants'	**Limitations** 'The review included some limitations such as lack of homogeneity between studies, different methodologies, different sample size and variations in the studied populations.'	
vii. Beltran[43] 20/12/2013 [3, all USA]	PTB, GA, BW, SGA	**PTB** 9 studies :7 cohorts and 2 time series; 8,913,266 births. 6/9 (67%) studies reported positive associations between increases in temperature and the risk of PTB, including 3 large studies (7,675,006 births in Japan and 101,870 births in Australia, and 132,691 births in Italy). Another study on 154,785 births in Australia examined the association between PTB and heat waves reported risks of PTB increased by 13% to 100% depending on the heat wave definition. Other studies focussing more precisely on the potential influence of temperature in the week and the few days preceding birth, first month or trimester found no association. This included two large studies (291,517 births in Germany, 482,765 births in England but extreme temperatures were not explored in these settings due to mild temperature). **mean GA** 3 cohort studies: 536,431 births. 2/3 studies reported inverse association between mean gestational age or length and average temperature during the month of birth (a large	'Further research should be preferentially conducted within the framework of international multicentric studies using harmonized methodologies. They would offer enhanced opportunities to disentangle the potential influence of different meteorological factors, thanks to the various combinations of these factors represented across Earth's climates. Investigating non-linear relationships between meteorological parameters and pregnancy outcomes appears important. Future studies need to measure, and if necessary adjust for, risk factors that exhibit	Not provided	

		study in Greece on 516,874 births) and between daily heat-humidity index (a study in Spain on 7,585 births). However, a study of 11,972 births in the USA during a period of heat wave (June–August 1995) detected no association between daily temperature and mean gestational length. **BW/SGA** 13 studies for BW and 1 study for SGA (9 cohort, 1 time series, and 3 ecological studies; 47,403,110 births with unreported size for 2 global studies) There was inverse association between temperature (heat stress index, annual average) temperature and mean birth weight in 3 studies. Three studies examined the average temperature exposure by pregnancy trimester and mean birth weight in term born infants. Significant increase in mean birth weight per 1 °C increase in the mean daily maximum temperature during the second trimester was reported in two studies (418,817 births in Ireland, and 3,333 births in Turkey) but a study of 8,516 births in New Zealand reported no effect of temperature “peaks” and “troughs” during any trimester on birth weight. Three other studies assessed similar associations but did not exclude preterm births and found inverse association between birthweight and meant temperature during the month of birth (a study of 516,874 births in Greece), positive associations between birth weights and mean daily maximum temperature in the first trimester (in a study of 225,545 births in Israel found). On the contrary, a study of 12,150 births in Scotland reported inverse associations between birth weight and mean ambient temperature in the mid 10-day period of the first trimester, no association for second trimester, and a positive association for the third trimester.	seasonal variability and may be correlated with meteorological factors such as nutritional patterns, air pollution and infections. Since nutritional pattern and maternal infections are seldom documented while meteorological stations are ubiquitous, research on the effects of meteorological conditions on pregnancy outcome might be most cost efficient if conducted within preexisting cohorts of nutrition and/or infections and pregnancy outcomes. They should ideally focus on individual indicators for exposure to meteorological conditions and cofactors, which would take into account time-activity patterns of pregnant women, and the mitigating effects of time spent indoors and associated heating, air conditioning and ventilation, on exposure. Future studies on birth weight should take into account the length of gestation as part of their study design, in order to disentangle the possible		

		Two studies (both from US; 37,100,000 births for 1972-1988 in cohort study, 4,921,561births for 1974-1978 and 1984-1988 in county-level ecological study) specifically showed an inverse relationship between extreme temperature episodes and mean birth weight and with higher number of days of extreme temperatures within each pregnancy trimester associating with the lower the mean birth weight, suggesting a possible inverse U-shaped relationship Three studies reported categorical birth weight; no association with term LBW for any trimester in a 134,846 births time-series study in Germany, association with very LBW of colder temperature during summer month in a 3,757,440 births population-based cohort study in Sweden and increase odds of SGA with average temperature in a 147,357 study from Australia. **Note**: We did not consider results on seasonality without temperature measurements.	effects of meteorology on intrauterine growth restriction and/or the length of gestation. Lastly, fine temporal exposure windows over the entire gestational period are needed to identify critical windows of vulnerability to meteorological stressors.'		
viii. Carolan-Olah[44] 12/03/2013 [2; both Australia]	PTB	7 studies: 5 retrospective cohort, 1 case-crossover, 1 ecological. All but two of the included studies found that high environmental temperature was related to an increase in preterm birth rates. Higher rates of preterm birth were linked to high environmental temperature among different subgroups; younger mothers, and among Black and Asian mothers but did not reach statistical significance.	'Health promotion is an important part of the professional midwife's role and, as such, midwives must be conversant on health determinants, including environmental influences. Moreover, midwives base their practice on the latest evidence, and current evidence suggests that the incidence of heatwaves is increasing. Global warming, and associated high environmental temperature, appears to contribute to increasing preterm birth rates,	**Strengths** No clear statement provided. **Limitations** 'Limitations of the review include a lack of homogeneity of studies and study characteristics, such as design, statistical approach, sample size and population, varied considerably from study to study. These factors limit the generalisability of results.'	

			although the exact nature of this relationship is unclear. Nonetheless, it is clear that pregnant women are vulnerable to heat stress. For this reason, it is prudent that midwives are aware of heat stress and can advise pregnant women to adopt supportive measures to protect their health and the health of their unborn baby, during periods of extreme heat. Such measures may include increasing fluid intake, remaining in a cool or airconditioned area and reducing activity levels to avoid exertion'		
ix. Strand[45] 18/02/2011 [3, all Australia]	PTB/GA, BW	**PTB/GA** 3 cohort studies; 541,249 plus unreported size in one study) One study reported mean weekly heat–humidity index in the hottest and coldest week of summer and winter and found non-significant rate of PTB. 2 studies reported at birth temperature, and one found significant increased risk and the other found no association. Another cohort study (11,792 births in Chicago, USA) reported and found no association with gestational age. **BW** 8 studies: 6 cohorts with 38,088,372 births and 2 ecological with unreported size where one gave only the median size of 5,558 in the global study. 2 studies reported for 1st trimester and both found significant reduction in BW	'More research is needed to clarify whether there is an adverse effect of ambient temperature on fetal health. New studies should use more sophisticated study designs such as population-based cohort studies that consider individual fetal outcomes and high-quality exposure data. The standardisation of methods would help make results more comparable. A non-linear relationship between temperature and	No clear statement at all. **Note:** Only outlined significant differences or limitations in the primary studies; in study design, statistical methods, exposure windows and birth outcome definitions.	

		4 studies reported for 2nd trimester/mean temperature in 2nd trimester where 1 each found significant reduction and increased (protective effect) in BW and 2 found non-significant protective effect (increased or positive association with BW) 2 studies reported for 3rd trimester and found significant reduction in BW in one and non-significant protective effect in the other. One of the trimester-specific results was on blacks/whites but almost same direction of findings. 2 ecological studies reported for mean temperature and both found significant reduction in BW. One study reported and found significant (for female) and non-significant (for male) increase in BW. One study reported and found significant reduction in BW for birth month mean temperature. Note: We did not consider results on seasonality without temperature assessment.	birth outcomes should be considered. Both exposure and birth outcomes should be clearly defined and crucial definitions such as 'stillbirth' should be further developed and standardised. Exposure windows should be made narrower, or at least be used consistently between studies. New studies should also use a large sample size and include as much information on the mother and baby as possible, which are especially important for stillbirth research because it is a rare event. Even though stillbirth is rare, it is absolutely devastating for the families involved, which makes it important to identify its causes. It is necessary and feasible to build on the current knowledge in order to prevent the occurrence of adverse birth outcomes and to ensure that newborn babies get a good start to their life, or even get to start their life at all.'		

Note: SB, Stillbirth; BW, Birth weight; LBW, Low birth weight; PTB, Preterm birth; GA, Gestational age

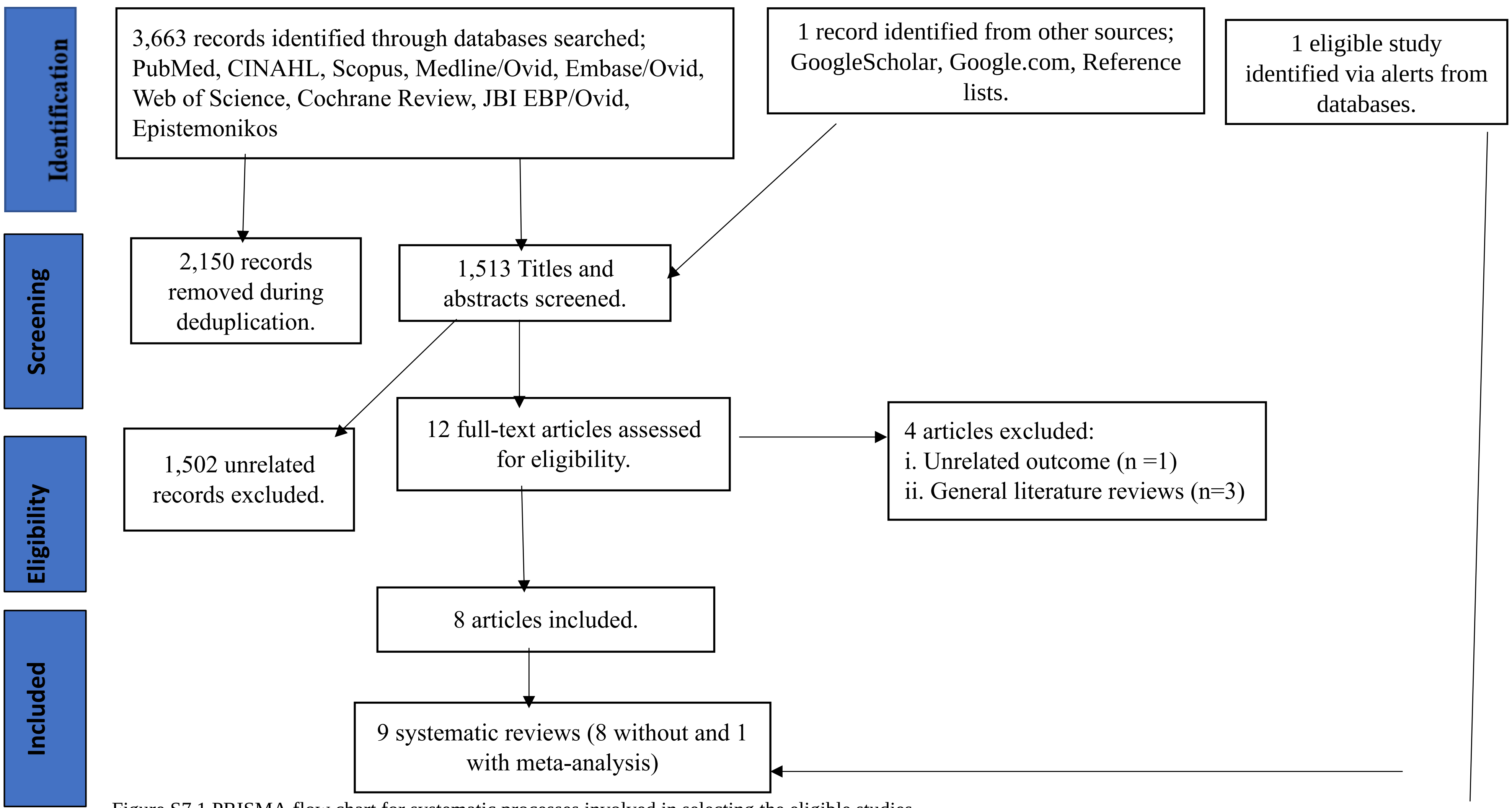

Figure S7.1 PRISMA flow chart for systematic processes involved in selecting the eligible studies.

First author, Year	1. Is the review question clearly and explicitly stated?	2. Were the inclusion criteria appropriate for the review question?	3. Was the search strategy appropriate?	4. Were the sources and resources used to search for studies adequate?[a]	5. Were the criteria for appraising studies appropriate?[b]	6. Was critical appraisal conducted by two or more reviewers independently?	7. Were there methods to minimize errors in data extraction?[c]	8. Were the methods used to combine studies appropriate?	9. Was the likelihood of publication bias assessed?	10. Were recommendations for policy and/or practice supported by the reported data?	11. Were the specific directives for new research appropriate?	Score (max=10)	Overall RoB
Sexton, 2021	Y	Y	Y	Y	Y	N	Y	Y	NA	Y	Y	9	L
Bekkar, 2020	Y	Y	Y	Y	N	N	N	Y	NA	Y	Y	7	M
Chersich, 2020*	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	9	L
Kuehn, 2017	Y	Y	Y	Y	U	N	N	Y	NA	Y	Y	7	M
Zhang, 2017	Y	Y	Y	Y	Y	N	N	Y	NA	Y	Y	8	M
Poursafa, 2015	Y	Y	Y	Y	N	N	Y	Y	NA	Y	Y	8	M
Beltran, 2013	Y	Y	Y	Y	N	N	N	Y	NA	Y	Y	7	M
Carolan-Olah,2013	Y	Y	Y	Y	Y	N	N	Y	NA	Y	Y	8	M
Strand, 2011	Y	Y	Y	Y	N	N	N	Y	NA	Y	Y	7	M
Y	9	9	9	9	4	0	3	9		9	9	**Average score = 7.8**	Average overall RoB
U	0	0	0	0	1	0	0	0		0	0		
N	0	0	0	0	4	9	6	0		0	0		

Figure S7.2. Summary of the risk of bias (RoB) assessment with Joanna Briggs Institute (JBI) critical appraisal checklist of the systematic reviews without meta-analysis for ambient air pollution and birth outcomes. (https://jbi-global-wiki.refined.site/space/MANUAL/3283910853/Appendix+10.1+JBI+Critical+Appraisal+Checklist+for+Systematic+reviews+and+Research+Syntheses)

[a]'Yes' if at least two electronic databases were searched

[b]'Yes' if standardised tools were used and results reported for each study, 'Unclear' if stated as done but results were not reported for each study.

[c]‘Yes’ if data extraction was performed by at least two reviewers independently.
* Included meta-analysis, hence maximum score is 11.

Legend	
Yes (Y)	
Unclear(U)	
No (N)	
Not applicable (NA)	
High (H)	
Moderate (M)	
Low (L)	

Appendix F: Supplementary materials for paper one of Chapter 8

Table S8.1.1 The cumulative relative risks of stillbirth stratified by season for 1st and 99th percentiles relative to season-specific median UTCI in Western Australia, 2000-2015.

	1st percentile, median UTCI			99th percentile, median UTCI		
Lag days	Transition (1.5 ºC, 14.1 ºC)	Winter (-1.3 ºC, 8.5 ºC)	Summer (9.6 ºC, 20.3 ºC)	Transition (30.8 ºC, 14.1 ºC)	Winter (20.9 ºC, 8.5 ºC)	Summer (33.7 ºC, 20.3 ºC)
0	1.12 (1.12, 1.13)	0.88 (0.88, 0.89)	1.04 (1.03, 1.05)	1.22 (1.21, 1.22)	0.82 (0.81, 0.83)	0.99 (0.98, 1.00)
0-1	1.23 (1.22, 1.24)	0.78 (0.78, 0.79)	1.06 (1.05, 1.07)	1.44 (1.42, 1.45)	0.69 (0.67, 0.70)	1.00 (0.98, 1.01)
0-2	1.33 (1.32, 1.35)	0.70 (0.69, 0.71)	1.06 (1.05, 1.08)	1.65 (1.62, 1.67)	0.58 (0.57, 0.60)	1.02 (1.00, 1.04)
0-3	1.42 (1.40, 1.44)	0.64 (0.63, 0.65)	1.04 (1.03, 1.06)	1.84 (1.81, 1.87)	0.50 (0.49, 0.52)	1.05 (1.03, 1.08)
0-4	1.49 (1.46, 1.51)	0.58 (0.57, 0.60)	1.01 (0.99, 1.03)	2.00 (1.97, 2.04)	0.44 (0.43, 0.46)	1.10 (1.07, 1.13)
0-5	1.54 (1.52, 1.57)	0.54 (0.53, 0.55)	0.97 (0.95, 0.99)	2.14 (2.09, 2.19)	0.40 (0.38, 0.41)	1.15 (1.12, 1.18)
0-6	1.58 (1.55, 1.61)	0.51 (0.50, 0.52)	0.92 (0.89, 0.94)	2.24 (2.19, 2.30)	0.36 (0.35, 0.37)	1.21 (1.18, 1.25)
0-13	1.62 (1.58, 1.66)	0.46 (0.44, 0.47)	0.56 (0.54, 0.58)	2.28 (2.21, 2.36)	0.27 (0.25, 0.28)	1.53 (1.47, 1.59)
0-21	1.72 (1.66, 1.78)	0.93 (0.89, 0.98)	0.40 (0.38, 0.42)	1.96 (1.88, 2.05)	0.40 (0.37, 0.43)	0.87 (0.82, 0.92)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Table S8.1.2 The cumulative relative risks of stillbirth for 1st and 99th percentiles relative to median UTCI (13.9 °C) with alternative degrees of freedom, Western Australia, 2000-2015.

Lag days	3 *df* for both predictor variable and lag spaces		3 *df* for predictor variable and 4 *df* for lag spaces	
	1st percentile (0.7 ºC) RR (95% CI)	99th percentile (31.7 ºC) RR (95% CI)	1st percentile (0.7 ºC) RR (95% CI)	99th percentile (31.7 ºC) RR (95% CI)
0	1.01 (1.00, 1.01)	1.04 (1.04, 1.05)	1.01 (1.01, 1.02)	1.14 (1.13, 1.14)
0-1	1.02 (1.01, 1.02)	1.09 (1.08, 1.10)	1.02 (1.01, 1.03)	1.21 (1.20, 1.23)
0-2	1.02 (1.01, 1.03)	1.14 (1.12, 1.15)	1.03 (1.02, 1.04)	1.24 (1.23, 1.26)
0-3	1.03 (1.02, 1.04)	1.19 (1.17, 1.20)	1.03 (1.02, 1.05)	1.26 (1.24, 1.27)
0-4	1.04 (1.03, 1.05)	1.24 (1.22, 1.26)	1.04 (1.03, 1.05)	1.27 (1.25, 1.28)
0-5	1.05 (1.03, 1.06)	1.29 (1.27, 1.31)	1.05 (1.03, 1.06)	1.29 (1.27, 1.31)
0-6	1.06 (1.04, 1.07)	1.34 (1.32, 1.37)	1.05 (1.04, 1.07)	1.32 (1.30, 1.34)
0-13	1.15 (1.13, 1.18)	1.56 (1.52, 1.60)	1.15 (1.13, 1.18)	1.63 (1.59, 1.67)
0-21	1.38 (1.34, 1.42)	1.22 (1.18, 1.26)	1.38 (1.34, 1.42)	1.24 (1.20, 1.28)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; *df*, degree of freedom

Table S8.1.3 The cumulative relative risks of stillbirth for 1st and 99th percentiles, relative to mean and an average of 'no thermal stress' range UTCI, Western Australia, 2000-2015.

Lag days	Mean UTCI (14.6 ºC) as reference		Average of the 'no thermal stress' range (17.5 ºC) as reference	
	1st percentile (0.7 ºC) RR (95% CI)	99th percentile (31.7 ºC) RR (95% CI)	1st percentile (0.7 ºC) RR (95% CI)	99th percentile (31.7 ºC) RR (95% CI)
0	1.02 (1.02, 1.03)	1.01 (1.01, 1.02)	1.02 (1.02, 1.03)	1.01 (1.01, 1.02)
0-1	1.04 (1.04, 1.05)	1.03 (1.02, 1.04)	1.04 (1.04, 1.05)	1.03 (1.02, 1.04)
0-2	1.06 (1.05, 1.07)	1.05 (1.04, 1.06)	1.06 (1.05, 1.07)	1.05 (1.04, 1.06)
0-3	1.08 (1.07, 1.09)	1.08 (1.07, 1.09)	1.08 (1.07, 1.09)	1.08 (1.07, 1.09)
0-4	1.10 (1.09, 1.11)	1.12 (1.10, 1.13)	1.10 (1.09, 1.11)	1.11 (1.10, 1.13)
0-5	1.12 (1.11, 1.13)	1.15 (1.13, 1.17)	1.11 (1.10, 1.13)	1.15 (1.13, 1.16)
0-6	1.14 (1.12, 1.15)	1.19 (1.17, 1.21)	1.13 (1.11, 1.15)	1.18 (1.16, 1.20)
0-13	1.24 (1.22, 1.26)	1.40 (1.37, 1.43)	1.22 (1.20, 1.24)	1.38 (1.35, 1.41)
0-21	1.32 (1.29, 1.35)	1.22 (1.19, 1.26)	1.32 (1.29, 1.36)	1.23 (1.19, 1.26)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Table S 8.1.4 The cumulative relative risks of stillbirth for 1st and 99th percentiles relative to median UTCI (13.9 °C) with alternative definitions of case day, Western Australia, 2000-2015*.

Case day	Lag days	1st percentile (0.7 °C) RR (95% CI)	99th percentile (31.7 °C) RR (95% CI)
1 day before delivery	0	1.00 (0.99, 1.00)	0.99 (0.99, 0.99)
	0-1	0.99 (0.99, 1.00)	0.99 (0.98, 1.00)
	0-2	0.99 (0.99, 1.00)	1.00 (0.99, 1.01)
	0-3	1.00 (0.99, 1.01)	1.01 (1.00, 1.02)
	0-4	1.00 (0.99, 1.01)	1.03 (1.02, 1.05)
	0-5	1.00 (0.99, 1.01)	1.06 (1.04, 1.07)
	0-6	1.01 (1.00, 1.02)	1.09 (1.07, 1.10)
	0-13	1.04 (1.02, 1.06)	1.29 (1.27, 1.32)
	0-21	1.02 (1.00, 1.05)	1.19 (1.15, 1.22)
On the delivery day	0	0.96 (0.95, 0.96)	0.98 (0.97, 0.98)
	0-1	0.92 (0.92, 0.93)	0.97 (0.96, 0.97)
	0-2	0.90 (0.89, 0.90)	0.96 (0.95, 0.97)
	0-3	0.88 (0.87, 0.89)	0.97 (0.96, 0.98)
	0-4	0.86 (0.85, 0.87)	0.98 (0.96, 0.99)
	0-5	0.85 (0.84, 0.87)	0.99 (0.98, 1.01)
	0-6	0.85 (0.84, 0.86)	1.01 (1.00, 1.03)
	0-13	0.85 (0.83, 0.86)	1.21 (1.19, 1.24)
	0-21	0.77 (0.75, 0.79)	1.27 (1.24, 1.31)

*Total included stillbirths = 2,836 (increased by one), Note: UTCI, Universal Thermal Climate Index in degree Celsius.

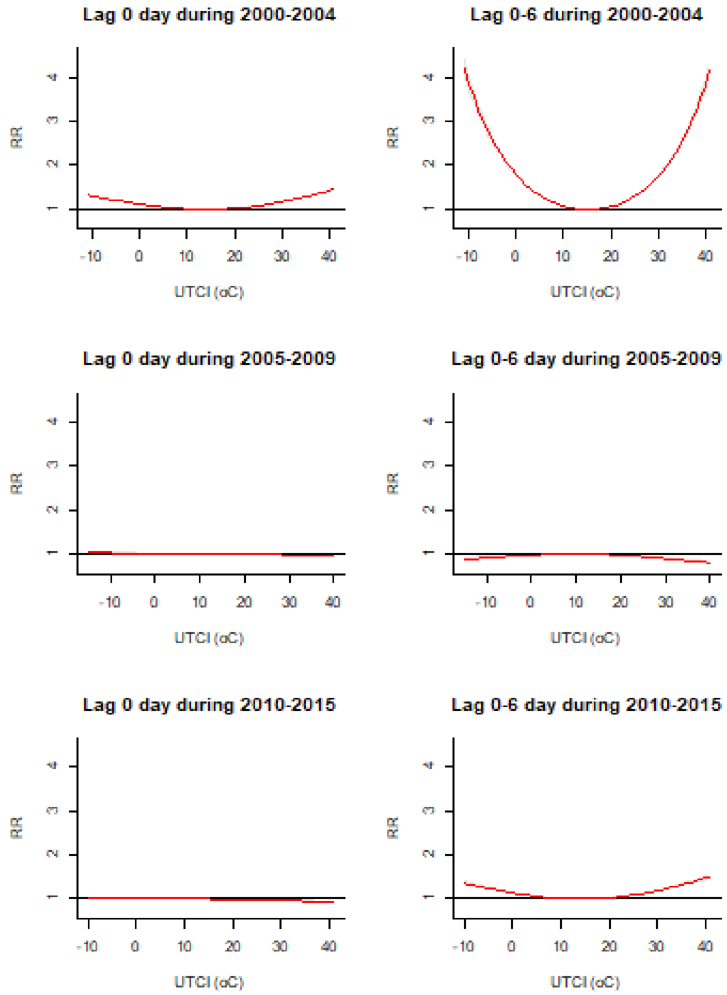

Figure S8.1.1 Temporal exposure-response curves of daily UTCI and immediate and six days cumulative relative risk of stillbirth using year-specific median UTCI of each year as reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals (CIs). Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Appendix G: Supplementary materials for paper two of Chapter 8

Table S8.2.1 The descriptive statistics of daily mean UTCI (ºC), Western Australia, 2000-2015.

Variable	Subgroup	Min	Mean (SD)	P1	P25	Median	P75	P99	Max
	All	-15.4	14.5 (6.7)	0.7	9.7	13.8	18.9	31.2	41.9
Season	Transition	-15.4	14.6 (5.7)	1.5	10.9	14.1	17.9	30.2	40.2
	Winter	-12.6	8.4 (4.1)	-1.3	5.9	8.5	10.9	20.3	31.9
	Summer	-1.3	20.5 (5.3)	9.5	16.5	20.2	24.2	33.3	41.9
Year	2000-2004	-11.0	14.1 (6.6)	0.5	9.4	13.5	18.6	30.7	41.9
	2005-2009	-15.4	14.0 (6.8)	0.2	9.3	13.4	18.5	31.1	41.3
	2010-2015	-10.2	15.1 (6.8)	1.5	10.3	14.5	19.7	31.7	41.1

Note: UTCI, Universal Thermal Climate Index in degree Celsius; SD, standard deviation; P1, P25, P75, and P99 are respective percentiles.

Table S8.2.2a The cumulative relative risks of spontaneous PTB stratified by season for 1st and 99th percentiles relative to overall median UTCI (13.8 ˚C) in Western Australia, 2000-2015.

Lag days	1st percentile of UTCI RR (95% CI)			99th percentile RR (95% CI)		
	Transition	Winter	Summer	Transition	Winter	Summer
0	1.01 (1.01, 1.02)	0.97 (0.97, 0.98)	0.99 (0.99, 0.99)	1.04 (1.03, 1.04)	0.99 (0.99, 0.99)	1.02 (1.02, 1.03)
0-1	1.02 (1.02, 1.03)	0.95 (0.94, 0.96)	0.98 (0.98, 0.99)	1.07 (1.06, 1.08)	0.98 (0.98, 0.99)	1.03 (1.02, 1.04)
0-2	1.03 (1.03, 1.04)	0.93 (0.92, 0.94)	0.97 (0.97, 0.98)	1.09 (1.08, 1.10)	0.98 (0.97, 0.99)	1.03 (1.02, 1.04)
0-3	1.04 (1.03, 1.05)	0.91 (0.90, 0.92)	0.97 (0.96, 0.97)	1.11 (1.10, 1.13)	0.98 (0.97, 0.99)	1.02 (1.00, 1.03)
0-4	1.04 (1.03, 1.05)	0.90 (0.88, 0.91)	0.96 (0.95, 0.97)	1.13 (1.12, 1.14)	0.99 (0.97, 1.00)	1.00 (0.98, 1.01)
0-5	1.05 (1.03, 1.06)	0.88 (0.87, 0.90)	0.96 (0.95, 0.96)	1.14 (1.12, 1.15)	0.99 (0.98, 1.00)	0.97 (0.96, 0.99)
0-6	1.05 (1.03, 1.06)	0.87 (0.86, 0.89)	0.95 (0.94, 0.96)	1.15 (1.13, 1.16)	1.00 (0.98, 1.01)	0.94 (0.93, 0.96)
0-13	0.99 (0.98, 1.01)	0.84 (0.82, 0.86)	0.92 (0.91, 0.93)	1.12 (1.10, 1.15)	1.15 (1.07, 1.12)	0.73 (0.71, 0.75)
0-21	0.84 (0.83, 0.86)	0.84 (0.81, 0.87)	0.86 (0.85, 0.88)	1.09 (1.06, 1.12)	1.24 (1.20, 1.28)	0.65 (0.63, 0.67)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table S8.2.2b The cumulative relative risks of spontaneous PTB stratified by season for 1st and 99th percentiles relative to season-specific median UTCI in Western Australia, 2000-2015.

Lag days	1st percentile, median UTCI			99th percentile, median UTCI		
	Transition (1.5 ºC, 14.1 ºC) RR (95% CI)	Winter (-1.3 ºC, 8.5 ºC) RR (95% CI)	Summer (9.5 ºC, 20.2 ºC) RR (95% CI)	Transition (30.2 ºC, 14.1 ºC) RR (95% CI)	Winter (20.3 ºC, 8.5 ºC) RR (95% CI)	Summer (33.3 ºC, 20.2 ºC) RR (95% CI)
0	1.01 (1.01, 1.02)	0.97 (0.97,0.98)	0.98 (0.98, 0.98)	1.04 (1.03, 1.04)	0.99 (0.99, 1.00)	1.01 (1.00, 1.01)
0-1	1.02 (1.02, 1.03)	0.95 (0.95, 0.96)	0.96 (0.96, 0.97)	1.07 (1.06, 1.08)	0.99 (0.98, 1.00)	1.01 (1.00, 1.02)
0-2	1.03 (1.02, 1.04)	0.93 (0.93, 0.94)	0.95 (0.94, 0.96)	1.09 (1.08, 1.10)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)
0-3	1.04 (1.03, 1.05)	0.92 (0.91, 0.93)	0.94 (0.93, 0.95)	1.11 (1.10. 1.13)	0.99 (0.98, 1.01)	0.99 (0.97, 1.00)
0-4	1.04 (1.03, 1.05)	0.91 (0.90, 0.92)	0.93 (0.92, 0.94)	1.13 (1.11, 1.14)	1.00 (0.98, 1.02)	0.97 (0.95, 0.98)
0-5	1.05 (1.03, 1.06)	0.90 (0.89, 0.91)	0.92 (0.91, 0.94)	1.14 (1.12, 1.15)	1.01 (0.99, 1.03)	0.94 (0.92, 0.96)
0-6	1.05 (1.03, 1.06)	0.89 (0.88, 0.91)	0.92 (0.90, 0.93)	1.14 (1.13, 1.16)	1.02 (1.00, 1.04)	0.91 (0.89, 0.93)
0-13	0.99 (0.97, 1.01)	0.89 (0.87, 0.91)	0.89 (0.87, 0.91)	1.12 (1.10, 1.15	1.17 (1.14, 1.21)	0.71 (0.69, 0.73)
0-21	0.84 (0.82, 0.86)	0.94 (0.91, 0.97)	0.80 (0.78, 0.83)	1.09 (1.06, 1.12)	1.39 (1.33, 1.45)	0.61 (0.58, 0.63)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table S8.2.3 The cumulative relative risks of spontaneous PTB stratified by type and sex for 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015.

Lag days	1st percentile of UTCI RR (95% CI)			99th percentile of UTCI RR (95% CI)		
	Extremely PTB	Very PTB	Moderate PTB	Extremely PTB	Very PTB	Moderate PTB
0	0.94 (0.93, 0.94)	1.08 (1.08, 1.08)	0.99 (0.99, 0.99)	1.13 (1.13, 1.13)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)
0-1	0.89 (0.89, 0.90)	1.15 (1.15, 1.16)	0.98 (0.98, 0.99)	1.25 (1.24, 1.26)	0.99 (0.98, 0.99)	1.02 (1.01, 1.02)
0-2	0.87 (0.87, 0.88)	1.21 (1.20, 1.21)	0.98 (0.97, 0.98)	1.35 (1.34, 1.36)	0.99 (0.98, 0.99)	1.02 (1.02, 1.03)
0-3	0.87 (0.86, 0.87)	1.25 (1.24, 1.26)	0.97 (0.97, 0.98)	1.43 (1.42, 1.44)	0.99 (0.98, 0.99)	1.03 (1.02, 1.04)
0-4	0.87 (0.87, 0.88)	1.28 (1.27, 1.29)	0.97 (0.96, 0.98)	1.48 (1.47, 1.50)	0.99 (0.98, 0.99)	1.03 (1.02, 1.04)
0-5	0.89 (0.88, 0.89)	1.30 (1.29, 1.31)	0.97 (0.96, 0.98)	1.52 (1.51, 1.53)	0.98 (0.98, 0.99)	1.03 (1.02, 1.04)
0-6	0.91 (0.90, 0.92)	1.31 (1.30, 1.32)	0.97 (0.96, 0.97)	1.54 (1.52, 1.55)	0.98 (0.97, 0.99)	1.03 (1.02, 1.04)
0-13	1.04 (1.02, 1.05)	1.26 (1.24, 1.27)	0.93 (0.91, 0.94)	1.45 (1.43, 1.47)	0.85 (0.84, 0.86)	1.02 (1.01, 1.04)
0-21	0.59 (0.58, 0.60)	1.32 (1.29, 1.34)	0.76 (0.75, 0.77)	1.66 (1.63, 1.69)	0.45 (0.44, 0.46)	1.05 (1.03, 1.07)
Lag days	Male	Female		Male	Female	
0	0.98 (0.98, 0.99)	1.00 (1.00, 1.01)		1.01 (1.01, 1.01)	1.02 (1.02, 1.02)	
0-1	0.98 (0.97, 0.98)	1.01 (1.00, 1.01)		1.03 (1.02, 1.03)	1.03 (1.02, 1.03)	
0-2	0.97 (0.97, 0.98)	1.00 (1.00, 1.01)		1.04 (1.04, 1.05)	1.03 (1.02, 1.04)	
0-3	0.97 (0.97, 0.98)	1.00 (0.99, 1.01)		1.06 (1.05, 1.07)	1.02 (1.01, 1.03)	
0-4	0.98 (0.97, 0.99)	0.99 (0.99, 1.00)		1.08 (1.07, 1.09)	1.01 (1.00, 1.02)	
0-5	0.99 (0.98, 0.99)	0.98 (0.98, 0.99)		1.10 (1.09, 1.11)	0.99 (0.98, 1.00)	
0-6	0.99 (0.99, 1.00)	0.97 (0.97, 0.98)		1.12 (1.11, 1.13)	0.97 (0.96, 0.98)	
0-13	1.00 (0.99, 1.01)	0.90 (0.89, 0.91)		1.24 (1.22, 1.25)	0.82 (0.80, 0.83)	
0-21	0.74 (0.72, 0.75)	0.85 (0.84, 0.86)		1.20 (1.18, 1.22)	0.82 (0.81, 0.84)	

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table S8.2.4 The cumulative relative risks of spontaneous PTB stratified by maternal smoking and marital statuses, and of race/ethnicity for 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015.

Maternal variable	Lag days	1st percentile of UTCI RR (95% CI)		99th percentile of UTCI RR (95% CI)	
Smoking status		Non-smoker	Smoker	Non-smoker	Smoker
	0	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	1.01 (1.01, 1.01)	1.03 (1.03, 1.04)
	0-1	0.99 (0.99, 0.99)	0.98 (0.98, 0.99)	1.01 (1.01, 1.02)	1.07 (1.06, 1.07)
	0-2	0.99 (0.99, 1.00)	0.97 (0.97, 0.98)	1.02 (1.01, 1.02)	1.10 (1.09, 1.10)
	0-3	0.99 (0.99, 1.00)	0.96 (0.95, 0.97)	1.01 (1.01, 1.02)	1.13 (1.12, 1.13)
	0-4	1.00 (0.99, 1.00)	0.95 (0.94, 0.95)	1.01 (1.00, 1.02)	1.15 (1.14, 1.16)
	0-5	1.00 (0.99, 1.01)	0.93 (0.92, 0.94)	1.01 (1.00, 1.02)	1.17 (1.16, 1.18)
	0-6	1.01 (1.00, 1.02)	0.92 (0.91, 0.92)	1.00 (0.99, 1.01)	1.19 (1.18, 1.21)
	0-13	1.01 (0.99, 1.02)	0.80 (0.79, 0.81)	0.97 (0.95, 0.98)	1.24 (1.22, 1.26)
	0-21	0.81 (0.80, 0.83)	0.69 (0.68, 0.71)	0.99 (0.97, 1.01)	1.09 (1.07, 1.11)
Marital status		Married	Unmarried	Married	Unmarried
	0	1.01 (1.01, 1.01)	0.92 (0.92, 0.92)	1.00 (1.00, 1.00)	1.07 (1.07, 1.07)
	0-1	1.02 (1.02, 1.02)	0.85 (0.85, 0.86)	1.00 (1.00, 1.01)	1.13 (1.12, 1.13)
	0-2	1.03 (1.03, 1.04)	0.79 (0.79, 0.80)	1.00 (1.00, 1.01)	1.18 (1.17, 1.18)
	0-3	1.04 (1.04, 1.05)	0.74 (0.74, 0.75)	1.00 (1.00, 1.01)	1.21 (1.20, 1.22)
	0-4	1.06 (1.05, 1.06)	0.70 (0.69, 0.70)	1.01 (1.00, 1.01)	1.23 (1.22, 1.24)
	0-5	1.07 (1.06, 1.08)	0.66 (0.65, 0.66)	1.01 (1.00, 1.02)	1.24 (1.23, 1.25)
	0-6	1.08 (1.07, 1.09)	0.62 (0.62, 0.63)	1.01 (1.00, 1.02)	1.24 (1.23, 1.25)
	0-13	1.10 (1.09, 1.11)	0.48 (0.47, 0.48)	1.02 (1.00, 1.03)	1.07 (1.06, 1.09)
	0-21	0.88 (0.87, 0.90)	0.44 (0.43, 0.45)	1.06 (1.04, 1.08)	0.87 (0.85, 0.89)
Race/ethnicity		Caucasian	Non-Caucasian	Caucasian	Non-Caucasian
	0	0.97 (0.97, 0.98)	1.05 (1.04, 1.05)	1.01 (1.00, 1.01)	1.03 (1.03, 1.03)
	0-1	0.96 (0.95, 0.96)	1.08 (1.07, 1.08)	1.01 (1.01, 1.02)	1.05 (1.05, 1.06)
	0-2	0.95 (0.94, 0.95)	1.10 (1.09, 1.10)	1.02 (1.01, 1.03)	1.07 (1.06, 1.08)
	0-3	0.94 (0.94, 0.95)	1.10 (1.09, 1.11)	1.02 (1.01, 1.03)	1.08 (1.08, 1.09)
	0-4	0.94 (0.94, 0.95)	1.10 (1.09, 1.10)	1.02 (1.02, 1.03)	1.09 (1.08, 1.10)
	0-5	0.95 (0.94, 0.96)	1.08 (1.07, 1.09)	1.03 (1.02, 1.04)	1.10 (1.09, 1.11)
	0-6	0.96 (0.95, 0.96)	1.06 (1.05, 1.07)	1.03 (1.02, 1.04)	1.10 (1.09, 1.11)
	0-13	0.99 (0.98, 1.00)	0.85 (0.84, 0.86)	1.02 (1.01, 1.04)	1.06 (1.04, 1.07)
	0-21	0.78 (0.76, 0.79)	0.79 (0.78, 0.80)	1.02 (1.00, 1.04)	1.02 (1.00, 1.03)
Area-level SES		High	Low	High	Low
	0	1.02 (1.02, 1.02)	0.98 (0.97, 0.98)	1.05 (1.04, 1.05)	0.99 (0.99, 1.00)
	0-1	1.04 (1.03, 1.04)	0.96 (0.96, 0.96)	1.08 (1.08, 1.09)	0.99 (0.99, 0.99)
	0-2	1.04 (1.04, 1.05)	0.95 (0.95, 0.96)	1.11 (1.10, 1.12)	0.99 (0.98, 1.00)
	0-3	1.05 (1.04, 1.05)	0.95 (0.94, 0.95)	1.13 (1.12, 1.13)	0.99 (0.98, 1.00)
	0-4	1.04 (1.04, 1.05)	0.95 (0.94, 0.96)	1.13 (1.12, 1.14)	0.99 (0.99, 1.00)
	0-5	1.04 (1.03, 1.04)	0.95 (0.95, 0.96)	1.13 (1.12, 1.14)	1.00 (0.99, 1.01)
	0-6	1.02 (1.02, 1.03)	0.96 (0.95, 0.97)	1.12 (1.11, 1.13)	1.00 (0.99, 1.01)
	0-13	0.87 (0.86, 0.88)	1.01 (0.99, 1.02)	1.02 (1.01, 1.04)	1.04 (1.03, 1.06)
	0-21	0.68 (0.67, 0.69)	0.85 (0.83, 0.86)	1.08 (1.06, 1.10)	0.99 (0.97, 1.01)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth; SES, Socioeconomic status.

Table S8.2.5 The cumulative relative risks of spontaneous PTB stratified by maternal age at delivery for 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015.

Lag days	1st percentile of UTCI RR (95% CI)			99th percentile of UTCI RR (95% CI)		
	≤ 19	20-34	≥ 35	≤ 19	20-34	≥ 35
0	0.99 (0.99, 0.99)	1.00 (1.00, 1.00)	0.97 (0.97, 0.97)	1.11 (1.11, 1.11)	0.99 (0.99, 1.00)	1.06 (1.06, 1.06)
0-1	0.98 (0.97, 0.98)	1.00 (1.00, 1.00)	0.95 (0.95, 0.95)	1.21 (1.20, 1.21)	0.99 (0.99, 0.99)	1.10 (1.10, 1.11)
0-2	0.95 (0.95, 0.96)	1.00 (1.00, 1.01)	0.93 (0.93, 0.94)	1.29 (1.28, 1.30)	0.99 (0.98, 1.00)	1.12 (1.11, 1.13)
0-3	0.92 (0.92, 0.93)	1.01 (1.00, 1.01)	0.92 (0.91, 0.93)	1.36 (1.35, 1.37)	0.99 (0.99, 1.00)	1.11 (1.11, 1.12)
0-4	0.89 (0.89, 0.90)	1.01 (1.01, 1.02)	0.91 (0.90, 0.92)	1.41 (1.40, 1.42)	1.00 (0.99, 1.01)	1.09 (1.08, 1.10)
0-5	0.86 (0.85, 0.86)	1.02 (1.01, 1.03)	0.90 (0.89, 0.91)	1.45 (1.44, 1.46)	1.01 (1.00, 1.02)	1.06 (1.05, 1.07)
0-6	0.82 (0.81, 0.83)	1.02 (1.02, 1.03)	0.89 (0.89, 0.90)	1.47 (1.46, 1.48)	1.01 (1.00, 1.02)	1.02 (1.01, 1.03)
0-13	0.61 (0.61, 0.62)	1.03 (1.02, 1.05)	0.80 (0.79, 0.81)	1.39 (1.38, 1.41)	1.06 (1.05, 1.08)	0.76 (0.75, 0.77)
0-21	0.57 (0.56, 0.58)	0.89 (0.90, 0.90)	0.51 (0.50, 0.52)	1.28 (1.26, 1.30)	1.00 (1.00, 1.02)	0.92 (0.91, 0.94)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table S8.2.6 The cumulative relative risks of spontaneous PTB for 1st and 99th percentiles relative to median UTCI (13.8 °C) with alternative degrees of freedom in Western Australia, 2000-2015.

	3 *df* for both predictor and lag space		3 *df* for predictor and 4 *df* for lag space	
Lag days	1st (0.7 ^{0}C) RR (95% CI)	99th (31.2 ^{0}C) RR (95% CI)	1st (0.7 ^{0}C) RR (95% CI)	99th (31.2 ^{0}C) RR (95% CI)
0	1.00 (0.99, 1.00)	1.02 (1.01, 1.02)	1.01 (1.00, 1.01)	1.07 (1.07, 1.08)
0-1	0.99 (0.99, 1.00)	1.03 (1.02, 1.04)	1.01 (1.00, 1.01)	1.10 (1.09, 1.11)
0-2	0.99 (0.98, 1.00)	1.04 (1.03, 1.05)	1.00 (0.99, 1.01)	1.10 (1.09, 1.11)
0-3	0.99 (0.98, 0.99)	1.05 (1.04, 1.06)	0.99 (0.99, 1.00)	1.08 (1.07, 1.09)
0-4	0.99 (0.98, 0.99)	1.06 (1.05, 1.07)	0.99 (0.98, 0.99)	1.07 (1.06, 1.08)
0-5	0.99 (0.98, 0.99)	1.06 (1.05, 1.07)	0.98 (0.97, 0.99)	1.05 (1.04, 1.06)
0-6	0.99 (0.98, 0.99)	1.06 (1.05, 1.07)	0.98 (0.97, 0.99)	1.04 (1.03, 1.06)
0-13	0.96 (0.95, 0.97)	1.04 (1.02, 1.05)	0.96 (0.95, 0.98)	1.06 (1.04, 1.08)
0-21	0.84 (0.83, 0.86)	0.96 (0.94, 0.98)	0.85 (0.83, 0.86)	0.97 (0.95, 0.99)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; df, degree of freedom; PTB. Preterm birth.

Table S8.2.7 The cumulative relative risks of spontaneous PTB for 1st and 99th percentiles, relative to mean and an average of 'no thermal stress' range UTCI in Western Australia, 2000-2015.

	Mean UTCI (14.5 ^{0}C)		Average of standard no thermal stress range (17.5 ^{0}C)	
Lag days	1st percentile (0.7 ^{0}C) RR (95% CI)	99th percentile (31.2 ^{0}C) RR (95% CI)	1st percentile (0.7 ^{0}C) RR (95% CI)	99th percentile (31.2 ^{0}C) RR (95% CI)
0	0.99 (0.99, 1.00)	1.01 (1.01, 1.02)	0.99 (0.99, 0.99)	1.01 (1.01, 1.01)
0-1	0.99 (0.98, 0.99)	1.03 (1.02, 1.03)	0.98 (0.98, 0.99)	1.02 (1.02, 1.03)
0-2	0.99 (0.98, 0.99)	1.04 (1.03, 1.04)	0.98 (0.97, 0.99)	1.03 (1.02, 1.04)
0-3	0.98 (0.98, 0.99)	1.04 (1.03, 1.05)	0.98 (0.97, 0.99)	1.04 (1.03, 1.04)
0-4	0.98 (0.98, 0.99)	1.05 (1.04, 1.05)	0.98 (0.97, 0.99)	1.04 (1.03, 1.05)
0-5	0.98 (0.98, 0.99)	1.05 (1.04, 1.06)	0.98 (0.97, 0.99)	1.04 (1.03, 1.05)
0-6	0.98 (0.98, 0.99)	1.05 (1.04, 1.06)	0.98 (0.97, 0.99)	1.04 (1.03, 1.05)
0-13	0.95 (0.94, 0.96)	1.03 (1.01, 1.04)	0.94 (0.93, 0.96)	1.02 (1.01, 1.03)
0-21	0.78 (0.76, 0.79)	1.01 (0.99, 1.03)	0.76 (0.75, 0.77)	0.99 (0.97, 1.00)

Note: UTCI, Universal Thermal Climate Index in degree Celsius

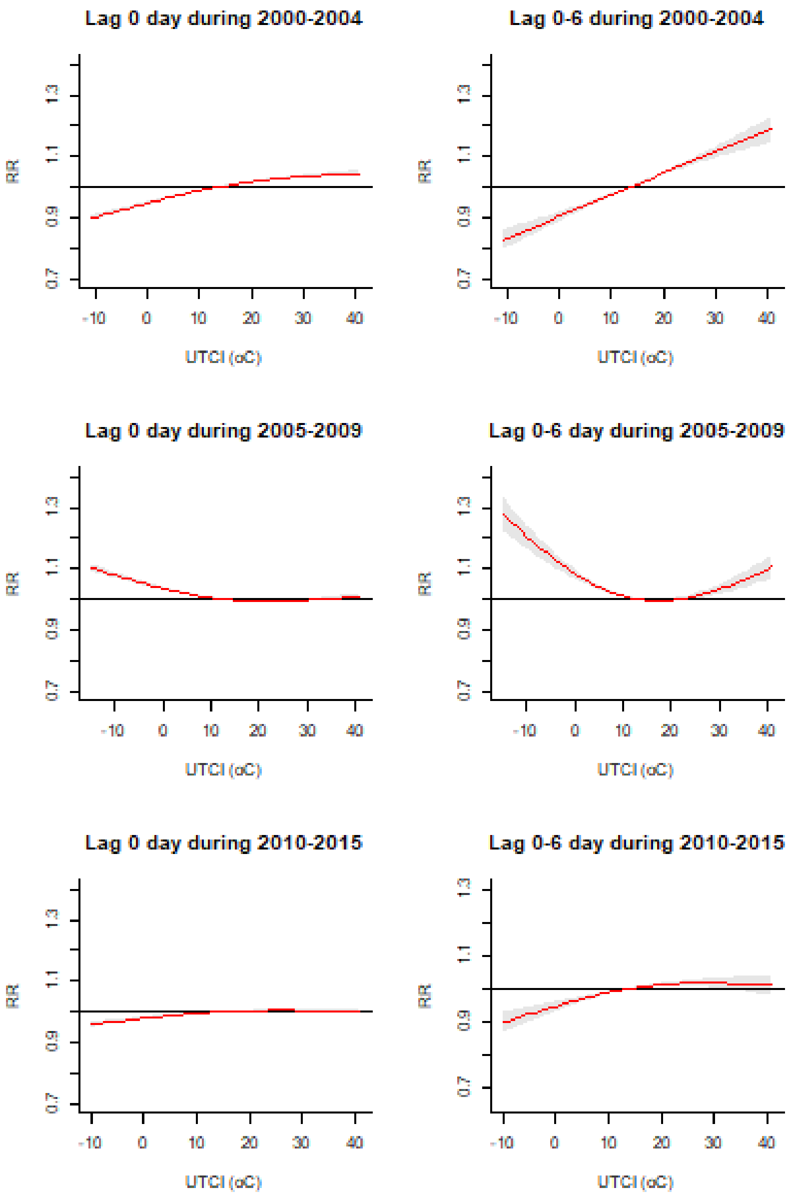

Figure S8.2.1 Year-grouped exposure-response curves of daily UTCI and immediate and six days cumulative relative risk of spontaneous PTB using year-specific median UTCI of each year as a reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals. Note: UTCI, Universal Thermal Climate Index in degree Celsius.

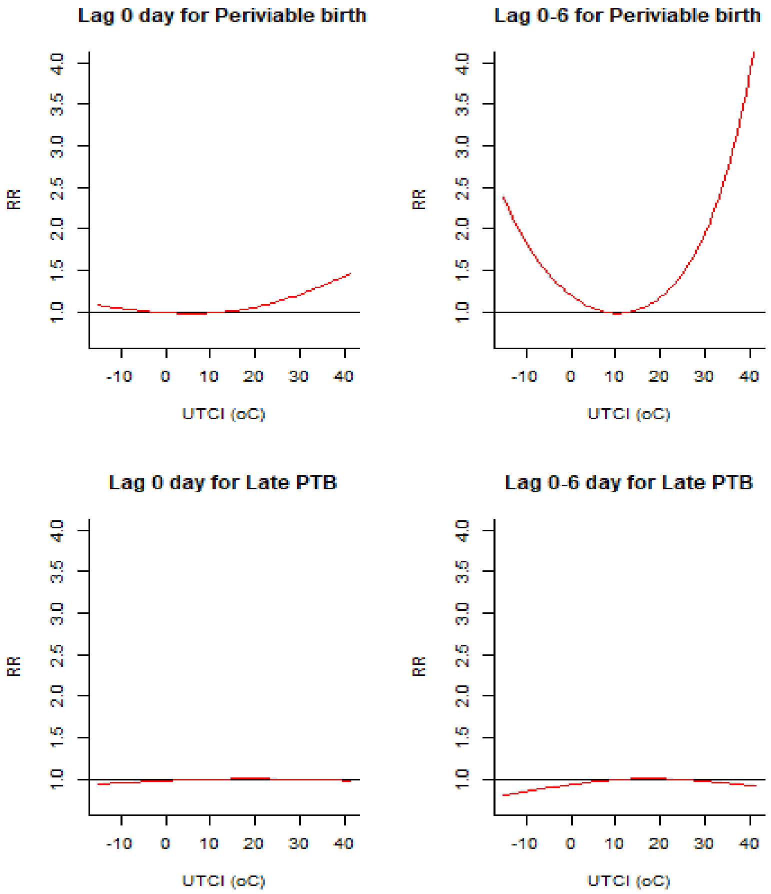

Figure S8.2.2 Exposure-response curves of daily UTCI and immediate and six days cumulative relative risk of spontaneous Periviable birth and late PTB using median UTCI of 13.8 ºC as reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals. Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Appendix H. Supplementary materials for Chapter 9

Table S9.1 Descriptive statistics of the average UTCI (℃) during twelve weeks preconception through to gestational weeks at delivery exposure periods without induced sPTB in Western Australia, 2000-2015 (N= 400,867 births)

Exposure periods	Min	Mean ± SD	Median	1st	5th	10th	IQR	90th	95th	99th	Max
Preconception to pregnancy	7.3	14.5 ± 2.5	14.2	10.2	11.9	12.8	1.2	15.4	17.4	26.0	31.2
Preconception	1.4	14.4 ± 5.2	14.0	5.8	7.6	8.2	8.8	20.9	22.0	29.5	35.8
Pregnancy	4.9	14.6 ± 2.9	14.2	9.6	11.3	11.9	2.9	16.7	18.3	26.7	34.1
1st Trimester	1.7	14.6 ± 5.2	14.2	5.9	7.7	8.3	8.8	20.9	22.0	29.6	36.0
2nd Trimester	1.6	14.6 ± 5.2	14.2	6.1	7.8	8.5	8.7	20.9	22.0	29.8	36.1
3rd Trimester	-1.1	14.5 ± 5.2	14.0	5.8	7.7	8.4	8.7	20.8	22.0	29.7	35.7

Note: UTCI, Universal Thermal Climate Index; SD, standard deviation; P1 to P99, first to 99th centiles; IQR, interquartile range= P75-P25; sPTB, spontaneous preterm birth.

Table S9.2 Weekly-specific UTCI exposure over 12- week preconception (-11 to 0) through to gestational week at delivery (1 to 42) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of Stillbirth in Western Australia, 2000–2015.

Week	P1 (10.2 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.4 ˚C)			P95 (17.4 ˚C)			P99 (26.1 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-11	1.003	0.918	1.096	1.060	0.978	1.150	1.055	0.989	1.125	0.978	15.40	1.012	1.026	0.951	1.108	1.040	0.931	1.161
-10	1.002	0.930	1.080	1.046	0.976	1.122	1.042	0.986	1.101	0.984	0.945	1.013	1.025	0.961	1.093	1.040	0.95	1.138
-9	1.001	0.940	1.066	1.033	0.973	1.096	1.03	0.982	1.080	0.99	0.955	1.015	1.024	0.970	1.081	1.040	0.968	1.116
-8	1.001	0.948	1.056	1.02	0.968	1.075	1.018	0.977	1.061	0.995	0.965	1.017	1.023	0.977	1.071	1.040	0.985	1.098
-7	1.00	0.952	1.050	1.008	0.961	1.058	1.008	0.97	1.047	1.001	0.974	1.021	1.022	0.981	1.064	1.040	0.997	1.084
-6	0.999	0.953	1.048	0.998	0.953	1.046	0.999	0.962	1.036	1.005	0.981	1.025	1.021	0.982	1.060	1.040	1.003	1.077
-5	0.999	0.951	1.049	0.990	0.943	1.038	0.991	0.954	1.029	1.009	0.989	1.029	1.02	0.981	1.060	1.040	1.002	1.079
-4	0.998	0.947	1.052	0.983	0.935	1.034	0.985	0.947	1.025	1.012	0.991	1.034	1.019	0.978	1.062	1.040	0.996	1.085
-3	0.998	0.944	1.055	0.979	0.928	1.032	0.981	0.941	1.023	1.014	0.992	1.037	1.019	0.976	1.065	1.039	0.99	1.092
-2	0.998	0.941	1.057	0.977	0.925	1.032	0.980	0.938	1.023	1.015	0.992	1.038	1.019	0.974	1.067	1.039	0.985	1.097
-1	0.997	0.940	1.058	0.979	0.926	1.034	0.981	0.939	1.025	1.014	0.991	1.038	1.020	0.973	1.068	1.039	0.982	1.099
0	0.997	0.941	1.057	0.983	0.931	1.037	0.985	0.944	1.028	1.012	0.989	1.035	1.020	0.974	1.068	1.039	0.983	1.098
1	0.997	0.944	1.053	0.991	0.941	1.043	0.993	0.953	1.033	1.008	0.987	1.030	1.021	0.977	1.067	1.038	0.986	1.093
2	0.998	0.949	1.049	1.002	0.956	1.052	1.003	0.966	1.042	1.003	0.983	1.023	1.023	0.982	1.066	1.038	0.993	1.086
3	0.998	0.951	1.047	1.016	0.970	1.064	1.016	0.980	1.054	0.996	0.977	1.016	1.025	0.985	1.066	1.038	0.998	1.079
4	0.999	0.952	1.048	1.030	0.982	1.079	1.028	0.991	1.068	0.991	0.971	1.011	1.026	0.986	1.068	1.037	0.999	1.076
5	1.00	0.950	1.052	1.040	0.989	1.093	1.038	0.997	1.079	0.986	0.966	1.007	1.028	0.986	1.072	1.036	0.996	1.078
6	1.001	0.949	1.056	1.045	0.992	1.101	1.043	1.001	1.087	0.984	0.962	1.006	1.029	0.985	1.075	1.035	0.991	1.081
7	1.002	0.948	1.059	1.047	0.993	1.105	1.044	1.001	1.089	0.984	0.962	1.006	1.030	0.985	1.077	1.034	0.988	1.082
8	1.003	0.949	1.061	1.046	0.992	1.103	1.043	1.000	1.087	0.985	0.963	1.007	1.031	0.986	1.078	1.033	0.986	1.082
9	1.005	0.952	1.061	1.042	0.99	1.097	1.038	0.997	1.081	0.987	0.966	1.009	1.032	0.988	1.077	1.031	0.985	1.080
10	1.007	0.955	1.061	1.036	0.986	1.088	1.032	0.993	1.073	0.99	0.970	1.011	1.032	0.990	1.076	1.030	0.986	1.076
11	1.009	0.96	1.061	1.028	0.981	1.077	1.024	0.988	1.062	0.995	0.975	1.014	1.032	0.992	1.073	1.029	0.987	1.072
12	1.011	0.964	1.061	1.019	0.975	1.065	1.016	0.981	1.051	0.999	0.981	1.018	1.032	0.994	1.071	1.027	0.988	1.067
13	1.014	0.969	1.061	1.010	0.969	1.053	1.007	0.974	1.040	1.004	0.987	1.022	1.031	0.995	1.069	1.025	0.990	1.062
14	1.016	0.973	1.061	1.001	0.961	1.042	0.998	0.966	1.030	1.009	0.992	1.027	1.031	0.995	1.068	1.024	0.991	1.058
15	1.019	0.977	1.063	0.993	0.954	1.034	0.989	0.959	1.021	1.014	0.997	1.031	1.030	0.995	1.067	1.022	0.990	1.055
16	1.022	0.980	1.066	0.986	0.946	1.027	0.982	0.951	1.014	1.018	1.000	1.036	1.030	0.994	1.067	1.021	0.989	1.054

17	1.026	0.984	1.070	0.980	0.940	1.022	0.976	0.945	1.009	1.021	1.003	1.039	1.029	0.992	1.067	1.019	0.987	1.052
18	1.029	0.987	1.073	0.976	0.936	1.019	0.972	0.940	1.005	1.024	1.006	1.042	1.028	0.990	1.067	1.018	0.985	1.052
19	1.033	0.990	1.077	0.974	0.932	1.017	0.968	0.936	1.002	1.026	1.007	1.045	1.027	0.989	1.066	1.017	0.983	1.051
20	1.037	0.994	1.081	0.972	0.93	1.016	0.966	0.933	1.000	1.027	1.008	1.046	1.025	0.987	1.065	1.015	0.982	1.050
21	1.041	0.997	1.085	0.972	0.93	1.016	0.965	0.932	0.999	1.028	1.009	1.047	1.024	0.986	1.064	1.014	0.980	1.049
22	1.045	1.002	1.090	0.973	0.931	1.017	0.965	0.931	0.999	1.028	1.009	1.047	1.023	0.984	1.062	1.013	0.979	1.048
23	1.049	1.006	1.094	0.975	0.933	1.019	0.965	0.932	1.000	1.027	1.009	1.047	1.021	0.983	1.061	1.012	0.978	1.047
24	1.053	1.011	1.098	0.978	0.936	1.021	0.967	0.934	1.001	1.026	1.008	1.045	1.020	0.982	1.059	1.010	0.977	1.045
25	1.058	1.016	1.102	0.982	0.941	1.025	0.970	0.937	1.003	1.025	1.007	1.044	1.018	0.981	1.056	1.009	0.976	1.044
26	1.063	1.021	1.106	0.987	0.946	1.030	0.973	0.941	1.007	1.023	1.005	1.042	1.016	0.980	1.054	1.008	0.975	1.042
27	1.068	1.026	1.111	0.993	0.952	1.036	0.977	0.945	1.011	1.021	1.002	1.039	1.015	0.978	1.052	1.007	0.975	1.041
28	1.073	1.031	1.117	1.000	0.958	1.044	0.982	0.949	1.017	1.018	1.000	1.036	1.013	0.977	1.05	1.006	0.974	1.039
29	1.078	1.035	1.123	1.007	0.964	1.053	0.988	0.954	1.023	1.015	0.996	1.033	1.011	0.974	1.049	1.005	0.972	1.039
30	1.083	1.039	1.130	1.016	0.970	1.064	0.995	0.959	1.031	1.011	0.992	1.031	1.009	0.971	1.049	1.004	0.971	1.039
31	1.089	1.041	1.138	1.025	0.976	1.076	1.002	0.964	1.041	1.007	0.987	1.028	1.007	0.967	1.049	1.003	0.968	1.039
32	1.094	1.044	1.147	1.035	0.982	1.091	1.009	0.968	1.052	1.003	0.982	1.025	1.005	0.962	1.050	1.002	0.965	1.041
33	1.100	1.045	1.158	1.046	0.988	1.107	1.018	0.973	1.065	0.999	0.975	1.022	1.003	0.956	1.052	1.001	0.961	1.043
34	1.106	1.046	1.169	1.057	0.993	1.125	1.026	0.977	1.078	0.994	0.969	1.019	1.001	0.95	1.054	1.000	0.956	1.046
35	1.111	1.046	1.181	1.069	0.998	1.145	1.036	0.981	1.093	0.989	0.962	1.017	0.999	0.943	1.057	0.999	0.951	1.050
36	1.117	1.045	1.194	1.081	1.003	1.166	1.045	0.985	1.110	0.984	0.955	1.014	0.996	0.936	1.061	0.998	0.946	1.054
37	1.123	1.044	1.208	1.094	1.008	1.189	1.056	0.989	1.127	0.979	0.947	1.012	0.994	0.928	1.065	0.998	0.940	1.059
38	1.129	1.043	1.223	1.108	1.012	1.213	1.066	0.993	1.145	0.974	0.939	1.010	0.992	0.920	1.069	0.997	0.934	1.064
39	1.136	1.042	1.238	1.122	1.017	1.238	1.077	0.996	1.164	0.968	0.931	1.007	0.990	0.912	1.074	0.996	0.927	1.069
40	1.142	1.040	1.254	1.136	1.021	1.264	1.088	1.000	1.184	0.963	0.923	1.005	0.988	0.904	1.079	0.995	0.921	1.075
41	1.148	1.038	1.270	1.15	1.025	1.291	1.099	1.004	1.204	0.957	0.914	1.003	0.985	0.887	1.084	0.994	0.914	1.081
42	1.154	1.035	1.287	1.165	1.029	1.319	1.111	1.007	1.225	0.952	0.906	1.000	0.983	0.887	1.089	0.993	0.907	1.088

Note: Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval; UTCI, Universal Thermal Climate Index; P1-P99; 1st -99th centile of UTCI

Table S9.3 Weekly-specific UTCI exposure over 12-week preconception (-11 to 0) through to gestational week at delivery (1 to 36) at different thresholds of UTCI using the median of 14.2 ˚C as a reference and the adjusted hazard ratios of sPTB in Western Australia, 2000–2015.

Week	P1 (10.2 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.4 ˚C)			P95 (17.4 ˚C)			P99 (26.1 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-11	0.979	0.943	1.014	0.988	0.963	1.016	0.993	0.970	1.016	1.005	0.987	1.025	1.013	0.985	1.042	1.048	0.998	1.101
-10	0.982	0.953	1.013	0.988	0.967	1.010	0.992	0.974	1.012	1.006	0.99	1.022	1.012	0.989	1.035	1.038	0.999	1.078
-9	0.986	0.961	1.011	0.989	0.971	1.007	0.992	0.977	1.008	1.006	0.993	1.019	1.010	0.992	1.029	1.028	1.000	1.057
-8	0.989	0.968	1.011	0.989	0.974	1.005	0.992	0.978	1.005	1.006	0.995	1.018	1.009	0.993	1.025	1.019	0.998	1.040
-7	0.992	0.972	1.013	0.990	0.976	1.004	0.992	0.979	1.004	1.007	0.996	1.017	1.008	0.994	1.022	1.010	0.993	1.028
-6	0.995	0.975	1.016	0.991	0.977	1.005	0.992	0.979	1.005	1.007	0.996	1.017	1.007	0.992	1.022	1.003	0.985	1.022
-5	0.998	0.976	1.021	0.992	0.977	1.007	0.992	0.979	1.006	1.007	0.995	1.018	1.006	0.991	1.022	0.997	0.975	1.020
-4	1.000	0.977	1.025	0.993	0.977	1.010	0.993	0.979	1.008	1.006	0.994	1.018	1.006	0.989	1.023	0.993	0.968	1.019
-3	1.002	0.978	1.028	0.995	0.978	1.012	0.994	0.980	1.009	1.005	0.993	1.018	1.006	0.988	1.023	0.990	0.964	1.018
-2	1.004	0.979	1.029	0.997	0.980	1.014	0.996	0.981	1.011	1.004	0.992	1.017	1.006	0.988	1.024	0.990	0.964	1.017
-1	1.005	0.981	1.029	0.999	0.983	1.016	0.998	0.984	1.013	1.003	0.991	1.015	1.007	0.99	1.024	0.992	0.968	1.016
0	1.005	0.983	1.028	1.002	0.986	1.018	1.001	0.987	1.015	1.001	0.99	1.012	1.008	0.992	1.024	0.996	0.976	1.016
1	1.005	0.982	1.028	1.005	0.989	1.021	1.004	0.990	1.018	0.999	0.987	1.010	1.009	0.994	1.025	1.003	0.984	1.023
2	1.004	0.979	1.031	1.008	0.990	1.027	1.008	0.992	1.024	0.996	0.983	1.009	1.011	0.993	1.030	1.012	0.985	1.039
3	1.005	0.977	1.035	1.011	0.991	1.031	1.011	0.993	1.029	0.995	0.980	1.009	1.011	0.990	1.033	1.016	0.983	1.051
4	1.009	0.981	1.037	1.012	0.993	1.032	1.011	0.994	1.029	0.994	0.980	1.009	1.009	0.989	1.030	1.013	0.980	1.047
5	1.013	0.988	1.039	1.013	0.995	1.031	1.010	0.994	1.025	0.995	0.983	1.008	1.005	0.987	1.024	1.005	0.978	1.033
6	1.018	0.995	1.040	1.012	0.997	1.028	1.008	0.994	1.021	0.997	0.986	1.008	1.001	0.985	1.018	0.995	0.975	1.016
7	1.021	0.999	1.043	1.011	0.996	1.027	1.005	0.992	1.019	0.998	0.988	1.009	0.998	0.983	1.013	0.986	0.971	1.003
8	1.022	1.000	1.045	1.010	0.994	1.026	1.003	0.990	1.017	0.999	0.989	1.011	0.996	0.980	1.011	0.981	0.979	0.998
9	1.022	0.998	1.046	1.008	0.992	1.024	1.002	0.988	1.016	1.001	0.989	1.012	0.995	0.979	1.011	0.978	0.988	0.998
10	1.020	0.996	1.044	1.006	0.990	1.023	1.000	0.986	1.015	1.001	0.990	1.013	0.995	0.979	1.011	0.978	0.965	0.999
11	1.017	0.993	1.040	1.004	0.988	1.02	0.999	0.985	1.013	1.002	0.991	1.013	0.996	0.98	1.012	0.981	0.96	1.002
12	1.013	0.990	1.035	1.002	0.987	1.018	0.998	0.985	1.012	1.002	0.991	1.013	0.997	0.982	1.013	0.985	0.958	1.005
13	1.008	0.987	1.029	1.000	0.985	1.015	0.998	0.985	1.010	1.003	0.992	1.013	0.999	0.985	1.014	0.99	0.959	1.009
14	1.003	0.984	1.023	0.998	0.984	1.012	0.997	0.985	1.009	1.003	0.993	1.013	1.002	0.988	1.016	0.996	0.964	1.013
15	0.999	0.980	1.017	0.996	0.983	1.009	0.997	0.986	1.008	1.003	0.994	1.012	1.004	0.991	1.018	1.003	0.970	1.018
16	0.995	0.977	1.012	0.995	0.983	1.008	0.997	0.986	1.008	1.003	0.994	1.012	1.007	0.994	1.020	1.01	0.996	1.023

17	0.991	0.974	1.009	0.994	0.982	1.007	0.997	0.986	1.008	1.003	0.994	1.012	1.009	0.997	1.023	1.016	1.003	1.029
18	0.989	0.972	1.006	0.994	0.981	1.006	0.997	0.986	1.008	1.003	0.993	1.012	1.012	0.998	1.025	1.021	1.008	1.034
19	0.988	0.970	1.006	0.994	0.981	1.007	0.998	0.986	1.009	1.003	0.993	1.012	1.013	0.999	1.027	1.025	1.012	1.039
20	0.988	0.970	1.007	0.994	0.981	1.008	0.998	0.986	1.010	1.002	0.993	1.013	1.014	1.000	1.028	1.028	1.014	1.043
21	0.990	0.972	1.009	0.996	0.982	1.009	0.999	0.987	1.011	1.002	0.992	1.013	1.015	1.000	1.029	1.030	1.015	1.045
22	0.993	0.974	1.012	0.997	0.984	1.011	0.999	0.987	1.012	1.002	0.992	1.013	1.015	1.001	1.029	1.030	1.015	1.045
23	0.997	0.978	1.015	1.000	0.986	1.013	1.000	0.988	1.013	1.002	0.992	1.012	1.014	1.000	1.029	1.029	1.015	1.045
24	1.002	0.984	1.020	1.002	0.989	1.016	1.001	0.989	1.013	1.002	0.992	1.012	1.014	1.000	1.028	1.028	1.013	1.042
25	1.008	0.990	1.026	1.005	0.993	1.019	1.002	0.991	1.014	1.002	0.992	1.012	1.013	0.999	1.026	1.025	1.011	1.039
26	1.015	0.998	1.032	1.009	0.996	1.022	1.003	0.992	1.015	1.002	0.993	1.011	1.011	0.998	1.024	1.021	1.008	1.035
27	1.023	1.006	1.039	1.013	1.001	1.025	1.005	0.994	1.016	1.002	0.993	1.011	1.009	0.997	1.022	1.017	1.004	1.030
28	1.031	1.015	1.048	1.017	1.005	1.029	1.006	0.995	1.017	1.002	0.993	1.011	1.007	0.995	1.020	1.012	1.000	1.024
29	1.040	1.024	1.057	1.021	1.009	1.034	1.007	0.997	1.018	1.002	0.993	1.011	1.005	0.992	1.018	1.006	0.994	1.019
30	1.050	1.033	1.068	1.026	1.013	1.039	1.009	0.998	1.020	1.001	0.992	1.011	1.002	0.989	1.016	1.000	0.987	1.013
31	1.061	1.043	1.080	1.031	1.017	1.045	1.010	0.998	1.022	1.001	0.992	1.011	1.000	0.986	1.014	0.993	0.979	1.008
32	1.072	1.052	1.093	1.036	1.021	1.051	1.012	0.999	1.025	1.001	0.991	1.012	0.997	0.982	1.012	0.987	0.970	1.003
33	1.084	1.061	1.107	1.041	1.025	1.058	1.013	0.999	1.028	1.001	0.989	1.013	0.994	0.977	1.011	0.979	0.961	0.998
34	1.096	1.070	1.122	1.047	1.028	1.066	1.015	0.998	1.031	1.001	0.988	1.015	0.991	0.972	1.010	0.972	0.951	0.994
35	1.108	1.079	1.138	1.052	1.031	1.074	1.016	0.998	1.035	1.001	0.986	1.016	0.988	0.967	1.009	0.965	0.940	0.989
36	1.121	1.088	1.155	1.058	1.035	1.082	1.018	0.997	1.039	1.001	0.984	1.018	0.985	0.962	1.008	0.957	0.930	0.985

Note: Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval; UTCI, Universal Thermal Climate Index; P1-P99; 1st -99th centile of UTCI

Table S9.4. Monthly-specific UTCI exposure over three months preconception (-2 to 0) through to gestational month at delivery (1 to 10) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of Stillbirth in Western Australia, 2000–2015.

Month	P1 (10.2 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.5 ˚C)			P95 (17.4 ˚C)			P99 (26.1 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.970	0.831	1.133	1.071	0.941	1.218	1.081	0.972	1.202	0.940	0.870	1.016	0.984	0.871	1.112	1.049	0.906	1.215
-1	0.968	0.856	1.095	1.051	0.950	1.162	1.062	0.979	1.152	0.952	0.897	1.010	0.987	0.900	1.082	1.037	0.933	1.154
0	0.967	0.868	1.078	1.033	0.948	1.126	1.046	0.976	1.120	0.962	0.915	1.012	0.990	0.915	1.070	1.027	0.944	1.116
1	0.970	0.869	1.084	1.020	0.936	1.112	1.032	0.964	1.105	0.971	0.923	1.022	0.992	0.914	1.076	1.018	0.936	1.107
2	0.978	0.869	1.101	1.014	0.924	1.112	1.024	0.952	1.102	0.977	0.925	1.033	0.992	0.905	1.087	1.012	0.920	1.112
3	0.993	0.879	1.122	1.017	0.924	1.118	1.022	0.948	1.103	0.980	0.926	1.038	0.991	0.900	1.092	1.009	0.912	1.116
4	1.014	0.902	1.140	1.028	0.938	1.127	1.026	0.954	1.104	0.980	0.927	1.035	0.989	0.900	1.086	1.009	0.914	1.115
5	1.042	0.936	1.160	1.046	0.961	1.139	1.036	0.968	1.109	0.976	0.927	1.027	0.985	0.903	1.074	1.013	0.924	1.110
6	1.075	0.974	1.187	1.072	0.988	1.163	1.050	0.983	1.121	0.970	0.924	1.018	0.980	0.904	1.063	1.019	0.935	1.109
7	1.114	1.005	1.235	1.103	1.009	1.206	1.068	0.993	1.148	0.962	0.913	1.013	0.974	0.894	1.063	1.026	0.938	1.123
8	1.157	1.021	1.312	1.139	1.019	1.273	1.088	0.993	1.192	0.952	0.893	1.016	0.968	0.869	1.078	1.035	0.926	1.157
9	1.204	1.023	1.418	1.179	1.020	1.363	1.111	0.987	1.252	0.942	0.866	1.025	0.961	0.835	1.106	1.046	0.903	1.211
10	1.255	1.018	1.547	1.222	1.016	1.470	1.136	0.976	1.322	0.932	0.836	1.038	0.955	0.797	1.143	1.057	0.874	1.277

Note: Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval; UTCI, Universal Thermal Climate Index; P1-P99; 1^{st} -99^{th} centile of UTCI

Table S9.5. Monthly-specific UTCI exposure over three months preconception (-2 to 0) through to gestational month at delivery (1 to 10) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of sPTB in Western Australia, 2000–2015.

Month	P1 (10.2 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.5 ˚C)			P95 (17.4 ˚C)			P99 (26.1 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	0.918	0.854	0.986	0.945	0.901	0.991	0.967	0.930	1.005	1.021	0.984	1.058	1.028	0.976	1.082	1.112	1.028	1.204
-1	0.990	0.939	1.043	0.993	0.959	1.028	0.997	0.970	1.024	1.003	0.978	1.028	1.009	0.973	1.046	1.030	0.986	1.076
0	1.049	0.995	1.107	1.032	0.996	1.070	1.020	0.992	1.050	0.988	0.962	1.015	0.994	0.957	1.033	0.971	0.932	1.012
1	1.074	1.014	1.138	1.049	1.009	1.091	1.031	0.999	1.064	0.982	0.953	1.012	0.989	0.948	1.033	0.949	0.902	0.999
2	1.050	0.997	1.106	1.035	0.999	1.072	1.024	0.996	1.053	0.986	0.960	1.012	0.997	0.959	1.037	0.974	0.931	1.019
3	1.001	0.955	1.049	1.005	0.974	1.038	1.007	0.982	1.033	0.995	0.972	1.019	1.011	0.976	1.048	1.026	0.989	1.064
4	0.967	0.919	1.017	0.984	0.951	1.018	0.995	0.968	1.023	1.002	0.977	1.029	1.020	0.981	1.059	1.068	1.025	1.113
5	0.968	0.920	1.018	0.985	0.951	1.020	0.994	0.966	1.023	1.003	0.976	1.030	1.015	0.976	1.056	1.075	1.029	1.122
6	1.000	0.955	1.046	1.005	0.974	1.037	1.004	0.978	1.030	0.997	0.973	1.022	1.000	0.965	1.036	1.049	1.010	1.090
7	1.057	1.016	1.099	1.040	1.011	1.069	1.022	0.998	1.045	0.987	0.966	1.009	0.976	0.946	1.008	1.002	0.968	1.037
8	1.135	1.085	1.187	1.087	1.053	1.122	1.045	1.018	1.073	0.974	0.950	0.999	0.949	0.915	0.983	0.942	0.900	0.986
9	1.228	1.152	1.308	1.142	1.092	1.193	1.072	1.033	1.113	0.960	0.926	0.994	0.919	0.874	0.966	0.879	0.819	0.943

Note: Models were fitted from distributed lag non-linear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; LCI, 95% lower confidential interval; UCI, 95% upper confidential interval; UTCI, Universal Thermal Climate Index; sPTB, spontaneous preterm birth; P1-P99; 1st -99th centile of UTCI

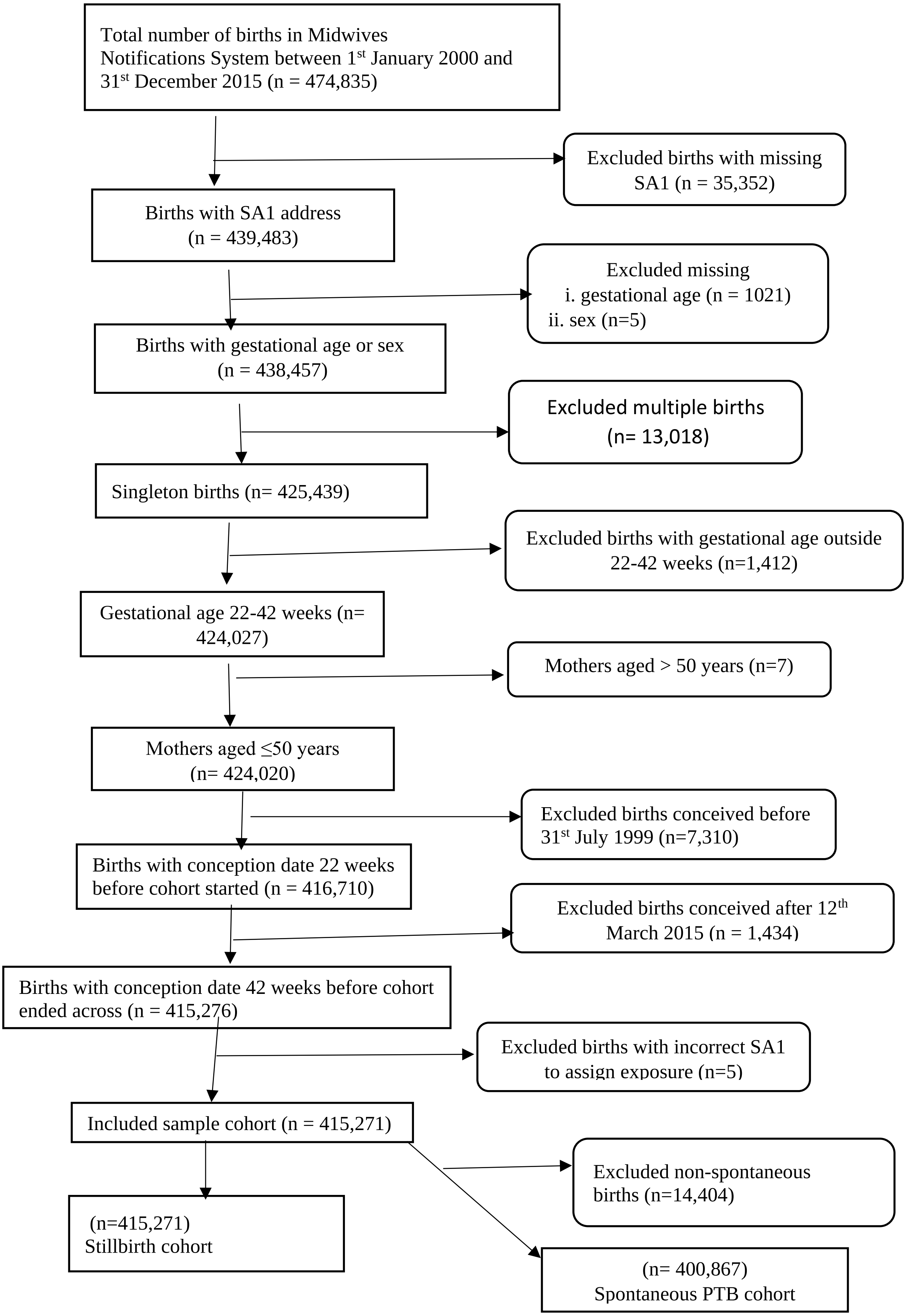

Figure S9.1. Flow chart for selecting the eligible births included in this study, Western Australia, 2000-2015. Note: SA1, statistical area level 1; PTB, preterm birth

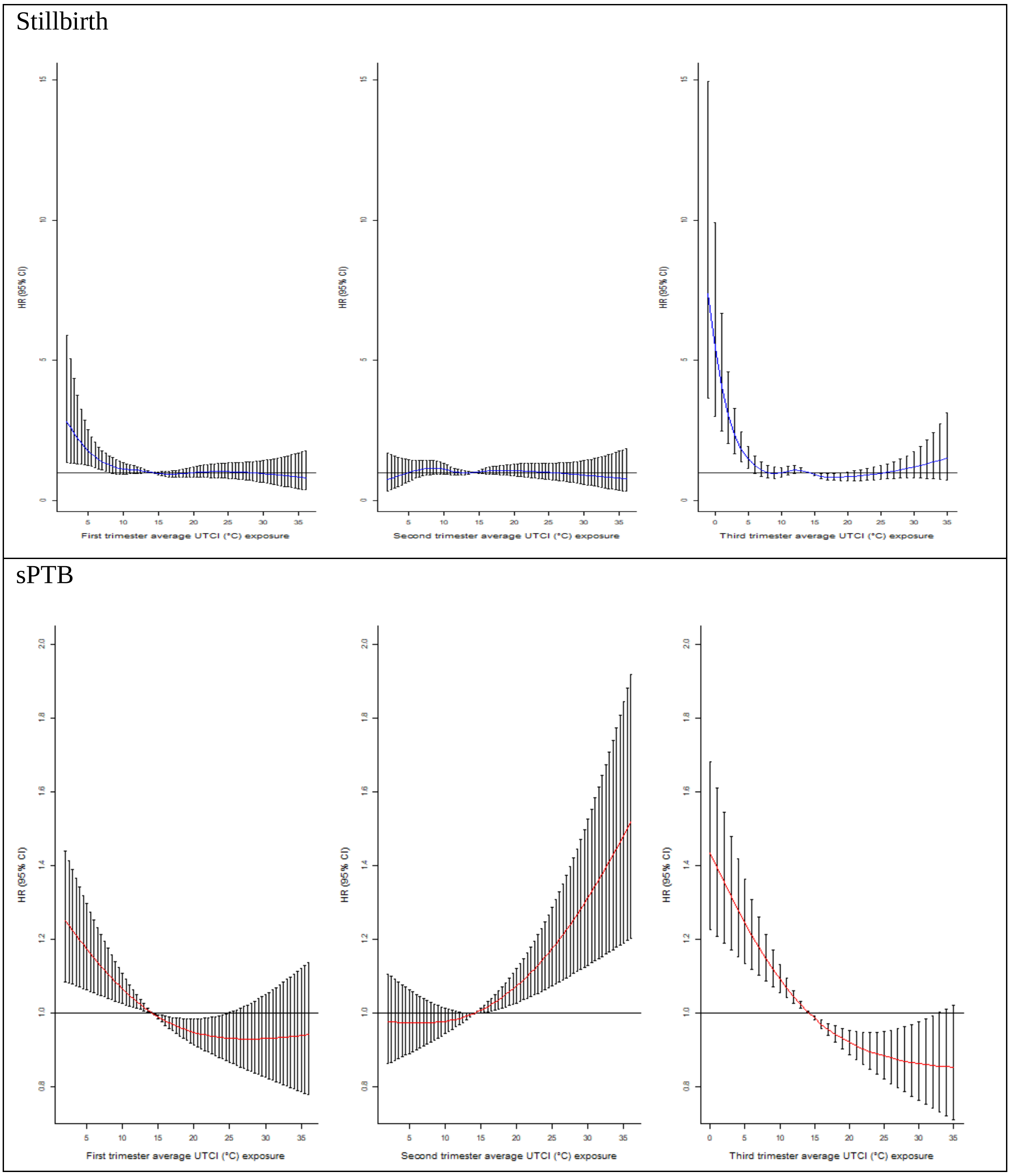

Figure S9.2 The exposure-response association between maternal trimester-average cumulative UTCI exposures with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB in Western Australia, 2000–2015. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

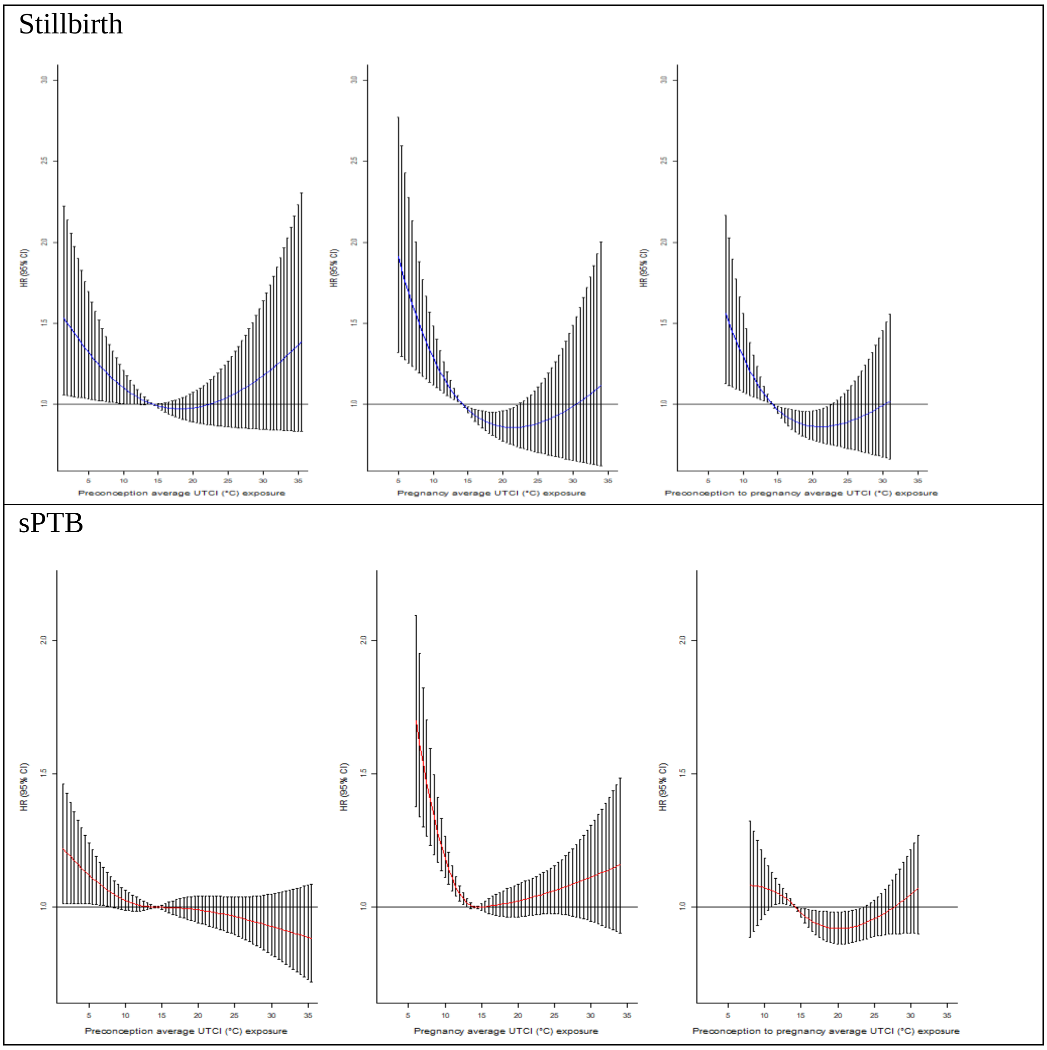

Figure S9.3 The exposure-response association between maternal cumulative UTCI exposures over preconception through to pregnancy with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB in Western Australia, 2000–2015. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

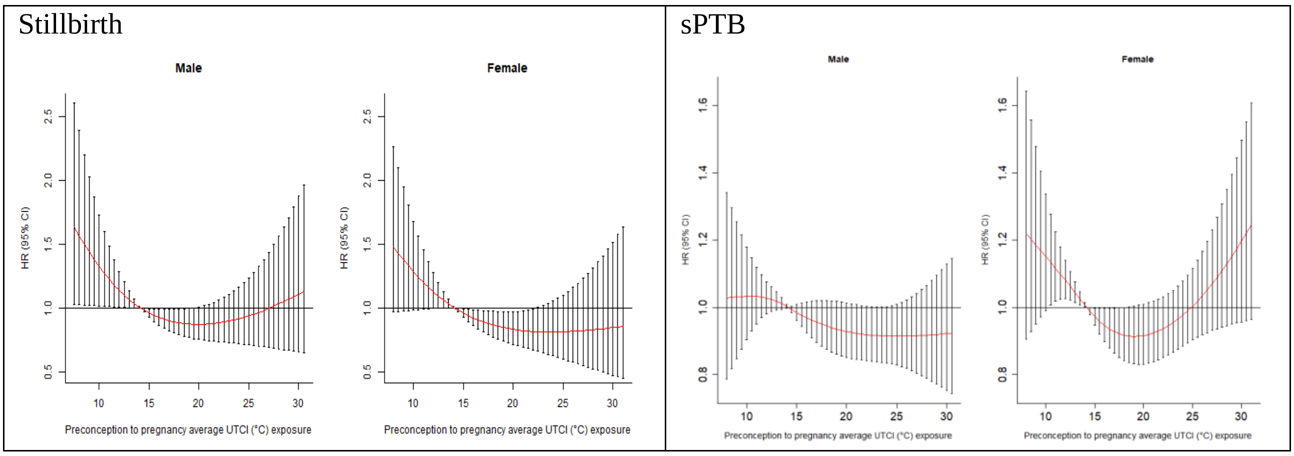

Figure S9.4 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by infant sex. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

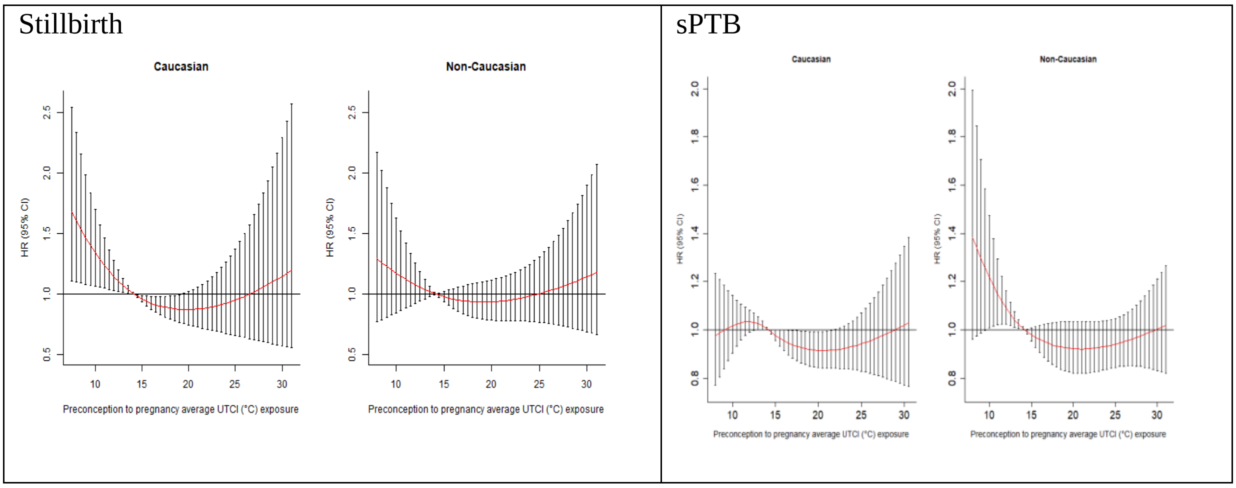

Figure S9.5 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by race or ethnicity. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for maternal age, infant sex, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

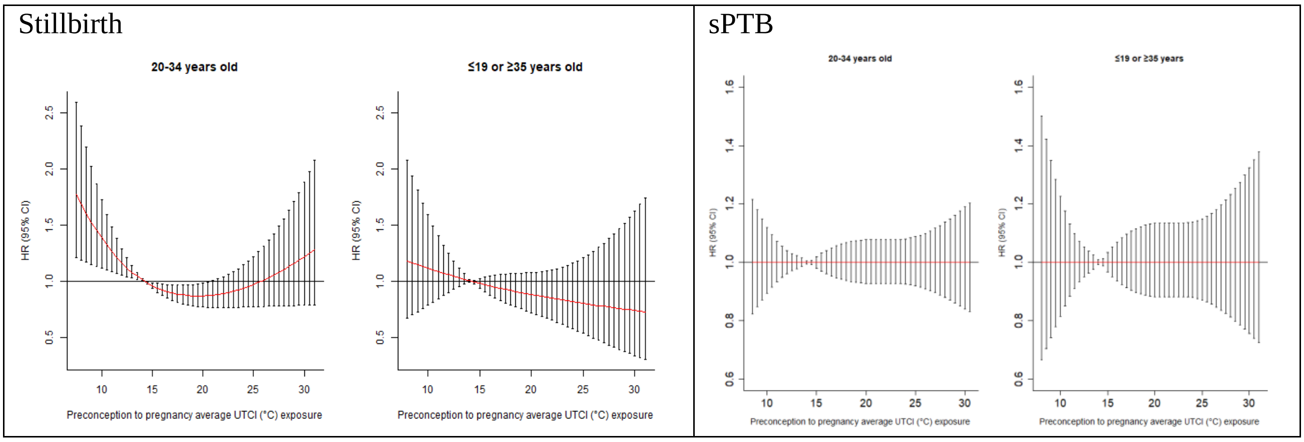

Figure S9.6 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by maternal age. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

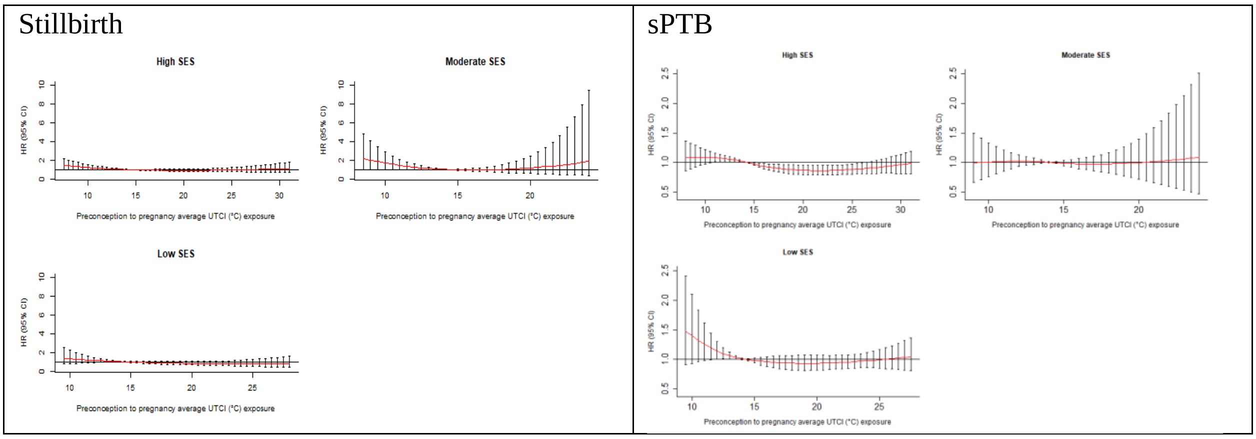

Figure S9.7 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by SES. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, marital status, smoking status, parity, remoteness, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index; SES, socioeconomic status

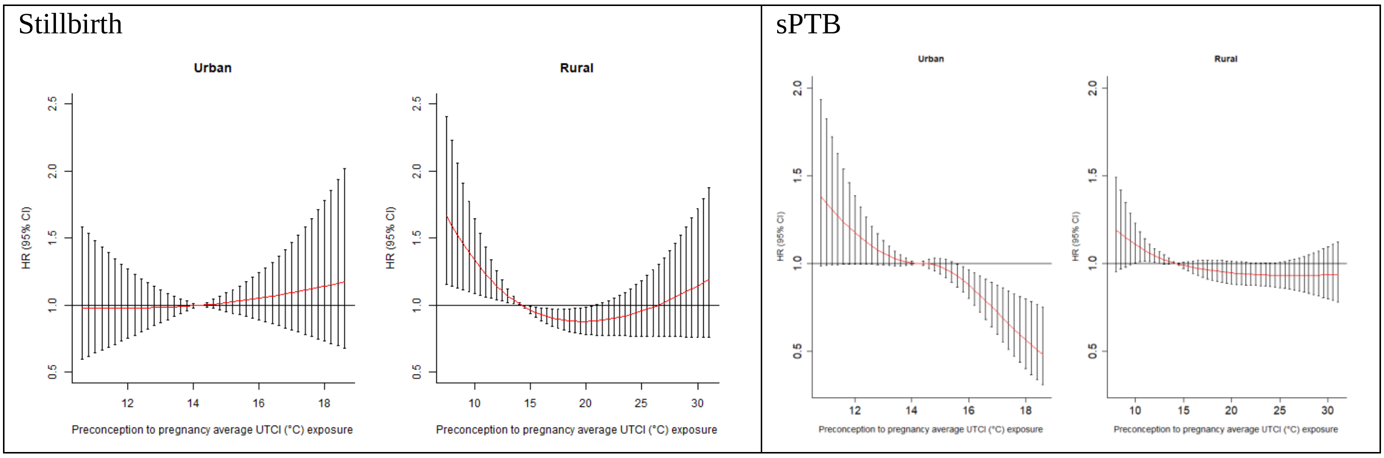

Figure S9.8 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by remoteness. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, marital status, smoking status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

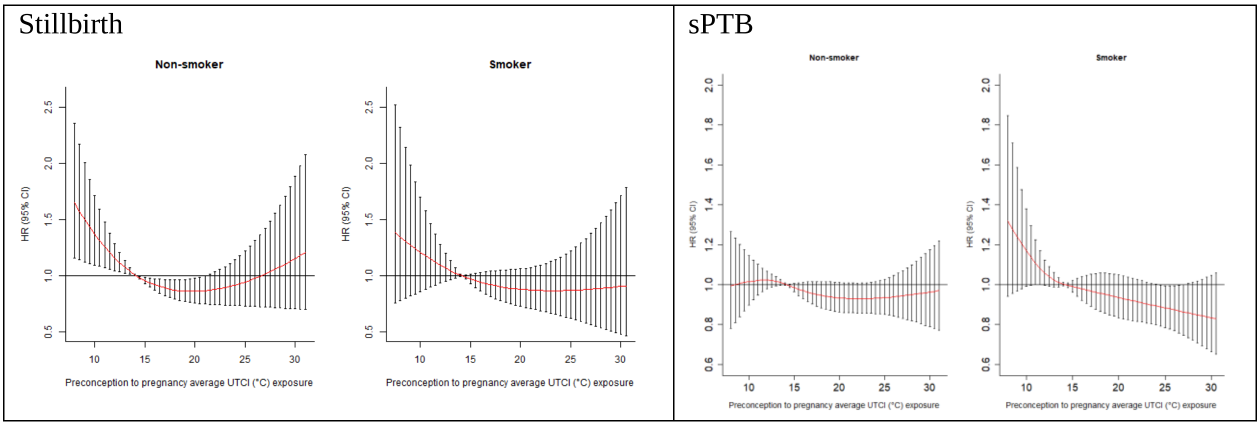

Figure S9.9 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by smoking status. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, marital status, remoteness, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

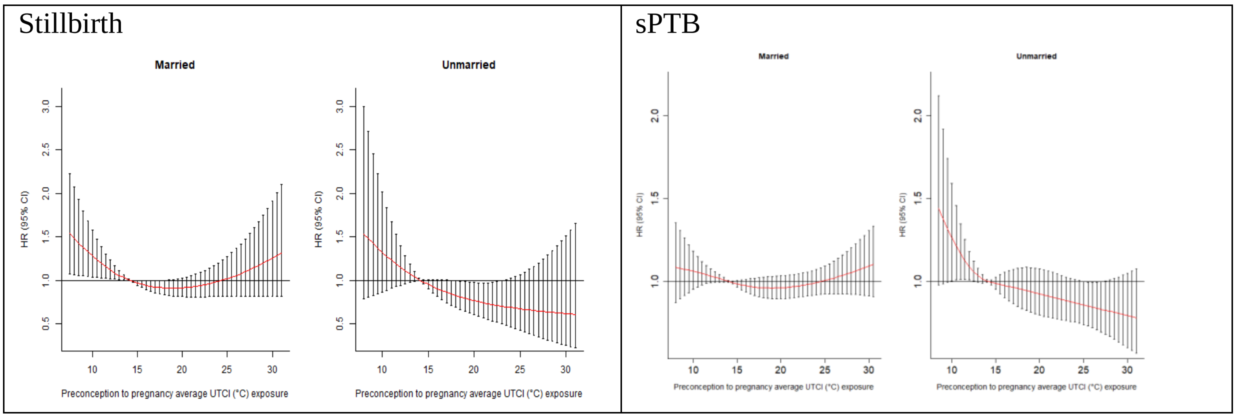

Figure S9.10 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by marital status. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

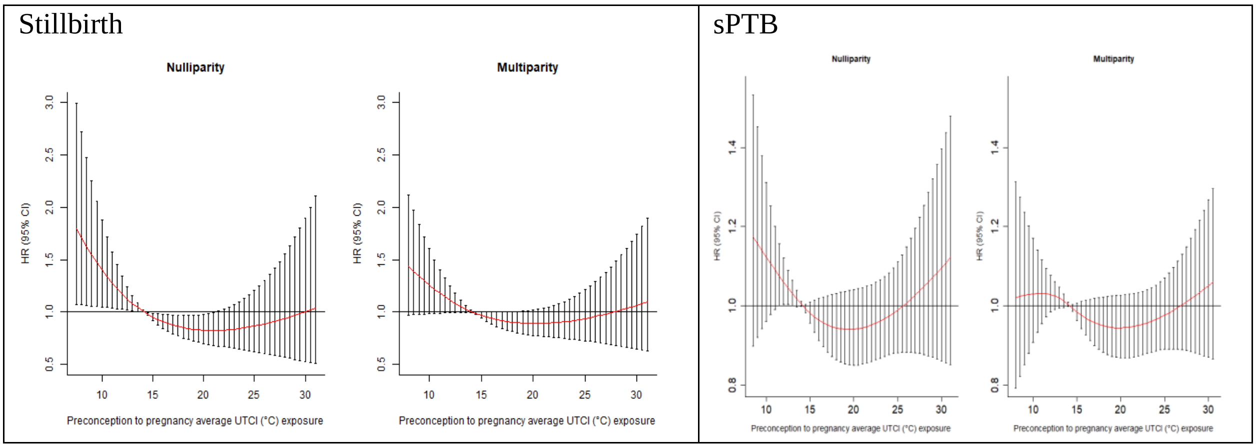

Figure S9.11 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by parity. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

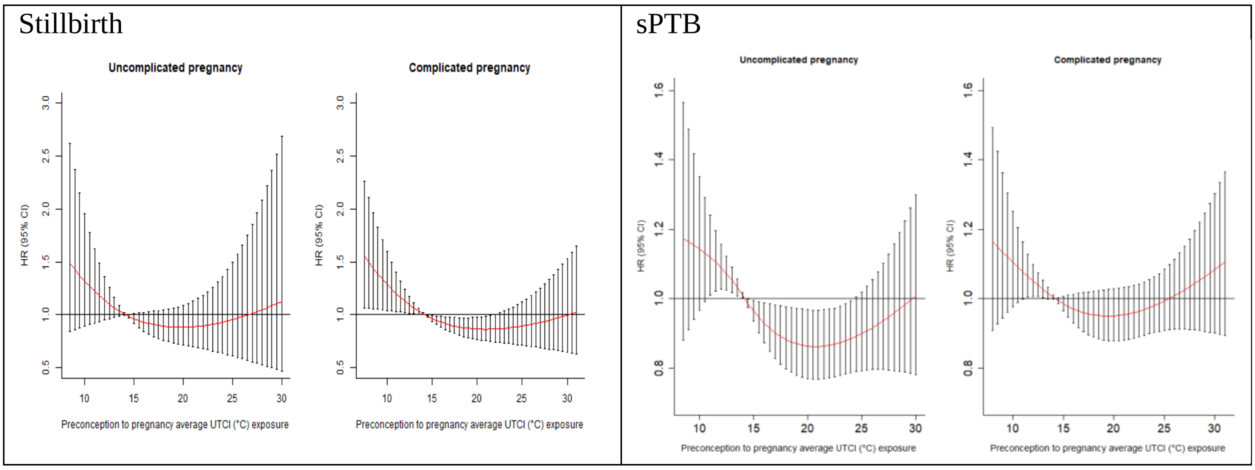

Figure S9.12 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB by pregnancy complications. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

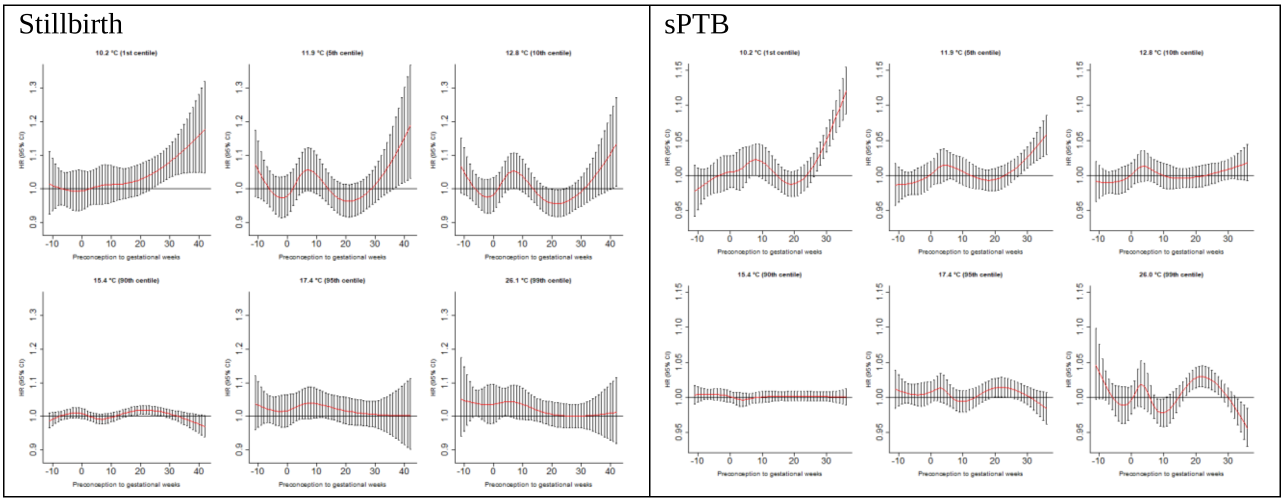

Figure S9.13 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to mean 14.5 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB. Mean rather than median UTCI was used as reference Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index

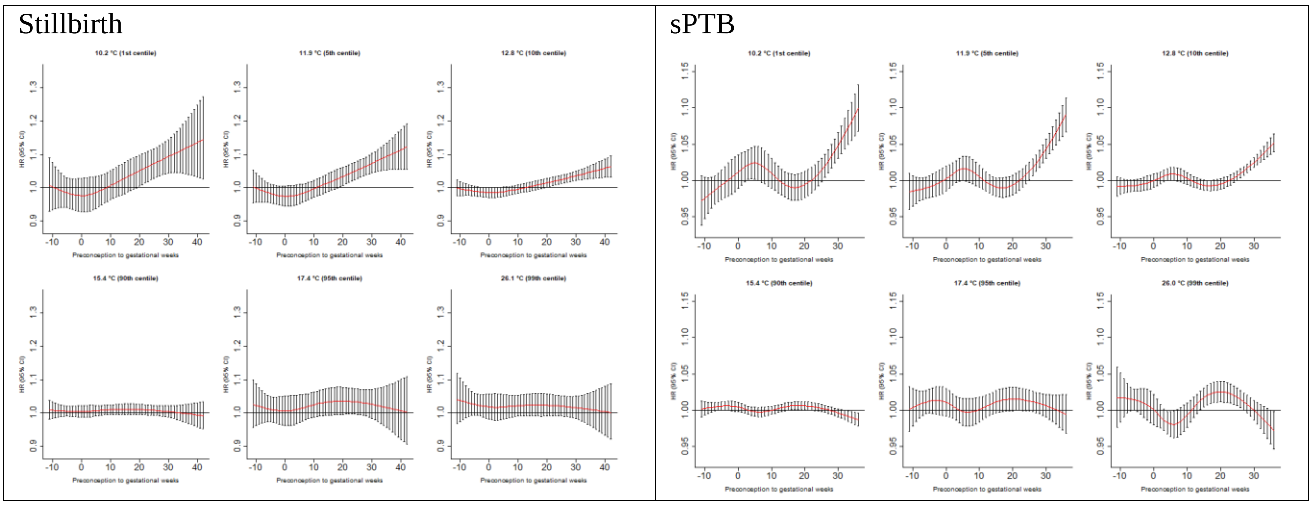

Figure S9.14 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to mean 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB. Degrees of freedom in constructing the crossbasis matrix were decreased by one for both exposure and exposure period. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index

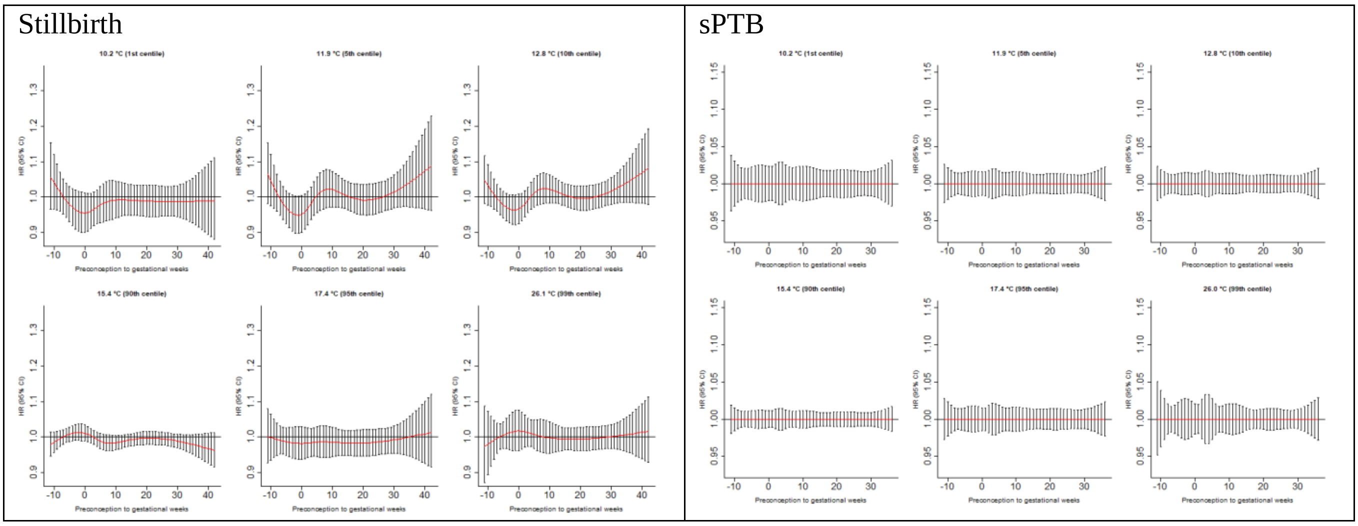

Figure S9.15 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to mean 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB. Used categorical instead of continuous maternal age. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index

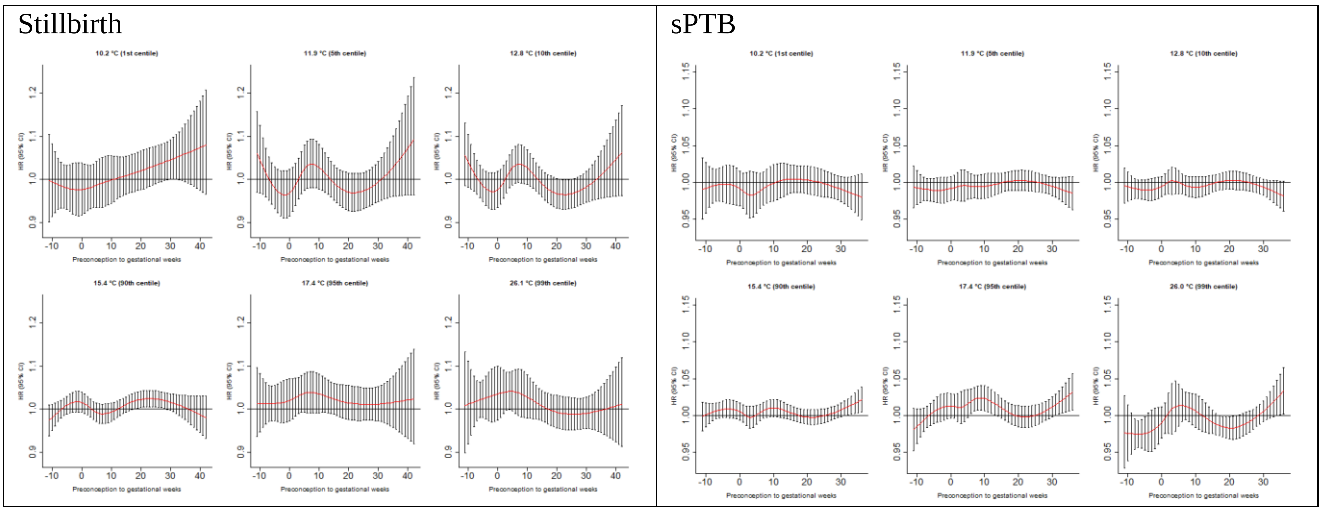

Figure S9.16 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to mean 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB. Adjusted for calendar month index (1 to 12) instead of four-season categories. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index

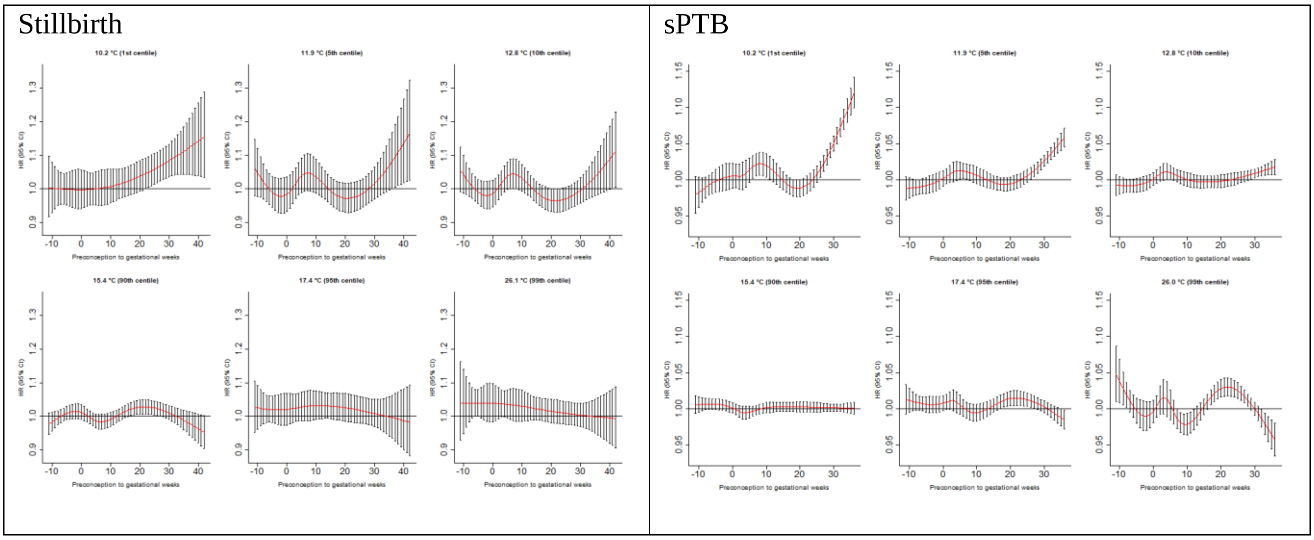

Figure S9.17 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to mean 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB. Included mother-specific clusters to account for repeated births by the same mother. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index

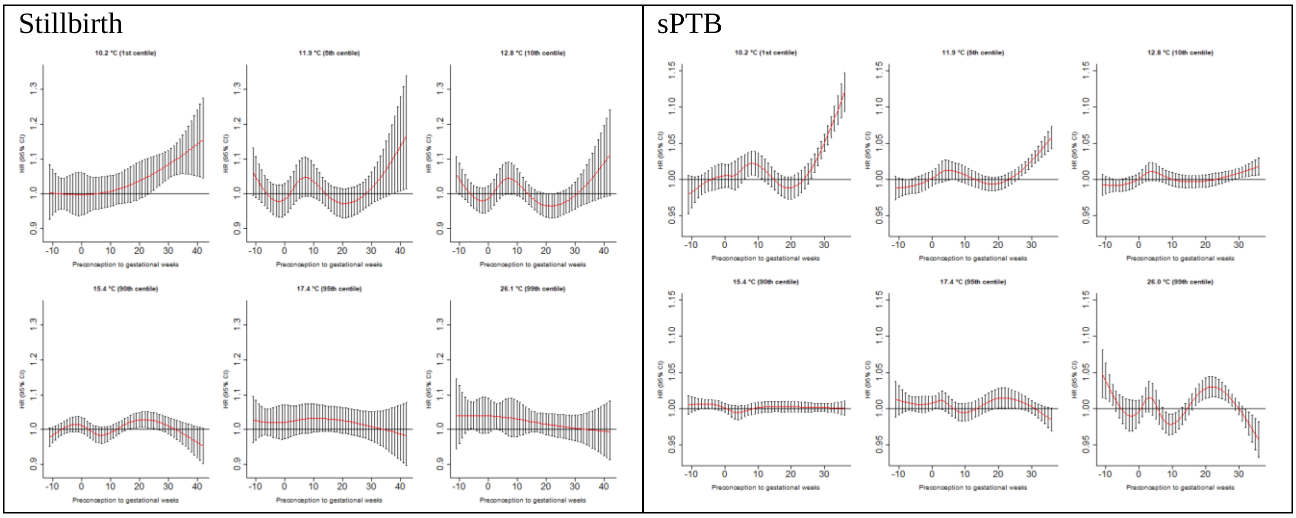

Figure S9.18 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to mean 14.2 ˚C and the hazard ratios HR (95% CI) of stillbirth and sPTB. Local government area-specific cluster was included to account for potential spatial clustering and maternal mobility. Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.

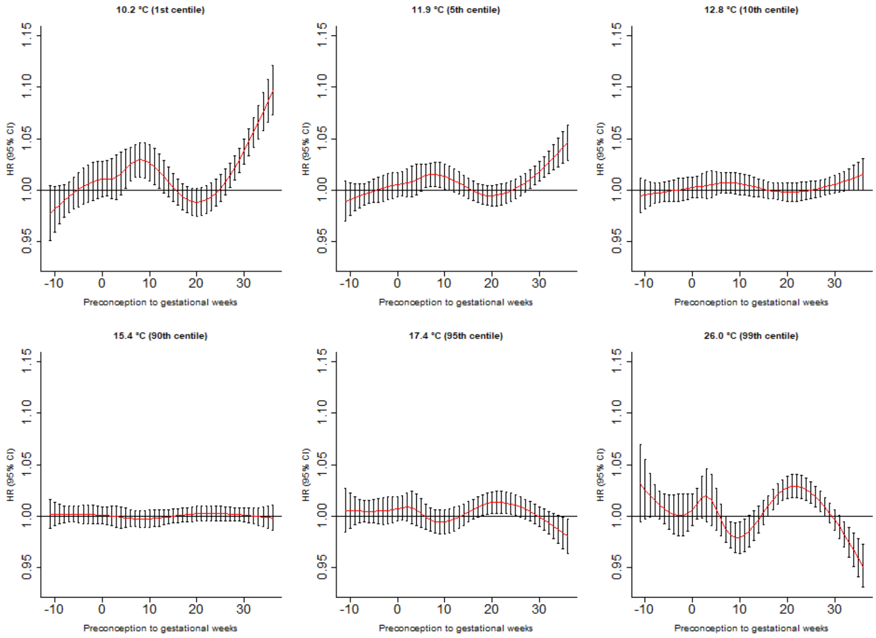

Figure S9.19 The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to mean 14.2 ˚C and the hazard ratios HR (95 % CI) of PTB. Analysed live singleton births (N= 413,348 births). Solid horizontal lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were adjusted for race or ethnicity, infant sex, maternal age, smoking status, remoteness, marital status, parity, socioeconomic status, and year and season of conception. Note: HR, hazard ratio; CI, confidence interval; PTB, Preterm birth; UTCI, Universal Thermal Climate Index.

Appendix I. Supplementary materials for Chapter 10

Table S10.1. Weekly-specific UTCI exposure over 12- week preconception (-11 to 0) through to gestational week at delivery (1 to 42) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of term SGA in Western Australia, 2000–2015.

Week	P1 (10.3 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.4 ˚C)			P95 (17.3 ˚C)			P99 (26.0 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-11	1.003	0.988	1.018	1.002	0.992	1.012	1.000	0.996	1.005	1.002	0.997	1.007	1.004	0.991	1.017	0.995	0.985	1.005
-10	1.002	0.988	1.016	1.001	0.992	1.010	1.000	0.996	1.005	1.002	0.997	1.006	1.004	0.992	1.016	0.995	0.985	1.005
-9	1.001	0.988	1.014	1.001	0.992	1.009	1.000	0.996	1.004	1.002	0.997	1.006	1.003	0.992	1.014	0.995	0.986	1.004
-8	1.000	0.988	1.013	1.000	0.992	1.008	1.000	0.996	1.004	1.001	0.997	1.005	1.003	0.992	1.013	0.995	0.987	1.003
-7	0.999	0.988	1.011	0.999	0.992	1.007	0.999	0.996	1.003	1.001	0.997	1.005	1.002	0.993	1.012	0.995	0.987	1.003
-6	0.998	0.988	1.009	0.999	0.992	1.006	0.999	0.996	1.003	1.001	0.998	1.005	1.002	0.993	1.011	0.995	0.988	1.002
-5	0.998	0.987	1.008	0.998	0.992	1.005	0.999	0.995	1.002	1.001	0.998	1.004	1.001	0.993	1.010	0.995	0.988	1.002
-4	0.997	0.987	1.007	0.998	0.991	1.004	0.999	0.995	1.002	1.001	0.998	1.004	1.001	0.993	1.009	0.995	0.989	1.002
-3	0.996	0.987	1.006	0.997	0.991	1.004	0.998	0.995	1.002	1.001	0.998	1.004	1.001	0.993	1.008	0.995	0.989	1.001
-2	0.995	0.986	1.005	0.997	0.991	1.003	0.998	0.995	1.001	1.001	0.998	1.004	1.000	0.993	1.007	0.995	0.989	1.001
-1	0.995	0.986	1.004	0.996	0.991	1.002	0.998	0.995	1.001	1.001	0.998	1.003	1.000	0.993	1.007	0.995	0.990	1.001
0	0.994	0.985	1.003	0.996	0.990	1.002	0.998	0.995	1.001	1.000	0.998	1.003	1.000	0.993	1.007	0.995	0.990	1.001
1	0.994	0.985	1.002	0.996	0.990	1.001	0.998	0.995	1.001	1.000	0.998	1.003	0.999	0.992	1.006	0.996	0.990	1.001
2	0.993	0.984	1.002	0.995	0.990	1.001	0.998	0.995	1.001	1.000	0.998	1.003	0.999	0.992	1.006	0.996	0.990	1.002
3	0.993	0.984	1.002	0.995	0.989	1.001	0.997	0.995	1.000	1.000	0.998	1.003	0.999	0.992	1.006	0.996	0.990	1.002
4	0.992	0.983	1.002	0.995	0.989	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.992	1.006	0.996	0.990	1.002
5	0.992	0.983	1.001	0.995	0.989	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.991	1.006	0.996	0.990	1.002

6	0.992	0.983	1.001	0.995	0.989	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.991	1.006	0.996	0.990	1.003
7	0.992	0.982	1.001	0.995	0.988	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.991	1.006	0.997	0.990	1.003
8	0.992	0.982	1.002	0.995	0.988	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.991	1.006	0.997	0.990	1.003
9	0.992	0.982	1.002	0.995	0.988	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.991	1.007	0.997	0.990	1.003
10	0.992	0.982	1.002	0.995	0.988	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.991	1.007	0.997	0.991	1.004
11	0.992	0.982	1.002	0.995	0.988	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.991	1.007	0.997	0.991	1.004
12	0.992	0.983	1.002	0.995	0.989	1.001	0.997	0.994	1.000	1.000	0.997	1.003	0.999	0.991	1.007	0.998	0.991	1.004
13	0.993	0.983	1.003	0.995	0.989	1.001	0.997	0.994	1.001	1.000	0.997	1.004	0.999	0.991	1.007	0.998	0.991	1.005
14	0.993	0.983	1.003	0.995	0.989	1.002	0.998	0.994	1.001	1.000	0.997	1.004	1.000	0.992	1.008	0.998	0.992	1.005
15	0.994	0.984	1.003	0.996	0.990	1.002	0.998	0.995	1.001	1.001	0.997	1.004	1.000	0.992	1.008	0.999	0.992	1.005
16	0.994	0.985	1.004	0.996	0.990	1.002	0.998	0.995	1.001	1.001	0.998	1.004	1.000	0.993	1.008	0.999	0.993	1.005
17	0.995	0.985	1.004	0.996	0.990	1.002	0.998	0.995	1.001	1.001	0.998	1.004	1.001	0.993	1.008	0.999	0.993	1.006
18	0.995	0.986	1.005	0.997	0.991	1.003	0.998	0.995	1.001	1.001	0.998	1.004	1.001	0.994	1.009	1.000	0.993	1.006
19	0.996	0.987	1.005	0.997	0.991	1.003	0.998	0.995	1.001	1.001	0.998	1.004	1.002	0.994	1.009	1.000	0.994	1.006
20	0.997	0.988	1.006	0.998	0.992	1.003	0.998	0.996	1.001	1.001	0.998	1.004	1.002	0.995	1.009	1.000	0.994	1.006
21	0.997	0.989	1.006	0.998	0.993	1.004	0.999	0.996	1.002	1.001	0.998	1.004	1.002	0.995	1.010	1.001	0.995	1.006
22	0.998	0.990	1.007	0.999	0.993	1.004	0.999	0.996	1.002	1.001	0.999	1.004	1.003	0.996	1.010	1.001	0.995	1.007
23	0.999	0.991	1.008	0.999	0.994	1.005	0.999	0.996	1.002	1.002	0.999	1.004	1.004	0.997	1.011	1.001	0.996	1.007
24	1.000	0.992	1.008	1.000	0.995	1.005	0.999	0.997	1.002	1.002	0.999	1.004	1.004	0.997	1.011	1.002	0.996	1.007
25	1.001	0.993	1.009	1.000	0.995	1.006	1.000	0.997	1.002	1.002	0.999	1.005	1.005	0.998	1.012	1.002	0.997	1.008
26	1.002	0.994	1.010	1.001	0.996	1.006	1.000	0.997	1.003	1.002	0.999	1.005	1.005	0.999	1.012	1.003	0.997	1.008
27	1.003	0.995	1.011	1.002	0.997	1.007	1.000	0.998	1.003	1.002	1.000	1.005	1.006	0.999	1.013	1.003	0.998	1.008

28	1.004	0.996	1.012	1.002	0.997	1.008	1.001	0.998	1.003	1.002	1.000	1.005	1.007	1.000	1.014	1.004	0.998	1.009
29	1.005	0.997	1.013	1.003	0.998	1.008	1.001	0.998	1.004	1.003	1.000	1.005	1.007	1.000	1.014	1.004	0.998	1.010
30	1.006	0.998	1.015	1.004	0.998	1.009	1.001	0.998	1.004	1.003	1.000	1.006	1.008	1.001	1.015	1.004	0.999	1.010
31	1.007	0.999	1.016	1.005	0.999	1.010	1.001	0.999	1.004	1.003	1.000	1.006	1.009	1.001	1.016	1.005	0.999	1.011
32	1.009	1.000	1.018	1.005	1.000	1.011	1.002	0.999	1.005	1.003	1.000	1.006	1.009	1.002	1.017	1.005	0.999	1.011
33	1.010	1.000	1.019	1.006	1.000	1.012	1.002	0.999	1.005	1.003	1.000	1.007	1.010	1.002	1.018	1.006	0.999	1.012
34	1.011	1.001	1.021	1.007	1.001	1.013	1.002	0.999	1.006	1.004	1.000	1.007	1.011	1.002	1.020	1.006	0.999	1.013
35	1.012	1.002	1.023	1.008	1.001	1.014	1.003	0.999	1.006	1.004	1.000	1.007	1.012	1.003	1.021	1.007	0.999	1.014
36	1.014	1.003	1.025	1.008	1.001	1.015	1.003	1.000	1.007	1.004	1.000	1.008	1.012	1.003	1.022	1.007	1.000	1.015
37	1.015	1.003	1.027	1.009	1.002	1.017	1.003	1.000	1.007	1.004	1.000	1.008	1.013	1.003	1.023	1.008	1.000	1.016
38	1.016	1.004	1.029	1.010	1.002	1.018	1.004	1.000	1.008	1.005	1.000	1.009	1.014	1.003	1.025	1.008	1.000	1.017
39	1.017	1.004	1.031	1.011	1.003	1.019	1.004	1.000	1.008	1.005	1.000	1.009	1.015	1.003	1.026	1.009	1.000	1.018
40	1.019	1.005	1.033	1.012	1.003	1.021	1.005	1.000	1.009	1.005	1.000	1.010	1.016	1.004	1.028	1.009	0.999	1.019
41	1.020	1.005	1.035	1.013	1.003	1.022	1.005	1.000	1.009	1.005	1.000	1.010	1.016	1.004	1.029	1.009	0.999	1.020
42	1.021	1.006	1.037	1.013	1.004	1.023	1.005	1.001	1.010	1.005	1.000	1.011	1.017	1.004	1.031	1.010	0.999	1.021

Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; P1-99, 1st-99th centiles; HR, hazard ratio; LCI and UCI, 95% lower and upper confidence intervals; SGA, small for gestational age

Table S10.2. Weekly-specific UTCI exposure over 12- week preconception (-11 to 0) through to gestational week at delivery (1 to 42) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of term LGA in Western Australia, 2000–2015.

Week	P1 (10.3 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.4 ˚C)			P95 (17.3 ˚C)			P99 (26.0 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-11	0.991	0.976	1.005	0.994	0.984	1.004	12.800	0.992	1.002	0.999	0.994	1.004	0.996	0.984	1.009	0.997	0.987	1.007
-10	0.991	0.978	1.005	0.994	0.985	1.003	0.997	0.993	1.002	0.999	0.994	1.004	0.996	0.985	1.008	0.998	0.988	1.007
-9	0.992	0.979	1.005	0.995	0.987	1.003	0.997	0.993	1.002	0.999	0.995	1.004	0.996	0.985	1.008	0.998	0.989	1.007
-8	0.993	0.981	1.005	0.995	0.988	1.003	0.998	0.994	1.002	0.999	0.995	1.003	0.996	0.986	1.007	0.999	0.991	1.008
-7	0.993	0.982	1.005	0.996	0.988	1.003	0.998	0.994	1.002	0.999	0.995	1.003	0.996	0.987	1.006	1.000	0.992	1.008
-6	0.994	0.983	1.005	0.996	0.989	1.003	0.998	0.995	1.002	0.999	0.995	1.002	0.996	0.988	1.005	1.000	0.993	1.008
-5	0.995	0.984	1.005	0.997	0.990	1.004	0.999	0.995	1.002	0.999	0.995	1.002	0.997	0.988	1.005	1.001	0.994	1.008
-4	0.995	0.986	1.005	0.997	0.991	1.004	0.999	0.996	1.002	0.999	0.996	1.002	0.997	0.989	1.004	1.002	0.995	1.008
-3	0.996	0.987	1.005	0.998	0.992	1.004	0.999	0.996	1.002	0.999	0.996	1.002	0.997	0.989	1.004	1.002	0.996	1.009
-2	0.996	0.987	1.006	0.998	0.992	1.004	0.999	0.997	1.003	0.999	0.996	1.001	0.997	0.989	1.004	1.003	0.997	1.009
-1	0.997	0.988	1.006	0.999	0.993	1.004	1.000	0.997	1.003	0.999	0.996	1.001	0.997	0.990	1.004	1.004	0.998	1.010
0	0.998	0.989	1.006	0.999	0.993	1.005	1.000	0.997	1.003	0.999	0.996	1.001	0.997	0.990	1.004	1.004	0.998	1.010
1	0.998	0.989	1.007	0.999	0.994	1.005	1.000	0.997	1.003	0.998	0.996	1.001	0.997	0.990	1.004	1.005	0.999	1.011
2	0.999	0.990	1.008	1.000	0.994	1.005	1.000	0.997	1.003	0.998	0.996	1.001	0.997	0.990	1.004	1.005	0.999	1.011
3	0.999	0.990	1.008	1.000	0.994	1.006	1.000	0.998	1.003	0.998	0.996	1.001	0.997	0.990	1.004	1.005	0.999	1.012
4	0.999	0.990	1.009	1.000	0.994	1.006	1.000	0.998	1.004	0.998	0.996	1.001	0.997	0.990	1.004	1.006	1.000	1.012
5	1.000	0.991	1.009	1.001	0.995	1.006	1.001	0.998	1.004	0.998	0.996	1.001	0.997	0.990	1.005	1.006	1.000	1.012
6	1.000	0.991	1.010	1.001	0.995	1.007	1.001	0.998	1.004	0.998	0.996	1.001	0.997	0.990	1.005	1.006	1.000	1.013
7	1.001	0.991	1.010	1.001	0.995	1.007	1.001	0.998	1.004	0.999	0.996	1.002	0.997	0.990	1.005	1.007	1.000	1.013
8	1.001	0.991	1.011	1.001	0.995	1.007	1.001	0.998	1.004	0.999	0.996	1.002	0.998	0.990	1.005	1.007	1.000	1.013
9	1.001	0.991	1.011	1.001	0.995	1.007	1.001	0.998	1.004	0.999	0.996	1.002	0.998	0.990	1.006	1.007	1.000	1.013

10	1.001	0.992	1.011	1.001	0.995	1.008	1.001	0.998	1.004	0.999	0.996	1.002	0.998	0.990	1.006	1.007	1.000	1.013
11	1.001	0.992	1.011	1.001	0.995	1.008	1.001	0.998	1.004	0.999	0.996	1.002	0.998	0.990	1.006	1.007	1.000	1.013
12	1.002	0.992	1.012	1.001	0.995	1.008	1.001	0.998	1.004	0.999	0.996	1.002	0.998	0.990	1.006	1.007	1.000	1.013
13	1.002	0.992	1.012	1.001	0.995	1.008	1.001	0.998	1.004	0.999	0.996	1.002	0.999	0.991	1.007	1.007	1.000	1.013
14	1.002	0.992	1.012	1.001	0.995	1.008	1.001	0.998	1.004	0.999	0.996	1.002	0.999	0.991	1.007	1.006	1.000	1.013
15	1.002	0.992	1.012	1.001	0.995	1.007	1.001	0.998	1.004	0.999	0.996	1.002	0.999	0.991	1.007	1.006	1.000	1.013
16	1.002	0.993	1.012	1.001	0.995	1.007	1.001	0.998	1.004	0.999	0.996	1.002	0.999	0.991	1.007	1.006	1.000	1.013
17	1.002	0.993	1.011	1.001	0.995	1.007	1.001	0.998	1.004	0.999	0.996	1.003	1.000	0.992	1.007	1.006	0.999	1.012
18	1.002	0.993	1.011	1.001	0.995	1.007	1.001	0.998	1.004	1.000	0.997	1.003	1.000	0.992	1.007	1.006	0.999	1.012
19	1.002	0.993	1.011	1.001	0.995	1.007	1.000	0.998	1.003	1.000	0.997	1.003	1.000	0.993	1.008	1.005	0.999	1.011
20	1.002	0.993	1.011	1.001	0.995	1.006	1.000	0.997	1.003	1.000	0.997	1.003	1.000	0.993	1.008	1.005	0.999	1.011
21	1.002	0.993	1.011	1.001	0.995	1.006	1.000	0.997	1.003	1.000	0.997	1.003	1.001	0.993	1.008	1.004	0.999	1.010
22	1.002	0.993	1.010	1.000	0.995	1.006	1.000	0.997	1.003	1.000	0.997	1.003	1.001	0.994	1.008	1.004	0.998	1.010
23	1.002	0.993	1.010	1.000	0.995	1.005	1.000	0.997	1.003	1.000	0.998	1.003	1.001	0.994	1.008	1.003	0.998	1.009
24	1.002	0.993	1.010	1.000	0.995	1.005	1.000	0.997	1.002	1.001	0.998	1.003	1.002	0.995	1.008	1.003	0.997	1.009
25	1.001	0.993	1.009	1.000	0.994	1.005	0.999	0.997	1.002	1.001	0.998	1.004	1.002	0.995	1.009	1.002	0.997	1.008
26	1.001	0.993	1.009	0.999	0.994	1.004	0.999	0.997	1.002	1.001	0.998	1.004	1.002	0.995	1.009	1.002	0.996	1.007
27	1.001	0.993	1.009	0.999	0.994	1.004	0.999	0.996	1.002	1.001	0.998	1.004	1.003	0.996	1.009	1.001	0.996	1.007
28	1.001	0.993	1.009	0.999	0.994	1.004	0.999	0.996	1.002	1.001	0.999	1.004	1.003	0.996	1.010	1.001	0.995	1.006
29	1.001	0.993	1.009	0.998	0.993	1.004	0.999	0.996	1.001	1.002	0.999	1.004	1.003	0.996	1.010	1.000	0.995	1.006
30	1.000	0.992	1.009	0.998	0.993	1.003	0.998	0.996	1.001	1.002	0.999	1.005	1.004	0.996	1.011	1.000	0.994	1.005
31	0.999	0.992	1.009	0.998	0.992	1.003	0.998	0.995	1.001	1.002	0.999	1.005	1.004	0.996	1.011	0.999	0.993	1.005

32	0.998	0.991	1.009	0.997	0.992	1.003	0.998	0.995	1.001	1.002	0.999	1.005	1.004	0.996	1.012	0.998	0.992	1.004
33	0.998	0.990	1.009	0.997	0.991	1.003	0.998	0.995	1.001	1.003	0.999	1.006	1.005	0.996	1.013	0.998	0.991	1.004
34	0.997	0.990	1.009	0.997	0.991	1.003	0.997	0.994	1.001	1.003	0.999	1.006	1.005	0.996	1.014	0.997	0.990	1.004
35	0.996	0.989	1.009	0.996	0.990	1.003	0.997	0.994	1.000	1.003	0.999	1.007	1.005	0.996	1.014	0.996	0.989	1.003
36	0.995	0.988	1.010	0.996	0.989	1.003	0.997	0.993	1.000	1.003	0.999	1.007	1.006	0.996	1.015	0.995	0.988	1.003
37	0.995	0.987	1.010	0.996	0.988	1.003	0.997	0.993	1.000	1.003	0.999	1.007	1.006	0.996	1.016	0.995	0.987	1.003
38	0.994	0.986	1.010	0.995	0.988	1.003	0.996	0.992	1.000	1.004	0.999	1.008	1.006	0.996	1.017	0.994	0.986	1.003
39	0.993	0.985	1.011	0.995	0.987	1.003	0.996	0.992	1.000	1.004	0.999	1.008	1.007	0.996	1.018	0.993	0.984	1.002
40	0.993	0.984	1.011	0.995	0.986	1.003	0.996	0.992	1.000	1.004	0.999	1.009	1.007	0.995	1.019	0.993	0.983	1.002
41	0.992	0.983	1.012	0.994	0.985	1.003	0.995	0.991	1.000	1.004	0.999	1.009	1.008	0.995	1.020	0.992	0.982	1.002
42	0.991	0.982	1.012	0.994	0.984	1.003	0.995	0.991	1.000	1.005	0.999	1.010	1.008	0.995	1.021	0.991	0.981	1.002

Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; P1-99, 1^{st}-99^{th} centiles; HR, hazard ratio; LCI and UCI, 95% lower and upper confidence intervals; LGA, large for gestational age

Table S10.3. Weekly-specific UTCI exposure over 12- week preconception (-11 to 0) through to gestational week at delivery (1 to 42) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of term LBW in Western Australia, 2000–2015.

Week	P1 (10.3 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.4 ˚C)			P95 (17.3 ˚C)			P99 (26.0 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-11	1.000	0.998	1.003	1.000	0.999	1.002	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.998	1.002	0.999	0.992	1.007
-10	1.000	0.998	1.002	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.998	1.002	1.000	0.992	1.007
-9	1.000	0.998	1.002	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.998	1.002	1.000	0.993	1.006
-8	1.000	0.998	1.002	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.998	1.002	1.000	0.994	1.006
-7	1.000	0.998	1.002	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.999	1.001	1.000	0.999	1.002	1.001	0.995	1.006
-6	1.000	0.998	1.001	1.000	0.999	1.001	1.000	0.999	1.000	1.000	1.000	1.001	1.000	0.999	1.002	1.001	0.996	1.006
-5	1.000	0.998	1.001	1.000	0.999	1.001	1.000	0.999	1.000	1.000	1.000	1.001	1.000	0.999	1.001	1.001	0.997	1.006
-4	1.000	0.998	1.001	1.000	0.999	1.001	1.000	0.999	1.000	1.000	1.000	1.001	1.000	0.999	1.001	1.001	0.997	1.005
-3	0.999	0.998	1.001	1.000	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.000	1.000	1.001	1.002	0.998	1.005
-2	0.999	0.998	1.000	1.000	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.001	1.002	0.999	1.005
-1	0.999	0.998	1.000	1.000	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.001	1.002	0.999	1.005
0	0.999	0.998	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.001	1.003	1.000	1.005
1	0.999	0.998	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.001	1.003	1.000	1.006
2	0.999	0.998	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.001	1.003	1.001	1.006
3	0.999	0.998	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.003	1.001	1.006
4	0.999	0.998	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.001	1.006
5	0.999	0.998	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.001	1.007
6	0.999	0.998	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.001	1.007
7	0.999	0.998	1.000	0.999	0.999	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.001	1.007
8	0.999	0.997	1.000	0.999	0.999	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.001	1.007
9	0.999	0.997	1.000	0.999	0.999	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.001	1.008

10	0.998	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.005	1.001	1.008
11	0.998	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.005	1.001	1.008
12	0.998	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.005	1.001	1.008
13	0.998	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.005	1.001	1.008
14	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.000	1.002	1.005	1.002	1.008
15	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.000	1.002	1.005	1.002	1.008
16	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.000	1.002	1.005	1.002	1.008
17	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.000	1.002	1.005	1.002	1.008
18	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.000	1.002	1.005	1.002	1.008
19	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
20	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
21	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
22	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
23	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
24	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
25	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
26	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
27	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.001	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
28	0.998	0.997	0.999	0.999	0.999	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
29	0.998	0.997	0.999	0.999	0.999	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.001	1.002	1.005	1.002	1.008
30	0.998	0.997	0.999	0.999	0.999	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.005	1.002	1.008
31	0.998	0.997	0.999	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.005	1.001	1.008

32	0.999	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.005	1.001	1.008
33	0.999	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.005	1.001	1.008
34	0.999	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.000	1.008
35	0.999	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.000	1.008
36	0.999	0.997	1.000	0.999	0.998	1.000	0.999	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.000	1.008
37	0.999	0.997	1.000	0.999	0.998	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	1.000	1.009
38	0.999	0.997	1.000	0.999	0.998	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	0.999	1.009
39	0.999	0.997	1.000	0.999	0.998	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	0.999	1.009
40	0.999	0.997	1.000	0.999	0.998	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	1.000	1.002	1.004	0.998	1.009
41	0.999	0.997	1.001	0.999	0.998	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	0.999	1.002	1.004	0.998	1.009
42	0.999	0.997	1.001	0.999	0.998	1.000	1.000	0.999	1.000	1.000	1.000	1.001	1.001	0.999	1.003	1.004	0.998	1.010

Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; P1-99, 1st-99th centiles; HR, hazard ratio; LCI and UCI, 95% lower and upper confidence intervals; LBW, low birth weight.

Table S10.4. Monthly-specific UTCI exposure over three months preconception (-2 to 0) through to gestational month at delivery (1 to 10) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of term SGA in Western Australia, 2000–2015.

Month	P1 (10.2 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.5 ˚C)			P95 (17.2 ˚C)			P99 (26.0 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	1.068	1.027	1.110	1.049	1.023	1.077	1.027	1.012	1.041	0.997	0.984	1.011	1.008	0.977	1.039	1.012	0.982	1.043
-1	1.047	1.014	1.080	1.031	1.010	1.053	1.016	1.005	1.028	0.999	0.988	1.009	1.006	0.982	1.031	1.012	0.988	1.037
0	1.028	1.000	1.057	1.015	0.997	1.034	1.007	0.997	1.017	1.000	0.991	1.009	1.005	0.984	1.025	1.013	0.993	1.034
1	1.014	0.985	1.043	1.002	0.984	1.021	1.000	0.991	1.010	1.001	0.992	1.010	1.004	0.984	1.025	1.014	0.994	1.035
2	1.005	0.975	1.035	0.995	0.976	1.014	0.996	0.986	1.006	1.003	0.993	1.012	1.004	0.982	1.027	1.016	0.994	1.039
3	1.003	0.972	1.034	0.993	0.974	1.013	0.995	0.984	1.005	1.004	0.993	1.014	1.006	0.983	1.030	1.019	0.996	1.043
4	1.008	0.977	1.039	0.998	0.979	1.017	0.997	0.987	1.008	1.004	0.994	1.015	1.010	0.986	1.034	1.023	1.000	1.047
5	1.018	0.990	1.048	1.008	0.989	1.026	1.002	0.993	1.012	1.005	0.995	1.015	1.014	0.992	1.037	1.027	1.006	1.050
6	1.035	1.008	1.061	1.022	1.005	1.039	1.010	1.001	1.019	1.005	0.996	1.014	1.019	0.999	1.040	1.033	1.013	1.053
7	1.055	1.030	1.080	1.040	1.024	1.056	1.020	1.012	1.029	1.006	0.997	1.014	1.025	1.006	1.045	1.038	1.020	1.058
8	1.079	1.053	1.105	1.061	1.045	1.078	1.031	1.023	1.040	1.006	0.997	1.015	1.032	1.012	1.053	1.045	1.025	1.065
9	1.106	1.075	1.137	1.085	1.066	1.104	1.044	1.034	1.054	1.006	0.996	1.017	1.040	1.015	1.065	1.051	1.027	1.075
10	1.134	1.095	1.174	1.110	1.086	1.134	1.057	1.045	1.069	1.006	0.993	1.019	1.047	1.016	1.079	1.058	1.028	1.088

Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; P1-99, 1st-99th centiles; HR, hazard ratio; LCI and UCI, 95% lower and upper confidence intervals; SGA, small for gestational age.

Table S10.5. Monthly-specific UTCI exposure over three months preconception (-2 to 0) through to gestational month at delivery (1 to 10) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of term LGA in Western Australia, 2000–2015.

Month	P1 (10.2 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.5 ˚C)			P95 (17.2 ˚C)			P99 (26.0 ˚C)		
	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI
-2	1.016	0.978	1.056	1.011	0.985	1.037	1.005	0.992	1.019	1.002	0.988	1.015	1.009	0.978	1.041	1.022	0.991	1.054
-1	1.011	0.980	1.044	1.005	0.984	1.026	1.002	0.991	1.013	1.002	0.991	1.012	1.007	0.984	1.032	1.026	1.002	1.052
0	1.007	0.979	1.036	0.999	0.981	1.018	0.999	0.989	1.009	1.002	0.993	1.011	1.006	0.986	1.027	1.031	1.009	1.053
1	1.004	0.976	1.033	0.995	0.977	1.013	0.996	0.987	1.006	1.002	0.993	1.011	1.006	0.985	1.026	1.034	1.013	1.056
2	1.003	0.973	1.034	0.993	0.974	1.012	0.995	0.985	1.005	1.002	0.992	1.012	1.006	0.984	1.029	1.036	1.013	1.059
3	1.005	0.974	1.036	0.994	0.974	1.013	0.995	0.985	1.006	1.003	0.992	1.013	1.007	0.984	1.032	1.036	1.012	1.061
4	1.009	0.979	1.040	0.997	0.978	1.016	0.997	0.986	1.007	1.004	0.993	1.014	1.010	0.987	1.034	1.035	1.011	1.059
5	1.016	0.987	1.045	1.002	0.984	1.021	1.000	0.990	1.009	1.005	0.995	1.015	1.014	0.992	1.037	1.032	1.010	1.055
6	1.024	0.998	1.051	1.010	0.993	1.027	1.003	0.994	1.012	1.006	0.997	1.015	1.018	0.998	1.039	1.029	1.008	1.049
7	1.034	1.010	1.059	1.019	1.004	1.034	1.008	1.000	1.016	1.008	0.999	1.017	1.024	1.004	1.043	1.024	1.005	1.043
8	1.045	1.020	1.071	1.029	1.013	1.045	1.013	1.005	1.022	1.010	1.001	1.019	1.029	1.009	1.050	1.018	0.999	1.038
9	1.058	1.028	1.088	1.040	1.022	1.059	1.019	1.009	1.028	1.012	1.001	1.022	1.036	1.011	1.061	1.013	0.990	1.036
10	1.070	1.034	1.108	1.052	1.029	1.075	1.025	1.013	1.036	1.013	1.000	1.027	1.042	1.011	1.074	1.007	0.978	1.036

Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; P1-99, 1st-99th centiles; HR, hazard ratio; LCI and UCI, 95% lower and upper confidence intervals; LGA, large for gestational age.

Table S10.6. Monthly-specific UTCI exposure over three months preconception (-2 to 0) through to gestational month at delivery (1 to 10) at different thresholds of UTCI using median of 14.2 ˚C as reference and the adjusted hazard ratios of term LBW in Western Australia, 2000–2015.

Month	P1 (10.2 ˚C)			P5 (11.9 ˚C)			P10 (12.8 ˚C)			P90 (15.5 ˚C)			P95 (17.2 ˚C)			P99 (26.0 ˚C)		
	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI	HR	LCI	UCI		
-2	1.002	0.993	1.012	1.001	0.996	1.007	1.001	0.997	1.004	0.999	0.996	1.002	0.998	0.991	1.005	0.994	0.967	1.022
-1	1.000	0.993	1.006	1.000	0.996	1.004	1.000	0.998	1.002	1.000	0.998	1.002	1.000	0.995	1.005	1.001	0.982	1.021
0	0.997	0.993	1.002	0.998	0.996	1.001	0.999	0.997	1.001	1.001	0.999	1.002	1.002	0.999	1.005	1.008	0.995	1.022
1	0.995	0.992	0.999	0.997	0.995	0.999	0.998	0.997	1.000	1.002	1.000	1.003	1.004	1.001	1.006	1.014	1.003	1.025
2	0.994	0.990	0.998	0.996	0.994	0.999	0.998	0.996	0.999	1.002	1.001	1.003	1.005	1.002	1.008	1.019	1.006	1.031
3	0.993	0.988	0.998	0.996	0.993	0.999	0.997	0.996	0.999	1.002	1.001	1.004	1.005	1.002	1.009	1.021	1.007	1.036
4	0.993	0.988	0.998	0.996	0.993	0.999	0.997	0.996	0.999	1.002	1.001	1.004	1.006	1.002	1.009	1.022	1.007	1.037
5	0.993	0.988	0.998	0.996	0.993	0.999	0.998	0.996	0.999	1.002	1.001	1.004	1.005	1.002	1.009	1.021	1.007	1.035
6	0.994	0.990	0.998	0.996	0.994	0.999	0.998	0.996	0.999	1.002	1.001	1.003	1.005	1.002	1.008	1.019	1.006	1.032
7	0.995	0.991	0.999	0.997	0.995	0.999	0.998	0.997	1.000	1.002	1.000	1.003	1.004	1.001	1.007	1.015	1.003	1.028
8	0.996	0.992	1.001	0.998	0.995	1.000	0.999	0.997	1.000	1.001	1.000	1.003	1.003	0.999	1.006	1.011	0.998	1.025
9	0.998	0.992	1.004	0.999	0.995	1.002	0.999	0.997	1.001	1.001	0.999	1.003	1.002	0.997	1.006	1.007	0.989	1.024
10	0.999	0.992	1.007	1.000	0.995	1.004	1.000	0.997	1.003	1.000	0.998	1.003	1.000	0.995	1.006	1.002	0.979	1.025

Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; P1-99, 1st-99th centiles; HR, hazard ratio; LCI and UCI, 95% lower and upper confidence intervals; LBW, low birth weight.

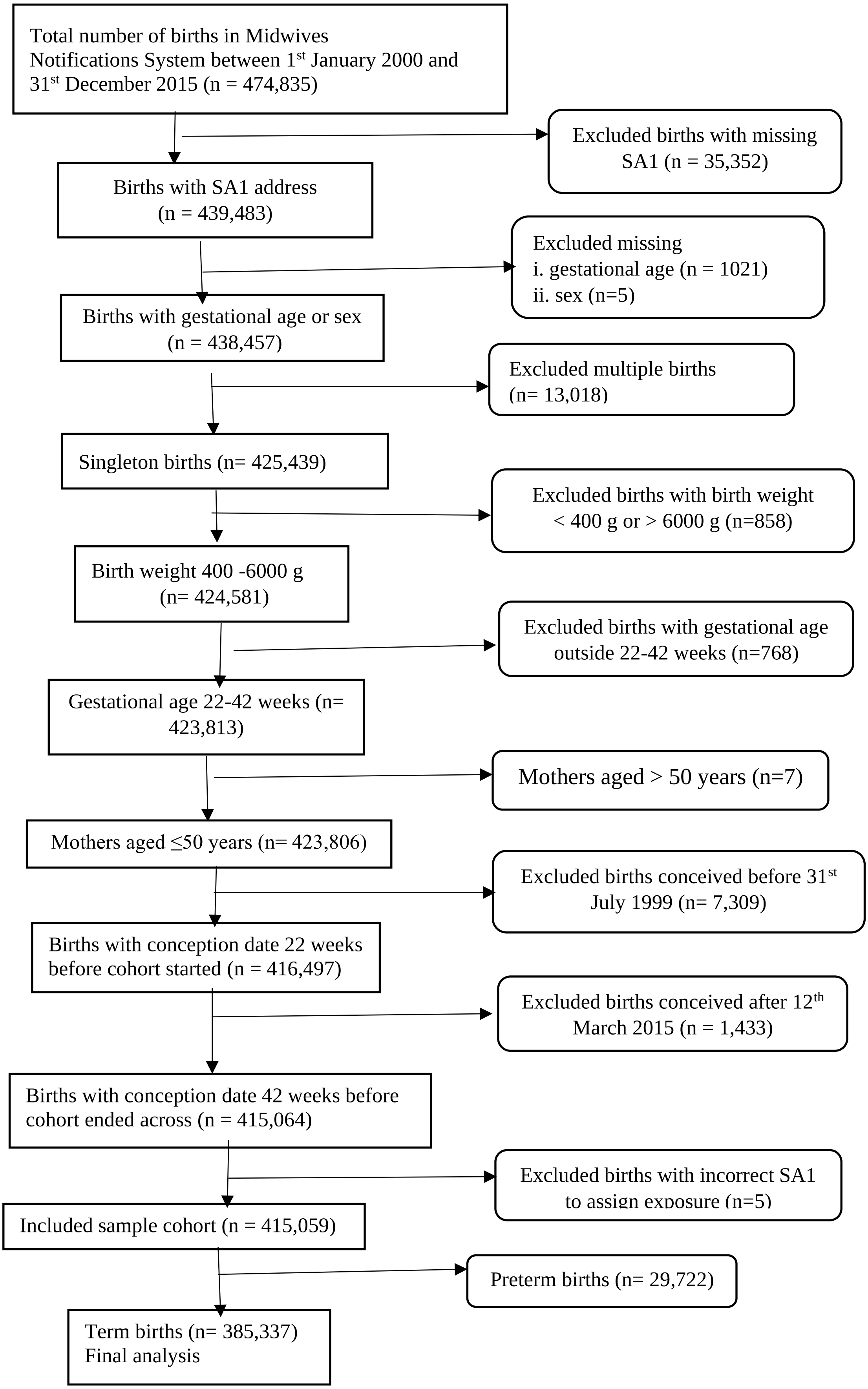

Figure S10.1. Flow chart for selecting the eligible births included in this study, Western Australia, 2000-2015. Note: SA1, statistical area level 1.

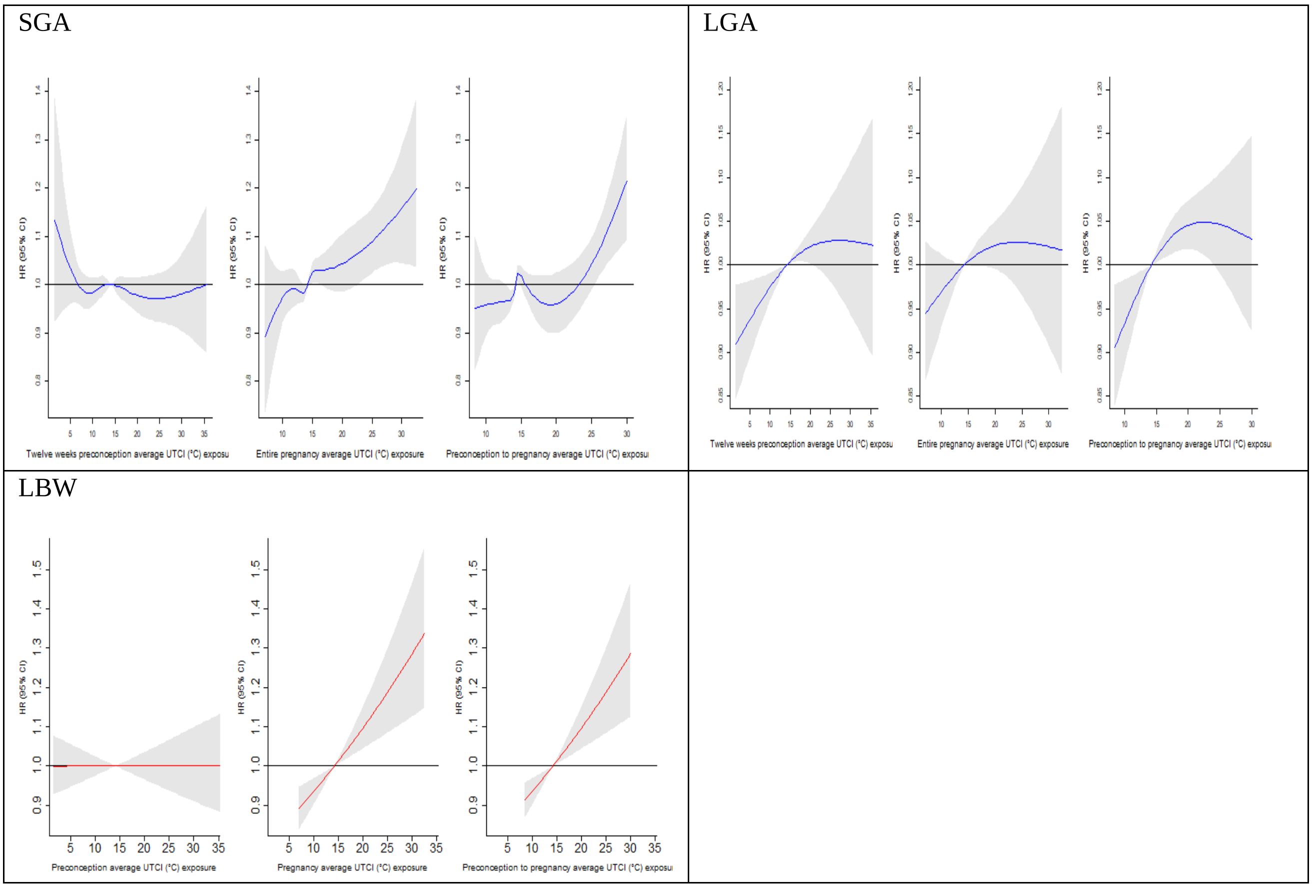

Figure S10.2. The exposure-response association between maternal cumulative UTCI exposures over twelve weeks preconception through to pregnancy with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW. Solid colour lines represent point estimates, and the whiskers represent 95% confidence intervals. All models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

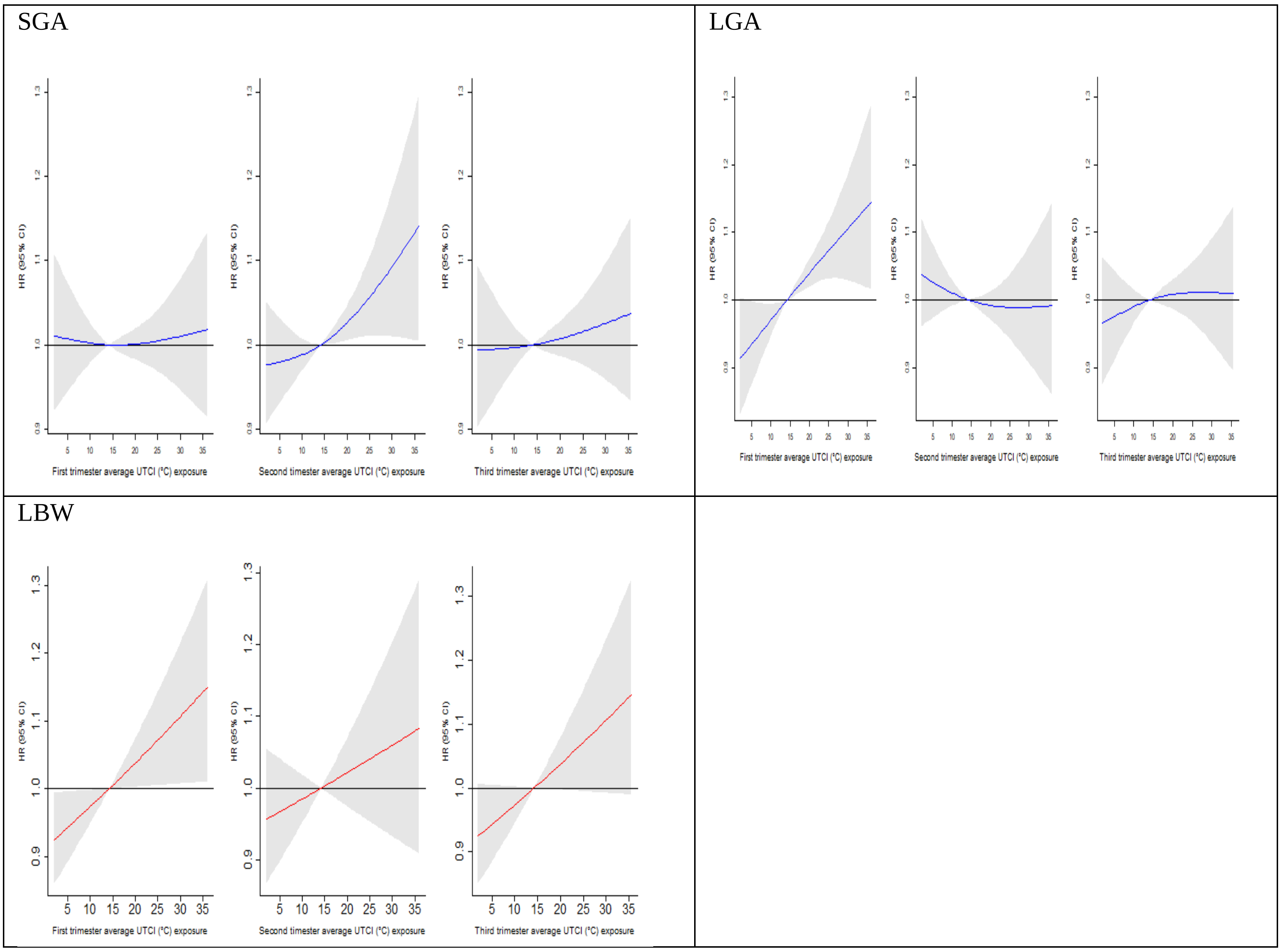

Figure S10.3. The exposure-response association between maternal trimester-average cumulative UTCI exposures with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW. Solid colour lines represent point estimates, and the whiskers represent 95% confidence intervals. All models were adjusted for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and month of conception. Note: HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

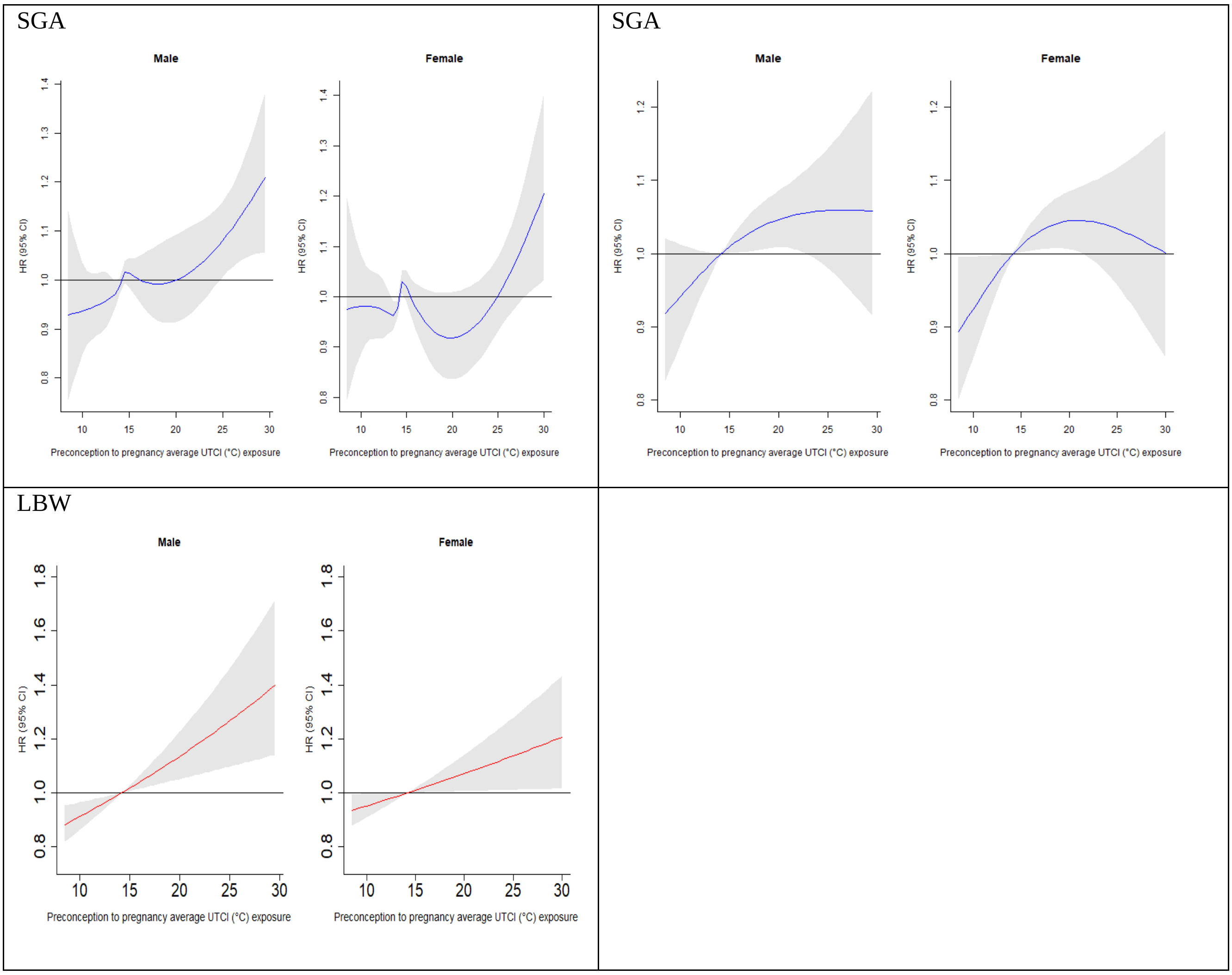

Figure S10.4. The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW by infant sex. Note: Model was adjusted for maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

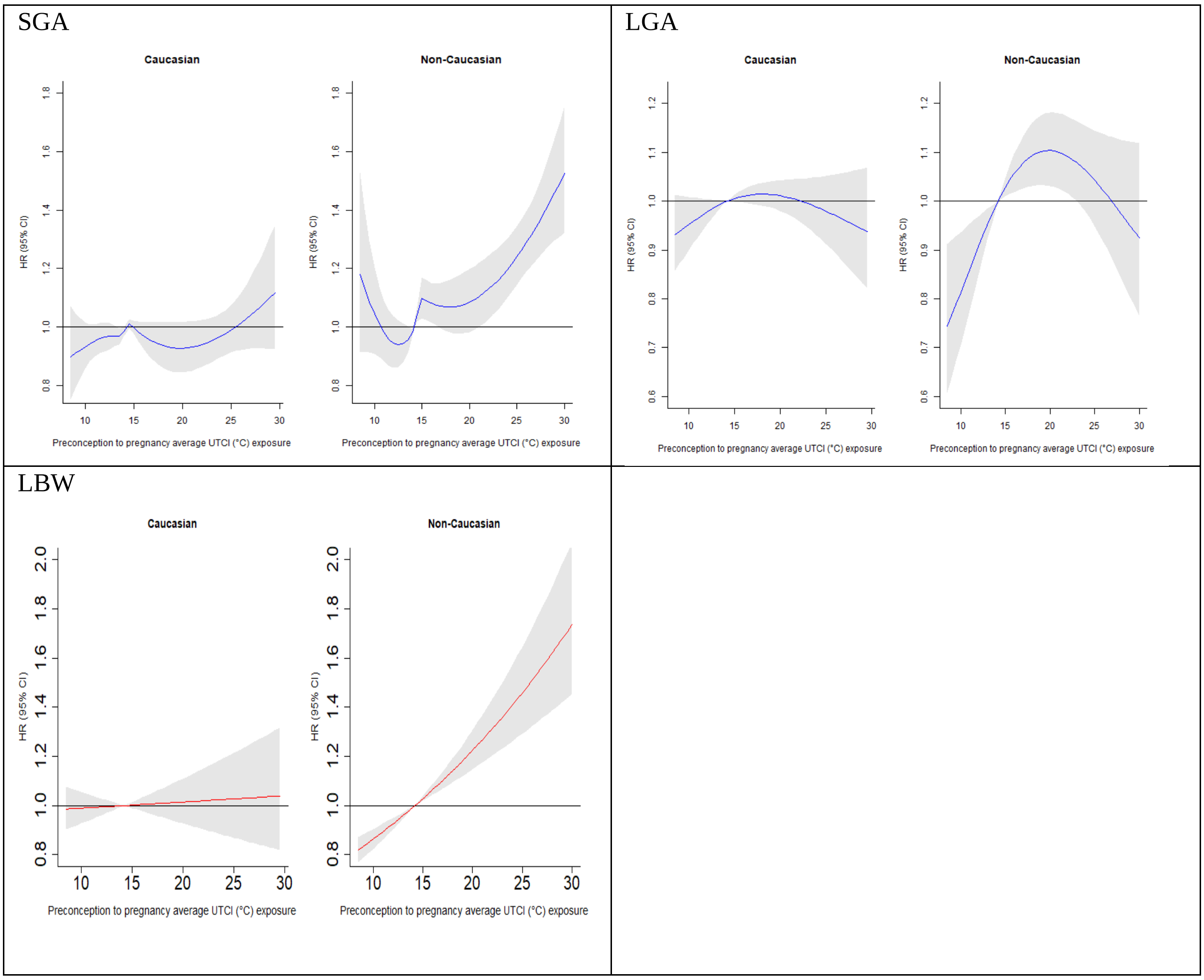

Figure S10.5. The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW by maternal race or ethnicity. Note: Model was adjusted for infant sex, maternal age, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

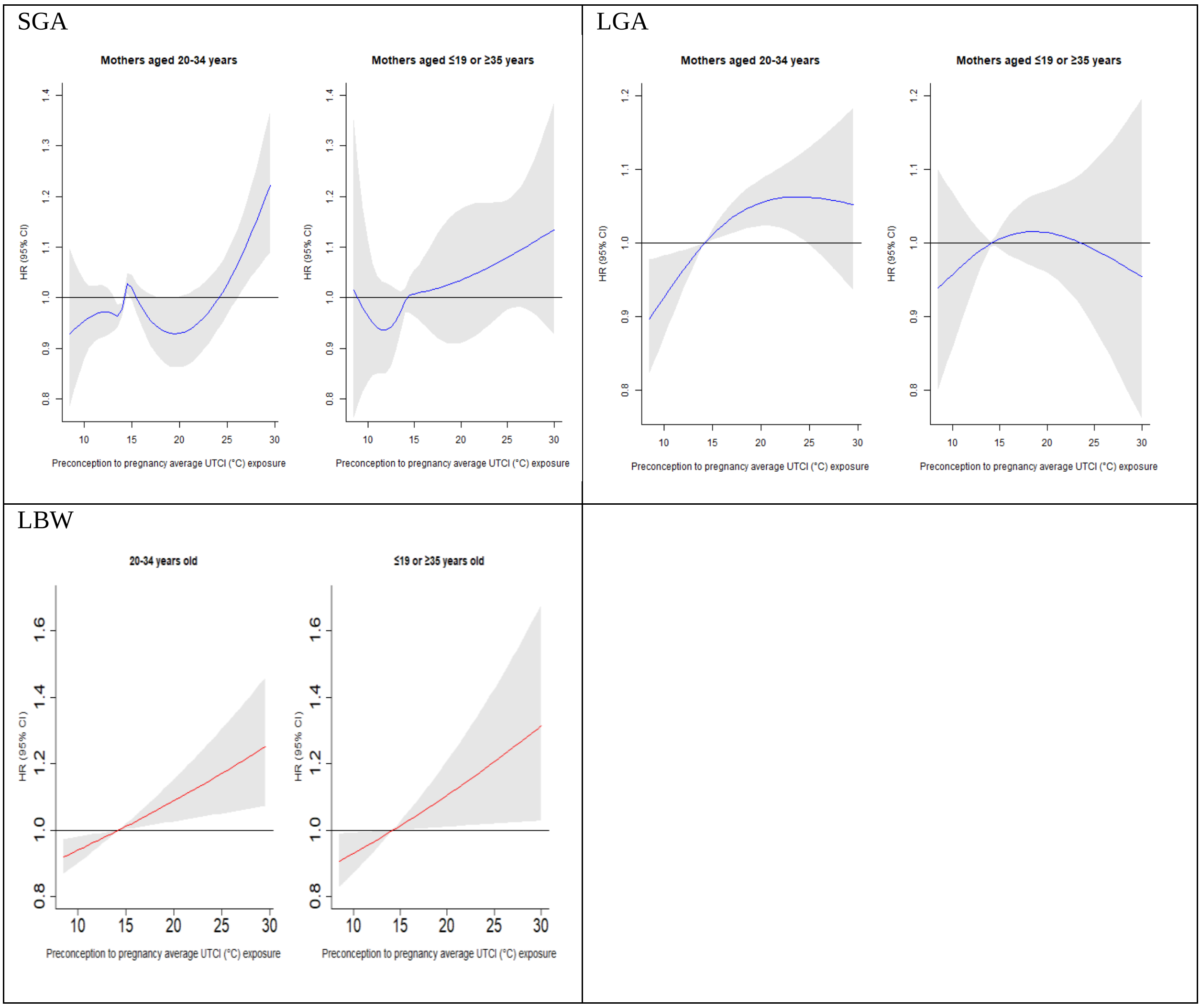

Figure S10.6. The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW by maternal age. Note: Model was adjusted for infant sex, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age. The analysis of ≤19 subgroup ran out of iterations and did not converge and was combined with ≥35 years; LBW, low birth weight.

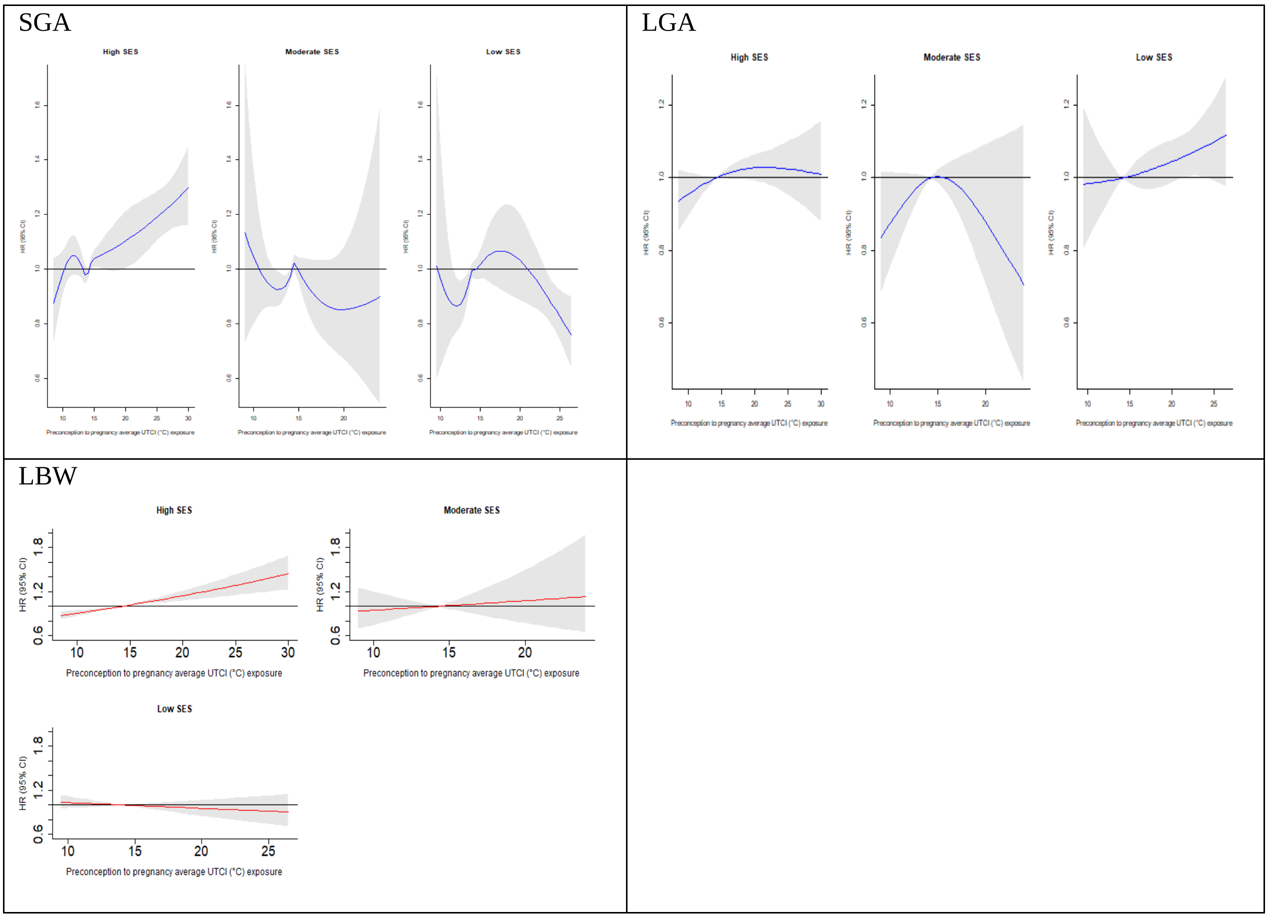

Figure S10.7. The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW by SES. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; SES, socioeconomic status; LBW, low birth weight.

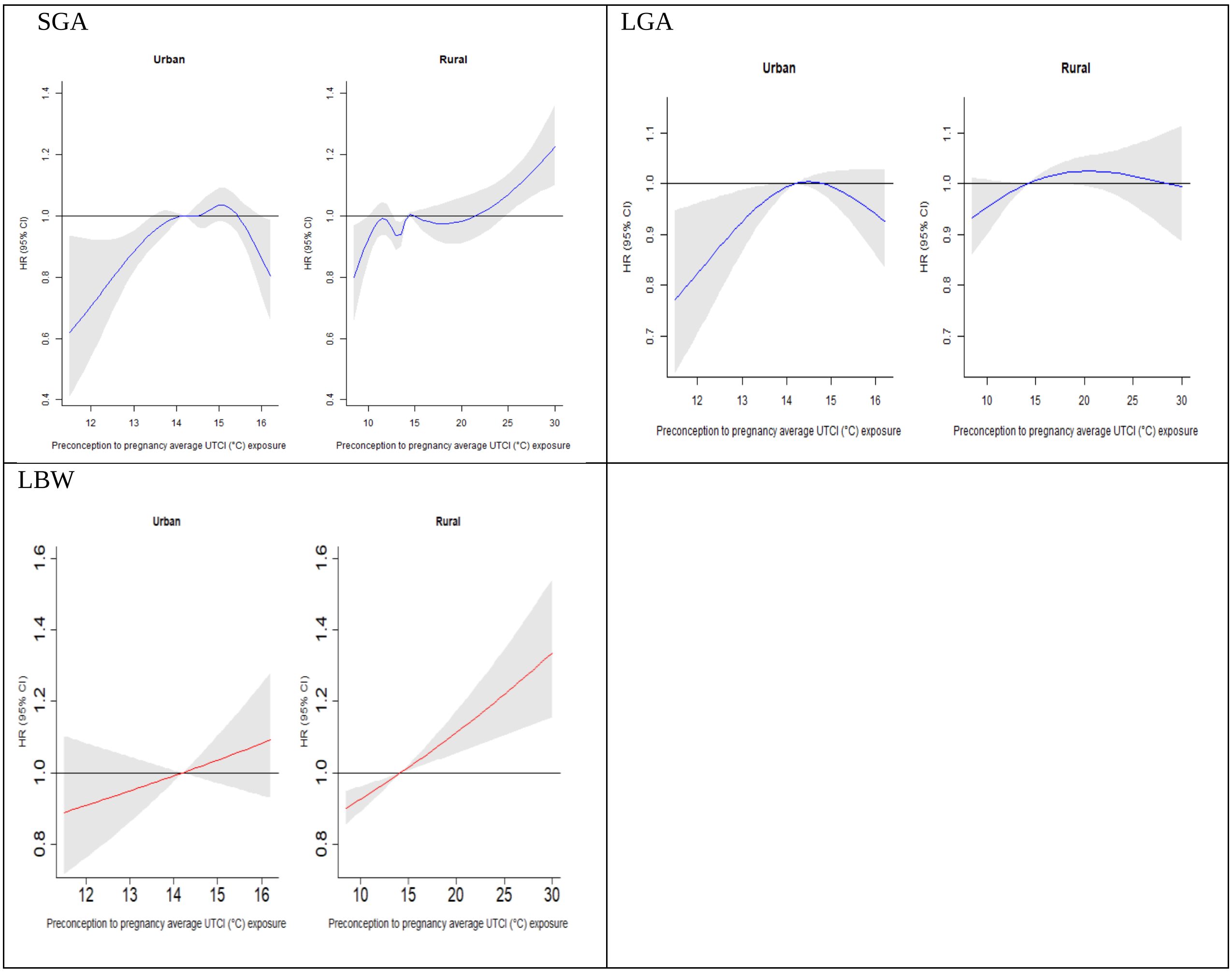

Figure S10.8. The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW by remoteness indicator or urbanicity. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age, LBW, low birth weight.

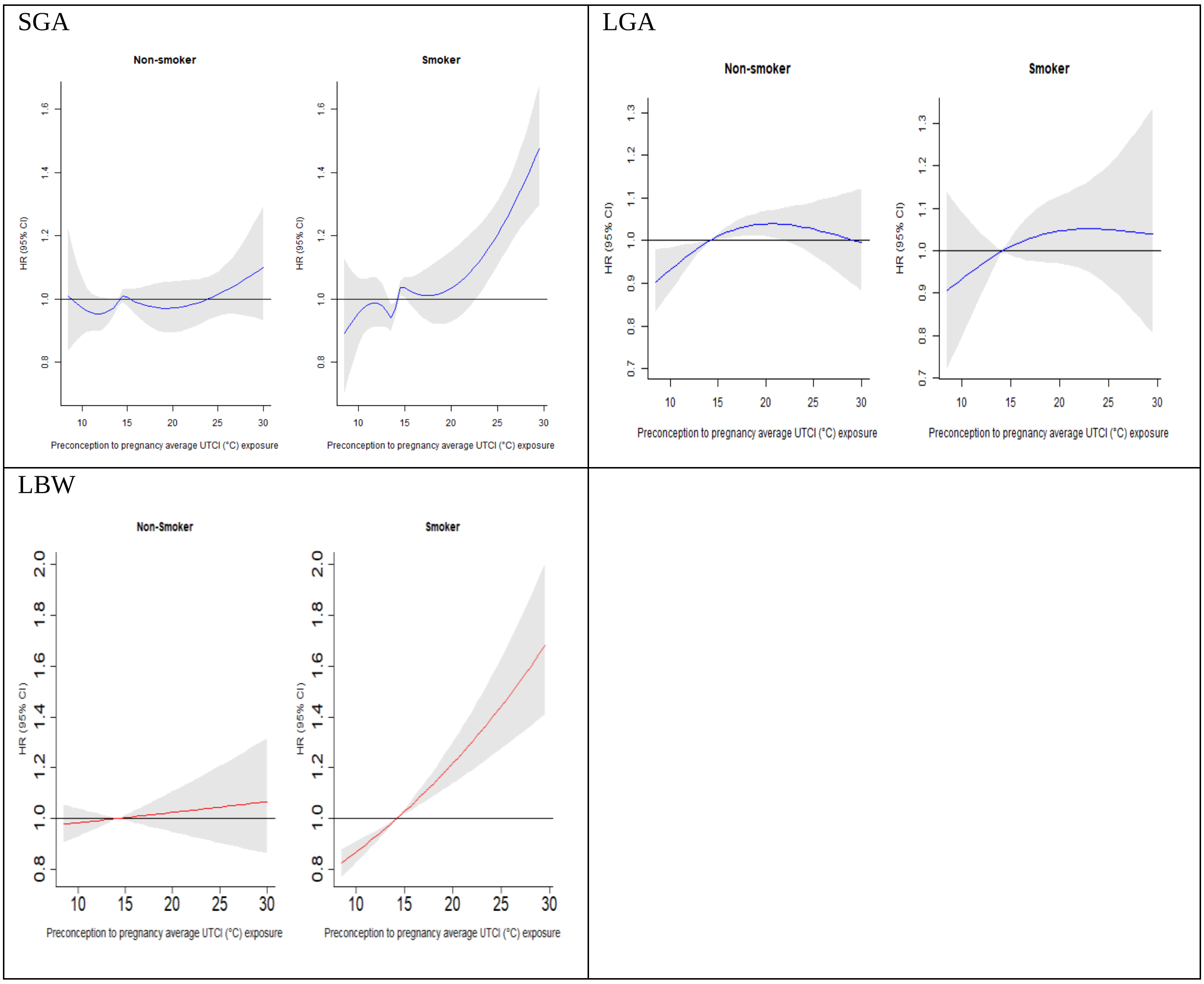

Figure S10.9. The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, LBW by maternal smoking status. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

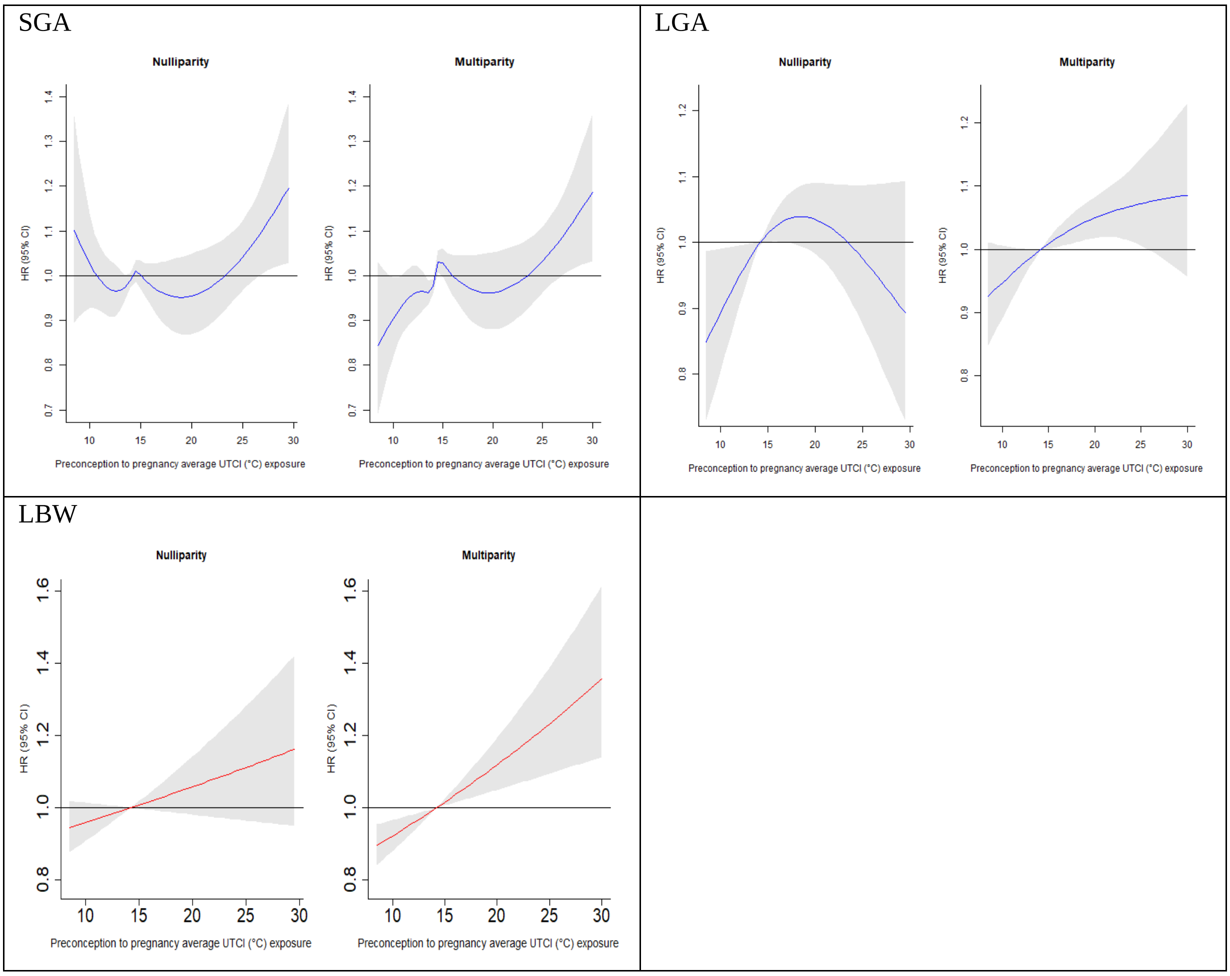

Figure S10.10. The exposure-response association between maternal cumulative average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW by parity. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

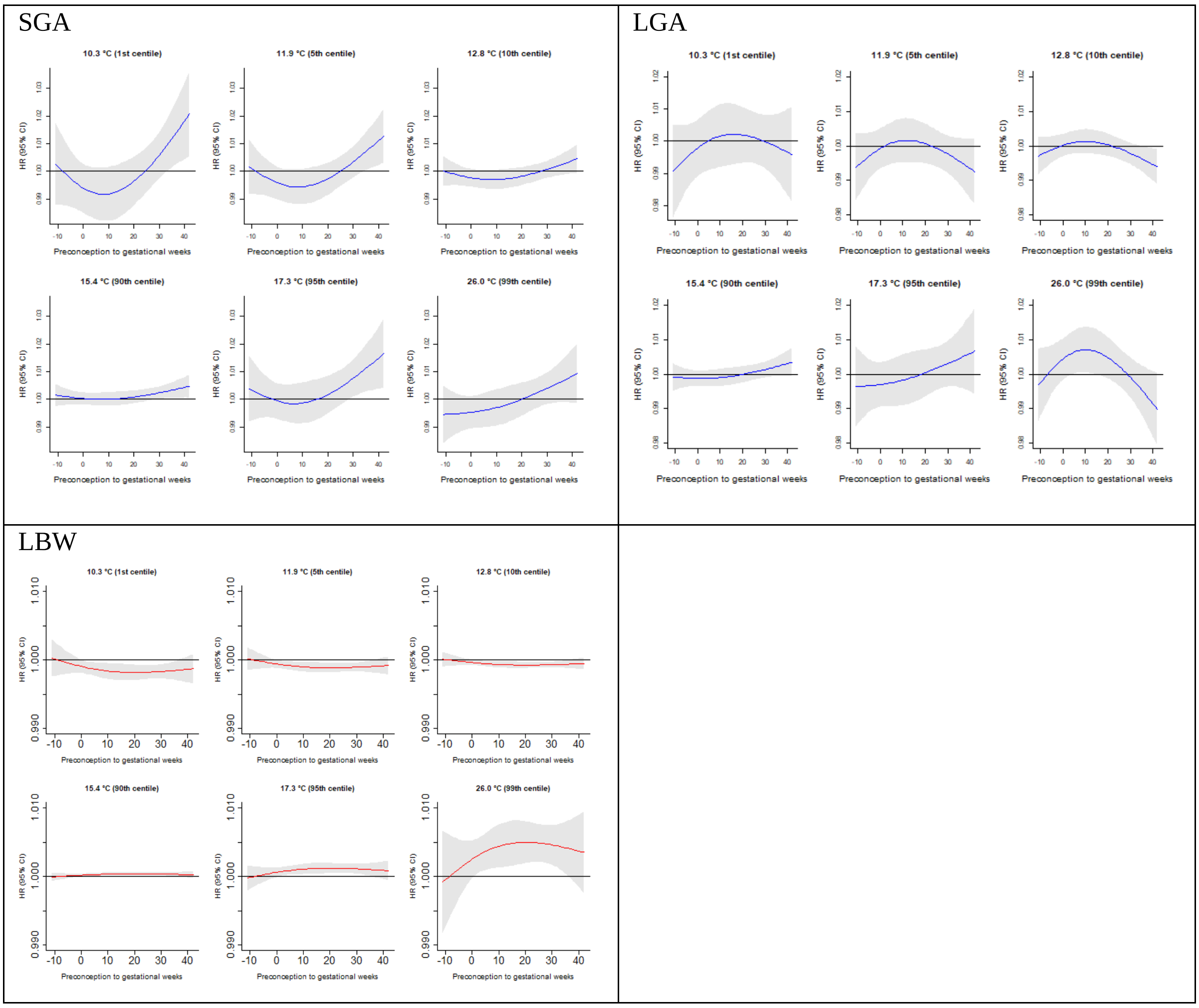

Figure S10.11. The exposure-response association between maternal weekly-specific average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to mean 14.5 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various thresholds of exposure. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

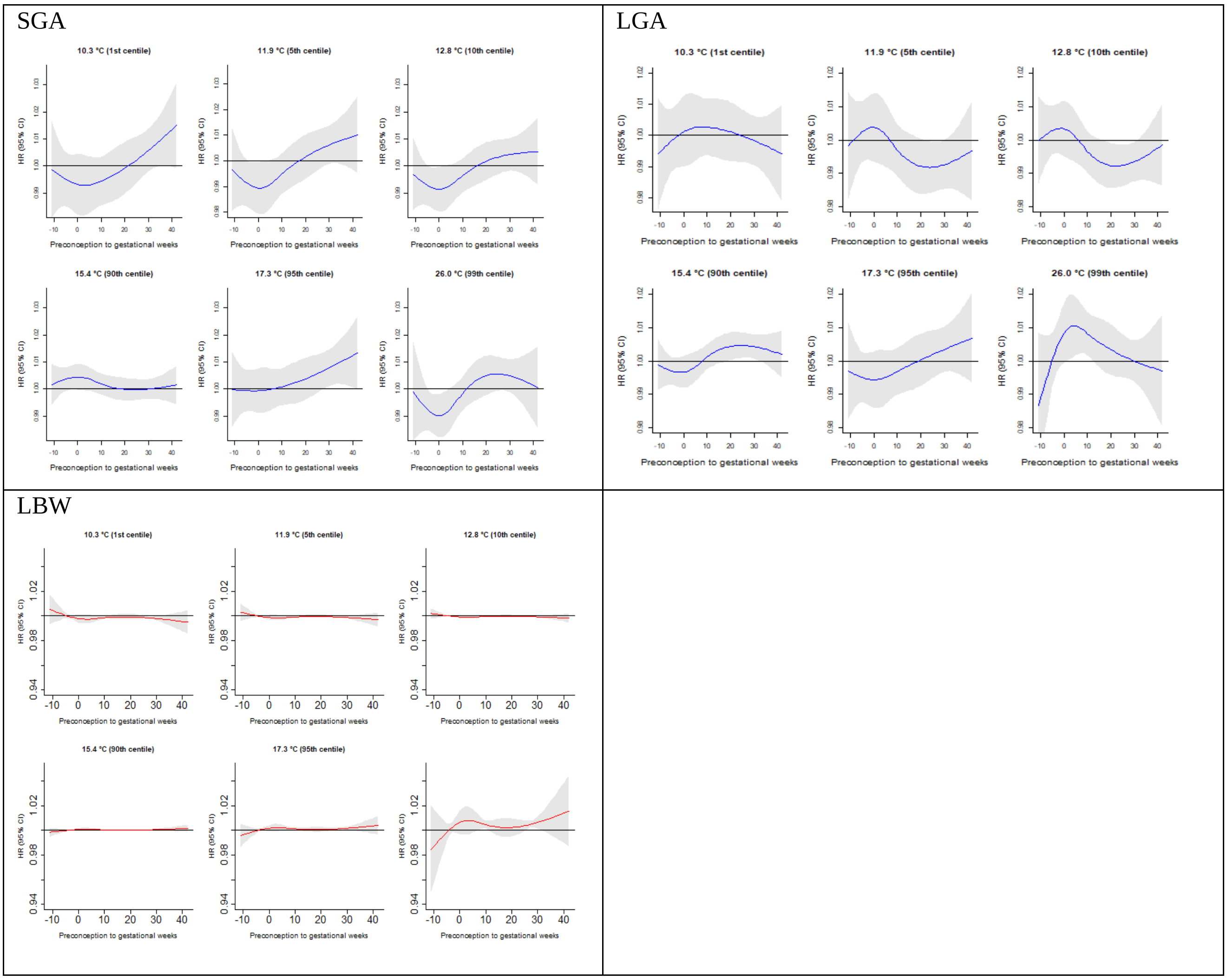

Figure S10.12. The exposure-response association between maternal weekly-specific average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various thresholds of exposure. Cross-basis was constructed by increasing the with degrees of freedom by one for exposure and exposure period, respectively. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

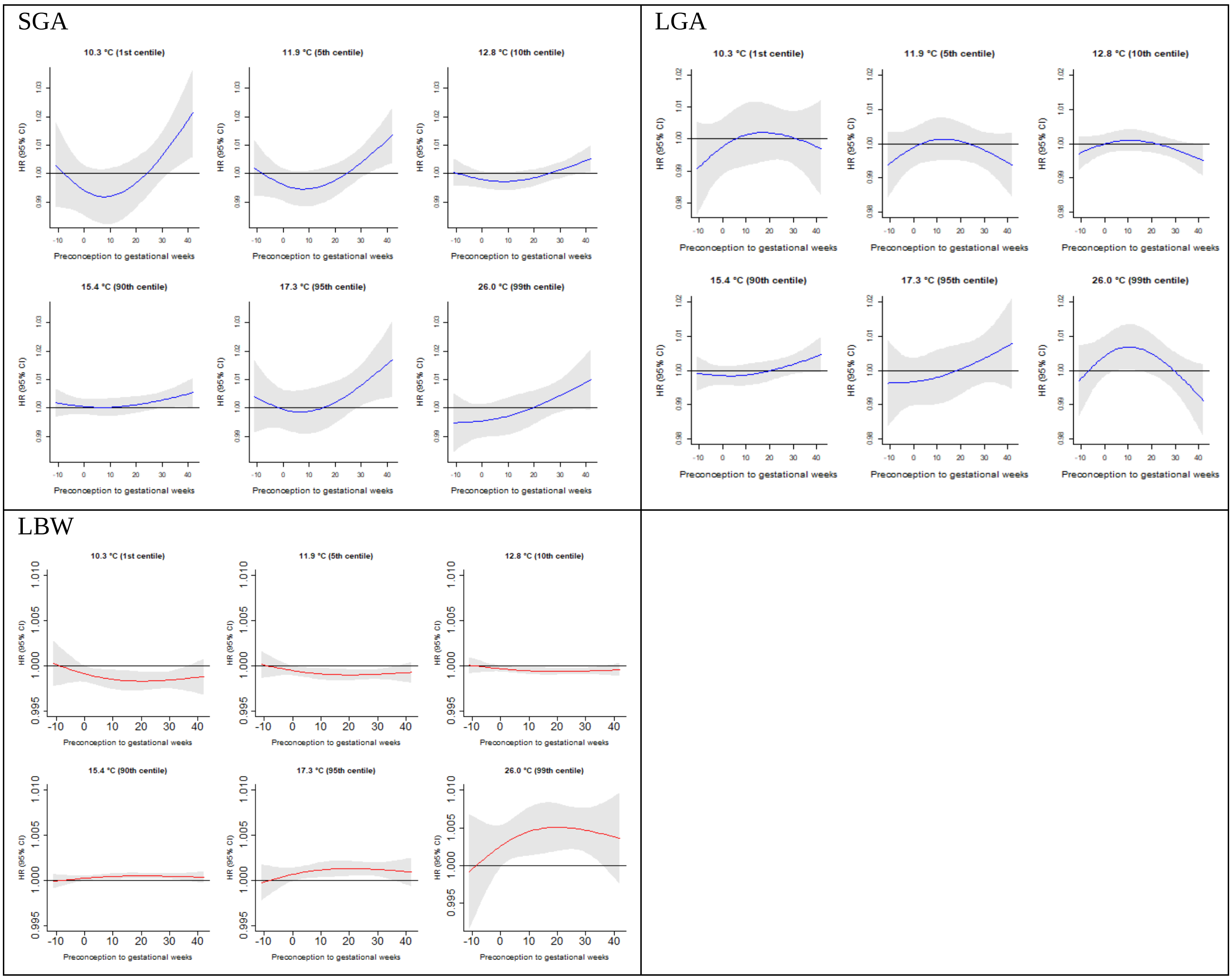

Figure S10.13. The exposure-response association between maternal weekly-specific average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various thresholds of exposure. Maternal age was adjusted as categorical instead of natural spline of the continuous variable. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

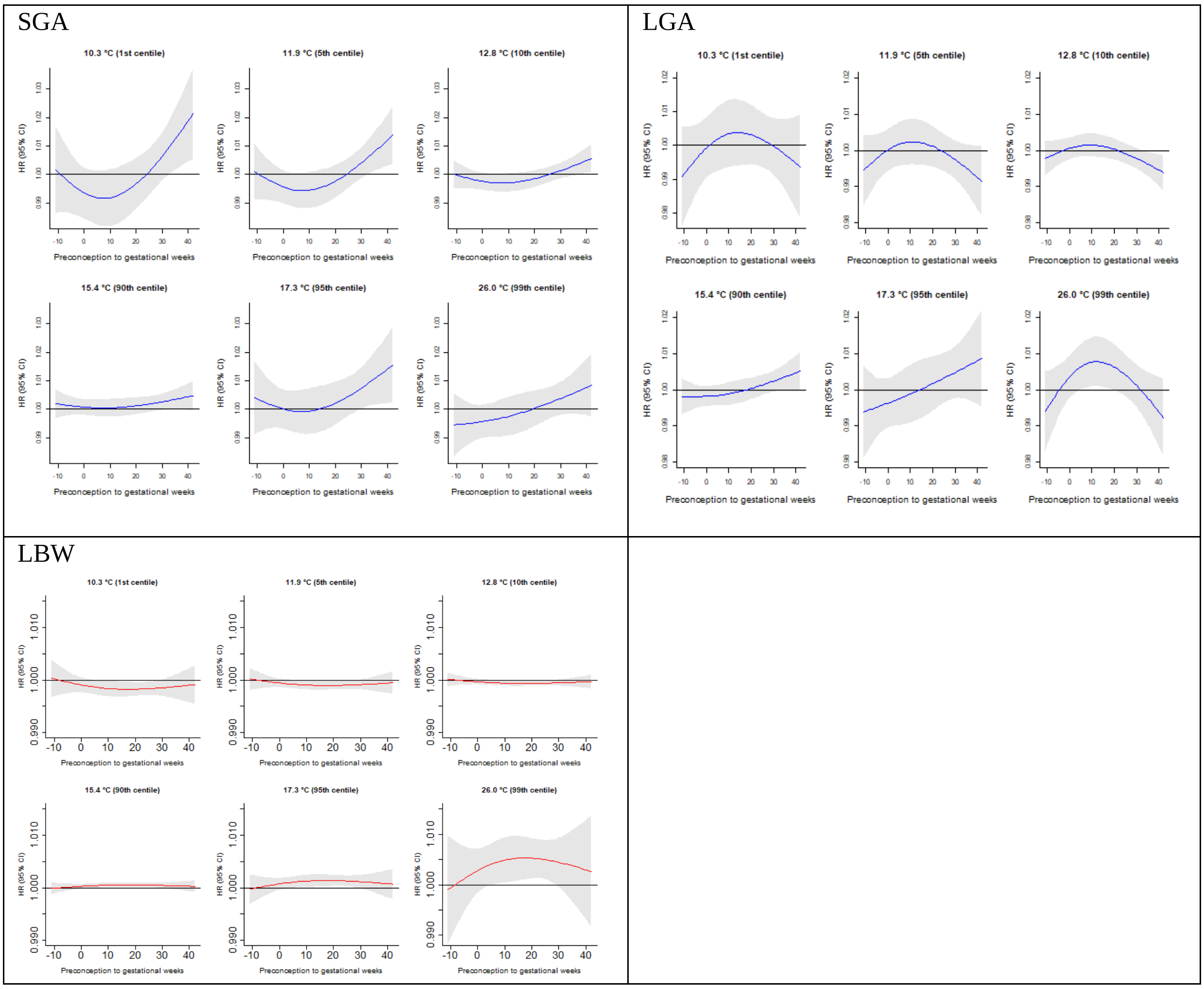

Figure S10.14. The exposure-response association between maternal weekly-specific average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various thresholds of exposure. Season of conception was adjusted as categorical (summer, spring, winter, and autumn) variable instead of calendar month index. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, year, and season of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

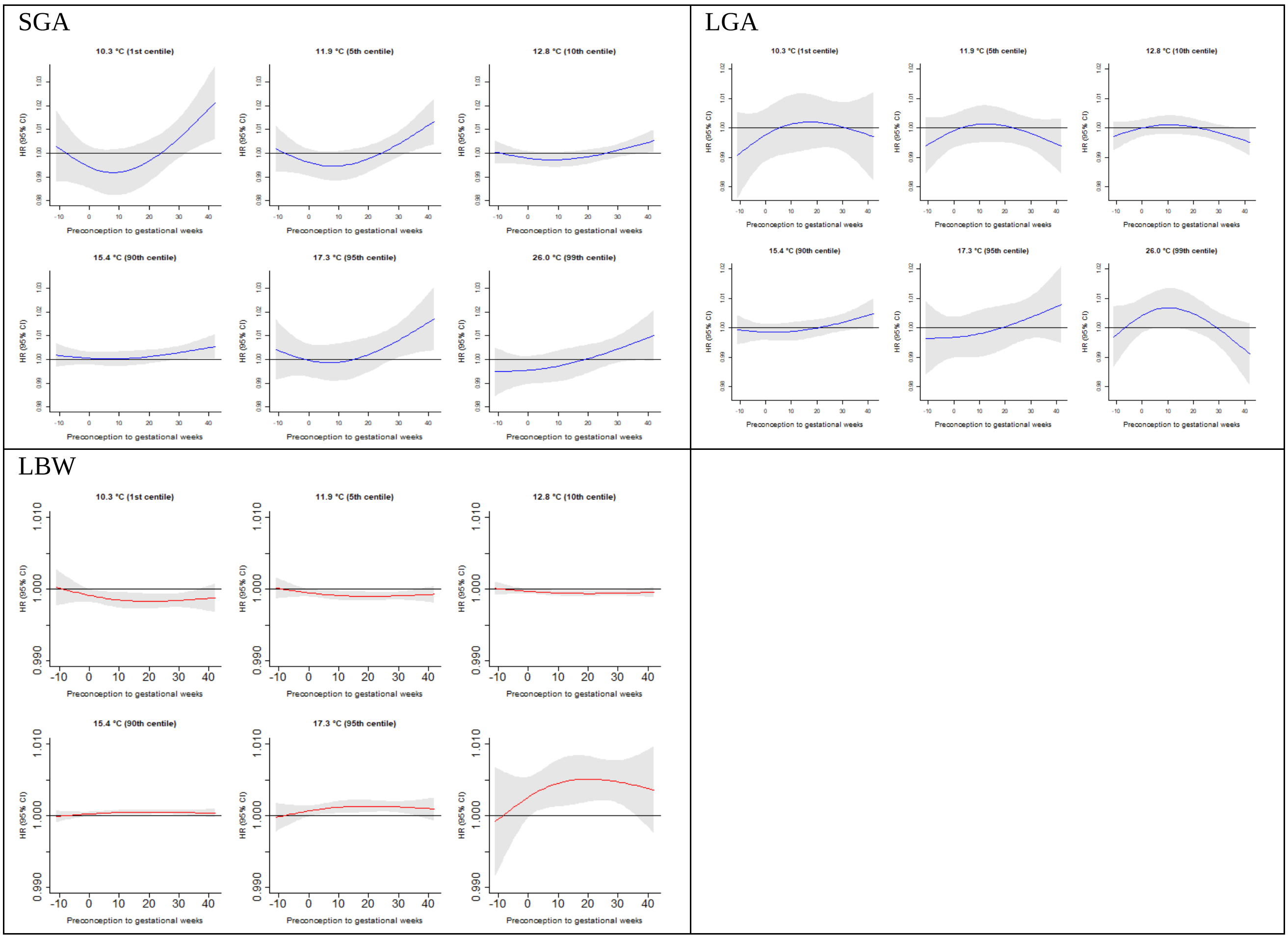

Figure S10.15. The exposure-response association between maternal weekly-specific average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various thresholds of exposure. Included mother-specific cluster was included to account for repeated births by the same mother. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, and year and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

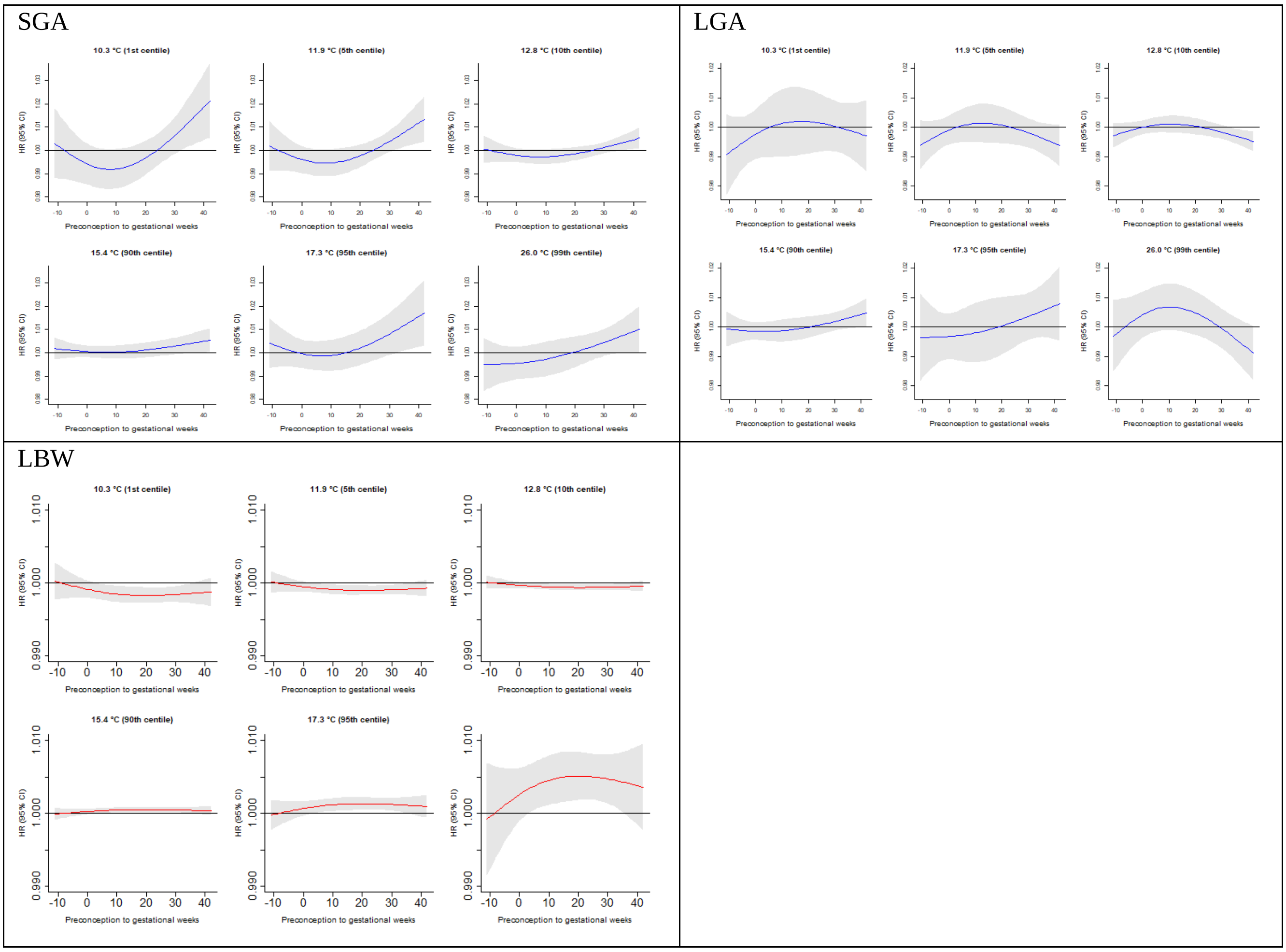

Figure S10.16. The exposure-response association between maternal weekly-specific average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various thresholds of exposure. Included local government area-specific cluster was included to account for potential spatial clustering and maternal mobility. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, and year and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

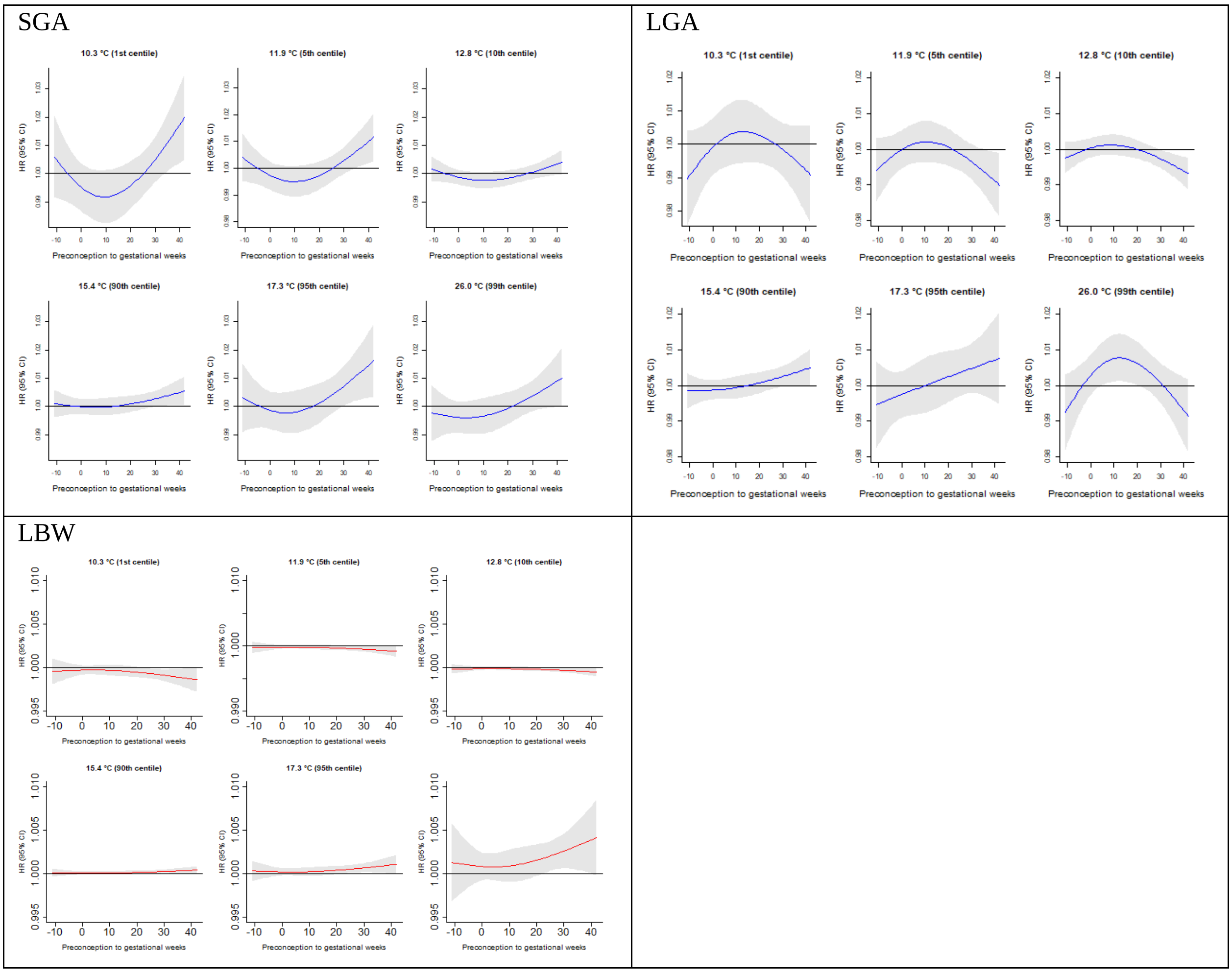

Figure S10.17. The exposure-response association between maternal weekly-specific average UTCI exposures over twelve weeks preconception through to gestational weeks at birth with reference to median 14.2 ˚C and the hazard ratios HR (95% CI) of term SGA, LGA, and LBW at various thresholds of exposure. All eligible births with 22-42 gestational weeks were analysed instead of only term births. Note: Model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, areal level socioeconomic status, and year and month of conception. UTCI, Universal Thermal Climate Index in degree Celsius; HR, hazard ratio; CI, confidential interval; SGA, small for gestational age; LGA, large for gestational age; LBW, low birth weight.

Appendix J: Supplementary materials for Chapter 11

Table S11.1 Descriptive statistics of UTCI by subgroups across the 260 districts in Ghana, 2012–2020 for 5,961,328 births, including 90,532 stillbirths.

		UTCI (˚C)									
Variable	Group	Mean (SD)	Median	Min	P1	P5	P10	90	P95	P99	Max
All	All	28.5 (2.0)	28.8	19.6	23.0	25.0	25.8	30.8	31.6	33.2	35.2
Season	Summer	28.3 (2.0)	28.3	1·9.7	23.4	25.1	25.8	30.6	31.5	33.3	35.2
	Winter	29.5 (2.0)	29.4	19.6	22.6	24.6	26.3	31.0	31.6	32.9	34.4
Population density (82/ 2368 persons/km^2)	Low*	28.9 (2.0)	29.0	21.1	23.5	25.4	26.2	31.3	32.1	33.5	35.2
	High*	28.2 (2.0)	28.6	19.6	22.7	24.6	25.5	30.4	30.8	32.3	35.1
GDP (28.6/534.9 per million US dollars)	Low	28.8 (2.0)	29.0	21.0	23.4	25.4	26.2	31.2	32.1	33.5	35.2
	High	28.3 (2,0)	28.6	19.6	22.7	24.6	25.5	30.5	30.9	32.4	35.1
$PM_{2.5}$ (58.0/61.7 µg/m^3)	Low	28.5 (2.2)	28.7	19.6	22.5	24.6	25.6	30.9	32.1	33.6	35.2
	High	28.6 (1.8)	28.8	21.5	23.8	25.3	26.0	30.7	31.2	32.2	34.1

Note. SD, standard deviation; UTCI, Universal Thermal Climate Index; P1 to P99, 5th to 99th percentiles; GDP, Gross Domestic Production (Purchasing Power Parity); US, United States; PM2.5; fine particulate matter at aerodynamic diameter ≤ 2.5 µm. * Overall means were computed to dichotomise the districts into low (≤ median) or high (> median) subgroups for each covariate.

Table S11.2 The estimated monthly relative risks (RRs) and 95% confidence intervals (95% CIs) of stillbirth at different percentiles relative to the median UTCI (28.8 °C) in Ghana, 2012-2020.

Lag months	1st (23.0 ºC)	10th (25.8 ºC)	25th (27.2 ºC)	75th (29.9 ºC)	90th (30.8 ºC)	95th (31.6)	99th (33.2 ºC)
0	0.96 (0.89, 1.03)	0.96 (0.92, 1.01)	0.98 (0.95, 1.00)	1.01 (1.00, 1.03)	1.02 (0.99, 1.05)	1.01 (0.97, 1.05)	0.96 (0.90, 1.02)
1	0.97 (0.93, 1.01)	0.96 (0.93, 0.99)	0.97 (0.95, 0.99)	1.02 (1.01, 1.03)	1.03 (1.01, 1.05)	1.02 (1.00, 1.05)	0.97 (0.93, 1.02)
2	0.99 (0.95, 1.03)	0.96 (0.93, 0.98)	0.97 (0.95, 0.98)	1.02 (1.01, 1.03)	1.03 (1.01, 1.05)	1.03 (1.00, 1.06)	0.98 (0.93, 1.03)
3	1.01 (0.97, 1.05)	0.97 (0.94, 1.00)	0.97 (0.95, 0.99)	1.02 (1.01, 1.03)	1.03 (1.01, 1.05)	1.03 (1.00, 1.05)	0.97 (0.92, 1.02)
4	1.03 (1.00, 1.06)	0.99 (0.96, 1.01)	0.98 (0.97, 1.00)	1.01 (1.01, 1.02)	1.02 (1.00, 1.03)	1.01 (0.98, 1.03)	0.94 (0.90, 0.98)
5	1.04 (1.01, 1.08)	1.01 (0.98, 1.03)	1.00 (0.98, 1.01)	1.00 (1.00, 1.01)	1.00 (0.98, 1.02)	0.99 (0.96, 1.01)	0.91 (0.87, 0.95)
6	1.04 (0.99, 1.08)	1.01 (0.98, 1.04)	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)	0.99 (0.97, 1.01)	0.98 (0.95, 1.00)	0.90 (0.85, 0.94)
7	1.00 (0.96, 1.04)	0.99 (0.96, 1.02)	0.99 (0.98, 1.01)	1.00 (0.99, 1.01)	1.00 (0.98, 1.02)	0.98 (0.96, 1.01)	0.93 (0.88, 0.97)
8	0.95 (0.91, 0.99)	0.95 (0.93, 0.98)	0.97 (0.96, 0.99)	1.01 (1.00, 1.02)	1.01 (0.99, 1.03)	1.01 (0.98, 1.04)	0.98 (0.94, 1.03)
9	0.89 (0.83, 0.95)	0.91 (0.87, 0.95)	0.95 (0.92, 0.97)	1.02 (1.01, 1.04)	1.04 (1.00, 1.07)	1.04 (1.00, 1.09)	1.06 (0.99, 1.14)

Table S11.3 The estimated immediate and cumulative relative risks (RRs) and 95% confidence intervals (95% CIs) of stillbirth at subgroup-specific 90th percentiles relative to the median UTCI in Ghana, 2012-2020.

	Season		Population density	
Lag month	Summer	Winter	Low	High
0	1.05 (0.98, 1.13)	1.09 (1.03, 1.15)	1.07 (1.02, 1.12)	1.03 (0.98, 1.08)
0-1	1.09 (0.97, 1.22)	1.13 (1.04, 1.22)	1.13 (1.05, 1.22)	1.06 (0.98, 1.14)
0-2	1.10 (0.96, 1.27)	1.12 (1.02, 1.24)	1.19 (1.08, 1.31)	1.08 (0.99, 1.18)
0-3	1.11 (0.94, 1.32)	1.10 (0.96, 1.26)	1.23 (1.09, 1.38)	1.09 (0.98, 1.21)
0-4	1.13 (0.93, 1.38)	1.10 (0.92, 1.32)	1.25 (1.09, 1.43)	1.10 (0.98, 1.24)
0-5	1.16 (0.92, 1.46)	1.13 (0.91, 1.40)	1.26 (1.08, 1.47)	1.10 (0.96, 1.25)
0-6	1.19 (0.92, 1.55)	1.19 (0.93, 1.52)	1.26 (1.06, 1.50)	1.09 (0.94, 1.26)
0-7	1.21 (0.91, 1.61)	1.26 (0.96, 1.66)	1.28 (1.05, 1.55)	1.09 (0.92, 1.28)
0-8	1.20 (0.89, 1.62)	1.33 (0.98, 1.79)	1.33 (1.07, 1.65)	1.09 (0.91, 1.31)
0-9	1.15 (0.84, 1.58)	1.37 (0.99, 1.90)	1.42 (1.11, 1.82)	1.10 (0.89, 1.36)
	GDP		$PM_{2.5}$	
Lag month	Low	High	Low	High
0	1.04 (0.99, 1.10)	1.02 (0.98, 1.06)	1.01 (0.97, 1.06)	1.05 (0.99, 1.11)
0-1	1.11 (1.02, 1.20)	1.04 (0.97, 1.11)	1.06 (0.99, 1.14)	1.08 (0.99, 1.18)
0-2	1.19 (1.07, 1.32)	1.05 (0.97, 1.14)	1.14 (1.04, 1.25)	1.10 (0.99, 1.22)
0-3	1.27 (1.12, 1.44)	1.06 (0.96, 1.16)	1.23 (1.09, 1.38)	1.11 (0.98, 1.26)
0-4	1.34 (1.15, 1.56)	1.05 (0.94, 1.17)	1.30 (1.14, 1.49)	1.11 (0.97, 1.28)
0-5	1.40 (1.18, 1.67)	1.04 (0.92, 1.18)	1.34 (1.15, 1.57)	1.11 (0.95, 1.30)
0-6	1.45 (1.19, 1.76)	1.03 (0.90, 1.18)	1.36 (1.14, 1.61)	1.12 (0.94, 1.33)
0-7	1.50 (1.21, 1.87)	1.02 (0.88, 1.19)	1.36 (1.12, 1.64)	1.14 (0.94, 1.38)
0-8	1.58 (1.24, 2.01)	1.02 (0.86, 1.22)	1.37 (1.11, 1.68)	1.18 (0.95, 1.46)
0-9	1.69 (1.29, 2.22)	1.04 (0.85, 1.27)	1.39 (1.10, 1.76)	1.25 (0.98, 1.59)

Note: GDP, Gross Domestic Product; UTCI, Universal Thermal Climate Index

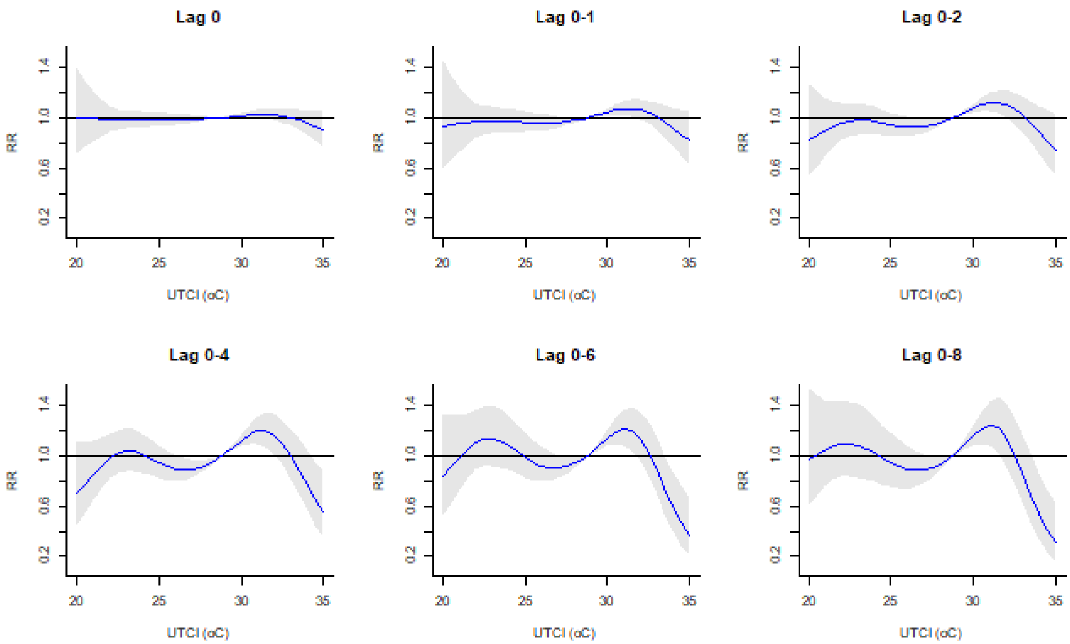

Figure S11.1 Unadjusted cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 °C).

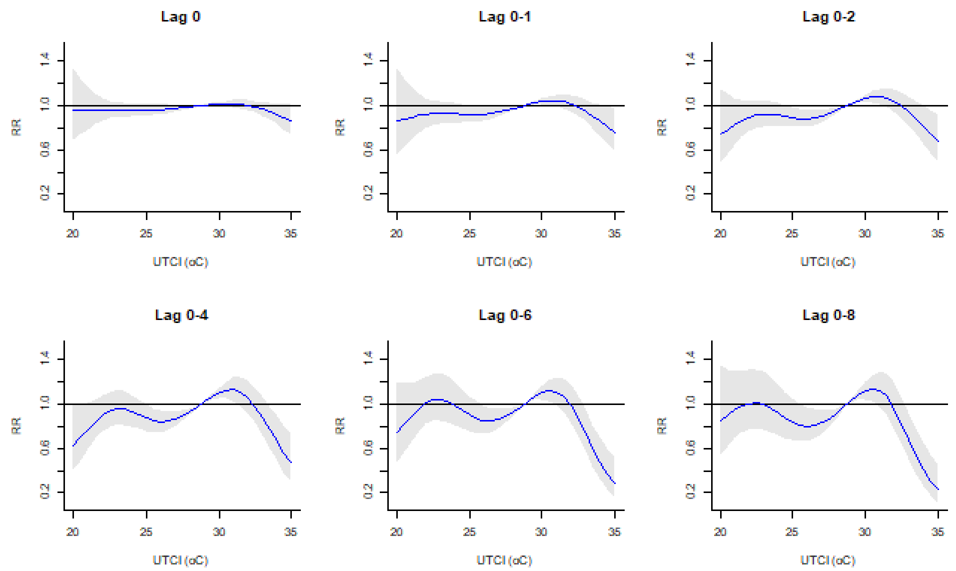

Figure S11.2 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 ºC) with $PM_{2.5}$ adjusted.

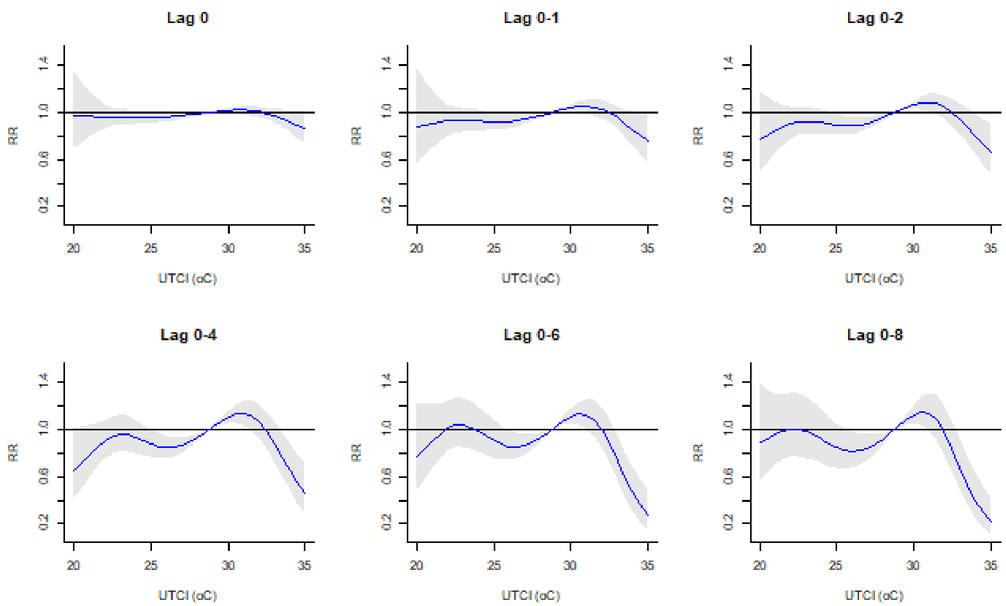

Figure S11.3 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 ºC) with population density and GDP included as linear terms.

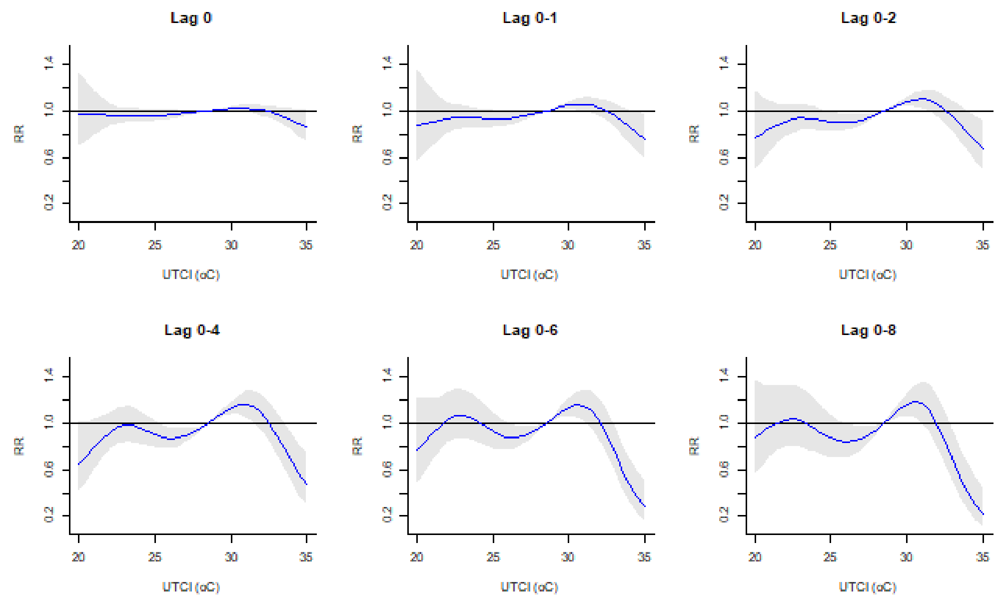

Figure S11.4 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the mean UTCI (28.5 ºC)

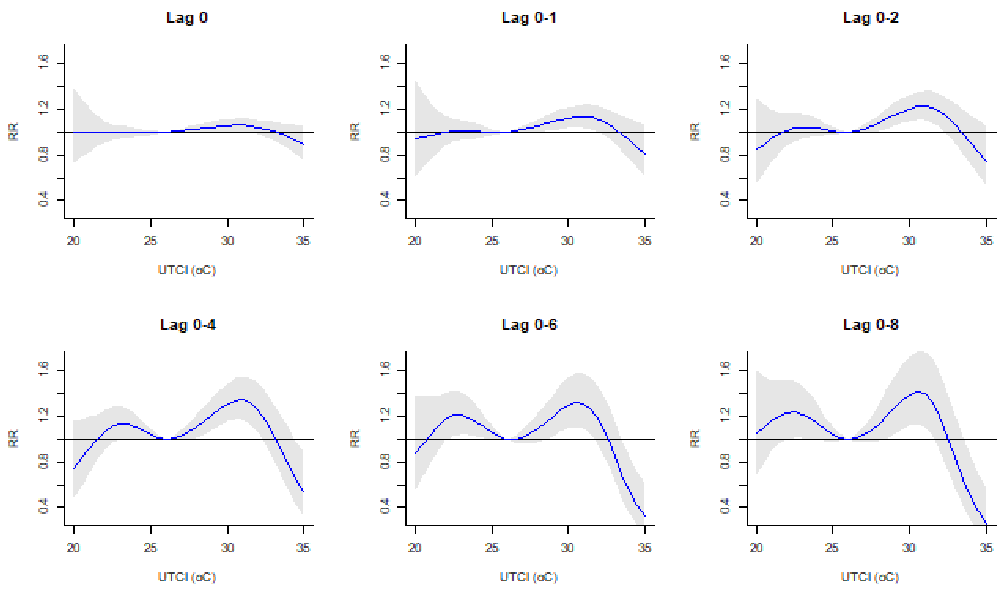

Figure S11.5 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the 26 ºC (upper value for the standard *no thermal stress* which was the closest to the median 28.8 ºC).

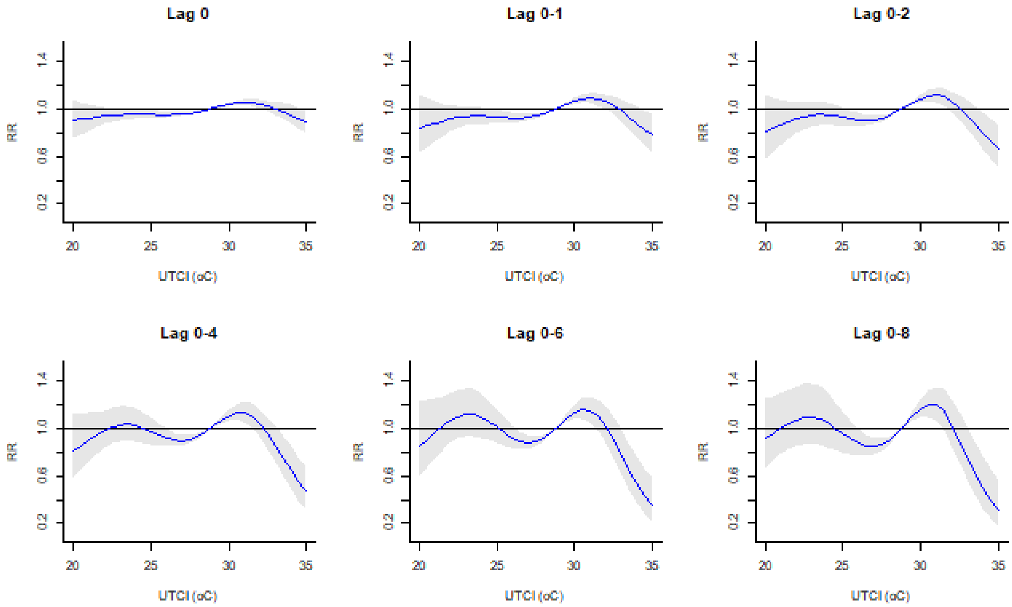

Figure S11.6 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 ºC) at 4 and 2 degrees of freedom for predictor and lag space dimensions, respectively.

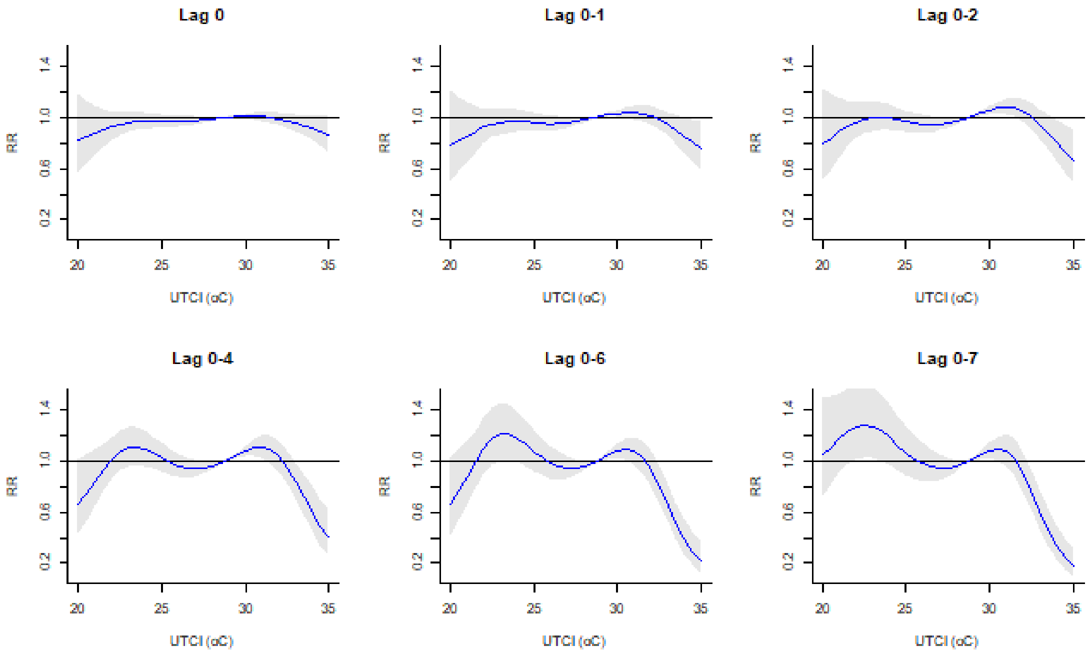

Figure S11.7 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 ºC) for maximum lag set at seven months.

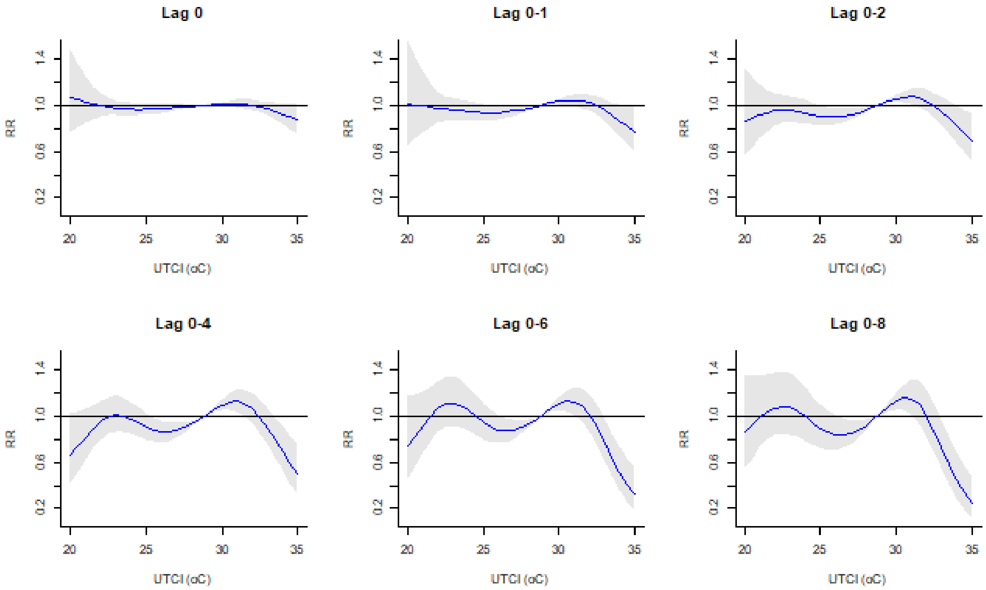

Figure S11.8 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 ºC) with natural spline of time replaced with year index.

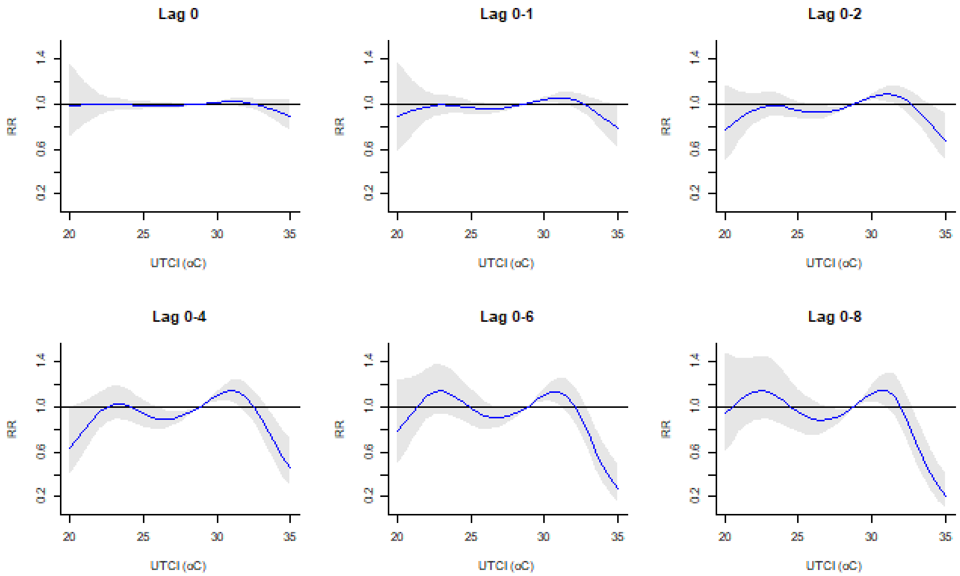

Figure S11.9 Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 ºC) without adjusting for month of birth.

Appendix K. Ambient Air Pollution, Extreme Temperatures and Birth Outcomes: A Protocol for an Umbrella Review, Systematic Review and Meta-Analysis

International Journal of *Environmental Research and Public Health*

MDPI

Study Protocol

Ambient Air Pollution, Extreme Temperatures and Birth Outcomes: A Protocol for an Umbrella Review, Systematic Review and Meta-Analysis

Sylvester Dodzi Nyadanu [1,2,*], Gizachew Assefa Tessema [2,3], Ben Mullins [2], Bernard Kumi-Boateng [4], Michelle Lee Bell [5] and Gavin Pereira [2,6,7]

1 Education, Culture and Health Opportunities (ECHO) Ghana, ECHO Research Group International, P. O. Box 424, Aflao, Ghana
2 School of Public Health, Curtin University, Perth, Kent Street, Bentley, Western Australia 6102, Australia; gizachew.tessema@curtin.edu.au (G.A.T.); b.mullins@curtin.edu.au (B.M.); gavin.f.pereira@curtin.edu.au (G.P.)
3 School of Public Health, University of Adelaide, Adelaide, South Australia 5000, Australia
4 Department of Geomatic Engineering, University of Mines and Technology, P. O. Box 237, Tarkwa, Ghana; kumi@umat.edu.gh
5 School of the Environment, Yale University, New Haven, CT 06511, USA; michelle.bell@yale.edu
6 Telethon Kids Institute, Northern Entrance, Perth Children's Hospital, Nedlands, Western Australia 6009, Australia
7 Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, 0473 Oslo, Norway
* Correspondence: sylvester.nyadanu@postgrad.curtin.edu.au

Received: 1 October 2020; Accepted: 18 November 2020; Published: 21 November 2020

check for updates

Abstract: Prenatal exposure to ambient air pollution and extreme temperatures are among the major risk factors of adverse birth outcomes and with potential long-term effects during the life course. Although low- and middle-income countries (LMICs) are most vulnerable, there is limited synthesis of evidence in such settings. This document describes a protocol for both an umbrella review (Systematic Review 1) and a focused systematic review and meta-analysis of studies from LMICs (Systematic Review 2). We will search from start date of each database to present, six major academic databases (PubMed, CINAHL, Scopus, MEDLINE/Ovid, EMBASE/Ovid and Web of Science Core Collection), systematic reviews repositories and references of eligible studies. Additional searches in grey literature will also be conducted. Eligibility criteria include studies of pregnant women exposed to ambient air pollutants and/or extreme temperatures during pregnancy with and without adverse birth outcomes. The umbrella review (Systematic Review 1) will include only previous systematic reviews while Systematic Review 2 will include quantitative observational studies in LMICs. Searches will be restricted to English language using comprehensive search terms to consecutively screen the titles, abstracts and full-texts to select eligible studies. Two independent authors will conduct the study screening and selection, risk of bias assessment and data extraction using JBI SUMARI web-based software. Narrative and semi-quantitative syntheses will be employed for the Systematic Review 1. For Systematic Review 2, we will perform meta-analysis with two alternative meta-analytical methods (quality effect and inverse variance heterogeneity) as well as the classic random effect model. If meta-analysis is infeasible, narrative synthesis will be presented. Confidence in cumulative evidence and the strength of the evidence will be assessed. This protocol is registered with PROSPERO (CRD42020200387).

Keywords: ambient air pollution; temperature; birth outcomes; perinatal outcomes; umbrella review; systematic review; meta-analysis; low and middle-income countries; LMICs

1. Introduction

Air pollution and extreme temperatures (heat/cold waves) are ubiquitous exposures that may explain a fraction of adverse birth outcomes (e.g., preterm birth, stillbirth and foetal growth restriction), pregnancy complications (e.g., miscarriage, pre-eclampsia and prelabour rupture of membranes) and longer-term effects (e.g., neurological, hormonal, respiratory and cardiovascular disorders) [1–4]. Environmental hazards contribute substantially to public health emergencies [5], with one in every nine deaths attributable to air pollution, ranking as the fifth leading risk factor of mortality [5,6]. Some common health-damaging air pollutants are gaseous air pollutants such as nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3), sulphur dioxide (SO_2), polycyclic aromatic hydrocarbons (PAH) [1,7,8] and particulate matter (PM), including those with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and ≤10 μm (PM_{10}) [9]. Although biological mechanisms are not fully established, there is accumulating evidence indicating that environmental hazards (e.g., air pollutants and extreme temperatures) might alter and trigger a cascade of pathophysiological responses, especially excess oxidative stress, and cardiovascular, immuno-inflammatory and metabolic alterations which affect prenatal development [10,11]. These patho-aetiological processes result in adverse reproductive outcomes which are exacerbated by obstetric or maternal health conditions, biologic, sociodemographic and behavioural risk factors [12–14].

With the increasing volume of relevant literature and the need for an understanding of the overall scientific evidence, systematic reviews and meta-analyses objectively synthesise scientific evidence to address environmental health questions [15], for informed decision-making by health practitioners, policy makers and other stakeholders [16–18]. Despite the mixed findings, syntheses of available literature have indicated possible associations between ambient air pollution and birth outcomes [19–25]. The literature that has examined extreme temperatures (heat/cold waves) and birth outcomes in original studies [26–28] and reviews [19,29–31] have also supported the hypothesis of positive associations. Systematic reviews and meta-analyses are crucial in harmonising the evidence but similar to original primary studies, they also have varied scope, quality and conclusions [32], and therefore the challenge of making evidence-based informed decisions resurfaces as reviews accumulate [16,33]. It is therefore prudent, logical and recommended [16] to perform umbrella reviews, a systematic synthesis of evidence from existing systematic reviews and meta-analyses [16,17]. A recent overview of meta-analyses on occupational exposures and pregnancy outcomes was conducted, concluding that maternal exposures to harmful substances can lead to many adverse pregnancy outcomes and birth defects [34]. Similar reviews of reviews (i.e., umbrella reviews) have been conducted for other exposures associated with birth outcomes, such as antenatal depression [35] and periodontal disease [36], but we are not aware of an equivalent study for associations between ambient environmental exposures, such as air pollution and/or extreme temperatures and birth outcomes. We conducted a preliminary search of PubMed and PROSPERO, which revealed one study that synthesised meta-analyses on environmental risk factors and pregnancy outcomes [32]. That study included only one meta-analytical result [25] on ambient air pollution and adverse birth outcomes and also noted that most meta-analyses did not follow meta-analysis methodological guidelines [32]. For ambient air pollution and birth outcomes, numerous systematic reviews and meta-analyses [19–25] have reported consistent positive associations and conclusions but with both statistically non-significant [20,23] and significant [22,25] associations of $PM_{2.5}$ with preterm birth (PTB), statistically non-significant [21,25] and significant [20] associations of PM_{10} with low birthweight (LBW) and statistically significant [22] and non-significant [20] associations of O_3 with PTB. Although the conclusions are consistent across the recent reviews on the increased risk of exposure–cause–effect, the mixed statistical significance and the varied scope of the reviews are likely to be perceived by policy makers or other stakeholders as confusing, resulting in delay in timely intervention. Similarly, variations in temperature metrics hindered meta-analysis in this domain but few systematic reviews without meta-analysis [19,30,31] from this relatively new and emerging area of research have also indicated negative impacts of extreme ambient air temperatures on pregnancy outcomes. Evaluating the importance and strength of the evidence through a well-planned umbrella review is now required to systematically and comprehensively synthesise the numerous existing systematic reviews and/or meta-analyses to inform current policies, to provide an explanation for associations and to inform future research directions [16,33].

The evidence in the existing reviews on ambient air pollution and/or temperature and birth outcomes [19–25,30,31,37] is heavily based on studies for high income countries while acknowledging lack of evidence from low-and middle-income countries (LMICs). Conceivably, this may be due to generally limited environmental health researches in developing countries such as Africa [38,39] and even in some East Asian and Pacific Island countries. Despite their limitations, analytical cross-sectional and ecological studies provide exploratory information to generate hypotheses for possible links between environmental factors and disease outcomes [18,40]. However, these study designs were excluded in previous reviews [20,21,24] which could lead to excluding evidence from under-resourced settings. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [41] and the proposal for Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [42] recommend broadening inclusion criteria to include most studies while implementing sensitivity and/or stratification. Stringent inclusion/exclusion criteria will improve the homogeneity among primary studies for valid cause-and-effect reviews, but this can limit the external generalisability and applicability of the findings [43]. Acknowledging the potential of these study designs in shedding light on the exposure-outcome association, recent reviews in environmental and occupational health are increasingly including ecological and analytical cross-sectional studies [22,23,44–46]. Moreover, searching databases alone is not necessarily sufficient to retrieve relevant studies [47] from LMICs and some reviews searched one [22] or two [20,25] databases. Notably, grey literature sources were not searched in previous reviews, which could also lead to missing yet relevant studies [43,47] from LMICs. A recent exploratory study on optimal database combinations for literature searches in systematic reviews concluded that optimal literature searches must search MEDLINE, EMBASE, Web of Science and Google Scholar (the first 200 relevant references) as a minimum requirement and any special topic databases to optimise adequate and efficient coverage of locating relevant studies [47].

Many would accept that populations within LMICs are possibly the most vulnerable to the effects of such exposures on perinatal endpoints given their already elevated health burden [48,49] but the quality of air in most LMICs is not monitored reliably as compared to high-income countries (HICs). Consequently, one conclusion made by Rees et al. [49] is that "we are not only potentially underestimating the impact we might also not know how bad it is until it is too late". Results from recent studies [38,39,50] using Demographic Health Survey (DHS) data and gridded satellite-based estimates of $PM_{2.5}$ across Africa indicate strong significant associations. For instance, exposure to early-life carbonaceous $PM_{2.5}$ increased the odds of neonatal mortality (OR: 1.22; 95% CI: 1.11–1.35) on the log $PM_{2.5}$ exposure level [38], higher odds for pregnancy loss cases with 26.64 μg/m^3 exposure than the control with 25.69 μg/m^3 exposure level (1.22; 1.107–1.137), and this included miscarriage (1.125; 1.109–1.142) and stillbirth (1.094; 1.05–1.38) per 10 μg/m^3 increase in $PM_{2.5}$ exposure [39]. Some researchers [38] have suggested lowering World Health Organization (WHO) air quality guidelines below the current 10 μg/m^3 total mass guideline for harmful carbonaceous $PM_{2.5}$ excluding dust and sea-salt levels [38]. Although studies from China are comparatively well-represented in previous reviews [20,51,52], relatively recent studies have been conducted in other LMICs such as India [53], South Africa [54] and across 33 African countries (using 68 surveys from 1998–2016) [39]. The tropical climatic zone of Sub-Saharan Africa adds to the impacts of extreme temperatures in these settings. A focussed systematic review and meta-analysis in LMICs on ambient air quality and temperature and the risk of adverse birth outcomes is required for these most vulnerable settings. A similar review, focussing on LMICs was planned for household air pollution and birth outcomes elsewhere [55].

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system is widely used in systematic reviews and meta-analyses, health technology assessment and clinical practice guidelines [56] and adopted by several national and international organisations [57,58]. However, direct utility of GRADE in environmental and occupational health reviews is challenging [58,59], which could have contributed to inability to evaluate the confidence in cumulative evidence in the previous reviews [19–25,30,31,37]. Fortunately, the Navigation Guide systematic review methodology refined GRADE for environmental health risk assessment of human observational studies [60] as reported recently [61,62]. A recent WHO review on effects of environmental noise on cardiovascular and metabolic diseases also modified GRADE [59] and such modifications have been applied elsewhere [44–46,63]. Thus, there is an opportunity to rate the confidence in cumulative evidence on the effects of air pollution and/or temperature by adapting the modified GRADE system [59,60] as well as translating the overall confidence into plausible toxicological effects per Navigation Guide criteria [61,62].

The aims of this study are therefore: (i) to systematically and comprehensively examine and synthesise the literature on the effects of ambient air pollution (and if reviews are available, temperature) on birth outcomes via umbrella review (Systematic Review 1); and (ii) to use first-order systematic review and meta-analysis to systematically synthesise the available evidence on the topic in the most vulnerable settings, LMICs (Systematic Review 2). Overall, this will improve knowledge of the associations between ambient air pollution and temperature and birth outcomes globally, provide an evidence-base to inform decision making and identify gaps for further research.

2. Materials and Methods

This systematic review protocol was developed using the statement and checklist of Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P) [64,65]. The conduct of the systematic review and meta-analysis will be guided by the PRISMA statement [66], the proposal for Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [42] and Joanna Briggs Institute (JBI) systematic reviews collaboration [33]. This review will include a comprehensive synthesis of evidence from existing systematic reviews and meta-analyses through an umbrella review approach (Systematic Review 1) and systematically evaluate the primary evidence from LMICs (Systematic Review 2)

2.1. Eligibility Criteria

Eligible studies in this review will address the objectives of the review according to the PECOS (Participants, Exposures, Comparators, Outcomes and Study design) statement [60,61] recommended for environmental and occupational health research.

2.1.1. Participants or Populations

The participants are pregnant women and foetuses (*in-utero* infants) at any period of pregnancy up to birth.

2.1.2. Exposures

The exposures to be included in this study are prenatal exposure to ambient (outdoor) air pollution and/or ambient air temperature. The most commonly used markers of ambient air pollution, nitrogen dioxide (NO_2) or nitrogen oxides (NOx), carbon monoxide (CO), ozone (O_3), sulphur dioxide (SO_2) [1,7,8], fine particulate matter (PM) at aerodynamic diameter ≤2.5 µm ($PM_{2.5}$) and coarse particles ≤10 µm (PM_{10}) or total suspended particles (TSP) [9] will be considered and as non-occupational exposures. Studies on temperature and birth outcomes used different metrics such as threshold temperature (mean or percentile with different durations), maximum temperature, heat-humid index, thermal heat sensation and heat index [30,31,67]. All reported metrics for temperature will be considered.

2.1.3. Comparators

The comparators (control groups) are pregnant women in the same study population and period with lower exposure levels with or without adverse birth outcomes as compared to those exposed to higher exposures with adverse birth outcomes.

2.1.4. Outcomes

The adverse perinatal outcomes of interest include: preterm birth (PTB; live birth before 37 completed gestational weeks, pregnancy loss (miscarriage and stillbirth), birth weight and foetal growth restrictions (term low birth weight, TLBW or LBW: birth weight <2500 g at ≥37 completed gestational weeks; and small-for-gestational age; SGA: birth weight below the 10th percentile for that gestational age and sex; and foetal or intrauterine growth restriction).

2.1.5. Study Designs

For both systematic reviews, we will include only quantitative human observational studies: prospective/retrospective cohort, case-control, analytical cross-sectional and ecological studies that examined long-term effects (that is, entire pregnancy or by trimesters) of ambient air pollution and/or temperature on birth outcomes. The analytical studies assessing short-term effects (e.g., last month of gestation and few weeks or days to birth), including daily time series and case-crossover studies, will be included and synthesis will be performed separately by exposure period. Randomised controlled trials (RCTs) are impractical in this domain, but any RCTs and/or natural human experiments will be included if identified.

Systematic Review 1(umbrella review) will include all systematic reviews with or without meta-analyses irrespective of geographical location or economic grouping. A systematic review and/or meta-analysis will be included if the review study specified inclusion/exclusion criteria, specified a search strategy in at least one literature database, clearly reported results on any of the exposure–outcome associations of interest (as defined in our PECO statement) as primary objective with details on the included primary studies [68] and included at least three primary studies for the exposure-outcome association of interest [69].

2.1.6. Exclusion Criteria

For both systematic reviews, studies investigating other reproductive health outcomes (e.g., pre-eclampsia) and studies using only distance from/to the source of exposure (e.g., distance to road) as proxy without empirical assessment of exposures will be excluded. Descriptive epidemiological studies (e.g., case reports, case series and descriptive cross-sectional), studies without full data/report (e.g., conference abstracts, letters to the editor and editorials), non-human studies (e.g., animal model and *in vitro*) and assisted-reproductive technology (e.g., *in vitro* fertilisation and embryo transfer) will be excluded.

Systematic Review 1(umbrella review) will exclude theoretical reviews or reviews incorporating theoretical studies or opinion as primary source of evidence.

Systematic Review 2 (systematic review and meta-analysis in LMICs) will include only primary studies conducted on participants from LMICs, using the current World Bank economic grouping [70]. No exclusion criterion will be applied to adjustment of confounding factors, but we will summarise the confounders adjusted in each study. Multi-country study that included both LMICs and high-income countries (HICs) will be selected but data will be retrieved for the included LMICs only.

2.2. Information Sources

Both published and grey literature will be sourced from: (i) six major bibliographic databases (PubMed, CINAHL, Scopus, MEDLINE via Ovid, EMBASE via Ovid and Web of Science Core Collection); (ii) systematic reviews repositories (Cochrane Database of Systematic Reviews, JBI Database of Systematic Reviews and Implementation Reports, and Epistemonikos; www.epistemonikos.org/); (iii) electronic grey literature databases, OpenGrey (http://www.opengrey.eu/) and WorldWideScience.org; (iv) Internet search engines, Google (www.google.com/) and Google Scholar (www.google.com/scholar/), to screen the first 200 hits for potentially relevant studies [47]; (v) World Health Organisation website; and (vi) references of eligible studies. Searches will be restricted to English language with no date limitations. The dates of searches will be recorded.

2.3. Search Strategy

We searched medical subject headings (MeSH) with key words related to the exposures (ambient air pollution and temperature) and the adverse birth outcomes based on terminologies used in recent reviews on the topic [19–25,29–31,37]. Comprehensive search terms using the relevant MeSH terms, key words and previous search terms will be developed (e.g., air pollution, particulate matter, temperature, climate change, heat, pregnancy outcome, birth outcome, birth weight, foetal growth, stillbirth, premature birth, preterm birth and small-for-gestational age). These search terms will be used within PubMed as template database to finalise an advanced search strategy using Boolean combination and will be modified where necessary for the rest of the databases and the other sources. The search terms within each search grid category will be expanded with "OR" and the two categories combined with "AND" to search in the "Title/Abstract". Example for PubMed is given in Table S1. For the umbrella review (Systematic Review 1), additional search terms "review" and "meta-analysis" will be applied to obtain previous systematic reviews and meta-analyses. A librarian from Faculty of Health Sciences, Curtin University with expertise in searching databases for systematic reviews will be consulted on the search strategies for each database. Reference lists of the eligible primary studies and previous reviews will also be searched manually to further identify potentially eligible studies that might be missed from the database literature search. Alerts will be set for each database, and we will also conduct literature search in PubMed and Scopus for the most recent publications as e-print or in-press ahead of publication over the last four months when we are close to completing the review. The dates of searches, including the last search, will be recorded.

2.4. Study Screening and Selection

All stages will be conducted independently by two researchers, with conflicts managed by discussion or with a third author. From the search, the titles of all identified citations with abstracts will be uploaded into *EndNote* library and duplicates removed. We will screen the title and abstract per the eligibility criteria. Potentially eligible studies will be retrieved and imported into Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI) web-based software [33,71]. The web-based all-in-one new JBI SUMARI software for conducting all types of review will be used to facilitate the review process [71]. The full text of the selected studies will be assessed comprehensively against the inclusion criteria within the JBI SUMARI system. All studies that do not meet the inclusion criteria will be excluded with reasons and presented in PRISMA flow chart [41]. Erratum or retraction status of the selected studies will be checked.

2.5. Quality (Risk of Bias) Assessment of Selected Studies

The methodological quality or risk of bias (RoB) of all selected eligible studies (previous systematic reviews and meta-analyses as well as the primary studies in LMICs) will be assessed by two authors independently with conflicts resolved by consensus or with a third investigator. A study design-specific standardised critical appraisal tools in JBI SUMARI software [71], detailed in the JBI reviewer's manual [33] will be used. The critical appraisal checklists have series of items to be checked as "yes", "no", "unclear" and rarely "not applicable". To rate the overall RoB of each study in this review, we will assign a score of 1 if a criterion is met (yes) and 0 if the criterion is either not met (no) or lack enough information to judge (unclear). The scores will be summed where high score indicates high quality or low RoB and vice versa.

2.5.1. Systematic Review 1 (Umbrella Review)

For the umbrella review (11 items), scores 0–5 will be classified as low quality (high RoB), 6–8 as moderate quality (moderate RoB) and 9–11 as high quality (low RoB) for the previous systematic reviews and/or meta-analyses. We will further assess the methodological quality of the included reviews with the revised AMSTAR (A MeaSurement Tool to Assess systematic Reviews, AMSTAR 2) critical appraisal tool [72] to clearly identify critical flaws in specific critical domains in rating the overall confidence in the results of each systematic review and/or meta-analysis as "high", "moderate", "low" and "critically low" (Boxes S1 and S2) [72].

2.5.2. Systematic Review 2 (Systematic Review and Meta-Analysis in LMICs)

Using the JBI critical appraisal checklists within the JBI SUMARI web-based software [71], cohort studies (11 items) of scores 0–5 will be classified as low quality (high RoB), 6–8 as moderate quality (moderate RoB) and 9–11 as high quality (low RoB); case-control studies (10 items) classified with 0–4, 5–7 and 8–10 scores for low, moderate and high quality, respectively; and cross-sectional (8 items) with 0–3, 4–6 and 7–8 scores for low, moderate and high quality, respectively. To our knowledge, critical appraisal checklists for ecological studies are not available and will be considered low quality by default (high RoB). If required, corresponding author(s) will be contacted for additional information for clarification. In such case, at least two attempts will be made to contact the corresponding author.

There are emerging and substantially consistent contextualised RoB criteria for observational human studies in environmental and occupational health [73]. We therefore modified an updated WHO evidence review's RoB for noise pollution and birth outcomes [44] by using information from Navigation Guide [61,62] and MOOSE [42] to obtain a precise and concise but comprehensive, transparent, reproducible, and objective RoB criteria (Table S2) for additional appraisal of the RoB of the primary studies in similar fashion [44,45]. The score for each domain will be presented and the overall RoB scores to rate each study as high quality (low RoB) if total score is 26–33 (at least 80% of maximum score 33), moderate quality (moderate RoB) if 17–25 (less than 26 but ≥50% of 33) and low quality (high RoB) for <17 (<50% of 33). All eligible studies will be included in the data synthesis irrespective of the results of the RoB [73] due to the non-consensus around quality rating and as recommended by the MOOSE group [42]. However, because results from subgroup and sensitivity analyses by RoB may lead to inconsistent results or spurious associations within strata due to collider-stratification bias [74], the proposed improved alternative meta-analytic quality effect model will be performed to account for RoB variance [74,75].

2.6. *Data Extraction and Management*

2.6.1. Systematic Review 1 (Umbrella Review)

Two authors will extract data from the selected studies with a data extraction tool (Table S3) developed according to the relevant data for the umbrella review as summarised in Table 1. The data extraction tool will be piloted prior to the full data extraction process. Any disagreements between the two authors will be resolved by consensus or with a third author.

Table 1. Key data extraction elements for Systematic Review 1 (umbrella review).

Data Element	Key Indicators
Publication data	First author, journal, publication date, number of citations (to be determined from Google Scholar prior to final data synthesis)
Aims and type of review	Aims/objectives, review type (systematic review, meta-analysis and systematic review and meta-analysis)
Literature search	Number and names of databases searched, date range of databases searched, language restriction and non-databases searched. Review guideline(s) used
Included primary studies	Number of included primary studies, country/continent of the included studies, number of each type of study design included and publication date range of included primary studies
Participants, exposures and outcomes	Total participants included in the review, description of study participants, exposure and outcome assessments
Risk of bias assessment	Risk of bias tool used to appraise the primary studies and the quality ratings
Data synthesis and results	Method of data synthesis, overall results (for meta-analyses, this will include pooled effect sizes and confidence intervals for whole pregnancy and/or trimester-specific or short-term period for air pollutants and any timeframe reported for extreme temperatures, heterogeneity measures, *p*-values and publication bias test, any reported estimates for subgroup/sensitivity analyses)
Conclusion, recommendations and limitations	Researchers' summary statement/conclusion or interpretation of the main findings (particularly from the abstract), overall recommendations and limitations
Funding and Conflict of interest	Yes/no for reporting of funding sources (and role of funders) and conflict of interest by authors
Protocol registration and publication	Yes/no for protocol registration and/or publication in peer-reviewed journal prior to the conduct of the review

2.6.2. Systematic Review 2 (Systematic Review and Meta-Analysis in LMICs)

Similarly, data will be extracted by two authors with a piloted data extraction tool (Table S4) according to the key data elements for the Systematic Review 2, as summarised in Table 2.

Table 2. Key data extraction elements for Systematic Review 2 (systematic review and meta-analysis in LMICs).

Data Element	Key Indicators
Publication data	First, journal, publication date
Study participants	Health data source/study population description, study/sampling period, geography (country or multi-country, region, state). maternal/neonatal factors (e.g., race/ethnicity, socioeconomic, marital status, comorbidities, sex and parity of birth), number of mothers and births (target, enrolled, follow-up rate, exclusion/inclusion criteria)
Methods	Study design, birth outcome (definition, assessment and prevalence or incidence in study population), exposure (sources and assessment methods, e.g., monitor, modelled, satellite imagery and hybrid method; and timeframe; e.g., whole pregnancy and trimester) and statistical methods
Results	Number of cases and controls in each study, exposure levels for each criteria air pollutant of interest and temperature (e.g., mean, median, quartiles/percentiles, range), main statistical findings (crude and adjusted effect estimates and reference unit with 95% confidence intervals and *p*-values for entire pregnancy period and by trimester or short-term and sex and any timeframe reported for the extreme temperatures), and adjustment of confounding factors (e.g., season of birth, pregnancy complications, smoking/alcohol, sociodemographic factors, infant's sex, co-pollutant)
Conclusion, recommendations and limitations	Researchers' summary statement/conclusion or interpretation of the main findings (particularly from the abstract), overall recommendations and limitations.
Funding and Conflict of interest	Yes/no for declaration of funding sources (and role of funders) and conflict of interest by authors

Results will be extracted for estimated effects for each criteria air pollutant and temperature separately for each study and LMIC-specific results for multi-country study that included both LMICs and HICs. If required, author(s) will be contacted for missing or additional data or to clarify the existing data through an email with two follow-up emails. In some cases, multiple studies may use the same underlying data (e.g., follow-up study). In this case, the most extensive data on the main findings of the study will be selected.

2.7. Data Synthesis and Statistical Analysis

2.7.1. Systematic Review 1 (Umbrella Review)

General characteristics and scope of each review will be summarised based on the data extracted (Table 2) using tables and figures with textual descriptions. Structured tabular and pictorial groupings of reviews will also be presented based on the meta-analytical model used (fixed and/or random); heterogeneity test (Cochran's Q and/or I^2); heterogeneity level (low, moderate, high or larger $I^2 > 50$); study period (categories of five-year intervals); number of databases used (1, 2–3 or >3), number of studies included in meta-analysis (≤5, 6–10, 11–20 or >20); and yes/no for searched grey literature, registered/published protocol, assessed and rated quality of included studies with a RoB tool, followed systematic review and/or meta-analysis guidelines, checked publication bias and the tests used and performed subgroup/sensitivity analyses. The methodological quality of each review will also be presented.

Following JBI umbrella review methodology, the core rationale for conducting an umbrella review is to systematically summarise the evidence from multiple top-tier bodies of evidence (systematic reviews and/or meta-analyses) on a given topic but not to re-synthesise the results of the previous reviews or synthesis with meta-analysis or meta-synthesis [16,33]. Thus, without statistically pooling the results of previous systematic reviews and meta-analyses, we will adapt a semi-quantitative approach to systematically evaluate the confidence in cumulative evidence across previous systematic reviews with meta-analyses as reported in other umbrella reviews [76–78]. The updated two grading scales in [76] will be used to judge the importance of each exposure at six levels (Table S5) and the strength of the evidence in terms of consistency in the findings of previous systematic reviews with meta-analyses and quality of included study designs at four levels as "convincing evidence" (CE), "probable evidence" (PE), "limited-suggestive evidence" (LSE) and "limited, no conclusive evidence" (LNCE) (Table S6). Combining the two grading scales will give overall epidemiological evidence of plausibility or not for a cause-and-effect association.

2.7.2. Systematic Review 2 (Systematic Review and Meta-Analysis in LMICs)

A minimum of five comparable studies for a birth outcome with adequate quantitative data will be required to conduct a meta-analysis for that birth outcome, otherwise only deep narrative synthesis will be undertaken. To be comparable, studies must address the same exposure timeframe (e.g., whole pregnancy), birth outcomes (e.g., preterm birth) and exposure (e.g., $PM_{2.5}$). The narrative synthesis will include summarising the characteristics of the study population, methodological quality, exposure measurements, birth outcome assessments, confounders adjusted and statistical significance of the effect estimates.

Main Meta-Analysis

We will conduct the meta-analysis and examine the potential publication bias with an open access meta-analysis package MetaXL version 5.3 [79]. The two novel meta-analytical models, the inverse variance heterogeneity (IVhet) and quality effect (QE) models, which use quasi-likelihood-based variance structures with no distributional assumptions [74,75,80–83], will be used. Unlike the random effects (RE) model, both IVhet (a modified fixed effect model) and the QE model favour large studies regardless of increasing heterogeneity and the robust QE model (a bias adjustment method without bias quantification but computes synthetic bias from the quality score) additionally favours studies with better methodological quality [75,80,81]. Comparatively, IVhet and QE models were demonstrated to outperform the conventional (random effect and fixed-effect) models with higher precision and probability of producing estimates closer to true effect sizes [74,75,80–84] and QE estimators also bypass collider-stratification bias (induced by stratification or meta-regression or leave-one-out sensitivity analyses based on RoB results) [74,75]. Several recent meta-analyses [44,45,85,86] have applied IVhet and QE models. The QE model will be used to report the main findings while supplementing results based on IVhet and RE models. We will pool the effect estimates for the entire pregnancy exposure period, and, if data allow, pooled estimates for specific exposure periods (trimester-specific and short-term measures) will also be performed. Because the effect estimates of dichotomous outcomes are mostly expressed as odd ratios (ORs), any relative risk (RR) reported will be converted to OR with the algorithm described elsewhere [87]. Overall (average) exposure levels for each criteria air pollutant and temperature for each study (and, if available, LMIC-specific for multi-country studies that included LMICs) will be summarised. For comparability across studies, a common reference scale of effect estimates will be calculated for increase in exposure per 10 μg/m^3 for $PM_{2.5}$ and PM_{10}; 10 part per billion (ppb) for nitrogen dioxide (NO_2), NOx and ozone (O_3); 5 ppb for sulphur dioxide (SO_2); and 1 part per million (ppm) for carbon monoxide (CO) as described previously [22]. The pooled effect sizes will be expressed as odd ratios (ORs) or hazard ratios (HRs) for dichotomous outcomes and weighted or standardised mean differences or linear regression beta coefficients for continuous outcomes. Forest plots will be used to visually summarise effect estimates with 95% confidence intervals (CIs). Statistical heterogeneity across studies will be evaluated with Cochran's Q statistic at $p < 0.1$ and percentage of inconsistency quantified with I^2 statistic, where 25%, 50% and 75%, respectively, indicate low, moderate and high degree of heterogeneity [88]. The statistical significance for the pooled effect estimates will be two-sided at $p < 0.05$.

Subgroup Meta-Analyses and Meta-Regression

Where data permit, series of subgroup analyses will be performed (and if possible meta-regression). This will include: study period (categories of five-year intervals), study region (e.g., Africa, Asia and Caribbean), country with the largest number of studies versus others, study designs (or longitudinal versus non-longitudinal), sample size (four categories), mean exposure levels (four categories), exposure data source and exposure assessment methods (e.g., monitor, modelled, satellite imagery and hybrid method) [37] and level of confounders adjusted for. We will also perform subgroup analysis by World Bank's economic group (low, lower-middle and upper-middle) [70], global gender gap index on the scale of 0 (inequality) to 1 (full gender equality) (0.0–0.2, worst; 0.3–0.5, bad; 0.6–0.8, good; and 0.9–1.00, best) [89], country's hunger and nutritional status with the global hunger index by severity scale (≤9.9, low; 10.0–19.9, moderate; 20.0–34.9, serious; 35.0–49.9, alarming; and ≥50.0, extremely alarming) [90], political stability index [91] (≤ −2.0, extremely weak; −2.0< to ≤ −1.0, very weak; −1.0 < to ≤ 0.0, weak; 0.0 < to ≤ 1.0, moderate; 1.0 < to ≤ 2.0, strong; and >2, very strong) and climatic zone (tropical, subtropical, temperate and polar/cold) [92].

Sensitivity Meta-Analyses

We will also evaluate the robustness of the result through leave-N-out sensitivity analyses by repeating analyses after removing N studies (e.g., outlying studies, studies with largest or smallest effect estimates and sample sizes and region with largest number of studies). This will indicate which single or combination of studies is/are primarily responsible for between-study heterogeneity.

Publication Bias

Potential publication and other forms of bias will be checked with the Doi plot and Luis–Furuya–Kanamori (LFK) index to detect and quantify asymmetry of the study effects in the Doi plots [93]. The Doi plots and LFK index were demonstrated to have greater power/sensitivity than the classic funnel plots and Egger's test, particularly obvious when the number of studies is small [79,84,93], and have been used elsewhere [44,45,85,86]. We will also report the funnel plots and Egger's regression *p*-values.

Confidence in Cumulative Evidence across Studies

Following the WHO contextualised version of GRADE for environmental and occupation health reviews [46,59] as applied in related reviews [44,45,63,94], we will determine the initial level of quality of evidence across studies based on the study designs and subsequently downgrade by considering GRADE criteria [56,95]: (i) the risk of bias across studies; (ii) inconsistency of results; (iii) indirectness of evidence; (iv) imprecision of the effect estimate; and (v) publication bias or evidence from only one high quality study. We will upgrade for: (i) large magnitude of effect estimate (RR > 1.5) [59]; (ii) a study reporting an association in the presence of accounting for all plausible residual confounders; and (iii) evidence of exposure dose–response gradient. The confidence in the cumulative evidence for each exposure and each birth outcome will be rated as "high", "moderate", "low" and "very low" certainty. We will apply Navigation Guide systematic review criteria [60–62] to translate the confidence in cumulative evidence ratings into strength of evidence of the health effect as "sufficient evidence of toxicity", "limited evidence of toxicity", "inadequate evidence of toxicity" and "evidence of lack of toxicity" (Table S7). Two authors will carry out the rating and discrepancies resolve by discussion or with a third author.

2.8. Ethics and Dissemination

Ethical approval is not required for this review of previously published studies. The findings will be disseminated by publication in peer-reviewed journals and/or conference presentations.

2.9. Review Registration

This review protocol was registered with International Prospective Register for Systematic Reviews (PROSPERO) under the identification code CRD42020200387.

2.10. Protocol Update

Any necessary amendments in the methods of the present protocol will be updated in PROSPERO and subsequently documented in the final reports with appropriate justifications for the amendments under the caption "Protocol Amendments".

2.11. Limitations of This Study

The meta-analysis for all exposure types and some planned subgroup or sensitivity analyses or meta-regression might not be performed due to potential small number of studies in LMICs. Due to diversity in extreme temperature metrics in the literature, results might not be combinable statistically. The English language restriction could result in missing some relevant studies, but this systematic bias is extremely minimal [96]. As a known limitation of umbrella reviews, a primary study has the potential to be reported in more than one review. However, this will be summarised and reported by computing the Corrected Coverage Area (CCA) index proposed by Pierper et al. [68] and considered in the interpretations.

2.12. Strengths of This Study

This is the first umbrella review planned to systematically synthesise and evaluate the epidemiological strength of evidence from existing systematic reviews and meta-analyses on the topic. This review will also specifically and rigorously examine evidence from the most vulnerable regions, LMICs. The use of new improved meta-analytic models (quality effects and inverse variance heterogeneity models) and identification of publication bias will improve the inference if the number of the included studies is small [74,75,80–84,93]. In addition to the general risk of bias (RoB) scales, this study will also assess the RoB in the primary studies using environmental exposure-outcome oriented RoB tool. Furthermore, unlike the previous reviews, this review will evaluate the confidence of the body of evidence with the WHO evidence review's modified GRADE [59] and also grade the plausible toxicological strength of the evidence according to Navigation Guide principle [60–62].

3. Conclusions

The prenatal stage is a very sensitive period for development in the life course and exposure to occupational and environmental hazards can have immediate and long-term negative impacts on the offspring [34]. The scientific evidence on environmental hazards (such as ambient air pollution and temperature) and reproductive health outcomes is large, of variable quality and largely unfamiliar to policy-makers, healthcare givers and patients; and compounded with no clear-cut roadmap for evidence evaluation, which could be impediments to timely evidence-based advice on preventive measures, including regulatory measures [57]. Many systematic reviews and/or meta-analyses on the topic with varied scope and quality have accumulated with similar conclusion on the adverse effect of the environmental exposures on perinatal outcomes but with differing statistical significance. Moreover, almost all the primary studies included in the previous reviews were from high-income countries and there is no clear information from the most vulnerable settings, LMICs. In addition to studies from China often captured in the previous reviews, recent studies [39,53,54] are emerging from other LMICs. Hence, synthesis of evidence in LMICs is now possible.

Employing an umbrella review to comprehensively synthesise existing systematic reviews and/or meta-analysis and then purposely pooling the evidence in LMICs with novel approaches, including improved robust meta-analytical QE model [74,75,81], grading the overall evidence with modified GRADE [59] as in previous environmental meta-epidemiology [44–46,63,94] and rating the strength of the cause-and-effect per Navigation Guide criteria [60–62] will contribute significantly to improved knowledge and inform future studies. We expect that this protocol will provide a succinct outline for searching, extracting and synthesising the relevant information.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/22/8658/s1, Table S1: Advanced literature search strategy in Title/Abstract for PubMed, Table S2: Risk of bias appraisal checklist for environmental health observational studies, Table S3: Data extraction tool for Systematic Review 1 (umbrella review), Table S4: Data extraction tool for Systematic Review 2 (systematic review and meta-analysis in LMICs), Table S5: Grading the importance of an exposure, Table S6: Grading the strength of evidence, Table S7: Strength of evidence of plausible toxicological effects of exposures on birth outcomes, Box S1: AMSTAR 2 critical domains in the conduct of review, Box S2: Rating overall confidence in the results of the existing reviews.

Author Contributions: Conceptualisation, S.D.N., G.A.T., B.M., B.K.-B. and G.P.; methodology, S.D.N., G.A.T., B.M., B.K.-B., M.L.B. and G.P.; writing—original draft preparation, S.D.N.; writing—review and editing, S.D.N., G.A.T., B.M., B.K.-B., M.L.B. and G.P.; supervision, B.M., G.A.T., B.K.-B. and G.P.; and project administration, S.D.N. All authors have read and agreed to the published version of the manuscript.

Funding: S.D.N. was funded by Curtin International Postgraduate Research Scholarship (CIPRS). G.P was funded by Australia National Health and Medical Research Council, grants number 1099655 and number 1173991, and the Research Council of Norway through its Centre of Excellence, grant number 262700.

Acknowledgments: We are very grateful for the expert assistance provided by the Faculty of Health Sciences librarian (Diana Blackwood). We are very grateful to the funders. We also appreciate the efforts of the editorial office and the reviewers to improve the quality of the article.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. World Health Organisation. *Air Pollution and Child. Health: Prescribing Clean Air*; WHO Press, World Health Organization: Geneva, Switzerland, 2018.
2. Ritz, B.; Wilhelm, M. Air pollution impacts on infants and children. In *Southern California Environmental Report Card*; UCLA Institute of the Environment: Los Angeles, CA, USA, 2008.
3. Xu, X.; Kan, H.; Ha, S. Ambient Air Pollution and Reproductive Health. In *The Impact of Air Pollution on Health, Economy, Environment and Agricultural Sources*; Mohamed, K., Ed.; IntechOpen: Rijeka, Croatia, 2011; pp. 93–116.
4. Mannucci, P.M.; Franchini, M. Health Effects of Ambient Air Pollution in Developing Countries. *Int. J. Environ. Res. Public Health* **2017**, *14*, 1048. [CrossRef] [PubMed]
5. World Health Organisation. *Ambient Air Pollution: A Global Assessment of Exposure and Burden of Disease*; WHO Press, World Health Organization: Geneva, Switzerland, 2016.
6. Health Effects Institute. *State of Global Air 2019. Special Report on Global Exposure to Air Pollution and Its Disease Burden*; Health Effects Institute: Boston, MA, USA, 2019.
7. Pereira, G.; Bell, M.L.; Lee, H.J.; Koutrakis, P.; Belanger, K. Sources of Fine Particulate Matter and Risk of Preterm Birth in Connecticut, 2000–2006: A Longitudinal Study. *Environ. Health Perspect.* **2014**, *122*, 1117–1122. [CrossRef] [PubMed]
8. World Health Organisation. *WHO Guidelines for Indoor air Quality: Selected Pollutants*; WHO Regional Office for Europe: Copenhagen, Denmark, 2010.
9. Hannam, K. The Effects of Air Pollution on Perinatal Outcomes in North West England. Ph.D. Thesis, Faculty of Medical and Human Sciences, School of Medicine Institute of Population Health and Institute of Human Development, University of Manchester, Manchester, UK, 2013.
10. Saenen, N.D.; Martens, D.S.; Neven, K.Y.; Alfano, R.; Bové, H.; Janssen, B.G.; Roels, H.A.; Plusquin, M.; Vrijens, K.; Nawrot, T.S. Air Pollution-Induced Placental Alterations: An interplay of oxidative stress, epigenetics, and the aging phenotype? *Clin. Epigenetics* **2019**, *11*, 124. [CrossRef] [PubMed]
11. Lin, V.W.; Baccarelli, A.A.; Burris, H.H. Epigenetics-a potential mediator between air pollution and preterm birth. *Environ. Epigenetics* **2016**, *2*, 1–8. [CrossRef]
12. Kannan, S.; Misra, D.P.; Dvonch, J.T.; Krishnakumar, A. Exposures to airborne particulate matter and adverse perinatal outcomes: A biologically plausible mechanistic framework for exploring potential effect modification by nutrition. *Environ. Health Perspect.* **2006**, *114*, 1636–1642. [CrossRef]
13. Slama, R.; Darrow, L.; Parker, J.; Woodruff, T.J.; Strickland, M.; Nieuwenhuijsen, M.; Glinianaia, S.; Hoggatt, K.J.; Kannan, S.; Hurley, F.; et al. Meeting report: Atmospheric pollution and human reproduction. *Environ. Health Perspect.* **2008**, *116*, 791–798. [CrossRef]
14. Erickson, A.C.; Arbour, L. The Shared Pathoetiological Effects of Particulate Air Pollution and the Social Environment on Fetal-Placental Development. *J. Environ. Public Health* **2014**, *2014*, 901017. [CrossRef]
15. Rooney, A.A.; Boyles, A.L.; Wolfe, M.S.; Bucher, J.R.; Thayer, K.A. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ. Health Perspect.* **2014**, *122*, 711–718. [CrossRef]
16. Aromataris, E.; Fernandez, R.; Godfrey, C.M.; Holly, C.; Khalil, H.; Tungpunkom, P. Summarizing systematic reviews: Methodological development, conduct and reporting of an umbrella review approach. *Int. J. Evid Based Health.* **2015**, *13*, 132–140. [CrossRef] [PubMed]
17. Hartling, L.; Chisholm, A.; Thomson, D.; Dryden, D.M. A descriptive analysis of overviews of reviews published between 2000 and 2011. *PLoS ONE* **2012**, *7*, e49667. [CrossRef] [PubMed]
18. World Cancer Research Fund/American Institute for Cancer. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*; AICR: Washington DC, USA, 2007.
19. Bekkar, B.; Pacheco, S.; Basu, R.; DeNicola, N. Association of Air Pollution and Heat Exposure with Preterm Birth, Low Birth Weight, and Stillbirth in the US: A Systematic Review. *JAMA Netw. Open* **2020**, *3*, e208243. [CrossRef] [PubMed]
20. Guo, L.Q.; Chen, Y.; Mi, B.B.; Dang, S.N.; Zhao, D.D.; Liu, R.; Wang, H.-L.; Yan, H. Ambient air pollution and adverse birth outcomes: A systematic review and meta-analysis. *J. Zhejiang Univ. Sci. B* **2019**, *20*, 238–252. [CrossRef] [PubMed]

21. Ji, Y.; Song, F.; Xu, B.; Zhu, Y.; Lu, C.; Xia, Y. Association between exposure to particulate matter during pregnancy and birthweight: A systematic review and a meta-analysis of birth cohort studies. *J. Biomed. Res.* **2017**, *33*, 56–68.
22. Klepac, P.; Locatelli, I.; Korosec, S.; Kunzli, N.; Kukec, A. Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges. *Environ. Res.* **2018**, *167*, 144–159. [CrossRef]
23. Li, X.; Huang, S.; Jiao, A.; Yang, X.; Yun, J.; Wang, Y.Y.; Xue, X.; Chu, Y.; Liu, F.; Liu, Y.; et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis. *Environ. Pollut.* **2017**, *227*, 596–605. [CrossRef]
24. Sun, X.; Luo, X.; Zhao, C.; Ng, R.W.C.; Lim, C.E.; Zhang, B.; Liu, T. The association between fine particulate matter exposure during pregnancy and preterm birth: A meta-analysis. *BMC Pregnancy Childbirth* **2015**, *15*, 300. [CrossRef]
25. Sapkota, A.; Chelikowsky, A.P.; Nachman, K.E.; Cohen, A.J.; Ritz, B. Exposure to particulate matter and adverse birth outcomes: A comprehensive review and meta-analysis. *Air Qual. Atmos. Health* **2010**, *5*, 369–381. [CrossRef]
26. Cox, B.; Vicedo-Cabrera, A.M.; Gasparrini, A.; Roels, H.A.; Martens, E.; Vangronsveld, J.; Forsberg, B.; Nawrot, T.S. Ambient temperature as a trigger of preterm delivery in a temperate climate. *J. Epidemiol. Community Health.* **2016**, *70*, 1191–1199. [CrossRef]
27. He, J.-R.; Liu, Y.; Xia, X.-Y.; Ma, W.-J.; Lin, H.-L.; Kan, H.-D.; Lu, J.-H.; Feng, Q.; Mo, W.-J.; Wang, P.; et al. Ambient Temperature and the Risk of Preterm Birth in Guangzhou, China (2001–2011). *Environ. Health Perspect.* **2016**, *124*, 1100–1106. [CrossRef]
28. Liu, X.; Xiao, J.; Sun, X.; Chen, Q.; Yao, Z.; Feng, B.; Cao, G.; Guo, L.; He, G.; Hu, J.; et al. Associations of maternal ambient temperature exposures during pregnancy with the risk of preterm birth and the effect modification of birth order during the new baby boom: A birth cohort study in Guangzhou, China. *Int. J. Hyg. Environ. Health* **2020**, *225*, 113481. [CrossRef]
29. Konkel, L. Taking the Heat: Potential Fetal Health Effects of Hot Temperatures. *Environ. Health Perspect.* **2019**, *127*, 102002. [CrossRef] [PubMed]
30. Kuehn, L.; McCormick, S. Heat Exposure and Maternal Health in the Face of Climate Change. *Int J. Environ. Res. Public Health* **2017**, *14*, 853. [CrossRef] [PubMed]
31. Zhang, Y.; Yu, C.; Wang, L. Temperature exposure during pregnancy and birth outcomes: An updated systematic review of epidemiological evidence. *Environ. Pollut.* **2017**, *225*, 700–712. [CrossRef] [PubMed]
32. Nieuwenhuijsen, M.J.; Dadvand, P.; Grellier, J.; Martinez, D.; Vrijheid, M. Environmental risk factors of pregnancy outcomes: A summary of recent meta-analyses of epidemiological studies. *Environ. Health* **2013**, *12*, 6. [CrossRef]
33. Joanna Briggs Institute. Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, Australia. Available online: https://reviewersmanual.joannabriggs.org/ (accessed on 21 May 2020).
34. Rahimi, R.; Moeindarbary, S.; Ghasempour, M.; Moghadam, T.G.; Heydari, O.; Bafghi, Z.R.; Norouziasl, S.; Abdi, F.; Ashrafinia, F.; Dadshahi, S. Maternal Occupational Exposures and Adverse Pregnancy Outcomes: An Overview of Meta- Analysis. *Int. J. Pediatrics* **2020**, *8*, 11341–11346.
35. Dadi, A.F.; Miller, E.R.; Bisetegn, T.A.; Mwanri, L. Global burden of antenatal depression and its association with adverse birth outcomes: An umbrella review. *BMC Public Health* **2020**, *20*, 173. [CrossRef]
36. Lavigne, S.E.; Forrest, J.L. An umbrella review of systematic reviews of the evidence of a causal relationship between periodontal disease and adverse pregnancy outcomes: A position paper from the Canadian Dental Hygienists Association. *Can. J. Dent. Hyg.* **2020**, *54*, 92–100.
37. Sun, X.; Luo, X.; Zhao, C.; Zhang, B.; Tao, J.; Yang, Z.; Ma, W.; Liu, T. The associations between birth weight and exposure to fine particulate matter (PM2.5) and its chemical constituents during pregnancy: A meta-analysis. *Environ. Pollut.* **2016**, *211*, 38–47. [CrossRef]
38. Goyal, N.; Karra, M.; Canning, D. Early-life exposure to ambient fine particulate air pollution and infant mortality: Pooled evidence from 43 low- and middle-income countries. *Int. J. Epidemiol.* **2019**, *48*, 1125–1141. [CrossRef]
39. Xue, T.; Zhu, T.; Geng, G.; Zhang, Q. Association between pregnancy loss and ambient PM2·5 using survey data in Africa: A longitudinal case-control study, 1998–2016. *Lancet Planet. Health* **2019**, *3*, e219–e225. [CrossRef]

40. World Cancer Research Fund/American Institute for Cancer. *Continuous Update Project Expert 2018*; World Cancer Research Fund and American Institute for Cancer Research: Washington, DC, USA, 2018.
41. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gotzsche, P.C.; Ioannidis, J.P.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* **2009**, *339*, b2700. [CrossRef] [PubMed]
42. Stroup, D.F.; Berlin, J.A.; Morton, S.C.; Olkin, I.; Williamson, G.D.; Rennie, D.; Moher, D.; Becker, B.J.; Sipe, T.A.; Thacker, S.B.; et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **2000**, *283*, 2008–2012. [CrossRef] [PubMed]
43. Almeida, C.P.B.D.; Goulart, B.N.G.D. How to avoid bias in systematic reviews of observational studies. *Rev. CEFAC* **2017**, *19*, 551–555. [CrossRef]
44. Dzhambov, A.M.; Lercher, P. Road Traffic Noise Exposure and Birth Outcomes: An Updated Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **2019**, *16*, 2522. [CrossRef]
45. Dzhambov, A.M.; Lercher, P. Road Traffic Noise Exposure and Depression/Anxiety: An Updated Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **2019**, *16*, 1434. [CrossRef]
46. Kempen, E.V.; Casas, M.; Pershagen, G.; Foraster, M. WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Cardiovascular and Metabolic Effects: A Summary. *Int. J. Environ. Res. Public Health* **2018**, *15*, 379. [CrossRef]
47. Bramer, W.M.; Rethlefsen, M.L.; Kleijnen, J.; Franco, O.H. Optimal database combinations for literature searches in systematic reviews: A prospective exploratory study. *BMC Syst. Rev.* **2017**, *6*, 245. [CrossRef]
48. Manisalidis, I.; Stavropoulou, E.; Stavropoulos, A.; Bezirtzoglou, E. Environmental and Health Impacts of Air Pollution: A Review. *Front. Public Health* **2020**, *8*, 14. [CrossRef]
49. Rees, N.; Wickham, A.; Choi, Y. *Silent Suffocation in Africa: Air Pollution Is a Growing Menace, Affecting the Poorest Children the Most*; United Nations Plaza: New York, NY, USA, 2019.
50. Heft-Neal, S.; Burney, J.; Bendavid, E.; Burke, M. Robust relationship between air quality and infant mortality in Africa. *Nature* **2018**, *559*, 254–258. [CrossRef]
51. Jacobs, M.; Zhang, G.; Chen, S.; Mullins, B.; Bell, M.; Jin, L.; Guo, Y.; Huxlety, R.; Pereiral, G. The association between ambient air pollution and selected adverse pregnancy outcomes in China: A systematic review. *Sci. Total Environ.* **2017**, *579*, 1179–1192. [CrossRef]
52. Zhu, P.F.; Zhang, Y.; Ban, J.; Li, T.T.; Shi, X.M. Air pollution and adverse birth outcome in China: A comprehensive review. *Chin. J. Epidemiol.* **2017**, *38*, 393–399.
53. Balakrishnan, K.; Ghosh, S.; Thangavel, G.; Sambandam, S.; Mukhopadhyay, K.; Puttaswamy, N.; Sadasivam, A.; Ramaswamy, P.; Johnson, P.; Kuppuswamy, R.; et al. Exposures to fine particulate matter (PM2.5) and birthweight in a rural-urban, mother-child cohort in Tamil Nadu, India. *Environ. Res.* **2018**, *161*, 524–531. [CrossRef] [PubMed]
54. Mitku, A.A.; Zewotir, T.; North, D.; Jeena, P.; Asharam, K.; Muttoo, S.; Naidoo, R.N. The spatial modification of the non-linear effects of ambient oxides of nitrogen during pregnancy on birthweight in a South African birth cohort. *Environ. Res* **2020**, *183*, 109239. [CrossRef] [PubMed]
55. Younger, A.; Alkon, A. Systematic Review of Adverse Birth Outcomes Associated with Household Air Pollution from Cooking Fuel in Low- and Middle-Income Countries. PROSPERO CRD42020152333. Available online: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020152333 (accessed on 19 May 2020).
56. Guyatt, G.; Oxman, A.D.; Akl, E.A.; Kunz, R.; Vist, G.; Brozek, J.; Norris, S.; Falck-Ytter, Y.; Glasziou, P.; Debeer, H. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J. Clin. Epidemiol.* **2011**, *64*, 383–394. [CrossRef]
57. Woodruff, T.J.; Sutton, P. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. *Health Aff.* **2011**, *30*, 931–937. [CrossRef]
58. Morgan, R.L.; Thayer, K.A.; Bero, L.; Bruce, N.; Falck-Ytter, Y.; Ghersi, D.; Guyatt, G.H.; Hooijmans, C.R.; Langendam, M.; Mandrioli, D.; et al. GRADE: Assessing the quality of evidence in environmental and occupational health. *Environ. Int.* **2016**, *92*, 611–616. [CrossRef]
59. van Kempen, E.E.M.M.; Casas, M.; Pershagen, G.; Foraster, M. *Cardiovascular and Metabolic Effects of Environmental Noise: Systematic Evidence Review in the Framework of the Development of the WHO Environmental Noise Guidelines for the European Region*; Report No.: RIVM Report 2017-0078; National Institute for Public Health and the Environment: Utrecht, The Netherlands, 2017.

60. Woodruff, T.J.; Sutton, P. The Navigation Guide systematic review methodology: A rigorous and transparent method for translating environmental health science into better health outcomes. *Environ. Health Perspect.* **2014**, *122*, 1007–1014. [CrossRef]
61. Chiu, W.; Johnson, N.; Moriarty, M.; Pulczinski, J.; Uwak, I.; Taiwo, S.; Lam, J.; Taylor, B.; Xu, X. Applying the Navigation Guide Systematic Review Methodology: Case Study #7. Association between Prenatal Exposures to Ambient Air Pollution and Birthweight. A Systematic Review of the Evidence Protocol. 2017. Available online: https://www.crd.york.ac.uk/PROSPEROFILES/58805_PROTOCOL_20170225.pdf (accessed on 13 June 2020).
62. Lam, J.; Sutton, P.; Kalkbrenner, A.; Windham, G.; Halladay, A.; Koustas, E.; Lawler, C.; Davidson, L.; Daniels, N.; Newschaffer, C.; et al. A Systematic Review and Meta-Analysis of Multiple Airborne Pollutants and Autism Spectrum Disorder. *PLoS ONE* **2016**, *11*, e0161851. [CrossRef]
63. Clark, C.; Crumpler, C.; Notley, A.H. Evidence for Environmental Noise Effects on Health for the United Kingdom Policy Context: A Systematic Review of the Effects of Environmental Noise on Mental Health, Wellbeing, Quality of Life, Cancer, Dementia, Birth, Reproductive Outcomes, and Cognition. *Int. J. Environ. Res. Public Health* **2020**, *17*, 393. [CrossRef]
64. Shamseer, L.; Moher, D.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. *BMJ* **2015**, *350*, g7647. [CrossRef]
65. Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *BMC Syst. Rev.* **2015**, *4*, 1. [CrossRef] [PubMed]
66. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Group, P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int. J. Surg.* **2010**, *8*, 336–341. [CrossRef] [PubMed]
67. Martinez, P.; Bandala, E.R. Heat Waves: A Growing Climate Change-related Risk. Brief for GSDR—2016 Update Secretariat of the United Nations; 2016. Available online: https://sustainabledevelopment.un.org/content/documents/967822_Martinez%20et%20al._Heat%20Waves_A%20Growing%20Climate%20Change-related%20Risk.pdf (accessed on 3 December 2019).
68. Pieper, D.; Antoine, S.L.; Mathes, T.; Neugebauer, E.A.; Eikermann, M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J. Clin. Epidemiol.* **2014**, *67*, 368–375. [CrossRef] [PubMed]
69. Beltran, A.J.; Wu, J.; Laurent, O. Associations of meteorology with adverse pregnancy outcomes: A systematic review of preeclampsia, preterm birth and birth weight. *Int. J. Environ. Res. Public Health* **2013**, *11*, 91–172. [CrossRef] [PubMed]
70. World Bank Country and Lending Groups. Available online: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. (accessed on 1 September 2020).
71. Munn, Z.; Aromataris, E.; Tufanaru, C.; Stern, C.; Porritt, K.; Farrow, J.; Lockwood, C.; Stephenson, M.; Moola, S.; Lizarondo, L.; et al. The development of software to support multiple systematic review types: The Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). *Int J. Evid. Based Healthc.* **2019**, *17*, 36–43. [CrossRef]
72. Shea, B.J.; Reeves, B.C.; Wells, G.; Thuku, M.; Hamel, C.; Moran, J.; Moher, D.; Tugwell, P.; Welch, V.; Kristjansson, E.; et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* **2017**, *358*, j4008. [CrossRef]
73. Rooney, A.A.; Cooper, G.S.; Jahnke, G.D.; Lam, J.; Morgan, R.L.; Boyles, A.L.; Ratcliffe, J.M.; Kraft, A.D.; Schünemann, H.J.; Schwingl, P.; et al. How credible are the study results? Evaluating and applying internal validity tools to literature-based assessments of environmental health hazards. *Environ. Int.* **2016**, *92*, 617–629. [CrossRef]
74. Stone, J.; Gurunathan, U.; Glass, K.; Munn, Z.; Tugwell, P.; Doi, S.A.R. Stratification by quality induced selection bias in a meta-analysis of clinical trials. *J. Clin. Epidemiol.* **2019**, *107*, 51–59. [CrossRef]
75. Stone, J.C.; Glass, K.; Munn, Z.; Tugwell, P.; Doi, S.A.R. Comparison of bias adjustment methods in meta-analysis suggests that quality effects modeling may have less limitations than other approaches. *J. Clin. Epidemiol.* **2020**, *117*, 36–45. [CrossRef]

76. O'Donoghue, G.; Kennedy, A.; Puggina, A.; Aleksovska, K.; Buck, C.; Burns, C.; Cardon, G.; Carlin, A.; Ciarapica, D.; Colotto, M.; et al. Socio-economic determinants of physical activity across the life course: A "DEterminants of DIet and Physical ACtivity" (DEDIPAC) umbrella literature review. *PLoS ONE* **2018**, *13*, e0190737. [CrossRef]
77. Sleddens, E.F.; Kroeze, W.; Kohl, L.F.; Bolten, L.M.; Velema, E.; Kaspers, P.; Kremers, S.P.; Brug, J. Correlates of dietary behavior in adults: An umbrella review. *Nutr Rev.* **2015**, *73*, 477–499. [CrossRef] [PubMed]
78. Sleddens, E.F.; Kroeze, W.; Kohl, L.F.; Bolten, L.M.; Velema, E.; Kaspers, P.J.; Brug, J.; Kremers, S.P.J. Determinants of dietary behavior among youth: An umbrella review. *Int. J. Behav. Nutr. Phys. Act.* **2015**, *12*, 7. [CrossRef] [PubMed]
79. Barendregt, J.J.; Doi, S.A. MetaXL User Guide. Version 5.3. Sunrise Beach, Queensland, Australia: EpiGear International Pty Ltd. Available online: www.epigear.com (accessed on 24 May 2020).
80. Doi, S.A.; Barendregt, J.J.; Khan, S.; Thalib, L.; Williams, G.M. Advances in the meta-analysis of heterogeneous clinical trials I: The inverse variance heterogeneity model. *Contemp. Clin. Trials.* **2015**, *45 Pt. A*, 130–138. [CrossRef]
81. Doi, S.A.; Barendregt, J.J.; Khan, S.; Thalib, L.; Williams, G.M. Advances in the meta-analysis of heterogeneous clinical trials II: The quality effects model. *Contemp. Clin. Trials.* **2015**, *45 Pt. A*, 123–129. [CrossRef]
82. Doi, S.A.R.; Barendregt, J.J.; Khan, S.; Thalib, L.; Williams, G.M. Simulation Comparison of the Quality Effects and Random Effects Methods of Meta-analysis. *Epidemiology* **2015**, *26*, e42–e44. [CrossRef] [PubMed]
83. Doi, S.A.R.; Furuya-Kanamori, L.; Thalib, L.; Barendregt, J.J. Meta-analysis in evidence-based healthcare: A paradigm shift away from random effects is overdue. *Int. J. Evid. Based Healthc.* **2017**, *15*, 152–160. [CrossRef] [PubMed]
84. Furuya-Kanamori, L.; Doi, S.A.R. Angry Birds, Angry Children, and Angry Meta-Analysts: A Reanalysis. *Perspect. Psychol. Sci.* **2016**, *11*, 408–414. [CrossRef] [PubMed]
85. Akaraci, S.; Feng, X.; Suesse, T.; Jalaludin, B.; Astell-Burt, T. A Systematic Review and Meta-Analysis of Associations between Green and Blue Spaces and Birth Outcomes. *Int. J. Environ. Res. Public Health* **2020**, *17*, 2494. [CrossRef]
86. Parisi, A.; Crump, J.A.; Glass, K.; Howden, B.P.; Furuya-Kanamori, L.; Vilkins, S.; Gray, D.J.; Kirk, M.D. Health Outcomes from Multidrug-Resistant Salmonella Infections in High-Income Countries: A Systematic Review and Meta-Analysis. *Foodborne Pathog. Dis.* **2018**, *15*, 428–436. [CrossRef]
87. Shrier, I.; Steele, R. Understanding the relationship between risks and odds ratios. *Clin. J. Sport Med.* **2006**, *16*, 107–110. [CrossRef]
88. Higgins, J.P.T.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **2003**, *327*, 557–560. [CrossRef] [PubMed]
89. World Economic Forum. The Global Gender Gap Index 2020 Rankings. Available online: http://reports.weforum.org/global-gender-gap-report-2020/the-global-gender-gap-index-2020-rankings/ (accessed on 5 November 2020).
90. von Grebmer, K.; Bernstein, J.; Alders, R.; Dar, O.; Kock, R.; Rampa, F.; Wiemers, M.; Acheampong, K.; Hanano, A.; Higgins, B.; et al. 2020 Global Hunger Index: One Decade to Zero Hunger: Linking Health and Sustainable Food Systems. Welthungerhilfe: Bonn, Germany; Concern Worldwide: Dublin, Germany, 2020; Available online: https://www.globalhungerindex.org/results.html and full report at https://www.globalhungerindex.org/pdf/en/2020.pdf; (accessed on 5 November 2020).
91. TheGlobalEconomy.com. Political Stability Index—Country Rankings. 2019. Available online: https://www.theglobaleconomy.com/rankings/wb_political_stability/#:~{}:text=Political%20stability%20index%20(%2D2.5,available%20from%201996%20to%202019 (accessed on 5 November 2020).
92. Meteoblue. General Climate Zones. Available online: https://content.meteoblue.com/nl/meteoscool/general-climate-zones (accessed on 5 November 2020).
93. Furuya-Kanamori, L.; Barendregt, J.J.; Doi, S.A.R. A new improved graphical and quantitative method for detecting bias in meta-analysis. *Int. J. Evid. Based Healthc.* **2018**, *16*, 195–203. [CrossRef] [PubMed]
94. Nieuwenhuijsen, M.J.; Ristovska, G.; Dadvand, P. WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Adverse Birth Outcomes. *Int J. Environ. Res. Public Health* **2017**, *14*, 1252. [CrossRef] [PubMed]

95. Balshem, H.; Helfand, M.; Schunemann, H.J.; Oxman, A.D.; Kunz, R.; Brozek, J.; Vist, G.E.; Falck-Ytter, Y.; Meerpohl, J.J.; Norris, S.L. GRADE guidelines: 3. Rating the quality of evidence. *J. Clin. Epidemiol.* **2011**, *64*, 401–406. [CrossRef] [PubMed]
96. Morrison, A.; Polisena, J.; Husereau, D.; Moulton, K.; Clark, M.; Fiander, M.; Mierzwinski-Urban, M.; Clifford, T.; Hutton, B.; Rabb, D. The effect of English-language restriction on systematic review-based meta-analyses: A systematic review of empirical studies. *Int. J. Technol Assess. Health Care* **2012**, *28*, 138–144. [CrossRef] [PubMed]

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Appendix L. Ambient particulate matter air pollution and stillbirth in Ghana: A difference-in-differences approach

Atmospheric Pollution Research 13 (2022) 101471

Contents lists available at ScienceDirect

Atmospheric Pollution Research

journal homepage: www.elsevier.com/locate/apr

Ambient particulate matter air pollution and stillbirth in Ghana: A difference-in-differences approach

Sylvester Dodzi Nyadanu[a,b,*], Gizachew Assefa Tessema[a,c], Ben Mullins[a], Bernard Kumi-Boateng[d], Anthony Adofo Ofosu[e], Gavin Pereira[a,f,g]

[a] Curtin School of Population Health, Curtin University, Perth, Kent Street, Bentley, Western Australia, 6102, Australia
[b] Education, Culture, and Health Opportunities (ECHO) Ghana, ECHO Research Group International, Aflao, Ghana
[c] School of Public Health, University of Adelaide, Adelaide, South Australia, 5000, Australia
[d] Department of Geomatic Engineering, University of Mines and Technology, P. O. Box 237, Tarkwa, Ghana
[e] Ghana Health Service, Private Mail Bag, Ministries, Accra, Ghana
[f] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, 0473, Oslo, Norway
[g] enAble Institute, Curtin University, Perth, Kent Street, Bentley, Western Australia, 6102, Australia

ARTICLE INFO

Keywords:
Ambient air pollution
Particulate matter
Stillbirth
Difference-in-differences

ABSTRACT

Sub-Saharan African countries, including Ghana, are known hotspots for fine particulate matter air pollution ($PM_{2.5}$) and stillbirths but lacked epidemiologic evidence. We investigated the association between $PM_{2.5}$ and stillbirth in Ghana. District-level stillbirth data were obtained from the Ghana Health Service for all 260 local districts from 2012 to 2019 for a total of 5,229,338 births, including 81,611 stillbirths. Spatiotemporal datasets, including satellite-derived $PM_{2.5}$, temperature, population density, and gross domestic product were linked with the birth data. We applied a variant difference-in-differences design with conditional quasi-Poisson regression to estimate the risk of stillbirth associated with annual $PM_{2.5}$ concentrations. We adjusted for relevant environmental and sociodemographic factors and performed subgroup analyses by population density and household air pollution. The average district-level annual stillbirth incidence was 29 (standard deviation = 55) per 1000 births. The annual average $PM_{2.5}$ concentration was 59.97 $\mu g/m^3$ (standard deviation = 9.75). Every 10 $\mu g/m^3$ increment in annual average $PM_{2.5}$ was associated with a 3% risk of stillbirth (RR); 1.03 (95% CI: 0.97, 1.09) for all-source $PM_{2.5}$ and 2% risk each for anthropogenic (RR = 1.02, 95% CI: 0.96, 1.07) and natural (RR = 1.02, 95% CI: 0.94, 1.11) sources. The association was higher for moderate or high subgroup, relative to low subgroup and higher in natural than anthropogenic sources of $PM_{2.5}$ exposures. Thus, there was some evidence for an adverse association between $PM_{2.5}$ exposure and stillbirth but estimates were less precise. Given that the district-level variation may be underpowered, stronger risk is expected in future high-quality individual-level longitudinal cohort studies in Ghana.

1. Introduction

Globally, 48 million stillbirths were recorded in the past two decades and 20 million babies are estimated to be stillborn in the next decade or by 2030 if the current rate of 2 million annual stillbirths between 2000 and 2019 continues (UN IGME, 2020). Low-and-middle-income countries (LMICs) accounted for 84% of the total stillbirths and Sub-Saharan Africa (SSA) and Southern Asia contributed to 75% of all stillbirths in 2019 (UN IGME, 2020). The SSA with 0.8 million stillbirths annually is the highest contributor to the global number of stillbirths, increasing from 27% in 2000 to 42% in 2019 (UN IGME, 2020). A stillbirth is a traumatic event that has a considerable psychosocial and

Abbreviations: LMICs, Low-and-middle-income countries; SSA, Sub-Saharan Africa; UN IGME, United Nations Inter-agency Group for Child Mortality Estimation; WHO, World Health Organisation; AQGs, Air Quality Guidelines; DID, Difference-in-differences; GSS, Ghana Statistical Service; GMHS, Ghana Maternal Health Surveys; GHS, Ghana Health Service; HEI, Health Effects Institute; CHIM, Centre for Health Information Management; AODs, Aerosol Optical Depths; GDP (PPP), Gross Domestic Production (Purchasing Power Parity).

Peer review under responsibility of Turkish National Committee for Air Pollution Research and Control.

* Corresponding author. Curtin School of Population Health, Curtin University, Perth, Kent Street, Bentley, Western Australia, 6102, Australia.
E-mail address: sylvester.nyadanu@postgrad.curtin.edu.au (S.D. Nyadanu).

https://doi.org/10.1016/j.apr.2022.101471
Received 19 January 2022; Received in revised form 4 May 2022; Accepted 29 May 2022

economic impact on families yet remains a 'neglected silent epidemic' (Aminu and van den Broek, 2019; UN IGME, 2020). The World Health Organization (WHO) defines stillbirth as a baby born with no signs of life at or after 28 weeks of gestation or with birth weight ≥1000 g or body length ≥35 cm (Aminu and van den Broek, 2019; McClure et al., 2015). The most commonly identified risk factors for stillbirth include asphyxia, placental or cord disorders, non-communicable disorders (such as gestational diabetes and hypertension), infections (such as malaria and syphilis), ruptured uterus, nutrition, lifestyle factors (such as tobacco and alcohol intake), birth interval, low birth weight, prematurity, parity, quality of antenatal care, healthcare system-related factors and many sociodemographic factors (such as maternal education and age) (Aminu et al., 2014; Lawn et al., 2016). However, the causes of approximately half of stillbirths in LMICs, particularly from SSA remain unknown, which is partly attributed to inadequate records of stillbirth cases in many SSA countries (Aminu et al., 2014; Aminu and van den Broek, 2019). In 2014, the Every Newborn Action Plan (ENAP) target was proposed to end preventable stillbirths and limit prevalence to 12 or fewer stillbirths per 1000 total births by 2030 (de Bernis et al., 2016; Lawn et al., 2016). However, considering the current trends and inability to identify the causes of stillbirth, most countries (particularly LMICs) are unlikely to meet this 2030 sustainable development goal for reducing stillbirths (Aminu and van den Broek, 2019; UN IGME, 2020). As a large proportion of stillbirths is preventable, identifying modifiable factors, including environmental risk factors, is critical for informed effective interventions to achieve the ENAP targets and the 2030 deadline (Aminu et al., 2014, 2019; de Bernis et al., 2016).

Ambient air pollution is currently not considered among the commonly reported risk factors for stillbirth. Nonetheless, population growth accompanied by growing urbanisation, industrialisation, and advancement in technology are increasing the levels of ambient air pollutants that affect human health (Manisalidis et al., 2020; Nyadanu et al., 2020). Among the major air pollutants, particulate matter is easily inhaled, causing respiratory, cardiovascular, reproductive, and neurodevelopmental disorders, cancers, and developmental morbidities (Johnson et al., 2021; Manisalidis et al., 2020; WHO, 2006a). Particulate matter is a mixture of liquid and solid particles of inorganic and organic substances suspended in air (Manisalidis et al., 2020). The particulate matter (PM) at aerodynamic diameter ≤10 μm (PM_{10}), ≤2.5 μm ($PM_{2.5}$), or < 0.1 μm (ultrafine particles) have all been associated with adverse health effects (Johnson et al., 2021; Manisalidis et al., 2020; WHO, 2006a). Inhalable $PM_{2.5}$ that is suspended in stable environments can stay travel over long distances of hundreds to thousands of kilometres (Li et al., 2019; WHO, 2006a). Based on the latest $PM_{2.5}$ estimates, globally more than half of the world population, particularly LMICs is exposed to levels of $PM_{2.5}$ that exceeded the then WHO Air Quality Guidelines (AQGs) annual average of 10 μg/m^3 (Shaddick et al., 2020; WHO, 2006b), and this will be much higher if compared to the updated AQGs annual average of 5 μg/m^3 (WHO, 2021). The major sources of $PM_{2.5}$ in SSA are biomass burning, dust from the Saharan desert dust, and some additional contributions from vehicular and industrial emissions (Abera et al., 2021; Bauer et al., 2019; Goyal et al., 2019). A recent systematic review and meta-analysis reported a 10% increase in the odds of stillbirth per 10 μg/m^3 increment in $PM_{2.5}$ exposure during the entire pregnancy period (odds ratio, OR = 1.103, 95% CI: 1.074, 1.131) (Zhang et al., 2021). Thus $PM_{2.5}$ could contribute to higher risk of stillbirth but is often not considered as a conventional risk factor. Due to its respirable size, $PM_{2.5}$ is easily transported (and more effectively during pregnancy due to the high maternal rate of metabolism) into the systemic circulation and is translocated across the placenta to the developing fetus (Erickson and Arbour, 2014; Johnson et al., 2021; Li et al., 2019). Toxic $PM_{2.5}$ particles have high oxidative potential (Johnson et al., 2021) to trigger pathophysiological and molecular processes that induce placental modifications, cause direct injury to the fetus, and cause hypoxia, which can increase the risk of stillbirth (Faiz et al., 2012; Li et al., 2019). Such effects can be exacerbated by other underlying conditions such as sociodemographic, psychosocial, and obstetrical factors (Erickson and Arbour, 2014; Kannan et al., 2006).

Although substantially high $PM_{2.5}$ concentrations (Abera et al., 2021; Agbo et al., 2021) and the highest burdens of stillbirth (Aminu and van den Broek, 2019; Lawn et al., 2016; UN IGME, 2020) have been observed in SSA, there is a paucity of epidemiologic studies from the region on this topic (Nyadanu et al., 2022). There is currently only one such study from Africa, which investigated the association between satellite-based $PM_{2.5}$ concentrations and stillbirths identified from the Demographic and Health Surveys (DHS) in 33 Africa countries (Xue et al., 2019). That study reported a 9% increase in the odds of stillbirths (OR = 1.09, 95% CI: 1.05, 1.14) per 10 μg/m^3 increment in $PM_{2.5}$ exposure during the entire pregnancy period (Xue et al., 2019). The study, however, relied on self-report, which is known to underreport and misreport stillbirth due to recall bias, survey-related methodological and reporting barriers, sociocultural beliefs, and psychosocial impacts (Kwesiga et al., 2021; McClure, 2020).

To effectively minimise confounding by design, a difference-in-differences (DID) approach, a 'double differencing' strategy has been suggested (Card and Krueger, 1994). The DID approach is a quasi-experimental design for studying causal effects in an observational study where randomised assignment of exposure is either infeasible or unethical (Wing et al., 2018) as is the case for environmental air pollutants. The DID design assumes that confounders varying across the groups are time-invariant, and time-varying confounders are group invariant (Wing et al., 2018). Wang and colleagues recently extended the DID design to multiple spatial units and periods in small area-level aggregated analysis to estimate causal effects of long-term $PM_{2.5}$ exposure on mortality within census tracts in New Jersey, USA (Wang et al., 2016). This *variant DID* design has been applied in several recent studies on ambient air pollution and mortality (Han et al., 2021; Leogrande et al., 2019; Renzi et al., 2019; Yu et al., 2020) and cancer hospitalization (Yu et al., 2021). The variant DID design is particularly suitable for cause-and-effect modelling with spatially aggregated time-series data.

This study aimed to estimate the association between clinically diagnosed stillbirth and $PM_{2.5}$ in Ghana, a SSA country for which no studies have been conducted on this topic.

2. Materials and methods

2.1. Study area

Ghana is a coastal West African country in SSA and situated along the Gulf of Guinea. Ghana's population at a growth rate of 2.1% according to 2021 census was 30.8 million with a population density of 129 persons/km^2 (GSS, 2021). The largest city, Accra is the capital. Administratively, Ghana is currently divided into 16 regions and further sub-divided into 260 local districts which are the lowest levels for policy implementations. The geographical unit of analysis in this study were these 260 local administrative districts in Ghana. The country has a tropical, warm, and humid climate with seasonal temperature variations characterised by the dry winter season and rainy summer season due to the African monsoon. The average annual temperature ranged from 26.1 °C along the coast to 28.9 °C at the driest northeast border where it can rise to 40 °C (Abbam et al., 2018). The state of global air report indicated an average $PM_{2.5}$ level of 35.0 μg/m^3 in 2017 (HEI, 2019a). Both the 2007 and 2017 Ghana Maternal Health Surveys (GMHS) indicated that 2% of pregnancies resulted in stillbirth (GSS, 2009, 2018). There is, however, substantial spatial variation in the stillbirth rate, such as the rate of 21 stillbirths/1000 births in the Northern part of Ghana (Nonterah et al., 2020), 32 stillbirths/1000 births in the middle part (Brong Ahafo) (Ha et al., 2012), and 27 stillbirths/1000 births in the southern part (Hohoe) (Agbozo et al., 2016).

2.2. Birth data

The Ghana Health Service (GHS) and other Health Agencies of the Ministry of Health coordinate all healthcare services at both public and private sectors in Ghana (CHIM, 2018; UG, 2018). An electronic health system, the Centre for Health Information Management (CHIM) of the GHS is used to routinely collect and report all health service information, including maternal health services from public and private health facilities across all local districts in the country (CHIM, 2018). These data are collated by district health directorates and remotely transferred into a centralised repository through the district health information management system. In this study, we obtained district-level birth data from 2012 to 2019 from the CHIM of GHS.

2.3. Fine particulate matter ($PM_{2.5}$) data

The total mass and the dust/sea-salts removed $PM_{2.5}$ global gridded datasets for 2012–2019 were obtained from the V4.GL.03 product of the Atmospheric Composition Analysis Group (Hammer et al., 2020; van Donkelaar et al., 2016). Briefly, this product estimated global annual $PM_{2.5}$ concentrations by combining and relating Aerosol Optical Depths (AODs) from multiple satellite observations with ground-based $PM_{2.5}$ monitoring measurements. Spatiotemporally varying geophysical relationships between the surface $PM_{2.5}$ and AODs were simulated by GEOS-Chem chemical transport model. Geographically weighted regression was then applied to the geophysical $PM_{2.5}$ estimates to calibrate the global surface $PM_{2.5}$ datasets at a spatial resolution of $0.01° \times 0.01°$ (approximately 1 km $\times$ 1 km) with cross-validation of $R^2 = 0.92$ (Hammer et al., 2020). It is, however, worth noting that the model performance will differ across countries and may be particularly low in LMICs with no or limited ground-level measurements. Ghana does air quality monitoring in limited locations, predominantly in the Greater Accra region where the capital city is located (WHO and Mudu, 2021). Using district centroids, we applied the zonal statistics technique with ArcGIS software (version 10.8.1) to obtain district-specific annual mean $PM_{2.5}$ for both total mass and dust/sea-salt removed. Following the approach adopted previously (Goyal et al., 2019), we assessed three types of $PM_{2.5}$. The first type was total mass (all-source). The second type was total mass excluding dust/sea-salts, and this was considered as from anthropogenic sources since biomass burning of aerosol particles from SSA is predominantly anthropogenic (Bauer et al., 2019; HEI, 2019b). The third type was from only dust/sea-salts and was considered from natural sources of $PM_{2.5}$, (estimated as total mass $PM_{2.5}$ − anthropogenic $PM_{2.5}$) (Goyal et al., 2019). Although, household or indoor air pollution also contribute to anthropogenic sources of $PM_{2.5}$ (HEI, 2019b), the available data on anthropogenic sources used here was considered outdoor exposure (Hammer et al., 2020). This global satellite-derived gridded $PM_{2.5}$ has been used in several studies across SSA where ground-based air quality data are not available (Bachwenkizi et al., 2021; Goyal et al., 2019; Heft-Neal et al., 2018; Xue et al., 2019), three South Asian countries (Xue et al., 2021), and elsewhere, such as Australia (Yu et al., 2020), China (Han et al., 2021), and Brazil (Yu et al., 2021), and particularly where air quality monitoring stations are sparse.

2.4. Temperature data

Monthly global gridded mean temperature and diurnal temperature range (maximum minus minimum) of daily measurements at 2 m above the ground were produced by the Climatic Research Unit gridded Time Series version 4 (CRU TS v4) product (Harris et al., 2020). The CRUTS v4 product was provided at $0.5° \times 0.5°$ spatial resolution of the global land surface climate dataset. It was derived by angular-distance weighting interpolation of monthly surface climatic variables from several networks of meteorological stations across the globe (Harris et al., 2020). The gridded monthly temperatures for 2012–2019 were processed with similar spatial techniques described earlier to obtain district-specific values. For each year, season-specific mean and standard deviation temperatures were derived. That is, yearly means and standard deviations in summer season (wet or rainy season: April–November) and winter season (dry or harmattan season: December–March) temperatures were estimated for each district.

2.5. Socioeconomic data

The socioeconomic status of each district was assessed with the global gridded dataset on total Gross Domestic Production (Purchasing Power Parity), GDP (PPP) in constant 2011 international United States dollars (Kummu et al., 2018). The GDP (PPP) data was estimated as a product of GDP per capita and gridded population from national and subnational datasets over the years 1990–2015. Spatiotemporally weighted interpolations and extrapolations were applied to produce the dataset at a spatial resolution of 5 arc-min (approximately 10 km at the equator) (Kummu et al., 2018). The GDP (PPP), representing total GDP in each grid cell was obtained for 2010–2015 and processed for district-specific annual values using similar procedures described earlier. We then applied linear interpolation functionality provided in the 'imputeTS' package (Moritz and Bartz-Beielstein, 2017) to extrapolate GDP (PPP) for the remaining years for the period 2012–2019.

2.6. Population density data

The global Gridded Population of the World, Version 4 (GPWv4) data produced by the Center for International Earth Science Information Network (CIESIN) of Columbia University (CIESIN, 2018) was used. The GPWv4 is a minimally modelled gridded population dataset created by extrapolating the raw census values from national or subnational input administrative units to a series of five target year intervals: 2000, 2005, 2010, 2015, and 2020 at a spatial resolution of 30 arc-seconds (approximately 1 km at the equator) (CIESIN, 2018). For this study, we obtained the dataset for 2015 and processed the district-specific population density (persons/km^2) within the ArcGIS environment as described earlier. Districts were then classified into three population density zones using tertiles: low ($n = 87$), moderate ($n = 87$), and high ($n = 86$).

2.7. Household air pollution data

We obtained Ghana Maternal Health Survey (GMHS) 2017 with the Geographical Positioning System coordinates for each cluster (GSS, 2018). District-level solid cooking fuel use was constructed as an indicator for household or indoor air pollution levels (Bickton et al., 2020; Weber et al., 2020). Briefly, we organised the number of households using biomass fuel or unclean cooking fuel (wood, charcoal, dung, kerosene, crop residues, shrubs, and coal) for all the 900 survey clusters (GSS, 2018). Inverse distance weighting geostatistical interpolation was applied within ArcGIS to generate a continuous raster of the number of households using polluted cooking fuel for the entire study area. District-specific values were extracted as described earlier. The districts were categorised into three household air pollution zones using tertiles: low ($n = 87$), moderate ($n = 87$), and high ($n = 86$).

2.8. Statistical analyses

We applied the variant DID design which is analogous to case-crossover and time-series designs (Lu and Zeger, 2007; Wang et al., 2016). For this, $PM_{2.5}$ exposure for everyone within a small area for each year could be assigned as an average exposure over the fine spatial grids without biasing the effect estimates due to exposure misclassification (Wang et al., 2016). This was found to additionally eliminate the problem of ecological fallacy associated with small areal-level aggregated analysis (Wang et al., 2016). This model is therefore suitable for ecological time-series analysis for causal modelling where the accessible data do not permit individual-level longitudinal cohort designs. The variant DID design assumes that the temporal differences in outcomes are related to differences in the exposures in the same populations within the location (Wang et al., 2016). Hence, the role of potential individual and behavioural factors is cancelled out since the comparisons are occurring within the same populations in the same location (Leogrande et al., 2019; Wang et al., 2016). Consequently, any spatiotemporal differences in the outcome occurrence are associated with the corresponding spatiotemporal differences between the observed and counterfactual exposures (Leogrande et al., 2019; Wang et al., 2016; Yu et al., 2020). We estimated the association between ambient $PM_{2.5}$ exposure and stillbirth using the variant DID approach with conditional quasi-Poisson regression. The association between year-to-year fluctuations in $PM_{2.5}$ concentrations and year-to-year differences in stillbirths within each district was estimated by comparing the same population to itself in the same district (260 districts) at different times (from 2012 to 2019) (Leogrande et al., 2019; Wang et al., 2016). By design, this inherently controlled for the unmeasured time-invariant confounders by removing all known and unknown confounding factors varying across areas (but fixed in time) and varying over time (but homogenous across space) (Leogrande et al., 2019; Renzi et al., 2019; Wang et al., 2016; Yu et al., 2020). This assumption in DID design (known as common or parallel trends assumption) implies that at constant $PM_{2.5}$ concentration or in the absence of $PM_{2.5}$ association with stillbirth, the unobserved differences among districts should be constant in every period and exhibit a common set of period-specific changes (Wing et al., 2018; Yu et al., 2020). Given that there is no statistical test for the common or parallel trends assumption, we used visual evidence to examine the annual trends and year-to-year volatility for relative changes in $PM_{2.5}$ and stillbirth rate over the 8-year periods (Wing et al., 2018; Yu et al., 2020). Following previous studies (Yu et al., 2020, 2021), we calculated and visually examine the proportional changes in the $PM_{2.5}$ concentrations and stillbirth rates in each district during 2012–2019 according to equations (1a) and (1b) below:

$$V_s = \frac{\sum_{t=2012}^{t=2019} V_{s,t}}{8} \tag{1a}$$

$$RC_{s,t} = \frac{V_{s,t} - V_s}{V_s} \times 100 \tag{1b}$$

where $V_{s,t}$: the annual values of the variables $PM_{2.5}$ concentration or stillbirth rate in spatial unit (district) s, year t.

V_s: the overall average of $V_{s,t}$ from 2012 to 2019 in each spatial unit s.

$RC_{s,t}$: the annual percent changes of the variables $PM_{2.5}$ concentration or stillbirth rate in spatial unit (district) s, year t.

To be a confounder under this assumption, the variable must vary differentially among districts and over time, and the variations must be associated with the district-level variations in $PM_{2.5}$ exposure and mean yearly change (Wang et al., 2016). Apart from the seasonal effects of temperature variations, we assumed no such confounder exists (Renzi et al., 2019; Wang et al., 2016). Thus, with the variant DID approach, we controlled for i) spatial-varying factors (and considered fixed in time) by using dummy variables for each district, ii) time-varying factors (but homogenous across the study area) by using dummy variables for each year, and iii) spatiotemporally varying covariates associated with $PM_{2.5}$, which we assumed to be seasonal temperatures in our base model and better captured by the means and standard deviations of summer and winter temperatures (Renzi et al., 2019; Shi et al., 2015; Wang et al., 2016). An increase in temperature in summer may have a different effect (and direction) as compared to an increase in temperature in winter (Shi et al., 2015; Wang et al., 2016). Therefore, to effectively account for the yearly seasonal confounding effect of temperature, we included mean summer and winter temperatures with their corresponding standard deviations separately in the model instead of annual mean temperature as reported previously (Han et al., 2021; Renzi et al., 2019; Wang et al., 2016; Yu et al., 2020, 2021). Specifically, DID design was formulated as

$$In\left[E\left(Y_{s,t}\right)\right] = \beta_0 + \beta_1 I_s + \beta_2 I_t + \beta_3 PM_{2.5,s,t} + \beta_4 T_{sum,s,t} + \beta_5 T_{win,s,t} + \beta_6 SD\left(T_{sum,s,t}\right) + \beta_7 SD\left(T_{win,s,t}\right) + offset\left(\ln\left(P_{s,t}\right)\right) \tag{2}$$

$Y_{s,t}$: the number of stillbirths in the spatial unit or district s (260 districts), year t (2012–2019).

I_s: dummy variable for district s

I_t: dummy variable for year t

$PM_{2.5,s,t}$: annual mean concentration of $PM_{2.5}$ in district s, year t.

$\beta_4 T_{sum,s,t}$ and $\beta_5 T_{win,s,t}$: means of summer and winter temperatures and their respective standard deviations (SD) in district s, year t.

$offset(\ln(P_{s,t}))$: an offset term using the natural logarithms of the total number of births in district s, year t.

β_0 , β_1 …. . β_7: intercept and slopes for the linear terms.

Due to many fixed effects from each district, and to account for overdispersion and autocorrelation of time-series data, we implemented a conditional quasi-Poisson regression modelling with the "gnm" package (Armstrong et al., 2014; Turner and Firth, 2020). The model parameters were estimated conditioning on the districts by specifying with the "eliminate" option to account for the district fixed effects while "eliminating" the variables that did not contribute to the maximum likelihood (Renzi et al., 2019; Turner and Firth, 2020). This generally improved the model fitting and computational efficiency (Armstrong et al., 2014; Turner and Firth, 2020). For our main analyses, we additionally adjusted for fetal sex (percentages of male and female births), maternal age at delivery (percentages of mothers that are teenagers, 10–19 years; young adults, 20–34 years, and older adults, ≥ 35 years), and GDP (PPP) per million US dollars. We examined three separate exposure-outcome associations; all-source $PM_{2.5}$, anthropogenic, and natural $PM_{2.5}$ sources.

2.9. Subgroup and sensitivity analyses

The effect modification was tested through stratification analyses by household air pollution and population density at three levels (low, moderate, and high). A separate model was fitted for each subgroup for each indicator for the three types of the $PM_{2.5}$ exposure. Furthermore, the risks in the moderate and high subgroups were compared to that of the low subgroup by estimating the ratio of relative risks (RRRs) and the corresponding 95% CIs with the Altman and Bland test of interaction effects (Altman and Bland, 2003; Hutchon, 2005).

Several sensitivity analyses were also undertaken to check the robustness of the main results. The interaction effect of temperature, GDP (PPP), and air pollution on stillbirth was tested by introducing product terms. To further check the effect of temperature variability, we replaced the means and standard deviations temperatures with the means and standard deviations of diurnal temperature ranges. To check the nonlinear association between temperature and stillbirth, we modelled the summer and winter temperatures with natural splines with 3 and 2 degrees of freedom, respectively (Renzi et al., 2019) and 2 degrees of freedom for GDP (PPP). Finally, we estimated the risk for 2-year-average (lag 0–1 year) of $PM_{2.5}$ concentrations. We reported relative risks (RRs) and 95% confidence intervals (95% CIs) of stillbirth per 10 $\mu g/m^3$ increment in annual average $PM_{2.5}$ exposures. All sensitivity analyses were performed for the three types of $PM_{2.5}$ exposures.

The results were interpreted without a dichotomised threshold for statistical significance as recommended in a recent editorial on statistical inference by the American Statistical Association (Wasserstein et al., 2019). All analyses were conducted using R software (version 4.1.1).

3. Results

3.1. Characteristics of the study population

The study included 5,229,338 births of which 81,611 were stillbirths over the 8 years with an overall district-level annual average of 2,514 births. The average cumulative incidence of stillbirth was 29 per 1000 births. The average (standard deviation) annual mean $PM_{2.5}$ concentration was 59.97 μg/m^3 (9.75) from all-source, 30.72 μg/m^3 (7.62) from anthropogenic sources and 29.25 μg/m^3(9.68) from natural sources. There were slight observable seasonal variations in temperatures with lower average temperature in wet season or summer (mean = 27.26 °C) than dry season or winter (mean = 28.50 °C) and similar pattern for diurnal temperature range in summer (mean = 8.09 °C) and winter (mean = 11.24 °C). There were slightly more male births (mean = 51%) than female (mean = 49%). Most of the mothers, 73% were young adults (20–34 years). The average GDP (PPP) was 283.78 (789.38) per million US dollars and the average persons per km^2 were 1128 (3044). On average, a total of 582 households used solid cooking fuels (Table 1).

The percentage changes in the $PM_{2.5}$ concentrations and stillbirth rates over the 8-year periods generally depicted common or parallel trends, except in 2013 and 2015 (Fig. 1), which visually supported our parallel trends assumption (Wing et al., 2018; Yu et al., 2020, 2021). Incidence of stillbirth and concentrations of $PM_{2.5}$ varied considerably across districts. For all-source $PM_{2.5}$, the district-level concentrations were lowest at the northern part of the country and highest through the eastern middle to the southern parts. The concentrations of $PM_{2.5}$ from anthropogenic sources increased from north to south. Conversely, natural sources of $PM_{2.5}$ increased from the southern to the northern districts (Fig. 2).

3.2. Association between $PM_{2.5}$ and stillbirth

The results of the main analyses provided the RR (95% CI) of stillbirth per 10 μg/m^3 increment in annual average $PM_{2.5}$. The adjusted estimate showed a 3% (RR = 1.03, 95% CI: 0.97, 1.09) higher risk of stillbirth with a 10 μg/m^3 increase in annual average all-source $PM_{2.5}$. Anthropogenic and natural sources independently were associated with a 2% higher risk of stillbirth: 1.02 (95% CI: 0.96, 1.07) from anthropogenic and 1.02 (95% CI: 0.94, 1.11) from natural $PM_{2.5}$. All effect estimates, however, included the null value within the confidence intervals (Table 2 and Fig. 3).

To further investigate effect modification, we repeated analyses for three subgroups of population density, and household or indoor air pollution (Table 2). The results of the subgroup analyses were generally consistent with the main results but with wide confidence intervals due to small sample sizes. The difference between two estimated relative risks showed slightly higher risks in moderate and high subgroups, relative to low subgroups in few instances, most of which included the null in the confidence interval (Table 3). Specifically, risk of stillbirth per 10 μg/m^3 increase in annual average all-source $PM_{2.5}$ is 4% higher in moderate (RRR = 1.04, 95% CI: 0.90, 1.20) household air pollution exposures as compared to the risk in low household air pollution exposure. Population density showed 1% higher risk in high relative to low subgroup per 10 μg/m^3 increase in annual average PM_2 from anthropogenic sources (RRR = 1.01, 95% CI: 0.86, 1.19). Similarly, moderate household air pollution exposures showed 1% higher risk (RRR = 1.01, 95% CI: 0.88, 1.16) as compared to low household air pollution exposure per 10 μg/m^3 increase in annual average $PM_{2.5}$ from anthropogenic sources. Natural $PM_{2.5}$ showed higher risks in moderate (RRR = 1.18, 95% CI:1.00, 1.40) and high (RRR = 1.02, 95% CI: 0.82, 1.28) subgroups as compared to low population density and higher risk in moderate (RRR = 1.03, 95% CI: 0.86, 1.24) as compared to low household air pollution (Table 3).

Except for interaction terms showing large and highly imprecise effect estimates, the sensitivity analyses results did not show substantial differences from the main analyses (Tables S1 and S2). Thus, the results were robust within the context of the data and the model assumptions.

Table 1
Descriptive statistics of annual birth outcomes, environmental and sociodemographic conditions across the 260 districts in Ghana, 2012–2019.

Variables	Mean	SD	Min	Percentiles			Max	*IQR
				25th	50th	75th		
Birth outcomes								
Births (N = 5,229,338)	2514.10	2653.18	150.00	1030.00	1919.00	3132.75	47835.00	2102.75
Stillbirths (N = 81,611)	39.24	57.96	0.00	6.00	22.00	50.00	578.00	44.00
Stillbirth incidence (per 1000)	29.18	55.36	0.00	3.20	10.80	29.52	712.48	26.32
Environmental data								
All sources $PM_{2.5}$ (μg/m^3)	59.97	9.75	38.40	51.50	60.50	68.50	81.40	17.00
Anthropogenic $PM_{2.5}$ (μg/m^3)	30.72	7.62	11.10	25.70	31.50	36.40	46.20	10.70
Natural $PM_{2.5}$ (μg/m^3)	29.25	9.68	14.10	21.60	25.75	37.40	56.20	15.80
Mean summer temperature (°C)	27.26	0.72	25.31	26.76	27.14	27.75	29.29	0.99
SD summer temperature (°C)	1.20	0.35	0.67	0.98	1.10	1.30	2.44	0.32
Mean winter temperature (°C)	28.50	0.68	27.02	27.92	28.48	29.05	30.18	1.13
SD winter temperature (°C)	1.29	0.68	0.34	0.72	1.14	1.74	3.29	1.02
Mean summer diurnal temperature range (°C)	8.09	1.27	5.52	7.25	8.19	8.66	11.04	1.41
SD summer diurnal temperature range (°C)	1.42	0.50	0.73	1.11	1.20	1.56	3.01	0.45
Mean winter diurnal temperature range (°C)	11.24	2.37	7.05	9.30	11.12	12.79	16.22	3.49
SD winter diurnal temperature range (°C)	0.88	0.42	0.05	0.54	0.82	1.18	2.05	0.64
Sociodemographic data								
Male (%)	50.95	2.52	32.92	49.84	50.89	51.92	97.95	2.08
Female (%)	48.94	2.62	2.05	48.02	49.08	50.12	67.08	2.10
Teen mothers (%)	13.26	4.37	0.27	10.96	14.07	16.30	24.64	5.34
Young adult mothers (%)	72.73	4.13	57.12	69.95	72.28	74.97	88.01	5.02
Adult mothers (%)	13.94	2.69	5.19	12.27	13.88	15.54	31.80	3.27
GDP (PPP)	283.78	789.38	0.83	24.48	50.34	106.51	5132.47	82.03
Population density (persons/km^2)	1127.86	3044.44	11.56	75.61	138.54	300.44	13585.83	224.83
Household air pollution (number of households)	581.58	555.29	9.00	225.75	437.50	688.75	3862.00	463.00

Note: *IQR, Interquartile range = 75th–25th percentiles; SD, standard deviation; GDP (PPP), Gross Domestic Production (Purchasing Power Parity) per million United States dollars; $PM_{2.5}$, particulate matter air pollution at aerodynamic diameter ≤2.5 μm; Anthropogenic $PM_{2.5}$ sources ($PM_{2.5}$ without sea salts and dusts); Natural $PM_{2.5}$ sources ($PM_{2.5}$ from sea-salts and dusts).

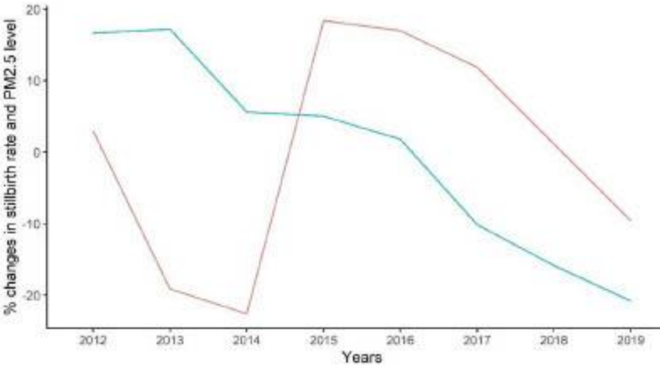

Fig. 1. The percentage changes in stillbirth rate and all-source $PM_{2.5}$ concentrations to visually test the parallel trends in $PM_{2.5}$ and stillbirth across 260 districts in Ghana during 2012–2019. Note: The percentage changes are the percent difference between the values of stillbirth rate (per 1000 births) or $PM_{2.5}$ in the district-specific to each year. The average of the values from 2012 to 2019 in each district, divided by the average of the values in each district-specific to the time from 2012 to 2019. $PM_{2.5}$, fine particulate matter at diameter of < 2.5 μm.

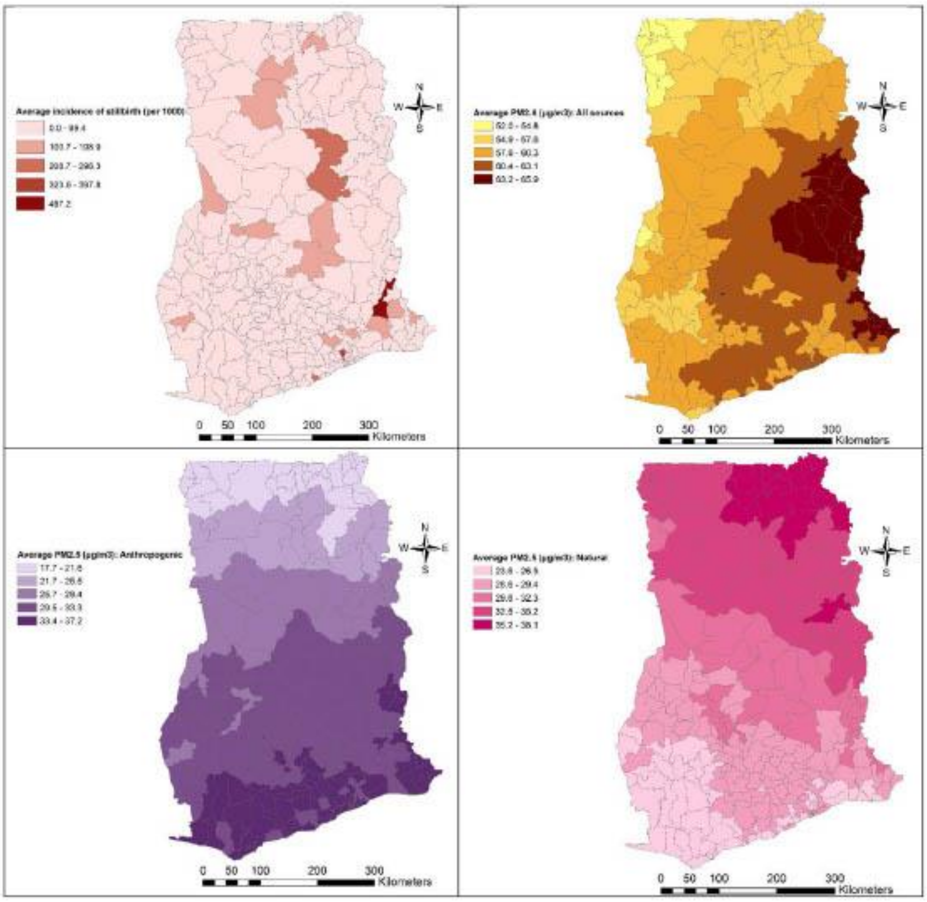

Fig. 2. Geographical distribution of the average incidence of stillbirth (per 1000 births) and the average annual $PM_{2.5}$ concentrations (μg/m^3) across the 260 districts in Ghana during 2012–2019 for all, anthropogenic, and natural sources. Equal interval classification method in ArcGIS was used. Note: $PM_{2.5}$, fine particulate matter at diameter of < 2.5 μm. The base map was obtained from https://data.humdata.org/dataset/ghana-administrative-boundaries.

Table 2
The relative risk (RR) and 95% confidence intervals (95% CI) of stillbirth per 10 μg/m³ increment in annual average $PM_{2.5}$ in Ghana, 2012–2019.

Model	Subgroups	$PM_{2.5}$ (All)	$PM_{2.5}$ (Anthropogenic)	$PM_{2.5}$ (All) (Natural)
Main Groups		1.03 (0.97, 1.09)	1.02 (0.96, 1.07)	1.02 (0.94, 1.11)
Population density	Low	1.17 (1.04, 1.31)	1.14 (1.03, 1.25)	0.95 (0.84, 1.09)
	Moderate	1.03 (0.95, 1.11)	0.97 (0.90, 1.05)	1.12 (1.01, 1.25)
	High	1.11 (0.99, 1.26)	1.15 (1.01, 1.32)	0.97 (0.81, 1.17)
Household air pollution	Low	1.04 (0.93, 1.16)	1.04 (0.93, 1.15)	1.01 (0.87, 1.17)
	Moderate	1.08 (0.99, 1.18)	1.05 (0.96, 1.15)	1.04 (0.93, 1.16)
	High	1.04 (0.94, 1.16)	1.04 (0.94, 1.15)	1.00 (0.85, 1.17)

Note. Adjusted for fetal sex, maternal age at delivery, means and standard deviations of summer and winter temperatures, and Gross Domestic Production (Purchasing Power Parity) per million United States dollars.

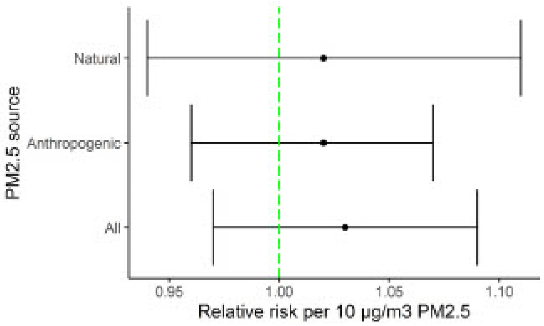

Fig. 3. Forest plot of the association between stillbirth per 10 μg/m³ increment in annual $PM_{2.5}$. Solid points represent point estimates of each group, and the whiskers represent 95% confidence intervals (CIs). The vertical green dotted line represents the reference for null association of 1.

Table 3
The ratio of relative risk (RRR) and 95% confidence intervals (95% CI) of stillbirth per 10 μg/m³ increment in annual average $PM_{2.5}$ in moderate and high as compared to low subgroups of population density and household air pollution in Ghana, 2012–2019.

Group variable	Subgroups	$PM_{2.5}$ (All)	$PM_{2.5}$ (Anthropogenic)	$PM_{2.5}$ (Natural)
Population density	Moderate	0.88 (0.77, 1.01)	0.85 (0.75, 0.96)	1.18 (1.00, 1.40)
	High	0.95 (0.80, 1.12)	1.01 (0.86, 1.19)	1.02 (0.82, 1.28)
Household air pollution	Moderate	1.04 (0.90, 1.20)	1.01 (0.88, 1.16)	1.03 (0.86, 1.24)
	High	1.00 (0.86, 1.16)	1.00 (0.86, 1.16)	0.99 (0.80, 1.23)

4. Discussion

4.1. Main findings and interpretations

We applied a DID approach to remove spatiotemporal confounding (Renzi et al., 2019; Wang et al., 2016) of the association between long-term $PM_{2.5}$ exposure and stillbirth in Ghana by design. Both $PM_{2.5}$ and stillbirth were very high in most districts across the country. The 8-year average all-source $PM_{2.5}$ in every district in Ghana exceeded even the highest WHO AQG annual average of 35 μg/m³ (interim target-1) (WHO, 2021). Based on point estimates, we found small positive associations between long-term exposure to all-source $PM_{2.5}$ and stillbirth in Ghana, and small at the same risk for both anthropogenic and natural sources of $PM_{2.5}$. Relative to the low subgroups of population density and household air pollution, the risks of stillbirth were slightly higher in moderate and high subgroups for all-source $PM_{2.5}$ exposure and higher in natural than anthropogenic sources of $PM_{2.5}$. However, effect estimates included null in the confidence intervals and were wide, which limited firm inference.

Africa has been putatively described as a hotspot for both air pollution and stillbirth (Abera et al., 2021; Agbo et al., 2021; Aminu and van den Broek, 2019; Lawn et al., 2016; UN IGME, 2020), but the lack of high-quality health registration systems and vital records (Froen et al., 2016) and the absence of routine air quality monitoring (Agbo et al., 2021; Amegah, 2018; Bauer et al., 2019) has hampered related research in this continent (Nyadanu et al., 2022). A recent case-control study used survey data across 33 Africa countries also reported a positive association between every 10 μg/m³ $PM_{2.5}$ increments and the odds of stillbirth (OR = 1.09, 95% CI: 1.05, 1.14) (Xue et al., 2019). The estimated risk in our study was of a lower magnitude (RR = 1.03, 95% CI: 0.97, 1.09). This could be due to several reasons such as differences in study designs, statistical analysis, effect estimate (RR against OR), exposure assessment (district level in one country against survey clusters across multiple countries), case definition (clinically diagnosed against self-reported verbal autopsy), level of residual confounding, and population demographics. However, our finding indicated a small positive association between $PM_{2.5}$ and stillbirth in Ghana with a 3% higher risk of stillbirth associated with all-source $PM_{2.5}$ after adequately controlling for potentially known and unknown confounders by design.

Although with a lower magnitude that also included the null in the confidence interval, our result for all-source $PM_{2.5}$ (RR = 1.03, 95% CI: 0.97, 1.09) per 10 μg/m³ increment showed a similar direction of positive association as compared to previous findings for entire pregnancy exposure per 10 μg/m³ $PM_{2.5}$ based on population-based cohort studies conducted in the USA (OR = 1.06, 95% CI: 0.99, 1.13) (Green et al., 2015) and China (OR = 1.14, 95% CI: 1.08, 1.20) (Zang et al., 2019) and other previous studies reported in the updated meta-analysis (Zhang et al., 2021). Many factors could contribute to the observed smaller effect estimate in our study. In addition to the differences in the study design, the population demographics, and chemical compositions of $PM_{2.5}$, and district-level variation may provide insufficient power to detect an effect as compared to the individual-level population-based cohort. Also, all the previous comparable studies reported the effect estimate with ORs. There are other major competing risk factors of stillbirth peculiar to LMICs such as poor healthcare system, malnutrition, and infectious diseases such as malaria (Aminu et al., 2014; Lawn et al., 2016). These unmeasured and possibly spatiotemporally varying risk factors could have attenuated or biased our risk estimates towards the null.

The recent updated systematic reviews and meta-analyses pooled effect estimate from seven studies (4 studies from the USA, 2 from China, and the one across 33 Africa countries based on the survey data) found 10% higher odds of stillbirth per 10 μg/m³ increment in $PM_{2.5}$ for whole pregnancy exposure (OR = 1.10, 95% CI: 1.07, 1.13) (Zhang et al., 2021). Another recent self-compared case-control study also linked the satellite-based $PM_{2.5}$ to the survey data in three South Asian countries

(India, Pakistan, and Bangladesh) and found 7% higher odds of stillbirth per 10 μg/m^3 increment in $PM_{2.5}$ (OR = 1.07, 95% CI: 1.02, 1.12) (Xue et al., 2021). This means that the epidemiologic studies conducted so far on the association between $PM_{2.5}$ and stillbirth have described evidence for elevated risk of stillbirth due to prenatal exposure to $PM_{2.5}$(Nyadanu et al., 2022)

In SSA, including Ghana, the major anthropogenic sources contributing to $PM_{2.5}$ are solid or fossil fuel for domestic needs, agriculture biomass burning, open burning of waste, and emissions from old vehicles or motorcycles (Abera et al., 2021; HEI, 2019b; Manisalidis et al., 2020). The observable spatial heterogeneity as in the mapped $PM_{2.5}$ and stillbirth imply that the observed exposure-outcome association could be elevated in certain local districts in the country. The northern parts where we observed the high concentrations of natural $PM_{2.5}$ sources (from dust and sea-salt) could be emerging largely from the Saharan desert dust especially during harmattan periods and unpaved roads (Abera et al., 2021; HEI, 2019b) since the northern parts of Ghana do not have sea. The northern parts are also economically less developed with a higher reliance on solid cooking fuel as compared to the southern parts (GSS, 2018). On the other hand, the comparatively higher levels of urbanisation and industrialisation in the southern parts could account for the higher concentrations of anthropogenic sources in the southern part with the associated increased risk of stillbirth. These sociodemographic factors are well-known risk factors for stillbirth in LMICs, particularly in SSA (Aminu et al., 2014) and as effect modifiers of $PM_{2.5}$ on stillbirth (Xie et al., 2021). These findings aligned with the conclusion from our recent umbrella review indicating that the plethora of evidence on the fetal developmental exposure to $PM_{2.5}$ and risk of adverse birth outcomes supports public health policies for reducing $PM_{2.5}$(Nyadanu et al., 2022), particularly for the susceptible populations and disproportionally exposed subgroups (Johnson et al., 2021). Future analyses of the association between the chemical constituents of $PM_{2.5}$ and stillbirth and joint mixture effects will contribute to further elucidating the specific emission sources for effective regulatory measures and public health intervention (Tanner et al., 2020; Zhang et al., 2021). Individual-level population-based cohort studies, especially prospective cohort with personal air pollution monitoring are required in SSA countries that are currently understudied (Nyadanu et al., 2022).

4.2. Biological mechanisms

The biological mechanisms underlying $PM_{2.5}$ prenatal exposure and the risk of stillbirth are not yet fully established due to the multifactorial nature of the pathobiology of stillbirth (Li et al., 2019). However, some causal pathways are emerging from biomarker and toxico-epigenomics from human observational and animal studies (Johnson et al., 2021; Lin et al., 2016; Marczylo et al., 2016; Saenen et al., 2019). The placenta is the organ for the transport of nutrients and the exchange of materials between the mother and fetus (Kannan et al., 2006). Hence, any toxicant, including air pollutants reaching the placenta will be deleterious to fetal development (Kannan et al., 2006; Li et al., 2019). This is because impaired placental physiology with fetal growth restriction or preterm labour is frequently implicated in the causal pathways for stillbirths (Lawn et al., 2016). Particulate matter enters the human transport systems by inhalation or ingestion and gets translocated into and across the placental barrier to the developing fetus, influencing the *in utero* environment (Lin et al., 2016; Manisalidis et al., 2020; Saenen et al., 2019). The molecules affect the systemic and placental vascular system, endothelial system, inflammatory cytokine productions, immune system, and metabolites, and produce oxidative stress during pregnancy (Erickson and Arbour, 2014; Johnson et al., 2021; Kannan et al., 2006). The effects of these pathophysiological responses, especially excess oxidative stress and endocrine disruptions induce placental modifications (Johnson et al., 2021; Lin et al., 2016; Saenen et al., 2019). The $PM_{2.5}$ generates reactive radical species which modulate conformational alterations or damage the functional biomolecules (lipids, proteins, and DNA) (Saenen et al., 2019;Nyadanu et al., 2022). The induced pathophysiological processes and alterations in placental molecular processes affect the pregnant woman and alter the phenotype and health of the fetus, including fetal death (Saenen et al., 2019; Zhang et al., 2021). The direct transfer of $PM_{2.5}$ across the fetoplacental interface also generates immuno-inflammatory reactions that block the transfer of oxygen and nutrients to the fetus, causing hypoxic damage and irreversible injury to the developing fetus which further increases the risk of stillbirth (Faiz et al., 2012; Li et al., 2019). The pathophysiological responses are also triggered by socio-economic factors, such as poor nutrition, poverty, occupation, low psychosocial support, stress, trauma, alcohol intake, and smoking which accelerate the increase in the effects of $PM_{2.5}$ (Erickson and Arbour, 2014; Johnson et al., 2021; Kannan et al., 2006; Nyadanu et al., 2022). Fundamentally, the biological factors of the mother and father interacting with the physical and social environments affect the birth outcomes (Erickson and Arbour, 2014; Kannan et al., 2006). It was also noted that exposure to $PM_{2.5}$ has a toxicological effect on male reproductive capacity with associated adverse pregnancy outcomes (Li et al., 2019).

4.3. Strengths and limitations

This study had many strengths. Firstly, this is the first study in Ghana and the first country-specific study in Africa to the best of our knowledge, to investigate the association between ambient $PM_{2.5}$ and stillbirth. Secondly, while the only known previous study conducted in 33 Africa countries used self-reported cases of stillbirth and provided OR (Xue et al., 2019), our study used clinically diagnosed stillbirths according to WHO standards and analysed the plausible causal association with a novel approach that adequately reduces the residual confounding effect by design, and we reported RR. Thirdly, the use of spatiotemporal high-resolution datasets improved the accuracy and precision of the assessments of the exposure and covariates. Fourthly, we also provided the risk of stillbirth by anthropogenic and natural sources of $PM_{2.5}$ in addition to the total mass which is relevant for public health intervention. Fifthly, unlike previous studies, we were able to investigate the modifying effect of household or indoor air pollution and showed that the effect was further increased among moderate subgroup as compared to low subgroup.

We also acknowledged some notable limitations in this study. Our analysis was based on a single-pollutant model. This is, however, a common practice because of the measurement error and biases associated with joint environmental exposure mixture analyses (Tanner et al., 2020) and the effect estimates of multi-pollutant models were often found to be robust to that of the single-pollutant models (Zhang et al., 2021). As a result, the meta-analyses conventionally pool only the effect estimates from single-pollutant models (Xie et al., 2021; Zhang et al., 2021). We were unable to investigate effects of constituent components of $PM_{2.5}$, other co-pollutants, the overall environmental mixture effects, and critical exposure windows which are very important for public health interventions and policy regulation for overall and specific emission sources (Tanner et al., 2020; Zhang et al., 2021). Although the aggregated variant DID design is closely related to the individual-level model and without ecological fallacy (Wang et al., 2016), its statistical power may not be sufficient as compared to high-quality individual-level longitudinal cohort studies. We did not have the individual-level datasets. Spatiotemporal confounding factors were adequately adjusted or controlled by design but residual confounding cannot be ruled out completely in observational studies (Leogrande et al., 2019). In our study, residual confounding only exists if a covariate varied differentially across districts over time and that such space-time differences were not adequately captured by the linear trends (Leogrande et al., 2019; Wang et al., 2016). Spatial variation within a location over time was analysed but empirical spatial neighbourhood or spill-over effect, residential mobility, and activity patterns of pregnant women from one district into the other were not accounted for. Despite the high performance of the $PM_{2.5}$ prediction model ($R^2 = 0.92$) (Hammer et al., 2020), this may be low in Ghana with very limited ground-level measurements. These exposure errors together with the uncertainties in the estimated satellite-based $PM_{2.5}$ may underestimate the estimated risk or bias the results towards the null (Xue et al., 2019). Also, there are known inadequate records of stillbirth cases in many SSA countries, including Ghana (Aminu et al., 2014; Aminu and van den Broek, 2019). Thus, it is also likely that the number of stillbirth cases could be more than the reported cases in this study since some birth deliveries might have occurred outside a health facility. However, the current GMHS reported an increase in institutional deliveries in Ghana from 54% in 2007 to 79% in 2017 (GSS, 2018).

5. Conclusion

Given the strengths amidst the limitations, our analysis showed a small magnitude of a positive association between long-term exposure to $PM_{2.5}$ and stillbirth in Ghana but with less precision. The association was higher for moderate and high subgroups of population density and household air pollution as compared to low subgroup but again with less precision. The district-level variation may not provide sufficient power to detect an effect as compared to the individual-level population-based cohort. Thus, the epidemiologic evidence is expected to be stronger in future studies if high-quality individual-level longitudinal cohort studies are conducted in Ghana. However, considering the strong association reported in individual-level longitudinal cohort studies from developed countries (Nyadanu et al., 2022), the small positive association found from the district-level analysis should not be underestimated as no effect to ignore any necessary environmental governance and policies to reduce the observed high level of $PM_{2.5}$ concentrations.

Informed consent

This study was approved by Curtin University Human Research Ethics Committee (Number HRE2020-0523) and Ghana Health Service Ethics Review Committee (Number GHS-ERC016/12/20). Participants' consent is not applicable since district-level aggregated data was used.

Funding

SDN was supported with funding from the Curtin International Postgraduate Research Scholarship. GAT was supported with funding from the Australia National Health and Medical Research Council (Grant number 1195716). GP was supported with funding from the Australia National Health and Medical Research Council (Grants number 1099655, 1173991), and the Research Council of Norway through its Centre of Excellence (Grant number 262700). The funders had no role in the study design, data collection, data analysis, data interpretation, and writing of the manuscript, or in the decision to publish the results.

Data availability

Apart from the birth data, all datasets are open access from the referenced sources. The data use agreement restricts us from making the birth data publicly available, but it can be requested from the Centre for Health Information Management of Ghana Health Service, Accra, Ghana.

Credit authorship statement

SDN: Conceptualisation, Methodology, Data curation, Formal analysis, Investigation, Writing—Original draft preparation, Writing—Critical Review and Editing, Project administration. GAT: Conceptualisation, Methodology, Investigation, Writing—Critical Review and Editing, Supervision, Project administration. BM: Conceptualisation, Methodology, Investigation, Writing—Critical Review and Editing, Supervision, Project administration. BK-B: Conceptualisation, Methodology, Writing—Critical Review and Editing, Supervision. AAO: Writing—Critical Review and Editing. GP: Conceptualisation, Methodology, Investigation, Writing—Critical Review and Editing, Supervision, Project administration. All authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are very grateful to the funders. The authors would like to thank Centre for Health Information Management of the Ghana Health Service for the birth data provision. We also appreciate Kalayu Mruts for his assistance to organise the piece of information from the Ghana maternal health survey data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apr.2022.101471.

References

Abbam, T., Johnson, F.A., Dash, J., Padmadas, S.S., 2018. Spatiotemporal variations in rainfall and temperature in Ghana over the twentieth century, 1900–2014. Earth Space Sci. 5 (4), 120–132. https://doi.org/10.1002/2017EA000327.

Abera, A., Friberg, J., Isaxon, C., Jerrett, M., Malmqvist, E., Sjöström, C., et al., 2021. Air quality in Africa: public health implications. Annu. Rev. Publ. Health 42, 193–210. https://doi.org/10.1146/annurev-publhealth-100119-113802.

Agbo, K.E., Walgraeve, C., Eze, J.I., Ugwoke, P.E., Ukoha, P.O., Van Langenhove, H., 2021. A review on ambient and indoor air pollution status in Africa. Atmos. Pollut. Res. 12 (2), 243–260. https://doi.org/10.1016/j.apr.2020.11.006.

Agbozo, F., Abubakari, A., Der, J., Jahn, A., 2016. Prevalence of low birth weight, macrosomia and stillbirth and their relationship to associated maternal risk factors in Hohoe Municipality, Ghana. Midwifery 40, 200–206. https://doi.org/10.1016/j.midw.2016.06.016.

Altman, D.G., Bland, J.M., 2003. Interaction revisited: the difference between two estimates. BMJ (Clin. Res. Ed.) 326 (7382). https://doi.org/10.1136/bmj.326.7382.219, 219-219.

Amegah, A.K., 2018. Proliferation of low-cost sensors. What prospects for air pollution epidemiologic research in Sub-Saharan Africa? Environ. Pollut. 241, 1132–1137. https://doi.org/10.1016/j.envpol.2018.06.044.

Aminu, M., van den Broek, N., 2019. Stillbirth in low- and middle-income countries: addressing the 'silent epidemic. Int. Health 11 (4), 237–239. https://doi.org/10.1093/inthealth/ihz015.

Aminu, M., Unkels, R., Mdegela, M., Utz, B., Adaji, S., van den Broek, N., 2014. Causes of and factors associated with stillbirth in low- and middle-income countries: a systematic literature review. BJOG 121 (Suppl. 4), 141–153. https://doi.org/10.1111/1471-0528.12995.

Aminu, M., Bar-Zeev, S., White, S., Mathai, M., van den Broek, N., 2019. Understanding cause of stillbirth: a prospective observational multi-country study from sub-Saharan Africa. BMC Pregnancy Childbirth 19 (1), 470. https://doi.org/10.1186/s12884-019-2626-7.

Armstrong, B.G., Gasparrini, A., Tobias, A., 2014. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. BMC Med. Res. Methodol. 14, 122. https://doi.org/10.1186/1471-2288-14-122.

Bachwenkizi, J., Liu, C., Meng, X., Zhang, L., Wang, W., van Donkelaar, A., et al., 2021. Fine particulate matter constituents and infant mortality in Africa: a multicountry study. Environ. Int. 156, 106739 https://doi.org/10.1016/j.envint.2021.106739.

Bauer, S., im, u., Mezuman, K., Gao, C., 2019. desert dust, industrialization, and agricultural fires: health impacts of outdoor air pollution in Africa. J. Geophys. Res. Atmos. 124 https://doi.org/10.1029/2018JD029336.

Bickton, F.M., Ndeketa, L., Sibande, G.T., Nkeramahame, J., Payesa, C., Milanzi, E.B., 2020. Household air pollution and under-five mortality in sub-Saharan Africa: an analysis of 14 demographic and health surveys. Environ. Health Prev. Med. 25 (1), 67. https://doi.org/10.1186/s12199-020-00902-4.

Card, D., Krueger, A.B., 1994. Minimum wages and employment: a case study of the fast-food industry in New Jersey and Pennsylvania. Am. Econ. Rev. 84 (4), 772–793. http://www.jstor.org/stable/2118030.

CHIM, 2018. Centre for health and information management of the policy planning, monitoring, and evaluation division (PPMED) of the Ghana health service (GHS) in collaboration with the system for health. In: The Health Sector in Ghana: Facts and

Figures. https://open.africa/dataset/4176f749-cfa8-4e32-9418-86cef78f9db6/resource/0bcf9b54-3e35-4543-95cd-fd4de953edff/download/factsfigures_2018.pdf. (Accessed 19 July 2021). Accessed.

CIESIN, Center for International Earth Science Information Network, Columbia University, 2018. Documentation for the gridded population of the world, version 4 (GPWv4), revision 11 data sets. In: Palisades NY: NASA Socioeconomic Data and Applications Center (SEDAC). https://doi.org/10.7927/H45Q4T5F.

de Bernis, L., Kinney, M.V., Stones, W., Ten Hoope-Bender, P., Vivio, D., Leisher, S.H., et al., 2016. Stillbirths: ending preventable deaths by 2030. Lancet 387 (10019), 703–716. https://doi.org/10.1016/s0140-6736(15)00954-x.

Erickson, A.C., Arbour, L., 2014. The shared pathoetiological effects of particulate air pollution and the social environment on fetal-placental development. J. Environ. Publ. Health, 901017. https://doi.org/10.1155/2014/901017, 2014.

Faiz, A.S., Rhoads, G.G., Demissie, K., Kruse, L., Lin, Y., Rich, D.Q., 2012. Ambient air pollution and the risk of stillbirth. Am. J. Epidemiol. 176 (4), 308–316. https://doi.org/10.1093/aje/kws029.

Froen, J.F., Myhre, S.L., Frost, M.J., Chou, D., Mehl, G., Say, L., et al., 2016. eRegistries: electronic registries for maternal and child health. BMC Pregnancy Childbirth 16, 11. https://doi.org/10.1186/s12884-016-0801-7.

Goyal, N., Karra, M., Canning, D., 2019. Early-life exposure to ambient fine particulate air pollution and infant mortality: pooled evidence from 43 low- and middle-income countries. Int. J. Epidemiol. 48 (4), 1125–1141. https://doi.org/10.1093/ije/dyz090.

Green, R., Sarovar, V., Malig, B., Basu, R., 2015. Association of stillbirth with ambient air pollution in a California cohort study. Am. J. Epidemiol. 181 (11), 874–882. https://doi.org/10.1093/aje/kwu460.

GSS, 2009. Ghana statistical service, Ghana health service (GHS), and macro international. In: Ghana Maternal Health Survey 2007. (Calverton, Maryland, USA: GSS, GHS, and Macro International). https://dhsprogram.com/pubs/pdf/FR227/FR227.pdf. (Accessed 11 August 2020).

GSS, 2018. Ghana Statistical Service, Ghana Health Service (GHS), and Macro International. Ghana Maternal Health Survey 2017. https://dhsprogram.com/pubs/pdf/FR340/FR340.pdf. (Accessed 11 August 2020).

GSS, Ghana Statistical Service, 2021. Ghana 2021 Population and Housing Census: General Report; Population of Regions and Districts. https://census2021.statsghana.gov.gh/gssmain/fileUpload/reportthemelist/2021%20PHC%20General%20Report%20Vol%203A_Population%20of%20Regions%20and%20Districts_181121.pdf. (Accessed February 2022).

Ha, Y.P., Hurt, L.S., Tawiah-Agyemang, C., Kirkwood, B.R., Edmond, K.M., 2012. Effect of socioeconomic deprivation and health service utilisation on antepartum and intrapartum stillbirth: population cohort study from rural Ghana. PLoS One 7 (7). https://doi.org/10.1371/journal.pone.0039050 e39050-e39050.

Hammer, M.S., van Donkelaar, A., Li, C., Lyapustin, A., Sayer, A.M., Hsu, N.C., et al., 2020. Global estimates and long-term trends of fine particulate matter concentrations (1998–2018). Environ. Sci. Technol. 54 (13), 7879–7890. https://doi.org/10.1021/acs.est.0c01764.

Han, C., Xu, R., Gao, C.X., Yu, W., Zhang, Y., Han, K., et al., 2021. Socioeconomic disparity in the association between long-term exposure to PM2.5 and mortality in 2640 Chinese counties. Environ. Int. 146, 106241 https://doi.org/10.1016/j.envint.2020.106241.

Harris, I., Osborn, T.J., Jones, P., Lister, D., 2020. Version 4 of the CRU TS monthly high-resolution gridded multivariate climate dataset. Sci. Data 7 (1), 109. https://doi.org/10.1038/s41597-020-0453-3.

Heft-Neal, S., Burney, J., Bendavid, E., Burke, M., 2018. Robust relationship between air quality and infant mortality in Africa. Nature 559 (7713), 254–258. https://doi.org/10.1038/s41586-018-0263-3.

HEI, Health Effects Institute, 2019a. State of Global Air 2019. Special Report on Global Exposure to Air Pollution and its Disease Burden. https://www.stateofglobalair.org/sites/default/files/soga_2019_report.pdf. (Accessed 27 November 2019).

HEI, Health Effects Institute, 2019b. Household air pollution-Ghana working group. In: Contribution of Household Air Pollution to Ambient Air Pollution in Ghana. Health Effects Institute, Boston, MA. Communication 19. https://www.healtheffects.org/system/files/Comm19-HAP-Ghana.pdf. (Accessed 20 July 2021).

08:47:27 Hutchon, D.J.R., 23 April 2015. Calculations for Comparing Two Estimated Relative Risks, 2005, Retrieved 10 January 2022 from. http://www.hutchon.net/CompareRR.htm.

Johnson, N.M., Hoffmann, A.R., Behlen, J.C., Lau, C., Pendleton, D., Harvey, N., et al., 2021. Air pollution and children's health—a review of adverse effects associated with prenatal exposure from fine to ultrafine particulate matter. Environ. Health Prev. Med. 26 (1) https://doi.org/10.1186/s12199-021-00995-5. Article 72.

Kannan, S., Misra, D.P., Dvonch, J.T., Krishnakumar, A., 2006. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environ. Health Perspect. 114 (11), 1636–1642. https://doi.org/10.1289/ehp.9081.

Kummu, M., Taka, M., Guillaume, J.H.A., 2018. Gridded global datasets for gross domestic product and human development index over 1990-2015. Sci. Data 5, 180004. https://doi.org/10.1038/sdata.2018.4.

Kwesiga, D., Tawiah, C., Imam, M.A., Tesega, A.K., Nareeba, T., Enuameh, Y.A.K., et al., 2021. Barriers and enablers to reporting pregnancy and adverse pregnancy outcomes in population-based surveys: EN-INDEPTH study. Popul. Health Metrics 19 (1), 15. https://doi.org/10.1186/s12963-020-00228-x.

10018 Lawn, J.E., Blencowe, H., Waiswa, P., Amouzou, A., Mathers, C., Hogan, D., et al., 2016. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet 387, 587–603. https://doi.org/10.1016/S0140-6736(15)00837-5.

Leogrande, S., Alessandrini, E.R., Stafoggia, M., Morabito, A., Nocioni, A., Ancona, C., et al., 2019. Industrial air pollution and mortality in the Taranto area, Southern Italy: a difference-in-differences approach. Environ. Int. 132, 105030 https://doi.org/10.1016/j.envint.2019.105030.

Li, Z., Tang, Y., Song, X., Lazar, L., Li, Z., Zhao, J., 2019. Impact of ambient PM(2.5) on adverse birth outcome and potential molecular mechanism. Ecotoxicol. Environ. Saf. 169, 248–254. https://doi.org/10.1016/j.ecoenv.2018.10.109.

Lin, V., Baccarelli, A., Burris, H., 2016. Epigenetics—a potential mediator between air pollution and preterm birth. Environ. Epigenet. 2, dvv008. https://doi.org/10.1093/eep/dvv008.

Lu, Y., Zeger, S.L., 2007. On the equivalence of case-crossover and time series methods in environmental epidemiology. Biostatistics 8 (2), 337–344. https://doi.org/10.1093/biostatistics/kxl013.

Manisalidis, I., Stavropoulou, E., Stavropoulos, A., Bezirtzoglou, E., 2020. Environmental and health impacts of air pollution: a review [review]. Front. Public Health 8, 14. https://doi.org/10.3389/fpubh.2020.00014.

Marczylo, E.L., Jacobs, M.N., Gant, T.W., 2016. Environmentally induced epigenetic toxicity: potential public health concerns. Crit. Rev. Toxicol. 46 (8), 676–700. https://doi.org/10.1080/10408444.2016.1175417.

McClure, E.M., 2020. Enhancing routine surveillance to improve stillbirth data. Lancet Global Health 8 (4), e464–e465. https://doi.org/10.1016/S2214-109X(20)30082-6.

McClure, E.M., Saleem, S., Goudar, S.S., Moore, J.L., Garces, A., Esamai, F., et al., 2015. Stillbirth rates in low-middle income countries 2010 - 2013: a population-based, multi-country study from the Global Network. Reprod. Health 12 (2). https://doi.org/10.1186/1742-4755-12-S2-S7. S7.

Moritz, S., Bartz-Beielstein, T., 2017. imputeTS: time series missing value imputation in R. R J 9 (1), 207–218 https://doi.org/Doi: 10.32614/RJ-2017-009.

WHO, World Health Organisation, Mudu, P., 2021. Ambient Air Pollution and Health in Accra, Ghana. World Health Organization. https://apps.who.int/iris/handle/10665/340678.

Nonterah, E.A., Agorinya, I.A., Kanmiki, E.W., Kagura, J., Tamimu, M., Ayamba, E.Y., et al., 2020. Trends and risk factors associated with stillbirths: a case study of the Navrongo War Memorial Hospital in Northern Ghana. PLoS One 15 (2), e0229013. https://doi.org/10.1371/journal.pone.0229013.

Nyadanu, S.D, Dunne, J., Tessema, G.A, Mullins, B., Kumi-Boateng, B., Bell, M.L, et al., 2022. Prenatal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of 36 systematic reviews and meta-analyses. Environ. Pollut. 306, 1–25. https://doi.org/10.1016/j.envpol.2022.119465.

Nyadanu, S.D., Tessema, G.A., Mullins, B., Kumi-Boateng, B., Bell, M.L., Pereira, G., 2020. Ambient air pollution, extreme temperatures and birth outcomes: a protocol for an umbrella review, systematic review and meta-analysis. Int. J. Environ. Res. Publ. Health 17 (22), 8658. https://www.mdpi.com/1660-4601/17/22/8658.

Renzi, M., Forastiere, F., Schwartz, J., Davoli, M., Michelozzi, P., Stafoggia, M., 2019. Long-term PM(10) exposure and cause-specific mortality in the Latium region (Italy): a difference-in-differences approach. Environ. Health Perspect. 127 (6), 67004 https://doi.org/10.1289/ehp3759.

Saenen, N.D., Martens, D.S., Neven, K.Y., Alfano, R., Bové, H., Janssen, B.G., et al., 2019. Air pollution-induced placental alterations: an interplay of oxidative stress, epigenetics, and the aging phenotype? Clin. Epigenet. 11 (1), 124. https://doi.org/10.1186/s13148-019-0688-z.

Shaddick, G., Thomas, M.L., Mudu, P., Ruggeri, G., Gumy, S., 2020. Half the world's population are exposed to increasing air pollution. NPJ Clim. Atmos. Sci. 3 (1), 23. https://doi.org/10.1038/s41612-020-0124-2.

Shi, L., Kloog, I., Zanobetti, A., Liu, P., Schwartz, J.D., 2015. Impacts of temperature and its variability on mortality in New England. Nat. Clim. Change 5, 988–991. https://doi.org/10.1038/nclimate2704.

Tanner, E., Lee, A., Colicino, E., 2020. Environmental mixtures and children's health: identifying appropriate statistical approaches. Curr. Opin. Pediatr. 32 (2), 315–320. https://doi.org/10.1097/mop.0000000000000877.

Turner, H., Firth, D., 2020. Generalized Nonlinear Models in R: an Overview of the Gnm Package version 1.1-1. https://cran.r-project.org/web/packages/gnm/vignettes/gnmOverview.pdf. (Accessed 2 May 2021). Accessed.

UG, University of Ghana School of Public Health, Ministry of Health and Ghana Health Services, 2018. State of the Nation's Health Report. https://publichealth.ug.edu.gh/sites/publichealth.ug.edu.gh/files/docs/state_of_the_nations_interior_final_compressed-compressed_2.pdf. (Accessed 19 July 2021). Accessed.

UN IGME, United Nations Inter-agency Group for Child Mortality Estimation, 2020. A Neglected Tragedy: the Global Burden of Stillbirths'. Report of the UN Inter-agency Group for Child Mortality Estimation. https://data.unicef.org/wp-content/uploads/2020/10/UN-IGME-2020-Stillbirth-Report-updated.pdf. (Accessed 16 July 2021). Accessed, 2020.

van Donkelaar, A., Martin, R.V., Brauer, M., Hsu, N.C., Kahn, R.A., Levy, R.C., et al., 2016. Global estimates of fine particulate matter using a combined geophysical-statistical method with information from satellites, models, and monitors. Environ. Sci. Technol. 50 (7), 3762–3772. https://doi.org/10.1021/acs.est.5b05833.

Wang, Y., Kloog, I., Coull, B.A., Kosheleva, A., Zanobetti, A., Schwartz, J.D., 2016. Estimating causal effects of long-term PM2.5 exposure on mortality in New Jersey. Environ. Health Perspect. 124 (8), 1182–1188. https://doi.org/10.1289/ehp.1409671.

Wasserstein, R.L., Schirm, A.L., Lazar, N.A., 2019. Moving to a world beyond "$p < 0.05$". Am. Statistician 73, 1–19. https://doi.org/10.1080/00031305.2019.1583913 sup.1.

Weber, E., Adu-Bonsaffoh, K., Vermeulen, R., Klipstein-Grobusch, K., Grobbee, D.E., Browne, J.L., et al., 2020. Household fuel use and adverse pregnancy outcomes in a Ghanaian cohort study. Reprod. Health 17 (1), 29. https://doi.org/10.1186/s12978-020-0878-3.

WHO, World Health Organisation, 2006a. Health Risks of Particulate Matter from Long-Range Transboundary Air Pollution. https://www.euro.who.int/__data/assets/pdf_file/0006/78657/E88189.pdf. (Accessed 11 October 2021). Accessed.

WHO, World Health Organisation, 2006b. WHO Global Air Quality Guidelines. Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. World Health Organization, Geneva. http://apps.who.int/iris/bitstream/handle/10665/69477/WHO_SDE_PHE_OEH_06.02_eng.pdf?sequence=1. (Accessed 7 April 2021). Accessed.

WHO, World Health Organisation, 2021. WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. World Health Organization. https://apps.who.int/iris/handle/10665/345329.

Wing, C., Simon, K., Bello-Gomez, R.A., 2018. Designing difference in difference studies: best practices for public health policy research. Annu. Rev. Publ. Health 39 (1), 453–469. https://doi.org/10.1146/annurev-publhealth-040617-013507.

Xie, G., Sun, L., Yang, W., Wang, R., Shang, L., Yang, L., et al., 2021. Maternal exposure to PM2.5 was linked to elevated risk of stillbirth. Chemosphere 283, 131169. https://doi.org/10.1016/j.chemosphere.2021.131169.

Xue, T., Zhu, T., Geng, G., Zhang, Q., 2019. Association between pregnancy loss and ambient PM2·5 using survey data in Africa: a longitudinal case-control study, 1998–2016. Lancet Planet. Health 3 (5), e219–ee225. https://doi.org/10.1016/s2542-5196(19)30047-6.

Xue, T., Guan, T., Geng, G., Zhang, Q., Zhao, Y., Zhu, T., 2021. Estimation of pregnancy losses attributable to exposure to ambient fine particles in south Asia: an epidemiological case-control study. Lancet Planet. Health 5 (1), e15–e24. https://doi.org/10.1016/S2542-5196(20)30268-0.

Yu, W., Guo, Y., Shi, L., Li, S., 2020. The association between long-term exposure to low-level PM2.5 and mortality in the state of Queensland, Australia: a modelling study with the difference-in-differences approach. PLoS Med. 17 (6), e1003141 https://doi.org/10.1371/journal.pmed.1003141.

Yu, P., Xu, R., Coelho, M.S.Z.S., Saldiva, P.H.N., Li, S., Zhao, Q., et al., 2021. The impacts of long-term exposure to PM2.5 on cancer hospitalizations in Brazil. Environ. Int. 154, 106671 https://doi.org/10.1016/j.envint.2021.106671.

Zang, H., Cheng, H., Song, W., Yang, M., Han, P., Chen, C., et al., 2019. Ambient air pollution and the risk of stillbirth: a population-based prospective birth cohort study in the coastal area of China. Environ. Sci. Pollut. Res. 26 (7), 6717–6724. https://doi.org/10.1007/s11356-019-04157-7.

Zhang, H., Zhang, X., Wang, Q., Xu, Y., Feng, Y., Yu, Z., et al., 2021. Ambient air pollution and stillbirth: an updated systematic review and meta-analysis of epidemiological studies. Environ. Pollut. 278, 116752 https://doi.org/10.1016/j.envpol.2021.116752.

Appendix M. Authorship attribution statement

Co-authors and acknowledgement	Conception and Design	Acquisition of Data and Method	Data Conditioning and Manipulation	Analysis and Statistical Method	Interpretation and Discussion	Critical Review and Editing
1. Prof. Gavin Pereira Curtin School of Population Health, Curtin University, Perth, Australia. E-mail: gavin.f.pereira@curtin.edu.au	√	√		√		√
Acknowledgement: Chapters 1 to 12 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 26/04/2023						
2. Dr. Gizachew A. Tessema Curtin School of Population Health, Curtin University, Perth, Australia. E-mail: gizachew.tessema@curtin.edu.au	√	√				√
Acknowledgement: Chapters 1 to 12 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 27/04/2023						
3. Prof. Ben Mullins Curtin School of Population Health, Curtin University, Perth, Australia. E-mail: b.mullins@curtin.edu.au	√					√
Acknowledgement: Chapters 1 to 12 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 27/04/2023						
4. Prof. Bernard Kumi-Boateng Department of Geomatic Engineering, University of Mines and Technology, P. O. Box 237, Tarkwa, Ghana E-mail: kumi@umat.edu.gh	√	√				√
Acknowledgement: Chapters 3 and 11 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 11/04/2023						
5. *Dr. Anthony A. Ofosu Ghana Health Service, Private Mail Bag, Ministries, Accra, Ghana. E-mail: anthony.ofosu@ghsmail.org						√
Acknowledgement: Chapter 11 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed:						

6. Prof. Michelle L. Bell School of the Environment, Yale University, New Haven, CT, 06511, USA. E-mail: michelle.bell@yale.edu	√					√
Acknowledgement: Chapter 3 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 17/04/ 2023						
7. Ms Jennifer Dunne Curtin School of Population Health, Curtin University, Perth, Australia. E-mail: jennifer.dunne1@curtin.edu.au		√		√		√
Acknowledgement: Chapter 3 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 11/04/2023						
8. Dr. Bereket Duko Curtin School of Population Health, Curtin University, Perth, Australia. E-mail: bereketduko.adema@curtin.edu.au				√		√
Acknowledgement: Chapter 3 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 11/04/2023						
9. Dr. Kevin Chai Curtin School of Population Health, Curtin University, Perth, Australia. E-mail: k.chai@curtin.edu.au			√			√
Acknowledgement: Chapter 10 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 26/04/2023						
10. Dr. Maayan Yitshak-Sade Icahn School of Medicine at Mount Sinai, Department of Environmental Medicine and Public Health, New York, NY, USA E-mail: maayan.yitshak-sade@mssm.edu						√
Acknowledgement: Chapter 10 I acknowledge that these represent my contribution to the above research output, and I have approved the final version. Signed: 11/04/2023						

*All attempts to reach Dr. Anthony A. Ofosu to sign his authorship contribution statement for the included published papers have been unsuccessful.

***Appendix N. Copyright Information**

Permissions Helpdesk <permissionshelpdesk@elsevier.com>
To: Sylvester Dodzi Nyadanu
Mon 17/04/2023 3:57 PM

Dear Sylvester Nyadanu,

Thank you so much for contacting us.

Please note that, as one of the authors of this article, you retain the right to reuse it in your thesis/dissertation. You do not require formal permission to do so. You are permitted to post this Elsevier article online if it is embedded within your thesis subject to proper acknowledgment;

Our preferred acknowledgement wording will be:

Example: "This article/chapter was published in Publication title, Vol number, Author(s), Title of article, Page Nos, Copyright Elsevier (or appropriate Society name) (Year)."

All the best for your thesis submission!

Kind regards,

Kaveri Thakuria

Senior Copyrights Coordinator

ELSEVIER | HCM - Health Content Management

Visit Elsevier Permissions

*All the papers included in the thesis were published in Elsevier journals.
The umbrella review protocol was published as open access in MDPI

Appendix O. Ethical approvals

Curtin University

Research Office at Curtin

GPO Box U1987
Perth Western Australia 6845

Telephone +61 8 9266 7863
Facsimile +61 8 9266 3793
Web research.curtin.edu.au

18-Sep-2020

Name: Ben Mullins
Department/School: School of Public Health
Email: B.Mullins@curtin.edu.au

Dear Ben Mullins

RE: Ethics Office approval
Approval number: HRE2020-0523

Thank you for submitting your application to the Human Research Ethics Office for the project **Spatio-temporal modelling and effects of fine particulate matter air pollution and extreme temperatures on birth outcomes in Ghana and Australia**.

Your application was reviewed through the Curtin University Low risk review process.

The review outcome is: **Approved**.

Your proposal meets the requirements described in the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*.

Approval is granted for a period of one year from **18-Sep-2020** to **17-Sep-2021**. Continuation of approval will be granted on an annual basis following submission of an annual report.

Personnel authorised to work on this project:

Name	Role
Mullins, Ben	CI
Nyadanu, Sylvester Dodzi	Student
Tessema, Gizachew	Co-Inv
Pereira, Gavin	Co-Inv

Approved documents:

Document

Standard conditions of approval

1. Research must be conducted according to the approved proposal
2. Report in a timely manner anything that might warrant review of ethical approval of the project including:
   - proposed changes to the approved proposal or conduct of the study
   - unanticipated problems that might affect continued ethical acceptability of the project
   - major deviations from the approved proposal and/or regulatory guidelines
   - serious adverse events
3. Amendments to the proposal must be approved by the Human Research Ethics Office before they are implemented (except where an amendment is undertaken to eliminate an immediate risk to participants)
4. An annual progress report must be submitted to the Human Research Ethics Office on or before the anniversary of approval and a completion report submitted on completion of the project
5. Personnel working on this project must be adequately qualified by education, training and experience for their role, or supervised

6. Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, that bears on this project
7. Changes to personnel working on this project must be reported to the Human Research Ethics Office
8. Data and primary materials must be retained and stored in accordance with the Western Australian University Sector Disposal Authority (WAUSDA) and the Curtin University Research Data and Primary Materials policy
9. Where practicable, results of the research should be made available to the research participants in a timely and clear manner
10. Unless prohibited by contractual obligations, results of the research should be disseminated in a manner that will allow public scrutiny; the Human Research Ethics Office must be informed of any constraints on publication
11. Approval is dependent upon ongoing compliance of the research with the Australian Code for the Responsible Conduct of Research, the National Statement on Ethical Conduct in Human Research, applicable legal requirements, and with Curtin University policies, procedures and governance requirements
12. The Human Research Ethics Office may conduct audits on a portion of approved projects.

Special Conditions of Approval

It is the responsibility of the Chief Investigator to ensure that any activity undertaken under this project adheres to the latest available advice from the Government or the University regarding COVID-19.

This letter constitutes low risk/negligible risk approval only. This project may not proceed until you have met all of the Curtin University research governance requirements.

Should you have any queries regarding consideration of your project, please contact the Ethics Support Officer for your faculty or the Ethics Office at hrec@curtin.edu.au or on 9266 2784.

22 November 2019

Dr Gavin Pereira
Curtin University
School of Public Health, Curtin University Kent
Street, Bentley
Bentley Western Australia 6102 Dear

Dr Pereira

PRN:	RGS0000003168
Project Title:	Inter-pregnancy interval, obstetric/morbidity history and adverse pregna ncy outcomes

Thank you for submitting the Amendment Form 22/11/2019 for the above project. The submission was reviewed and approved on behalf of the HREC on 22 November 2019.

Approval to extend ethics approval to 29 November 2021 has been provided in accordance with the HREC Terms of Reference and Standard Operating Procedures which are available on the HREC's website. The submission will be tabled for information at the next HREC meeting on 11 December 2019.

As the CPI you must ensure that the project is conducted at all sites under the conditions of approval for this project. The next progress report for this project is due on 29 November 2019.

This letter constitutes ethical approval only. If this project is conducted at multiple sites utilising this HREC's approval, a copy of this letter must be made available to all site PIs to maintain authorisation from their site.

If you require further information, please contact the HREC Office on 08 9222 4278 or hrec@health.wa.gov.au. To find the original letter, click here when logged into RGS.

Yours sincerely

Michelle King
Executive Ethics Officer
Department of Health WA Human Research Ethics Committee

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Digital Address: GA-050-3303
Mob: +233-50-3539896
Tel: +233-302-681109
Fax + 233-302-685424
Email: ethics.research@ghsmail.org

My Ref. GHS/RDD/ERC/Admin/App/20/511
Your Ref. No.

17th December, 2020

Sylvester Dodzi Nyadanu
Curtin University, School of Public Health,
GPO Box U1987, Perth,
Western Australia 6845

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	**GHS-ERC 016/12/20**
Study Title	Spatiotemporal Modelling and Effects of Fine Particulate Matter Air Pollution and Extreme Temperatures on Birth Outcomes in Ghana and Australia.
Approval Date	17th December, 2020
Expiry Date	16th December, 2021
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

- Submission of a yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report after completion of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

You are kindly advised to adhere to the national guidelines or protocols on the prevention of COVID -19

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED...

Dr. Cynthia Bannerman
(GHS ERC Chairperson)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra

Appendix P. R codes for DLNM model in Cox model and quasi-Poisson regressions

P1. R syntax for DLNM Cox regression modelling (Western Australia)

```
library(data.table)
library(tidyverse)
library(dlnm)
library(splines)
library(survival)

#Import analytical data (coxdata) in wide format.
#Weekly specific exposure analysis
#Define lagged exposure matrix with crossbasis function in 'dlnm' package
expomat<-as.matrix(coxdata[,34:87]) #Index of  exposure for preconception to birth (-11 to  42 weeks)
cb<-crossbasis(expomat, lag = c(-11,42),argvar = list(fun="ns", df=6), arglag = list(fun="ns",knots=logknots(54,df=3)))
# Select covariables; covalist. Note: ga is gestational age in weeks and SGA is small for gestational age as binary outcome
#Fit Cox regression with 'survival' package
sgamod<- coxph(Surv(ga,SGA)~cb +covlist,data = coxdata,na.action = na.exclude)
#Check Cox PH model assumption
cox.zph(sgamod)
# Use time-by-covariate interaction terms (e.g: sex+sex:ga) for covariates that violated the assumption (ie. p < 0.05) in the final model.
sgamod1<-coxph(Surv(ga,SGA)~cb+covlist, data=coxdata, na.action = na.exclude)
# Use AIC (sgamod1) to select the model with the smallest AIC after varying 2-7 degree of freedom in constructing the crossbasis matrix

#Get exposure values at centiles over the preconception to birth exposure (P1, P5, P10, P50, P90, P95, P99)
myperct<- quantile(coxdata$precon_pregm, probs = c(0.01,0.05,0.10,0.50, 0.90,0.95,0.99), na.rm = T)
#Predictions at various exposure centiles (P1, P5, P10, P90, P95, P99) using median (P50) as reference
predhr<-crosspred(cb,sgamod1,cen =P50, at=c(P1, P5, P10, P90, P95, P99)  ## values of P1 to P99 were used
#Plot and save at selected centiles of exposure
png("SGA for weekly exposure at various exposure centiles.png", width = 800, height = 550)
par(mfrow=c(2,3),cex.lab=1.2)
plot.crosspred(predhr,var = P1, ylab="HR (95% CI)",col="blue",ylim=c(0.977,1.035),
xlab="preconception to gestational weeks", main= "P1 °C (1st centile)")
plot.crosspred(predhr,var = P5, ylab="HR (95% CI)",col="blue",ylim=c(0.977,1.035),
xlab="preconception to gestational weeks", main= "P5 °C (5th centile)")
plot.crosspred(predhr,var = P10, ylab="HR (95% CI)",col="blue",ylim=c(0.977,1.035),
xlab="onception to gestational weeks", main= "P10 °C (10th centile)")
plot.crosspred(predhr,var = P90, ylab="HR (95% CI)",col="blue",ylim=c(0.977,1.035),
xlab="preconception to gestational weeks", main= "P90 °C (90th centile)")
plot.crosspred(predhr,var = P95, ylab="HR (95% CI)",col="blue",ylim=c(0.977,1.035),
xlab="preconception to gestational weeks", main= "P95 °C (95th centile)")
plot.crosspred(predhr,var = P99, ylab="HR (95% CI)",col="blue",ylim=c(0.977,1.035),
xlab="preconception to gestational weeks", main= "P99 °C (99th centile)")
dev.off()

#Extract weekly specific HRs (95% CI)
#Extract HR fit
fit.table <- as.data.frame(predhr$matRRfit)
colnames(fit.table) <- paste0("HR.", colnames(fit.table))
fit.table <- fit.table %>%   mutate(utci = as.numeric(row.names(fit.table)))
#Extract 95% CI
lci.table <- as.data.frame(predhr$matRRlow)
colnames(lci.table) <- paste0("lci.", colnames(lci.table))
```

```
uci.table <- as.data.frame(predhr$matRRhigh)
colnames(uci.table) <- paste0("uci.", colnames(uci.table))
# Combine RR fit and 95%CIs
pred.table <- bind_cols(fit.table, lci.table, uci.table)
# Save prediction as csv
write_csv(pred.table,file = path.SGA main results.csv")
```

#Cumulative exposures analyses

```
#Construct unlagged exposure matrices with onebasis function in 'dlnm' package
obprecon<-onebasis(coxdata$precon,"ns",df=5)
obpreg<-onebasis(coxdata$pregnancy,"ns",df=5)
obprecpreg<-onebasis(coxdata$precon_preg,"ns",df=5)
#Fit Cox regression with 'survival' package
sgamodcum<-coxph(Surv(ga,SGA)~obprecon+obpreg+ covalist, data = coxdata,na.action = na.exclude)
sgamodcum1<-coxph(Surv(ga,SGA)~obprecpreg+ covalist, data = coxdata,na.action = na.exclude)

#Predictions and plot
pcum1<- crosspred(obprecon,sgamodcum, cen =P50)
pcum2<- crosspred(obpreg,sgamodcum, cen =P50)
pcum3<- crosspred(obprecpreg,sgamodcum1, cen =P50)

png("SGA by precon to pregnancy.png", width = 900, height = 550)
par(mfrow=c(1,3),cex.lab=1.2)
plot.crosspred(pcum1,ylab="HR (95% CI)",col="blue",ylim=c(0.75,1.4),xlim=c(0,40),
xlab="Twelve weeks preconception average UTCI (°C) exposure")
plot.crosspred(pcum2,ylab="HR (95% CI)",col="blue",ylim=c(0.75,1.4),xlim=c(0,40),
xlab="Entire pregnancy average UTCI (°C) exposure")
plot.crosspred(pcum3,ylab="HR (95% CI)",col="blue",ylim=c(0.75,1.4),xlim=c(0,40),
xlab="Preconception to pregnancy average UTCI (°C) exposure")
dev.off()
#Prediction and extract HR (95% CI) for at selected exposure centiles. Note: repeat for each cumulative exposure
predhr<-crosspred(obprecpreg, sgamodcum,cen =P50, at=c(P1,P99))
fit.table <- as.data.frame(predhr$allRRfit)
colnames(fit.table) <- paste0("HR.", colnames(fit.table))
fit.table <- fit.table %>% mutate(utci = as.numeric(row.names(fit.table)))
lci.table <- as.data.frame(predhr$allRRlow)
colnames(lci.table) <- paste0("lci.", colnames(lci.table))
uci.table <- as.data.frame(predhr$allRRhigh)
colnames(uci.table) <- paste0("uci.", colnames(uci.table))
pred.tablec <- bind_cols(fit.table, lci.table, uci.table)
# Save prediction as csv
write_csv(pred.tablec, file = path.SGA by precon_pregnancy.csv")
```

P2. R syntax for DLNM quasi-Poisson regression modelling (Ghana)

```
library(tidyverse)
library(data.table)
library(lubridate)
library(tsModel)
library(gnm)
library(splines)
library(dlnm)

#Import analytical data (mydat) in long format.
#define matrices of lagged terms for monthly Universal Thermal Climate Index (UTCI) and PM2.5
# set maximum lag of 9 months
lagci<- tsModel::Lag(mydat$utci, group = mydat$ID, k = 0:9) ## ID is district ID
lagpm<-tsModel::Lag(mydat$pm2.5,group = mydat$ID, k=0:9)
#Remove year 2011 from lagged heat index and PM2.5 as birth data covered 2012 to 2020 but 2011 exposure was included to obtain lagged exposures for births at early months of 2012
lagci <- lagci[mydat$Year > 2011,]
lagpm <- lagpm[mydat$Year > 2011,]
#Remove year 2011 from the mydat data
mydat <-mydat[mydat$Year > 2011,]
#Re-define time indicator to set 1 to Jan 2012
mydat$dateid<-mydat$dateid -12
## Create year index by setting first year (in this case 2012) to 1
mydat$Yi<-mydat$Year-2011
#Create factors and the spatial conditioning stratum as district (ID) nested in region (RI)
mydat<-mydat %>% mutate_at(c("ID", "RI", "Yi","Month"),factor)
mydat$stratum<-as.factor(mydat$RI:mydat$ID)

##Define UTCI cross-basis matrix
ciknots<-equalknots(mydat$utci, fun = "ns", df=3)
cilagknots = equalknots(0:9,df=3)
cbhi<-crossbasis(lagci, argvar = list(fun="ns", knots=ciknots),
                           arglag = list(fun="ns",knots=cilagknots))
#Define PM2.5 cross-basis matrix
pmknots<-equalknots(mydat$pm2.5, fun = "ns",df=7)
pmlagknots = equalknots(0:9,df=7)
cbpm<-crossbasis(lagpm, argvar = list(fun="ns", knots=pmknots),
                          arglag = list(fun="ns",knots=pmlagknots))
# For linear PM2.5 relationship modelling use the function 'lin' for the exposure
cbpm<-crossbasis(lagpm, argvar = list(fun="lin"),
                          arglag = list(fun="ns",knots=pmlagknots))
#quasi-Poisson regression modelling conditioned on stratum.
```

```
cpr<-gnm(nsb ~cbpm+cbhi+season+ns(dateid,df=36)+male+female+teen+adult+old+
HAP+ns(PD,df=2)+ns(GDP, df=2),offset = log(total birth),family=quasipoisson,
eliminate = stratum,na.action = "na.exclude", data = mydat)
## HAP is number of households using solid or biomass fuel; PD is population density, and GDP is gross domestic product
AIC(cpr) ## As AIC is not obtainable straightforward in quasi-Poisson, Poisson model was run to select the model with the smallest AIC after varying 2-5 degree of freedom in constructing the crossbasis matrix

#Linear PM2.5-stillbirth relationship
#Predict at 5, 10, 20.5,23.3
predrr<-crosspred(cbpm,cpr,cen =0, at=c(5, 10, 20.5,23.3),cumul = T)
#Plot for individual lag
png("SB linear for each lag.png", width = 900, height = 600)
par(mfrow=c(2,2),cex.lab=1.2,cex.axis=1.2)
plot.crosspred(predrr,var = 5, ylab="RR (95% CI)",col="red",
xlab="Lag months", ci="lines", cumul = F,ylim=c(0.96,1.04),
main= "Per 5 µg/m3 increment")
plot.crosspred(predrr,var = 10, ylab="RR (95% CI)",col="red",
xlab="Lag months",ci="lines",cumul = F,ylim=c(0.96,1.04),
main= "Per 10 µg/m3 increment")
plot.crosspred(predrr,var =20.5, ylab="RR (95% CI)",col="red",
xlab="Lag months",ci="lines",cumul = F,ylim=c(0.96,1.04),
main= "Per IQR (20.5 µg/m3) increment")
plot.crosspred(predrr,var =23.3, ylab="RR (95% CI)",col="red",
xlab="Lag months", ci="lines",cumul = F,ylim=c(0.96,1.04),
main= "Per median (23.3 µg/m3) increment")
dev.off()

#Plot for cumulative exposures
png("SB lin cumlag.png", width = 900, height = 600)
par(mfrow=c(2,2),cex.lab=1.2,cex.axis=1.2)
plot.crosspred(predrr,var = 5, ylab="RR (95% CI)",col="red",
xlab="Cumulaive lag months", ci="lines", cumul = T,ylim=c(0.89,1.15),
main= "Per 5 µg/m3 increment")
plot.crosspred(predrr,var = 10, ylab="RR (95% CI)",col="red",
xlab="Cumulative lag months",ci="lines",cumul = T,ylim=c(0.89,1.15),
main= "Per 10 µg/m3 increment")
plot.crosspred(predrr,var =20.5, ylab="RR (95% CI)",col="red",
xlab="CUmulative lag months",ci="lines",cumul = T,ylim=c(0.89,1.15),
main= "Per IQR (20.5 µg/m3) increment")
plot.crosspred(predrr,var =23.3, ylab="RR (95% CI)",col="red",
xlab="Cumulative lag months", ci="lines",cumul = T,ylim=c(0.89,1.15),
```

```
main= "Per median (23.3 µg/m3) increment")
dev.off()

#For nonlinear association
#Get values for the 1st, 5th, 10th,,50th,75th, 90th, 95th, and 99th percentiles of pm2.5
myperct<- quantile (mydat$pm2.5, probs = c(0.01,0.05,0.1,0.5,0.90,0.95,0.99),
                na.rm = TRUE); myperct
#Predictions at various exposure centiles using 5 and 10 ug/m3 as references
predrr<-crosspred(cbpm,cpr,cen=5,at=c(9.9,12.2, 23.3,38.0,57.8,67.7,86.0), cumul=TRUE)
#Plot at selected percentiles of exposure
#For each lag
png("SB nonlin for each lag.png", width = 900, height = 600)
par(mfrow=c(2,3),cex.lab=1.2, cex.axis=1.2)
plot.crosspred(predrr,var =9.9, ylab="RR (95% CI)",col="red",
xlab="Lag months", ci="lines",ylim=c(0.76,1.32),
main= "1st centile (9.9 µg/m3)")
plot.crosspred(predrr,var=12.2, ylab="RR (95% CI)",col="red",
xlab="Lag months", ci="lines",ylim=c(0.76,1.32),
main= "5th centile (12.2 µg/m3)")
plot.crosspred(predrr,var = 23.3, ylab="RR (95% CI)",col="red",
xlab="Lag months",ci="lines",ylim=c(0.76,1.32),
main= "50th centile (23.3 µg/m3)")
plot.crosspred(predrr,var =57.8, ylab="RR (95% CI)",col="red",
xlab="Lag months", ci="lines",ylim=c(0.76,1.32),
main= "90th centile (57.8 µg/m3)")
plot.crosspred(predrr,var =67.7, ylab="RR (95% CI)",col="red",
xlab="Lag months", ci="lines",ylim=c(0.76,1.32),
main= "95th centile (67.7 µg/m3)")
plot.crosspred(predrr,var =86, ylab="RR (95% CI)",col="red",
xlab="Lag months", ci="lines",ylim=c(0.76,1.32),
main= "99th centile (86 µg/m3)")
dev.off()

#Cumulative plot
png("SB nonlin.png", width = 900, height = 600)
par(mfrow=c(2,3),cex.lab=1.2, cex.axis=1.2)
plot.crosspred(predrr,var =9.9, ylab="RR (95% CI)",col="red",
xlab=" Cumulative lag months", ci="lines", cumul = T, ylim=c(0.68,2.5),
main= "1st centile (9.9 µg/m3)")
plot.crosspred(predrr,var=12.2, ylab="RR (95% CI)",col="red",
xlab="Cumulative lag months", ci="lines",cumul = T,ylim=c(0.68,2.5),
main= "5th centile (12.2 µg/m3)")
```

```
plot.crosspred(predrr,var = 23.3, ylab="RR (95% CI)",col="red",
xlab="Cumulative lag months",ci="lines",cumul = T,ylim=c(0.68,2.5),
main= "50th centile (23.3 µg/m3)")
plot.crosspred(predrr,var =57.8, ylab="RR (95% CI)",col="red",
xlab=" Cumulative lag months", ci="lines",cumul = T,ylim=c(0.68,2.5),
main= "90th centile (57.8 µg/m3)")
plot.crosspred(predrr,var =67.7, ylab="RR (95% CI)",col="red",
xlab="Cumulative lag months", ci="lines",cumul = T,ylim=c(0.68,2.5),
main= "95th centile (67.7 µg/m3)")
plot.crosspred(predrr,var =86, ylab="RR (95% CI)",col="red",
xlab=" Cumulative lag months", ci="lines",cumul = T,ylim=c(0.68,2.5),
main= "99th centile (86 µg/m3)")
dev.off()

#Extract the cumulative association
#Extract RR fit
fit.tablec <- as.data.frame(predrr$cumRRfit)
colnames(fit.tablec) <- paste0("RR.", colnames(fit.tablec))
fit.tablec <- fit.tablec %>%   mutate(utci = as.numeric(row.names(fit.tablec)))
#Extract 95% CI
lci.tablec <- as.data.frame(predrr$cumRRlow)
colnames(lci.tablec) <- paste0("lci.", colnames(lci.tablec))
uci.tablec <- as.data.frame(predrr$cumRRhigh)
colnames(uci.tablec) <- paste0("uci.", colnames(uci.tablec))
#Combine cumm RR fit and 95% CIs
pred.tablec <- bind_cols(fit.tablec, lci.tablec, uci.tablec)
#Save prediction table as csv
write_csv (pred.tablec, "path SB_PM2.5 nonlin.csv")
#Extract individual lags
#Extract RR fit
fit.table <- as.data.frame(predrr$matRRfit)
colnames(fit.table) <- paste0("RR.", colnames(fit.table))
fit.table <- fit.table %>%   mutate(pm2.5 = as.numeric(row.names(fit.table)))
#Extract 95% CI
lci.table <- as.data.frame(predrr$matRRlow)
colnames(lci.table) <- paste0("lci.", colnames(lci.table))
uci.table <- as.data.frame(predrr$matRRhigh)
colnames(uci.table) <- paste0("uci.", colnames(uci.table))
# Combine RR fit and 95%CIs
pred.table <- bind_cols(fit.table, lci.table, uci.table)
# Save prediction table as csv
write_csv (pred.table, "path.SB_PM2.5 lin each lag.csv")
```

Appendix Q. References for supplementary materials

1. Edwards L, Wilkinson P, Rutter G, Milojevic A. Health effects in people relocating between environments of differing ambient air pollution concentrations: A literature review. *Environ Pollut* 2022; *292*:118314. https://doi.org/https://doi.org/10.1016/j.envpol.2021.118314.

2. Walter CM, Schneider-Futschik EK, Hall NL, Sly PD, Head BW, Knibbs LD. The health impacts of ambient air pollution in Australia: A systematic literature review. *Intern Med J* 2021. https://doi.org/10.1111/imj.15415.

3. Luo D, Kuang T, Chen Y-X, Huang Y-H, Zhang H, Xia Y-Y. Air pollution and pregnancy outcomes based on exposure evaluation using a land use regression model: A systematic review. *Taiwanese Journal of Obstetrics and Gynecology* 2021; *60*(2):193-215. https://doi.org/https://doi.org/10.1016/j.tjog.2021.01.004.

4. Bekkar B, Pacheco S, Basu R, DeNicola N. Association of Air Pollution and Heat Exposure With Preterm Birth, Low Birth Weight, and Stillbirth in the US: A Systematic Review. *JAMA Network Open* 2020; *3*(6):e208243-e208243. https://doi.org/10.1001/jamanetworkopen.2020.8243.

5. Heo S, Fong KC, Bell ML. Risk of particulate matter on birth outcomes in relation to maternal socio-economic factors: a systematic review. *Environ Res Lett* 2019; *14*(12. https://doi.org/10.1088/1748-9326/ab4cd0.

6. Yuan L, Zhang Y, Gao Y, Tian Y. Maternal fine particulate matter (PM2.5) exposure and adverse birth outcomes: an updated systematic review based on cohort studies. *Environ Sci Pollut Res Int* 2019; *26*(14):13963-13983. https://doi.org/10.1007/s11356-019-04644-x.

7. Tsoli S, Ploubidis GB, Kalantzi O-I. Particulate air pollution and birth weight: A systematic literature review. *Atmos Pollut Res* 2019; *10*(4):1084-1122. https://doi.org/10.1016/j.apr.2019.01.016.

8. Grippo A, Zhang J, Chu L, Guo Y, Qiao L, Zhang J, et al. Air pollution exposure during pregnancy and spontaneous abortion and stillbirth. *Rev Environ Health* 2018; *33*(3):247-264. https://doi.org/10.1515/reveh-2017-0033.

9. Westergaard N, Gehring U, Slama R, Pedersen M. Ambient air pollution and low birth weight - are some women more vulnerable than others? *Environ Int* 2017; *104*:146-154. https://doi.org/10.1016/j.envint.2017.03.026.

10. Jacobs M, Zhang G, Chen S, Mullins B, Bell M, Jin L, et al. The association between ambient air pollution and selected adverse pregnancy outcomes in China: A systematic review. *Sci Total Environ* 2017; *579*:1179-1192. https://doi.org/10.1016/j.scitotenv.2016.11.100.

11. Shah PS, Balkhair T, Knowledge Synthesis Group on Determinants of Preterm LBWb. Air pollution and birth outcomes: a systematic review. *Environ Int* 2011; *37*(2):498-516. https://doi.org/10.1016/j.envint.2010.10.009.

12. Bonzini M, Carugno M, Grillo P, Mensi C, Bertazzi PA, Pesatori AC. Impact of ambient air pollution on birth outcomes: systematic review of the current evidences. *Med Lav* 2010; *101*(5):341-363. Published 2010/11/26.

13. Bosetti C, Nieuwenhuijsen MJ, Gallus S, Cipriani S, La Vecchia C, Parazzini F. Ambient particulate matter and preterm birth or birth weight: a review of the literature. *Arch Toxicol* 2010; *84*(6):447-460. https://doi.org/10.1007/s00204-010-0514-z.

14. Ghosh R, Rankin J, Pless-Mulloli T, Glinianaia S. Does the effect of air pollution on pregnancy outcomes differ by gender? A systematic review. *Environ Res* 2007; *105*(3):400-408. https://doi.org/10.1016/j.envres.2007.03.009.

15. Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. *Epidemiol* 2004; *15*(1):36-45. https://doi.org/10.1097/01.ede.0000101023.41844.ac.

16. Gong C, Wang J, Bai Z, Rich DQ, Zhang Y. Maternal exposure to ambient PM2.5 and term birth weight: A systematic review and meta-analysis of effect estimates. *Sci Total Environ* 2022; *807*:150744. https://doi.org/https://doi.org/10.1016/j.scitotenv.2021.150744.

17. Zhu W, Zheng H, Liu J, Cai J, Wang G, Li Y, et al. The correlation between chronic exposure to particulate matter and spontaneous abortion: A meta-analysis. *Chemosphere* 2022; *286*:131802. https://doi.org/https://doi.org/10.1016/j.chemosphere.2021.131802.
18. Ju L, Li C, Yang M, Sun S, Zhang Q, Cao J, et al. Maternal air pollution exposure increases the risk of preterm birth: Evidence from the meta-analysis of cohort studies. *Environ Res* 2021; *202*:111654. https://doi.org/10.1016/j.envres.2021.111654.
19. Xie G, Sun L, Yang W, Wang R, Shang L, Yang L, et al. Maternal exposure to PM2.5 was linked to elevated risk of stillbirth. *Chemosphere* 2021; *283*:131169. https://doi.org/https://doi.org/10.1016/j.chemosphere.2021.131169.
20. Rappazzo KM, Nichols JL, Rice RB, Luben TJ. Ozone exposure during early pregnancy and preterm birth: A systematic review and meta-analysis. *Environ Res* 2021; *198*:111317. https://doi.org/10.1016/j.envres.2021.111317.
21. Zhang H, Zhang X, Wang Q, Xu Y, Feng Y, Yu Z, et al. Ambient air pollution and stillbirth: An updated systematic review and meta-analysis of epidemiological studies. *Environ Pollut* 2021; *278*:116752. https://doi.org/10.1016/j.envpol.2021.116752.
22. Uwak I, Olson N, Fuentes A, Moriarty M, Pulczinski J, Lam J, et al. Application of the navigation guide systematic review methodology to evaluate prenatal exposure to particulate matter air pollution and infant birth weight. *Environ Int* 2021; *148*:106378. https://doi.org/10.1016/j.envint.2021.106378.
23. Simoncic V, Enaux C, Deguen S, Kihal-Talantikite W. Adverse Birth Outcomes Related to NO2 and PM Exposure: European Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2020; *17*(21. https://doi.org/10.3390/ijerph17218116.
24. Thayamballi N, Habiba S, Laribi O, Ebisu K. Impact of Maternal Demographic and Socioeconomic Factors on the Association Between Particulate Matter and Adverse Birth Outcomes: a Systematic Review and Meta-analysis. *Journal of Racial and Ethnic Health Disparities* 2020. https://doi.org/10.1007/s40615-020-00835-2.
25. Li C, Yang M, Zhu Z, Sun S, Zhang Q, Cao J, et al. Maternal exposure to air pollution and the risk of low birth weight: A meta-analysis of cohort studies. *Environ Res* 2020; *190*:109970. https://doi.org/10.1016/j.envres.2020.109970.
26. Ji Y, Song F, Xu B, Zhu Y, Lu C, Xia Y. Association between exposure to particulate matter during pregnancy and birthweight: a systematic review and a meta-analysis of birth cohort studies. *J Biomed Res* 2017. https://doi.org/10.7555/JBR.31.20170038.
27. Liu C, Sun J, Liu Y, Liang H, Wang M, Wang C, et al. Different exposure levels of fine particulate matter and preterm birth: a meta-analysis based on cohort studies. *Environ Sci Pollut Res Int* 2017; *24*(22):17976-17984. https://doi.org/10.1007/s11356-017-9363-0.
28. Li X, Huang S, Jiao A, Yang X, Yun J, Wang Y, et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis. *Environ Pollut* 2017; *227*:596-605. https://doi.org/10.1016/j.envpol.2017.03.055.
29. Zhang K LY, Zhao H, Guo J, Gehendra M, Qiu H, Wu S, He D. Association between atmospheric particulate matter and adverse pregnancy outcomes in the populationInt J Clin Exp Med. *Int J Clin Exp Med* 2016; *9*(11):20594-20604.
30. Siddika N, Balogun HA, Amegah AK, Jaakkola JJ. Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence. *Occup Environ Med* 2016; *73*(9):573-581. https://doi.org/10.1136/oemed-2015-103086.
31. Sun X, Luo X, Zhao C, Zhang B, Tao J, Yang Z, et al. The associations between birth weight and exposure to fine particulate matter (PM2.5) and its chemical constituents during pregnancy: A meta-analysis. *Environ Pollut* 2016; *211*:38-47. https://doi.org/10.1016/j.envpol.2015.12.022.

32. Sun X, Luo X, Zhao C, Chung Ng RW, Lim CE, Zhang B, et al. The association between fine particulate matter exposure during pregnancy and preterm birth: a meta-analysis. *BMC Pregnancy Childbirth* 2015; *15*:300. https://doi.org/10.1186/s12884-015-0738-2.
33. Lamichhane DK, Leem JH, Lee JY, Kim HC. A meta-analysis of exposure to particulate matter and adverse birth outcomes. *Environ Health Toxicol* 2015; *30*:e2015011. https://doi.org/10.5620/eht.e2015011.
34. Zhu X, Liu Y, Chen Y, Yao C, Che Z, Cao J. Maternal exposure to fine particulate matter (PM2.5) and pregnancy outcomes: a meta-analysis. *Environ Sci Pollut Res Int* 2015; *22*(5):3383-3396. https://doi.org/10.1007/s11356-014-3458-7.
35. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res* 2012; *117*:100-111. https://doi.org/10.1016/j.envres.2012.05.007.
36. Sapkota A, Chelikowsky AP, Nachman KE, Cohen AJ, Ritz B. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. *Air Quality, Atmosphere & Health* 2010; *5*(4):369-381. https://doi.org/10.1007/s11869-010-0106-3.
37. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol* 2014; *67*(4):368-375. https://doi.org/10.1016/j.jclinepi.2013.11.007.
38. Sexton J, Andrews C, Carruthers S, Kumar S, Flenady V, Lieske S. Systematic review of ambient temperature exposure during pregnancy and stillbirth: Methods and evidence. *Environ Res* 2021; *197*:111037. https://doi.org/10.1016/j.envres.2021.111037.
39. Chersich MF, Pham MD, Areal A, Haghighi MM, Manyuchi A, Swift CP, et al. Associations between high temperatures in pregnancy and risk of preterm birth, low birth weight, and stillbirths: systematic review and meta-analysis. *BMJ* 2020; *371*:m3811. https://doi.org/10.1136/bmj.m3811.
40. Kuehn L, McCormick S. Heat Exposure and Maternal Health in the Face of Climate Change. *Int J Environ Res Public Health* 2017; *14*(8. https://doi.org/10.3390/ijerph14080853.
41. Zhang Y, Yu C, Wang L. Temperature exposure during pregnancy and birth outcomes: An updated systematic review of epidemiological evidence. *Environ Pollut* 2017; *225*:700-712. https://doi.org/10.1016/j.envpol.2017.02.066.
42. Poursafa P, Keikha M, Kelishadi R. Systematic review on adverse birth outcomes of climate change. *J Res Med Sci* 2015; *20*(4):397-402. Published 2015/06/26.
43. Beltran AJ, Wu J, Laurent O. Associations of meteorology with adverse pregnancy outcomes: a systematic review of preeclampsia, preterm birth and birth weight. *Int J Environ Res Public Health* 2013; *11*(1):91-172. https://doi.org/10.3390/ijerph110100091.
44. Carolan-Olah M, Frankowska D. High environmental temperature and preterm birth: a review of the evidence. *Midwifery* 2014; *30*(1):50-59. https://doi.org/10.1016/j.midw.2013.01.011.
45. Strand LB, Barnett AG, Tong S. The influence of season and ambient temperature on birth outcomes: a review of the epidemiological literature. *Environ Res* 2011; *111*(3):451-462. https://doi.org/10.1016/j.envres.2011.01.023.