Curtin School of Population Health

THE APPLICATION OF SIMULATION TO QUANTIFYING THE INFLUENCE OF BIAS IN PERINATAL EPIDEMIOLOGY

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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 acknowledgement 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 work that has been published in a peer-reviewed journal and detailed contributions and signed statements from all co-authors are presented in **Appendix A.** The permission to reproduce the material from the publishers can be found in **Appendix B**.

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 Department of Health Western Australia Human Research Ethics Committee; Approval Number #2016/51; 14 September 2016 and the Curtin University Human Research Ethics Committee (EC00262), Approval Number #RDHS-30-16; 23 February 2016.

Signature:

Jennifer Dunne
Date: 28th April 2023

Statement from Principal Supervisor

Jennifer Dunne's thesis has been prepared in accordance with the guidelines for a Doctor of Philosophy thesis by publication and I am recommending the thesis now be sent for examination.

Signature:

Gavin Pereira

Date: 28th April 2023

Abstract

Perinatal epidemiology is the study of the distribution, determinants and sequelae of perinatal events. As randomised controlled trials are neither practical, feasible, nor ethical in pregnant women, much of the information that has informed our understanding of causal effects in perinatal epidemiology have been derived from observational studies. Due to the non-random nature of observational data, perinatal epidemiological studies are often prone to various types of bias. Yet there remains a lack of clarity around the magnitude or direction of such biases.

Simulation is a powerful tool that has the potential to quantify the influence of bias in aetiological associations. Simulation involves computational experiments in which pseudo random sampling generates data to replicate bias mechanisms, enabling the illustration and quantification of multiple types of bias (selection, confounding and information), and facilitating the rapid testing of simulation models under multiple scenarios. Despite the seemingly benefits of simulation to quantitative bias analysis, there has been limited evidence of their application in perinatal epidemiology.

This thesis considered the utility of simulation to quantify the influence of bias in perinatal epidemiology through three inter-related aims:

1. To review and explore the existing literature on the application of simulation methods as an approach to quantify the influence of bias in perinatal epidemiology.
2. To design, implement and analyse a series of simulation studies to quantify the magnitude and direction of bias in perinatal epidemiology to address issues from methodological challenges that may lead to spurious inference on associations between pregnancy exposures and adverse birth outcomes.
3. To develop a framework for the application of simulation to quantify bias in perinatal epidemiology.

To address the specific aims of this thesis, various studies and simulation methodologies were undertaken. The findings from a systematic review identified that simulation was effective in the quantification of bias in perinatal epidemiology; however, there was a lack of uniformity in the design, implementation and reporting of simulation studies. The limitations of these studies reinforced the need for a framework

to guide perinatal epidemiologists on the development of simulation studies to quantify bias. The application of simulation in included studies in this thesis demonstrated its broad utility in perinatal epidemiology. Simulation methods were employed with traditional epidemiological regression modelling and the *e*-value for confounding to investigate the role of unmeasured confounding in association between pregnancy complications across successive pregnancies. Here, the application of simulation strengthened the validity of the epidemiological findings. Simulation studies extricated the role of the *collider* in selection bias mechanisms and its influence on mediated associations, providing methodologies and reproducible simulation code that can be applied by other researchers to quantify the influence of bias across a range of perinatal epidemiological associations. Lastly, a framework was developed to guide epidemiologists on the design, implementation and reporting of simulation studies to quantify bias.

Taken together, this body of work demonstrated that simulation is a potent method to quantify the influence of bias in perinatal epidemiology. The methods demonstrated in this thesis have to potential to aid epidemiologists to increase their understanding of, and quantify, the influence of pervasive bias mechanisms in perinatal epidemiology.

Publications included in this Thesis

Peer-reviewed articles published

1. **Dunne J**, Tessema GA, Ognjenovic M, Pereira G. Quantifying the influence of bias in reproductive and perinatal epidemiology. *Annals of Epidemiology* 2021;63:86-101. Doi:10.1016/j.annepidem.2021.07.033
2. **Dunne J**, Tessema GA, Pereira G. The role of confounding in the association between pregnancy complications and subsequent preterm birth: a cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2022;129:4-101. Doi:10.1111/1471-0528.17007
3. **Dunne J**, Tessema GA, Gebremedhin AT, Pereira G. Bias in the association between advanced maternal age and stillbirth using left truncated data. *Scientific Reports* 12(1):1-9. Doi:10.1038/s41598-022-23719-3

Peer-reviewed articles submitted for publication

4. **Dunne J**, Tessema GA, Gebremedhin AT, Pereira G. B**i**as in the mediated association between maternal obesity and caesarean section delivery: a simulation study. Submitted to *Statistics in Medicine.*
5. **Dunne, J,** Tessema GA, Pereira G. The application of simulation to quantifying bias: a framework for epidemiologists. Submitted to the *European Journal of Epidemiology*.

Conference Presentations from this Thesis

Peer-reviewed conference abstracts

1. **Dunne J**, Tessema GA, Pereira G. Bias in the exposure-outcome associations when using left truncated birth datasets. *International Journal of Population Data Science* 2022;7(3). Oral presentation
2. **Dunne J**, Tessema GA, Pereira G. Confounding in the association between pregnancy complications and subsequent preterm birth. *International Journal of Epidemiology* 2021;50:1. Oral presentation
3. **Dunne J**, Tessema GA, Ognjenovic M, Pereira G. The application of simulation to quantifying the influence of bias in reproductive and perinatal epidemiology. *International Journal of Epidemiology* 2021;50:1. Oral presentation

Conference presentations

4. **Dunne J**, Tessema GA, Pereira G. Bias due to left truncation in the exposure-outcome associations. *Society for Epidemiologic Research Fall 2022 Meeting.* Oral presentation
5. **Dunne J**, Tessema GA, Ognjenovic M, Pereira G. Quantifying the influence of bias in reproductive and perinatal epidemiology through simulation. *Society for Epidemiologic Research 2021 Meeting*. Poster presentation

Media release

Curtin university “Study shows preterm birth risk most strongly linked to pre-eclampsia”, 9th December 2021

Statement of Contribution

My contribution to each of the included publications has been detailed and endorsed by co-authors in **Appendix A.**

Publication	**My contribution**
1. Quantifying the influence of bias in reproductive and perinatal epidemiology	Designed and managed the project. Developed the search strategy. Conducted the initial database searches and extracted the data. Analysed the results. Wrote the manuscript, wrote the original responses to reviewer comments, and complied the manuscript and reviewer comments to include co-author suggestions.
2. The role of confounding in the association between pregnancy complications and subsequent preterm birth: a cohort study.	Designed and managed the project. Wrote the R code. Conducted the data analysis. Wrote the manuscript, wrote the original responses to reviewer comments, and complied the manuscript and reviewer comments to include co-author suggestions.
3. Bias in the association between advanced maternal age and stillbirth using left truncated data.	Designed and managed the project. Conceived the computational model. Wrote the R code. Conducted the data analysis. Wrote the manuscript, wrote the original responses to reviewer comments, and complied the manuscript and reviewer comments to include co-author suggestions.
4. Bias in the mediated association between maternal obesity and caesarean section delivery: a simulation study	Designed and managed the project. Conceived the computational model. Wrote the R code. Conducted the data analysis. Wrote the manuscript, wrote the original responses to reviewer comments, and

	complied the manuscript and reviewer comments to include co-author suggestions.
5. The application of simulation to quantifying bias: a framework for epidemiologists	Designed and managed the project. Conceived the framework and the computational model. Wrote the R code. Conducted the data analysis. Wrote the manuscript, wrote the original responses to reviewer comments, and complied the manuscript to include co-author suggestions.

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Appendix I Media release

Curtin University (https://www.curtin.edu.au)

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(/NEWS/CATEGORY/)

Study shows preterm birth risk most strongly linked to pre-eclampsia

09 DEC 2021 | Yasmine Phillips

Copy Link Share Print

Women who gave birth to a premature baby after developing pre-eclampsia were 17 times more likely to experience another preterm birth if pre-eclampsia emerged again, new Curtin University research has found.

The study, published in the *British Journal of Obstetrics and Gynaecology*, examined more than 125,000 women who experienced two consecutive singleton births in Western Australia from 1998 to 2015.

About 27,000 babies are born prematurely – or before 37 weeks' gestation – across Australia each year, with preterm birth the leading cause of death and morbidity in children up to five years of age in the developed world.

Lead author and PhD candidate Jennifer Dunne, from Curtin's School of Population Health, said the findings showed the strongest link between preterm birth and pregnancies complicated by pre-eclampsia, a serious pregnancy condition that is usually characterised by high blood pressure, protein in the urine and severe swelling.

"When both pregnancies were complicated by pre-eclampsia, the risk of a subsequent preterm birth increased 10-fold after an initial term birth and 17-fold when the first birth was preterm, compared to women who had an uncomplicated first pregnancy," Ms Dunne said.

"This study also found that there was a three-fold higher risk of women experiencing a subsequent case of pre-eclampsia after a preterm birth in the first pregnancy that was not complicated by pre-eclampsia.

"Until recently, a first birth at full term was considered a reduced risk for a preterm delivery in the next pregnancy. However, there is emerging evidence that a complicated first pregnancy, regardless of whether the baby was delivered early or at full term, increases the subsequent risk of a baby being born prematurely."

Ms Dunne said the main pregnancy complications examined included pre-eclampsia, placental abruption (the detachment from the wall of the womb), small-for-gestational age and perinatal death (a stillbirth or a neonatal death in the first 28 days).

"Having any of the four complications in their first pregnancy puts women at an increased risk of a preterm birth in their next pregnancy, regardless of whether that first birth ended at full term or preterm," Ms Dunne said.

"Likewise, women whose first pregnancy ended in a preterm delivery were at an increased risk for each pregnancy complication in the second pregnancy.

"The findings of this study will help clinicians to better identify women who are at an increased risk of a either a preterm birth or complications in their subsequent pregnancies. Further research is now needed to reveal the specific pathways that explain these strong links between pregnancy complications and preterm births, whether they be genetic, pathological, and behavioural or other recurrent issues."

The research was supervised by Professor Gavin Pereira and co-authored by Dr Gizachew Tessema, also from Curtin's School of Population Health.

The full paper, '*The role of confounding in the association between pregnancy complications and subsequent preterm birth: a cohort study*', can be viewed online here (https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.17007).

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List of Abbreviations

BMI	Body mass index
CI	Confidence interval
CS	Caesarean section
DAG	Directed acyclic graphs
ICD	International Classification of Diseases
LBW	Low birth weight
MNS	Midwifery Notifications System
OR	Odds ratio
PE	Pre-eclampsia
RR	Relative risk
SEIFA	Socio-Economic Index for Areas
U	Unmeasured confounder
US	United States
WA	Western Australia

Thesis Outline

This thesis has seven chapters comprising an introduction to the topic (Chapter One), five original research chapters (Chapters Two to Six) and a discussion (Chapter Seven). The original research is a combination of published manuscripts (Chapters Two to Four) and two manuscripts under peer review (Chapter Five and Six).

Chapter One: Introduction

The aim of this opening chapter was to include sufficient background information on key concepts of importance in the application of simulation to the quantification of the influence of bias. Bias from selection, information and confounding is pervasive in perinatal aetiology. Data that informs perinatal epidemiological studies is left truncated as the sample population is restricted to a pre-specified gestational cut-off. Bias from confounding is impactful due to causal factors that are unmeasured or unknown to a study. Moreover, the physiology of pregnancy is complicated, with many influencing factors that are potentially yet undiscovered. Bias compromises the validity of a study. Yet, the practice of quantifying the influence of bias in perinatal epidemiological studies remains low. The application of simulation, empirical computer experiments, have the potential to quantify the influence of multiple types of bias on a range of exposure-outcome associations commonly found in perinatal epidemiology. However, there is a lack of guidance for researchers in the design, implementation and analysis of simulation studies for the prime purpose of bias analysis. This chapter placed the contribution of this thesis amongst these knowledge gaps.

Chapter Two: The application of simulation to quantify bias

The first step of this PhD project was to map out how simulation had been applied as a method to quantify bias in perinatal epidemiology. To fill this knowledge gap, a systematic review was conducted of the application of simulation as a method to quantify the magnitude and influence of bias in reproductive and perinatal epidemiology. The findings indicated that, although the number of simulation studies remained low, there was increasing application for bias analysis in more recent years. There was a lack of conformity in the design, implementation, analysis and reporting of the included simulation studies. Few studies provided simulation code, which

impeded the reproducibility of their results. These limitations informed recommendations for best practice in the application of simulation to quantify the influence of bias, which underpinned the design, implementation and analysis of subsequent simulation studies in this thesis (Chapter Four and Five) and the development of a framework (Chapter Six). This chapter (Publication One) was peer-reviewed and published in *Annals of Epidemiology.*

Chapter Three: The role of confounding

This chapter examined the role of confounding in the association between complications in first pregnancy and the subsequent risk of preterm birth. The study applied traditional epidemiological methods (regression models) to measure the associations between pre-eclampsia, placental abruption, small-for-gestational age and perinatal deaths (stillbirth and neonatal death within 28 days of birth) with subsequent preterm birth. Included in this study was a brief simulation in which a relevant but unknown confounder of maternal obesity was simulated to determine its influence on the observed associations between pregnancy complications and subsequent preterm birth. To measure the role of confounding, the *e*-value for confounding was computed to determine the magnitude of unmeasured confounding in the observed associations. The main finding of this study indicated that recurrent confounding was unlikely as any such unmeasured confounder would have to be uncharacteristically large explain away the observed associations between pregnancy complications and subsequent preterm birth. This chapter (Publication Two) was peer-reviewed and published in *BJOG: An International Journal of Obstetrics & Gynaecology.*

Chapter Four: Bias due to left truncation

Chapter Four quantified the magnitude and influence of bias from the use of left truncated birth data in the association between advancing maternal age and stillbirth. The bias mechanism occurs as the cause of the left truncation (restriction to pregnancies that survived past 20 gestational weeks) was influenced by both the exposure and an unmeasured factor, which also affected the outcome. The simulation was based on an observed cohort and range of plausible parameters derived from published literature. The findings of this simulation study revealed that the exclusion of early pregnancy losses (prior to 20 gestational weeks) produced minimal bias in the

association between advancing maternal age and stillbirth. This study (Publication Three) was peer-reviewed and published in *Scientific Reports.*

Chapter Five: Bias in mediated associations

This chapter quantified the influence of bias due to unmeasured confounding in the association between maternal obesity and caesarean section delivery when mediated by the pregnancy complication of pre-eclampsia. The magnitude and direction of bias was quantified under the three most common scenarios: 1) mediator-outcome confounding, 2) mediator-outcome confounding affected by the exposure, and 3) exposure-mediator confounding. The simulation was based on an observed cohort and a range of plausible parameters. The strongest evidence of bias was due to exposure-mediator confounding, contrasting with the mediator-outcome confounding which produced minimal bias. This study (Publication Four) has been submitted to *Statistics in Medicine.*

Chapter Six: A framework to apply simulation to bias analysis

Chapter Six introduced a framework for the application of simulation to quantify the magnitude and direction of biases in perinatal epidemiology. This framework provides guidance to researchers in the design, implementation and reporting of simulation studies for the prime purpose of bias analysis. Underpinning this framework are five steps: 1) study aim, 2) causal logic, 3) data generation processes, 4) implementation, and, 5) reproducibility of the study. Included in this chapter is a reproducible simulation which demonstrated the implementation of the frame to quantify bias. This study (Publication Five) has been submitted to the *European Journal of Epidemiology*.

Chapter Seven: Discussion

This final chapter discusses the thesis research outcomes and summarises the relevance of each of the chapters in achieving the thesis aims. This chapter also highlights the strengths and limitations of the thesis, discusses the significance of simulation as a method for bias analysis in perinatal epidemiology, and makes suggestions for future research.

Chapter One: Introduction

This chapter provides a comprehensive introduction and description to the application of simulation to quantifying bias in perinatal epidemiology. It begins with a brief overview of causal inference and bias mechanisms commonly found in perinatal epidemiological studies. It then provides background to simulation and the role it can play in quantifying the influence of bias. This introductory chapter also highlights the knowledge gaps that are filled by this PhD project and includes the research aim and objectives of the thesis.

1.1 Background

Pregnancy is often a time of joy for families. Yet, for some mothers and babies, pregnancy can be a dangerous period. The physiology of pregnancy is complex. Understanding the causal associations between exposures and outcomes is challenging due to many unseen and possibly unforeseen factors. Increasing our understanding of the complex causal associations between exposures during pregnancy and adverse outcomes will improve the quality of the evidence-based information that many clinicians and families rely upon. Epidemiology mainly focuses on the distributions and determinants of diseases in a specific population. Since its earliest inception, the field of epidemiology has expanded from a singular focus on infectious diseases to broader chronic and non-communicable diseases. To support this aetiology, formalised assumptions and statistical methods have been developed to ensure our understanding of cause and effect. More recently, the rapid growth in computing power has increased the feasibility of analysing big datasets using complex methodologies in epidemiology. However, the application of such data is prone to various types of bias due to the non-random nature of observational studies. The application of simulation methods, which are computer-based experiments using pseudo-generated data, are placed to improve causality in epidemiology, as they can quantify the magnitude and direction of multiple types of bias mechanisms that distort exposure-outcome associations derived from observational studies.

1.2 Complications of pregnancy

Although pregnancy is a natural life transition, both mothers and babies are susceptible to many adverse events during the pregnancy period. Perinatal epidemiology has been instrumental in identifying risk factors for these adverse events, leading to the development of medical interventions and practices that improved health outcomes associated with pregnancy and birth.[1] In Australia, these improvements have resulted in very low maternal mortality rates of 6 deaths per 100,000 women giving birth,[2] compared to the average global rate of 12 deaths per 100,000 women giving birth in high-income countries.[3] Yet, Australia continues to report a higher perinatal mortality rate (9.1 deaths per 1,000 women giving birth),[2] compared to the standardised average in high-income countries (4 deaths per 1,000 women giving birth).[3] Contributing to high perinatal mortality rate were stillbirths which

accounted for 6.8[2] deaths per 1,000 women giving birth, with the underlying causes remaining unexplained in up to half of all Australian stillbirths.[4]

Changing demographics in Australia, as in many similar high-income countries, are presenting new challenges in reducing adverse events during pregnancy. Two main challenges relevant to this thesis are the increasing prevalence of advanced maternal age (≥ 35 years) and the increasing prevalence of maternal obesity (body mass index (BMI) ≥ 30kg/m^2), both of which are associated with an increased incidence of pregnancy complications and adverse birth outcomes.[5, 6] Some evidence shows that in high-income countries the delay in reproduction to later years is often attributed to access to effective contraception, greater workforce participation, and difficulties in finding a life partner.[7] Advances in assisted reproductive technologies have also contributed to an increase in the prevalence of very advanced maternal age (i.e. women who are greater than 45 years at the time of birth).[8] Globally, the prevalence of obesity in women of reproductive ages is increasing, significantly impacting maternal and perinatal outcomes in women entering pregnancy with a higher BMI.[9] Over 20% of all births in Australia in 2015 were to women who were clinically obese, which is defined as a BMI ≥ 30kg/m^2.[10, 11] Perinatal epidemiologists have established a strong association between advancing maternal age and maternal obesity with a range of adverse outcomes,[5, 6, 12] with the incidence increasing monotonically for each additional year of maternal age and unit increase in BMI.[12, 13] Further, there is evidence that the risk factors associated with advanced maternal age and maternal obesity are increased in the presence of comorbidities, such as gestational mellitus diabetes and hypertensive disorders.[12, 14] These risk factors and comorbidities are also independently associated with increased risk of pregnancy loss, perinatal mortality, sequelae of fetal growth restriction, and congenital malformations.[12, 14-16]

Early pregnancy losses (prior to 20 gestational weeks) are not an uncommon outcome of pregnancy.[17] Although the exact aetiology of miscarriage (also known as spontaneous abortions) remains unknown, they are widely acknowledged to result from a complex interaction between multiple factors (environmental, genetic, hormonal, and immunology).[17-20] Advancing maternal age has been reported as a strong independent risk factor for early pregnancy loss in the first trimester, with evidence of an incremental increase in risk for each year after 30 years.[17] Women who are overweight (BMI 25- 29.9kg/m^2) or obese (BMI ≥ 30kg/m^2) are also at increased

risk of early pregnancy loss, with the reported risk almost 40% higher in mothers who are obese compared to those with a normal BMI (BMI 18.5- 24.9kg/m^2).[21]

Adverse outcomes and complications of pregnancy relevant to studies contained in this thesis include stillbirth, preterm birth, pre-eclampsia, placental abruption and small-for-gestational age. Stillbirth is defined as the fetal death of a baby either antepartum (fetal death prior to the birth of a baby of ≥20 gestational weeks or >400 grams birthweight) or intrapartum (fetal death of the baby during labour).[22] Despite the absolute risk of stillbirth being low in high-income countries, such as Australia, it has not declined in line with advances in perinatal and obstetric care.[23] There is a strong interaction between stillbirths and preterm birth (defined as a birth prior to the 37th gestational week of pregnancy),[22] with 80% of all stillbirths in high-income countries being born preterm.[24] Pre-eclampsia, characterised by the presence of hypertension or proteinuria in pregnancy,[25] is the most common serious medical disorder of pregnancy.[26] In Australia, the prevalence of mild and severe pre-eclampsia is 5-10% and 2%, respectively.[27] Pre-eclampsia is also associated with adverse events in Australia, accounting for between 5-10% of preterm birth, 10% of perinatal mortality and 15% of maternal mortality.[26] Placental abruption results from the early separation of the placenta from the lining of the uterus before labour has progressed beyond the second stage.[28] This relatively rare, yet very serious, pregnancy complication occurs in between 0.5-1.5% of pregnancies in high-income countries.[29] Adverse pregnancy outcomes resulting from placenta abruption include preterm birth, asphyxia, stillbirth or perinatal mortality.[28] Small –for-gestational age babies generally have a birthweight below the 10th percentile for babies of the same gestational age and sex.[30] Babies that are small-for-gestational age have more than twice the risk of stillbirth[23] and an increased risk for neonatal death (death within 28 days of birth)[31] compared to babies that are not small-for-gestational age.

There is a complex interplay between the above pregnancy outcomes (stillbirth, preterm birth, pre-eclampsia, placental abruption and small-for-gestational age) that may be due to biological and environmental exposures that are not fully understood. It has been purported that there are shared underlying mechanisms underpinning the complex interaction between pregnancy complications.[32] Often referred to as the *Great Obstetrical Syndrome*, ischemic placental diseases are thought to be associated with disorders of the placental,[33] preterm birth,[34] intrauterine growth and stillbirth.[35, 36]

Furthermore, advancing maternal age and increments in BMI are associated with each of the aforementioned pregnancy outcomes. Increasing our understanding of how a pregnancy exposure can influence perinatal outcomes is imperative to informing the creation of effective preventative health that seeks to improve health outcomes for mothers and babies.

1.3 Causal inference

Historically, much of epidemiology was concerned with establishing association (i.e. smoking is a cause of lung cancer);[37] however, there have been increasing movements by experts in the field towards establishing true causal inference in recent decades.[37-41] Causal inference can be defined in basic terms as the process of determining that an exposure was the 'true cause' of the effect or outcome that was observed.[42] More broadly, causal inference can be considered a multi-disciplinary science, comprising areas of philosophy, biostatistics, epidemiology, artificial intelligence and machine learning.[37] This contrasts with traditional epidemiological methods which are broadly interested as to whether an effect is present or not.[41]

Common criteria for establishing causation in modern epidemiology are what came to be known as the Bradford Hill's Criteria;[43] comprising a list of nine aspects to be considered by researchers to distinguish between causal and non-causal associations (strength; consistency; specificity; temporality; biological gradient; plausibility; coherence; experimental evidence; analogy).[43] Despite the wide acceptance of Bradford Hill's Criteria, the criterion has remained controversial overtime as to whether they are too prescriptive for establishing causation.[44-47] It should be noted, however, that Hill considered the above criteria to be viewpoints,[43] and it is generally considered that not all the criterion have to be met for causation to exist.[43] Over time, the interpretation of each criterion has evolved to accommodate complementary research tools and data methods, yet the underlying checklist continues to guide researchers.[48]

In general, establishing causation is a complicated process as a given outcome could be caused by more than one causal mechanism; thereby, the joint action of multi-causality must be considered with any of the components having either strong or weak effects.[41] To complicate matters further, the strength of an effect may alter an outcome, or the effects themselves may not necessarily influence the outcome at the same time.[41] It is therefore unsurprising that one of the requirements of a good study design

that can infer causality is expert knowledge on the topic of interest.[49] A qualitive approach that is similar to Hill's "consistency" is triangulation. Triangulation occurs in aetiological epidemiology when different methodological associations containing different sources of bias are compared to determine if the obtained effect estimates is similar.[50] Here, it would be expected that the effect estimates would only be the same if all sources were unbiased. Although a promising method to establish causal inference, a limitation of triangulation is access to data and considerations around the pooling of such data.[50] Consequently, there are no exact criteria that can be universally applied to determine the true validity of a causal inference. However, sources of potential bias need to be identified and their influence either removed or quantified to reduce uncertainty around causal effects.

One of the earliest advocates for causality, and possibly less known in statistical science, was Barbara Stoddard Burks, who obtained her PhD from Stanford University in 1929.[51] During her academic career in social science, she applied causal diagrams (originally developed by Sewall Wright, a biometrician)[52] to explain her research and identified colliders (a common effect of two variables) and their biasing influence.[53] A more well-known study of the influence of selection bias is the Berkson's bias, which came to light in 1946.[54] This type of bias arose in a case-control study in which the case and the controls were not comparable as the probability of hospitalisation was higher amongst cases who had two or more diseases compared to the controls from a healthy population.[55] Since the mid-19th century, there has been a rapid growth in statistical methods to minimise the influence of bias. However, due to the non-random nature of observational studies they are prone to various biases (selection, confounding and information) that cannot be accounted for fully using statistical methods. As it is not possible to completely remove bias, it is often recommended that epidemiologist employ caution when interpreting their results. Consequently, it is important that epidemiologists identify and quantify the influence of potential biases in order to reduce uncertainty prior to reporting causal associations.

1.4 Overview of bias in perinatal epidemiology

Quite simply, bias can be conceived as some deviation from the truth. In epidemiology, bias can result from systematic errors in the study design or data analysis that consistently produce an incorrect estimate of the exposure-outcome association.[56] By

contrast with random error in which there is a chance difference between the observed and true association, systematic errors do not decrease as the study size increases.[56]

Perinatal epidemiological studies are vulnerable to unique methodological challenges that can lead to biased exposure-outcome associations if not adequately addressed. A major challenge for researchers is that the study population themselves are incompletely observable due to high attrition from conception to when a pregnancy has been established.[57] Although the true attrition rate remains unknown, it is estimated that there are 2,500 early pregnancy losses per 10,000 implantations[57] due to spontaneous and induced abortion. As the detection of early pregnancy loss is not always clinically diagnosed nor apparent to women, there are feasibility issues in conducting longitudinal studies to identify all conceptions due to methodological complexities (i.e. difficulty in identifying the cohort of women who did not intend to become pregnant and had a missed miscarriage) and associated monetary expenditure.[58]

Moreover, perinatal epidemiology often relies on birth registries that are restricted to pregnancies that survive beyond a specified gestational age.[59] In Australia, as in many high-income countries, birth datasets are restricted to pregnancies that survive past 20 gestational weeks or have a birth weight >400 grams.[60] This is a selection bias as the individuals in the sample (women with a pregnancy beyond 20 gestational weeks) differ systematically from the population of interest (i.e. pregnant women). A further source of selection bias is that in some cases the birth datasets are restricted to live births,[61] thus conditioning on the 'survival' leads to distorted associations. Inadvertently, conditioning on a collider variable, a variable that is a common effect of an exposure and outcome, can lead to specious exposure-outcome associations.[62] Further challenging for researchers is conditioning on intermediaries/mediator variables that lie on the causal pathway.[59] Such challenges are evident in the difficulty of handling gestational age or birthweight variables that lie on the causal pathway between exposures and outcomes,[59] as intersecting birthweight-specific and gestational age-specific mortality curves can lead to paradoxical associations.[63]

The influence of unmeasured confounders, a variable that is related to the exposure and outcome which may account for the observed association, is a broader epidemiological issue. However, it is highly unlikely that any association observed in perinatal exposure-outcomes is not subject to some degree of bias from confounders

that are either unavailable in the dataset or even unknown to the researcher. This is particularly true when we consider that exposures during the pre-conception period, which are often unavailable, can lead to adverse events over the life-course of the pregnancy and beyond.[64, 65]

Misclassification bias is particularly pertinent in perinatal epidemiology due to the potential for measurement error of exposure(s), potential confounder(s) and outcome(s).[66] A previous cause for concern was the potential for misclassification of gestational age due to the varied methods of calculation (fetal ultrasound measurement; first day of the last menstrual period; time of in vitro fertilisation; based on clinical judgement after birth);[66] however, the increased use of fetal ultrasound in many countries has reduced this potential bias. In recent years, there has been increasing awareness of the potential for misclassification in the ascertainment of environmental exposures.[67-69] Further, due to left truncation of birth datasets there is potential for misclassification of the true interpregnancy or interbirth intervals due to unobservable early pregnancy losses.[70] It should also be noted that misclassification bias can be introduced during the data analysis phase by researchers through categorisation of continuous data,[71] including varying cut off consideration used for exposure or outcome variables. This is particularly pertinent in sibling comparison studies, where the categorising of variables such as the interpregnancy interval and birthweight for gestational age percentile may compromise statistical power and can introduce selection bias for discordant pairs.[72]

The above is a brief and selective summary of the types of biases that are likely to be impactful when conducting perinatal epidemiological studies. This thesis will focus primarily on three interrelated influences of bias relevant to perinatal epidemiology; selection bias, collider bias and the influence of unmeasured confounders. The descriptions of these types of bias will be expanded throughout this chapter and quantified through simulation studies in chapters three (bias due to confounding), chapter four (selection bias and collider bias) and chapter five (collider bias and bias due to confounding).

Confounding

A confounder is an extraneous variable that influences both the exposure and outcome of interest but is not part of their causal pathway (Figure 1.1).[73] Nearly all observational studies will adjust for measured confounders[74] using methods such as stratification,

multivariate linear regression, and logistic regression.[75] Therefore, consideration must be given to identifying the appropriate set of confounders to adjust for in order to produce plausible associations[76] as confounding can result when researchers fail to correctly adjust for all relevant confounders, leading to the masking of the true exposure-outcome associations.[77] An overestimation of the effect sizes can occur when researchers adjust for apparent differences between study groups when they do not exist.[78] Traditionally, strategies to decide whether a variable is a confounder that should be adjusted for largely rely on statistical approaches, such as forward and backward stepwise selection,[76] the change in time approach,[76] or penalised regression.[79] More promisingly, a review[80] of 299 observational studies published in 2015 found that 50% of authors reported using prior knowledge or causal graphs for selecting confounding variables; yet 37% of the included studies failed to provide sufficient detail on their methods of variable selection.

One conundrum in perinatal epidemiology is where to include prior pregnancy outcomes as a confounder. Many epidemiologists do adjust for prior pregnancy outcomes as they are often predictive of future adverse outcomes; however, this is not an appropriate method when the aim is to produce unbiased estimate of an exposure on an current outcome as the prior outcome is likely associated with current outcome and the exposure.[81] Here, adjustment for the prior pregnancy outcome can produce a bias effect as this seemingly confounder variable may be a collider variable.[81] Therefore, it is strongly recommended that causal diagrams or direction acyclic graphs (DAGs) are used to explore the nature of the proposed causal association to identify relevant confounders.[76, 81, 82]

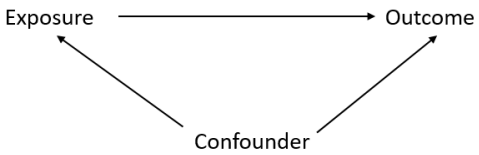


Figure 1.1 Causal diagram showing the causal pathway between an exposure and outcome in the presence of a confounder

Even with the best attempts to address confounding in perinatal epidemiology, there will always remain some degree of residual confounding[83] largely due to omission of relevant variables that were unknown to the study, those that cannot be measured or

those variables that are yet undiscovered.[84] Furthermore, measurement errors in the classification of confounding variables can also contribute to residual confounding.[85] In instances when a moderate effect is evident, epidemiological observations may be considered less robust to bias due to difficulties in controlling for unknown or unobservable confounders that can distort the results and be responsible for creating an observed association that may not be exist.[73] To take one example, if a study is reporting the association between a maternal exposure and perinatal outcome, the association may not be due to the maternal exposure but to a factor that directly affects both the exposure and outcome that is unknown to the study or not included in the available clinical dataset.[73, 74, 86] Determining if an observed association is due to unmeasured confounding is critical to determining plausible causal effects; however, quite often unmeasured confounding is not adequately addressed in epidemiological studies.[87-89]

Collider bias

In contrast to the aforementioned bias associated with failure to control for confounding, incorrectly conditioning on a common effect of exposure and outcome (through restriction, stratification, or regression adjustment) will induce collider bias.[90] Thus conditioning on a collider, or a variable influenced by the collider, will induce biased association exposure-outcome associations.[62] A simple form of collider bias can be viewed in Figure 1.2 in which the collider is a variable in which two arrows collide. Adjusting for this variable in a regression model will induce a specious association between the exposure and the outcome[3] through the causal pathway of *Exposure →Collider←Outcome* that was previously blocked.[39] In general, it is strongly advised that epidemiologists use causal diagrams or DAGS to distinguish between confounders and colliders during the study design phase.[91]

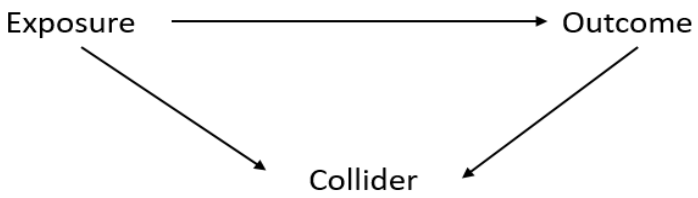


Figure 1.2 Causal diagram showing the causal pathway between an exposure and outcome in the presence of a collider variable

Examples of a collider variable that can be incorrectly adjusted for in perinatal epidemiology is gestational age and birthweight as they lie on the causal pathway between exposure and outcomes.[92-94] Preterm birth and low birth weight are predictors of infant morbidity and mortality but may also be due to other pathological factors that cause both preterm birth and low birth weight and infant morbidity and mortality.[93, 94] Consequently, the practice of stratifying on a potential intermediate has previously led to the intersection of gestational age-specific and birthweight-specific mortality curves.[63] This has been evidenced when low birth-weight infants from populations with higher infant mortality have better survival rates compared to low birth-weight infants from a lower-risk population. As Basso and Wilcox (2009)[92] explained, this can result from the presence of unmeasured confounders influencing the variable of birth weight and making it a collider. This bias results as conditioning on (or including in a regression analysis) a collider opens a back-door causal pathway between the exposure and outcome that leads to biased exposure-outcome associations.[39] As you can see in Figure 1.3, when the variable of LBW is influence by an unmeasured confounder, which also influences the outcome, then the variable of LBW becomes a collider variable. Conditioning on LBW (or including it in a regression analysis) opens a back-door pathway between the exposure and the outcome via *Exposure → LBW ← U → Outcome.*

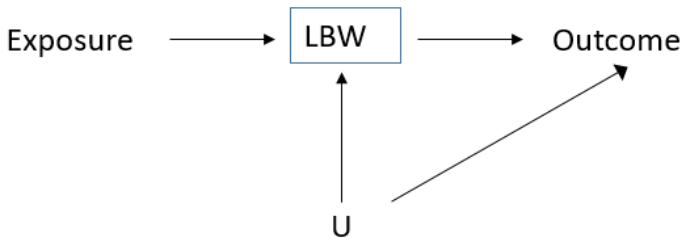


Figure 1.3 Causal diagram showing the causal pathway between an exposure and outcome in the presence of a mediator. There is a causal pathway between an exposure and outcome when low birth-weight (LBW) is a mediator on the pathway between the exposure and the outcome but is also influenced by an unmeasured confounder (U) that also influences the outcome. Here LBW is a collider variable.

Conditioning on LBW will open a backdoor causal pathway from *Exposure* → *LBW* ← *U* → *Outcome* that can lead to biased exposure-outcome effect estimates.

Collider bias resulting from restriction and stratification will be discussed in more detail under selection bias.

Selection bias

Selection bias results from factors related to the selection of the study cohort. In its simplest form, selection bias indicates that participants in a study are systematically different from those that were not included.[95] Random sampling is the most effective method to prevent selection bias, yet this is not possible in observational studies.[96] Rather, the onus is largely upon the researchers to ensure that measures to prevent or minimise the influence of selection bias are enacted during the study design period. Although selection bias can never be completely controlled in observational studies, it is important for perinatal epidemiologists to have a comprehensive understanding of the various avenues in which selection bias can lead to spurious associations. Bias from selection commonly occurs when the exposure and outcome, or even a cause of these variables, influences the probability of being selected into the study population.[97] This is pertinent in perinatal epidemiology where the selection into a pregnancy cohort is restricted to pregnancies that survive beyond a specified gestational period (generally 20 gestational weeks in high-income countries).[59] Left truncation is missing person-time information, where time zero is not detected in the timeline.[59, 98, 99] It is imbedded in all perinatal epidemiology studies as women are recruited after conception.[100] Consequently, an unknown proportion of the source population is absent due to pregnancy losses prior to the enrolment period.[100] Bias from left truncation casts doubt on the validity of observational studies in which truncation varies by risk factors associated with the outcome of interest.[101] Birth datasets from which perinatal epidemiologist draw their effect estimates are left truncated. In high-income countries, such as Australia and the US, selection into a birth dataset is restricted to those pregnancies that survive beyond 20 gestational weeks or >400g birth weigth.[59] In low and middle-income countries, selection into a birth cohort is restricted to pregnancies that survive beyond 28 gestational weeks or >1000g birth weight.[102] Furthermore, in many countries birth datasets are often restricted to live-births, thereby excluding all pregnancy losses from 20 gestational weeks including

neonatal deaths.[103] This left truncation results in a type of selection bias called live-birth bias.[61, 104-106] However, the issue of left truncation is not solely linked to birth datasets. All perinatal studies as subjected to left truncation as recruitment into a cohort is often restricted until some pre-specified point when the pregnancy is deemed viable.[107] Moreover, studies that are interested in pre-pregnancy exposures are additionally left truncated as women with sub-fertility or those who chose not to become pregnancy are excluded.[108]

The bias mechanism that underpins left-truncation bias and live birth bias is called *collider-stratification*. This bias mechanism results from conditioning on a collider that represents a variable that is either restricted or stratified. The most famous example is the smoking birth-weight paradox originally described by Yerushalmy[109] in 1971. Here, neonatal mortality rates among low birth-weight infants of smokers were found to be substantially lower than the neonatal mortality rates among low birth-weight infants of non-smokers; conversely, with the reverse true at higher birth-weights.[109] Since then, this study has been replicated in different studies and populations (altitude vs low altitude,[93] infants of older vs young mothers,[110] ethnicity[111]). More commonly called the 'birthweight' paradox, these effects occur regardless of whether the conditioned intermediate is birth-weight or gestational length.[112] Below, I have presented the most common example of the smoking birthweight paradox. If we consider the example in Figure 1.4, birthweight is a collider variable, blocking the causal pathway it is on (Smoking → Birthweight) ensuring that the only causal pathway is the direct association between the exposure and outcome (Smoking → Neonatal mortality). By stratifying on the variable of birthweight, a spurious association is induced between smoking and neonatal mortality through the collider birthweight and the unmeasured confounder (Smoking → Birthweight ← U → Neonatal mortality).

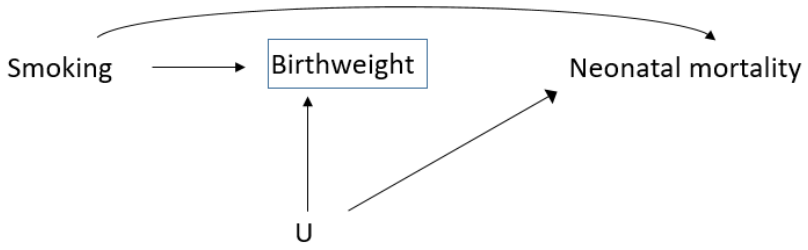


Figure 1.1 Causal diagram showing the causal pathway between an exposure and outcome in the presence of *collider-stratification*. There is a causal pathway between an exposure of smoking and an outcome of neonatal mortality in the presence of a collider variable of birthweight and an unmeasured confounder. This causal diagram depicts the smoking 'birthweight' paradox, which is depicted by *collider-stratification* resulting from stratifying on the collider variable of birthweight.

Depletion of susceptibles

A variation of *collider-stratification bias* is *depletion of susceptibles*. Here, the susceptibles are individuals who have a higher baseline risk or are more susceptible to the outcome.[113] Overtime, a depletion of these susceptibles will lead to an overall decrease in the prevalence of individuals that are at risk of the outcome within the study cohort.[114] In general, this *depletion of susceptibles* will lead to an attenuation of effect size towards the null by amounts that increase with the incidence of the outcome, the variance of the susceptibility and the impact of the susceptibility on the outcome.[105]

Depletion of susceptibles bias can operate independently or in conjunction with collider-stratification mechanism; whereby there is an even greater *depletion of susceptibles*. This is because the depletion is dependent on the joint effects of the exposure and the unmeasured variable U (Figure 1.5). A potential example of this type of bias is in environmental epidemiology where nitrogen dioxide exposure in pregnancy is associated with an increased risk of preterm birth.[115] Here, it is plausible that the exposure of $N0_2$ could induce early pregnancy loss preferentially in those people who also have the factor U, which may be a genetic influence. This group is a subset of pregnancies that are susceptible to the outcome of preterm birth that is differential from individual who are only exposed to $N0_2$.

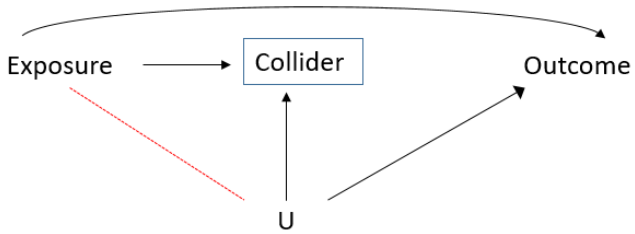


Figure 1.5 Causal diagram showing the causal pathway between an exposure and outcome in the presence of *depletion of susceptibles.* There is a causal pathway between an exposure and outcome in the presence of a collider variable and an unmeasured confounder. This causal diagram depicts collider bias with the *depletion of susceptibles*. When there is an interaction between the exposure and the unmeasured variable U (as depicted by the red dashed line) there is an increase in the prevalence of the collider for those individuals that are exposure to both the exposure and the unmeasured variable U.

M bias

Another variation of the *collider-stratification* bias is *M bias,* which occurs when the collider-stratification bias results through variables that are ancestors of the exposure and outcome (Figure 1.6).[116, 117] Here, the collider variable has no causal association with the exposure or the outcome. Rather, it is indirectly association with both the exposure and the outcome through the causes (ancestors) of the exposure and the outcome.[116, 117] The bias is a results of Berkson's paradox[54] as both the independent unmeasured confounders *U1* and *U2* become dependent once the collider variable is conditioned.[116, 117]

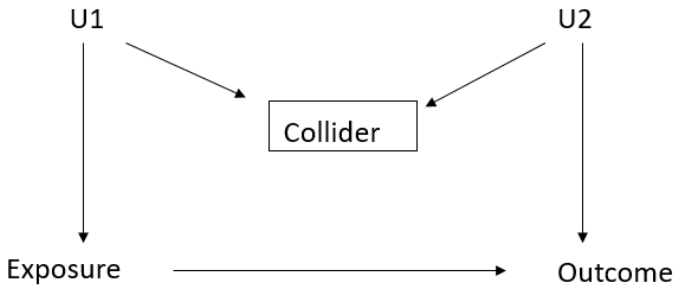


Figure 1.6 Causal diagram showing the causal pathway between an exposure and outcome in the presence of *M-bias.* There is a causal pathway between an exposure and outcome in the presence of a collider variable and two ancestor unmeasured confounders *U1* and *U2*. This causal diagram depicts *M-bias* where the two independent variables of *U1* and *U2* become dependent when conditioning on the collider variable leading to a spurious association.

1.5 Statistical approaches to minimise bias

Much bias can be minimised through a good study design, thus reducing the propensity of a study to bias from poor selection processes, misclassification of variables, and the inclusion of important confounding factors. However, as previously

discussed, it is not possible to address all study design issues that lead to biased exposure-outcome associations, particularly in perinatal epidemiology, where we rely on clinical or administrative data that is left truncated and many variables on causal pathways that are unobservable. Not surprisingly, there is a large body of statistical tools (sensitivity analysis, stratified, analysis, matching, and regression) to minimise the effect biases from selection, information, and confounding. As it is not possible to describe every statistical tool, below is a summary of the most accessible and commonly implemented statistical tools by perinatal epidemiologist.

Selection bias is generally minimised by techniques such as propensity score matching[118] and probability weighting (inverse probability weighting).[119] However, limitations of these methods are the reliance on information of the entire population[120] and their assumption of no influence of unmeasured confounding.[118, 119] A number of distinct methods are available to help researchers to mitigate the effects of bias from confounding, the most promising of which seems to be the G-methods, comprising of G-formula, marginal structure models and structured nested models.[121] These methods create models using different exposure scenarios to generate potential outcome effects, under a less restrictive set of conditions compared to standard regression models.[122] Multiple imputation provides a general purpose approach to handle information bias due to missing data.[123] Traditional approaches employed by researchers include replacing missing values with values imputed some an observed data, using a missing category indicator or carrying forward the last value.[123] All these approaches to minimise bias from missing data can lead to bias themselves. Further, none of the above-mentioned methods to minimise the influence of bias are able to quantify the influence of bias when the bias interacts between the exposure, the outcome and unmeasured confounding.

1.6 *E*-values

E-values were investigated as they are the most commonly used approach to the assessment of the potential influence of unmeasured confounding. *E*-values provide an alternative method for sensitivity analysis of unmeasured confounding in observational studies and were included in Chapter 3. Although not a method to minimise bias, the uptake of e-value has been strong in the epidemiological community[124] since the original ground-breaking paper in 2017.[125] The most popular *e*-value is for confounding, which assess the strength of the effect size needed to

explain away potential bias. The *e*-value[125] calculates the minimum strength of the exposure-confounder and outcome-confounder association needed for the confounder to completely explain the observed exposure-outcome association. Here, a small *e*-value would indicate that a small amount of bias from unmeasured confounding would be required to explain away an observed effect,[125] or that the effect sizes observed are not robust to bias from unmeasured confounding. Conversely, a large *e*-value would indicate that a larger amount of bias from unmeasured confounding would be required to explain the observed effect.[125] Also reported is the *e*-value for the lower limit of the 95% confidence interval which represents the level of confounding from unmeasured or unknown variables required to render the interval estimate null.*[126]*

The *e*-value for confounding has proven to be a highly topical method[124, 127-133] Criticisms levelled include their relationship with effect estimates is monotonic[124, 130] and that they are prone to potential misinterpretations[124, 130, 133] by researchers. Determining how small an *e*-value would need to be to be of concern remains unclear;[133] however, the author's recommend that researchers should interpret the *e*-value within the context of their research question.[134] The *e*-value was originally proposed as an alternative to sensitivity analysis,[125] yet critics have argued that *e*-values cannot provide valid and precise estimates of effects that could only be obtained using more complex sensitivity analysis methods.[124, 127, 130, 133] Further criticism include that focusing on bias from unmeasured confounding is oversimplified as bias required to explain away an observed effect could be due to other sources of bias (selection and information) that may act together.[127] However supporters of the *e*-values for confounding acknowledge that *e*-values are first step in calculating of the amount of potential bias from unmeasured confounding, rather than to replace more complicate analysis to identify missing values or quantify measurement error.[128, 129] To address these concerns, the authors VanderWeelee and Mathur (2020) responded with a best-practice guideline for reporting of *e*-values.[132] In addition to the *e*-value for confounding, *e*-values have been developed for selection bias,[135] misclassification bias and multiple types of bias;[136] although their uptake has lagged by comparison to that of the *e*-value for confounding.

1.7 The application of simulation

Epidemiologists derive effect estimates of an exposure on an outcome in specific populations, using sample data from a representative population. However, it is rare for researchers to have full access to data that would enable unbiased exposure-outcome associations. Simulation studies are empirical studies in which missing data can be simulated,[137-140] based on observed cohorts or prior published literature, to test biased assumptions and draw clearer associations that may be closer to the 'true association'. A simulation itself can be considered a computational experiment that requires the creation of data by a pseudo-random sampling method,[139] which is the use of an algorithm to generate values that follow a given distribution.[141, 142]

In health research, simulation studies are more widely used to test and compare the performance of statistical methods to minimise the influence of bias.[139] However, they are under-utilised in their application to quantify bias more broadly in epidemiology. The quantification of bias is often an intractable problem that cannot be fully solved by closed form mathematical expressions. One of the key assets of simulation studies is that they enable epidemiologists to increase their understanding of the influence of a range of bias in aetiological associations. This results as the actual process of generating the data requires epidemiologists to fully immerse in the causal pathways between an exposure and outcome. Unlike mathematical solutions, the process of generating a simulation usually begins with a causal diagram or a DAG. Parameters in a simulation study can be fully simulated or based on observed data, which can inform the exposure, outcome and confounder variables, thereby, ensuring that the simulation model has real-world context. The main advantage of simulation studies is that multiple scenarios can be generated in which the biased parameters of interest can be varied (i.e. such as values for unknown or unmeasured confounding variables that possibly influence the exposure-outcome association). Due to increased computing power, the running of simulation models is fast and multiple scenarios can be run within a short time-frame.

The reasons that simulation studies are more commonly conducted by statisticians rather than epidemiologist remains speculative; a lack of guidance in the design and implementation of simulation studies,[139] lack of skills in statistical modelling[140] and a lack of interest in exploring new research methods have been cited as potential barriers.[139] Further negating the application of simulation to quantify the influence of

bias in perinatal epidemiology, is the oft-cited reports that simulation studies are prone to poor design, analysis and reporting.[139] In response to the negativity surrounding simulation studies, a number of researcher groups have attempted to educate researchers and reviewers on the design, implementation and reporting of a good quality simulation study; however their purpose has been largely limited to simulation as a tool to test the performance of statistical methods.[139, 143-145] In 2013 the STRengthening Analytical Thinking for Observational Studies (STRATOS) group[140] was established to educate and upskills researchers in the application of simulation studies. Recent outputs by STRATOS members include a platform for planning for planning simulation studies with a focus on testing statistical methods[139] and more relevant to this PhD project a tutorial on quantifying misclassification bias.[146] Although these publications have been positively received, uptake of simulation studies with the prime purpose of quantifying the influence of bias in epidemiology has remained limited

Simulation methods have evolved from a foundation of bias analysis methods, which traditionally applied mathematical formulae to compare an observed dataset with a hypothetical dataset.[45] In 2014, a seminal paper was published by Lash et al.,[147] which informed best practices when quantifying the influence of bias under the overarching term 'quantitative bias analysis'.[148] Although not a guide to simulation as a method, their paper provides a direction for the assignment of plausible values to bias parameters in order to determine the influence of bias on exposure-outcome associations.[148] Types of quantitative bias analysis techniques include simple sensitivity analysis, multidimensional analysis, probabilistic analysis and multiple bias analysis.[149, 150] With the exception of multiple bias modelling, these approaches are limited to analysing one type of bias at a time. Additional limitations of the application of these methods include the ability to only assess fixed variables,[151] inability to assess multiple biases at once[152] or in the case of multiple bias modelling, the biases must be independent of each other;[153] none of which reflect reality (see Table 1.1 for further details).

Table 1.1 Types of bias analysis methods and their characteristics

Bias analysis method	**Bias parameters**	**Number of biases analysis**	**Limitations**

Simple sensitivity analysis	One fixed value assigned to each bias parameter	One at a time	Assess only fixed one variable
Multidimensional analysis	More than one value assigned to each bias parameters	One at a time	Assess multiple fixed variables
Probabilistic analysis	Probability distributions assigned to each bias parameter	One at a time	Cannot assess multiple biases
Multiple bias modelling	Probability distributions assigned to bias parameters	Multiple biases at once	Bias are independent of each other

Previous simulation studies in perinatal epidemiology applied simulation methods to explain paradoxical associations, such as the smoking birth-weight paradox.[100, 101, 154]. Yet, simulation methods have the potential to quantify the influence of bias under more commonly applied scenarios, particularly when the epidemiological effects reported seem to conform to expectations. The application of simulation can quantify multiple types of biases simultaneously, moving away from the *quantitative bias analysis* methods proposed by Lash et al.[147, 150] in which the type of bias should be prioritised by order of the bias that is deemed to be most impactful on the observed association. Some additional limitations under the *quantitative bias analysis* methods proposed by Lash et al.[147] was the assertion that bias analysis was only essential when the findings were informing action or policy, or when it is expected that the bias could explain a finding. By contract, simulation methods can provide a tool to quantify the magnitude and direction of multiple types of bias simultaneously that can be rapidly tested under multiple scenarios. The application of simulation can provide new knowledge on the influence of bias on common perinatal aetiological associations that are potentially biased yet seem to conform to expectations.

As highlighted earlier in this chapter, bias is ubiquitous in perinatal epidemiology and quantifying the influence of various types of bias is valuable step in strengthening the validity of epidemiological studies. However, there remains a lack of good practice in the design, implementation, and analysis of simulation studies that quantify bias,[155] which is further compounded by a lack of confidence in the application of simulation

as a method to facilitate bias analysis by researchers.[139] In order for perinatal epidemiologists to develop the skillset required to apply simulation methods to quantify the influence of multiple biases across a range of research questions, a unifying framework of quantitative bias analysis methods and simulation methods is required.

1.8 Summary of gaps in knowledge

Bias is omnipresent in perinatal epidemiology, yet it is rarely quantified. Bias is generally addressed by researchers qualitatively through a descriptive explanation of different potential sources of bias in their studies, which is generally limited to the discussion section of research papers. Researchers rarely discuss the influence of bias on the direction and magnitude on their observed effects nor quantify the extent to which bias could influence their results.

The left truncation of data is evident in all perinatal studies as the sample population will always be restricted to pregnancies that reach a pre-specified gestational age cut-off. Further complicating the aetiology of perinatal associations is the influence of factors that are unknown to the study, unmeasured or undiscovered. The influence of these 'unmeasured confounders' on variables that are mediators, or variables that are either restricted or stratified on, can create a *collider bias* mechanism when those 'unmeasured confounders' also influence the outcome; threating the validity of exposure-outcome associations. The applied simulation studies conducted in this PhD thesis were focused on this *collider bias* mechanism that resulted from common occurrences in perinatal epidemiology, that is selection bias that results from the left truncation of birth data and the influence of unmeasured confounding on mediators (i.e. pregnancy complications) that are often mediate an association between pregnancy exposures and adverse birth outcomes. The studies conducted in this thesis also addressed changing demographics in Australia and other high-income countries, focusing on exposures of advancing maternal age and maternal obesity, their association with early pregnancy loss and other adverse outcomes, such as stillbirth and pregnancy complications of caesarean section delivery, preterm birth, pre-eclampsia, placental abruption, and small-for-gestational age.

A hypothesis of this PhD project is that if the mechanisms that lead to bias in paradoxical associations (such as the 'smoking –birthweight' paradox) hold true, then these same bias mechanisms would also lead to distorted effect estimates in other observational associations, even when the results seem to conform to expectations.

Simulations are powerful tools that can increase our undertaking of potential biases in epidemiology. They have the potential to quantify the magnitude and direction of multiple biases that influence the associations between exposures and outcomes under commonly applied scenarios in perinatal epidemiology. However, to date it is unknown the full extent to which simulation methods have been applied to quantify the influence of bias in perinatal epidemiology**.**

It is not expected or common for researchers to conduct even a basic analysis of bias when they share their research findings. This presents a problem when those same results are used to inform policy to drives improvements in population health. The lack of guidance in the design, implementation and analysis of simulation studies to quantify bias likely hinders their application by perinatal epidemiologists. A framework is required to assist epidemiologists to undertake simulation studies for the purpose of undertaking quantitative bias analysis. This will make simulation methodologies accessible to perinatal epidemiologists and, thereby, increase understanding of the causal mechanisms that have the potential to distort the observed effects of perinatal exposures on birth outcomes.

1.9 Thesis aims and objectives

The overarching aim of this thesis was to determine the utility of simulation methods to quantify the influence of a range biases commonly found in perinatal epidemiology. To achieve this, the thesis is organised into three inter-related study aims and objectives that addressed the knowledge gaps identified in the above chapter.

Aim1: To review and explore the existing literature on the application of simulation methods as an approach to quantify the influence of bias in perinatal epidemiology.

> **Objective 1.1:** To systematically search, compile, synthesis and critically review the current evidence on the application of simulation to quantify the magnitude and direction of bias in perinatal and reproductive epidemiology (Chapter Two).

Aim 2: To design, implement and analyse a series of simulation studies to quantify the magnitude and direction of bias in perinatal outcomes to address issues from methodological challenges that may lead to spurious inference on associations between pregnancy exposures and adverse birth outcomes.

Objective 2.1: To investigate the consequences of unmeasured confounding on the association between pregnancy complications over two successive pregnancies (Chapter Three).

Objective 2.2: To quantify the influence bias resulting from the use of left-truncated datasets (birth registries) in which early pregnancy losses prior to 20 gestational weeks are excluded (Chapter Four).

Objective 2.3: To quantify the influence of unmeasured confounding in mediated associations (Chapter Five).

Aim 3: To develop a framework for the application of simulation to quantify bias in perinatal epidemiologists.

Objective 3.1: To incorporate best practice for the application of simulation methods to quantify the influence of bias into a framework to guide researchers in the design, implementation, analysis and reporting of simulation studies in perinatal epidemiology (Chapter Six).

The studies that were conducted to fulfil this aim and objectives are described in Chapters two to six.

Chapter Two: The application of simulation to quantify bias

This chapter addressed Aim 1 and Objective 1.1 of the thesis.

Aim 1: To review and explore the existing literature on the application of simulation methods as an approach to quantify the influence of bias in perinatal epidemiology.

> **Objective 1.1:** To systematically search, compile, synthesise and critically review the current evidence on the application of simulation to quantify the magnitude and direction of bias in perinatal and reproductive epidemiology.

The content of this chapter is covered by Publication One. It provides a synthesised summary of the application of simulation to quantify the influence of bias in reproductive and perinatal epidemiology. As limiting this review to perinatal epidemiology would exclude by design all reproductive factors that could potentially introduce bias later in the perinatal period, a decision was made to include, rather than exclude reproductive epidemiology, thereby enhancing the understanding of the application of simulation to quantify the influence of bias. This chapter highlighted specific areas for improvement in the development, analysis and reporting of simulation methods that would enable researchers to better quantify the magnitude and direction of bias in reproductive and perinatal epidemiology.

The version that appears in this thesis is of an article that has been through peer-review with *Annals of Epidemiology* but has not been through the copyediting process. The contribution of co-authors, Professor Gavin Pereira, Dr Gizachew A. Tessema and Milica Ognjenovic are detailed in the author attribution statements in Appendix A.

Dunne J, Tessema GA, Ognjenovic M, Pereira G. Quantifying the influence of bias in reproductive and perinatal epidemiology. *Annals of Epidemiology* 2021;63:86-101. doi:10.1016/j.annepidem.2021.07.033

A copy of this publication has been provided in Appendix C. Supplementary material for this chapter are available in Appendix D.

2.1 Abstract

The application of simulated data in epidemiological studies enables the illustration and quantification of the magnitude of various types of bias commonly found in observational studies. This was a review of the application of simulation methods to the quantification of bias in reproductive and perinatal epidemiology and an assessment of value gained. A search of published studies available in English was conducted in August 2020 using PubMed, Medline, Embase, CINAHL, and Scopus. A gray literature search of Google and Google Scholar, and a hand search using the reference lists of included studies was undertaken. Thirty-nine papers were included in this study, covering information (n =14), selection (n = 14), confounding (n = 9), protection (n=1), and attenuation bias (n=1). The methods of simulating data and reporting of results varied, with more recent studies including causal diagrams. Few studies included code for replication. Although there has been an increasing application of simulation in reproductive and perinatal epidemiology since 2015, overall this remains an underexplored area. Further efforts are required to increase knowledge of how the application of simulation can quantify the influence of bias, including improved design, analysis and reporting. This will improve causal interpretation in reproductive and perinatal studies.

2.2 Introduction

Reproductive and perinatal epidemiology seeks to establish the effects of exposures on maternal and neonatal outcomes before, during and after pregnancy.[156] As randomised controlled trials cannot always be conducted in pregnant women for ethical reasons[97], well-designed observational studies have provided information to increase the understanding of causal effects in reproductive and perinatal health.[97] Due to the non-random nature of observational studies, they can be prone to bias,[97] influencing causal inference. Bias results from systematic errors in study design, conduct or data analysis, and unlike random error, does not decrease as study size increases.[56] To strengthen the validity of associations drawn from observational studies, it is therefore important to identify and evaluate potential sources of bias.

Reproductive and perinatal studies are vulnerable to unique methodological challenges. The study population themselves are widespread from preconception to birth stages, and include populations that are difficult to define, such as women who may conceive in the future.[157] Proving an additional challenge is that the study

populations are incompletely observed due to high attrition from the preconception period through to birth.[157] Thereby, by the time pregnancy is established, an extensive cohort attrition has already occurred; estimated to be 2,500 early pregnancy losses per 10,000 implantations.[57] Consequently, the use of birth register datasets, which are generally restricted to specific periods and in many cases live births, can introduce bias because the sample is thus restricted.[59] Conditioning on intermediaries that are on the causal pathway also proves problematic.[59] Conditioning on a collider, a common effect of the exposure and outcome, or a variable influenced by the collider, can induce a specious association between the exposure and outcome.[62] One such example of such challenges in perinatal epidemiology is how to deal with gestational-age-specific or birth-weight-specific associations that lie on the causal pathway between exposure(s) and an outcome.[59] Reproductive and perinatal epidemiological studies are also impacted by information bias, a measurement error of exposures, outcomes and potential confounders.[66] For example, gestational age can be calculated using various methods: fetal ultrasound measurement, first day of the last menstrual period, time of in vitro fertilisation, or based on clinical judgement after birth.[66] All these measures are prone to some degree of misclassification, not all of which are at random.[66] Additionally, information bias can be introduced during the data analysis phase, such as the incorrect categorisation of continuous data.[71] Thus, selection, confounding and information bias are ubiquitous in reproductive and perinatal research,[59, 157] compromising study validity.[158]

Quantitative bias analysis methods to estimate systematic errors in epidemiology are available,[147] the basic principle of which is to assign plausible values to bias parameters to determine the influence of bias.[148] However, there are a number of limitations in the available methods. Sensitivity analysis, a standard practice, only assesses one binary variable independently.[151] A limitation of multiple bias analysis modelling is the assumption that the bias are independent, which may not reflect actuality.[153] More recent methods have been developed to calculate the effects of unmeasured mediators; however, unless the mediator is binary the study will require a large number of parameters.[125] In recent years, quantitative bias analysis methods have been expanded to include simulation,[148] empirical experiments that involve applying epidemiological modelling to simulated bias parameters.[139] Computer simulations comprise a broad range of computational practices that vary across

disciplinary fields.[159] This review is interested in simulations that replicate complex causal structures, thereby allowing the illustration and quantification of bias by comparing scenarios for the observed association with alternative scenarios.[146] One of the main benefits of simulation is that it enables researchers to conduct numerous experiments, exploring complex causal pathways between exposures and outcomes. This has been greatly facilitated by technological advances that have led to improved computation speed at lower cost. While simulation as a method is well-established,[159] there is a paucity of research using simulations to quantify bias across epidemiology in general.[139] The reasons for the limited application of simulation as a method to quantify bias in reproductive and perinatal epidemiology could be due to several factors. Notably, there is a lack of guidance in the design and implementation of simulation,[139] combined with researchers with a limited skillset in statistical modelling[140] and a lack of interest in exploring new research methods.[139] Further to this, adoption of simulation may be impeded by negative reports that studies that use simulation are prone to poor design, analysis and reporting.[139]

Although the problems of bias in observational studies are well-acknowledged, reviews of the application of methods to address this bias remain limited.[160] Further, no study has documented how simulation methods have been applied in the quantification of bias in reproductive or perinatal epidemiology, which would otherwise be of interest to those who would wish to apply simulation within this field. To address this, we aimed to systematically review the published literature to provide an assessment of the value gained in reproductive and perinatal research, and to identify best practices in the application of simulation in the quantification of bias.

2.3 Methods

Search strategy

A systematic search of four databases (PubMed, Medline, EMBASE, CINAHL and Scopus) was conducted from the start of indexing to the 31st August 2020. Search strategies for each database used the particular databases controlled vocabulary (e.g., medical subject headings (Mesh) terms) and free-text terms (Appendix D). A search on Google and Google Scholar was undertaken to identify gray literature (i.e. literature that has not been formally published in a peer-reviewed indexed format) using simulation methods in perinatal and reproductive epidemiology. A combination of key terms were used: simulat* AND bias AND (reproductive OR perinatal). Due to the large

nature of search results in Google Scholar, the search was limited to the first 100 results returned sorted by relevance. To capture articles that may have been indexed incorrectly, further data collection was completed using a systematic retrospective snowball sample. Here, a hand search was conducted using the reference lists of included studies to identify additional relevant articles. All references were exported to Endnote X9 (Thomson Reuters).

Study selection

Studies identified by the search strategy were initially screened for eligibility by the primary author. The initial eligibility criteria, based on an abstract and title screen, was: 1) examination of the bias types as defined in the search, and 2) focused on reproductive or perinatal outcomes as defined in the search (Appendix D). Studies were excluded using *a priori* exclusion criteria as follows: 1) does not include reproductive or perinatal outcomes in humans, 2) are conference abstracts, review papers (systematic, narrative or literature), editorials or opinion letters, and 3) are not published in English. Studies that fulfilled these criteria were obtained for a full-text review to determine if simulated data is applied as a method to quantify bias. Studies were excluded if the details of the simulation process were not included in the article. Title and abstract screening were undertaken by the primary author. For the full-text screening, a second independent reviewer (MO) conducted a dual review for a sub-sample (20%) of the records. When conflicts for including/excluding articles between the two reviewers occurred, a third independent reviewer (GT) was involved for a final decision.

Data extraction

Studies were retrieved for inclusion through a two-stage process according to the inclusion/exclusion criteria specified above. The key characteristics and methodology details were tabulated and discussed. Standard bibliographic information (authors, and journal year of publication) was extracted. Additionally, the objectives of each study were extracted, type of bias, exposure and outcomes, original cohort (if any), simulation method, simulation analysis, simulation results, author's conclusions, and the key findings of the simulation study. Studies were reported according to the type of bias. We reported study features such as the use of causal diagrams and statistical software, including the availability of code.

2.4 Results

Our searches returned 1,390 records through bibliographic databases and an additional 171 records from gray literature searches. After removing duplicates 913 unique titles and abstracts remained of which 90 articles were retrieved for full-text screen. Of the 90 studies eligible for the full-text screening, 51 were excluded (Appendix D). The principal reason for exclusions were that the studies did not quantify bias as the primary aim study (n=31). Other reasons for exclusion included not applying simulation or where the application of simulation were not core to the article (n=8). Eight studies did not apply simulated data and four studies applied simulation for the purpose of learning in a clinical environment. A total of 39 articles met the inclusion criteria as the studies applied simulation methods to the quantification of bias in reproductive or perinatal epidemiology. The process of study identification, screening and inclusion is summarised in Figure 2.1. The included studies covered three main areas of bias: information (n =14), selection (n = 14) and confounding (n = 9). One study quantified protection bias, defined by the authors as 'the effect of the ability to protect against giving birth to an unintended child' in measures of time-to-pregnancy.[161] Another study investigated the effects of attenuation in study designs used to determine the cumulative probability of pregnancy.[162] Overall, perinatal outcomes were examined in 27 studies and 12 studies examined reproductive outcomes. The timeline of the studies ranged from 1983 to 2019, with 18 studies published since 2015 (Figure 2.2). See Appendix D for a summary of the study characteristics.

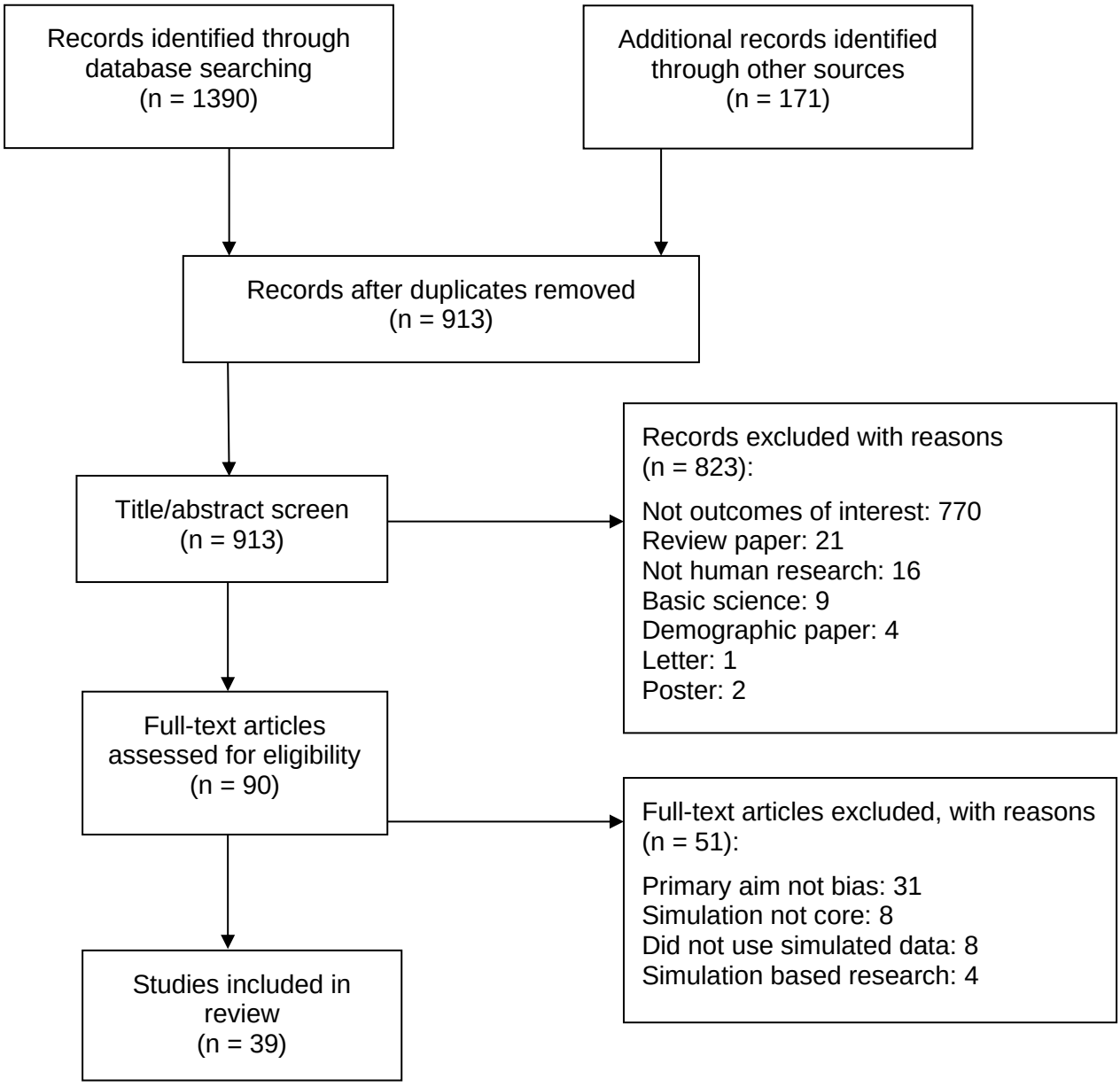


Figure 2.1 Flowchart of the study selection process

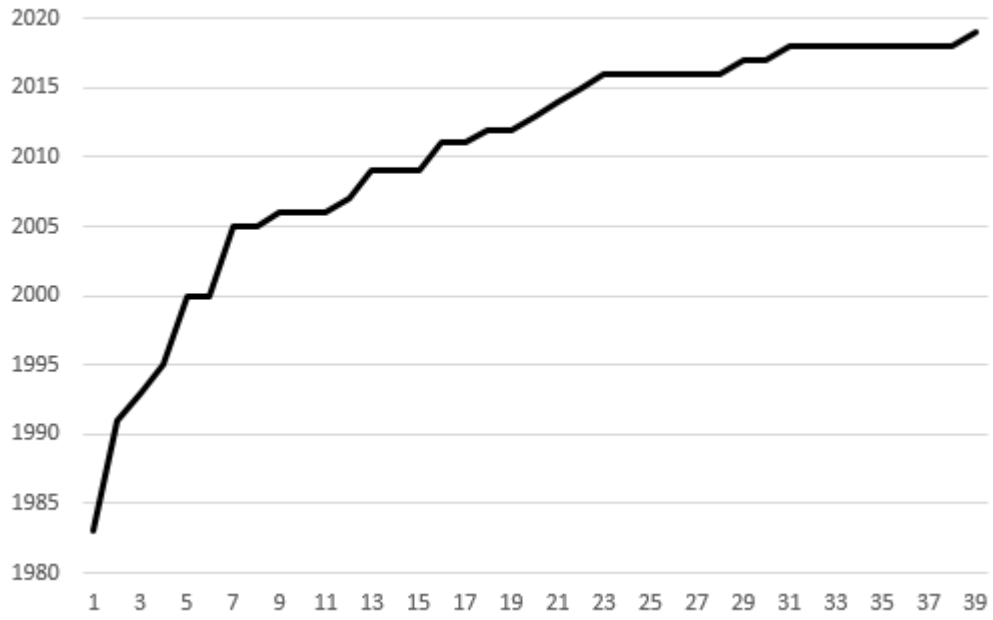


Figure 2.2 Number of included studies (n=39) by publication year

Information bias

Of the studies that quantified information bias, all quantified misclassification bias. The earliest published reproductive study[163] investigated reporting errors resulting from collecting self-reported data in a time-to-pregnancy study, producing bias towards the null. One study[164] investigated the potential magnitude of error resulting from loss to follow up in studies of fertility, noting that the return of pregnant drop-outs to the study biased cumulative pregnancy rates.[164] Four studies examined misclassification bias associated with gestational age. One study[165] examined misclassification bias caused by errors in gestational age on spontaneous abortion studies. Another study[166] evaluated the impact of misspecifying the distributions of weight gain and gestational age using directed acyclic diagrams to inform the simulation. A later study[167] specified a model that investigated Gaussian measurement error in gestational age on the subsequent risk of preterm birth, finding that parameter estimation was mostly unbiased. Lastly, a study[168] used gestational age at arrest of development to reduce misclassification bias for time-varying exposures on the risk of miscarriage. Three articles investigated misclassification bias in studies of the impact of pollutants on perinatal outcomes. The first study[69] applied simulation to estimate bias in relative risk

estimates due to exposure misclassification in disinfection by-product in birthweight studies. A 2016 study[67] evaluated the impact of uncertainty in estimated Perfluorooctanoic acid drinking-water concentrations on estimated serum concentrations and pre-eclampsia. A later study[68] applied simulation to determine the impact of maternal residential mobility during pregnancy on identifying critical windows of susceptibility to term low birth weight from weekly exposure to particulate matter less than or equal to 10$_{\mu m}$ in aerodynamic diameter (PM_{10}). A study from 2014[169] evaluated bias arising from misclassification of pre-pregnancy body mass index and its association with early preterm births. Another study,[170] quantified the extent to which current measures of gestational weight gain could bias the relationship between maternal weight gain and risk of preterm birth. One study[171] demonstrated how the correction for misclassification in a time-varying exposure of influenza vaccination using survival analysis. Another study[172] demonstrated that bias increased with advancing gestational age at antiretroviral therapy initiation and the introduction of gestational age measurement error. The final study investigated the ability of the propensity score to reduce confounding bias in the presence of non-differential misclassification of treatment.[173] The authors showed in the presence of even moderate misclassification, all methods (adjustment, weighting, matching and stratification) increased bias estimates.[173]

Selection bias

Of the three studies that examined bias in reproductive outcomes, the earliest[174] evaluated how the availability of contraception and induced abortion might bias studies of time trends in couple's fertility. The second reproductive study[175] focused on selection bias in pregnancy samples for time-to-pregnancy, with the authors finding that even when fecundity decreased with age, the estimation of the effect of age showed the opposite trend. Another reproductive study[98] investigated bias from left truncation in time-to-pregnancy, demonstrating that fixed or variable differential left truncation can bias results either towards or away from the null. A perinatal study[99] investigated left truncation bias in spontaneous abortion studies when the exposure is maternal smoking, with the simulation suggesting that a difference in 10 days or more in gestational age at entry biased the odds ratio of spontaneous abortion by more than 20%. Lisonkova and Joseph[101] investigated whether left truncation bias could explain the negative association between smoking and pre-eclampsia, finding a protective

effect of pre-eclampsia given smoking even in simulations that did not require assumptions about early pregnancy loss. Kinlaw and colleagues[100] then examined the sensitivity of the assumptions in the Lisonkova and Joseph study, suggesting that the earlier study's results were highly dependent on assumptions regarding the strength of association between abnormal placentation and pre-eclampsia, resulting in less bias than the Lisonkova and Joseph study[101] suggested. Another study[154] also examined the smoking pre-eclampsia paradox with results indicating that the biased effect of smoking was estimated to reduce the odds of pre-eclampsia by 28% and after stratification by gestational age at delivery by 75%.

Three studies examined collider-stratification bias. The first study[176] investigated the 'birthweight' paradox, where birthweight specific mortality curves cross after stratification by smoking status. Another study[94] quantified selection bias when adjusting for gestational age, which was considered as the collider variable where preterm birth was a predictor for neonatal mortality. Here, conditioning on the collider of gestational age led to the reversal of exposure-outcome association.[94] A later study on the effect of asthma medication during pregnancy on major congenital malformations[177] evaluated the potential impact of selection bias due to conditioning on a collider of delivery after 20 weeks gestation. This study found that selection bias could be partially mitigated by controlling for other variables that are not colliders, on exposure-outcome pathway.[177] One study[178] quantified the impact of initial selection into the national birth dataset on different associations between well-established risk factors and pregnancy outcomes. Another study[179] illustrated how selection bias affecting studies restricted to very preterm births should be carefully interpreted, as pre-eclampsia can appear to reduce the risk of adverse neonatal outcomes. A later study[172] hypothesized that the lower risk of preterm birth amongst women who initiate antiretroviral therapy during pregnancy compared to those already receiving therapy is due to selection bias. In this study, selection bias increased with advancing gestational age at therapy initiation and the introduction of gestational age measurement error.[172] Another study[180] used simulation to demonstrate how conditioning on live birth can induce selection bias in studies of drug effects on pregnancy complications when fetal death is a competing risk or is also caused by the complication. Another study[181] quantified both selection and misclassification bias in

studies of reproductive abortion-related mortality, applying explicit assumptions in a multiple-bias analysis model.

Confounding bias

The earliest reproductive paper in this review examined bias arising from inadequate statistical control that impacts gravidity and gravidity-specific relative risks.[182] Another study[183] quantified potential sources of bias related to seasonal variation in reproductive failures, demonstrating that seasonal planning differences in subfecund females lead to variations in reproductive failures. A later study[184] found that differential persistence in pregnancy attempts, which are age-dependent, leads to the observation that older women conceive faster on average unless unsuccessful waiting times are considered. The final reproductive study[185] highlighted fixed cohort bias in pregnancy studies when estimating the effects of seasonal exposures on birth outcomes. When shorter and longer pregnancies are missing, bias can be substantial, changing the estimated effect of temperature on gestational length.[185] One perinatal study[186] postulated that the relationship between birthweight and mortality could be explained by confounding factors that decrease birthweight and also increase mortality. The same authors expanded their previous model in a later study[92] to demonstrate that the addition of a simple exposure could produce a paradoxical reversal of risk among small babies. A later study[187] considered the effects of time-varying covariates such as weight gain on preterm delivery when their mutual dependence relies on gestational age. The study suggested that failure to account for confounding effects of time on gestational weight gain produced a stronger association between higher weight gain and later delivery.[187] One study[188] investigated bias when gestational age acting as a mediator between maternal asthma and small for gestational age. Here, the authors consider small for gestational age to be an absorbing variable, that is the observed association between the exposure and small for gestational age solely reflected the direct effect of the exposure on birth weight.[188] The final perinatal study[189] used simulation to quantify cluster-level confounding of the effect of caesarean section on the Apgar score, finding that preferential within-cluster matching approach showed a good performance in the presence of big and small clusters.

Simulation methods

Of the 39 included studies, 24 studies based their simulations on an original cohort; three studies based their simulations on previously published papers with the remaining twelve studies creating hypothetical cohorts. Key findings related to the types of bias investigated and the simulation methods applied are summarised in Table 2.1. Nine studies used Monte Carlo simulation methods for data generation. One study used a hidden Markov model to account for measurement error in gestational age.[167] The primary method of statistical analysis was logistic regression, with sixteen studies reporting odds ratios. Cox regression models were used to calculate hazard ratios in eight studies. Relative risks were reported in six studies. Two reproductive studies[92, 186] produced mortality curves and one[175] produced Kaplan-Meier curves for waiting time-to-pregnancy. One perinatal study produced generate birthweight-specific mortality curves stratified on a binary risk factor of interest.[154]

Eleven studies used causal diagrams to represent their causal research question and inform their simulation studies. One reproductive study applied a causal diagram in a study of time trends in fertility.[174] Two perinatal studies used a directed acyclic diagram (DAG) where gestational age was the potential mediator between the exposure of interest and birth weight.[94, 188] A study on information bias, used DAGs to depict the correlation between weight gain and gestational age longitudinally across gestation before building simulations.[166] Three studies used DAGs to describe the smoking-pre-eclampsia paradox.[100, 154, 176] Another study used a DAG to illustrate collider-stratification bias when conditioning on live birth.[180] Two studies used DAGs to illustrate bias resulting from restriction to live births in pharmacological studies,[177, 180] and one study illustrated measurement error in a pharmacological study.[173] Nineteen studies disclosed their statistical software. R were the most commonly used in eight studies, Five authors used SAS, four used STATA, one used Microsoft Excel and an early study (from 1993) used BASIC. One study used a combination of R and MATLAB. Six studies made their code available online and two others agreed to make code available upon request. (Appendix D contains a checklist for the application of simulation in studies that quantify bias using observational data).

Table 2.1 Summary of the key findings related to the types of bias investigated and simulation methods applied by the included studies (n=39).

		N (%)
Type of bias examined	Information	14 (36)
	Selection	14 (36)
	Confounding	9 (23)
	Protection	1 (2.5)
	Attenuation	1 (2.5)
	Multiple types	4 (10)
Area of main focus	Perinatal	27 (69)
	Reproductive	12 (31)
Source of data for simulation	Register/database	24 (61)
	Simulation	12 (31)
	Previous study	3 (8)
Causal diagram provided	Yes	11 (28)
Source of bias parameters	Previous study	28 (72)
	Not stated	11 (28)
Simulation iterations	Reported in study	24 (62)
	Minimum	100
	Mode	1,000
	Maximum	100,000
Code availability	Available online	6 (15)
Type of software used	Available upon request	2 (5)
	R	8 (21)
	SAS	5 (13)
	STATA	4 (10)
	Other*	3 (8)

*Other included Microsoft Excel, Basic and Matlab

2.5 Discussion

Although it is standard practice to report potential sources of bias, this review highlights that few reproductive and perinatal epidemiological studies have applied simulation to quantitatively evaluate bias. This is the first review of the application of simulation to quantifying the influence of bias, providing a catalogue of diverse application in the field. This is an important topic due to the potential to improve causal inference by providing context for observational results. Our findings highlight that although simulation is a promising method for quantifying the influence of bias, it remains infrequently utilised in reproductive and perinatal studies. Nonetheless, there has been a significant increase in its application to evaluate bias in this specific field since 2015. As might be expected, there were considerable differences in how the simulations were designed, presented, and reported, revealing a range of specific areas where improvement can be made.

One of the main advantages of simulation is the potential to investigate scenarios that were not directly observed or cannot be directly observed, scenarios in which the true underlying causal effect of an exposure on an outcome can be bounded but is generally unknown.[158] This is particularly relevant in perinatal research where the study population is incompletely observable, in part due to perinatal databases restricting to specified gestational time-periods in pregnancy. This issue is not unique to registries, as prospective cohorts are also usually limited to “recognised” pregnancies. As evidenced in this review, such left truncation can result in bias toward the null, bias away from the null, and loss of precision.[98, 100, 101, 190] Importantly, simulating a population for unmeasured confounders can not only improve precision but can potentially highlight the impact of rare pathologies on adverse outcomes.[92] Further, simulation can illustrate bias when stratifying on an intermediate such as gestational age or birth weight, which can lead to unexpected results such as the intersection of mortality curves.[92, 98, 186] Simulation can also demonstrate whether collider-stratification results in a level of bias that would be of concern,[92, 98, 179, 180, 186] as the incorrect handling of colliders can yield paradoxical associations. [92, 98, 179, 180, 186] This is a valid concern for researchers, as conditioning on a collider such as gestational length will introduce bias, regardless of whether that collider is restricted on or adjusted for in a model.[179] As demonstrated in this review, simulation is a valuable method to correct estimates for potential measurement error. A true

representation of the causal pathway would typically consider more than one type of bias, yet only four of the reviewed studies considered more than one type of bias.[166, 172, 179, 181] However, it remains unclear whether there is a lack of confidence or lack of interest by researchers has led to the limited application of simulation in multiple bias analysis in reproductive and perinatal epidemiology.

This review highlighted several attributes that were common to the included studies. The first is the use of causal diagrams to inform the development of the simulation. Causal diagrams are powerful tools that can aid researchers in constructing models based on hypothesized biologic mechanisms in order to produce the least biased effect estimates possible.[191] Considerable literature has been published on the best approach to the application of causal diagrams, more recently with perinatal examples.[191, 192] Despite the evidence that information bias has a clear and helpful representation within the causal diagram framework,[193] there remains limited application of causal diagrams in the wider epidemiological context. The second attribute common to the included studies was the careful selection of bias parameters to represent effect sizes within the bounds of associations. A common caveat acknowledged in the included studies was that the simulation was only as good as the assumptions that informed the parameters.[100, 101, 154, 172, 177, 181] Bias parameters and the causal structures that underpin the simulations are largely based on researcher knowledge and previously published literature. Although such caveats are unavoidable, a general limitation of the included studies was the lack of clarity from where the estimated bias parameters were derived. Overall, a limitation of the application of simulation in epidemiology, which was also evidenced in this review, is that the simulations are often over-simplified and do not reflect the true complexity of the true causal association. Nonetheless, the application of simulation was an improvement, as it accounted for greater complexity of the underlying true causal pathways than observational studies alone.

Scientific evidence is strengthened by the replication of important findings by multiple independent studies; however, replication may not be always feasible due to costs and difference in the context where the epidemiological population data were drawn.[194] An attainable minimum standard can be reproducibility, where independent investigators subject their original data to their analysis and interpretations based on published protocols and code.[194] The reporting of simulation protocols and the release

of code are important considerations in reproductive and perinatal epidemiology,[139] enabling researchers to identify bias scenarios commonly found in all reproductive and perinatal research questions. However, only a handful of included studies in this review shared their code in the public domain. Increasing study reproducibility can elucidate processes that produce contradictory results. A working example of contradictory results was evident in this review in regards to the paradoxical inverse association between maternal smoking and pre-eclampsia.[100, 101] One study proposed that left truncation bias was responsible for a protective effect of maternal smoking on pre-eclampsia, based on the assumption that there was no direct effect of smoking on pre-eclampsia but an indirect effect through abnormal placentation.[101] Another research group examined the sensitivity of these conclusions, constructing a new simulation model using published estimates to frame their bias parameters.[100] These authors concluded that under more empirical assumptions, bias from left truncation does not fully account for the inverse association between maternal smoking and pre-eclampsia.[100] Rather, when left truncation may result from the exposure, researchers should describe the target population and parameter of interest prior to assessing potential bias.[100]

There are no published guidelines for the development and application of simulation studies in epidemiology for the purpose of bias analysis. A 2014 paper provided a guide for conducting and presenting quantitative bias analysis research studies, highlighting the importance of diagrams to establish causal pathway and the careful selection bias parameter.[147] In recent years, several epidemiological studies have been published under the framework of quantitative bias analysis.[195] As evidenced in this review, the number of studies publishing under the quantitative bias analysis framework is limited[169] compared to the number of studies applying simulation in bias analysis. This may indicate that a broader approach for the development, analysis and reporting of studies applying simulation in bias analysis is required. In 2013 the STRengthening Analytical Thinking for Observational Studies (STRATOS) group was established to guide health researchers to meet the rapid development of statistical methodology.[140] Recently, members of the STRATOS simulation study panel published a guide on the application of statistical simulations in health research, which included a helpful example of measurement error in confounding and exposure variables.[146] Yet it could be considered a potential missed opportunity to consider the

impact of bias more holistically, including complications from selection bias and the dangers of stratifying or adjusting for colliders in observational studies. Overall, there remains a lack of guidance to inform researchers of the practical steps in the development, analysis and reporting of simulation for the quantification of the influence of multiple types of bias in observational epidemiological studies.

The strength of this review was a comprehensive search strategy that included keyword searches and citations indexes of key sources of simulation in reproductive and epidemiology studies that investigated bias. This review also considered the application of simulated data to different types of bias in the broad research areas of reproductive and perinatal health. Our search strategy restricted studies to those that described simulation methods within the paper. Consequently, we may have excluded studies that included simulation methods in supplementary material or those quantifying bias through other methods. Due to a lack of formal critical appraisal tools for simulation studies, an additional limitation is that this study did not conduct a quality assessment of the included studies. Although the included studies' primary aims centred on bias analysis with simulation as an integral component, the simulation itself was not always their central focus. As such, the studies did not need to report all important aspects of their simulations to achieve their study aims. Finally, as we intended to identify the extent to which simulation has been applied in the field, the types of applications of simulation, and potential advantages of simulation, we did not evaluate the degree to which the simulations in each study were effective in achieving the respective individual study aims.

2.6 Conclusion

The use of simulation to quantify bias in reproductive and perinatal epidemiology remains relatively limited. The use of causal diagrams and the reporting of simulation code is minimal. The current applications and examples of simulation demonstrated that such techniques can be implemented to more comprehensively investigate associations. Simulation should be considered as a complementary method in observational studies, rather than a competing method of analysis. It is possible that the potential of simulation to address common issues of bias in reproductive and perinatal epidemiology is under-emphasized due to an overall lack of knowledge in the process of their application, lack of the necessary computational skillset among researchers in the field, lack of a well-established reporting standard, or possibly the

lack of knowledge on potential applications. Increased adoption could be achieved through a more holistic approach to research regarding simulation methodology, which might include cataloguing successful applications of simulation, development of protocols for reporting of simulations studies, complementary application of simulation in observational studies to address bias and sharing of simulation code.

Chapter Three: The role of confounding

This chapter contributed to Aim 2 and fully met Objective 2.1 of the thesis.

Aim 2: To design, implement and analyse a series of simulation studies to quantify the magnitude and direction of bias in perinatal outcomes to address issues from methodological challenges that may lead to spurious inference on associations between pregnancy exposures and adverse birth outcomes.

> **Objective 2.1:** To investigate the consequences of unmeasured confounding on the association between pregnancy complications over two successive pregnancies.

The content of this chapter is covered by Publication Two. This study investigated the consequences of unmeasured confounding on the association between (preeclampsia, placental abruption, small-for-gestational age and perinatal deaths) with a subsequent preterm birth. Using *e*-values and a simulation, this study demonstrated that recurrent confounding is unlikely as any such unmeasured confounder would have to be uncharacteristically large explain away the observed associations.

The version that appears in this thesis is of an article that has been through peer-review with *BJOG*: *An International Journal of Obstetrics & Gynaecology* but has not been through the copyediting process. The contribution of co-authors, Professor Gavin Pereira and Dr Gizachew A. Tessema are detailed in the author attribution statements in Appendix A.

Dunne J, Tessema GA, Pereira G. The role of confounding in the association between pregnancy complications and subsequent preterm birth: a cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2022;129:4-101. doi:10.1111/1471-0528.17007

A copy of this publication has been provided in Appendix C. Supplementary material for this chapter are available in Appendix E.

3.1 Abstract

Objectives

To estimate the degree of confounding necessary to explain the associations between complications in first pregnancy and the subsequent risk of preterm birth.

Design

Population based cohort study.

Setting

Western Australia.

Participants

Women (n=125,473) who gave birth to their first and second singleton children between 1998 and 2015.

Main outcome measures

Relative risk of the subsequent preterm birth (<37 gestational weeks) with complications of pre-eclampsia, placental abruption, small-for-gestational age and perinatal death (stillbirth and neonatal death within 28 days of birth). We derived *e*-values to determine the minimum strength of association for an unmeasured confounder to explain away an observed association.

Results

Complications in first pregnancy were associated with higher risk of a subsequent preterm birth. Relative risks were significantly higher when the complication was recurrent, with the exception of first term perinatal death. The association with subsequent preterm birth was strongest when pre-eclampsia was recurrent. The risk of subsequent preterm birth with pre-eclampsia was 11.87 (95% confidence interval (CI) 9.52 to 14.79) times higher after a first term birth with pre-eclampsia and 64.04 (95% CI 53.58 to 76.55) times higher after a preterm first birth with pre-eclampsia, than an uncomplicated term birth. E-values were 23.22 and 127.58 respectfully.

Conclusions

The strong associations between recurrent pre-eclampsia, placental abruption and small-for-gestational age with preterm birth supports the hypothesis of shared underlying causes that persist from pregnancy to pregnancy. High *e*-values suggest that recurrent confounding is unlikely, as any such unmeasured confounder would have to be uncharacteristically large.

3.2 Introduction

There is strong evidence that a previous preterm birth is a predictor of a subsequent one,[196-198] suggesting the presence of persistent causal factors in the mother or her environment.[199] The assumption that a term birth in first pregnancy can be considered sufficient to imply a reduced risk for a future preterm birth has been refuted by recent studies.[200-202] These studies reported that term first births, complicated by either pre-eclampsia, placental abruption, small-for-gestational age, stillbirth or neonatal death, were associated with elevated risks of subsequent preterm birth, leading the authors of those studies to conclude that there are likely shared underlying pathologic mechanisms persisting from pregnancy to pregnancy.[200-202]

One pathway that explains the association between complicated term birth and subsequent preterm birth is that the complications can also reoccur.[203, 204] Recurrence has been well-established for pre-eclampsia,[205] placental abruption[206] and small-for-gestational age,[207] complications pertaining to ischemic placental diseases,[27] with these complications acting as risk factors for preterm birth.[196-198] Another more complex explanation is that each complication is associated with an increased risk of other complications,[203, 208] which is supportive of the hypothesis of shared underlying mechanisms.[203] Further supportive of a shared underlying mechanism are observations for associations with preterm birth in the "reverse" direction. For example, more recent studies have established associations between preterm first birth and risk of pre-eclampsia[204] and stillbirth[209] in the next birth.

The most well-cited candidate for the shared underlying mechanism is the *Great Obstetrical Syndrome,*[32] ischemic placental diseases that are associated with disorders of deep placentation,[33] preterm birth,[34] and late stillbirth.[35, 36] However, the shared causal pathway is not necessarily biological. Environmental confounders such as socio-economic status, income, age, education and body mass index have previously been identified as risk factors for pregnancy complications[202] and preterm birth.[210] If environmental risk factors and underlying biological mechanisms that cause complications of pre-eclampsia, placental abruption, small-for-gestational age and perinatal death are shared with preterm birth, these associations would persist from pregnancy to pregnancy. Although incomplete control for confounding is inevitable in non-randomised studies,[73, 77] it is possible to estimate the amount of confounding needed to explain away observed associations, which would thereby allow qualitative

assessment as to whether such confounding is likely. We hypothesise that the associations between pregnancy complications exist and that they are largely explained by recurrence of the complications themselves. We aimed to estimate the magnitude of these associations and to establish the degree of evidence for shared underlying pathways by estimating the degree of confounding necessary to explain away these associations.

3.3 Methods

Data sources

We conducted a retrospective population-based cohort study using perinatal records from the Midwives Notification System in Western Australia (WA), a statutory data collection of all live births and stillbirths with either a final gestational length of ≥20 weeks or a birth weight > 400 grams.[211] This de-identified and validated dataset[212] was cross-referenced with Death Registrations obtained from the WA Registry of Births, Deaths and Marriages using a linkage key provided by the Data Linkage Branch of the WA Department of Health.[213] Hospitalisation records were identified from Hospital Morbidity Data Collection for WA using the Australian Modification of International Classification of Diseases (ICD-10-AM) coded diagnostic information for pregnancy complications.[214] As data on chronic co-morbidities and smoking status were not routinely and comprehensively collected until 1998, analysis was restricted to women who gave birth (live birth or stillbirth) within the period 1998–2015.

Study cohort

The study cohort consisted of women who delivered their first two singleton births (live birth or stillbirth) in WA, during the period 1998-2015. From a starting population of 299,166 women who gave birth during this period, we sequentially excluded: multiple births (n=3,276; 1.1%); duplicate parity (n=28; <0%); parity greater than 1 (n=36,892; 12.3%); gestational age <20 or >= 45 weeks (n=76; <0%); birth weight by gestational age z score > 5 (n=6; <0%); women with only one birth (n=133,415; 44.6%). After these exclusions, the final eligible study population was 125,473 women with first and second births (live birth or stillbirth) in WA (Figure 3.1).

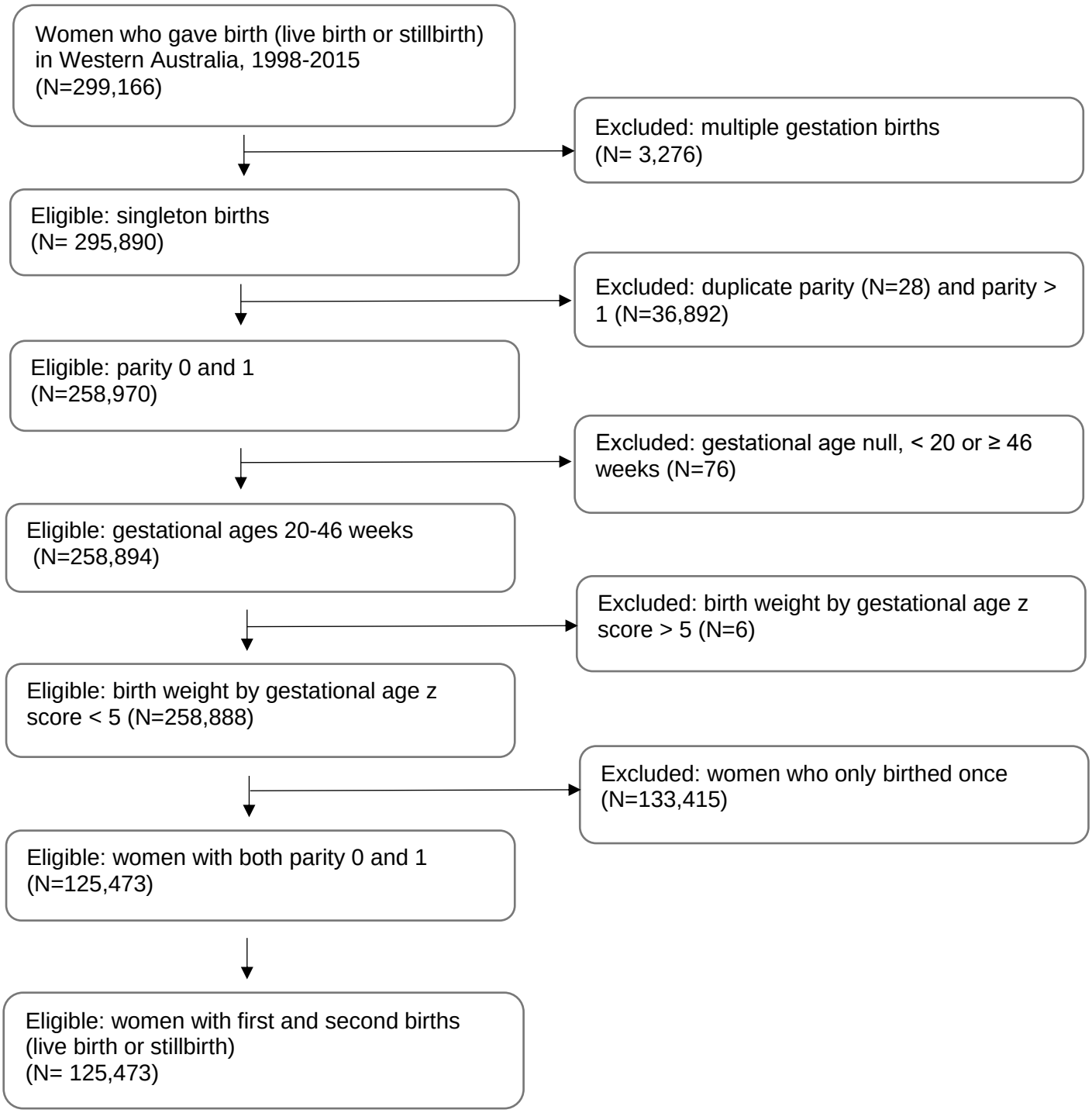


Figure 3.1 Selection of eligible birth records included in this study, Western Australia, 1998-2015

Exposure and outcome ascertainment

The four variables used to identify a shared pathway were pre-eclampsia, placental abruption, small-for-gestational age, and perinatal death (hereon *complications*). Pre-eclampsia (ICD-9: 642.4, 642.5, 642.6, 642.7 and ICD-10: 011, 014, 015) and placental abruption (ICD-9: 641.20 and ICD-10: 045) were obtained from hospital

discharge ICD-9 and ICD-10 diagnosis. Small-for-gestational age was derived using the Australian national centiles and defined with the 3rd percentile for singleton births to exclude more constitutionally mall births.[215] Perinatal death included stillbirths and neonatal deaths, where stillbirth is defined as fetal death after 20 gestational weeks or ≥ 400 grams birthweight, and neonatal death is the death of a live born baby in the first 28 days of life. Preterm birth was defined as a live birth or stillbirth delivered before 37 weeks of gestation. Gestational age at birth was derived from dating ultrasounds.[216]

Based on the hypothesis that the complications and preterm birth share common mechanisms, complications in the first pregnancy (exposure) would be associated with the risk of preterm birth in the second pregnancy (outcome). Similarly, preterm birth in the first pregnancy (exposure) would be associated with complications in the second pregnancy (outcome). Associations were investigated separately for each complication (hereon *primary complication*). Because associations can be induced by the recurrence of complications independent of preterm birth, and recurrence of preterm birth independent of complications, outcomes and exposures were categorised with levels to account for such recurrence. Specifically, for the association between first pregnancy complication and preterm birth in the second pregnancy we defined (i) six exposure groups: uncomplicated term birth, uncomplicated preterm birth, term birth without primary complication (i.e. had a complication other than the primary complication), term birth with primary complication, preterm birth without primary complication (i.e. had a complication other than the primary complication), and preterm birth with the primary complication and (ii) three preterm outcomes: preterm birth with no complications, preterm birth including the primary complication, and complicated preterm birth excluding the primary complication. To avoid introducing collider bias from conditioning on preterm birth, the association between preterm birth in first pregnancy was limited to pregnancy complications at second term birth.

Confounders

Adjustment was made for known confounders that may contribute to the associations between complications and preterm birth. These factors included maternal age, ethnicity, smoking during pregnancy, year of delivery, socio-economic status, inter-pregnancy interval and change of father between the first and second birth. To avoid introducing bias from factors that may have changed since first pregnancy, maternal age, smoking, year of delivery, and socio-economic status were adjusted at the time

of first pregnancy. Ethnicity was classified as Caucasian, Aboriginal Torres Strait Islander and other. Smoking during pregnancy was dichotomised as non-smoking vs smoking. Socio-economic status was derived by the Australian Bureau of Statistics as the Socio-Economic Indexes of Areas (SEIFA) at a geographic area for the maternal residence at the time of birth, with lower values indicating an area that is relatively disadvantaged compared to an area with a higher score.[217] Inter-pregnancy interval was defined as the length of time between the delivery date of the first pregnancy and the estimated conception date of the second pregnancy.

Statistical analysis

We used robust Poisson regression models to calculate relative risks with 95% confidence intervals for the association between complications in the first pregnancy and the risk of preterm birth in second pregnancy. The Poisson model was chosen because the results approximate those obtained from a log-binomial model when the outcome is rare and the sample sizes are large,[218] and overcome problems with convergence[219] commonly associated with log-binomial models. Robust standard errors were applied to derive the confidence intervals. Separate models were run for each primary complication (pre-eclampsia, placental abruption, small-for-gestational age, and perinatal death), with reference set as uncomplicated first term pregnancy. When preterm birth in first pregnancy was the exposure and pregnancy complications at term the outcome, the reference was term birth in the first pregnancy. We presented unadjusted relative risks and relative risks after adjustment for potential confounding variables.

E-values provide a method to gauge the minimum strength of association required to explain away exposure-unmeasured confounders and unmeasured confounder-outcomes associations.[125] A *large e*-value indicates that considerable unmeasured confounding is needed to expound an observed effect estimate. Conversely, a *small e*-value indicates that less unmeasured confounding is needed to explain an observed effect estimate.[125] The *e*-value for the lower limit of the 95% confidence interval is the level of confounding needed to render the interval estimate null, and thereby alter inference.[220] To address the potential impact of bias from unmeasured confounding in our study, *e*-values were calculated and presented for the unadjusted and adjusted relative risks.

Simulation

We undertook a brief simulation exercise to determine if the inclusion of a well-established known confounding variable could explain the association between complications in the first pregnancy and subsequent preterm birth. Body mass index (BMI) is a commonly adjusted confounder in perinatal studies; yet is unavailable in the WA data prior to 2016. As maternal height and maternal weight were readily available for births delivered after 2012, we were able to directly estimate BMI and thereby derive obesity (BMI ≥ 30kg/m^2) for the period 2012-2015. We then applied logistic regression to simulate obesity at the first birth that was not associated with preterm second birth while preserving the correlations in the data between obesity and the other observed variables. Applying the same statistical approach as the main analysis, we re-analysed the data adjusting for the same confounders as before but with the addition of the new simulated obesity. A simulation was run for each exposure-outcome association, with iteration until convergence of the new obesity-adjusted relative risks, which was defined as no change at the third decimal place.

All data analyses and simulations were conducted using R v4.0.5.[221]

3.4 Results

Study population characteristics

In total, 125,493 women had two consecutive births (live birth or stillbirth) in WA between 1998 and 2015. Women were more likely to be in the 25-29 years age group (33.3%) at first birth, Caucasian (83.9%), and reported not smoking during pregnancy (86.5%) (Table 3.1). The majority of the study sample had a SEIFA score greater than 1000 (58.4%) which is slightly above the national average (50%).[217] The most common inter-pregnancy interval was 24-59 months (34.1%). The prevalence of preterm birth in first pregnancy was 7.4%, pre-eclampsia was 4.5%, placental abruption was 0.3%, small-for-gestational age was 3%, and, perinatal death was 0.9%. The prevalence of preterm birth in an uncomplicated second pregnancy was 3.7%.

Table 3.1 Characteristics of the 125,473 women who gave birth between 1998 and 2015 in Western Australia.

Characteristics	N (%)
Maternal age at first-birth (years):	
< 20	18,352 (14.6)
20-24	21,747 (17.3)
25-29	41,779 (33.3)
30-34	37,250 (29.7)
35-39	6,103 (4.9)
40+	242 (0.2)
Ethnicity:	
Caucasian	105,293 (83.9)
Aboriginal Torre Strait Islander	5,470 (4.4)
Other	14,710 (11.7)
Maternal smoking status at first-birth:	
No	108,518 (86.5)
Yes	16,955 (13.5)
SEIFA score at first-birth:	
< 700	279 (0.2)
700-800	1,044 (0.8)
800-900	8,443 (6.7)
900-1000	32,664 (26.1)
>1000	73,312 (58.4)
Missing	9,731 (7.8)
Inter-pregnancy interval (months):	
< 6	4,108 (3.3)
6-11	18,759 (15)
12-17	28,534 (22.7)
18-23	23,229 (18.5)
24-59	42,731 (34.1)
60-120	7,326 (5.8)
>120	786 (0.6)
Year at first-birth:	
1998-1999	22,421 (17.9)
2000-2004	38,307 (30.5)
2005-2009	43,766 (34.9)

2010-2016	20,979 (16.7)
Outcome in 1st pregnancy:	
Preterm	9,240 (7.4)
Term	116,233 (92.6)
Pre-eclampsia	5,644 (4.5)
Placental abruption	435 (0.3)
Small-for-gestational age	3,781 (3)
Perinatal death	1,174 (0.9)

Association between complications at first birth and preterm second birth

The strongest associations were observed between first pregnancy pre-eclampsia and subsequent preterm birth when both pre-eclampsia and preterm birth were recurrent (RR 67.69, 95% CI 56.82 to 80.63) (Table 3.2). The risk of subsequent preterm birth remained elevated when first pregnancy was term and pre-eclampsia was recurrent (RR 11.94, 95% CI 9.60 to 14.86). There was insufficient evidence to suggest that first preterm birth complicated by pre-eclampsia confers greater risk on subsequent complicated preterm birth without recurrent pre-eclampsia (RR 3.67, 95% CI 2.49 to 5.42), than an uncomplicated preterm birth (RR 3.70, 95% CI 3.21 to 4.27). Corresponding *e*-values for associations that involved either recurrence of pre-eclampsia or recurrence of preterm birth were high (> 6). In the absence of recurrence of pre-eclampsia or preterm birth, smaller associations were observed. Strong associations were also observed between placental abruption in first term pregnancy and subsequent preterm birth (RR 11.79, 95% CI 4.37 to 31.83) when placental abruption was recurrent. When the first preterm birth was complicated by placental abruption, the risk of a subsequent preterm birth remained elevated when placental abruption was recurrent (RR 10.47, 95% CI 3.37 to 32.51) and when the subsequent pregnancy was complicated without recurrent placental abruption (RR 10.80, 95% CI 6.69 to 18.00). Corresponding *e*-values for the associations of the recurrence of placental abruption and preterm birth were high (>20). There was a weak association between first term pregnancy with placental abruption and subsequent complicated preterm birth without recurrent placental abruption (RR 1.35, 95% CI 0.34 to 5.37). There was no association between first term birth with placental abruption and the subsequent risk of uncomplicated preterm birth. Corresponding *e*-values were low (≤2) with confidence limits of 1.

Table 3.2 Relative risk and assessment of unmeasured confounding in the association between complications in first pregnancy and preterm

1st pregnancy	2nd pregnancy					
	Preterm birth with no complications[a]		**Complicated preterm birth including primary complication[a]**		**Complicated preterm birth excluding primary complication[a]**	
Complication status	**Adjusted* RR (95% CI)**	**E-value[b] for RR (lower 95% CI[c])**	**Adjusted* RR (95% CI)**	**E-value[b] for RR (lower 95% CI[c])**	**Adjusted* RR (95% CI)**	**E-value[b] for RR (lower 95% CI[c])**
Term no complication	Reference[d]	Reference[d]	Reference[d]	Reference[d]	Reference[d]	Reference[d]
Pre-eclampsia:						
Term[e]	1.22 (1.05, 1.41)	1.73 (1.29)	11.87 (9.52, 14.79)	23.22 (18.53)	1.75 (1.29, 2.38)	2.89 (1.89)
Preterm[f]	3.70 (3.21, 4.27)	6.87 (5.58)	64.04 (53.58, 76.55)	127.58 (106.65)	3.67 (2.49, 5.42)	6.80 (4.41)
Placental abruption:						
Term[e]	1.00 (0.51, 1.98)	1.04 (1)	11.79 (4.37, 31.83)	23.08 (8.20)	1.35 (0.34, 5.37)	2.03 (1)
Preterm[f]	5.40 (4.16, 7.01)	10.27 (7.78)	10.47 (3.37, 32.51)	20.43 (6.20)	10.80 (6.49, 18.00)	21.10 (12.45)
Small –for-gestational age:						
Term[e]	1.62 (1.42, 1.84)	2.62 (2.20)	4.30 (2.78, 6.66)	8.07 (5.00)	2.39 (1.83, 3.11)	4.21 (3.06)
Preterm[f]	3.66 (2.86, 4.69)	6.78 (5.16)	32.68 (19.87, 53.74)	64.86 (39.24)	9.69 (6.60, 14.25)	18.87 (12.67)
Perinatal death:						

Term[e]	3.00 (2.22, 4.05)	5.45 (3.87)	1.29 (0.32, 5.17)	1.90 (1)	2.80 (0.91, 8.61)	5.04 (1)
Preterm[f]	4.22 (3.61, 4.93)	7.91 (6.68)	5.23 (3.36, 8.14)	9.93 (6.17)	12.72 (8.90, 18.18)	24.93(17.28)

[a] complications included are pre-eclampsia, placental abruption, small-for-gestational age and perinatal death; [b] The e-values for the effect estimates are the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and outcome to fully explain away the association between preterm birth in first pregnancy and complications in the second term pregnancy; [c] The e-values for the limit of the 95% confidence interval (CI) closest to the null denote the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have to shift the confidence interval to include the null value; [d] uncomplicated term birth; [e] term birth with primary complication; [f] preterm birth with primary complication

*Adjusted for ethnicity, maternal age at first-birth, smoking status at first-birth, socioeconomic status at first-birth, time period of first-birth, inter-pregnancy interval, and change of father between first and second birth.

The associations were strong when small-for-gestational age and preterm birth were recurrent (RR 32.68, 95% CI 19.87 to 53.74) compared to a first term uncomplicated pregnancy. Preterm birth in first pregnancy confers a greater risk on the subsequent risk of complicated preterm birth when small-for-gestational was not recurrent (RR 9.69, CI, 6.60 to 14.25), in contrast to the subsequent risk of preterm birth without complications (RR 3.6, 95% CI 2.86 to 4.69). Corresponding *e*-values for associations that involved recurrence of small-for-gestational age were high (> 6). In the absence of recurrence of preterm birth or small-for-gestational age, smaller associations were observed, with first term pregnancy complicated by small-for-gestational age weakly associated with subsequent uncomplicated preterm birth (RR 1.62, 95% CI 1.42 to 1.84) with a corresponding *e*-value (2.20). There was a stronger association between a first preterm birth with perinatal death and subsequent complication preterm birth without recurrent perinatal death (RR 12.72, CI 8.90 to 18.18) compared to when the subsequent pregnancy was uncomplicated (RR 4.22, 95% CI 3.62 to 4.93) and when perinatal death was recurrent (RR 5.34, CI 3.36 to 8.14). Conversely, the risk of subsequent preterm birth was higher after a first term birth with perinatal death (RR 3.00, 95% CI 2.22 to 4.05), compared to when perinatal death was recurrent (RR 1.29, 95% CI 0.32 to 5.17). The corresponding *e*-values were 5.45 and 1.90 respectively.

Association between preterm first birth and complications at second birth

When we compared women whose first pregnancy ended in preterm birth to those with a first term birth, there was an increased risk of each complication in second pregnancy. This was particularly true for pre-eclampsia, for which we observed a three-fold higher risk after preterm birth in the first pregnancy (Table 3.3). Generally, there was very slight attenuation after adjustment for known confounders in models when preterm birth was considered the exposure or the outcome of interest.

Table 3.3 Relative risk and assessment of unmeasured confounding in the association between preterm birth in first pregnancy and complications in the second term pregnancy

1st pregnancy	2nd pregnancy							
	Pre-eclampsia		**Placental abruption**		**Small-for-gestational age**		**Perinatal death**	
	Adjusted* RR (95% CI)	**E-value[a] for RR (lower 95% CI[b])**	**Adjusted* RR (95% CI)**	**E-value[a] for RR (lower 95% CI[b])**	**Adjusted* RR (95% CI)**	**E-value[a] for RR (lower 95% CI[b])**	**Adjusted* RR (95% CI)**	**E-value[a] for RR (lower 95% CI[b])**
Term birth	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Preterm birth	3.58 (3.12 to 4.11)	6.62 (5.69)	1.71 (1.03 to 2.83)	2.81 (1.22)	1.85 (1.60 to 2.15)	3.11 (2.57)	1.02 (0.53 to 1.93)	1.14 (1)

[a] The e-values for the effect estimates are the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the exposure and outcome to fully explain away the association between preterm birth in first pregnancy and complications in the second term pregnancy; [b] The e-values for the limit of the 95% confidence interval (CI) closest to the null denote the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have to shift the confidence interval to include the null value.

*Adjusted for ethnicity, maternal age at first-birth, smoking status at first-birth, socioeconomic status at first-birth, time period of first-birth, inter-pregnancy interval, and change of father between first and second birth.

Simulation results

After the simulated confounder of obesity was included, each model was iterated 50 times until convergence was achieved at the third decimal point. When the outcome was uncomplicated preterm birth, there was no difference in relative risks from any of the complications in first pregnancy. There were marginal differences in the relative risks after the simulated confounder was included when the outcome was a subsequent preterm birth complicated with the recurrent pregnancy complication. Overall, the simulation demonstrated that the inclusion of the confounder obesity did not alter the relative risks.

3.5 Discussion

This study examined the role of confounding in the association between pregnancy complications across two subsequent pregnancies. Women with previous pre-eclampsia, small-for-gestational age or perinatal death in first pregnancy were at increased risk for a subsequent preterm birth, regardless of whether their first birth was term or preterm. Placental abruption was the exception with an increased risk of uncomplicated subsequent preterm birth observed only after a first preterm birth. Moreover, preterm birth in first pregnancy was associated with an increased risk of complications in second pregnancy, excluding perinatal death. We were able to demonstrate that substantial confounding would be required to explain away the strong associations observed. Maternal obesity was simulated, demonstrating that the inclusion of a single well-established confounder is not enough to weaken the strong observed associations.

The findings that pre-eclampsia, small-for-gestational age, and perinatal death in a first pregnancy, at either term or preterm, present an increased risk of a subsequent preterm birth support the hypothesis of shared underlying mechanisms. This is reinforced by the findings that preterm birth in the first pregnancy increased the risk of pre-eclampsia, placental abruption, and small-for-gestational age in the next pregnancy. We found that placental abruption at first term birth was not a risk for a subsequent uncomplicated preterm birth. Moreover, the increased risk of subsequent preterm birth with a recurrence of placental abruption was higher after a term birth compared to preterm. These findings may result from situations in which an elective delivery at term occurs before spontaneous labour, leading to uncertainty regarding the true recurrence rate of placental abruption.[222] The strong effect for the associations

between recurrent pre-eclampsia, placental abruption, and small-for-gestational age on preterm birth suggests the presence of strong maternal specific factors that persist from pregnancy to pregnancy. The exception was perinatal death, for which we observed higher risks for a subsequent preterm birth when the complication was not recurrent after a first term birth. This may in part be due to the variability in the influence of placental causes for stillbirth[223] and neonatal death[224] compared to the other complications, and increased health surveillance after the occurrence of said complication in first pregnancy.[225] Adjustment for known confounders had almost no influence on the point estimates of associations between pregnancy complications suggesting the true causal mechanisms are a complex interplay between environmental and biological factors.[32]

To explore the sensitivity of our results to confounding, we applied *e*-values, a relatively new method to quantify the minimum strength of association an unmeasured confounder would need to explain away the exposure-outcome relation.[125] Interpreting the *e*-value within the context of our effect sizes, the large *e*-values suggest large unmeasured confounder(s) are required to explain away the strength of the association between complications of pregnancy. In particular, an unmeasured confounder would have to be extremely high to explain the association between pre-eclampsia in a preterm first birth and a subsequent preterm birth with recurring pre-eclampsia (*e*-value 127.58). Although it is improbable that a single unmeasured variable could confound the strong associations evidenced between pregnancy complications and subsequent preterm birth, we included a simulated variable of maternal obesity as a sensitivity analysis. As expected, simulated maternal obesity did not influence the effect size, supporting previous observations that the shared and unknown underlying mechanisms are a possible interaction between complex biological and environmental exposures.[32]

Comparison to other studies

Our study is the first to report the results of associations between pregnancy complications and subsequent risk of preterm birth for first births at term and preterm. Although direct comparison to other studies is constrained by differences between exposure and reference groups, several past studies support our findings.[125, 196-198, 202, 204, 206, 209, 226-229] There is consistent evidence for the recurrence of preterm birth,[196-198] most notably when the previous preterm birth occurred with early onset pre-

eclampsia.[202, 227] One study reported an increased risk for recurrent placental abruption after a term first birth compared to preterm birth,[228] another study reported almost three-fold higher odds of preterm birth (compared to a term birth) after a small-for-gestational preterm birth,[226] and a study reported that previous all-cause infant death (up to 365 days post-birth) was associated with a two-fold increase in the risk of a subsequent preterm birth.[229] Only two studies considered the reverse associations between a first preterm birth and complications,[204, 209] with one study reporting an increased risk of term pre-eclampsia in second pregnancy[204] and the other reporting a higher risk of stillbirth, after preterm birth.[209] The findings of these studies support the premise of shared underlying mechanisms between pregnancy complications and preterm birth.

More recently, researchers have turned their attention to the subsequent risk of preterm birth from complications when the first birth is term.[196-198] Finding similar results to ours, a study from Norway[201] reported a two-fold increase in the risk of preterm birth when the previous births were term with at least one complication (pre-eclampsia, placental abruption, small-for-gestational age, stillbirth or neonatal mortality) compared to an uncomplicated first term birth. Consistent with our study, the authors also found little evidence for confounding by known demographic and lifestyle factors.[201] Findings from another study provide further support that complications of pre-eclampsia, small-for-gestational age, and perinatal mortality at first term birth increased the subsequent risk of preterm birth.[202] A study from the United States reported similar associations between subsequent preterm birth for first term complications (small-for-gestational age, placental abruption and neonatal death); however, a *protective* association was observed between term births with pre-eclampsia and subsequent preterm birth.[200] An alternative explanation for these results is that the adjustment for placental abruption and small-for-gestational age (potential mediators) introduced collider bias.[230] The findings of these studies add weight to the hypothesis that there are shared underlying causal mechanisms influencing outcomes even when the first birth is term.

Strengths and limitations

This study provided a comprehensive analysis considering multiple scenarios of the interactions between pregnancy complications. A strength was the application of *e*-values to measure the strength of potential confounding required to explain results. An

additional strength of this study was that pregnancy complications for this analysis were drawn from population-based birth data, linking each woman across two pregnancies, enabling the study of relatively rare outcomes with precision. Inevitably, as with most observational studies, these data may also be prone to a degree of misclassification. Furthermore, our findings are not necessarily generalisable to higher order parities than those included in our cohort, although it is uncertain as to why underlying causal pathways would differ. Another limitation is that we were also not able to include women who gave birth to their first child or subsequent child out of the state.

3.6 Conclusion

The evidence for shared casual risk factors between pregnancy complications and preterm birth in this study is strong. The high e-values indicate that substantial confounding would be needed to explain away these associations. However, these findings alone do not provide direct evidence that the shared risk factors are of placental origin or biological origin. Further research is required to elucidate specific pathways that explain these associations whether genetic or pathologic, behavioural or other recurrent mechanisms.

Chapter Four: Bias due to left truncation

This chapter contributed to Aim 2 of the thesis and met Objective 2.2.

Aim 2: To design, implement and analyse a series of simulation studies to quantify the magnitude and direction of bias in perinatal outcomes to address issues from methodological challenges that may lead to spurious inference on associations between pregnancy exposures and adverse birth outcomes.

> **Objective 2.2:** To quantify the influence bias resulting from the use of left-truncated datasets (birth registries) in which early pregnancy losses prior to 20 gestational weeks are excluded.

The content of this chapter is covered by Publication Three. This chapter quantified the magnitude and influence of bias due the use of left truncated birth data in the association between advancing maternal age and stillbirth in a simulation study. This simulation study is reproducible with published code and a full disclosure of the informing data parameters.

The version that appears in this thesis is of an article that has been through peer-review with *Scientific Reports* but has not been through the copyediting process. The contribution of co-authors, Professor Gavin Pereira, Dr Gizachew A. Tessema and Dr Amanuel T. Gebremedhin are detailed in the author attribution statements in Appendix A.

Dunne J, Tessema GA, Gebremedhin AT, Pereira G. Bias in the association between advanced maternal age and stillbirth using left truncated data. *Scientific Reports* 2022;12:19214. doi:10.1038/s41598-022-23719-3

A copy of this publication has been provided in Appendix C. Supplementary material for this chapter are available in Appendix F.

4.1 Abstract

The left-truncation of birth datasets to those that survive past a specified gestational age (usually 20 gestational weeks) leads to biased exposure-outcome associations in perinatal epidemiology. Here, the exposure itself may impact selection into the study. Collider-stratification bias results when the cause of this restriction (early pregnancy loss) is influenced by the exposure and an unmeasured confounder. The aim of this study is to estimate the magnitude of bias resulting from left truncated data in the association between advanced maternal age and stillbirth. We simulated data for the causal pathway under a collider-stratification mechanism. Using an original birth cohort and a range of plausible values we simulated parameters for the prevalence of early pregnancy loss, and unmeasured confounder *U* and odds ratios for selection effects (maternal age → early pregnancy loss, *U* → pregnancy loss, *U* → stillbirth). We compared the simulation scenarios to the observed birth cohort that was truncated to pregnancies that survived beyond 20 gestational weeks. We found evidence of marginal downward bias, which was most prominent for women aged 40+ years. Overall, we conclude that the magnitude of bias due to left truncation is minimal in the association between advanced maternal age and stillbirth.

4.2 Introduction

It is considered that women with advanced maternal age (>35 years of age) have an increased risk of stillbirth.[5] However, the magnitude of this increased risk is unclear when using birth data that is restricted to pregnancies that survive beyond a specified gestational week,[97] as the exposure may impact selection into the study and thus mask the true observation of outcomes. In high-income countries, selection into a study is generally restricted to pregnancies that survive beyond 20 gestational weeks.[59] Thus, the use of left truncated birth registries and cohort studies that recruit women during a specific period of pregnancy, will produce biased estimates in perinatal exposure-outcome associations. The mechanism that leads to these biased associations is collider stratification bias. This occurs as conditioning on a collider, a common effect of an exposure and an outcome, induces a correlation between the exposure and a confounder.[231] As the confounder also affects the outcome, conditioning on the collider leads to a specious association that is either strengthened or reversed between the exposure and outcome.[232] The most well-known example of collider-stratification bias in perinatal epidemiology is the birth-weight paradox.[112] In this example, stratifying on

birth weight produces a cross-over of the birth-weight mortality curves, such that low birth weight babies with smoking mothers have a lower mortality rates than low birth weight babies with non-smoking mothers.[109] However, the collider-stratification mechanism that underpins bias resulting from left truncated data is more difficult to address analytically as selection is based on an attrition processes that we cannot observe in data, i.e. early pregnancy loss.

With estimates of 2,500 early pregnancy losses per 10,000 implantations,[57] an extensive cohort attrition has already occurred prior to pregnancy being established due to spontaneous and induced abortion. The exact aetiology of spontaneous abortion remains unclear, although it is widely acknowledged that they result from interaction between hormonal, immunology, genetic and environmental factors.[17-20] Parental age is considered to be a strong risk factor for early pregnancy loss,[17, 233] with the risk of early pregnancy loss slightly elevated in younger mothers before rising sharply in older mothers (≥35 years).[17] The continuing trend of advanced maternal age and high rates of stillbirth in high-income countries have led many researchers to examine the association between the exposure of advanced maternal age and the outcome of stillbirth, defined as fetal death at 20 gestational weeks or more. Advancing maternal age (≥35 years) has been identified is an independent risk factor for stillbirth,[5] with the increased risk of stillbirth not accounted for by increased prevalence of other maternal comorbities.[23] In studies that use left truncated datasets (i.e. missing pregnancies prior to 20 gestational weeks), the differential impact of maternal age on early pregnancy loss will lead to biased estimates in the relationship between advanced maternal age and stillbirth. Whether the bias is of concern will depend on its magnitude and direction, which remain unclear. Because early pregnancy losses are unobserved, simulations are a useful tool for exploring the influence of bias resulting from such left truncated data on the effects of exposure prior to pregnancy on birth outcomes.[234] In this simulation study, we aimed to quantify the influence of bias due to left truncation and selection in utero on the association between the exposure of advancing maternal age and the risk of stillbirth in a population representative of high-income countries.

4.3 Methods

The motivation for this study was to quantify the influence of bias due to left truncated birth data in the association between advanced maternal age at conception and stillbirth. Using data from the Midwives Notification Systems (MNS) in Western Australia, we compared effect estimates with those from simulated models in which we adjusted for the influence of selection bias under a range of plausible scenarios. For this study, we considered early pregnancy loss as fetal death prior to 20 gestational weeks; and stillbirth when fetal deaths occurred at 20 gestational weeks or later.[212]

Observed cohort

The observed cohort consisted of women who had a singleton birth in Western Australia between 1998 and 2015 (births=483,466), derived from the MNS.[212] This de-identified and validated dataset contains all births in Western Australia with either a gestational length ≥20 gestational weeks or a birth weight > 400 grams.[212] We cross-referenced the MNS with Death Registrations obtained from the WA Registry of Births, Deaths and Marriages using a linkage key provided by the Data Linkage Branch of the WA Department of Health.[213] Hospitalisation records were identified from the Hospital Morbidity Data Collection for WA using the Australian Modification of International Classification of Diseases (ICD-9:779.9; ICD-10:P45 and P96.9) coded diagnostic information for stillbirth.[214] We categorised maternal age into five- year age groups (20-24, 25-29, 30-34, 35-39 and 40+ years). As the primary interest of this study is the biological impact of advancing age on stillbirth, women younger than 20 years were excluded in both the observed cohort and simulation study.

Bias structure

The causal diagram (Figure 4.1) illustrates the bias resulting from restriction to births that survive past 20 gestational weeks. Here, the exposure *A* (maternal age, a proxy for aging) affects early pregnancy loss *L*. An unmeasured confounder *U* is causally associated with increased risk of pregnancy loss *L* and the outcome of stillbirth *S*. Both the exposure *A* and the unmeasured confounder *U* independently affect early pregnancy loss *L,* which is a collider. Thus, by excluding pregnancies that end in loss prior to 20 weeks gestation (*L*=1), or conditioning on *L*, a back-door pathway is opened from maternal age to stillbirth through the pregnancy loss *L* and the unknown

confounder *U*. This bias is commonly known as collider-stratification bias. An assumption implicit in the causal diagram is that maternal age causes early pregnancy loss, however, after attaining a gestational length close to viability (here 20 gestational weeks), maternal age has no direct influence on risk of stillbirth.

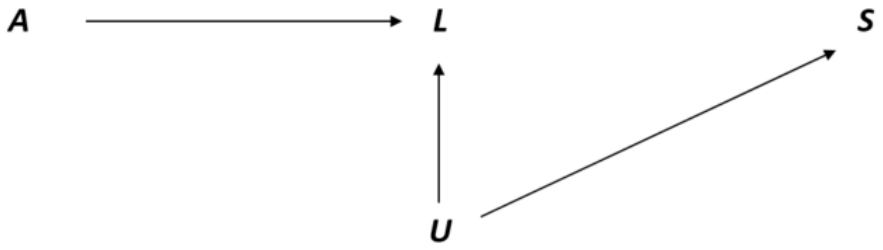


Figure 4.1 Directed acyclic graph of the structure of collider-stratification bias. The exposure maternal age *A* affects early pregnancy loss *L*, which is also affected by the independent risk factor *U*, inducing a back-door pathway between exposure *A* and the outcome of stillbirth *S*.

Simulation

To quantify the influence of the collider-stratification bias on the association between advanced maternal age and stillbirth, we simulated a population of 500,000 conceptions which is approximately the number of births in the observed cohort. We generated data for the maternal age exposure *A*, unmeasured confounder *U*, early pregnancy loss *L* and the outcome of stillbirth *S*. Maternal age variable *A* was normally distributed, with the mean and standard deviation derived from the Gaussian distribution of age in the observed cohort. As per the observed cohort, we categorised maternal age into five-year age groups. The early pregnancy loss variable *L*, the unmeasured variable *U* and the stillbirth variable *S* were binary variables. The prevalence of *L* (π_L) was set to 12.8%,[17] 20%[235] and 30%[236] to reflect a realistic range of early pregnancy loss as reported in high-income countries. The baseline prevalence of *S* was set to 0.7% to reflect the incidence of stillbirth in the observed cohort. We set the prevalence of *U* (π_U) to 0.15, 0.30 and 0.50, to reflect a range of plausible scenarios.

The overall causal pathway [*A* -> *L* <- *U* -> *S*] that represents the collider-stratification bias was broken down to smaller pathways [*A* -> *L*, *U* -> *L*, *U* -> *S*], which we deemed

'selection effects'. All selection effects were modelled in terms of odds ratios (ORs) so that simulation probabilities were bounded between 0 and 1. For the selection effect *A -> L,* we assigned each individual an underlying risk of early pregnancy loss based on their biological age at conception, which was drawn from a Bernoulli model based on results from a 2019 Norwegian study[17] of the effects of maternal age on early pregnancy loss. The Norwegian study[17] reported the lowest risk of miscarriage among women aged 25-29 (9.8%), with an absolute lowest risk at age 27 (9.5%) and the highest risk at age 45 (53.6%). As we were unable to ascertain the increasing risk of early pregnancy loss for women aged older than 45 years, we limited our simulation study to women aged between 20 and 45 years. In our Bernoulli model we used non-parametric regression to capture the nonlinearity of the association between the exposure and early pregnancy loss using LOESS (locally weighted scatterplot smoothing)[237] (Figure 4.2).

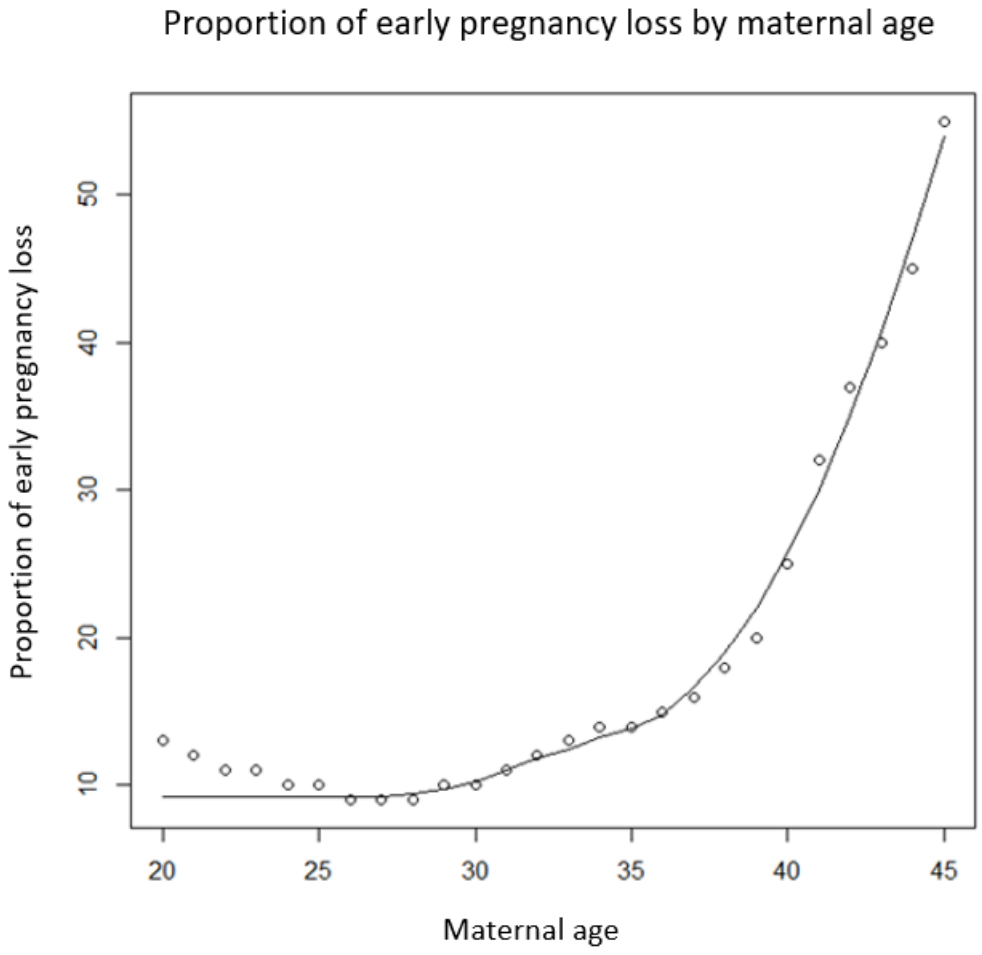


Figure 4.2 Risk of early pregnancy loss according to maternal age with locally weighted scatterplot smoothing curve.

The probability of early pregnancy loss for each conception *i* (assuming a monotonic risk by maternal age) was estimated using the equation below:

$$P(L_i) = \frac{\exp(\beta_0 + \beta_1 A_i + \beta_2 U_i)}{1 + \exp(\beta_0 + \beta_1 A_i + \beta_2 U_i)}$$

Selection effects for *U* -> *L* and *U* -> *S* were set to an equal OR from a range of 1.5, 2.0, 2.5 and 3.0. To isolate the bias mechanism we firstly assumed a true null effect of maternal age on stillbirth (i.e. there is no direct causal effect of *A* -> *S*). We further considered a scenario in which there was an interaction between the unmeasured confounder *U* and maternal age *A* on early pregnancy loss *L* in conjunction with the collider-stratification mechanism. Often called depletion of susceptibles, the interaction of *A*U* increases the prevalence of early pregnancy loss for those that are exposed to both the exposure *A* and *U* (Appendix F). Selection effects for *A*U* were set to an equal OR as with the selection effects for *U* -> *L* and *U* -> *S,* with a range set to 1.5, 2.0, 2.5 and 3.0. To enable a direct comparison with the observed cohort, we then considered a third scenario in which we assumed a true effect of maternal age on stillbirth *A* -> *S* (Appendix F). Here each individual was assigned a probability of stillbirth drawn from a Bernoulli model based on the risk of stillbirth from their biological age of the observed cohort at conception (Appendix F). To capture the nonlinearity of this direct association between the exposure maternal age *A* and the outcome of stillbirth *S* we conducted non-parametric regression with LOESS.[237]

Analysis

We estimated the OR for the association between the exposure and outcome in the observed cohort and the simulated populations. We performed logistic regression of stillbirth with maternal age as the exposure to obtain the OR, which approximates the risk ratio because the outcome of stillbirth is rare in Western Australia.[238] We exponentiated the mean of the point estimates obtained from 100 iterations for each scenario to obtain $OR_{AS|L=0}$, which represents the OR for the effect of *A* on *S* for pregnancies in which early pregnancy loss did not occur (*L*=0). We then derived the

percentile-based 95% simulation intervals (SI) of the OR mean using 500 bootstrap replications.

We initially examined the collider-stratification bias under a range of plausible assumptions by varying the selection effects (OR_{UL} and OR_{US}) and the prevalence of both *L* and *U* as described above. In the first scenario, the simulation is conducted under the null hypothesis of no association between advancing maternal age *A* with the exposure of stillbirth *S*. In the second scenario we simulated a collider-stratification mechanism with an association between the exposure *A* and the unmeasured confounder *U*. As in the first scenario, we conducted the simulation under a hypothesis of no association between advancing maternal age *A* and stillbirth *S*. In both scenario one and scenario two we assumed that there is no causal effect, and therefore the value of $OR_{AS|L=0}$ was set to 1. Consequently, we interpreted the results such that the greater the departure of $OR_{AS|L=0}$ from 1 the greater the magnitude of the bias.

For the third scenario in which we assumed a true effect of *A -> S,* we were able to undertake a direct comparison with the observed cohort. For $OR_{AS|L=0}$ in this scenario, we simulated collider-stratification mechanism without an association between exposure *A* and the unmeasured confounder *U* and assumed a true effect of the exposure *A* on the outcome stillbirth *S*. Here the greater difference between $OR_{AS|L=0}$ and OR_{AS} (the observed cohort without the simulated bias), the greater the magnitude of bias. Furthermore, to eliminate possible model misspecification due to the categorisation of maternal age, we undertook a sensitivity analysis in which we simulated the true null association between the exposure maternal age *A* and the outcome of stillbirth *S* with input parameters π_L =0.20, π_U =0.15, OR_{UL}=1.5, OR_{US}=1.5 for each whole year of maternal age (Appendix F). All data analyses and simulations were conducted using R v4.0.5.[239]

4.4 Results

Overall, the bias was minimal under a true null association between the exposure maternal age *A* and the outcome of stillbirth *S*. In scenario one, we considered a collider-stratification bias where the exposure maternal age *A* and the unmeasured confounder *U* independently effected early pregnancy loss (Appendix F). Here the magnitude of bias was generally weak for women aged 35-39 years, with departure

from 1 not evidenced until the selection effects (OR_{UL} and OR_{US}) were set to a minimum of 2.5 and regardless of the values of π_L and π_U. For example, the $OR_{AS|L=0}$ for women aged 35-39 years was 0.98 (SI 0.97 to 0.99) with input parameters of π_L =0.128, π_U=0.30, OR_{UL}=3.0, OR_{US}=3.0. For women aged 40+ years there was evidence of increasing bias when the magnitudes of the selection effects increased (OR_{UL} and OR_{US}) regardless of the values of π_L and π_U (Figure 4.3). The largest departure from the null for women aged 40+ years was evident with input parameters of π_L =0.128, π_U=0.30, OR_{UL}=3.0, OR_{US}=3.0 ($OR_{AS|L=0}$ 0.92 SI 0.90 to 0.94).

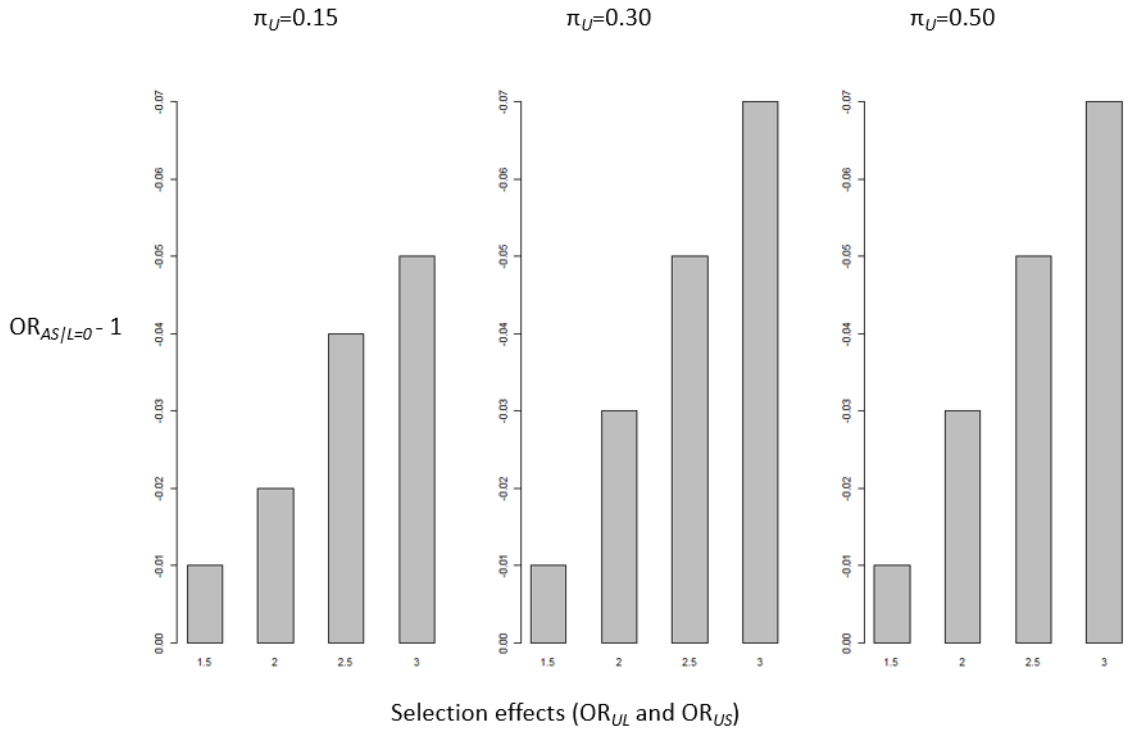


Figure 4.3 Collider-stratification bias of $OR_{AS|L=0}$ -1 under the true null effect of maternal age on stillbirth for women aged 40+ years, where the bias represents the departure from the null. Average odds ratio ($OR_{AS|L=0}$) with $\pi_{L=}$ 0.20 and with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects OR_{UL} and OR_{US} (1.5, 2.0, 2.5, 3.0). Each scenario was iterated 100 times.

In the second scenario, when we considered the collider-stratification mechanism with an interaction between the exposure *A* and the unmeasured confounder *U*, we found a greater departure from the null for women aged 40+ compared to scenario one. In this scenario, we also found that the magnitude of the bias increased with increasing values of π_L and π_U (Figure 4.4). The strongest evidence of bias was evident in women aged 40+ years with π_L =0.30, π_U=0.30, OR_{UL}=3.0, OR_{US}=3.0 (OR 0.87 SI 0.84 to

0.89) (Appendix F). For women aged 35-39 years, there no evidence of bias when the selection effects (OR_{UL}, $OR_{US,}$ OR_{AU}) were set to 1.5 and 2.0, regardless of the values of π_L and $\pi_{U.}$ The greatest departure from the null was evidenced ($OR_{AS|L=0}$ 0.98 SI 0.97 to 0.99) when π_L =0.30, OR_{UL}=3.0, OR_{US}=3.0, OR_{AU}=3.0 and π_U was set to either 0.15, 0.30 or 0.50.

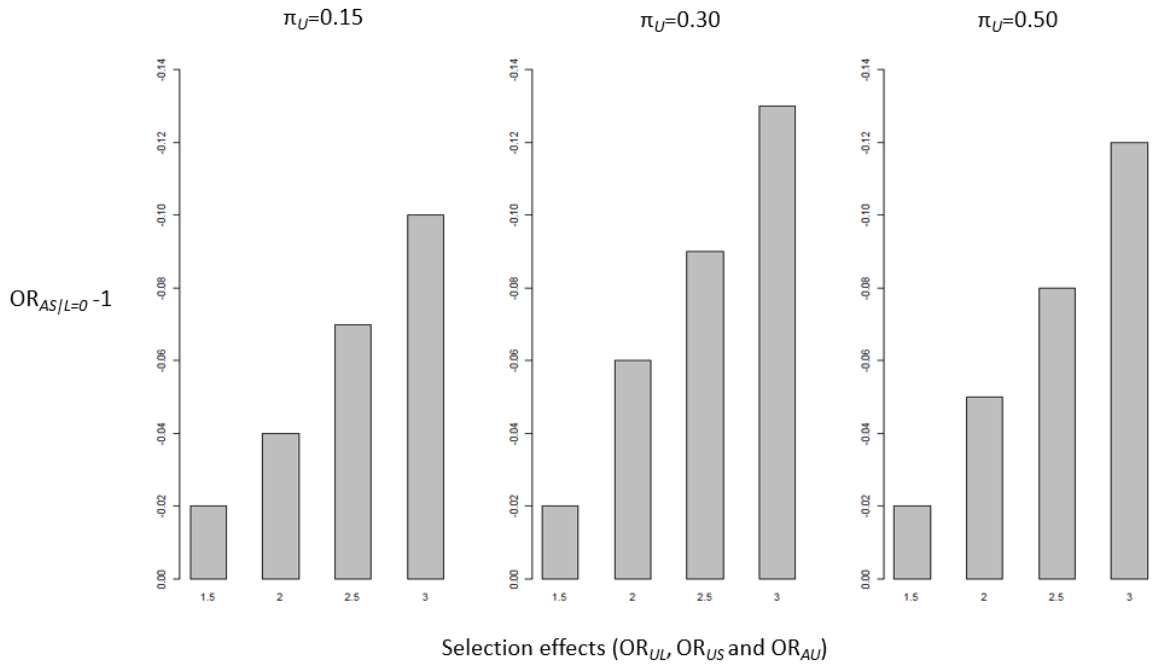


Figure 4.4 Collider-stratification bias of $OR_{AS|L=0}$ -1 under the true null effect of maternal age on stillbirth for women aged 40+ years with an interaction between exposure *A* and the unmeasured confounder *U*, where the bias represents the departure from the null. Average odds ratio ($OR_{AS|L=0}$) with $\pi_{L=}$ 0.30 and with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects (OR_{UL}, $OR_{US,}$ OR_{AU}). Each scenario was iterated 100 times.

In the observed cohort, the association between maternal age and stillbirth presented as a U-shape, with the lowest risk for women aged 25-29 (OR 0.98 95% CI 0.90 to 1.17). The OR_{AS} for women aged 35-39 years was 1.23 (95% CI 1.11 to 1.37), increasing to 1.74 (95% CI 1.42 to 2.12) for women aged 40+. In scenario three we simulated the biased collider-stratification pathway (without interaction between the exposure *A* and the unmeasured confounder *U*) with a direct effect of the exposure *A* on the outcome *S* (with data drawn from the observed cohort). We found evidence of minimal downward bias when we compared the results from this simulation with the observed cohort in which we assumed there was no influence from unmeasured

confounders nor selection bias (Appendix F). Women aged 35-39 years had an OR_{AS} of 1.23 (95% CI 1.11 to 1.37) in the observed cohort which was only marginally higher than the average $OR_{AS|L=0}$ of 1.21 in the simulated scenario three. The greater departure from the results of the observed cohort for women aged 35-39 years ($OR_{AS|L=0}$ 1.18 SI 1.17 to 1.20) was evident with input parameters of $\pi_{L=}$ 0.20, π_U=0.30, OR_{UL}=3.0, OR_{US}=3.0. In the observed cohort, women aged 40+ years had an OR_{AS} of 1.74 (95% CI 1.42 to 2.12) and we found a greater departure from the observed cohort in general (Figure 4.5). For example, with input parameters of parameters $\pi_{L=}$ 0.20, π_U=0.30, OR_{UL}=3.0, OR_{US}=3.0 the $OR_{AS|L=0}$ for women aged 40+ years was 1.58 (SI 1.56 to 1.61).

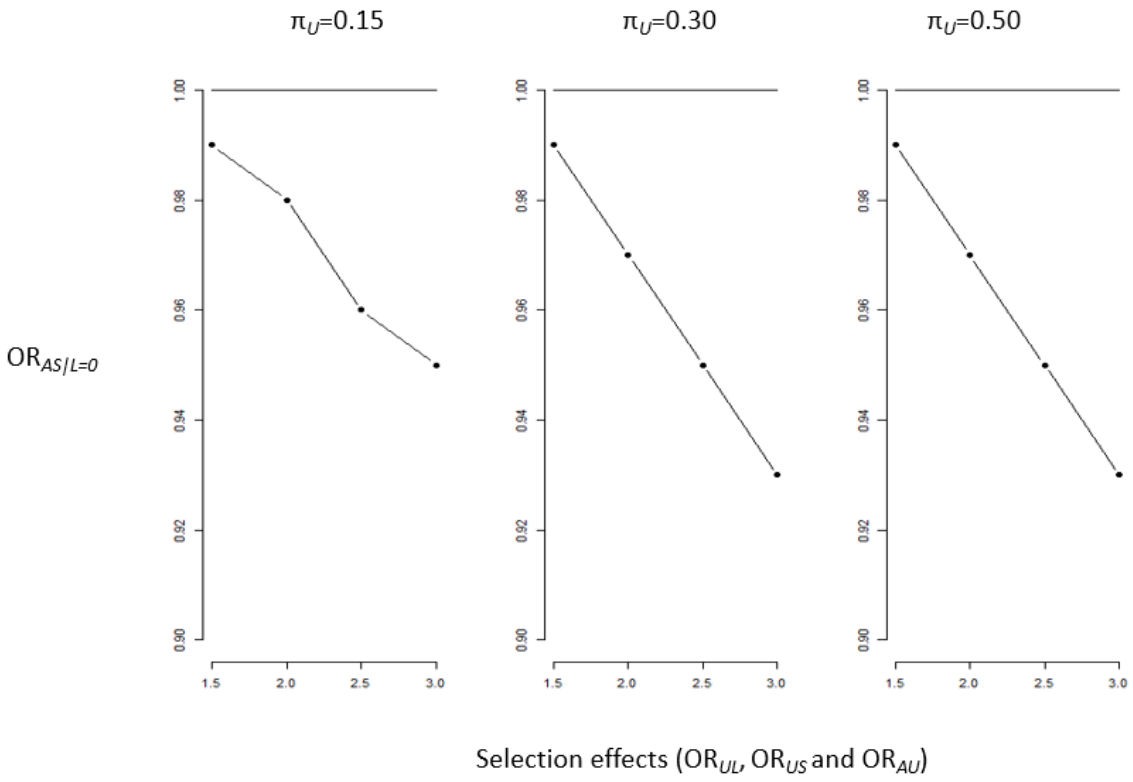


Figure 4.5 The upper straight line represents the results of the observed cohort for women aged 40+ years assuming no influence of an unmeasured confounder or selection bias. The lower lines represent the collider-stratification bias of $OR_{AS|L=0}$ assuming a true effect of maternal age on stillbirth for women aged 40+ years without an interaction between exposure *A* and the unmeasured confounder *U.* Average odds ratio with $\pi_{L=}$ 0.20 and with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects (OR_{UL} and OR_{US}). Each scenario was iterated 100 times.

When we simulated the true null association between exposure maternal age *A* and the outcome of stillbirth *S* (input parameters $\pi_{L=}$ 0.20, π_U=0.15, OR_{UL}=1.5, OR_{US}=1.5)

by each maternal age in the sensitivity analysis, we found that the structure of bias was similar to when maternal age was categorised by 5-year age groups (Appendix F).

4.5 Discussion

Establishing the magnitude and direction of bias from unobserved early pregnancy losses on exposure-outcome associations is essential in improving our understanding of aetiological associations in perinatal epidemiology. In this simulation study, we quantified the magnitude and direction of bias due to left truncation and selection in utero on the association between the exposure of advancing maternal age and the risk of stillbirth. Our findings suggest that the exclusion of early pregnancy loss in perinatal epidemiological studies likely biases effect estimates downwards. However, we found that the magnitude of bias was generally marginal, with a maximum $OR_{AS|L=0}$ of 0.87 for women aged 40+ years when we considered a true null effect of advancing maternal age on stillbirth. The strength of this bias was primarily dependent on the selection effects of the unmeasured confounder on the collider of early pregnancy loss *L* (OR_{UL}), the exposure of advancing maternal age *A* (OR_{AU}) and the outcome of stillbirth *S* (OR_{US}).

Direct comparison to other studies was constrained by differences between exposure-outcome associations and the structure of the collider-stratification bias; however, the small magnitude of bias in this study is consistent with other studies that examined the collider-stratification mechanism for other perinatal outcomes,[100, 101, 104, 105, 154, 176, 180, 240] such as the smoking-birthweight paradox.[100, 101, 112, 154] Our findings, and those of others, suggest that the bias resulting from a collider-stratification mechanism would need to be very strong to produce an association that reverses the observed causal effects, and that this would primarily occur in scenarios where the effect of the unmeasured confounder would be quite large. It remains uncertain as to whether it is plausible that such a large causal effect would remain unknown or unobservable. On this basis, we limited the selection effects of *U* (OR_{UL} and OR_{US}) to a realistic range from 1.5 to an upper limit of 3.0. We found that the stronger the selection effects of *U* (OR_{UL} and OR_{US}), the stronger the magnitude of bias regardless of the prevalence of early pregnancy loss *L* or the prevalence of the unmeasured confounder *U*. Simulation studies that considered an interaction between an unmeasured confounder and the

exposure found evidence of a stronger magnitude of bias in comparison to simulations without an interaction effect.[104, 105] Often called *depletion of susceptibles*, this interaction between the susceptible factor (in our study this would be advancing maternal age) increases the depletion of early pregnancy loss among those who experience the unmeasured confounder.[106, 241] Although our study showed an increase in the magnitude of bias when we considered a depletion effect, it was only evident for women aged 40+ years. One of the benefits of this study was that we could directly compare the difference between $OR_{AS|L=0}$ and OR_{AS} (the observed cohort without the simulated bias). Here, we found that the magnitude of downward bias was negligible for women aged 35-39 years and minimal for women aged 40+. Overall, our findings indicate that the influence of bias due to left truncation and selection in utero is not sufficient to have a substantial effect on the strength of the association between advancing maternal age and stillbirth.

As simulation studies are only as valid as their assumptions, we used published literature and an observed cohort to support our assumptions of the magnitude of the underlying causal effects when quantifying the influence of bias in the association between advancing maternal age and stillbirth. Advancing maternal age has previously been established as a strong independent risk factor for early pregnancy loss in the first trimester,[17] with risks increasing incrementally after the age of 30 years. Although the absolute risk of second trimester pregnancy loss is small in comparison to first semester, there is an incremental increase for women of advancing age.[242] Using data from a 2019 Norwegian study[17]we were able to model this incremental increase in risk of early pregnancy loss *L* prior to 20 gestational weeks for each year of maternal age from 20 to 45 years in our simulations. We accounted for a variety of early pregnancy loss scenarios from 12.8%[17] a mid-range of 20%[235] and an upper level of 30%.[236] As our simulations are hypothetical scenarios in which all conceptions are selected, it is also likely that induced abortions would present a small competing risk to stillbirth. However, the Norwegian study,[17] from which our lowest prevalence (12.8%) of early pregnancy loss is derived, did correct for induced abortions, finding very little difference in the overall estimate of miscarriage.[17] Although the absolute risk of stillbirth is low in high-income countries, it has not declined in recent decades despite advances in perinatal and obstetric care.[23] For women aged 40+ years, the risk of stillbirth increases earlier in pregnancy than for younger women, with a women

aged 40+ having a greater risk of stillbirth at 39 gestational weeks compared to a younger women at 41 weeks.[242] Using data from our large observed cohort in Western Australia, we built models that accounted for the differential impact of the exposure advancing age *A* on the outcome of stillbirth *S* in a high-income setting. Our careful definition of our exposure variable advancing maternal age *A,* accounting for the differential impact on the early pregnancy loss *L* and stillbirth *S*, ensure our simulations are reflective of real world interactions between variables.

The exact biological mechanism of the higher risk of maternal age remains uncertain, with many of the potential shared risk factors for early pregnancy loss and stillbirth unobservable prior to the outcome. Possible suggestions include utero-placental dysfunction predisposing some women to adverse fetal outcomes including early pregnancy loss and stillbirth.[16] Infections can increase risk of early pregnancy loss and stillbirth, infecting the fetus via the placenta [243] with many infections asymptomatic. Fetal chromosomal abnormalities are the most common cause of early pregnancy loss in the first trimester, accounting for 50% of non-recurrent pregnancy losses.[244, 245] There is an increased chromosomal anomaly rate (approx. 20%) in women aged 35+ years compared to younger women in sporadic and recurrent pregnancy losses.[246] Here, chromosomal anomalies would be an ideal candidate for the unobserved variable in our second simulation scenario. Increasing advanced age predisposes mothers to increasing risk of chromosomal anomalies that increase the risk of early pregnancy loss. Notwithstanding the collider-stratification mechanism, unmeasured confounders can lead to biased exposure-outcome effect estimates in either direction. Making assumptions about such confounders that are unobservable or unknown is challenging for researchers. Given the existence of causal factors that are not measured or remain to be discovered, researchers will continue to be required to make reasonable assumptions in relation to the strength and role of such unobservable confounders in the causal pathway, as we have done in our simulation study.

Quite often, the influence of collider-stratification bias is only examined when unexpected associations are observed in epidemiological studies.[100, 101, 105, 154, 176, 240] As the use of left truncated data is ubiquitous in perinatal in epidemiology, due to restriction of studies until a time when pregnancy is either observed or deemed viable, the quantification of bias should be no less important in studies when an expected

association is observed. Nonetheless, there are some caveats for interpreting our simulation results. The estimates in our simulation study are based on simple scenarios with all the variables having a binary response. We further assumed that there are no other forms of bias such as misclassification, nor the effects of multiple unmeasured confounders. There may also be a mediator variable, such as a pregnancy disease, that mitigates the association between advancing maternal age and stillbirth. An additional limitation of this study on the effect of ageing on stillbirth is that we did not consider selection bias prior to conception; that is women of advancing maternal age have a higher risk of infertility.[247]

In this simulation study, we have quantified the magnitude and influence of bias from left-truncated perinatal data caused by studying cases prevalent from a specified gestation age, rather than including all cases in a conception or pregnancy cohort. We know that conditioning on the collider (early pregnancy loss prior to 20 weeks gestational weeks) will produce biased estimated in perinatal exposure-outcome associations. Using realistic assumptions, we found the magnitude of bias was generally minimal when using data that is left truncated due to early pregnancy loss on the association between the exposure of advancing maternal age and the outcome of stillbirth. When we considered a true association between the exposure and outcome, we observed a small downward bias which was stronger for women aged 40+ years. In our specific research question, in which the exposure is advancing maternal age, our findings indicated that the influence of bias due to selection in utero (and thereby left truncation) is not sufficient to have a substantial effect on the association with stillbirth. That is not to say that other researchers, with a different research question, would not find stronger evidence of bias when using left truncated birth data. However, as we demonstrated in this simulation, the strength of the bias is driven primarily by the prevalence and strength of the unmeasured confounder *U* rather than selection in utero. Although it is unlikely that such large unmeasured confounders exist, researcher should consider the influence of collider-stratification bias when using left-truncated data within the context of their own studies.

Chapter Five: Bias in mediated associations

This chapter contributed to Aim 2 of the thesis and met Objective 2.3.

Aim 2: To design, implement and analyse a series of simulation studies to quantify the magnitude and direction of bias in perinatal outcomes to address issues from methodological challenges that may lead to spurious inference on associations between pregnancy exposures and adverse birth outcomes.

> **Objective 2.3:** To quantify the influence of unmeasured confounding in mediated associations.

The content of this chapter is covered by Publication Four. This study quantified the magnitude and direction of bias from unmeasured confounding in the association between maternal obesity and caesarean section delivery when mediated by the pregnancy complication of pre-eclampsia. This study is reproducible with published code and a full disclosure of the informing data parameters.

The version that appears in this thesis is of an article that has been submitted for peer-review to *Statistics in Medicine*. The contribution of co-authors, Professor Gavin Pereira, Dr Gizachew A. Tessema and Dr Amanuel T. Gebremedhin are detailed in the author attribution statements in Appendix A.

Supplementary material for this chapter are available in Appendix G.

5.1 Abstract

Background:

Bias from unmeasured confounding has the potential to distort mediated exposure-outcome associations. The aim of this simulation study was to quantify the influence of unmeasured confounding in the association between maternal obesity and caesarean section delivery when mediated by the pregnancy complication of pre-eclampsia.

Methods:

Bias from unmeasured confounding in the mediated association was simulated under three common scenarios: 1) mediator-outcome confounding, 2) mediator-outcome confounding affected by the exposure, and 3) exposure-mediator confounding. Using an observed cohort from Western Australia, we simulated data for a range of values for the prevalence of maternal obesity, pre-eclampsia, caesarean section delivery and an unmeasured confounder *U*. We also simulated the odds ratio for the selection effects (maternal obesity → pre-eclampsia, maternal obesity → *U*, pre-eclampsia → caesarean section delivery, *U* → maternal obesity, *U* → pre-eclampsia, *U* → caesarean section delivery) based on realistic assumptions drawn from the observed cohort and prior published literature.

Results:

Overall, we found the strongest bias due to exposure-mediator confounding, producing an upward bias that increased with the prevalence and the strength of *U*. Bias due to mediator-outcome confounding was minimal; however, when we simulated the mediator-outcome confounding affected by the exposure, there was evidence of an upward bias.

Conclusion:

In all three scenarios, the influence of bias from unmeasured confounding association between maternal obesity and caesarean section when mediated by pre-eclampsia was dependent on the prevalence and the strength of the unmeasured confounder *U*. Bias was strongest in scenarios in which there was an association between maternal obesity and the unmeasured confounder *U.*

5.2 Introduction

There is a strong association between maternal obesity and having a caesarean section delivery.[248, 249] However, it is likely that the true association is mediated by other pregnancy complications that are on the causal pathway between the exposure of maternal obesity and the outcome of caesarean section delivery.[250, 251] Determining the true association between exposure and outcomes when there are mediating variables proves a statistical challenge for researchers.[77, 252, 253] For example, it is inadvisable to condition on a variable that occurs after the exposure, as that variable may have been caused by the exposure itself and may mediate the causal pathway between the exposure and the outcome.[84, 230] One solution to address this dilemma is the use of causal mediation analysis which is based on the assumption of temporal precedence of the exposure, mediator and the outcome, i.e. exposures precede the mediator and the mediator precedes the outcome.[252-254] However, one of the main limitations of causal mediation analysis is the reliance on strict assumptions, including the assumption of no unmeasured confounding.[252, 253, 255] Yet for many associations from etiological observational studies, there is likely to be at least some degree of confounding from variables that are unknown to the study or unobserved.[74] A recent review[256] of the application of mediation analysis methods used in observational epidemiological studies (published between 2015 and 2019) found that only three out of the 174 included studies undertook a sensitivity analysis for unmeasured confounding when mediation was the primary analysis. This might indicate the difficulty for researchers to apply methods, such as the application of the potential outcomes framework,[257] to address the influence of unmeasured confounders in mediated associations when conducting observational studies.

Although obesity *per se* is not acknowledged in clinical guidelines as an indication for caesarean section delivery,[258] the body of research to date has only focused on the total effect of maternal obesity on caesarean section delivery.[248-250, 259-266] That maternal obesity has been identified as an independent risk factor for caesarean section deliveries has significant implications due to the associated risks of surgical and anaesthetic complications.[258] After delivery, obese women (body mass index (BMI) ≥ 30 kg/m^2) are at increased risk of postpartum haemorrhage, post-partum anaemia, and endometriosis compared to mothers whose BMI is within the *normal* range (18.5 to 24.9 kg/m^2).[258] The risk of wound infection also doubles for every 5-unit

increase in BMI.[258] Thus, medical experts recommend caution when planning to undertake a caesarean section delivery in women with a high BMI (≥ 30 kg/m^2).[258] A systematic review and meta-analysis[249] suggested pregnancy complications of pre-eclampsia, gestational diabetes and macrosomia as possible mediators in the association between maternal obesity and caesarean section delivery. This simulation study will investigate the influence of unmeasured confounding on the association between maternal obesity and caesarean-section delivery when mediated by the pregnancy complication of pre-eclampsia. Pre-eclampsia is defined as the presence of hypertension or proteinuria in pregnancy,[25] and is strongly associated with maternal obesity[267] and caesarean section delivery.[268]

Mediation analysis is a relevant approach to determine the association between maternal obesity and caesarean section delivery when accounting from the influence of possible mediators but its value is limited in the presence of unmeasured confounding in the mediated associations. If unmeasured confounding is present, the estimates for the direct and indirect (mediated) effects may be over- or under-estimated. In such cases, where a potential unmeasured confounder affects the mediator and the outcome (known as mediator-outcome confounding), conditioning on the mediator (which acts as a collider as it is the common descendant of the exposure and the unmeasured confounder) can lead to a specious association.[231, 232] However, this phenomenon of collider bias due to unmeasured confounding can also materialise in the mediator-outcome confounding affected by the exposure and exposure-mediator confounding. The purpose of this simulation study was to quantify the magnitude and direction of the influence of unmeasured confounding on the association between maternal obesity and caesarean section delivery when mediated by the pregnancy complication of pre-eclampsia, under three common scenarios: 1) mediator-outcome confounding, 2) mediator-outcome confounding affected by the exposure, and 3) exposure-mediator confounding.

5.3 Methods

We quantified the magnitude and direction of bias resulting from the influence of unmeasured confounding in the association between the exposure (maternal obesity) and the outcome (caesarean section delivery) when mediated by a pregnancy complication (pre-eclampsia) under three scenarios: 1) mediator-outcome

confounding, 2) mediator-outcome confounding affected by the exposure, and 3) exposure-mediator confounding. As per the World Health Organization criteria,[269] we defined the exposure of maternal obesity as a BMI greater than or equal to 30 kg/m^2.

Observed cohort

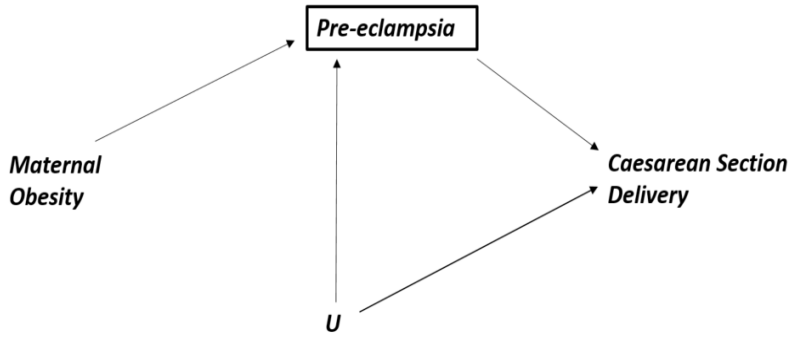
Our simulation cohort was derived from an observed cohort in Western Australia, which provided data on maternal obesity, pre-eclampsia and caesarean section delivery. The observed cohort consisted of women who had a singleton birth between 2012 and 2015 (n = 128,167) and was obtained from the Midwives Notification System, a de-identified and validated dataset containing all births in Western Australia with either a gestational length ≥ 20 gestational weeks or a birth weight > 400 grams.[212] The data was limited to collection from the period 2012-2015 as data on maternal height and maternal weight were unavailable prior to that period. Therefore, we were only able to directly estimate BMI and thereby derive obesity (BMI ≥ 30 kg/m^2) for the period 2012-2015. We identified hospitalisation records from the Hospital Morbidity Data Collection for West Australia using the Australian Modification of International Classification of Diseases (pre-eclampsia ICD-9:624.4, 624.5, 624.7 and ICD-10:011, 014; caesarean section delivery ICD-9:669.7 and ICD-10:O82) coded diagnostic information for pre-eclampsia and caesarean section delivery.[214]

Bias structure

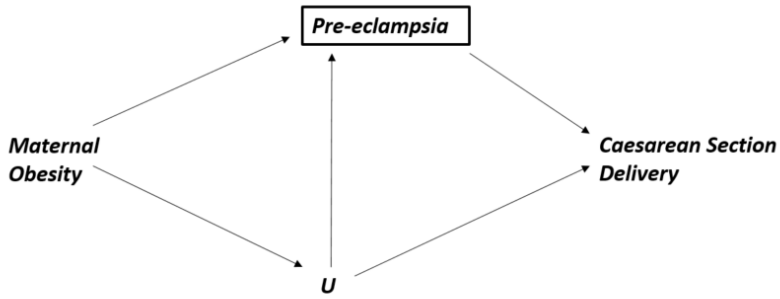
The causal diagram (Figure 5.1) illustrates the bias mechanisms resulting from the influence of unmeasured confounding when we adjust for a mediator variable under the three scenarios: 1) mediator-outcome confounding (Figure 5.1a); 2) mediator-outcome confounding affected by the exposure (Figure 5.1b); and 3) exposure-mediator confounding (Figure 5.1c). In Figure 1a, an unmeasured confounder *U* is causally associated with increased risk of pre-eclampsia and the outcome of caesarean section delivery. Here, both maternal obesity exposure and the unmeasured confounder *U* independently affect pre-eclampsia, rendering it a collider variable. Thus, by adjusting for pre-eclampsia in a model, a back-door pathway is opened from maternal obesity to caesarean section delivery through the mediator pre-eclampsia and the unknown confounder *U*. This bias is commonly known as *collider bias* and leads to inflation or deflation of the exposure on the outcome due to mediator-outcome confounding. Figure 5.1b is an extension of Figure 5.1a with an additional

unidirectional association between the exposure and *U* in conjunction with mediator-outcome confounding. In Figure 5.1c, there is exposure-mediator confounding when *U* affects both the exposure and the mediator. Here there is no direct influence *U* on the outcome. In all three scenarios, the influence of the unmeasured confounding *U* and the exposure variable on the mediator of pre-eclampsia have led to a *collider bias* mechanism, which has the potential to distort the observed effect.

(a) mediator-outcome confounding



(b) mediator-outcome confounding affected by the exposure



(c) exposure-mediator confounding

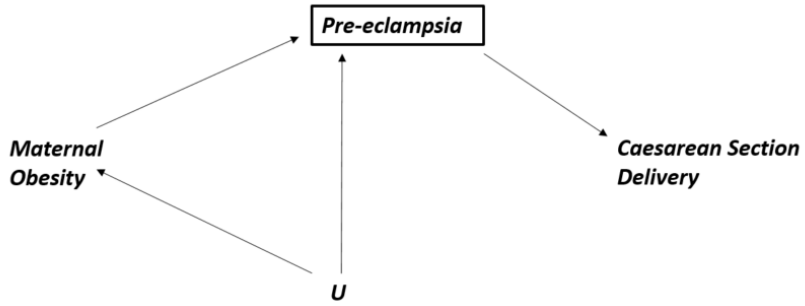


Figure 5.1 (a-c). Directed acyclic graphs representing the collider bias in the association between obesity and caesarean section delivery when mediated by the pregnancy complication of pre-eclampsia and in the presence of an influencing unmeasured confounding *U.*

Simulation

To quantify the influence of the *collider bias* on the mediated association between maternal obesity and caesarean section delivery, we simulated a population of 128,000 conceptions, which was approximately the number of births in the observed cohort during the study period (2012-2015). We generated data for the maternal obesity exposure *OB*, the mediator pre-eclampsia *PE*, an unmeasured confounder *U*, and the outcome of caesarean section delivery *CS*. All variables were binary. The baseline prevalence of maternal obesity *OB* was derived from a binomial distribution with a probability of 20% based on the observed cohort. The baseline prevalence of *CS* was set to 34.5% to reflect the incidence of caesarean section delivery *CS* in the observed cohort. We set the prevalence of *U* (π_U) to 0.15, 0.30 and 0.50, to reflect a range of potential conditions.

We considered each causal pathway as selection effects [*OB* → *PE*, *PE* →*CS*, *U* → *PE*, *U* → *CS, OB* →*U,* and *U*→*OB*], which were modelled in terms of odds ratios (ORs), with simulation probabilities bounded between 0 and 1. The selection effects of [*OB* → *PE*, *PE* →*CS*] were ORs derived from the observed cohort. Selection effects [*U*→*PE*, *U*→*CS, OB* →*U,* and *U*→*OB*] for the influence of the unmeasured confounder *U* were varied and set to an equal OR of 1.5, 2.5 and 3.5. The probability of *PE* was estimated using the formulae:

$$P(PE \mid OB, U) = \frac{\exp(\beta_0 + \beta_1 OB + \beta_2 U)}{1 + \exp(\beta_0 + \beta_1 OB + \beta_2 U)}$$

(Scenario 1)

$$P(PE \mid OB, U) = \frac{\exp(\beta_0 + \beta_1 OB + \beta_2 U + \beta_3 OB.U)}{1 + \exp(\beta_0 + \beta_1 OB + \beta_2 U + \beta_3 OB.U)}$$

(Scenario 2 and 3)

As we are only interested in quantifying the influence of bias from unmeasured confounding (indirect association), we assumed a true null direct effect of maternal obesity *OB* on caesarean section delivery *CS* (i.e. there is no direct causal effect of *OB* → *CS* in the causal diagram in Figure 5.1). The probability formula for the outcome of caesarean section delivery is presented below for scenarios 1 and 2:

$$P(CS \mid PE, U) = \frac{\exp(\gamma_0 + \gamma_1 PE + \gamma_1 U)}{1 + \exp(\gamma_0 + \gamma_1 PE + \gamma_1 U)}$$

The probability formula for the outcome of caesarean section delivery for scenario 3 is:

$$P(CS \mid PE, U) = \frac{\exp(\gamma_0 + \gamma_1 PE)}{1 + \exp(\gamma_0 + \gamma_1 PE)}$$

Analysis

We performed logistic regression of caesarean section delivery *CS* with maternal obesity *OB* when mediated by pre-eclampsia *PE* to obtain ORs in the simulated population. To obtain the ORs, we exponentiated the mean of the point estimates obtained from 100 iterations for each scenario, which represent the ORs for the effect of *OB* on *CS* when mediated by pre-eclampsia *PE*. Percentile-based 95% simulation intervals (SI) of the OR mean were derived using 500 bootstrap replicates. The collider bias was examined under a range of plausible assumptions by varying the selection effects ($OR_{U.PE}$, $OR_{U.CS}$, $OR_{OB.U}$, $OR_{U.OB}$, and $OR_{OB.U}$) and the prevalence of *U* as described above. This simulation models were conducted under the null hypothesis of no direct causal effect of maternal obesity *OB* on caesarean section delivery *CS*. As such, we interpreted the results that the greater the departure of OR from 1, the greater the magnitude of the bias. All data analyses and simulations were conducted using R v4.0.5.[239] Reproducible code for each scenario is available in the supplementary materials.

5.4 Results

Overall, we found that bias resulting from the influence of unmeasured confounding increased across each of the scenarios from mediator-outcome confounding to mediator-outcome confounding affected by the exposure, with the strongest bias results from exposure-mediator confounding. When we simulated mediator-outcome confounding in the association between maternal obesity and caesarean-section delivery, we found that the magnitude of bias was generally weak and in an upward direction (Figure 5.2). For example, the $OR_{CS\sim O|PE,U}$ was 1.03 (95% SI 1.03 to 1.03) with input parameters of π_U=0.15, OR_{UPE}=1.5, OR_{UCS}=1.5. The magnitude of the bias did not increase until input parameters were set to π_U=0.50, OR_{UPE}=3.5, OR_{UCS}=3.5, producing the maximum result of $OR_{OCS|PE}$ 1.04 (95% SI 1.04 to 1.05).

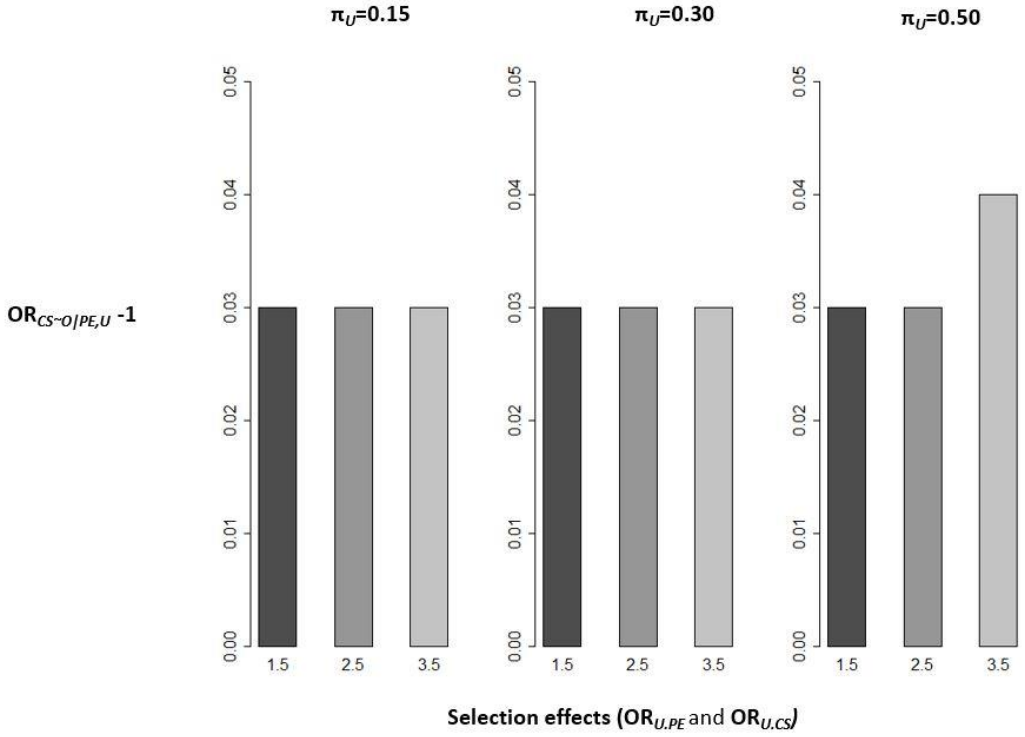


Figure 5.2 Collider bias of $OR_{CS\sim O|PE,U}$ -1 under the true null effect of maternal obesity *OB* on caesarean section delivery *CS* when mediated by pre-eclampsia *PE* and the presence of one unmeasured confounder *U* (Scenario 1: mediator-outcome confounding). Bias represents the departure from the null. Average odds ratio $OR_{CS\sim O|PE,U}$ with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects $OR_{U.PE}$ and $OR_{U.CS}$ (1.5, 2.5, 3.5). Each scenario was iterated 100 times.

There was stronger evidence of upwards bias when we extended scenario 1 to include the influence of the exposure on the unmeasured confounder (scenario 2) (Figure 5.3). Here, the minimum bias for $OR_{CS\sim O|PE,U}$ was 1.04 (95% SI 1.03 to 1.04) with input parameters of π_U=0.15, $OR_{U.PE}$=1.5, $OR_{U.CS}$=1.5. The magnitude of the bias increased when the prevalence of the unmeasured confounder *U* and the strength of the selection effects ($OR_{UPE,}$ OR_{UCS} and OR_{EU}) increased. This produced a strong biased $OR_{OCS|PE,U}$ of 1.10 (95% SI 1.09 to 1.10) when the parameters were set to π_U=0.50, $OR_{U.PE}$=3.5, $OR_{U.CS}$=3.5 and $OR_{PE.U}$=3.5.

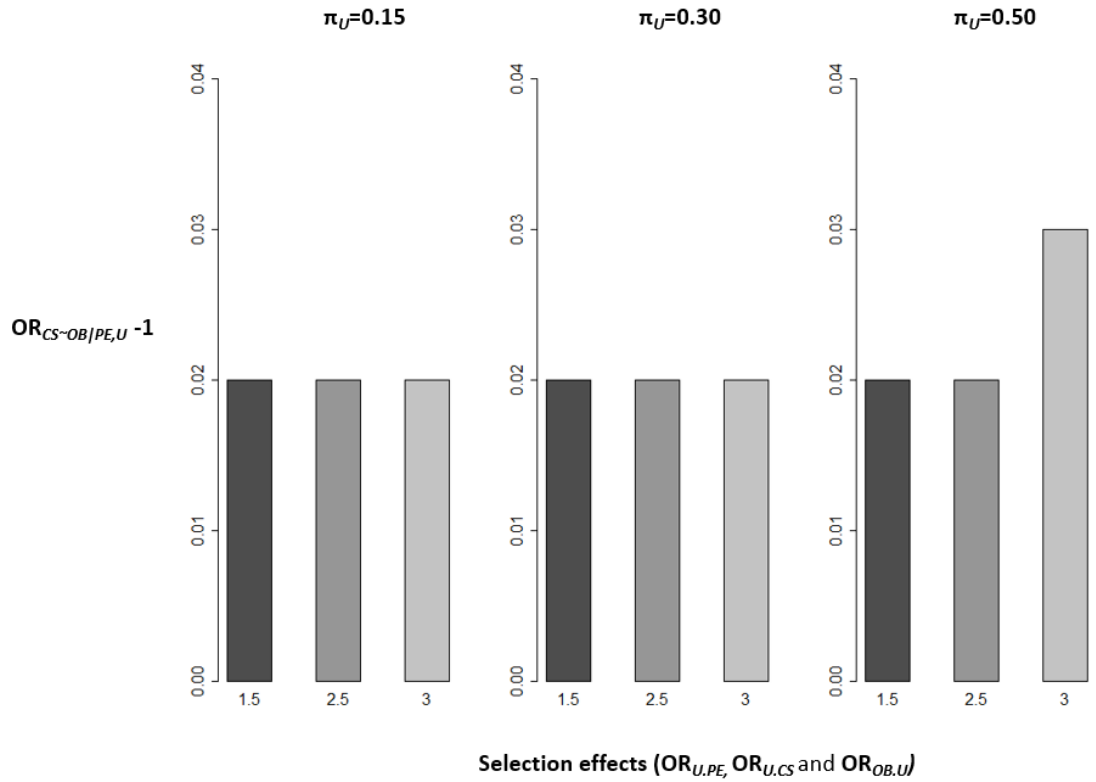


Figure 5.3. Collider bias of OR $_{CS\sim OB|PE,U}$ -1 under the true null effect of maternal obesity *OB* on caesarean section delivery *CS* when mediated by pre-eclampsia *PE* and the presence of one unmeasured confounder *U* (Scenario 2: mediator-outcome confounding when affected by the exposure). Bias represents the departure from the null. Average odds ratio OR $_{CS\sim O|PE}$ with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects $OR_{U.PE,}$ $OR_{U.CS}$ *and* $OR_{OB.U}$ (1.5, 2.5, 3.5). Each scenario was iterated 100 times.

Scenario 3 (exposure-mediator confounding) produced the strongest evidence of upwards bias from the influence of unmeasured confounding in the mediated association between maternal obesity and caesarean-section delivery. For example, the $OR_{CS\sim O|PE}$ was 1.04 (95% SI 1.04 to 1.04) with input parameters of $OR_{U.PE}$=1.5,

$OR_{U.OB}$=1.5 and when the π_U was 0.15 and 0.30. The strongest evidence of bias occurred when the input parameters were set to π_U=0.50, $OR_{U.PE}$=3.5, $OR_{U.OB}$=3.5, producing the maximum result of $OR_{CS\sim O|PE}$ 1.17 (95% SI 1.17 to 1.18). Results for each scenario are presented in tabular format in the supplementary materials.

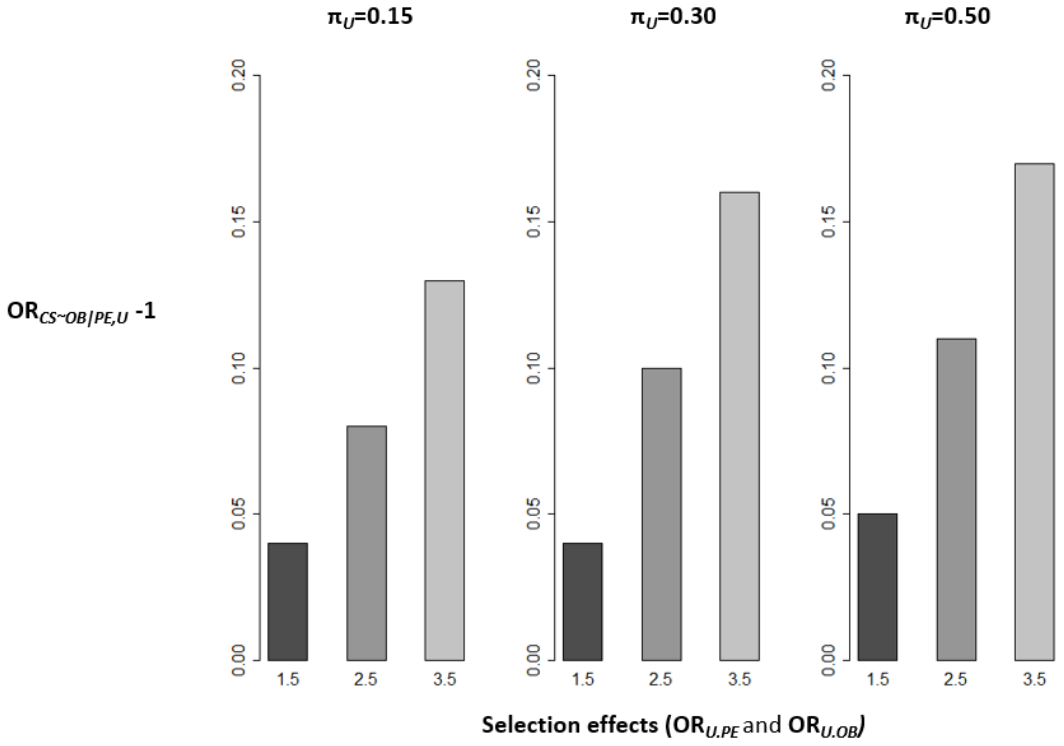


Figure 5.4 Collider bias of OR $_{CS\sim O|PE}$ -1 under the true null effect of maternal obesity *OB* on caesarean section delivery *CS* when mediated by pre-eclampsia *PE* and the presence of one unmeasured confounder *U* (Scenario 3: exposure-mediator confounding). Bias represents the departure from the null. Average odds ratio OR $_{CS\sim O|PE}$ with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects $OR_{U.PE}$ and $OR_{U.OB}$ (1.5, 2.5, 3.5). Each scenario was iterated 100 times.

5.5 Discussion

To increase our understanding of exposure-outcome associations in epidemiological studies, we must disentangle potential causal pathways that link exposures with outcomes. Despite the strong assumptions required, causal mediation analysis continues to be a commonly applied tool, leading to uncertainty of the validity of results reported by causal mediation analysis studies. As assumptions about unmeasured confounders cannot be tested using observed data, simulations are a powerful tool to

determine the influence of bias due to confounding in epidemiological associations. The purpose of this simulation study was to quantify the magnitude and direction of bias in mediated associations due to the influence of unmeasured confounding under three common scenarios. The strongest bias was evident when we considered the influence of exposure-mediator confounding on the mediated association between maternal obesity and caesarean section delivery. The bias was marginal under mediator-outcome confounding, however, it increased when there was an effect of the exposure on the mediator-outcome confounding. Overall, we found that the strength of the bias in the mediation associations was influenced by the prevalence and strength of the influencing unmeasured confounder *U*.

The prevalence of obesity in women of reproductive ages is increasing globally, significantly impacting maternal and perinatal outcomes in women when they enter pregnancy with a higher BMI.[9] In parallel, caesarean section delivery rates are also increasingly common, having risen by 14% globally since 1990.[270] As of 2014, Australia had a caesarean section delivery rate of 34 per 100 live births, exceeding the OECD (Organisation for Economic Co-operation and Development) average of 28 per 100 live births.[271] This has also been evidenced in Western Australia, with the incidence of caesarean section delivery of 34.8% in our observed cohort. In 2019, a group of experts in the US proposed a framework[272] for the impact of maternal obesity on the risk of caesarean section delivery in which they posited that obesity operates through potential mediating pathways including but not limited to pregnancy complications and pregnancy comorbidities. Our simulation study examined one potential causal pathway via the pregnancy complication of pre-eclampsia, the most common reason for therapeutic interruption of pregnancy.[268] Maternal obesity is a risk factor for all types of pre-eclampsia, with a raise in BMI increasing the risk, from mild to severe forms.[267] There are a number of potential influencing factors in the inter-related relationship between maternal obesity, pre-eclampsia and caesarean section delivery that are not necessarily readily available to researchers when conducting a mediation analysis. One such plausible factor is leptin, a hormone that is secreted from adipose tissue that is controlled by the obesity gene,[273] with increasing percent of body fat associated with increasing concentrations of leptin. Leptin also plays an important role during pregnancy with the placenta producing leptin, thereby high levels of maternal leptin levels in obesity can adversely impact fetal growth and development.[274]

Furthermore, leptin can inhibit the intensity and frequency of myometrial contractions which can lead to caesarean-section delivery.[275] As leptin concentrations are higher in women with pre-eclampsia,[276] leptin is a potential unmeasured influencing factor in scenario 1 and 2. Another plausible factor worth considering is maternal deficit in dietary intake, particularly in calcium, protein, essential vitamins and essential fatty acids.[267] Maternal obesity is associated with insulin resistance and systemic inflammation, mechanisms that are conductive to pre-eclampsia, supporting scenario 3. As the physiology of pregnancy is complicated, it is possible that there are other factors that are impactful on the association between the exposure of maternal obesity, the outcome of caesarean section delivery and the mediator of pre-eclampsia that remain unknown or are yet to be fully elucidated.

As the presence of unmeasured confounding can rarely be ruled out in epidemiological associations,[74] quantifying the influence of bias from unmeasured confounding is essential to increase our understanding of causal effects in mediated associations. Simulation is a valuable tool to advance our understanding of the influence of bias in such mediated associations,[234] as through the data generation process it is possible to examine multiple scenarios in which bias can be corrected for. Simulation studies been used to test bias resulting from misclassification of variables in mediation analysis.[277-282] In more recent years, a number of bias methods have been proposed to explore the sensitivity of mediation analysis to the influence of unmeasured confounding;[252, 253, 255, 283-287] however, many of these methods have focused on mediator-outcome confounding[255, 283, 285, 287] or are often reliant on specific assumptions.[284, 286] In this study, we have simulated models in which the effect of the unmeasured confounding on the outcome given the exposure and mediator, and the relationship between each variable is pre-specified, based on assumptions drawn from an observed cohort or published literature. We found that the mediated association was more sensitive to the influence of the unmeasured confounder from the exposure-mediator compared to the mediator-outcome, a finding that was shared with simulation study[281] that undertook a sensitivity analysis of the influence of unmeasured confounding on the direct and indirect effects. As it is not uncommon for the effect of a pregnancy exposure on an outcome to be mediated through a complication of pregnancy, this simulation model can be applied to other perinatal epidemiological associations.

Quite often in perinatal epidemiology, the association between maternal exposures and adverse outcomes are mediated by other complications. The influence of unmeasured confounders can create a *collider bias* mechanism that has the potential to distort the mediated association. Quantifying the influence of this bias cannot be undertaken using observational data, therefore simulations studies such as this, enable the quantification of the influence of unmeasured confounding under a number of scenarios that replicate real world examples. The simulations here evaluated the sensitivity of unmeasured mediator-outcome, mediator-outcome when affected by the exposure and exposure-mediator confounding. However, a limitation of these simulations is that they are based on simple scenarios, the most prominent is that there is only one mediator variable in each of the scenarios. However, we undertook the simulations under strong associations (high prevalence and strength of the influence of the unmeasured confounder *U*) which would also be taken to represent the influence of multiple mediators. Additionally, to minimise the complexity and maintain the interpretability of the simulation scenarios, we assumed that there was no misclassification in any of the variables and that all variables were binary. Finally, like any metric, BMI is an imperfect as a measure to determine maternal obesity and adiposity[288] but is relevant to this topic and has been almost universally adopted in past studies.

In this simulation study, we calculated the effect of maternal obesity on caesarean section delivery in the presence of a mediator of pre-eclampsia and the influence of an unmeasured confounder *U*. In our three simulation scenarios, the influence of the unmeasured confounder *U* created a collider of the mediator of pre-eclampsia, leading to biased estimates in the mediated exposure-outcome association. We found evidence of bias across all three scenarios, with the strongest evidence due to the influence of exposure-mediator confounding, which was closely followed by the mediator-outcome confounding affected by the exposure. Further, we found that the strength of the bias was directly related to the prevalence and strength to the unmeasured confounder, with the weakest evidence of bias presenting when the prevalence of the unmeasured confounder was small (15%) and the strength of the OR was minimal (OR 1.5) across all three scenarios. We recommend that all researchers undertake analysis to investigate the mechanisms in which the influence

of unmeasured confounding can impact their mediated exposure-outcome associations, in addition to causal mediation analysis.

Chapter Six: A framework to apply simulation to bias analysis

This chapter fulfilled Aim 3 and objective 3.1 of the thesis.

Aim 3: To develop a framework for the application of simulation to quantify bias in perinatal epidemiologists.

> **Objective 3.1:** To incorporate best practice for the application of simulation methods to quantify the influence of bias into a framework to guide researchers in the design, implementation, analysis and reporting of simulation studies in perinatal epidemiology.

The content of this chapter is covered by Publication Five. This study provides a framework to guide epidemiologists in the design, implementation and reporting of simulation studies with the prime purpose of quantifying the influence of bias in aetiological associations. This framework includes a simulation study to demonstrate the application of the framework to quantify bias in the association between maternal BMI and preterm birth. This chapter was written in the style of an educational note, translating the simulation methods applied in this thesis through the provision of an education tool for epidemiologists in the application of simulation to quantify the influence of bias.

The version that appears in this thesis is of an article that has been submitted for peer-review to *European Journal of Epidemiology.* The contribution of co-authors, Professor Gavin Pereira and Dr Gizachew A. Tessema are detailed in the author attribution statements in Appendix A.

Supplementary material for this manuscript is available in **Error! Reference source not found.**H.

6.1 Abstract

Due to the observational nature of epidemiological studies, they are prone to one or more type of bias (information, selection, confounding). In particular, reproductive and perinatal epidemiological studies are subject to unique methodological challenges due to unobservable events from pre-conception to birth and the clustering of outcomes across successive pregnancies or multiple births. Therefore, to strengthen the validity of associations drawn from observational studies, it is important that researchers are able to identify and evaluate potential sources of bias.

Simulations studies involve computational methods to create data by pseudo-random sampling. They are ideal to quantify bias as the process of generating data allows greater control of the biased parameters of interest. Commonly used to test statistical methods, simulation studies are under-used in epidemiology, yet have the potential to quantify the influence of a range of biases simultaneously on aetiological associations. Current simulation studies in reproductive and perinatal epidemiology lack uniformity in their design, analysis, and reporting. The absence of guidance in the application of simulation to quantify the influence of bias has hampered researchers and peer reviewers.

This paper proposes a framework to guide epidemiologists in the application of simulation studies to quantify the magnitude and direction of biases in epidemiological studies. Using a perinatal example, we applied the framework to a simple simulation that quantified the influence of selection bias on the association between maternal BMI and preterm birth. This framework was aimed with highlighting the application of simulation methods to quantify the influence of various types of bias common in observational research, and to increase their application in the practice of quantitative bias analysis in epidemiological studies.

6.2 Introduction

Due to the non-random nature of observational studies, they are prone to various biases.[56] A great deal of literature has been published to increase the understanding of the influence of bias in observational studies,[74, 117, 158, 170, 231, 232, 289] including the development of methods to minimise their influence.[119, 122, 290-292] However, much less consideration has been given to quantifying the influence of bias on reported exposure-outcome associations.[293] To strengthen the validity of associations drawn from observational studies, researchers need to be able to identify and evaluate potential sources of bias. Simulation studies are one method that can aid researchers in quantifying the influence of bias in aetiological associations. In short, simulations are computational methods that allow greater control when generating important bias parameters. This enables researchers to create models that represent complex real-life conditions, which can then be tested under a range of scenarios. However, a potential barrier to the application of simulation studies in epidemiology is its seemingly complicated application and the lack of guidance in their design, implementation and reporting.

Research conducted by Lash *et al*.[147-150, 169] propagated the term *quantitative bias analysis* in epidemiology. Their 2014 paper[147] provided a list of best practices when quantifying the influence of bias. The same authors later developed an online tool in which epidemiologist can assign plausible values to bias parameters in order to determine the influence of bias.[148] Despite the diligent guidance of Lash *et al.,* the uptake of quantitative bias analysis methods in epidemiology has remained low with a recent systematic review identifying only 24 standalone bias analysis studies that applied their framework over a 14 years period.[195] Although it should be noted that a further 123 undertook a bias analysis as a secondary analysis which is encouraging;[195] however, these numbers are overshadowed by the vast number of epidemiological studies published in the same period. A more recent paper[155] published by the same research group, critiqued three examples of what the authors deemed suboptimal bias analysis studies. Here, the authors noted that attention to good practices in the presentation, explanation and interpretation of bias remains lacking.[155] We concur with their statements and believe that quantitative bias analysis is a worthwhile endeavour that should be undertaken to strengthen the validity of epidemiological studies.

Some of the limitations of the early *quantitative bias analysis* methods was the assertion that bias should only be analysed under recommended situations, such that the findings of a study were informing policy development or when it was expected that bias could explain away a finding.[147] It is the assertion of the authors of this paper that bias should be quantified if there is plausibility of an influence on exposure-outcome associations that may alter inference. The application of a causal diagram will be sufficient to determine if there is any such influence. Simulation methods also enable the quantification of multiple types of bias simultaneously, moving away from the need to prioritised the quantification of bias by the order of the most influential factor.[147] However, the design of high-quality simulations that reflect complex situations that lead to biased exposure-outcome associations can be challenging for researchers. Furthermore, assessing the integrity of published simulation studies is both challenging for reviewers and other researchers. Simulation studies and concerns about their reporting has been an issue for a long time, with the first paper guiding the reporting of computational statistical results published in 1975.[296] Since then, there have been several papers guiding researchers to improve the planning, implementation, and reporting of their simulation studies with the specific aim of testing or comparing statistical methods.[139, 143-145] The STRengthening Analytical Thinking for Observational Studies (STRATOS) group[140] was created to meet the increased interest in the application of simulation in statistical methodology. This initiative has a broad interest in the application of statistical simulation in health research.[146] A 2018 paper by Morris *et al*.,[139] produced a primer of a detailed systematic approach to planning simulation studies for the purpose of testing statistical methods.[139] A more recent paper provided a tutorial on generating Monte Carlo simulations in epidemiology for quantitative bias analysis; however, a framework to guide researchers and reviewers on the application of simulation methods for the prime purpose of quantifying the influence of bias in epidemiological modelling remains lacking.[234]

Simulation as a method for quantitative bias analysis has the potential to assess the influence of multiple types of bias through the design, implementation and analysis of simulation models that reflect true causal pathways between exposures and outcomes. One of the main benefits of simulation studies in epidemiology is the ability to conduct numerous experiments on the complex causal pathway between exposures

and outcomes to ascertain the magnitude and direction of multiple biases. Technological advances in recent decades have led to improved computation speed at a lower cost, with complex simulations being able to run on hardware that is easily accessible, which in theory should have supported the increased adoption of simulation studies in epidemiology. In order for researchers to become more confident in the application of simulation to quantify the influence of multiple biases across a range of epidemiological research questions, a unifying framework of quantitative bias analysis methods and simulation methods is required. The purpose of this paper is to introduce epidemiologists to the benefits of using simulation studies to quantify the magnitude and direction of biases. Building on the prior work of experts in simulation modelling and quantitative bias analysis methods, we aim to provide a primer framework to guide researchers on the design, implementation, analysis, and reporting of simulation studies for the prime purpose of quantitative bias analysis.

6.3 Framework

As with any other study, when planning a simulation study to quantify bias, researchers should first produce a protocol detailing how the study will be designed, implemented, and analysed for transparency and to facilitate understanding. A good simulation study protocol should document the specific aims of the studies, a graphical display of the causal association, the procedures for generating data, details of how the study will be implemented, analysed and reported, and the simulation source code to support the reproducibility of the study. The framework proposed here will provide guidance to epidemiologists to quantify the magnitude and direction of potential biases that undermine the validity of exposure-outcome associations. See Figure 6.1 for the proposed framework on the design, implementation, analysis, and reporting of simulation studies to quantify the influence of bias. This framework was informed by the findings of the previously published review of the application of simulation to quantify bias in reproductive and perinatal epidemiology[234] and drew inspiration from previously published frameworks for bias analysis[147, 297] or simulation studies to test and compare statistical methods.[137-139, 146]

The framework is supported by a demonstrated simulation example of selection bias in perinatal epidemiology. All observational studies are prone to bias; however, selection bias is particularly problematic in perinatal epidemiology. A major challenge

for researchers is that the study population itself is difficult to define as only pregnancies to fertile couples can be observed.[157] Furthermore, by a time when pregnancy is recognised an extensive attrition of the conceptions has already occurred[62] due to spontaneous and induced abortions. Further compounding this selection bias, is that most epidemiologists rely on birth data obtained from administrate databases that are left truncated,[294] with selection into a study restricted to those pregnancies that survive pass a specified gestational age; ranging from 16 gestational weeks in Nordic countries to 28 gestational weeks in low and middle-income countries.[60]

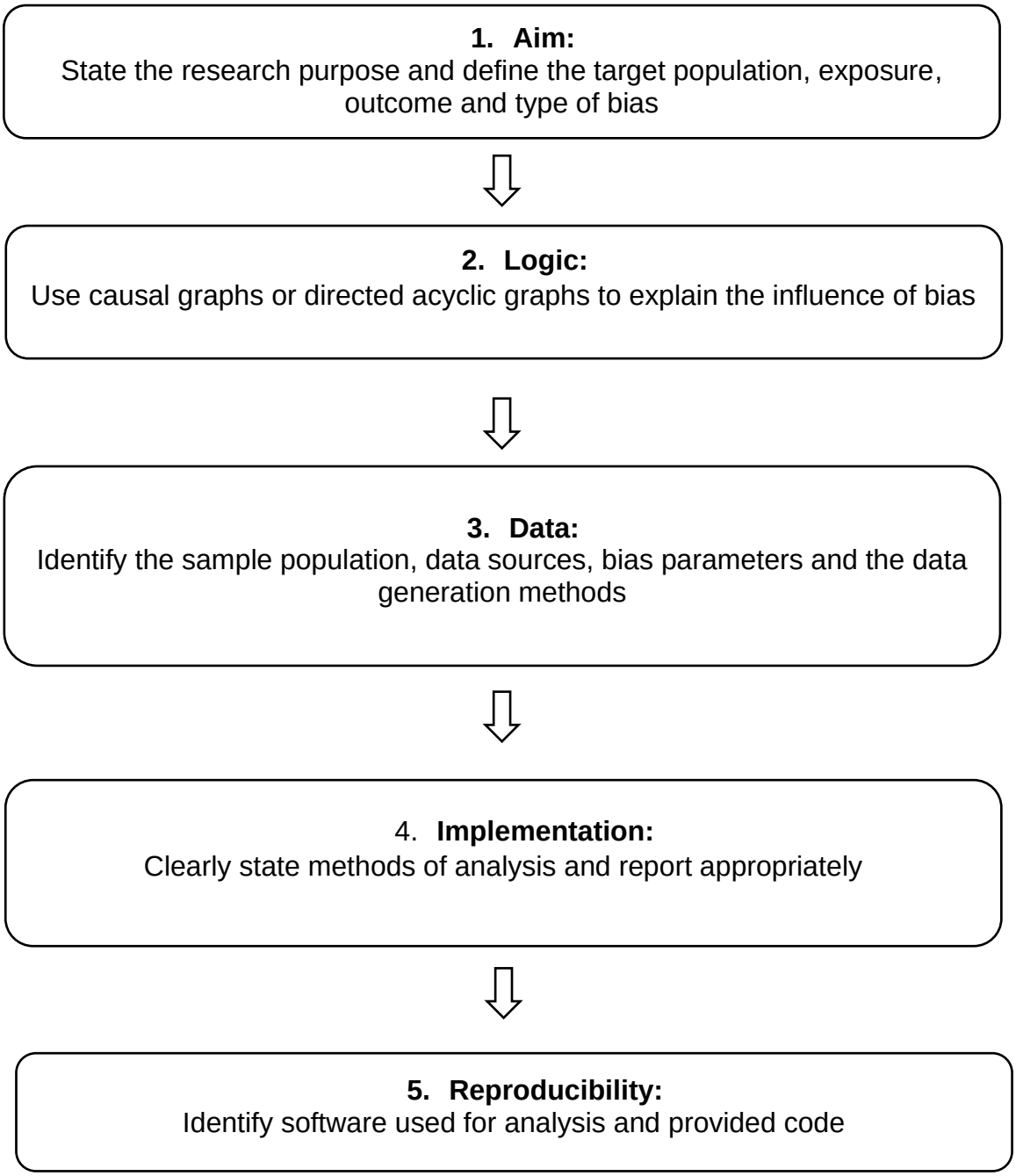


Figure 6.1 Flowchart of the framework for applying simulation to quantifying bias in observational studies.

1. Aim

State the research purpose, define exposure and outcomes, the target population and, the types of bias(es) to be quantified

1.1 Purpose of the simulation – explain the background and clearly state the aim of the simulation in the research study

1.2 Exposure(s) and outcome(s) – define the exposure and outcomes which will be included in the simulation model

1.3 Target population – clearly define the population of interest to the study

1.4 Type(s) of bias – state the types of bias that the simulation model will be quantifying

The simulation study should have clearly defined aims that are established prior to commencement of the study. The overarching purpose of a simulation study for bias analysis requires detailed description of the types of biases to be quantified. The aims should also clearly state the research question of interest and the target population. It should also include a defined exposure, outcome and any other variables that are considered on the causal pathway between the exposure and outcome when quantifying bias.

2. Logic

Use causal diagrams to explain the influence of bias

2.1 Graphs – describe the influence of bias using causal diagrams or direct acyclic graphs.

It would be remiss of any researcher that aims to undertake a simulation study to omit a causal diagram that conceptualises the causal associations between each of the relevant variables (exposure, outcomes and other variables). The most popular graphical tool for causal diagrams is directed acyclic graphs (DAGs).[298] DAGs provide researchers with a tool to graphically represent and increase understanding of causal associations between exposures and outcomes.[299] Akin to conceptual diagrams, DAGs operate with formal rules which define causal effect and increase the identification of bias.[293] Each variable is depicted as nodes, which are connected to each other by unidirectional arrows or arcs to depict the hypothesised relationships between them.[293, 300] The arrow between two nodes assumed the existence and direction of a causal relationship; however, it does not denote the magnitude nor the direction (i.e. positive or negative) of that relationship.[293, 300] A DAG is considered *acyclic* as no variable (node) can cause itself at a particular moment in time.[293, 300] Further, DAGs are not able to determine if the causal relationship is linear or non-linear, nor if the relationship is parametric or not. The absence of a direct effect of one

variable on another is evidenced by the absence of an arrow between them.[301] However, it is important to note that the arrows themselves are not completely deterministic. In perinatal research questions this would mean that not all women who are exposed will experience an outcome, rather that the exposure is hypothesised to cause the outcome in at least some of the women.[299]

The benefit of using a tool like DAGs is that they make unstated relationships between variables explicit. This can help researchers to decide which variables to collect, which variables to adjust for, to differentiate between a confounder and a collider and to identify the sources of bias.[76, 82] A recent review [6] of the application of DAGs to identify confounders in applied health research noted inconsistencies in reporting of technical details (target estimand(s) of interest, the DAG and the DAG-implied adjustment sets). The authors then identified eight recommendations for the application of DAGs to improve utility and transparency.[6] Tools that enables the application of DAGs include the popular online user-friendly interface of DAGitty and the DAGitty R software packages.[302] Modules for the application of DAGs are also available in STATA.

3. Data

Identify the sample population, data sources, bias parameters and the data generation methods

3.1 Population – provide clear details of the base population

3.2 Data sources – clearly state the data sources that inform the simulation. This could be an observed cohort or data from previously published literature.

3.3 Bias parameters – provide the parameters applied to the model that drive the influence of the bias

3.4 Data generation – report how probability distributions were assigned to the bias parameters

As one of the main benefits of simulation studies is their ability to quantify the influences of multiple types of biases under different scenarios; an important step in producing a valid study is the explicit description of the data generating mechanisms for each variable. These data-generating mechanisms are based on the causal diagram or a previously created DAG. The pre-specified assumptions that inform this data generation could be derived from an observed cohort or based on prior published

research. To ensure the transportability of bias parameters that inform the simulation model, it is important that the sources of these assumptions are explicitly stated and described in detail. If the simulated dataset is derived from an observed cohort, important details of that observed cohort should be reported, including when the data was collected, by what means and the general characteristics of the sample, including whether the dataset has previously been validated.

Variables that are endogenous (i.e. changed by its relationship with another variable) should be represented by a probability formula. The distribution of all other variables is determined by variable type. For example, the researcher may assume that dichotomous variables are binomially distributed, and continuous variables are either normally or uniformly distributed. The relationships between each variable in the model must be specified and it is recommended to include probability distribution formulae for all endogenous variables. Data-generation can be undertaking using statistical software popular with epidemiologists such as SAS, STATA and R programming, including functions to facilitate the simulation of data. Alternatively, programming languages such as Python, C and C++ are also viable.

4. Implementation

Clearly state methods of analysis and report appropriately

4.1 Analysis – clearly state the analysis methods applied to the simulation. Details should include all methods, results, diagnostics, and code used during the implementation of the model.

4.2 Reporting results – restate the assumptions of the simulation and clearly report the results, focusing on whether the model explains the reported estimate.

As in standard epidemiological studies, the selection of an appropriate statistic is an important step that should be considered during the study design period. Regression modelling is one of the most commonly applied analysis methods in aetiological epidemiology.[303] Models include but are not limited to linear regression for continuous outcomes, logistic regression for binary outcomes, Cox regression for time-to-event data, and Poisson regression for frequencies and rates.[304] Prior to conducting the analysis, consideration should be given how to store estimates after each iteration. Researchers should also decide how they will summarise the estimates once all the

iterations have been performed. Simulation can generate a large amount of results that need to be summarised and displayed in a clear and concise manner, with graphical displays preferred over tabular format.[305] The number of times a simulation will be iterated should be considered a prior. The greater the number of iterations, the less random error will be present. However, an additional consideration in determining the number of iterations should be available computational power. After each simulation iteration has been performed and each estimate stored and summarised, it is necessary to evaluate the performance of the simulation model from different scenarios or observed data. Evaluating the performance of the simulation study to provide a meaningful measure of the influence of bias can be achieved by a comparison of the simulated vs observed data or comparison of different bias mechanism scenarios.

5. Reproducibility

Identify software used for analysis and provide source code

5.1 Model assumptions - if assumptions of the model are summarised in the methods section, use online appendices to elaborate on their details.

5.2 Software - the software used for data analysis should be highlighted in the methods, including and any relevant packages or functions.

5.3 Code sharing - all source code for the simulation should be made available online, preferably without necessitating a request from the researcher(s).

A cornerstone of scientific research is its replication. Scientific evidence is strengthened when important findings can be replicated by multiple independent researchers using different datasets.[194] However, in some circumstances replicating an epidemiological finding may be limited due to lack of generalisation across different demographic populations. Yet, a basic minimum any research study should be achieving is reproducibility, whereby independent researchers can test the reliability of a prior finding using the same data and methods.[306] However, reproducibility itself can only be achieved when the data, code, methodology and the software is available.[306] A recent review of the application of simulation in reproductive and

perinatal epidemiology found only six out of 39 simulation studies made their source code available online.[234]

6.4 An example of simulation to quantify the influence of bias

In this section, we present a simple simulation study that quantifies the influence of bias in the association between maternal body mass index (BMI) and preterm birth to demonstrate the application of the above framework. The methods applied in this study have been inspired by a previous published study that quantified selection bias in the association between maternal advancing age and stillbirth.[294] Each subsection of the framework is highlighted in the subsequent text.

Aim

The aim of this simulation study is to quantify the influence of selection bias (Framework: 1.1; 1.4) on the association between the exposure of maternal BMI and the outcome of preterm birth (Framework: 1.2) in pregnancies in Western Australia between 2012 and 2015 (Framework: 1.3).

Causal logic

The bias mechanism as illustrated in the causal diagram (Figure 6.2) results from the exclusion of miscarriage prior to 20 gestational weeks, a restriction commonly applied in birth datasets in high-income countries. The exposure of maternal BMI affects miscarriage, which is influenced by an unknown or unmeasured confounder *U* (possibly a genetic factor) that also influences the outcome of preterm birth. Here, the selection of pregnancies that survive beyond 20-gestational weeks induced a back-door causal pathway from the exposure to the outcome via the collider variable of miscarriage and *U*. Commonly known at the *collider-stratification bias*, the left truncation of pregnancy and birth studies can lead to distorted exposure-outcome associations (Framework: 2.1).

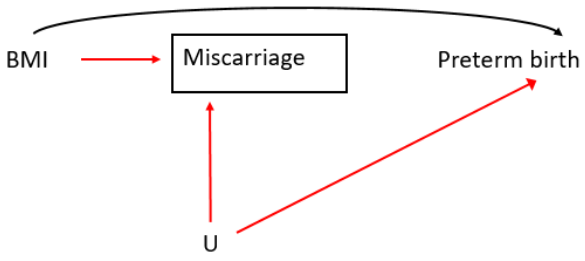


Figure 6.2 Directed acyclic graph depicting the causal structure of selection bias in the association between maternal body mass index (BMI) and preterm birth. Commonly referred to as *collider-stratification bias*, the exposure maternal BMI affects miscarriage, which is also affected by the independent risk factor *U*, inducing a back-door pathway between exposure and the outcome of preterm birth.

Data

The simulated data in study was derived from an observed birth cohort in Western Australia. It included all women (n= 124,806) who had a singleton birth between 2012 and 2015 (Framework: 3.1) derived from the Midwives Notification Systems, a de-identified and validated dataset that captures >99% of all births in the jurisdiction with a gestational age length ≥20 gestational weeks or a birth weight > 400 grams[212] (Framework: 3.2). We then simulated a population of 125,000 conceptions, with data generated for the variables of BMI, miscarriage, *U* and preterm birth. The baseline prevalence of miscarriage was set to 20%, which is a commonly reported statistic for pregnancy loss prior to 20 gestational weeks.[235] The baseline prevalence of BMI and preterm birth were derived from the observed birth cohort. The prevalence of *U* was varied from a low prevalence of 15% to 20%, 40% and 50%.

The causal pathway (highlighted in red) [BMI→ Miscarriage ← *U* → Preterm birth] represent the collider-stratification mechanism. We can further break this causal pathway down [BMI → Miscarriage, Miscarriage ← *U* and *U* → Preterm birth]. Each pathway can be deemed a *selection effect,* with a simulated probability bounded between 0 and 1. The selection effect BMI → Miscarriage was drawn from a Bernoulli model based on a study[307] that reported the effect of BMI on miscarriage using Australian data. The selection effects of *U* → Miscarriage and *U* → Preterm birth were modelled in terms of equal odds ratios from modestly strong to very strong effect: OR 1.5, 2.5, 3.5 (Framework: 3.3).

The probability formula (Framework: 3.4) for miscarriage for each conception in the study can be represented by the below equation where *BMI* represent BMI, *M* miscarriage and *U* the unmeasured confounder:

$$P(M \mid BMI, U) = \frac{\exp\left(\beta_0 + \beta_1 BMI + \beta_2 U\right)}{1 + \exp\left(\beta_0 + \beta_1 BMI + \beta_2 U\right)}$$

As we are only interested in quantifying the influence of bias, we assumed a true null effect of BMI on preterm birth in this simulated example. Therefore, the probability

formula for the outcome of preterm birth is represented by the below formula (Framework: 3.4):

$$P(PTB \mid U) = \frac{\exp\left(\gamma_0 + \gamma_1 U_i\right)}{1 + \exp\left(\gamma_0 + \gamma_1 U_i\right)}$$

Implementation

Simple logistic regressions were performed of preterm birth with BMI to obtain the odds ratio. The mean of the point estimate was obtained from 100 iterations for each scenario. The percentile-based 95% simulation intervals (SI) of the OR mean were derived using 500 bootstrap replications. For the purpose of interpretation, the results of BMI were categorised as follows: underweight (BMI < 18.5 kg/m^2), normal (set as reference) (BMI 18.5- 24.99 kg/m^2), overweight (BMI 25- 29.9kg/m^2) and obese (BMI ≥ 30kg/m^2). All data analysis and simulation were conducted using R v4.2.1[239] (Framework 4.1).

This simulation indicated that the influence of bias due to collider-stratification was marginal in the association between maternal BMI and preterm birth, and only prominent for women that met the BMI criteria for underweight. When the prevalence of *U* was strong (50%) and the strength of the selection effects (*U* → miscarriage and *U* → Preterm birth) were set to an equal OR 3.5, there was evidence of a downwards bias was for women that were underweight (OR 0.92 95% SI 0.92 to 0.93). Using the same parameters, there was a marginal upwards bias for women with a BMI that meet the criteria for overweight (OR 1.04 95% SI 1.04 to 1.05) and obese (1.04 95% SI 1.04-1.05) (Framework: 4.2).

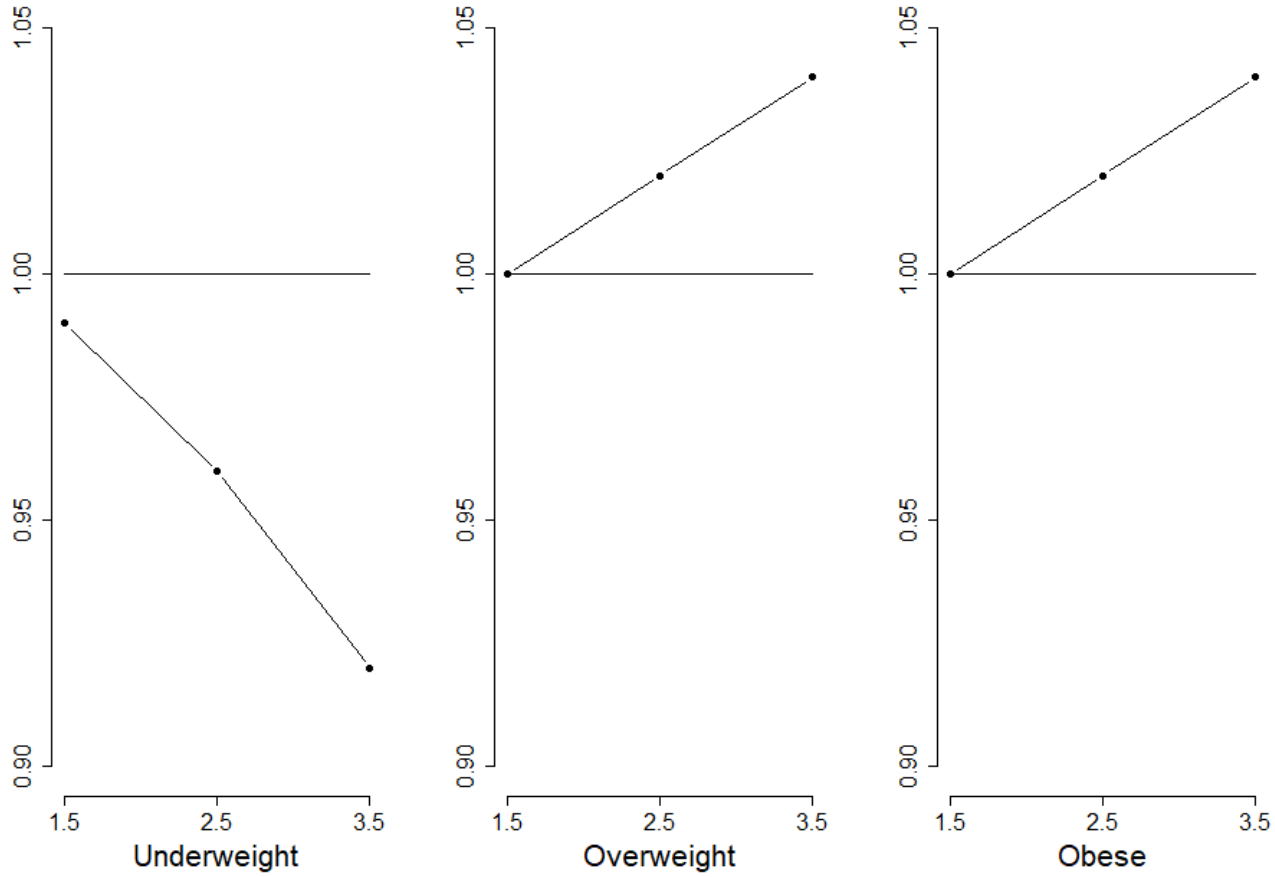


Figure 6.3 Collider-stratification bias of OR of body mass index on preterm birth, where the bias represents the departure from the null. Average odds ratio when the prevalence of *U* was 50% and the selection effects for *U* → miscarriage and *U* → Preterm birth ranged from 1.5, 2.5 to 3.5 for women who were underweight, overweight, and obese. Each scenario was iterated 100 times.

Reproducibility

An extract of the simulation function in R programming (Framework 5.2) to quantify the influence of selection bias on the association between maternal BMI and preterm birth is included below (Figure 6.4) The full reproducible code for the simulation model undertaken in this framework is available in the supplementary materials (Framework: 5.1: 5.3). This will enable other researchers to reproduce this simple example of collider-stratification bias.

```
results=foreach(i=1:100,.packages=c("MASS","sandwich","lmtest","tidyverse","Rlab","dplyr","matrix
Stats"),.combine=rbind) %dopar% {
  rboundednorm <- function(n, mymean, mysd, min = 15, max = 40) {
   a = pnorm(c(min, max), mymean, mysd)
   z = runif(n, a[1], a[2])
   qnorm(z, mymean, mysd)}
        n=128000;pU=0.50;min.bpL=19.43;or1=3.5;bY=0.738;or2=3.5
        set.seed(i)
        bias <- data.frame("id" = 1:n) %>%
        mutate(BMI= rboundednorm(n, mymean=BMI.mean, mysd=BMI.sd), #create BMI
                bMiscarriage = (min.bpL +
                BMI.to.misc(BMIvec=BMI,min.BMI=x2[p2==min(p2)],min.risk=min(p2)))/100,
                b_Miscarriage = bMiscarriage / (1 - bMiscarriage),
                U = rbern(n, pU),
                prob_Miscarriage = plogis(log(b_Miscarriage) + log(or1)*U),
                Miscarriage = rbern(n, prob_Miscarriage), #miscarriage
                pPTB = plogis(log(bY) + log(or2)*U),
                PTB = rbern(n, pPTB))  %>% #preterm birth
                mutate(BMI_cat = cut(BMI,breaks=c(15, 18.5, 25, 30,Inf),
                labels=c("underweight","normal", "overweight", "obese"), include.lowest=TRUE),
                BMI_cat = relevel(BMI_cat, ref ="normal"))#set normal BMI as reference
        #fit a logistic model
        log_model <- bias %>% glm(formula = PTB ~ BMI_cat, family = binomial(link = "logit"),
        data = ., subset = Miscarriage==0)
        ct=coeftest(log_model, vcov = sandwich)
        ci=confint(ct)
        c(ct[-1,1],ci[-1,1],ci[-1,2])
}
```

Figure 6.4 Extract of R code for simulation study to quantify the influence of selection bias on the association between maternal body mass index and preterm birth.

6.5 Conclusion

This framework included in this paper will provide guidance to epidemiologists in the application of simulation methods to quantify the magnitude and direction of bias under a range of plausible scenarios. A benefit of simulation methods is that the influence of multiple types of bias can be computed in one model. This enables researchers to investigate bias mechanisms that replicated complex real-life scenarios. However, for researchers unexperienced with computation simulation, it is preferable to start with a small uncomplicated simulation model and build towards increased complexity. The included simulation example is one such simple example, including only four variables. It is intended to provide epidemiologists with a working demonstration that they can apply to their own work and research questions. This simple simulation is fully reproducible using the R code provided.

In this paper, we proposed a framework to apply simulation methods to quantify the influence of bias in epidemiology. However, it should be noted that even adhering to the best of frameworks will not necessarily guarantee that a study is deemed optimal or valid. Nonetheless, adhering to the framework provided here will ensure that simulation studies that seek to quantify the influence of bias in epidemiological associations have provided sufficient details to enable the wider research community to validate their findings and advance our collective knowledge.

Chapter Seven: Discussion

This thesis project addressed the overall aim of demonstrating that the application of simulation is a powerful tool in quantifying the influence of bias in perinatal epidemiology. Further, this thesis project has filled the knowledge gaps identified in Chapter One and achieved each of the three specific aims of the thesis. This chapter presents a summary of the main findings from each of the five publications that addressed the specific aims of the thesis, explores the significance of the findings and includes recommendations for future research.

This thesis project achieved the overall aim of demonstrating the application of simulation to quantify the influence of bias in perinatal epidemiology. Using three inter-related study aims and objectives, this thesis addressed the knowledge gaps identified in Chapter One. The systematic review in Chapter two demonstrated that simulation had utility in the quantification of bias; however, the method was under-applied and there was a lack of conformity in study design, implementation, analysis and reported was noted.

This thesis adds to quantitative bias analysis methods by demonstrating the suitability of simulation as a methodology to support bias analysis. Chapter Three demonstrated simulation as a complementary method to traditional epidemiological methods. One of the main benefits of simulation is the ability to quantify multiple types of bias simultaneously. This was demonstrated in Chapters Four and Five, in which applied simulation studies quantified the influence of bias under common mechanisms in perinatal epidemiology, in particular the influence of left truncation bias on perinatal exposure-outcome associations. The included framework in Chapter Six extends on recommended best practices in quantitative bias analysis by providing a targeted educational tool to guide epidemiologists in the application of simulation to quantify bias.

7.1 The application of simulation to quantify bias

Aim 1: To review and explore the existing literature on the application of simulation methods as an approach to quantify the influence of bias in perinatal epidemiology.

A systematic review was carried out at the onset of this PhD project (Publication One) to fulfil the first aim of the thesis. Based on this systematic review,[234] there was a limited number publications applying simulation methods to quantify bias in reproductive and perinatal epidemiology (n=39), ranging in time from 1983 to 2019. The included simulation studies presented a heterogeneity in their design, implementation and reporting of their results. Nonetheless, this review[234] did highlight some clear best practices in the application of simulation to quantifying bias; including the use of causal diagrams to illustrate the influence of the bias(es) and a clear declaration of data parameters that informed the development of the simulation models. Few studies included the simulation code, reducing the reproducibility of their

studies; however, the practice of sharing simulation code was becoming increasingly common in studies published post 2015.

This was the first and only review[234] of the application of simulation as a method to quantify the influence of bias in perinatal epidemiology. The included studies demonstrated that simulation is beneficial in the quantification the magnitude and strength of bias and has potential to be applied more comprehensively to investigate bias in perinatal associations. Since 2019, only three studies[104, 105, 308] were published that applied simulation to quantify the influence of bias in reproductive or perinatal epidemiology, independent of the research included in this PhD project. The lack of research activity in bias analysis during the course of the PhD (April 2020 to April 2023) could be contributed to the Covid-19. It is plausible that during this time epidemiologists temporarily moved away from methods-based research to focus on tracking and preventing the spread of Covid-10 globally. Nonetheless, this paucity of simulation studies to quantify bias in perinatal epidemiology reinforces the need for guidance to support perinatal epidemiologist on best practices in the application of simulation to quantify the influence of bias.

In 2021, two studies[104, 105] applied simulation to quantify the influence of live-birth bias on environmental exposures in perinatal epidemiology, with both studies also quantifying the influence of depletion of susceptibles. The first simulation study reported that exposure to environmental hazards induced a live-birth bias, which was increased for women who were socially vulnerable.[104] The second simulation study[105] was undertaken to try to explain a previously reported[309] paradoxical association between exposure to nitrogen dioxide during pregnancy and the subsequent development of autism spectrum disorder in offspring. The findings of both studies[104, 105] indicated that bias was strongest when both live-birth bias and the depletion of susceptibles mechanisms were present. The most recent study by Jayaweera and colleagues (2023)[308] used a Monte Carlo simulation to estimate self-managed abortion effectiveness account for bias from misclassification of self-reported outcomes and selection bias due to loss of follow-up. They found that bias-adjusted estimates were similar to the observed effect estimated in a cross-sectional study, with the level of bias dependent on the chosen bias parameters. These recent studies included important factors that meet the requirements of best practice in applying simulation to

quantify the influence of bias; including the use of causal diagrams, the clear declaration of data sources and bias parameters, and the inclusion of reproducible simulation code.

The findings of this study indicated the simulation methods are an important tool in quantitative bias analysis; however, the lack of simulation studies undertaken in reproductive and perinatal epidemiology suggests a clear need for a framework to upskill epidemiologist in their application. This review highlighted best practices for the application of simulation to quantify bias which informed the subsequent development of the simulation studies included in this thesis, and the development of a framework to guide researchers in their study design, implementation, analysis and reporting of simulation studies to quantify bias in perinatal epidemiology as presented in Chapter Six.

7.2 Quantifying the magnitude and direction of bias in perinatal epidemiology

Aim 2: To design, implement and analyse a series of simulation studies to quantify the magnitude and direction of bias in perinatal epidemiology to address issues from methodological challenges that may lead to spurious inference on associations between pregnancy exposures and adverse birth outcomes.

The role of confounding

Unmeasured confounding is routinely acknowledged in research papers yet its impact on aetiological associations is rarely addressed. The influence of unmeasured confounding in the association between pregnancy complications and a subsequent preterm birth was investigated in Chapter Three to address objective 2.1 of this thesis. Traditional epidemiological methods (regression models) were combined with simulation and the *e*-value for confounding to estimate the degree of confounding necessary to explain the observed associations between complications in first pregnancy and the subsequent risk of a preterm birth (Publication Two)[310].

The simulation in this study generated data for maternal obesity, a potentially important confounding variable as it is considered a risk factor for the development of pregnancy complications and preterm birth.[6, 9, 267, 311] By re-analysing the original data and adjusting for the same observed confounders plus the new simulated maternal obesity, this simple simulation demonstrated that the inclusion of a single confounder was not enough to weaken the observed associations between pregnancy

complications across two successive pregnancies. This is unsurprising given the strengths of the associations and their subsequent e-values that were observed in the study. *E*-values for confounding are a powerful tool to determine how robust the observed association are to bias.[125, 132, 220] The high *e*-values observed in this study suggest that any unmeasured confounding would have to be extremely high to explain away the observed associations, particularly for the association between pre-eclampsia in a preterm first birth and a subsequent preterm birth with recurring pre-eclampsia (e-value 127.58). It is highly improbable that a single unmeasured confounder, or multiple unmeasured confounders working together, could explain away the observed association.

The findings of this Western Australian study supported the previous evidence from the US[200, 202] and Norway,[201] that a previous pregnancy complicated by pre-eclampsia, placental abruption, small-for-gestational age or perinatal death can increase the risk of a subsequent preterm birth, regardless of whether the first birth was preterm or term. This would indicate that there are shared and unknown underlying mechanisms that influences the recurrence of a pregnancy association across successive pregnancies.[32] A plausible candidate for these mechanisms is the emerging evidence that latent cardiovascular disease risk factors could explain the associations between pregnancy complications across successive pregnancies.[312] This hypothesis is supported by the circular relationship between cardiovascular disease and pregnancy complications, with markers of cardiovascular disease, such as obesity, hypertension and diabetes, increasing the risk of pregnancy complications[313], and pregnancy complications themselves predicting the subsequent development of cardiovascular disease.[314]

The study[310] demonstrated how simulation and novel methods, such as the *e*-value, can support traditional epidemiological methods by providing evidence to strengthen the validity of observed associations.

Bias due to left truncation

Much of the evidence on perinatal epidemiological effects are derived from pregnancy data that is left truncated. This is problematic when examining aetiological associations between an exposure in early pregnancy and a subsequent adverse

perinatal event, as the cause of the exposure could influence selection into the study cohort. The influence of bias due to the application of left-truncated datasets (birth registries), in which early pregnancy losses prior to 20 gestational weeks are excluded, was quantified in Chapter Four to address objective 2.2 of the thesis. A simulation study was undertaken to quantify the magnitude and direction of bias due to the left truncation of birth data in the association between advanced maternal age and stillbirth (Publication Three).[294] This study hypothesised that bias occurs when early pregnancy loss (<20 gestational weeks) is influenced by both the exposure and the unmeasured confounder, creating a backdoor causal pathway between the exposure of advancing maternal age and the outcome of stillbirth. The mechanism for this bias is commonly referred to as *collider-stratification.*

The findings of this study strongly suggested that for left truncation bias to be influential, the prevalence and strength of the unmeasured confounder must be strong. Specific to this study, an unmeasured confounder would have to be highly prevalent (≥50%) in the population of pregnant women and have an impactful effect (OR ≥ 3.0) to produce significant bias. It is unlikely that such plausible confounders exist that would be capable of inducing such strong bias. In this simulation study, evidence of marginal bias was only found for women aged 40+ years, which is comprehensible given that this group had the most susceptibility to early pregnancy loss and stillbirth, in comparison to the other age categories. Similar findings were also reported by US based researchers[104, 105] that examined *live-birth bias*, a bias that results from *collider-stratification* mechanism in studies that restrict their birth dataset to pregnancies that results in live-births only.[157] A study by Leung et al.[105] attempted to explain away the protective effect of the ambient air pollutant of nitrogen dioxide during pregnancy on the subsequent development of autism spectrum disorder in early childhood.[106, 309] This causal association was purported to results from live-birth bias ,where the OR was per 5.85 parts per billion increase in nitrogen dioxide exposure during pregnancy (median, 16.8 ppb; range, 7.5–31.2 ppb) was 0.77 (95% confidence interval: 0.59, 1.00), when mutually adjusting for post-natal exposure to nitrogen dioxide.[106, 309] Leung et al. could only replicate the bias when both *collider-stratification bias* and the *depletion of susceptibles* mechanisms worked together and the prevalence of U was 75% with an OR strength of 3.0.[105] This seems to suggest that bias mechanisms from one selection event alone are not sufficient to produce such an inverse association;

there may, in fact, be a combination of biasing factors from misclassification, mediation and selection bias acting together to produce spurious inverse associations.

As demonstrated in my study, bias due to left-truncation is not likely to be sufficient to substantially distort exposure-outcome associations in perinatal epidemiological studies. As the application of left truncated data is pervasive in perinatal in epidemiology, these findings will be reassuring to perinatal epidemiologist who are interested in the association between pregnancy exposures and perinatal outcomes.

Bias in mediated associations

The handling of mediator variables in perinatal epidemiology can be problematic, particularly the mediator of gestational age or birthweight. Adjusting for mediators of gestational age or birthweight will produce intersecting birthweight-specific and gestational age-specific mortality curves can lead to paradoxical associations.[74, 92, 157, 186] However, it is not uncommon for pregnancy complications to mediate associations between an exposure in pregnancy and a subsequent adverse outcome. Causal mediation analysis is a method that enables researchers to separate the total effect of an exposure-outcome association into a direct and indirect effect (mediated). Yet, causal mediation analysis is highly restricted to the strict assumption that there is no influence of unmeasured confounders.[252, 253, 255] The influence unmeasured confounding on a mediator will render that mediator a collider and lead to biased results.[231, 232] Chapter Five addressed objective 2.3 of the thesis: to quantify the influence of unmeasured confounding in mediated associations. To estimate the magnitude and direction of bias from unmeasured confounding in the association between maternal obesity and caesarean section delivery when mediated by the pregnancy complication of pre-eclampsia, a simulation study (Publication Four) quantified the *collider bias* mechanism in mediated associations under three common scenarios: 1) mediator-outcome confounding, 2) mediator-outcome confounding affected by the exposure, and 3) exposure-mediator confounding.

The findings indicated that bias was strongest when the unmeasured confounder influenced the mediator of pre-eclampsia and the exposure of maternal obesity (exposure-mediator confounding). This confounding scenario has received less attention from researchers compared to mediator-outcome confounding,[255, 283, 287] which produced very minimal bias in my study. These findings are important,

particularly when using observational data as the exposure itself cannot be randomised. However, as per the previous simulation study (Publication Three)[294] we found that the strength of the bias was directly related to the prevalence and strength of the unmeasured confounder, with the weakest evidence of bias presenting when the prevalence of the unmeasured confounder was small (15%) and the strength of the OR was minimal (OR 1.5) across all three scenarios. The findings of this study support the need to undertake a quantitative bias analysis to investigate the mechanisms in which the influence of unmeasured confounding can impact their mediated exposure-outcome associations, in addition to causal mediation analysis.

7.3 A framework to guide the application of simulation for bias analysis

Aim 3: To develop a framework for the application of simulation to quantify bias in perinatal epidemiologists.

Chapter Six addressed a key research gap on the lack of guidance for perinatal epidemiologists in the application of simulation methods for the purpose of bias analysis, and addressed the final aim of the thesis. The requirement for a practical guide on the application of simulation was further evidenced in the systematic review (Publication One)[234], which found a lack of conformity in the methods of designing, implementing and reporting of simulation studies for bias analysis in reproductive and perinatal epidemiology. Furthermore, the identification of best practices from the systematic review informed the development of this framework (Publication Five) to guide perinatal epidemiologists in the design, implementation and reporting of simulation studies to quantify the influence of bias in perinatal aetiological associations.

The framework is composed of five steps to guide perinatal epidemiologist through the development of simulation studies to quantify bias: 1) clearly define the *aim*, including the research purpose, the target population, exposure and outcome, 2) use *causal diagrams* to explain the influence of potential biases, 3) identify the *sample population, data sources, bias parameters* and the *data generation methods*, 4), clearly state the methods of *analysis* and *report* appropriately, and 5) provide *reproducible code.* This framework also included a simulation study, which provides a building block for perinatal epidemiologist to start undertaking quantitative bias analysis for their own research questions.

Applying the framework to the included simulation studies in this thesis (Publication Three and Four), I first clearly identified the study aim and then created a causal diagram to illustrate the bias mechanisms. I explicitly declared the sources of my data and the assumptions that informed the development of the simulation model. In both the simulation studies, an observed cohort from Western Australia informed the simulated population. This data for this observed cohort was derived from probabilistic linked datasets in Western Australia, including the Midwives Notification System and the WA Registry of Births, Deaths and Marriages using a linkage key provided by the Data Linkage Branch of the WA Department of Health.[213] Both simulation studies undertook logistic regression modelling to calculate the biased estimate of the exposure on the outcome. Results were subsequently reported using figures and tables. I also included my simulation code. By following all five steps of the framework, I have ensured that my simulation studies have high reproducibility.

Both the simulation example included in the framework, and the simulation studies undertaken in this thesis, are fully reproducible. Researchers can use the provided simulation code to determine the influence of bias in their exposure-outcome associations. Implementing the steps highlighted in this framework will enable the standardisation of reporting, reproducibility, better comparisons between studies and consequently improve research synthesis. The provision of this framework can advance our collective knowledge about bias mechanisms and the nature in which they can distort our observed associations; thereby improving causal inference in perinatal epidemiology.

7.4 Significance

This thesis has made a significant contribution to the field of quantitative bias analysis by 1) demonstrating that simulation methods are powerful tool quantity the influence of bias, 2) undertaking simulation studies that quantified the magnitude and direction under multiple bias mechanisms, and 3) developing a framework to guide other researchers to apply simulation to quantify bias.

The initial review (Publication One) indicated that simulation studies are a potentially powerful tool in quantitative bias analysis; however, they are under-utilised in perinatal epidemiology. This thesis demonstrated that simulation methods can be used to supplement traditional epidemiological methods to account for important variables that

are unavailable to a study in Publication Two. As demonstrated in Publication Three (bias due to left truncation) and Publication Four (bias in mediated associations), simulation models can replicate complex bias mechanisms that may be unknown or seen by researchers. Furthermore, the simulation studies demonstrated that it is possible to test simulation models under multiple scenarios and quantified the influence of multiple types of bias simultaneously.

A significant contribution of this thesis was the quantification of the influence of left truncated birth data in perinatal epidemiological studies. Although, live-birth bias has been previously explored as a bias mechanism, in countries such as Australia and many European countries, birth data includes stillbirths so live-birth bias is not an issue. This restriction of data to only include pregnancies that survived past 20 gestational weeks was problematic when researchers were drawing associations between exposures in early pregnancy and adverse perinatal outcomes. Quantifying the magnitude and direction of this bias can assure perinatal epidemiologists that the influence of bias on the observed exposure-outcome associations is minimal. – assuming that they is no other influencing bias mechanism.

Much research has been dedicated to developing methods in which the influence of mediator-outcome confounding in mediation analysis. However, the findings of publication four indicate that mediator-outcome bias is insignificant, with the strong bias evidence in the exposure-mediator association. Although, ours in not the first study to find these results. These findings should act as a cautionary note to other researchers to carefully draw their causal association using a diagram.

The final significant contribution to perinatal epidemiology was the development of a framework to guide other researchers to undertake simulation studies to quantify bias. This framework provides five steps to guide perinatal epidemiologist in the development, implementation and reporting of simulation studies to quantify bias. The inclusion of a simulation study will reinforce the steps of the framework, providing a visualisation of a simple simulation study which can act as a building block for other research questions.

7.5 Strengths and limitations

The systematic review was novel, as no similar review had previously undertaken that investigated the application of simulation to quantify bias in reproductive and perinatal

epidemiology. This systematic review was also an important step of the thesis as it identified best practices in the application of simulation, which later informed the development of the simulation studies and underpinned the steps in the framework to guide perinatal epidemiologist on the application of simulation to in bias analysis.

This thesis demonstrated that simulation can supplement traditional epidemiological methods by generating data for important variables that are missing from perinatal datasets. Quite often bias is only quantified in perinatal epidemiology in an attempt to explain away an association that seems counter-intuitive. Therefore, a strength of this thesis was the application of simulation studies to quantify bias in common perinatal associations when the results seem to conform to expectations. That the research questions quantified bias in associations that are relevant to the changing demographics (i.e. advancing maternal age and increasing maternal obesity) of perinatal research in high-income countries is an additional strength.

The outputs of the simulation studies addressed important bias mechanisms, particularly increasing our understanding of the *collider bias* mechanism which underpins selection biases and its influence in mediated associations. A strength of the simulation studies included the clear use of DAGs to map the causal pathway between exposure and outcomes, highlighting bias mechanisms that may be otherwise hidden to researchers. The data source for the included studies was derived from probabilistic linked datasets in Western Australia, which are routinely validated and are of high quality.[315] A major strength of the simulation studies was the inclusion of the simulation code, which can be adapted by other researchers to replicate their study findings using their own data. A major output of this thesis was the development of a framework to guide the development, implementation and reporting of simulation studies to quantify bias. This filled a much needed research gap and has the potential to increase the application of simulation and the undertaking of quantitative bias analysis. The simulation approach adopted in this thesis captures the sensitivity of results to different assumptions and types of bias, ensuring high quality inference. This approach can provide a stronger evidence-base for the effect of preventative actions, policy interventions and clinical practice.

A limitation of simulation models is that simplifying assumptions must be made. Such assumptions arise, for example, from the examination of a limited set of factors in the

causal model, the need to hold some aspects of the study parameters constant while varying others, or the practical need to limit to a specific range of parameters to improve interpretation. Therefore, a common criticism of quantitative bias analyses is that the scenarios are not truly representative of real-world situations. However, the work completed in this PhD thesis should be considered a building block on which more complex simulations can be built to replicate more complicated bias mechanisms. An additional limitation of the simulation studies may be the inclusion of only one unmeasured confounder in the simulation models. However, it may be considered that an unmeasured confounder that is both strong in prevalence and strength may comprise multiple smaller unmeasured confounders. An additional limitation of the simulation models included in this thesis is that the included variables were categorical. This is not uncommon in perinatal epidemiology where risk factors and outcomes often have binary classifications. The same principles apply to simulation studies when risk factors and outcomes occur on a continuum. The model family, link function and error distributions can be amended accordingly. The inclusion of time-varying exposures or risk factors was not explicitly modelled in the simulation models included in this thesis. As simulations are based on substantive knowledge of the data generating mechanisms, time-varying exposures prove challenging due to the need to observe individuals over time. Nonetheless, my approach to the design of the included simulations, which included explicit specifications of the theoretical model in the form of DAGs, is generalisable to time-varying factors, which can be included in the DAG by including time in the definition of the variable.[316] A final limitation is that the included simulations did not quantify bias from misclassification, which is a common source of bias, particularly when exposure or outcome assessment is challenging (e.g. environmental exposures, latent variables, self-reported states, and non-specific diagnostic criteria). This was beyond the scope of this PhD thesis as the inclusion of misclassification of the exposure and/or outcome in addition to selection bias and bias from the influence of confounding would generate an impractical number of combinations to investigate in a single thesis. Nonetheless an achievable activity when using simulation methods and should be considered for future research.

7.6 Direction for future research

This thesis demonstrated that simulation methods are a powerful tool to quantifying the influence of bias in perinatal epidemiology. As established in this thesis, simulation

methods do not have to be complicated; they can complement traditional epidemiological studies to strengthen the validity of results. For example, simulation can generate data for important variables that are omitted from a dataset - variables that could potentially explain the observed exposure-outcome association. Simulation can also correct for misclassified variables, a common source of bias due to inaccuracies in the exposure, outcome and confounding variables. Simulations of this nature are a relatively simple exercise that should be achievable for all perinatal epidemiologists. The increase of well-designed pre-conception cohort studies may provide richer data, including a better set of adjustment variables. However, there would always remain a degree of bias from confounders that are unknown (i.e. not yet discovered) and bias from self-reported variables, such as maternal smoking. Therefore, future researchers should consider the use of simulation to account for omitted variables in statistical modelling and to correct for misclassified variables; this will prevent the reporting of biased estimated effects and improve causal inference in perinatal epidemiology.

The simulation studies included in this thesis made use of DAGs to illustrate bias mechanisms. This is a practice that all perinatal epidemiologist should undertake prior to their data analysis. Graphically drawing the associations between variables will reveal potential sources of bias that may not be obvious to researchers otherwise. DAGs are useful in identifying *collider* variables, particularly those that may be mistaken for confounders. One such example is *M Bias,* where bias results from conditioning on a variable that is caused by two other variables, one of which is the cause of the exposure and the other is the cause of the outcome.[317] A naive approach may involve adjustment for all three variables - the collider, the cause of the exposure and the cause of the outcome - believing that such adjustment will “control” for any spurious associations attributable to all pathways involving these variables, when in fact it will lead to a bias of the observed associations, the direction of which can be either upward or downward. To avoid the perils of such hidden bias mechanisms, perinatal epidemiologists must draw a DAG to illustrate the causal relationship amongst their set of included variables prior to undertaking data analysis. Ideally, the inclusion of a DAG should be mandated in peer-reviewed publications that report perinatal aetiological associations.

Although DAGs are a vital tool to illuminate complex bias mechanisms that are more difficult to avoid in perinatal research, they only tell us one part of the bias analysis story. In order to increase our understanding of the consequences of bias mechanisms, we must undertake a quantitative analysis to determine the magnitude and direction of the influence of bias on perinatal aetiological associations. The undertaking of simulation studies to quantify bias is a worthwhile activity that enables researchers to strengthen the validity of perinatal associations drawn from observational studies. The included simulation studies in this thesis have high reproducibility, which combined with the provision of a framework on the application of simulation to quantify bias, makes simulation methodologies more accessible to researchers. Bias analysis is a very important facet of epidemiological research; therefore, more research that quantifies the influence of bias is necessary. The application of simulations is an achievable methodology that all perinatal epidemiologist need to develop skills in. To strengthen the validity of perinatal associations, future researchers should apply simulation to quantify bias in addition to the reporting of traditional epidemiological methods.

Moving forward, perinatal epidemiologists need to apply simulation to increase our understanding of paradoxical associations, an intractable problem in perinatal epidemiology and one that cannot necessarily be resolved by closed form mathematical expressions. Using the traditional example of the birthweight paradox, researchers have tried to explain the protective effect of maternal smoking on neonatal mortality[94, 109-112, 176] (or pre-eclampsia[100, 101, 154]) from different bias mechanisms (collider-stratification due to conditioning on birth weight[94, 100, 101, 109-112, 154, 166, 176] or gestational age[154] and left truncation[100, 318]). Despite numerous attempts, researchers have not been able to fully explain this inverse association. It is plausible that mechanisms required to induce such strong bias is due to a complex interaction between bias mechanisms of selection, confounding and misclassification. Simulation has the potential to solve this riddle, elucidating these obscure mechanisms that can lead to paradoxical associations. These counter-intuitive associations are also likely subjected to publication bias and therefore their prevalence in perinatal epidemiology may be underestimated. Future researchers should apply simulation methodologies to increase our understanding of these complex and elusive bias mechanisms that have the potential to obfuscate perinatal aetiological associations.

7.7 Conclusion

This thesis has confirmed that simulation is a dynamic tool to quantifying the influence of bias in perinatal epidemiology. There should be no doubt that quantification of bias is a worthwhile activity, as it enables researchers to strengthen the validity of perinatal associations drawn from observational studies. Simulation methodologies have a number of advantages that make them integral to quantitative bias analysis. Simulations can account for data that is missing, misclassified and replicate complex bias mechanisms that are often not obviously visible to researchers, nor are answerable by closed form mathematical expressions. Simulations can rapidly conduct numerous experiments to test bias mechanisms across a range of scenarios that represent real-life situations.

The simulation studies in this thesis have demonstrated the application of simulation to quantify important bias mechanisms that are common to perinatal epidemiology. The included studies extricated the role of the *collider* in selection bias and mediated associations, providing a methodology that can be applied to quantify the influence of bias across a range of perinatal epidemiological associations. The development of a framework supports perinatal epidemiologists to develop skills in the quantification of bias; thereby increasing the breadth of studies that undertake quantitative bias analysis in epidemiology. Taken together, the included studies make the application of simulation to quantify bias more accessible to perinatal epidemiologists.

The ubiquity of bias in observational studies necessitates further research to provide clarity on the influence of bias mechanisms common to perinatal epidemiological studies. Researchers should consider the application of simulation studies to quantify the magnitude and direction of such bias mechanisms in addition to traditional epidemiological methods. Moving forward, simulation methodologies have the potential to explain paradoxical associations and elucidate the complex bias mechanisms from which they evolve.

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APPENDICES

Appendix A Author's contributions

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To whom it may concern,

I, Jennifer Dunne, contributed (managed the project, developed the search strategy, conducted the initial database searches, extracted the data, analysed the results, wrote the manuscript, complied the final manuscript and reviewer's response, including co-author suggestions) to the publication titled "Quantifying the influence of bias in reproductive and perinatal epidemiology through simulation" by J Dunne, GA Tessema, M Ognjenovic, G Pereira. 2021. *Annals of Epidemiology* 63:86-101. Doi:10.1016/j.annepidem.2021.07.033.

19/01/2023

I, as co-author, endorse that this level of contribution by the candidate indicated above is appropriate.

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To whom it may concern,

I, Jennifer Dunne, contributed (managed the project, conducted the data analysis, wrote the manuscript, complied the final manuscript and reviewer's response, including co-author suggestions) to the publication entitled "The role of confounding in the association between pregnancy complications and subsequent preterm birth: a cohort study" by J Dunne, GA Tessema, G Pereira. 2021. *BJOG: An International Journal of Obstetrics & Gynaecology 129:6*:890-899. Doi: 10.1111/1471-0528.17007.

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To whom it may concern,

I, Jennifer Dunne, contributed (designed and managed the project, conceived the computational model, wrote the R code, conducted the data analysis, wrote the manuscript, complied the final manuscript and reviewer's response, including co-author suggestions) to the publication titled "Bias in the association between advanced maternal age and stillbirth using left truncated data" by J Dunne, GA Tessema, AT Gebremedhin, G Pereira. *Scientific Reports* 12(1):1-9. Doi:10.1038/s41598-022-23719-3.

14/02/2023

I, as co-author, endorse that this level of contribution by the candidate indicated above is appropriate.

Name	**Signature**	**Date**
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14/03/2023

I, as co-author, endorse that this level of contribution by the candidate indicated above is appropriate.

Name	**Signature**	**Date**
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Appendix B Copyright information

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Quantifying the influence of bias in reproductive and perinatal epidemiology through simulation

Author: Jennifer Dunne,Gizachew A Tessema,Milica Ognjenovic,Gavin Pereira

Publication: Annals of Epidemiology

Publisher: Elsevier

Date: November 2021

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Appendix C Publications in the thesis

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Review Article

Quantifying the influence of bias in reproductive and perinatal epidemiology through simulation

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ABSTRACT

Purpose: The application of simulated data in epidemiological studies enables the illustration and quantification of the magnitude of various types of bias commonly found in observational studies. This was a review of the application of simulation methods to the quantification of bias in reproductive and perinatal epidemiology and an assessment of value gained.

Methods: A search of published studies available in English was conducted in August 2020 using PubMed, Medline, Embase, CINAHL, and Scopus. A gray literature search of Google and Google Scholar, and a hand search using the reference lists of included studies was undertaken.

Results: Thirty-nine papers were included in this study, covering information ($n = 14$), selection ($n = 14$), confounding ($n = 9$), protection ($n = 1$), and attenuation bias ($n = 1$). The methods of simulating data and reporting of results varied, with more recent studies including causal diagrams. Few studies included code for replication.

Conclusions: Although there has been an increasing application of simulation in reproductive and perinatal epidemiology since 2015, overall this remains an underexplored area. Further efforts are required to increase knowledge of how the application of simulation can quantify the influence of bias, including improved design, analysis and reporting. This will improve causal interpretation in reproductive and perinatal studies.

Introduction

Reproductive and perinatal epidemiology seeks to establish the effects of exposures on maternal and neonatal outcomes before, during and after pregnancy [1]. As randomized controlled trials cannot always be conducted in pregnant women for ethical reasons [2], well-designed observational studies have provided information to increase the understanding of causal effects in reproductive and perinatal health [2]. Due to the non-random nature of observational studies, they can be prone to bias [2], influencing causal inference. Bias results from systematic errors in study design, conduct or data analysis, and unlike random error, does not decrease as study size increases [3]. To strengthen the validity of associations drawn from observational studies, it is therefore important to identify and evaluate potential sources of bias.

Reproductive and perinatal studies are vulnerable to unique methodological challenges. The study population themselves are widespread from preconception to birth stages, and include populations that are difficult to define, such as women who may conceive in the future [4]. Proving an additional challenge is that the study populations are incompletely observed due to high attrition from the preconception period through to birth [4]. Thereby, by the time pregnancy is established, an extensive cohort attrition has already occurred; estimated to be 2500 early pregnancy losses per 10,000 implantations [5]. Consequently, the use of birth register datasets, which are generally restricted to specific periods and in many cases live births, can introduce bias because the sam-

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.

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1047-2797/

ple is thus restricted [6]. Conditioning on intermediaries that are on the causal pathway also proves problematic [6]. Conditioning on a collider, a common effect of the exposure and outcome, or a variable influenced by the collider, can induce a specious association between the exposure and outcome [7]. One such example of such challenges in perinatal epidemiology is how to deal with gestational-age-specific or birth-weight-specific associations that lie on the causal pathway between exposure(s) and an outcome [6]. Reproductive and perinatal epidemiological studies are also impacted by information bias, a measurement error of exposures, outcomes and potential confounders [8]. For example, gestational age can be calculated using various methods: fetal ultrasound measurement, first day of the last menstrual period, time of in vitro fertilization, or based on clinical judgement after birth [8]. All these measures are prone to some degree of misclassification, not all of which are at random [8]. Additionally, information bias can be introduced during the data analysis phase, such as the incorrect categorization of continuous data [9]. Thus, selection, confounding and information bias are ubiquitous in reproductive and perinatal research [4,6], compromising study validity [10].

Quantitative bias analysis methods to estimate systematic errors in epidemiology are available [11], the basic principle of which is to assign plausible values to bias parameters to determine the influence of bias [12]. However, there are a number of limitations in the available methods. Sensitivity analysis, a standard practice, only assesses one binary variable independently [13]. A limitation of multiple bias analysis modelling is the assumption that the bias are independent, which may not reflect actuality [14]. More recent methods have been developed to calculate the effects of unmeasured mediators; however, unless the mediator is binary the study will require a large number of parameters [15]. In recent years, quantitative bias analysis methods have been expanded to include simulation [12], empirical experiments that involve applying epidemiological modelling to simulated bias parameters [16]. Computer simulations comprise a broad range of computational practices that vary across disciplinary fields [17]. This review is interested in simulations that replicate complex causal structures, thereby allowing the illustration and quantification of bias by comparing scenarios for the observed association with alternative scenarios [18]. One of the main benefits of simulation is that it enables researchers to conduct numerous experiments, exploring complex causal pathways between exposures and outcomes. This has been greatly facilitated by technological advances that have led to improved computation speed at lower cost. While simulation as a method is well-established [17], there is a paucity of research using simulations to quantify bias across epidemiology in general [16]. The reasons for the limited application of simulation as a method to quantify bias in reproductive and perinatal epidemiology could be due to several factors. Notably, there is a lack of guidance in the design and implementation of simulation [16], combined with researchers with a limited skillset in statistical modelling [19] and a lack of interest in exploring new research methods [16]. Further to this, adoption of simulation may be impeded by negative reports that studies that use simulation are prone to poor design, analysis and reporting [16].

Although the problems of bias in observational studies are well-acknowledged, reviews of the application of methods to address this bias remain limited [20]. Further, no study has documented how simulation methods have been applied in the quantification of bias in reproductive or perinatal epidemiology, which would otherwise be of interest to those who would wish to apply simulation within this field. To address this, we aimed to systematically review the published literature to provide an assessment of the value gained in reproductive and perinatal research, and to identify best practices in the application of simulation in the quantification of bias.

Methods

Search strategy

A systematic search of four databases (PubMed, Medline, EMBASE, CINAHL and Scopus) was conducted from the start of indexing to the August 31, 2020. Search strategies for each database used the particular databases controlled vocabulary (e.g., medical subject headings (Mesh) terms) and free-text terms (Appendix A). A search on Google and Google Scholar was undertaken to identify gray literature (i.e. literature that has not been formally published in a peer-reviewed indexed format) using simulation methods in perinatal and reproductive epidemiology. A combination of key terms were used: simulat* AND bias AND (reproductive OR perinatal). Due to the large nature of search results in Google Scholar, the search was limited to the first 100 results returned sorted by relevance. To capture articles that may have been indexed incorrectly, further data collection was completed using a systematic retrospective snowball sample. Here, a hand search was conducted using the reference lists of included studies to identify additional relevant articles. All references were exported to Endnote X9 (Thomson Reuters).

Study selection

Studies identified by the search strategy were initially screened for eligibility by the primary author. The initial eligibility criteria, based on an abstract and title screen, was: 1) examination of the bias types as defined in the search, and 2) focused on reproductive or perinatal outcomes as defined in the search (Appendix A). Studies were excluded using *a priori* exclusion criteria as follows: 1) does not include reproductive or perinatal outcomes in humans, 2) are conference abstracts, review papers (systematic, narrative or literature), editorials or opinion letters, and 3) are not published in English. Studies that fulfilled these criteria were obtained for a full-text review to determine if simulated data is applied as a method to quantify bias. Studies were excluded if the details of the simulation process were not included in the article. Title and abstract screening were undertaken by the primary author. For the full-text screening, a second independent reviewer (MO) conducted a dual review for a sub-sample (20%) of the records. When conflicts for including/excluding articles between the two reviewers occurred, a third independent reviewer (GT) was involved for a final decision.

Data extraction

Studies were retrieved for inclusion through a two-stage process according to the inclusion and/or exclusion criteria specified above. The key characteristics and methodology details were tabulated and discussed. Standard bibliographic information (authors, and journal year of publication) was extracted. Additionally, the objectives of each study were extracted, type of bias, exposure and outcomes, original cohort (if any), simulation method, simulation analysis, simulation results, author's conclusions, and the key findings of the simulation study. Studies were reported according to the type of bias. We reported study features such as the use of causal diagrams and statistical software, including the availability of code.

Results

Our searches returned 1390 records through bibliographic databases and an additional 171 records from gray literature searches. After removing duplicates 913 unique titles and abstracts remained of which 90 articles were retrieved for full-text screen.

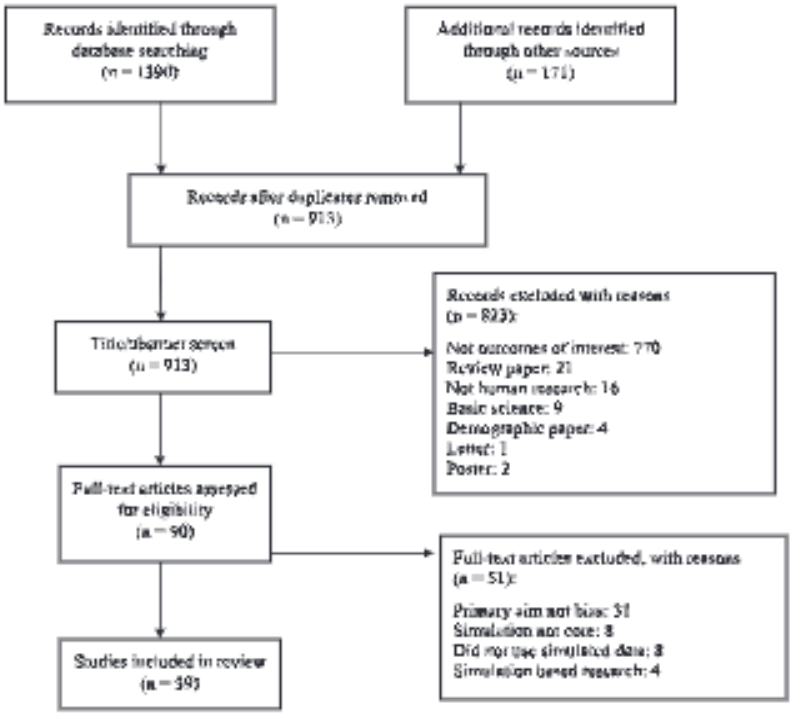

Fig. 1. Flowchart of the study selection process.

Of the 90 studies eligible for the full text screening, 51 were excluded (See Appendix B for reasons for full-text exclusions). The principal reason for exclusions were that the studies did not quantify bias as the primary aim study ($n = 31$). Other reasons for exclusion included not applying simulation or where the application of simulation were not core to the article ($n = 8$). Eight studies did not apply simulated data and four studies applied simulation for the purpose of learning in a clinical environment. A total of 39 articles met the inclusion criteria as the studies applied simulation methods to the quantification of bias in reproductive or perinatal epidemiology. The process of study identification, screening and inclusion is summarised in Figure 1. The included studies covered three main areas of bias: information ($n = 14$), selection ($n = 14$) and confounding ($n = 9$). One study quantified protection bias, defined by the authors as 'the effect of the ability to protect against giving birth to an unintended child' in measures of time-to-pregnancy [21]. Another study investigated the effects of attenuation in study designs used to determine the cumulative probability of pregnancy [22]. Overall, perinatal outcomes were examined in 27 studies and 12 studies examined reproductive outcomes. The timeline of the studies ranged from 1983 to 2019, with 18 studies published since 2015 (Fig. 2). See Appendix C for a summary of the study characteristics.

Information bias

Of the studies that quantified information bias, all quantified misclassification bias. The earliest published reproductive study [23] investigated reporting errors resulting from collecting self-reported data in a time-to-pregnancy study, producing bias towards the null. One study [24] investigated the potential magnitude of error resulting from loss to follow up in studies of fertility, noting that the return of pregnant drop-outs to the study biased cumulative pregnancy rates [24]. Four studies examined misclassification bias associated with gestational age. One study [25] examined misclassification bias caused by errors in gestational age on spontaneous abortion studies. Another study [26] evaluated the impact of mis specifying the distributions of weight gain and gestational age using directed acyclic diagrams to inform the simulation. A later study [27] specified a model that investigated Gaussian measurement error in gestational age on the subsequent risk of preterm birth, finding that parameter estimation was mostly unbiased. Lastly, a study [28] used gestational age at arrest of development to reduce misclassification bias for time-varying exposures on the risk of miscarriage. Three articles investigated misclassification bias in studies of the impact of pollutants on perinatal outcomes. The first study [29] applied simulation to estimate bias in relative risk estimates due to exposure misclassification in disinfection by-product in birthweight studies. A 2016 study [30] evaluated the impact of uncertainty in estimated Perfluorooctanoic acid drinking-water concentrations on estimated serum concentrations and pre-eclampsia. A later study [31] applied simulation to determine the impact of maternal residential mobility during pregnancy on identifying critical windows of susceptibility to term low birth weight from weekly exposure to particulate matter less than or equal to $10_{\mu m}$ in aerodynamic diameter (PM_{10}). A study from 2014,[33] evaluated bias arising from misclassification of pre-pregnancy body mass index and its association with early preterm births. Another study [33], quantified the extent to which current measures of gestational weight gain could bias the relationship between maternal weight gain and risk of preterm birth. One study [34] demonstrated how the correction for misclassifica-

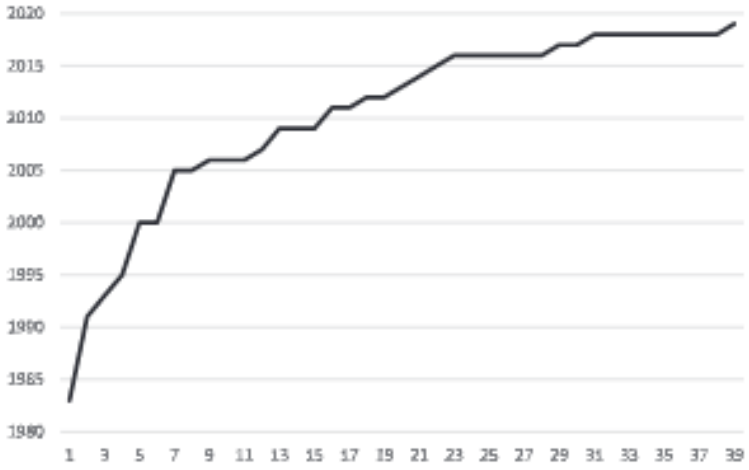

Fig. 2. Number of included studies (n = 39) by publication year.

tion in a time-varying exposure of influenza vaccination using survival analysis. Another study [35] demonstrated that bias increased with advancing gestational age at antiretroviral therapy initiation and the introduction of gestational age measurement error. The final study investigated the ability of the propensity score to reduce confounding bias in the presence of non-differential misclassification of treatment [36]. The authors showed in the presence of even moderate misclassification, all methods (adjustment, weighting, matching and stratification) increased bias estimates [36].

Selection bias

Of the three studies that examined bias in reproductive outcomes, the earliest [37] evaluated how the availability of contraception and induced abortion might bias studies of time trends in couple's fertility. The second reproductive study [38] focused on selection bias in pregnancy samples for time-to-pregnancy, with the authors finding that even when fecundity decreased with age, the estimation of the effect of age showed the opposite trend. Another reproductive study [39] investigated bias from left truncation in time-to-pregnancy, demonstrating that fixed or variable differential left truncation can bias results either towards or away from the null. A perinatal study [40] investigated left truncation bias in spontaneous abortion studies when the exposure is maternal smoking, with the simulation suggesting that a difference in 10 days or more in gestational age at entry biased the odds ratio of spontaneous abortion by more than 20%. Lisonkova and Joseph [41] investigated whether left truncation bias could explain the negative association between smoking and pre-eclampsia, finding a protective effect of pre-eclampsia given smoking even in simulations that did not require assumptions about early pregnancy loss. Kinlaw et al. [42] then examined the sensitivity of the assumptions in the Lisonkova and Joseph study, suggesting that the earlier study's results were highly dependent on assumptions regarding the strength of association between abnormal placentation and pre-eclampsia, resulting in less bias than the Lisonkova and Joseph study [41] suggested. Another study [43] also examined the smoking pre-eclampsia paradox with results indicating that the biased effect of smoking was estimated to reduce the odds of pre-eclampsia by 28% and after stratification by gestational age at delivery by 75%.

Three studies examined collider-stratification bias. The first study [44] investigated the 'birthweight' paradox, where birthweight specific mortality curves cross after stratification by smoking status. Another study [45] quantified selection bias when adjusting for gestational age, which was considered as the collider variable where preterm birth was a predictor for neonatal mortality. Here, conditioning on the collider of gestational age led to the reversal of exposure-outcome association [45]. A later study on the effect of asthma medication during pregnancy on major congenital malformations [46] evaluated the potential impact of selection bias due to conditioning on a collider of delivery after 20 weeks gestation. This study found that selection bias could be partially mitigated by controlling for other variables that are not colliders, on exposure-outcome pathway [46]. One study [47] quantified the impact of initial selection into the national birth dataset on different associations between well-established risk factors and pregnancy outcomes. Another study [48] illustrated how selection bias affecting studies restricted to very preterm births should be carefully interpreted, as pre-eclampsia can appear to reduce the risk of adverse neonatal outcomes. A later study [35] hypothesized that the lower risk of preterm birth amongst women who initiate antiretroviral therapy during pregnancy compared to those already receiving therapy is due to selection bias. In this study, selection bias increased with advancing gestational age at therapy initiation and the introduction of gestational age measurement error [35]. Another study [49] used simulation to demonstrate how conditioning on live birth can induce selection bias in studies of drug effects on pregnancy complications when fetal death is a competing risk or is also caused by the complication. Another study [50] quantified both selection and misclassification bias in studies of reproductive abortion-related mortality, applying explicit assumptions in a multiple-bias analysis model.

Confounding bias

The earliest reproductive paper in this review examined bias arising from inadequate statistical control that impacts gravidity and gravidity-specific relative risks [51]. Another study [52] quantified potential sources of bias related to seasonal variation in reproductive failures, demonstrating that seasonal planning differences in subfecund females lead to variations in reproductive failures. A later study [53] found that differential persistence in preg-

Table 1
Summary of the key findings related to the types of bias investigated and simulation methods applied by the included studies (n = 39)

		n (%)
Type of bias examined	Information	14 (36)
	Selection	14 (36)
	Confounding	9 (23)
	Protection	1 (2.5)
	Attenuation	1 (2.5)
	Multiple types	4 (10)
Area of main focus	Perinatal	27 (69)
	Reproductive	12 (31)
Source of data for simulation	Register/database	24 (61)
	Simulation	12 (31)
	Previous study	3 (8)
Causal diagram provided	Yes	11 (28)
Source of bias parameters	Previous study	28 (72)
	Not stated	11 (28)
Simulation iterations	Reported in studyMinimumModeMaximum	24 (62)1001,000100,000
Code availabilityType of software used	Available onlineAvailable upon requestRSASSTATAOther*	6 (15)2 (5)8 (21)5 (13)4 (10)3 (8)

* Other included Microsoft Excel, Basic and Matlab.

nancy attempts, which are age-dependent, leads to the observation that older women conceive faster on average unless unsuccessful waiting times are considered. The final reproductive study [54] highlighted fixed cohort bias in pregnancy studies when estimating the effects of seasonal exposures on birth outcomes. When shorter and longer pregnancies are missing, bias can be substantial, changing the estimated effect of temperature on gestational length [54]. One perinatal study [55] postulated that the relationship between birthweight and mortality could be explained by confounding factors that decrease birthweight and also increase mortality. The same authors expanded their previous model in a later study [56] to demonstrate that the addition of a simple exposure could produce a paradoxical reversal of risk among small babies. A later study [57] considered the effects of time-varying covariates such as weight gain on preterm delivery when their mutual dependence relies on gestational age. The study suggested that failure to account for confounding effects of time on gestational weight gain produced a stronger association between higher weight gain and later delivery [57]. One study [58] investigated bias when gestational age acting as a mediator between maternal asthma and small for gestational age. Here, the authors consider small for gestational age to be an absorbing variable, that is the observed association between the exposure and small for gestational age solely reflected the direct effect of the exposure on birth weight [58]. The final perinatal study [59] used simulation to quantify cluster-level confounding of the effect of caesarean section on the Apgar score, finding that preferential within-cluster matching approach showed a good performance in the presence of big and small clusters.

Simulation methods

Of the 39 included studies, 24 studies based their simulations on an original cohort; three studies based their simulations on previously published papers with the remaining twelve studies creating hypothetical cohorts. Key findings related to the types of bias investigated and the simulation methods applied are summarized in Table 1. Nine studies used Monte Carlo simulation methods for data generation. One study used a hidden Markov model to account for measurement error in gestational age [27]. The primary method of statistical analysis was logistic regression, with sixteen studies reporting odds ratios. Cox regression models were used to calculate hazard ratios in eight studies. Relative risks were reported in six studies. Two reproductive studies [55,56] produced mortality curves and one [38] produced Kaplan-Meier curves for waiting time-to-pregnancy. One perinatal study produced generate birthweight-specific mortality curves stratified on a binary risk factor of interest [44].

Eleven studies used causal diagrams to represent their causal research question and inform their simulation studies. One reproductive study applied a causal diagram in a study of time trends in fertility [37]. Two perinatal studies used a directed acyclic diagram (DAG) where gestational age was the potential mediator between the exposure of interest and birth weight [45,58]. A study on information bias, used DAGs to depict the correlation between weight gain and gestational age longitudinally across gestation before building simulations [26]. Three studies used DAGs to describe the smoking-pre-eclampsia paradox [42–44]. Another study used a DAG to illustrate collider-stratification bias when conditioning on live birth [49]. Two studies used DAGs to illustrate bias resulting from restriction to live births in pharmacological studies [46,49], and one study illustrated measurement error in a pharmacological study [36]. Nineteen studies disclosed their statistical software. R were the most commonly used in eight studies, Five authors used SAS, four used STATA, one used Microsoft Excel and an early study (from 1993) used BASIC. One study used a combination of R and MATLAB. Six studies made their code available online and two others agreed to make code available upon request. (Appendix D contains a checklist for the application of simulation in studies that quantify bias using observational data).

Discussion

Although it is standard practice to report potential sources of bias, this review highlights that few reproductive and perinatal epidemiological studies have quantitatively evaluated bias. This is the first review of the application of simulation to quantifying the influence of bias, providing a catalogue of diverse application in the field. This is an important topic due to the potential to improve causal inference by providing context for observational results. Our findings highlight that although simulation is a promising method for quantifying the influence of bias, it remains infrequently utilized in reproductive and perinatal studies. Nonetheless, there has been a significant increase in its application to evaluate bias in this specific field since 2015. As might be expected, there were considerable differences in how the simulations were designed, presented, and reported, revealing a range of specific areas where improvement can be made.

One of the main advantages of simulation is the potential to investigate scenarios that were not directly observed or cannot be directly observed, scenarios in which the true underlying causal effect of an exposure on an outcome can be bounded but is gen-

erally unknown [10]. This is particularly relevant in perinatal research where the study population is incompletely observable, in part due to perinatal databases restricting to specified gestational time-periods in pregnancy. This issue is not unique to registries, as prospective cohorts are also usually limited to "recognized" pregnancies. As evidenced in this review, such left truncation can result in bias toward the null, bias away from the null, and loss of precision [41,42,61,63]. Importantly, simulating a population for unmeasured confounders can not only improve precision but can potentially highlight the impact of rare pathologies on adverse outcomes [56]. Further, simulation can illustrate bias when stratifying on an intermediate such as gestational age or birth weight, which can lead to unexpected results such as the intersection of mortality curves [44,55,56]. Simulation can also demonstrate whether collider-stratification results in a level of bias that would be of concern [42–44,49,62], as the incorrect handling of colliders can yield paradoxical associations [42–44,49,62]. This is a valid concern for researchers, as conditioning on a collider such as gestational length will introduce bias, regardless of whether that collider is restricted on or adjusted for in a model [62]. As demonstrated in this review, simulation is a valuable method to correct estimates for potential measurement error. A true representation of the causal pathway would typically consider more than one type of bias, yet only four of the reviewed studies considered more than one type of bias [26,35,50,62]. However, it remains unclear whether there is a lack of confidence or lack of interest by researchers has led to the limited application of simulation in multiple bias analysis in reproductive and perinatal epidemiology.

This review highlighted several attributes that were common to the included studies. The first is the use of causal diagrams to inform the development of the simulation. Causal diagrams are powerful tools that can aid researchers in constructing models based on hypothesized biologic mechanisms in order to produce the least biased effect estimates possible [64]. Considerable literature has been published on the best approach to the application of causal diagrams, more recently with perinatal examples [64,65]. Despite the evidence that information bias has a clear and helpful representation within the causal diagram framework [66], there remains limited application of causal diagrams in the wider epidemiological context. The second attribute common to the included studies was the careful selection of bias parameters to represent effect sizes within the bounds of associations. A common caveat acknowledged in the included studies was that the simulation was only as good as the assumptions that informed the parameters [35,41–43,46,50]. Bias parameters and the causal structures that underpin the simulations are largely based on researcher knowledge and previously published literature. Although such caveats are unavoidable, a general limitation of the included studies was the lack of clarity from where the estimated bias parameters were derived. Overall, a limitation of the application of simulation in epidemiology, which was also evidenced in this review, is that the simulations are often over-simplified and do not reflect the true complexity of the true causal association. Nonetheless, the application of simulation was an improvement, as it accounted for greater complexity of the underlying true causal pathways than observational studies alone.

Scientific evidence is strengthened by the replication of important findings by multiple independent studies; however, replication may not be always feasible due to costs and difference in the context where the epidemiological population data were drawn [67]. An attainable minimum standard can be reproducibility, where independent investigators subject their original data to their analysis and interpretations based on published protocols and code [67]. The reporting of simulation protocols and the release of code are important considerations in reproductive and perinatal epidemiology [16], enabling researchers to identify bias scenarios commonly found in all reproductive and perinatal research questions. However, only a handful of included studies in this review shared their code in the public domain. Increasing study reproducibility can elucidate processes that produce contradictory results. A working example of contradictory results was evident in this review in regards to the paradoxical inverse association between maternal smoking and pre-eclampsia [41,42]. One study proposed that left truncation bias was responsible for a protective effect of maternal smoking on pre-eclampsia, based on the assumption that there was no direct effect of smoking on pre-eclampsia but an indirect effect through abnormal placentation [41]. Another research group examined the sensitivity of these conclusions, constructing a new simulation model using published estimates to frame their bias parameters [42]. These authors concluded that under more empirical assumptions, bias from left truncation does not fully account for the inverse association between maternal smoking and pre-eclampsia [42]. Rather, when left truncation may result from the exposure, researchers should describe the target population and parameter of interest prior to assessing potential bias [42].

There are no published guidelines for the development and application of simulation studies in epidemiology for the purpose of bias analysis. A 2014 paper provided a guide for conducting and presenting quantitative bias analysis research studies, highlighting the importance of diagrams to establish causal pathway and the careful selection bias parameter [11]. In recent years, several epidemiological studies have been published under the framework of quantitative bias analysis [68]. As evidenced in this review, the number of studies publishing under the quantitative bias analysis framework is limited [32] compared to the number of studies applying simulation in bias analysis. This may indicate that a broader approach for the development, analysis and reporting of studies applying simulation in bias analysis is required. In 2013 the STRengthening Analytical Thinking for Observational Studies (STRATOS) group was established to guide health researchers to meet the rapid development of statistical methodology [19]. Recently, members of the STRATOS simulation study panel published a guide on the application of statistical simulations in health research, which included a helpful example of measurement error in confounding and exposure variables [18]. Yet it could be considered a potential missed opportunity to consider the impact of bias more holistically, including complications from selection bias and the dangers of stratifying or adjusting for colliders in observational studies. Overall, there remains a lack of guidance to inform researchers of the practical steps in the development, analysis and reporting of simulation for the quantification of the influence of multiple types of bias in observational epidemiological studies.

The strength of this review was a comprehensive search strategy that included keyword searches and citations indexes of key sources of simulation in reproductive and epidemiology studies that investigated bias. This review also considered the application of simulated data to different types of bias in the broad research areas of reproductive and perinatal health. Our search strategy restricted studies to those that described simulation methods within the paper. Consequently we may have excluded studies that included simulation methods in supplementary material or those quantifying bias through other methods. Due to a lack of formal critical appraisal tools for simulation studies, an additional limitation is that this study did not conduct a quality assessment of the included studies. Although the included studies' primary aims centered on bias analysis with simulation as an integral component, the simulation itself was not always their central focus. As such, the studies did not need to report all important aspects of their simulations to achieve their study aims. Finally, as we intended to identify the extent to which simulation has been applied in the field, the types of applications of simulation, and potential advantages of simulation, we did not evaluate the degree to which the

simulations in each study were effective in achieving the respective individual study aims.

Conclusion

The use of simulation to quantify bias in reproductive and perinatal epidemiology remains relatively limited. The use of causal diagrams and the reporting of simulation code is minimal. The current applications and examples of simulation demonstrated that such techniques can be implemented to more comprehensively investigate associations. Simulation should be considered as a complementary method in observational studies, rather than a competing method of analysis. It is possible that the potential of simulation to address common issues of bias in reproductive and perinatal epidemiology is under-emphasized due to an overall lack of knowledge in the process of their application, lack of the necessary computational skillset among researchers in the field, lack of a well-established reporting standard, or possibly the lack of knowledge on potential applications. Increased adoption could be achieved through a more holistic approach to research regarding simulation methodology, which might include cataloguing successful applications of simulation, development of protocols for reporting of simulations studies, complementary application of simulation in observational studies to address bias, and sharing of simulation code.

Acknowledgments

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Appendix A. Search strategy by database

Simulat* AND Bias AND (Perinatal OR Reproductive)		
Bias	**Perinatal OR Reproductive**	
Pubmed (includes simulat*[tiab] with the below search terms) Bias[mh] OR Selection bias*[tiab] OR confound* bias*[tiab] OR collider*[tiab] OR truncat* bias*[tiab] OR censor* bias*[tiab] OR misclass* bias*[tiab] OR measurement bias*[tiab]	Pregnancy[mh] OR Pregnancy complications[mh] OR Infant Death[mh] OR Fetal Development[mh] OR *birth*[tiab] OR perinatal[tiab] OR neonatal[tiab] OR fetal[tiab] OR foetal[tiab] OR abortion[tiab] OR pregnancy termination[tiab] OR preterm[tiab] OR premature labour[tiab] OR small for gestational age[tiab] OR macrosomia[tiab] OR anomalies[tiab] OR malformations[tiab] OR defects[tiab] OR pregnancy hypertension[tiab] OR placenta previa[tiab] OR placenta praevia[tiab] OR intrauterine growth retardation[tiab] OR pregnancy loss[tiab] OR premature rupture membranes[mh]	Reproductive techniques[mh] OR Embryonic and Fetal Development[mh] OR Fertilization[mh] OR Fertility[mh] OR fecund*[tiab] OR placent*[tiab] OR reproductive tech*[tiab] OR blastocyst transfer[tiab] OR tubal embryo[tiab] OR fertil*[tiab] OR test-tube[tiab] OR steril*[mh]
Medline (includes simulat*.ti,ab with the below search terms) Bias/exp OR Selection bias*.ti,ab OR Confound* bias*.ti,ab OR collider* bias*.ti,ab OR truncat* bias*.ti,ab OR censor* bias*.ti,ab OR misclass* bias*.ti,ab OR measurement bias*.ti,ab	Pregnancy/exp OR Pregnancy complications/exp OR Infant Death/exp OR Fetal Development/exp OR birth*.ti,ab OR perinatal.ti,ab OR neonatal.ti,ab OR fetal.ti,ab OR foetal.ti,ab OR abortion.ti,ab OR pregnancy termination.ti,ab OR preterm.ti,ab OR premature labour.ti,ab OR small for gestational age.ti,ab OR macrosomia.ti,ab OR anomalies.ti,ab OR malformations.ti,ab OR defects.ti,ab OR pregnancy hypertension.ti,ab OR placenta previa.ti,ab OR placenta praevia.ti,ab OR intrauterine growth retardation.ti,ab OR pregnancy loss.ti,ab OR premature rupture membrane.ti,ab	Reproductive techniques/exp OR Embryonic and Fetal Development/exp OR Fertilization/exp OR Fertility/exp OR fecund*.ti,ab OR placent*.ti,ab OR reproductive tech*.ti,ab OR blastocyst transfer.ti,ab OR tubal embryo.ti,ab OR fertil*.ti,ab OR test-tube.ti,ab OR steril*.ti,ab
EMBASE (includes simulat*.ti,ab with the below search terms) Bias/exp OR Selection bias*.ti,ab OR Confound* bias*.ti,ab OR collider* bias*.ti,ab OR truncat* bias*.ti,ab OR censor* bias*.ti,ab OR misclass* bias*.ti,ab OR measurement bias*.ti,ab	Pregnancy/exp OR Pregnancy complications/exp OR Infant Death/exp OR Fetal Development/exp OR birth*.ti,ab OR perinatal.ti,ab OR neonatal.ti,ab OR fetal.ti,ab OR foetal.ti,ab OR abortion.ti,ab OR pregnancy termination.ti,ab OR preterm.ti,ab OR premature labour.ti,ab OR small for gestational age.ti,ab OR macrosomia.ti,ab OR anomalies.ti,ab OR malformations.ti,ab OR defects.ti,ab OR pregnancy hypertension.ti,ab OR placenta previa.ti,ab OR placenta praevia.ti,ab OR intrauterine growth retardation.ti,ab OR pregnancy loss.ti,ab OR premature rupture membrane.ti,ab	Reproductive techniques/exp OR Embryonic and Fetal Development/exp OR Fertilization/exp OR Fertility/exp OR fecund*.ti,ab OR placent*.ti,ab OR reproductive tech*.ti,ab OR blastocyst transfer.ti,ab OR tubal embryo.ti,ab OR fertil*.ti,ab OR test-tube.ti,ab OR steril*.ti,ab

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(continued)

Simulat* AND Bias AND (Perinatal OR Reproductive)		
Bias	**Perinatal OR Reproductive**	
CINAHL (includes TI simulat* AND AB simulat* with the below search terms)		
MH Bias OR TI "selection bias*" OR AB "selection bias*" OR TI "confound* bias*"OR AB "confound* bias*" OR TI "collider* bias*" OR AB "collider* bias*" OR TI "truncat* bias*" OR AB "truncat* bias*" OR TI "censor* bias*" OR AB "censor* bias*"OR TI "misclass* bias*"OR AB "misclass* bias*" OR TI "measurement bias*" OR AB "measurement bias*"	MH Pregnancy OR MH "Pregnancy complications" OR MH "Infant Death" OR MH "Fetal Development" OR TI *birth* OR AB *birth* OR TI perinatal OR AB perinatal OR TI neonatal OR AB neonatal OR TI fetu OR AB fetal OR TI foetal OR AB foetal OR TI abortion OR AB abortion OR TI "pregnancy termination" OR AB "pregnancy termination" OR TI preterm OR AB preterm OR TI "premature labour" OR AB "premature labour" OR TI "small for gestational age" OR AB "small for gestational age" OR TI macrosomia OR AB macrosomia OR TI anomalies OR AB anomalies OR TI malformations OR AB malformations OR TI defects OR AB defects OR TI "pregnancy hypertension" OR AB "pregnancy hypertension" OR TI "placenta previa" OR AB "placenta previa" OR TI "placenta praevia" OR AB "placenta praevia" OR TI "intrauterine growth retardation" OR AB "intrauterine growth retardation" OR TI "pregnancy loss" OR AB "pregnancy loss" OR TI "premature rupture membranes" OR AB "premature rupture membranes"	MH "Reproductive techniques" OR MH "Embryonic and Fetal Development" OR MH Fertilization OR MH Fertility OR TI fecund* OR AB fecund* OR TI placent* OR AB placent* OR TI "reproductive tech*" OR AB "reproductive tech*" OR TI "blastocyst transfer" OR AB "blastocyst transfer" OR TI "tubal embryo" OR AB "tubal embryo" OR TI fertile* OR AB fertil* OR TI test-tube OR AB test-tube OR TI steril* OR AB steril*
SCOPUS (includes ALL(simulat*) with the below search terms)		
TITLE-ABS-KEY("selection bias*" OR "confound* bias*" OR "collider* bias*" OR "truncat* bias*" OR "censor* bias*" OR "misclass* bias*" OR "measurement bias*")	TITLE-ABS-KEY(Pregnancy OR (Pregnancy complication) OR (Infant Death) OR (Fetal Development) OR *birth* OR perinatal OR neonatal OR fetal OR foetal OR abortion OR "pregnancy termination" OR preterm OR "premature labour" OR "small for gestational age" OR macrosomia OR anomalies OR malformations OR defects OR "pregnancy hypertension" OR "placenta previa" OR "placenta praevia" OR "intrauterine growth retardation" OR "pregnancy loss" OR "premature rupture membranes")	TITLE-ABS-KEY((Reproductive techniques) OR (Embryonic and Fetal Development) OR Fertil?zation OR Fertility OR fecund* OR placent* OR "reproductive tech*" OR "blastocyst transfer" OR "tubal embryo" OR fertil* OR test-tube OR steril*)

Appendix B. Records excluded at full-text screening with reasons

1. Adebayo et al. Analyzing infant mortality with geoadditive categorical regression models: A case study for Nigeria. Economics and Human Biology 2004, 2(2):229-244
   Reason for exclusion: The primary aim is not to quantify bias.
2. Aiken et al. Management of fetal malposition in the second stage of labor: A propensity score analysis. American Journal of Obstetrics and Gynecology 2015 212(3):335e1-335e7
   Reason for exclusion: This study did not use simulated data.
3. Bang et al. Estimating treatment effects in studies of perinatal transmission of HIV. Biostatistics 2004 5(1):31-43
   Reasons for exclusion: The primary aim is not to quantify bias.
4. Basso et al. The performance of several indicators in detecting recall bias. Epidemiology 1997 8(3):269-274
   Reasons for exclusion: The primary aim is not to quantify bias.
5. Brubaker et al. Vaginal progesterone in women with twin gestations complicated by short cervix: A retrospective cohort study. BJOG 2015 122(5):712-718
   Reasons for exclusion: This study did not use simulated data.
6. Chaemsaithong et al. Uterine artery pulsatility index in the first trimester: assessment of intersonodiagramer and intersampling site measurement differences. Journal of Maternal-Fetal and Neonatal Medicine 2018 31(17):2276-2283
   Reasons for exclusion: The primary aim is not to quantify bias.
7. Cies et al. Population pharmacokinetics of gentamicin in neonates with hypoxemic-ischemic encephalopathy receiving controlled hypothermia. Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy 2018 38(11):1120-1129
   Reasons for exclusion: The primary aim is not to quantify bias.
8. Cirillo et al. The human factor: does the operator performing the embryo transfer significantly impact the cycle outcome? Human Reproduction 2020 35(2):275-282
   Reasons for exclusion: This study did not use simulated data.
9. De Oliveira et al. A random-censoring Poisson model for underreported data. Statistics in Medicine 2017 36(30):4873-4892
   Reasons for exclusion: The primary aim is not to quantify bias.
10. Ding et al. Estimating effect of environmental contaminants on women's subfecundity for the MoBa study data with an outcome-dependent sample scheme. Biostatistics 2014 15(4):636-650
    Reasons for exclusion: The primary aim is not to quantify bias.
11. Gard et al. A coarsened multinomial regression model for perinatal mother to child transmission of HIV. BMC Medical Research Methodology 2008 8(1):46-46
    Reasons for exclusion: The primary aim is not to quantify bias.
12. Hatch et al. Evaluation of selection bias in an internet-based study of pregnancy planners. Epidemiology 2016 27(1):98-104

Reasons for exclusion: This study did not use simulated data.

13. Heinke et al. Quantification of selection bias in studies of risk factors for birth defects among livebirths. Paediatric & Perinatal Epidemiology 2020 34(6):655-664
Reasons for exclusion: The application of simulation was not core to the paper.
14. Honein et al. Modeling the potential public health impact of prepregnancy obesity on adverse fetal and infant outcomes. Obesity 2013 21(8):1276-1283
Reasons for exclusion: The primary aim is not to quantify bias.
15. Horton et al. A population-based approach to analyzing pulses in time series of hormone data. Statistics in Medicine 2017 36(16):2576-2589
Reasons for exclusion: The primary aim is not to quantify bias.
16. Howards et al. Adjusting for bias due to incomplete case ascertainment in case-control studies of birth defects. Practice of Epidemiology 2015 181(8):595-607
Reasons for exclusion: The application of simulation was not core to this paper.
17. Janssen et al. Towards rational dosing algorithms for vancomycin in neonates and infants based on population pharmacokinetic modeling. Antimicrobial Agents & Chemotherapy 2016 60(2):1013-1021
Reasons for exclusion: The primary aim is not to quantify bias.
18. Jiang et al. Causal Mediation Analysis in the Presence of a Misclassified Binary Exposure. Epidemiological Methods 2019 1(8)
Reasons for exclusion: The primary aim is not to quantify bias.
19. Kim et al. Flexible Bayesian human fecundity models. Bayesian Analysis 2012 7(4):771-800
Reasons for exclusion: The primary aim is not to quantify bias.
20. Kim et al. A model-based approach to detection limits in studying environmental exposures and human fecundity. Statistics in Biomedicine 2019 11:524-547
Reasons for exclusion: The application of simulation is not core to the study.
21. Kone et al. Heckman-type selection models to obtain unbiased estimates with missing measures outcome: theoretical considerations and an application to missing birth weight data. BMC Medical Research Methodology 2019 19(1):231
Reasons for exclusion: The primary aim is not to quantify bias.
22. Kovacevic et al. Fetal aortic valvuloplasty: investigating institutional bias in surgical decision-making. Ultrasound in Obstetrics & Gynecology 2014 44(5):538-544
Reasons for exclusion: This is simulation based research.
23. Lau. On the heterogeneity of fecundability. Lifetime Data Analysis 1996 2(4):403-415
Reasons for exclusion: The primary aim is not to quantify bias.
24. Manuel et al. Matched case-control data with a misclassified exposure: what can be done with instrumental variables? Biostatistics 2019 0:1-18
Reasons for exclusion: The application of simulation was not core to the study.
25. Marston et al. The effects of HIV on fertility by infection duration: evidence from African population cohorts before antiretroviral treatment availability. AIDS 2017 31(1):S61-S76
Reasons for exclusion: The study did not use simulated data.
26. Molitor et al. Using Bayesian graphical models to model biases in observational studies and to combine multiple sources of data: application of low birth weight and water disinfection by-products. Journal of Royal Statistical Society 2009 172:615-637
Reason for exclusion: The application of simulation was not core to the study.
27. Nadler et al. Clinicians can accurately assign Apgar scores to video recordings of simulated neonatal resuscitations. Simulation in Healthcare: Journal of the Society for Medical Simulation 2010 5(4):204-212
Reasons for exclusion: This is simulation based research.
28. Osei et al. What happened to the IUD in Ghana? African Journal of Reproductive Health 2005 9(2):76-91
Reasons for exclusion: The primary aim is not to quantify bias.
29. Parry et al. An online tool for investigating clinical decision making. Information for Health and Social Care 2004 29(1):75-85
Reasons for exclusion: This is simulation based research.
30. Piao et al. Semiparametric model and inference for spontaneous abortion data with a cured proportion and biased sampling. Biostatistics 2018 19(1):54-70
Reasons for exclusion: The primary aim is not to quantify bias.
31. Radin et al. Maternal recall error in retrospectively reported time-to-pregnancy: an assessment and bias analysis. Paediatric and Perinatal Epidemiology 2015 29(6):576-588
Reasons for exclusion: The application of simulation was not core to this paper.
32. Rosenbaum. Confidence intervals for uncommon but dramatic responses to treatment. Biometrics 2007 63(4):1164-1171
Reasons for exclusion: This study did not use simulated data.
33. Rousson et al. Stabilizing cumulative incidence estimation of pregnancy outcome with delayed entries. Biometrical Journal 2019 61:1290-1302
Reasons for exclusion: The application of simulation was not core to the paper.
34. Sallmen et al. Selection bias due to parity-conditioning in studies of time trends in fertility. Epidemiology 2015 26(1):85-90
Reasons for exclusion: The application of simulation was not core to the paper.
35. Sampson et al. Predictive performance of a gentamicin population pharmacokinetic model in neonates receiving full-body hypothermia. Therapeutic Drug Monitoring 2014 36(5):584-589
Reasons for exclusion: The primary aim is not to quantify bias.
36. Shaffer et al. Analysis of neonatal clinical trials with twin births. BMC Medical Research Methodology 2009 9(1):12-21.
Reasons for exclusion: The primary aim is not to quantify bias.
37. Slager et al. Stoppage: an issue for segregation analysis. Genetic Epidemiology 2001 20:328-339
Reasons for exclusion: The primary aim is not to quantify bias.
38. Stott-Miller et al. Increased risk of orofacial clefts associated with maternal obesity: case-control study and Monte Carlo-based bias analysis. Paediatric & Perinatal Epidemiology 2010 24(5):502-512
Reasons for exclusion: The primary aim is not to quantify bias.

39. Takada et al. Practical approaches for design and analysis of clinical trials of infertility treatments: crossover designs and the Mantel-Hansel method are recommended. Pharmaceutical Statistics: Journal of the Pharmaceutical Industry 2015 14(3):198–204
Reasons for exclusion: The primary aim is not to quantify bias.
40. Van Eekelen et al. A comparison of the beta-geometric model with landmarking for dynamic prediction of time to pregnancy. Biometrical Journal 2019 62(1):175–190
Reasons for exclusion: The primary aim is not to quantify bias.
41. Van Os et al. Influence of cut-off value on prevalence of short cervical length. Ultrasound in Obstetrics & Gynecology 2017 49(3):330–336
Reasons for exclusion: The primary aim is not to quantify bias.
42. Venkatacharya. An examination of a certain bias due to truncation in the context of simulation models of human reproduction. The Indian Journal of Statistics 1969 31(3/4):397–412
Reasons for exclusion: This primary aim is not the application of simulation to quantify bias.
43. Weinberg et al. Efficiency and bias in studies of early pregnancy loss. Epidemiology 1992 3(1):17–22
Reasons for exclusion: The primary aim is not to quantify bias.
44. Weinberg et al. Pitfalls inherent in retrospective time-to-event studies: the example of time to pregnancy. Statistics in Medicine 1993 12:867–879
Reasons for exclusion: This is a statistical study whose primary aim is not the quantification of bias.
45. Wilbaux et al. Characterizing and forecasting individual weight changes in term neonates. Journal of Pediatrics 2016 173:101–107
Reasons for exclusion: The primary aim is to not to quantify bias.
46. Williams & Nix. Bias in risk estimation: application to Down's syndrome screening. Statistics in Medicine 2002 21(17):2495–2509
Reasons for exclusion: The primary aim is the demonstration of a method.
47. Wilson et al. Confounder selection via penalized credible regions. Biometrics 2014 70(4):852–861
Reasons for exclusion: The primary aim is not the application of a simulation to quantify bias.
48. Wilson et al. Bayesian distributed lag interaction models to identify perinatal windows of vulnerability in children's health. Biostatistics 2017 18(3):537–552
Reasons for exclusion: The primary aim is not to quantify bias.
49. Yland et al. Methodological approaches to analyzing IVF data with multiple cycles. Human Reproduction 2019 34(3):549–557
Reasons for exclusion: The study did not apply simulation.
50. Zekavat et al. A computational model of 1,5-AG dynamics during pregnancy. Physiological Reports 2017 5(16):13375
Reasons for exclusion: The primary aim is not to quantify bias.
51. Zelop et al. Cardiac arrest during pregnancy: ongoing clinical conundrum. American Journal of Obstetrics & Gynecology 2018 219(1):51–61
Reasons for exclusion: The study applied simulation based research.

Appendix C. Supplementary Table 1. Summary of the characteristics of the studies quantifying bias ($n = 39$) in the review

First author (year of publication)	Aim(s) of the simulation	Key findings of the simulation	Author's conclusion
Olsen[51] (1983)	To demonstrate bias resulting from the inadequate control of exogenous effects in gravidity and pregnancy order specific rates.	In the simulated scenarios where the number of women with low gravidity is high in the exposed group, the odds ratio will be too low when using inadequate statistical control. Conversely, high numbers of women with high gravidity in the exposed group will lead to an overestimated odds ratio.	Stratification based on either pregnancy order or gravidity alone can occasionally produce misleading results.
Baird[23] (1991)	To examine reporting errors from collecting data on time-to-pregnancy.	Substantial power was lost in detecting weak exposures yet exposures that reduce fecundability by 50%, could still be detected with 80% power in samples of about 100 women (half of which were exposed to a possible toxin).	Data from a brief measure of time-to-pregnancy can produce bias toward the null and concomitant loss of power due to non-differential misclassification. Women with short and long times to pregnancy had less misclassification compared to women who required 5–13 menstrual cycles to conceive.
Doody[24] (1993)	To investigate the potential magnitude of error resulting from loss to follow up in studies of fertility.	Using a range of clinical plausible assumptions, very large deviations were noted from loss to follow-up in the direction of elevated cumulative pregnancy rates. On a percentage basis, the largest effects were seen in groups that have the lowest monthly fecundity rates and the lowest cure rates.	Loss to follow-up can lead to a systematic error in the reporting of excess pregnancy, raising fecundity rates. The later return of pregnant drop-outs to the study introduced major confounding effects in the simulation. These effects were most evident in women with lower fecundity rates, lower 'cured' women (where 'cured' is fertility restored due to treatment), higher drop-outs, and higher pregnant drop-out return rates.

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First author (year of publication)	Aim(s) of the simulation	Key findings of the simulation	Author's conclusion
Basso[52] (1995)	To evaluate the influence of the magnitude of bias on seasonal patterns of reproductive failures.	Under conditions that were more extreme than those observed in the original cohort, bias related to differential pregnancy planning was marginal in the simulation.	Correcting for seasonal patterns in reproductive failures may eliminate bias associated with the seasonal variation in pregnancy planning.
Basso[53] (2000)	To determine whether a differential persistence in pregnancy attempt is a source of bias in time-to-pregnancy estimates.	Simulating moderate changes in planning behavior modified the waiting time distributions significantly. Persistence in trying to become pregnant was age-related.	Time-to-pregnancy studies are vulnerable to bias due to differential compliance in pregnancy planning. Relative risk measures can be biased up to 20% under realistic circumstances.
Juul[38] (2000)	To demonstrate selection bias associated with restriction to completed pregnancies in retrospective study designs.	The simulation showed that even if each women's fecundity decreased with age, estimation of the effect of age may show the opposite trend when restricted to completed pregnancies.	The different fecundability classes (high fecund; low fecund; age-dependent) becomes differentially distorted in the various age groups when the sampling based on completed pregnancies.
Sallmen[37] (2005)	To evaluate whether contraception and induced abortion might bias the direct study of time trends in fertility.	Comparing bias across two study designs, the strength of the bias is weaker in infertility study designs compared to time-to-pregnancy study designs; however the bias remains substantial	Dependent on the study design (time-to-pregnancy or infertility) access to effective contraception and elective abortion can bias the fertility rates, despite no actual change in fertility.
Wright[29] (2005)	To examine bias due to exposure misclassification from the use of weighted and unweighted exposure metrics (disinfection by-product) on fetal development.	The simulation showed that the attenuation of the true effect of the exposure was diminished when town mean concentrations with large variability were down-weighted.	The weighted town mean analysis produced less misclassification bias; but at the cost of greater variability in the effect estimates compared to the unweighted results.
Basso[55] (2006)	To explore confounding bias in the observed association between birth weight and neonatal mortality.	An observed steep gradient of risk for small babies at term could be produced by rare confounders, impacting associations between fetal growth and mortality.	A high rate of mortality in small babies could be explained by the presence of rare and unmeasured confounders that underlie the association of birth weight with mortality.
Howards[25] (2006)	To examine misclassification bias caused by errors in gestational age.	In this simulation, errors in gestational age dating did not bias Cox regression if 1) the error is not differential by exposure, 2) differential error by exposure is small, or 3) due to the tail of the distributions.	Pregnancies ending in spontaneous abortion are more likely to have errors in their gestational ages than pregnancies ending in live birth. However, bias resulting from these errors is likely to be marginal.
Mohr[60] (2006)	To evaluate two methods for constructing confidence limits for estimates of selection bias of relative risk estimates in perinatal cohort studies.	The effect of differential participation was modelled, resulting in small estimated effect on the risk estimates, even after adjustment for minimal confounding. Although some of the confidence intervals were wide, the bias was never larger than sixteen.	The two methods (logarithm of relative odds ratio and non-parametric bootstrap) used to compute confidence intervals give very similar results with the simulation study showing coverage probabilities were close to the 95% nominal level. As the logarithm of relative odds ratio is simpler to implement, it is a valid choice when the selection bias is modest.
Howards[40] (2007)	To assess the magnitude of bias introduced by fitting logistic versus Cox models using left-truncated data.	The simulation suggested that bias in the odds ratio will exceed 20% when average gestational age at entry for the exposed versus the unexposed differs by ten days or more. This was observed due to possible socioeconomic factors, such as education and ethnicity.	For variables where the exposure is associated with entry time, logistic regression may be subject to bias. Given that left truncation in studies may be related to exposure or important covariates, Cox regression model may be a better fit.
Basso[56] (2009)	To demonstrate the intersection of mortality curves due to the presence of unmeasured confounders.	In this simulation model, the addition of a single exposure (one that reduces birth weight and independently increases mortality) reversed the risk of mortality among small babies. Furthermore, the model explicitly showed how the mix of high- and low-risk babies within a given stratum of birth weight produced lower mortality for high-risk babies at low birth weights.	The intersection of mortality curves can be explained by the presence of confounding variables and the unequal mix of those variables across the birth weight distribution.

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First author (year of publication)	Aim(s) of the simulation	Key findings of the simulation	Author's conclusion
Key[21] (2009)	To quantify the effects of protection bias from accidental pregnancies on fecundity in time-to-pregnancy studies.	To see a change in the trend of fecundity, the simulations required extreme and implausible trends in accidental pregnancies and unrealistic sample sizes.	Protection bias probably does exist, however it is quantitatively not very important. In any study of fecundity trends or cross-cultural differences, the proportion of accidental pregnancies can be used to screen for the presence of this bias.
Whitcomb[44] (2009)	To quantify the collider-stratification bias between smoking and neonatal death.	When birth weight is a proxy for other causally related variables, inclusion in regression models of neonatal mortality generates an over-adjustment.	This study illustrated that when the birth weight–mortality relation is subject to substantial uncontrolled confounding, the bias on estimates of effect adjusted for birthweight may be sufficient to yield opposite causal conclusions. Therefore a factor that posed increased risk now appears protective.
Strand[54] (2011)	To quantify fixed cohort bias when estimating the effects of season and seasonal exposures on birth outcomes.	Using a fixed cohort does not only bias the estimated effects of the season (e.g., month of conception), but can also bias the estimated effects of seasonal exposures (e.g. air pollution and temperature).	This study demonstrated that the size of the fixed cohort bias can be substantial, causing great changes in the months that most affect gestational length and changed the estimated effect of temperature on gestational length.
Wilcox[45] (2011)	To explore bias resulting from adjustment when gestational age is a mediator.	The simulations demonstrated that under plausible conditions, reversal of exposure-outcome associations can occur due to collider bias.	Unmeasured risk factors complicate inference about the risk of morbidity outcomes due to immaturity alone. Adjustment for gestational age is likely to produce biased estimates.
Ahrens[34] (2012)	To correct for exposure misclassification when using survival analysis with a time-varying exposure	Correction for misclassification bias in a simulation could result in a much greater change in effect estimates depending on the magnitude and pattern of exposure misclassification.	In this simulation, correction for misclassification of prenatal influenza vaccination resulted in an adjusted hazard ratio that was slightly higher and less precise than the conventional analysis.
Hutcheon[33] (2012)	To quantify bias from conventional gestational weight gain measures on the relationship between maternal weight gain and risk of preterm birth.	Bias was likely due to a positive correlation between the adequacy ratio and gestational duration, resulting from increased differences between observed and expected weights as the pregnancy progressed.	Conventional measures of gestational weight gain introduce a significant degree of bias when assessing the relationship between gestational weight gain and risk of preterm birth < 32 gestational weeks.
Schisterman[61] (2013)	To demonstrate selection bias using truncated data in a time-to-pregnancy study.	Fixed or variable non-differential left truncation will results in a loss of precision. Fixed or variable differential left truncation will result in a bias either towards or away from the null, including a loss of precision.	Null-bias can be induced when events occur prior to truncation time. When deaths occur before the truncation time, identifying if these prior events are likely associated with exposure is important.
Lash[32] (2014)	To evaluate the direction, magnitude, and uncertainty in estimates as a result of misclassification bias from pre-pregnancy body mass index on early preterm births.	The applications of probabilistic-bias analysis to frequency-weighted datasets using simulation enabled the same conceptual correction to be applied to each data record. This allowed the covariates required for adjustment to account for misclassification.	Probabilistic bias analyses suggested that the association between underweight and early preterm birth was overestimated by the conventional approach. However, the associations between over-weight categories and early preterm birth were underestimated.
Lisonkova[41] (2015)	To determine whether left truncation bias could explain the paradoxical association between smoking and pre-eclampsia.	The simulation yielded a protective effect of pre-eclampsia given smoking. This protective effect of smoking was also evident in simulations that did not require assumptions about early pregnancy loss rates.	Left truncation bias due to differential rates of early pregnancy loss among smokers is a reasonable explanation for the inverse association between maternal smoking and pre-eclampsia.
Arpino[50] (2016)	To reduce bias due to cluster level confounders (hospitals and sample size) on estimates of caesarean section treatment on the 5-min Apgar score.	The simulations suggest that when the average cluster size is about 100 units, the bias of within cluster matching can be rather high. With smaller clusters of size 50, the results were even more negative when using pure within-cluster matching. The proposal of a preferential within-cluster matching is a better alternative in these cases.	The preferential within-cluster matching approach, combining the advantages of within-cluster and between cluster matching, showed a relatively good performance both in the presence of big and small clusters.

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First author (year of publication)	Aim(s) of the simulation	Key findings of the simulation	Author's conclusion
Avanasa[30] (2016)	To evaluate the impact of bias in estimated perfluorooctanoate drinking-water concentrations on the association with pre-eclampsia.	Using variables for uncertainty exposures allowed for specification of correlations in exposure measurement errors across years and individuals with shared exposure sources, in contrast to standard epidemiological models that assume independence of the measurement errors.	The correlated exposure uncertainty can substantially change estimated perfluorooctanoate serum concentrations, but results had only minor impacts on the association between perfluorooctanoate and pre-eclampsia.
Gerdts[50] (2016)	To quantify selection and misclassification bias in reproductive abortion-related mortality.	Using simulated data in multiple-bias analysis allowed for explicit assumptions to replace implicit assumptions through the quantification of selection bias and sensitivity/specificity.	After adjustment for selection bias, misclassification, and random error, there was approximately 20% increase in the reported proportion of abortion related deaths.
Hinkle[26] (2016)	To evaluate the impact of mis specifying the distributions of weight gain and gestational age.	Adjusting for gestational age, total weight gain will obtain unbiased estimates of the true association with neonatal mortality, assuming no unmeasured confounding. The simulation model permitted flexibility in identifying the most appropriate relationship between potential confounders with the exposure and outcome.	Using directed acyclic graphs and simulation, gestational weight gain is recognized as a time-varying exposure. There was no true association between weight gain and neonatal mortality. Adjusting for gestational age achieved unbiased estimates of the association between total gestational weight gain and neonatal mortality.
Luque-Fernandez**(2016)	To determine if selection bias could explain the paradoxical association between smoking pregnancy and pre-eclampsia as being a consequence.	Applying a simulated probabilistic sensitivity analysis, the inverse association of smoking on pre-eclampsia shifted from a 28% risk reduction to a non-significant bias-adjusted effect of 22% risk increase of pre-eclampsia for smokers compared with non-smokers.	Selection bias is evident from two sources. The first is conditioning on the collider of gestational weeks at delivery. The second source is the omittance of important confounders associated with smoking and pre-eclampsia, given that some pregnancies will not be selected into the population because they are left truncated.
Mitchell[57] (2016)	To investigate bias due to effect of gestational age on the time-varying confounder of gestational weight gain and it's association with preterm delivery.	The results of the simulations suggest that the survival model with interpolated gestational weight gain performs extremely well under various effect sizes, with no discernible bias and nominal coverage. When weight was measured only intermittently, an unbiased and precise hazard ratio estimate can be achieved.	Hazard ratio estimates can be accurately and precisely estimated under a survival model with linear interpolation of weight gain. This study emphasized the importance of accounting for the confounding effect of time. Not doing so could result in misleading inference.
Kinlaw[42] (2017)	To examine the sensitivity of Lisonkova & Joseph simulation study on the inverse association between maternal smoking and pre-eclampsia.	The simulation confirmed that the previous findings by Lisonkova and Joseph (2015) are highly dependent on assumptions regarding the strength of association between abnormal placentation and pre-eclampsia. Other factors might introduce additional biasing pathways from smoking to pre-eclampsia.	Left truncation does not appear to fully explain the inverse association between smoking and pre-eclampsia. Conceptualizing early loss as a competing event for pre-eclampsia clarifies the consequences of analytic decisions intended to address potential collider bias.
Lefebvre[58] (2017)	To investigate confounding bias from small-for-gestational age on birthweight related outcomes.	The simulations highlight that in addition to gestational age, both outcome variables (low) birthweight and small-for-gestational age must be considered in studies that rely on these perinatal outcomes.	Small-for-gestational age is an absorbing variable: the observed association between the exposure and small-for-gestational age solely reflects the direct effect of the exposure on birth weight.
Albert[27] (2018)	To examine measurement error in gestational age on subsequent risk of preterm birth.	Under the correctly specified model assuming a Gaussian distributed measurement error, parameter estimation is nearly unbiased. For all, except the polynomial terms for the regression relating gestational age to birth weight, the average asymptotic standard errors are close to the reported Monte Carlo estimates. This suggests the variance estimation for important parameter estimates performs well.	The authors showed the importance of properly accounting for measurement error in transition probabilities across multiple pregnancies. Analyses with the hidden Markov models found that the odds ratio for smoking on preterm birth was substantially larger when the first pregnancy was not preterm.

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First author (year of publication)	Aim(s) of the simulation	Key findings of the simulation	Author's conclusion
Schnitzer[46] (2018)	To assess the extent of selection bias due to the delayed inclusion of pregnancies.	An advantage of the simulation study is the ability to investigate the estimation bias, standard error, and power of the statistical estimator.	Not all sources of bias threaten the overall validity of the conclusions; it is important to investigate the potential size of bias in relation to effect estimates. While delayed pregnancy can produce substantial bias in pregnancy drug studies, simulation is an effective method for producing estimates of the size of the bias.
Snowden[62] (2018)	To examine bias in associations from studies restricted to preterm births are potentially biased.	The simulation provided a simple demonstration of collider-stratification bias, calculated (i.e. gestational length is 'conditioned on') when there is uncontrolled mediator-outcome confounding, regardless of whether gestational length is 'restricted on' or adjusted for in a model.	Among very preterm births, nearly all babies are born with pathologies that increase the risk of adverse outcomes. Babies exposed to one factor (e.g. pre-eclampsia) are compared with babies who have a mix of other pathologies; thereby, selection bias affects studies carried out among very preterm births.
Stoner[35] (2018)	To quantify selection bias in the effect of immediate versus delayed antiretroviral therapy initiation on preterm birth in HIV-infected women.	Non-differential measurement error generally produced bias toward the null. In this simulation with selection bias, increased measurement error increased the number of preterm births and the number who were excluded as they delivered prior to initiation of treatment.	Selection bias increases with 1) lower thresholds of prematurity when women initiate treatment later in pregnancy, and 2) measurement error in gestational age dating.
Suarez[49] (2018)	To estimate collider-stratification bias when conditioning on live birth.	When unmeasured covariates are positively associated with exposures, confounding is introduced into the exposure-outcome relationship in addition to selection bias. Bias is thereby no longer predictable and is dependent on which bias is stronger, confounding or selection.	A downward bias was observed in the relative risk estimates of antidepressant use and pre-eclampsia when restricted to live birth, but only when the covariates of obesity was not associated with antidepressant use. This study demonstrated that if the exposure of interest is also a strong risk factor for stillbirth, substantial bias can result.
Sundermann[28] (2018)	To quantify bias from misattributed exposure time on estimates of miscarriage risk.	Exposures after arrest of development are unlikely to affect pregnancy outcome. Using estimated gestational arrest at development instead of miscarriage to determine time at risk, allowed for more precise estimate of the risk of pregnancy loss associated with time-varying exposures.	Using gestational age at arrest of development to assign time at risk reduced the misclassification bias and variance of effect estimates for time-varying exposures.
Warren[31] (2018)	To quantify the impact of exposure misclassification from maternal residential mobility during pregnancy on defining weekly exposure to air pollution.	The simulation study showed that the distance travelled may be a more important factor in terms of exposure misclassification than the proportion of the population who move during pregnancy. Mobilizing larger distances would increase the geographical variability of ambient air pollution and therefore lead to larger exposure classification.	Even when a larger proportion of the pregnant population moves residence a short distance from their usual vicinity between conception and delivery, there is relatively little impact on critical window identification for PM_{10} and term low birth weight.
Wood[36] (2018)	To investigate the ability of the propensity score to reduce confounding bias in the presence of non-differential misclassification of treatment.	The simulation demonstrated that the impact of sensitivity and specificity on bias is strongly related to prevalence of exposure: as exposure prevalence decreases and/or outcomes are continuous rather than categorical, the effect of misclassification is magnified.	Propensity score matching more often produced estimates with worse coverage and greater bias, although in the presence of even moderate misclassification, all methods (adjustment, weighting, matching and stratification) increased in bias.
Eijkemans[22] (2019)	To investigate bias in study designs that estimate the cumulative probability of pregnancy.	The simulations showed that all four study designs (incident cohort; prevalent cohort; pregnancy-based; current duration approach) analyzed by proportional hazards regression suffered from attenuation bias. However, this bias could be reduced by censuring analysis at six months follow-up.	Focusing on the effect of exposures during the first six months of unprotected intercourse through censoring partly removes bias from attenuation.

Appendix D. Checklist for the application of simulation in studies that quantify bias using observational data

Section/subsection	Recommendation
Aim	
1.1 Purpose of the simulation	Explain the background and clearly state the aim of the simulation in the research study.
1.2 Exposure(s) and outcome(s)	Define the exposure and outcomes that will be included in the simulation model.
1.3 Type(s) of bias	State the types of bias that the simulation model will be quantifying.
Logic	
2.1 Causal graphs	Describe the simulation logic using causal diagrams.
2.2 Probability formula (optional)	Provide details on any probability formula that will inform the simulation.
Data	
3.1 Population	Provide clear details of the base population, including whether an original cohort is used or the population is simulated. If the population is simulated, describe the assumptions in details that inform the dataset.
Data sources	Clearly state the data sources that inform the simulation of the population and/or the assumptions of the model.
3.3 Bias parameters	Provide the parameters applied to the model, and details of the source of these parameters. If using prior published literature, also include references.
3.4 Data generation	Report how probability distributions were assigned to the bias parameters.
Implementation	
4.1 Summarize analysis of the simulation	Clearly state the analysis methods applied to the simulation. Details should include all methods, results, diagnostics and code used during the implementation of the model.
4.2 Report results of simulation	Restate the assumptions of the simulation and clearly report the results, focusing on whether the model explains the reported estimate.
Reproducibility	
5.1 Model assumptions	If assumptions of the model are summarized in the methods section, use online appendices to elaborate on details, including probability formulas.
5.2 Software	Provide a clear statement of the software used to conduct the simulation.
Code sharing	Make the code available, preferably online with the published paper.

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Research Article
Epidemiology

The role of confounding in the association between pregnancy complications and subsequent preterm birth: a cohort study

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Objective To estimate the degree of confounding necessary to explain the associations between complications in a first pregnancy and the subsequent risk of preterm birth.

Design Population-based cohort study.

Setting Western Australia.

Population Women (n = 125 473) who gave birth to their first and second singleton children between 1998 and 2015.

Main outcome measures Relative risk (RR) of a subsequent preterm birth (<37 weeks of gestation) with complications of pre-eclampsia, placental abruption, small-for-gestational age and perinatal death (stillbirth and neonatal death within 28 days of birth). We derived *e*-values to determine the minimum strength of association for an unmeasured confounding factor to explain away an observed association.

Results Complications in a first pregnancy were associated with an increased risk of a subsequent preterm birth. Relative risks were significantly higher when the complication was recurrent, with the exception of first-term perinatal death. The association with subsequent preterm birth was strongest when pre-eclampsia was recurrent. The risk of subsequent preterm birth with pre-eclampsia was 11.87 (95% CI 9.52–14.79) times higher after a first term birth with pre-eclampsia, and 64.04 (95% CI 53.58–76.55) times higher after a preterm first birth with pre-eclampsia, than an uncomplicated term birth. The *e*-values were 23.22 and 127.58, respectively.

Conclusions The strong associations between recurrent pre-eclampsia, placental abruption and small-for-gestational age with preterm birth supports the hypothesis of shared underlying causes that persist from pregnancy to pregnancy. High *e*-values suggest that recurrent confounding is unlikely, as any such unmeasured confounding factor would have to be uncharacteristically large.

Keywords Confounding, *e*-values, placental abruption, pre-eclampsia, preterm birth, small-for-gestational age.

Tweetable abstract First pregnancy complications are associated with a higher risk of subsequent preterm birth, with evidence strongest for pregnancies complicated by pre-eclampsia.

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Introduction

There is strong evidence that a previous preterm birth is a predictor of a subsequent preterm birth,[1–3] suggesting the presence of persistent causal factors in the mother or her environment.[4] The assumption that a term birth in first pregnancy can be considered sufficient to imply a reduced risk for a future preterm birth has been refuted by recent studies.[5–7] These studies reported that term first births complicated by pre-eclampsia, placental abruption, small-for-gestational age, stillbirth or neonatal death were associated with elevated risks of subsequent preterm birth, leading the authors to conclude that there are likely shared underlying pathological mechanisms persisting from pregnancy to pregnancy.[5–7]

One pathway that explains the association between complicated term birth and subsequent preterm birth is that the complications can also reoccur.[8,9] Recurrence has been well established for pre-eclampsia,[10] placental abruption[11] and small-for-gestational age,[12] complications linked to ischaemic placental diseases,[13] with these complications acting as risk factors for preterm birth.[5–7] Another more

complex explanation is that each complication is associated with an increased risk of other complications,[8,14] which is supportive of the hypothesis of shared underlying mechanisms.[8] Further supportive of a shared underlying mechanism are observations for associations with preterm birth in the 'reverse' direction. For example, more recent studies have established associations between preterm first birth and risk of pre-eclampsia[15] and stillbirth[16] in the next birth.

The most well-cited candidates for the shared underlying mechanism are the *great obstetrical syndromes*,[17] ischaemic placental diseases that are associated with disorders of deep placentation,[18] preterm birth[19] and late stillbirth.[20,21] However, the shared causal pathway is not necessarily biological. Environmental confounding factors such as socio-economic status, income, age, education and body mass index have previously been identified as risk factors for pregnancy complications[7] and preterm birth.[22] If environmental risk factors and underlying biological mechanisms that cause complications of pre-eclampsia, placental abruption, small-for-gestational age and perinatal death are shared with preterm birth, these associations would persist from pregnancy to pregnancy. Although incomplete control for confounding is inevitable in non-randomised studies,[23,24] it is possible to estimate the extent of confounding needed to explain away observed associations, which would thereby allow qualitative assessment as to whether such confounding is likely. We hypothesise that the associations between pregnancy complications exist and that they are largely explained by the recurrence of the complications themselves. We aimed to estimate the magnitude of these associations and to establish the degree of evidence for shared underlying pathways by estimating the degree of confounding necessary to explain away these associations.

Methods

Data sources

We conducted a retrospective population-based cohort study using perinatal records from the Midwives Notification System in Western Australia (WA), a statutory data collection of all live births and stillbirths with either a final gestational length of ≥20 weeks or a birthweight of >400 g.[25] This de-identified and validated dataset[26] was cross-referenced with death registrations obtained from the WA Registry of Births, Deaths and Marriages using a linkage key provided by the Data Linkage Branch of the WA Department of Health.[27] Hospitalisation records were identified from the Hospital Morbidity Data Collection for WA using the Australian Modification of International Classification of Diseases (ICD-10-AM) coded diagnostic information for pregnancy complications.[28] As data on chronic co-morbidities and smoking status were not routinely and comprehensively collected until 1998, analysis was restricted to women who gave birth (live birth or stillbirth) within the period 1998–2015.

Study cohort

The study cohort consisted of women who delivered their first two singleton births (live birth or stillbirth) in WA, during the period 1998–2015. From a starting population of 299 166 women who gave birth during this period, we sequentially excluded: multiple births (n = 3276; 1.1%); duplicate parity (n = 28; <0%); parity of >1 (n = 36 892; 12.3%); gestational age <20 or ≥45 weeks (n = 76; <0%); birthweight by gestational age z-score of >5 (n = 6; <0%); and women with only one birth (n = 133 415; 44.6%). After these exclusions, the final eligible study population was 125 473 women with first and second births (live birth or stillbirth) in WA (Figure 1).

Exposure and outcome ascertainment

The four variables used to identify a shared pathway were pre-eclampsia, placental abruption, small-for-gestational age and perinatal death (herein referred to as 'complications'). Pre-eclampsia (ICD-9, 642.4, 642.5, 642.6, 642.7; ICD-10, 011, 014, 015) and placental abruption (ICD-9, 641.20; ICD-10, 045) were obtained from hospital discharge ICD-9 and ICD-10 diagnosis. Small-for-gestational age was derived using the Australian national centiles and defined as the third percentile for singleton births, so as to exclude more constitutionally small births.[29] Perinatal death included stillbirths and neonatal deaths, where stillbirth is defined as fetal death after 20 weeks of gestation or with birthweights of ≥400 g, and neonatal death is the death of a liveborn baby in the first 28 days of life. Preterm birth was defined as a live birth or stillbirth delivered before 37 weeks of gestation. Gestational age at birth was derived from dating ultrasounds.[30]

Based on the hypothesis that the complications and preterm birth share common mechanisms, complications in the first pregnancy (exposure) would be associated with the risk of preterm birth in the second pregnancy (outcome). Similarly, preterm birth in the first pregnancy (exposure) would be associated with complications in the second pregnancy (outcome). Associations were investigated separately for each complication (herein referred to as 'primary complication'). Because associations can be induced by the recurrence of complications independent of preterm birth, and recurrence of preterm birth independent of complications, outcomes and exposures were categorised with levels to account for such recurrence. Specifically, for the association between first-pregnancy complications and preterm birth in the second pregnancy we defined: (i) six exposure groups, including uncomplicated term birth, uncomplicated preterm birth, term birth without primary complication (i.e. had a complication other than the primary complication), term birth with primary complication, preterm birth

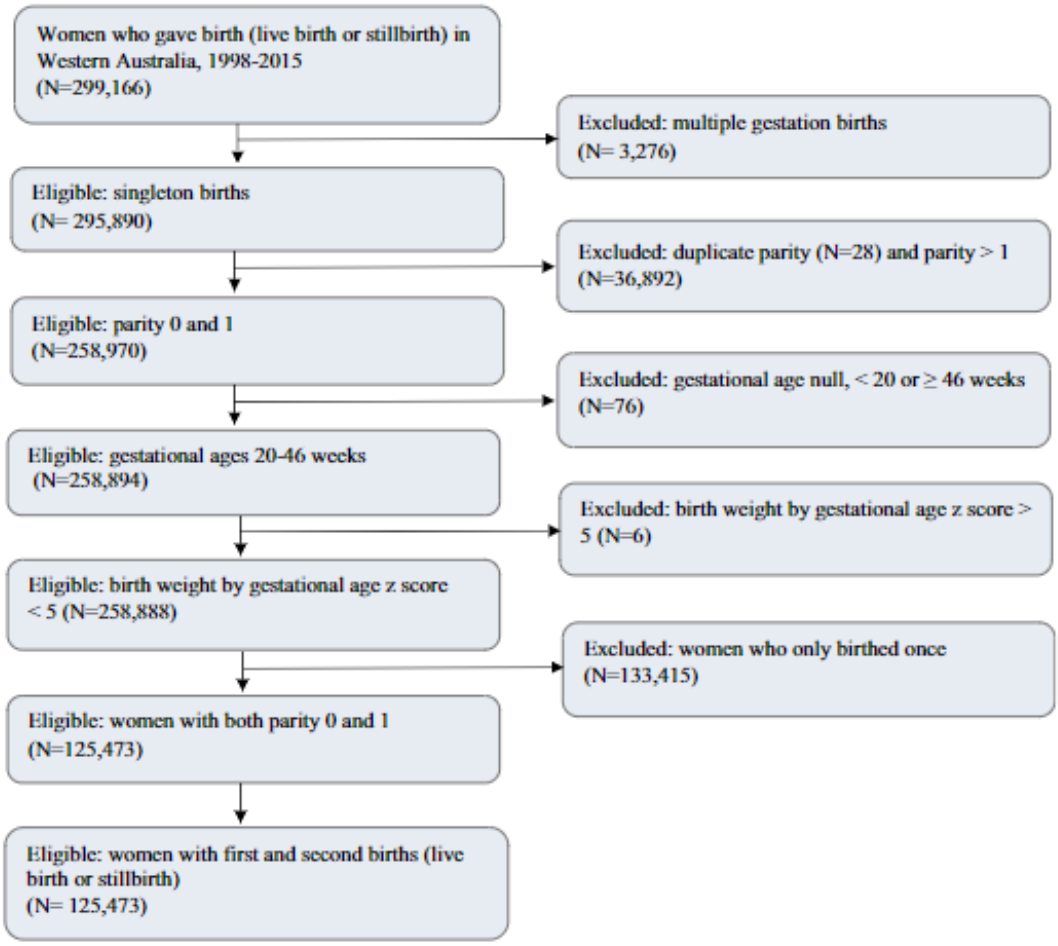

Figure 1. Selection of eligible birth records included in this study, Western Australia, 1998–2015.

without primary complication (i.e. had a complication other than the primary complication) and preterm birth with the primary complication; and (ii) three preterm outcomes, including preterm birth with no complications, preterm birth including the primary complication and complicated preterm birth excluding the primary complication. To avoid introducing collider bias from conditioning on preterm birth, the association between preterm birth in the first pregnancy was limited to pregnancy complications at the second term birth.

Confounding factors

Adjustment was made for known confounding factors that may contribute to the associations between complications and preterm birth. These factors included maternal age, ethnicity, smoking during pregnancy, year of delivery, socio-economic status, inter-pregnancy interval and change of father between the first and second birth. To avoid introducing bias from factors that may have changed since the first pregnancy, maternal age, smoking, year of delivery and socio-economic status were adjusted at the time of the first pregnancy. Ethnicity was classified as white, Aboriginal Torres Strait Islander and other. Smoking during pregnancy was dichotomised as non-smoking versus smoking. Socio-economic status was derived by the Australian Bureau of Statistics as the Socio-Economic Indexes of Areas (SEIFA) at a geographic area for the maternal residence at the time of birth, with lower values indicating an area that is

relatively disadvantaged compared with an area with a higher score.[31] Inter-pregnancy interval was defined as the length of time between the delivery date of the first pregnancy and the estimated conception date of the second pregnancy.

Statistical analysis

We used robust Poisson regression models to calculate relative risks with 95% confidence intervals for the association between complications in the first pregnancy and the risk of preterm birth in the second pregnancy. The Poisson model was chosen because the results approximate those obtained from a log-binomial model when the outcome is rare and the sample sizes are large,[32] and overcome the problems with convergence commonly associated with log-binomial models.[33] Robust standard errors were applied to derive the confidence intervals. Separate models were run for each primary complication (pre-eclampsia, placental abruption, small-for-gestational age and perinatal death), with the reference set as uncomplicated first-term pregnancy. When preterm birth in the first pregnancy was the exposure and pregnancy complications at term the outcome, the reference was term birth in the first pregnancy. We presented unadjusted relative risks and relative risks after adjustment for potential confounding factors.

E-values provide a method to gauge the minimum strength of association required to explain away unmeasured exposure confounding factors and unmeasured confounder–outcome associations.[34] A large *e*-value indicates that considerable unmeasured confounding is needed to expound an observed effect estimate. Conversely, a small *e*-value indicates that less unmeasured confounding is needed to explain an observed effect estimate.[34] The *e*-value for the lower limit of the 95% confidence interval is the level of confounding needed to render the interval estimate null, and thereby alter the inference.[35] To address the potential impact of bias from unmeasured confounding in our study, *e*-values were calculated and presented for the unadjusted and adjusted relative risks.

Simulation

We undertook a brief simulation exercise to determine whether the inclusion of a well-established known confounding factor could explain the association between complications in the first pregnancy and subsequent preterm birth. Body mass index (BMI) is a commonly adjusted confounding factor in perinatal studies, yet is unavailable in the WA data prior to 2016. As maternal height and maternal weight were readily available for births delivered after 2012, we were able to directly estimate BMI and thereby derive obesity (BMI 30 kg/m^2) for the period 2012–2015. We then applied logistic regression to simulate obesity at the first birth that was not associated with preterm second birth while preserving the correlations in the data between obesity and the other observed variables. Applying the same statistical approach as the main analysis, we re-analysed the data adjusting for the same confounding factors as before but with the addition of the new simulated obesity. A simulation was run for each exposure–outcome association, with iteration until convergence of the new obesity-adjusted relative risks, which was defined as no change at the third decimal place.

All data analyses and simulations were conducted using R 4.0.5.[36]

Results

Study population characteristics

In total, 125 493 women had two consecutive births (live birth or stillbirth) in WA between 1998 and 2015. Women were more likely to be aged 25–29 years (33.3%) at first birth, white (83.9%) and reported not smoking during pregnancy (86.5%) (Table 1). The majority of the study sample had a SEIFA score of >1000 (58.4%), which is slightly above the national average (50%).[37] The most common inter-pregnancy interval was 24–59 months (34.1%). In the first pregnancy the prevalence of preterm birth was 7.4%, pre-eclampsia was 4.5%, placental abruption was 0.3%, small-for-gestational age was 3%, and perinatal death was 0.9%. The prevalence of preterm birth in an uncomplicated second pregnancy was 3.7%.

Associations between complications at the first birth and second preterm birth

The strongest associations were observed between pre-eclampsia in the first pregnancy and subsequent preterm birth when both pre-eclampsia and preterm birth were recurrent (RR 67.69, 95% CI 56.82–80.63) (Table 2). The risk of subsequent preterm birth remained elevated when the first pregnancy was term and when pre-eclampsia was recurrent (RR 11.94, 95% CI 9.60–14.86). There was insufficient evidence to suggest that a first preterm birth complicated by pre-eclampsia confers greater risk on subsequent complicated preterm birth without recurrent pre-eclampsia (RR 3.67, 95% CI 2.49–5.42) than an uncomplicated preterm birth (RR 3.70, 95% CI 3.21–4.27). Corresponding *e*-values for associations that involved either the recurrence of pre-eclampsia or the recurrence of preterm birth were high (>6). In the absence of recurrence of pre-eclampsia or preterm birth, smaller associations were observed. Strong associations were also observed between placental abruption in a first term pregnancy and subsequent preterm birth (RR 11.79, 95% CI 4.37–31.83) when placental abruption was recurrent. When the first preterm birth was complicated by placental abruption, the risk of a subsequent preterm birth remained elevated when placental abruption

Table 1. Characteristics of the 125 473 women who gave birth between 1998 and 2015 in Western Australia

Characteristics	*n* (%)
Maternal age at first birth (years)	
<20	18 352 (14.6)
20 24	21 747 (17.3)
25 29	41 779 (33.3)
30 34	37 250 (29.7)
35 39	6103 (4.9)
40+	242 (0.2)
Ethnicity	
White	105 293 (83.9)
Aboriginal Torre Strait Islander	5470 (4.4)
Other	14 710 (11.7)
Maternal smoking status at first birth	
No	108 518 (86.5)
Yes	16 955 (13.5)
SEIFA score at first birth	
<700	279 (0.2)
700 800	1044 (0.8)
800 900	8443 (6.7)
900 1000	32 664 (26.1)
>1000	73 312 (58.4)
Missing	9731 (7.8)
Inter-pregnancy interval (months)	
<6	4108 (3.3)
6 11	18 759 (15)
12 17	28 534 (22.7)
18 23	23 229 (18.5)
24 59	42 731 (34.1)
60 120	7326 (5.8)
>120	786 (0.6)
Year at first birth	
1998 1999	22 421 (17.9)
2000 2004	38 307 (30.5)
2005 2009	43 766 (34.9)
2010 2016	20 979 (16.7)
Outcome in first pregnancy	
Preterm	9240 (7.4)
Term	116 233 (92.6)
Pre-eclampsia	5644 (4.5)
Placental abruption	435 (0.3)
Small-for-gestational age	3781 (3)
Perinatal death	1174 (0.9)

was recurrent (RR 10.47, 95% CI 3.37–32.51) and when the subsequent pregnancy was complicated without recurrent placental abruption (RR 10.80, 95% CI 6.69–18.00). Corresponding *e*-values for the associations of the recurrence of placental abruption and preterm birth were high (>20). There was a weak association between a first term pregnancy with placental abruption and a subsequent complicated preterm birth without recurrent placental abruption (RR 1.35, 95% CI 0.34–5.37). There was no association between a first term birth with placental abruption and the subsequent risk of uncomplicated preterm birth. Corresponding *e*-values were low (≤2) with confidence limits of 1.

The associations were strong when small-for-gestational age and preterm birth were recurrent (RR 32.68, 95% CI 19.87–53.74) compared with a first term uncomplicated pregnancy. Preterm birth in the first pregnancy confers a greater risk on the subsequent risk of complicated preterm birth when small-for-gestational age was not recurrent (RR 9.69, 95% CI 6.60–14.25), in contrast to the subsequent risk of preterm birth without complications (RR 3.6, 95% CI 2.86–4.69). Corresponding *e*-values for associations that involved recurrence of small-for-gestational age were high (>6). In the absence of recurrence of preterm birth or small-for-gestational age, smaller associations were observed, with a first term pregnancy complicated by small-for-gestational age weakly associated with a subsequent uncomplicated preterm birth (RR 1.62, 95% CI 1.42–1.84), with a corresponding *e*-value (2.20). There was a stronger association between a first preterm birth with perinatal death and a subsequent complicated preterm birth without recurrent perinatal death (RR 12.72, 95% CI 8.90–18.18), compared with when the subsequent pregnancy was uncomplicated (RR 4.22, 95% CI 3.62–4.93) and when perinatal death was recurrent (RR 5.34, 95% CI 3.36–8.14). Conversely, the risk of subsequent preterm birth was higher after a first term birth with perinatal death (RR 3.00, 95% CI 2.22–4.05), compared with when perinatal death was recurrent (RR 1.29, 95% CI 0.32–5.17). The corresponding *e*-values were 5.45 and 1.90, respectively.

Associations between preterm first birth and complications at second birth

When we compared women whose first pregnancy ended in preterm birth with women with a first term birth, there was an increased risk of each complication in second pregnancy. This was particularly true for pre-eclampsia, for which we observed a three-fold higher risk after preterm birth in the first pregnancy (Table 3). Generally, there was very slight attenuation after adjustment for known confounding factors in models when preterm birth was considered the exposure or the outcome of interest.

Simulation results

After the simulated confounding factor of obesity was included, each model was iterated 50 times until convergence was achieved at the third decimal point. When the outcome was uncomplicated preterm birth, there was no difference in relative risks from any of the complications in first pregnancy. There were marginal differences in the relative risks after the simulated confounding factor was

Table 2. Relative risk and assessment of unmeasured confounding in the association between complications in the first pregnancy and preterm birth in the second pregnancy

First pregnancy	Second pregnancy					
	Preterm birth with no complications[a]		Complicated preterm birth including primary complication[a]		Complicated preterm birth excluding primary complication[a]	
Complication status	Adjusted[g] RR (95% CI)	e-value[b] for RR (lower 95% CI[c])	Adjusted[g] RR (95% CI)	e-value[b] for RR (lower 95% CI[c])	Adjusted[g] RR (95% CI)	e-value[b] for RR (lower 95% CI[c])
Term, no complications	Reference[d]	Reference[d]	Reference[d]	Reference[d]	Reference[d]	Reference[d]
Pre-eclampsia						
Term[e]	1.22 (1.05 1.41)	1.73 (1.29)	11.87 (9.52 14.79)	23.22 (18.53)	1.75 (1.29 2.38)	2.89 (1.89)
Preterm[f]	3.70 (3.21 4.27)	6.87 (5.58)	64.04 (53.58 76.55)	127.58 (106.65)	3.67 (2.49 5.42)	6.80 (4.41)
Placental abruption						
Term[e]	1.00 (0.51 1.98)	1.04 (1)	11.79 (4.37 31.83)	23.08 (8.20)	1.35 (0.34 5.37)	2.03 (1)
Preterm[f]	5.40 (4.16 7.01)	10.27 (7.78)	10.47 (3.37 32.51)	20.43 (6.20)	10.80 (6.49 18.00)	21.10 (12.45)
Small-for-gestational age						
Term[e]	1.62 (1.42 1.84)	2.62 (2.20)	4.30 (2.78 6.66)	8.07 (5.00)	2.39 (1.83 3.11)	4.21 (3.06)
Preterm[f]	3.66 (2.86 4.69)	6.78 (5.16)	32.68 (19.87 53.74)	64.86 (39.24)	9.69 (6.60 14.25)	18.87 (12.67)
Perinatal death						
Term[e]	3.00 (2.22 4.05)	5.45 (3.87)	1.29 (0.32 5.17)	1.90 (1)	2.80 (0.91 8.61)	5.04 (1)
Preterm[f]	4.22 (3.61 4.93)	7.91 (6.68)	5.23 (3.36 8.14)	9.93 (6.17)	12.72 (8.90 18.18)	24.93(17.28)

[a]Complications included are pre-eclampsia, placental abruption, small-for-gestational age and perinatal death.
[b]The e-values for the effect estimates are the minimum strength of association on the risk ratio scale that an unmeasured confounding factor would need to have with both the exposure and the outcome to fully explain away the association between preterm birth in the first pregnancy and complications in the second term pregnancy.
[c]The e-values for the limit of the 95% CI closest to the null denote the minimum strength of association on the risk ratio scale that an unmeasured confounding factor would need to shift the confidence interval to include the null value.
[d]Uncomplicated term birth.
[e]Term birth with primary complication.
[f]Preterm birth with primary complication.
[g]Adjusted for ethnicity, maternal age at first birth, smoking status at first birth, socio-economic status at first birth, time period of first birth, inter-pregnancy interval and change of father between first and second birth.

included when the outcome was a subsequent preterm birth complicated with a recurrent pregnancy complication. Overall, the simulation demonstrated that the inclusion of the confounding factor of obesity did not alter the relative risks.

Discussion

This study examined the role of confounding in the association between pregnancy complications across two subsequent pregnancies. Women with previous pre-eclampsia, small-for-gestational age or perinatal death in the first pregnancy were at increased risk for a subsequent preterm birth, regardless of whether their first birth was term or preterm. Placental abruption was the exception, with an increased risk of uncomplicated subsequent preterm birth observed only after a first preterm birth. Moreover, preterm birth in the first pregnancy was associated with an increased risk of complications in a second pregnancy, excluding perinatal death. We were able to demonstrate that substantial confounding would be required to explain away the strong associations observed. Maternal obesity was simulated, demonstrating that the inclusion of a single well-established confounding factor is not enough to weaken the strong observed associations.

The findings that pre-eclampsia, small-for-gestational age and perinatal death in a first pregnancy, at either term or preterm, present an increased risk of a subsequent preterm birth support the hypothesis of shared underlying mechanisms. This is reinforced by the findings that preterm birth in the first pregnancy increased the risk of pre-eclampsia, placental abruption and small-for-gestational age in the next pregnancy. We found that placental abruption in a first term birth was not a risk for a subsequent uncomplicated preterm birth. Moreover, the increased risk of subsequent preterm birth with a recurrence of placental abruption was higher after a term birth compared with a

Table 3. Relative risk and assessment of unmeasured confounding in the association between preterm birth in a first pregnancy and complications in the second term pregnancy

First pregnancy	Second pregnancy							
	Pre-eclampsia		Placental abruption		Small-for-gestational age		Perinatal death	
	Adjusted* RR (95% CI)	e-value** for RR (lower 95% CI***)	Adjusted* RR (95% CI)	e-value** for RR (lower 95% CI***)	Adjusted* RR (95% CI)	E-value** for RR (lower 95% CI***)	Adjusted* RR (95% CI)	e-value** for RR (lower 95% CI***)
Term birth	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Preterm birth	3.58 (3.12 4.11)	6.62 (5.69)	1.71 (1.03 2.83)	2.81 (1.22)	1.85 (1.60 2.15)	3.11 (2.57)	1.02 (0.53 1.93)	1.14 (1)

*Adjusted for ethnicity, maternal age at first birth, smoking status at first birth, socio-economic status at first birth, time period of first birth, inter-pregnancy interval and change of father between first and second birth.
**The e-values for the effect estimates are the minimum strength of association on the risk ratio scale that an unmeasured confounding factor would need to have with both the exposure and the outcome to fully explain away the association between preterm birth in the first pregnancy and complications in the second term pregnancy.
***The e-values for the limit of the 95% CI closest to the null denote the minimum strength of association on the risk ratio scale that an unmeasured confounding factor would need to shift the confidence interval to include the null value.

preterm birth. These findings may result from situations in which an elective delivery at term occurs before spontaneous labour, leading to uncertainty regarding the true recurrence rate of placental abruption.[38] The strong effect for associations between recurrent pre-eclampsia, placental abruption and small-for-gestational age with preterm birth suggests the presence of strong maternal-specific factors that persist from pregnancy to pregnancy. The exception was perinatal death, for which we observed higher risks for a subsequent preterm birth when the complication was not recurrent after a first term birth. This may in part be due to the variability in the influence of placental causes for stillbirth[39] and neonatal death,[40] compared with the other complications, and with increased health surveillance after the occurrence of those complications in the first pregnancy.[41] Adjustment for known confounding factors had almost no influence on the point estimates of associations between pregnancy complications, suggesting that the true causal mechanisms are a complex interplay between environmental and biological factors.[17]

To explore the sensitivity of our results to confounding we applied *e*-values, a relatively new method to quantify the minimum strength of an association that an unmeasured confounding factor would need to explain away the exposure–outcome relationship.[34] Interpreting the *e*-value within the context of our effect sizes, the large *e*-values suggest that large unmeasured confounding factors are required to explain away the strength of the associations between complications of pregnancy. In particular, an unmeasured confounding factor would have to be extremely high to explain the association between pre-eclampsia in a preterm first birth and a subsequent preterm birth with recurring pre-eclampsia (*e*-value 127.58). Although it is improbable that a single unmeasured variable could confound the strong associations evidenced between pregnancy complications and a subsequent preterm birth, we included a simulated variable of maternal obesity as a sensitivity analysis. As expected, simulated maternal obesity did not influence the effect size, supporting previous observations that the shared and unknown underlying mechanisms are a possible interaction between complex biological and environmental exposures.[17]

Comparison with other studies

Our study is the first to report the results of associations between pregnancy complications and subsequent risk of preterm birth for first births at term and preterm. Although direct comparison with other studies is constrained by differences between exposure and reference groups, several past studies support our findings.[1–3,7,11,15,16,42–45] There is consistent evidence for the recurrence of preterm birth,[1–3] most notably when the previous preterm birth occurred with early-onset pre-eclampsia.[7,43] One study reported an increased risk for recurrent placental abruption after a term first birth, compared with preterm birth,[44] another study reported almost three-fold higher odds of preterm birth (compared with a term birth) after a small-for-gestational preterm birth,[42] and a study reported that previous all-cause infant death (up to 365 days post-birth) was associated with a two-fold increase in the risk of a subsequent preterm birth.[45] Only two studies considered the reverse associations

between a first preterm birth and complications,[15,16] with one study reporting an increased risk of term pre-eclampsia in a second pregnancy[15] and the other reporting a higher risk of stillbirth after preterm birth.[16] The findings of these studies support the premise of shared underlying mechanisms between pregnancy complications and preterm birth.

More recently, researchers have turned their attention to the subsequent risk of preterm birth from complications when the first birth is term.[5–7] Finding similar results to ours, a study from Norway reported a two-fold increase in the risk of preterm birth when the previous births were term with at least one complication (pre-eclampsia, placental abruption, small-for-gestational age, stillbirth or neonatal mortality), compared with an uncomplicated first term birth.[6] Consistent with our study, the authors also found little evidence for confounding by known demographic and lifestyle factors.[6] Findings from another study provide further support that complications of pre-eclampsia, small-for-gestational age and perinatal mortality at a first term birth increased the subsequent risk of preterm birth.[7] A study from the USA reported similar associations between a subsequent preterm birth and complications (small-for-gestational age, placental abruption and neonatal death) in a first term birth; however, a *protective* association was observed between term births with pre-eclampsia and subsequent preterm birth.[5] An alternative explanation for these results is that the adjustment for placental abruption and small-for-gestational age (potential mediators) introduced collider bias.[46] The findings of these studies add weight to the hypothesis that there are shared underlying causal mechanisms influencing outcomes, even when the first birth is term.

Strengths and limitations of study

This study provided a comprehensive analysis considering multiple scenarios of the interactions between pregnancy complications. A strength was the application of *e*-values to measure the strength of potential confounding required to explain the results. An additional strength of this study was that pregnancy complications for this analysis were drawn from population-based birth data linking each woman across two pregnancies, enabling the study of relatively rare outcomes with precision. Inevitably, as with most observational studies, these data may also be prone to a degree of misclassification. Furthermore, our findings are not necessarily generalisable to higher order parities than those included in our cohort, although it is uncertain as to why the underlying causal pathways would differ. Another limitation is that we were not able to include women who gave birth to their first child or a subsequent child out of the state.

Conclusion

The evidence for shared casual risk factors between pregnancy complications and preterm birth in this study is strong. The high *e*-values indicate that substantial confounding would be needed to explain away these associations. However, these findings alone do not provide direct evidence that the shared risk factors are of placental origin or biological origin. Further research is required to elucidate specific pathways that explain these associations, whether genetic, pathologic, behavioural or other recurrent mechanisms.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

JD and GP conceived and designed the study. GP obtained access to the data. JD conducted the data analysis and drafted the article. GAT and GP provided important insight during the data analysis. All authors contributed to the interpretation of the data and critically revised the article. All authors had full access to tables and figures in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. GP is the guarantor. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Details of ethics approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for this study was obtained from the Human Research Ethics Committee, Department of Health, Western Australia (HREC approval 2016/51).

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Data availability statement

No additional data are available. The lead author (JD) affirms that the article is an honest, accurate and

transparent account of the study being reported. No important aspects of the study have been omitted, and any discrepancies from the study as originally planned have been explained.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Causal diagram illustrating the potential causal relationship between complications in a first pregnancy and subsequent preterm birth.

Table S1. Prevalence of complications in second pregnancy in the subsequent risk of preterm birth.

Table S2. Relative risk for the association between complications in the first pregnancy and preterm birth in the second pregnancy.

Table S3. *E*-values for unmeasured confounding of the relative risk of subsequent preterm birth from complications in the first pregnancy.

Table S4. Relative risk for the association between complications in the first pregnancy and preterm birth in the second pregnancy after simulating obesity. ■

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Bias in the association between advanced maternal age and stillbirth using left truncated data

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Restriction to analysis of births that survive past a specified gestational age (typically 20 weeks gestation) leads to biased exposure-outcome associations. This bias occurs when the cause of restriction (early pregnancy loss) is influenced by both the exposure and unmeasured factors that also affect the outcome. The aim of this study is to estimate the magnitude of bias resulting from left truncated data in the association between advanced maternal age and stillbirth. We simulated data for the causal pathway under a collider-stratification mechanism. Simulation parameters were based on an observed birth cohort from Western Australia and a range of plausible values for the prevalence of early pregnancy loss, unmeasured factor *U* and the odds ratios for the selection effects. Selection effects included the effects of maternal age on early pregnancy loss, *U* on early pregnancy loss, and *U* on stillbirth. We compared the simulation scenarios to the observed birth cohort that was truncated to pregnancies that survived beyond 20 gestational weeks. We found evidence of marginal downward bias, which was most prominent for women aged 40 + years. Overall, we conclude that the magnitude of bias due to left truncation is minimal in the association between advanced maternal age and stillbirth.

It is considered that women with advanced maternal age (> 35 years of age) have an increased risk of stillbirth[1]. However, the magnitude of this increased risk is unclear when using birth data that is restricted to pregnancies that survive beyond a specified gestational week[2], as the exposure may impact selection into the study and thus mask the true observation of outcomes. In high-income settings, selection into a study is generally restricted to pregnancies that survive beyond 20 gestational weeks[3], a time when pregnancy is considered clinically viable. Thus, the use of left truncated birth registries and cohort studies that recruit women during a specific period of pregnancy, will produce biased estimates in perinatal exposure-outcome associations. The mechanism that leads to these biased associations is collider stratification bias. This occurs as conditioning on a collider, a common effect of an exposure and an outcome, induces a correlation between the exposure and a confounder[4]. If the confounder also affects the outcome, conditioning on the collider leads to a specious association that is either strengthened or reversed between the exposure and outcome[5]. The most well-known example of collider-stratification bias in perinatal epidemiology is the birth-weight paradox[6]. In this example, stratifying on birth weight produces a cross-over of the birth-weight mortality curves, such that low birth weight babies with smoking mothers have a lower mortality rates than low birth weight babies with non-smoking mothers[7]. However, the collider-stratification mechanism that underpins bias resulting from left truncated data is more difficult to address analytically as selection is based on an attrition processes that we cannot observe in data, i.e. early pregnancy loss.

With estimates of 2500 early pregnancy losses per 10,000 implantations[8], an extensive cohort attrition has already occurred prior to pregnancy being established due to spontaneous and induced abortion. The exact aetiology of spontaneous abortion remains unclear, although it is widely acknowledged that they result from interaction between hormonal, immunology, genetic and environmental factors[9–12]. Parental age is considered to be a strong risk factor for early pregnancy loss[11,13], with the risk of early pregnancy loss slightly elevated in younger mothers before rising sharply in older mothers (≥ 35 years)[11]. The continuing trend of advanced maternal age and high rates of stillbirth in high-income settings have led many researchers to examine the association

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Figure 1. Directed acyclic graph (DAG) of the structure of collider-stratification bias. The exposure maternal age *A* affects early pregnancy loss *L*, which is also affected by the independent risk factor *U*, inducing a back-door pathway between exposure *A* and the outcome of stillbirth *S*.

between the exposure of advanced maternal age and the outcome of stillbirth, defined as fetal death at 20 gestational weeks or more. Advancing maternal age (≥ 35 years) has been identified is an independent risk factor for stillbirth[1], with the increased risk of stillbirth not accounted for by increased prevalence of other maternal comorbities[14]. In studies that use left truncated datasets (i.e. missing pregnancies prior to 20 gestational weeks), the differential impact of maternal age on early pregnancy loss will lead to biased estimates in the relationship between advanced maternal age and stillbirth. Whether the bias is of concern will depend on its magnitude and direction, which remain unclear. Because early pregnancy losses are unobserved, simulations are a useful tool for exploring the influence of bias resulting from such left truncated data on the effects of exposure prior to pregnancy on birth outcomes[15]. In this simulation study, we aimed to quantify the influence of bias due to left truncation and selection in utero on the association between the exposure of advancing maternal age and the risk of stillbirth in a population representative of high-income settings.

Methods

The motivation for this study was to quantify the influence of bias due to left truncated birth data in the association between advanced maternal age at conception and stillbirth. Using data from the Midwives Notification Systems (MNS) in Western Australia, we compared effect estimates with those from simulated models in which we adjusted for the influence of selection bias under a range of plausible scenarios. For this study, we considered early pregnancy loss as fetal death prior to 20 gestational weeks; and stillbirth when fetal deaths occurred at 20 gestational weeks or later[16].

Observed cohort. The observed cohort consisted of women who had a singleton birth in Western Australia between 1998 and 2015 (births = 483,466), derived from the MNS[16]. This de-identified and validated dataset contains all births in Western Australia with either a gestational length ≥ 20 gestational weeks or a birth weight > 400 g[16]. We cross-referenced the MNS with Death Registrations obtained from the WA Registry of Births, Deaths and Marriages using a linkage key provided by the Data Linkage Branch of the WA Department of Health[17]. Hospitalisation records were identified from the Hospital Morbidity Data Collection for WA using the Australian Modification of International Classification of Diseases (ICD-9:779.9; ICD-10:P45 and P96.9) coded diagnostic information for stillbirth[18]. We categorised maternal age into five- year age groups (20–24, 25–29, 30–34, 35–39 and 40 + years). As the primary interest of this study is the biological impact of advancing age on stillbirth, women younger than 20 years were excluded in both the observed cohort and simulation study.

Bias structure. The causal diagram (Fig. 1) illustrates the bias resulting from restriction to births that survive past 20 gestational weeks. Here, the exposure *A* (maternal age, a proxy for aging) affects early pregnancy loss *L*. An unmeasured confounder *U* is causally associated with increased risk of pregnancy loss *L* and the outcome of stillbirth *S*. Both the exposure *A* and the unmeasured confounder *U* independently affect early pregnancy loss *L*, which is a collider. Thus, by excluding pregnancies that end in loss prior to 20 weeks gestation ($L = 1$), or conditioning on *L*, a back-door pathway is opened from maternal age to stillbirth through the pregnancy loss *L* and the unknown confounder *U*. This bias is commonly known as collider-stratification bias. An assumption implicit in the causal diagram is that maternal age causes early pregnancy loss, however, after attaining a gestational length close to viability (here 20 gestational weeks), maternal age has no direct influence on risk of stillbirth.

Simulation. To quantify the influence of the collider-stratification bias on the association between advanced maternal age and stillbirth, we simulated a population of 500,000 conceptions which is approximately the number of births in the observed cohort. We generated data for the maternal age exposure *A*, unmeasured confounder *U*, early pregnancy loss *L* and the outcome of stillbirth *S*. Maternal age variable *A* was normally distributed, with the mean and standard deviation derived from the Gaussian distribution of age in the observed cohort. As per the observed cohort, we categorised maternal age into five-year age groups (20–24; 25–29; 30–34; 35–39; 40–45) and excluded mothers younger than 20 years. The early pregnancy loss variable *L*, the unmeasured variable *U* and the stillbirth variable *S* were binary variables. The prevalence of *L* (π_L) was set to 12.8%[11], 20%[19] and 30%[20] to reflect a realistic range of early pregnancy loss as reported in high-income settings. The baseline prevalence of *S* was set to 0.7% to reflect the incidence of stillbirth in the observed cohort. We set the prevalence of *U* (π_U) to 0.15, 0.30 and 0.50, to reflect a range of plausible scenarios.

The overall causal pathway $[A \rightarrow L \leftarrow U \rightarrow S]$ that represents the collider-stratification bias was broken down to smaller pathways $[A \rightarrow L, U \rightarrow L, U \rightarrow S]$, which we deemed 'selection effects'. All selection effects were modelled in terms of odds ratios (ORs) so that simulation probabilities were bounded between 0 and 1. For the selection effect $A \rightarrow L$, we assigned each individual an underlying risk of early pregnancy loss based on their biological age

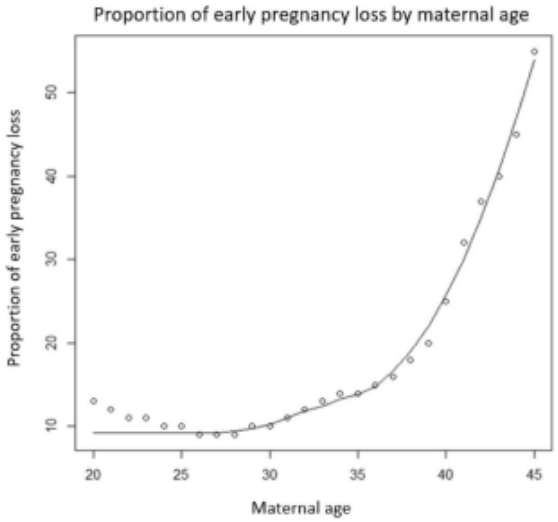

Figure 2. Risk of early pregnancy loss according to maternal age with locally weighted scatterplot smoothing curve.

at conception, which was drawn from a Bernoulli model based on results from a 2019 Norwegian study[11] of the effects of maternal age on early pregnancy loss. The Norwegian study[11] reported the lowest risk of miscarriage among women aged 25–29 (9.8%), with an absolute lowest risk at age 27 (9.5%) and the highest risk at age 45 (53.6%). As we were unable to ascertain the increasing risk of early pregnancy loss for women aged older than 45 years, we limited our simulation study to women aged between 20 and 45 years. In our Bernoulli model we used non-parametric regression to capture the nonlinearity of the association between the exposure and early pregnancy loss using LOESS (locally weighted scatterplot smoothing)[21] (Fig. 2).

The probability of early pregnancy loss for each conception i (assuming a monotonic risk by maternal age) was estimated using the equation below:

$$P(L_i) = \frac{\exp(\beta_0 + \beta_1 A_i + \beta_2 U_i)}{1 + \exp(\beta_0 + \beta_1 A_i + \beta_2 U_i)}.$$

Selection effects for $U \rightarrow L$ and $U \rightarrow S$ were set to an equal OR from a range of 1.5, 2.0, 2.5 and 3.0. To isolate the bias mechanism we firstly assumed a true null effect of maternal age on stillbirth (i.e. there is no direct causal effect of $A \rightarrow S$). We further considered a scenario in which there was an interaction between the unmeasured confounder U and maternal age A on early pregnancy loss L in conjunction with the collider-stratification mechanism. Often called depletion of susceptibles, the interaction of $A*U$ increases the prevalence of early pregnancy loss for those that are exposed to both the exposure A and U (Fig. S1). Selection effects for $A*U$ were set to an equal OR as with the selection effects for $U \rightarrow L$ and $U \rightarrow S$, with a range set to 1.5, 2.0, 2.5 and 3.0. To enable a direct comparison with the observed cohort, we then considered a third scenario in which we assumed a true effect of maternal age on stillbirth $A \rightarrow S$ (Fig. S2). Here each individual was assigned a probability of stillbirth drawn from a Bernoulli model based on the risk of stillbirth from their biological age of the observed cohort at conception (Fig. S3). To capture the nonlinearity of this direct association between the exposure maternal age A and the outcome of stillbirth S we conducted non-parametric regression with LOESS[21].

Analysis. We estimated the OR for the association between the exposure and outcome in the observed cohort and the simulated populations. We performed logistic regression of stillbirth with maternal age as the exposure to obtain the OR, which approximates the risk ratio because the outcome of stillbirth is rare in Western Australia[22]. We exponentiated the mean of the point estimates obtained from 100 iterations for each scenario to obtain $OR_{AS|L=0}$, which represents the OR for the effect of A on S for pregnancies in which early pregnancy loss did not occur ($L = 0$). We then derived the percentile-based 95% simulation intervals (SI) of the OR mean using 500 bootstrap replications.

We initially examined the collider-stratification bias under a range of plausible assumptions by varying the selection effects (OR_{UL} and OR_{US}) and the prevalence of both L and U as described above. In the first scenario, the simulation is conducted under the null hypothesis of no association between advancing maternal age A with the exposure of stillbirth S. In the second scenario we simulated a collider-stratification mechanism with an association between the exposure A and the unmeasured confounder U. As in the first scenario, we conducted the simulation under a hypothesis of no association between advancing maternal age A and stillbirth S. In both

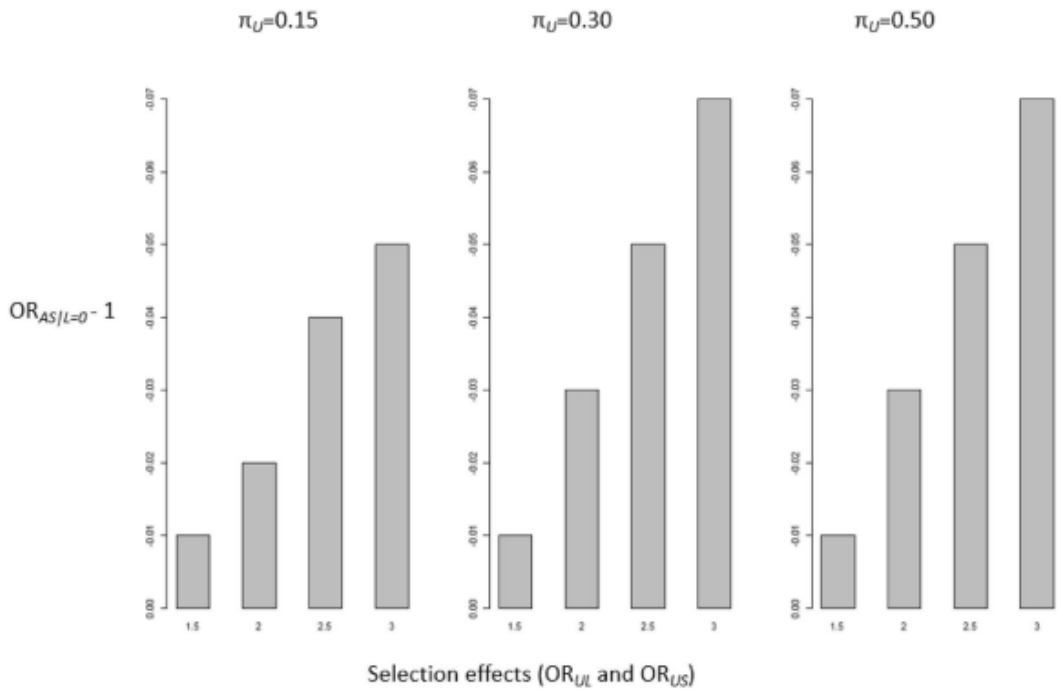

Figure 3. Collider-stratification bias of $OR_{AS|L=0} - 1$ under the true null effect of maternal age on stillbirth for women aged 40 + years, where the bias represents the departure from the null. Average odds ratio ($OR_{AS|L=0}$) with π_L = 0.20 and with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects OR_{UL} and OR_{US} (1.5, 2.0, 2.5, 3.0). Each scenario was iterated 100 times.

scenario one and scenario two we assumed that there is no causal effect, and therefore the value of $OR_{AS|L=0}$ was set to 1. Consequently, we interpreted the results such that the greater the departure of $OR_{AS|L=0}$ from 1 the greater the magnitude of the bias.

For the third scenario in which we assumed a true effect of $A \rightarrow S$, we were able to undertake a direct comparison with the observed cohort. For $OR_{AS|L=0}$ in this scenario, we simulated collider-stratification mechanism without an association between exposure A and the unmeasured confounder U and assumed a true effect of the exposure A on the outcome stillbirth S. Here the greater difference between $OR_{AS|L=0}$ and OR_{AS} (the observed cohort without the simulated bias), the greater the magnitude of bias. Furthermore, to eliminate possible model misspecification due to the categorisation of maternal age, we undertook a sensitivity analysis in which we simulated the true null association between the exposure maternal age A and the outcome of stillbirth S with input parameters $\pi_L = 0.20$, $\pi_U = 0.15$, $OR_{UL} = 1.5$, $OR_{US} = 1.5$ for each whole year of maternal age (Fig. S5). All data analyses and simulations were conducted using R v4.0.5[23].

Ethical approval. This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for this study was obtained from the Human Research Ethics Committee, Department of Health, Western Australia (HREC approval 2016/51) with a waiver of participants' informed consent, particularly due to the implausibility of obtaining retrospective consent for de-identified secondary data.

Results

Overall, the bias was minimal under a true null association between the exposure maternal age A and the outcome of stillbirth S. In scenario one, we considered a collider-stratification bias where the exposure maternal age A and the unmeasured confounder U independently effected early pregnancy loss (Table S1). Here the magnitude of bias was generally weak for women aged 35–39 years, with departure from 1 not evidenced until the selection effects (OR_{UL} and OR_{US}) were set to a minimum of 2.5 and regardless of the values of π_L and π_U. For example, the $OR_{AS|L=0}$ for women aged 35–39 years was 0.98 (SI 0.97 to 0.99) with input parameters of $\pi_L = 0.128$, $\pi_U = 0.30$, $OR_{UL} = 3.0$, $OR_{US} = 3.0$. For women aged 40 + years there was evidence of increasing bias when the magnitudes of the selection effects increased (OR_{UL} and OR_{US}) regardless of the values of π_L and π_U (Fig. 3). The largest departure from the null for women aged 40 + years was evident with input parameters of $\pi_L = 0.128$, $\pi_U = 0.30$, $OR_{UL} = 3.0$, $OR_{US} = 3.0$ ($OR_{AS|L=0}$ 0.92 SI 0.90 to 0.94).

In the second scenario, when we considered the collider-stratification mechanism with an interaction between the exposure A and the unmeasured confounder U, we found a greater departure from the null for women aged

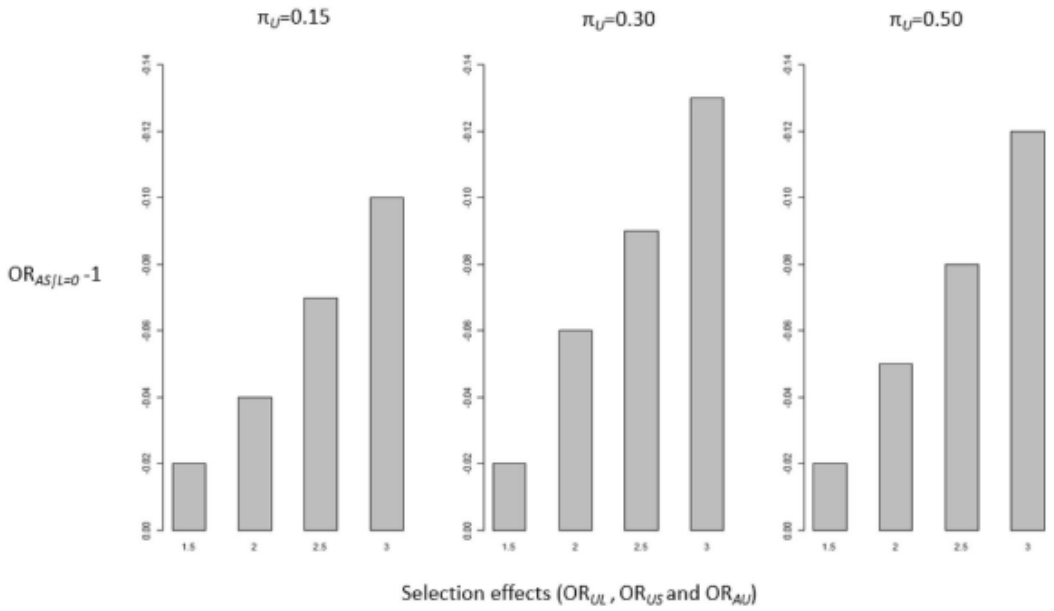

Figure 4. Collider-stratification bias of $OR_{AS|L=0} - 1$ under the true null effect of maternal age on stillbirth for women aged 40 + years with an interaction between exposure *A* and the unmeasured confounder *U*, where the bias represents the departure from the null. Average odds ratio ($OR_{AS|L=0}$) with π_L 0.30 and with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects (OR_{UL}, OR_{US}, OR_{AU}). Each scenario was iterated 100 times.

40 + compared to scenario one. In this scenario, we also found that the magnitude of the bias increased with increasing values of π_L and π_U (Fig. 4). The strongest evidence of bias was evident in women aged 40 + years with $\pi_L = 0.30$, $\pi_U = 0.30$, $OR_{UL} = 3.0$, $OR_{US} = 3.0$ (OR 0.87 SI 0.84 to 0.89) (Table S2). For women aged 35–39 years, there no evidence of bias when the selection effects (OR_{UL}, OR_{US}, OR_{AU}) were set to 1.5 and 2.0, regardless of the values of π_L and π_U. The greatest departure from the null was evidenced ($OR_{AS|L=0}$ 0.98 SI 0.97 to 0.99) when $\pi_L = 0.30$, $OR_{UL} = 3.0$, $OR_{US} = 3.0$, $OR_{AU} = 3.0$ and π_U was set to either 0.15, 0.30 or 0.50.

In the observed cohort, the association between maternal age and stillbirth presented as a U-shape, with the lowest risk for women aged 25–29 (OR 0.98 95% CI 0.90 to 1.17). The OR_{AS} for women aged 35–39 years was 1.23 (95% CI 1.11 to 1.37), increasing to 1.74 (95% CI 1.42 to 2.12) for women aged 40 +. In scenario three we simulated the biased collider-stratification pathway (without interaction between the exposure *A* and the unmeasured confounder *U*) with a direct effect of the exposure *A* on the outcome *S* (with data drawn from the observed cohort). We found evidence of minimal downward bias when we compared the results from this simulation with the observed cohort in which we assumed there was no influence from unmeasured confounders nor selection bias (Table S3). Women aged 35–39 years had an OR_{AS} of 1.23 (95% CI 1.11 to 1.37) in the observed cohort which was only marginally higher than the average $OR_{AS|L=0}$ of 1.21 in the simulated scenario three. The greater departure from the results of the observed cohort for women aged 35–39 years ($OR_{AS|L=0}$ 1.18 SI 1.17 to 1.20) was evident with input parameters of π_L 0.20, $\pi_U = 0.30$, $OR_{UL} = 3.0$, $OR_{US} = 3.0$. In the observed cohort, women aged 40 + years had an OR_{AS} of 1.74 (95% CI 1.42 to 2.12) and we found a greater departure from the observed cohort in general (Fig. 5). For example, with input parameters of parameters π_L 0.20, $\pi_U = 0.30$, $OR_{UL} = 3.0$, $OR_{US} = 3.0$ the $OR_{AS|L=0}$ for women aged 40 + years was 1.58 (SI 1.56 to 1.61).

When we simulated the true null association between exposure maternal age *A* and the outcome of stillbirth *S* (input parameters π_L 0.20, $\pi_U = 0.15$, $OR_{UL} = 1.5$, $OR_{US} = 1.5$) by each maternal age in the sensitivity analysis, we found that the structure of bias was similar to when maternal age was categorised by 5-year age groups (Fig. S5).

Discussion

Establishing the magnitude and direction of bias from unobserved early pregnancy losses on exposure-outcome associations is essential in improving our understanding of aetiological associations in perinatal epidemiology. In this simulation study, we quantified the magnitude and direction of bias due left truncation and selection in utero on the association between the exposure of advancing maternal age and the risk of stillbirth. Our findings suggest that the exclusion of early pregnancy loss in perinatal epidemiological studies likely biases effect estimates downwards. However, we found that the magnitude of bias was generally marginal, with a maximum $OR_{AS|L=0}$ of 0.87 for women aged 40 + years when we considered a true null effect of advancing maternal age on stillbirth. The strength of this bias was primarily dependent on the selection effects of the unmeasured confounder on the

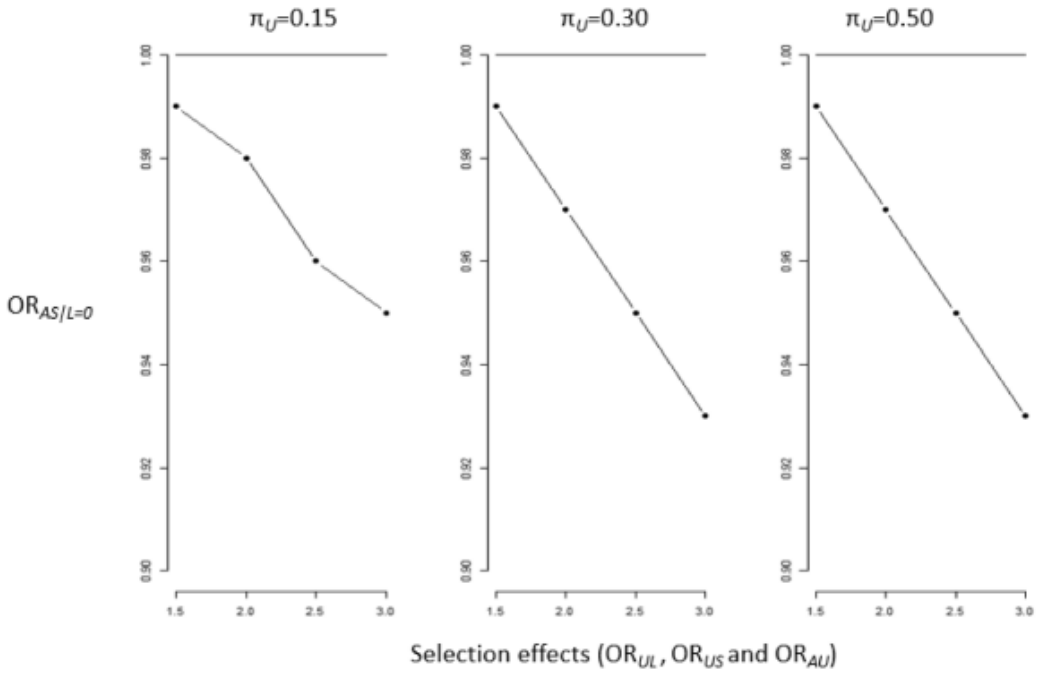

Figure 5. The upper straight line represents the results of the observed cohort for women aged 40 + years assuming no influence of an unmeasured confounder or selection bias. The lower lines represent the collider-stratification bias of $OR_{AS|L=0}$ assuming a true effect of maternal age on stillbirth for women aged 40 + years without an interaction between exposure *A* and the unmeasured confounder *U*. Average odds ratio with $\pi_{L=}$ 0.20 and with varying input parameters for π_U (0.15, 0.30, 0.50) and the selection effects (OR_{UL} and OR_{US}). Each scenario was iterated 100 times.

collider of early pregnancy loss *L* (OR_{UL}), the exposure of advancing maternal age *A* (OR_{AU}) and the outcome of stillbirth *S* (OR_{US}).

Direct comparison to other studies was constrained by differences between exposure-outcome associations and the structure of the collider-stratification bias; however, the small magnitude of bias in this study is consistent with other studies that examined the collider-stratification mechanism for other perinatal outcomes[24–32], such as the smoking-birthweight paradox[6,24,26,27]. Our findings, and those of others, suggest that the bias resulting from a collider-stratification mechanism would need to be very strong to produce an association that reverses the observed causal effects, and that this would primarily occur in scenarios where the effect of the unmeasured confounder would be quite large. It remains uncertain as to whether it is plausible that such a large causal effect would remain unknown or unobservable. On this basis, we limited the selection effects of *U* (OR_{UL} and OR_{US}) to a realistic range from 1.5 to an upper limit of 3.0. We found that the stronger the selection effects of *U* (OR_{UL} and OR_{US}), the stronger the magnitude of bias regardless of the prevalence of early pregnancy *L* or the prevalence of the unmeasured confounder *U*. Simulation studies that considered an interaction between an unmeasured confounder and the exposure found evidence of a stronger magnitude of bias in comparison to simulations without an interaction effect[25,30]. Often called *depletion of susceptibles*, this interaction between the susceptible factor (in our study this would be advancing maternal age) increases the depletion of early pregnancy loss among those who experience the unmeasured confounder[33,34]. Although our study showed an increase in the magnitude of bias when we considered a depletion effect, it was only evident for women aged 40 + years. One of the benefits of this study was that we could directly compare the difference between $OR_{AS|L=0}$ and OR_{AS} (the observed cohort without the simulated bias). Here, we found that the magnitude of downward bias was negligible for women aged 35–39 years and minimal for women aged 40 +. Overall, our findings indicate that the influence of bias due to left truncation and selection in utero is not sufficient to have a substantial effect on the strength of the association between advancing maternal age and stillbirth.

As simulation studies are only as valid as their assumptions, we used published literature and an observed cohort to support our assumptions of the magnitude of the underlying causal effects when quantifying the influence of bias in the association between advancing maternal age and stillbirth. Advancing maternal age has previously been established as a strong independent risk factor for early pregnancy loss in the first trimester[11], with risks increasing incrementally after the age of 30 years. Although the absolute risk of second trimester pregnancy loss is small in comparison to first semester, there is an incremental increase for women of advancing

age[35]. Using data from a 2019 Norwegian study[11] we were able to model this incremental increase in risk of early pregnancy loss *L* prior to 20 gestational weeks for each year of maternal age from 20 to 45 years in our simulations. We accounted for a variety of early pregnancy loss scenarios from 12.8%[11] a mid-range of 20%[19] and an upper level of 30%[20]. As our simulations are hypothetical scenarios in which all conceptions are selected, it is also likely that induced abortions would present a small competing risk to stillbirth. However, the Norwegian study[11], from which our lowest prevalence (12.8%) of early pregnancy loss is derived, did correct for induced abortions, finding very little difference in the overall estimate of miscarriage[11]. Although the absolute risk of stillbirth is low in high-income countries, it has not declined in recent decades despite advances in perinatal and obstetric care[14]. For women aged 40 + years, the risk of stillbirth increases earlier in pregnancy than for younger women, with a women aged 40 + having a greater risk of stillbirth at 39 gestational weeks compared to a younger women at 41 weeks[35]. Using data from our large observed cohort in Western Australia, we built models that accounted for the differential impact of the exposure advancing age *A* on the outcome of stillbirth *S* in a high-income setting. Our careful definition of our exposure variable advancing maternal age *A*, accounting for the differential impact on the early pregnancy loss *L* and stillbirth *S*, ensure our simulations are reflective of real world interactions between variables.

The exact biological mechanism of the higher risk of maternal age remains uncertain, with many of the potential shared risk factors for early pregnancy loss and stillbirth unobservable prior to the outcome. Possible suggestions include utero-placental dysfunction predisposing some women to adverse fetal outcomes including early pregnancy loss and stillbirth[36]. Infections can increase risk of early pregnancy loss and stillbirth, infecting the fetus via the placenta[37] with many infections asymptomatic. Fetal chromosomal abnormalities are the most common cause of early pregnancy loss in the first trimester, accounting for 50% of non-recurrent pregnancy losses[38,39]. There is an increased chromosomal anomaly rate (approx. 20%) in women aged 35 + years compared to younger women in sporadic and recurrent pregnancy losses[40]. Here, chromosomal anomalies would be an ideal candidate for the unobserved variable in our second simulation scenario. Increasing advanced age predisposes mothers to increasing risk of chromosomal anomalies that increase the risk of early pregnancy loss. Notwithstanding the collider-stratification mechanism, unmeasured confounders can lead to biased exposure-outcome effect estimates in either direction. Making assumptions about such confounders that are unobservable or unknown is challenging for researchers. Given the existence of causal factors that are not measured or remain to be discovered, researchers will continue to be required to make reasonable assumptions in relation to the strength and role of such unobservable confounders in the causal pathway, as we have done in our simulation study.

Quite often, the influence of collider-stratification bias is only examined when unexpected associations are observed in epidemiological studies[24–29]. As the use of left truncated data is ubiquitous in perinatal in epidemiology, due to restriction of studies until a time when pregnancy is either observed or deemed viable, the quantification of bias should be no less important in studies when an expected association is observed. Nonetheless, there are some caveats for interpreting our simulation results. The estimates in our simulation study are based on simple scenarios with all the variables having a binary response. We further assumed that there are no other forms of bias such as misclassification, nor the effects of multiple unmeasured confounders. There may also be a mediator variable, such as a pregnancy disease, that mitigates the association between advancing maternal age and stillbirth. An additional limitation of this study on the effect of ageing on stillbirth is that we did not consider selection bias prior to conception; that is women of advancing maternal age have a higher risk of infertility[41].

In this simulation study, we have quantified the magnitude and influence of bias from left-truncated perinatal data caused by studying cases prevalent from a specified gestation age, rather than including all cases in a conception or pregnancy cohort. We know that conditioning on the collider (early pregnancy loss prior to 20 weeks gestational weeks) will produce biased estimated in perinatal exposure-outcome associations. Using realistic assumptions, we found the magnitude of bias was generally minimal when using data that is left truncated due to early pregnancy loss on the association between the exposure of advancing maternal age and the outcome of stillbirth. When we considered a true association between the exposure and outcome, we observed a small downward bias which was stronger for women aged 40 + years. In our specific research question, in which the exposure is advancing maternal age, our findings indicated that the influence of bias due to selection in utero (and thereby left truncation) is not sufficient to have a substantial effect on the association with stillbirth. That is not to say that other researchers, with a different research question, would not find stronger evidence of bias when using left truncated birth data. However, as we demonstrated in this simulation, the strength of the bias is driven primarily by the prevalence and strength of the unmeasured confounder *U* rather than selection in utero. Although it is unlikely that such large unmeasured confounders exist, researcher should consider the influence of collider-stratification bias when using left-truncated data within the context of their own studies.

Data availability

The data that supports the findings of this study are owned by the government departments who approved the linkage and use of the data for this study. The current Human Research Ethics Committee approvals were obtained for public sharing and presentation of data on results only, meaning the unit-record level data used in this study cannot be shared by the authors. The steps involved in seeking permission for the use of the original data in this study is the same for all researchers. Researchers who wish to replicate our results can apply directly to Data Linkage, Department of Health, Western Australia. The steps to apply for data are described at https://www.datalinkage-wa.org.au.

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Author contributions
J.D. and G.P. conceived and designed the study. G.P. obtained access to data. J.D. conducted the data analysis and drafted the initial version of the manuscript. G.A.T., A.T.G. and G.P. provided important insight during the data analysis. All authors contributed in the interpretation of the data and critically revised the manuscript. All authors had full access to tables and figures in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. G.P. is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests
The authors declare no competing interests.

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Appendix D Supplementary material for Publication One

Supplementary Table S2.1 Search strategy by database

Simulat* AND Bias AND (Perinatal OR Reproductive)		
Bias	**Perinatal OR**	**Reproductive**
Pubmed (includes simulat*[tiab] with the below search terms)		
Bias[mh] OR Selection bias*[tiab] OR confound* bias*[tiab] OR collider*[tiab] OR truncat* bias*[tiab] OR censor* bias*[tiab] OR misclass* bias*[tiab] OR measurement bias*[tiab]	Pregnancy[mh] OR Pregnancy complications[mh] OR Infant Death[mh] OR Fetal Development[mh] OR *birth*[tiab] OR perinatal[tiab] OR neonatal[tiab] OR fetal[tiab] OR foetal[tiab] OR abortion[tiab] OR pregnancy termination[tiab] OR preterm[tiab] OR premature labour[tiab] OR small for gestational age[tiab] OR macrosomia[tiab] OR anomalies[tiab] OR malformations[tiab] OR defects[tiab] OR pregnancy hypertension[tiab] OR placenta previa[tiab] OR placenta praevia[tiab] OR intrauterine growth retardation[tiab] OR pregnancy loss[tiab] OR	Reproductive techniques[mh] OR Embryonic and Fetal Development[mh] OR Fertilization[mh] OR Fertility[mh] OR fecund*[tiab] OR placent*[tiab] OR reproductive tech*[tiab] OR blastocyst transfer[tiab] OR tubal embryo[tiab] OR fertil*[tiab] OR test-tube[tiab] OR steril*[tiab]

	premature rupture membranes[tiab]	
Medline (includes simulat*:ti,ab with the below search terms)		
Bias/exp OR Selection bias*.ti,ab OR Confound* bias*.ti,ab OR collider* bias*.ti,ab OR truncat* bias*.ti,ab OR censor* bias*.ti,ab OR misclass* bias*.ti,ab OR measurement bias*.ti,ab	Pregnancy/exp OR Pregnancy complications/exp OR Infant Death/exp OR Fetal Development/exp OR birth*.ti,ab OR perinatal.ti,ab OR neonatal.ti,ab OR fetal.ti,ab OR foetal.ti,ab OR abortion.ti,ab OR pregnancy termination.ti,ab OR preterm.ti,ab OR premature labour.ti,ab OR small for gestational age.ti,ab OR macrosomia.ti,ab OR anomalies.ti,ab OR malformations.ti,ab OR defects.ti,ab OR pregnancy hypertension.ti,ab OR placenta previa.ti,ab OR placenta praevia.ti,ab OR intrauterine growth retardation.ti,ab OR pregnancy loss.ti,ab OR premature rupture membrane.ti,ab	Reproductive techniques/exp OR Embryonic and Fetal Development/exp OR Fertilization/exp OR Fertility/exp OR fecund*.ti,ab OR placent*.ti,ab OR reproductive tech*.ti,ab OR blastocyst transfer.ti,ab OR tubal embryo.ti,ab OR fertil*.ti,ab OR test-tube.ti,ab OR steril*.ti,ab
EMBASE (includes simulat*:ti,ab with the below search terms)		

Bias/exp OR Selection bias*.ti,ab OR Confound* bias*.ti,ab OR collider* bias*.ti,ab OR truncat* bias*.ti,ab OR censor* bias*.ti,ab OR misclass* bias*.ti,ab OR measurement bias*.ti,ab	Pregnancy/exp OR Pregnancy complications/exp OR Infant Death/exp OR Fetal Development/exp OR birth*.ti,ab OR perinatal.ti,ab OR neonatal.ti,ab OR fetal.ti,ab OR foetal.ti,ab OR abortion.ti,ab OR pregnancy termination.ti,ab OR preterm.ti,ab OR premature labour.ti,ab OR small for gestational age.ti,ab OR macrosomia.ti,ab OR anomalies.ti,ab OR malformations.ti,ab OR defects.ti,ab OR pregnancy hypertension.ti,ab OR placenta previa.ti,ab OR placenta praevia.ti,ab OR intrauterine growth retardation.ti,ab OR pregnancy loss.ti,ab OR premature rupture membrane.ti,ab	Reproductive techniques/exp OR Embryonic and Fetal Development/exp OR Fertilization/exp OR Fertility/exp OR fecund*.ti,ab OR placent*.ti,ab OR reproductive tech*.ti,ab OR blastocyst transfer.ti,ab OR tubal embryo.ti,ab OR fertil*.ti,ab OR test-tube.ti,ab OR steril*.ti,ab
CINAHL (includes TI simulat* AND AB simulat* with the below search terms)		
MH Bias OR	MH Pregnancy OR MH “Pregnancy complications”	MH “Reproductive techniques” OR MH “Embryonic and Fetal

TI “selection bias*” OR AB “selection bias*” OR TI “confound* bias*”OR AB “confound* bias*” OR TI “collider* bias*” OR AB “collider* bias*” OR TI “truncat* bias*” OR AB “truncat* bias*” OR TI “censor* bias*” OR AB “censor* bias*”OR TI “misclass* bias*”OR AB “misclass* bias*” OR TI “measurement bias*” OR AB “measurement bias*”	OR MH “Infant Death” OR MH “Fetal Development” OR TI *birth* OR AB *birth* OR TI perinatal OR AB perinatal OR TI neonatal OR AB neonatal OR TI feta OR AB fetal OR TI foetal OR AB foetal OR TI abortion OR AB abortion OR TI “pregnancy termination” OR AB “pregnancy termination” OR TI preterm OR AB preterm OR TI “premature labour” OR AB “premature labour” OR TI “small for gestational age” OR AB “small for gestational age” OR TI macrosomia OR AB macrosomia OR TI anomalies OR AB anomalies OR TI malformations OR AB malformations OR TI defects OR AB defects OR TI “pregnancy hypertension” OR AB “pregnancy hypertension” OR TI “placenta previa” OR AB “placenta previa” OR TI “placenta praevia” OR AB “placenta praevia” OR TI “intrauterine growth retardation” OR AB “intrauterine growth	Development” OR MH Fertilization OR MH Fertility OR TI fecund* OR AB fecund* OR TI placent* OR AB placent* OR TI “reproductive tech*” OR AB “reproductive tech*” OR TI “blastocyst transfer” OR AB “blastocyst transfer” OR TI “tubal embryo” OR AB “tubal embryo” OR TI fertile* OR AB fertil* OR TI test-tube OR AB test-tube OR TI steril* OR AB steril*

	retardation" OR TI "pregnancy loss" OR AB "pregnancy loss" OR TI "premature rupture membranes" OR AB "premature rupture membranes"	
SCOPUS (includes ALL(simulat*) with the below search terms)		
TITLE-ABS-KEY("selection bias*" OR "confound* bias*" OR "collider* bias*" OR "truncat* bias*" OR "censor* bias*" OR "misclass* bias*" OR "measurement bias*")	TITLE-ABS-KEY(Pregnancy OR {Pregnancy complication} OR {Infant Death} OR {Fetal Development} OR *birth* OR perinatal OR neonatal OR fetal OR foetal OR abortion OR "pregnancy termination" OR preterm OR "premature labour" OR "small for gestational age" OR macrosomia OR anomalies OR malformations OR defects OR "pregnancy hypertension" OR "placenta previa" OR "placenta praevia" OR "intrauterine growth retardation" OR "pregnancy loss" OR "premature rupture membranes")	TITLE-ABS-KEY({Reproductive techniques} OR {Embryonic and Fetal Development} OR Fertili?ation OR Fertility OR fecund* OR placent* OR "reproductive tech*" OR "blastocyst transfer" OR "tubal embryo" OR fertil* OR test-tube OR steril*)

Supplementary Table S2.2 Records excluded at full-text screening with reasons

1. Adebayo et al. Analyzing infant mortality with geoadditive categorical regression models: A case study for Nigeria. Economics and Human Biology 2004, 2(2):229-244
   Reason for exclusion: The primary aim is not to quantify bias.

2. Aiken et al. Management of fetal malposition in the second stage of labor: A propensity score analysis. American Journal of Obstetrics and Gynecology 2015 212(3):335e1-335e7
   Reason for exclusion: This study did not use simulated data.

3. Bang et al. Estimating treatment effects in studies of perinatal transmission of HIV. Biostatistics 2004 5(1):31-43
   Reasons for exclusion: The primary aim is not to quantify bias.

4. Basso et al. The performance of several indicators in detecting recall bias. Epidemiology 1997 8(3):269-274
   Reasons for exclusion: The primary aim is not to quantify bias.

5. Brubaker et al. Vaginal progesterone in women with twin gestations complicated by short cervix: A retrospective cohort study. BJOG 2015 122(5):712-718
   Reasons for exclusion: This study did not use simulated data.

6. Chaemsaithong et al. Uterine artery pulsatility index in the first trimester: assessment of intersonodiagramer and intersampling site measurement differences. Journal of Maternal-Fetal and Neonatal Medicine 2018 31(17):2276-2283
   Reasons for exclusion: The primary aim is not to quantify bias.

7. Cies et al. Population pharmacokinetics of gentamicin in neonates with hypoxemic-ischemic encephalopathy receiving controlled hypothermia. Pharmacotherapy: The Journal of Human Pharmacology & Drug Therapy 2018 38(11):1120-1129
   Reasons for exclusion: The primary aim is not to quantify bias.

8. Cirillo et al. The human factor: does the operator performing the embryo transfer significantly impact the cycle outcome? Human Reproduction 2020 35(2):275-282
   Reasons for exclusion: This study did not use simulated data.

9. De Oliveira et al. A random-censoring Poisson model for underreported data. Statistics in Medicine 2017 36(30):4873-4892
   Reasons for exclusion: The primary aim is not to quantify bias.

10. Ding et al. Estimating effect of environmental contaminants on women's subfecundity for the MoBa study data with an outcome-dependent sample scheme. Biostatistics 2014 15(4):636-650
    Reasons for exclusion: The primary aim is not to quantify bias.

11. Gard et al. A coarsened multinomial regression model for perinatal mother to child transmission of HIV. BMC Medical Research Methodology 2008 8(1):46-46
    Reasons for exclusion: The primary aim is not to quantify bias.

12. Hatch et al. Evaluation of selection bias in an internet-based study of pregnancy planners. Epidemiology 2016 27(1):98-104
    Reasons for exclusion: This study did not use simulated data.

13. Heinke et al. Quantification of selection bias in studies of risk factors for birth defects among livebirths. Paediatric & Perinatal Epidemiology 2020 34(6):655-664
    Reasons for exclusion: The application of simulation was not core to the paper.

14. Honein et al. Modeling the potential public health impact of prepregnancy obesity on adverse fetal and infant outcomes. Obesity 2013 21(8):1276-1283
    Reasons for exclusion: The primary aim is not to quantify bias.

15. Horton et al. A population-based approach to analyzing pulses in time series of hormone data. Statistics in Medicine 2017 36(16):2576-2589
    Reasons for exclusion: The primary aim is not to quantify bias.

16. Howards et al. Adjusting for bias due to incomplete case ascertainment in case-control studies of birth defects. Practice of Epidemiology 2015 181(8):595-607
    Reasons for exclusion: The application of simulation was not core to this paper.

17. Janssen et al. Towards rational dosing algorithms for vancomycin in neonates and infants based on population pharmacokinetic modeling. Antimicrobial Agents & Chemotherapy 2016 60(2):1013-1021
    Reasons for exclusion: The primary aim is not to quantify bias.

18. Jiang et al. Causal Mediation Analysis in the Presence of a Misclassified Binary Exposure. Epidemiological Methods 2019 1(8)
    Reasons for exclusion: The primary aim is not to quantify bias.

19. Kim et al. Flexible Bayesian human fecundity models. Bayesian Analysis 2012 7(4):771-800
    Reasons for exclusion: The primary aim is not to quantify bias.

20. Kim et al. A model-based approach to detection limits in studying environmental exposures and human fecundity. Statistics in Biomedicine 2019 11:524-547
    Reasons for exclusion: The application of simulation is not core to the study.

21. Kone et al. Heckman-type selection models to obtain unbiased estimates with missing measures outcome: theoretical considerations and an application to missing birth weight data. BMC Medical Research Methodology 2019 19(1):231
    Reasons for exclusion: The primary aim is not to quantify bias.

22. Kovacevic et al. Fetal aortic valvuloplasty: investigating institutional bias in surgical decision-making. Ultrasound in Obstetrics & Gynecology 2014 44(5):538-544
    Reasons for exclusion: This is simulation based research.

23. Lau. On the heterogeneity of fecundability. Lifetime Data Analysis 1996 2(4):403-415
    Reasons for exclusion: The primary aim is not to quantify bias.

24. Manuel et al. Matched case-control data with a misclassified exposure: what can be done with instrumental variables? Biostatistics 2019 0:1-18
    Reasons for exclusion: The application of simulation was not core to the study.

25. Marston et al. The effects of HIV on fertility by infection duration: evidence from African population cohorts before antiretroviral treatment availability. AIDS 2017 31(1):S61-S76

Reasons for exclusion: The study did not use simulated data.

26. Molitor et al. Using Bayesian graphical models to model biases in observational studies and to combine multiple sources of data: application of low birth weight and water disinfection by-products. Journal of Royal Statistical Society 2009 172:615-637
    Reason for exclusion: The application of simulation was not core to the study.

27. Nadler et al. Clinicians can accurately assign Apgar scores to video recordings of simulated neonatal resuscitations. Simulation in Healthcare: Journal of the Society for Medical Simulation 2010 5(4):204-212
    Reasons for exclusion: This is simulation based research**.**

28. Osei et al. What happened to the IUD in Ghana? African Journal of Reproductive Health 2005 9(2):76-91
    Reasons for exclusion: The primary aim is not to quantify bias.

29. Parry et al. An online tool for investigating clinical decision making. Information for Health and Social Care 2004 29(1):75-85
    Reasons for exclusion: This is simulation based research.

30. Piao et al. Semiparametric model and inference for spontaneous abortion data with a cured proportion and biased sampling. Biostatistics 2018 19(1):54-70
    Reasons for exclusion: The primary aim is not to quantify bias.

31. Radin et al. Maternal recall error in retrospectively reported time-to-pregnancy: an assessment and bias analysis. Paediatric and Perinatal Epidemiology 2015 29(6):576-588
    Reasons for exclusion: The application of simulation was not core to this paper.

32. Rosenbaum. Confidence intervals for uncommon but dramatic responses to treatment. Biometrics 2007 63(4):1164-1171
    Reasons for exclusion: This study did not use simulated data.

33. Rousson et al. Stabilizing cumulative incidence estimation of pregnancy outcome with delayed entries. Biometrical Journal 2019 61:1290-1302
    Reasons for exclusion: The application of simulation was not core to the paper.

34. Sallmen et al. Selection bias due to parity-conditioning in studies of time trends in fertility. Epidemiology 2015 26(1):85-90
    Reasons for exclusion: The application of simulation was not core to the paper.

35. Sampson et al. Predictive performance of a gentamicin population pharmacokinetic model in neonates receiving full-body hypothermia. Therapeutic Drug Monitoring 2014 36(5):584-589
    Reasons for exclusion: The primary aim is not to quantify bias.

36. Shaffer et al. Analysis of neonatal clinical trials with twin births. BMC Medical Research Methodology 2009 9(1):12-21.
    Reasons for exclusion: The primary aim is not to quantify bias.

37. Slager et al. Stoppage: an issue for segregation analysis. Genetic Epidemiology 2001 20:328-339
    Reasons for exclusion: The primary aim is not to quantify bias.

38. Stott-Miller et al. Increased risk of orofacial clefts associated with maternal obesity: case-control study and Monte Carlo-based bias analysis. Paediatric & Perinatal Epidemiology 2010 24(5):502-512
    Reasons for exclusion: The primary aim is not to quantify bias.

39. Takada et al. Practical approaches for design and analysis of clinical trials of infertility treatments: crossover designs and the Mantel-Hansel method are recommended. Pharmaceutical Statistics: Journal of the Pharmaceutical Industry 2015 14(3):198-204
    Reasons for exclusion: The primary aim is not to quantify bias.

40. Van Eekelen et al. A comparison of the beta-geometric model with landmarking for dynamic prediction of time to pregnancy. Biometrical Journal 2019 62(1):175-190
    Reasons for exclusion: The primary aim is not to quantify bias.

41. Van Os et al. Influence of cut-off value on prevalence of short cervical length. Ultrasound in Obstetrics & Gynecology 2017 49(3):330-336
    Reasons for exclusion: The primary aim is not to quantify bias.

42. Venkatacharya. An examination of a certain bias due to truncation in the context of simulation models of human reproduction. The Indian Journal of Statistics 1969 31(3/4):397-412
    Reasons for exclusion: This primary aim is not the application of simulation to quantify bias.

43. Weinberg et al. Efficiency and bias in studies of early pregnancy loss. Epidemiology 1992 3(1):17-22
    Reasons for exclusion: The primary aim is not to quantify bias.

44. Weinberg et al. Pitfalls inherent in retrospective time-to-event studies: the example of time to pregnancy. Statistics in Medicine 1993 12:867-879
    Reasons for exclusion: This is a statistical study whose primary aim is not the quantification of bias.

45. Wilbaux et al. Characterizing and forecasting individual weight changes in term neonates. Journal of Pediatrics 2016 173:101-107
    Reasons for exclusion: The primary aim is to not to quantify bias.

46. Williams & Nix. Bias in risk estimation: application to Down's syndrome screening. Statistics in Medicine 2002 21(17):2495-2509
    Reasons for exclusion: The primary aim is the demonstration of a method.

47. Wilson et al. Confounder selection via penalized credible regions. Biometrics 2014 70(4):852-861
    Reasons for exclusion: The primary aim is not the application of a simulation to quantify bias.

48. Wilson et al. Bayesian distributed lag interaction models to identify perinatal windows of vulnerability in children's health. Biostatistics 2017 18(3):537-552
    Reasons for exclusion: The primary aim is not to quantify bias.

49. Yland et al. Methodological approaches to analyzing IVF data with multiple cycles. Human Reproduction 2019 34(3):549-557
    Reasons for exclusion: The study did not apply simulation.

50. Zekavat et al. A computational model of 1,5-AG dynamics during pregnancy. Physiological Reports 2017 5(16):13375
    Reasons for exclusion: The primary aim is not to quantify bias.

51. Zelop et al. Cardiac arrest during pregnancy: ongoing clinical conundrum. American Journal of Obstetrics & Gynecology 2018 219(1):51-61

Reasons for exclusion: The study applied simulation based research.

Supplementary Table S2.3 Summary of the characteristics of the studies quantifying bias (n=39) in the review.

First author (year of publication)	Aim(s) of the simulation	Key findings of the simulation	Author's conclusion
Olsen (1983)	To demonstrate bias resulting from the inadequate control of exogenous effects in gravidity and pregnancy order specific rates.	In the simulated scenarios where the number of women with low gravidity is high in the exposed group, the odds ratio will be too low when using inadequate statistical control. Conversely, high numbers of women with high gravidity in the exposed group will lead to an overestimated odds ratio.	Stratification based on either pregnancy order or gravidity alone can occasionally produce misleading results.
Baird (1991)	To examine reporting errors from collecting data on time-to-pregnancy.	Substantial power was lost in detecting weak exposures yet exposures that reduce fecundability by 50%, could still be detected with 80% power in samples of about 100 women (half of which were exposed to a possible toxin).	Data from a brief measure of time-to-pregnancy can produce bias toward the null and concomitant loss of power due to non-differential misclassification. Women with short and long times to pregnancy had less misclassification compared to women who required 5-13 menstrual cycles to conceive.

Doody (1993)	To investigate the potential magnitude of error resulting from loss to follow up in studies of fertility.	Using a range of clinical plausible assumptions, very large deviations were noted from loss to follow-up in the direction of elevated cumulative pregnancy rates. On a percentage basis, the largest effects were seen in groups that have the lowest monthly fecundity rates and the lowest cure ratios.	Loss to follow-up can lead to a systematic error in the reporting of excess pregnancy, raising fecundity rates. The later return of pregnant drop-outs to the study introduced major confounding effects in the simulation. These effects were most evident in women with lower fecundity rates, lower 'cured' women (where 'cured' is fertility restored due to treatment), higher drop-outs, and higher pregnant drop-out return rates.
Basso (1995)	To evaluate the influence of the magnitude of bias on seasonal patterns of reproductive failures.	Under conditions that were more extreme than those observed in the original cohort, bias related to differential pregnancy planning was marginal in the simulation.	Correcting for seasonal patterns in reproductive failures may eliminate bias associated with the seasonal variation in pregnancy planning.
Basso (2000)	To determine whether a differential persistence in pregnancy attempt is a source of bias in time-to-pregnancy estimates.	Simulating moderate changes in planning behaviour modified the waiting time distributions significantly. Persistence in trying to become pregnant was age-related.	Time-to-pregnancy studies are vulnerable to bias due to differential compliance in pregnancy planning. Relative risk measures can be biased up to 20% under realistic circumstances.

Juul (2000)	To demonstrate selection bias associated with restriction to completed pregnancies in retrospective study designs.	The simulation showed that even if each women's fecundity decreased with age, estimation of the effect of age may show the opposite trend when restricted to completed pregnancies.	The different fecundability classes (high fecund; low fecund; age-dependent) becomes differentially distorted in the various age groups when the sampling based on completed pregnancies.
Sallmen (2005)	To evaluate whether contraception and induced abortion might bias the direct study of time trends in fertility.	Comparing bias across two study designs, the strength of the bias is weaker in infertility study designs compared to time-to-pregnancy study designs; however the bias remains substantial	Dependent on the study design (time-to-pregnancy or infertility) access to effective contraception and elective abortion can bias the fertility rates, despite no actual change in fertility.
Wright (2005)	To examine bias due to exposure misclassification from the use of weighted and unweighted exposure metrics (disinfection by-product) on fetal development.	The simulation showed that the attenuation of the true effect of the exposure was diminished when town mean concentrations with large variability were down-weighted.	The weighted town mean analysis produced less misclassification bias; but at the cost of greater variability in the effect estimates compared to the unweighted results.
Basso (2006)	To explore confounding bias in the observed association	An observed steep gradient of risk for small babies at term could be produced by	A high rate of mortality in small babies could be explained by the presence of

	between birth weight and neonatal mortality.	rare confounders, impacting associations between fetal growth and mortality.	rare and unmeasured confounders that underlie the association of birth weight with mortality.
Howards (2006)	To examine misclassification bias caused by errors in gestational age.	In this simulation, errors in gestational age dating did not bias Cox regression if 1) the error is not differential by exposure, 2) differential error by exposure is small, or 3) due to the tail of the distributions.	Pregnancies ending in spontaneous abortion are more likely to have errors in their gestational ages than pregnancies ending in live birth. However, bias resulting from these errors is likely to be marginal.
Nohr (2006)	To evaluate two methods for constructing confidence limits for estimates of selection bias of relative risk estimates in perinatal cohort studies.	The effect of differential participation was modelled, resulting in small estimated effect on the risk estimates, even after adjustment for minimal confounding. Although some of the confidence intervals were wide, the bias was never larger than sixteen.	The two methods (logarithm of relative odds ratio and non-parametric bootstrap) used to compute confidence intervals gave very similar results with the simulation study showing coverage probabilities were close to the 95% nominal level. As the logarithm of relative odds ratio is simpler to implement, it is a valid choice when the selection bias is modest.
Howards (2007)	To assess the magnitude of bias introduced by fitting	The simulation suggested that bias in the odds ratio will exceed 20% when average	For variables where the exposure is associated with entry time, logistic regression

	logistic versus Cox models using left-truncated data.	gestational age at entry for the exposed versus the unexposed differs by ten days or more. This was observed due to possible socioeconomic factors, such as education and ethnicity.	may be subject to bias. Given that left truncation in studies may be related to exposure or important covariates, Cox regression model may be a better fit.
Basso (2009)	To demonstrate the intersection of mortality curves due to the presence of unmeasured confounders.	In this simulation model, the addition of a simple exposure (one that reduces birth weight and independently increases mortality) reversed the risk of mortality among small babies. Furthermore, the model explicitly showed how the mix of high- and low-risk babies within a given stratum of birth weight produced lower mortality for high-risk babies at low birth weights.	The intersection of mortality curves can be explained by the presence of confounding variables and the unequal mix of those variables across the birth weight distribution.
Key (2009)	To quantify the effects of protection bias from accidental pregnancies on fecundity in time-to-pregnancy studies.	To see a change in the trend of fecundity, the simulations required extreme and implausible trends in accidental pregnancies and unrealistic sample sizes.	Protection bias probably does exist, however it is quantitatively not very important. In any study of fecundity trends or cross-cultural differences, the proportion of accidental pregnancies can be used to screen for the presence of this bias.

Whitcomb (2009)	To quantify the collider-stratification bias between smoking and neonatal death.	When birth weight is a proxy for other causally related variables, inclusion in regression models of neonatal mortality generates an over-adjustment.	This study illustrated that when the birth weight–mortality relation is subject to substantial uncontrolled confounding, the bias on estimates of effect adjusted for birthweight may be sufficient to yield opposite causal conclusions. Therefore a factor that posed increased risk now appears protective.
Strand (2011)	To quantify fixed cohort bias when estimating the effects of season and seasonal exposures on birth outcomes.	Using a fixed cohort does not only bias the estimated effects of the season (e.g., month of conception), but can also bias the estimated effects of seasonal exposures (e.g. air pollution and temperature).	This study demonstrated that the size of the fixed cohort bias can be substantial, causing great changes in the months that most affect gestational length and changed the estimated effect of temperature on gestational length.
Wilcox (2011)	To explore bias resulting from adjustment when gestational age is a mediator.	The simulations demonstrated that under plausible conditions, reversal of exposure-outcome associations can occur due to collider bias.	Unmeasured risk factors complicate inference about the risk of morbidity outcomes due to immaturity alone. Adjustment for gestational age is likely to produce biased estimates.

Ahrens (2012)	To correct for exposure misclassification when using survival analysis with a time-varying exposure	Correction for misclassification bias in a simulation could result in a much greater change in effect estimates depending on the magnitude and pattern of exposure misclassification.	In this simulation, correction for misclassification of prenatal influenza vaccination resulted in an adjusted hazard ratio that was slightly higher and less precise than the conventional analysis.
Hutcheon (2012)	To quantify bias from conventional gestational weight gain measures on the relationship between maternal weight gain and risk of preterm birth.	Bias was likely due to a positive correlation between the adequacy ratio and gestational duration, resulting from increased differences between observed and expected weights as the pregnancy progressed.	Conventional measures of gestational weight gain introduce a significant degree of bias when assessing the relationship between gestational weight gain and risk of preterm birth ≤ 32 gestational weeks.
Schisterman (2013)	To demonstrate selection bias using truncated data in a time-to-pregnancy study.	Fixed or variable non-differential left truncation will results in a loss of precision. Fixed or variable differential left truncation will result in a bias either towards or away from the null, including a loss of precision.	Null-bias can be induced when events occur prior to truncation time. When deaths occur before the truncation time, identifying if these prior events are likely associated with exposure is important.
Lash[319318318319319319319319319319319319319319319319318317317316] (2014)	To evaluate the direction, magnitude, and uncertainty in estimates as a result of misclassification bias from pre-pregnancy	The applications of probabilistic-bias analysis to frequency-weighted datasets using simulation enabled the same conceptual correction to be applied to each data	Probabilistic bias analyses suggested that the association between underweight and early preterm birth was overestimated by the

	body mass index on early preterm births.	record. This allowed the covariates required for adjustment to account for misclassification.	conventional approach. However, the associations between over-weight categories and early preterm birth were underestimated.
Lisonkova (2015)	To determine whether left truncation bias could explain the paradoxical association between smoking and pre-eclampsia.	The simulation yielded a protective effect of pre-eclampsia given smoking. This protective effect of smoking was also evident in simulations that did not require assumptions about early pregnancy loss rates.	Left truncation bias due to differential rates of early pregnancy loss among smokers is a reasonable explanation for the inverse association between maternal smoking and pre-eclampsia.
Arpino (2016)	To reduce bias due to cluster level confounders (hospitals and sample size) on estimates of caesarean section treatment on the 5-min Apgar score.	The simulations suggest that when the average cluster size is about 100 units, the bias of within cluster matching can be rather high. With smaller clusters of size 50, the results were even more negative when using pure within-cluster matching. The proposal of a preferential within-cluster matching is a better alternative in these cases.	The preferential within-cluster matching approach, combining the advantages of within-cluster and between cluster matching, showed a relatively good performance both in the presence of big and small clusters.
Avanasai (2016)	To evaluate the impact of bias in estimated	Using variables for uncertainty exposures	The correlated exposure uncertainty can substantially

	perfluorooctanoate drinking-water concentrations on the association with pre-eclampsia.	allowed for specification of correlations in exposure measurement errors across years and individuals with shared exposure sources, in contrast to standard epidemiological models that assume independence of the measurement errors.	change estimated perfluorooctanoate serum concentrations, but results had only minor impacts on the association between perfluorooctanoate and pre-eclampsia.
Gerdts (2016)	To quantify selection and misclassification bias in reproductive abortion-related mortality.	Using simulated data in multiple-bias analysis allowed for explicit assumptions to replace implicit assumptions through the quantification of selection bias and sensitivity/specificity.	After adjustment for selection bias, misclassification, and random error, there was approximately 20% increase in the reported proportion of abortion related deaths.
Hinkle[166] (2016)	To evaluate the impact of mis-specifying the distributions of weight gain and gestational age.	Adjusting for gestational age, total weight gain will obtain unbiased estimates of the true association with neonatal mortality, assuming no unmeasured confounding. The simulation model permitted flexibility in identifying the most appropriate relationship between potential confounders with the exposure and outcome.	Using directed acyclic graphs and simulation, gestational weight gain is recognised as a time-varying exposure. There was no true association between weight gain and neonatal mortality. Adjusting for gestational age achieved unbiased estimates of the association between total gestational weight gain and neonatal mortality.

Luque-Fernandez (2016)	To determine if selection bias could explain the paradoxical association between smoking pregnancy and pre-eclampsia as being a consequence.	Applying a simulated probabilistic sensitivity analysis, the inverse association of smoking on pre-eclampsia shifted from a 28% risk reduction to a non-significant bias-adjusted effect of 22% risk increase of pre-eclampsia for smokers compared with non-smokers.	Selection bias is evident from two sources. The first is conditioning on the collider of gestational weeks at delivery. The second source is the omittance of important confounders associated with smoking and pre-eclampsia, given that some pregnancies will not be selected into the population because they are left truncated.
Mitchell (2016)	To investigate bias due to effect of gestational age on the time-varying confounder of gestational weight gain and it's association with preterm delivery.	The results of the simulations suggest that the survival model with interpolated gestational weight gain performs extremely well under various effect sizes, with no discernible bias and nominal coverage. When weight was measured only intermittently, an unbiased and precise hazard ratio estimate can be achieved.	Hazard ratio estimates can be accurately and precisely estimated under a survival model with linear interpolation of weight gain. This study emphasised the importance of accounting for the confounding effect of time. Not doing so could result in misleading inference.
Kinlaw (2017)	To examine the sensitivity of Lisonkova & Joseph simulation study on the inverse association between	The simulation confirmed that the previous findings by Lisonkova and Joseph (2015) are highly dependent on assumptions regarding the	Left truncation does not appear to fully explain the inverse association between smoking and pre-eclampsia. Conceptualizing early loss as

	maternal smoking and pre-eclampsia.	strength of association between abnormal placentation and pre-eclampsia. Other factors might introduce additional biasing pathways from smoking to pre-eclampsia.	a competing event for pre-eclampsia clarifies the consequences of analytic decisions intended to address potential collider bias.
Lefebvre (2017)	To investigate confounding bias from small-for-gestational age on birthweight related outcomes.	The simulations highlight that in addition to gestational age, both outcome variables (low) birthweight and small-for-gestational age must be considered in studies that rely on these perinatal outcomes.	Small-for-gestational age is an absorbing variable: the observed association between the exposure and small-for-gestational age solely reflects the direct effect of the exposure on birth weight.
Albert (2018)	To examine measurement error in gestational age on subsequent risk of preterm birth.	Under the correctly specified model assuming a Gaussian distributed measurement error, parameter estimation is nearly unbiased. For all, except the polynomial terms for the regression relating gestational age to birth weight, the average asymptotic standard errors are close to the reported Monte Carlo estimates. This suggests the variance estimation for important parameter estimates performs well.	The authors showed the importance of properly accounting for measurement error in transition probabilities across multiple pregnancies. Analyses with the hidden Markov models found that the odds ratio for smoking on preterm birth was substantially larger when the first pregnancy was not preterm.

Schnitzer (2018)	To assess the extent of selection bias due to the delayed inclusion of pregnancies.	An advantage of the simulation study is the ability to investigate the estimation bias, standard error, and power of the statistical estimator.	Not all sources of bias threaten the overall validity of the conclusions; it is important to investigate the potential size of bias in relation to effect estimates. While delayed pregnancy can produce substantial bias in pregnancy drug studies, simulation is an effective method for producing estimates of the size of the bias.
Snowden (2018)	To examine bias in associations from studies restricted to preterm births are potentially biased.	The simulation provided a simple demonstration of collider-stratification bias, calculated (i.e. gestational length is 'conditioned on') when there is uncontrolled mediator-outcome confounding, regardless of whether gestational length is 'restricted on' or adjusted for in a model.	Among very preterm births, nearly all babies are born with pathologies that increase the risk of adverse outcomes. Babies exposed to one factor (e.g. pre-eclampsia) are compared with babies who have a mix of other pathologies; thereby, selection bias affects studies carried out among very preterm births.
Stoner (2018)	To quantify selection bias in the effect of immediate versus delayed antiretroviral therapy initiation on	Non-differential measurement error generally produced bias toward the null. In this simulation with selection bias, increased measurement error	Selection bias increases with 1) lower thresholds of prematurity when women initiate treatment later in pregnancy, and 2)

	preterm birth in HIV-infected women.	increased the number of preterm births and the number who were excluded as they delivered prior to initiation of treatment.	measurement error in gestational age dating.
Suarez (2018)	To estimate collider-stratification bias when conditioning on live birth.	When unmeasured covariates are positively associated with exposures, confounding is introduced into the exposure-outcome relationship in addition to selection bias. Bias is thereby no longer predictable and is dependent on which bias is stronger, confounding or selection.	A downward bias was observed in the relative risk estimates of antidepressant use and pre-eclampsia when restricted to live birth, but only when the covariates of obesity was not associated with antidepressant use. This study demonstrated that if the exposure of interest is also a strong risk factor for stillbirth, substantial bias can result.
Sundermann (2018)	To quantify bias from misattributed exposure time on estimates of miscarriage risk.	Exposures after arrest of development are unlikely to affect pregnancy outcome. Using estimated gestational arrest at development instead of miscarriage to determine time at risk, allowed for more precise estimate of the risk of pregnancy loss associated with time-varying exposures.	Using gestational age at arrest of development to assign time at risk reduced the misclassification bias and variance of effect estimates for time-varying exposures.

Warren (2018)	To quantify the impact of exposure misclassification from maternal residential mobility during pregnancy on defining weekly exposure to air pollution.	The simulation study showed that the distance travelled may be a more important factor in terms of exposure misclassification than the proportion of the population who move during pregnancy. Mobilising larger distances would increase the geographical variability of ambient air pollution and therefore lead to larger exposure classification.	Even when a larger proportion of the pregnant population moves residence a short distance from their usual vicinity between conception and delivery, there is relatively little impact on critical window identification for PM_{10} and term low birth weight.
Wood (2018)	To investigate the ability of the propensity score to reduce confounding bias in the presence of non-differential misclassification of treatment.	The simulation demonstrated that the impact of sensitivity and specificity on bias is strongly related to prevalence of exposure: as exposure prevalence decreases and/or outcomes are continuous rather than categorical, the effect of misclassification is magnified.	Propensity score matching more often produced estimates with worse coverage and greater bias, although in the presence of even moderate misclassification, all methods (adjustment, weighting, matching and stratification) increased in bias.
Eijkemans (2019)	To investigate bias in study designs that estimate the cumulative probability of pregnancy.	The simulations showed that all four study designs (incident cohort; prevalent cohort; pregnancy-based; current duration approach) analysed by proportional hazards regression suffered	Focusing on the effect of exposures during the first six months of unprotected intercourse through censoring partly removes bias from attenuation.

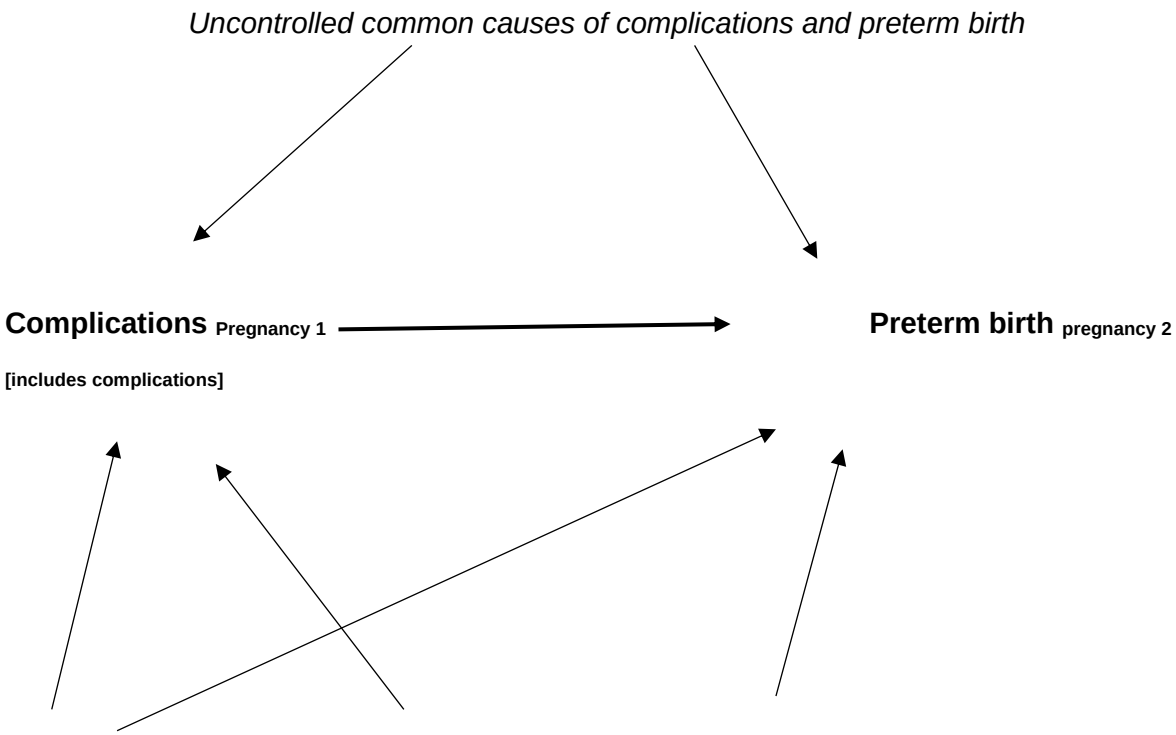
		from attenuation bias. However, this bias could be reduced by censuring analysis at six months follow-up.

Supplementary Table S2.4 Checklist for the application of simulation in studies that quantify bias using observational data

Section/subsection	Recommendation
1. Aim	
1.1 Purpose of the simulation	Explain the background and clearly state the aim of the simulation in the research study.
1.2 Exposure(s) and outcome(s)	Define the exposure and outcomes that will be included in the simulation model.
1.3 Type(s) of bias	State the types of bias that the simulation model will be quantifying.
2. Logic	
2.1 Causal graphs	Describe the simulation logic using causal diagrams.
2.2 Probability formula (optional)	Provide details on any probability formula that will inform the simulation.
3. Data	
3.1 Population	Provide clear details of the base population, including whether an original cohort is used or the population is simulated. If the population is simulated, describe the assumptions in details that inform the dataset.
3.2 Data sources	Clearly state the data sources that inform the simulation of the population and/or the assumptions of the model.
3.3 Bias parameters	Provide the parameters applied to the model, and details of the source of these parameters. If using prior published literature, also include references.
3.4 Data generation	Report how probability distributions were assigned to the bias parameters.
4. Implementation	

4.1 Summarise analysis of the simulation	Clearly state the analysis methods applied to the simulation. Details should include all methods, results, diagnostics and code used during the implementation of the model.
4.2 Report results of simulation	Restate the assumptions of the simulation and clearly report the results, focusing on whether the model explains the reported estimate.
5. **Reproducibility**	
5.1 Model assumptions	If assumptions of the model are summarised in the methods section, use online appendices to elaborate on details, including probability formulas.
5.2 Software	Provide a clear statement of the software used to conduct the simulation.
5.3 Code sharing	Make the code available, preferably online with the published paper.

Appendix E Supplementary material for Publication Two



Supplementary Figure S3.1. This causal diagram illustrates the potential causal relationship between complications in first pregnancy and subsequent preterm birth. Obesity represents a simulated confounder. Second pregnancy complications are included in the outcome of preterm birth to prevent collider bias that would be induced by conditioning on them when estimating the effect of first pregnancy complications on subsequent preterm birth. [*variable*] represents the adjustment of known confounders. Uncontrolled common causes of complications and preterm birth are not included in the model.

Supplementary Table S3.1 Prevalence of complications in second pregnancy in the subsequent risk of preterm birth

1st pregnancy	2nd pregnancy									
	Preterm birth with no complications[a]			Complicated preterm birth including primary complication[a]			Complicated preterm birth excluding primary complication[a]			
Complication status	N(%)			N(%)			N(%)			
	Yes	No	Unknown	Yes	No	Unknown	Yes	No	Unknown	**Total**
Reference[b]	3,897 (3.7)	103,240 (95.5)	901 (0.8)	-	-	-	-	-	-	108,128
Pre-eclampsia	-	-	-	252 (0.2)	103,240 (95.5)	4,636 (4.3)	649 (0.6)	103,240 (95.5)	4,239 (3.9)	108,128
Placental abruption	-	-	-	154 (0.1)	103,240 (95.5)	4,734 (4.4)	742 (0.7)	103,240 (95.5)	4,146 (3.8)	108,128
Small-for-gestational age	-	-	-	145 (0.1)	103,240 (95.5)	4,743 (4.4)	754 (0.7)	103,240 (95.5)	4,134 (3.8)	108,128
Perinatal death	-	-	-	467 (0.4)	103,240 (95.5)	4,421 (4.1)	434 (0.4)	103,240 (95.5)	4,454 (4.1)	108,128
Pre-eclampsia:										
PE02[c]	1,315 (19.8)	5,175 (77.8)	160 (2.4)	77 (1.2)	5,175 (77.8)	1,398 (21)	83 (1.2)	5,175 (77.8)	1,392 (20.9)	6,650
PE03[d]	225 (6.9)	3,386 (91.3)	66 (1.8)	20 (0.5)	3,386 (91.3)	301 (8.1)	46 (1.2)	3,386 (91.3)	275 (7.4)	3,707

PE04[e]	185 (4.4)	3,839 (91.8)	158 (3.8)	115 (2.7)	3,839 (91.8)	228 (5.5)	43 (1)	3,839 (91.8)	300 (7.2)	4,182
PE05[f]	201 (17.9)	855 (76)	69 (6.1)	21 (1.9)	855 (76)	249 (22.1)	48 (4.3)	855 (76)	222 (19.7)	1,125
PE06[g]	174 (11.9)	1054 (72.1)	234 (16)	208 (14.2)	1054 (72.1)	200 (13.7)	26 (1.8)	1054 (72.1)	382 (26.1)	1,462
Missing	0 (0)	215 (98.2)	*	0 (0)	215 (98.2)	*	0 (0)	215 (98.2)	*	219
Placental abruption:										
PA02[c]	1,469 (18.4)	6,135 (76.9)	370 (4.6)	31 (0.4)	6,135 (76.9)	1,808 (22.7)	338 (4.2)	6,135 (76.9)	1,501 (18.8)	7,974
PA03[d]	432 (5.5)	7,235 (91.7)	221 (2.8)	19 (0.2)	7,235 (91.7)	634 (8)	199 (2.5)	7,235 (91.7)	454 (5.8)	7,888
PA04[e]	8 (3.7)	203 (93.5)	6 (2.8)	*	203 (93.5)	10 (4.6)	*	203 (93.5)	12 (5.5)	217
PA05[f]	174 (16.7)	794 (76.1)	76 (7.3)	9 (0.9)	794 (76.1)	241 (23.1)	67 (6.4)	794 (76.1)	183 (17.5)	1,044
PA06[g]	45 (20.6)	156 (71.6)	17 (7.8)	*	156 (71.6)	59 (27.1)	14 (6.4)	156 (71.6)	48 (22)	218
Missing	*	*	*	0 (0)	*	*	*	*	*	*
Small-for-gestational age:										
SGA02[c]	1,469 (18.4)	6,135 (76.9)	370 (4.6)	27 (0.3)	6,135 (76.9)	1,812 (22.7)	342 (4.3)	6,135 (76.9)	1,497 (18.8)	7,974
SGA03[d]	215 (4.6)	4,296 (92.3)	143 (3.1)	9 (0.2)	4,296 (92.3)	349 (7.5)	131 (2.8)	4,296 (92.3)	227 (4.9)	4,654
SGA04[e]	225 (6.6)	3,078 (90.9)	84 (2.5)	25 (0.7)	3,078 (90.9)	284 (8.4)	59 (1.7)	3,078 (90.9)	250 (7.4)	3,387
SGA05[f]	166 (19.1)	654 (75.1)	51 (5.9)	5 (0.6)	654 (75.1)	212 (24.3)	46 (5.3)	654 (75.1)	171 (19.6)	871
SGA06[g]	55 (14)	296 (75.1)	43 (10.9)	18 (4.6)	296 (75.1)	80 (20.3)	25 (6.3)	296 (75.1)	73 (18.5)	394
Missing	0 (0)	65 (100)	0 (0)	0 (0)	65 (100)	0 (0)	0 (0)	65 (100)	0 (0)	65
Perinatal death:										

PD02[c]	1,469 (18.4)	6,135 (76.9)	370 (4.6)	69 (0.9)	6,135 (76.9)	1,770 (22.2)	300 (3.8)	6,135 (76.9)	1,539 (19.3)	7,974
PD03[d]	401 (5.1)	7,172 (92)	222 (2.8)	52 (0.7)	7,172 (92)	571 (7.3)	167 (2.1)	7,172 (92)	456 (5.8)	7,795
PD04[e]	39 (12.6)	266 (85.8)	5 (1.6)	*	266 (85.8)	42 (13.5)	*	266 (85.8)	41 (13.2)	310
PD05[f]	71 (17.7)	294 (73.1)	37 (9.2)	13 (3.2)	294 (73.1)	95 (23.6)	24 (6)	294 (73.1)	84 (20.9)	402
PD06[g]	150 (17.4)	657 (76)	57 (6.6)	22 (2.5)	657 (76)	185 (21.4)	35 (4.1)	657 (76)	172 (19.9)	864
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0

[a] complications included are pre-eclampsia, placental abruption, small-for-gestational age and stillbirth; [b] uncomplicated term birth; [c] uncomplicated preterm birth; [d] term birth without primary complication; [e] term birth with primary complication; [f] preterm birth without primary complication; [g] preterm birth with primary complication
*observations with less than 5 counts were not reported

Supplementary Table S3.2 Relative risk for the association between complications in first pregnancy and preterm birth in the second pregnancy

1st pregnancy	2nd pregnancy					
	Preterm birth with no complications[a]		Complicated preterm birth including primary complication[a]		Complicated preterm birth excluding primary complication[a]	
Complication status	**Unadjusted RR (CI)**	**Adjusted* RR (CI)**	**Unadjusted RR (CI)**	**Adjusted* RR (CI)**	**Unadjusted RR (CI)**	**Adjusted* RR (CI)**
No complication	Reference[b]	Reference[b]	Reference[b]	Reference[b]	Reference[b]	Reference[b]
Pre-eclampsia:						
PE02[c]	5.45 (5.15 to 5.77)	5.16 (4.87 to 5.46)	6.02 (4.67 to 7.76)	5.38 (4.52 to 7.53)	2.53 (2.01 to 3.17)	2.37 (1.89 to 2.97)
PE03[d]	1.88 (1.67 to 2.13)	1.67 (1.48 to 1.89)	2.41 (1.53 to 3.80)	2.27 (1.43 to 3.58)	2.15 (1.59 to 2.89)	1.83 (1.35 to 2.47)
PE04[e]	1.24 (1.07 to 1.43)	1.22 (1.05 to 1.41)	11.94 (9.60 to 14.86)	11.87 (9.52 to 14.79)	1.77 (1.30 to 2.41)	1.75 (1.29 to 2.38)
PE05[f]	5.12 (4.50 to 5.82)	4.35 (3.80 to 4.98)	9.85 (6.34 to 15.29)	10.10 (6.38 to 15.99)	8.51 (6.39 to 11.32)	6.81 (5.06 to 9.16)
PE06[g]	3.81 (3.31 to 4.39)	3.70 (3.21 to 4.27)	67.69 (56.82 to 80.63)	64.04 (53.58 to 76.55)	3.85 (2.62 to 5.68)	3.67 (2.49 to 5.42)
Placental abruption:						

PA02[c]	5.20 (4.92 to 5.49)	4.93 (4.66 to 5.22)	3.83 (2.30 to 4.96)	3.25 (2.21 to 4.78)	7.32 (6.45 to 8.30)	6.99 (6.15 to 7.94)
PA03[d]	1.52 (1.38 to 1.67)	1.42 (1.29 to 1.56)	1.76 (1.09 to 2.83)	1.62 (1.00 to 2.61)	3.75 (3.21 to 4.38)	3.57 (3.05 to 4.17)
PA04[e]	1.02 (0.52 to 2.01)	1.00 (0.51 to 1.98)	12.97 (5.85 to 34.68)	11.79 (4.37 to 31.83)	1.37 (0.34 to 5.44)	1.35 (0.34 to 5.37)
PA05[f]	4.83 (4.21 to 5.55)	4.11 (3.56 to 4.75)	7.52 (3.86 to 14.68)	6.39 (3.16 to 12.92)	10.91 (5.57 to 13.87)	10.12 (7.86 to 13.02)
PA06[g]	6.02 (4.65 to 7.80)	5.40 (4.16 to 7.01)	12.67 (4.08 to 39.29)	10.47 (3.37 to 32.51)	11.54 (6.95 to 19.16)	10.80 (6.49 to 18.00)
Small-for-gestational age:						
SGA02[c]	5.20 (4.92 to 5.49)	4.94 (4.67 to 5.22)	3.12 (2.07 to 4.71)	2.89 (1.92 to 4.35)	7.28 (6.43 to 8.25)	7.00 (6.16 to 7.94)
SGA03[d]	1.28 (1.12 to 1.47)	1.26 (1.10 to 1.44)	1.49 (0.76 to 2.92)	1.51 (0.77 to 2.97)	4.08 (3.40 to 4.90)	4.02 (3.34 to 4.83)
SGA04[e]	1.83 (1.61 to 2.09)	1.62 (1.42 to 1.84)	5.74 (3.76 to 8.77)	4.30 (2.78 to 6.66)	2.59 (1.99 to 3.37)	2.39 (1.83 to 3.11)
SGA05[f]	5.44 (4.74 to 6.26)	4.63 (4.00 to 5.36)	5.41 (2.23 to 13.15)	5.73 (2.33 to 14.09)	9.06 (6.79 to 12.09)	8.18 (6.07 to 11.03)
SGA06[g]	4.21 (3.30 to 5.38)	3.66 (2.86 to 4.69)	40.87 (25.36 to 65.86)	32.68 (19.87 to 53.74)	10.74 (7.32 to 15.76)	9.69 (6.60 to 14.25)
Perinatal death:						
PD02 [c]	5.20 (4.92 to 5.49)	4.93 (4.67 to 5.22)	2.47 (1.92 to 3.18)	2.34 (1.82 to 3.00)	11.14 (9.63 to 12.87)	10.69 (9.23 to 12.39)
PD03[d]	1.42 (1.29 to 1.57)	1.34 (1.21 to 1.48)	1.60 (1.20 to 2.13)	1.52 (1.14 to 2.02)	5.44 (4.55 to 6.49)	5.14 (4.30 to 6.14)
PD04[e]	3.44 (2.56 to 4.62)	3.00 (2.22 to 4.05)	1.66 (0.42 to 6.61)	1.29 (0.32 to 5.17)	2.66 (0.86 to 8.24)	2.80 (0.91 to 8.61)
PD05[f]	5.23 (4.24 to 6.46)	4.65 (3.76 to 5.76)	9.40 (5.48 to 16.13)	8.09 (4.72 to 13.85)	18.03 (12.13 to 26.79)	16.19 (10.89 to 24.07)

PD06[g]	5.00 (4.31 to 5.79)	4.22 (3.61 to 4.93)	7.20 (4.72 to 10.96)	5.23 (3.36 to 8.14)	12.08 (8.63 to 16.91)	12.72 (8.90 to 18.18)

[a] complications included are pre-eclampsia, placental abruption, small-for-gestational age and stillbirth; [b] uncomplicated term birth; [c] uncomplicated preterm birth; [d] term birth without primary complication; [e] term birth with primary complication; [f] preterm birth without primary complication; [g] preterm birth with primary complication

*Adjusted for ethnicity, maternal age at first-birth, smoking status at first-birth, socioeconomic status at first-birth, time period of first-birth, inter-pregnancy interval, and change of father between first and second birth.

Supplementary Table S3.3 E-values for unmeasured confounding of the relative risk of subsequent preterm birth from complications in first pregnancy

1st pregnancy	2nd pregnancy					
	Preterm birth with no complications[a]		Complicated preterm birth including primary complication[a]		Complicated preterm birth excluding primary complication[a]	
Complication status	**E-value unadjusted RR (lower 95% CI)**	**E-value adjusted* RR (lower 95% CI)**	**E-value unadjusted RR (lower 95% CI)**	**E-value adjusted* RR (lower 95% CI)**	**E-value unadjusted RR (lower 95% CI)**	**E-value adjusted* RR (lower 95% CI)**
No complication	Reference[b]	Reference[b]	Reference[b]	Reference[b]	Reference[b]	Reference[b]
Pre-eclampsia:						
PE02[b]	10.37 (9.77)	9.78 (9.20)	11.52 (8.81)	11.14 (8.50)	4.49 (3.44)	4.18 (2.19)
PE03[c]	3.17 (2.72)	2.73 (2.32)	4.26 (2.43)	3.96 (2.22)	3.71 (2.57)	3.05 (2.03)
PE04[d]	1.78 (1.35)	1.73 (1.29)	23.38 (18.69)	23.22 (18.53)	2.94 (1.93)	2.89 (1.89)
PE05[f]	9.71 (8.48)	8.17 (7.07)	19.18 (12.16)	19.68(12.23)	16.50 (12.27)	13.09 (9.59)
PE06[g]	7.08 (6.07)	6.87 (5.58)	134.87 (113.18)	127.58 (106.65)	7.17 (4.67)	6.80 (4.41)
Placental abruption:						
PA02[b]	9.86 (9.31)	9.34 (8.80)	6.21 (4.02)	5.95 (3.84)	14.11 (12.38)	13.49 (11.78)
PA03[c]	2.40(2.10)	2.19 (1.90)	2.91 (1.41)	2.61 (1.0)	6.96 (5.88)	6.59 (5.55)

PA04[d]	1.16 (1)	1.04 (1.0)	25.44 (9.18)	23.08 (8.20)	2.08 (1.0)	2.03 (1.0)
PA05[f]	9.14 (7.89)	7.69 (6.59)	14.53 (7.17)	12.27 (5.78)	21.30 (16.62)	19.73 (15.21)
PA06[g]	11.52 (8.76)	10.27 (7.78)	24.83 (7.63)	20.43 (6.20)	22.57 (13.38)	21.10 (12.45)
Small-for-gestational age:						
SGA02[b]	9.86 (9.31)	9.34 (8.81)	5.70 (3.57)	5.22 (3.23)	14.04 (12.33)	13.47 (11.81)
SGA03[c]	1.88 (1.49)	1.84 (1.44)	2.35 (1)	2.39 (1)	7.63 (6.25)	7.50 (6.14)
SGA04[d]	3.07 (2.60)	2.62 (2.20)	10.96 (7.00)	8.07 (5.00)	4.62 (3.40)	4.21 (3.06)
SGA05[f]	10.36 (8.94)	8.73 (7.47)	10.29 (3.88)	10.94 (4.10)	17.61 (13.07)	15.85 (11.61)
SGA06[g]	7.89 (6.05)	6.78 (5.16)	81.24 (50.3)	64.86 (39.24)	20.97 (14.13)	18.87 (12.67)
Perinatal death:						
PD02[b]	9.86 (9.31)	9.34 (8.80)	4.38 (3.25)	4.10 (3.04)	21.76 (18.75)	20.87 (17.94)
PD03[c]	2.20 (1.90)	2.02 (1.72)	2.58 (1.69)	2.40 (1.54)	10.35 (8.58)	9.75 (8.06)
PD04[d]	6.34 (4.56)	5.45 (3.87)	2.70 (1)	1.90 (1)	4.77 (1)	5.04 (1)
PD05[f]	9.94 (7.94)	8.78 (7.00)	18.29 (10.44)	15.66 (8.91)	35.55(23.77)	31.87 (21.26)
PD06[g]	9.47 (8.09)	7.91 (6.68)	13.87 (8.92)	9.93 (6.17)	23.65 (16.75)	24.93(17.28)

[a] complications included are pre-eclampsia, placental abruption, small-for-gestational age and stillbirth; [b] uncomplicated term birth; [c] uncomplicated preterm birth; [d] term birth without primary complication; [e] term birth with primary complication; [f] preterm birth without primary complication; [g] preterm birth with primary complication

*Adjusted for ethnicity, maternal age at first-birth, smoking status at first-birth, socioeconomic status at first-birth, time period of first-birth, inter-pregnancy interval, and change of father between first and second birth.

Supplementary Table S3.4 Relative risk for the association between complications in first pregnancy and preterm birth in the second pregnancy after simulating obesity

1st pregnancy	2nd pregnancy					
	Preterm birth with no complications[a]		Complicated preterm birth including primary complication[a]		Complicated preterm birth excluding primary complication[a]	
Complication status	**Adjusted* RR (CI)**	**Simulation adjusted* RR (CI)**	**Adjusted* RR (CI)**	**Simulation adjusted* RR (CI)**	**Adjusted* RR (CI)**	**Simulation adjusted* RR (CI)**
No complication	Reference[b]	Reference[b]	Reference[b]	Reference[b]	Reference[b]	Reference[b]
Pre-eclampsia:						
PE02[c]	5.16 (4.87 to 5.46)	5.16 (4.87 to 5.46)	5.83 (4.52 to 7.53)	5.83 (4.51 to 7.52)	2.37 (1.89 to 2.97)	2.37 (1.89 to 2.97)
PE03[d]	1.67 (1.48 to 1.89)	1.67 (1.48 to 1.89)	2.27 (1.43 to 3.58)	2.36 (1.43 to 3.58)	1.83 (1.35 to 2.47)	1.83 (1.35 to 2.47)
PE04[e]	1.22 (1.05 to 1.41)	1.22 (1.05 to 1.41)	11.87 (9.52 to 14.79)	11.90 (9.55 to 14.84)	1.75 (1.29 to 2.38)	1.75 (1.29 to 2.38)
PE05[f]	4.35 (3.80 to 4.98)	4.35 (3.80 to 4.98)	10.10 (6.38 to 15.99)	10.09 (6.38 to 15.97)	6.81 (5.06 to 9.16)	6.80 (5.06 to 9.16)
PE06[g]	3.70 (3.21 to 4.27)	3.70 (3.21 to 4.27)	64.04 (53.58 to 76.55)	63.87 (53.43 to 76.35)	3.67 (2.49 to 5.42)	3.67 (2.49 to 5.41)

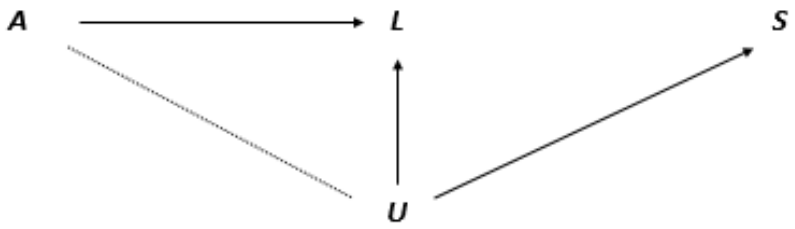
Placental abruption:						
PA02[c]	4.93 (4.66 to 5.22)	4.93 (4.66 to 5.22)	3.25 (2.21 to 4.78)	3.24 (2.20 to 4.77)	6.99 (6.15 to 7.94)	6.98 (6.15 to 7.93)
PA03[d]	1.42 (1.29 to 1.56)	1.42 (1.29 to 1.56)	1.62 (1.00 to 2.61)	1.62 (1.00 to 2.62)	3.57 (3.05 to 4.17)	3.57 (3.05 to 4.17)
PA04[e]	1.00 (0.51 to 1.98)	1.00 (0.51 to 1.98)	11.79 (4.37 to 31.83)	11.98 (4.45 to 32.27)	1.35 (0.34 to 5.37)	1.35 (0.34 to 5.39)
PA05[f]	4.11 (3.56 to 4.75)	4.11 (3.56 to 4.75)	6.39 (3.16 to 12.92)	6.33 (3.13 to 12.80)	10.12 (7.86 to 13.02)	10.11 (7.86 to 13.01)
PA06[g]	5.40 (4.16 to 7.01)	5.40 (4.16 to 7.01)	10.47 (3.37 to 32.51)	10.50 (3.39 to 32.59)	10.80 (6.49 to 18.00)	10.84 (6.50 to 18.05)
Small-for-gestational age:						
SGA02[c]	4.94 (4.67 to 5.22)	4.94 (4.67 to 5.22)	2.89 (1.92 to 4.35)	2.89 (1.92 to 4.35)	7.00 (6.16 to 7.94)	6.99 (6.16 to 7.93)
SGA03[d]	1.26 (1.10 to 1.44)	1.26 (1.10 to 1.44)	1.51 (0.77 to 2.97)	1.50 (0.76 to 2.96)	4.02 (3.34 to 4.83)	4.03 (3.35 to 4.84)
SGA04[e]	1.62 (1.42 to 1.84)	1.62 (1.42 to 1.84)	4.30 (2.78 to 6.66)	4.31 (2.78 to 6.67)	2.39 (1.83 to 3.11)	2.38 (1.83 to 3.11)
SGA05[f]	4.63 (4.00 to 5.36)	4.63 (4.00 to 5.36)	5.73 (2.33 to 14.09)	5.72 (2.33 to 14.06)	8.18 (6.07 to 11.03)	8.19 (6.07 to 11.04)
SGA06[g]	3.66 (2.86 to 4.69)	3.66 (2.86 to 4.69)	32.68 (19.87 to 53.74)	32.89 (19.98 to 54.13)	9.69 (6.60 to 14.25)	9.64 (6.56 to 14.18)
Perinatal death:						

PD02 [c]	4.93 (4.67 to 5.22)	4.93 (4.67 to 5.22)	2.34 (1.82 to 3.00)	2.34 (1.82 to 3.00)	10.69 (9.23 to 12.39)	10.68 (9.21 to 12.37)
PD03[d]	1.34 (1.21 to 1.48)	1.34 (1.21 to 1.48)	1.52 (1.14 to 2.02)	1.52 (1.14 to 2.02)	5.14 (4.30 to 6.14)	5.14 (4.30 to 6.15)
PD04[e]	3.00 (2.22 to 4.05)	3.00 (2.22 to 4.05)	1.29 (0.32 to 5.17)	1.29 (0.32 to 5.17)	2.80 (0.91 to 8.61)	2.81 (0.91 to 8.66)
PD05[f]	4.65 (3.76 to 5.76)	4.65 (3.76 to 5.76)	8.09 (4.72 to 13.85)	8.09 (4.72 to 13.85)	16.19 (10.89 to 24.07)	16.14 (10.87 to 24.00)
PD06[g]	4.22 (3.61 to 4.93)	4.22 (3.61 to 4.93)	5.23 (3.36 to 8.14)	5.22 (3.36 to 8.14)	12.72 (8.90 to 18.18)	12.71 (8.90 to 18.17)

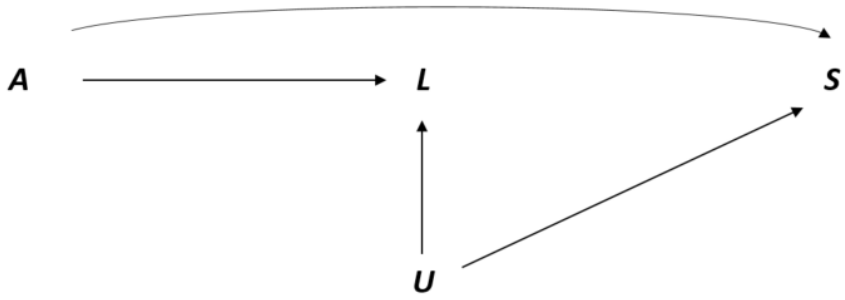
[a] complications included are pre-eclampsia, placental abruption, small-for-gestational age and stillbirth; [b] uncomplicated term birth; [c] uncomplicated preterm birth; [d] term birth without primary complication; [e] term birth with primary complication; [f] preterm birth without primary complication; [g] preterm birth with primary complication

*Adjusted for ethnicity, maternal age at first-birth, smoking status at first-birth, socioeconomic status at first-birth, time period of first-birth, inter-pregnancy interval, and change of father between first and second birth.

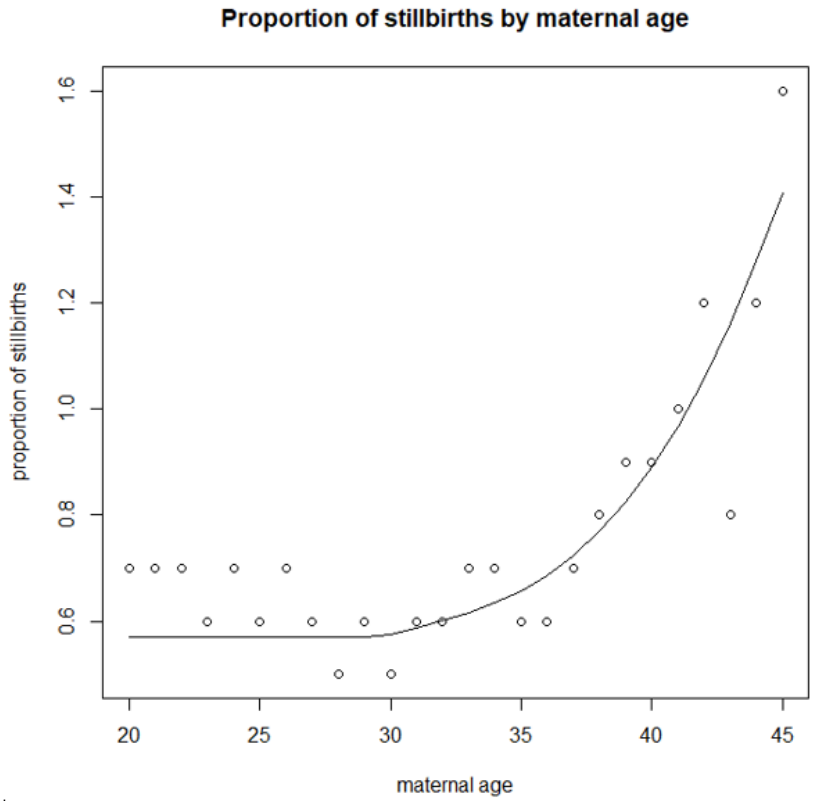
Appendix F Supplementary material for Publication Three



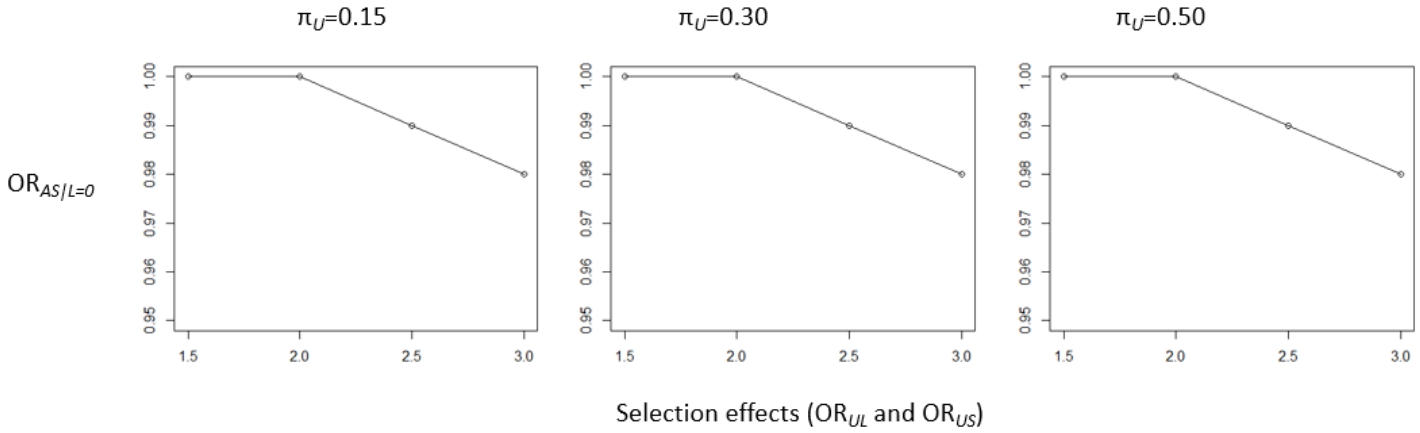
Supplementary Figure S4.1 Directed acyclic graph (DAG) of the structure of collider-stratification bias with interaction between the exposure and the unmeasured confounder U. The exposure maternal age *A* affects early pregnancy loss *L*, which is also affected by the independent risk factor *U*, inducing a back-door pathway between exposure *A* and the outcome of stillbirth *S*. When there is an interaction between *A* and *U* (depicted by dashed line), there is an increase in the prevalence of early pregnancy loss L for those that are exposed to both the exposure maternal age *A* and the unmeasured confounder *U*.



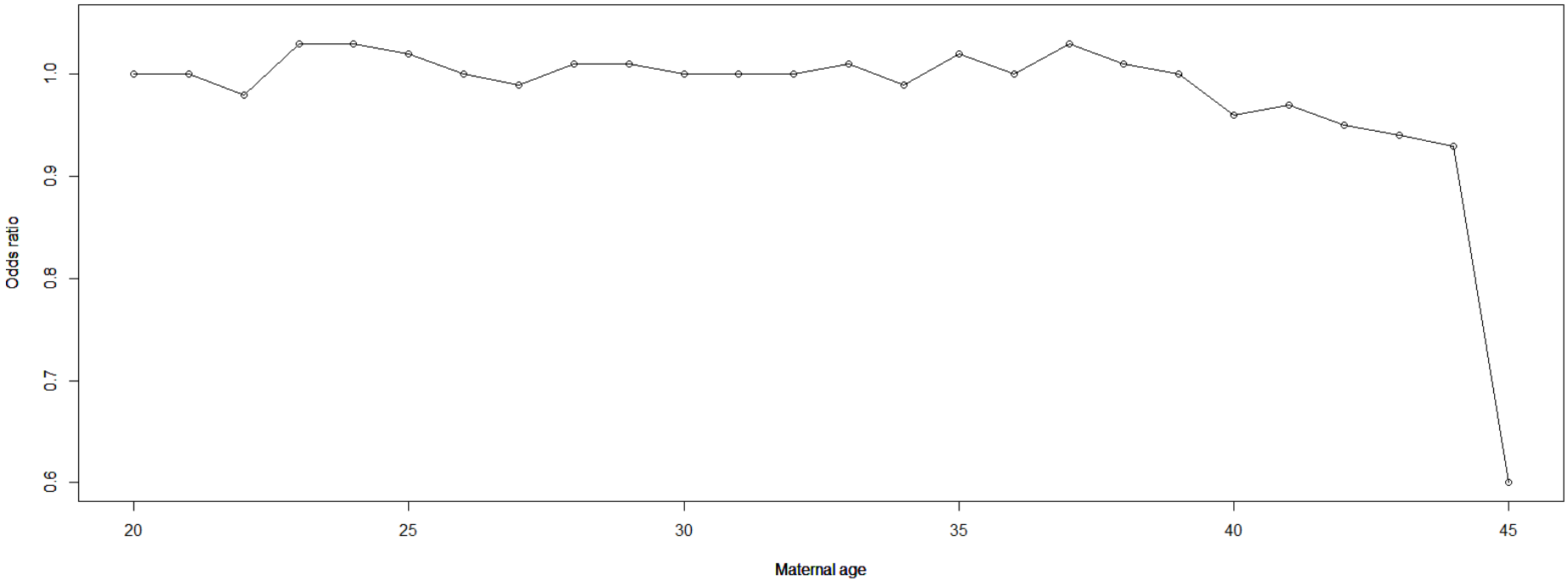
Supplementary Figure S4.2 Directed acyclic graph (DAG) of the structure of collider-stratification bias. The exposure maternal age *A* affects pregnancy loss *L*, which is also affected by the independent risk factor *U*, inducing a back-door pathway between exposure *A* and the outcome of stillbirth *S*. Here, there is a true effect of maternal age *A* on the outcome of stillbirth *S*.



Supplementary Figure S4.3 Risk of stillbirth according to maternal age based on a non-parametric regression model with locally weighted scatterplot smoothing to capture the nonlinearity of the association between maternal age and the outcome of stillbirth.



Supplementary Figure S4.4 Collider-stratification bias of $OR_{AS|L=0}$ under the true null effect of maternal age on stillbirth for women aged 35-39 years. Average odds ratio assuming with $\pi_{L=}$ 0.20 and varying input parameters for π_U and the selection effects (OR_{UL} and OR_{US}). Each scenario was simulated 100 times.



Supplementary Figure S4.5 Average odds ratio (OR) for the association between the exposure maternal age *A* and the outcome of stillbirth *S* over 100 simulations assuming a true null effect the and input of one unmeasured confounder *U* by each maternal year.

Supplementary Table S4.1 Average odds ratio (OR) and 95% simulation intervals (SIs) for the association between the exposure maternal age *A* and the outcome of stillbirth *S* over 100 simulations assuming a true null effect and the input of one unmeasured confounder *U*.

Selection effects			Average OR for maternal age on stillbirth (95% SI)				
π_L	π_U	OR_{UL} and OR_{US}	20-24	25-29	30-34	35-39	40+
0.128	0.15	1.5	1.00 (0.98 to 1.01)	0.99 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.99 (0.97 to 1.01)
		2.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.98 (0.95 to 1.00)
		2.5	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.96 (0.94 to 0.98)
		3.0	1.00 (0.99 to 1.02)	1.00 (0.99 to 1.01)	Ref	0.98 (0.98 to 0.99)	0.94 (0.92 to 0.96)
	0.30	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.99 (0.96 to 1.01)
		2.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.97 (0.95 to 0.99)
		2.5	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.94 (0.92 to 0.96)
		3.0	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	0.98 (0.97 to 0.99)	0.92 (0.90 to 0.94)
	0.50	1.5	1.00 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.99 (0.97 to 1.01)
		2.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.97 (0.95 to 0.99)
		2.5	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.94 (0.92 to 0.96)
		3.0	1.00 (1.00 to 1.01)	1.01 (1.00 to 1.01)	Ref	0.98 (0.98 to 0.99)	0.93 (0.91 to 0.94)
0.20	0.15	1.5	0.99 (0.98 to 1.01)	0.99 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.99 (0.96 to 1.01)
		2.0	1.00 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.98 (0.96 to 1.00)

		2.5	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.96 (0.94 to 0.99)
		3.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.98 (0.97 to 0.99)	0.95 (0.93 to 0.97)
	0.30	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.99 (0.96 to 1.01)
		2.0	1.00 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.97 (0.94 to 0.99)
		2.5	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.95 (0.92 to 0.97)
		3.0	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	0.98 (0.97 to 0.99)	0.93 (0.91 to 0.95)
	0.50	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.99 (0.97 to 1.01)
		2.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.97 (0.95 to 0.99)
		2.5	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.95 (0.93 to 0.98)
		3.0	1.00 (0.99 to 1.01)	1.01 (1.00 to 1.01)	Ref	0.98 (0.97 to 0.99)	0.93 (0.91 to 0.95)
0.30	0.15	1.5	1.00 (0.98 to 1.01)	0.99 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.02)	0.99 (0.96 to 1.02)
		2.0	1.00 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.98 (0.95 to 1.01)
		2.5	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.99 (0.98 to 1.01)	0.96 (0.94 to 0.99)
		3.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.95 (0.93 to 0.98)
	0.30	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.99 (0.96 to 1.02)
		2.0	1.00 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.98 (0.75 to 1.26)
		2.5	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.95 (0.92 to 0.98)
		3.0	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	0.98 (0.97 to 0.99)	0.94 (0.91 to 0.96)

	0.50	1.5	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.02)	1.00 (0.97 to 1.03)
		2.0	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.99 (0.96 to 1.01)
		2.5	1.00 (0.99 to 1.01)	1.01 (1.00 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.96 (0.94 to 0.99)
		3.0	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	0.98 (0.97 to 0.98)	0.94 (0.92 to 0.96)

$OR_{AS|L=0}$ odds ratio for the association between the exposure maternal age *A* and the outcome stillbirth *S* when early pregnancy loss *L* is set to 0; SI simulation intervals; π_L early pregnancy loss; π_U unmeasured confounder; OR_{UL} odds ratio for the association between the unmeasured confounder *U* and early pregnancy loss *L*; OR_{US} odds ratio for the association between the unmeasured confounder *U* and stillbirth *S*

Supplementary Table S4.2 Average odds ratio (OR) and 95% simulation intervals (SI) for the biased association between maternal age *A* and stillbirth *S* over 100 simulations for one single unmeasured *U*, assuming a true null effect of maternal age *A* on stillbirth *S* and an interaction between *U* and the exposure of maternal age *A*.

Selection effects			Average OR for maternal age on stillbirth (95% SI)				
π_L	π_U	$OR_{UL,}$ OR_{US} OR_{AU}	20-24	25-29	30-34	35-39	40+
0.128	0.15	1.5	0.99 (0.98 to 1.01)	0.99 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.98 (0.96 to 1.01)
		2.0	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.98 (0.96 to 1.00)
		2.5	0.99 (0.98 to 1.00)	0.99 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.97 (0.95 to 0.99)
		3.0	0.99 (0.98 to 1.00)	0.99 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.96 (0.93 to 0.97)
	0.30	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.99 (0.97 to 1.02)
		2.0	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.98 (0.96 to 1.00)
		2.5	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	1.00 (1.00 to 1.01)	0.96 (0.94 to 0.98)
		3.0	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.95 (0.93 to 0.97)
	0.50	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	1.00 (0.98 to 1.02)
		2.0	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.98 (0.96 to 1.00)
		2.5	0.99 (0.98 to 1.00)	0.99 (0.99 to 1.00)	Ref	1.00 (1.00 to 1.01)	0.97 (0.95 to 0.99)
		3.0	0.99 (0.98 to 1.00)	0.99 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.95 (0.93 to 0.97)
0.20	0.15	1.5	0.99 (0.98 to 1.01)	0.99 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.99 (0.97 to 1.01)

		2.0	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.98 (0.95 to 1.00)
		2.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.96 (0.93 to 0.98)
		3.0	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	0.99 (0.98 to 1.00)	0.94 (0.92 to 0.96)
	0.30	1.5	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.99 (0.96 to 1.01)
		2.0	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.97 (0.95 to 0.99)
		2.5	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.94 (0.92 to 0.96)
		3.0	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	0.99 (0.98 to 1.00)	0.92 (0.90 to 0.94)
	0.50	1.5	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.99 (0.96 to 1.01)
		2.0	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.97 (0.95 to 0.99)
		2.5	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.94 (0.92 to 0.96)
		3.0	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.00)	Ref	0.99 (0.98 to 1.00)	0.92 (0.90 to 0.94)
0.30	0.15	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.98 (0.95 to 1.01)
		2.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.96 (0.93 to 0.99)
		2.5	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.93 (0.90 to 0.96)
		3.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.98 (0.97 to 0.99)	0.90 (0.88 to 0.92)
	0.30	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.00)	Ref	1.00 (0.99 to 1.01)	0.98 (0.95 to 1.00)
		2.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.94 (0.92 to 0.97)
		2.5	1.00 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.91 (0.88 to 0.93)
		3.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	0.98 (0.97 to 0.99)	0.87 (0.84 to 0.89)

	0.50	1.5	0.99 (0.98 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.98 (0.95 to 1.00)
		2.0	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	Ref	1.00 (0.99 to 1.01)	0.95 (0.92 to 0.97)
		2.5	1.00 (0.99 to 1.01)	1.01 (1.00 to 1.01)	Ref	0.99 (0.98 to 1.00)	0.92 (0.89 to 0.94)
		3.0	1.00 (0.99 to 1.01)	1.00 (1.00 to 1.01)	Ref	0.98 (0.98 to 0.99)	0.88 (0.86 to 0.90)

$OR_{AS|L=0}$ odds ratio for the association between the exposure maternal age *A* and the outcome stillbirth *S* when early pregnancy loss *L* is set to 0; SI simulation intervals; π_L early pregnancy loss; π_U unmeasured confounder; OR_{UL} odds ratio for the association between the unmeasured confounder *U* and early pregnancy loss *L*; OR_{US} odds ratio for the association between the unmeasured confounder *U* and stillbirth *S*; OR_{AU} odds ratio for the association between the advanced maternal age *A* and the unmeasured confounder *U*

Supplementary Table S4.3 Average odds ratio (OR) and 95% simulation intervals (SIs) for the association between the exposure maternal age *A* and the outcome of stillbirth *S* over 100 simulations assuming a true effect and the input of one unmeasured confounder *U*.

Selection effects			Average OR for maternal age on stillbirth (95% SI)				
			20-24	25-29	30-34	35-39	40+
Original Cohort (OR 95% CI)			1.16 (1.05 to 1.29)	0.98 (0.90 to 1.17)	Ref	1.23 (1.11 to 1.37)	1.74 (1.42 to 2.12)
π_L	π_U	OR_{UL} and OR_{US}	20-24	25-29	30-34	35-39	40+
0.128	0.15	1.5	0.94 (0.93 to 0.95)	0.94 (0.93 to 0.95)	Ref	1.21 (1.20 to 1.23)	1.71 (1.67 to 1.74)
		2.0	0.94 (0.93 to 0.95)	0.94 (0.94 to 0.95)	Ref	1.21 (1.22 to 1.35)	1.69 (1.66 to 1.71)
		2.5	0.95 (0.93 to 0.96)	0.95 (0.94 to 0.95)	Ref	1.20 (1.19 to 1.22)	1.67 (1.64 to 1.69)
		3.0	0.95 (0.94 to 0.96)	0.95 (0.94 to 0.96)	Ref	1.19 (1.18 to 1.21)	1.62 (1.60 to 1.65)
	0.30	1.5	0.94 (0.93 to 0.95)	0.94 (0.94 to 0.95)	Ref	1.21 (1.20 to 1.22)	1.69 (1.66 to 1.72)
		2.0	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.95)	Ref	1.21 (1.19 to 1.22)	1.67 (1.64 to 1.69)
		2.5	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)	Ref	1.20 (1.19 to 1.21)	1.62 (1.60 to 1.65)
		3.0	0.95 (0.94 to 0.96)	0.95 (0.94 to 0.96)	Ref	1.19 (1.18 to 1.20)	1.58 (1.55 to 1.60)
	0.50	1.5	0.94 (0.93 to 0.95)	0.94 (0.94 to 0.95)	Ref	1.21 (1.20 to 1.23)	1.67 (1.65 to 1.71)
		2.0	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)	Ref	1.21 (1.20 to 1.22)	1.66 (1.64 to 1.69)
		2.5	0.95 (0.94 to 0.96)	0.95 (0.95 to 0.96)	Ref	1.20 (1.19 to 1.21)	1.61 (1.59 to 1.63)

		3.0	0.95 (0.94 to 0.96)	0.95 (0.95 to 0.96)	Ref	1.19 (1.18 to 1.20)	1.57 (1.55 to 1.59)
0.20	0.15	1.5	0.94 (0.93 to 0.95)	0.94 (0.93 to 0.95)	Ref	1.21 (1.20 to 1.23)	1.70 (1.67 to 1.74)
		2.0	0.94 (0.93 to 0.95)	0.94 (0.93 to 0.95)	Ref	1.21 (1.19 to 1.22)	1.69 (1.66 to 1.72)
		2.5	0.94 (0.93 to 0.96)	0.95 (0.94 to 0.95)	Ref	1.20 (1.19 to 1.21)	1.66 (1.63 to 1.69)
		3.0	0.95 (0.93 to 0.96)	0.95 (0.94 to 0.95)	Ref	1.19 (1.18 to 1.20)	1.63 (1.60 to 1.66)
	0.30	1.5	0.94 (0.92 to 0.95)	0.94 (0.94 to 0.95)	Ref	1.21 (1.20 to 1.22)	1.69 (1.66 to 1.72)
		2.0	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.95)	Ref	1.21 (1.19 to 1.22)	1.66 (1.63 to 1.69)
		2.5	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)	Ref	1.20 (1.19 to 1.21)	1.62 (1.60 to 1.65)
		3.0	0.95 (0.93 to 0.96)	0.95 (0.94 to 0.96)	Ref	1.18 (1.17 to 1.20)	1.58 (1.56 to 1.61)
	0.50	1.5	0.94 (0.93 to 0.95)	0.94 (0.94 to 0.95)	Ref	1.21 (1.20 to 1.23)	1.69 (1.66 to 1.72)
		2.0	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)	Ref	1.21 (1.20 to 1.22)	1.65 (1.62 to 1.68)
		2.5	0.95 (0.94 to 0.96)	0.95 (0.94 to 0.96)	Ref	1.20 (1.19 to 1.21)	1.62 (1.60 to 1.64)
		3.0	0.95 (0.94 to 0.96)	0.95 (0.95 to 0.96)	Ref	1.19 (1.18 to 1.20)	1.58 (1.56 to 1.61)
0.30	0.15	1.5	0.94 (0.93 to 0.96)	0.94 (0.93 to 0.95)	Ref	1.21 (1.20 to 1.23)	1.69 (1.66 to 1.73)
		2.0	0.94 (0.93 to 0.96)	0.94 (0.94 to 0.95)	Ref	1.21 (1.19 to 1.22)	1.67 (1.64 to 1.71)
		2.5	0.94 (0.93 to 0.96)	0.95 (0.94 to 0.96)	Ref	1.20 (1.19 to 1.22)	1.66 (1.62 to 1.70)
		3.0	0.95 (0.93 to 0.96)	0.95 (0.94 to 0.95)	Ref	1.20 (1.18 to 1.21)	1.63 (1.60 to 1.67)
	0.30	1.5	0.94 (0.92 to 0.95)	0.94 (0.94 to 0.95)	Ref	1.21 (1.20 to 1.23)	1.68 (1.65 to 1.72)

		2.0	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)	Ref	1.20 (1.19 to 1.22)	1.66 (1.63 to 1.69)
		2.5	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)	Ref	1.19 (1.18 to 1.21)	1.63 (1.60 to 1.66)
		3.0	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.96)	Ref	1.18 (1.17 to 1.20)	1.59 (1.56 to 1.63)
	0.50	1.5	0.94 (0.93 to 0.95)	0.95 (0.94 to 0.95)	Ref	1.21 (1.20 to 1.23)	1.68 (1.64 to 1.71)
		2.0	0.95 (0.93 to 0.96)	0.95 (0.94 to 0.96)	Ref	1.21 (1.19 to 1.22)	1.67 (1.63 to 1.70)
		2.5	0.95 (0.93 to 0.96)	0.96 (0.95 to 0.96)	Ref	1.20 (1.18 to 1.21)	1.63 (1.60 to 1.66)
		3.0	0.95 (0.93 to 0.96)	0.95 (0.94 to 0.96)	Ref	1.18 (1.17 to 1.19)	1.59 (1.55 to 1.62)

OR_{AS} odds ratio for the association between the advanced maternal age *A* and the outcome of stillbirth *S*; SI simulation intervals; π_L early pregnancy loss; π_U unmeasured confounder; OR_{UL} odds ratio for the association between the unmeasured confounder *U* and early pregnancy loss *L*; OR_{US} odds ratio for the association between the unmeasured confounder *U* and stillbirth *S*; OR_{AS} odds ratio for the association between the advanced maternal age *A* and the outcome of stillbirth *S*

Simulation code

age->early pregnancy loss<-U->stillbirth

n	sample size
p	prevalence of U
min.bpl	baseline risk of early pregnancy loss (derived from Figure 1)
or1	odds ratio for the U-early pregnancy loss effect
bY	baseline odds of exposure (derived from original cohort)
or2	odds ratio for the U-stillbirth effect

```
Results = foreach ( i=1:100, .packages = c("MASS","sandwich","lmtest","tidyverse","Rlab","dplyr","matrixStats"), .combine=rbind)  %dopar% {
        rboundednorm <- function(n, mymean, mysd, min = 20, max = 45) {
                a = pnorm(c(min, max), mymean, mysd)
                z = runif(n, a[1], a[2])
                qnorm(z, mymean, mysd)}
                n=500000;p=0.5;min.bpL=9.25;or1=1.5;bY=0.007;or2=1.5
        set.seed(i)
        bias <- data.frame("id" = 1:n) %>%
        mutate(age = rboundednorm(n, mymean=age.mean_std, mysd=age.sd_std),
        bpL = (min.bpL + age.to.misc(agevec=age,min.age=x2.2[p2.2==min(p2.2)],min.risk=min(p2.2)))/100,
        bL = bpL / (1 - bpL),
                U = rbern(n,p),
                prob_loss = plogis(log(bL) + log(or1)*U),
                loss = rbern(n, prob_loss),
                pY = plogis(log(bY) + log(or2)*U),
                Y = rbern(n, pY)) %>%
                mutate(age_cat = cut(age,breaks=c(10, 20, 24, 29, 35, 40, Inf),
                labels=c("<20", "20-24", "25-29", "30-34", "35-39", "40+"), include.lowest=TRUE),
                age_cat = relevel(age_cat, ref ="30-34"))#30-34 years set as reference
   # fit a logistic model among live births
   log_model <- bias %>% glm(formula = Y ~ age_cat,family = binomial(link = "logit"),
        data = ., subset = loss==0)
   ct=coeftest(log_model, vcov = sandwich)
   ci=confint(ct)
   c(ct[-1,1],ci[-1,1],ci[-1,2])
}
```

Appendix G Supplementary material for Publication Four

Supplementary Table S5.1 Average odds ratio (OR) and 95% simulation intervals (SIs) for the mediator-outcome confounding (Scenario 1) on the association between the exposure maternal obesity *OB* and the outcome of caesarean birth delivery *CS* with a mediator of pre-eclampsia *PE* (assuming a true null direct effect) over 100 simulations and the input of one unmeasured confounder *U.*

Selection effects		Average OR for maternal obesity on caesarean delivery (95% SI)
π_U	$OR_{U.PE}$ and $OR_{U.CS}$	
0.15	1.5	1.03 (1.02 to 1.02)
	2.5	1.03 (1.03 to 1.03)
	3.5	1.03 (1.03 to 1.03)
0.30	1.5	1.03 (1.02 to 1.03)
	2.5	1.03 (1.03 to 1.03)
	3.5	1.03 (1.03 to 1.04)
0.50	1.5	1.03 (1.02 to 1.03)
	2.5	1.03 (1.03 to 1.04)
	3.5	1.04 (1.04 to 1.05)

SI simulation intervals; π_U unmeasured confounder; $OR_{U.PE}$ odds ratio for the association between the unmeasured confounder *U* and the mediator of pre-eclampsia; $OR_{U.CS}$ odds ratio for the association between the unmeasured confounder *U* and caesarean section delivery

Supplementary Table S5.2 Average odds ratio (OR) and 95% simulation intervals (SIs) for the mediator-outcome confounding affected by the exposure (Scenario 2) on the association between the exposure maternal obesity *OB* and the outcome of caesarean birth delivery *CS* with a mediator of pre-eclampsia *PE* (assuming a true null direct effect) over 100 simulations and the input of one unmeasured confounder *U.*

Selection effects		Average OR for maternal obesity on caesarean delivery (95% SI)
π_U	$OR_{U.PE,}$ $OR_{U.CS}$ and $OR_{OB.U}$	
0.15	1.5	1.04 (1.03 to 1.04)
	2.5	1.06 (1.06 to 1.06)
	3.5	1.08 (1.07 to 1.08)
0.30	1.5	1.04 (1.04 to 1.04)
	2.5	1.06 (1.06 to 1.07)
	3.5	1.08 (1.08 to 1.09)
0.50	1.5	1.04 (1.04 to 1.04)
	2.5	1.07 (1.07 to 1.07)
	3.5	1.10 (1.09 to 1.10)

SI simulation intervals; π_U unmeasured confounder; $OR_{U.PE}$ odds ratio for the association between the unmeasured confounder *U* and the mediator of pre-eclampsia; $OR_{U.CS}$ odds ratio for the association between the unmeasured confounder *U* and caesarean section delivery; $OR_{OB.U}$ odds ratio for the association between the exposure of maternal obesity and the unmeasured confounder *U*

Supplementary Table S5.3 Average odds ratio (OR) and 95% simulation intervals (SIs) for the exposure-mediator confounding affected by the exposure (Scenario 3) on the association between the exposure maternal obesity *OB* and the outcome of caesarean birth delivery *CS* with a mediator of pre-eclampsia *PE* (assuming a true null direct effect) over 100 simulations and the input of one unmeasured confounder *U.*

Selection effects		Average OR for maternal obesity on caesarean delivery (95% SI)
π_U	$OR_{U.PE}$ and $OR_{U.OB}$	
0.15	1.5	1.04 (1.04 to 1.04)
	2.5	1.08 (1.08 to 1.08)
	3.5	1.13 (1.12 to 1.13)
0.30	1.5	1.04 (1.04 to 1.04)
	2.5	1.10 (1.09 to 1.10)
	3.5	1.16 (1.15 to 1.16)
0.50	1.5	1.05 (1.04 to 1.05)
	2.5	1.11 (1.11 to 1.11)
	3.5	1.17 (1.17 to 1.18)

SI simulation intervals; π_U unmeasured confounder; $OR_{U.PE}$ odds ratio for the association between the unmeasured confounder

Simulation code

```
library(boot)
library(foreach)
#Scenario 1: Mediator-outcome confounding

#n          sample size 128000
#pe         prevalence of preeclampsia (2.75) based on observed data
#pU         prevalence of U
#or1        odds ratio for the OB->PE effect (OR1.99)based on observed data
#or2        odds ratio for the U-> PE effect (varied)
#bY         baseline odds of outcome based on MNS
#or3        odds ratio for the PE-> CS effect (OR2.39) based on observed data
#or4        odds ratio for the U-> CS effect (varied)


res1=foreach(i=1:100,.packages=c("MASS","sandwich","lmtest","tidyverse","Rlab","dplyr","matrixStats"),.combine=rbind) %dopar% {
        n=128000;pe=0.0275;pU=0.50;or1=1.99;or2=1.5;bY=0.3454;or3=2.39;or4=1.5
        set.seed(i)
        bias <- data.frame("id" = 1:n) %>%
        mutate(obesity = rbinom(n,size=1,prob=0.20),
                bPE = plogis(log(pe) + log(or1)*obesity),
                b_PE = bPE / (1 - bPE),
                U = rbern(n, pU),
                prob_PE = plogis(log(b_PE) + log(or2)*U),
                PE = rbern(n, prob_PE),
                pCS = plogis(log(bY) + log(or3)*PE+ log(or4)*U),
               CS = rbern(n, pCS))
        log_model <- glm(formula = CS ~ obesity, family = binomial(link = "logit"), data = bias)
        ct=coeftest(log_model, vcov = sandwich)
        ci=confint(ct)
        c(ct[-1,1],ci[-1,1],ci[-1,2])
}

  meanf = function(myvar,index){return(mean(myvar[index],na.rm=TRUE))}
  set.seed(123)
  myboot = boot(data=res1,statistic=meanf,R=500)

  ORmean = boot(data=res1[,1],statistic=meanf,R=500)
  exp(ORmean$t0)
  ORCI = boot.ci(ORmean, conf=0.95,type="perc")
  exp(ORCI$perc[,4:5])
```

```
Mod1 <- paste("OR ", formatC(exp(ORmean$t0),digits=2,format="f"),"
(",formatC(exp(ORCI$perc[,4]),digits=2,format="f"),
        ",",formatC(exp(ORCI$perc[,5]),digits=2,format="f"),")",sep="")
Mod1
```

#Scenario 2: Mediator-outcome confounding affected by the exposure

```
#n          sample size 128000
#pe         prevalence of preeclampsia (2.75) based on observed data
#pU         prevalence of U
#or1        odds ratio for the OB-> PE effect (OR1.99)based on observed data
#or2        odds ratio for the U-> PE effect (varied)
#bY         baseline odds of outcome based on MNS
#or3        odds ratio for the PE-> CS effect (OR2.39) based on observed data
#or4        odds ratio for the U-> CS effect (varied)
#or5        odds ratio for the OB-> U effect (varied)

res2=foreach(i=1:100,.packages=c("MASS","sandwich","lmtest","tidyverse","Rlab","dpl
yr","matrixStats"),.combine=rbind) %dopar% {
        n=128000;pe=0.0275;pU=0.3;or1=1.99;or2=1.5;bY=0.3454;or3=2.39;or4=1.
5;or5=1.5
        set.seed(i)
        bias <- data.frame("id" = 1:n) %>%
        mutate(obesity = rbinom(n,size=1,prob=0.20),
                bPE = plogis(log(pe) + log(or1)*obesity),
                b_PE = bPE / (1 - bPE),
                U = rbern(n, pU),
                prob_PE = plogis(log(b_PE) + log(or2)*U + log(or5)),
               PE = rbern(n, prob_PE),
               pCS = plogis(log(bY) + log(or3)*PE+ log(or4)*U),
               CS = rbern(n, pCS))
        log_model <- glm(formula = CS ~ obesity, family = binomial(link = "logit"), data
= bias)
        ct=coeftest(log_model, vcov = sandwich)
        ci=confint(ct)
        c(ct[-1,1],ci[-1,1],ci[-1,2])
}

  meanf = function(myvar,index){return(mean(myvar[index],na.rm=TRUE))}
  set.seed(123)
  myboot = boot(data=res2,statistic=meanf,R=500)

  ORmean = boot(data=res2[,1],statistic=meanf,R=500)
  exp(ORmean$t0)
  ORCI = boot.ci(ORmean, conf=0.95,type="perc")
  exp(ORCI$perc[,4:5])
```

```
Mod2 <- paste("OR ", formatC(exp(ORmean$t0),digits=2,format="f"),"
(",formatC(exp(ORCI$perc[,4]),digits=2,format="f"),
        ",",formatC(exp(ORCI$perc[,5]),digits=2,format="f"),")",sep="")
Mod2
```

#Scenario 3: Exposure-mediator confounding

```
#n          sample size 128000
#pe         prevalence of preeclampsia (2.75) based on observed data
#pU         prevalence of U
#or1        odds ratio for the OB->PE effect (OR1.99) based on observed data
#or2        odds ratio for the U-> PEeffect - vary
#bY         baseline odds of outcome based on MNS
#or3        odds ratio for the PE->CS effect (OR2.39) based on observed data
#or4        odds ratio for the U->OB effect - vary


res3=foreach(i=1:100,.packages=c("MASS","sandwich","lmtest","tidyverse","Rlab","dpl
yr","matrixStats"),.combine=rbind) %dopar% {
        n=128000;pe=0.0275;pU=0.15;or1=1.99;or2=1.5;or3=2.39;bY=0.3454;or4=1
.5;
        set.seed(i)
        bias <- data.frame("id" = 1:n) %>%
        mutate(
                U = rbern(n, pU),
                p_obesity=plogis(log(0.2/(1-0.2)) + log(or4)*U)
                obesity=rbern(n,p_obesity),
                bPE = plogis(log(pe) + log(or1)*obesity),
                b_PE = bPE / (1 - bPE),
                prob_PE = plogis(log(b_PE) + log(or2)*U),
                PE = rbern(n, prob_PE),
                pCS = plogis(log(bY) + log(or3)*PE),
                CS = rbern(n, pCS))
        log_model <- bias %>% glm(formula = CS ~ obesity, family = binomial(link =
"logit"),  data = .)
        ct=coeftest(log_model, vcov = sandwich)
        ci=confint(ct)
        c(ct[-1,1],ci[-1,1],ci[-1,2])
}

  meanf = function(myvar,index){return(mean(myvar[index],na.rm=TRUE))}
  set.seed(123)
  myboot = boot(data=res3,statistic=meanf,R=500)

  ORmean = boot(data=res3[,1],statistic=meanf,R=500)
  exp(ORmean$t0)
  ORCI = boot.ci(ORmean, conf=0.95,type="perc")
  exp(ORCI$perc[,4:5])
```

```
Mod3 <- paste("OR ", formatC(exp(ORmean$t0),digits=2,format="f"),"
(",formatC(exp(ORCI$perc[,4]),digits=2,format="f"),
        ",",formatC(exp(ORCI$perc[,5]),digits=2,format="f"),")",sep="")
Mod3
```

Appendix H Supplementary material for Publication Five

Supplementary Table S6.1 Framework for the application of simulation in studies that quantify bias using observational data

Section/subsection	Recommendation
1. Aim	
1.1 Purpose of the simulation	Explain the background and clearly state the aim of the simulation study.
1.2 Exposure(s) and outcome(s)	Define the exposure(s), outcome(s), and other relevant variable(s) that will be included in the simulation study
1.3 Target population	Clearly define the population of interest to the study
1.4 Type(s) of bias	State the types of bias that the simulation model will be quantifying.
2. Logic	
2.1 Graphs	Describe the influence of bias using causal diagrams or direct acyclic graphs.
3. Data	
3.1 Population	Provide clear details of the base population.
3.2 Data sources	Clearly state the data sources that inform the simulation. This could be an observed cohort or data from previously published literature.
3.3 Bias parameters	Provide the parameters applied to the model that drive the influence of the bias

3.4 Data generation	Report how probability distributions were assigned to the bias parameters.
4. Implementation	
4.1 Analysis of simulation	Clearly state the analysis methods applied to the simulation. Details should include all methods, results, diagnostics, and programming code used to implement the analysis.
4.2 Report results of the simulation	Restate the assumptions of the bias analysis and clearly report the results, focusing on whether the model explains the reported estimate.
5. Reproducibility	
5.1 Model assumptions	If assumptions of the model are summarised in the methods section, use online appendices to elaborate on details.
5.2 Software	Provide a clear statement of the software used to conduct the simulation.
5.3 Code sharing	Make the code available, preferably online with the published paper.

Simulation code

```
#                SIMULATION STUDY: BMI AND PTB FRAMEWORK EXAMPLE
#
# Underweight <18.5; Normal 18.5-24.9; Overweight 25-29.9; Obese >30
#
#                INSTALL PACKAGES & LIBRARIES
#
#install.packages("doParallel", repos="http://cran.r-project.org")
#install.packages("foreach", repos="http://cran.r-project.org")
#install.packages("boot", repos="http://cran.r-project.org")
library(foreach)
library(doParallel)
library(boot)

#                SET PARALLEL COMPUTING

num.clusters=detectCores()-1
registerDoParallel(num.clusters)
getDoParWorkers() #Number of clusters used

#                MISCARRIAGE AS A FUNCTION OF BMI

# BMI~miscarriage association as per
https://pubmed.ncbi.nlm.nih.gov/35232386/
# x BMI in whole levels from 15 to 40
# y Proportion of miscarriage
x1 <- seq(15, 40, 1)
y1 <-
100*c(0.21,0.21,0.205,0.205,0.20,0.20,0.19,0.19,0.195,0.20,0.20,0.20
5,0.21,0.22,0.23,0.23,0.24,0.24,0.245,0.25,0.25,0.26,0.26,0.27,0.27,
0.27)

#Model for miscarriage based on BMI
#Local regression smoother. Smoothness controlled by "span"
model <- loess(y1~x1,span=2/3)
summary(model)

#New data with a finer granularity
x2 <- seq(15, 40, 0.01) #new BMI
p2 <- predict(model,newdata=x2) #prediction of miscarriages at these
new BMI

#Plot - good fit
plot(x1, y1, xlab = "maternal BMI", ylab = "Proportion of
miscarriage", main = "Proportion of miscarriage by BMI")
lines(x2, p2)
```

```
#Check BMI at which miscarriage is lowest
x2[p2==min(p2)] #21.96 BMI
min(p2) #19.43

#Function to estimate theoretical probability of miscarriage
assuming risk does not increase until the aforementioned BMI of
21.96
BMI.to.misc <- function(BMIvec,min.BMI,min.risk){
 misc=predict(model,newdata=BMIvec)
 misc[BMIvec<=min.BMI]=misc[BMIvec>min.BMI]=0
 misc[BMIvec>min.BMI]=misc[BMIvec>min.BMI]-min.risk
 return(misc)
}


#Plot - good fit from BMI of 21.96

min.risk=min(p2)

plot(x1, y1, xlab = "Maternal BMI", ylab = "Proportion of
miscarriage", main = "Proportion of miscarriage by BMI",pch=19,
cex.lab=1.5, col.lab="blue", axes=F, frame.plot=TRUE)

lines(x1,
min.risk+BMI.to.misc(BMIvec=x1,min.BMI=x2[p2==min(p2)],min.risk=min(
p2)), pch=19) #Very good fit.


#                SET SIM PARAMETERS
# mean of normally distributed exposure.
BMI.mean=26.02 ## Derived from observed data

# sd standard deviation of normally distributed exposure
BMI.sd=5.59 ## Derived from observed data


#                SIMULATION MODEL

#BMI -> Miscarriage <- U -> PTB

#           BMI->M->U<-PTB
#n         sample size 125000 (close match to selected sample from
observed data)
#pEPL      prevalence of M set to 20% - represents a common
statistic for miscarriage
#pU        prevalence of U - range from moderate to high (20:50)
#min.bpL   Minimum risk of early pregnancy loss set to 19.43
(derived from Bernoulli model)
#or1       odds ratio for the U-> EPL effect range from RR of
1.5;2;3
```

```
#or2       odds ratio for the U->PTB effect range from RR of 1.5;2;3
#bY        baseline prevalence of PTB based on MNS (set to 7.38%)


results=foreach(i=1:100,.packages=c("MASS","sandwich","lmtest","tidy
verse","Rlab","dplyr","matrixStats"),.combine=rbind) %dopar% {
   rboundednorm <- function(n, mymean, mysd, min = 15, max = 40) {
    a = pnorm(c(min, max), mymean, mysd)
    z = runif(n, a[1], a[2])
    qnorm(z, mymean, mysd)}
      n=128000;pU=0.50;min.bpL=19.43;or1=3.5;bY=0.738;or2=3.5
       set.seed(i)
      bias <- data.frame("id" = 1:n) %>%
      mutate(BMI= rboundednorm(n, mymean=BMI.mean, mysd=BMI.sd),
             bMiscarriage = (min.bpL +
             BMI.to.misc(BMIvec=BMI,min.BMI=x2[p2==min(p2)],min.risk=
             min(p2)))/100,b_Miscarriage = bMiscarriage / (1 -
             bMiscarriage),
             U = rbern(n, pU),
             prob_Miscarriage = plogis(log(b_Miscarriage) +
            log(or1)*U),
             Miscarriage = rbern(n, prob_Miscarriage), #miscarriage
             pPTB = plogis(log(bY) + log(or2)*U),
             PTB = rbern(n, pPTB))  %>% #preterm birth
             mutate(BMI_cat = cut(BMI,breaks=c(15, 18.5, 25, 30,Inf),
             labels=c("underweight","normal", "overweight", "obese"),
            include.lowest=TRUE),BMI_cat = relevel(BMI_cat, ref
            ="normal"))
      #fit a logistic model
      log_model <- bias %>% glm(formula = PTB ~ BMI_cat, family =
      binomial(link  = "logit"),data = ., subset = Miscarriage==0)
       ct=coeftest(log_model, vcov = sandwich)
       ci=confint(ct)
       c(ct[-1,1],ci[-1,1],ci[-1,2])
}


    meanf =
function(myvar,index){return(mean(myvar[index],na.rm=TRUE))}
    myboot = boot(data=results,statistic=meanf,R=500)

    ORmeanUnderweightboot =
boot(data=results[,1],statistic=meanf,R=500)
    exp(ORmeanUnderweightboot$t0)
    ORCIUnderweightboot = boot.ci(ORmeanUnderweightboot,
conf=0.95,type="perc")
    exp(ORCIUnderweightboot$perc[,4:5])
```

```
    ORmeanOverweightboot =
boot(data=results[,2],statistic=meanf,R=500)
    exp(ORmeanOverweightboot$t0)
    ORCIOverweightboot = boot.ci(ORmeanOverweightboot,
conf=0.95,type="perc")
    exp(ORCIOverweightboot$perc[,4:5])

    ORmeanObeseboot = boot(data=results[,3],statistic=meanf,R=500)
    exp(ORmeanObeseboot$t0)
    ORCIObeseboot = boot.ci(ORmeanObeseboot, conf=0.95,type="perc")
    exp(ORCIObeseboot$perc[,4:5])


#bind results into one line
SimulationResults <- paste("Underweight OR ",
formatC(exp(ORmeanUnderweightboot$t0),digits=2,format="f"),"
(",formatC(exp(ORCIUnderweightboot$perc[,4]),digits=2,format="f"),
      ",",formatC(exp(ORCIUnderweightboot$perc[,5]),digits=2,format=
"f"),")"," Overweight OR ",
formatC(exp(ORmeanOverweightboot$t0),digits=2,format="f"),
      "
(",formatC(exp(ORCIOverweightboot$perc[,4]),digits=2,format="f"),","
,formatC(exp(ORCIOverweightboot$perc[,5]),digits=2,format="f"),")","
Obese OR ",

formatC(exp(ORmeanObeseboot$t0),digits=2,format="f"),"(",formatC(exp
(ORCIObeseboot$perc[,4]),digits=2,format="f"),",",formatC(exp(ORCIOb
eseboot$perc[,5]),digits=2,format="f")
      ,")",sep="" )
SimulationResults
```

Appendix I Media release

Curtin University (https://www.curtin.edu.au)

NEWS AT CURTIN (HTTPS://WWW.CURTIN.EDU.AU/NEWS)

Home > News at Curtin > Media release > Study shows preterm birth risk most strongly linked to pre-eclampsia

(/NEWS/CATEGORY/)

Study shows preterm birth risk most strongly linked to pre-eclampsia

09 DEC 2021 | Yasmine Phillips

Copy Link Share Print

Women who gave birth to a premature baby after developing pre-eclampsia were 17 times more likely to experience another preterm birth if pre-eclampsia emerged again, new Curtin University research has found.

The study, published in the *British Journal of Obstetrics and Gynaecology*, examined more than 125,000 women who experienced two consecutive singleton births in Western Australia from 1998 to 2015.

About 27,000 babies are born prematurely – or before 37 weeks' gestation – across Australia each year, with preterm birth the leading cause of death and morbidity in children up to five years of age in the developed world.

Lead author and PhD candidate Jennifer Dunne, from Curtin's School of Population Health, said the findings showed the strongest link between preterm birth and pregnancies complicated by pre-eclampsia, a serious pregnancy condition that is usually characterised by high blood pressure, protein in the urine and severe swelling.

"When both pregnancies were complicated by pre-eclampsia, the risk of a subsequent preterm birth increased 10-fold after an initial term birth and 17-fold when the first birth was preterm, compared to women who had an uncomplicated first pregnancy," Ms Dunne said.

"This study also found that there was a three-fold higher risk of women experiencing a subsequent case of pre-eclampsia after a preterm birth in the first pregnancy that was not complicated by pre-eclampsia.

"Until recently, a first birth at full term was considered a reduced risk for a preterm delivery in the next pregnancy. However, there is emerging evidence that a complicated first pregnancy, regardless of whether the baby was delivered early or at full term, increases the subsequent risk of a baby being born prematurely."

Ms Dunne said the main pregnancy complications examined included pre-eclampsia, placental abruption (the detachment from the wall of the womb), small-for-gestational age and perinatal death (a stillbirth or a neonatal death in the first 28 days).

"Having any of the four complications in their first pregnancy puts women at an increased risk of a preterm birth in their next pregnancy, regardless of whether that first birth ended at full term or preterm," Ms Dunne said.

"Likewise, women whose first pregnancy ended in a preterm delivery were at an increased risk for each pregnancy complication in the second pregnancy.

"The findings of this study will help clinicians to better identify women who are at an increased risk of a either a preterm birth or complications in their subsequent pregnancies. Further research is now needed to reveal the specific pathways that explain these strong links between pregnancy complications and preterm births, whether they be genetic, pathological, and behavioural or other recurrent issues."

The research was supervised by Professor Gavin Pereira and co-authored by Dr Gizachew Tessema, also from Curtin's School of Population Health.

The full paper, '*The role of confounding in the association between pregnancy complications and subsequent preterm birth: a cohort study*', can be viewed online here (https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.17007).