Curtin School of Population Health

EFFECTS OF INTERPREGNANCY INTERVAL ON PREGNANCY COMPLICATIONS IN A HIGH-INCOME COUNTRY

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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.

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.

Amanuel Tesfay Gebremedhin

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List of abbreviations

ABS	Australian Bureau of Statistics
ACOG	American College of Obstetricians and Gynaecologists
APH	Antepartum haemorrhage
AOR	Adjusted odds ratio
AR	Absolute risk
ART	Artificial Reproductive Treatment
BMI	Body mass index
CI	Confidence interval
CS	Caesarean section
DAG	Directed Acyclic Graphs
GDM	Gestational diabetes melilites
GH	Gestational hypertension
HDP	Hypertensive disorders of pregnancy
HMDC	Hospital Morbidity Data Collection
HREC	Human Research Ethics Committee
IBI	Interbirth interval
ICD	International Classification of Diseases
IPDLN	International Population Data Linkage Network
IPI	Interpregnancy interval
IQR	Inter quantile range
IRSD	Index of Relative Social Disadvantage
LBW	Low birth weight
LMIC	Low-and Middle-Income Countries
LMP	Last menstrual period

MNS	Midwifery Notifications System
NHMRC	National Health and Medical Research Council
NOS	Newcastle-Ottawa Scale
OLS	Ordinary least square
OR	Odds ratio
PE	Preeclampsia
PROM	Premature rupture of membrane
PTB	Preterm birth
QR	Quantile regression
RR	Relative risk
SEIFA	Socio-Economic Index for Areas
SER	Society for Epidemiologic Research
SES	Socio Economic Status
SPER	Society for Paediatric and Perinatal Epidemiologic Research
UK	United Kingdom
US	United States
VBAC	Vaginal birth after caesarean
WA	Western Australia
WHO	World Health Organization
WADLS	Western Australian Data Linkage System

Abstract

Interpregnancy interval (IPI) is the time between birth and the start of the subsequent pregnancy and has been examined extensively regarding its link with child outcomes. Much less is known on its association with maternal outcomes, including gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy (HDPs). The World Health Organization (WHO) recommends waiting at least two years following a live birth and at least six months following a miscarriage or induced abortion. However, these recommendations are heavily driven by studies from low and middle-income populations, which might not be relevant for high-income population, where the changing obstetric profile (increasing maternal age and chronic morbidities) is most relevant. This thesis examined the associations between IPI and pregnancy complications to inform the evidence-based IPI recommendations in high-income settings.

Using high-quality, validated, population-based datasets on more than 350,000 consecutive pregnancies from Western Australia (WA) Data linkage System, gathered over more than 35 years in WA, we seek a better understanding of the associations between IPIs and pregnancy complications.

We used a novel within-mother (matched) design, matching pregnancies to the same mother to better control the potential unmeasured confounders known to bias associations. Findings from the within-mother analysis found insufficient evidence to suggest that short IPIs (<6 months) increases the risks of HDPs and GDM. Long IPIs (≥24 months) were associated with an increased risk of HDPs. The results of this thesis further indicated that the associations between IPIs and pregnancy complications vary by maternal age and previous complications at birth prior to IPI. The risks of HDPs and GDM following long IPIs (≥36 months) were more remarkable for mothers older than 35 years. The risks of antepartum haemorrhage and premature rupture of membrane at shorter IPIs (<6 months) were greater for mothers younger than 20 years.

There was insufficient evidence for an increased risk of preeclampsia or GDM at shorter IPIs (<18 months) for mothers with previous experience with these conditions. For mothers with no previous GDM, short IPIs (<18 months) were associated with a lower risk of GDM. Furthermore, the results suggest that IPIs were longer after HDPs. However, the extent of the delay was relatively small and did not differ across the IPI continuum.

The synthesis of the studies from this thesis, in conjunction with other studies, supported the adverse association between long intervals with HDPs and an inconsistent but accumulating evidence of association with an increased risk of uteroplacental bleeding disorders. The meta-analysed results also found insufficient evidence of adverse association of short IPIs (<6 months) with HDPs.

Overall, these findings challenge the current recommendations on birth spacing, including WHO, and questions their applicability to high-income settings such as Australia.

Keywords: Birth spacing, interpregnancy interval, birth intervals, pregnancy complications, gestational diabetes, hypertensive disorders of pregnancy, preeclampsia, within-mother, matched analysis, sibling design, population-based, data linkage

Dedication

For my amazing wife and love

Tirhas

whose sacrificial care for our children and me made it possible to complete this thesis,

and for our beloved children, ***Christian*** *and* ***Eyoab,*** *who have been patient and understanding throughout these doctoral years*

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Statement of contribution

Curtin School of Population Health provided the environment which supported the PhD candidate to undertake this project. The candidate was responsible for conceiving, designing, data management and statistical analyses, interpretation and drafting of the manuscript included in this thesis. Papers included in this thesis report original research I conducted during my Higher Degree by Research candidature and is not subject to any obligations or contractual agreement with a third party that would constrain its inclusion in this thesis. I am the primary author of all the papers.

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The detailed contributions and signed statements of all co-authors are included in Appendix A. The permission to reproduce the material from the publishers can be found in the Appendix D.

Publications included in this thesis

Peer-reviewed articles published

Study One: Gebremedhin AT, Regan AK, Ball S, Betrán AP, Foo D, Gissler M, Håberg SE, Malacova E, Marinovich ML, Pereira G. Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study. *Annals of epidemiology* 2019;39:33-8. e33 (incorporated in chapter 4).

Study Two: Gebremedhin AT, Regan AK, Ball S, Betrán AP, Foo D, Gissler M, Håberg SE, Malacova E, Marinovich ML, Pereira G. Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study. *Paediatric and Perinatal Epidemiology* 2020. doi:10.1111/ppe.12668 (incorporated in chapter 5).

Study Three: Gebremedhin AT, Tessema GA, Regan AK, Pereira G. Association between interpregnancy interval and hypertensive disorders of pregnancy: Effect modification by maternal age. *Paediatric and Perinatal Epidemiology 2021*. doi:10.1111/ppe.12774 (in press) (incorporated in chapter 6).

Gebremedhin AT, Regan AK, Malacova E, Marinovich ML, Ball S, Foo D, et al. Effects of interpregnancy interval on pregnancy complications: protocol for systematic review and meta-analysis. *BMJ Open*. 2018; 8:e025008 (incorporated in chapter 9).

Peer-reviewed articles submitted for publication

Study Four: Gebremedhin AT, Tessema GA, Regan AK, Pereira G. Association between interpregnancy interval and pregnancy complications by previous history of complications: a population-based cohort study. Under review in *BMJ Open* (incorporated in chapter 7).

Unpublished manuscripts

Study Five: Gebremedhin AT, Tessema GA, Regan AK, Pereira G. The influence of pregnancy complications on interpregnancy interval: a quantile regression analysis (incorporated in chapter 8).

Study Six: Gebremedhin AT, Mruts KB, Tessema GA, Malacova E, Marinovich ML, Ball S, Foo D, Regan AK, Pereira G. Effects of interpregnancy interval on pregnancy complications: a systematic review and meta-analysis (incorporated in chapter 9).

Other relevant publications during candidature

Srinivasjois RM, **Gebremedhin A,** Malacova E, Pereira G. Do adults born preterm deliver preterm babies? A record linkage study from Western Australia. *Journal of Maternal-Fetal & Neonatal Medicine.* 2021:1-4.

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Marinovich ML, Regan AK, Gissler M, Magnus MC, Haberg SE, Mayo JA, Shaw GM, Bell J, Nassar N, Ball S, **Gebremedhin AT**, Marston C, de Klerk N, Betran AP, Padula AM, et al. Associations between interpregnancy interval and preterm birth by previous preterm birth status in four high-income countries: a cohort study. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2020. NOV 24.

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Marinovich ML, Regan AK, Gissler M, Magnus MC, Haberg SE, Padula AM, Mayo JA, Shaw GM, Ball S, Malacova E, **Gebremedhin AT**, Nassar N, Marston C, de Klerk N, Betran AP, et al. Developing evidence-based recommendations for optimal interpregnancy intervals in high-income countries: protocol for an international cohort study. *BMJ Open* 2019;9:e027941.

Conference presentations from this thesis

Peer-reviewed conference abstracts

Gebremedhin A[1], Regan, Annette., Periera, Gavin, Malacova, Eva. Linking midwives and hospital morbidity data to investigate the effect of interpregnancy interval on gestational diabetes: a 35-year cohort study in Western Australia. International Population Data Linkage Conference. Banff, Alberta, Canada 2018. https://doi.org/10.23889/ijpds.v3i4.944 (***Oral presentation***)

Gebremedhin A. The effect of interpregnancy interval on preeclampsia by previous preeclampsia status; a population-based cohort study in Western Australia, 1980–2015. 24th Annual Congress of the Perinatal Society of Australia and New Zealand (PSANZ) Bridging Gaps in Perinatal Care. Sydney Convention Centre, NSW, Australia: Journal of Pediatrics and Child Health; 2020:138-53. https://doi.org/10.1111/jpc.14868 (***Poster presentation***)

Conference presentations

Gebremedhin A, Regan, Annette., Marinovich, Luke., Pereira, Gavin. Interpregnancy interval and risk of preeclampsia for women with and without previous preeclampsia: a population-based cohort study in Western Australia, 1980-2015. SPER annual conference Minnesota, USA 2019 (***Oral presentation***)

Gebremedhin A, Regan, Annette., Periera, Gavin, Malacova, Eva. Effect of interpregnancy interval on preeclampsia in a high-income country. Australasian Epidemiological Association (AEA). Fremantle, WA, Australia 2018 (***Mini-Oral presentation***)

Gebremedhin A, Regan, Annette., Marinovich, Luke., Periera, Gavin. The effect of Interpregnancy interval on hypertensive disorders during pregnancy and gestational diabetes;

[1] I have been awarded the competitive 'IPDLN student travel bursary' and Curtin Student Guild's PhD Conference Grant

a retrospective matched cohort study. Mark Liveris Research Student Seminar. Curtin University, Bentley, WA, Australia2018 (***Oral presentation***)

Gebremedhin A. Interpregnancy interval and pregnancy complications Perinatal Research Symposium Curtin University, Bentley, WA, Australia. 2018 (***Oral presentation***)

Klebanoff M, Ahrens, Katherine., **Gebremedhin, Amanuel**[2]., Pereira, Gavin,. Good epi, bad epi: Is short birth spacing really that bad? Society for Epidemiologic Research (SER) 52 annual meeting Minnesota, USA 2019 (***Oral presentation***)

Media release

Curtin University. Conceiving within six months of birth does not increase risk of diabetes [Internet]. 2019 [updated December 4. Available from: https://news.curtin.edu.au/media-releases/conceiving-within-six-months-of-birth-does-not-increase-risk-of-diabetes/

[2] Awarded SER travel scholarship

Chapter 1: THESIS 'ROADMAP'

1.1 AIM AND SCOPE

This research aimed to examine the effect of interpregnancy interval on pregnancy complications following the development and applications of methods for which a causal association is better established. The primary outcomes of interest were gestational diabetes, preeclampsia and gestational hypertension. However, other pregnancy complications were also incorporated across the studies including, uteroplacental bleeding disorders (placenta previa and placental abruption) and premature rupture of membrane (PROM).

1.2 APPROACH TO ADRESS THE AIM

This thesis has been divided into interrelated sub-studies, each of which is presented as a chapter. All sub-studies were conducted on populations of Western Australia (WA) using a large population-based cohort of longitudinally linked perinatal and hospital records from 1980-2015. A wide range of pregnancy complications was incorporated into the literature review (Chapter 2), from which gestational diabetes and hypertensive disorders of pregnancy emerged as primary outcomes of interest. Following this literature review which focused on the definition, risk factors and epidemiology of IPI and pregnancy complications, this thesis presents an overview of the methodological gaps regarding the current state of knowledge and novel epidemiological designs and approaches in the IPI literature (Chapter 3). This chapter comprehensively describes the study designs, measures and datasets employed in this thesis. Subsequent chapters (Chapter 4-7) focus on the causal effect of interpregnancy interval on the primary outcomes of interest - gestational diabetes (Chapter 4) and hypertensive disorders of pregnancy (Chapter 5)- applying various novel causal inference designs and analytical approaches. Next, the modifying role of maternal age and previous complications on the association between IPIs and pregnancy complications was presented (Chapter 6 and 7). Following this, quantile regression was employed to investigate if complications at first pregnancy delay subsequent pregnancy (Chapter 8). Finally, the results from this thesis are synthesised with the currently available evidence of an association between IPI and pregnancy complications and conclusions drawn (Chapter 9). This chapter also discusses the major strengths and limitations of the project.

1.3 STRUCTURE OF THE THESIS

This thesis has ten chapters, including this introductory chapter (Chapter 1), each presenting a review of the literature, methods, and results under specific study aims and overall discussion.

Chapter 2: Literature review

This chapter presents a comprehensive literature review on the definitions, risk factors and biological pathways by which IPI can lead to an increased risk of pregnancy complications. A summary of methodological limitations and gaps in the current state of knowledge is also described. Matters relating to causal inference and design alternatives were also included in this chapter.

Chapter 3: Methodology

This chapter provides an overview of the study design, methods and statistical approaches employed to address the aims and objectives identified in Chapter 2. It also provides a more comprehensive description of the data sources used to achieve the primary studies' aims in the thesis.

Chapter 4: Interpregnancy interval and gestational diabetes

Conventional approaches used to assess the association between IPIs, and pregnancy complications are sometimes more prone to confounding bias. To overcome this concern, (i) a 'matched' or 'within-mother comparison' design and (ii) a 'negative control' analyses were employed to investigate the association between IPI and gestational diabetes. The term "effect" in this thesis is used to describe estimated associations – regression coefficients or their transformations – and is not used to confer causation. This chapter (Study One) was peer-reviewed and published in *Annals of Epidemiology*.[1]

Chapter 5: Interpregnancy interval and hypertensive disorders of pregnancy

A similar design described in Chapter 4 was applied to examine the effects of IPIs on hypertensive disorders of pregnancy (preeclampsia and gestational hypertension). Directed acyclic graphs (DAGs) were employed to present the potential pathways between IPI and hypertensive disorders of pregnancy. A restricted cubic spline approach was applied to understand non-linear associations better. This study (Study Two) addressed a significant knowledge gap in the literature, clarifying that partner change did not explain associations between IPI and preeclampsia. This chapter was peer-reviewed and published in *Paediatric and Perinatal Epidemiology*.[2]

Chapter 6: Interpregnancy interval and pregnancy complications: Effect modification by maternal age

The potential modifying effect of maternal age in the association between IPIs and pregnancy complications is unknown. In this chapter (Study Three), the "optimal IPIs", defined as the IPI at which risk was minimum, were estimated for each complication of interest by maternal age and risk profile. This is the first time optimal IPIs are presented for each complication by maternal age and risk status. This chapter is accepted for publication at *Paediatric and Perinatal Epidemiology* journal and is currently in press.

Chapter 7: Interpregnancy interval and pregnancy complications: Effect modification by the previous history of complications

In addition to maternal age, previous pregnancy complications are major potential modifiers of the effect of IPIs on pregnancy complications, yet such effect modification has not been comprehensively investigated. This chapter (Study Four) presented both absolute and relative risks of gestational diabetes and preeclampsia for mothers with and without previous experience with these conditions throughout the IPI continuum. This chapter is currently under review at *BMJ Open*.

Chapter 8: The influence of pregnancy complications on interpregnancy interval

Examining the role of pregnancy complications in delaying IPI helps to understand the potential confounding effect of previous complications in the association between IPIs and subsequent complications. This chapter employed a quantile regression to assess the hypothesis that complications at first pregnancy delay subsequent pregnancy and visualise whether this effect is consistent across the IPI continuum. This study (Study Five) was used as a methodological supplement to overcome the methodological limitations of the epidemiological design (i.e., matched) employed in the chapters presenting findings related to specific aims of the study/project in the thesis (Chapters 4-8).

Chapter 9: Synthesis of the results from this thesis with the current body of literature: a systematic review and meta-analyses

This chapter provided a focused discussion and synthesis of the studies from this thesis along with other studies that have emerged on the association between IPIs and pregnancy complications. This was implemented through a systematic review of the association between birth spacing and various pregnancy complications, with meta-analyses to pool results with others identified in the systematic review (Study Six). Pooled results are reported for the effect

of IPIs on gestational diabetes, preeclampsia, and gestational hypertension. The remaining gaps and future research needed in the field is also outlined in this chapter.

Chapter 10: Discussion and conclusion

This chapter summarises and integrates the main findings from each study included in this thesis, reviews the strengths and limitations, and discusses the implications for evidence-based IPI recommendations and future epidemiological research.

Chapter 2: LITERATURE REVIEW

An introduction to the topic

2.1 PREAMBLE

This chapter begins with a background to the topic (section 2.2). It reviews the literature on the following topics: the epidemiology of pregnancy complications (section 2.3) which provides a summary of the updated global and national context of selected pregnancy complications; briefly described definitions of birth spacing, including the primary exposure, IPI, its epidemiology and risk factors (section 2.4). This chapter also included a comprehensive review of literature on the factors associated with IPI and, the link between birth spacing and pregnancy complications (section 2.5); the biological pathways of IPI and pregnancy complications (section 2.6); methodological limitations and gaps (section 2.7); and comprehensive reviews on causal inference and quasi-experimental designs (sections 2.8). Sections 2.9 and 2.10 highlighted the study's conceptual framework and the overall summary of the literature review, respectively. This chapter finally presented the research questions and aims of the thesis (section 2.11).

2.2 BACKGROUND

Pregnancy is a time of great joy and hope for many families. However, some pregnancies end tragically with maternal or fetal death or cause severe maternal or child impairment.[3] Globally, around 287,000 women die every year due to complications related to pregnancy and childbirth or the postpartum period. Another 5.7 million suffer severe or long-lasting illness caused by complications during pregnancy or childbirth.[4, 5] Majority of these morbidities and mortalities occur in resource-limited countries.[5] Although maternal mortality and severe morbidity are much lower in high-income countries, and they can contribute to significant health and economic burden to families and communities in these countries.

2.3 THE EPIDEMIOLOGY OF PREGNANCY COMPLICATIONS

Pregnancy complications are health problems that occur during pregnancy and include hypertensive disorders during pregnancy (HDPs; preeclampsia, eclampsia and gestational hypertension), gestational diabetes (GDM), maternal sepsis, uteroplacental bleeding disorders (placental abruption, placenta praevia), premature rupture of membranes and obstructed labor.[6, 7]

2.3.1 Gestational diabetes

GDM is defined as abnormal glucose tolerance in the mother, complicating pregnancy, childbirth or the puerperium with onset or first recognition during pregnancy.[8] It is one of the most common complications during pregnancy and an important contributor to a greater risk of perinatal complications. Globally, due to variations in population and diagnostic criteria implemented, the incidence varies from 1% to 25%, with the Middle East and North Africa with the highest incidence, followed by Southeast Asia, Western Pacific, South and Central America, Africa and North America and Caribbean. In Australia, GDM diagnosis is made based on the 75g OGTT with one or more of (fasting plasma glucose level of ≥5.1 mmol/L or one hour post 75g oral glucose load ≥ 10.0 mmol/L or two-hour post 75g oral glucose load ≥8.5 mmol/L) when first detected during pregnancy.[9] However, diagnostic criteria vary by country. For instance, the international association of diabetes in pregnancy study group endorsed a 75-g oral glucose tolerance test (OGTT). In contrast, in the US and some other countries, GDM is usually screened and diagnosed based on the two-step screening strategy (with a 3-h,100-g OGTT after an abnormal 1-h, 50g glucose challenge test.[10] Women with GDM are at increased risk for hypertensive disorders, caesarean delivery and perinatal metabolic disturbances resulting in stillbirth, preterm birth and macrosomia.[11-13]In Australia, in 2016-17, the national incidence of GDM was 15%, with slightly higher rates in the Australian Capital Territory and the Northern Territory (17%) and lower in WA (12%).[14]

Certain risk factors, which include interpregnancy weight gain, short IPIs, advanced maternal age, history of adverse pregnancy outcome and obesity, are thought to place a woman at increased risk for GDM or its recurrence.[15-20]

According to Australia Institute of Health and Welfare (AIHW) report the rate of mothers diagnosed with gestational diabetes in Australia was tripled from 5% to 15% in the year between 2000-01 and 2016-17 with similar pattern across all age groups and all states and territories. Among others, the changing of diagnostic and testing guidelines as well as increasing risk factors in the population are the main.[14] Among several diagnostic criteria's globally, the original criteria of 1964 (derivation of which are still widely accepted) were based on the prediction of the development of maternal diabetes.[21] In 1991, the consensus criteria for the diagnosis of GDM was formulated as national guidelines for testing and diagnosis of GDM in Australia by the Australian Diabetes in Pregnancy Society (ADIPS). These guidelines have been widely sued for almost decades. In 2010, a new consensus guideline was developed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) with

Australasian representation following publication of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study in 2008. Moreover, the establishment of National Gestational Diabetes Register (NGDR) by Diabetes Australia in 2011 and endorsement of the IADPSG guidelines by WHO in 2013, and by ADIPS in 2014 were prominent changes that might had an impact on creating awareness, practice of screening, testing and diagnosis of GDM in Australia. These prominent timelines in regard to the changes in guidelines over time and their potential influence is presented on Chapter-7 (Supplemental Figure 7-3). Other factors that may influence GDM incidence rates over time include, increased overweight and obesity rates, maternal age and immigration.[22]

2.3.2 Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDPs) include gestational hypertension (new hypertension without proteinuria), chronic hypertension, preeclampsia and eclampsia. HDPs are among the leading causes of maternal mortality and stillbirths that complicates around 4%–10% of pregnancies worldwide.[23-25] Gestational hypertension (GH), also referred to as pregnancy-induced hypertension, is characterised by the new onset of hypertension after 20 weeks of gestation, in the absence of proteinuria or other maternal organ dysfunction. GH affects 5-8% of pregnancies, and women who progress to severe GH based on the degree of blood pressure elevation have usually worse perinatal outcomes than do women with mild PE.[26] Preeclampsia (PE), a systematic syndrome characterised by hypertension (≥140mmHg systolic and ≥90mmHg diastolic blood pressure) and proteinuria (≥300mg/day or other maternal organ dysfunction), usually begins after the second half of pregnancy in women whose blood pressure had been normal.[27, 28] PE complicates 3%–5% of pregnancies worldwide with possible maternal (placental abruption, eclampsia) and neonatal (fetal growth restriction, preterm birth) complications.[29, 30] Eclampsia is severe complications of preeclampsia with generalised seizures or comma (or both) in the absence of other neurologic conditions.[31] Even though maternal deaths are infrequent in Australia, preeclampsia and its associated complications are responsible for around 15 per cent of maternal deaths.[32]

Several risk factors have been identified as risk factors for preeclampsia and gestational hypertension. Factors that increase risk include older maternal age, pre-existing medical conditions such as chronic hypertension and gestational diabetes, family history of preeclampsia, renal diseases and obesity.[33-37]

Preeclampsia has been described as “a disease of first pregnancy” and more associated with primiparity (4-5 times prevalent than among multiparous).[33, 34] Risk factors of PE among multiparous women include IPI,[16, 33, 37-39] previous adverse pregnancy outcomes,[39, 40] partner change,[41-44] and previous history of PE.[34, 40, 45] Decreased risk of hypertensive disorders of pregnancy has been associated with smoking, previous abortion (spontaneous or induced) and pregnancy with the same partner.[33, 36, 41, 46, 47]

2.3.3 Utero placental bleeding disorders

Utero placental bleeding disorder or antepartum haemorrhage (APH) is defined as bleeding from or into the genital tract, usually occurring from 24 weeks of gestation and prior to the baby's birth. APH complicates 3-5% of pregnancies and is one of the leading causes of maternal and fetal morbidity and mortality worldwide.[48, 49]

The two most common placental bleeding disorders are placental abruption and placenta praevia. Placental abruption is premature separation of the normally situated placenta from the uterine wall prior to delivery and occurs in about 3-10 per 1000 births. It is associated with up to one-quarter of all perinatal deaths.[49-51] Placenta praevia, a leading causes of vaginal bleeding during pregnancy, is a complication in which the placenta attaches in the lower uterine segment, covers or comes close to the internal cervical os. This condition has been reported to complicate 1 in 200 deliveries and has been associated with up to 5% of all perinatal deaths.[52] Placenta praevia is also associated with an increased risk of perinatal complications, including preterm birth, low birth weight, and associated morbidity.[53, 54] In Australia, according to 2018 report, the incidences ranged from 2.2-10.0 per 1000 women who gave birth and 1.4-6.0 per 1000 women for placenta praevia and placental abruption respectively.[55]

The aetiology of uteroplacental bleeding disorders is not well-understood, but identified risk factors include short IPIs, advanced maternal age, multiparity, smoking, folate deficiency, previous abortions, previous caesarean delivery, hypertensive disorders of pregnancy and prior placenta praevia or placental abruption.[52, 56-61]

2.3.4 Premature rupture of membranes

Premature rupture of membranes (PROM) is defined as prelabor rupture of the fetal membranes before uterine contractions. Approximately 8% - 10% of term pregnancies experience PROM and are typically associated with worse fetal and neonatal outcomes due to chorioamnionitis or premature delivery. Less commonly, it is also associated with stillbirth and perinatal death.[62-64] It may occur at term (≥37 weeks of gestation) or preterm (<37 weeks of gestation); the latter

is termed as preterm PROM (pPROM) and complicates 2-5% of all pregnancies, but associated with 40% - 50% of all preterm deliveries and can result in significant neonatal morbidity and mortality.[65-67] PROM was one of the most common complications in women who gave birth in WA, with a prevalence of 3.5%.[68]

In most cases, the cause of PROM is not fully understood but is likely multifactorial. Reported risk factors include ascending bacterial infection from women's genital tract (the most widely speculated factor),[69] advanced maternal age, nulliparity,[70] interpregnancy intervals,[15, 61, 71, 72] and smoking.[70, 73] Other factors, such as race/ethnicity, multiple pregnancies, history of PROM or prematurity and increased body mass index (BMI), have also been identified as risk factors for PROM.[61, 72, 74]

2.3.5 Uterine rupture

Uterine rupture is a rare complication of pregnancy in which the wall of the uterus tears during pregnancy or childbirth. It is a severe complication potentially leading to severe adverse outcomes among mothers and their infants. In high-income countries, it can occur in women who have a previous history of caesarean delivery.[75] Other known or suspected risk factors include maternal age, induction of labor, instrumental vaginal delivery and IPIs.[76-78] In high-income countries, although the prevalence of uterine rupture is low, with a median incidence of '5.3 per 10,000 births',[75] it is linked with increased maternal and neonatal mortality and long term complications.[25, 79, 80]

2.3.6 Labor dystocia

Labor dystocia, defined as slow or difficult labor or delivery, has been the most commonly reported indication for caesarean deliveries. It accounts for approximately half of primary caesarean births.[81, 82] Labor dystocia, accounted for an estimated 2.8% of the maternal causes of death globally, [83] with an incidence between 21 and 37% among nulliparous women and between 2 and 8% among parous women.[84-86]

There is limited literature on the incidence and risk factors of labor dystocia. Although identified by few studies, the risk factors include nulliparity, advanced maternal age, obesity, and other clinical characteristics, including induction of labor.[87-89] A dose-response relationship of labor dystocia has also been reported with both IPIs and short stature.[86, 90]

2.4 INTERPREGNANCY INTERVAL: DEFINITIONS, EPIDEMIOLOGY AND RISK FACTORS

2.4.1 Definition of IPI

The importance of birth spacing has been a focus for perinatal and family planning researchers and policy-makers since the early1980s.[91] Previous research on the association of birth spacing and infant, child and maternal health have used various definitions of such intervals. The common types of pregnancy interval measures used in the literature are described below and illustrated in Figure 2-1.

- Interpregnancy interval (IPI), or birth to pregnancy interval, is the most commonly used interval estimate and defined as the time interval between the birth of one child and conception of the subsequent pregnancy. Most often, only previous pregnancies ending in live births prior to the interval are considered in the calculation (time from 'Birth1' to 'Pregnancy1', 'Termination' to 'Pregnancy3' or time from 'Birth2' to 'Pregnancy4'; Figure 2-1), although this is usually due to limitations of data availability related to the difficulty in identifying and/or registering pregnancy loss prior to viability. Consequently, pregnancies before the interval ending in miscarriage or induced abortions (time interval between 'Pregnancy1' and 'Pregnancy2'; Figure 2-1) are left unaccounted.[92]

- Interdelivery interval (IDI) or interbirth interval (IBI) is defined as the time between two consecutive live births. The IBI interval does not include intervening non-live births (abortions and fetal deaths). Consequently, this measure does not take into consideration the time between 'pregnancy1' to 'termination', because it ended with non-live birth (Figure 1). IBI includes the length of the subsequent pregnancy, requiring an assumption that the gestational length of the subsequent pregnancy does not bias associations. Characterisation of IBI is highly sensitive to the definition of a "birth", which can vary from as early as 16 weeks of pregnancy in countries with fetal registries to 28 weeks of pregnancy in lower to middle-income countries. With its limitations, IBI remains as a useful proxy measure of interpregnancy intervals in several population surveys in low-and middle-income countries with limited information on the date of conception.[93]

- Inter-outcome interval (IOI) is defined as the interval between two consecutive pregnancy outcomes, irrespective of the outcome of pregnancy. As all pregnancies

are evaluated, this measure provides a better risk assessment for stillbirth or abortion (spontaneous or induced). In IOI, the starting and/or endpoints can be non-live birth (e.g., 'Termination' as an endpoint for 'IOI1' and as starting point for 'IOI2' measures; Figure 2-1). Using this measure, short intervals, by definition, are more likely to contain abortions, stillbirths, and premature births than IPI.

For this study, I used the Interpregnancy interval (IPI) - the period between the delivery date of the previous pregnancy and the conception date of the subsequent pregnancy-for all registered pregnancies as defined by the World Health Organisation (WHO).[94] This definition is also widely accepted in the literature.[95-98]

2.4.2 Definition of short and long IPIs

To date, there is no uniform international definition of short or long intervals. Short and long IPIs usually refers to less than six months and more than 60 months, respectively.[99] However, the definition has ranged from less than six months [16, 71, 72, 100-102] to less than 18 months,[103] or less than 24 months,[19, 86, 104, 105] for short IPIs, and more than 24 months,[19, 20, 72, 106] more than 60,[15, 71, 107, 108] to 120 months or more [86, 97] for long IPIs. Furthermore, IPI categories of <6, 6-11, 12-17, 18-23 (reference), 24-59, 60-119 and ≥120 months is recommended and commonly used in previous studies.[16, 38, 71, 97, 109] According to Klebanoff *et al.*,[110] an "optimal" interval between pregnancies is defined as the interval associated with the greatest likelihood of giving birth to a healthy infant and minimal risk of adverse maternal and perinatal outcomes. WHO recommends at least 24 months before conception of the subsequent pregnancy after a live birth and a minimum 6-month interval after miscarriage or induced abortion.[94] This interval was consistent with the WHO and United Nations Children's Fund (UNICEF) recommendation of continuing breastfeeding until two years.

Identifying optimal IPIs can promote healthy spacing of pregnancy that could reduce the risks to both mothers and children. Thus, it is crucial to investigate the association between IPIs and pregnancy complications and identify the optimal IPIs with minimal risk for infant and mothers. Women can potentially have some control over their informed decisions about pregnancy timing and spacing to attain a healthy pregnancy.

2.4.3 Patterns of IPI

The harmful consequences of postponing pregnancy are well known, especially at a later maternal age. Nevertheless, mothers from industrialised high-income settings seem to have an increasing trend towards longer IPIs.[111-113] For example, in the US, the median IPI was found

to be 23.8 months in 1999,[113] but increased to 24-29 months in 2014.[111] Similarly, an unpublished document that analysed data using WA linked records has shown that in WA, the median IPI increased from 19 months in the year 1990 to 21 months in 2010.[114]

2.4.4 Factors influencing IPI

Previous research has shown that IPI varies by various maternal characteristics, suggesting that certain women are more prone to risks posed by short and long IPIs.[115-119] Various factors that are known to be associated with IPIs include maternal age, birth order, parity, smoking, breastfeeding status, contraceptive use, marital status, fecundity and pregnancy intention.[116-122] Similarly, markers of maternal social disadvantage, including socioeconomic status (SES), access to prenatal care, level of education and race/ethnicity, were also IPI correlates in various studies from high-income settings.[115, 120, 123] Despite inconsistent measures of SES, studies show that IPIs (short and long) are associated with SES.[118, 124, 125]

In high-income settings such as Australia, several studies have shown that shorter IPIs are more common among women of advanced age,[117, 119, 126] teenage mothers, [116, 126] and non-Caucasian women.[111, 117, 127] Of particular concern are mothers who started childbearing later and are trying to achieve their fertility goal. Parity is another factor known to influence IPI. Mothers with higher-order parity have shorter intervals, [116, 128]. Therefore, effects attributed to short IPIs may indicate the biological risks associated with higher parity or social disadvantages of a large family. Short IPIs are common among women with unintended pregnancies,[111, 117, 129] and women who smoke tobacco or drink alcohol during pregnancy.[127]

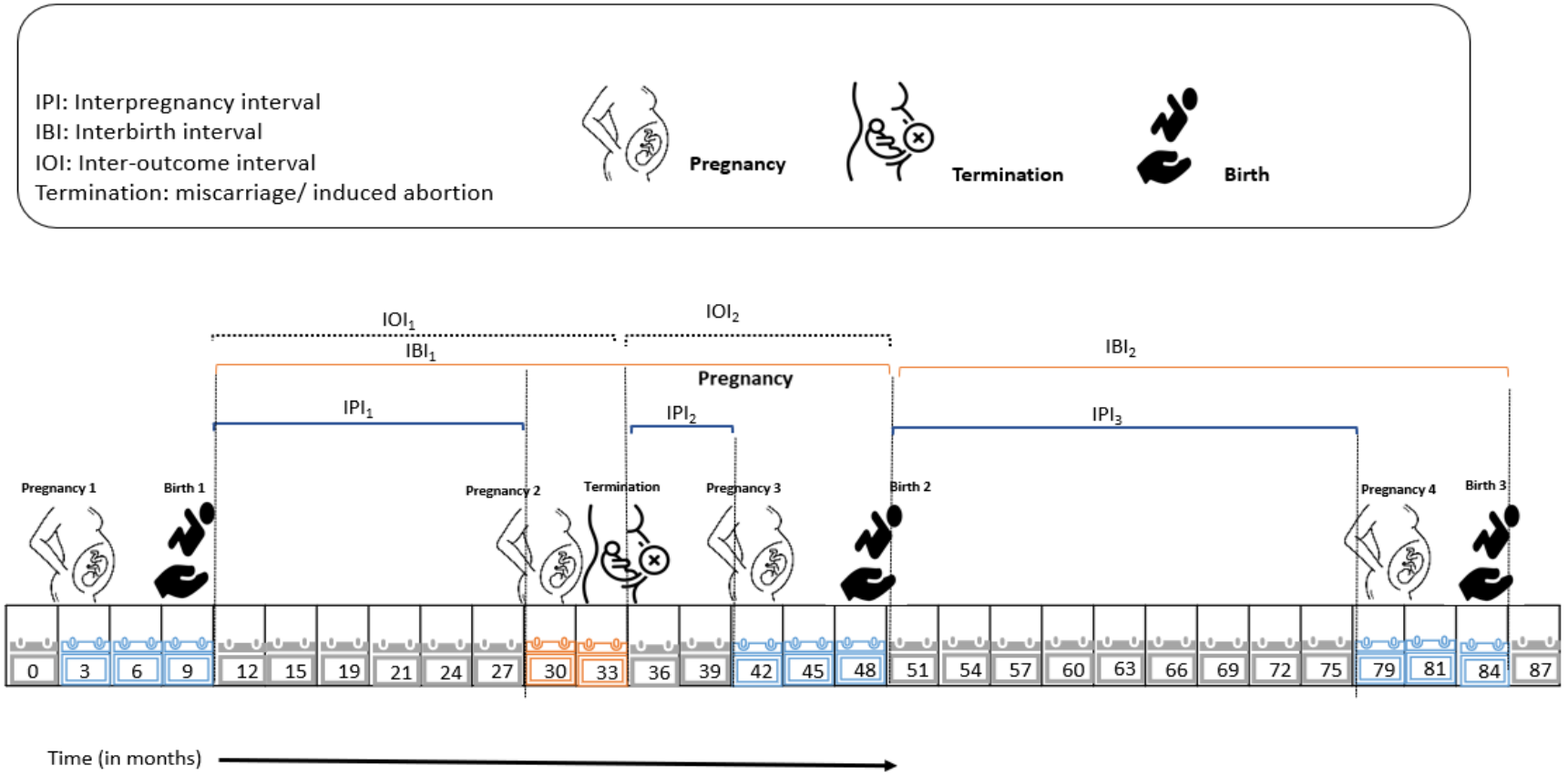

Figure 2-1 Birth spacing terminologies and interval types

Icons adapted from Noun project, licensed under CC BY 3.0 US; Figure adapted from WHO, 2005[94]

Long IPI is also associated with partner change, time of cohabitation, subfertility and change in behavioural factors.[41, 122, 130] Moreover, few studies reported that the presence of hypertensive complications such as preeclampsia, gestational diabetes and placental disorders are associated with long IPI, a marker of fecundity.[122, 131] Outcomes of the preceding pregnancy are also associated with birth and interpregnancy intervals. For example, pregnancies that ended with fetal death, miscarriage, premature birth or stillbirth tend to be followed by short birth or interpregnancy intervals.[91, 123, 124, 132]

In summary, in addition to IPI,[15, 101] factors that may be associated with increased risk of pregnancy complications would include advanced maternal age,[59, 133, 134] inadequate prenatal care,[135, 136] prepregnancy BMI,[137, 138] previous complications,[11, 139, 140] previous caesarean delivery,[59, 77, 79, 141] genetic factors[142, 143] and smoking.[41, 46] IPI has also been identified as a potentially modifiable risk factor for adverse pregnancy outcomes, with both short and long IPIs found to be associated with various pregnancy outcomes,[99, 144-146] yet only a few studies have investigated the association between IPIs and pregnancy complications.[15, 16, 101, 147]

2.5 ASSOCIATION BETWEEN IPI AND PREGNANCY COMPLICATIONS

Numerous studies have reported that both short and long IPIs were associated with increased risk of adverse pregnancy outcomes, including stillbirth, small for gestational age (SGA), preterm delivery, and neonatal death.[99, 102, 113, 148] Conversely, investigating the effect of IPI on pregnancy complications has received less attention and results from existing studies have been more heterogeneous (Table 2-1).[15, 16, 71, 101]

Short IPIs are associated with increased risk of preeclampsia,[101, 103] gestational hypertension,[71, 101] gestational diabetes,[15, 16, 19] placental abruptions and placenta praevia,[15, 52, 59, 104] PROM,[15, 101, 149] and uterine rupture for women who previously delivered by caesarean section.[150-152] However, a recent study found that women with short intervals have a lower risk of labor dystocia.[85] The reported associations between IPI (short and long) with pregnancy complications have been consistent in studies conducted in low-and middle-income,[15, 71, 101]and high-income settings.[16, 104, 149] Several large cohort studies have published contradictory results reporting protective effect or no significant association of short intervals with preeclampsia,[15, 16, 153, 154] gestational hypertension,[100, 155] gestational diabetes[61, 100, 155] and PROM.[71] In contrast to other complications such as gestational diabetes, studies revealed that long IPIs (mainly >60 months or >75 months) are associated with an increased risk of preeclampsia,[15, 41, 45, 101, 139, 154] and gestational hypertension.[71, 101, 155] Few studies have reported an association of long IPIs

with increased risks of gestational diabetes,[16, 20] and PROM.[15, 71] Although a dose-response association was observed between IPI and labor dystocia, [86] the association of long IPIs with uteroplacental bleeding disorders were examined in a limited number of studies and findings were inconsistent. [15, 59, 156]

Studies on the adverse causal associations of long IPIs and pregnancy complications has received much less attention in the literature. While the claimed association is vulnerable to confounding through maternal age, previous complications, subfertility and partner change, studies suggest consistent associations with hypertensive complications,[15, 71, 101] and labor dystocia.[85, 86] However, contrary to these findings, results from a recent large population-based study from Canada did not support the hypothesised association between long IPIs and adverse maternal outcomes.[16] This study replicated a design that matched pregnancies to the same mothers (within-mother comparison), that was first proposed to study the causal association of IPI and perinatal outcomes by Ball et al.[97] This design matched pregnancies to the same women, thereby accounting for all potential unmeasured or poorly measured time-invariant confounders that may induce spurious association between IPI and maternal or perinatal outcomes. The majority of the research into the association between IPI and pregnancy complications has primarily based on conventional unmatched retrospective cohort studies.[15, 20, 71, 100] This raises the possibility that, despite efforts to adjust for possible confounders, the reported associations may not be due to IPI itself but rather due to unmeasured or poorly measured maternal factors.

Moreover, several other studies also showed that factors that may be associated with increased risk of pregnancy complications including maternal age,[59, 133, 134] SES[115, 120, 123] parity,[116, 128] previous complications,[11, 139, 140] smoking,[41, 46] prenatal care,[135, 136] pre-pregnancy BMI,[137, 138] and previous caesarean delivery[59, 77, 79, 141] have also been found to be linked with short or long IPIs.[15, 41, 101, 117, 119, 126] A key question when examining the effect of short or long IPIs on pregnancy complications is whether the associations are independent of these factors. Pertinent risk factors to consider in this respect are parity, maternal age, SES, smoking and maternal co-morbidity status.[38, 109] While several hypotheses have been proposed (see section 2.6), a possible mechanism for the causal association between IPIs and pregnancy complications is yet less clear. Further investigation addressing potential confounders are therefore required. Previous literature on the association between IPIs and pregnancy complications is summarised in Table 2-1below.

Table 2-1 Summary of previous literature investigating associations of pregnancy spacing and pregnancy complications and their effect modifiers

Author, year, Location (study period); study size	Study Design	Interval categories (months)	Outcomes	Variables controlled¶	Findings
Conde-Agudelo *et al* 2000[15], 18 Latin American Countries (1985-1997); (N=456,889)	Cohort	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	PE, GDM, PROM	1, 3, 8, 11, 12, 15, 16, 18, 21, 22	Short IPIs (<6 months) was associated with increased risks of PROM (aOR:1.7, 95% CI:1.5, 1.9) and third-trimester bleeding (aOR:1.7; 95% CI: 1.4, 2.2). Long IPI (>60 months) was associated with increased risks of PE with aOR of 1.8 (95% CI: 1.7-1.9) and eclampsia with aOR of 1.8 (95% CI: 1.4, 2.3). Reported no significant association of short or long IPI and GDM.
Cecatti *et al* 2008[71], Brazil (1986-2000); (N=14,930)	Cohort	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	GH, PROM	1, 11, 12, 14, 15, 16, 18, 19, 22	Long intervals (>60 months) were significantly associated with a higher risk of PROM (aOR:1.57; 95% CI:1.20, 2.06). A non-significant increased risk of GH associated with long IPIs (>60 months) with aOR of 1.24 (95% CI: 0.89, 1.72). No significant increased association was observed between short IPIs and maternal outcomes examined.
Razzaque *et al* 2005[101], Bangladesh (1996-200); (N=11,112)	Cohort	IPI, <6; 6-14; 15-26; 27-50[a]; 51-74; ≥75	PE, GH, PROM	1, 8, 13, 22, 23	Hypertensive disorders of pregnancy are significantly higher for women with short (<6 months), AORs: 2.19 and 1.66 for PE and GH respectively) or long IPIs (>75 months), aORs:2.44 for both PE and GH, as compared to IPI of 27-50 months. PROM is significantly higher following IPI of 6-14 months, aOR: 2.86 [No CI provided].
Skjaerven *et al* 2002[130], Norway (1967-1998); (N=551,478)	Cohort	IBI, <12[a]; 12-24	PE	1[§], 3, 7, 21	After adjustment for partner change, the risk of PE significantly increased for each 1-year increase in a birth interval with an aOR of 1.12 (95% CI: 1.11, 1.13) for each 1-year increase in the birth interval from first to second pregnancy), and aOR:1.12, 95% CI: 1.10, 1.14) from second to third pregnancy. For IBI ≥10 years, the risk of PE among multiparous women was similar to that of nulliparous.
Hanley *et al* 2017[16], Canada (2000-2015); (N=38,178)	Cohort[¥]	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	GDM, PE	1[£], 3, 11, 16, 21, 22	Unmatched analyses: Short and long IPIs were associated with an increased risk of GDM with aOR of 1.47; (95% CI: 1.26, 1.72) for IPIs of <6 months and aOR of 1.32 (95% CI: 1.8,1.48) for IPI >60 months. Only women with long IPIs (≥60months) were at elevated risk of PE (aOR:1.31; 95% CI 1.09, 1.58). Women with short IPIs (less than 18–23 months) at a slightly lower risk of PE. Matched analyses: Gestational diabetes was significantly associated with short IPIs. The risk of GDM was considerably higher among women with short IPI (<6 months) with aOR of 1.35 (95% CI: 1.02, 1.80). An IPI of 12–18 months was associated with significantly lower odds of PE with aOR of 0.71 (95% CI: 0.54,0.94).
Schummers *et al* 2018 [126], Canada (2004-2014); (N=148,544)	Cohort[‡]	IPI, (spline), 3, 6, 9, 12, 18[a]	Maternal mortality or severe morbidity[b]	1[c], 2[c], 14[c, d], 15[c], 16[c]	Risks of maternal mortality or severe morbidity (composite outcome) increased for women with advanced maternal age (≥35 years) for IPIs of 3, 6, 9, and 12 versus 18 months, but null or protective associations for women aged 20-34 years.

Author, year, Location (study period); study size	Study Design	Interval categories (months)	Outcomes	Variables controlled[¶]	Findings
Haight *et al* 2019[100], USA (2013-2016); (N=2,362,656)	Cohort	IPI, <6; 6-11; 12-17; 18-23[a];	GDM, GH	1[*], 2, 6, 8, 12, 14, 15, 16, 18	Shorter IPIs (<6, 6-11 and 12-17 months) were associated with slightly lower risks of gestational diabetes (aRR range:0.89-0.98) and gestational hypertension (aRR range: 0.93-0.95), with associations attenuated or remained flat with increased maternal age. Short IPIs (<6 months) was associated with a slightly increased risk of maternal morbidity (a composite measure), and this association did not vary by maternal age. However, IPI of 6-11 months showed an increasing trend across age, showing a higher risk of maternal morbidity for women with advanced maternal age (≥35 years).
Trogstad *et al* 2001[157], Norway (1967-1998); (N=547,328)	Cohort	IBI, ≤12; 13-60[a]; 61-120; 121-180;>180	PE recurrence	1[§], 3, 7, 21	Women with no previous PE The risk of PE in the second pregnancy increased with increasing birth interval. Compared to reference category of 12-60 months, short (≤12 months) and long (>60 months) birth intervals were associated with increased risk of PE (aOR:1.52; 95% CI: 1.20,1.93 for birth intervals ≤12 months; aOR of 1.64 (95% CI: 1.54, 1.75) for intervals 61 to 120 months). There was no association between birth interval and preeclampsia in women with previous PE. Women with previous PE The risk of PE decreased with increasing birth interval, but not significantly. Reduced risk of preeclampsia was observed in mothers who changed partner in the second pregnancy but only for women without PE in the first pregnancy.
Wang *et al* 2018[19], China (2011-2017); (N=128)	Cohort	IPI, <24; ≥24[a]	GDM recurrence	1[£], 8, 11, 12, 22	After adjustment for confounders including BMI, IPI of <24 months was associated with a higher risk of GDM recurrence (aOR:10.6; 95% CI: 2.1, 53.1)
Blumenfeld *et al* 2014[104], USA (2009-2010); (N=137,915)	Cohort	IPI, <6; 6-23; 24-59[a]; >60	Placental abruption	1, 3, 11, 12	Short (<6 months) and long (>60 months) IPIs were associated with an increased risk of placental abruption with aOR of 1.8 (95% CI: 1.2, 2.7) for IPI <6 months and AOR of1.2 (95% CI: 1.0, 1.4) for IPI>60 months.
Getahun et al 2006[52], USA (1989-1997); (N=156,475)	Cohort	IPI, <12; 12-17; 18-23; 24-35; 36-41; 42-47; ≥48	Placental abruption & placenta previa	1, 8, 15, 16, 17, 18	Short IPI (<12 months) was associated with an increased risk of placental abruption regardless of method of delivery in the first pregnancy. Short birth interval (<12 months interval from birth to caesarean delivery) was also associated with an increased risk of placenta previa.

PE: Preeclampsia; GDM: gestational diabetes mellites; GH: gestational hypertension; PROM: premature rupture of membrane; AOR: Adjusted odds ratio; [a] reference category; [b] outcome included death according to vital records, organ failure, unanticipated surgical procedure, blood transfusion of >3 units, ventilation, or admission to ICU; [c] variables measured at index birth before the interval [d] Nulliparity; [¶] Variables controlled by adjustment, restriction, matching or stratification; [¥] reported both matched & unmatched models; [*]maternal age at index birth; [£] maternal age at the time of each birth; [§]maternal age at later birth

Variables controlled: 1, maternal age; 2, SES; 3,previous pregnancy complications; 4, gestational age or birth weight; 5, maternal country of birth; 6, race/ethnicity; 7, paternal change; 8, maternal education; 9, maternal occupation; 10, plurality; 11, maternal conditions; 12, maternal BMI; 13, gravidity; 14, parity/birth order; 15, prenatal care; 16, smoking; 17, alcohol use; 18, marital/co-habitation status; 19, obstetric history; 20, infant sex; 21, birthyear/month; 22, previous perinatal outcome; 23, proxy for SES (e.g. religion, HH space)

2.6 BIOLOGICAL PATHWAYS OF IPI AND PREGNANCY COMPLICATIONS

The mechanism by which short or long intervals between pregnancies affects pregnancy outcomes has been debated. Although there are a few hypotheses, to date, no single prevailing framework or hypothesis has emerged.[110, 158, 159] Postulated hypotheses to explain the association between IPIs and pregnancy complications are briefly described below.

2.6.1 Recovery time hypothesis

This hypothesis suggests short IPI may predispose women to adverse pregnancy complications due to short recovery time between pregnancies, resulting in depletion of maternal nutrients or insufficient healing of the uterine scar. There are two hypothesised pathways for this theory:

(a) Maternal depletion hypothesis: Maternal nutrients could be depleted during pregnancy and the early postpartum period and may not be replenished sufficiently for a woman with closely -spaced pregnancies due to insufficient recovery time.[160-162] These depleted nutrients have been in part linked to the pathogenesis of PROM.[163] This is likely to be a predominant issue in low-income settings, following the effects of malnutrition. However, multiple studies from high-income settings have reported a low level of nutrients in the postpartum period.[164-166] Moreover, insufficient time to lose weight from previous pregnancy due to short IPI may increase the chance of beginning the next pregnancy without sufficiently reducing the weight gained in the previous pregnancy, thereby increasing the risk of developing gestational diabetes.[16, 167] There is also a shred of growing evidence supporting the 'nutrient depletion hypothesis'. Folic acid and iron are mobilised from maternal reserves during pregnancy and lactation and must be replaced before conceiving another pregnancy. Depleted maternal folate concentrations, particularly during mid-pregnancy until six months postpartum, can weaken connective tissues by preventing collagen cross-linking. This may contribute to poor pregnancy outcomes in women with short IPIs.[161, 167] A study by van Eijsden et al.[164] found that associations between short IPIs and perinatal outcomes were strongest among women who did not use folic acid-containing supplements, a weak association for late users and no association among early users. Furthermore, a recent study adds to the literature that short intervals were associated with a trend to increased risk to adverse pregnancy outcomes, notably in the absence of folic acid supplement use.[168]

(b) Incomplete healing of uterine scar: In women who previously delivered by caesarean section and attempt a trial of labor to have a vaginal delivery in subsequent pregnancies (trial of labor), short IPIs are associated with an increased risk of rupture of the uterus, through the

hypothetical pathways of incomplete healing of the uterine scar.[152, 169, 170] Regarding this, Dicle et al.,[171] in the assessment of incision healing after caesarean delivery using magnetic resonance imaging, found that the complete restoration of uterine anatomy needed at least six months.

2.6.2 Physiologic regression hypothesis

This hypothesis was first postulated by Zhu *et al*.,[113] and stated that long-spacing between pregnancies results in gradual loss of physiological adaptations of the reproductive system developed during the preceding pregnancy. This results in a return to similar physiological phenomena of primigravida women.[113] The hypothesis has been suggested to elucidate the association between long IPIs with labor dystocia,[113] and preeclampsia.[15]

2.6.3 Abnormal process of remodelling of endometrial blood vessels

This hypothesis proposed by Conde-Agudelo *et al.*[15] postulated that the normal process of remodelling of endometrial blood vessels after childbirth might be interfered with by closely spaced pregnancies leading to subsequent uteroplacental under perfusion, thus increasing the risk for placental abruption and placenta praevia. However, this hypothesis is uncommonly mentioned in the IPI literature as a pathway to explain the association between short intervals and pregnancy complications.

2.6.4 Carry-over effect hypothesis

This theory hypothesised that there is a carry-over effect of an unresolved inflammatory process, including sub-clinical infections, from the previous birth. This hypothesis was grounded on a finding that the recurrence of inflammation in the subsequent pregnancy is linked with pathohistological inflammation of the placenta.[172, 173] The effect of short IPI on PROM could be supported by this hypothesis.[149]

2.6.5 Hypotheses relating to confounding

Also known as the *systematic bias hypothesis*, the increased risk of pregnancy complications might be attributed to factors associated with both IPIs and pregnancy complications that may imply a spurious association between IPIs and the complications. For instance, short IPIs are more likely to be unwanted or mistimed and are common among teenage and non-Caucasian women.[117] Given that these population groups are more likely to experience socioeconomic disadvantage, this could lead to an association between short IPIs and maternal complications.[16, 110, 158, 159] Likewise, some studies show that, among others, sub-fecundity and advanced maternal age are associated with long IPIs and adverse pregnancy outcomes, and

these factors may induce a spurious relationship between IPIs and pregnancy complications under investigation.[16, 122, 130]

Generally, the existing literature, including findings from systematic reviews,[38, 96, 147] suggests that short intervals are associated with increased risks of uterine rupture in women attempting vaginal birth after previous caesarean delivery and uteroplacental bleeding disorders. Likewise, long IPIs (>60 months) is associated with an increased risk of preeclampsia and labor dystocia. However, several studies that examined this association were limited by sample size, potential confounding bias, inconsistent use of terms and classifications of IPI or outcome. There is insufficient evidence of an association between short IPIs and maternal complications such as preeclampsia and gestational diabetes. Particularly, studies that employed complementary epidemiological designs such as matched (with-in mother comparison aka sibling) analyses are extremely limited.[16] Such analyses may help in re-evaluating the causal association between IPI and pregnancy complications. To my knowledge, there is only one study that re-examined long-established empirical findings of the association between IPIs with preeclampsia and gestational diabetes with a design that allows examining causal association.[16]

Furthermore, some factors could potentially modify the reported associations between IPIs and pregnancy complications, such as maternal age,[126] previous complications[130, 157, 174] and previous perinatal losses.[132] Similarly, previous caesarean section, SES, and race/ethnicity are also potential effect modifiers of the association.[109] Even though there has been a growing literature on these possible effect measure modifiers of the association between IPI and certain pregnancy complications,[126, 130, 157, 174] there is much less evidence to inform a recommendation.

Collectively, the current literature underscores the need for more studies investigating the causal association of IPIs on pregnancy complications and possible effect measure modification of factors such as maternal age and previous complications.

2.7 METHODOLOGICAL LIMITATIONS AND GAPS IN THE CURRENT STATE OF KNOWLEDGE

Previous literature indicates short and long intervals are associated with an increased risk of adverse maternal and perinatal outcomes.[15, 102, 175] These findings and other supportive evidence have led the WHO to recommend individuals wait at least two years following a live birth before conceiving again.[94] However, there is a paucity of studies that examined the association between IPIs and pregnancy complications. [16, 38, 96, 147] Studies that investigated the

association varied in their statistical strength and consideration of potential confounding variables in their analyses.

Some large-scale cohort studies have been conducted[16, 38, 96], but these studies offer conflicting results regarding the associations of IPI and pregnancy complications. The largest of these studies, and the basis for the WHO recommendation regarding birth spacing, examined data from perinatal surveillance systems of 17 Latin American and Caribbean (low and middle-income) countries, which might not be relevant to high-income countries such as Australia. Despite this being a multi-country study and a relatively large sample size (n=456,889 parous women delivering singleton infants), the study had several limitations. Even though the study controlled for some socio-demographic factors (i.e., maternal education and marital status), they failed to include other potential confounders like family income, parity and race. This study was also based on the analysis of hospital-based records, and the accuracy of the diagnoses registered may vary.

The majority of the existing research on the association of IPI and complications during pregnancy are subject to several methodological limitations. Firstly, interbirth interval (IBI) is commonly used as a measure of birth spacing as opposed to IPI, especially in low-income settings.[38, 147] As it is clearly described earlier in this chapter and Figure 2-1, IBIs are the sum of the IPI and the subsequent pregnancy duration. Therefore, pregnancy complications that are linked with shorter pregnancy duration, such as preeclampsia, will have systematically short IBIs than women without these complications. This systematic difference may create bias related to reverse causation (i.e., short IBI will be a result of, rather than the cause of, the complication). This bias does not occur when using IPI as a measure of spacing.[109] There also appears a significant inconsistency in the current literature in defining intervals and considering consistent IPI categorisation. Discrepancies in the operational definition of intervals can further limit the ability to interpret and draw conclusions across studies examining the effect of birth spacing. Studies that use IPI as a measure of pregnancy spacing also face the challenge of accurately estimating gestational age based on self-reported last menstrual period (LMP). Eventually, this will affect the accuracy of IPI estimation.[94] Due to the reverse J-shaped relationship between IPI and various pregnancy outcomes previously reported,[102, 128] use of a recommended reference category of 18-23 helps to avoid a comparator group with heterogeneous risk. However, despite the large body of literature supporting the association, several recent studies cast doubt on whether IPI is causally responsible for adverse pregnancy outcomes in high-income countries.[16, 97-99] These investigators have argued that much of the

apparent association between IPIs and adverse pregnancy outcomes in past studies is attributable to confounding factors, not IPI itself. In support of this explanation, a large population-based study using linked administrative records from WA was the first to apply a within-mother (matched) analysis to evaluate the causal effect of IPI on adverse pregnancy outcomes.[97] To our knowledge, only one study has applied an alternative design to investigate the effect of IPI on pregnancy complications (gestational diabetes and preeclampsia).[16]

Although the underlying mechanisms of the association between IPI and pregnancy complications are poorly understood, few studies have employed tools such as directed-acyclic-graphs (DAG) to make transparent causal assumptions for a conceptual framework to delineate relationships and support their causal claim. Both short and long IPIs have been associated with a higher risk of pregnancy complications (Table 2-1). The tendency of recurring pregnancy complications, including GDM and PE, is also a well-established finding.[176, 177] Studies have also reported that mothers with long IPIs have an increased risk of pregnancy complication recurrence.[178] Little is known whether these pregnancy complications influence IPI. If this association exists, previous pregnancy complications have the potential to create a spurious association of IPI with subsequent pregnancy complications, which poses questions regarding the nature of causation. Furthermore, the patterns of the reported associations of IPI and increased risk of pregnancy outcomes cannot be captured if IPI is modelled as a continuous linear variable in regression analyses and may produce biased estimates.[109] To date, no study has employed a flexible approach such as restricted cubic spline to estimate the association of IPI and pregnancy complications that account for a potential non-linear relationship.

Finally, although there has been growing interest in IPI research,[16, 96, 100] there is a paucity of studies, and no recommendation for optimal interval based on factors (e.g., maternal age and obstetric history) hypothesised to modify the effect of IPI on pregnancy complications. There is also a lack of updated and comprehensive synthesis of the evidence of an association between IPI and pregnancy complications (Table 2-2).

Hence, evidence-based recommendations derived from large, population-based self-matched cohort data are needed for examining the causal effect of IPIs on pregnancy complications and in subpopulations of women, including women with a history of pregnancy complications in high-income settings.

Table 2-2 Summary of current gaps in knowledge

Area 1- Exposure assessment
• Many studies examining the association of birth spacing, and pregnancy complications have been restricted to the use of IBI as opposed to IPI • Many studies employed inconsistent exposure definition   o Use of inaccurate gestational age estimation in defining interval (e.g., self-report of LMP) • Most studies used IPI categories not consistent with current recommendations
Area 2- Study population and setting

• Large population-based studies are limited
  o Many studies were limited by small sample sizes
  o Many studies were focused on analyses of data extracted from hospital settings
• Case-ascertainment of the outcome of interest from both perinatal and hospital records is rare
• Majority of the evidence base for WHO recommendations were based on associations between IPI and pregnancy outcomes observed in studies from Low- and Middle-income countries (LMICs)

Area 3- Causal assumption
• A paucity of studies that employed a quasi-experimental design such as matching (within-mother studies)– that adjusts for potential known or unmeasured/inaccurately measured confounding variables • To date, no studies have employed DAG as a conceptual framework to explain the association of IPI and pregnancy complications and inform the choice of variables to include in their adjusted analyses • Little is known if previous complications such as GDM and PE delay subsequent pregnancy and whether the size of this effect is consistent • Studies that account for the non-linear nature of the association between IPIs and complications is limited
Area 4- IPI recommendations
• To date, no studies have evaluated the potential effect modification of maternal age on the association between IPI and complications during pregnancy • Insufficient evidence if the association between IPI and pregnancy complications varies by previous experience with these conditions • No current recommendations for the optimal IPI based on maternal age and obstetric history
Area 5- Evidence synthesis
• Lack of updated and comprehensive synthesis of the evidence of an association between IPI and pregnancy complications

Abbreviations: IBI; Interbirth interval; IPI: interpregnancy interval; LMP: Last menstrual period; GDM: Gestational diabetes mellitus; PE: preeclampsia

2.8 CAUSAL INFERENCE

2.8.1 Historical perspective

In perinatal epidemiology, researchers seek to establish the effects of reproductive events that occurred before, during or after pregnancy on adverse pregnancy outcomes among dynamic and complex populations, including pregnant women and their infants. Due to biological interrelatedness and vulnerability, scientific research questions related to these populations frequently face several ethical and methodological challenges.[179, 180] These challenges include the inability to ethically and practicably randomise IPI to participants,[180] Randomisation to interventions that modify IPI are poor proxies for direct randomisation of IPI because they are limited by the take-up and effectiveness of the intervention. Epidemiological studies on this topic are therefore observational in nature. As a result, non-experimental studies are prone to bias, which can be related to the design, selection, measurement, or presentation of the result.[181] Nonetheless, causal inference remains possible by triangulation - application of causal approaches, use of different sources of data, application of methods in various population settings, and use of complementary study designs.[182] However, its uptake in perinatal epidemiology and specifically on IPI research is relatively recent.[109, 183] Common problems of observational studies which impede causal inference include: (a) selection bias - when the selection of exposed or unexposed subjects in a study are somehow related to the outcome of interest; b) confounding - the presence of common causes for the exposure and outcome of interest; c) measurement bias in the exposure, covariate or outcome of interest; and d) possibility of reverse causation – an association between an exposure and an outcome is not due to direct causality from exposure to the outcome, but rather the outcome results in a change in the exposure.

2.8.2 Challenges of conventional study designs on IPI research

Despite the growing body of literature on the associations between IPI and adverse pregnancy outcomes across populations using various epidemiological designs and plausible hypothetical mechanisms proposed, numerous recent studies cast doubt on whether IPI is causally responsible for the adverse maternal and perinatal outcomes in high-income settings. [97, 98, 184] The main issues are twofold: (i) it is unethical and infeasible to randomise IPI to mothers, and (ii) almost all studies have used essentially the same design, typically retrospective cohort studies that employ between-women comparisons, and therefore are prone to similar sources of bias, thereby limiting causal inference by impeding triangulation. Observational studies are

considered essential in examining associations between IPIs and perinatal outcomes. [38, 109] However, addressing confounding has continued to be an important methodological challenge. Given that previous research on this area has relied mainly on traditional epidemiological designs, it raises the possibility that, despite previous efforts to adjust for potential confounders, the association could still be confounded by unmeasured or poorly measured maternal factors.

The conventional epidemiological study designs (between-mother comparison) compare outcomes between women regarding the presence or absence of the exposure to the risk factors under investigation (IPI in this case). Compared to randomised trials, the conventional designs have several advantages, including lower cost and data availability. However, inferring causality by limiting inference to only studies that employ these designs is problematic. These conventional designs have the potential to be confounded by factors that influence both IPIs and the adverse pregnancy outcome in question. Such factors could include various aspects of SES, race/ethnicity, smoking status, and maternal age.[38, 97, 109, 185] Moreover, observational studies, such as longitudinal or birth cohorts, generally assumes that confounding characteristics have been identified and measured with little error. However, the presence of residual confounding (inadequately measured confounders) or unmeasured factors can lead to spurious associations and conclusions about exposures and outcomes of interest.[186]

2.8.3 Defining causal inference

Causal inference is the process of determining whether a causal relationship exists. It is a broad and multi-disciplinary scientific framework linked to statistics, epidemiology, philosophy, economics, and computer science.[179] There appears various techniques and concepts aiming to formalise the assumptions required to claim causality.[185, 187, 188] As several methods have advanced lately to encompass more modern strategies for causal inferences, there has been a growing interest in applying graphic tools such as causal diagrams (e.g., DAGs). DAGs are causal diagrams that provide a structured way to present an overview of the causal research question and its context.[189, 190] Besides, DAGs can also inform the choice of variables to collect during design or variables to include in the adjusted analyses, differentiating confounders from mediators and identifying selection bias.[179, 189]

2.8.4 Quasi-experimental design alternatives

Quasi-experimental designs are studies that aim to demonstrate causality between an intervention and an outcome without applying randomisation. These approaches are based on individuals who are not randomly assigned to conditions but use design features to account for

possible confounding.[191] There exist numerous quasi-experimental designs, but some are less relevant for the research questions of the topic of this thesis. Therefore, a further description will be limited to a subset of those that are relevant. Recently, novel analytical approaches have been increasingly applied among observational studies aiming to improve causal inference in epidemiology.[98, 109, 190, 192, 193] These approaches include family-based designs such as sibling comparison studies, natural experiments, and novel statistical approaches such as propensity score and marginal structural models.[109, 193]

Sibling comparison

In most observational studies investigating the causal effect of a given exposure such as IPIs, differences in exposure status related to their risk of developing the outcome may lead to spurious associations. To address this problem, quasi-experimental methods such as sibling-comparison, also referred to as "matched", "within-women", or "within-mother" comparison designs have been proposed recently in which each woman is compared with herself.[97, 184, 194] By comparing a woman with herself, the approach inherently controls for characteristics (measured or unmeasured) that do not change over time, such as early-life exposure, genetics, or characteristics that remain strongly correlated overtime for mothers throughout their consecutive pregnancies such as SES.[97, 184]

Unlike the conventional approach, the sibling-comparison approach enables inferences that are based purely on within-mother effects. In the absence of confounding bias, we will expect similar effects of the exposure (IPI in this case). However, in the presence of confounding, the conventional approach will give biased estimates of the effects of the exposure.[97]

Nonetheless, it should be noted that, despite the strength of sibling comparison designs, there are limitations. For example, this design cannot control for unmeasured time-varying factors that change between pregnancies such as breastfeeding practices, a sudden deterioration in health, change in family circumstances such as divorce and change of partner unless these factors are adjusted during analyses. The presence of such confounders can produce results that are more biased than conventional designs.[195] Analysis of one of the common analytic strategies of this design, conditional logistic regression (fixed-effect model), only includes mothers who had an adverse outcome in one but not the other of their pregnancies (i.e., only mothers with discordant outcomes contribute to the analyses). Moreover, cohort studies require long follow-up time to observe a representative IPI distribution, and typically large databases such as longitudinal population-based records are used for this reason. The main criticism, however, lies in the generalisability of the findings obtained using this design.[184, 196, 197]

Specifically, IPI studies that employ sibling comparison designs have the limitation of excluding small families, as their analyses are inevitably restricted to mothers with three or more pregnancies (contributing two or more IPIs).

Likewise, there are arguments that the validity of the conclusion drawn from sibling designs depends on the assumption that pregnancy outcomes following the first IPI do not affect those following a subsequent IPI (absence of carryover effects).[109] Though the extent to which the presence of the carryover effect would bias estimates from sibling comparison designs is yet unclear, there are circumstances where carryover effects are likely to be present. For example, there is likely to be an exposure-to-exposure carryover effect if we consider "Caesarean delivery" as exposure of interest because the chance of caesarean delivery in second pregnancy considerably increases following previous caesarean delivery.[198] As a possible remedy for this carryover effect, recent suggestions consider examining the potential of the effect subjected to birth order by presenting results stratified by birth order.[109] Moreover, 'cousin-comparisons', a type of family-based quasi-experimental design, has also been recently suggested when carryover effects are suspected to be a problem.[199]

Furthermore, a negative control design is a supplementary design used to rule out possible non-causal interpretation of findings by performing a study where the hypothesised causal mechanism is removed.[193, 194] For example, in the absence of confounding, IPI cannot be associated with the outcome of the sibling born prior to the IPI. An observed association in this situation would indicate either the presence of family confounding, genetic or environmental or a violation of the assumption that the sibling outcome does not affect the subsequent IPI. Under such an approach, the post-birth interval here serves as a "negative control" exposure, which helps to identify the presence of confounding.[194]

Natural experiment

The term "natural experiment" is defined as: "Naturally occurring circumstances in which subsets of the population have different levels of exposure to a supposed causal factor, in a situation resembling an actual experiment where human subjects would be randomly allocated to groups.[200] Natural experiments are often used to study events in which controlled experimentation is not possible. Randomised controlled trials (RCT), a research design considered to be a gold standard in epidemiologic studies, are not useful in such questions for which random assignment is either impractical or unethical. Due to the lack of direct control of the assignment process, any attempt to infer a potential causal relationship between exposure to the intervention and outcome of interest must rely on either natural experiment or statistical

tool or both.[201] Natural experiments, when properly conducted and analysed, have the potential to control for most of the unknown or unmeasured confounders. Changes in policy or clinical practices such as access to paid parental leave, financial incentives, paid parental leave are good examples that may create appropriate circumstances for an applicability of a natural experiment in the pregnancy spacing research, where exposure to an intervention might approximate random assignment.[109] Researchers in Australia have used a 'Baby Bonus', a federal tax rebate scheme, as a natural experiment regarding fertility policies. They found that the Baby Bonus exerted a small but significant effect on fertility rates, possibly changing the interval distribution.[202] Depending on application possibilities, there are various techniques/methods of natural experiment, including commonly used such as difference-in-differences, interrupted time series and regression discontinuity designs.[201]

Statistical approaches

Other than the most common analytic approaches, such as correctly adjusting for potential confounders in multiple regression models, various other novel approaches have been suggested, such as propensity score analysis and marginal structural models.[190, 192] A propensity score is the probability of treatment/exposure assignment conditional on observed baseline characteristics. Conditioning on the propensity score (i.e., matching or adjusting) on the average results in measured characteristics being balanced between exposed and non-exposed groups and thus remove the potential confounding effect.[192] Marginal structural models are a modification of propensity score approaches, which provides a means to account for time-dependant confounding and aims to approximate the findings of an RCT using inverse-probability-of-treatment weighted estimators.[190] Unlike RCTs and natural experiments design, the downside of these statistical approaches is their limited ability to rely on the potential measured confounders available in the dataset. There is still a potential for confounding from unmeasured factors. To quantify the importance of each of the model's parameters, including the role of an unmeasured confounder, researchers usually conduct a sensitivity or bias analyses. [203, 204] Recently, there is a growing interest in using "E-value" as a complementary approach to sensitivity analyses to evaluate the extent to which unmeasured confounding may have influenced the observed association in observational studies.[126] The E-value provides the minimum strength of association on the risk ratio scale that unmeasured confounder must have with both treatment and outcome to negate the observed exposure-outcome association.[204]

Triangulation of causal inference approaches

As the different causal inference methods have different assumptions, strengths and limitations, "triangulation" of findings from multiple designs to conclude is mandatory. Combining multiple methodological approaches provides a more nuanced understanding of the causal associations. If the estimated causal associations are consistent across methodological approaches, the chance that these designs are biased is low.[193] For example, findings of the presence of confounding bias identified through sibling comparison design can be triangulated with conventional between-women designs and supplementary information such as negative control analyses and E-values.

2.9 CONCEPTUAL FRAMEWORK

A conceptual framework was developed after reviewing the literature, mainly adapting two existing models (conceptual hierarchical,[205] and McCarthy and Maine's[206]). The framework takes into consideration a comprehensive range of factors that are hypothesized to affect the pregnancy complications, theoretical concepts, and biological pathways for the effect of short and long IPIs on pregnancy complications. The framework (Figure 2-2) summarises the factors affecting pregnancy complications termed proximate, intermediate, and distal determinants. It also illustrates the hypothesised causal pathway of the effect of short and long IPIs on pregnancy complications, proposed by Conde-Agudelo *et al*.[167]

2.10 SUMMARY OF THE LITERATURE REVIEW

Overall, a growing body of literature has examined the association between IPI and adverse perinatal and maternal outcomes. While much of the existing literature supports the association of short and long IPIs with pregnancy outcomes, studies that evaluated the association with pregnancy complications are limited in number. The literature on the effect of IPIs on gestational diabetes found a quite small number of studies with conflicting results. Many studies were subjected to several methodological limitations related to exposure assessment, study population and setting (hospital-based vs population-based), and causal inference. Although the effect of long IPI on hypertensive disorders of pregnancy is relatively well established and consistent, much less is known if the association is causal and if findings from previous research are derived by confounding factors.

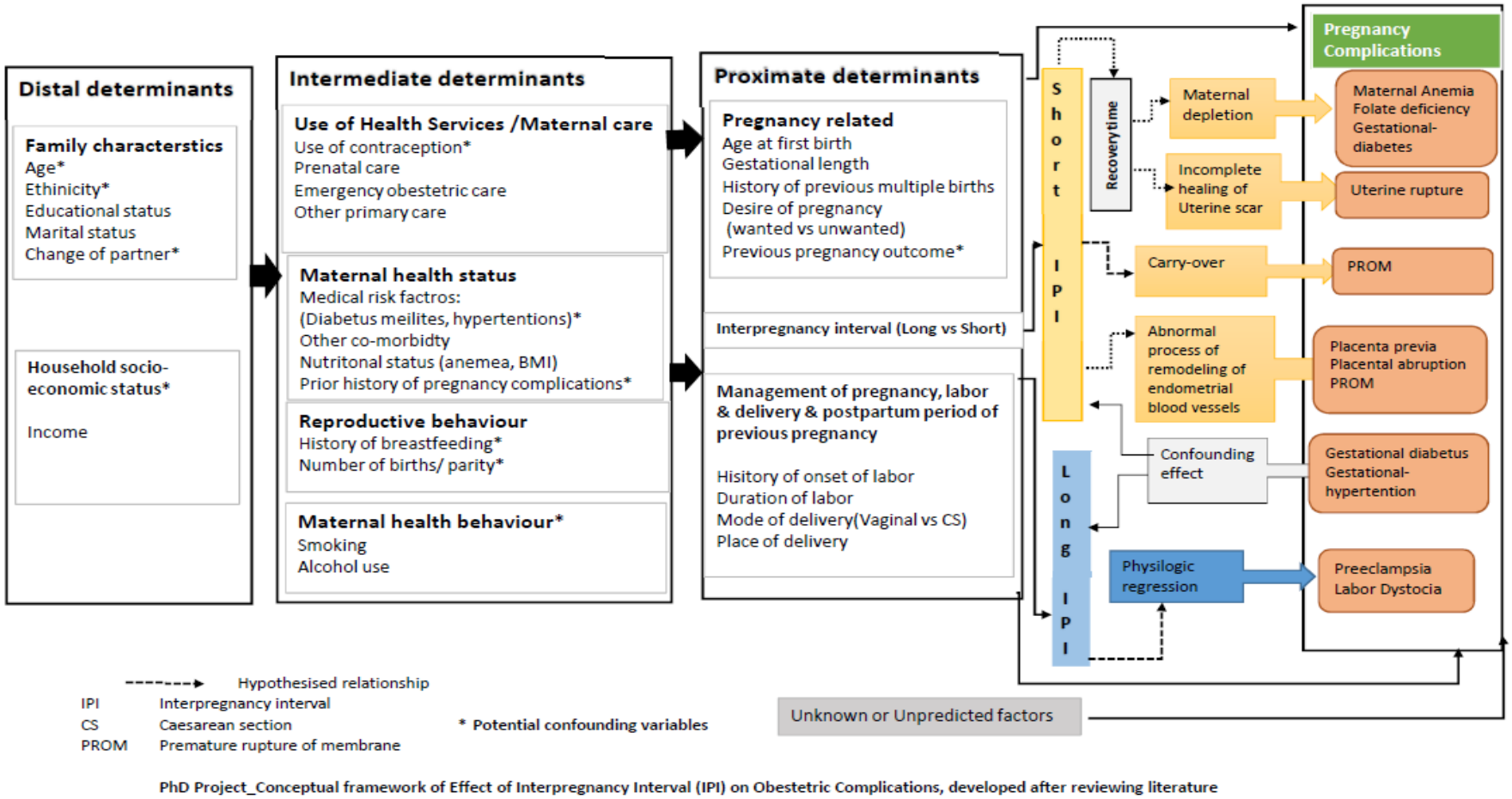

Figure 2-2. Conceptual framework, the effect of IPI on pregnancy complications, adapted from McCarthy and Maine, [206] and Conde-Agudelo *et al* [205]

Studies that employed complementary epidemiological designs such as matching, which ensures that examined associations between IPIs and outcomes of interest are entirely based on within-mother (not between-mother) effects are extremely limited. The literature also noted that much of the evidence and the basis for the IPI recommendations by the WHO was based on limited studies from low- and middle-income settings, and the applicability of these recommendations to high-income settings such as Australia is uncertain. WA has the unique opportunity to contribute to the current literature on IPI research at the population level through its extensive data linkage capabilities to establish a more than 35 years longitudinal cohort.

2.11 RESEARCH QUESTIONS AND STUDY AIMS

The current study intended to use available data sources in WA to fill a significant knowledge gap that has not been addressed for women in high-income countries.

- *What are the effects of IPI on pregnancy complications after removing confounding due to differences between mothers (matched analysis)?* To date, only one study employed matched analysis for investigating the effect of IPIs on pregnancy complications but only considered a few pregnancy complications (gestational diabetes and preeclampsia). Additionally, the study has not controlled for one of the potential confounders (parity).
- *What are the optimal IPIs associated with the lowest risk of pregnancy complications*? The optimal IPIs, an interval at which minimal risk of adverse maternal complications is observed, is still unclear, and currently, there is no clear recommendation.
- *What are the context-specific IPI recommendations*? Identifying optimal IPIs is needed for sub-populations, e.g., for women with a history of pregnancy complications (gestational diabetes, preeclampsia) and maternal age category.

To answer these research questions outlined above, this thesis is organised into four interrelated study aims.

Aim 1. To assess the effect of IPIs on pregnancy complications in WA.

Objective 1.1: To examine the association between IPI and gestational diabetes using both within-mother and between-mother comparisons (Chapter 4).

Objective 1.2: To examine the association between IPI and hypertensive disorders of pregnancy using both within-mother and between-mother comparisons (Chapter 5).

Aim 2. To assess the effect modification role of maternal age and previous pregnancy complications in the association between IPIs and pregnancy complications

Objective 2.1: To examine if the association between IPIs and pregnancy complications varies by maternal age (Chapter 6).

Objective 2.2: To examine if the association between IPI and pregnancy complications varies by previous experience with these conditions (Chapter 7).

Aim 3: To examine the influence of pregnancy outcomes at first pregnancy on IPI

Objective 3.1: To ascertain whether preeclampsia, gestational hypertension, and gestational diabetes at first pregnancy influence subsequent pregnancy and whether the size of the effect varies with IPI distribution (Chapter 8).

Aim 4: To synthesise the current evidence on the effect of IPIs on pregnancy complications

Objective 4.1: To update, compile, synthesise and critically review the current evidence on the association between short and long birth or interpregnancy intervals on pregnancy complications, specifically preeclampsia, gestational hypertension, gestational diabetes, placental abruption, placenta praevia, PROM, uterine rupture for women attempting vaginal delivery after prior caesarean delivery and labor dystocia (Chapter 9).

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Chapter 3: METHODS

Brief summary of methods applied in the thesis

3.1 PREAMBLE

This chapter provides a general overview of the study designs, participants, and data sources to address the aims identified in Chapter 2. Various epidemiological approaches were employed, and the most appropriate design to answer each research question was selected. Designs included unmatched and matched population-based retrospective cohort and negative control exposure for the main and supplementary analyses. This chapter provides an overview of each of the approaches utilised. While each chapter of results (Chapter 4-9) provides a more detailed description of specific methods and participants and statistical approaches used.

3.2 OVERVIEW OF STUDY DESIGN, POPULATION AND VARIABLES

3.2.1 Study design and population

This thesis is based on prospectively collected retrospective analyses of a population-based cohort of mothers who gave birth within the study period 1980-2015 in WA.

For the studies reported in Chapter 4 (Study One) and 5 (Study Two), we mainly employed a within-mother design to examine the causal association between IPI and pregnancy complications. We also presented results from the traditional (unmatched) design to compare our findings with previous studies. The analytic cohort in the first aim included 103,909 mothers with two or more consecutive pregnancies (n=254,137 pregnancies) within the study period in WA. Matched analysis (using conditional logistic regression) restricts the analyses to births from non-concordant strata (informative strata, e.g., mothers experienced PE for at least one, but not all of their pregnancies). Of the eligible 254,137 pregnancies, 21,007 were informative for PE, 11,402 for GH, and 18,873 for GDM. Results from this analysis are described in Chapter 4 and 5 for gestational diabetes and HDPs, respectively. Depending on the specific objective in each study, the study population was further limited to certain groups (e.g., sensitivity analyses).

Study Three (Chapter 6) included a population-based retrospective cohort of mothers with at least two consecutive singleton pregnancies (n=430,615) during the study period. This study presented results in the overall population (without stratification) and stratified by maternal age categories. The study population vary for each group, with 95,369 (22.1%) in the young age group (<20 years) and 17,021 (3.9%) in the older age group (≥35 years).

In study Four (Chapter 7), we included two cohorts, mothers with their first two consecutive pregnancies (n= 252,368) and three consecutive pregnancies (n=96,315) during the study period to assess the modifying role of previous complications (PE and GDM) on the association between IPIs and pregnancy complications.

Study Five (Chapter 8) also included mothers with their first two consecutive singleton pregnancy (parity 0 and 1) at 20-44 weeks of gestation, yielding a total of 251,892 mothers.

For all studies included in this thesis, we based our eligibility on mothers (i) with consecutive singleton births; (ii) with at least two birth records; (iii) whose children birth years is consistent with parity (consecutive); (iv) gestational age at 20-44 weeks of gestation; and (v) mothers with non-missing information. However, as at least two intervals (at least three pregnancies) are required for matching, mothers with only two birth records were also excluded in Studies One and Two. The study population and selection of eligible birth records is discussed in detail in the relevant result chapters (Chapter 4-8).

3.2.2 Study variables

Outcomes

In this thesis, the primary outcomes of interest were gestational diabetes, preeclampsia and gestational hypertension. We also examined the following outcomes across the studies in this thesis, including placenta previa, placental abruption and PROM. These complications were ascertained from the Midwives Notification System (MNS) and the Hospital Morbidity Data Collection (HMDC) data sources. Datasets were linked centrally by the Data Linkage Branch of the WA Department of Health. We used the International Classification of Diseases (ICD-9 through to ICD-10-AM [Australian Modification]) diagnostic codes (Table 3-1Table 3-2) to define the outcomes. The MNS dataset includes specific items to indicate these complications (Appendix C1). The context and definitions for data items included in the MNS guideline[1] are briefly summarised below.

- Gestational diabetes: Condition arising during this pregnancy is diagnosed using the Australasian Diabetes in Pregnancy Consensus Statement.
- Preeclampsia: Diagnosis of a condition arising after 20 weeks gestation as defined using the Australasian Hypertension in Pregnancy Consensus Statement. Preeclampsia is a multi-system disorder unique to human pregnancy characterised by hypertension and involvement of one or more other organ systems and/or the foetus. Proteinuria is the most commonly recognised additional feature after hypertension but should not be considered mandatory to make the clinical diagnosis. A diagnosis of preeclampsia can be made when hypertension arises after 20 weeks gestation and is accompanied by one or more of the following: renal involvement, haematological involvement, liver

involvement, neurological involvement, pulmonary oedema, fetal growth restriction, placental abruption.

- Gestational hypertension: Condition arising as new onset of hypertension after 20 weeks gestation without any maternal or fetal features of preeclampsia. Followed by a return of blood pressure to normal within three months post-partum -which feature would be unknown at the time of reporting.
- Placenta praevia: Bleeding from the placenta positioned over or very near the internal cervical os.
- Placental abruption: Bleeding from the placenta that has been totally or partially abruptly separated from the uterine wall before the infant's birth.
- Antepartum haemorrhage (APH)-other: Bleeding from the uterus where the cause is other than placenta praevia or abruption, i.e. trauma, unknown cause
- Prelabour rupture of membranes: Rupture of membranes at any gestation and at any time before the onset of labor.

It should be noted that preeclampsia coding in the ICD-9 included mild preeclampsia cases, while ICD-10 (from 1st-7th edition), introduced in 1999, combines mild preeclampsia with gestational hypertension; this might increase the incidence of preeclampsia in the ICD-9 as compared to ICD-10.

Table 3-1 International Classification of Diseases and related conditions (ICD-9/10th revision-Australian Modification) codes used to identify the complications

Complications	ICD-9/ICD-9-CM	ICD-10-AM
Preeclampsia	642.4, 642.5, 642.7	O14, O11
Gestational hypertension	642.3	O13
Gestational diabetes	648.8	O24.4
Premature rupture of membrane	658.1-658.2	O42.-
Placental abruption	641.2	O45.-
Placenta previa, with or without haemorrhage	641.0-641.1	O44.-
Antepartum haemorrhage (APH), not elsewhere classified	641.3-641.9	O46.-

Exposure

The exposure of interest, IPI, was calculated prior to exclusions as the time between the delivery date of the first eligible birth and the estimated conception date of the subsequent pregnancy. We computed the conception date by subtracting the last pregnancy's delivery date

from its gestational age at birth. Ultrasound was routinely used to estimate gestational age at birth, while the last menstrual period was used if ultrasound is not available. When used as category (Studies One and Two), the exposure variable (IPI) was categorised as follows: less than six months, 6-11 months, 12-17 months, 18-23 months (reference), 24-59 months, 60-119 months and ≥120 months. In studies Three to Five, IPI was treated as continuous (Chapter 6-8).

Independent variables

This study included the following covariates/confounders in the multivariable analyses: socio-demographic variables: maternal age (categorised as <20, 20-24, 25-29, 30-34, 35-39 and ≥40 years), birth year, marital status, race/ethnicity (Caucasian vs non-Caucasian) Socio-economic status (SES) and infant sex; Chronic conditions: known chronic diabetes, known chronic hypertension and history of obesity; pregnancy/birth-related information: parity, birth type (live born vs stillborn) and infant weight. We categorised marital status in to married, never married, widowed/divorced/ separated and unknown. We also included smoking status during pregnancy, fertility treatment and paternal age variables in several sensitivity analyses across the studies.

SES was derived by the Australian Bureau of Statistics as the Socio-Economic Index of Areas - Index of Relative Socio-economic Disadvantage (IRSD) at a geographic area (Census District, average: 225 dwellings) for the maternal residence at the time of birth which we categorised into quintiles. It is a composite measure of disadvantage using household income, unemployment status, internet connection, the highest level of education, unemployment, occupation type, low rental payments, single-parent family status, disability, overcrowding, and English-language competency.

3.2.3 Analytic approach

In this thesis, appropriate epidemiological designs and statistical approaches were employed to achieve the study aims.

For all studies, we first summarise the characteristics of each cohort at index birth during the study period. Then the study population was presented by outcome and exposure of interest as appropriate.

For studies One and Two (Chapter 4 and 5), we fitted a conditional logistic/Poisson regression adjusted for prognostic score (predicted log odds of each outcome based on adjustment variables from baseline data), which is analogous to propensity score, as a means to adjust

time-varying covariates (e.g., maternal age) without introducing multi-collinearity. For comparison purposes, we also reported results from unconditional logistic regression. Adjusted odds ratios (ORs) or Risk ratios (RRs) and their 95% confidence interval (CIs) were also provided. For studies Three and Four (Chapter 6 and 7), we used Generalised linear models (GLM) fitted using Poisson distribution and log link function to report RRs. IPI was modelled using restricted cubic splines to allow the most flexible characterization of the relationship with each pregnancy complication.[2] Using post-estimation calculations ('*xblc'* command in Stata), we also estimated absolute risk (ARs) for each outcome of interest according to a 1-month increment of IPI.

Study Five uniquely employed quantile regression analyses, an extension of linear regression well suited to addressing the research question of how pregnancy complications at first pregnancy are associated with changes in the response variable (IPI) at specific quantile revel. For example, the association can be estimated and visualised for mothers at the low end of the IPI distribution (e.g., 25th percentile of IPI [short]) or at the higher end (e.g., 75th percentile of IPI [long].

Different timing of confounding/ covariate ascertainment was used across the papers in the thesis. For example, in Studies One (Chapter 4) and Two (Chapter 5), covariates measured at the time of each delivery, whereas in Studies Three to Five (Chapter 6-8), covariates measured at birth prior to the interval were used. For clarifying any uncertainties, sensitivity analyses were also conducted when necessary.

Table 3-2 Presents the summary of the analytic cohort, study variables and analysis considerations for each study included in the thesis.

Table 3-2 Summary of methods for each of the analyses included in the thesis

Chapter	Analytic cohort	Exposure variables/s	Outcome variable/s	Confounders/covariates	Design/Analyses considerations
4	103,909 women; 254,137 pregnancies	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; 60-119, ≥120	GDM	Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity[£], marital status, fetal sex, history of obesity, GH and known chronic hypertension, and smoking[¥]	Within-mother (matched) design; between-mother (unmatched) design; negative control exposure analysis; prognostic score adjustment for the matched model; sensitivity of results for parity, stillbirths, time-period, previous GDM
5			PE, GH	Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity[£], marital status, fetal sex, history of obesity, known chronic diabetes, GDM, partner change, and smoking[¥]	Matched and unmatched design; DAGs; prognostic score adjustment for the matched model; non-linear association, restricted cubic spline (RCS); generalisability of the finding from matched design; potential causal intermediates of the association; sensitivity for parity, stillbirths, and time-period
6	All births to mothers with at least two consecutive births (430,615 pregnancies)	IPI modelled using RCS with knots placed at 3, 6, 12, 18, 24, 36, 48 months of IPI	PE, GH, GDM, PROM, APH (composite outcome)	SES, parity, birth year, ethnicity, marital status; smoking[¥], fertility treatment[¥] and paternal age[¥] Effect modifier: maternal age (categorical :<20, 20-24, 25-29, 30-34, ≥35 years)	Estimated and plotted absolute risk (ARs) at a 1-month increment of IPI by maternal age and risk profile; covariates selected at birth prior to IPI, E-values; sensitivity of results for parity, definitions of APH, time-period, and timing of covariate adjustment
7	Mothers with their first two (n=252,368) and three (n=96,315) consecutive births		PE, GDM	Maternal age, SES, birth year, ethnicity, marital status at birth prior to IPI and partner change at recent birth, smoking[¥], fertility treatment[¥] and paternal age[¥]; Effect modifier: previous history of complications (PE, GDM)	Estimated and plotted ARs (and risk differences) at 1-month increment of IPI by previous complications and risk profile; covariates selected at birth prior to IPI, E-values; sensitivity of results for choice of timing of the modifier and covariate adjustment, parity, and time-period
8	Mothers with their first two consecutive births (n=251,892)	PE, GDM and GH at first birth	IPI, continuous (months)	Maternal age, SES, birth year, infant sex, ethnicity, marital status, birth status (liveborn vs stillborn), and infant weight	Reported results from linear (OLS) and Quantile regression; adjusted for potential confounders measured at birth prior to the interval

[£] included only in the unmatched model; PE, preeclampsia; GH, gestational hypertension; PROM, premature rupture of membrane; APH, Antepartum haemorrhage; OLS, ordinary least square; [¥] variables included in sensitivity analyses

3.3 DESCRIPTION OF DATA SOURCES

3.3.1 Data linkage overview

Data or record linkage is a methodology for bringing information from multiple sources linked to the same person, family, place or event while maintaining privacy.[3, 4] It offers a powerful mechanism for conducting longitudinal research and evaluating various health-related outcomes across populations.[5] To date, linked administrative health records collected over several years can generate improved statistical power needed to detect rare outcomes such as perinatal mortality; describing population disease burden as well as epidemiological risk assessment.[6, 7] Health service research such as healthcare utilisation and evaluation of longitudinal health outcomes in clinical populations are also areas of application of record linkage. As most projects utilise available administrative datasets, record linkage is often less costly than collecting primary data for large study populations such as surveys. Record linkage also allows a large or entire population to be studied. Which minimise the common challenges related to non-participation and attrition bias encountered in survey-based research designs.[8, 9] It is also less subjective to recall and social desirability biases. However, limitations of record linkage include concerns over the quality, accuracy, consistency, completeness and comparability of data nor primarily collected for research purpose.[4, 10]

As IPIs are relevant for mothers with at least two pregnancies and matching requires at least three pregnancies (i.e. two IPIs), the total population study will ensure enough sample size and sufficient follow up to answer the research questions of the study.

The two main types of linkage algorithms, deterministic and probabilistic, have been successfully implemented in previous studies.[11-13] The deterministic linkage is used to identify records of the same person using a unique identifier (e.g., Social security number). In Scandinavian countries, the presence of a single unique personal identification number for each resident used in all administrative contexts makes it possible to use deterministic linkage.[14] 'Probabilistic linkage' uses statistical theory to link each pattern of matching variable agreement with a chance that record pairs exhibiting the pattern are a match. It is based on the assumption that no single match between variables common to the source databases will identify a client with complete reliability.[15, 16] Studies indicate that probabilistic linkages for health administrative databases have high sensitivity (74 to 98%) and specificity (99 to 100%).[17] In Australia, data linkage uses probabilistic algorithms to match individual

demographic information such as name, date of birth, sex and postcode across several databases.[6, 9]

3.3.2 Data linkage in WA

The data linkage system in WA was developed in 1970, and the WA Data Linkage System (WADLS) was formally established in 1995, the longest operating Australia linkage system.[3] It was a collaborative development by the WA Department of Health, the University of Western Australia, Curtin University and the Telethon Kids Institute. The Data Linkage Branch creates links between data collections from the WA Department of Health and other government departments. The system comprises seven core data sets, including Hospital Morbidity, Emergency Department; Midwives Notifications; Mental Health; Cancer Registry; Births, Deaths, Marriages, and Electoral Roll records. The linkage process at the Data Linage Branch is multi-faceted and includes various automated subprocess designed to reduce the chance of error. These linkages are maintained using rigorous, privacy-sensitive protocols with probabilistic matching, and extensive clerical review.[8] The WADLS has a 'separation principle' in place, which was developed to protect privacy by separating the demographic data and clinical data when it is provided for linkage. This principle ensures that researchers only receive clinical or service data and use the encrypted keys to link other details needed for analysis.[8] The quality of these routinely linked data sources is high. A recent audit of the MNS found that more than 96% of demographic and obstetric information were correctly recorded.[18] The HMDS data are also used for health service monitoring and Key Performance Indicator reporting in the state.[19]

3.3.3 Data sources

Midwives Notifications System (MNS)

The MNS is a legally mandated perinatal data collection that routinely collects information on maternal demographics, pregnancy details, health conditions, labor and delivery details, including pregnancy complications. It also comprises a history of previous pregnancy outcomes, pre-existing medical conditions, and caesarean section data. The notifications comprise of nearly all births (>99%) in WA of an infant with gestational age >20 weeks or birth weight of >400g (if the gestation is unknown), including live births and stillbirths. The details of the data variables list for this dataset are provided in (Appendix C1). The system encompasses data from public and private hospitals, public-funded homebirth midwives, private practice midwives, midwives, nurses, or medical practitioners at any site who first

provided care to a woman who gave birth.[20] The MNS is a rich source of data and the basis of the annual report for 'WA's Mothers and Babies'. This study used MNS records from 1 January 1980 and 31 December 2015.

Hospital Morbidity Data Collections (HMDC)

HMDC records include information on all episodes of care, including diagnosis (using ICD-9/10), admission dates, and discharge for all hospital separations. The databases contain data related to all patients admitted to any health service in WA (acute and psychiatric hospitals (public and private) and private day surgeries. The written medical discharge summaries are translated to the principal diagnosis code and up to 20 additional diagnosis code based on ICD-9/10-AM) by trained clinical coders. The HMDC also includes details of all procedures performed. The details of the HMDC data variables list are provided in (Appendix C2).

Data were extracted from the HMDC for all hospital admissions for the mother occurring during pregnancy in the period between 1 January 1980 and 31 December 2015.

All variables included in the analyses were obtained from the two primary data sources, MNS and HMDC. However, we also extracted a few variables from the birth registration (e.g., paternal age) and family connections databases (e.g., Father's unique ID for partner change variable).

3.3.4 Data quality and validation

The quality of routinely collected data sources in WA is high. A recent validation study on MNS records found that MNS had a high accuracy (97.9%), sensitivity (23%) and positive predictive value of 75% for preeclampsia and excellent sensitivity and positive predictive value for gestational diabetes. As to my knowledge, there is no validation study for HMDS in WA in regard to the outcomes of interest. However, validity study for other morbidity outcomes such as cancer, psychiatric disorders as well as other comorbid outcomes including diabetes and asthma indicates that HMDS had relatively high specificity (range:0.98-0.99) for most of the outcomes, higher Positive Predictive Value (PPV) range:[0.62-0.97] for most of the conditions.[21, 22] This suggested that HMDS can be a valid tool to asses morbidities among the general hospitalised population. A descriptive analysis of inter-rater agreement[23, 24] between MNS and HMDS for the study cohort included in this thesis is presented in (Supplemental Table 7-5).

3.4 ETHICAL APPROVAL

This study was part of a larger project (NHMRC APP1099655: Evidence-based recommendations for interpregnancy interval in high-income countries), funded by the National Health and Medical Research Council (APP1099655) and approved by the Human Research Ethics Committee (Project 2016/51) of the Department of Health, WA. A WA Health Declaration of Confidentiality was signed by the PhD Candidate, to ensure data is kept confidential.

3.5 REFERENCES

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Chapter 4: INTERPREGNANCY INTERVAL AND GESTATIONAL DIABETES

Study One. The effect of IPI on gestational diabetes: A retrospective matched cohort study

4.1 PREAMBLE

Study One of the thesis employed the largest population-based retrospective cohort study that examined the association between interpregnancy interval and gestational diabetes using conditional logistic regression (matching pregnancies to the same mother) among mothers who gave birth in WA during the period 1980-2015. The unconditional logistic regression (traditional approach) was also produced to compare the results of previous unmatched designs.

The results described in this chapter were published in *Annals of Epidemiology*:

Gebremedhin AT, Regan AK, Ball S, Betrán AP, Foo D, Gissler M, Håberg SE, Malacova E, Marinovich ML, Pereira G. Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study. *Annals of epidemiology* 2019;39:33-8. e3

A copy of this publication has been provided in Appendix B.

4.2 ABSTRACT

Purpose: To examine the association between interpregnancy interval (IPI) and gestational diabetes using both within-mother and between-mother comparisons.

Methods: A retrospective cohort study of 103,909 women who delivered three or more consecutive singleton births (n=358,046) between 1 January 1980 and 31 December 2015 in Western Australia. The association between IPI and gestational diabetes was estimated using conditional logistic regression, matching pregnancies to the same mother and adjusted for factors that vary within-mother across pregnancies. For comparison with previous studies, we also applied unmatched logistic regression (between-mother analysis).

Results: The conventional between-mother analysis resulted in adjusted odds ratios (aOR) of 1.13 (95% CI, 1.06-1.21) for intervals of 24-59 months and 1.51 (95% CI, 1.33-1.70) for intervals of 120 or more months, compared with IPI of 18-23 months. In addition, short IPIs were associated with lower odds of gestational diabetes with (aOR: 0.89; 95% CI, 0.82-0.97) for 6-11 months and (aOR: 0.92; 95% CI, 0.85-0.99) for 12-17-months. In comparison, the adjusted within-mother matched analyses showed no statistically significant association between IPIs and gestational diabetes. All effect estimates were attenuated using the within-mother matched model.

Conclusion: Our findings do not support the hypothesis that short IPI (<6 months) increases the risk of gestational diabetes and suggest that observed associations in previous research might be attributable to confounders that vary between mothers.

Keywords: Interpregnancy intervals, birth intervals, gestational diabetes, pregnancy complications, matched analysis, birth spacing

4.3 INTRODUCTION

Gestational diabetes is one of the major pregnancy complications that affect 6-13% of pregnancies worldwide.1 Pregnancies complicated by gestational diabetes have an increased risk of caesarean section, high blood pressure and greater risk of perinatal complications, including perinatal death.[2-5]

The length of time between previous delivery and subsequent conception (interpregnancy interval [IPI]) has been extensively evaluated with respect to its association with birth outcomes.[6-9] However, there is relatively less research on its association with pregnancy complications.

It has previously been observed that both short and long IPIs increase the risk of gestational diabetes.[10-14] However, the inference was limited due to small sample sizes, reliance on hospital-based cohorts, insufficient control for important confounders (for example, socioeconomic status [SES]) and biased IPI length measurements, such as the use of birth-to-birth intervals or birth-to-outcome intervals instead of birth to conception.

The World Health Organization (WHO) and the American College of Obstetricians and Gynaecologists recommend that women should wait at least two years, and at least 18 months after live birth before commencing their next pregnancy, respectively.[15, 16] However, the suitability of these recommendations for mothers in high-income countries is uncertain as the recommendations emanating from studies from low-income and middle-income settings conducted prior to the early 2000s.

Several hypotheses have been postulated, including the "maternal depletion" and "physiologic regression" hypotheses;[8, 17, 18] however, a causal effect of IPI on pregnancy complications has not yet been elucidated. Recently, researchers have posited that the association between IPI and increased risk of adverse perinatal outcomes might be attributed to confounding factors ("systematic bias" hypothesis).[9, 14, 19] It remains plausible that the previously reported associations between IPI and gestational diabetes may be explained by risk factors that tend to persist within-mothers across pregnancies and potentially vary greatly between mothers.[9, 14] Complementary within-mother matched analyses offer an opportunity to account for within-mother effects. This study aimed to examine the association between IPI and gestational diabetes employing both matched pregnancies within the same mother and unmatched between-mother comparisons in a high-income setting.

4.4 METHODS

4.4.1 Data source and study population

We conducted a retrospective cohort study using matched and unmatched approaches to examine the association between IPI and risk of gestational diabetes for all mothers who gave birth between January 1st, 1980, and December 31st, 2015 in Western Australia (WA). We sourced maternal, infant and birth information from the Midwives Notification System (MNS), a population-wide registry of all births (>99%) with at least 20 weeks' gestation or with birthweight >400 grams if the gestational length is unknown.20 Hospitalization records were identified from Hospital Morbidity Data Collection (HMDC), which includes information on all hospitalizations in the state, with the Australian Modification of International Classification of Diseases (ICD-10-AM) coded diagnostic information and procedures performed.[21] Ethics approval was obtained from the Human Research Ethics Committee (2016/51) of the Department of Health, WA.

Our analyses included all mothers with at least three consecutive singleton births (at least two IPIs) at 20-44 weeks of gestation in WA within the study period. Of the original total of 487,297 mothers who gave birth in the study period, we sequentially excluded mothers who delivered multiples (n=4,381); mothers who delivered only once during the study period (n=189,269); and mothers for whom parity, as recorded in the birth record, was discordant with the order of the birth dates of her children (n=5,902). These exclusions resulted in a sample of 287,745 mothers with ≥2 consecutive births eligible for analysis (Figure 4-1). We further excluded mothers who had missing information (for example, gestational age, SES, maternal age, negative IPI) for one or more pregnancies (n=7,109). Finally, we excluded mothers with fewer than two intervals (n=176,727), leaving 103,909 mothers included in the final analyses.

4.4.2 Measures

4.4.3 Outcome assessment

The outcome of interest, gestational diabetes, was ascertained from the MNS notifications and hospital separation codes consistent with gestational diabetes (ICD-9-AM: 648.8, ICD-10-AM: O24.4).

4.4.4 Exposure

The exposure, IPI, was defined as the length of time between the delivery date of the previous pregnancy and the estimated conception date of the subsequent pregnancy (date of birth minus

gestational age at birth). Gestational age at birth was based on dating ultrasounds or last menstrual period when ultrasound was not available. We used IPI as a categorical variable, grouped into seven categories (<6 months, 6-11 months, 12-17 months, 18-23 months (reference), 24-59 months, 60-119 months, or 120 or more months), which is consistent with WHO recommendations and categories used in past studies.[9, 14, 22]

4.4.5 Independent variables

For the within-mother matched analyses, we adjusted for factors that can vary between births to the same mother. Specifically, we adjusted for maternal age at the time of each delivery (categorical variable: 14-19, 20-24, 25-29, 30-34, 35-39, or 40 years or older), parity, birth year (continuous), SES, fetal sex, marital status, history of obesity, known pre-existing hypertension and gestational hypertension. SES was derived by the Australian Bureau of Statistics as the Socio-Economic Index of Areas - Index of Relative Socio-economic Disadvantage at a geographic area for the maternal residence at the time of birth,[23] which we categorized into quintiles.

4.4.6 Statistical analysis

We summarized the socio-demographic and medical conditions of the cohort at their first pregnancy during the study period. Conditional logistic regression (accounting for matching pregnancies to the same mother) was used to estimate odds of gestational diabetes as a function of IPI categories, comparing pregnancies within-mothers. Under this approach, effect estimates also controlled for unmeasured characteristics that remained stable or strongly correlated over time for mothers throughout their consecutive pregnancies. This enables inference that is based purely on within-mother effects.[7, 9, 14]

To estimate the total effect of IPI, we repeated our matched analyses without adjustment for maternal age at the time of each delivery and birth year. In the absence of residual time-varying confounding or selection bias, we would expect similar effects of IPI on gestational diabetes in both between-mother and within-mother comparisons. It is plausible that if unmeasured persistent confounders exist, the unconditional logistic regression may result in biased estimates.[9]

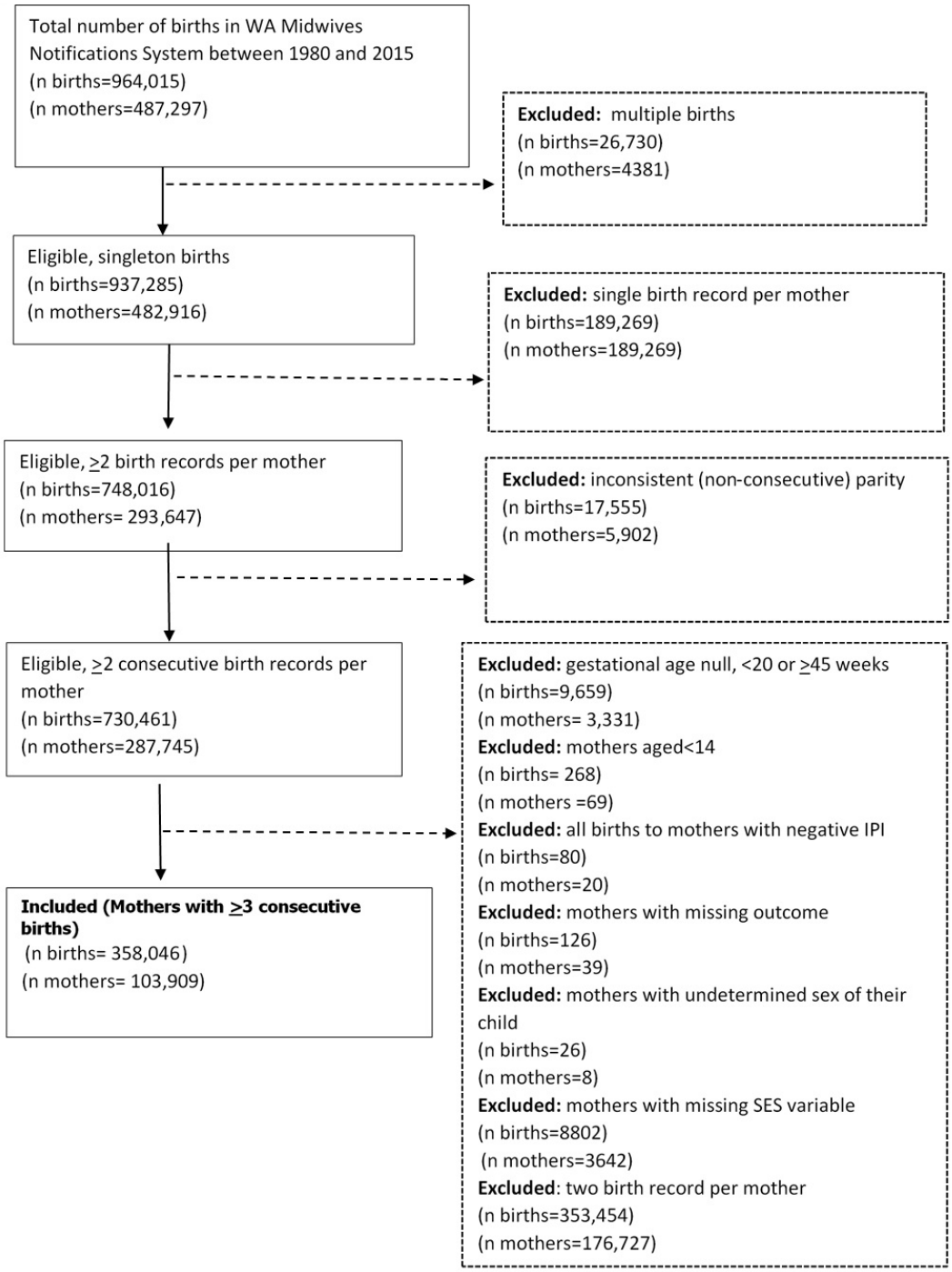

Figure 4-1. Selection of eligible birth records included in this study – Western Australia, 1980-2015

For comparison with previous unmatched studies, we also applied unmatched logistic regression that additionally adjusted for measured covariates that vary between mothers, such as race/ethnicity. To minimize multicollinearity between time-varying covariates (such as maternal age at the time of each delivery and birth year), our within-mother model was adjusted for a prognostic score defined as the logit of the probability of the outcome regressed on the adjustment variables from an unmatched model. This results in the estimation of the direct effect of IPI and allows the whole cohort to contribute to the adjustment for the underlying risk of the outcome.[24]

4.4.7 Supplementary analysis

We further estimated the association of gestational diabetes with post-birth IPI. In the absence of confounding factors, gestational diabetes should not be associated with the IPI that follows this birth. An observed association between gestational diabetes and this post-birth IPI indicates the presence of factors in a mother influencing both the risk of gestational diabetes and the IPI, potentially leading to bias estimates. Thus, the post-birth IPI serves as a "negative control" exposure that estimates the effect of mother-level confounding.[19, 25, 26]

4.4.8 Sensitivity analysis

To ascertain the sensitivity of our results to higher-order parity and inclusion of stillbirths, we conducted separate analyses restricted to the first three births for all mothers with births at parity 0, 1, and 2 and to mothers with at least three consecutive live births, respectively. To explore if our results are sensitive to the time period of the cohort, we restricted our further analyses to consecutive births after the 1st of September 1997, after which smoking status and pre-existing chronic conditions were routinely recorded, and ultrasound scans were more common [Supplemental Table 4-2, Model 2a-c]. Finally, we included a sensitivity analysis restricted to mothers who had no gestational diabetes in their first pregnancy to ascertain if the effect of IPI differs for those with and without gestational diabetes in the first pregnancy [Supplemental Table 4-3].

All analyses were performed using STATA version 15.1 (Stata Corporation, College Station, Texas, USA). We reported unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CIs) for each model.

4.5 RESULTS

At study entry, defined as mothers' first birth occurring during the study period, the majority of women were generally free from chronic hypertension, diabetes and obesity. There were 1,716 (1.6%) mothers who had a diagnosis of gestational diabetes at study entry (Table 4-1). For all births included in the cohort, the incidence of gestational diabetes during the study period was 4% (Table 4-2).

There were 16,548 (6%) births which occurred after an IPI of 0-5 months, 45,076 (18%) after 6-11 months, 50,528 (20%) after 12-17 months; 37,352 (15%), after 18-23 months; 78,909 (31%) after IPI of 24-59 months, 21,780 (9%) births after 60-119 months and 3,944 (1.6%) of births after 120 or more months. Gestational diabetes diagnoses were more common among mothers in the older age groups and in mothers with longer IPIs (Table 4-2). Moreover, mothers with shorter IPIs tended to be younger and non-Caucasian. Observation of longer IPIs was more prevalent late in the study period (1995 onwards) [Supplemental Table 4-1].

Compared to an IPI of 18-23 months, unmatched adjusted analysis showed lower odds of gestational diabetes for 6-11-month intervals (adjusted odds ratio (aOR), 0.89; 95% CI, 0.82-0.97) and 12-17-month intervals (aOR: 0.92; 95% CI, 0.85-0.99) (Table 4-3). However, an IPI of 24 months or more was associated with greater odds of gestational diabetes. The greatest adjusted effect was observed for IPIs of 120 or more months (aOR:1.51; 95% CI, 1.33-1.70).

Conditional logistic regression restricts analyses to births from informative (non-concordant) strata (mothers), which in this study were mothers who experienced gestational diabetes for at least one, but not all of their births. There were 18,873 births to mothers with non-concordant gestational diabetes. The unadjusted within-mother comparison indicated that an IPI of 24 months or longer was associated with greater odds of gestational diabetes compared to an interval of 18-23 months, with OR ranging from 1.40 (95% CI, 1.26-1.55) for 24-59 months interval, to 3.65 (95% CI, 2.95-4.52) for IPI of 120 or more months.

After full adjustment for covariates including, maternal age at the time of each delivery and birth year, matched analyses showed a statistically non-significant lower odd of gestational diabetes for short IPIs as compared to reference category of 18-23 months, with aOR of 0.88 (95% CI, 0.75-1.05) for IPI lower than six months and 0.90 (95% CI, 0.79-1.02) for IPI of 12-17 months.

Table 4-1 Socio-demographic characteristics and medical conditions of the study cohort of mothers at their first birth during the study period (n=103,909 mothers) in WA, 1980-2015

Characteristics	**Mothers, N (%)**
Total number of mothers	103,909
Maternal age at first birth (years)	
<25	56,901 (54.8)
25-29	32,988 (31.7)
30-34	12,467 (12.0)
35-39	1,521 (1.5)
40 or older	32 (0.03)
Marital status	
Married	83,875 (80.7)
Never married	19,221 (18.5)
Widowed, divorced, separated	618 (0.6)
Unknown	195 (0.2)
Race/ethnicity	
Caucasian	88,106 (84.8)
Aboriginal/Torres Strait Islander	8,267 (7.9)
Asian*	1,986 (1.9)
African	600 (0.6)
Others**	4,950 (4.8)
Birth year	
1980-1984	20,264 (19.5)
1985-1989	17,681 (17.0)
1990-1994	16,811 (16.2)
1995-1999	16,053 (15.4)
2000-2004	15,538 (15.0)
2005-2009	14,448 (13.9)
2010-2015	3,114 (3.0)
SES in quintiles	
<20th percentiles (most disadvantaged)	20,398 (19.6)
20-39th percentile	21,679 (20.8)
40-59th percentile	21,914 (21.1)
60-79th percentile	20,648 (19.9)

≥80th percentile (least disadvantaged)		19,270 (18.6)
Chronic conditions		
Known chronic hypertension		259 (0.3)
Known chronic diabetes		181 (0.2)
Known obesity history		237 (0.2)
Pregnancy characteristics		
Pregnancy complications	Gestational diabetes	1,716 (1.6)
	Gestational hypertension	2,400 (2.3)
Fetal sex	Male	54,132 (52.1)
Parity	0	96,314 (92.7)
	1	4,977 (4.8)
	2	1,636 (1.6)
	≥3	374 (1.0)

¥ Row percentages

However, we observed a statistically non-significant increased odds of gestational diabetes for long IPI compared to an 18-23-month IPI, with aORs ranging from 1.07 (95% CI, 0.95-1.20) for IPI of 24-59 months to 1.08 (95% CI, 0.93-1.25) for IPI of 60 months or longer.

The results of our sensitivity analyses [Supplemental Table 4-2] restricted to mothers with their first three consecutive births [Model 2a], and a cohort that only included live births [Model 2b] were consistent with the effect estimates obtained from our main analyses. However, statistically significant lower odds of gestational diabetes were observed for shorter IPIs of 0-5 months and 12-17 months in the model that excluded stillbirths [Model 2b]. Additionally, we observed a negligible difference in the association between IPI and gestational diabetes when we restricted our cohort to births from September 1997 onwards, for which more information was available for adjustment, although this induced a 65% reduction in sample size [Model 2c]. We observed a little difference in the effect estimates with and without excluding mothers with gestational diabetes in their first pregnancy [Supplemental Table 4-3].

In general, our sensitivity analyses collectively supported a weak adverse association of long IPIs and gestational diabetes, similar to those reported in the main analyses.

The adjusted model from the supplementary analyses indicated that the short post-birth IPI of 6 months or less was statistically significantly associated with gestational diabetes in the previous pregnancy (aOR:1.25; 95% CI, 1.03-1.52).

Table 4-2 Characteristics of study population of births by gestational diabetes status for all births to mothers with at least three consecutive births during the study period (n=254,137 births) in WA, 1980-2015

Characteristics	Total	Gestational diabetes
	Births (N)	**Births, N (%)** [¥]
Total number of births	254,137	10,032 (4)
Interpregnancy interval (months)		
0-5	16,548	539 (3.3)
6-11	45,076	1,261 (2.8)
12-17	50,528	1,509 (3.0)
18-23	37,352	1,272 (3.4)
24-59	78,909	3,526 (4.5)
60-119	21,780	1,499 (6.9)
120 or more	3,944	426 (10.8)
Maternal age at time of each delivery (years)		
<25	53,083	915 (1.7)
25-29	83,808	2,430 (2.9)
30-34	77,280	3,407 (4.4)
35-39	34,138	2,603 (7.6)
40 or older	5,828	677 (11.6)
Race/ethnicity		
Caucasian	209,073	6,803 (3.3)
Non-Caucasian	45,064	3,229 (7.2)
Birth year		
1980-1984	12,277	30 (0.3)
1985-1989	35,264	238 (0.7)
1990-1994	41,065	765 (1.9)
1995-1999	40,560	1,353 (3.3)
2000-2004	39,082	1,613 (4.1)
2005-2009	43,408	2,098 (4.8)
2010-2015	42,481	3,935 (9.3)
SES in quintiles		
<20th percentiles (most disadvantaged)	51,221	2,232 (4.4)
20-39th percentile	49,930	1,915 (3.8)
40-59th percentile	49,689	1,846 (3.7)
60-79th percentile	50,968	2,027 (4.0)
≥80th percentile (least disadvantaged)	52,329	2,012 (3.8)
Marital status		
Married	229,549	8,873 (3.8)
Never married	19,588	887 (4.5)
Widowed, divorced, separated	4,156	225 (5.4)
Unknown	844	47 (5.6)

[¥] Row percentages

However, the long post-birth IPIs of 24 or more months was not associated with gestational diabetes in this model with aOR of 1.04 (95% CI, 0.91-1.18) for post-birth IPI of 24-59 months and 1.18 (95% CI, 0.78-1.79) for 120 or more months [Supplemental Table 4-4].

4.6 DISCUSSION

4.6.1 Principal findings

Both the between-mother adjusted and within-mother unadjusted models indicate that IPIs of 24 months or longer were associated with greater odds of gestational diabetes than an interval of 18-23 months. In contrast, pregnancies that followed IPIs shorter than 18-23 months had lower odds of gestational diabetes. However, the fully adjusted within-mother analyses showed no statistically significant association between short and long IPIs and gestational diabetes.

4.6.2 Meaning of the findings

Point estimates from within-mother analyses were lower than those from between-mother analyses, and estimates from the within-mother analyses were attenuated after full adjustment for covariates, indicating that the influence of IPI could be partially explained by the pathway through time-varying confounders, most notably maternal age. Longer IPIs are inherently linked to increasing maternal age, which is a well-established risk factor for gestational diabetes.[2, 27] Contrary to the findings of previous between-mother comparisons,[13, 14] which showed that short IPIs were statistically significantly associated with increased risk of gestational diabetes, our results did not support the existence of an adverse association between short IPIs and gestational diabetes. This finding is consistent with previous unmatched cohort studies [6, 28], and a recent case-control study.[29] However, our findings for long IPIs are consistent with findings of other studies.[12, 14, 29]

The associations observed in the unmatched between-mother comparisons were attenuated in the within-mother comparisons. This suggests that the observed effects of short and long IPIs in the unmatched between-mother comparison and previous similar unmatched studies likely were influenced by factors that remain stable for mothers throughout their pregnancies (e.g. persistent lifestyle factors, SES) but vary much more between women.

Table 4-3 Odds Ratios (ORs) and 95% CIs for the association between interpregnancy interval and gestational diabetes for births to mothers with at least three consecutive births during the study period (n=103,909 mothers, n=254,137 births) in WA, 1980-2015

	Unmatched			**Matched**		
IPI in months	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** ǂ	**Informative strata, n (%)** ¥	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** ǂǂ	**Adjusted OR (95% CI)** ǂǂǂ
0-5	0.95 (0.86-1.05)	1.01 (0.91-1.12)	1,305 (6.9)	**0.78 (0.67-0.91)**	**0.80 (0.68-0.95)**	0.88 (0.75-1.05)
6-11	**0.81 (0.75-0.88)**	**0.89 (0.82-0.97)**	2,954 (15.7)	**0.79 (0.70-0.89)**	**0.84 (0.74-0.96)**	0.92 (0.80-1.05)
12-17	**0.87 (0.80-0.94)**	**0.92 (0.85-0.99)**	3,297 (17.5)	**0.83 (0.74-0.93)**	**0.86 (0.76-0.98)**	0.90 (0.79-1.02)
18-23	1.00 (reference)	1.00 (reference)	2,489 (13.2)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24-59	**1.32 (1.24-1.41)**	**1.13 (1.06-1.21)**	6,096 (32.3)	**1.40 (1.26-1.55)**	**1.29 (1.15-1.44)**	1.07 (0.95-1.20)
60-119	**2.09 (1.94-2.26)**	**1.32 (1.22-1.43)**	2,216 (11.7)	**2.28 (2.01-2.57)**	**1.96 (1.71-2.23)**	1.08 (0.93-1.25)
120 or more	**3.42 (3.06-3.85)**	**1.51 (1.33-1.70)**	516 (2.7)	**3.65 (2.95-4.52)**	**3.02 (2.41-3.80)**	1.02 (0.77-1.34)

Bold indicates statistical significance at the 5% level.

Models adjusted for the following variables: ǂ Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, fetal sex, history of obesity, gestational hypertension and known chronic hypertension; ǂǂ Prognostic score for gestational diabetes by parity, SES, marital status, fetal sex, history of obesity, gestational hypertension, and known chronic hypertension; ǂǂǂ Prognostic score for gestational diabetes by maternal age at the time of each delivery (categorical), birth year, parity, SES, marital status, fetal sex, history of obesity, gestational hypertension and known chronic hypertension; ¥ Number and percentage of informative strata of gestational diabetes for each IPI category for births to mothers with at least three consecutive births

Our long IPI findings are consistent with those from a recent matched study of a Canadian cohort,[14] which reported that matched analyses resulted in statistically non-significant associations between long IPIs and gestational diabetes. However, our findings differ for short IPIs, as the Canadian study reported greater odds of gestational diabetes for short IPIs lower than six months. The observed differences may be due to unmeasured confounding that could arise from the lack of adjustment for known risk factors (SES, parity) or differences in susceptibility of the study populations to IPI in the Canadian study.[14] Future research would benefit from exploring the role of pregnancy complications at mothers first birth, as it remains possible that the effect of IPI might be modified by gestational diabetes in first birth. In our cohort, there were 3,906 total pregnancies among mothers who had gestational diabetes during their first pregnancy, and 1,525 (39%) pregnancies were complicated by recurrent gestational diabetes.

Our supplementary analyses using post-birth IPI established the presence of confounding of the association between IPI and gestational diabetes by factors that vary between women [Supplemental Table 4-4]. Specifically, short post-birth IPIs (<6 months) was associated with increased odds of gestational diabetes in the previous pregnancy. Intuitively, a pregnancy complication cannot be caused by an exposure that occurs after that complication. This result provides justification for the within-mother design because it demonstrates confounding at the mother-level.[19, 25] The lack of association between long post-birth IPI and gestational diabetes might indicate that such confounding is less of a concern for longer intervals.

4.6.3 Strengths and Limitations

We sourced our cohort from highly reliable population-based perinatal information ascertained from hospital separations and midwives' notifications. To our knowledge, this is the largest population-based study to examine the association between IPIs and gestational diabetes among mothers with at least three consecutive births (two intervals) using within-mother comparison (matching pregnancies of the same mother). The within-mother design provides estimates based on a cohort of mothers who have experienced pregnancies with and without the complication of interest (gestational diabetes). The premise of this design is that it accounts to a larger extent for environmental and genetic confounders that can vary between mothers.

There were some limitations to our study. Firstly, we restricted our analyses to the outcomes of more than two births for each mother to enable the matching of at least two IPIs. Thus, although our design achieves greater interval validity, there remains the possibility of selection bias. Secondly, we attempted to control time-varying confounders but were unable to measure some variables that may have significance (e.g., pre-pregnancy weight change). However, matched analyses were statistically non-significant, and adjustment for such variables would have likely attenuated effect estimates

further, and our conclusions would have remained unchanged. Thirdly, it should be acknowledged that chronic conditions were not routinely collected until 1997 and without good capture until 2000. However, our sensitivity analyses suggested that the effect estimates were consistent between the main analyses, and births restricted to 1997 onwards with complete information. Finally, as with all retrospective cohort studies that use comprehensive perinatal records, we were unable to identify pregnancy loss before 20 weeks of gestation. However, gestational diabetes usually occurs later in pregnancy, and if any bias is introduced by truncation of pregnancies after 20 weeks of gestation, this is likely to be limited to survivor bias. Even though information on pregnancy loss may be relevant to consider, findings from a recent study reported insufficient evidence for differences in pregnancy losses by IPI.[30]

In conclusion, there was insufficient statistical evidence for a harmful association between short IPI (<6 months) and gestational diabetes in our cohort. Our findings do not support the hypothesis that short IPI (<6 months) increases the risk of gestational diabetes and suggests that observed associations in previous studies were possibly attributable to residual confounding.

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4.8 SUPPLEMENTARY MATERIAL

Supplemental Table 4-1 Characteristics of the study population of all births to mothers with at least three consecutive births during the study period (n=254,137 births) in WA, 1980-2015

Characteristics	**Interpregnancy Interval (months)**						
	<6	**6-11**	**12-17**	**18-23**	**24-59**	**60-119**	**120 or more**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Total (n=254,137)	16,548 (6.5)	45,076 (17.7)	50,528 (19.9)	37,352 (14.7)	78,909 (31.1)	21,780 (8.6)	3,944 (1.6)
Gestational diabetes (GDM), n (%): 10,032 (4)							
Yes	539(3.3)	1,261(2.8)	1,509(3.0)	1,272(3.4)	3,526(4.5)	1,499(6.9)	426(10.8)
Maternal age at time of each delivery (years)							
<25	6,656 (40.2)	13,032 (28.9)	11,872 (23.5)	7,747 (20.7)	12,871 (16.3)	905 (4.2)	0 (0.0)
25-29	5,395 (32.6)	15,905 (35.3)	17,822 (35.3)	13,023 (34.9)	25,743 (32.6)	5,733 (26.3)	187 (4.7)
30-34	3,220 (19.5)	11,627 (25.8)	14,883 (29.5)	11,610 (31.1)	26,394 (33.5)	8,378 (38.5)	1,168 (29.6)
35-39	1,130 (6.8)	4,024 (8.9)	5,290 (10.5)	4,397 (11.8)	12,040 (15.3)	5,528 (25.4)	1,729 (43.8)
40 or older	147 (0.9)	488 (1.1)	661 (1.3)	575 (1.5)	1,861 (2.4)	1,236 (5.7)	860 (21.8)
Marital status							
Married	14,263 (86.2)	41,118 (91.2)	46,825 (92.7)	34,438 (92.2)	70,892 (89.8)	18,705 (85.9)	3,308 (83.9)
Never married	1,948 (11.8)	3,303 (7.3)	3,074 (6.1)	2,382 (6.4)	6,312 (8.0)	2,178 (10.0)	391 (9.9)
Widowed, divorced, separated	282 (1.7)	545 (1.2)	497 (1.0)	419 (1.1)	1,429 (1.8)	772 (3.5)	212 (5.4)
Unknown	55 (0.3)	110 (0.2)	132 (0.3)	113 (0.3)	276 (0.4)	125 (0.6)	33 (0.8)
Race/ethnicity							
Caucasian	12,299 (74.3)	37,050 (82.2)	42,262 (83.6)	31,413 (84.1)	64,944 (82.3)	17,801 (81.7)	3,304 (83.8)
Non-Caucasian	4,249 (25.7)	8,026 (17.8)	8,266 (16.4)	5,939 (15.9)	13,965 (17.7)	3,979 (18.3)	640 (16.2)
Birth year							
1980-1984	1,452 (8.8)	3,698 (8.2)	3,545 (7.0)	1,973 (5.3)	1,609 (2.0)	0 (0.0)	0 (0.0)
1985-1989	2,460 (14.9)	7,173 (15.9)	8,132 (16.1)	5,862 (15.7)	10,641 (13.5)	996 (4.6)	0 (0.0)
1990-1994	2,569 (15.5)	7,315 (16.2)	8,381 (16.6)	6,260 (16.8)	13,059 (16.6)	3,275 (15.0)	206 (5.2)
1995-1999	2,433 (14.7)	6,807 (15.1)	7,725 (15.3)	5,787 (15.5)	13,192 (16.7)	3,931 (18.1)	685 (17.4)
2000-2004	2,327 (14.1)	6,367 (14.1)	7,201 (14.3)	5,545 (14.9)	12,652 (16.0)	4,125 (18.9)	865 (21.9)
2005-2009	2,828 (17.1)	7,398 (16.4)	8,023 (15.9)	5,943 (15.9)	13,443 (17.0)	4,686 (21.5)	1,087 (27.6)
2010-2015	2,479 (15.0)	6,318 (14.0)	7,521 (14.9)	5,982 (16.0)	14,313 (18.1)	4,767 (21.9)	1,101 (27.9)
SES [¥]							
1	4,602 (27.8)	9,386 (20.8)	9,482 (18.8)	6,905 (18.5)	15,507 (19.7)	4,603 (21.1)	736 (18.7)
2	3,712 (22.4)	9,070 (20.1)	9,563 (18.9)	7,096 (19.0)	15,245 (19.3)	4,445 (20.4)	799 (20.3)
3	3,283 (19.8)	8,994 (20.0)	9,909 (19.6)	7,367 (19.7)	15,073 (19.1)	4,276 (19.6)	787 (20.0)
4	2,749 (16.6)	8,938 (19.8)	10,450 (20.7)	7,684 (20.6)	15,976 (20.3)	4,328 (19.9)	843 (21.4)
5	2,202 (13.3)	8,688 (19.3)	11,124 (22.0)	8,300 (22.2)	17,108 (21.7)	4,128 (19.0)	779 (19.8)

[¥] Categorized as quintiles (1= most disadvantaged to 5= least disadvantaged

Supplemental Table 4-2 Odds Ratios (OR) and 95% confidence intervals for the association between interpregnancy interval and gestational diabetes for births to (Model 2a) mothers with three consecutive births (parity 0,1,2); (Model 2b) mothers with at least three consecutive live births; (Model 2c) mothers with at least three consecutive births during the end of the study period (Sept 1997 onwards) in WA, 1980-2015

	Unmatched		**Matched**		
IPI in months	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** [ǂ]	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)** [#]	**Adjusted OR (95% CI)** [##]
Gestational diabetes					
Model 2a: (n=96,354 mothers, n=192,708 births)					
0-5	0.99 (0.87-1.12)	**1.14 (1.00-1.30)**	0.82 (0.66-1.03	0.83 (0.66-1.05)	0.94 (0.75-1.19)
6-11	**0.86 (0.78-0.95)**	0.97 (0.87-1.07)	0.89 (0.75-1.05)	0.93 (0.78-1.11)	1.01 (0.84-1.20)
12-17	**0.88 (0.79-0.96)**	0.94 (0.85-1.03)	**0.82 (0.70-0.96)**	**0.86 (0.73-1.01)**	0.91 (0.76-1.07)
18-23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24-59	**1.34 (1.24-1.45)**	**1.14 (1.05-1.24)**	**1.44 (1.25-1.65)**	**1.37 (1.18-1.58)**	1.11(0.95-1.29)
60-119	**2.16 (1.97-2.38)**	**1.36 (1.23-1.50)**	**2.42 (2.03-2.88)**	**2.22 (1.85-2.66)**	1.19 (0.97-1.45)
120 or more	**3.82 (3.32-4.38)**	**1.60 (1.38-1.86)**	**3.13 (2.39-4.10)**	**2.72 (2.06-3.59)**	0.92 (0.65-1.30)
Model 2b: (n=100,286 mothers, n=244,125 births)					
0-5	0.90 (0.81-1.01)	0.96 (0.86-1.07)	**0.74 (0.63-0.88)**	**0.75 (0.62-0.90)**	**0.82 (0.68-0.98)**
6-11	**0.80 (0.74-0.87)**	**0.88 (0.81-0.96)**	**0.75 (0.66-0.85)**	**0.82 (0.71-0.94)**	0.87 (0.76-1.01)
12-17	**0.85 (0.79-0.92)**	**0.91 (0.83-0.98)**	**0.79 (0.70-0.89)**	**0.83 (0.73-0.95)**	**0.86 (0.76-0.99)**
18-23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24-59	**1.33 (1.25-1.42)**	**1.14 (1.07-1.22)**	**1.40 (1.26-1.55)**	**1.28 (1.14-1.43)**	1.10 (0.97-1.23)
60-119	**2.11 (1.95-2.29)**	**1.34 (1.23-1.45)**	**2.26 (1.99-2.56)**	**1.90 (1.65-2.18)**	1.13 (0.97-1.31)
120 or more	**3.45 (3.08-3.88)**	**1.52 (1.34-1.72)**	**3.66 (2.93-4.56)**	**2.95 (2.32-3.73)**	1.13 (0.86-1.50)
Model 2c: (n=40,405 mothers, n=93,716 births)					
0-5	0.91 (0.79-1.04)	1.05 (0.91-1.21)	**0.77 (0.62-0.95)**	0.83 (0.66-1.04)	0.91 (0.72-1.15)
6-11	**0.82 (0.74-0.91)**	0.93 (0.84-1.03)	**0.74 (0.63-0.87)**	0.84 (0.70-1.00)	0.90 (0.75-1.07)
12-17	0.91 (0.82-1.01)	0.97 (0.88-1.07)	**0.79 (0.67-0.92)**	0.89 (0.75-1.06)	0.92 (0.77-1.09)
18-23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24-59	**1.32 (1.20-1.44)**	**1.15 (1.07-1.27)**	**1.41 (1.22-1.62)**	**1.32 (1.13-1.54)**	1.07 (0.91-1.25)
60-119	**2.01 (1.80-2.25)**	**1.33 (1.19-1.49)**	**2.18 (1.81-2.63)**	**2.05 (1.67-2.51)**	1.05 (0.84-1.31)
120 or more	**2.78 (2.07-3.74)**	1.28 (0.95-1.74)	**1.94 (1.16-3.26)**	**2.03 (1.16-3.55)**	0.61 (0.30-1.24)

Bold indicates significance at the 5% level. Model 2a and 2b were adjusted for the following variables: [ǂ] maternal age at the time of each delivery (categorical), birth year, parity, SES, race/ethnicity, marital status, fetal sex, history of obesity; gestational hypertension and known chronic hypertension; [#] Prognostic score for GDM of parity, SES, marital status, fetal sex, history of obesity; gestational hypertension, and known chronic hypertension; [##] Prognostic score for GDM of maternal age at the time of each delivery (categorical), parity, birth year, SES, marital status, fetal sex, history of obesity; gestational hypertension and known chronic hypertension; Model 2c: includes all variables in Model 2a plus smoking during pregnancy

Supplemental Table 4-3 Odds Ratios (OR) and 95% confidence intervals for the association between interpregnancy interval and gestational diabetes for births to (Model-A) mothers with at least three consecutive births during the study period (n=103,909 mothers, n=254,137 births); (Model-B) mothers with at least three consecutive births during the study period, excluding mothers with gestational diabetes in the first pregnancy (n=102,193 mothers, n=250,231 births) in Western Australia, 1980-2015

IPI in months	**Unmatched**			
	Unadjusted OR (95% CI)		**Adjusted OR (95% CI)** [ǂ]	
	Model A	**Model B**	**Model A**	**Model B**
0-5	0.95 (0.86-1.05)	0.97(0.86-1.08)	1.01 (0.91-1.12)	1.00 (0.89-1.13)
6-11	**0.81 (0.75-0.88)**	**0.79 (0.72-0.87)**	**0.89 (0.82-0.97)**	**0.86 (0.79-0.95)**
12-17	**0.87 (0.80-0.94)**	**0.84 (0.77-0.91)**	**0.92 (0.85-0.99)**	**0.88 (0.81-0.96)**
18-23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24-59	**1.32 (1.24-1.41)**	**1.42 (1.32-1.52)**	**1.13 (1.06-1.21)**	**1.21 (1.13-1.30)**
60-119	**2.09 (1.94-2.26)**	**2.40 (2.21-2.61)**	**1.32 (1.22-1.43)**	**1.52 (1.40-1.66)**
≥120	**3.42 (3.06-3.85)**	**4.07 (3.61-4.58)**	**1.51 (1.33-1.70)**	**1.83 (1.61-2.08)**

IPI in months	**Matched**							
	Informative strata, n (%) [¥]		**Unadjusted OR (95% CI)**		**Adjusted OR (95% CI)** [♯]		**Adjusted OR (95% CI)** [♯♯]	
	Model A	**Model B**	**Model A**	**Model B**	**Model A**	**Model B**	**Model A**	**Model B**
0-5	1,305 (6.9)	1,202 (6.9)	**0.78 (0.67-0.91)**	**0.77 (0.65-0.91)**	**0.80 (0.68-0.95)**	**0.79 (0.67-0.95)**	0.88 (0.75-1.05)	0.87 (0.73-1.05)
6-11	2,954 (15.7)	2,665 (15.3)	**0.79 (0.70-0.89)**	**0.79 (0.70-0.89)**	**0.84 (0.74-0.96)**	**0.84 (0.73-0.96)**	0.92 (0.80-1.05)	0.91 (0.79-1.05)
12-17	3,297 (17.5)	3,004 (17.2)	**0.83 (0.74-0.93)**	**0.82 (0.72-0.93)**	**0.86 (0.76-0.98)**	**0.84 (0.74-0.96)**	0.90 (0.79-1.02)	0.87 (0.76-1.00)
18-23	2,489 (13.2)	2,262 (12.9)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24-59	6,096 (32.3)	5,685 (32.6)	**1.40 (1.26-1.55)**	**1.43 (1.29-1.60)**	**1.29 (1.15-1.44)**	**1.33 (1.19-1.50)**	1.07 (0.95-1.20)	1.10 (0.97-1.24)
60-119	2,216 (11.7)	2,128 (12.2)	**2.28 (2.01-2.57)**	**2.37 (2.08-2.69)**	**1.96 (1.71-2.23)**	**2.04 (1.77-2.34)**	1.08 (0.93-1.25)	1.11 (0.95-1.29)
≥120	516 (2.7)	504 (2.9)	**3.65 (2.95-4.52)**	**3.75 (3.02-4.67)**	**3.02 (2.41-3.80)**	**3.07 (2.43-3.88)**	1.02 (0.77-1.34)	1.01 (0.75-1.34)

Bold indicates significance at the 95% confidence level.

Models adjusted for the following variables: [ǂ] Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, fetal sex, history of obesity, gestational hypertension and known chronic hypertension; [♯] Prognostic score for gestational diabetes by parity, SES, marital status, fetal sex, history of obesity, gestational hypertension, and known chronic hypertension; [♯♯] Prognostic score for gestational diabetes by maternal age at the time of each delivery (categorical), birth year, parity, SES, marital status, fetal sex, history of obesity, gestational hypertension and known chronic hypertension; [¥] Number and percentage of informative strata of gestational diabetes for each IPI category for births to mothers with at least three consecutive births.

Supplemental Table 4-4 Odds Ratios ORs) and 95% confidence intervals for the association between post-birth interpregnancy interval (interval between second and third births) and gestational diabetes in the second birth for mothers with three consecutive births during the study period (n=96,354 births) in Western Australia, 1980-2015

IPI in months	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ǂ
	Gestational diabetes¥	
0-5	**1.36 (1.13-1.65)**	**1.25 (1.03-1.52)**
6-11	**1.00 (0.86-1.16)**	0.94 (0.81-1.10)
12-17	1.05 (0.91-1.22)	1.02 (0.88-1.18)
18-23	1.00 (reference)	1.00 (reference)
24-59	0.93 (0.82-1.06)	1.04 (0.91-1.18)
60-119	**0.67 (0.55-0.81)**	0.96 (0.79-1.16)
120 or more	**0.54 (0.36-0.81)**	1.18 (0.78-1.79)

¥ Predicting gestational diabetes of second-born (parity one births) using post-pregnancy IPI (interval between second born and third born births); ǂ Model adjusted for maternal age (categorical), birth year, parity, SES, race/ethnicity, marital status, fetal sex, history of obesity, gestational hypertension and known chronic hypertension

Chapter 5: INTERPREGNANCY INTERVAL AND HYPERTENSIVE DISORDERS OF PREGNANCY

Study Two. IPI and hypertensive disorders of pregnancy: A population-based cohort study

5.1 PREAMBLE

This chapter contains results from Study Two contributing to this thesis. Methods and definitions employed in Study One (Chapter 4) were expanded upon to investigate the association between IPI and hypertensive disorders of pregnancy. This study is the first to employ a large-population-based matched design to examine the role of partner change in the association between IPI and preeclampsia, addressing a significant knowledge gap in the literature.

This study was published in *Paediatric and Perinatal Epidemiology* in 2020 and is included in this chapter with permission of the publisher:

Gebremedhin AT, Regan AK, Ball S, Betrán AP, Foo D, Gissler M, Håberg SE, Malacova E, Marinovich ML, Pereira G. Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study. *Paediatr Perinat Epidemiol* 2020. doi:10.1111/ppe.12668

A copy of this publication is provided in Appendix B.

5.2 ABSTRACT

Background: Despite extensive research on risk factors and mechanisms, the extent to which interpregnancy interval (IPI) affects hypertensive disorders of pregnancy in high-income countries remains unclear.

Objective: To examine the association between IPI and hypertensive disorders of pregnancy in a high-income country setting using both within-mother and between-mother comparisons.

Methods: A retrospective, population-based cohort study was conducted among 103,909 women who delivered three or more consecutive singleton births (n=358,046) between 1980 and 2015 in Western Australia. We used conditional Poisson regression with robust variance, matching intervals of the same mother and adjusted for factors that vary within-mother across pregnancies to investigate the association between IPI categories (reference 18-23 months) and the risk of hypertensive disorders of pregnancy. For comparison with previous studies, we also applied unmatched Poisson regression (between-mother analysis).

Results: The incidence of preeclampsia and gestational hypertension during the study period was 4% and 2%, respectively. For the between-mother comparison, mothers with intervals of 6-11 months had a lower risk of preeclampsia with an adjusted relative risk (RR) 0.92 (95% confidence interval [CI] 0.85, 0.98) compared to the reference category of 18-23 months. With the within-mother design, we estimated a larger effect of long IPI on the risk of preeclampsia (RR 1.29, 95% CI 1.18, 1.42 for 60-119 months; and RR 1.30, 95% CI 1.10, 1.53 for intervals ≥120 months) compared to 18-23 months. Short IPIs were not associated with hypertensive disorders of pregnancy.

Conclusions: In our cohort, longer IPIs were associated with an increased risk of preeclampsia. However, there was insufficient evidence to suggest that short IPIs (<6 months) increases the risks of hypertensive disorders of pregnancy.

Keywords: Interpregnancy interval; pregnancy complications; hypertensive disorders of pregnancy; within-mother; birth spacing

5.3 INTRODUCTION

Globally, hypertensive disorders of pregnancy affect 2-10% of pregnancies and are among the most significant contributors to perinatal and maternal mortality and morbidity.[1] Hypertensive disorder of pregnancy can lead to severe complications, including eclampsia, abruptio placentae, fetal growth restriction and preterm birth.[2-5]

Interpregnancy interval (IPI) is defined as the length of time between delivery and the conception date of the subsequent pregnancy and has been evaluated extensively with respect to its association with perinatal outcomes.[6-9] However, less attention has been given towards its association with pregnancy complications.[10, 11] The World Health Organization (WHO) and the American College of Obstetricians and Gynaecologists suggest intervals of at least two years and at least 18 months following live births respectively.[12, 13] The applicability of these recommendations for mothers in high-income countries is uncertain as they were based on large studies in low- and middle-income settings. The extent to which these recommendations are relevant for minimising effects on pregnancy complications remains unclear. Despite extensive research on risk factors and mechanisms,[14] the aetiology of hypertensive disorders of pregnancy has not been completely elucidated. Studies that examine risk factors have typically focused on preeclampsia for nulliparous mothers.[2, 3, 15] Among parous mothers, longer IPI,[7, 16] change of partner,[17-19] and history of preeclampsia[3, 20] have been associated with an increased risk of preeclampsia or gestational hypertension.

Different hypotheses have been proposed as causal effects of IPI on pregnancy complications.[21] The *maternal depletion hypothesis* proposes that mothers with closely spaced pregnancies have less time to recover from the physiological stress of their previous pregnancy.[22, 23] The *physiologic regression hypothesis* suggests that longer pregnancy intervals result in the gradual loss of childbearing capacities, which are developed during the preceding pregnancy, and thereby result in regression to a similar physiological state to that of primigravida.[21] However, a competing explanation posits that the increased risk of pregnancy complications might be attributed to confounding factors that are associated with both IPIs and pregnancy complications (the *systematic bias hypothesis*). [24] It remains plausible that much of the observed association between pregnancy complications and perinatal outcomes in past studies may be attributable to risk factors that vary between mothers but tend to persist between pregnancies within-mothers. [24-26] Complementary within-mother analyses offer an opportunity to investigate factors that account for these effects.

We examined the association between IPI and hypertensive disorders during pregnancy in a high-income country setting using both within-mother and between-mother comparisons.

5.4 METHODS

5.4.1 Study design

We conducted a retrospective population-based matched and unmatched cohort study on the association between IPI and the risk of hypertensive disorders of pregnancy for all mothers who gave birth within the period 1980 to 2015 in Western Australia (WA).

5.4.2 Data sources and analytic sample

Maternal, infant and birth information were obtained from the Midwives Notification System, which has been validated,[27] and includes > 99% of births in WA of at least 20 weeks gestation or birthweight ≥ 400 g if the gestational length was unknown.[28] Hospitalisation records were obtained from the Hospital Morbidity Data Collection, which includes information on all hospitalizations in the state with International Classification of Diseases (ICD- 9/10th revision-Australian Modification) coded diagnoses and procedures.[29] Data sources and the study protocol have been described elsewhere.[30, 31] Our analyses included all mothers with at least two consecutive IPIs at 20-44 weeks of gestation in WA within the period 1980 and 2015. Of the original total of 487,297 mothers, we sequentially excluded mothers who delivered multiples; mothers who delivered only once during the study period; mothers whose children's birth years were inconsistent with parity; mothers whose IPIs were negative; and mothers who had missing gestational length, birth outcomes, age, infant sex, and socioeconomic status. These exclusions resulted in 287,745 mothers with two or more consecutive births (Figure 5-1). Finally, we excluded mothers with fewer than two intervals, leaving 103,909 eligible women with 358,046 births. There were 254,137 births in the analytic cohort because each of the first (parity 0) births does not have an IPI.

5.4.3 Exposure

Interpregnancy interval was defined as the length of time between the delivery date of the previous pregnancy and the estimated conception date of the subsequent pregnancy (date of birth minus gestational age at birth). Gestational age at birth was estimated as the best clinical estimate from dating ultrasounds or last menstrual period when ultrasound was not available. Intervals were grouped into seven categories (<6, 6-11, 12-17, 18-23 (reference), 24-59, 60-119, and ≥ 120 months). These categories are consistent with the WHO recommendations and categories used in previous studies.[24, 25, 32, 33]

5.4.4 Outcomes

Midwives notifications and hospital separation codes consistent with preeclampsia (ICD-9:642.4, 642.5, 642.7, ICD-10: O14, O11) and gestational hypertension without proteinuria (ICD-9: 642.3, ICD-10: O13) were used to define outcome variables. The definitions and diagnosis of hypertensive

disorders of pregnancy were based on the Australian Hypertension in Pregnancy Consensus Statement.[28]

5.4.5 Covariates

Information on potential confounding factors, including maternal age, delivery year, marital status, parity, fetal sex, race/ethnicity, and pre-existing maternal medical conditions (diabetes, hypertension, history of obesity) were also obtained from hospitalisations and midwives notifications. Race/ethnicity was classified as Caucasian versus non-Caucasian. Socio-economic status (SES) was derived by the Australian Bureau of Statistics Index of Relative Socio-economic Disadvantage at a geographic area for the maternal residence at the time of birth,[34] and categorised into quintiles. We obtained the family linkages from the WA Family Connections database.

5.4.6 Statistical analysis

Directed acyclic graphs (DAGs) were created based on existing literature and recent recommendations to present the potential pathway between IPI (short & long) and hypertensive disorders of pregnancy (Supplemental Figure 5-1 & Supplemental Figure 5-2).[33] We used a within-mother design, matching pregnancies to the same mothers, comparing pregnancies within-mothers (to control for unmeasured characteristics that do not change over time or remain strongly correlated over time). This enables inference that is based purely on within-mother effects, minimises the need for additional adjustment, and has been successfully applied previously.[24-26]

In the absence of residual time-varying confounding and selection bias, the unmatched and matched models, will report similar effects of IPI. It is plausible that if unmeasured persistent confounders exist, the unmatched model may result in biased estimates.[24] A conditional Poisson regression with robust variance was used to estimate unadjusted and adjusted relative risk (RR) and 95% confidence interval (CI) for the associations between IPIs and risk of hypertensive disorders of pregnancy for the within-mother model.[35-38] For comparison with the unmatched design of previous studies, we also generated results by Generalised linear models (GLM) fitted using a Poisson distribution with a log link function for these associations, comparing pregnancies between mothers.

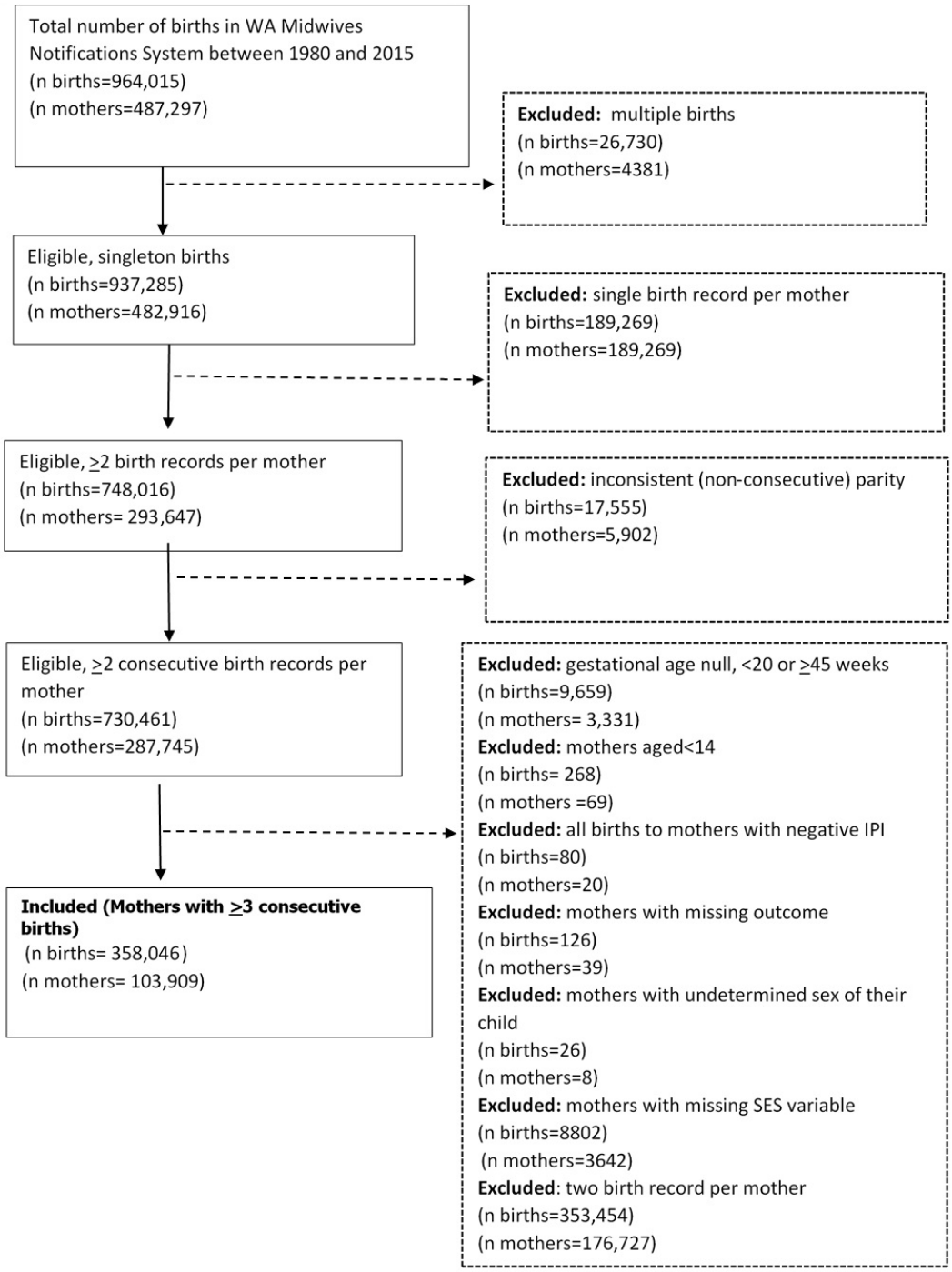

Figure 5-1. Selection of eligible birth records included in this study – Western Australia, 1980-2015

For the matched analysis, we adjusted for factors that vary between births. Specifically, we adjusted for maternal age (categorized as 14-19, 20-24, 25-29, 30-34, 35-39, or ≥40 years), parity, birth year and SES (quintiles), sex, history of obesity; pre-existing diabetes, gestational diabetes and partner change. Because time-varying adjustment variables can be proxies for IPI, which can introduce multicollinearity, we adjusted for a prognostic score, an analogue to propensity score defined as the logit of the probability of the outcome regressed on the adjustment variables from the baseline cohort.[39-41] This process ensures the whole cohort is used to estimate changes in the underlying risk of the pregnancy complication and results in the estimation of the direct effect of IPI. To estimate the total effect of IPI, we repeated analyses without adjustment for age and birth year. In the between-mother analysis, we adjusted for the same variables as we did in the within-mother analysis plus factors that can vary between mothers, such as race/ethnicity. We used STATA version 16.0 (Stata Corporation, College Station, Texas, USA), with the *xtpoisson* command to run the matched analysis (conditional Poisson regression), and the *glm* command to run the unmatched analysis (generalised linear models).[37] We used DAGitty v2.3 to select covariates fulfilling minimally sufficient adjustment sets.[42]

5.4.7 Missing data

We undertook a complete case analysis. The proportion of missing data was small and ranged from 0.07% for maternal age to 2.6% for gestational age. Multiple imputation was not performed. Approximately 5% of the missingness was due to lack of availability of data prior to year 1997, and this bias was assessed by sensitivity analyses.

5.4.8 Sensitivity analyses

To ascertain the sensitivity of our results to higher-order parity and inclusion of stillbirths, we conducted two separate supplementary analyses restricted to the first three births for all mothers with births at parity 0, 1 and 2 and analysis restricted to mothers with at least three consecutive live births. To explore the potential effects of measurement error/missingness, which would have occurred more commonly during the earlier years of the cohort when there was a lower likelihood that births had ultrasound-confirmed gestation as well as to investigate the potential influence of maternal smoking, which was routinely captured in the perinatal data collection from September 1997 onwards,[28] we conducted a separate analysis restricted to consecutive births after September 1997. To explore the role of partner change in the association between IPI and preeclampsia, we conducted a multivariable analysis with different levels of adjustment

(unadjusted, fully adjusted, adjusted for non-time-varying risk factors). To check whether the characteristics of women included in the matched analyses (mothers with informative strata) differed from those mothers with non-informative strata, we presented the baseline characteristics at their first pregnancy during the study period for these groups. Furthermore, to assess the generalizability of the cohort used in our within-mother analysis, we applied a conventional Poisson regression on a restricted cohort to births from mothers with informative strata obtained from within-mother analysis and compared to results of between-mother analysis obtained from the main cohort**.** Finally, we examined IPI as a continuous measure using restricted cubic spline with a Poisson model and conditional-Poisson model for the between- and within-mother analyses, respectively. We used a spline with five knots placed at 6, 12, 18, 24, 48, 60 and 120 months of the IPI distribution (Supplemental Figure 5-3 & Supplemental Figure 5-4).

5.4.9 Ethical approval

This research was approved by the Human Research Ethics Committee (2016/51) from the Department of Health, WA. The Ethics Committee approval was accepted on 14 September 2016.

5.5 RESULTS

Study entry for each mother was defined as their first birth during the study period. At study entry, the majority of women were generally free of chronic hypertension, diabetes and obesity (Table 5-1). More than half (55%) of the mothers were under 25 years, married (81%), or Caucasian (85%).

For all births included in the cohort, the incidence of preeclampsia and gestational hypertension during the study period was 4% and 2%, respectively (Table 5-2). Approximately 6% of births occurred after an IPI of 0-5 months, 20% after 12-17 months, 15% after 18-23 months, and 1.5% after more than 120 months. Gestational hypertension diagnosis was more common among mothers in the older age groups, whereas preeclampsia diagnosis was more common among younger mothers (Supplemental Table 5-1).

Table 5-1 Socio-demographic characteristics and medical conditions of the study cohort of mothers at their first birth during the study period (n=103,909 mothers) in WA, 1980-2015

Characteristics		Mothers, N (%)
Maternal age at first birth (years)		
<25		56,901 (54.8)
25-29		32,988 (31.7)
30-34		12,467 (12.0)
35-39		1,521 (1.5)
40 or older		32 (0.03)
Marital status		
Married		83,875 (80.7)
Never married		19,221 (18.5)
Widowed, divorced, separated		618 (0.6)
Unknown		195 (0.2)
Race/ethnicity		
Caucasian		88,106 (84.8)
Aboriginal/Torres Strait Islander		8,267 (7.9)
Asian [a]		1,986 (1.9)
African		600 (0.6)
Others [b]		4,950 (4.8)
Birth year		
1980-1984		20,264 (19.5)
1985-1989		17,681 (17.0)
1990-1994		16,811 (16.2)
1995-1999		16,053 (15.4)
2000-2004		15,538 (15.0)
2005-2009		14,448 (13.9)
2010-2015		3,114 (3.0)
SES in quintiles		
<20th percentiles (most disadvantaged)		20,398 (19.6)
20-39th percentile		21,679 (20.8)
40-59th percentile		21,914 (21.1)
60-79th percentile		20,648 (19.9)
≥80th percentile (least disadvantaged)		19,270 (18.6)
Chronic conditions		
Known chronic hypertension		259 (0.3)
Known chronic diabetes		181 (0.2)
Known obesity history		237 (0.2)
Pregnancy characteristics		
Pregnancy complications	Gestational diabetes	1,716 (1.6)
	Preeclampsia	9,928 (9.6)
	Gestational hypertension	2,400 (2.3)
Infant sex	Male	54,132 (52.1)
Parity	0	96,314 (92.7)
	1	4,977 (4.8)
	2	1,636 (1.6)
	≥3	374 (1.0)

[a] including Indian; [b] including Polynesian & Maori

IPI and risk of preeclampsia estimated by between-mother comparisons

Compared to an IPI of 18-23 months, the unmatched adjusted analysis showed a lower risk of preeclampsia for 6-11-month intervals (adjusted RR 0.92, 95% CI 0.85, 0.98) (Table 5-3).

Longer IPIs were associated with a greater risk of preeclampsia after adjustment for confounders (Table 5-3). Compared to an IPI of 18-23 months, the greatest adjusted effects were observed for IPIs of ≥120 months. IPI of 24 months or greater remained associated with increased risk of all hypertensive disorders of pregnancy after adjustment, with greatest effects observed for preeclampsia. Mothers with shorter IPI of 6-11 had a slightly lower risk of preeclampsia than IPI of 18-23 months.

IPI and risk of preeclampsia estimated by within-mother comparisons

In the matched analysis after adjustment, no increased risk of preeclampsia was observed for short IPI (<17 months), while for longer IPIs, we found an increased risk of preeclampsia. Relative to 18-23-months, the two longest IPI categories had a greater risk of preeclampsia. Similarly, longer IPIs were associated with a greater risk of gestational hypertension (Supplemental Table 5-2).

Partner change and risk of preeclampsia

In our cohort, only 10% of mothers changed their partner during the study period. The proportion of mothers who changed partners ranged from two per cent for those with IPI <6 months to 63% for those with long IPIs (≥120 months) (Table 5-2). We observed a negligible difference in risk of preeclampsia for mothers who changed partner compared to those who did not change partner (Supplemental Table 5-6).

Among women who did not change their partner between pregnancies, compared to IPI 18-23 months, the risk of preeclampsia was associated with an increase in IPI. Similar associations were observed among mothers who did not change their partner between pregnancies. Shorter intervals were not associated with an increased risk of preeclampsia. The associations were attenuated in the within-mother analysis, but the patterns of the associations were similar to the between-mother analyses (Table 5-4).

Sensitivity analysis

The results from matched and unmatched models restricted to mothers with the first three consecutive births were consistent with those based on mothers with at least three consecutive births (Supplemental Table 5-3). Similarly, point estimates were consistent with those obtained

after exclusion of stillbirths (Supplemental Table 5-4). There was a negligible difference in the association between IPI and hypertensive disorders of pregnancy when the cohort was restricted to births from September 1997 onwards, for which more information was available for adjustment. The precision of the effect estimates was reduced due to a 65% reduction in the sample size (Supplemental Table 5-5). In the sensitivity analysis, the harmful associations with longer IPI persisted regardless of partner change in both within and between-mother comparisons. A negligible difference in risk of preeclampsia was observed for mothers who changed partner compared to those who did not change (Supplemental Table 5-6).

Mothers included in the within-mother analyses (mothers with informative strata) had a similar profile of characteristics at baseline, except that mothers in the informative strata had a higher incidence of pregnancy complications (Supplemental Table 5-7). Moreover, the pattern of association was similar when we ran a conventional Poisson regression on the cohort restricted to informative strata obtained from within-mother analysis (Supplemental Table 5-8). However, estimates were attenuated after this restriction.

When examined as a nonlinear function, the risk remained unchanged until 20 months and increased linearly thereafter for the between-mother analyses (Supplemental Figure 5-3). For the within-mother analyses, the risk remained unchanged until 20 months, increased linearly until 80 months and did not change thereafter (Supplemental Figure 5-4). In general, all other findings were very similar to those reported for the main analysis and collectively supported the hypothesis of an adverse association between long IPIs and hypertensive disorders of pregnancy.

Table 5-2 Characteristics of the study population of all births to mothers with at least two consecutive intervals during the study period (n=254,137 births) in WA, 1980-2015

Characteristics	Interpregnancy Interval (months)						
	0-5 N (%)	6-11 N (%)	12-17 N (%)	18-23 N (%)	24-59 N (%)	60-119 N (%)	>=120 N (%)
Total (n=254,137)	16,548 (6.5)	45,076 (17.7)	50,528(19.9)	37,352 (14.7)	78,909 (31.1)	21,780 (8.6)	3,944 (1.6)
Preeclampsia, n (%): 9,863 (4)							
Yes	623 (3.7)	1,562 (3.5)	1,805 (3.6)	1,373 (3.7)	3,154 (4.0)	1,097 (5.0)	249 (6.3)
Gestational hypertension, n (%): 4,710 (2)							
Yes	251 (1.5)	645 (1.4)	816 (1.6)	612 (1.6)	1,660 (2.1)	566 (2.6)	160 (4.1)
Maternal age at time of each delivery (years)							
<25	6,656 (40.2)	13,032 (28.9)	11,872 (23.5)	7,747 (20.7)	12,871 (16.3)	905 (4.2)	0 (0.0)
25-29	5,395 (32.6)	15,905 (35.3)	17,822 (35.3)	13,023 (34.9)	25,743 (32.6)	5,733 (26.3)	187 (4.7)
30-34	3,220 (19.5)	11,627 (25.8)	14,883 (29.5)	11,610 (31.1)	26,394 (33.5)	8,378 (38.5)	1,168 (29.6)
35-39	1,130 (6.8)	4,024 (8.9)	5,290 (10.5)	4,397 (11.8)	12,040 (15.3)	5,528 (25.4)	1,729 (43.8)
≥40	147 (0.9)	488 (1.1)	661 (1.3)	575 (1.5)	1,861 (2.4)	1,236 (5.7)	860 (21.8)
Marital status							
Married	14,263 (86.2)	41,118 (91.2)	46,825 (92.7)	34,438 (92.2)	70,892 (89.8)	18,705 (85.9)	3,308 (83.9)
Never married	1,948 (11.8)	3,303 (7.3)	3,074 (6.1)	2,382 (6.4)	6,312 (8.0)	2,178 (10.0)	391 (9.9)
Divorced [b]	282 (1.7)	545 (1.2)	497 (1.0)	419 (1.1)	1,429 (1.8)	772 (3.5)	212 (5.4)
Unknown	55 (0.3)	110 (0.2)	132 (0.3)	113 (0.3)	276 (0.4)	125 (0.6)	33 (0.8)
Race/ethnicity							
Caucasian	12,299 (74.3)	37,050 (82.2)	42,262 (83.6)	31,413 (84.1)	64,944 (82.3)	17,801 (81.7)	3,304 (83.8)
Non-Caucasian	4,249 (25.7)	8,026 (17.8)	8,266 (16.4)	5,939 (15.9)	13,965 (17.7)	3,979 (18.3)	640 (16.2)
Birth year							
1980-1984	1,452 (8.8)	3,698 (8.2)	3,545 (7.0)	1,973 (5.3)	1,609 (2.0)	0 (0.0)	0 (0.0)
1985-1989	2,460 (14.9)	7,173 (15.9)	8,132 (16.1)	5,862 (15.7)	10,641 (13.5)	996 (4.6)	0 (0.0)
1990-1994	2,569 (15.5)	7,315 (16.2)	8,381 (16.6)	6,260 (16.8)	13,059 (16.6)	3,275 (15.0)	206 (5.2)
1995-1999	2,433 (14.7)	6,807 (15.1)	7,725 (15.3)	5,787 (15.5)	13,192 (16.7)	3,931 (18.1)	685 (17.4)
2000-2004	2,327 (14.1)	6,367 (14.1)	7,201 (14.3)	5,545 (14.9)	12,652 (16.0)	4,125 (18.9)	865 (21.9)
2005-2009	2,828 (17.1)	7,398 (16.4)	8,023 (15.9)	5,943 (15.9)	13,443 (17.0)	4,686 (21.5)	1,087 (27.6)
2010-2015	2,479 (15.0)	6,318 (14.0)	7,521 (14.9)	5,982 (16.0)	14,313 (18.1)	4,767 (21.9)	1,101 (27.9)
SES in quintiles [a]							
1	4,602 (27.8)	9,386 (20.8)	9,482 (18.8)	6,905 (18.5)	15,507 (19.7)	4,603 (21.1)	736 (18.7)
2	3,712 (22.4)	9,070 (20.1)	9,563 (18.9)	7,096 (19.0)	15,245 (19.3)	4,445 (20.4)	799 (20.3)
3	3,283 (19.8)	8,994 (20.0)	9,909 (19.6)	7,367 (19.7)	15,073 (19.1)	4,276 (19.6)	787 (20.0)
4	2,749 (16.6)	8,938 (19.8)	10,450 (20.7)	7,684 (20.6)	15,976 (20.3)	4,328 (19.9)	843 (21.4)
5	2,202 (13.3)	8,688 (19.3)	11,124 (22.0)	8,300 (22.2)	17,108 (21.7)	4,128 (19.0)	779 (19.8)
Partner							
Same	14,458 (87.4)	41,264 (91.5)	46,276 (91.6)	33,568 (89.9)	63,062 (79.9)	10,360 (47.6)	811 (20.6)
Different	341 (2.1)	785 (1.7)	1,074 (2.1)	1,279 (3.4)	8,775 (11.1)	8,544 (39.2)	2,470 (62.6)
Unknown	1,749 (10.6)	3,027 (6.7)	3,178 (6.3)	2,505 (6.7)	7,072 (8.9)	2,876 (13.2)	663 (16.8)

[a] Categorized as quintiles (1= most disadvantaged to 5= least disadvantaged); [b] includes widowed and separated

5.6 DISCUSSION

5.6.1 Principal findings

This large population-based matched study examined the association of hypertensive disorders during pregnancy with IPI in mothers with at least two intervals (three consecutive births). The results of the within-mother unadjusted model indicate that IPI of ≥ 60 months was associated with a greater risk of hypertensive disorders of pregnancy compared to an interval of 18-23 months. Pregnancies that followed IPIs shorter than 6-11 months had a lower risk of gestational hypertension. Both the within-mother and between-mother analyses showed a greater risk of hypertensive disorders following long IPI (≥ 24 months) than IPI of 18-23-months. Conversely, our results do not support the existence of an adverse association between short IPI and hypertensive disorders of pregnancy.

5.6.2 Strengths of the study

Our cohort drew from highly reliable sources of population-based perinatal information ascertained from hospital separations and midwives' notifications. To our knowledge, this is the largest matched study to investigate the association between hypertensive disorders of pregnancy with IPI.

5.6.3 Limitations of the data

Our study has several limitations. Firstly, to facilitate the matched study, our cohort was restricted to the outcomes of more than two births for each woman. Although this design achieves greater internal validity, it does so at the potential cost of external generalizability if the biological effect of IPI is different for those populations not included in our study. Secondly, as with most retrospective cohort studies that use comprehensive perinatal records, we lacked data on pregnancy loss before 20 weeks of gestation. Finally, data on chronic co-morbidities were not routinely and comprehensively collected until 1997. However, results were consistent with those after restriction to births from 1997 onwards.

Table 5-3 Relative Risks (RRs) and 95% confidence intervals for the association between interpregnancy interval and preeclampsia for births to mothers with at least two consecutive intervals during the study period (n=103,909 mothers, n=254,137 births) in WA, 1980-2015

	Unmatched			**Matched**		
IPI in months	Unadjusted RR (95% CI)	Adjusted RR (95% CI) [a]	Informative strata, n (%) [b]	Unadjusted RR (95% CI)	Adjusted RR (95% CI) [c]	Adjusted RR (95% CI) [d]
Preeclampsia						
0-5	1.02 (0.93, 1.12)	0.98 (0.89, 1.07)	1,474 (7.0)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)
6-11	0.94 (0.88, 1.01)	0.92 (0.85, 0.98)	3,599 (17.1)	0.95 (0.88, 1.03)	0.95 (0.87, 1.03)	0.95 (0.87, 1.02)
12-17	0.97 (0.91, 1.04)	0.96 (0.89, 1.03)	3,912 (18.6)	1.00 (0.92, 1.08)	0.99 (0.92, 1.07)	0.99 (0.92, 1.07)
18-23	1.00 (Reference)	1.00 (Reference)	2,933 (13.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.09 (1.02, 1.16)	1.13 (1.06, 1.20)	6,606 (31.5)	1.03 (0.96, 1.11)	1.04 (0.97, 1.12)	1.05 (0.97, 1.12)
60-119	1.37 (1.27, 1.48)	1.52 (1.40, 1.65)	2.043 (9.7)	1.26 (1.15, 1.38)	1.28 (1.17, 1.41)	1.29 (1.18, 1.42)
≥120	1.72 (1.51, 1.96)	1.95 (1.68, 2.25)	440 (2.1)	1.27 (1.08, 1.49)	1.29 (1.09, 1.52)	1.30 (1.10, 1.53)

Models adjusted for the following variables: **[a]** Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; **[c]** Prognostic score for each outcome by parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; **[d]** Prognostic score for each outcome by maternal age at time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change.

[b] Number and percentage of informative strata of preeclampsia and gestational hypertension for each IPI category for births to mothers with at least two consecutive IPIs.

5.6.4 Interpretation

Point estimates from within-mother analyses were lower than those from between-mother analyses, implying that more conservative conclusions would be drawn from the results of the within-mother analyses. Estimates from the within-mother analyses were attenuated after additional adjustment for covariates, indicating that the influence of IPI was partially explained by the pathway through maternal age or time period. For example, longer IPI can result in advanced maternal age, a well-established risk factor for hypertensive pregnancy complications.[43, 44] Although it is plausible that the effect of IPI on pregnancy complications differs by outcome status (live birth vs stillbirth), sensitivity analysis revealed that associations did not differ after restriction to live births. This may be due to the small number of stillbirths in our cohort. The association between IPI and hypertensive disorders of pregnancy can vary by parity and calendar year. However, our results were not sensitive to the restriction of mothers with three consecutive births or to births from 1997 onwards.

Our finding of greater risk of hypertensive disorders during pregnancy for longer IPIs in both between-mother and within-mother comparisons, with the effect slightly smaller in the matched models, is consistent with the previous studies.[6, 45, 46] Our results do not support the hypothesis of an adverse association between short IPI on hypertensive disorders of pregnancy, which differs from previous studies.[47, 48] Our results are consistent with previous research using unmatched designs regarding the association between longer IPIs and hypertensive disorders of pregnancy,[6, 7, 45, 49] as well as with the recent matched study conducted by Hanley *et al.* [25] which reported an association between shorter IPIs (6-11 months) and lower risk of preeclampsia. However, that study reported no association between long IPI and preeclampsia/eclampsia. The differences observed between the studies may be due to the differences in the definitions of outcome variables, adjustment variables (smoking, parity, partner change), or differences in susceptibility of the study populations to IPI (selection bias).

The observation of potential protective effects for short intervals and harmful effects for longer intervals might be explained by the physiological regression hypothesis; a pathway by which multiparous mothers with long IPI return to a similar physiological state of nulliparous mothers as protective benefits of a previous birth are gradually lost over time.[21]

Table 5-4 Relative Risks (RRs) and 95% confidence intervals for the association between interpregnancy interval and preeclampsia for births to mothers with at least two consecutive intervals during the study period stratified by status of partner change (n= 100,751 mothers, n=233,068 births) in WA, 1980- 2015

	Unmatched					
IPI in months	**Same partner (n=209,797)**			**Different partner (n=23,271)**		
	N (%)	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [a]**	**N (%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [a]**
0-5	14,457 (6.9)	1.05 (0.96, 1.16)	0.99 (0.90, 1.09)	341 (1.5)	0.55 (0.24, 1.28)	0.62 (0.26, 1.45)
6-11	41,264 (19.7)	0.94 (0.87, 1.01)	0.91 (0.84, 0.98)	786 (3.4)	0.95 (0.58, 1.57)	0.99 (0.60, 1.63)
12-17	46,275 (22.1)	0.95 (0.89, 1.03)	0.94 (0.87, 1.01)	1,074 (4.6)	1.19 (0.78, 1.82)	1.23 (0.81, 1.88)
18- 23	33,568 (16.0)	1.00 (Reference)	1.00 (Reference)	1,281 (5.5)	1.00 (Reference)	1.00 (Reference)
24-59	63,062 (30.1)	1.08 (1.01, 1.16)	1.12 (1.05, 1.20)	8,775 (37.7	1.27 (0.92, 1.74)	1.26 (0.92, 1.74)
60-119	10,360 (4.9)	1.45 (1.31, 1.60)	1.57 (1.42, 1.74)	8,544 (36.7)	1.41 (1.03, 1.93)	1.45 (1.04, 2.02)
≥120	811 (0.4)	1.91 (1.47, 2.46)	2.05 (1.59, 2.65)	2,470 (10.6)	1.91 (1.36, 2.68)	2.14 (1.47, 3.11)
	Matched					
	Same partner (n=209,797)			**Different partner (n=23,271)**		
IPI in months	**Informative strata, n (%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [b]**	**Informative strata, n (%)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [b]**
0-5	1,104 (7.4)	1.04 (0.93, 1.17)	1.03 (0.91, 1.16)	8 (2.0)	0.44 (0.10, 1.96)	0.44 (0.10, 2.04)
6-11	2,803 (18.7)	0.95 (0.87, 1.04)	0.94 (0.86, 1.03)	18 (4.4)	1.16 (0.46, 2.88)	1.12 (0.43, 2.92)
12-17	3,138 (21.0)	0.98 (0.90, 1.07)	0.98 (0.90, 1.07)	26 (6.3)	1.14 (0.44, 2.92)	1.09 (0.41, 2.88)
18- 23	2,323 (15.5)	1.00 (Reference)	1.00 (Reference)	37 (9.0)	1.00 (Reference)	1.00 (Reference)
24-59	4,576 (30.6)	1.01 (0.93, 1.09)	1.03 (0.95, 1.11)	186 (45.4)	1.67 (0.81, 3.46)	1.83 (0.92, 3.67)
≥60 [c]	1,016 (6.8)	1.24 (1.10, 1.40)	1.29 (1.14, 1.45)	135 (32.9)	1.83 (0.85, 3.95)	2.23 (1.05, 4.73)

The total included n=233,068 births (excluding births with unknown partner change status); [a] Adjusted for maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, and gestational diabetes; [b] Prognostic score for preeclampsia by maternal age at the time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, and gestational diabetes; [c] merged IPI category as there were few observations in the ≥120 IPI category

.

The role of partner change across pregnancies has been debated in epidemiological studies of risk factors for preeclampsia.[16, 18, 19, 48]

In this large population-based cohort of singleton births in WA, after adjusting for smoking and other confounders, associations implied that women who changed partners between pregnancies were not at increased risk of preeclampsia in both between-mother and within-mother analyses, which is consistent with previous studies.[48, 50] We also observed that long IPI is strongly associated with increased risk of preeclampsia regardless of partner change. The primipaternity (immune maladaptation) hypothesis postulates that the protective effect of multiparity is lost with partner change, which could confound the association between preeclampsia and IPI if partner change influences IPI and is associated with preeclampsia risk.[18, 19, 51, 52]

However, for our cohort, there was little indication of elevated risks of preeclampsia for mothers who changed partner compared to those who did not, while effect estimates were slightly higher for mothers who changed partner. It is plausible that mothers who change partner have other risk factors that place them at elevated risk of preeclampsia. Some authors have argued that both partner change and preeclampsia may influence IPI and suggest controlling for underlying maternal conditions in addition to IPI while studying the effect of partner change on preeclampsia to prevent collider-stratification bias.[53] To assess the magnitude of potential collider-stratification bias in the association between partner change and preeclampsia, we reported estimates for partner change with and without adjustment for IPI. The RR for partner change decreased toward unity when IPI was included, which was also found to be the case in the study by Zhang *et al*.[53, 54] However, the protective effect of partner change persisted after adjustment for underlying maternal conditions. These analyses did not include smoking status during pregnancy. However, in the sub-cohort for which smoking status was known, the associations of IPI and change of partner with the risk of preeclampsia remained relatively unchanged. Our findings are consistent with several studies on preeclampsia, [16, 48, 50] and a study on placental abruption.[55] Future studies would benefit from applying complementary matched designs and exploring whether previous pregnancy complications modify the effect of IPI on pregnancy complications.[50, 54, 55]

5.6.5 Conclusions

Longer interpregnancy intervals (≥24 months) were associated with increased risk of hypertensive pregnancy complications and that the total effect was partially attributable to

advanced maternal age. There was insufficient statistical evidence to support the claim that short IPIs (<6 months) increases risks of pregnancy complications in this cohort and suggests that these complications may not be due to IPI itself, but rather, may be due to maternal confounding factors.

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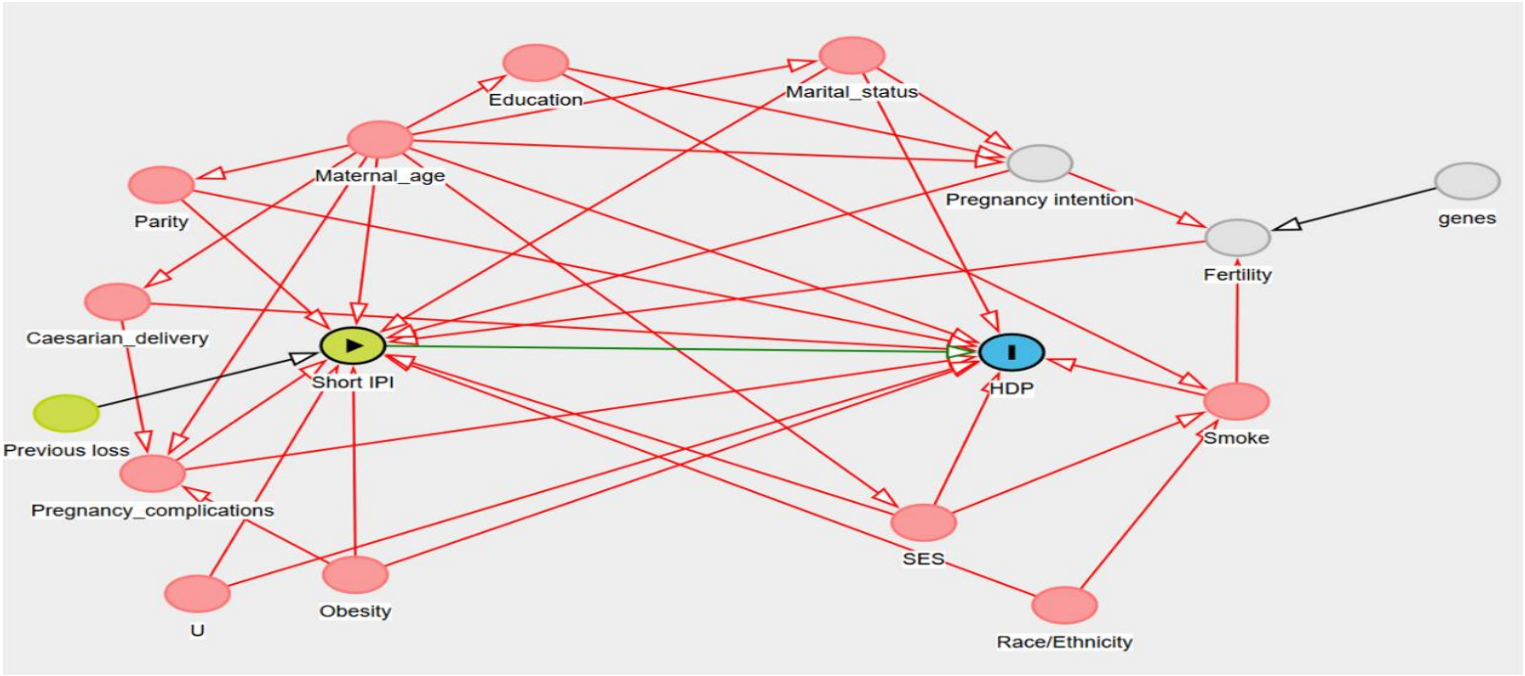
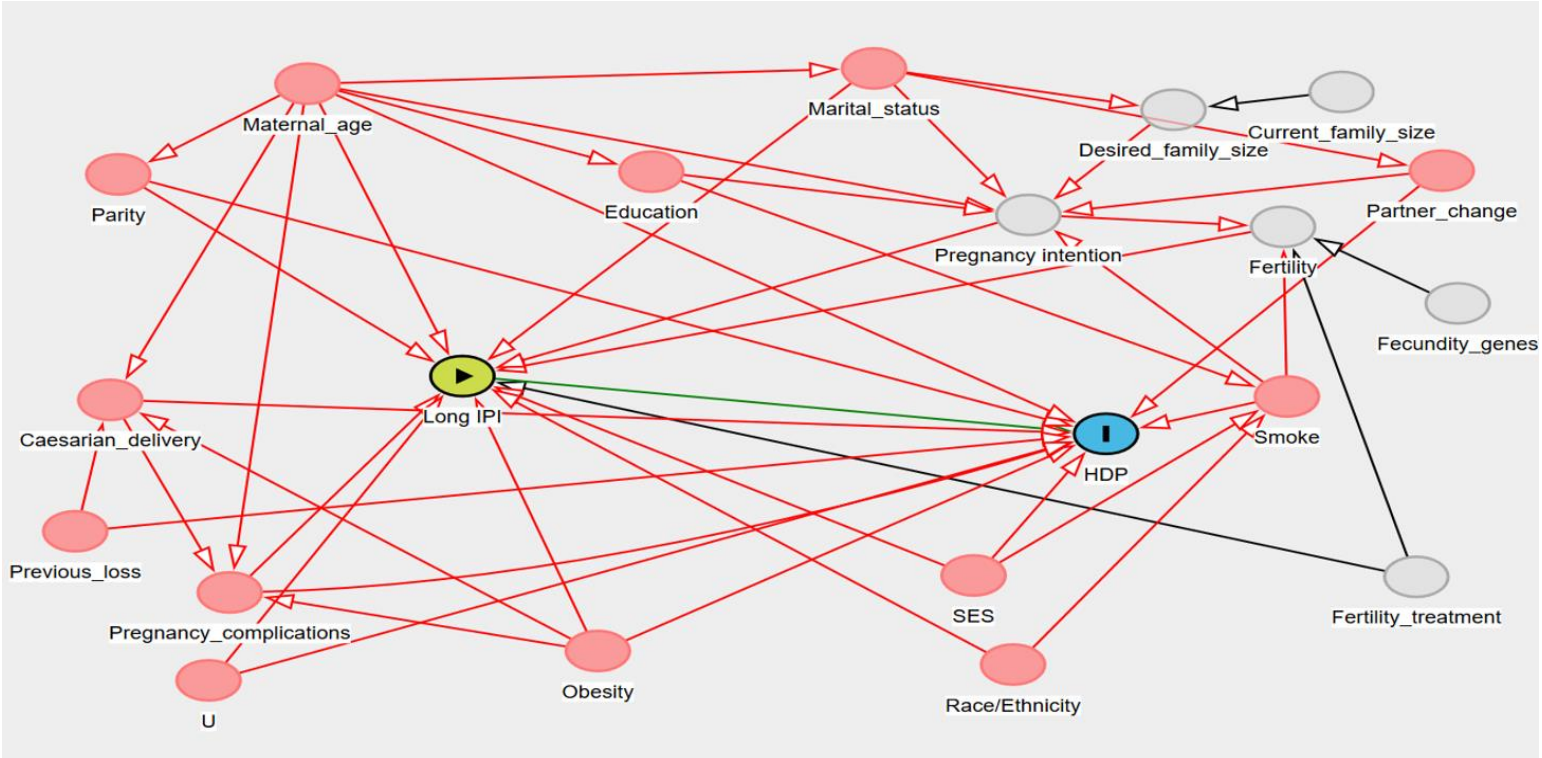
5.8 SUPPLEMENTARY MATERIAL



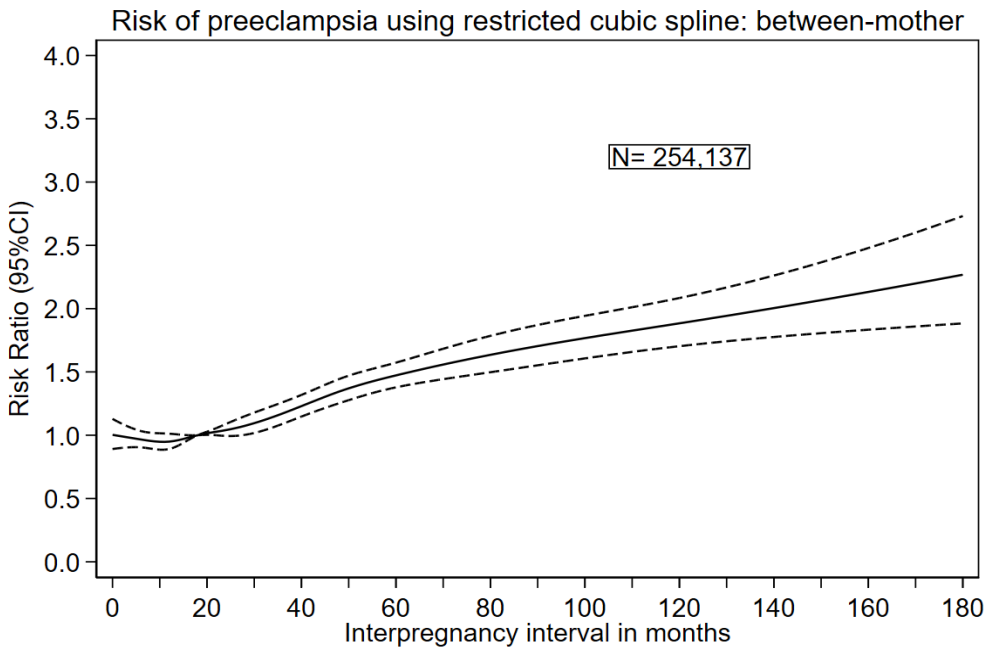
Supplemental Figure 5-1 Directed acyclic graphs representing the association between short interpregnancy interval and hypertensive disorders of pregnancy.

IPI: interpregnancy interval; HDP: Hypertensive disorders of pregnancy (preeclampsia and gestational hypertension); Outcome, exposure, measured covariates and unmeasured covariates are represented by blue, green, red and grey colour respectively; U-unmeasured and unknown confounders; The minimal set of adjustment sets for estimating the total effect of short IPI on HDP are: Marital status, maternal age, obesity, parity, pregnancy complications, SES, smoking and U. In our study, control for U (unknown and unmeasured confounders) is represented using matching (within-mother comparison).

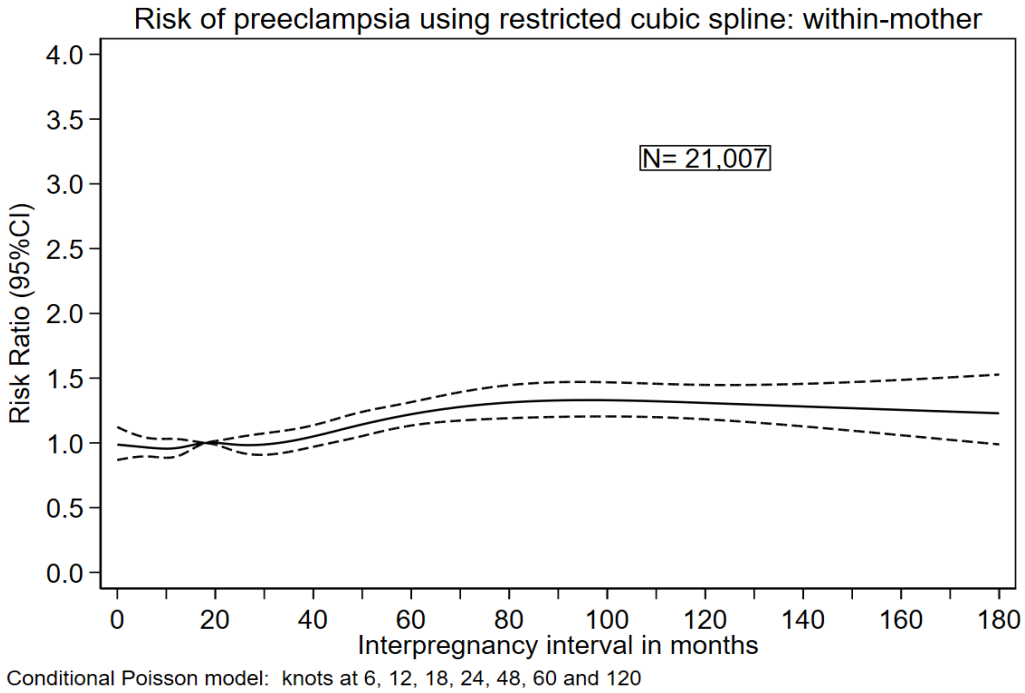


Supplemental Figure 5-2 Directed acyclic graphs representing the association between long interpregnancy interval and hypertensive disorders of pregnancy

IPI: interpregnancy interval; HDP: Hypertensive disorders of pregnancy (preeclampsia and gestational hypertension); Outcome, exposure, measured covariates and unmeasured covariates are represented by blue, green, red and grey colour respectively; U-unmeasured and unknown confounders; The minimal set of adjustment sets for estimating the total effect of long IPI on HDP are: Maternal age, obesity, parity, pregnancy complications, partner change, SES, smoking and U. In our study, control for U (unknown and unmeasured confounders) is represented using matching (within-mother comparison)



Supplemental Figure 5-3: **Restricted cubic spline for interpregnancy interval using between-mother approach.** Multivariate risk ratio of preeclampsia as a function of interpregnancy interval in months. Data are fitted by a restricted cubic spline using Poisson regression model with robust variance and controlled for maternal age at time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change. The 95% CIs are indicated by dashed lines.



Supplemental Figure 5-4: **Restricted cubic spline for interpregnancy interval using within-mother approach.** Multivariate risk ratio of preeclampsia as a function of interpregnancy interval in months. Data are fitted by a restricted cubic spline using Conditional Poisson regression model with robust variance and controlled for Prognostic score for preeclampsia by maternal age at time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change. The 95% CIs are indicated by dashed lines.

Supplemental Table 5-1 Characteristics of study population by pregnancy complication for all births to mothers with at least two consecutive intervals during the study period (n=254,137 births) in WA, 1980-2015

	Pregnancy complications		
Characteristics	**Total**	**Preeclampsia N (%)**	**Gestational hypertension N (%)**
Total No	254,137	9,863 (4)	4,710 (2)
Interpregnancy interval (months)			
0-5	16,548	623 (3.8)	251 (1.5)
6-11	45,076	1,562 (3.5)	645 (1.4)
12-17	50,528	1,805 (3.6)	816 (1.6)
18-23	37,352	1,373 (3.7)	612 (1.6)
24-59	78,909	3,154 (4.0)	1,660 (2.1)
60-119	21,780	1,097 (5.0)	566 (2.6)
≥120	3,944	249 (6.3)	160 (4.1)
Maternal age at time of each delivery (years)			
<25	53,083	2,135 (4.0)	788 (1.5)
25-29	83,808	3,318 (3.9)	1,382 (1.6)
30-34	77,280	2,843 (3.7)	1,515 (2.0)
35-39	34,138	1,296 (3.8)	812 (2.4)
≥40	5,828	1,296 (3.8)	213 (3.6)
Race/ethnicity			
Caucasian	209,073	8,143 (3.9)	3,906 (1.9)
Non- Caucasian	45,064	1,720 (3.8)	804 (1.8)
Birth year			
1980-1984	12,277	646 (5.3)	1 (0.0)
1985-1989	35,264	1,758 (5.0)	3 (0.0)
1990-1994	41,065	2,024 (4.9)	269 (0.6)
1995-1999	40,560	2,140 (5.3)	653 (1.6)
2000-2004	39,082	1,398 (3.6)	1,581 (4.1)
2005-2009	43,408	1,009 (2.3)	1,196 (2.7)
2010-2015	42,481	888 (2.1)	1,007 (2.4)
SES in quintiles [a]			
1	51,221	2,343 (4.6)	950 (1.8)
2	49,930	2,149 (4.3)	999 (2.0)
3	49,689	1,984 (4.0)	909 (1.8)
4	50,968	1,820 (3.6)	966 (1.9)
5	52,329	1,567 (3.0)	886 (1.7)

Supplemental Table 5-2 Relative Risks (RRs) and 95% confidence intervals for the association between interpregnancy interval and gestational hypertension for births to mothers with at least two consecutive intervals during the study period (n=103,909 mothers, n=254,137 births

	Unmatched			Matched		
IPI in months	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [a]**	**Informative strata, n (%) [b]**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [c]**	**Adjusted RR (95% CI) [d]**
			Gestational hypertension			
0-5	0.93 (0.80, 1.07)	0.93 (0.80, 1.07)	743 (6.7)	0.90 (0.76, 1.06)	0.90 (0.76, 1.06)	0.91 (0.77, 1.07)
6-11	0.87 (0.78, 0.97)	0.91 (0.82, 1.02)	1,807 (16.4)	0.88 (0.77, 0.99)	0.88 (0.78, 0.99)	0.89 (0.78, 1.01)
12-17	0.99 (0.89, 1.09)	1.02 (0.92, 1.13)	2,002 (18.1)	1.01 (0.90, 1.15)	1.02 (0.90, 1.15)	1.01 (0.89, 1.14)
18-23	1.00 (Reference)	1.00 (Reference)	1,512 (13.3)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.28 (1.17, 1.41)	1.20 (1.09, 1.31)	3,565 (32.3)	1.21 (1.08, 1.34)	1.20 (1.08, 1.34)	1.16 (1.04, 1.30)
60-119	1.59 (1.42, 1.78)	1.30 (1.15, 1.47)	1,159 (10.5)	1.30 (1.14, 1.50)	1.31 (1.14 1.50)	1.15 (1.00, 1.32)
≥120	2.48 (2.09, 2.94)	1.70 (1.40, 2.06)	254 (2.3)	1.95 (1.53, 2.49)	1.97 (1.55, 2.52)	1.48 (1.16, 1.90)

Models adjusted for the following variables: [a] Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [c] Prognostic score for each outcome by parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [d] Prognostic score for each outcome by maternal age at the time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [b] Number and percentage of informative strata of preeclampsia and gestational hypertension for each IPI category for births to mothers with at least two consecutive IPIs

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Supplemental Table 5-3 Relative Risks (RRs) and 95% CIs for the association between IPI and pregnancy complications for births to mothers with only two consecutive intervals (parity 0, 1 and 2) during the study period (n=96,354 mothers, n=192,708 births) in WA, 1980-2015

	Unmatched but restricted to mothers with three births		Matched and restricted to mothers with three births		
IPI in months	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [a]**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [b]**	**Adjusted RR (95% CI) [c]**
			Preeclampsia		
0-5	1.04 (0.93, 1.16)	0.97 (0.87, 1.09)	0.97 (0.85, 1.11)	0.97 (0.85, 1.11)	0.97 (0.85, 1.11)
6-11	0.94 (0.87, 1.02)	0.90 (0.83, 0.98)	0.92 (0.83, 1.01)	0.92 (0.83, 1.01)	0.91 (0.83, 1.01)
12-17	0.98 (0.90, 1.05)	0.96 (0.88, 1.03)	0.96 (0.88, 1.06)	0.96 (0.88, 1.06)	0.96 (0.87, 1.05)
18-23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.05 (0.98, 1.13)	1.10 (1.03, 1.18)	0.98 (0.90, 1.07)	1.02 (0.93, 1.11)	1.02 (0.93, 1.11)
60-119	1.40 (1.28, 1.53)	1.60 (1.45, 1.77)	1.23 (1.10, 1.37)	1.30 (1.16, 1.45)	1.32 (1.17, 1.48)
≥120	1.63 (1.39, 1.90)	1.95 (1.64, 2.32)	1.18 (0.97, 1.45)	1.22 (0.99, 1.49)	1.24 (1.01, 1.52)
			Gestational hypertension		
0-5	0.94 (0.79, 1.12)	0.94 (0.79, 1.12)	0.92 (0.74, 1.14)	0.92 (0.74, 1.14)	0.93 (0.75, 1.15)
6-11	0.92 (0.81, 1.05)	0.95 (0.84, 1.08)	0.95 (0.81, 1.11)	0.95 (0.81, 1.11)	0.96 (0.82, 1.13)
12-17	1.03 (0.91, 1.16)	1.05 (0.94, 1.19)	1.06 (0.91, 1.24)	1.06 (0.91, 1.23)	1.06 (0.91, 1.24)
18-23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.29 (1.16, 1.44)	1.22 (1.09, 1.35)	1.18 (1.03, 1.35)	1.18 (1.03, 1.35)	1.14 (1.00, 1.31)
60-119	1.60 (1.40, 1.83)	1.35 (1.16, 1.56)	1.21 (1.02, 1.44)	1.21 (1.02, 1.44)	1.08 (0.90, 1.29)
≥120	2.66 (2.18, 3.24)	1.95 (1.56, 2.45)	1.95 (1.43, 2.64)	1.94 (1.43, 2.63)	1.52 (1.11, 2.09)

Models adjusted for the following variables: [a] Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [b] Prognostic score for each outcome by parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [c] Prognostic score for each outcome by maternal age at the time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change

Supplemental Table 5-4 Relative Risks (RRs) and 95% CIs for the association between IPI and pregnancy complications for births to mothers with at least two consecutive intervals of live births during the study period (n=100,286 mothers, n=244,125 births) in WA, 1980-2015

	Unmatched		Matched		
IPI in months	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [a]**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [b]**	**Adjusted RR (95% CI) [c]**
			Preeclampsia		
0-5	0.95 (0.86, 1.05)	0.90 (0.82, 1.00)	0.95 (0.84, 1.06)	0.94 (0.84, 1.06)	0.94 (0.84, 1.05)
6-11	0.93 (0.86, 1.00)	0.90 (0.83, 0.97)	0.93 (0.86, 1.01)	0.93 (0.85, 1.01)	0.93 (0.85, 1.01)
12-17	0.96 (0.89, 1.03)	0.94 (0.88, 1.01)	0.98 (0.91, 1.06)	0.98 (0.90, 1.06)	0.98 (0.90, 1.06)
18- 23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.09 (1.03, 1.17)	1.15 (1.08, 1.22)	1.03 (0.96, 1.11)	1.05 (0.97, 1.13)	1.05 (0.98, 1.13)
60-119	1.39 (1.29, 1.51)	1.57 (1.44, 1.71)	1.27 (1.16, 1.40)	1.29 (1.18, 1.42)	1.31 (1.19, 1.44)
≥120	1.76 (1.54, 2.01)	2.04 (1.76, 2.36)	1.27 (1.08, 1.50)	1.29 (1.08, 1.52)	1.30 (1.10, 1.53)
			Gestational hypertension		
0-5	0.86 (0.74, 1.01)	0.86 (0.73, 1.00)	0.85 (0.71, 1.00)	0.85 (0.72, 1.01)	0.86 (0.72, 1.01)
6-11	0.87 (0.78, 0.97)	0.90 (0.80, 1.01)	0.86 (0.76, 0.98)	0.86 (0.76, 0.98)	0.89 (0.78, 0.98)
12-17	0.97 (0.87, 1.08)	1.00 (0.90, 1.11)	1.00 (0.88, 1.14)	1.00 (0.88, 1.14)	1.00 (0.88, 1.14)
18- 23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.28 (1.16, 1.40	1.21 (1.10, 1.33)	1.21 (1.08, 1.35)	1.20 (1.08, 1.34)	1.14 (1.02, 1.27)
60-119	1.60 (1.43, 1.80)	1.34 (1.19, 1.52)	1.33 (1.15, 1.53)	1.32 (1.15, 1.52)	1.11 (0.96, 1.28)
≥120	2.55 (2.15, 3.03)	1.81 (1.49, 2.20)	1.99 (1.56, 2.55)	1.96 (1.54, 2.51)	1.35 (1.06, 1.74)

Models adjusted for the following variables: [a] Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [b] Prognostic score for each outcome by parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [c] Prognostic score for each outcome by maternal age at the time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change

Supplemental Table 5-5 RRs and 95% CIs for the association between IPI & pregnancy complications for births to mothers with at least two consecutive intervals during the end of the study period (Sept 1997 onwards) (n=40,336 mothers, n=93,543 births) in WA, 1980-2015

	Unmatched		Matched		
IPI in months	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [a]**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI) [b]**	**Adjusted RR (95% CI) [c]**
			Preeclampsia		
0-5	0.99 (0.82, 1.21)	0.91 (0.75, 1.11)	1.00 (0.80, 1.26)	1.01 (0.80, 1.26)	1.00 (0.80, 1.25)
6-11	0.88 (0.76, 1.03)	0.85 (0.73, 0.98)	0.95 (0.80, 1.13)	0.95 (0.79, 1.13)	0.94 (0.79, 1.12)
12-17	1.06 (0.91, 1.22)	1.04 (0.90, 1.20)	1.06 (0.89, 1.25)	1.06 (0.89, 1.26)	1.05 (0.89, 1.25)
18- 23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.05 (0.92, 1.19)	1.07 (0.94, 1.22)	0.99 (0.84, 1.16)	1.01 (0.86, 1.19)	1.03 (0.88, 1.21)
60-119	1.34 (1.12, 1.60)	1.44 (1.19, 1.75)	1.09 (0.88, 1.26)	1.14 (0.92, 1.42)	1.20 (0.96, 1.50)
≥120	1.62 (0.96, 2.74)	1.70 (0.98, 2.94)	0.93 (0.47, 1.83)	0.93 (0.46, 1.85)	1.02 (0.52, 2.03)
			Gestational hypertension		
0-5	1.02 (0.85, 1.23)	0.98 (0.81, 1.17)	1.13 (0.92, 1.40)	1.14 (0.92, 1.40)	1.13 (0.92, 1.39)
6-11	0.92 (0.80, 1.06)	0.89 (0.77, 1.03)	0.94 (0.80, 1.10)	0.94 (0.80, 1.10)	0.93 (0.79, 1.09)
12-17	1.08 (0.94, 1.23)	1.06 (0.93, 1.21)	1.10 (0.94, 1.30)	1.10 (0.93, 1.29)	1.10 (0.93, 1.29)
18- 23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.17 (1.03, 1.32)	1.22 (1.08, 1.37)	1.09 (0.95, 1.26)	1.10 (0.96, 1.27)	1.11 (0.97, 1.29)
60-119	1.05 (0.87, 1.26)	1.19 (0.99, 1.44)	0.84 (0.68, 1.04)	0.85 (0.69, 1.05)	0.88 (0.71, 1.09)
≥120	1.41 (0.84, 2.39)	1.73 (1.01, 2.95)	1.17 (0.56, 2.43)	1.15 (0.55, 2.39)	1.21 (0.58, 2.53)

Models adjusted for the following variables: [a] Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, smoking during pregnancy, known chronic diabetes, gestational diabetes, and partner change; [b] Prognostic score for each outcome by parity, SES, marital status, infant sex, history of obesity, smoking during pregnancy, known chronic diabetes, gestational diabetes, and partner change; [c] Prognostic score for each outcome by maternal age at the time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, smoking during pregnancy, known chronic diabetes, gestational diabetes, and partner change

Supplemental Table 5-6 RRs and 95% CIs for the association between IPI, partner change and preeclampsia for births to mothers with at least two consecutive intervals during the study period (n=103,909 mothers, n=254,137 births) in WA, 1980-2015

	Unmatched				Matched				
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)			Unadjusted RR (95% CI)	Adjusted RR (95% CI)			
Variables		**Model A**	**Model B**	**Model C**		**Model D**	**Model E**	**Model F**	**Model G**
Partner									
Same	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Different	1.13 (1.06, 1.21)	1.23 (1.15, 1.31)	0.93 (0.86, 0.99)	0.97 (0.90, 1.04)	1.15 (1.06, 1.24)	1.16 (1.07, 1.25)	1.01 (0.93, 1.11)	1.00 (0.92, 1.09)	1.00 (0.92, 1.10)
Unknown	1.10 (1.02, 1.17)	1.05 (0.97, 1.14)	1.03 (0.96, 1.10)	0.94 (0.87, 1.02)	1.00 (0.90, 1.12)	0.98 (0.88, 1.10)	0.94 (0.84, 1.06)	0.91 (0.81, 1.02)	0.90 (0.81, 1.01)
IPI in months									
0-5	1.02 (0.93, 1.12)	-	1.02 (0.93, 1.12)	0.98 (0.88, 1.07)	1.00 (0.90, 1.11)	-	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)	0.99 (0.90, 1.10)
6-11	0.94 (0.88, 1.01)	-	0.94 (0.87, 1.01)	0.92 (0.85, 0.98)	0.95 (0.88, 1.03)	-	0.95 (0.88, 1.03)	0.95 (0.87, 1.03)	0.94 (0.87, 1.02)
12-17	0.97 (0.91, 1.04)	-	0.97 (0.91, 1.04)	0.96 (0.89, 1.03)	1.00 (0.92, 1.08)	-	1.00 (0.92, 1.08)	0.99 (0.92, 1.07)	0.99 (0.92, 1.07)
18- 23	1.00 (Reference)	-	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	-	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.09 (1.02, 1.16)	-	1.09 (1.03, 1.16)	1.13 (1.06, 1.20)	1.03 (0.96, 1.11)	-	1.03 (0.96, 1.11)	1.05 (0.97, 1.12)	1.05 (0.98, 1.13)
60-119	1.37 (1.27, 1.48)	-	1.40 (1.29, 1.52)	1.52 (1.40, 1.65)	1.26 (1.15, 1.38)	-	1.26 (1.14, 1.38)	1.29 (1.17, 1.42)	1.30 (1.18, 1.44)
≥120	1.72 (1.51, 1.96)	-	1.79 (1.56, 2.05)	1.95 (1.68, 2.25)	1.27 (1.08, 1.49)	-	1.26 (1.06, 1.50)	1.29 (1.09, 1.53)	1.30 (1.10, 1.55)

Models adjusted for the following variables: Model A - maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, and gestational diabetes (excluding IPI); Model B - partner change and IPI; Model C - risk factors included in Model A and IPI**;** Model D - prognostic score for preeclampsia using maternal age at the time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, and gestational diabetes (excluding IPI); Model E - partner change and IPI; Model F - prognostic score for each outcome using parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, and gestational diabetes; Model G - risk factors for Model D and IPI.

Supplemental Table 5-7 Socio-demographic characteristics and medical conditions of the study cohort of mothers at the study entry included during the study period (n=103,909 mothers) based on informative strata in WA, 1980-2015

Characteristics		Mothers, N (%)	
		Informative strata (n=7,991) [a]	**Non-informative strata (n=95,918)**
Maternal age at first birth (years)			
<25		4,928 (61.7)	51,973 (54.2)
25-29		2,260 (28.3)	30,728 (32.0)
30-34		711 (8.9)	11,756 (12.3)
35-39		90 (1.1)	1,431 (1.5)
40 or older		2 (0.0)	30 (0.03)
Marital status			
Married		36,157 (77.1)	77,718 (81.0)
Never married		1,768 (22.1)	17,453 (18.2)
Widowed, divorced, separated		58 (0.7)	560 (0.6)
Unknown		8 (0.1)	187 (0.2)
Race/ethnicity			
Caucasian		6,670 (83.5)	81,436 (84.9)
Aboriginal/Torres Strait Islander		944 (11.8)	7,323 (7.6)
Asian [b]		34 (0.4)	1,935 (2.0)
African		24 (0.5)	566 (0.6)
Others [c]		292 (3.6)	4,658 (4.8)
Birth year			
1980-1984		2,216 (27.7)	18,048 (18.8)
1985-1989		1,731 (21.6)	15,950 (16.6)
1990-1994		1,586 (19.8)	15,225 (15.9)
1995-1999		1,134 (14.2)	14,919 (15.5)
2000-2004		717 (8.9)	14,821 (15.4)
2005-2009		511 (6.4)	13,937 (14.5)
2010-2015		96 (1.2)	3,018 (3.1)
SES in quintiles			
<20th percentiles (most disadvantaged)		1,963 (24.6)	18,435 (19.2)
20-39th percentile		1,812 (22.7)	19,867 (20.7)
40-59th percentile		1,679 (21.0)	20,2235 (21.1)
60-79th percentile		1,394 (17.4)	19,254 (20.1)
≥80th percentile (least disadvantaged)		1,143 (14.3)	18,127 (18.9)
Chronic conditions			
Known chronic hypertension		76 (0.9)	183 (0.2)
Known chronic diabetes		31 (0.40)	150 (0.2)
Known obesity history		42 (0.5)	195 (0.2)
Pregnancy characteristics			
Pregnancy complications	Gestational diabetes	184 (2.3)	1,532 (1.6)
	Preeclampsia	2,966 (37.1)	6,962 (7.3)
	Gestational hypertension	417 (5.2)	1,983 (2.1)
Infant sex	Male	4,194 (52.5)	49,938 (52.1)
Parity	0	7,264 (90.9)	89,050 (92.8)
	1	452 (5.6)	4,525 (4.7)
	2	165 (2.1)	1,471 (1.5)
	≥3	110 (1.4)	872 (0.9)

[a] Informative strata obtained from conditional Poisson regression of preeclampsia model [b] including Indian; [c] including Polynesian & Maori

Supplemental Table 5-8 Adjusted Relative Risks (RRs) and 95% confidence intervals for the association between IPI and hypertensive disorders of pregnancy for births to mothers included in the main cohort (n=254,137 births); and mothers included in the within-mother analysis (informative strata) (n=21,007 births, preeclampsia model; n=11,042 births, gestational hypertension model) during the study period in WA, 1980-2015

IPI in months	**Unadjusted RR (95% CI)**		**Adjusted RR (95% CI)**	
	Main Cohort	**Informative Strata**	**Main Cohort [a]**	**Informative Strata [a]**
	Preeclampsia			
0-5	1.02 (0.93, 1.12)	0.90 (0.84, 0.97)	0.98 (0.89, 1.07)	0.95 (0.88, 1.02)
6-11	0.94 (0.88, 1.01)	0.93 (0.88, 0.98)	0.92 (0.85, 0.98)	0.95 (0.90, 1.00)
12-17	0.97 (0.91, 1.04)	0.99 (0.94, 1.04)	0.96 (0.89, 1.03)	0.99 (0.94, 1.04)
18-23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.09 (1.02, 1.16)	1.02 (0.97, 1.07)	1.13 (1.06, 1.20)	1.04 (1.00, 1.09)
60-119	1.37 (1.27, 1.48)	1.15 (1.08, 1.21)	1.52 (1.40, 1.65)	1.19 (1.12, 1.26)
≥120	1.72 (1.51, 1.96)	1.21 (1.10, 1.32)	1.95 (1.68, 2.25)	1.19 (1.07, 1.31)
	Gestational hypertension			
0-5	0.93 (0.80, 1.07)	0.83 (0.74, 0.94)	0.93 (0.80, 1.07)	0.92 (0.82, 1.03)
6-11	0.87 (0.78, 0.97)	0.88 (0.81, 0.96)	0.91 (0.82, 1.02)	0.92 (0.85, 1.00)
12-17	0.99 (0.89, 1.09)	1.01 (0.93, 1.09)	1.02 (0.92, 1.13)	1.01 (0.93, 1.09)
18-23	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.28 (1.17, 1.41)	1.15 (1.07, 1.23)	1.20 (1.09, 1.31)	1.12 (1.04, 1.20)
60-119	1.59 (1.42, 1.78)	1.21 (1.11, 1.31)	1.30 (1.15, 1.47)	1.09 (1.00, 1.19)
≥120	2.48 (2.09, 2.94)	1.56 (1.39, 1.74)	1.70 (1.40, 2.06)	1.23 (1.08, 1.40)

Models adjusted for the following variables: [a] Maternal age at the time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change

Chapter 6: INTERPREGNANCY INTERVAL AND PREGNANCY COMPLICATIONS BY MATERNAL AGE

Study Three. Associations between IPI and pregnancy complications: Effect modification by maternal age

6.1 PREAMBLE

Though there is a growing body of literature on the association between IPI and pregnancy complications, the potential effect-modifying role of maternal age on this association remains unclear. This chapter, third study (Study Three) that contributed to this thesis, evaluated whether the association between IPI and pregnancy complications is modified by maternal age. In this study, the potential role of other factors explaining and differences was assessed in several sensitivity analyses.

This chapter reports the extended text version of a paper accepted for publication at *Paediatric and Perinatal Epidemiology* journal:

Gebremedhin AT, Tessema GA, Regan AK, Pereira G. Association between interpregnancy interval and hypertensive disorders of pregnancy: Effect modification by maternal age. *Paediatric and perinatal Epidemiology 2021*. doi:10.1111/ppe.12774

A copy of this publication is provided in Appendix B.

6.2 ABSTRACT

Background: Short and long interpregnancy intervals (IPIs) are associated with increased risk of pregnancy complications, yet whether this association is modified by maternal age remains unclear.

Objective: To examine if the association between IPI and pregnancy complications varies by maternal age at birth prior to IPI.

Methods: We conducted a population-based cohort study of all mothers with at least one consecutive IPI (n=430,615 singleton pregnancies) from 1980 to 2015 in Western Australia (WA). The main outcomes were preeclampsia, gestational diabetes, gestational hypertension, premature rupture of membrane (PROM), and antepartum haemorrhage composite (APH). We estimated the risk of each outcome for 3-60 months of IPI according to maternal age at birth prior to IPI [<20 years, 20-24, 25-29, 30-34 and ≥35 years]. We modelled IPI using restricted cubic splines and reported adjusted relative risk (RRs) with 95% CI at 3, 6, 12, 24, 36, 48 and 60 months, with 18 months as reference.

Results: The risk of preeclampsia was increased at 6 months compared to 18 months; RR (1.31, 95% CI 1.00, 1.71) for mothers 35 years or older, but not for mothers younger than 20 years (RR 0.84, 95% CI 0.73, 0.95). The increased risk of gestational diabetes and gestational hypertension at longer IPI (60 months) was more pronounced for mothers older than 35 years than mothers younger than 20 years. The risk of APH and PROM at short IPIs (<6 months) was greater for younger women.

Conclusion: In our cohort, associations between IPI and pregnancy complications varied by maternal age.

Keywords: interpregnancy interval; pregnancy complications; birth intervals; birth spacing; maternal age

6.3 INTRODUCTION

Interpregnancy interval (IPI), or the length of time between the end of one pregnancy and conception of the next, has been associated with adverse outcomes among mothers and their infants.[1-4] Research suggests that short and long IPIs are associated with an increased risk of pregnancy complications, including preeclampsia, gestational diabetes, antepartum haemorrhage and premature rupture of membranes (PROM).[1,3,5,6] To reduce these risks, the World Health Organization (WHO) and various clinical guidelines recommend that women wait at least 18-24 months before conceiving another child.[7-9]

In many high-income countries, there has been an increasing proportion of women who delay initiation of childbearing.[10] Maternal age is a well-established risk factor for various pregnancy complications.[1,11-13] Women who have delayed childbearing until later in life and are planning to become pregnant are likely to plan to have their subsequent child sooner than later to minimise the effects of diminishing fecundability.[13] However, shorter IPI can also introduce additional risk, independently of age.[1,14] Although some studies have examined the association between IPI and birth outcomes by maternal age,[11,13,15,16] few maternal outcomes, such as pregnancy complications, have been evaluated in relation to IPI by maternal age.[11,13]

Given the increasing number of women delaying initiation of childbearing in many high-income countries, evaluating the relationship between IPI and pregnancy complications by maternal age is warranted. This study aimed to examine whether the association between IPI and pregnancy complications varies by maternal age at the time of birth prior to the IPI.

6.4 METHODS

6.4.1 Study design

We conducted a population-based, record linked cohort study drawn from all mothers with at least two consecutive singleton pregnancies in the period of 1980-2015 in Western Australia (WA).

6.4.2 Data sources and study population

Maternal, infant and birth information were obtained from the Midwives Notification System, a validated database[17] that includes >99% of births in WA of at least 20 weeks' gestation or birthweight of 400 g or more if the gestational age was unknown.[18] We sourced hospitalization records from Hospital Morbidity Data Collection, which includes information on all hospitalizations in the state with International Classification of Diseases (ICD-9/10th revision-

Australian Modification) coded diagnoses.[19] Data sources and study protocol has been published elsewhere.[3,20] Birth records were probabilistically linked based on maternal information to identify all births to individual women during the study period.

From the original total of 487,297 mothers, we sequentially excluded mothers who delivered multiples; mothers who delivered only once during the study period; mothers whose children's birth years were inconsistent with the parity and mothers who had missing gestational age, pregnancy outcomes, age, and socio-economic status. These exclusions resulted in 280,637 eligible mothers who contributed 711,252 pregnancies. Finally, 430,615 pregnancies were included in the final analysis because each of the first (parity 0) births does not have an IPI.

6.4.3 Exposure

Interpregnancy interval (IPI) was calculated prior to exclusions as the time between the delivery date of the first eligible birth during the study period and the estimated conception date of the subsequent pregnancy (date of birth minus gestational age at birth). Gestational age at birth was estimated as the best clinical estimate from dating ultrasounds or last menstrual period when ultrasound was not available.

6.4.4 Outcomes

The outcomes of interest were ascertained from midwives notifications and hospital separation data in the state, with the International Classification of Diseases (ICD-9 through to ICD-10-AM [Australian Modification]) diagnostic codes consistent with preeclampsia (ICD-9/ICD-9-CM: 642.4, 642.5, 642.7, ICD-10-AM: O14, O11); gestational hypertension without proteinuria (ICD-9-AM: 642.3, ICD-10-AM: O13); gestational diabetes (ICD-9/ICD-9-CM: 648.8, ICD-10-AM: O24.4-); placenta previa, with or without haemorrhage (ICD-9/ICD-9-CM: 641.0-641.1, ICD-10-AM: O44.-); placental abruption (ICD-9/ICD-9-CM : 641.2, ICD-10-AM: O45.-); antepartum haemorrhage (APH), not elsewhere classified (ICD-9/ICD-9-CM: 641.3-641.9, ICD-10-AM: O46.-) and; premature rupture of membrane (PROM) (ICD-9/ICD-9-CM: 658.1-658.2, ICD-10-AM: O42.-). We also included a composite outcome, Antepartum haemorrhage -composite (APH), that included placenta previa, placental abruption and unspecified APH.

6.4.5 Covariates

We controlled for potential confounding factors measured at the birth prior to the interval and included birth year, marital status, nulliparity, race/ethnicity and paternal age. Race/ethnicity was classified as Caucasian versus non-Caucasian. Marital status was categorised as married,

never married, widowed/divorced/ separated and unknown. Socio-economic status (SES) was derived by the Australian Bureau of Statistics Index of Relative Socio-economic Disadvantage at a geographic area for the maternal residence at the time of birth,[21] and categorised into quintiles.

6.4.6 Statistical analysis

We examined the association between IPI and each pregnancy complication in the overall population and stratified by maternal age categories at birth prior to the IPI (<20 years, 20 to 24 years, 25 to 29 years, 30 to 34 years, and 35 years or more) using Generalised linear models (GLM) fitted using a Poisson distribution with a log link function. We first tabulated the incidence of each pregnancy complication by IPI (categorised to <6, 6-11, 12-17, 18-23, 24-59, and ≥60 months). We modelled IPI as a continuous variable using restricted cubic splines to allow curvilinear shapes with knots placed at 3, 6, 12, 18, 24, 36 and 48 months of IPI. We predicted the absolute risk of each pregnancy complication in 1-month increments of IPI from 3 to 60 months using post estimation calculations.[22]

For each outcome, the unadjusted model included the IPI spline terms only, and the adjusted model included covariates measured at birth prior to IPI: birth year, nulliparity, SES, marital status, race/ethnicity and paternal age. All the unstratified models were also adjusted for maternal age at birth prior to the IPI. To examine the potential variability of the relationship between IPI and each pregnancy complication by maternal age category, we estimated the predicted absolute risk at population-representative and relevant covariates values at birth prior to IP. The predicted risks were estimated at the lowest risk values of all covariates for the low-risk group (nulliparous, Caucasian, married, least disadvantaged SES, birth year set to 2010 at birth prior to the IPI and at higher risk values of the covariates for high-risk groups (non-nulliparous, Caucasian, non-married, highly disadvantaged SES and birth year set to 2010 at birth prior to the IPI) separately. We then plotted the predicted risks with 95% CIs at 1-month increments of IPI for the whole cohort and stratified by maternal age group to illustrate the shapes of the risk curves. For tabulated results, we presented relative risks (RRs) with 95% CIs at 3, 6, 12, 24, 36, 48 and 60 months of IPI, with 18 months as the reference group. Robust variance estimation was used to account for non-dependence of more than two IPIs for the same women.[23]

6.4.7 Missing data

Because the proportion of missing data was small (range 0.04% for maternal age to 1.2% for SES), we carried out a complete case analysis. The majority of missing data was due to lack of availability of information (e.g. SES) prior to the year 1997, and we evaluated this bias using sensitivity analyses.

6.4.8 Sensitivity analyses

We conducted a sensitivity analysis for the component outcomes of APH-composite, which includes placenta praevia, abruptio placentae and unspecified APH (Supplemental Table 6-2). To ascertain the sensitivity of our results to higher-order parity, we conducted a separate analysis restricted to mothers who were nulliparous at the index pregnancy. (Supplemental Table 6-3) We further included a sensitivity analysis restricted to consecutive births after the year 1997 for which more information on potential confounders including paternal age, fertility treatment (assuming that these pregnancies were more likely to be intended), and smoking were available for adjustment.[18] (Supplemental Table 6-4). We used E-values to estimate the minimum strength of association, on the risk ratio scale, that any unmeasured confounder would need to have with both IPI and each pregnancy complication to fully explain away the observed association, conditional on the measured covariates.[24] (Supplemental Table 6-5). All analyses were performed using STATA version 16.1 (Stata Corporation, College Station, Texas, USA).

6.4.9 Ethical approval

This research was approved by the Human Research Ethics Committee (2016/51) from the Department of Health, WA.

6.5 RESULTS

Cohort description

Approximately 5% of births occurred after an IPI of <6 months, 15% after 18-23 months and 10% after 60 or more months. One-third of pregnancies were to mothers of age 25-29 years at birth prior to IPI (139,756 [32.5%], 95,369 (22%) were to mothers younger than 20 years, and 17,021 (4%) were to mothers older than 35 years at birth before the IPI (Table 6-1).

At study entry (before the IPI), a greater proportion of mothers were nulliparous, socio-economically disadvantaged, married, and Caucasian. There were also more smokers and socio-economically disadvantaged mothers in the short (<6 months) and long IPI (≥24 months)

categories than other IPI categories. Aboriginal/TSI mothers were highly represented in the less than 6-month IPI category. During the study period, we observed a decreasing trend in the intervals shorter than two years and a relatively increasing trend for intervals longer than 2 years (Table 6-1).

IPI distribution

The distribution of IPI differed by maternal age at birth prior to IPI. For mothers younger than 20 years at birth prior to IPI compared to mothers older than 35 years, short IPIs (<6 months) were more common (8.0% vs 5.3%). However, for mothers older than 35 years, long IPI (≥60 months) were less common as compared to mothers younger than 20 years at birth prior to IPI (2% vs 16%) (Supplemental Figure 6-1).

Incidence of pregnancy complications by IPI category

The overall incidences of preeclampsia, gestational hypertension, gestational diabetes, APH, and PROM were 3.9%, 1.9%, 3.4%, 5.1% and 5.3%, respectively (Table 6-2). Associations between IPI and APH or PROM followed a U-shaped curve; this trend was less apparent for preeclampsia, gestational hypertension and gestational diabetes (Figure 6-1). The lowest incidence for IPIs at 12-17 months for APH and PROM, and at 6-11 months for the other outcomes. Incidences were relatively higher after IPIs <6 months and ≥ 24 months (Table 6-2). For younger mothers, APH and PROM incidence were generally higher compared to mothers older than 35 years. In contrast, for older mothers, the incidence of gestational diabetes and gestational hypertension were higher as compared to younger mothers at birth before the IPI (Table 6-2).

IPI and risk of pregnancy complications prior to age stratification

Prior to age-stratification, harmful associations were most pronounced for shorter IPIs for pre-eclampsia (RR 1.09, 95% CI 1.00, 1.18), APH (RR 1.24, 95% CI 1.16, 1.32), and PROM (RR 1.14, 95% CI 1.07, 1.22) at three months of IPI compared to 18 months (Table 6-3). In contrast, harmful associations were most pronounced for longer intervals for gestational hypertension (RR 1.62, 95% CI 1.51, 1.73) and gestational diabetes (RR 1.97, 95% CI 1.89, 2.06) at 60 months of IPI compared to 18 months. For these complications, there was relatively more evidence that shorter IPIs of less than 18 months was associated with lower risk than at IPIs of 18 months.

IPI and risk of pregnancy complications by age

After age stratification, associations between shorter IPIs of <6 months and gestational hypertension and gestational diabetes were inconsistent across age groups (Table 6-3). However, for APH and PROM, adverse associations with short intervals was relatively more consistent across age groups. Risks of all complications after intervals longer than 24 to 36 months were consistently higher than those for intervals of 18 months, with some evidence of stronger associations with preeclampsia and APH for older mothers (30-34 years, ≥35 years) than mothers in the other younger age groups.

We observed an increased risk of preeclampsia at shorter IPIs with RR (1.31, 95% CI 1.00, 1.71) for mothers 35 years or older, but not for mothers younger than 20 years (RR 0.84, 95% CI 0.73, 0.95) for IPIs of 6 months compared to 18 months. Interestingly, no increased risks of gestational hypertension (RR 0.72, 95% CI 0.59, 0.87) and gestational diabetes (RR 0.73, 95% CI 0.62, 0.86) were observed at 6 months IPI compared to 18 months IPI for mothers younger than 20 years at birth before the IPI. The increased risk of preeclampsia (PE) at longer IPIs was more pronounced at 60 months for mothers older than 35 years (RR_{PE} 1.73, 95% CI 1.33, 2.25) than mothers younger than 20 years at birth prior to the IPI (RR_{PE} 1.20, 95% CI 1.08, 1.33).

Similarly, the increased risk of gestational hypertension and gestational diabetes at longer IPI (60 months) was more pronounced for mothers aged 30-34 years (RR_{GH} 1.82, 95% CI 1.57, 2.18; RR_{GDM} 2.02, 95% CI 1.84, 2.22) than mothers younger than 20 years (RR_{GH} 1.37, 95% CI 1.19, 1.57; RR_{GDM} 1.70, 95% CI 1.52, 1.91), respectively.

Table 6-1 Characteristics of the study population at birth prior to IPI for all births to mothers with at least two consecutive births by IPI (N=430,615 pregnancies) – WA, 1980-2015

Characteristics		Interpregnancy Interval, No. (%) of pregnancies						
		All	**<6**	**6-11**	**12-17**	**18-23**	**24-59**	**>=60**
		All (N=430615)	**(n=23,041)**	**(n=70,372)**	**(n=86,522)**	**(n=67,760)**	**(n=141,541)**	**(n=41,379)**
Maternal age, y	<20	95,369 (22.1)	7,567 (32.8)	14,789 (21.0)	14,945 (17.3)	11,612 (17.1)	31,235 (22.1)	15,221 (36.8)
	20-24	105,034 (24.4)	6,002 (26.0)	16,914 (24.0)	19,670 (22.7)	15,394 (22.7)	34,281 (24.2)	12,773 (30.9)
	25-29	139,756 (32.5)	5,683 (24.7)	22,348 (31.8)	30,145 (34.8)	24,098 (35.6)	47,413 (33.5)	10,069 (24.3)
	30-34	73,435 (17.1)	2,894 (12.6)	12,695 (18.0)	17,461 (20.2)	13,649 (20.1)	23,753 (16.8)	2,983 (7.2)
	≥35	17,021 (3.9)	895 (3.9)	3,626 (5.2)	4,301 (5.0)	3,007 (4.4)	4,859 (3.4)	333 (0.8)
Nulliparity		391593 (90.9)	20,375 (88.4)	63,680 (90.5)	79,399 (91.8)	62,390 (92.1)	128,934 (91.1)	36,815 (89.0)
Time period	1980-1984	76,752 (17.8)	4,157 (18.0)	12,288 (17.5)	15,180 (17.5)	11,643 (17.2)	24,855 (17.6)	8,629 (20.9)
	1985-1989	66,201 (15.4)	3,522 (15.3)	11,043 (15.7)	13,083 (15.1)	9,970 (14.7)	21,435 (15.1)	7,148 (17.3)
	1990-1994	65,468 (15.2)	3,456 (15.0)	9,987 (14.2)	12,179 (14.1)	9,731 (14.4)	22,140 (15.6)	7,975 (19.3)
	1995-1999	63,337 (14.7)	3,165 (13.7)	9,533 (13.5)	11,601 (13.4)	9,355 (13.8)	21,523 (15.2)	8,160 (19.7)
	2000-2004	60,828 (14.1)	3,032 (13.2)	9,393 (13.3)	11,399 (13.2)	9,415 (13.9)	21,351 (15.1)	6,238 (15.1)
	2005-2009	63,494 (14.7)	3,305 (14.3)	10,515 (14.9)	13,520 (15.6)	10,841 (16.0)	22,097 (15.6)	3,216 (7.8)
	2010-2015	34,535 (8.0)	2,404 (10.4)	7,613 (10.8)	9,560 (11.0)	6,805 (10.0)	8,140 (5.8)	13 (0.0)
SES in quintiles	<20 percentile (most disadvantaged)	94,845 (22.0)	6,797 (29.5)	15,595 (22.2)	17,047 (19.7)	13,151 (19.4)	30,745 (21.7)	11,510 (27.8)
	20-39 percentile	92,929 (21.6)	5,464 (23.7)	15,234 (21.6)	17,886 (20.7)	13,908 (20.5)	30,495 (21.5)	9,942 (24.0)
	40-59 percentile	87,434 (20.3)	4,507 (19.6)	14,150 (20.1)	17,588 (20.3)	14,024 (20.7)	28,983 (20.5)	8,182 (19.8)
	60-79 percentile	81,247 (18.9)	3,566 (15.5)	13,336 (19.0)	17,183 (19.9)	13,566 (20.0)	26,814 (18.9)	6,782 (16.4)
	≥80 percentile (least disadvantaged)	74,160 (17.2)	2,707 (11.7)	12,057 (17.1)	16,818 (19.4)	13,111 (19.3)	24,504 (17.3)	4,963 (12.0)
Marital status	Married	355504 (82.6)	17,309 (75.1)	59,217 (84.1)	75,054 (86.7)	58,589 (86.5)	116,562 (82.4)	28,773 (69.5)
	Never married	71383 (16.6)	5,471 (23.7)	10,510 (14.9)	10,831 (12.5)	8,658 (12.8)	23,734 (16.8)	12,179 (29.4)
	Widowed, divorced, separated	2556 (0.6)	195 (0.8)	415 (0.6)	378 (0.4)	313 (0.5)	886 (0.6)	369 (0.9)
	Unknown	1172 (0.3)	66 (0.3)	230 (0.3)	259 (0.3)	200 (0.3)	359 (0.3)	58 (0.1)
Race/Ethnicity	Caucasian	362697 (84.2)	17,641 (76.6)	59,036 (83.9)	74,215 (85.8)	58,563 (86.4)	118,850 (84.0)	34,392 (83.1)
	Aboriginal/TSI	30725 (7.1)	3,038 (13.2)	5,204 (7.4)	5,432 (6.3)	3,976 (5.9)	9,682 (6.8)	3,393 (8.2)
	Asian [a]	12784 (3.0)	634 (2.8)	1,939 (2.8)	2,538 (2.9)	1,967 (2.9)	4,787 (3.4)	919 (2.2)
	African	2450 (0.6)	150 (0.7)	524 (0.7)	536 (0.6)	347 (0.5)	770 (0.5)	123 (0.3)
	Others [b]	21959 (5.1)	1,578 (6.8)	3,669 (5.2)	3,801 (4.4)	2,907 (4.3)	7,452 (5.3)	2,552 (6.2)
Fertility treatment [c]		5340 (1.3)	17,641 (76.6)	59,036 (83.9)	74,215 (85.8)	58,563 (86.4)	118,850 (84.0)	34,392 (83.1)
Smoking [d]		29310 (15.6)	2,637 (26.0)	4,790 (15.1)	4,663 (11.8)	3,876 (12.4)	9,911 (16.1)	3,433 (26.1)

[a] including Indian; [b] including Polynesian & Maori; [c] fertility treatment information missing for 190169 (44.2%); [d] smoking information missing for 242960 (56.4%)

Optimal IPI

For mothers of all ages, risks were minimal at intervals of approximately 12 months for APH and PROM and at intervals of 6 months for preeclampsia, gestational hypertension, and gestational diabetes (Figure 6-1, Supplemental Table 6-2). However, Optimal IPI varied by maternal age prior to the IPI (Figure 6-2). For mothers older than 35 years, risks were lowest for intervals between 12 and 18 months for preeclampsia, at 12 months for APH, between 6 and 12 months for gestational hypertension and PROM, and less than 12 months for gestational diabetes. For mothers at other ages, the intervals at which risks were lowest were less clear but appeared to be between 6 and 18 months. At all ages, risks of preeclampsia, gestational hypertension, and gestational diabetes for mothers with intervals longer than 24 months were generally as high or higher than those for mothers with intervals at six months.

For mothers younger than 20 years, risks of APH and PROM for mothers with intervals longer than 36 months were generally as high or higher than those with intervals of 6 months (Figure 6-2,Supplemental Table 6-6).

We estimated the predicted absolute risk of each outcome according to IPI for all mothers and by maternal age, calculated at representative values of each risk factor (Figure 6-1 & Figure 6-2). These graphs can inform optimal IPI by comparing estimated risks of each outcome based on mothers age category and risk profile (Supplemental Figure 6-2, Supplemental Figure 6-3, Supplemental Figure 6-4, below). For example, mothers younger than 20 years at prior birth with a low-risk profile and IPI of 6 months have predicted risk of 1.2% for preeclampsia, 2.1% for gestational hypertension, 2.1% for gestational diabetes, 6.4% for APH and 7.3% for PROM. These predicted risks can be compared with risks among mothers older than 35 years with the same IPI (6 months), who have predicted risks of 2.4% for preeclampsia, 2.0% for gestational hypertension, 5.8% for gestational diabetes, 5.4% for APH and 4.1% for PROM.

The pattern of the effect of IPI on pregnancy complications do not differ by maternal age in both mothers with low and high-risk profiles. However, mothers with advanced maternal age at birth prior to the IPI had markedly higher risks of gestational diabetes and preeclampsia. In comparison, APH and PROM risks were higher for younger women across the IPI continuum than mothers from other age groups (Figure 6-2,Supplemental Table 6-6).

Table 6-2 Counts and percentages of outcomes by IPI, stratified by maternal age at birth prior to IPI (N=430,615 pregnancies) – WA, 1980-2015

	Interpregnancy Interval, No. (%) of pregnancies						
	All	<6mo	6-11mo	12-17mo	18-23mo	24-59mo	≥60mo
Preeclampsia							
All mothers	16,893 (3.9)	879 (3.8)	2,425 (3.4)	3,024 (3.5)	2,479 (3.6)	5,809 (4.1)	2,277 (5.5)
<20	3,850 (4.0)	249 (3.3)	532 (3.6)	610 (4.1)	428 (3.7)	1,250 (4.0)	781 (5.1)
20-24	4,548 (4.3)	229 (3.8)	643 (3.8)	804 (4.1)	655 (4.3)	1,518 (4.4)	699 5.5)
25-29	5,384 (3.8)	245 (4.3)	756 (3.4)	978 (3.2)	867 (3.6)	1,941 (4.1)	597 (5.9)
30-34	2,486 (3.4)	112 (3.8)	373 (2.9)	515 (2.9)	426 (3.1)	884 (3.7)	176 (5.9)
≥35	625 (3.7)	44 (4.9)	121 (3.3)	117 (2.7)	103 (3.4)	216 (4.4)	24 (7.2)
Gestational hypertension							
All mothers	8,124 (1.9)	351 (1.5)	1,026 (1.5)	1,421 (1.6)	1,179 (1.7)	2,963 (2.1)	1,184 (2.8)
<20	1,921 (2.0)	95 (1.3)	224 (1.5)	259 (1.7)	216 (1.8)	684 (2.2)	443 (2.9)
20-24	1,969 (1.9)	90 (1.5)	266 (1.6)	289 (1.5)	279 (1.8)	689 (2.0)	356 (2.8)
25-29	2,478 (1.7)	92 (1.6)	276 (1.2)	463 (1.5)	392 (1.6)	966 (2.0)	289 (2.8)
30-34	1,366 (1.9)	52 (1.8)	194 (1.5)	315 (1.8)	219 (1.6)	503 (2.1)	83 (2.8)
≥35	390 (2.3)	22 (2.5)	66 (1.8)	95 (2.2)	73 (2.4)	121 (2.5)	13 (3.9)
Gestational diabetes							
All mothers	17,018 (3.4)	766 (3.3)	2,071 (2.9)	2,758 (3.2)	2,336 (3.5)	6,193 (4.4)	2,894 (7.0)
<20	3,251 (3.4)	164 (2.2)	302 (2.0)	363 (2.4)	339 (2.9)	1,143 (3.6)	940 (6.2)
20-24	3,317 (3.2)	161 (2.7)	363 (2.2)	430 (2.2)	383 (2.5)	1,129 (3.3)	851 (6.6)
25-29	5,183 (3.7)	202 (3.5)	614 (2.7)	859 (2.8)	714 (3.0)	2,027 (4.3)	767 (7.6)
30-34	3,989 (5.4)	179 (6.2)	563 (4.4)	808 (4.6)	661 (4.8)	1,485 (6.3)	293 (9.8)
≥35	1,278 (7.5)	60 (6.7)	229 (6.3)	298 (6.9)	239 (7.9)	409 (8.4)	43 (12.9)
Antepartum haemorrhage (APH) composite [a]							
All mothers	21,854 (5.1)	1,350 (5.8)	3,287(4.7)	3,905(4.5)	3,233 (4.7)	7,550 (5.3)	2,529 (6.1)
<20	5,982 (6.3)	484 (6.4)	921 (6.2)	867 (5.8)	707 (6.1)	2,095 (6.7)	908 (6.0)
20-24	5,369 (5.1)	316 (5.3)	784 (4.6)	889 (4.5)	778 (5.1)	1,784 (5.2)	818 (6.4)
25-29	6,135 (4.4)	317 (5.6)	851 (3.8)	1,214 (4.0)	991 (4.1)	2,164 (4.6)	598 (5.9)
30-34	3,458 (4.7)	183 (6.3)	555 (4.4)	728 (4.2)	594 (4.4)	1,210 (5.1)	188 (6.3)
≥35	910 (5.4)	50 (5.6)	176 (4.8)	207 (4.8)	163 (5.4)	297 (6.1)	17 (5.1)
PROM [b]							
All mothers	22,908 (5.3)	1,413 (6.1)	3,256 (4.6)	4,006 (4.6)	3,226 (4.7)	7,918 (5.6)	3,089 (7.5)
<20	7,217 (7.6)	571 (7.6)	1,054 (7.1)	1,066 (67.1)	842 (7.3)	2,362 (7.6)	1,322 (8.7)
20-24	5,377 (5.1)	368 (6.1)	706 (4.2)	871 (4.43)	713 (4.6)	1,835 (5.4)	884 (6.9)
25-29	6,041 (4.3)	277 (4.8)	817 (3.6)	1,073 (3.5)	957 (3.9)	2,235 (4.7)	682 (6.7)
30-34	3,437 (4.7)	148 (5.1)	520 (4.1)	802 (4.6)	565 (4.1)	1,219 (5.1)	183 (6.1)
≥35	836 (4.9)	49 (5.5)	159 (4.4)	194 (4.5)	149 (4.9)	267 (5.5)	18 (5.4)

[a] composite outcome of placental abruption, placenta previa and antepartum haemorrhage unspecified; [b] Premature rupture of membrane

Sensitivity analyses

Our results were not sensitive to the definition of the composite outcome for APH, which included placenta previa, abruptio placenta and unspecified APH (Supplemental Table 6-1,Supplemental Table 6-2). The results of our sensitivity analysis restricted to nulliparous mothers were consistent with those obtained from our primary analyses (Supplemental Table 6-3). We observed little difference in the associations between IPI and pregnancy complications when we restricted our cohort to births from September 1997 (Supplemental Table 6-4). The E-values for the observed relative risk for these pregnancy complications varied from 1.10 to 2.30 for short and 1.16 to 3.72 for long IPIs, which indicated considerable unmeasured confounders would need to negate the observed associations (Supplemental Table 6-5).

6.6 DISCUSSION

6.6.1 Principal findings

In this large population-based cohort, we observed an increased risk of APH and PROM after short IPIs (<6 months); and increased risk for the majority of the pregnancy complications following long IPIs (>36 months), and these findings persisted after stratification by age. Very short IPIs were associated with a higher risk of APH and PROM complications, with effects slightly higher for younger age groups. Similarly, long IPIs were associated with an elevated risk of HDPs, and GDM among mothers older than 35 years compared to younger mothers at birth prior to the IPI. We observed a protective association of shorter IPIs (<6 months) for preeclampsia, gestational hypertension, and gestational diabetes for mothers younger than 20 years. Generally, the predicted risks following short or long IPIs for APH and PROM were lower at advanced maternal age than at younger ages but higher at advanced maternal age than at younger ages for HDPs, or GDM.

6.6.2 Strengths of the study

This large cohort was sourced from highly reliable population-based perinatal information spanning more than three decades (1980-2015). Examining the non-linear relationships between IPI and various pregnancy complications for each maternal age group before the interval and presenting absolute risks, which previously have not been well studied, allowed us to clearly observe the presence of a “dose-response” relationship and better clarification of optimal IPI.

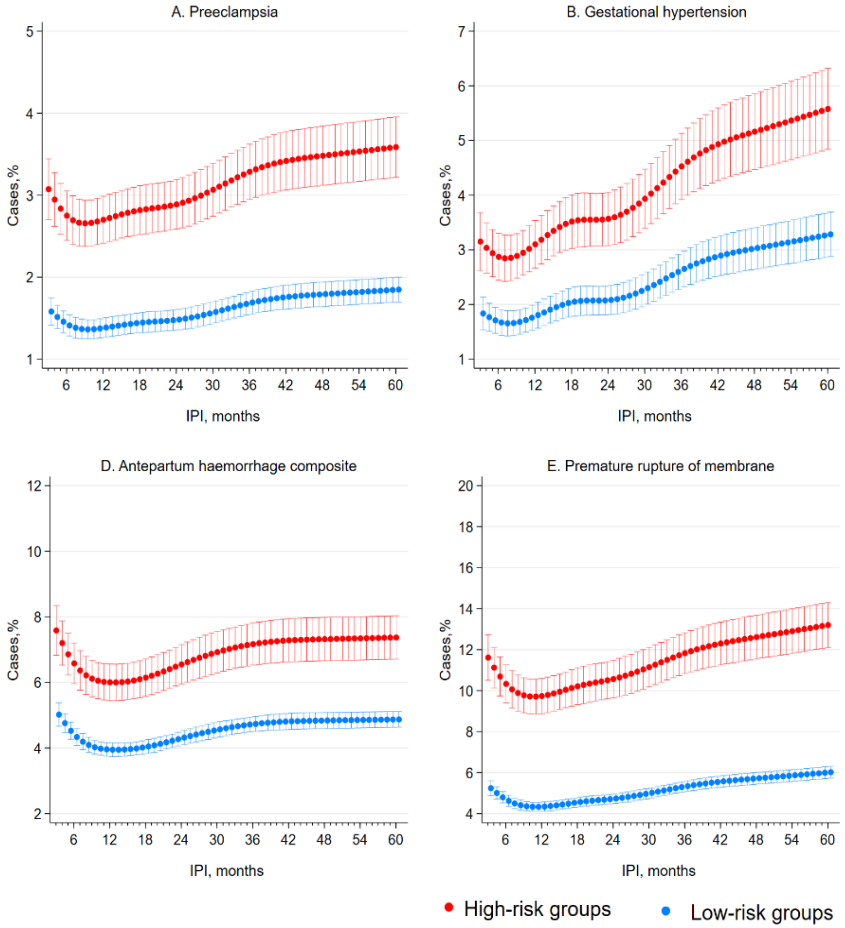


Figure 6-1 Predicted absolute risk of pregnancy complications with 95 % confidence intervals according to IPI for all mothers.

Predicted absolute risks for low-risk group are reported at representative values of covariates: nulliparous, Caucasian, married, least-disadvantaged SES, average maternal age (25-29 years) and birth year in 2010 at birth prior to the IPI; Predicted risks for high-risk group are reported at representative values of covariates: non-nulliparous, non-Caucasian, non-married, highly disadvantaged SES, advanced maternal age (≥35 years) and birth year in 2010 at birth prior to the IPI; nulliparity at birth prior to the IPI included in the high-risk group for preeclampsia and gestational hypertension.

Our findings provide more clinically applicable information on the effect of different IPI values on the risk of various pregnancy complications according to maternal age.

6.6.3 Limitations of the data

Like other observational studies, our study was limited by the potential for unmeasured or residual confounding factors that we were unable to due to lack of availability. However, our sensitivity analyses revealed that substantial unmeasured confounding would be required to fully explain the observed associations (Supplemental Table 6-5). As ultrasound was less common during the earlier periods of our cohort, diagnoses of the uteroplacental bleeding disorders included in our study may have been subject to a degree of misclassification. However, results from our sensitivity analysis restricted to births after 1997 did not meaningfully change our estimates.

6.6.4 Interpretation

Regardless of age, for many of the pregnancy complications included in the study, we demonstrated risks were minimal at intervals of approximately 6-12 months and not substantially higher at around 24 months, after which the risk increased. Specifically, APH and PROM have U-shaped associations with IPI for all maternal ages, and the optimal IPIs were at approximately 12 months. However, the U-shaped association was less clear for preeclampsia, gestational hypertension, and gestational diabetes. We observed minimal risks at intervals of around 6 months for preeclampsia, gestational hypertension, and gestational diabetes. Mothers older than 35 years had minimal risk at 12 months for APH, between 6 and 12 months for gestational hypertension and PROM, less than 12 months for gestational diabetes, and around 12 and 18 months for preeclampsia. This finding was consistent with a recent finding from the US, which indicated a relatively shorter IPI of 12-24 months found to have a lesser risk of outcomes for women of all ages.[13]

However, the observed pattern was slightly different for mothers younger than 20 years for preeclampsia, for whom risks were lower at six months and started to rise up to around 12 months. The reason to explain this observation remains unclear.

Table 6-3 Adjusted Relative Risk (RRs) comparing estimated risks of each outcome at 3, 6, 12, 18, 24, 36, 48, and 60 months of IPI with estimated risks following 18 months intervals to mothers with at least two consecutive births during the study period (n=430,615 pregnancies)

	Interpregnancy Interval, RR (95% CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
Preeclampsia								
All mothers	1.09 (1.00, 1.18)	0.98 (0.92, 1.04)	0.96 (0.90, 1.02)	1.00 (Reference)	1.03 (0.98, 1.07)	1.17 (1.12, 1.23)	1.24 (1.19, 1.30)	1.28 (1.22, 1.34)
<20	0.97 (0.83, 1.13)	0.84 (0.73, 0.95)	1.06 (0.93, 1.21)	1.00 (Reference)	0.97 (0.87, 1.08)	1.10 (0.99, 1.23)	1.17 (1.05, 1.30)	1.20 (1.08, 1.33)
20, 24	1.03 (0.88, 1.21)	0.94 (0.83, 1.05)	1.01 (0.90, 1.13)	1.00 (Reference)	1.03 (0.94, 1.13)	1.14 (1.04, 1.25)	1.19 (1.09, 1.30)	1.23 (1.12, 1.34)
25-29	1.20 (1.03, 1.39)	1.07 (0.96, 1.18)	0.90 (0.82, 1.00)	1.00 (Reference)	1.04 (0.96, 1.12)	1.19 (1.09, 1.29)	1.28 (1.18, 1.39)	1.33 (1.23, 1.44)
30-34	1.12 (0.90, 1.40)	0.98 (0.85, 1.14)	0.88 (0.77, 1.02)	1.00 (Reference)	1.01 (0.90, 1.13)	1.15 (1.02, 1.30)	1.27 (1.12, 1.43)	1.36 (1.21, 1.53)
≥35	1.44 (0.96, 2.15)	1.31 (1.00, 1.71)	0.95 (0.71, 1.27)	1.00 (Reference)	1.31 (1.05, 1.65)	1.33 (1.02, 1.73)	1.46 (1.13, 1.88)	1.73 (1.33, 2.25)
Gestational hypertension								
All mothers	0.89 (0.78, 1.01)	0.81 (0.74, 0.89)	0.88 (0.80, 0.96)	1.00 (Reference)	1.02 (0.95, 1.09)	1.30 (1.21, 1.40)	1.49 (1.39, 1.60)	1.62 (1.51, 1.73)
<20	0.67 (0.52, 0.85)	0.72 (0.59, 0.87)	0.91 (0.75, 1.11)	1.00 (Reference)	1.05 (0.90, 1.22)	1.17 (1.00, 1.37)	1.27 (1.10, 1.47)	1.37 (1.19, 1.57)
20-24	0.84 (0.65, 1.08)	0.86 (0.71, 1.03)	0.80 (0.67, 0.96)	1.00 (Reference)	0.97 (0.84, 1.11)	1.16 (1.00, 1.34)	1.34 (1.17, 1.55)	1.48 (1.29, 1.69)
25-29	1.04 (0.85, 1.31)	0.78 (0.66, 0.93)	0.82 (0.71, 0.96)	1.00 (Reference)	1.01 (0.90, 1.14)	1.42 (1.26, 1.61)	1.70 (1.51, 1.92)	1.87 (1.66, 2.10)
30-34	1.14 (0.82, 1.57)	0.92 (0.75, 1.14)	1.06 (0.88, 1.28)	1.00 (Reference)	1.08 (0.93, 1.26)	1.42 (1.20, 1.69)	1.65 (1.40, 1.95)	1.82 (1.57, 2.18)
≥35	1.18 (0.70, 1.98)	0.74 (0.52, 1.06)	0.82 (0.58, 1.16)	1.00 (Reference)	0.89 (0.67, 1.19)	1.07 (0.77, 1.48)	1.30 (0.95, 1.79)	1.51 (1.06, 2.15)
Gestational diabetes								
All mothers	0.98 (0.90, 1.07)	0.90 (0.84, 0.96)	0.91 (0.86, 0.97)	1.00 (Reference)	1.11 (1.06, 1.16)	1.46 (1.39, 1.54)	1.73 (1.65, 1.81)	1.97 (1.89, 2.06)
<20	0.70 (0.58, 0.85)	0.73 (0.62, 0.86)	0.78 (0.66, 0.91)	1.00 (Reference)	1.10 (0.98, 1.24)	1.33(1.18, 1.51)	1.53 (1.36, 1.71)	1.70 (1.52, 1.91)
20-24	0.94 (0.78, 1.14)	0.90 (0.78, 1.04)	0.93 (0.80, 1.08)	1.00 (Reference)	1.08 (0.96, 1.21)	1.47 (1.31, 1.66)	1.78 (1.58, 2.00)	2.04 (1.81, 2.31)
25-29	1.09 (0.92, 1.28)	0.96 (0.85, 1.07)	0.91 (0.82, 1.02)	1.00 (Reference)	1.10 (1.02, 1.20)	1.58 (1.45, 1.72)	1.90 (1.75, 2.07)	2.15 (1.99, 2.33)
30-34	1.37 (1.16, 1.62)	1.00 (0.89, 1.13)	1.00 (0.89, 1.12)	1.00 (Reference)	1.15 (1.06, 1.26)	1.52 (1.38, 1.67)	1.78 (1.62, 1.95)	2.02 (1.84, 2.22)
≥35	0.85 (0.62, 1.17)	0.79 (0.65, 0.96)	0.89 (0.74, 1.06)	1.00 (Reference)	1.11 (0.96, 1.29)	1.12 (0.94, 1.32)	1.29 (1.08, 1.53)	1.56 (1.29, 1.88)
Antepartum haemorrhage (APH) composite								

	Interpregnancy Interval, RR (95% CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
All mothers	1.24 (1.16, 1.32)	1.07 (1.01, 1.12)	0.98 (0.93, 1.03)	1.00 (Reference)	1.07 (1.02, 1.11)	1.16 (1.11, 1.21)	1.18 (1.14, 1.23)	1.19 (1.14, 1.24)
<20	1.15 (1.03, 1.29)	1.09 (0.99, 1.20)	1.01 (0.91, 1.12)	1.00 (Reference)	1.10 (1.02, 1.20)	1.14 (1.04, 1.25)	1.11 (1.02, 1.20)	1.08 (1.00, 1.17)
20-24	1.06 (0.92, 1.21)	1.02 (0.92, 1.13)	0.90 (0.81, 0.99)	1.00 (Reference)	1.03 (0.94, 1.11)	1.07 (0.98, 1.17)	1.12 (1.03, 1.21)	1.15 (1.06, 1.25)
25-29	1.47 (1.29, 1.67)	1.05 (0.96, 1.16)	1.01 (0.92, 1.11)	1.00 (Reference)	1.08 (1.01, 1.16)	1.17 (1.08, 1.27)	1.22 (1.13, 1.32)	1.27 (1.18, 1.37)
30-34	1.47 (1.23, 1.76)	1.12 (0.99, 1.26)	1.00 (0.89, 1.13)	1.00 (Reference)	1.04 (0.94, 1.14)	1.22 (1.10, 1.36)	1.31 (1.18, 1.45)	1.35 (1.21, 1.50)
≥35	1.13 (0.78, 1.62)	1.01 (0.80, 1.25)	0.95 (0.76, 1.18)	1.00 (Reference)	1.10 (0.91, 1.33)	1.25 (1.01, 1.55)	1.26 (1.02, 1.56)	1.23 (0.94, 1.61)
PROM								
All mothers	1.14 (1.07, 1.22)	1.01 (0.96, 1.07)	0.95 (0.91, 1.00)	1.00 (Reference)	1.04 (1.00, 1.08)	1.18 (1.13, 1.23)	1.26 (1.21, 1.32)	1.33 (1.28, 1.38)
<20	0.98 (0.89, 1.09)	0.99 (0.90, 1.08)	0.92 (0.84, 1.01)	1.00 (Reference)	0.98 (0.91, 1.06)	1.02 (0.94, 1.10)	1.07 (0.99, 1.15)	1.12 (1.04, 1.20)
20-24	1.21 (1.06, 1.37)	0.98 (0.88, 1.08)	0.91 (0.82, 1.01)	1.00 (Reference)	1.02 (0.94, 1.11)	1.14 (1.05, 1.25)	1.24 (1.14, 1.35)	1.31 (1.21, 1.42)
25-29	1.29 (1.12, 1.48)	1.08 (0.98, 1.19)	0.94 (0.86, 1.04)	1.00 (Reference)	1.11 (1.03, 1.20)	1.30 (1.20, 1.41)	1.43 (1.32, 1.54)	1.55 (1.44, 1.67)
30-34	1.14 (0.94, 1.38)	0.98 (0.86, 1.11)	1.04 (0.93, 1.17)	1.00 (Reference)	1.02 (0.93, 1.13)	1.27 (1.14, 1.41)	1.37 (1.24, 1.52)	1.41 (1.27, 1.57)
≥35	1.25 (0.88, 1.78)	0.90 (0.71, 1.15)	1.02 (0.80, 1.28)	1.00 (Reference)	1.00 (0.82, 1.22)	1.30 (1.03, 1.62)	1.39 (1.12, 1.73)	1.39 (1.06, 1.83)

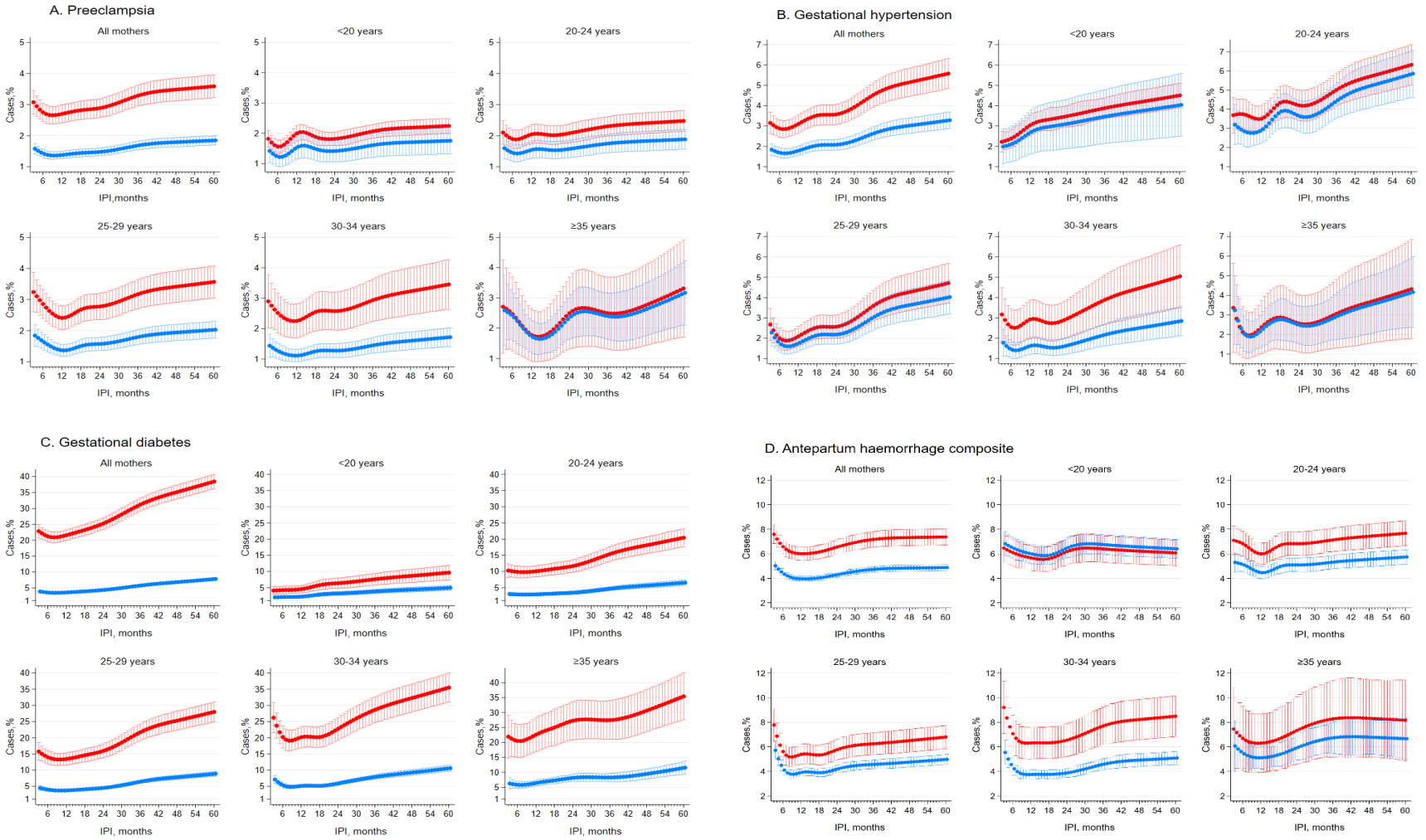
Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of IPI. Models were adjusted for SES, nulliparity, birth year, ethnicity, marital status birth prior to the IPI with risks estimated at population average values for 18-month IPI. All the unstratified models using the overall population were adjusted for maternal age.

Our results are supported by previous studies indicating short IPIs are associated with increased risk of pregnancy complications, including APH (placental abruption, placenta previa) and PROM,[6,25] and long IPIs associated with an elevated risk of the majority of pregnancy complications.[1,3,26] Unlike other studies,[1,14] our finding of protective associations with shorter IPIs for hypertensive disorders and gestational diabetes is consistent with a recent US study.[11]

In accordance with recent recommendations,[27] we adjusted for maternal age before the IPI. However, the observed increased risk of pregnancy complications for mothers with long IPIs can be confounded by maternal age at the time of the complication. Our findings indicate that as IPI exceeds one to two years, the influence of age begins to dominate the risks on the outcome. The consistent associations observed for all pregnancy complications at longer IPIs (>36 months) can be explained by confounding by maternal age at outcome of pregnancy.

6.6.5 Conclusions

Given the increasing trend in delayed childbearing, it is essential to evaluate whether the risks of pregnancy complications associated with IPI may be influenced by maternal age. For our cohort, associations between pregnancy complications and IPI varied by maternal age, with optimal IPI in the range of 6-18 months, which is shorter than those recommended. The current World Health Organization (WHO) and various regional clinical guidelines suggest at least 18-24 months before conceiving another child irrespective of other maternal characteristics. Our study challenges this “one size fits all” recommendation for an optimal IPI and suggests the optimal IPI may vary depending on the cohort's maternal age and risk profile. Hence, a more tailored approach to family planning counselling may be required to improve health.


A. Preeclampsia
All mothers
<20 years
20-24 years
25-29 years
30-34 years
≥35 years
B. Gestational hypertension
All mothers
<20 years
20-24 years
25-29 years
30-34 years
≥35 years
C. Gestational diabetes
All mothers
<20 years
20-24 years
25-29 years
30-34 years
≥35 years
D. Antepartum haemorrhage composite
All mothers
<20 years
20-24 years
25-29 years
30-34 years
≥35 years
Cases,%
IPI,months
IPI, months

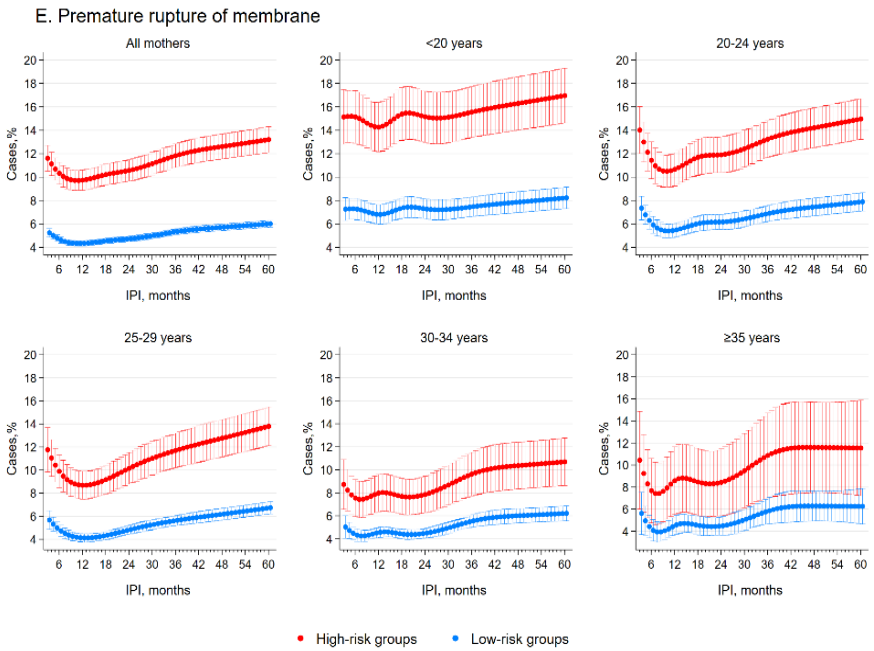


Figure 6-2 Predicted absolute risk of (95% CIs) of pregnancy complications according to IPI stratified by maternal age at birth prior to the IPI

Pregnancy complications include preeclampsia (A), gestational hypertension (B), gestational diabetes (C), antepartum haemorrhage composite (D) and premature rupture of membrane (E). Predicted risks for low-risk group are reported at representative values of covariates :nulliparous, Caucasian, married, least-disadvantaged SES and birth year in 2010 at birth prior to the IPI; Predicted risks for high-risk group are reported at representative values of covariates: non-nulliparous, non-Caucasian, non-married, highly disadvantaged SES and birth year in 2010 at birth prior to the IPI; nulliparity at birth prior to the IPI included in the high-risk group for preeclampsia and gestational hypertension; for the unstratified predictions (all mothers in the cohort) we used average maternal age (25-29 years) at birth prior to the IPI for low-risk group

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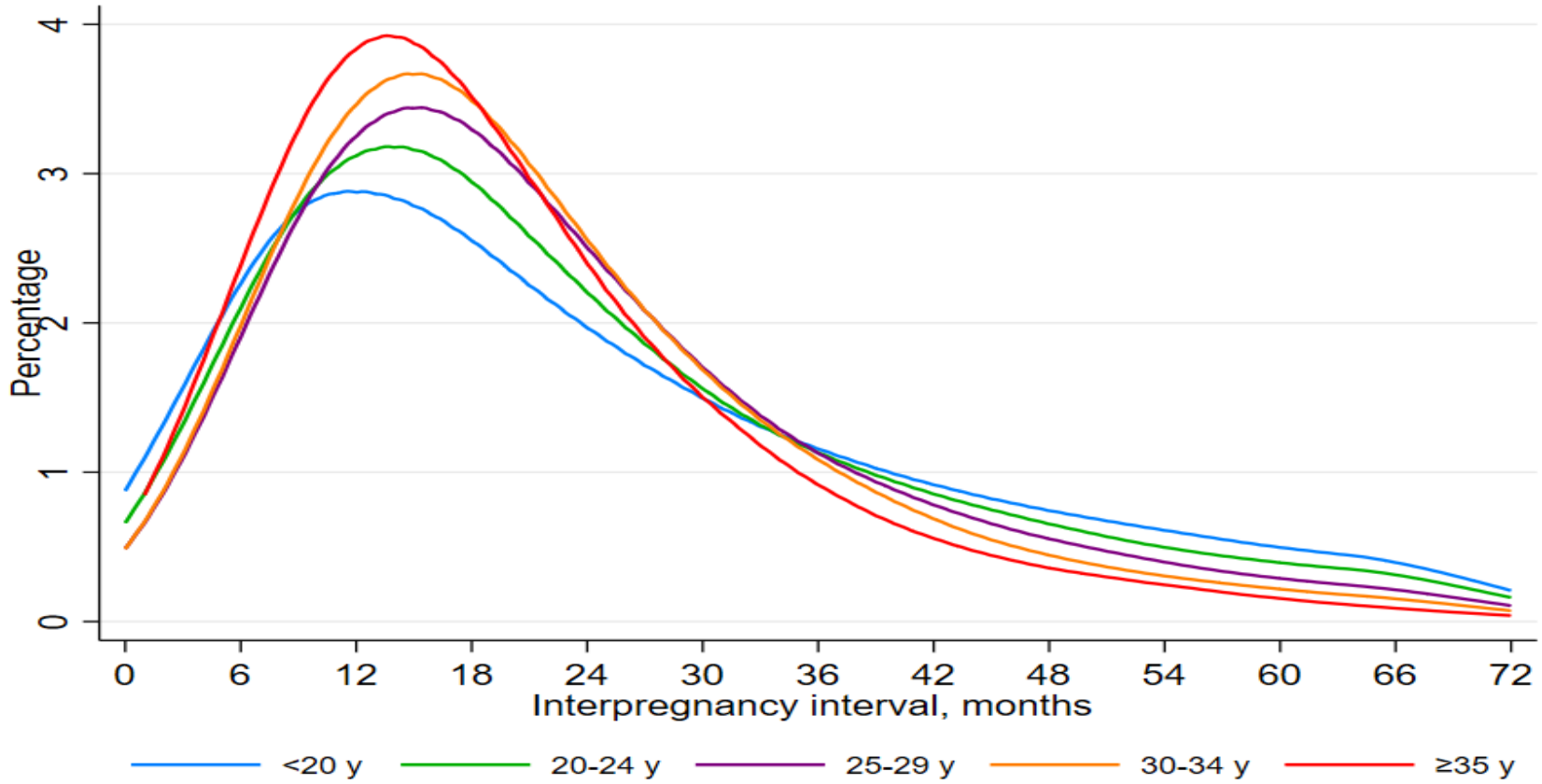
6.8 SUPPLEMENTARY MATERIAL



Supplemental Figure 6-1 Distribution of interpregnancy interval by maternal age at birth prior to IPI for mothers during the study period

Supplemental Table 6-1 Counts and percentages of outcomes according to Interpregnancy interval categories, stratified by maternal age at birth prior to IPI during the study period (n=430,615 pregnancies) – Western Australia, 1980-2015

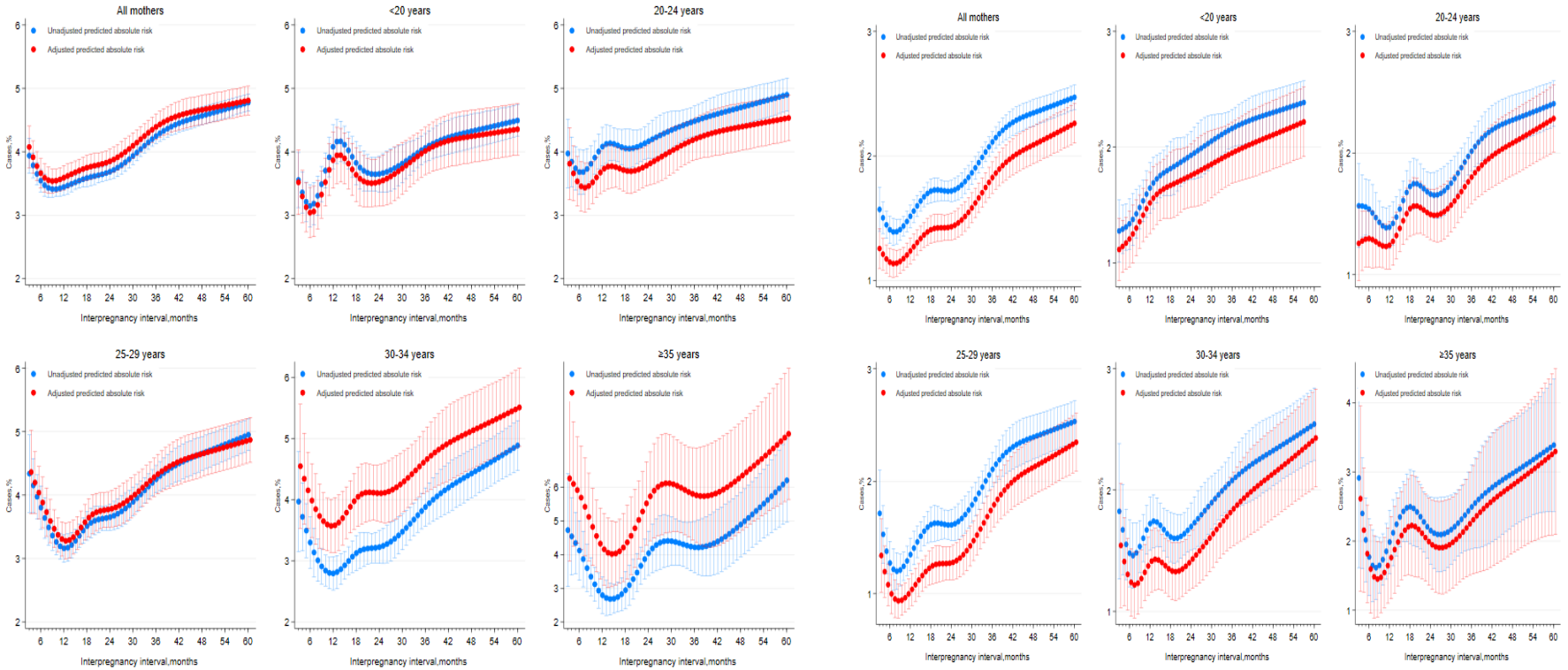
	All	<6mo	6-11mo	12-17mo	18-23mo	24-59mo	≥60mo
Placenta Previa							
All mothers	4780 (1.1)	251 (1.1)	649 (0.9)	815 (0.9)	740 (1.1)	1654 (1.2)	671 (1.6)
<20	978 (1.0)	72 (0.9)	149 (1.0)	126 (0.8)	106 (0.9)	320 (1.0)	205 (1.4)
20-24	1007 (1.0)	46 (0.7)	114 (0.7)	156 (0.8)	150 (0.9)	330 (1.0)	211 (1.6)
25-29	1518 (1.1)	79 (1.4)	204 (0.9)	278 (0.9)	255 (1.1)	517 (1.1)	185 (1.8)
30-34	976 (1.3)	44 (1.5)	127 (1)	198 (1.1)	174 (1.3)	373 (1.6)	60 (2.0)
≥35	301 (1.7)	10 (1.1)	55 (1.5)	57 (1.3)	55 (1.8)	114 (2.4)	10 (3.0)
Abruptio Placenta							
All mothers	3496 (0.8)	258 (1.1)	581 (0.8)	635 (0.7)	470 (0.7)	1165 (0.8)	387 (0.9)
<20	1013 (1.1)	90 (1.2)	177 (1.2)	131 (0.8)	113 (0.9)	351 (1.1)	151 (1.0)
20-24	899 (0.8)	63 (1.1)	155 (0.9)	153 (0.8)	116 (0.7)	282 (0.8)	130 (1.0)
25-29	973 (0.7)	56 (1.0)	143 (0.6)	218 (0.7)	138 (0.6)	334 (0.7)	84 (0.8)
30-34	504 (0.7)	36 (1.2)	84 (0.6)	114 (0.6)	93 (0.7)	159 (0.7)	18 (0.6)
≥35	107 (0.6)	13 (1.4)	22 (0.6)	19 (0.4)	10 (0.3)	39 (0.8)	4 (1.2)
Antepartum hemorrhage-unspecified							
All mothers	15966 (3.7)	1015 (4.4)	2405 (3.4)	2875 (3.3)	2417 (3.6)	5585 (3.9)	1669 (4.0)
<20	4651 (4.8)	381 (5.0)	714 (4.8)	695 (4.6)	584 (5.0)	1657 (5.3)	620 (4.1)
20-24	4000 (3.8)	243 (4.0)	588 (3.5)	681 (3.5)	596 (3.8)	1357 (4.0)	535 (4.2)
25-29	4349 (3.1)	228 (4.0)	590 (2.6)	866 (2.8)	714 (3.0)	1565 (3.3)	386 (3.8)
30-34	2356 (3.2)	125 (4.3)	400 (3.1)	486 (2.8)	404 (3.0)	819 (3.4)	122 (4.1)
≥35	610 (3.6)	38 (4.3)	113 (3.1)	147 (3.4)	119 (4.0)	187 (3.8)	6 (1.8)

Supplemental Table 6-2 Adjusted RRs comparing estimated risks of component outcomes of APH at 3, 6, 12, 18, 24, 36, 48, and 60 months of IPI with estimated risks following 18 months intervals to mothers with at least two births during the study period (n=430,615 pregnancies)

	Interpregnancy interval, RR (95% CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
Placenta Previa								
All mothers	1.14 (0.97, 1.32)	0.98 (0.87, 1.09)	0.86 (0.77, 0.96)	1.00 (Reference)	1.03 (0.94, 1.13)	1.17 (1.07, 1.28)	1.28 (1.17, 1.40)	1.37 (1.26, 1.50)
<20	1.07 (0.79, 1.46)	1.13 (0.88, 1.47)	0.95 (0.73, 1.24)	1.00 (Reference)	0.99 (0.80, 1.24)	1.15 (0.92, 1.43)	1.23 (1.00, 1.52)	1.28 (1.04, 1.56)
20-24	0.88 (0.62, 1.24)	0.73 (0.56, 0.96)	0.72 (0.55, 0.91)	1.00 (Reference)	0.98 (0.80, 1.18)	0.99 (0.80, 1.20)	1.10 (0.90, 1.34)	1.22 (1.00, 1.49)
25-29	1.48 (1.13, 1.95)	1.12 (0.92, 1.36)	0.89 (0.73, 1.08)	1.00 (Reference)	1.00 (0.86, 1.16)	1.13 (0.96, 1.33)	1.28 (1.09, 1.49)	1.41 (1.21, 1.63)
30-34	1.21 (0.84, 1.74)	0.86 (0.67, 1.10)	0.89 (0.70, 1.12)	1.00 (Reference)	1.05 (0.87, 1.25)	1.35 (1.10, 1.64)	1.48 (1.21, 1.79)	1.52 (1.24, 1.84)
≥35	0.81 (0.35, 1.84)	1.00 (0.66, 1.52)	0.84 (0.56, 1.28)	1.00 (Reference)	1.41 (1.02, 1.95)	1.48 (1.02, 2.16)	1.57 (1.09, 2.26)	1.77 (1.17, 2.68)
Abruptio Placenta								
All mothers	1.64 (1.40, 1.92)	1.35 (1.19, 1.54)	1.16 (1.02, 1.32)	1.00 (Reference)	1.14 (1.03, 1.27)	1.22 (1.09, 1.36)	1.20 (1.08, 1.34)	1.20 (1.08, 1.33)
<20	1.57 (1.19, 2.08)	1.46 (1.14, 1.86)	1.18 (0.91, 1.54)	1.00 (Reference)	1.34 (1.09, 1.66)	1.34 (1.07, 1.69)	1.24 (1.00, 1.54)	1.21 (0.98, 1.48)
20-24	1.33 (0.95, 1.87)	1.37 (1.07, 1.75)	1.20 (0.93, 1.55)	1.00 (Reference)	1.06 (0.86, 1.30)	1.14 (0.91, 1.42)	1.18 (0.95, 1.47)	1.24 (1.00, 1.53)
25-29	1.75 (1.27, 2.40)	1.27 (0.99, 1.61)	1.15 (0.91, 1.44)	1.00 (Reference)	1.06 (0.88, 1.29)	1.20 (0.98, 1.47)	1.22 (1.00, 1.48)	1.21 (1.00, 1.47)
30-34	2.00 (1.34, 3.00)	1.20 (0.87, 1.65)	1.05 (0.77, 1.43)	1.00 (Reference)	1.05 (0.81, 1.37)	1.03 (0.77, 1.37)	0.97 (0.73, 1.30)	0.93 (0.68, 1.25)
≥35	5.13 (2.31, 11.40)	2.17 (1.06, 4.44)	1.66 (0.82, 3.33)	1.00 (Reference)	1.62 (0.87, 3.01)	2.46 (1.26, 4.82)	2.44 (1.27, 4.69)	2.41 (1.14, 5.09)
APH unspecified								
All mothers	1.20 (1.11, 1.29)	1.03 (0.97, 1.09)	0.95 (0.89, 1.00)	1.00 (Reference)	1.05 (1.00, 1.10)	1.14 (1.08, 1.19)	1.13 (1.08, 1.19)	1.10 (1.05, 1.16)
<20	1.08 (0.95, 1.22)	1.02 (0.91, 1.14)	0.95 (0.85, 1.07)	1.00 (Reference)	1.08 (0.98, 1.18)	1.08 (0.97, 1.19)	1.02 (0.93, 1.12)	0.97 (0.89, 1.07)
20-24	1.07 (0.92, 1.25)	1.00 (0.88, 1.12)	0.88 (0.78, 0.99)	1.00 (Reference)	1.00 (0.91, 1.11)	1.07 (0.97, 1.18)	1.09 (0.99, 1.21)	1.09 (0.99, 1.20)
25-29	1.45 (1.24, 1.70)	0.98 (0.87, 1.11)	0.99 (0.89, 1.11)	1.00 (Reference)	1.09 (1.00, 1.19)	1.18 (1.07, 1.29)	1.20 (1.09, 1.31)	1.22 (1.12, 1.33)
30-34	1.47 (1.18, 1.82)	1.20 (1.03, 1.39)	0.99 (0.86, 1.15)	1.00 (Reference)	1.04 (0.92, 1.17)	1.20 (1.05, 1.36)	1.27 (1.12, 1.45)	1.32 (1.15, 1.50)
≥35	1.08 (0.71, 1.65)	0.91 (0.70, 1.19)	0.88 (0.67, 1.15)	1.00 (Reference)	1.01 (0.80, 1.27)	1.08 (0.83, 1.42)	1.00 (0.76, 1.32)	0.88 (0.60, 1.28)

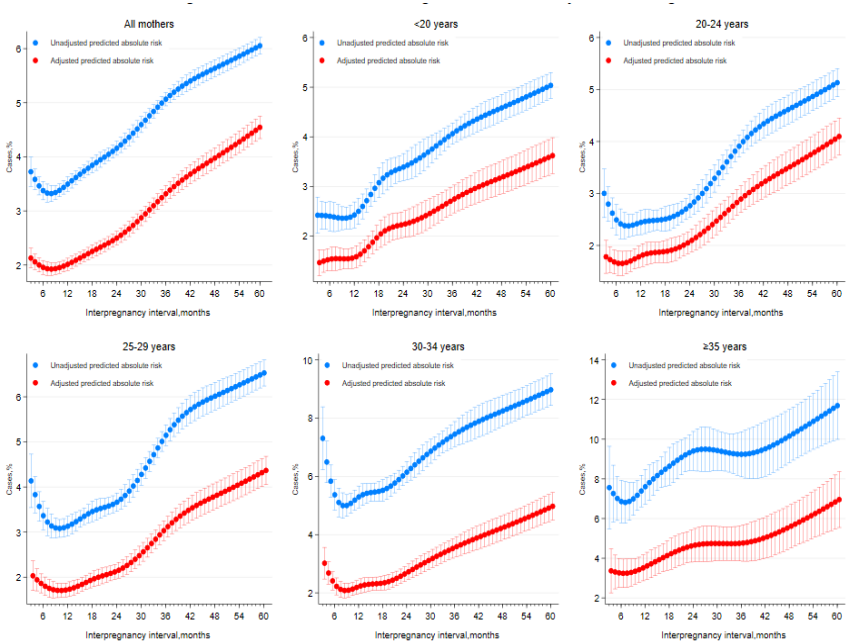
A. Preeclampsia

B. Gestational hypertension

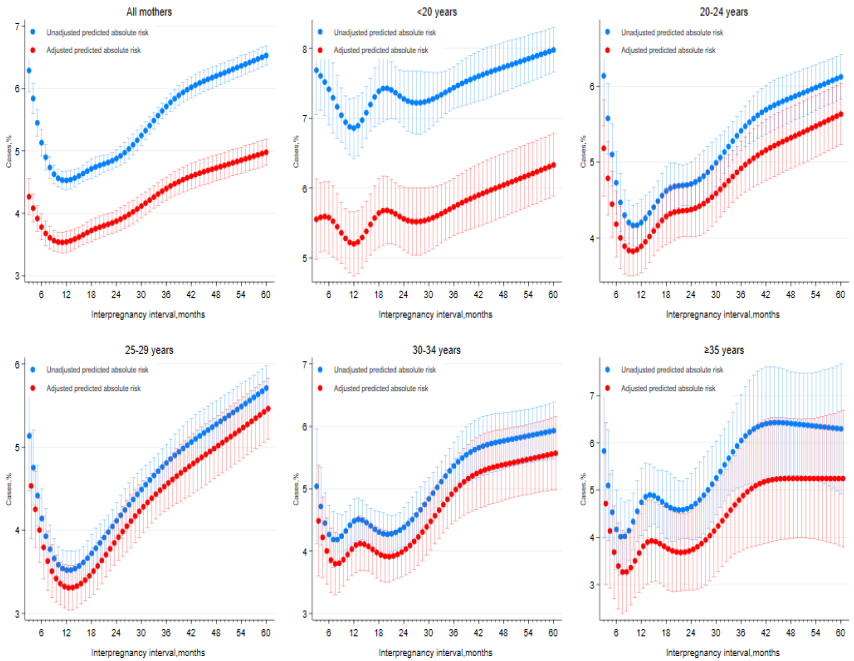


Supplemental Figure 6-2 Unadjusted and adjusted predicted risk of preeclampsia (A) and gestational hypertension (B) at each IPI length from 3 to 60 months according to maternal age at birth prior to IPI

C. Gestational diabetes

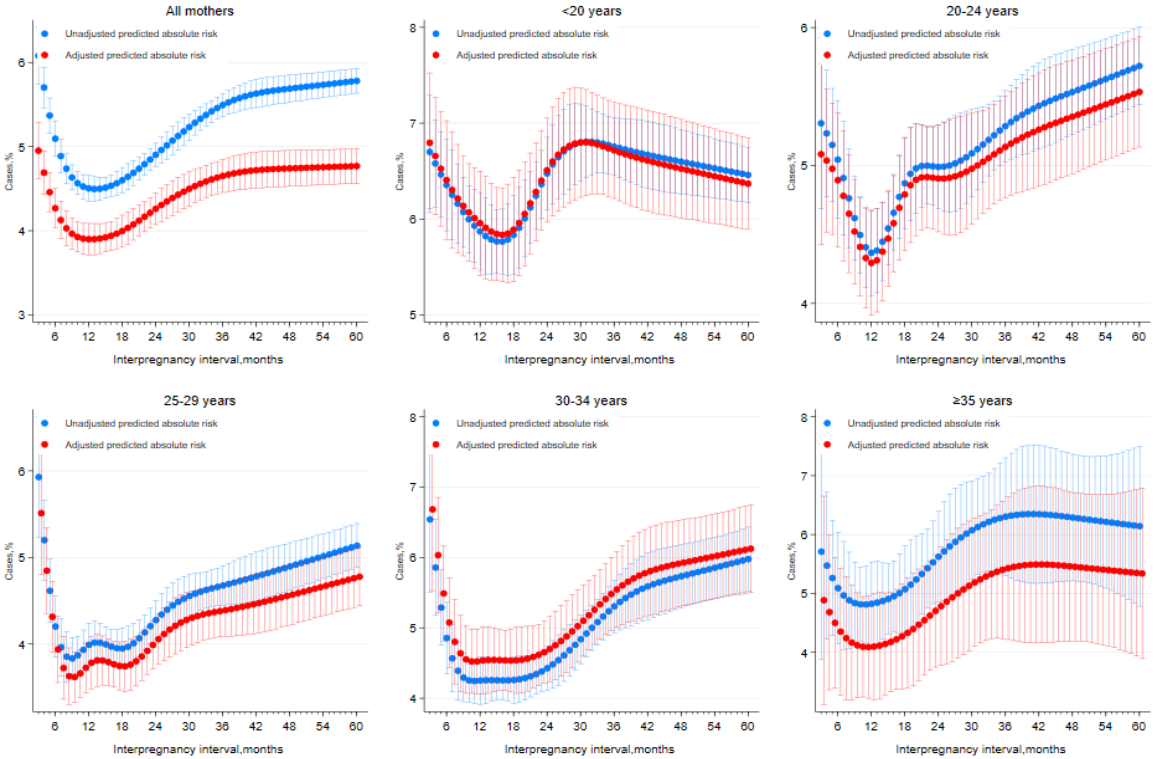


D. Premature rupture of membrane



Supplemental Figure 6-3 Unadjusted and adjusted predicted risk of gestational diabetes (C) and premature rupture of membrane (D) at each IPI length from 3 to 60 months according to maternal age at birth prior to IPI

E. Antepartum haemorrhage composite



Supplemental Figure 6-4 Unadjusted and adjusted predicted risk of antepartum haemorrhage composite at each IPI length from 3 to 60 months according to maternal age at birth prior to IPI

Supplemental Table 6-3 Adjusted Relative Risk (RRs) comparing estimated risks of each outcome at 3, 6, 12, 18, 24, 36, 48, and 60 months of IPI with estimated risks following 18 months intervals for births to nulliparous mothers at birth prior to IPI (n= 252,368 pregnancies)

	Interpregnancy interval, RR (95% CI)							
Outcome	3 **months**	6 **months**	12 **months**	18 **months**	24 **months**	36 **months**	48 **months**	60 **months**
Preeclampsia								
All mothers	1.15 (1.04, 1.28)	0.98 (0.91, 1.06)	0.9 (0.84, 0.97)	1.00 (Reference)	1.03 (0.97, 1.09)	1.17 (1.10, 1.25)	1.24 (1.17, 1.32)	1.28 (1.20, 1.36)
<20	0.98 (0.79, 1.22)	0.79 (0.66, 0.96)	0.93 (0.78, 1.11)	1.00 (Reference)	0.90 (0.78, 1.05)	0.96 (0.82, 1.12)	1.01 (0.87, 1.17)	1.04 (0.90, 1.20)
20-24	1.08 (0.88, 1.33)	0.99 (0.85, 1.14)	1.00 (0.87, 1.16)	1.00 (Reference)	1.06 (0.95, 1.19)	1.15 (1.02, 1.31)	1.19 (1.05, 1.35)	1.23 (1.09, 1.39)
25-29	1.27 (1.05, 1.54)	1.05 (0.92, 1.19)	0.86 (0.76, 0.97)	1.00 (Reference)	1.06 (0.96, 1.17)	1.25 (1.13, 1.39)	1.35 (1.22, 1.49)	1.39 (1.26, 1.54)
30-34	1.07 (0.79, 1.44)	0.96 (0.80, 1.15)	0.85 (0.72, 1.01)	1.00 (Reference)	1.01 (0.88, 1.16)	1.12 (0.97, 1.30)	1.23 (1.07, 1.42)	1.32 (1.14, 1.53)
≥35	1.92 (1.20, 3.07)	1.20 (0.86, 1.69)	0.8 (0.57, 1.14)	1.00 (Reference)	1.22 (0.92, 1.61)	1.35 (1.00, 1.84)	1.56 (1.16, 2.09)	1.84 (1.34, 2.54)
Gestational hypertension*								
All mothers	1.02 (0.86, 1.20)	0.79 (0.70, 0.89)	0.86 (0.77, 0.96)	1.00 (Reference)	1.05 (0.96, 1.14)	1.37 (1.25, 1.50)	1.57 (1.44, 1.72)	1.72 (1.58, 1.87)
<20	0.53 (0.35, 0.80)	0.57 (0.41, 0.78)	0.67 (0.50, 0.91)	1.00 (Reference)	0.97 (0.77, 1.22)	0.92 (0.73, 1.17)	1.01 (0.81, 1.26)	1.11 (0.90, 1.37)
20-24	0.81 (0.58, 1.13)	0.72 (0.57, 0.93)	0.76 (0.59, 0.96)	1.00 (Reference)	0.93 (0.77, 1.12)	1.15 (0.95, 1.40)	1.37 (1.14, 1.65)	1.52 (1.28, 1.81)
25-29	1.43 (1.10, 1.87)	0.81 (0.66, 1.00)	0.87 (0.72, 1.05)	1.00 (Reference)	1.10 (0.96, 1.28)	1.60 (1.37, 1.87)	1.85 (1.60, 2.15)	1.99 (1.72, 2.30)
30-34	1.19 (0.80, 1.77)	1.02 (0.80, 1.31)	1.11 (0.89, 1.39)	1.00 (Reference)	1.15 (0.96, 1.37)	1.52 (1.25, 1.86)	1.79 (1.47, 2.18)	2.06 (1.70, 2.51)
≥35	1.41 (0.76, 2.58)	0.70 (0.46, 1.07)	0.81 (0.54, 1.22)	1.00 (Reference)	0.95 (0.69, 1.31)	1.16 (0.80, 1.68)	1.49 (1.04, 2.13)	1.87 (1.28, 2.73)
Gestational diabetes								
All mothers	1.04 (0.92, 1.17)	0.9 (0.83, 0.98)	0.89 (0.83, 0.96)	1.00 (Reference)	1.13 (1.06, 1.20)	1.50 (1.41, 1.60)	1.81 (1.70, 1.93)	2.12 (1.99, 2.25)
<20	0.48 (0.31, 0.76)	0.60 (0.43, 0.84)	0.77 (0.56, 1.05)	1.00 (Reference)	1.14 (0.90, 1.44)	1.43 (1.12, 1.83)	1.71 (1.33, 2.20)	2.01 (1.51, 2.68)
20-24	0.90 (0.67, 1.22)	0.94 (0.75, 1.17)	0.84 (0.67, 1.05)	1.00 (Reference)	1.12 (0.95, 1.32)	1.6 (1.34, 1.91)	1.98 (1.68, 2.35)	2.31 (1.95, 2.74)
25-29	1.09 (0.88, 1.35)	0.89 (0.76, 1.03)	0.83 (0.72, 0.95)	1.00 (Reference)	1.07 (0.96, 1.18)	1.51 (1.35, 1.69)	1.83 (1.65, 2.04)	2.07 (1.86, 2.29)
30-34	1.49 (1.21, 1.84)	1.07 (0.93, 1.23)	1.02 (0.90, 1.17)	1.00 (Reference)	1.21 (1.09, 1.34)	1.54 (1.37, 1.73)	1.82 (1.63, 2.04)	2.17 (1.94, 2.43)
≥35	1.02 (0.70, 1.48)	0.78 (0.62, 0.98)	0.89 (0.72, 1.10)	1.00 (Reference)	1.14 (0.95, 1.35)	1.13 (0.92, 1.39)	1.29 (1.05, 1.59)	1.59 (1.26, 1.99)
Antepartum hemorrhage (APH) composite								
All mothers	1.18 (1.08, 1.30)	1.04 (0.97, 1.11)	0.93 (0.87, 0.99)	1.00 (Reference)	1.08 (1.02, 1.13)	1.2 (1.13, 1.27)	1.23 (1.17, 1.30)	1.24 (1.18, 1.31)
<20	1.12 (0.93, 1.35)	1.11 (0.95, 1.29)	1.02 (0.87, 1.19)	1.00 (Reference)	1.15 (1.01, 1.30)	1.13 (0.99, 1.29)	1.08 (0.95, 1.23)	1.06 (0.94, 1.20)
20-24	0.98 (0.81, 1.18)	1.02 (0.88, 1.16)	0.81 (0.71, 0.93)	1.00 (Reference)	1.02 (0.92, 1.14)	1.07 (0.95, 1.21)	1.13 (1.01, 1.27)	1.17 (1.05, 1.31)

	Interpregnancy interval, RR (95% CI)							
Outcome	3 **months**	6 **months**	12 **months**	18 **months**	24 **months**	36 **months**	48 **months**	60 **months**
25-29	1.34 (1.12, 1.61)	0.95 (0.84, 1.08)	0.95 (0.85, 1.06)	1.00 (Reference)	1.07 (0.97, 1.17)	1.24 (1.13, 1.37)	1.33 (1.21, 1.47)	1.40 (1.27, 1.54)
30-34	1.49 (1.18, 1.88)	1.12 (0.96, 1.29)	0.99 (0.86, 1.14)	1.00 (Reference)	1.1 (0.98, 1.24)	1.27 (1.12, 1.44)	1.36 (1.20, 1.55)	1.45 (1.27, 1.65)
≥35	0.98 (0.62, 1.55)	1.01 (0.78, 1.31)	0.82 (0.63, 1.06)	1.00 (Reference)	1.07 (0.86, 1.33)	1.25 (0.97, 1.61)	1.27 (0.99, 1.62)	1.22 (0.87, 1.71)
PROM								
All mothers	1.17 (1.07, 1.28)	0.99 (0.93, 1.06)	0.96 (0.90, 1.03)	1.00 (Reference)	1.03 (0.98, 1.09)	1.23 (1.17, 1.30)	1.34 (1.27, 1.41)	1.39 (1.32, 1.47)
<20	0.97 (0.82, 1.15)	0.95 (0.83, 1.10)	0.91 (0.79, 1.05)	1.00 (Reference)	0.93 (0.83, 1.04)	0.95 (0.84, 1.07)	1.01 (0.90, 1.13)	1.06 (0.95, 1.19)
20-24	1.28 (1.08, 1.52)	0.97 (0.84, 1.12)	0.96 (0.83, 1.10)	1.00 (Reference)	1.01 (0.90, 1.13)	1.25 (1.11, 1.41)	1.38 (1.23, 1.54)	1.44 (1.29, 1.61)
25-29	1.24 (1.02, 1.50)	1.06 (0.93, 1.20)	0.93 (0.83, 1.05)	1.00 (Reference)	1.16 (1.06, 1.27)	1.41 (1.28, 1.56)	1.53 (1.39, 1.69)	1.63 (1.48, 1.79)
30-34	1.04 (0.81, 1.34)	0.90 (0.77, 1.05)	1.03 (0.90, 1.17)	1.00 (Reference)	0.93 (0.83, 1.04)	1.25 (1.10, 1.41)	1.37 (1.21, 1.55)	1.37 (1.20, 1.56)
≥35	1.33 (0.87, 2.03)	0.96 (0.74, 1.25)	1.01 (0.78, 1.32)	1.00 (Reference)	1.00 (0.80, 1.25)	1.34 (1.04, 1.72)	1.39 (1.08, 1.78)	1.32 (0.95, 1.83)

[*] (n= 251,990); Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for SES, nulliparity, birth year, ethnicity, marital status at birth prior to IPI with 18-month of IPI as reference. All the unstratified models using the overall population were adjusted for maternal age.

Supplemental Table 6-4 Adjusted Relative Risk (RRs) comparing estimated risks of each outcome at 3, 6, 12, 18, 24, 36, 48, and 60 months of IPI with estimated risks following 18 months intervals to mothers with at least two consecutive births at the end of the study period (1997 onwards [n=175,986 pregnancies].

	Interpregnancy interval, RR (95% CI)							
Outcome	3 **months**	6 **months**	12 **months**	18 **months**	24 **months**	36 **months**	48 **months**	60 **months**
Preeclampsia								
All mothers	1.13 (0.96, 1.33)	0.86 (0.76, 0.97)	1.02 (0.91, 1.14)	1.00 (Reference)	1.00 (0.91, 1.09)	1.17 (1.06, 1.29)	1.23 (1.12, 1.36)	1.25 (1.14, 1.38)
<20	1.21 (0.86, 1.70)	0.77 (0.55, 1.07)	1.60 (1.17, 2.20)	1.00 (Reference)	1.14 (0.89, 1.47)	1.17 (0.88, 1.55)	1.15 (0.88, 1.50)	1.21 (0.93, 1.56)
20-24	1.00 (0.71, 1.41)	0.69 (0.52, 0.91)	0.94 (0.71, 1.23)	1.00 (Reference)	0.87 (0.71, 1.08)	0.96 (0.76, 1.20)	1.02 (0.82, 1.26)	1.03 (0.84, 1.28)
25-29	1.17 (0.88, 1.57)	0.90 (0.73, 1.12)	1.00 (0.82, 1.21)	1.00 (Reference)	1.02 (0.88, 1.19)	1.21 (1.03, 1.43)	1.26 (1.08, 1.49)	1.27 (1.08, 1.48)
30-34	0.96 (0.63, 1.45)	0.87 (0.68, 1.12)	0.94 (0.75, 1.17)	1.00 (Reference)	0.90 (0.75, 1.08)	1.25 (1.02, 1.52)	1.41 (1.16, 1.71)	1.42 (1.17, 1.74)
≥35	1.33 (0.70, 2.54)	1.20 (0.80, 1.80)	0.78 (0.51, 1.19)	1.00 (Reference)	1.26 (0.90, 1.77)	1.19 (0.81, 1.76)	1.42 (0.97, 2.07)	1.86 (1.24, 2.80)
Gestational hypertension*								
All mothers	0.96 (0.82, 1.12)	0.82 (0.73, 0.91)	0.92 (0.83, 1.02)	1.00 (Reference)	0.96 (0.88, 1.05)	1.08 (0.98, 1.18)	1.11 (1.01, 1.21)	1.09 (1.00, 1.19)
<20	0.74 (0.51, 1.06)	0.81 (0.61, 1.08)	1.06 (0.80, 1.41)	1.00 (Reference)	1.06 (0.85, 1.33)	0.95 (0.74, 1.21)	0.94 (0.75, 1.18)	0.99 (0.80, 1.23)
20-24	0.90 (0.66, 1.21)	0.75 (0.59, 0.95)	0.77 (0.61, 0.97)	1.00 (Reference)	0.86 (0.71, 1.03)	0.85 (0.70, 1.04)	0.87 (0.72, 1.05)	0.85 (0.71, 1.02)
25-29	1.03 (0.78, 1.36)	0.75 (0.61, 0.92)	0.84 (0.71, 1.01)	1.00 (Reference)	0.92 (0.80, 1.06)	1.22 (1.05, 1.42)	1.26 (1.09, 1.46)	1.16 (1.00, 1.35)
30-34	1.18 (0.82, 1.68)	0.96 (0.76, 1.22)	1.09 (0.88, 1.35)	1.00 (Reference)	1.06 (0.89, 1.26)	1.23 (1.01, 1.50)	1.31 (1.08, 1.59)	1.36 (1.11, 1.67)
≥35	1.11 (0.59, 2.07)	0.84 (0.57, 1.23)	0.9 (0.62, 1.32)	1.00 (Reference)	0.86 (0.62, 1.19)	0.97 (0.67, 1.41)	1.00 (0.68, 1.47)	0.95 (0.59, 1.53)
Gestational diabetes								
All mothers	1.01 (0.91, 1.13)	0.9 (0.83, 0.97)	0.96 (0.89, 1.03)	1.00 (Reference)	1.11 (1.05, 1.18)	1.45 (1.37, 1.55)	1.70 (1.60, 1.80)	1.92 (1.81, 2.04)
<20	0.72 (0.53, 0.97)	0.61 (0.46, 0.81)	0.83 (0.64, 1.08)	1.00 (Reference)	1.12 (0.92, 1.37)	1.29 (1.05, 1.60)	1.45 (1.19, 1.77)	1.64 (1.35, 1.99)
20-24	0.90 (0.69, 1.17)	0.90 (0.73, 1.10)	0.97 (0.79, 1.19)	1.00 (Reference)	1.08 (0.92, 1.26)	1.48 (1.26, 1.75)	1.78 (1.52, 2.08)	2.03 (1.74, 2.36)
25-29	1.00 (0.81, 1.22)	0.94 (0.82, 1.08)	0.94 (0.83, 1.07)	1.00 (Reference)	1.09 (0.99, 1.21)	1.50 (1.34, 1.66)	1.76 (1.59, 1.95)	1.96 (1.77, 2.17)
30-34	1.32 (1.09, 1.61)	0.98 (0.86, 1.12)	1.03 (0.91, 1.16)	1.00 (Reference)	1.15 (1.05, 1.27)	1.55 (1.39, 1.73)	1.76 (1.58, 1.96)	1.93 (1.73, 2.16)
≥35	1.01 (0.72, 1.42)	0.82 (0.67, 1.02)	0.88 (0.72, 1.07)	1.00 (Reference)	1.08 (0.92, 1.28)	1.09 (0.89, 1.32)	1.26 (1.03, 1.53)	1.53 (1.22, 1.92)
Antepartum hemorrhage (APH) composite								
All mothers	1.19 (1.08, 1.32)	1.05 (0.97, 1.13)	0.98 (0.91, 1.06)	1.00 (Reference)	1.07 (1.00, 1.14)	1.15 (1.08, 1.24)	1.17 (1.10, 1.25)	1.18 (1.11, 1.26)
<20	1.29 (1.07, 1.57)	1.12 (0.94, 1.34)	1.03 (0.86, 1.24)	1.00 (Reference)	1.12 (0.96, 1.30)	1.13 (0.96, 1.33)	1.08 (0.93, 1.25)	1.04 (0.90, 1.20)

	Interpregnancy interval, RR (95% CI)							
Outcome	3 **months**	6 **months**	12 **months**	18 **months**	24 **months**	36 **months**	48 **months**	60 **months**
20-24	0.89 (0.70, 1.14)	0.94 (0.79, 1.13)	0.93 (0.78, 1.11)	1.00 (Reference)	1.05 (0.91, 1.21)	1.03 (0.89, 1.20)	1.04 (0.90, 1.21)	1.07 (0.93, 1.23)
25-29	1.33 (1.08, 1.63)	0.98 (0.84, 1.14)	0.98 (0.85, 1.13)	1.00 (Reference)	1.06 (0.95, 1.19)	1.14 (1.01, 1.29)	1.21 (1.07, 1.36)	1.29 (1.15, 1.45)
30-34	1.26 (0.97, 1.64)	1.14 (0.97, 1.33)	0.96 (0.83, 1.13)	1.00 (Reference)	1.02 (0.90, 1.16)	1.22 (1.06, 1.40)	1.31 (1.14, 1.51)	1.35 (1.17, 1.57)
≥35	0.97 (0.60, 1.57)	1.01 (0.78, 1.32)	1.00 (0.77, 1.29)	1.00 (Reference)	1.12 (0.90, 1.40)	1.38 (1.07, 1.79)	1.26 (0.97, 1.64)	1.07 (0.71, 1.59)
PROM								
All mothers	1.06 (0.97, 1.17)	1.02 (0.95, 1.09)	0.98 (0.92, 1.06)	1.00 (Reference)	1.03 (0.97, 1.09)	1.13 (1.06, 1.20)	1.16 (1.10, 1.24)	1.18 (1.11, 1.25)
<20	0.92 (0.77, 1.10)	1.03 (0.89, 1.19)	0.94 (0.80, 1.09)	1.00 (Reference)	0.97 (0.86, 1.10)	0.96 (0.84, 1.09)	0.97 (0.86, 1.10)	0.98 (0.87, 1.10)
20-24	1.03 (0.84, 1.26)	0.96 (0.82, 1.13)	0.93 (0.79, 1.09)	1.00 (Reference)	1.02 (0.90, 1.16)	1.14 (0.99, 1.30)	1.18 (1.04, 1.34)	1.18 (1.04, 1.34)
25-29	1.19 (0.97, 1.45)	0.99 (0.87, 1.14)	0.97 (0.85, 1.10)	1.00 (Reference)	1.05 (0.95, 1.17)	1.14 (1.02, 1.27)	1.20 (1.08, 1.34)	1.26 (1.13, 1.40)
30-34	1.07 (0.82, 1.39)	1.06 (0.90, 1.23)	1.10 (0.95, 1.27)	1.00 (Reference)	1.01 (0.89, 1.14)	1.23 (1.08, 1.41)	1.31 (1.15, 1.49)	1.33 (1.16, 1.53)
≥35	1.47 (0.99, 2.18)	0.97 (0.74, 1.27)	0.98 (0.75, 1.28)	1.00 (Reference)	1.14 (0.91, 1.43)	1.22 (0.94, 1.58)	1.17 (0.90, 1.52)	1.12 (0.78, 1.60)

* (n=175,718)

Supplemental Table 6-5 E-values to quantify the minimum strength of association that unmeasured confounders would need to have with both IPI and each outcome, conditional on the measured covariates, to fully explain the observed association between IPI and pregnancy complications

		E-values for RR, (E-value for CI)						
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
Preeclampsia								
All mothers	1.40 (1.00)	1.16 (1.00)	1.25 (1.00)	Reference	1.20 (1.00)	1.61 (1.48)	1.78 (1.66)	1.87 (1.76)
<20	1.21 (1.00)	1.67 (1.28)	1.31 (1.00)	Reference	1.21 (1.00)	1.43 (1.00)	1.62 (1.30)	1.69 (1.37)
20-24	1.21 (1.00)	1.32 (1.00)	1.10 (1.00)	Reference	1.21 (1.00)	1.56 (1.24)	1.66 (1.40)	1.74 (1.48)
25-29	1.66 (1.00)	1.31 (1.00)	1.46 (1.00)	Reference	1.24 (1.00)	1.66 (1.40)	1.87 (1.64)	2.01 (1.76)
30-34	1.48 (1.00)	1.16 (1.00)	1.53 (1.00)	Reference	1.10 (1.00)	1.56 (1.16)	1.85 (1.48)	2.06 (1.71)
≥35	2.21 (1.00)	1.94 (1.00)	1.28 (1.00)	Reference	1.95 (1.28)	1.99 (1.16)	2.28 (1.51)	2.85 (1.99)
Gestational hypertension								
All mothers	1.49 (1.00)	1.74 (1.46)	1.53 (1.25)	Reference	1.16 (1.00)	1.92 (1.71)	2.32 (2.10)	2.58 (2.36)
<20	2.35 (1.59)	2.12 (1.53)	1.43 (1.00)	Reference	1.28 (1.00)	1.62 (1.00)	1.83 (1.40)	2.04 (1.62)
20-24	1.74 (1.00)	1.63 (1.00)	1.77 (1.00)	Reference	1.21 (1.00)	1.61 (1.11)	2.04 (1.62)	2.32 (1.93)
25-29	1.34 (1.00)	1.81 (1.28)	1.70 (1.21)	Reference	1.16 (1.00)	2.21 (1.18)	2.79 (2.38)	3.14 (2.73)
30-34	1.59 (1.00)	1.36 (1.00)	1.31 (1.00)	Reference	1.34 (1.00)	2.10 (1.59)	2.60 (2.06)	3.04 (2.45)
≥35	1.61 (1.00)	2.12 (1.00)	1.84 (1.00)	Reference	1.56 (1.00)	1.24 (1.00)	1.85(1.00)	2.32 (1.24)
Gestational diabetes								
All mothers	1.28 (1.00)	1.56 (1.36)	1.46 (1.28)	Reference	1.43 (1.31)	2.26 (2.13)	2.85 (2.71)	3.39 (3.21)
<20	2.12 (1.59)	1.96 (1.53)	1.88 (1.46)	Reference	1.43 (1.00)	2.04 (1.69)	2.49 (2.13)	2.89 (2.52)
20-24	1.28 (1.00)	1.53 (1.00)	1.25 (1.00)	Reference	1.43 (1.00)	2.38 (2.04)	3.06 (2.68)	3.66 (3.27)
25-29	1.21 (1.00)	1.39 (1.00)	1.49 (1.16)	Reference	1.40 (1.11)	2.49 (2.23)	3.18 (2.89)	3.72 (3.39)
30-34	1.81 (1.34)	1.28 (1.00)	1.28 (1.00)	Reference	1.56 (1.31)	2.32 (2.06)	2.87 (2.58)	3.43 (3.10)
≥35	1.77 (1.00)	1.88 (1.36)	1.59 (1.00)	Reference	1.40 (1.00)	1.48 (1.00)	1.92 (1.46)	2.54 (1.99)
Antepartum hemorrhage (APH) composite								

	E-values for RR, (E-value for CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
All mothers	1.76 (1.59)	1.34 (1.11)	1.16 (1.00)	Reference	1.34 (1.16)	1.59 (1.45)	1.64 (1.54)	1.66 (1.54)
<20	1.56 (1.21)	1.40 (1.00)	1.11 (1.00)	Reference	1.46 (1.16)	1.54 (1.28)	1.46 (1.16)	1.37 (1.00)
20-24	1.31 (1.00)	1.16 (1.00)	1.46 (1.11)	Reference	1.16 (1.00)	1.34 (1.00)	1.48 (1.21)	1.56 (1.31)
25-29	2.30 (1.90)	1.28 (1.00)	1.11 (1.00)	Reference	1.37 (1.11)	1.62 (1.37)	1.74 (1.51)	1.85 (1.64)
30-34	2.30 (1.76)	1.48 (1.00)	1.00 (1.00)	Reference	1.24 (1.00)	1.74 (1.43)	1.94 (1.64)	2.04 (1.71)
≥35	1.51 (1.00)	1.00 (1.00)	1.28 (1.00)	Reference	1.43 (1.00)	1.81 (1.11)	1.83 (1.16)	1.76 (1.00)
PROM								
All mothers	1.54 (1.34)	1.11 (1.00)	1.28 (1.00)	Reference	1.24 (1.00)	1.64 (1.51)	1.83 (1.71)	1.99 (1.88)
<20	1.16 (1.00)	1.11 (1.00)	1.39 (1.00)	Reference	1.16 (1.00)	1.16 (1.00)	1.34 (1.00)	1.48 (1.24)
20-24	1.71 (1.31)	1.16 (1.00)	1.43 (1.00)	Reference	1.16 (1.00)	1.54 (1.28)	1.78 (1.54)	1.95 (1.71)
25-29	1.91 (1.48)	1.37 (1.00)	1.32 (1.00)	Reference	1.46 (1.00)	1.92 (1.51)	2.21 (1.97)	2.47 (2.24)
30-34	1.54 (1.00)	1.16 (1.00)	1.24 (1.00)	Reference	1.16 (1.00)	1.85 (1.54)	2.08 (1.78)	2.17 (1.85)
≥35	1.81 (1.00)	1.46 (1.00)	1.16 (1.00)	Reference	1.00 (1.00)	1.92 (1.21)	2.13 (1.48)	2.13 (1.31)

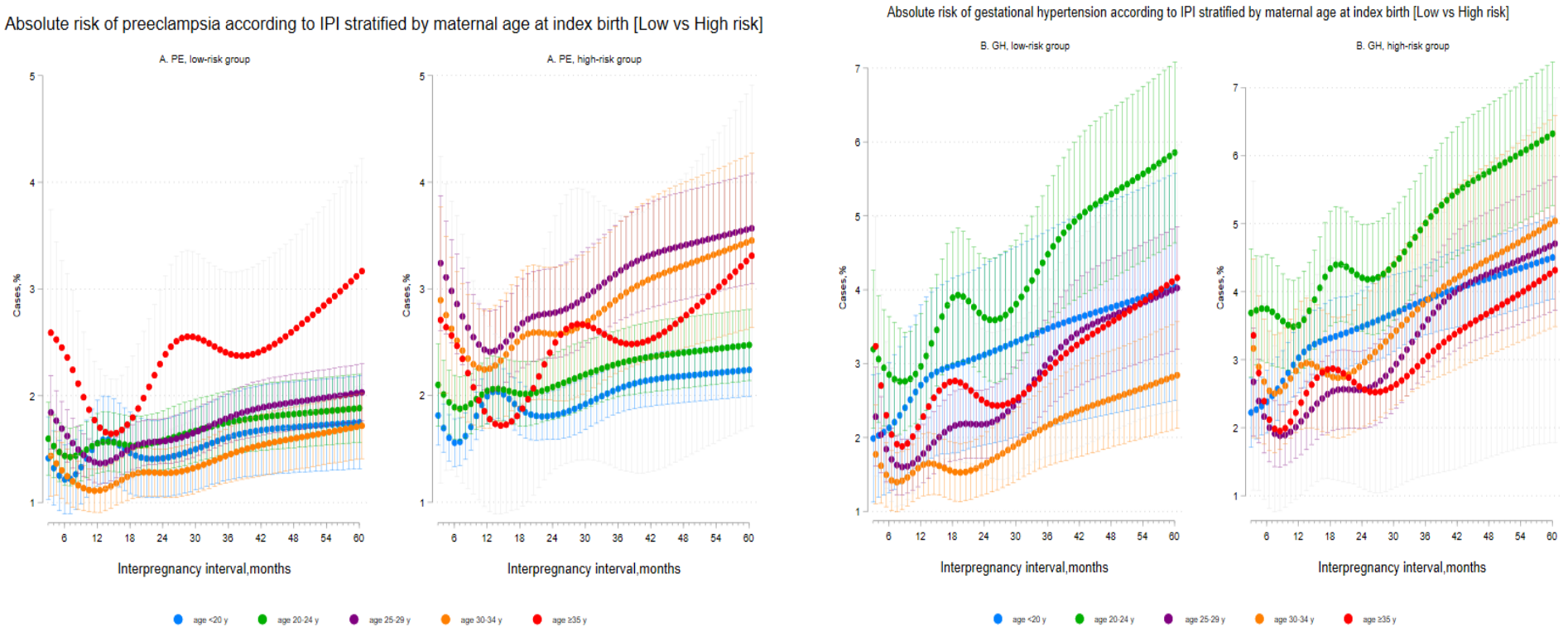
Supplemental Table 6-6 Predicted absolute risk of pregnancy complications according to Interpregnancy interval categories, stratified by maternal age at birth prior to IPI during the study period (n= 430,615)

	Interpregnancy interval, Absolute risk (95% CI)							
Outcome	3 **months**	6 **months**	12 **months**	18 **months**	24 **months**	36 **months**	48 **months**	60 **months**
Preeclampsia								
Low risk group								
All mothers	1.6 (1.4, 1.7)	1.4 (1.3, 1.5)	1.4 (1.3, 1.5)	1.4 (1.3, 1.6)	1.5 (1.4, 1.6)	1.7 (1.6, 1.8)	1.8 (1.6, 1.9)	1.8 (1.7, 2.0)
<20	1.4 (1.0, 1.8)	1.2 (0.9, 1.5)	1.6 (1.2, 2.0)	1.5 (1.1, 1.8)	1.4 (1.1, 1.8)	1.6 (1.2, 2.0)	1.7 (1.3, 2.1)	1.8 (1.3, 2.2)
20-24	1.6 (1.3, 1.9)	1.4 (1.2, 1.7)	1.6 (1.3, 1.8)	1.5 (1.3, 1.8)	1.6 (1.3, 1.9)	1.7 (1.5, 2.0)	1.8 (1.5, 2.1)	1.9 (1.6, 2.2)
25-29	1.8 (1.5, 2.2)	1.6 (1.4, 1.9)	1.4 (1.2, 1.6)	1.5 (1.3, 1.7)	1.6 (1.4, 1.8)	1.8 (1.6, 2.0)	1.9 (1.7, 2.2)	2.0 (1.8, 2.3)
30-34	1.4 (1.1, 1.8)	1.2 (1.0, 1.5)	1.1 (0.9, 1.3)	1.3 (1.0, 1.5)	1.3 (1.0, 1.5)	1.5 (1.2, 1.7)	1.6 (1.3, 1.9)	1.7 (1.4, 2.0)
≥35	2.6 (1.4, 3.7)	2.4 (1.6, 3.1)	1.7 (1.2, 2.2)	1.8 (1.2, 2.4)	2.4 (1.7, 3.1)	2.4 (1.6, 3.2)	2.6 (1.8, 3.5)	3.2 (2.1, 4.2)
High risk group								
All mothers	3.1 (2.7,3.4)	2.8 (2.4,3.1)	2.7 (2.4,3.0)	2.8 (2.5,3.1)	2.9 (2.6,3.2)	3.3 (2.9,3.6)	3.5 (3.1,3.8)	3.6 (3.2,4.0)
<20	1.8 (1.5, 2.1)	1.6 (1.3, 1.8)	2.0 (1.7, 2.3)	1.9 (1.6, 2.1)	1.8 (1.6, 2.0)	2.1 (1.8, 2.3)	2.2 (1.9, 2.4)	2.2 (2, 2.5)
20-24	2.1 (2.0, 2.0)	1.9 (2.0, 2.0)	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)	2.1 (2.0, 2.0)	2.3 (2.0, 3.0)	2.4 (2.0, 3.0)	2.5 (2.0, 3.0)
25-29	3.2 (2.6, 3.9)	2.9 (2.4, 3.3)	2.4 (2.0, 2.8)	2.7 (2.3, 3.1)	2.8 (2.4, 3.2)	3.2 (2.7, 3.6)	3.4 (2.9, 3.9)	3.6 (3.1, 4.1)
30-34	2.9 (2.0, 3.8)	2.5 (1.9, 3.2)	2.3 (1.7, 2.8)	2.6 (1.9, 3.2)	2.6 (1.9, 3.2)	2.9 (2.2, 3.6)	3.2 (2.4, 4.0)	3.5 (2.6, 4.3)
≥35	2.7 (1.2, 4.2)	2.5 (1.2, 3.7)	1.8 (0.9, 2.6)	1.9 (1.0, 2.8)	2.5 (1.3, 3.7)	2.5 (1.3, 3.7)	2.8 (1.4, 4.1)	3.3 (1.7, 4.9)
Gestational hypertension*								
Low risk group								
All mothers	1.8 (1.5, 2.1)	1.7 (1.4, 1.9)	1.8 (1.6, 2.0)	2.1 (1.8, 2.3)	2.1 (1.8, 2.3)	3 .0 (2.3, 3.0)	3.0 (2.7, 3.4)	3.3 (2.9, 3.7)
<20	2.0 (1.0, 3.0)	2.1 (1.0, 3.0)	2.7 (2.0, 4.0)	3.0 (2.0, 4.0)	4.0 (2.0, 4.0)	3.5 (2.0, 5.0)	3.8 (2.0, 5.0)	4.0 (2.0, 6.0)
20-24	1.7 (1.1, 2.3)	1.7 (1.2, 2.3)	1.6 (1.1, 2.1)	2.0 (1.4, 2.6)	1.9 (1.3, 2.5)	2.3 (1.6, 3.0)	2.7 (1.9, 3.5)	2.9 (2.1, 3.8)
25-29	2.3 (1.6, 2.9)	1.7 (1.3, 2.1)	1.8 (1.4, 2.2)	2.2 (1.7, 2.6)	2.2 (1.7, 2.7)	3.1 (2.4, 3.7)	3.7 (2.9, 4.4)	4.0 (3.2, 4.9)
30-34	1.8 (1.1, 2.4)	1.4 (1.0, 1.8)	1.6 (1.2, 2.1)	1.5 (1.1, 1.9)	1.7 (1.2, 2.1)	2.2 (1.6, 2.7)	2.6 (1.9, 3.2)	2.8 (2.1, 3.6)
≥35	3.2 (1.5, 5.0)	2.0 (1.1, 2.9)	2.3 (1.4, 3.2)	2.8 (1.7, 3.8)	2.5 (1.5, 3.4)	2.9 (1.7, 4.1)	3.6 (2.1, 5.1)	4.2 (2.4, 6.0)
High risk group								

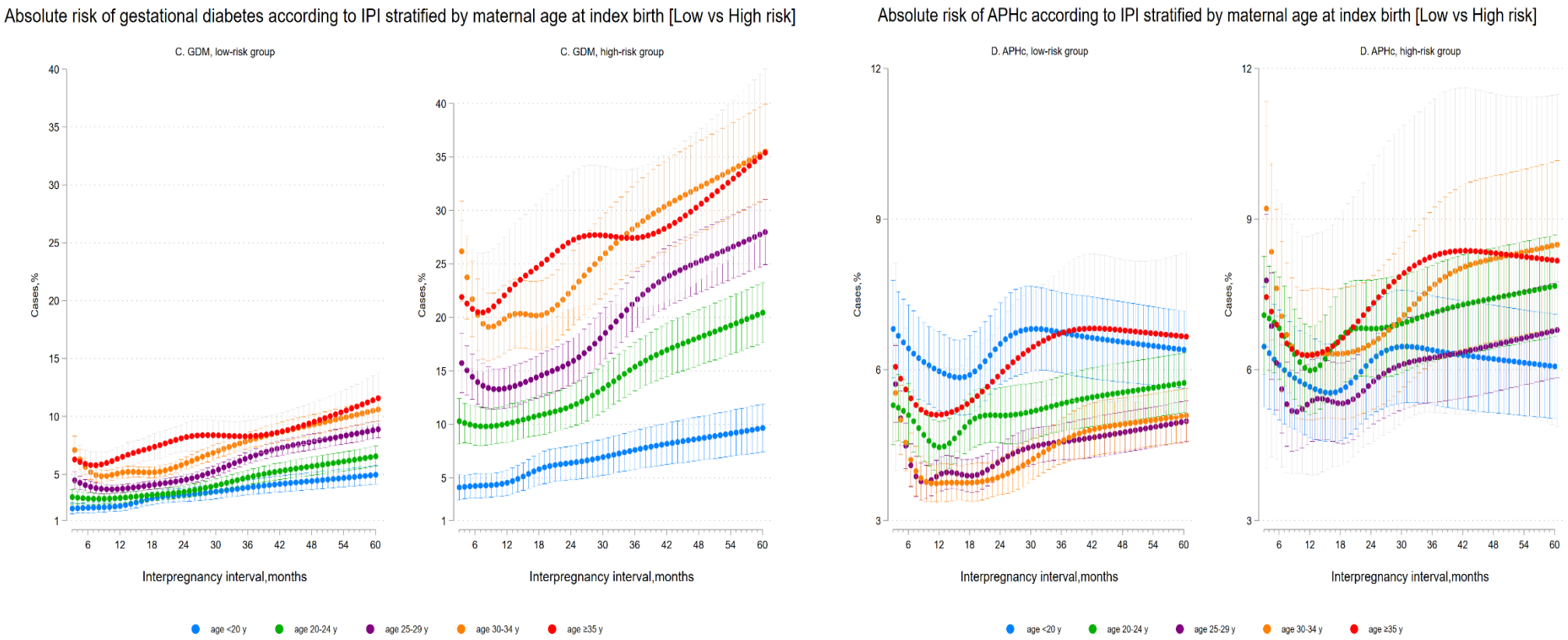
Outcome	Interpregnancy interval, Absolute risk (95% CI)							
	3 **months**	6 **months**	12 **months**	18 **months**	24 **months**	36 **months**	48 **months**	60 **months**
All mothers	3.2 (2.6, 3.7)	2.9 (2.4, 3.3)	3.1 (2.7, 3.5)	3.5 (3.0, 4.0)	3.6 (3.1, 4.1)	4.5 (3.9, 5.1)	5.2 (4.5, 5.9)	5.6 (4.8, 6.3)
<20	2.2 (1.7, 2.7)	2.4 (1.9, 2.8)	3.0 (2.5, 3.5)	3.3 (2.8, 3.9)	3.5 (3.0, 4.0)	3.9 (3.4, 4.4)	4.2 (3.6, 4.8)	4.5 (3.9, 5.1)
20-24	3.7 (2.7, 4.6)	3.7 (3, 4.5)	3.5 (2.8, 4.2)	4.3 (3.5, 5.2)	4.2 (3.4, 5.0)	5.0 (4.2, 5.9)	5.8 (4.8, 6.8)	6.3 (5.3, 7.4)
25-29	2.7 (1.9, 3.5)	2.0 (1.5, 2.5)	2.1 (1.6, 2.6)	2.5 (2.0, 3.1)	2.6 (2.0, 3.1)	3.6 (2.8, 4.4)	4.3 (3.4, 5.2)	4.7 (3.7, 5.7)
30-34	3.2 (1.9, 4.5)	2.5 (1.7, 3.4)	2.9 (2.0, 3.9)	2.7 (1.9, 3.6)	3.0 (2.0, 3.9)	3.9 (2.7, 5.1)	4.5 (3.1, 5.9)	5.0 (3.5, 6.6)
≥35	3.4 (1.1, 5.6)	2.1 (0.8, 3.4)	2.4 (1.0, 3.7)	2.9 (1.2, 4.5)	2.6 (1.1, 4.0)	3.1 (1.3, 4.8)	3.7 (1.6, 5.9)	4.3 (1.8, 6.8)
Gestational diabetes								
Low risk group								
All mothers	3.9 (3.5, 4.2)	3.5 (3.3, 3.8)	3.6 (3.4, 3.8)	3.9 (3.7, 4.2)	4.4 (4.1, 4.6)	5.8 (5.5, 6.1)	6.9 (6.5, 7.2)	7.8 (7.4, 8.2)
<20	2.0 (1.6, 2.5)	2.1 (1.7, 2.6)	2.3 (1.8, 2.7)	2.9 (2.4, 3.5)	3.2 (2.7, 3.8)	3.9 (3.2, 4.5)	4.4 (3.7, 5.2)	5.0 (4.1, 5.8)
20-24	3.0 (2.4, 3.7)	2.9 (2.4, 3.4)	3.0 (2.5, 3.4)	3.2 (2.7, 3.7)	3.5 (3.0, 4.0)	4.7 (4.1, 5.4)	5.7 (4.9, 6.5)	6.6 (5.7, 7.4)
25-29	4.5 (3.7, 5.2)	3.9 (3.4, 4.4)	3.8 (3.4, 4.1)	4.1 (3.7, 4.5)	4.5 (4.1, 4.9)	6.5 (6.0, 7.0)	7.8 (7.2, 8.5)	8.9 (8.1, 9.6)
30-34	7.1 (5.9, 8.3)	5.2 (4.5, 5.8)	5.2 (4.7, 5.7)	5.2 (4.7, 5.7)	6.0 (5.5, 6.5)	8.0 (7.3, 8.7)	9.3 (8.4, 10.2)	10.6 (9.6, 11.6)
≥35	6.3 (4.3, 8.2)	5.8 (4.7, 6.9)	6.5 (5.5, 7.5)	7.4 (6.2, 8.5)	8.2 (7, 9.4)	8.3 (6.9, 9.7)	9.5 (7.9, 11.2)	11.6 (9.4, 13.8)
High risk group								
All mothers	22.8 (20.7, 24.9)	21.2 (19.5, 22.9)	21.6 (19.9, 23.3)	23.3 (21.5, 25)	25.3 (23.4, 27.1)	31.2 (29.2, 33.2)	35.2 (33, 37.4)	38.5 (36.2, 40.7)
<20	4.1 (2.9, 5.3)	4.2 (3.1, 5.4)	4.5 (3.4, 5.7)	5.8 (4.3, 7.3)	6.4 (4.8, 8.0)	7.6 (5.8, 9.4)	8.7 (6.6, 10.7)	9.7 (7.4, 11.9)
20-24	10.3 (8.2, 12.4)	9.9 (8.1, 11.7)	10.1 (8.3, 11.8)	10.8 (9.0, 12.7)	11.7 (9.8, 13.6)	15.4 (13.1, 17.6)	18.1 (15.5, 20.7)	20.4 (17.6, 23.3)
25-29	15.7 (13, 18.5)	14 (11.9, 16)	13.5 (11.5, 15.4)	14.6 (12.6, 16.6)	15.9 (13.8, 18.1)	21.7 (19.1, 24.3)	25.3 (22.4, 28.2)	28.0 (24.9, 31)
30-34	26.2 (21.5, 30.9)	20.2 (16.8, 23.6)	20.2 (16.9, 23.4)	20.2 (17, 23.4)	22.8 (19.3, 26.3)	28.6 (24.6, 32.6)	32.3 (28, 36.6)	35.5 (31.1, 40)
≥35	21.9 (14.7, 29.1)	20.5 (15, 26)	22.6 (17, 28.2)	25 (18.9, 31.1)	27.3 (20.9, 33.6)	27.5 (21, 34)	30.6 (23.6, 37.7)	35.4 (27.6, 43.2)
Antepartum hemorrhage (APH) composite								
Low risk group								
All mothers	5.0 (4.7, 5.4)	4.3 (4.1, 4.6)	3.9 (3.7, 4.2)	4.0 (3.8, 4.3)	4.3 (4.1, 4.5)	4.7 (4.5, 5.0)	4.8 (4.6, 5.1)	4.9 (4.6, 5.1)
<20	6.8 (5.8, 7.8)	6.4 (5.6, 7.3)	6.0 (5.2, 6.8)	5.9 (5.1, 6.7)	6.5 (5.7, 7.3)	6.7 (5.9, 7.5)	6.6 (5.8, 7.4)	6.4 (5.6, 7.2)
20-24	5.3 (4.5, 6.1)	5.1 (4.5, 5.7)	4.5 (3.9, 5.0)	5.0 (4.4, 5.5)	5.1 (4.5, 5.6)	5.3 (4.8, 5.9)	5.6 (5.0, 6.1)	5.7 (5.1, 6.3)
25-29	5.7 (4.9, 6.5)	4.1 (3.7, 4.5)	3.9 (3.6, 4.3)	3.9 (3.6, 4.2)	4.2 (3.9, 4.5)	4.6 (4.2, 4.9)	4.8 (4.4, 5.2)	5.0 (4.6, 5.4)
30-34	5.5 (4.6, 6.5)	4.2 (3.7, 4.7)	3.7 (3.4, 4.1)	3.8 (3.4, 4.1)	3.9 (3.5, 4.3)	4.6 (4.1, 5.1)	4.9 (4.4, 5.4)	5.1 (4.5, 5.6)
≥35	6.1 (4.0, 8.1)	5.4 (4.3, 6.6)	5.1 (4.2, 6.0)	5.4 (4.4, 6.4)	6.0 (4.9, 7.0)	6.7 (5.4, 8.1)	6.8 (5.4, 8.2)	6.7 (5.0, 8.3)

Outcome	Interpregnancy interval, Absolute risk (95% CI)							
	3 **months**	6 **months**	12 **months**	18 **months**	24 **months**	36 **months**	48 **months**	60 **months**
High risk group								
All mothers	7.6 (6.8, 8.3)	6.6 (6.0, 7.2)	6.0 (5.4, 6.6)	6.1 (5.6, 6.7)	6.6 (6.0, 7.1)	7.2 (6.5, 7.8)	7.3 (6.7, 8.0)	7.4 (6.7, 8.0)
<20	6.5 (5.3, 7.7)	6.1 (5.0, 7.2)	5.7 (4.6, 6.7)	5.6 (4.6, 6.6)	6.2 (5.1, 7.3)	6.4 (5.3, 7.5)	6.2 (5.1, 7.3)	6.1 (5.0, 7.1)
20-24	7.1 (5.9, 8.3)	6.8 (5.8, 7.8)	6.0 (5.1, 6.9)	6.6 (5.7, 7.6)	6.8 (5.9, 7.8)	7.1 (6.2, 8.1)	7.4 (6.4, 8.4)	7.7 (6.7, 8.7)
25-29	7.8 (6.5, 9.1)	5.6 (4.7, 6.5)	5.4 (4.6, 6.2)	5.3 (4.5, 6.1)	5.8 (4.9, 6.6)	6.2 (5.4, 7.1)	6.5 (5.6, 7.4)	6.8 (5.8, 7.7)
30-34	9.2 (7.1, 11.3)	7.1 (5.6, 8.6)	6.3 (5.0, 7.6)	6.3 (5.0, 7.6)	6.5 (5.2, 7.9)	7.7 (6.2, 9.2)	8.2 (6.6, 9.9)	8.5 (6.8, 10.2)
≥35	7.4 (4.0, 10.9)	6.7 (4.1, 9.3)	6.3 (3.9, 8.7)	6.6 (4.1, 9.2)	7.3 (4.6, 10.1)	8.3 (5.2, 11.4)	8.3 (5.1, 11.5)	8.2 (4.9, 11.5)
PROM								
Low risk group								
All mothers	5.2 (4.9, 5.6)	4.6 (4.4, 4.9)	4.3 (4.1, 4.6)	4.6 (4.3, 4.8)	4.7 (4.5, 5.0)	5.3 (5.1, 5.6)	5.7 (5.4, 6.0)	6.0 (5.7, 6.3)
<20	7.3 (6.3, 8.2)	7.3 (6.3, 8.2)	6.8 (6.0, 7.7)	7.4 (6.5, 8.3)	7.3 (6.4, 8.1)	7.5 (6.6, 8.3)	7.9 (7.0, 8.8)	8.2 (7.3, 9.1)
20-24	7.4 (6.3, 8.4)	5.9 (5.2, 6.6)	5.5 (4.9, 6.1)	6.1 (5.4, 6.7)	6.2 (5.5, 6.8)	6.9 (6.2, 7.6)	7.5 (6.7, 8.2)	7.9 (7.1, 8.7)
25-29	5.7 (4.9, 6.5)	4.7 (4.2, 5.2)	4.1 (3.7, 4.5)	4.4 (4.0, 4.7)	4.8 (4.5, 5.2)	5.6 (5.2, 6.1)	6.2 (5.7, 6.7)	6.7 (6.2, 7.3)
30-34	5.0 (4.0, 6.0)	4.3 (3.8, 4.9)	4.6 (4.1, 5.0)	4.4 (4.0, 4.8)	4.5 (4.1, 4.9)	5.6 (5.0, 6.1)	6.0 (5.4, 6.6)	6.2 (5.6, 6.9)
≥35	5.6 (3.7, 7.5)	4.1 (3.1, 5.0)	4.6 (3.7, 5.4)	4.5 (3.6, 5.4)	4.5 (3.6, 5.4)	5.9 (4.7, 7.1)	6.3 (4.9, 7.6)	6.3 (4.6, 7.9)
High risk group								
All mothers	11.6 (10.5, 12.7)	10.3 (9.4, 11.3)	9.7 (8.9, 10.6)	10.2 (9.3, 11.1)	10.6 (9.6, 11.5)	11.8 (10.8, 12.8)	12.6 (11.5, 13.7)	13.2 (12.1, 14.3)
<20	15.1 (12.8, 17.5)	15.1 (12.9, 17.4)	14.3 (12.2, 16.4)	15.4 (13.1, 17.6)	15.1 (13, 17.3)	15.5 (13.4, 17.7)	16.3 (14.0, 18.6)	17.0 (14.6, 19.3)
20-24	14.0 (12.0, 16.0)	11.4 (9.9, 13.0)	10.7 (9.2, 12.1)	11.7 (10.1, 13.2)	11.9 (10.4, 13.4)	13.2 (11.7, 14.8)	14.2 (12.5, 15.9)	15.0 (13.2, 16.7)
25-29	11.8 (9.8, 13.7)	9.9 (8.5, 11.3)	8.7 (7.5, 9.9)	9.2 (7.9, 10.4)	10.1 (8.8, 11.5)	11.7 (10.2, 13.2)	12.8 (11.1, 14.4)	13.8 (12.1, 15.5)
30-34	8.7 (6.6, 10.9)	7.5 (5.9, 9.2)	8.0 (6.4, 9.6)	7.7 (6.1, 9.3)	7.9 (6.3, 9.4)	9.6 (7.7, 11.5)	10.4 (8.3, 12.4)	10.7 (8.6, 12.8)
≥35	10.4 (6.0, 14.9)	7.7 (4.8, 10.6)	8.6 (5.5, 11.6)	8.5 (5.4, 11.5)	8.4 (5.4, 11.5)	10.9 (7.0, 14.7)	11.6 (7.5, 15.7)	11.5 (7.2, 15.9)

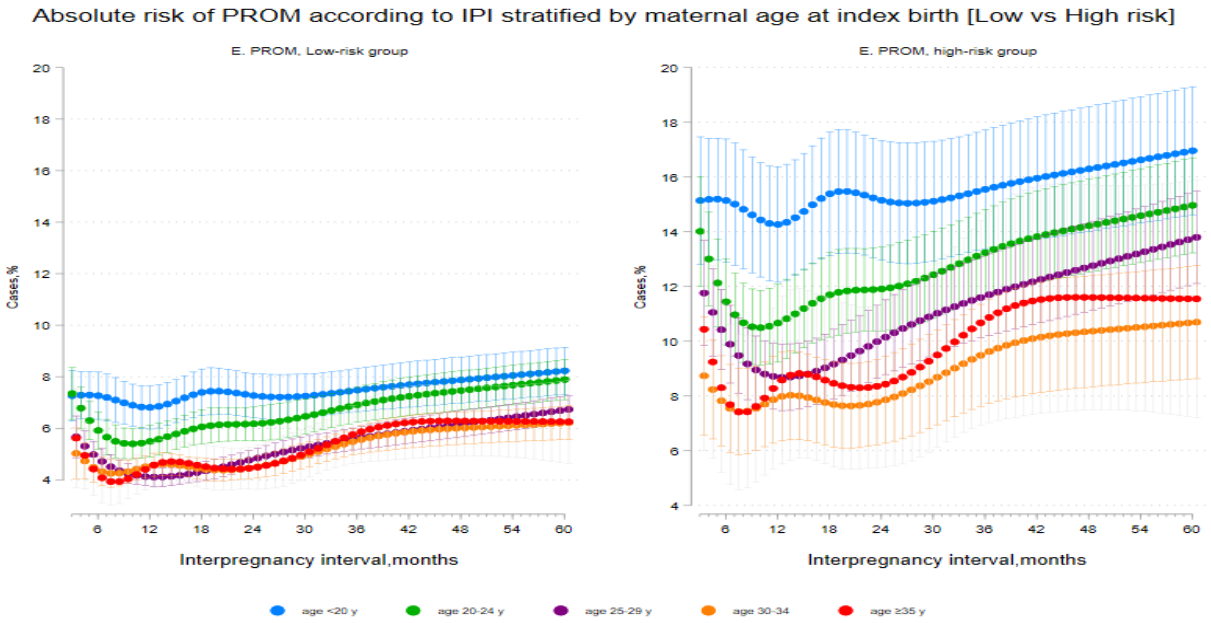
* (n=421,912); Data are predicted absolute risk (in %) (95% confidence interval); Predicted risks for low-risk group are reported at representative values of covariates :nulliparous, Caucasian, married, least-disadvantaged SES and birth year in 2010 at birth prior to IPI; Predicted risks for high-risk group are reported at representative values of covariates: non-nulliparous, Caucasian, non-married, highly disadvantaged SES and birth year in 2010 at birth prior to IPI; nulliparity at birth prior to IPI included in the high-risk group for preeclampsia and gestational hypertension; for the unstratified predictions (all mothers in the cohort) we used average maternal age (25-29 years) at birth prior to IPI for low-risk group while advanced maternal age (≥35 years)at birth prior to IPI for the high-risk group.



Supplemental Figure 6-5 Predicted risk of preeclampsia and gestational hypertension at each IPI length from 3 to 60 months according to maternal age at birth prior to IPI and risk profile



Supplemental Figure 6-6 Predicted risk of gestational diabetes and APH-composite at each IPI length from 3 to 60 months according to maternal age at birth prior to IPI and risk profile



Supplemental Figure 6-7 Predicted risk of PROM at each IPI length from 3 to 60 months according to maternal age at birth prior to IPI and risk profile

Chapter 7: INTERPREGNANCY INTERVAL AND PREGNANCY COMPLICATIONS BY PREVIOUS HISTORY OF COMPLICATIONS

Study Four. Associations between IPI and pregnancy complications: Effect modification by previous history of complications

7.1 PREAMBLE

This study was based on findings from Study Three, on the increased risk of preeclampsia with long interval between pregnancies, aimed to examine whether this effect is influenced by a history of previous complications (e.g., preeclampsia). Unlike other studies, this study presented the estimated risk of preeclampsia and gestational diabetes (outcomes) for each 1 month of IPI increment (exposure modelled using cubic spline), separately for mothers with and without history of these complications in their previous pregnancies.

This study (Study Four) is currently under review (second round) at *BMJ Open*.

7.2 ABSTRACT

Objective: To examine if the association between interpregnancy interval (IPI) and pregnancy complications varies by previous experience with these conditions.

Design and setting: Population-based longitudinally linked cohort study in Western Australia (WA).

Participants: Mothers who had their first two (n=252,368) and three (n=96,315) consecutive singleton births in WA between 1980 and 2015.

Outcome measures: We estimated risk of preeclampsia (PE) and gestational diabetes (GDM) for 3 to 60 months of IPI according to previous history of each outcome. We modelled IPI using restricted cubic splines and reported adjusted relative risk (RRs) with 95% CI at 3,6,12, 24, 36, 48 and 60 months, with 18 months as reference.

Results: Risks of PE and GDM were 9.5%, 2.6% in first pregnancies, with recurrence rates of 19.3% and 41.5% in second pregnancy for PE and GDM respectively. The absolute risk of GDM ranged from 30% to 43% across the IPI range for mothers with previous GDM compared to 2% to 8% for mothers without previous GDM. For mothers with no previous PE, greater risks were observed for IPIs at 3 months (RR 1.24, 95% CI 1.07, 1.43) and 60 months (RR 1.40, 95% CI 1.29, 1.53) compared to 18 months. There was insufficient evidence for increased risk of PE at shorter IPIs of <18 months for mothers with previous PE. Shorter IPIs of <18 months were associated with lower risk than at IPIs of 18 months for mothers with no previous GDM.

Conclusions: The associations between IPIs and risk of PE or GDM on subsequent pregnancies is modified by previous experience with these conditions. Mothers with previous complications had higher absolute (AR), but lower relative risks (RR) than mothers with no previous complications. However, IPI remains a potentially modifiable risk factor for mothers with previous complicated pregnancies.

Keywords: interpregnancy interval; gestational diabetes; preeclampsia, birth intervals; birth spacing

7.3 INTRODUCTION

Preeclampsia (PE) and gestational diabetes (GDM) remain the most significant contributors to perinatal and maternal mortalities and morbidities, complicating 2-10% and 6-13% of pregnancies worldwide, respectively.[1,2] These complications have a higher tendency of recurrence in subsequent pregnancies. Studies have reported a recurrence rate of 7 to 20% for PE and 30 to 70% for GDM, respectively.[3-6]

Interpregnancy interval (IPI), the length of time between pregnancies, has been identified as a potentially modifiable risk factor for adverse perinatal outcomes, with short and long IPIs found to be associated with adverse outcomes.[7-10] Based on these associations, various clinical guidelines and World Health Organization (WHO) recommend that women wait at least 18-24 months before conceiving another child.[11-13]

Recently, there has been growing literature on the association between IPIs and the recurrence of pregnancy complications.[14-16] However, there is currently no recommendation for the optimal interval based on obstetric history, and there is limited evidence to inform such a recommendation.

This study aimed to examine whether the association between IPI and pregnancy complications was modified by previous obstetric history, specifically PE and GDM. In addition, we estimated the absolute risk of these complications associated with short and long IPIs, to better inform decision-making regarding optimal IPIs.

7.4 METHODS

7.4.1 Study design

We conducted a population-based, longitudinal cohort study of mothers with at least two consecutive singleton pregnancies in the period of 1980-2015 in Western Australia (WA).

7.4.2 Data sources and study population

We obtained maternal, infant and birth information from the Midwives Notification System, a validated database[17] that includes >99% of births in WA of at least 20 weeks' gestation or birthweight of 400 g or more if the gestational age was unknown.[18] We sourced hospitalization records from Hospital Morbidity Data Collection, which includes information on all hospitalizations in the state with International Classification of Diseases (ICD-9/10th revision-Australian Modification) coded diagnoses.[19] Data sources and study protocol has been

published elsewhere.[10,20] Birth records were probabilistically linked based on maternal information to identify all births to individual women during the study period.

From total of 487,297 mothers, we sequentially excluded mothers who delivered multiples; mothers who had only one pregnancy during the study period; mothers whose children's birth years were inconsistent with the parity and mothers who had missing gestational age, pregnancy outcomes, age, and socio-economic status (SES). These exclusions resulted in 280,637 eligible mothers who contributed 711,252 pregnancies. Finally, we included 252,368 mothers with their first two (parity 0, 1) and 96,315 mothers with their first three consecutive singleton births (parity 0, 1, 2) in the analytic cohort (Supplemental Figure 7-1).

7.4.3 Exposure

Interpregnancy interval (IPI) was calculated prior to exclusions as the time between the delivery date of the first eligible birth during the study period and the estimated conception date of the subsequent pregnancy (date of birth minus gestational age at birth). Gestational age at birth was estimated as the best clinical estimate from dating ultrasounds or last menstrual period when ultrasound was not available.

7.4.4 Outcomes

The outcomes of interest were ascertained from midwives notifications and hospital separation data in the state, with the International Classification of Diseases (ICD-9 through to ICD-10-AM [Australian Modification]) diagnostic codes consistent with preeclampsia (PE) (ICD-9/ICD-9-CM: 642.4, 642.5, 642.7, ICD-10-AM: O14, O11) and gestational diabetes (GDM) (ICD-9/ICD-9-CM: 648.8, ICD-10-AM: O24.4-).

7.4.5 Covariates

We controlled for potential confounding factors measured at the birth prior to the interval and included birth year, maternal age, marital status, parity, race/ethnicity and SES. We also included a partner change status, which identifies if a mother changed partner either between first and second or between second and third pregnancies. Race/ethnicity was classified as Caucasian versus non-Caucasian. Marital status was categorised as married, never married, widowed/divorced/ separated and unknown. Socio-economic status (SES) was derived by the Australian Bureau of Statistics Index of Relative Socio-economic Disadvantage at a geographic area for the maternal residence at the time of birth,[21] and categorised into quintiles.

7.4.6 Statistical analysis

We examined the association between IPI and pregnancy complication (GDM and PE) stratified by the previous history of each complication using Generalised linear models (GLM) fitted using a Poisson distribution with a log link function. We first tabulated the incidence of each pregnancy complication by IPI (categorised to <6, 6-11, 12-17, 18-23, 24-59, and ≥60 months). We modelled IPI as a continuous variable with a flexible, non-linear approach, restricted cubic splines, with knots placed at 3, 6, 12, 18, 24, 36 and 48 months of IPI. We then estimated the absolute risk of each pregnancy complication in 1-month increments of IPI from 3 to 60 months using post estimation calculations.[22]

For each outcome, the unadjusted model included the IPI spline terms only, and the adjusted model included covariates measured at birth prior to IPI: birth year, SES, marital status, race/ethnicity, and partner change status at recent birth. Maternal age was modelled using restricted cubic splines with 4 knots at the 5^{th}, 35^{th}, 65^{th} and 95^{th} percentiles (ages 18, 24, 29 and 35). We also adjusted for parity (categorised as nulliparous, parity 1, and 2) for the association between IPI and complications to ascertain the sensitivity of our results to higher-order parity (Supplemental Table 7-2). To examine the potential variability of the relationship between IPI and each outcome by the previous history of complications, we estimated the predicted absolute risk at the following covariates values: Caucasian, married, average SES, average maternal age and birth year set to 2010 at birth before the IPI. We then plotted the predicted risks with 95% confidence intervals (CIs) at 1-month increments of IPI for each outcome stratified by the previous history of complications to illustrate the shapes of the risk curves. We presented relative risks (RRs) with 95% CIs at 3, 6, 12, 24, 36, 48 and 60 months of IPI, with 18 months as the reference for tabulated results. Robust (sandwich) variance estimation was used to account for the dependence of more than one outcome per mother.[23]

7.4.7 Missing data

Because the proportion of missing data was small (<3%, range 0.04% for maternal age to 1.2% for SES), we carried out a complete case analysis. The majority of missing data was due to lack of availability of information (e.g. SES) before the year 1997, and we evaluated this bias using sensitivity analyses.

7.4.8 Sensitivity analyses

We conducted a sensitivity analyses to examine the effect of choice of timing of the effect modifier (presence of complication for any previous pregnancy as opposed to complication

experienced at the immediate previous pregnancy) by including all mothers with at least two consecutive pregnancies during the study period (Supplemental Table 7-2). We further included a sensitivity analysis restricted to consecutive births after the year 1997 for which more information on potential confounders including paternal age, fertility treatment (assuming that these pregnancies were more likely to be intended), and smoking were available for adjustment[18] (Supplemental Table 7-3). We also performed a sensitivity analysis to examine whether our results differed by the timing of covariate adjustment (i.e., covariates at birth before the interval versus at the time of the outcome (Supplemental Table 7-4). To examine if our results were sensitive to the difference in reporting of the outcome and definitions change from ICD-9 to ICD-10, we conducted a separate analyses for gestational hypertension and a composite outcome of hypertensive disorder of pregnancy (gestational hypertension and preeclampsia combined) for the main cohort (Supplemental Table 7-6). Additionally, to examine if our results were sensitive to the possibility of misclassification of the outcome, related to the source of the outcome (outcomes recorded in both database as opposed to in either) we conducted a sensitivity analyses for gestational diabetes by comparing the effect estimates for GDM recorded in either MNS or HMDS as opposed to GDM recorded in both databases for the main cohort (Supplemental Table 7-7). Finally, To examine if our results are influenced by the fixed cohort bias, we conducted a sensitivity analyses (Supplemental Table 7-8) by restricting our cohort to sibling pairs when the first born baby was born before 1 January 2010 (which provides at least 5 years of follow-up time). All analyses were performed using STATA version 16.1 (Stata Corporation, College Station, Texas, USA).

7.4.9 Patient and public involvement

Members of the community *Healthy Pregnancies Consumer Reference Group* provided community and consumer perspectives to this study. This group also provided an insight into issues that affect their pregnancy planning decisions, contextualise results and provided participant experience.

7.5 RESULTS

Cohort characteristics

Maternal age at birth of first child peaked between 25 and 29 years. IPIs were more commonly within 24-59 months (31.7%); 4.8% and 7.8% of mothers had IPIs of <6 months and ≥60 months, respectively. The distribution of IPIs was similar for mothers with and without previous complications (Table 7-1).

Incident and recurrent risks of pregnancy complications

Risks of preeclampsia (PE) in first and second pregnancy were 9.5% and 2.4%, respectively, with a recurrence rate of 19.3% at a second pregnancy. The risk of gestational diabetes (GDM) was 2.6% in both first and second pregnancies, with a recurrence rate of 41.5% at second pregnancy (Supplemental Table 7-1). The incidence of GDM increased over the study period with steep increases after 2000 (an incidence of 3.2% in 2000 versus 8.9% in 2015) (Supplemental Figure 7-2).

The lowest incidence at second birth was observed for IPIs of 6-11 months for both preeclampsia and gestational diabetes. Incidences were relatively higher for IPIs <6 months and ≥ 24 months (Table 7-2). The recurrence risks were generally higher for both complications at IPIs <6 months and ≥60 months (Supplemental Table 7-1). The proportion of PE cases increased with pregnancy duration, from 1.4% at 20 weeks to 31.4% at 32 weeks of gestation age with higher proportion at around 28-32 weeks of gestation (Supplemental Figure 7-3).

Absolute risk of pregnancy complications by IPI and previous complication status

The absolute risks of preeclampsia in the second birth were higher for mothers with previous preeclampsia than mothers with no previous preeclampsia across the IPI continuum (Table 7-2). The absolute risks of preeclampsia ranged between 14 and 16% for previous preeclampsia and 1% to 2% for mothers with no previous preeclampsia, with the highest risk at IPI <6 or >60 months and lowest at around 12 months for mothers with previous preeclampsia. For mothers with no previous preeclampsia, the intervals at which risks were lowest were less clear but appeared to be around 12 months (Table 7-2, Figure 7-1, panel A).

The absolute risks of gestational diabetes ranged from 30 to 43% for mothers with previous gestational diabetes versus 2 to 8% for mothers with no previous gestational diabetes. Risks of gestational diabetes were most minor at intervals between 6 and 12 months for both mothers with and without previous gestational diabetes (Table 7-2, Figure 7-1, panel B).

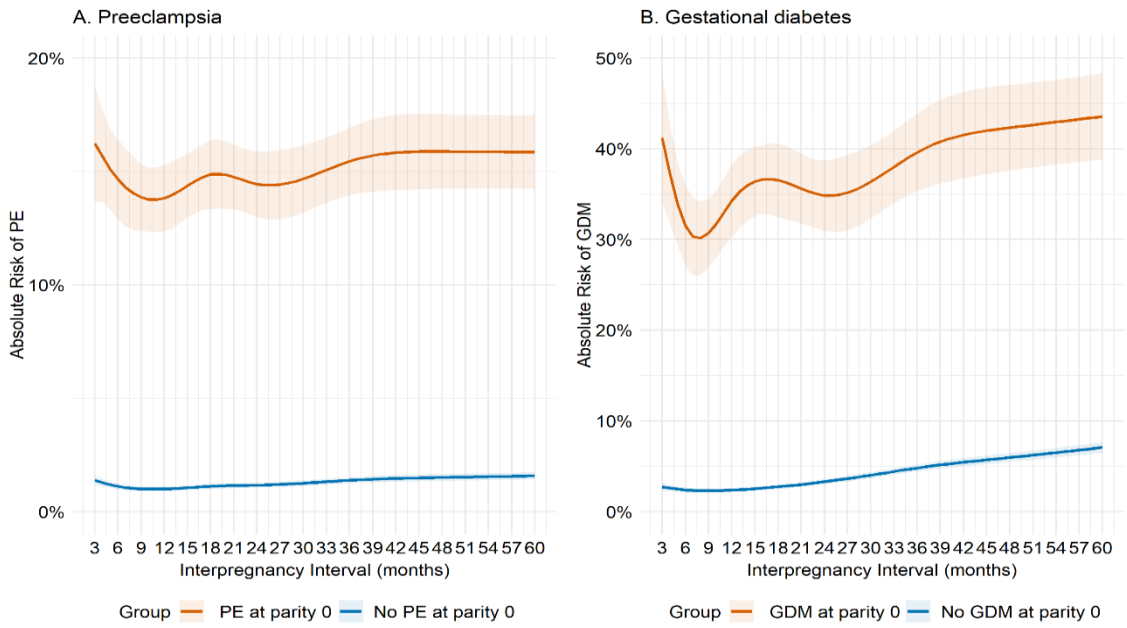


Figure 7-1 Predicted absolute risks (95 % CIs) at each IPI from 3 to 60 months according to previous history for (A) preeclampsia, and (B) gestational diabetes for mothers with first two consecutive pregnancies. Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (25.1) and birth year in 2010 at birth before the IPI. GDM, gestational diabetes; PE, preeclampsia

Table 7-1 Maternal characteristics at first pregnancy by previous pregnancy complications, WA 1980-2015

Characteristics			Preeclampsia		Gestational diabetes	
		Total	No previous PE	Previous PE	No previous GDM	Previous GDM
		N=252,368	N=228,407	N=23,961	N=245,764	N=6,604
Maternal age, y	<20	43,473 (17.2)	38,999 (17.1)	4,474 (18.7)	43,035 (17.5)	438 (6.6)
	20-24	57,209 (22.7)	51,194 (22.4)	6,015 (25.1)	56,334 (22.9)	875 (13.2)
	25-29	87,480 (34.7)	79,285 (34.7)	8,195 (34.2)	85,233 (34.7)	2,247 (34.0)
	30-34	51,537 (20.4)	47,291 (20.7)	4,246 (17.7)	49,332 (20.1)	2,205 (33.4)
	≥35	12,669 (5.0)	11,638 (5.1)	1,031 (4.3)	11,830 (4.8)	839 (12.7)
Time period	1980-1984	32,982 (13.1)	29,087 (12.7)	3,895 (16.3)	32,940 (13.4)	42 (0.6)
	1985-1989	35,703 (14.1)	31,397 (13.7)	4,306 (18.0)	35,583 (14.5)	120 (1.8)
	1990-1994	36,940 (14.6)	32,881 (14.4)	4,059 (16.9)	36,492 (14.8)	448 (6.8)
	1995-1999	37,012 (14.7)	32,715 (14.3)	4,297 (17.9)	36,070 (14.7)	942 (14.3)
	2000-2004	37,260 (14.8)	33,998 (14.9)	3,262 (13.6)	36,031 (14.7)	1,229 (18.6)
	2005-2009	43,151 (17.1)	40,458 (17.7)	2,693 (11.2)	41,303 (16.8)	1,848 (28.0)
	2010-2015	29,320 (11.6)	27,871 (12.2)	1,449 (6.0)	27,345 (11.1)	1,975 (29.9)
SES in quintiles	<20th percentile (Most disadvantaged)	46,991 (18.6)	42,087 (18.4)	4,904 (20.5)	45,883 (18.7)	1,108 (16.8)
	20-39th percentile	51,517 (20.4)	46,271 (20.3)	5,246 (21.9)	50,295 (20.5)	1,222 (18.5)
	40-59th percentile	52,503 (20.8)	47,506 (20.8)	4,997 (20.9)	51,107 (20.8)	1,396 (21.1)
	60-79th percentile	51,922 (20.6)	47,140 (20.6)	4,782 (20.0)	50,462 (20.5)	1,460 (22.1)
	>=80th percentile (Least disadvantaged)	49,435 (19.6)	45,403 (19.9)	4,032 (16.8)	48,017 (19.5)	1,418 (21.5)
Marital status	Married	215,196 (85.3)	194,800 (85.3)	20,396 (85.1)	209,351 (85.2)	5,845 (88.5)
	Others	37172 (14.7)	33607 (14.7)	3565 (14.9)	36413 (14.8)	759 (11.5)
Race/Ethnicity	Caucasian	219,562 (87.0)	198,137 (86.7)	21,425 (89.4)	214,645 (87.3)	4,917 (74.5)
Interpregnancy Interval, months	<6	12,104 (4.8)	11,006 (4.8)	1,098 (4.6)	11,780 (4.8)	324 (4.9)
	6-11	42,470 (16.8)	38,678 (16.9)	3,792 (15.8)	41,267 (16.8)	1,203 (18.2)
	12-17	55,218 (21.9)	50,237 (22.0)	4,981 (20.8)	53,737 (21.9)	1,481 (22.4)
	18-23	42,934 (17.0)	38,880 (17.0)	4,054 (16.9)	41,751 (17.0)	1,183 (17.9)
	24-59	79,950 (31.7)	71,980 (31.5)	7,970 (33.3)	77,890 (31.7)	2,060 (31.2)
	≥60	19,692 (7.8)	17,626 (7.7)	2,066 (8.6)	19,339 (7.9)	353 (5.3)
Partner change [a]	Yes	15,789 (6.3)	14,307 (6.3)	1,482 (6.2)	15,572 (6.3)	217 (3.3)
Smoking	Yes	17,239 (13.6)	16,062 (13.7)	1,177 (12.7)	16,705 (13.8)	534 (9.6)
Fertility treatment	Yes	4,185 (2.7)	3,872 (2.7)	313 (2.4)	3,882 (2.6)	303 (4.9)

Data are presented in n(%) based on study cohort that consists of first 2 pregnancies ; [a] measured at second pregnancy; PE, preeclampsia; GDM, gestational diabetes

We next estimated the predicted absolute risk of each outcome associated with IPI according to presence or absence of previous complications for the sub-cohort of mothers with their first three consecutive pregnancies (parity 0, 1, 2), calculated at representative values of each risk factor (Table 7-3, Figure 7-2, panel A & panel B). The predicted risk of preeclampsia for mothers with no preeclampsia in their first and second births (No PE-No PE group) ranged between 0.7 to 0.9% for IPIs of <24 months, lowest at around 24 months and increased with IPI afterwards. For mothers with a history of preeclampsia in either first or second births, the intervals at which risks were lowest were less clear but appeared to be around 6 months, with elevated risk at 12 months of IPI for both groups. However, the predicted risk of preeclampsia was markedly higher for mothers with a history of preeclampsia in their recent pregnancy (12-21% for No PE-PE group) compared to mothers with preeclampsia in their first, but not second birth (5 to 7% for PE-No PE group. These risks were even more pronounced in the third birth for mothers who developed preeclampsia in their first and second births (24 to 33% for PE-PE group) (Table 7-3, Figure 7-2, panel A).

Generally, the predicted absolute risk of gestational diabetes at third pregnancy differed by mothers' previous history of GDM. Absolute risks were relatively lower for mothers without GDM in their first and second pregnancies (2 to7% for No GDM-No GDM group), slightly higher for mothers with pregnancies complicated by GDM during the second but not the first (14 to22% for No GDM-GDM group), and substantially higher for mothers who developed GDM during their first and second pregnancies (55 to 70% for GDM-GDM group). For mothers with no history of GDM in both pregnancies (No GDM-No GDM group), risks were minimal at IPI of <18 months, but risks increased consistently with increasing IPI.

For mothers with GDM in first but not second (GDM-No GDM group) and mothers with GDM in their first and second pregnancies (GDM-GDM group), risks were minimal at intervals of approximately 18 months. In contrast, minimal risks were observed at around 24 months for mothers with GDM in their second but not first pregnancy. Interestingly, for most of these groups except mothers with no history of previous GDM (No GDM-No GDM group), risks were higher at IPIs of <6 months (Figure 7-2).

Table 7-2 Adjusted Relative Risk (RRs) and predicted absolute risks (ARs) of pregnancy complications according to IPI stratified by pregnancy complication at first pregnancy for mothers with their first two consecutive births during the study period (n=252,368 mothers)

	Interpregnancy interval, Absolute risk (95% CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
Preeclampsia								
Previous PE								
RR (95% CI)	1.09 (0.94-1.25)	0.99 (0.89-1.09)	0.93 (0.85-1.03)	1.00 (Reference)	0.97 (0.90-1.05)	1.04 (0.95-1.13)	1.06 (0.98-1.16)	1.06 (0.98-1.15)
AR % (95% CI)	16.3 (13.8, 18.9)	14.7 (12.9, 16.4)	13.8 (12.3, 15.3)	14.8 (13.2, 16.4)	14.4 (12.9, 15.9)	15.5 (14.0, 17.0)	16.0 (14.3, 17.6)	15.9 (14.3, 17.6)
RD % (95% CI)	1.5 (-1.00.6, 4.1)	-0.1 (-1.7, 1.5)	-1.0 (-2.5, 0.4)	Reference	-0.4 (-1.6, 0.8)	0.7 (-0.7, 2.1)	1.2 (-0.3, 2.6)	1.1 (-0.4, 2.6)
No previous PE								
RR (95% CI)	1.24 (1.07-1.43)	1.00 (0.90-1.11)	0.90 (0.81-0.99)	1.00 (Reference)	1.04 (0.96-1.13)	1.23 (1.13-1.35)	1.34 (1.23-1.46)	1.40 (1.29-1.53)
AR % (95% CI)	1.5 (1.3, 1.8)	1.1 (1.0, 1.3)	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.4 (1.3, 1.5)	1.6 (1.4, 1.8)	1.7 (1.5, 1.9)
RD % (95% CI)	0.4 (0.2, 0.7)	0.1 (-0.1, 0.2)	-0.1 (-0.2, 0.01)	Reference	0.1 (-0.0, 0.1)	0.3 (0.2, 0.4)	0.5 (0.4, 0.6)	0.6 (0.5, 0.8)
Gestational diabetes								
Previous GDM								
RR (95% CI)	1.11 (0.95-1.29)	0.87 (0.78-0.97)	0.94 (0.85-1.04)	1.00 (Reference)	0.96 (0.88-1.04)	1.07 (0.98-1.18)	1.14 (1.05-1.25)	1.18 (1.07-1.29)
AR % (95% CI)	39.7 (30.1, 49.2)	30.3 (23.5, 37.1)	32.6 (24.5, 40.7)	35.3 (28.0, 42.6)	33.3 (25.4, 41.2)	38.6 (31.8, 45.5)	41.5 (35.1, 47.8)	43.2 (38.3, 48.2)
RD % (95% CI)	4.4 (-2.6, 11.3)	-5.0 (-9.0, -0.9)	-2.7 (-6.7, 1.3)	Reference	-2.0 (-5.4, 1.4)	3.3 (-0.5, 7.2)	6.2 (1.9, 10.5)	7.9 (2.1, 13.9)
No previous GDM								
RR (95% CI)	1.00 (0.85-1.16)	0.87 (0.78-0.97)	0.87 (0.79-0.96)	1.00 (Reference)	1.20 (1.11-1.29)	1.75 (1.62-1.90)	2.18 (2.01-2.35)	2.58 (2.38-2.79)
AR % (95% CI)	3.0 (2.5, 3.4)	2.4 (2.2, 2.7)	2.3 (2.1, 2.6)	2.7 (2.4, 2.9)	3.2 (3.0, 3.5)	4.9 (4.5, 5.2)	6.3 (5.8, 6.8)	7.6 (7.0, 8.3)
RD % (95% CI)	0.3 (-0.2, 0.8)	-0.2 (-0.5, 0.1)	-0.3 (-0.6, -0.1)	Reference	0.5 (0.4, 0.9)	2.2 (1.9, 2.5)	3.6 (3.2, 4.1)	4.90 (4.4, 5.6)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for maternal age, SES, birth year, ethnicity, marital status at birth prior to IPI and partner change at recent birth with 18-month of IPI as reference. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (25.1) and birth year in 2010 at birth prior to the IPI; *PE, preeclampsia; GDM, gestational diabetes*

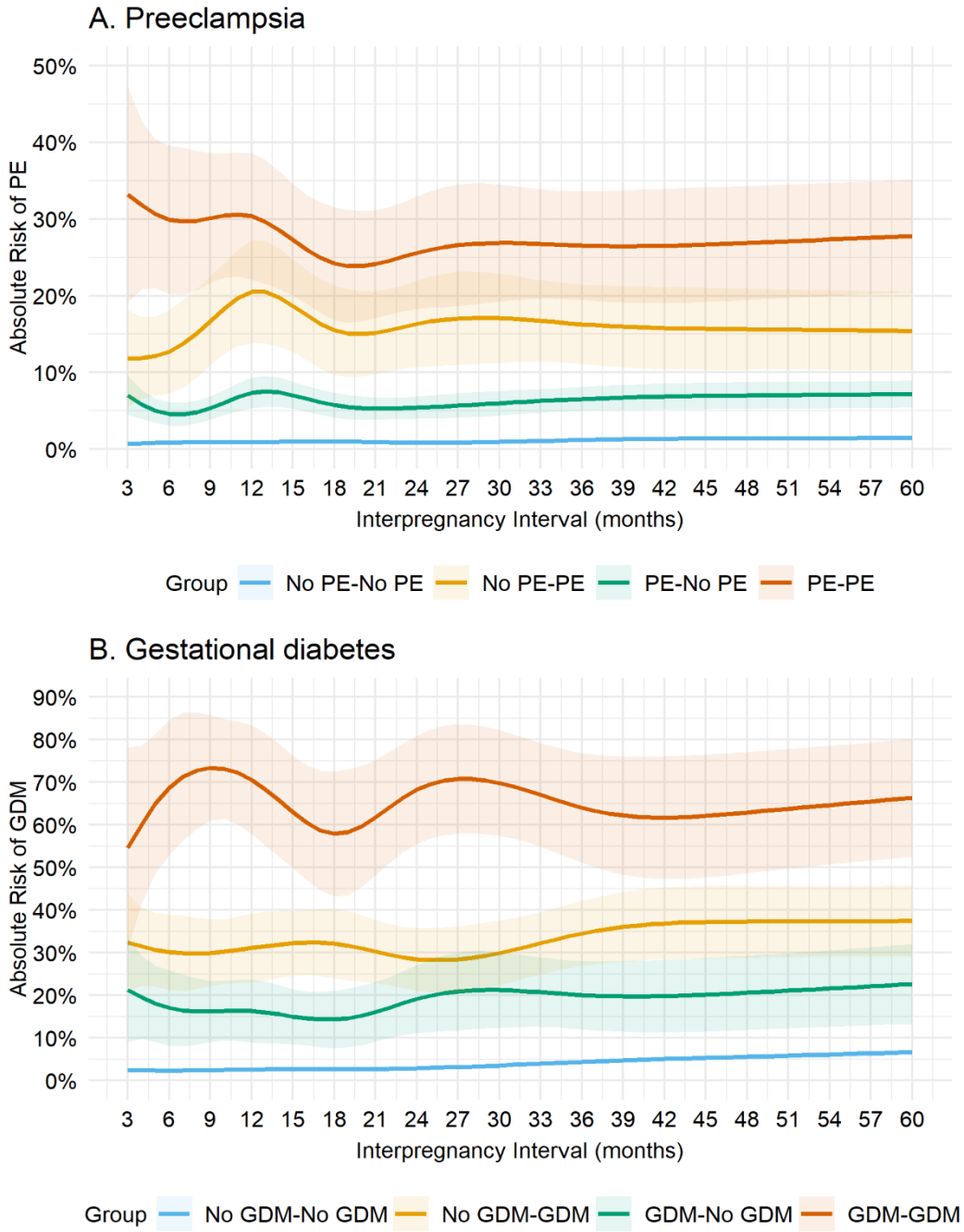


Figure 7-2 Predicted absolute risks (95 % CIs) at each IPI from 3 to 60 months according to previous histories for (A) preeclampsia, and (B) gestational diabetes for mothers with first three consecutive pregnancies. Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (26.5) and birth year in 2010 at birth prior to the IPI. Abbreviations: *GDM, gestational diabetes; PE, preeclampsia*

Relative Risks of IPI on preeclampsia by previous preeclampsia status

For mothers with no previous preeclampsia at parity 0, there was a "J-shaped" relationship between IPI and preeclampsia at parity 1, with greater risk for IPIs at 3 months (RR 1.24, 95% CI 1.07, 1.43) and 60 months (RR 1.40, 95% CI 1.29, 1.53) compared to 18 months. However, for mothers with preeclampsia at parity 0, there was insufficient evidence for an association between IPI and PE at parity 1, with consistently lower RRs than mothers with no previous preeclampsia for all IPIs (Table 7-2).

Relative Risks of IPI on gestational diabetes by previous gestational diabetes status

There was relatively more evidence that shorter IPIs of less than 18 months was associated with lower risk than at IPIs of 18 months for mothers with no previous GDM. In contrast, adverse associations were more pronounced at longer intervals (RR 1.18, 95% CI 1.07, 1.29) and (RR 2.58, 95% CI 2.38, 2.79) at 60 months of IPI for mothers with and without previous GDM, respectively. The "J-shaped" relationship between IPI and GDM was less clear for mothers with previous GDM as compared to mothers who no previous GDM. These general patterns were also evident in an analysis of mothers with three consecutive pregnancies. The estimates for IPIs longer than 36 months were attenuated for mothers with at least one pregnancy complicated (PE or GDM) compared to mothers with no complications in their first and second pregnancies (Table 7-2, Figure 7-2, Panel A & B).

Sensitivity analysis

The results of our sensitivity analysis to the choice of timing of the effect modifier (complications for any previous pregnancy as opposed to a complication at the immediate pervious pregnancy) were consistent with the main analyses (Supplemental Table 7-1). There was a negligible difference in the associations between IPI and pregnancy complications when we adjusted for additional covariates, including smoking and paternal age (Supplemental Table 7-2). Similarly, we observed a slight difference in the association when we adjusted for variables during the outcome of interest (Supplemental Table 7-3). Additional analyses that examined to check if the results were sensitive to the ICD-9 to ICD-10 changes revealed a very similar finding to those reported in the main analyses and collectively support that the associations between IPI and risk of hypertensive disorders of pregnancy on subsequent pregnancies varied by previous history of these hypertensive complications (Supplemental Table 7-6). However, our descriptive analysis revealed that the changes from ICD-9 to ICD-10 in the year 1999 corresponded with shifting of preeclampsia incidence at first birth from

7.6% in the year 1999 to 4.9% in the year 2005 (Supplemental Figure 7-2), which suggests that the impact of ICD version can have a role in explaining the higher incidence of preeclampsia in the cohort. A sensitivity analyses that examined for a possible misclassification of the outcome revealed a slightly higher effect estimates (both RR and AR) for the outcomes with concordant records in both datasets as compared to the main analysis. Our main result reported a conservative estimate and the 'true' estimates might be higher than reported in this thesis. However, the sensitivity analyses supported the main findings of this thesis and support that associations between IPI gestational diabetes is higher for mothers with previous gestational diabetes (Supplemental Table 7-7). The effect estimates of the model with a restricted cohort to examine sensitivity of our results to fixed cohort bias were similar with the main results (Supplemental Table 7-8).

7.6 DISCUSSION

7.6.1 Principal findings

In this large retrospective cohort, we observed an increased risk of preeclampsia for short and long IPIs compared to 18 months, but only for mothers with no previous preeclampsia. Adverse associations of IPI with GDM were observed at longer intervals of >36 months for both mothers with and without previous GDM. However, IPIs of less than 18 months was associated with a lower risk of GDM compared to IPI of 18 months in mothers with no previous GDM. Generally, the predicted absolute risks following short or long IPIs for PE and GDM were higher for mothers with previous complications than mothers with no previous pregnancy complications, most notably when the complication was experienced for the more recent birth.

7.6.2 Strengths of the study

This large cohort was sourced from highly reliable population-based perinatal information ascertained from hospital separations and perinatal database. To our knowledge, this is the largest population-based study to examine the non-linear relationships between IPI and pregnancy complications based on previous complication status. Modelling IPI flexibly allows for the estimation of risk curves and better clarification of optimal IPI. Our findings provide more clinically applicable information on the effect of different IPIs on the risk of PE and GDM based on the previous history of these complications.

7.6.3 Limitations of the data

In interpreting our findings, the following limitations must be considered. As we estimated risks at each IPI based on comparing outcomes of different women (between-women), our results might be biased due to unmeasured confounding. Recently, studies that have employed within-women (matched designs) have reported substantially attenuated associations between IPI and pregnancy complications, owing to unmeasured or residual confounding.[9,10,24]

Table 7-3 Adjusted Relative Risk (RRs) and predicted absolute risks (ARs) of pregnancy complications according to IPI stratified by pregnancy complications at their first and/or second pregnancy for mothers with their first three consecutive births during the study period (n=96,315 mothers

	Interpregnancy interval, Absolute risk (95% CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
Preeclampsia								
No PE-No PE								
RR (95% CI)	0.72 (0.51-1.01)	0.87 (0.71-1.08)	0.94 (0.76-1.16)	1.00 (Reference)	0.87 (0.74-1.03)	1.22 (1.03-1.43)	1.41 (1.22-1.65)	1.46 (1.27-1.69)
AR % (95% CI)	0.7 (0.47, 0.93)	0.9 (0.66, 1.05)	0.9 (0.73, 1.10)	1.0 (0.79, 1.17)	0.9 (0.69, 1.01)	1.2 (1.00, 1.38)	1.4 (1.15, 1.62)	1.4 (1.19, 1.68)
RD % (95% CI)	-0.3 (-0.6, -0.03)	-0.1 (-0.33, -0.07)	-0.1 (-0.3, 0.1)	Reference	-0.1 (-0.3, 0.02)	0.2 (0.02, 0.38)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)
No PE-PE								
RR (95% CI)	0.77 (0.45-1.32)	0.83 (0.58-1.18)	1.30 (0.93-1.82)	1.00 (Reference)	1.05 (0.80-1.37)	1.05 (0.78-1.40)	1.01 (0.76-1.33)	0.99 (0.75-1.31)
AR % (95% CI)	14.9(6.8, 23.1)	15.6 (8.6, 22.6)	22.2 (15.2, 29.3)	18.4 (11.4, 25.4)	18.4 (12.0, 24.7)	20.5 (13.1, 27.9)	17.2 (11.6, 22.9)	16.9 (11.4, 22.4)
RD % (95% CI)	-3.5 (-11.3, 4.3)	-2.8 (-8.9, 3.3)	3.8 (-2.7, 10.4)	Reference	-0.03 (-5.1, 5.0)	2.1 (-3.6, 7.8)	-1.19 (-6.5, 4.2)	-1.5 (-6.6, 3.7)
PE-No PE								
RR (95% CI)	1.21 (0.87-1.69)	0.81 (0.61-1.07)	1.26 (0.96-1.65)	1.00 (Reference)	0.95 (0.76-1.17)	1.13 (0.91-1.42)	1.21 (0.97-1.49)	1.23 (1.00-1.52)
AR % (95% CI)	6.9 (4.4, 9.4)	4.6 (3.1, 6.1)	7.3 (5.3, 9.3)	5.8 (4.1, 7.4)	5.3 (3.9, 6.7)	6.4 (4.9, 8.0)	6.9 (5.2, 8.6)	6.6 (4.8, 8.5)
RD % (95% CI)	1.2 (-1.3, 3.6)	-1.2 (-2.7, 0.4)	1.6 (-0.3, 3.4)	Reference	-0.5 (-1.8, 0.8)	0.7 (-0.7, 2.1)	1.1 (-0.3, 2.5)	0.9 (-1.0, 2.7)
PE-PE								
RR (95% CI)	1.31 (0.92-1.89)	1.20 (0.93-1.55)	1.22 (0.95-1.56)	1.00 (Reference)	1.05 (0.86-1.29)	1.08 (0.87-1.35)	1.10 (0.89-1.36)	1.13 (0.92-1.39)
AR % (95% CI)	37.2 (21.8, 52.6)	30.9 (21.2, 40.6)	31.1 (23.0, 39.3)	24.1 (16.9, 31.2)	27.1 (19.5, 34.7)	29.2 (21.0, 37.4)	27.9 (20.5, 35.3)	28.3 (21.1, 35.5)
RD % (95% CI)	13.1 (-1.8, 28.0)	6.8 (-1.3, 15.0)	7.1 (-0.7, 14.8)	Reference	3.1 (-3.3, 9.4)	5.2 (-2.6, 12.9)	3.9 (-2.4, 10.1)	4.3 (-1.7, 10.3)
Gestational diabetes								
No GDM-No GDM								
RR (95% CI)	0.94 (0.73-1.21)	0.90 (0.74-1.09)	0.99 (0.82-1.19)	1.00 (Reference)	1.11 (0.97-1.27)	1.71 (1.48-1.97)	2.18 (1.91-2.49)	2.60 (2.29-2.95)
AR % (95% CI)	2.6 (1.9, 3.2)	2.4 (1.9, 2.8)	2.6 (2.2, 2.9)	2.5 (2.2, 2.9)	2.9 (2.5, 3.3)	4.4 (3.9, 4.9)	5.7 (5.0, 6.4)	7.0 (6.1, 7.9)
RD % (95% CI)	0.01 (-0.7, 0.7)	-0.2 (-0.7, 0.3)	0.00 (-0.5, 0.5)	Reference	0.3 (-0.04, 0.7)	1.9 (1.4, 2.3)	3.2 (2.6, 3.8)	4.5 (3.6, 5.3)
No GDM-GDM								
RR (95% CI)	1.01 (0.75-1.36)	0.95 (0.75-1.19)	0.97 (0.77-1.23)	1.00 (Reference)	0.90 (0.74-1.10)	1.06 (0.88-1.29)	1.14 (0.95-1.37)	1.14 (0.96-1.37)
AR % (95% CI)	30.6 (19.6, 41.6)	24. (14.6, 34.7)	28.5 (20.2, 36.7)	32.2 (24.6, 39.8)	25.5 (17.9, 33.2)	34.9 (27.8, 41.9)	38.5 (30.6, 46.3)	36.4 (28.6, 44.2)
RD % (95% CI)	-1.6 (-12.7, 9.5)	-7.6 (-17.5, 2.4)	-3.7 (-12.5, 5.0)	Reference	-6.6 (-14.2, 0.9)	2.7 (-4.3, 9.7)	6.3 (-0.7, 13.3)	4.2 (-2.8, 11.2)

Outcome	Interpregnancy interval, Absolute risk (95% CI)							
	3 months	6 months	12 months	18 months	24 months	36 months	48 months	60 months
GDM-No GDM								
RR (95% CI)	1.43 (0.84-2.44)	1.17 (0.75-1.81)	1.13 (0.73-1.74)	1.00 (Reference)	1.29 (0.92-1.82)	1.37 (0.94-1.99)	1.40 (0.97-2.01)	1.51 (1.06-2.16)
AR % (95% CI)	20.7 (11.8, 29.6)	27.2 (13.9, 40.5)	17.2 (10.6, 23.8)	7.8 (4.0, 11.7)	19.5 (13.1, 25.9)	18.5 (12.9, 24.1)	22.1 (14.9, 29.3)	17.2 (11.7, 22.7)
RD % (95% CI)	12.9 (3.7, 22.1)	19.4 (5.4, 33.4)	9.3 (2.2, 16.4)	Reference	11.7 (5.4, 17.9)	10.6 (4.9, 16.3)	14.3 (7.1, 21.4)	9.4 (4.6, 14.1)
GDM-GDM								
RR (95% CI)	0.94 (0.62-1.42)	1.19 (0.93-1.51)	1.22 (0.97-1.54)	1.00 (Reference)	1.18 (0.98-1.43)	1.10 (0.89-1.36)	1.08 (0.88-1.33)	1.15 (0.93-1.42)
AR % (95% CI)	54.6 (31.1, 78.1)	75.5 (61.5, 89.6)	77.8 (66.5, 89.1)	70.3 (52.9, 87.7)	73.7 (64.0, 83.4)	79.1 (62.3, 95.9)	64.5 (52.0, 77.1)	73.9 (55.5, 92.4)
RD % (95% CI)	-3.3 (-12.1, 5.6)	5.3 (-8.1, 18.6)	7. (-4.9, 19.9)	0.00 (0.00, 0.00)	3.4 (-10.3, 17.1)	8.7 (-0.1, 17.6)	-5.8 (-20.3, 8.9)	3.6 (-6.9, 14.2)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for maternal age, SES, birth year, ethnicity, marital status at birth prior to IPI and partner change at recent birth with 18-month of IPI as reference. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (26.5) and birth year in 2010 at birth prior to the IPI; *PE, preeclampsia; GDM, gestational diabetes*

Although the information on fecundity was not available, variability in fecundity would be smaller for this cohort, which consisted of mothers who had two or more births. A standard limitation of IPI studies, including ours, is the lack of information on dates of miscarriage and gestational age at miscarriage. Finally, because it is both unethical and infeasible to randomise IPI to mothers, we cannot rule out the possibility of bias attributable to the observational design employed in our study. It should be noted that due to small number of events at extremes of IPI for mothers with complications at both of their previous births (PE-PE; GDM-GDM groups) the predicted risks presented should be interpreted cautiously. Furthermore, our findings should be interpreted as average population risks rather than individual-level risks. We expect individual risks will be more variable than the population averages in our study.

7.6.4 Interpretation

We observed that mothers with previous complications had higher absolute risks for developing recurrent complications than their counterparts across the IPI continuum. Risks were minimal at IPIs approximately between 6 and 12 months for both complications. In line with a well-documented recurrence effect of PE and GDM,[6,16] our results show that mothers who had previous PE or GDM had approximately eight-fold and five-fold increase in absolute risk of PE and GDM in the subsequent pregnancy as compared to mothers with no previous complications respectively. But, most notably, the range of absolute risk for mothers with no previous PE and previous PE (12% to 15%) and for mothers with no previous GDM and previous GDM (30% to 40%) was substantially greater than the observed increase in risk between IPIs (1% to2% for PE and 2% to 8% for GDM). That is, the dominant factor contributing to risk was the previous pregnancy complication, not the IPI. For mothers with no previous PE, where we observed a relatively larger relative risk of short and long IPIs, there was a small increase in absolute risk for both short and long IPIs (~1% for PE and ~5% for GDM). Additionally, for mothers with previous PE or GDM the increased risks were relatively larger across IPI (2% for PE and 8% for GDM), but again the added risk due to IPIs was relatively low as compared to the higher risk of recurrence. This implies that previous pregnancy complications were more important than IPIs in contributing to the risk of PE or GDM in subsequent pregnancies.

Previous studies have shown associations between both short and long IPIs and increased risk of pregnancy complications in the subsequent pregnancy.[9,10,16,25] We showed that, for mothers with no previous complications, IPI is associated with an increased risk of complications in subsequent pregnancies. Similarly, consistent with our findings, the risk of PE in the second

pregnancy increased with increasing IPI for only mothers with no history of PE.[14] The observed higher risks at shorter IPIs (<6 months) for mothers with complications in either both or immediately preceding pregnancy can be explained by the *maternal depletion hypothesis*,[26] whereby shorter intervals may not allow sufficient time for recovery from physiological stress at the maternal-fetal interface of a previous pregnancy. The adverse associations observed at longer IPIs for these complications might be attributable to loss of physiologic adaptation under the hypothesis that the benefits of a previous birth in terms of physiological adaptation are gradually lost.[26] Unmeasured variables such as changes in body mass index, pregnancy intention can also confound the association between IPI and pregnancy complications.[27] However, results from our sensitivity analysis examining the inclusion of potential confounders (e.g., smoking, paternal age, infertility status), did not change our estimates (Supplemental Table 7-3).

7.6.5 Conclusions

This population-based cohort study revealed that the associations between IPI and risk of PE or GDM on subsequent pregnancies varied by presence/absence of these complications in previous pregnancies. The absolute risks following short or long IPIs for both PE and GDM were consistently higher for mothers with the presence of the condition in previous pregnancy. Risk differences varied more across IPIs for mothers with previous pregnancy complications as compared to without the condition in previous pregnancy. However, relative risks were higher for mothers without the condition in previous pregnancy.

Therefore, if the associations observed in this study reflect true effects, although more pregnancy complications can be prevented by avoiding sub-optimal IPIs for women with a history of previous pregnancy complications (because of their higher baseline level of risk). Proportionally more pregnancy complications are attributable to sub-optimal IPI for mothers without a history of the pregnancy complications (because of their higher relative risks).

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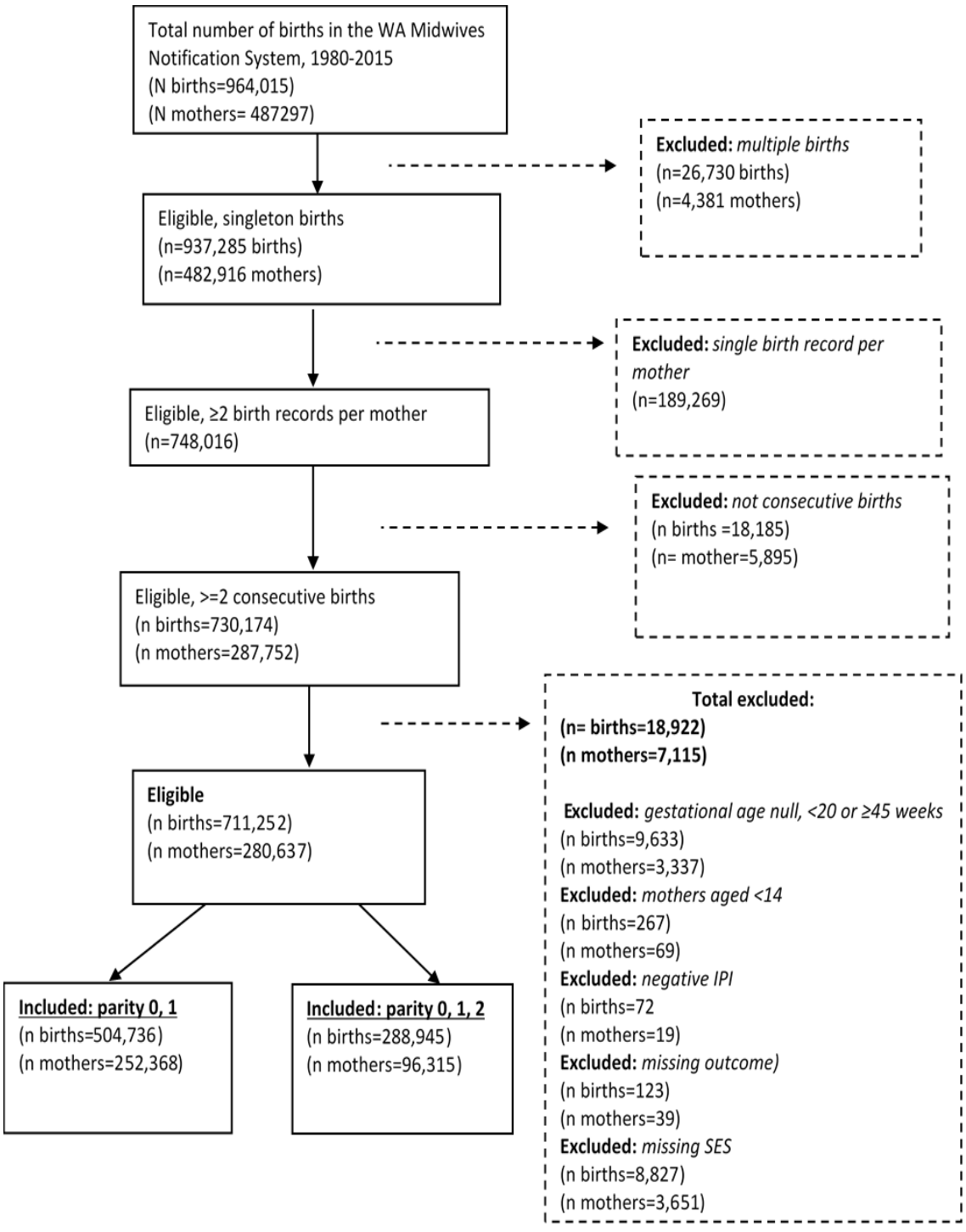
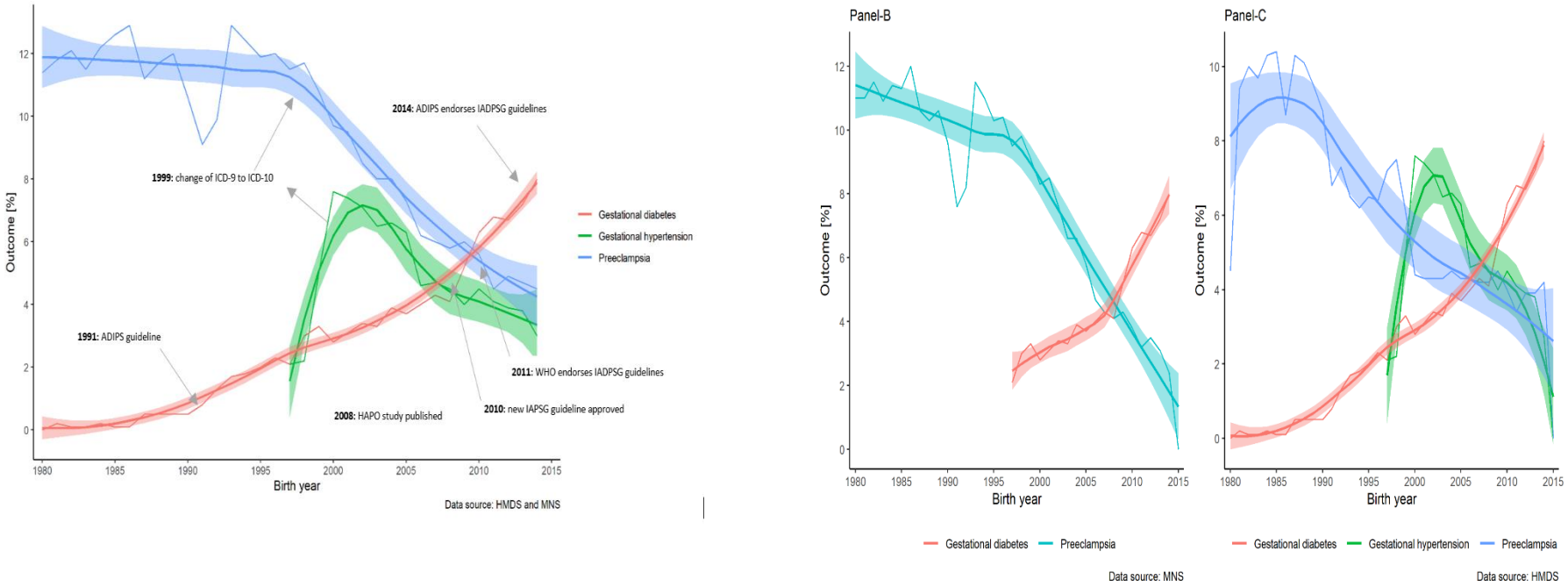
7.8 SUPPLEMENTARY MATERIAL

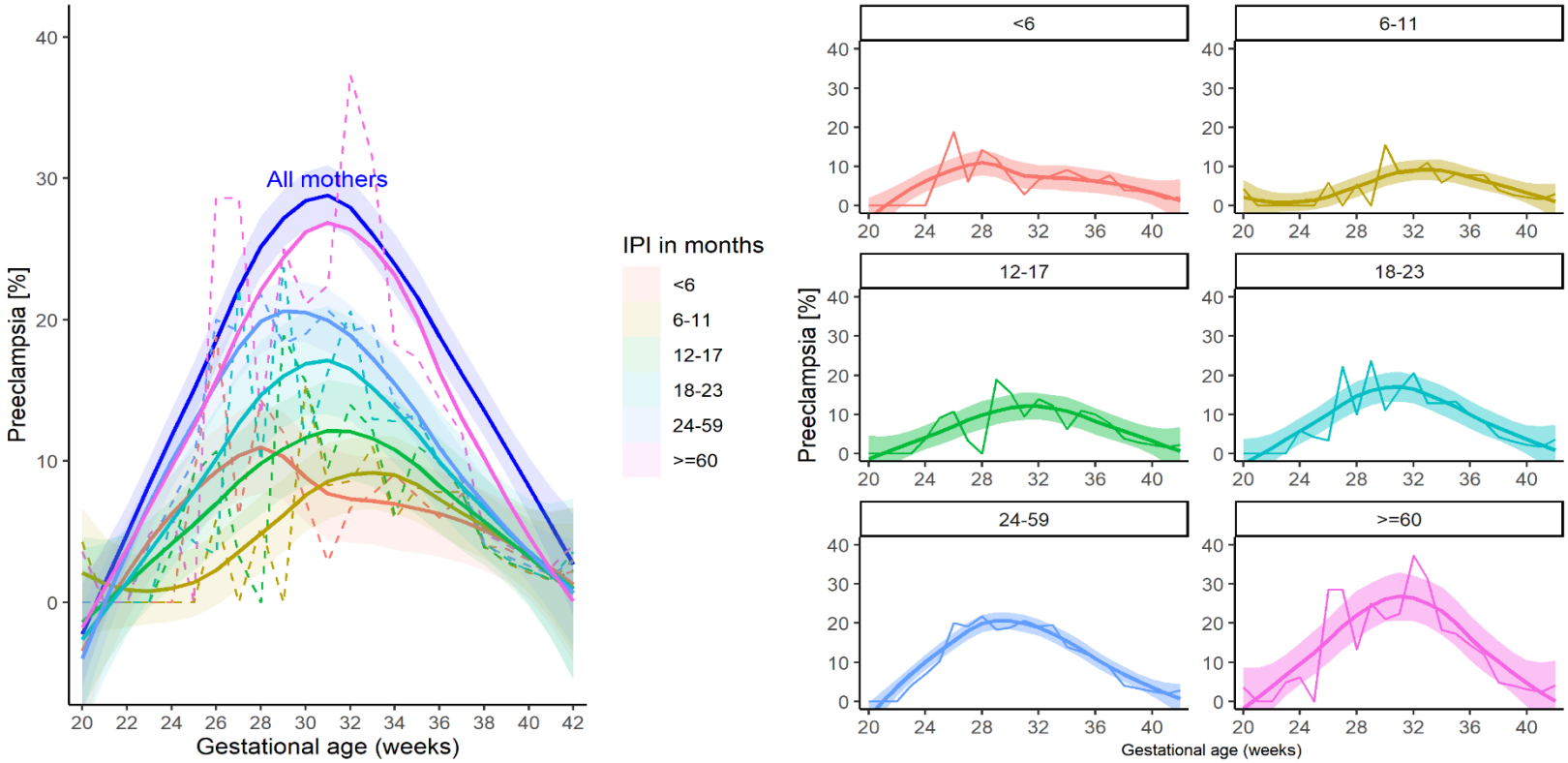


Supplemental Figure 7-1 Inclusion and exclusion of study cohorts



Abbreviations: ICD: International Classification of diseases; ADIPS: Australian Diabetes in Pregnancy Society ; IAPSG: International Assocation of Diabetes in Pregnancy Study Groups; HAPO: Hyperglycemia and Adverse Outcomes Study; MNS: Midwifery Notifications System; HMDS: Hospital Morbidity Data System

Supplemental Figure 7-2 Proportion of pregnancy complications at first pregnancy over study period (1980-2015), WA



Supplemental Figure 7-3 Proportion of preeclampsia at first pregnancy at each gestational age stratified by IPI groups, WA, 1980-2015

Supplemental Table 7-1 Counts and percentage of pregnancy complications during first and second singleton pregnancies by interpregnancy interval for mothers with first two consecutive births during the study period

	Interpregnancy Interval, No. (%) of pregnancies						
	Total	<6	6-11	12-17	18-23	24-59	≥60
	252,368	12,104 (4.8)	42,470 (16.8)	55,218 (21.9)	42,934 (17.0)	79,950 (31.7)	19,692 (7.8)
Preeclampsia							
First birth	23,961 (9.5)	1,098 (4.6)	3,792 (15.8)	4,981 (20.8)	4,054 (16.9)	7,970 (33.3)	2,066 (8.6)
Second birth	5,387 (2.4)	271 (2.5)	748 (1.9)	1,012 (2.0)	835 (2.1)	1,813 (2.5)	708 (4.0)
First and second	4,635 (19.3)	227 (20.7)	701 (18.5)	947 (19.0)	796 (19.6)	1,547 (19.4)	417 (20.2)
Gestational diabetes							
First birth	6,604 (2.6)	324 (4.9)	1,203 (18.2)	1,481 (22.4)	1183 (17.9)	2060 (31.2)	353 (5.3)
Second birth	6,349 (2.6)	228 (1.9)	708 (1.7)	1,022 (1.9)	885 (2.1)	2,427 (3.1)	1,079 (5.6)
First and second	2,739 (41.5)	142 (43.8)	444 (36.9)	614 (41.5)	484 (40.9)	890 (43.2)	165 (46.7)

Supplemental Table 7-2 Adjusted Relative Risk (RRs) and predicted absolute risks (ARs) of pregnancy complications at their last birth according to IPI stratified by pregnancy complications at any previous pregnancy (n=280,637 mothers)

	Interpregnancy interval, Absolute risk (95% CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
Preeclampsia								
Any previous PE (n=28,431 mothers)								
AR (95% CI)	1.08 (0.93-1.25)	1.00 (0.91-1.11)	1.03 (0.94-1.14)	1.00 (Reference)	0.99 (0.92-1.07)	1.05 (0.97-1.13)	1.06 (0.98-1.14)	1.05 (0.97-1.13)
AR % (95% CI)	12.8 (12.1, 16.6)	11.8 (11.7, 14.8)	12.5 (12.3, 15.1)	12.2 (11.9, 14.6)	12.2 (11.9, 14.4)	12.7 (12.6, 15.1)	12.5 (12.7, 15.4)	12.6 (12.6, 15.3)
RD % (95% CI)	0.6 (-1.4, 2.6)	-0.3 (-1.7, 1.0)	0.33 (-0.9, 1.6)	Reference	-0.03 (-1.0, 1.0)	0.5 (-0.0, 1.6)	0.3 (-0.8, 1.3)	0.4 (-0.8, 1.6)
No any previous PE (n=252,206 mothers)								
RR (95% CI)	1.09 (0.93-1.29)	1.01 (0.91-1.13)	0.94 (0.85-1.05)	1.00 (Reference)	1.03 (0.95-1.11)	1.29 (1.18-1.40)	1.42 (1.31-1.54)	1.49 (1.37-1.61)
AR % (95% CI)	1.1 (1.0, 1.4)	1.0 (0.9, 1.3)	0.9 (0.9, 1.1)	1.0 (0.99, 1.2)	1.0 (1.0, 1.2)	1.3 (1.3, 1.5)	1.4 (1.4, 1.7)	1.5 (1.5, 1.8)
RD % (95% CI)	0.1 (-0.1, 0.3)	0.02 (-0.10, 0.1)	-0.06 (-0.16, 0.05)	Reference	0.04 (-0.05, 0.1)	0.3 (0.2, 0.4)	0.5 (0.3, 0.6)	0.5 (0.4, 0.7)
Gestational diabetes								
Any previous GDM (n=10,001 mothers)								
RR (95% CI)	1.02 (0.90-1.15)	0.91 (0.83-1.00)	0.94 (0.86-1.02)	1.00 (Reference)	0.98 (0.92-1.05)	1.08 (1.00-1.16)	1.13 (1.05-1.21)	1.14 (1.06-1.23)
AR % (95% CI)	38.2 (30.3, 46.0)	33.8 (27.4, 40.2)	34.9 (27.5, 42.3)	37.7 (31.4, 44.0)	37.0 (30.4, 43.5)	40.9 (35.4, 46.5)	42.8 (38.0, 47.7)	43.6 (38.6, 48.7)
RD % (95% CI)	0.4 (-4.7, 5.6)	-3.9 (-7.4, -0.4)	-2.81 (-6.5, 0.8)	Reference	-0.8 (-3.6, 2.1)	3.2 (-0.03, 6.4)	5.08 (1.4, 8.8)	5.9 (2.3, 9.5)
No any previous GDM (n=270,636 mothers)								
RR (95% CI)	0.89 (0.77-1.03)	0.86 (0.78-0.95)	0.95 (0.87-1.04)	1.00 (Reference)	1.18 (1.11-1.26)	1.72 (1.61-1.85)	2.12 (1.98-2.27)	2.50 (2.34-2.68)
AR % (95% CI)	2.6 (2.3, 3.0)	2.5 (2.2, 2.7)	2.7 (2.5, 2.9)	2.8 (2.6, 3.0)	3.4 (3.1, 3.6)	5.0 (4.7, 5.3)	6.3 (5.9, 6.7)	7.6 (7.1, 8.1)
RD % (95% CI)	-0.1 (-0.6, 0.3)	-0.3 (-0.6, -0.1)	-0.1 (-0.4, 0.2)	Reference	0.6 (0.4, 0.8)	2.2 (1.9, 2.5)	3.5 (3.1, 3.9)	4.8 (4.4, 5.3)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for maternal age, parity, SES, birth year, ethnicity, marital status at birth prior to IPI and partner change at recent birth with 18-month of IPI as reference. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (25.1) and birth year in 2010 at birth prior to the IPI; *PE, preeclampsia; GDM, gestational diabetes*

Supplemental Table 7-3 Adjusted Relative Risk (RRs) and predicted absolute risks (ARs) of pregnancy complications at parity 1 according to IPI stratified by pregnancy complication at parity 0 for a cohort of mothers with their first two consecutive births at the end of the study period (1997 onwards) (n=119,902 mothers

	Interpregnancy interval, Absolute risk (95% CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
Preeclampsia								
Previous PE								
RR (95% CI)	1.23 (0.94-1.61)	0.88 (0.73-1.07)	0.94 (0.79-1.12)	1.00 (Reference)	0.9 (0.78-1.04)	0.96 (0.83-1.13)	0.98 (0.84-1.14)	0.95 (0.81-1.11)
AR % (95% CI)	17.7 (12.7, 22.7)	12.7 (9.5, 15.9)	13.60 (10.2, 17.1)	14.5 (11.2, 17.8)	13.0 (9.7, 16.4)	13.9 (11.2, 16.6)	14.1 (11.2, 17.1)	13.7 (10.6, 16.7)
RD % (95% CI)	3.2 (-1.7, 8.1)	-1.8 (-4.5, 0.9)	-0.9 (-3.4, 1.7)	Reference	-1.5 (-3.5, 0.6)	-0.60 (-3.0, 1.8)	-0.4 (-2.8, 2.0)	-0.8 (-3.2, 1.5)
No previous PE								
RR (95% CI)	1.31 (1.00-1.71)	0.94 (0.77-1.15)	0.99 (0.82-1.19)	1.00 (Reference)	0.99 (0.86-1.15)	1.26 (1.07-1.48)	1.38 (1.17-1.63)	1.43 (1.21-1.69)
AR % (95% CI)	1.5 (1.1, 1.90)	0.9 (0.7, 1.1)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.9 (0.7, 1.0)	1.2 (1.0, 1.4)	1.5 (1.2, 1.8)	1.6 (1.3, 1.9)
RD % (95% CI)	0.7 (0.2, 1.1)	0.1 (-0.1, 0.2)	0.01 (-0.2, 0.2)	Reference	0.02 (-0.1, 0.2)	0.4 (0.2, 0.6)	0.7 (0.4, 0.9)	0.8 (0.5, 1.1)
Gestational diabetes								
Previous GDM								
RR (95% CI)	1.10 (0.94-1.29)	0.85 (0.76-0.96)	0.93 (0.83-1.04)	1.00 (Reference)	0.93 (0.85-1.02)	1.05 (0.95-1.16)	1.12 (1.02-1.24)	1.15 (1.04-1.28)
AR % (95% CI)	38.8 (26.3, 51.2)	28.9 (20.1, 37.8)	31.4 (20.0, 42.7)	34.9 (24.9, 44.9)	31.6 (20.5, 42.6)	37.2 (27.1, 47.3)	40.0 (30.2, 49.9)	42.5 (35.9, 49.2)
RD % (95% CI)	3.9 (-3.8, 11.6)	-5.9 (-10.4, -1.5)	-3.5 (-8.0, 1.0)	Reference	-3.3 (-7.1, 0.5)	2.4 (-1.9, 6.6)	5.2 (0.7, 9.6)	7.7 (0.7, 14.6)
No previous GDM								
RR (95% CI)	1.03 (0.85-1.23)	0.89 (0.78-1.00)	0.96 (0.85-1.07)	1.00 (Reference)	1.22 (1.12-1.34)	1.73 (1.57-1.90)	2.10 (1.91-2.31)	2.49 (2.26-2.73)
AR % (95% CI)	2.8 (2.2, 3.3)	2.2 (1.9, 2.5)	2.3 (2.0, 2.6)	2.4 (2.1, 2.7)	3.0 (2.6, 3.3)	4.4 (3.9, 4.8)	5.6 (5.0, 6.2)	6.7 (6.0, 7.4)
RD % (95% CI)	0.4 (-0.2, 0.9)	-0.2 (-0.5, 0.1)	-0.09 (-0.4, 0.2)	Reference	0.6 (0.3, 0.8)	2.0 (1.6, 2.4)	3.2 (2.7, 3.7)	4.3 (3.7, 5.0)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for maternal age, SES, birth year, ethnicity, smoking, fertility treatment, paternal age, marital status at birth prior to IPI and partner change at recent birth with 18-month of IPI as reference. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); Predicted absolute risks are reported at representative values of covariates: Caucasian, married, not smoking, no fertility treatment, average paternal age (age group; 25-34 years), average SES, average maternal age (25.1) and birth year in 2010 at birth prior to the IPI; *PE, preeclampsia; GDM, gestational diabetes*

Supplemental Table 7-4 Adjusted Relative Risk (RRs) and predicted absolute risks (ARs) of pregnancy complications at parity 2 according to IPI stratified by pregnancy complications at parity 0 and parity 1 (n=96,315 mothers)

	Interpregnancy interval, Absolute risk (95% CI)							
Outcome	**3 months**	**6 months**	**12 months**	**18 months**	**24 months**	**36 months**	**48 months**	**60 months**
Preeclampsia								
No PE-No PE								
RR (95% CI)	0.68 (0.48-0.96)	0.84 (0.68-1.05)	0.92 (0.75-1.13)	1.00 (Reference)	0.88 (0.75-1.04)	1.27 (1.08-1.51)	1.53 (1.31-1.80)	1.63 (1.39-1.93)
AR % (95% CI)	0.7 (0.4, 0.9)	0.8 (0.6, 1.0)	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	0.9 (0.8, 1.1)	1.4 (1.1, 1.6)	1.6 (1.4, 1.9)	1.8 (1.5, 2.1)
RD % (95% CI)	-0.4 (-0.7, -0.1)	-0.2 (-0.4, 0.02)	-0.1 (-0.3, 0.1)	Reference	-0.1 (-0.3, 0.05)	0.3 (0.1, 0.5)	0.6 (0.4, 0.8)	0.7 (0.5, 1.0)
No PE-PE								
RR (95% CI)	0.77 (0.45-1.32)	0.84 (0.59-1.19)	1.25 (0.90-1.75)	1.00 (Reference)	1.05 (0.80-1.37)	1.04 (0.77-1.40)	1.02 (0.76-1.35)	1.02 (0.76-1.36)
AR % (95% CI)	15.3 (6.4, 24.3)	16.3 (8.7, 23.8)	24.0 (16.3, 31.6)	19.2 (12.3, 26.2)	19.5 (13.5, 25.6)	19.8 (14.0, 25.5)	18.4 (12.7, 24.2)	17.7 (11.9, 23.5)
RD % (95% CI)	-3.9 (-12.3, 4.5)	-2.9 (-9.5, 3.6)	4.7 (-2.4, 11.8)	Reference	0.3 (-5.3, 5.9)	0.6 (-5.3, 6.4)	-0.8 (-7.9, 6.3)	-1.5 (-9.2, 6.2)
PE-No PE								
RR (95% CI)	1.21 (0.86-1.69)	0.8 (0.60-1.07)	1.26 (0.96-1.65)	1.00 (Reference)	0.95 (0.77-1.18)	1.15 (0.92-1.43)	1.22 (0.99-1.51)	1.25 (1.01-1.55)
AR % (95% CI)	8.1 (4.9, 11.3)	5.2 (3.4, 7.0)	8.4 (6.0, 10.7)	6.5 (4.7, 8.3)	6.2 (4.6, 7.8)	7.4 (5.8, 9.0)	7.9 (6.0, 9.7)	8.1 (6.3, 9.9)
RD % (95% CI)	1.6 (-1.4, 4.6)	-1.3 (-3.0, 0.5)	1.9 (-0.3, 4.0)	Reference	-0.3 (-1.7, 1.1)	0.9 (-0.8, 2.5)	1.4 (-0.4, 3.2)	1.6 (-0.03, 3.2)
PE-PE								
RR (95% CI)	1.36 (0.94-1.95)	1.23 (0.95-1.58)	1.23 (0.96-1.57)	1.00 (Reference)	1.06 (0.86-1.30)	1.1 (0.89-1.38)	1.12 (0.90-1.39)	1.15 (0.93-1.43)
AR % (95% CI)	44.2 (26.9, 61.5)	37.8 (26.8, 48.8)	37.6 (28.3, 46.9)	29.3 (21.5, 37.2)	31.7 (23.8, 39.6)	33.4 (25.9, 41.0)	31.90 (24.3, 39.5)	31.0 (22.7, 39.3)
RD % (95% CI)	14.8 (-1.5, 31.3)	8.5 (-0.9, 17.9)	8.3 (-0.6, 17.1)	Reference	2.4 (-4.3, 9.0)	4.1 (-3.1, 11.3)	2.6 (-5.0, 10.2)	1.7 (-7.202, 10.5)
Gestational diabetes								
No GDM-No GDM								
RR (95% CI)	1.10 (0.85-1.42)	1.01 (0.84-1.23)	1.05 (0.87-1.26)	1.00 (Reference)	1.05 (0.92-1.20)	1.44 (1.24-1.66)	1.64 (1.43-1.87)	1.74 (1.52-2.00)
AR % (95% CI)	3.0 (2.2, 3.9)	2.7 (2.2, 3.3)	2.8 (2.3, 3.2)	2.6 (2.2, 3.0)	2.7 (2.4, 3.1)	3.7 (3.3, 4.1)	4.2 (3.7, 4.7)	4.5 (3.9, 5.0)
RD % (95% CI)	0.4 (-0.4, 1.3)	0.1 (-0.4, 0.7)	0.2 (-0.3, 0.7)	0.00 (0.00, 0.00)	0.12 (-0.2, 0.5)	1.1 (0.6, 1.5)	1.6 (1.1, 2.003)	1.8 (1.3, 2.3)
No GDM -GDM								
RR (95% CI)	1.04 (0.77-1.41)	0.97 (0.77-1.22)	0.98 (0.78-1.24)	1.00 (Reference)	0.89 (0.74-1.08)	1.02 (0.84-1.24)	1.07 (0.89-1.28)	1.04 (0.87-1.26)
AR % (95% CI)	42.1 (29.9, 54.2)	35.0 (25.8, 44.2)	37.3 (29.5, 45.1)	39.7 (31.4, 48.0)	31.7 (24.4, 38.9)	38.2 (31.1, 45.0)	39.6 (31.4, 47.8)	36.3 (26.4, 46.2)
RD % (95% CI)	2.3 (-10.1, 14.7)	-4.7 (-14.6, 5.2)	-2.5 (-11.5, 6.5)	0.00 (0.00, 0.00)	-8.1 (-16.4, 0.2)	-1.5 (-9.8, 6.8)	-0.14 (-8.9, 8.6)	-3.4 (-14.4, 7.6)
GDM-No GDM								

Outcome	Interpregnancy interval, Absolute risk (95% CI)							
	3 months	6 months	12 months	18 months	24 months	36 months	48 months	60 months
RR (95% CI)	1.47 (0.85-2.52)	1.23 (0.79-1.90)	1.14 (0.74-1.77)	1.00 (Reference)	1.25 (0.89-1.76)	1.28 (0.88-1.86)	1.27 (0.88-1.83)	1.34 (0.93-1.93)
AR % (95% CI)	29.0 (15.4, 42.6)	31.5 (15.6, 47.4)	23.7 (14.2, 33.2)	13.4 (7.6, 19.2)	23.0 (15.3, 30.7)	19.0 (12.7, 25.4)	18.7 (12.1, 25.4)	12.7 (4.6, 20.8)
RD % (95% CI)	15.6 (1.6, 29.6)	18.1 (1.4, 34.8)	10.3 (-0.2, 20.7)	0.00 (0.00, 0.00)	9.6 (2.1, 17.1)	5.6 (-0.6, 11.9)	5.3 (-0.7, 11.4)	-0.7 (-7.525 6.2)
GDM-GDM								
RR (95% CI)	0.97 (0.65-1.45)	1.19 (0.93-1.52)	1.21 (0.96-1.52)	1.00 (Reference)	1.15 (0.95-1.39)	1.07 (0.86-1.32)	1.04 (0.84-1.28)	1.07 (0.87-1.33)
AR % (95% CI)	58.7 (34.2, 83.2)	66.7 (52.6, 80.8)	69.9 (59.6, 80.1)	64.2 (50.0, 78.5)	68.8 (58.6, 79.0)	76.5 (60.1, 93.0)	65.4 (50.4, 80.4)	77.0 (54.2, 99.9)
RD % (95% CI)	-5.5 (-27.6, 16.6)	2.5 (-14.6, 19.6)	5.6 (-9.1, 20.4)	0.00 (0.00, 0.00)	4.6 (-7.5, 16.6)	12.3 (1.2, 23.5)	1.2 (-9.8, 12.1)	12.8 (-2.6, 28.1)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for SES, birth year, ethnicity, marital status, and partner change at the time of the outcome (third birth) with 18-month of IPI as reference. We modelled maternal age using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (31.2) and birth year in 2010 at the time of the outcome. *PE, preeclampsia; GDM, gestational diabetes*

Supplemental Table 7-5 Rates of pregnancy complications by data source in the study cohort of mothers with their first two consecutive births during the study period, WA, 1980-2015 [n=503,980 births**]**

	Rates of outcome by data source (% [n/N])				
Outcomes	**MNS**	**HMDS**	**MNS or HMDS**	**MNS and HMDS**	**kappa***
PE	5.6 [28,482/504,736]	4.6 [22,940/503,980]	6.7 [33,983/504,736]	3.6 [17,439/487,437]	0.66 [0.65-0.67]
GDM	2.4 [12,019/504,736]	2.5 [12,686/503,980]	3.1 [15,692/504,736]	1.8 [9,013/497,303]	0.72[0.71-0.73]
GH	4.1 [220/5,378]	2.3 [11,735/503,980]	2.3 [11,828/503,980]	2.5 [127/5,117]	0.47[0.42-0.53]
HDP	5.7 [28,702/504,736]	6.8 [34,338/504,736]	8.2 [41,545/504,736]	4.4 [21,595/484,686]	0.66[0.65-0.66]

*Kappa statistics for MNS vs HMDS; PE: Preeclampsia; GH; Gestational hypertension; GDM: Gestational diabetes; HDP: Hypertensive disorders of pregnancy [composite outcome of PE and GH]; MNS: Midwifery Notification System; HMDS: Hospital Morbidity Data System

Supplemental Table 7-6 Adjusted Relative Risk (RRs) and predicted absolute risks (ARs) of pregnancy complications according to IPI stratified by pregnancy complication at first pregnancy for mothers with their first two consecutive births during the study period (n=252,368 mothers): Gestational hypertension and hypertensive disorders of pregnancy as a composite outcome

	Interpregnancy interval (months), risk estimates (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
Gestational hypertension								
Previous GH								
RR (95% CI)	1.06 (0.76-1.49)	0.89 (0.71-1.11)	1.00 (0.82-1.23)	1 (Reference)	0.96 (0.81-1.13)	1.03 (0.86-1.24)	1.05 (0.87-1.27)	1.05 (0.87-1.27)
AR % (95% CI)	18.3(12.3, 24.3)	13.3 (10.2, 16.4)	14.0 (11.2, 16.8)	14.1 (11.3, 16.9)	13.3 (10.6, 16.0)	14.8 (12.0, 17.6)	17.8 (13.9, 21.6)	17.3 (13.7, 20.9)
RD % (95% CI)	4.21 (-1.97, 10.40)	-0.80 (-3.94, 2.35)	-0.11 (-2.91, 2.69)	Reference	-0.82 (-3.17, 1.54)	0.71 (-1.92, 3.35)	3.67 (-0.22, 7.57)	3.23 (-0.31, 6.78)
No previous GH								
RR (95% CI)	1.04 (0.87-1.26)	0.79 (0.69-0.90)	0.82 (0.72-0.93)	1 (Reference)	1.06 (0.96-1.17)	1.42 (1.28-1.58)	1.66 (1.50-1.84)	1.82 (1.65-2.01)
AR % (95% CI)	2.9 (2.3, 3.4)	2.0 (1.7, 2.3)	2.0 (1.8, 2.2)	2.4 (2.1, 2.7)	2.6 (2.30, 2.8)	3.6 (3.2, 3.9)	4.4 (3.9, 4.8)	4.9 (4.4, 5.5)
RD % (95% CI)	0.46 (-0.08, 1.00)	-0.38 (-0.68, -0.08)	-0.40 (-0.68, -0.12)	Reference	0.16 (-0.08, 0.40)	1.18 (0.86, 1.50)	1.95 (1.53, 2.37)	2.54 (2.02, 3.05)
Hypertensive disorder of pregnancy (composite outcome)								
Previous HDP								
RR (95% CI)	1.1 (0.98-1.23)	0.94 (0.87-1.03)	0.93 (0.86-1.01)	1 (Reference)	0.97 (0.91-1.03)	1.05 (0.98-1.12)	1.09 (1.02-1.17)	1.11 (1.03-1.18)
AR % (95% CI)	25.6 (22.6, 28.6)	21.8 (19.8, 23.8)	21.2 (19.4, 22.9)	22.7 (20.9, 24.6)	22.0 (20.3, 23.7)	24.1 (22.4, 25.8)	25.3 (23.4, 27.2)	25.8 (23.9, 27.8)
RD % (95% CI)	2.90 (-0.19, 6.00)	-0.93 (-2.85, 1.00)	-1.54 (-3.28, 0.20)	Reference	-0.74 (-2.18, 0.71)	1.41 (-0.27, 3.09)	2.56 (0.78, 4.34)	3.11 (1.17, 5.05)
No previous HDP								
RR (95% CI)	1.19 (1.04-1.36)	0.97 (0.88-1.07)	0.9 (0.82-0.99)	1 (Reference)	1.06 (0.99-1.14)	1.32 (1.22-1.42)	1.45 (1.34-1.57)	1.53 (1.41-1.66)
AR % (95% CI)	2.6 (2.2, 2.9)	1.9 (1.7, 2.1)	1.7 (1.6, 1.9)	1.9 (1.7, 2.0)	2.0 (1.8, 2.2)	2.6 (2.4, 2.8)	3.0 (2.7, 3.3)	3.3 (3.0, 3.6)
RD % (95% CI)	0.70 (0.35, 1.05)	0.07 (-0.13, 0.26)	-0.15 (-0.32, 0.02)	Reference	0.14 (0.00, 0.28)	0.73 (0.55, 0.91)	1.14 (0.91, 1.37)	1.43 (1.16, 1.70)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for maternal age, SES, birth year, ethnicity, marital status at birth prior to IPI and partner change at recent birth with 18-month of IPI as reference. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (25.1) and birth year in 2010 at birth prior to the IPI; *GH, gestational hypertension ; HDP, hypertensive disorders of pregnancy*

Supplemental Table 7-7 Adjusted Relative Risk (RRs) and predicted absolute risks (ARs) of gestational diabetes according to IPI stratified by gestational diabetes at first pregnancy for mothers with their first two consecutive births during the study period [comparison based on source of record]

	Interpregnancy interval (months), risk estimates (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
Gestational diabetes [recorded in either MNS or HMDS]								
Previous GDM [n=6,604]								
RR (95% CI)	1.11 (0.95-1.29)	0.87 (0.78-0.97)	0.94 (0.85-1.04)	1.00 (Reference)	0.96 (0.88-1.04)	1.07 (0.98-1.18)	1.14 (1.05-1.25)	1.18 (1.07-1.29)
AR % (95% CI)	39.7 (30.1, 49.2)	30.3 (23.5, 37.1)	32.6 (24.5, 40.7)	35.3 (28.0, 42.6)	33.3 (25.4, 41.2)	38.6 (31.8, 45.5)	41.5 (35.1, 47.8)	43.2 (38.3, 48.2)
RD % (95% CI)	4.4 (-2.6, 11.3)	-5.0 (-9.0, -0.9)	-2.7 (-6.7, 1.3)	Reference	-2.0 (-5.4, 1.4)	3.3 (-0.5, 7.2)	6.2 (1.9, 10.5)	7.9 (2.1, 13.9)
No previous GDM [n=245,764]								
RR (95% CI)	1.00 (0.85-1.16)	0.87 (0.78-0.97)	0.87 (0.79-0.96)	1.00 (Reference)	1.20 (1.11-1.29)	1.75 (1.62-1.90)	2.18 (2.01-2.35)	2.58 (2.38-2.79)
AR % (95% CI)	3.0 (2.5, 3.4)	2.4 (2.2, 2.7)	2.3 (2.1, 2.6)	2.7 (2.4, 2.9)	3.2 (3.0, 3.5)	4.9 (4.5, 5.2)	6.3 (5.8, 6.8)	7.6 (7.0, 8.3)
RD % (95% CI)	0.3 (-0.2, 0.8)	-0.2 (-0.5, 0.1)	-0.3 (-0.6, -0.1)	Reference	0.5 (0.4, 0.9)	2.2 (1.9, 2.5)	3.6 (3.2, 4.1)	4.90 (4.4, 5.6)
Gestational diabetes [concordant records]								
Previous GDM [n=3,254]								
RR (95% CI)	1.22 (0.99-1.51)	0.85 (0.71-1.00)	0.95 (0.81-1.11)	1.00 (Reference)	0.91 (0.79-1.04)	1.02 (0.89-1.19)	1.10 (0.95-1.27)	1.13 (0.97-1.31)
AR % (95% CI)	45.5 (31.4, 59.7)	31.8 (19.3, 44.3)	36.7 (22.8, 50.6)	37.6 (25.5, 49.8)	35.5 (21.3, 49.6)	39.2 (26.2, 52.3)	43.6 (27.5, 59.80)	38.1 (30.3, 45.9)
RD % (95% CI)	7.9 (-2.2, 18.1)	-5.8 (-11.6, -0.01)	-0.3 (-7.0, 5.2)	Reference	-2.2 (-7.6, 3.2)	1.6 (-4.1, 7.3)	6.0 1.0, 13.0)	0.5 (-8.0, 9.0)
No previous GDM [n=242,538]								
RR (95% CI)	0.99 (0.80-1.22)	0.84 (0.72-0.97)	0.87 (0.76-1.00)	1.00 (Reference)	1.21 (1.10-1.34)	1.93 (1.73-2.15)	2.54 (2.29-2.82)	3.16 (2.86-3.50)
AR % (95% CI)	2.1 (1.6, 2.5)	1.6 (1.4, 1.9)	1.6 (1.40, 1.8)	1.8 (1.6, 2.0)	2.2 (2.0, 2.5)	3.7 (3.3, 4.1)	5.1 (4.5, 5.7)	6.5 (5.7, 7.3)
RD % (95% CI)	0.3 (-0.2, 0.7)	-0.2 (-0.5, 0.1)	-0.2 (-0.4, 0.03)	Reference	0.4 (0.2, 0.6)	1.9 (1.6, 2.2)	3.3 (2.8, 3.8)	4.7 (4.0, 5.4)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for maternal age, SES, birth year, ethnicity, marital status at birth prior to IPI and partner change at recent birth with 18-month of IPI as reference. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (25.1) and birth year in 2010 at birth prior to the IPI**;** *PE, preeclampsia; GDM, gestational diabetes; MNS: Midwifery Notification System; HMDS: Hospital Morbidity Data Collection*

Supplemental Table 7-8 Adjusted Relative Risk (RRs) of preeclampsia according to IPI stratified by preeclampsia at first pregnancy for mothers with their first two consecutive births during the study period (analyses restricted to sibling pairs when the first baby was born **before 1 January 2010**; sensitivity analyses for fixed cohort bias)

	Interpregnancy interval (months), risk estimates (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
Preeclampsia								
Previous PE								
A: main cohort								
RR (95% CI)	1.09 (0.94-1.25)	0.99 (0.89-1.09)	0.93 (0.85-1.03)	1 (Reference)	0.97 (0.90-1.05)	1.04 (0.95-1.13)	1.06 (0.98-1.16)	1.06 (0.98-1.15)
B: restricted cohort								
RR (95% CI)	1.07 (0.92-1.24)	0.99 (0.90-1.10)	0.94 (0.85-1.04)	1 (Reference)	0.96 (0.89-1.04)	1.03 (0.95-1.13)	1.06 (0.98-1.16)	1.06 (0.98-1.15)
No previous PE								
A: main cohort								
RR (95% CI)	1.24 (1.07-1.43)	1 (0.90-1.11)	0.9 (0.81-0.99)	1 (Reference)	1.04 (0.96-1.13)	1.23 (1.13-1.35)	1.34 (1.23-1.46)	1.4 (1.29-1.53)
B: restricted cohort								
RR (95% CI)	1.4 (1.21-1.64)	1.12 (1.03-1.23)	1.01 (0.96-1.06)	1 (Reference)	1.18 (1.08-1.29)	1.41 (1.29-1.53)	1.52 (1.39-1.67)	1.59 (1.45-1.74)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for maternal age, SES, birth year, ethnicity, marital status at birth prior to IPI and partner change at recent birth with 18-month of IPI as reference. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); Predicted absolute risks are reported at representative values of covariates: Caucasian, married, average SES, average maternal age (25.1) and birth year in 2010 at birth prior to the IPI; *PE: Preeclampsia*

Chapter 8: THE INFLUENCE OF PREGNANCY COMPLICATIONS ON INTERPREGNANCY INTERVAL

Study Five. The influence of birth outcomes and pregnancy complications on IPI: A Quantile regression analyses

8.1 PREAMBLE

This chapter (Study Five) is a methodological supplementation (a form of detailed supplementary analyses) designed to answer a critical question whether the consistent findings of an increased risk of complications with long intervals (Chapter 4-7) is influenced by the presence of complications at previous pregnancy (a 'health selection process').

8.2 ABSTRACT

Background: It is well established that short and long interpregnancy intervals (IPIs) are associated with subsequent pregnancy complications. However, little is known whether previous pregnancy complications prolong subsequent IPI.

Methods: We included 251,892 mothers who gave birth to their first two singletons in Western Australia, 1980–2015. Using quantile regression, we investigated whether gestational diabetes, hypertension or preeclampsia in first pregnancy influenced IPI to subsequent pregnancy and whether effects were consistent across the IPI distribution. We considered intervals at the 25th centile of the distribution as 'short' and 75th centile as 'long'.

Results: The average IPI was 26.6 months. It was 0.56 months (95% CI: 0.25-0.88 months) and 1.12 months (95% CI: 0.56 – 1.68 months) longer after preeclampsia, and gestational hypertension respectively. There was insufficient evidence to suggest that the association between previous pregnancy complications and IPI differed by the extent of the interval. However, associations with marital status, race/ethnicity and stillbirth contributed in either shortening or prolonging IPIs differently across the distribution of IPI.

Conclusion: Mothers with preeclampsia and gestational hypertension had slightly longer subsequent interpregnancy intervals than mothers whose pregnancies were not complicated by these conditions. However, the extent of the delay was small (<2 months).

Keywords: quantile regression; interpregnancy interval; pregnancy complications; birth intervals, birth spacing

8.3 INTRODUCTION

Interpregnancy interval (IPI), the period between the end of one pregnancy and conception of the next, has been associated with adverse pregnancy complications.[1, 2] Both short and long IPIs are associated with a greater risk of gestational diabetes and hypertensive complications of pregnancy (preeclampsia, gestational hypertension) in subsequent pregnancies.

It is well established that pregnancy complications have a higher tendency to recur.[3, 4] A recent meta-analysis reported that mothers with long IPIs had an increased risk of recurrent preeclampsia.[3] However, little is known about whether pregnancy complications in a previous pregnancy may influence IPI. If such an association exists, in the presence of recurrence, previous pregnancy complications have the potential to confound the estimated effects of IPI on subsequent pregnancy complications. Moreover, maternal characteristics including age, socio-economic status (SES), race/ethnicity and parity have been associated with both IPI and pregnancy complications.[1, 2, 5] It remains plausible that previously reported associations between IPI on subsequent pregnancy complications were confounding by recurrence risks of complications or underlying characteristics.

This study aimed to ascertain whether preeclampsia, gestational hypertension, and gestational diabetes at first pregnancy influence subsequent IPI and whether the size of this effect varies with IPI distribution.

8.4 METHODS

8.4.1 Design, participants and data sources

We conducted a longitudinal study of mothers who gave birth to their first two singletons (parity 0 and 1) at 20-44 weeks of gestation in Western Australia (WA) between 1980 - 2015. We obtained birth records from the Midwives Notification System (MNS) and maternal hospitalization records from Hospital Morbidity Data Collection.[6, 7] Data sources have been described in detail in our protocol.[8]

Inclusion and exclusion criteria

From 487,297 mothers who gave birth in WA during the study period, we sequentially excluded 229,260 mothers with multiple births, only one birth or non-consecutive parity. These exclusions left 258,037 mothers with the first two consecutive singleton births eligible for analysis. We further excluded mothers who had implausible or missing information for key

covariates (gestational age, SES, maternal age, IPI, and infant weight) (n=6,145), leaving 251,892 mothers (503,784 births) included in the final analyses (Supplemental Figure 8-1).

8.4.2 Outcome

The outcome of interest, IPI, was calculated as the length of time (in months) between the delivery date of the first pregnancy and the estimated conception date of the second pregnancy.[8, 9]

8.4.3 Covariates

Pregnancy complications at parity 0 were ascertained from the MNS and hospital separation codes indicating preeclampsia (ICD-9-AM: 642.4, 642.5, 642.7, ICD-10: O14, O11), gestational hypertension without proteinuria (ICD-9-AM: 642.3, ICD-10: O13) and gestational diabetes (ICD-9-AM: 648.8, ICD-10: O24.4). We considered additional risk factors possibly related to IPI, including maternal age (years) at first birth (continuous), birth year (per 10 years, continuous), SES (per interquartile range, continuous), infant sex, marital status (married vs non-married), race/ethnicity (Caucasian vs Non-Caucasian), birth status (liveborn vs stillborn) and infant weight (per 100g, continuous).

8.4.4 Statistical analysis

We described the baseline characteristics of mothers at their first birth (parity 0) during the study period. We also summarized the distribution of IPI for each covariate of interest. Analysis of variance and Tukey's post-hoc comparisons were used to determine group differences. The Kolmogorov-Smirnov test was used to evaluate the statistical significance of the differences between the distributions.

We used Ordinary Least Squares (OLS) regression to estimate the effect of pregnancy complications and other risk factors on the mean IPI. To obtain differences in the distributions of IPIs, we also employed Quantile Regression (QR), which has been widely used in the analysis of birth weight [10, 11] and recently applied in the context of IPI.[12] We applied QR with IPI divided into 20 quantiles (i.e. every 5th centile) and considered intervals at the 25th centile of the distribution as 'short' and 75th centile as 'long'. Estimates were adjusted for all other covariates except that both hypertensive complications were not included in the same models. We performed the analysis with the 'quantreg' package in R (R Core Team, 2018).

8.5 RESULTS

Cohort characteristics

Of the eligible 258,037 women with their first two consecutive pregnancies between 1980 and 2015, 6,145 were excluded due to missing information on key covariates (gestational length, SES, maternal age, IPI, and infant weight), leaving 251,892 women eligible for analyses (Supplemental Figure 8-1) Mean (± SD) age at study entry (first delivery) was 25.29 (5.2) and peaked between 25-29 years. The majority of the mothers were married and Caucasian (Table 8-1). The prevalence of gestational diabetes, preeclampsia and gestational hypertension at study entry was 2.6%, 9.5% and 2.8%, respectively.

Distribution of IPI

IPI was skewed with a median of 20 months (IQR 12-32 months). The 25th (short) and 75th centiles (long) correspond to 12-month and 32-month interpregnancy intervals. Older mothers had shorter median intervals, and unmarried mothers, non-Caucasian and had lower SES, had longer median IPI (Table 8-1). Kolmogorov-Smirnov tests confirmed that the IPI distributions after preeclampsia, gestational hypertension, and gestational diabetes differed from the IPI distribution after pregnancies without these complications ($p<0.001$, $p=0.027$ and $p<0.001$, respectively).

Interpregnancy interval after pregnancy complications

OLS results indicated that compared to average IPI in all women, mean IPIs were longer in women with either hypertension or preeclampsia in first pregnancy but not after gestational diabetes. Overall, IPIs were 0.56 months (95% CI: 0.25-0.88 months) longer after preeclampsia and 1.12 months (95% CI: 0.56 – 1.68 months) longer after gestational hypertension than after pregnancies without these complications (Supplemental Table 8-1). The large overlap between the OLS and QR results indicated that the association between pregnancy complications and IPI did not differ by the extent of the pregnancy delay (Figure 8-1, Figure 8-2, Figure 8-3).

Table 8-1 Socio-demographic, medical conditions and pregnancy characteristics of mothers at parity 0 (n=251,892 mothers) in Western Australia, 1980-2015

Characteristics	Category	N (%)	IPI months	
			Mean (SE)	Median
		251,892	26.6 (0.05)	20
Maternal age at first birth (years)	14-19	31,377 (12.5)	35.6 (0.19) [a]	24
	20-24	69,128 (27.4)	29.1 (0.11) [a]	20
	25-29	87,246 (34.6)	24.6 (0.06) [a]	19
	30-34	51,477 (20.4)	22.6 (0.07) [a]	19
	≥35	12,664 (5.1)	20.4 (0.12) [a]	17
Marital status	Married	214,666 (85.2)	24.7 (0.04) [a]	19
	Not married	37,226 (14.8)	37.5 (0.18)	26
Ethnicity	Caucasian	219,067 (87.1)	26.4 (0.05) [a]	19
	Non-Caucasian	32,825 (13.0)	27.9 (0.14) [a]	21
Birth year	1980-1984	32,768 (13.0)	26.7 (0.14) [a]	19
	1985-1989	35,599 (14.1)	27.3 (0.14) [a]	20
	1990-1994	36,853 (14.6)	29.7 (0.15) [b]	21
	1995-1999	36,925 (14.6)	30.1 (0.14) [b]	21
	2000-2004	37,190 (14.7)	28.5 (0.12) [a]	21
	2005-2009	43,178 (17.1)	24.5 (0.08) [a]	20
	2010-2015	29,379 (11.6)	18.1 (0.06) [a]	16
SES quintiles	Quintile 1 (most disadvantaged)	51,766 (20.5)	29.1 (0.12) [a]	20
	Quintile 2	52,029 (20.6)	27.3 (0.11) [a]	20
	Quintile 3	51,583 (20.5)	26.6 (0.10) [a]	13
	Quintile 4	49,302 (19.6)	25.4 (0.09) [a]	13
	Quintile 5 (least disadvantaged)	47,212 (18.7)	24.4 (0.09) [a]	19
Pregnancy/birth characteristics of first pregnancy				
Gestational diabetes	Yes	6,614 (2.6)	23.8 (0.23) [a]	19
	No	245,278 (97.4)	26.6 (0.04)	20
Preeclampsia	Yes	23,899 (9.5)	27.7 (0.16) [a]	21
	No	227,993 (90.5)	26.4 (0.05)	13
Gestational hypertension	Yes	7,116 (2.8)	26.3 (0.26) [b]	20
	No	244,776 (97.2)	26.6 (0.04)	20
Infant sex	Male	129,952 (51.6)	26.5 (0.06) [b]	20
	Female	121,940 (48.4)	26.7 (0.07)	20
Birth status	Stillborn	2,001 (0.8)	15.4 (0.51) [a]	7
	Liveborn	249,891 (99.2)	26.7 (0.05)	20
Infant weight (grams)	<1000	1,840 (0.7)	20.1 (0.54) [a]	12
	1000-1499	1,275 (0.5)	27.2 (0.76) [a, c]	20
	1500-2499	11,435 (4.5)	27.9 (0.24) [a]	20
	2500-3499	141,728 (56.3)	26.8 (0.06) [a]	20
	3500-3999	73,590 (29.2)	26.2 (0.08) [a]	19
	>=4000	22,024 (8.7)	26.3 (0.16) [a, d]	19

[a] mean difference is significant; [b] mean difference not significant; [c] mean difference is significant with infant weight <1000g only; [d] mean difference not significant with infants weighed 2500-3499g and 3500-3999g. [a-d] Posthoc comparison at the 0.05 level using Tukey's HSD mean difference; SE: standard error

Interpregnancy interval after other risk factors

For mothers in the lower quantiles (short IPI), there was insufficient evidence for an effect of infant sex, birth weight and mother's age on IPI (Figure 8-2 and Figure 8-3)

Among mothers with IPIs below the 50th percentile, maternal age did not contribute to shorten the IPI, neither did infant sex or birth weight of the first child. However, among mothers in the upper quantiles (long IPIs) (especially those in the top 20th percentile), maternal age played an increasing role on IPI (higher age reduced the IPI up to 2 months the those with the longest IPI) (Figure 8-2)

For mothers in the upper quantiles, the effect of an IQR increase in SES was to shorten the IPI by less than one month (ß $_{tau=0.75}$=-0.39, SE=0.09). Similarly, for mothers), the effect of a 1-year increase in age and a 10-year increase in birth year were to decrease the IPI by approximately half a month and one and half months respectively (ß $_{tau=0.75}$=-0.49, SE=0.01, ß $_{tau=0.75}$=-1.34, SE=0.07). The effect of a 500g increase in birth weight was associated with a delayed IPI of half a month for mothers who had long IPI (ß $_{tau=0.75}$=-0.47, SE=0.05).

There was sufficient evidence that the IPI associations with marital status, race/ethnicity and stillbirth differed by the extent of the pregnancy delay. Nonetheless, the effect of being non-married on IPI was different at the two ends of the IPI distribution (ß $_{tau=0.25}$=2.07, SE=0.09, ß $_{tau=0.75}$=15.67, SE=0.34), exhibiting an increasing trend (25th to 75th percentile). Similarly, being non-Caucasian was associated with a delayed interval of approximately two and a half months for mothers in the upper quantiles of IPI (ß $_{tau=0.75}$=2.54, SE=0.21). Stillbirth had a strong association with shortening IPI, with a greater effect for mothers who had long IPI (ß $_{tau=0.25}$=-8.85, SE=0.07, ß $_{tau=0.75}$=-16.64, SE=0.48) (Figure 8-3).

8.6 DISCUSSION

Using data from a large population cohort of mothers with their first two births, we used quantile regression to ascertain whether pregnancy complications at first pregnancy influences subsequent IPI and verify whether changes occur along the IPI distribution. To our knowledge, no studies have investigated the influence of pregnancy complications on IPI or whether this effect is consistent across the IPI distribution. We observed that mothers with hypertensive complications had slightly longer IPIs (<2 months) than those without the complications. The prolongation was similar in the lower (short) and upper (long) quantiles of IPI distributions.

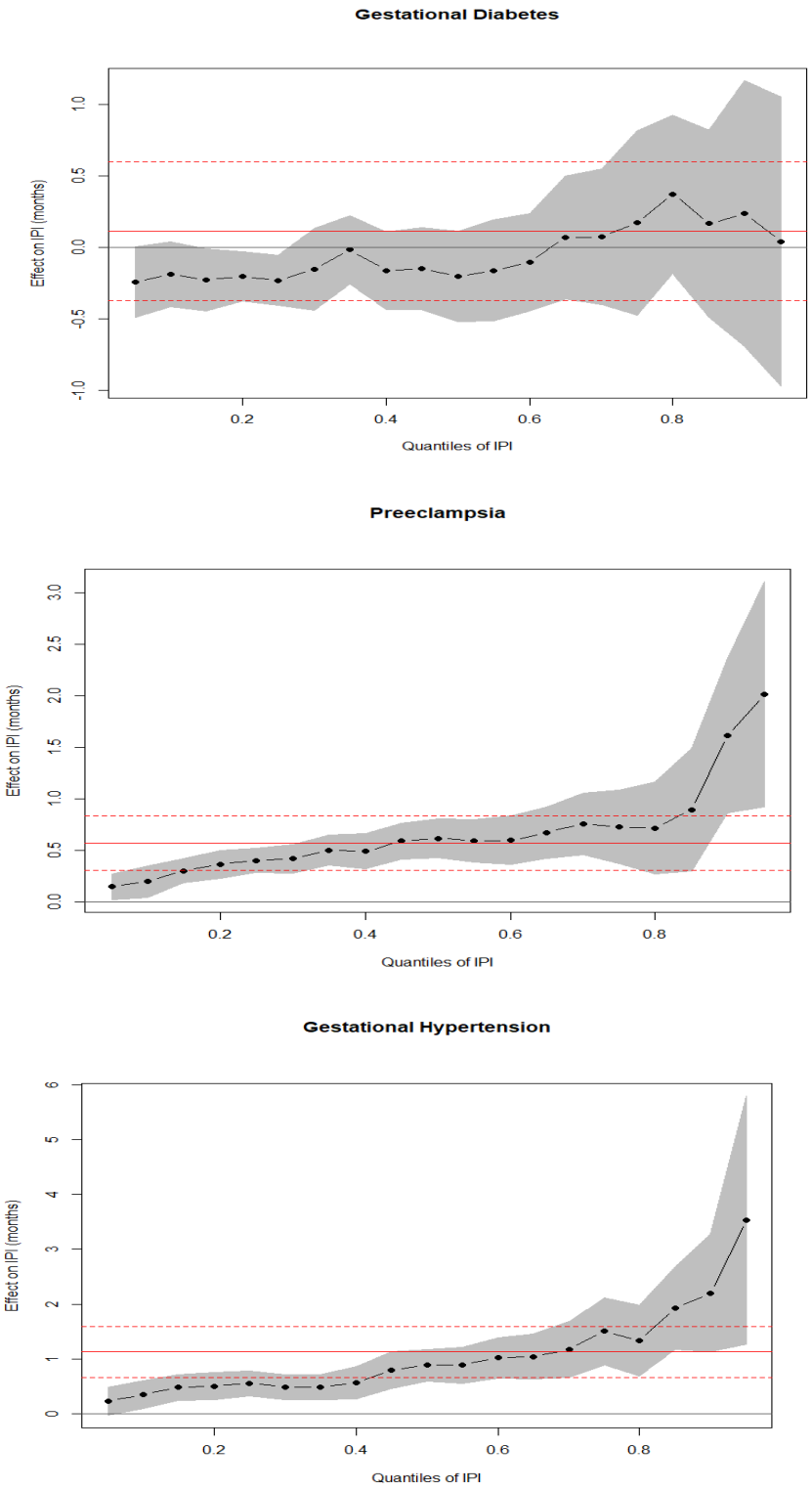


Figure 8-1 Effect of gestational diabetes, preeclampsia and gestational hypertension on different quantiles of IPI distribution

Studies have revealed that mother's age, SES, race/ethnicity and marital status are among factors either delaying or shortening IPI.[2, 5, 13] Those studies however did not examine the entire distribution of IPI, and usually examined IPI as binary outcome, which could rather be sensitive to the cutoff used to define short or long IPI.

Our analysis shows that the magnitude of association with other risk factors differed across the IPI distribution. For SES, maternal age and infant weight, the direction of effect on pregnancy intervals differed between mothers in the lower and upper IPI quantiles. Increased SES was associated with an increase in IPI of <0.5 months for mothers who had shorter intervals (<25th centile, 12 months) but a decrease in IPI of 0.5 to 2 months for mothers in the upper quantile (>75th centile, 32 months). Similarly, a 1-year increase in maternal age was associated with a negligible increase in IPI for mothers who had shorter intervals but a 0.5 to 2 month decreases in IPI for mothers who had longer intervals. Over time, the decreasing trend in IPI was more pronounced for mothers with longer intervals, for whom the decrease ranged from 2 to 8 months per decade.

The QR models' results also indicate that for most of the risk factors, the magnitude of associations was substantially larger at higher IPI quantiles. The effect of stillbirth and birth year in shortening IPI was almost twice and around four times larger at the 75th compared to the 25th quantile. In comparison, the effect of being non-married in delaying IPI was almost eight times larger than its effect on mothers with short IPI. A similar large positive association of race/ethnicity was observed on mothers in the upper quantile, which suggests that being non-Caucasian has a substantial impact in delaying IPI in mothers in the upper quantile. However, it has a negligible effect on the IPI distribution below the median.

In contrast, mother's age, SES and birth weight factors delayed IPI in mothers with short IPI, while shortened the interval in mothers with long IPI, a finding that is missed in the OLS model. This revealed that these risk factors may have multiple distinct effect on IPI, which differ across the distribution. For instance, marital status, SES, race/ethnicity and mother's age has been associated with increased risk of both short and long IPIs.[5]

Together with the increasing trends in maternal age in Australia, these results lead to a hypothesis of potential future improvements in birth outcomes attributable to reductions in longer intervals rather than short intervals. Increases in birth weight of 100g were associated with small <0.2 month increases in IPI for mothers with shorter intervals and <0.8 month decreases in IPI for mothers with longer intervals.

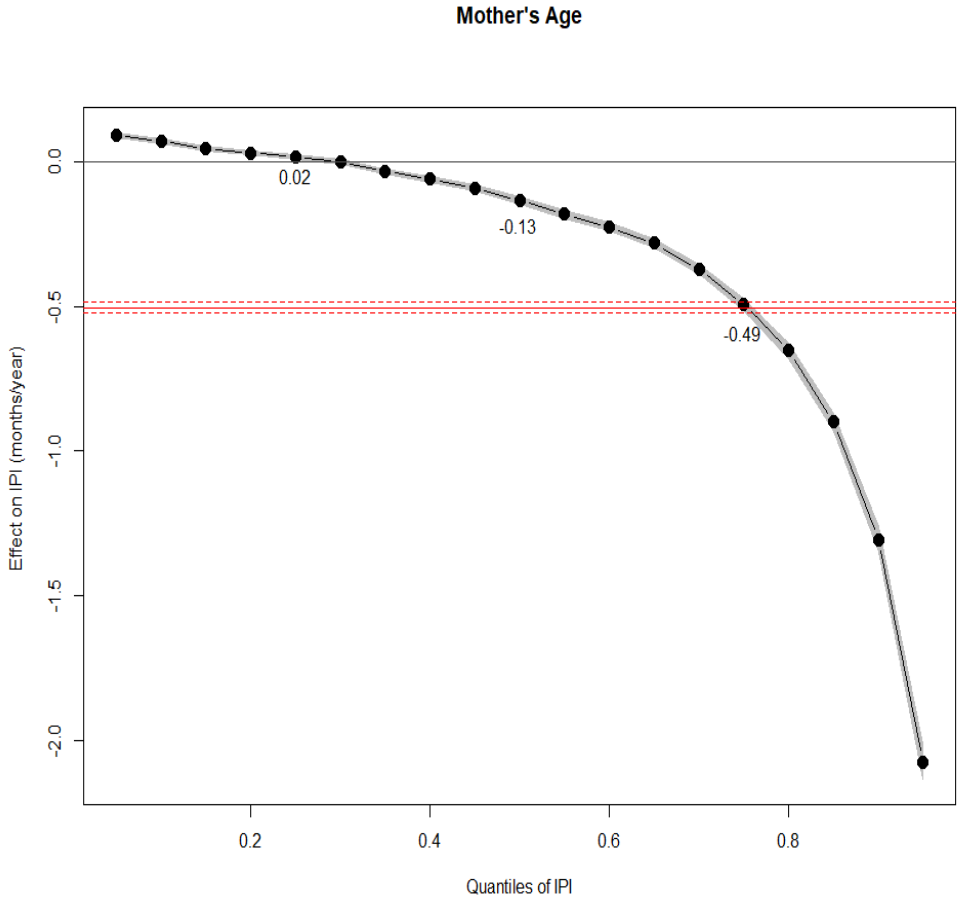


Figure 8-2 Association between a one-year increase in mother's age and IPI in months at deciles of the IPI distribution.

The horizontal solid line (red in colour) shows the average IPI change, -0.5 months, associated with a one-year increase in mother's age linear regression (OLS) coefficients with its 95% CI (parallel dashed lines). The vertical distance of a solid dot from the horizontal axis shows the effect of a one-year increase in mother's age on IPI for the chosen quantile (0.02 months increase in IPI for mothers in the 25th quantile (short IPI), a 0.13 months decrease in IPI for mothers with median IPI and a 0.49 months decrease in IPI for mothers in the 75th quantile (long IPI). Model covariates include birth year, SES, sex, marital status, race/ethnicity, birth status, infant weight, gestational diabetes, gestational hypertension and preeclampsia. Here, the QR coefficients measure the influence of maternal age in the lower quantiles (mothers with short IPI), in the median quantile (mothers with median IPI) and in the upper quantiles (mothers with long IPI) distributions of mothers interpregnancy interval. Differences across quantiles of the conditional distribution of IPI indicate heterogeneous effects of explanatory variables.

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The OLS estimates show that, on average, mothers who were not in a married (or *de facto*) relationship had a 10-month longer mean IPI. Using QR, we showed that marital status has a significant positive effect across all groups (quantiles). However, the effect was largely attributable to mothers with longer IPIs, for whom the difference ranged from 15 to 30 months. Consistent with our previous results, IPIs are much shorter after stillbirth.[14] Moreover, our results indicate that for mothers with longer intervals, stillbirth was associated with interval reductions of more than one year.

In conclusion, IPIs were longer after hypertensive pregnancy complications, but the extent of the delay was small (<2 months) and did not differ across the IPI distribution. This implies that the role of recurrent complications in the association between IPI on subsequent pregnancy complications is minimal. In contrast, the magnitude of associations with marital status, race/ethnicity and stillbirth varied across the IPI distribution. We caution that our effect estimates should not be interpreted as causal but rather elucidate the inconsistency of the magnitude of associations with risk factors across the IPI distribution.

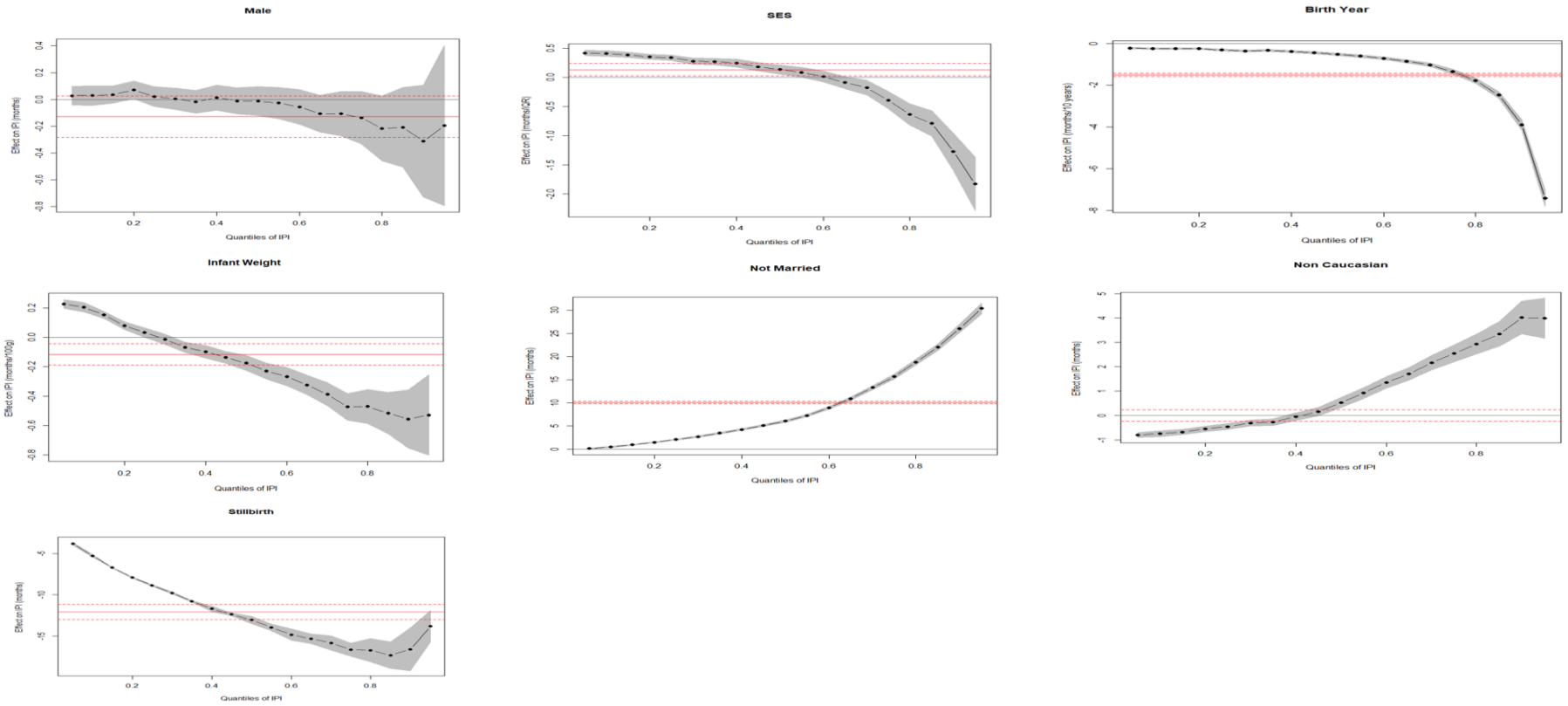

Figure 8-3 Graphical presentation of Quantile Regression results

A graphical presentation of the QR results. With all other covariates held constant, the straight solid line in each graph represents the OLS estimate with its CI, while the curves represent the coefficients of the QR models in different quantiles of IPI, with 95% CI of these estimates shaded.

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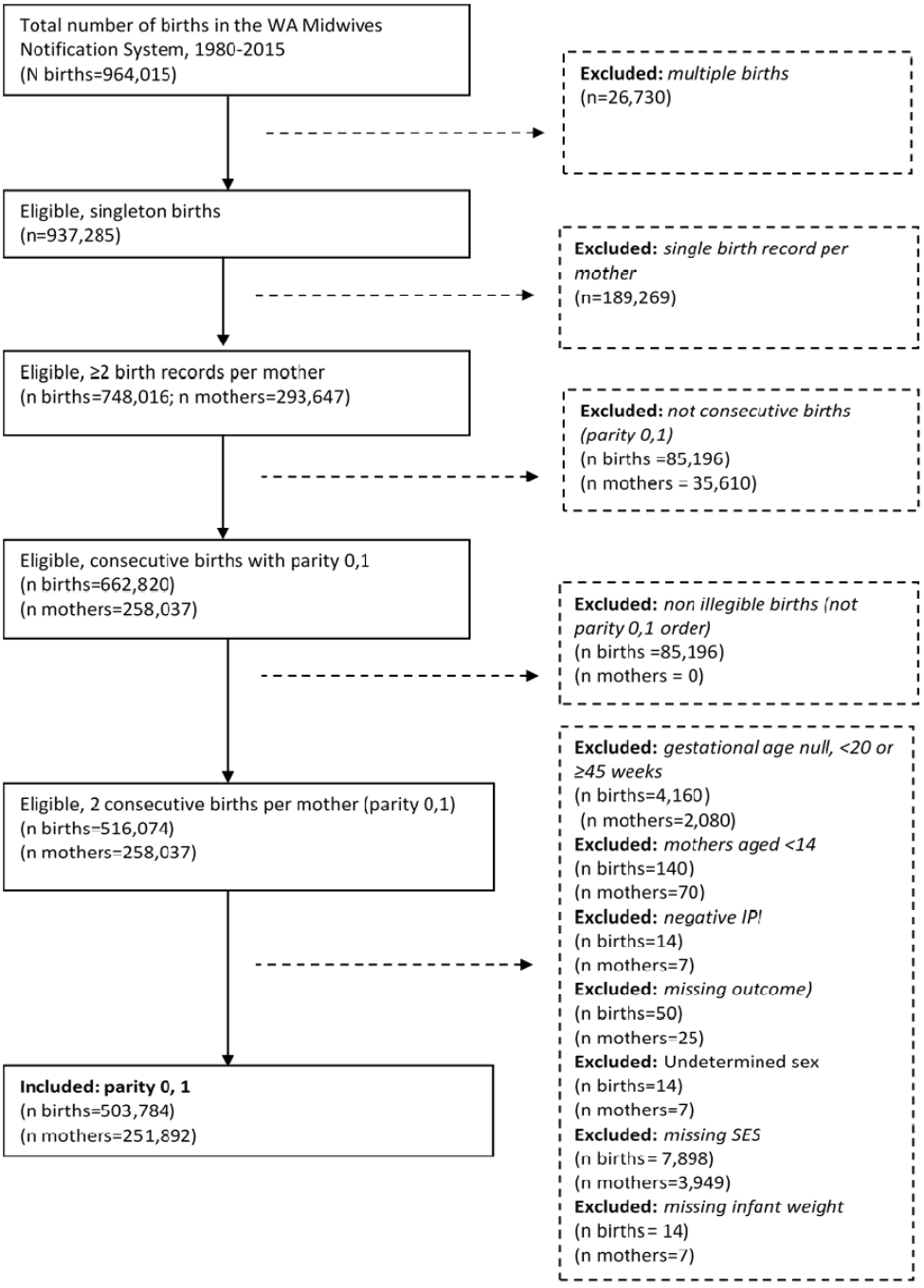
8.8 SUPPLEMENTARY MATERIAL



Supplemental Figure 8-1 Inclusions and exclusions for study cohorts defined by parity 0,1

Supplemental Table 8-1 Coefficients and 95% Confidence Intervals from Quantile Regression of interpregnancy interval (months) on pregnancy complications and other risk factors at parity 0 (n=251,892 mothers) in Western Australia, 1980-2015

Variable	OLS [a]	25th Percentile	50th Percentile	75th Percentile
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Gestational diabetes [b]	0.11 (-0.47, 0.69)	-0.23 (-0.53, 0.07)	-0.20 (-.065, 0.25)	0.17 (-0.69,1.04)
Preeclampsia [c]	0.56 (0.25, 0.88) **	0.40 (0.24, 0.57) **	0.62 (0.37, 0.86) **	0.73 (0.26,1.19) **
Gestational hypertension [d]	1.12 (0.56, 1.68) **	0.55 (0.25, 0.85) **	0.88 (0.45,1.32) **	1.50 (0.67,2.33) **
Pregnancy induced hypertension	0.46 (0.17, 0.75) **	0.36 (0.21, 0.51) **	0.53 (0.31, 0.76) **	0.57 (0.13, 1.00) **
Infant sex				
Male	-0.12 (-0.31, 0.05)	0.02 (-0.07, 0.12)	-0.01 (-0.15, 0.13)	-0.13 (-0.41,0.14)
SES, per IQR	0.13 (0.01, 0.25) **	0.33 (0.27, 0.40) **	-0.13 (0.04, 0.23) **	-0.39 (-0.57, -0.21) **
Ethnicity				
Non-Caucasian	0.006 (-0.27, 0.28)	-0.44 (-0.59, -0.30) **	0.53 (0.31, 0.75) **	2.54 (2.13, 2.96) **
Mother's age (years)	-0.50 (-0.52, -0.48) **	0.02 (0.00, 0.03) **	-0.13 (-0.15, -0.12) **	-0.49 (-0.52, -0.46) **
Birth year, per 10 year	-1.50 (-1.60, -1.40) **	-0.31 (-0.36, -0.26) **	-0.52 (-0.60, -0.44) **	-1.34 (-1.49, -1.19) **
Marital status				
Not married	10.10 (9.81,10.38) **	2.07 (1.93, 2.22) **	6.06 (5.84, 6.28) **	15.67(15.25,16.09) **
Infant weight, per 500g	-0.11 (-0.20, -0.03) **	0.03 (-0.01, 0.07)	-0.17 (-0.24, -0.11) **	-0.47 (0.60, -0.34) **
Stillbirth	-12.07 (-13.15, -10.98) **	-8.85 (-9.41, -8.28) **	-13.05 (-13.89, -12.21) **	-16.64 (-18.25, -15.04) **

** p<0.05; [a] OLS: Ordinary Least Squares; [b] Adjusted for all covariates listed in the table; [c] Adjusted for all covariates listed in the table except gestational hypertension; [d] Adjusted for all covariates listed in the table except preeclampsia; IQR: Inter quantile range

Chapter 9: INTERPREGNANCY INTERVAL AND PREGNANCY COMPLICATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Study Six. Synthesis of the results from this thesis with the current body of literature

9.1 PREAMBLE

Informed by published *systematic review protocol* (Appendix B1), this chapter comprises an updated synthesised summary of the current evidence of the association between IPI and a wide range of pregnancy outcomes by including published studies from inception-October 2020. This chapter also comprehensively described the limitations of the available evidence and directions for future research. This study (Study Six) is the first to present a meta-analysed association of IPI with preeclampsia, gestational hypertension and gestational diabetes.

As this chapter aimed to present the updated available evidence on birth spacing and maternal complications to date, two of the studies included in this thesis (Studies One and Two) also contributed to the review and meta-analyses. This may result in unavoidable repetition, particularly in the discussion of findings.

9.2 ABSTRACT

Background and aims: Investigating the effect of IPI on pregnancy complications has received little attention, and the few studies conducted have shown mixed results. This systematic review aims to provide the best available scientific evidence on the association between birth or interpregnancy interval and pregnancy complications.

Method and analysis: A search was conducted using Ovid/MEDLINE, EMBASE, CINAHL, Scopus, Web of Science, and PubMed databases to identify peer-reviewed articles addressing the association between birth or interpregnancy interval and pregnancy complications (inception to October 2020). At least two reviewers independently performed screening, data extraction and quality assessment. The Newcastle-Ottawa (NOS) tool was used to assess the quality of studies. We performed a qualitative synthesis of all included studies. Meta-analyses of adjusted odds ratio (aOR) with 95% confidence intervals (CIs) were used to derive a pooled estimate of the association between various interval categories and selected outcomes (preeclampsia, gestational hypertension, gestational diabetes).

Results: Of the total 776 unique articles, 147 met eligibility criteria. Short IPIs (<6 months) were not associated with increased risks of preeclampsia (pooled aOR: 0.96, 95% CI: 0.86, 1.06), gestational hypertension (pooled aOR: 0.96, 95% CI: 0.87, 1.06), or gestational diabetes (pooled aOR: 0.91, 95% CI: 0.85, 0.98) as compared to 18-23 months. Short birth or interpregnancy intervals (<6 or <12) months were associated with increased risk of uterine rupture, placenta praevia, placental abruption, and premature rupture of membrane. Compared to 18-23 months, IPI of ≥60 months increased the risk of preeclampsia (pooled aOR: 1.60, 95% CI: 1.37, 1.87) and gestational diabetes (pooled aOR: 1.34, 95% CI: 1.26, 1.43).

Conclusion: There was insufficient evidence of harmful associations of short IPIs (<6 months) and hypertensive disorders of pregnancy. We found consistent evidence for an association between long intervals and hypertensive disorders of pregnancy (preeclampsia and gestational hypertension) and labor dystocia, and inconsistent but accumulating evidence for increased risk of placenta praevia, placental abruption and premature rupture of membranes.

9.3 BACKGROUND

The importance of birth spacing has been a focus for perinatal researchers and policy-makers for nearly a century.[1,2] The length of time between birth and beginning of the subsequent pregnancy (interpregnancy interval or IPI) or the birth of the next child (inter-birth interval or IBI) is associated with an increased risk of adverse pregnancy outcomes in the subsequent pregnancy, among others, preterm birth, low birth weight, small for gestational age and preeclampsia. [2-5] Although it has received less attention, there has been an increasing interest in its association with pregnancy complications.[6-9] Pregnancy spacing has also been viewed as a potentially modifiable risk factor for adverse maternal and perinatal outcomes for planned pregnancies.

A previous systematic review published in 2007 found that women with short IPIs are at increased risk for labor dystocia, uterine rupture, and uteroplacental bleeding disorders (placental abruption and placenta praevia). Long IPIs were also independently associated with an increased risk of preeclampsia.[3] These findings, in addition to other supportive evidence, have led the WHO to recommend waiting at least two years between live birth and conception of the next child.[2] There is a growing body of literature that recognises the association between short IPIs and risk of premature rupture of membrane (PROM),[10,11] placental abruption, placenta praevia,[7,12,13] uterine rupture for women who previously delivered by caesarean section,[9,14] and gestational diabetes.[15] Similarly, long IPIs have long been associated with increased risk of preeclampsia[16,17] and labor dystocia.[18,19]

A recent review by Hutcheon *et al.* (2018), which focused on the association of short IPIs and adverse maternal outcomes in high-resource settings, also suggested evidence of association of short IPIs with increased risk of gestational diabetes, uterine rupture, and decreased risk of preeclampsia.[20]

Although previous reviews[3,20,21] have suggested that IPI is associated with the risk of various maternal outcomes, the strength of the evidence supporting the association is still unclear. These reviews did not identify a sufficient number of studies to pool data from studies,[3,20,21] limited to few maternal outcomes (i.e., maternal haemorrhage, premature rupture of membrane (PROM),[21] or have not included results from studies published in the last decade.[3,21] Additionally, the most recent review on this topic,[20] only evaluated studies examining the association between short IPI and pregnancy outcomes from high-income settings (mainly, US/Canada). Further systematic documentation and literature synthesis on the effect of IPI on

various pregnancy complications with a view to a meta-analysis of the outcomes will be important to inform women, their family, and clinicians of risks and set and provide an evidence-based revision of guidelines. By updating the current state of knowledge in IPI research, this review will provide a basis for guiding future studies and future global policies for family planning.

This systematic review and meta-analyses examined the effect of birth and interpregnancy intervals on pregnancy complications.

9.4 METHODS

9.4.1 Data sources and search strategies

We conducted a systematic review and meta-analyses in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Appendix B2),[22,] which was conducted per our published protocol.[23] We searched peer-reviewed studies examining birth or interpregnancy intervals and pregnancy complications using the Ovid/Medline, Scopus, EMBASE, CINAHL, Web of Science, and PubMed databases from inception to 30 October 2020. We used a combination of medical subject headings (MeSH) and keywords related to IPI and pregnancy complications without any restrictions on time period, study type, or geographic setting (Appendix B3). Search terms for the exposure included *interpregnancy interval, birth interval, birth spacing, pregnancy interval, pregnancy spacing, birth to birth interval, birth to conception interval*. In addition to specific outcome search terms, terms for pregnancy complications included *obstetric complication, pregnancy complication, maternal complication, maternal morbidity, and maternal outcome.* These searches were limited to studies on humans that were published in English. The reference list of all identified relevant records was searched for additional studies. The authors were not contacted for additional unpublished data. The study protocol was registered with PROSPERO under the identification code: CRD42018088578.

9.4.2 Eligibility criteria

Inclusion criteria

Included studies were required to fulfil the following criteria

1. The study population consisted of multiparous women with information on the length of interval between two consecutive pregnancies.
2. Studies that have evaluated the association between IPI and pregnancy complications using cohort (prospective or retrospective), cross-sectional, case-control or randomised controlled trial designs
3. Studies have investigated IPI or birth interval as the primary exposure. *Interpregnancy interval is* defined as the length of time between the end of a pregnancy and the start of the next pregnancy. *Birth interval* is defined as the time elapsed between the end of one pregnancy and the end of the subsequent pregnancy.

The outcomes of interest in this review were pregnancy complications, set *a priori*: preeclampsia, gestational hypertension, gestational diabetes, placental abruption, placenta praevia, PROM, uterine rupture for women attempting vaginal delivery after prior caesarean delivery and labor dystocia.

Exclusion criteria

Studies were excluded based on three criteria. (a). Non-primary studies: case series or reports, editorials, letters to the editor, or reviews without original data. (b). Studies with insufficient information on adjusted effect (e.g., unclear adjustment variable, missing confidence interval estimates) (c). Studies that did not investigate IPI or IBI as the primary exposure. Studies were also excluded if the primary aim of the studies were predictive as opposed to etiologic, as they will have insufficient information on the effect estimates.

9.4.3 Data abstraction, study quality and analyses

All unique studies identified from each electronic database were imported into an *EndNote* library. Further screening of titles and abstracts regarding eligibility criterion was facilitated using Covidence, web-based software that allows collation of search results, screening abstracts and full-text articles, extraction of data from selected articles, and tools to record and resolve conflicts and export data. For each included study, three independent reviewers extracted details of the articles and further evaluated the full records of those eligible articles (ATG, DF, KBM). The following information was extracted from each included study: author

and year published, country study conducted, World Bank income classification of countries (at the time of publication), design, outcome, sample size, exposure and outcome definition, exposure and outcome frequencies, effect estimates (unadjusted and adjusted), adjustment or matching variables and response rate (where indicated).

Risk of bias (quality) assessment

The risk of bias for included studies was assessed by two independent reviewers using the Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort and cross-sectional studies.[24] Discrepancies were discussed, and if consensus was not reached, a third reviewer was consulted.

The NOS for cohort studies includes an assessment of the risk of bias across three domains. The first domain evaluates the selection of exposed and non-exposed groups and exposure ascertainment with a maximum of four stars. Accordingly, studies achieved a star if the exposed cohort was derived from the general community or was a population-based study, the non-exposed group is drawn from the same community as the exposed, used clinical records or linkage to extract or calculate IPI or IBI. Studies attained an additional star if an outcome of interest was not present at the beginning of the study. Studies obtained a maximum of two stars in the comparability of the cohorts' domain if they adjust, match, or stratify for maternal age and socioeconomic status, SES (one star), and additionally known confounders (another star). The third domain evaluates three aspects: the outcome definition, adequacy of follow-up for an outcome to occur, and adequacy of follow-up of cohorts (related to loss to follow-up). Studies achieved a star if they had a clear definition of the outcome or reported the assessment based on ICD-codes or used record linkage, and another star if they allowed sufficient time for women to have a second pregnancy. Studies also achieved an additional star if they reported complete follow-up or studies reported the subjects lost to follow-up (or response rate), and loss to follow-up was unlikely to introduce bias.

Similarly, the NOS for Case-control studies includes an assessment of the risk of bias across three domains. In the selection domain (maximum of four stars), studies are awarded a star if the cases are ascertained with independent validation, are representative of series of cases or controls are selected from the community. Another star is awarded if controls had no history of diseases (endpoint). Studies obtained a maximum of two stars in the comparability of the case and control domain if they adjust, match, or stratify for maternal age and SES (one star) and additionally known confounders (another star). The third domain evaluates three aspects of the exposure: exposure ascertainment, the method of ascertainment for cases and controls,

and non-response rate. Studies achieved a star if they used clinical records or linkage to extract/calculate IPI or IBI, the same method of ascertainment for cases and controls, and an additional star if both cases and controls have a similar response rate.

Studies could score up to nine stars. For the purpose of this review, we defined a study as at low risk of bias for NOS of ≥7, moderate risk of bias for <7 NOS >5 and high-risk of bias for NOS≤4. We referred to high-quality studies for those with low-risk bias, moderate quality for studies with moderate risk of bias, and low-quality studies for those with a high risk of bias in the NOS quality assessment tool. However, we supplemented these classifications with descriptive commentary on the quality of each study further to the NOS score assessments by focusing on each studies strengths and limitations, which included comments on the internal and external validity of specific studies (Supplemental Table 9-1).

9.4.4 Statistical analyses

We performed a qualitative synthesis of all included studies (n=41) using author-defined birth or interpregnancy interval categories for each of the eight pregnancy complications included. For studies where interval categories were consistent to the extent that results could be pooled, we additionally performed meta-analyses. We pooled the adjusted odds ratios (OR) for associations between the pregnancy complications and IPIs classified as <6, 6-11, 12-17, 24-59, and 60+ months compared to 18-23 months (reference category) using inverse-variance weighted random-effects meta-analyses. [25] We reported the I^2 statistic as a measure of statistical heterogeneity between studies.[26]A sub-group analysis by country was not performed due to a small number of studies available for analyses. The level of statistical significance was set equal to 0.05. Analyses were performed in Stata/IC version 16.1(College Station, TX).

9.5 RESULTS

In total, 776 studies were screened, and 147 met inclusion criteria (Figure 9-1); 105 articles were excluded following full-text review. The most prevalent reasons for exclusion were, studies reported non-desired outcome (n=40), the absence of any comparison of outcomes by IPI (n=17), only abstract or commentary (n=8), not desired population (n=14), not a primary study (n=8), mainly predictive studies (n=9), insufficient information on IPI and/or outcome (n=4) or reporting of pregnancy complications as a composite outcome (n=2). Furthermore, we also excluded studies (n=3) that used the same dataset in multiple reports. Four additional relevant articles were identified from the reference lists of included publications and were included, leaving 41 studies (5 case-control,[27-31] 1 cross-sectional,[32] and 35 cohort) included in

the narrative synthesis. Of the 41 included studies, six were suitable[6,8,33-36] for meta-analysis for three outcomes (PE=3; GDM=4 and GH=3). The most common reasons for exclusion from meta-analyses were that the IPI categories provided were not comparable (n=30), the interval was reported as a continuous variable or no confidence interval or standard error was reported (n=5).

Studies were excluded from qualitative synthesis for the following reasons, non-specific maternal outcomes (e.g., uterine scar failure, placenta accreta),[37-43] a composite maternal outcome,[44,45] conducted on special obstetric population,[46-48] or reported a separate effect estimate by strata of interest (e.g. partner change or race).[17,49-51] Studies were also excluded due to the same dataset used in multiple reports,[52-54] and no IPI reference category specified.[55]

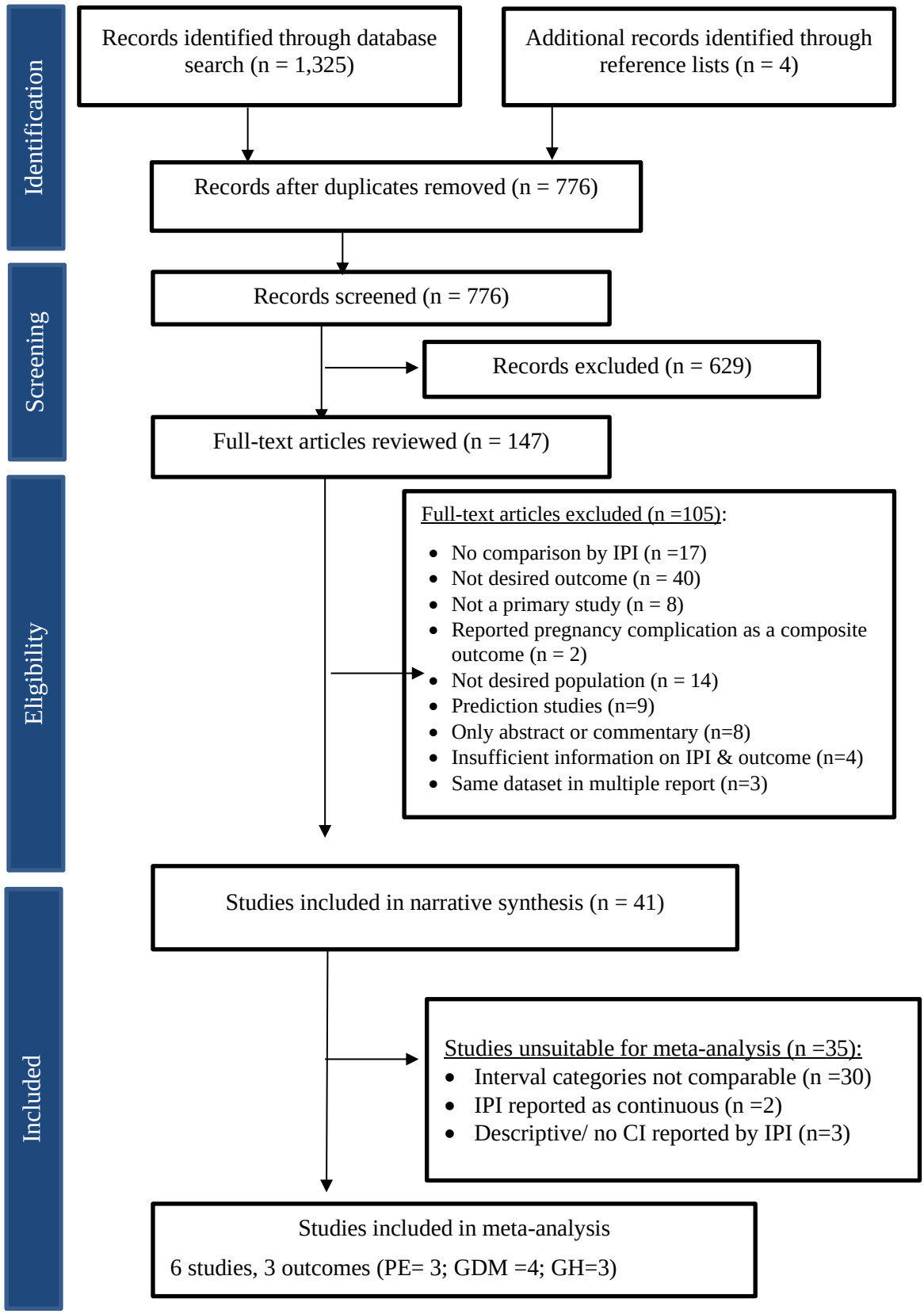


Figure 9-1 Flow diagram of studies included in the review

Studies examined preeclampsia(n=15),[6-8,28,29,34,56-64] gestational hypertension (n=6),[8,32,33,36,63,65] gestational diabetes (n=9),[6,13,34-36,65-68] placental abruption (n=2),[7,69] placenta previa (n=2),[13,70] premature rupture of membrane (n=9),[11,13,30,32-34,63,64,71] uterine rupture among women attempting vaginal birth after caesarean (n=10),[9,14,27,31,72-77] and labor dystocia (n=2).[18,19] Most studies examined more than one pregnancy outcome. Most of the cohort or cross-sectional studies had large sample size ranging from 11,112[63] to 2,362,656.[36] Only three studies had sample size < 1000 pregnancies.[64,68,71] The number of case subjects for the case-control studies ranged from 36 to 2,332 pregnancies.[28,29]

Eighteen studies were from the US or Canada (US: 16; Canada; 2), seven from Europe (UK: 2; Norway: 4; Sweden: 1), four from Australia, five from sub-Saharan Africa (Ethiopia: 1; Nigeria:1; Rwanda:1; Tanzania: 2), four from Asia (Bangladesh: 1; China: 1; South Korea:1; Armenia:1), and three were from Latin America and the Caribbean (Brazil: 1; multiple countries: 2) (Table 9-1).

Our study revealed a small number of studies (7 cohorts, two case-control, and one cross-sectional) from low-income settings where the effect of birth interval (mainly short) seems to matter greatly.[78] It is plausible that the association between birth intervals and pregnancy complications is different in countries with a higher baseline risk of these complications (e.g., sub-Saharan African countries).

A review of the risk of bias indicated that studies generally performed well on NOS for sample selection and comparability. Nevertheless, it performed poorly for exposure and outcome measurement (Supplemental Table 9-1, Supplemental Figure 9-1). While most studies scored ≥3 stars for sample selection (n=38/41) and 15 studies scored the maximum two stars for comparability, only seven studies scored one star for exposure/outcome measurement. Generally, 27 of the 41 studies met the criteria for low risk of bias, 12 moderate and three high risk of bias (Supplemental Figure 9-1). Five[3,6,8,35,36] of the six studies included in the meta-analyses were deemed high-quality cohort studies, with only one study rated as having a moderate risk of bias (Figure 9-2).[33] All these studies that were included in the meta-analysis used IPI as an interval definition.

27 of the 41 studies met high-quality criteria (low risk of bias),12 moderate and three low quality (Supplemental Table 9-1, Supplemental Figure 9-1). The majority of studies that were rated as good quality (> 8 stars) accounted for a measure of socioeconomic position and maternal age. Among the studies deemed to be higher quality, three studies employed a matched (within-mother comparison or aka sibling) design,[6,8,35,] which controls for time-invariant confounders using mothers as their own control.

Table 9-1 Summary of studies evaluating the association between interpregnancy interval and pregnancy complications

Author (s), Year	Year(s) of births included	Country	Study Design	Interval type (exposure), categories (months)	Outcome/s	Study population (N)
Low- & Middle-Income Countries						
Cecatti *et al* 2008[33]	1986-2000	Brazil	Retrospective Cohort	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	GH (n= 1,337), PROM (n=1,983)	Non-nulliparous women who delivered a single foetus after >22 weeks or when the weight of the conceptus was >500g (N=14,930)
Conde-Agudelo *et al* 2000[34]	1985-1997	18 Latin American Countries	Retrospective Cohort	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	PE (n=1,946), GDM (n=7,310), PROM (n=30,612)	Only parous women delivering singleton infants and whose previous pregnancy ended in live birth or fetal death after 19 weeks gestation (N=456,889)
Habimana-Kabano *et al* 2015[32]	2005-2010	Rwanda	Cross-sectional	IPI, ≤12; 13-18; 19-23; 24-59[a]; ≥60	GH (n=195 calculated), PROM (n=605 calculated)	Women who were transferred from health care centres located in the hospital catchment area (N=2,500)
Harutyunyan *et al* 2013[28]	2008-2009	Armenia	Case control	IBI, <59[a]; ≥60	PE	Multiparous women with PE and no PE during last pregnancy (Case=36; control=148)
Lilungulu *et al* 2015[64]	2012-2013	Tanzania	Prospective Cohort	IPI, <18; ≥18[a]	PE (n=35), PROM (n=78)	Pregnant women with Short IPI and Normal IPI at the time of admission (N=450)
Mignini *et al* 2016[58]	1990-2009	Latin America	Retrospective Cohort	IPI, 3-11; 12-23[a]; 24-35; 36-47; 48-59; 60-71; 72-83; 84-95; 96-107; 108-119	PE (n=25939; calculated)	Women delivering two consecutive infants during the study period (N=894, 476 women)
Onwuka *et al*, 2020[71]	2015-2016	Nigeria	Prospective cohort	IPI, <18; ≥18[a]	PROM (n=10)	Pregnant women receiving antenatal care in a tertiary hospital (n=271 pregnant mothers)
Razzaque *et al* 2005[63]	1996-2002	Bangladesh	Retrospective Cohort	IPI, <6; 6-14; 15-26; 27-50[a]; 51-74; ≥75	PE, GH, PROM	pregnant women who came to a community HC for ANC check-up during the study period (N=11,112 pregnancies)
Sanga *et al* 2020[59]	2000-2015	Tanzania	Retrospective Cohort	IPI, <24; 24-59[a]; ≥60	PE (n=270)	Women with at least two births recorded in the medical birth registry (N=6,612)
Workineh *et al* 2018[30]	2017	Ethiopia	Case-control	IBI, <24; 24-60[a]	PROM	Cases: mothers who admitted to the labor waiting room and had term premature rupture of membrane before the initiation of labor which is confirmed by clinical features (cases=75; controls=223)

High-Income Countries						
Al-Zirqi *et al* 2017[72]	1967-2008	Norway	Retrospective Cohort	IBI, <16; ≥16[a]	Uterine rupture (n=51)	Women undergoing a second delivery with a history of prior caesarean delivery (n=34550)
Blumenfeld *et al* 2014[69]	2009-2010	USA	Retrospective Cohort	IPI, <6; 6-23; 24-59[a]; >60	Placental abruption (n=1,017)	Singleton pregnancies undergoing first- and second-trimester prenatal serum screening, with expected dates of delivery in 2009 and 2010 (N=137,915)
Bujold *et al* 2002[73]	1988-2000	Canada	Retrospective Cohort	IBI, ≤24; >24[a]	Uterine rupture (n=21)	Women with a previous low transverse caesarean delivery and no previous vaginal delivery who undergo a trial of labor from 1988 to 2000 in a tertiary care centre (N=1,527)
Bujold *et al* 2010[31]	1987-2004	USA	Case control	IBI, ≤24; ≥24[a]	Uterine rupture	Women with a single prior low transverse CS experienced uterine rupture during a trial of labor (cases; n=96). For each case, three women who underwent a trial of labor without uterine rupture were included (Controls; n=288)
Cho *et al* 2015[56]	2006-2010	South Korea	Retrospective Cohort	IBI, 12[a]; 24; 36; 48	PE (n=1,473)	Women who had their first delivery during 2006 and their subsequent delivery between 2007 and 2010 (N=127,723)
Cunningham *et al* 2019[14]	2006-2012	USA	Retrospective Cohort	IPI, <12; 12-23; 24-59[a]; ≥60	Uterine rupture (n=249)	Mothers with singleton live births with or without prior caesarean delivery (N=1,034,522)
De silva and Thoma *et al* 2019[9]	2014-2017	USA	Retrospective Cohort	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	Uterine rupture (n=2,109)	Non-first-born singleton births to US resident women, with previous caesarean delivery (N=2,116,847)
Fitzpatrick *et al* 2012[27]	2009-2010	UK	Case control	IPI, <12; 12-23; ≥24[a]	Uterine rupture	Cases were all women in the UK identified as having a uterine rupture (N=159). Controls were defined as any woman delivering a foetus or infant with previous caesarean delivery who had not suffered from a uterine rupture (N=607)
Gebremedhin *et al* 2019[35]	1980-2015	Australia	Retrospective Cohort	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	GDM (n= 10,032)	Mothers with at least three consecutive singletons non-first births during the study period delivered at 20-40 weeks' gestation (N=103,909 mothers;254,137 births)

Gebremedhin *et al* 2020[8]	1980-2015	Australia	Retrospective Cohort	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	PE (n=9,863), GH (n=4,710)	Mothers with at least three consecutive singletons non-first births during the study period delivered at 20-40 weeks' gestation (N=103,909 mothers;254,137 births)
Gurol-Urganci *et al* 2011[70]	2000-2009	England	Retrospective Cohort	IBI, <12; 12-23; 24-35[a]; 36-47; 48-59; ≥60	Placenta previa (n=2,118; calculated 5.3/1000)	All women who gave birth to singleton first and second baby from 1st April 2000-Feb 2009 (N=399,674)
Haight *et al* 2019[36]	2013-2016	USA	Retrospective Cohort	IPI, <6; 6-11; 12-17; 18-23[a];	GDM (n= 111,534), GH (n=75,170)	Non-firstborn singleton live births of at least 21 weeks gestation to U.S. resident women whose last pregnancy ended in a live birth (N=2,362,656)
Hanley *et al* 2017[6]	2000-2015	Canada	Retrospective Cohort	IPI, <6; 6-11; 12-17; 18-23[a]; 24-59; ≥60	GDM (n=2,202 at second pregnancy; n=3,319 at third pregnancy; PE (n=796 at second and 1,093 at third pregnancies)	Women with at least three singleton deliveries delivered at 20-44wk' gestation (N = 38 178 women; N = 76, 356 second and third births)
Hercus *et al* 2018[57]	2011-2012	Australia	Retrospective Cohort	IBI, ≤48[a]; >48	PE(n=82)	Multigravida women giving birth at the Lyell McEwin Hospital, Adelaide, Australia (N=2,003 pregnancies)
Huang *et al* 2002[74]	1997-2000	USA	Retrospective Cohort	IBI, <19; ≥19[a]	Uterine rupture (n=3)	Patients with previous caesarean delivery who attempted VBAC (N=1,185)
Huber *et al* 2018[13]	2009-2011	USA	Retrospective Cohort	IBI, ≤18; 19-35; ≥36[a]	PROM (n=81), PPROM (n=287), Placenta Previa (n=175), GDM (n=236)	women with at least two live births and aged 18-40 years and who can provide information on IBI (n=2,212)
Kaczmarczyk *et al* 2007[75]	1983-2001	Norway	Retrospective Cohort	IPI, <12; 12-36[a]; >36	Uterine rupture (n=274)	Swedish women delivering two single, consecutive births between 1983 and 2001 (N=300,200 women)
Khambalia *et al* 2013[66]	2001-2019	Australia	Retrospective Cohort	IPI, continuous	Gestational diabetes (3,689)	Women without a pre-existing diagnosis of Type 1 or Type 2 diabetes at the time of first pregnancy and with at least a first and second birth (N=318, 447 pregnancies)
Lu *et al* 2002[67]	1991-1999	USA	Retrospective Cohort	IPI, ≤24[a]; >24	Gestational diabetes (n=37)	Women with a singleton pregnancy who received prenatal care and who were delivered within the institution during their first two consecutive pregnancies (N=3,710)

Mostello *et al* 2002[29]	1989-1997	USA	Case control	IPI, continuous	PE	Cases:2,332 women with PE in second pregnancy; Control 2,370 women without PE in second pregnancy
Mostello *et al* 2010[61]	1989-1997	USA	Retrospective Cohort	IBI, 0-12; 12-23; 24-48[a]; >48	PE recurrence	Women who delivered their first two singleton pregnancies at >20 weeks gestation whose first pregnancies were complicated by preeclampsia (N=17, 773)
Rohde *et al* 2019[7]	1989-2055	USA	Retrospective Cohort	IBI, <12; 12-48[a]; >48	PE (n=118), placental abruption recurrence (n=46)	All multiparous women in Missouri who delivered their first two singleton pregnancies between 20 and 44 weeks of gestation (N=2,069)
Sandstrom et *al* 2012[19]	1992-2006	Sweden	Retrospective Cohort	IPI, <12; 12-47[a]; 48-83; ≥84	Labor dystocia (n=12,599)	Women who gave birth to their first and second infants in a cephalic presentation at >=27 weeks of gestation with spontaneous onset of labor (N=239,953)
Shipp *et al* 2001[76]	1984-1996	USA	Retrospective Cohort	IBI, ≤18; >18[a]	Uterine rupture (n=29)	Women attempting a vaginal birth after previous caesarean delivery (N=2,409)
Shree *et al* 2017[11]	2003-2013	USA	Retrospective Cohort	IPI, ≤6, 7-23; ≥24[a]	PPROM (n=6,797)	Women with singleton deliveries between 2003 and 2013 with delivery date available for the current and prior delivery (N=474,957)
Skjaerven *et al.* 2002[60]	1967-1998	Norway	Retrospective Cohort	IBI, continuous	PE (n=8,900)	551,478 women who had two or more singleton deliveries; 209,423 women who had three or more singleton deliveries
Stamilio *et al* 2007[77]	1995-2000	USA	Retrospective Cohort	IPI, < 6; >6; IBI, 0-5;6-11;12-17;18-59[a]; ≥ 60	Uterine rupture (n=128)	Pregnant women with at least one prior caesarean delivery who attempted vaginal birth after caesarean delivery between 1995 & 2000 (N= 13,331)
Trogstad *et al* 2001[62]	1967-1998	Norway	Retrospective Cohort	IBI, ≤12; 13-60[a]; 61-120; 121-180;>180	PE recurrence	All women with first and second singleton delivery in Norway(N=547,238)
Wang *et al* 2018[68]	2011-2017	China	Retrospective Cohort	IPI, <24; ≥24[a]	GDM recurrence	Women with gestational diabetes mellitus in the first pregnancy (N=128)
Yee *et al* 2016[65]	2011-2012	USA	Retrospective Cohort	IBI, 4-17; 18-36[a]; 37-60; >60	GH (n=66,184), GDM (n=95,845)	Primiparous women with singleton live births having their second baby (N=1,964,523)

Zhu *et al* 2006[18]	1994-2002	USA	Retrospective Cohort	IPI, <24[a]; 24-47, 48-71; 72-95; 96-119; >=120	Labor dystocia (n=92,020)	Multiparous women who were delivered of a singleton infant (N=648,025 births)

PROM: Premature rupture of membrane; PPROM: Preterm premature rupture of membrane; PE: Preeclampsia; GDM: Gestational diabetes; GH: Gestational hypertension; IBI: Inter birth interval; VBAC: Vaginal birth after caesarean

Exposure definitions and the reference interval used for estimation of the association varied by study. Definitions of "short" interpregnancy interval was most commonly <12 months (n=13) but ranged from <6 months (n=11) to <24 months (n=4). More than half of the studies (n=25) used interpregnancy interval, and the remaining 16 studies used interbirth interval (IBI) as the measure of pregnancy spacing. The quality of exposure ascertainment also varies across studies. If mothers reported wrong/uncertain LMP (misclassifications), risk estimates will be biased. Similarly, studies that have used IBI can produce a biased estimate as the gestational age of the subsequent pregnancy is itself an outcome that the pregnancy interval can influence.[79] Outcome definition and quality of ascertainment also varied across the studies included in the review. Generally, population-based linked studies had quality outcome data and have either used ICD codes, variables ascertained from different databases [6,8,35] or data abstracted by two independent observers.[31,73]

There was a variation in the choice of model confounders/adjustments of studies. Several studies did not consider variables (either using adjustment, stratification, or matching) that could potentially confound the relationship between birth interval and pregnancy complications. Likely confounders include SES, maternal age, parity, previous child death, intervening pregnancy loss, presence of previous complications and partner change.

While most studies adjusted for maternal age (n= 34) and previous pregnancy complications (e.g., preeclampsia) [n=22], only twelve published studies adjusted for previous perinatal outcome (stillbirth or neonatal death) [n=12], smoking (n=17) and race/ethnicity (n=17) (eTable 2). Other common covariates included SES (n=15), obstetric history (n=14), maternal health conditions (n=13), and marital or cohabitation status (n=10). Only six studies adjusted for birth year. Studies infrequently (n<5) included other social factors (e.g., household size, occupation, religion, country of birth), pregnancy intention, and alcohol use for adjustment. Even though 11 studies adjusted for parity or birth order, only three considered gravidity in their analysis.[18,63,74]

Among 19 studies that reported associations of hypertensive disorders of pregnancy and birth interval, only four[8,29,60,62] adjusted for partner change (all high-quality studies). Intervening pregnancy loss was accounted for in only five studies.[18,32,34,63,72]

All of the high-quality studies, except four[70,73,76,77], used population-based data, including two studies that employed a matched within-mother matched design. Though the within-mother studies achieve an excellent internal validity, their external validity (generalisability) is limited

due to the nature of the design in restricting to mothers with three or more pregnancies and discordant outcomes (Figure 9-2).

Studies rated as moderate quality included only hospital births,[32,33,69,74]self-reported outcomes/exposure,[13,27,28,30] or short follow-up time to observe the effect of long IPI on the outcome of interest.[56,65] Studies rated as poor quality generally adjusted for fewer variables (SES, parity, race),[57,64,71] participants were not included randomly;[64] used self-reported LMP and date of birth;[64] included populations only from single hospital [57,64,71] which represents higher risk pregnancies.

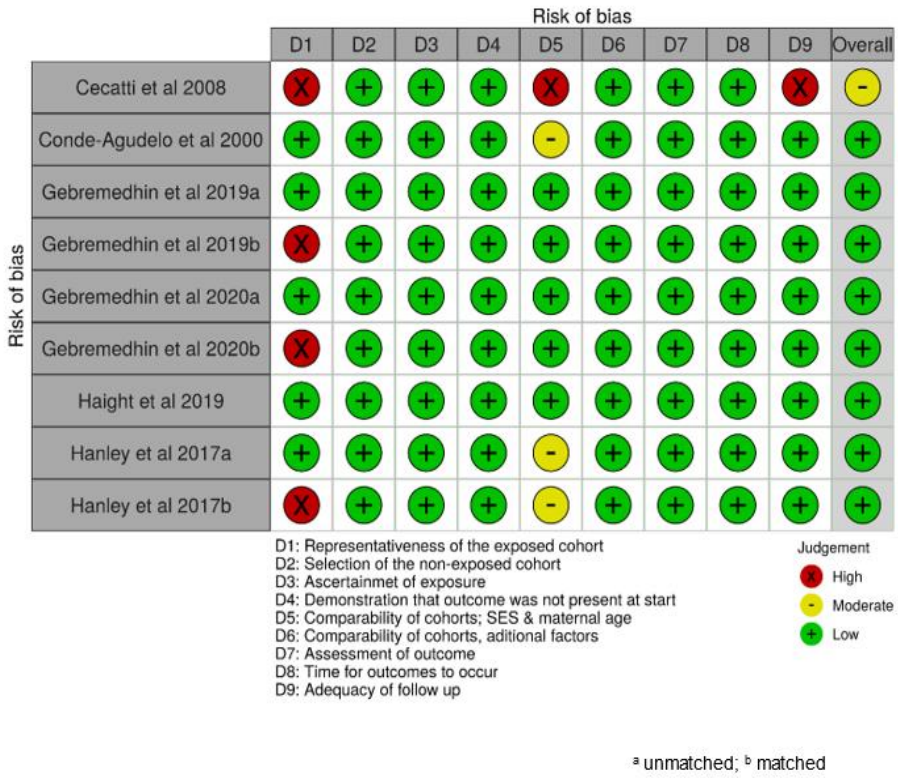


Figure 9-2 Methodological quality of studies included in the meta-analyses according to Newcastle-Ottawa Scale criteria

9.5.1 Preeclampsia

Among 15 studies (2 case-control and 13 cohorts) that assessed the relationship between pregnancy spacing and preeclampsia, three cohort studies were specifically on special obstetric population (women with previous preeclampsia) or recurrence,[61,62] and women with placental abruption at first pregnancy,[7] respectively. Of these studies, eight used IPI as a measure of interval[6,8,29,34,58,59,63,64] and two studies employed within-mother design.[6,8]

Among nine studies that provided effect estimates for the association between short IPI and preeclampsia, a short interval was defined as an IPI of less than six months,[6,8,34,63] less than 18 months,[64] or less than 24 months[59] and birth interval of less than two years,[56] or less than 12 months.[7,58]

Seven out of these nine studies reported a null,[7,8,34] or lower risk of preeclampsia with short intervals.[6,56,58,59] Risk estimates were not attenuated for an additional adjustment to maternal age and SES.[7,8]

Only two studies, both from low -income settings, reported an increased risk of preeclampsia after short IPI, less than six months,[63] or less than 18 months.[64] However, these studies were considered at high risk of bias,[64] or did not report the confidence interval of the estimates (Supplemental Figure 9-2).[63]

Among high-quality studies, two studies based on population cohorts in Canada[6] and Australia,[8] that employed within-mother design evaluated the relationship between short IPI and preeclampsia. These studies matched pregnancies to the same mothers to control unmeasured characteristics that do not change over time or remain strongly correlated between women's pregnancies. Results indicated that in reference to 18-23 months, an IPI of 6-11 months the reduced risk of preeclampsia (aOR 0.71(95% CI: 0.54, 0.94) in a study by Hanley *et al.* (2017),[6] and an aOR of 0.92 (95% CI:0.82, 1.03) in a study by Gebremedhin *et al.* (2020). [8] In both matched studies, the effect estimates were attenuated as compared to the unmatched studies.

In pooled adjusted analysis, IPI <6 months was not associated with a statistically significant increase in the risk of preeclampsia (pooled aOR: 0.96, 95% CI 0.86, 1.06) with moderate heterogeneity (I^2=55.5%). For IPI of 6-11 months, the OR suggested there was marginal evidence for lower odds of preeclampsia compared to IPIs of 18-23 months (pooled aOR: 0.89, 95% CI 0.79, 1.00) with heterogeneity in study results (I^2=74.2%) (Figure 9-3)

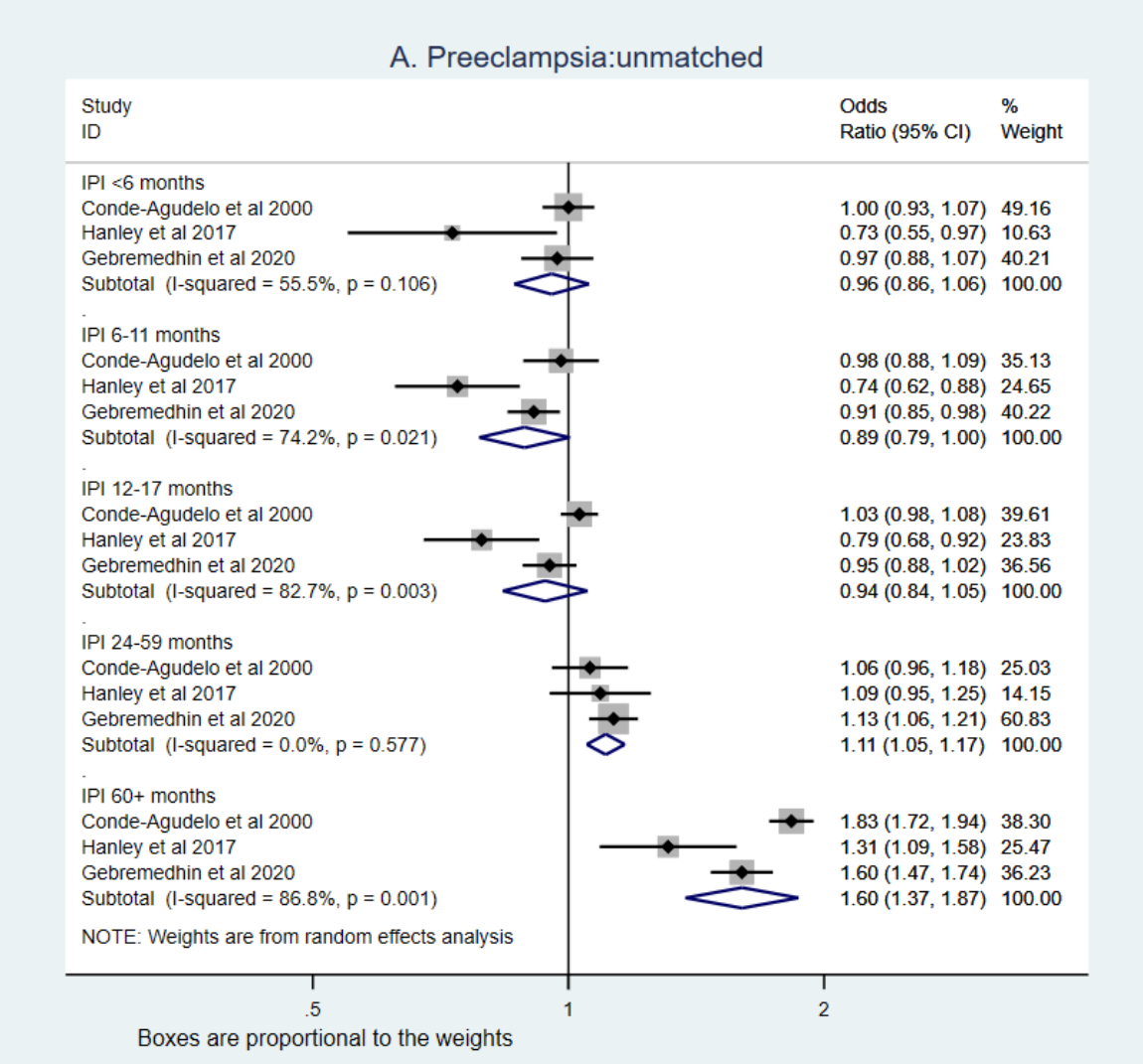


Figure 9-3 Meta-analysis of adjusted odds ratios of preeclampsia for various IPI categories compared to IPI 18-23 months

Eleven out of twelve studies that examined the association of preeclampsia with long intervals reported a statistically significant association suggesting a dose-response relationship.[6-8,28,29,34,56-58,60,63] Adjusted odds ratio of preeclampsia associated with long interval ranged from 1.83 (95% CI 1.03-3.24) for a birth interval of >4 years vs ≤4 years for a study rated as poor quality,[57] and 2.90 (95% CI 1.07-7.86) for a birth interval of ≥5 years vs <5 years in a study with moderate quality,[28] and 1.83 (95% CI 1.72-1.94) for IPI ≥60 months vs 18-23 months in a study deemed to be high-quality.[34]

Similarly, the two high quality matched studies[6,8] provide support for the earlier findings of unmatched studies on the associations between higher risk of preeclampsia and long intervals (≥60 months of IPI), with point estimates for the matched studies ranging from aOR=1.39 (95% CI 0.97, 2.00)[6] to aOR=1.42 (95% CI 1.26, 1.60).[8]

The studies by Mostello *et al.* (2010),[61] Skjaerven *et al.* (2002),[60] and Gebremedhin *et al.* (2020)[8] that adjusted for partner change between pregnancies reported similar findings of an association between increased risk of preeclampsia and long intervals as those that did not adjust for partner change.

Compared to 18-23 months of IPI, the pooled results revealed an association of long IPIs and preeclampsia with a dose-response pattern with a pooled OR of 1.11 (95% CI: 1.05, 1.17) and I^2=0.0% for IPI of 24-59 months; and a pooled OR of 1.60 (95% CI: 1.37, 1.87); I^2=86.8% for IPI of ≥60 months (Figure 2). This finding was confirmed in the pooled results of high-quality matched studies, with pooled OR of 1.15 (95% CI: 0.94, 1.40) and I^2=63.4% for IPI of 24-59 months; and pooled OR of 1.42 (95% CI: 1.27, 1.58) with little statistical heterogeneity (I^2=0.0%) for IPI of ≥60 months (Supplemental Figure 9-3).

9.5.2 Gestational hypertension

The association between interpregnancy or birth interval and gestational hypertension was evaluated in six moderate[32,33,65] to high-quality studies,[8,36,63] of which three studies were suitable for meta-analysis.[8,33,36] A study by Haight *et al.* (2019) [36] only evaluated for the shorter IPIs (less than 24 months) associations.

Of these five studies reporting on short IPI, defined as <6 months[8,33,36,63] or ≤12 months[32], a large cohort study from the US[36] with 2.36 million births identified a lower odds of gestational hypertension compared to an IPI of 18-23 months (aOR: 0.95; 0.93, 0.98). Gebremedhin *et al* (2020) [8] reported an aOR of 0.92 (95% CI: 0.79, 1.07) for IPI <6 months compared to 18-23 months. Similarly, Yee *et al.* (2016)[65] reported aOR of 0.98 (95% CI; 0.94, 1.02) for a birth interval of 4-17 months compared to 18-36 months (eFigure 4). Conversely, two studies reported an increase in the odds of gestational hypertension for an IPI <6 months ranging in magnitude from an aOR:1.36 (95% CI:0.91, 2.04)[33] for <6 vs 18-23 months to an aOR: 1.66 (95% CI not provided)[63] for <6 vs 24-59 months.

The point estimates were consistently lower after full adjustment for potential covariates. For example, a large cohort study from the US reported an increased risk of gestational hypertension for IPI <6 months before adjustment with an unadjusted OR of 1.06 (95% CI: 1.03, 1.08). However, after adjustment for confounders, the association even reversed with aOR of 0.95 (95% CI: 0.93, 0.98).

Likewise, a population-based cohort study from Australia[8] using within-mother design found attenuated estimates compared to their between-mother comparison, with further attenuation

after full adjustment for time-variant confounders (aOR:0.91; 95% CI; 0.77, 1.07) (Supplemental Figure 9-4).

The findings for IPI or birth interval of ≥60 months and risk of gestational hypertension are similar to preeclampsia findings. Long intervals were associated with an increased odd of gestational hypertension with aOR ranging from 1.24 (95% CI: 0.89, 1.72)[33] to 1.36 (95% CI: 1.20, 1.54).[8]

The association between long IPI and gestational hypertension was examined in the same within-mother study from Australia,[8] results indicate increased risk of gestational hypertension for long IPI (>60 months) with lower estimates than between-mother comparison studies (aOR:1.22; 95% CI; 1.04, 1.44) (Supplemental Figure 9-4).

In pooled adjusted analyses, the aOR for gestational hypertension was 0.96 (95% CI: 0.87, 1.06) with moderate heterogeneity (I^2=37.6%) for an IPI <6 months and 0.93 (95% CI 0.91, 0.95) with little variation in study findings due to heterogeneity (I^2=0.0%) for an IPI 6-11 months as compared to 18-23 months. For IPI of ≥60 months, the pooled aOR suggested there was a significant increase in odds of gestational hypertension compared to 18-23 months (pooled OR:1.34; 95% CI 1.20, 1.51) with no statistical heterogeneity (I^2=0.0%) (Figure 9-4).

9.5.3 Gestational diabetes

Nine studies, with high[6,8,34,36,66,67]to moderate[13,65,68] quality, examined the association between IPI and gestational diabetes.

Of the seven studies that reported associations for short interval defined as IPI <6 months,[6,8,34,36] IPI <24 months,[68] IBI ≤18 months,[13] or 4-17 months[65] four studies[8,13,36,65] did not find significantly increased risks for gestational diabetes. Conversely, studies from Latin America countries,[34]Canada[6] and China[68] reported an increased risk of gestational diabetes with point estimates ranging from aOR: 1.02 (95% CI: 0.74, 1.41)[34] to 1.47 (95% CI: 1.26, 1.72).[6]

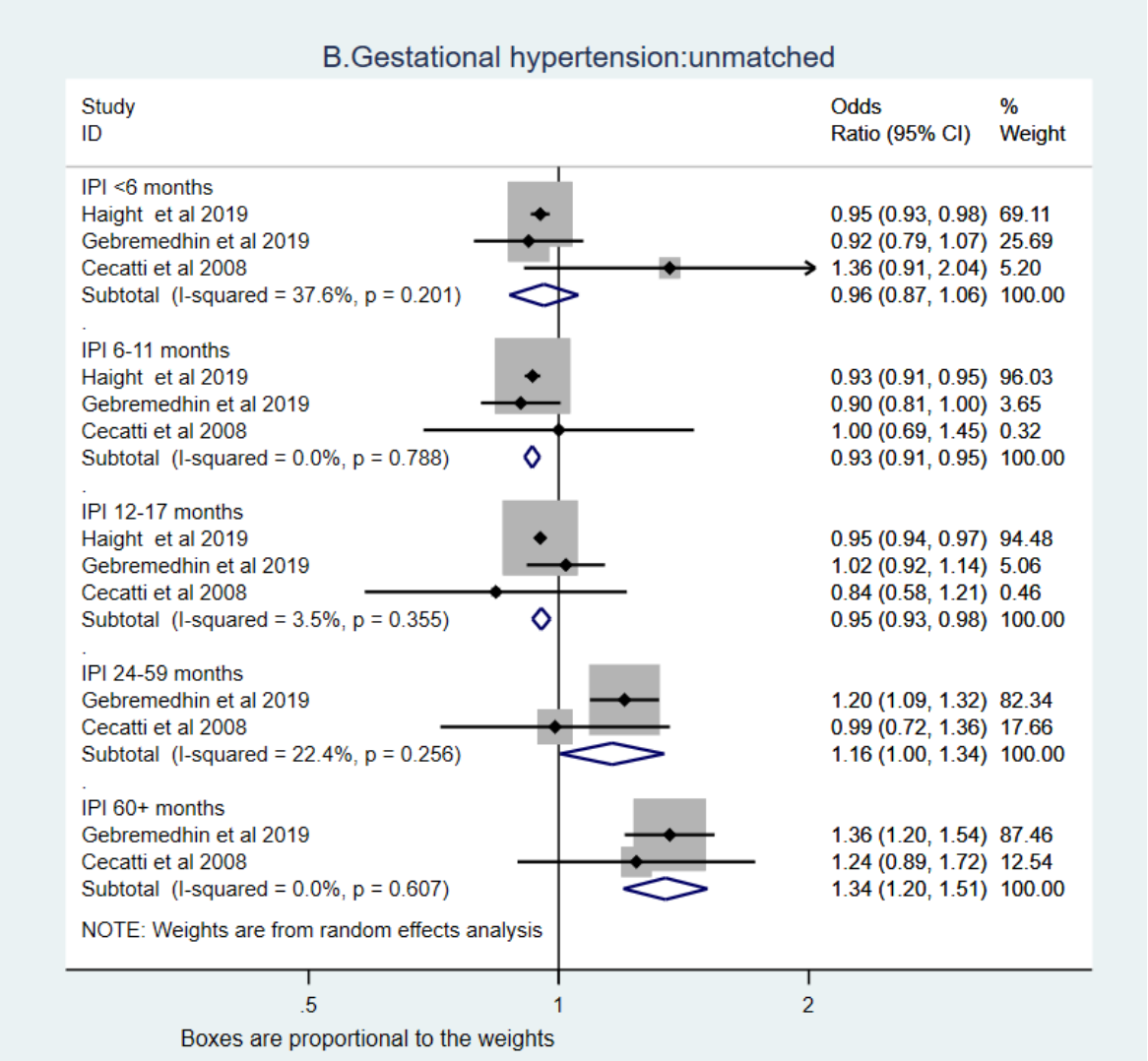


Figure 9-4 Meta-analysis of adjusted odds ratios of gestational hypertension for various IPI categories compared to IPI 18-23 months.

Short IPI (<6 months) were not associated with an increased risk of gestational diabetes in the matched analyses of the Australian study[8] (aOR:0.88; 95% CI:0.74, 1.04), but was associated with an increased risk in the Canadian study (aOR:1.36; 95% CI: 1.02, 1.79).[6]

Among seven studies that assessed the association between gestational diabetes and long intervals defined as IPI ≥60,[6,8,34,65] IPI ≥24,[67,68] or IBIs of ≥36 months[13] an increased risk of gestational diabetes was reported in five studies,[6,8,34,66,67] the association was null in one [65] and suggestive of non-significant decreased risk in another.[13]

Adjusted odds ratios of GDM associated with long interval ranged from 1.32 (95% CI 1.18-1.48) [8] to aOR:1.32 (95% CI: 1.26-1.48)[6] for IPI ≥60 months vs 18-23 months.

Two of the matched studies[6,8] reported increased risk in gestational diabetes for long IPIs (>60 months) compared to 18-23 months, with aOR of 1.02 (95% CI: 0.79-1.31)[6], and 1.07 (95% CI: 0.93, 1.23)[8]. However, none of the estimates was statistically significant.

Compared to 18-23 months of IPI, the pooled results suggest significantly decreased odds of gestational diabetes for shorter IPIs of 6-11 months (pooled OR: 0.91; 95% CI: 0.85, 0.98; I^2=75.8%), and for IPI of 12-17 months (pooled OR: 0.95; 95% CI: 0.89, 1.01; I^2=64.6%). For IPI of ≥60 months, the pooled adjusted odds ratio indicated there was an increase in odds of gestational diabetes compared to 18-23 months (pooled OR:1.34; 95% CI 1.26, 1.43) with little statistical heterogeneity (I^2=0.0%) (Figure 9-5).

A similar finding was observed in the pooled results of two within-mother matched studies.[6,8] The pooled odds ratio for IPI ≥60 months was associated with an increase in the odds of gestational diabetes (pooled OR: 1.04; 95% CI: 0.94, 1.20) with little statistical heterogeneity (I^2=0.0%), although these pooled estimates were not statistically significant (Supplemental Figure 9-6).

9.5.4 Placental abruption and placenta praevia

Utero-placental bleeding complications were evaluated in four studies.[7,13,69,70] Two studies[13,70] reported placental abruption, and two others[7,69] assessed placenta praevia as an outcome. In all of these moderate[7,13,69] to high[7,70] quality studies, a moderate to strong harmful association was reported for short intervals, with point estimates for placental abruption ranging from aOR:1.89 (95% CI 0.54, 6.59) for IBI ≤ 1 year vs 1-4 years[7]to aOR:1.90 (95% CI 1.30, 3.00) for IPI <6 vs 24-59 months,[69] and placenta praevia with an aOR of 2.08 (95% CI 1.53, 2.83)[70] for IBI < 1 year vs 2-3 years to an aOR of 2.58 (95% CI 1.10, 6.05)[13] for IBI ≤ 18 vs ≥ 36 months.

A high-quality study by Conde-Agudelo *et al.* (2000)[34] also reported that an IPI of 5 months or less is associated with a higher risk of third-trimester bleeding (placenta praevia with haemorrhage and placental abruption) with an aOR: 1.7 (95% CI:1.4, 2.2) for <6 months vs 18-23 months. Among two studies[7,70] that reported association of these bleeding complications with long intervals, an increased risk of placenta praevia was reported for birth intervals of more than five years in one study[70], while a study by Rohde *et al.* (2019)[7] reported a lower risk (recurrence) of placental abruption for the long birth interval (>4 years vs 1-4 years) (Supplemental Figure 9-5).

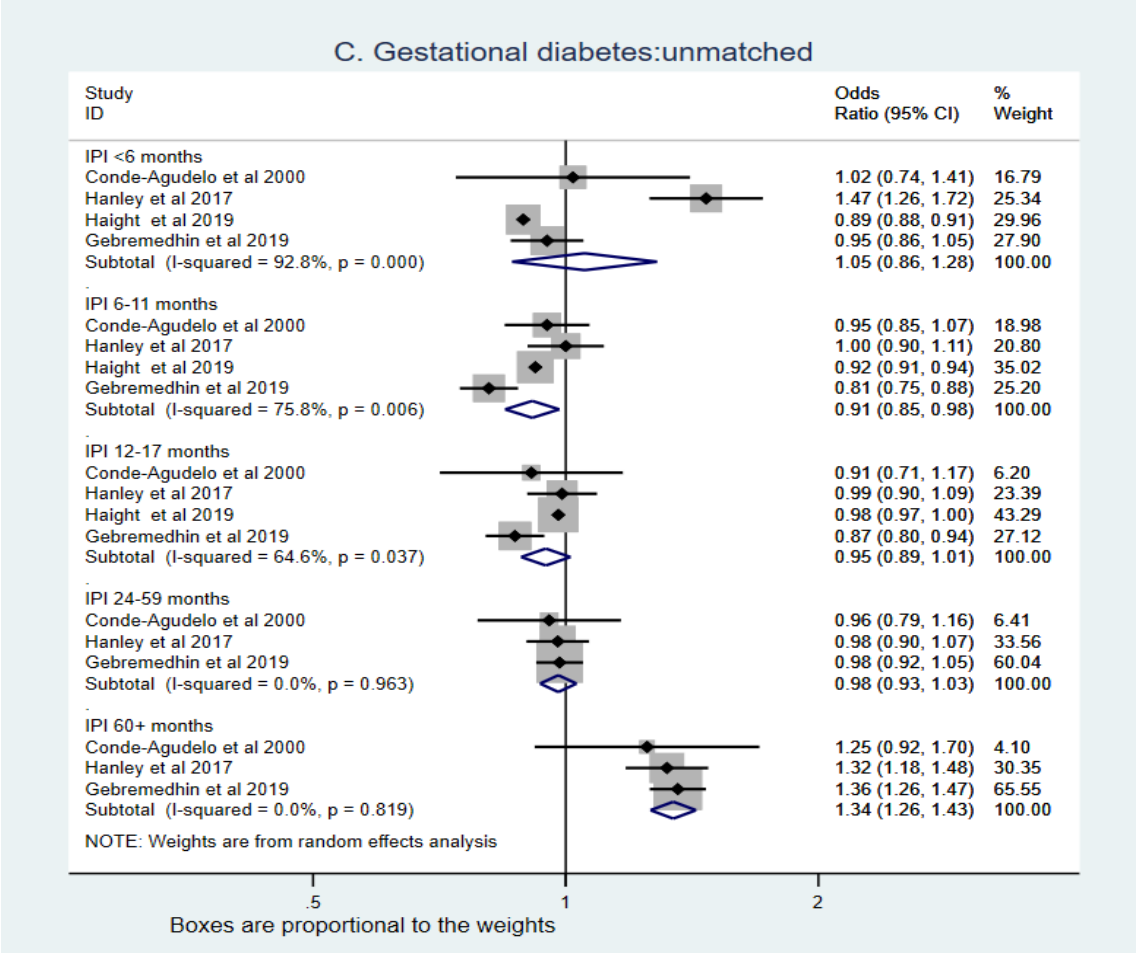


Figure 9-5 Meta-analysis of adjusted odds ratios of gestational diabetes for various IPI categories compared to IPI 18-23 months.

9.5.5 Premature rupture of membrane

Premature rupture of membrane was assessed in seven cohort,[11,13,33,34,63,64,71] One case –control[30] and one cross-sectional study.[32] Among the eight studies that evaluated the association of PROM with short intervals, one low quality,[64] four moderate[13] to high[11,34,63] quality studies reported statistically significant aOR for IPI <6 months [11,34]or IPI 6-14 months,[63] IBI ≤18 months.[13,64] Of these studies, all reported aOR ≥ 1.22. Three low to moderate quality studies reported significantly increased risks for IPI <6 months,[33] <12 months,[32] or less than 18 months.[71] Of the three studies that reported an IPI of ≥ 60 months, two identified an increase in the odds of PROM compared to an IPI 18-23 (aOR: 1.57; 95% CI 1.20, 2.06),[33]and an adjusted odds ratio of 1.03 (95% CI 0.93, 1.14).[34]

One moderate quality cross-sectional study reported a 34% increase in the risk of PROM for an IPI of five years or more.[32] Additionally, an IBI of 2-5 years was associated with a lower risk of PROM in a moderate quality case-control study (aOR:0.25; 95% CI 0.13, 0.48) for IBI 2-5 years vs <2 years (Supplemental Figure 9-7).[30]

9.5.6 Uterine rupture among mothers attempting vaginal birth after caesarean delivery

Uterine rupture was examined in two case-control[31,75] and eight cohort studies.[9,14,27,72-74,76,77]Among the nine moderate[27,31]to high quality studies[9,14,72,73,75-77]seven reported statistically significant aOR for intervals of IPI <6months,[9,77]IPI <12 months,[14,27] IBI less than 16 months,[72]18 months,[76]19 months, and IBI ≤24 months.[73] Of which studies reported an OR ranging from 2.30 (95% CI 1.10, 5.40) for <16 vs ≥16 months[72] to 3.12 (95% CI 1.62, 6.02) for IBI ≤24 vs >24 months.[27]One study reported an aOR: 3.05 (95% CI 1.36, 6.87) for IPI <6 vs 18-59 months.[77] De silva and Thoma *et al.* (2019) reported a dose-response association of IPI length and increased risk of uterine rupture, with a strong association at IPI of <6 months with an aOR: 2.78 (95% CI: 2.29, 3.39) for <6 vs 18-23 months, to aOR:0.83 (95% CI 0.69, 1.00) for IPI ≥60 vs 18-23 months.[9] The dose-response association was also reported in the high-quality cohort study by Bujold *et al.* (2002).[73] Three moderate[31,74] to high[75]quality studies did not find a statistically significant increased risk for short intervals defined as IPI<12 months[75], IBI <24, [31] or <19 months (Supplemental Figure 9-8).[74]

9.5.7 Labor dystocia

Two high-quality cohort studies in US[18] and Sweden[19] assessed the association of IPI and labor dystocia. Zhu et al. (2006)[18] reported a harmful association of IPI and labor dystocia in dose-response fashion with the lowest observed aOR of 1.06 (95% CI 1.04, 1.08) for 2-3 vs <2 years to higher observed aOR of 1.50 (95% CI 1.45, 1.56) for IPI ≥10 vs <2 years. Similarly, a study by Sandstorm *et al.* (2012)[19] reported a similar dose-response association with an aOR ranging from 1.36 (95% CI: 1.26, 1.46) for IPI 4-7 vs 1-4 years to aOR: 1.74 (95% CI 1.53, 1.97). Compared to IPI 4-7 years, IPI <1 year was associated with lower odds of dystocia in the same study (aOR: 0.91; 95% CI 0.85, 0.97) (Supplemental Figure 9-8).[19]

9.6 SPECIAL OBSTETRIC POPULATION STUDIES

9.6.1 By previous preeclampsia status

For intervals following previous preeclampsia, short birth intervals of less than one year were associated with increased risk of preeclampsia in studies from Norway[62] and the US[61] IBIs of 61-120 [62] and four years or more[61] also increased the risk of preeclampsia recurrence in subsequent pregnancies. In both of these studies,[61,62] adjusted for partner change and maternal age, potential confounding factors related to birth interval and preeclampsia (eFigure 4). Interestingly, the findings from Trogstad *et al.* (2001)[62] indicated that the risk for recurrent preeclampsia (risk of preeclampsia for women with a history of preeclampsia) in subsequent pregnancies decreased with longer intervals (Supplemental Figure 9-4). Studies from Norway,[60,62] and Australia[8] also assessed the risk of preeclampsia according to IPI and change of partner between pregnancies. Skjaerven *et al.* (2002),[60

and Gebremedhin *et al.* (2020)[8] reported increased risk of preeclampsia with long IPIs even after adjusting[60] or stratifying the analysis by partner change.[8] In a stratified analysis, a study by Trogstad *et al.* that included 527,268 women without previous preeclampsia and no change in partner reported adjusted odds ratios for preeclampsia of 2.35 (95% CI: 1.47, 3,77) for birth interval >15 years vs 1-5 years and aOR 2.69 (95% CI: 1.89, 3.83) for women changed partner between pregnancies.[62]

9.6.2 By previous gestational diabetes status

For intervals following previous gestational diabetes, the risk of gestational diabetes was higher for mothers with short IPI in one study,[68] and mothers with long IPI in another.[66] (Supplemental Figure 9-5). However, none of the studies reported separate associations by previous gestational diabetes status.

In general, findings of studies that conditioned the previous pregnancy outcome suggest that the relative risks of pregnancy outcome in the subsequent pregnancies by IPI are larger if the previous pregnancy was not complicated. In contrast, this group's absolute risk is lower compared to mothers with a previous complicated pregnancy.[80]

9.7 HETEROGENEITY OF STUDIES IN GENERAL

The I^2 values might not be informative for IPI studies, which tend to be population-based studies with a large sample size and therefore have narrow confidence intervals. With high precision of individual study, effects come with a high I^2 values because the variability between studies, which is the difference between individual study point estimates, is always going to much greater than the variability within individual studies (e.g., average CI widths). For instance, the point estimates for long IPI exposure (>60 months) for preeclampsia as an outcome (Figure 9-3) are close to each other. However, their CIs do not overlap (due to inherent differences in the population at risk). The possible explanation for this could be due to precise effect estimates owing to the large sample size of these population-based studies. In addition, it is also possible that the I^2 heterogeneity test could have excessive power for studies with a large sample size.

9.8 DISCUSSION

Pregnancy spacing has been identified as a potentially modifiable risk factor for various perinatal outcomes and has continued to be promoted as an essential component of family planning strategies.[81-83] Associations were investigated with preeclampsia, gestational hypertension, gestational diabetes, uteroplacental bleedings disorders (placental abruption and placenta praevia), uterine rupture, PROM and labor dystocia. Although 41 studies investigated associations with pregnancy complications, there were few studies conducted on any specific complication.

Even though the quality of many of the unmatched studies included in our review was limited due to confounding, we found consistent evidence for associations of long intervals with an increased risk of HDPs. The most consistent evidence of an association was observed for an IPI ≥60 vs 18-23 months with preeclampsia, gestational hypertension and gestational diabetes. IPIs of more than two years was associated with an 11% to 60% increased risk of preeclampsia. Likewise, our pooled estimates of moderate[33] to high[8,36] quality studies indicated that IPIs of more than two years was associated with a 16-34% increased risk of gestational hypertension. Furthermore, this finding was corroborated by studies that used a matched within-mother design, which controls for time-invariant confounders.[6,8,35] However, it remains controversial whether the link between short IPIs and adverse pregnancy outcomes is causal or due to unmeasured confounding by persistent maternal factors.

Additionally, intervening pregnancy loss can also influence the effects of long IPIs on pregnancy complications, as mothers with intervening pregnancy loss likely have longer IPIs.[79] Other studies have also suggested that prior induced abortion or miscarriage are associated with the risk of hypertensive disorders of pregnancy.[84] It is plausible that studies that cannot account for intervening pregnancy loss have biased associations at longer intervals.

There was insufficient evidence to indicate adverse associations of short IPIs (<6 months) with HDPs and GDM. In contrast, the pooled results suggest consistent evidence of lower risk of these complications for an IPI 6-11 months (and possibly 12-17 months), with little heterogeneity across studies. Our systematic review indicated that short intervals might be associated with increased risk of placenta praevia, placental abruption and premature rupture of membrane. These findings corroborate with the recovery time hypothesis, which suggests shorter intervals may not allow sufficient time for recovery from inflammation of a previous pregnancy,[46,50] folate deficiency, especially during the first trimester of pregnancy[85] and genes that regulate the folate metabolism.[49,86]

Among women attempting vaginal birth after prior caesarean delivery, there was evidence of a more consistent strong association of short intervals (defined as IPI <6 months or <12 months and IBI <16 months, <18 months, <19 or ≤24 months) and increased risk of uterine rupture.

The m*aternal depletion* is one of the major hypotheses used to explain the biological pathway through which short intervals may lead to adverse pregnancy complications. This hypothesis proposes that closely spaced pregnancies do not allow sufficient time to recover from the physiological stress of their previous pregnancy.[87,88] Additional hypotheses related to 'recovery time' focuses on proposed pathways of poor pregnancy outcomes associated with time to recover from the increased inflammatory changes from the previous pregnancy (specifically PROM),[50] as well as interference of short interval in the normal process of remodelling of endometrial blood vessels after delivery (specifically placental abruption and placenta praevia).[89,90] Likewise, the consistent strong association

between short intervals and the increased risk of uterine rupture can be explained through incomplete healing of the uterine scar after caesarean delivery.[89,91]

The physiologic regression hypotheses might explain the harmful effect of long intervals on pregnancy complications (mainly HDPs and labor dystocia)*;* a mechanism by which mothers physiologically become similar to nulliparous women if another pregnancy is not timely conceived due to gradual loss of the protective benefit of a previous birth over time.[18,89]

A competing explanation is a '*systematic bias hypotheses',* which postulated that the association between IPIs and pregnancy complications is attributed to confounding factors.[92] Several factors are associated with pregnancy complications, including age, socio-economic position, unplanned pregnancies, smoking and other social determinants that can confound the association with IPI.[92-94] Included studies varied in how the studies addressed these potential confounding variables. However, the reported evidence of association for preeclampsia, gestational hypertension and gestational diabetes has been supported by pooled results of high-quality matched studies (strong internal validity). The evidence of association of IPI and these complications were not strongly attenuated in the pooled results of the matched study, which leads us to believe that these associations are likely to exist. It should be noted that the pooled findings are limited to a small number of matched studies currently available,[6,8,35] but also matched studies have potentially limited external generalizability.[93] However, a study by Gebremedhin et al.[8] found a negligible difference of findings by higher-order parity and characteristics of the informative strata population to the broader analytic cohort, which suggests possible applicability of the findings from the matched studies to mothers with two consecutive births.

This review identified studies that evaluated the relationship between birth or interpregnancy interval and various maternal outcomes but not included in the qualitative syntheses as they did not meet the inclusion criteria.–Nonetheless, the findings of the excluded studies support the evidence of association of long intervals (not shorter) and increased risk of hypertensive disorders of pregnancy.[17,40,43,44,53] Shorter intervals were associated with increased risk of uterine rupture in women attempting vaginal birth after previous caesarean delivery,[38,39,47,54,95] and uteroplacental bleeding complications.[46,49]

9.8.1 Strengths

This review included independent reviewers, assessed a broad search strategy capturing the largest number of publications and relatively good quality observational studies with adequate observation time (study period), screening and data quality. Studies included in the meta-analyses deemed to be moderate to high quality and large population-based cohorts. Our review also included several

recently published studies that used within-mother design, which provide a novel approach to control for the potential confounding factors. Furthermore, this review adheres to recommended guidelines for conducting systematic reviews (i.e., PRISMA) and meta-analyses (i.e., MOOSE).

9.8.2 Limitations

Similar to other systematic reviews and meta-analyses, synthesis is limited by the quality of original studies. There was considerable variation in exposure and outcome definitions, data collection methods (maternal recall in a few of the studies, while the majority used information from databases) and study quality. We included strengths and limitations of each study included in the qualitative synthesis on top of the risk of bias score assessment using NOS to evaluate the overall quality of each study. In our synthesis, only ten studies were from LMICs (and only three in meta-analyses), Of which eight of them are deemed to be moderate[28,30,32,33] to high[34,58,59,63] quality. Generally, higher-quality studies reported lower effect estimates. Considerable number of studies have used personal interview or hospital records as opposed to ultrasound dating or the use of vital records to compute interpregnancy interval. Second, several studies did not adjust for potential confounders or adjusted for variables that may lie on the causal pathway, leading to either spurious association or over adjustment bias.

Moreover, providing conclusive evidence on the relationship between birth or interpregnancy intervals with some maternal outcomes (uteroplacental bleeding disorders and labor dystocia) is challenged by the number of available studies. Thirdly, inconsistent use of exposure definition limited the ability to synthesize results. We recommend the use of the following IPI categories for future studies: <6 months, 6-11 months, 12-17 months, 18-23 months [reference], 24-59 months, 60-119 months, and ≥120 months. Future research which applies the same categories would facilitate comparison to previous studies. Additionally, most of the population-based studies lacked data on pregnancy losses before 20 weeks of gestation. In addition, studies that used interbirth interval and studies that did not account for intervening pregnancy loss are prone to misclassification (exposure) bias.

Even though the pooled estimates from this review did not include studies that used IBI as a definition, a considerable number of studies included in the qualitative analysis used IBI as a definition. As the interbirth interval measure does not consider non-live births that occurred between live births and if the index pregnancy ends prematurely, there is a direct relationship between short birth intervals and adverse pregnancy complications, which creates a bias toward a shorter IPI. Thus, the findings from original studies that used IBI as a measure of the interval should be interpreted cautiously. Finally, despite rigorous literature search, a publication bias cannot be avoided entirely.

This review is a comprehensive and systematic evidence synthesis including meta-analyses to assess the effect of short and long intervals on the available evidence. Our findings are generally in line with previously published reviews.[3,20,21,96] These reviews reported that short intervals are associated with increased risk of uteroplacental bleeding disorders and uterine rupture, and decreased risk of labor dystocia and preeclampsia.[3,20] they also supported a harmful association of long intervals with preeclampsia[3,96] and labor dystocia.[3] The review by Hutcheon *et al.* (2019)[20] also suggested an increased risk of gestational diabetes associated with short IPIs <6 months. However, our meta-analyses of 4 large moderate to high-quality cohort studies did not support such a conclusion, with inconsistent finding across studies. Further research using additional data sources and rigorous methods would be valuable in this regard.

In conclusion, we found that among moderate to high-quality studies included, short birth or in interpregnancy interval (<6 or <12) are associated with increased risk of uterine rupture, placenta praevia, placental abruption, and PROM. There is clear and consistent evidence of the harmful effect of long IPIs on various pregnancy complications, mainly HDPs (preeclampsia, gestational hypertension), labor dystocia. However, there is insufficient evidence of harmful association of short intervals (IPIs <6 months) with preeclampsia, gestational hypertension and gestational diabetes.

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9.10 SUPPLEMENTARY MATERIAL

Supplemental Table 9-1 Quality of selected case-control, cohort and cross-sectional studies of interpregnancy interval and pregnancy complications (N=41), based on Newcastle-Ottawa Scale criteria.[3]

Author, Year	Data source	Selection	Comparability	Outcome/ Exposure	Total Score; Risk of bias	Comment
Low- & Middle-Income Countries						
Cecatti *et al.* 2008[33]	Medical record	★★★	★	★★	6; Moderate risk	*Strengths:* large sample size, multiple outcomes, adjusted for a majority of confounding variables *Weaknesses*: Hospital-based database, the analysis did not account for pregnancy losses, Possibility of selection bias (records with insufficient data to calculate IPI were excluded.
Conde-Agudelo *et al.* 2000[34]	Perinatal information system Database of Latin America	★★★★	★	★★★	8;Low risk	*Strengths:* large multi-country database *Weaknesses*: large database, but not population-based, not adjusted for potential confounders, e.g. SES, race, pregnancy intention
Habimana-Kabano *et al* 2015[32]	Medical record	★★★	★	★★	6; Moderate risk	*Strengths:* adequate sample size, multiple outcomes *Weaknesses*: hospital-based study did not adjust for additional known confounding factors (smoking, pregnancy loss). Possibility of selection bias; did not report CI of estimates
Harutyunyan *et al.* 2013[28]	Medical record	★★	★	★★	5; Moderate risk	*Strengths:* explored IPI as a category and continuous

[3] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 1 December 2018.

Author, Year	Data source	Selection	Comparability	Outcome/ Exposure	Total Score; Risk of bias	Comment
						Weaknesses: variables collected through a self-reported telephone interview, did not adjust for potential confounders (maternal age, SES, parity), small sample size, Possibility of selection bias.
Lilungulu *et al.* 2015[64]	Interview (self-report)	★★	★		3; High risk	*Strengths:* multiple maternal and perinatal outcomes studied *Weaknesses*: Poor external validity: groups selected by matching on maternal age only, which can introduce selection bias. These groups may have differences in other characteristics, and participants were not included randomly (purposive sampling); study excluded women with medical conditions in pregnancy and previous pregnancy complications. Poor internal validity: recall bias (LMP and date of births were self-reported)
Mignini *et al.* 2016[58]	Perinatal Information System database	★★★★	★	★★★	8; Low risk	*Strengths:* Good external validity: multi-country, large population-based cohort *Weaknesses*: fair internal validity: did not adjusted for potential confounders (SES, smoking, pregnancy loss)
Onwuka *et al.*, 2020[71]	Hospital records	★★		★	3; High risk	*Strength: a* prospective study *Weaknesses*: small sample size, facility-based, not adjusted for SES, maternal age
Razzaque *et al.* 2005[63]	Matlab DSS database	★★	★★	★★★	7; Low risk	*Strengths:* large sample size, adequate follow-up period *Weaknesses*: Poor external validity: prone to selection bias (analysis included only for women who came to a health facility for ANC), reported only point estimates (no CIs)
Sanga *et al.* 2020[59]	Medical birth registry	★★★★	★	★★	7; Low risk	*Strengths:* adequate follow-up period, adjusted for common confounding factors, outcome extracted from hospital record *Weaknesses*: more prone to selection bias (women selected if they have consecutive >=2 deliveries at the same hospital.
Workineh *et al.* 2018[30]	Interview (self-report) and medical records	★★	★★	★★	6; Moderate risk	*Strengths:* good outcome ascertainment (the outcome was confirmed using clinical features and examination), adjusted for potential confounders (maternal age, SES)

Author, Year	Data source	Selection	Comparability	Outcome/ Exposure	Total Score; Risk of bias	Comment
						Weaknesses: self-reported exposure (subjected to recall bias). Possibility of selection bias
High-Income Countries						
Al-Zirqi *et al.* 2017[72]	Medical birth registry of Norway	★★★★	★	★★★	7; Low risk	*Strengths: large population-based cohort, adequate follow-up time, outcome ascertained using two data sources* *Weaknesses*: did not adjust for SES.
Blumenfeld *et al.* 2014[69]	California Prenatal Screening Program linked to live birth and hospital discharge records in birth cohort database	★★★	★	★★	6; Moderate risk	*Strengths:* large sample size, good outcome and covariates ascertainment using both birth certificate and hospital discharge records. *Weaknesses*: Poor external validity: (included selected group of users), the possibility of measurement error (due to lack of data on the exact date of live birth), did not adjust for SES, pregnancy loss; Accuracy of birth certificate data is poor
Bujold *et al.* 2002[73]	Medical record	★★★★	★	★★★	8; Low risk	*Strengths:* information extracted by two independent observers. Used validated database (three sources) *Weaknesses*: did not adjust for SES
Bujold *et al.* 2010[31]	Medical records from multi centres	★★★	★	★★	6; Moderate risk	*Strengths:* information extracted by two independent observers. *Weaknesses*: did not adjust for maternal age, SES, Possibility of selection bias
Cho *et al.* 2015[56]	Korea National Health Insurance claims database	★★★★	★	★	6; Moderate risk	*Strengths:* large sample size, nationally representative, effects presented by the previous history of PE, *Weaknesses*: Relatively short follow-up time for observing the effect of IPI, adjusted for SES
Cunningham *et al.* 2019[14]	Vital statistics birth records	★★★★	★	★★★	8; Low risk	*Strengths:* Population-based cohort, large sample size *Weaknesses*: did not adjusted for potential confounders (maternal age, SES and parity).
De silva and Thoma *et al.* 2019[9]	US birth certificate data	★★★★	★★	★★★	9; Low risk	*Strengths:* adjusted for most important confounders *Weaknesses*: Accuracy of birth certificate data is poor.

Author, Year	Data source	Selection	Comparability	Outcome/ Exposure	Total Score; Risk of bias	Comment
Fitzpatrick *et al.* 2012[27]	UK Obstetrics Surveillance system (UKOSS)	★★	★★	★★	6; Moderate risk	*Strengths: a* nationally representative population-based case-control study *Weaknesses*: data collection technique (mail system) prone to misclassification bias
Gebremedhin *et al.* 2019[35]	Population-based registries-Midwives notifications and Hospital Morbidity Data System	★★★★	★★	★★★	9; Low risk	*Strengths: unmatched:* good external validity: large population-based cohort; *Weaknesses*: unmatched: Poor internal validity, not adjusted for BMI, pregnancy loss
		★★★	★★	★★★	8; Low risk	*Strengths: matched: good internal validity:* quality-controlled database *Weaknesses*: matched: Poor external validity: analysis restricted to women with three or more birth (a subset of the target population)
Gebremedhin *et al.* 2020[8]	Population-based registries-Midwives notifications and Hospital Morbidity Data System	★★★★	★★	★★★	9; Low risk	*Strengths: unmatched: good external validity: large population-based cohort* *Weaknesses*: unmatched: Poor internal validity, not adjusted for BMI, pregnancy loss
		★★★	★★	★★★	8; Low risk	*Strengths: matched: good internal validity: quality-controlled database* *Weaknesses*: matched: Poor external validity: analysis restricted to women with three or more birth (a subset of the target population)
Gurol-Urganci *et al.* 2011[70]	Hospital Episode Statistics (HES)	★★★★	★★	★★	8; Low risk	*Strengths: large sample size, adequate follow-up time, adjusted for potential confounders including deprivation, maternal age)* *Weaknesses*: authors did not describe the potential bias of missing information. Half of the eligible population were excluded due to missing of information on parity which likely introduces selection bias.
Haight *et al.* 2019[36]	US birth certificate data	★★★★	★★	★★	8; Low risk	*Strengths:* large sample size, examined maternal age at index birth *Weaknesses*: analysed data from the subset of states that had implemented revised birth certificate and accuracy of birth certificate data is poor. did not adjusted for potential confounders (intention and breastfeeding),

Author, Year	Data source	Selection	Comparability	Outcome/ Exposure	Total Score; Risk of bias	Comment
Hanley *et al.* 2017[6]	British Columbia Perinatal Data Registry	★★★★	★	★★★	8; Low risk	*Strengths: <u>unmatched</u>: good external validity*: large population-based cohort *Weaknesses*: <u>unmatched:</u> Poor internal validity, not adjusted for SES, parity, BMI, infertility
		★★★	★	★★★	7; Low risk	*Strengths: <u>matched</u>: good internal validity:* quality-controlled database *Weaknesses:* <u>matched:</u> Poor external validity: analysis restricted to women with three or more birth (a subset of the target population), not adjusted for SES and parity
Hercus *et al.* 2018[57]	Hospital records	★★	★	★	4; High risk	*Strengths: adjusted for smoking and paternity change* *Weaknesses*: did not adjusted for other potential confounders like SES, maternal age); not adequate follow-up period; hospital-based data
Huang *et al.* 2002[74]	Patient chart	★★★★	★	★	6;Moderate risk	*Strengths:* *Weaknesses*: short follow-up period, not adjusted for potential confounders: age, SES, smoking. 21% of participants excluded due to missing. Only three cases of uterine rupture
Huber *et al.* 2018[13]	Pregnancy Risk Assessment Monitoring System from two states in US (Mississippi and Tennessee)	★★★	★★	★	6; Moderate risk	*Strengths:* observed multiple outcomes, adjusted for major confounders *Weaknesses*: GDM, and placenta previa, and IBI, were Self-reported. Information on PROM abstracted from birth certificate
Kaczmarczyk *et al.* 2007[75]	Swedish Birth Register	★★★★	★	★★★	8; Low risk	*Strength:* population study, adequate follow-up period, large sample size *Weaknesses*: not adjusted for SES, the possibility of outcome misclassification bias (due to use of different ICD-definition for outcome)
Khambalia *et al.* 2013[66]	NSW Perinatal Data and the	★★★★	★	★★★	8; Low risk	*Strengths:* large population-based prospective cohort, adequate follow-up time, used validated risk factors and outcomes

Author, Year	Data source	Selection	Comparability	Outcome/ Exposure	Total Score; Risk of bias	Comment
	Admitted Patients Data					*Weaknesses*: did not adjust for potential confounders (SES, pregnancy loss), authors did not describe the potential bias of missing information.
Lu *et al.* 2002[67]	Comprehensive perinatal database	★★★★	★	★★	7; Low risk	*Strengths:* adequate follow-up time and sample size, analysis *restricted to women who had no GDM in their first pregnancy* *Weaknesses*: did not adjusted for potential confounders like SES, maternal age, parity).
Mostello *et al.* 2002[53]	Missouri maternally linked birth and fetal death certificates.	★★★	★★	★	6; Moderate risk	*Strengths:* large population-based, case-control study *Weaknesses*: Accuracy of birth certificate data is poor. Did not adjusted for partner change, parity and pregnancy intention
Mostello *et al.* 2010[61]	Missouri maternally linked birth and fetal death certificates.	★★★★	★	★★	7; Low risk	*Strengths:* large population-based cohort, adequate follow-up time *Weaknesses*: did not adjust for potential confounders (SES, pregnancy loss, smoking), authors did not describe the potential bias of missing information. The accuracy of birth certificate data is poor
Rohde *et al.* 2019[7]	maternally-linked Missouri birth registry	★★★★	★	★★	7; Low risk	*Strengths:* population-based *Weaknesses*: analysis restricted to women with abruptio placenta in the first pregnancy, not adjusted for potential confounders: SES
Sandstrom et al. 2012[19]	Swedish population-based Medical Birth Register	★★★★	★	★★	7; Low risk	*Strengths:* large population-based cohort, quality-controlled medical records, adequate follow-up time *Weaknesses*: did not adjusted for SES, Women with induced labor were excluded, missing data likely to introduce bias, authors did not examine the potential bias from these missing data.
Shipp *et al.* 2001[76]	Medical records	★★★★	★	★★	7; Low risk	*Strengths:* adequate follow-up period *Weaknesses*: analysis restricted to women with one prior caesarean delivery and no previous vaginal deliveries. Did not adjust for SES, Possibility of selection bias
Shree *et al.* 2017[11]	Missouri birth certificate Database	★★★★	★★	★★★	9; Low risk	*Strengths:* large sample size, adjusted to the majority of known confounding variables, long follow-up time *Weaknesses*: Accuracy of birth certificate data is poor
Skjaerven *et al.* 2002[60]	Medical Birth Registry of Norway	★★★★	★	★★★	7; Low risk	*Strengths:* population-based, adequate follow-up time *Weaknesses*: not adjusted for potential confounders: SES, smoking

Author, Year	Data source	Selection	Comparability	Outcome/ Exposure	Total Score; Risk of bias	Comment
Stamilio *et al.* 2007[77]	Medical record/hospital data	★★★★	★★	★★★	8; Low risk	*Strengths:* a multi-centre, record-based, retrospective cohort study *Weaknesses*: The database included only year of prior delivery (not date), which introduces the misclassification bias of IPI.
Trogstad *et al.* 2001[62]	Administrative data	★★★★	★	★★★	8; Low risk	*Strengths:* large sample size, population-based cohort, presented estimates stratified by PE history and paternal change status. *Weaknesses*: did not adjust for SES, pregnancy loss
Wang *et al.* 2018[68]	MCH hospital database	★★★	★	★★	6; Moderate risk	*Strengths:* adequate follow-up time, *Weaknesses*: Poor external validity (analysis restricted to primiparous, diet treated GDM in first pregnancy), did not adjusted for potential confounders like SES, parity). The study excluded multiparous and mothers with pre-existing diabetes at first birth,
Yee *et al.* 2016[65]	Vital Statistics Natality birth certificate registry	★★★	★★	★	6; Moderate risk	*Strengths:* Large sample size, considered multiple outcomes *Weaknesses*: included only primiparous women, short follow-up time, used IDI, Accuracy of birth certificate data is poor.
Zhu *et al.* 2006[97]	Birth certificate linked to Michigan Inpatient Database	★★★★	★	★★★	8; Low risk	*Strengths: large population-based cohort, adequate follow-up time* *Weaknesses*: did not adjust for potential confounders (SES, maternal morbidities). The accuracy of birth certificate data is poor.

Supplemental Table 9-2 Covariates included in analysis of interpregnancy interval and pregnancy complications among selected studies (n=41)

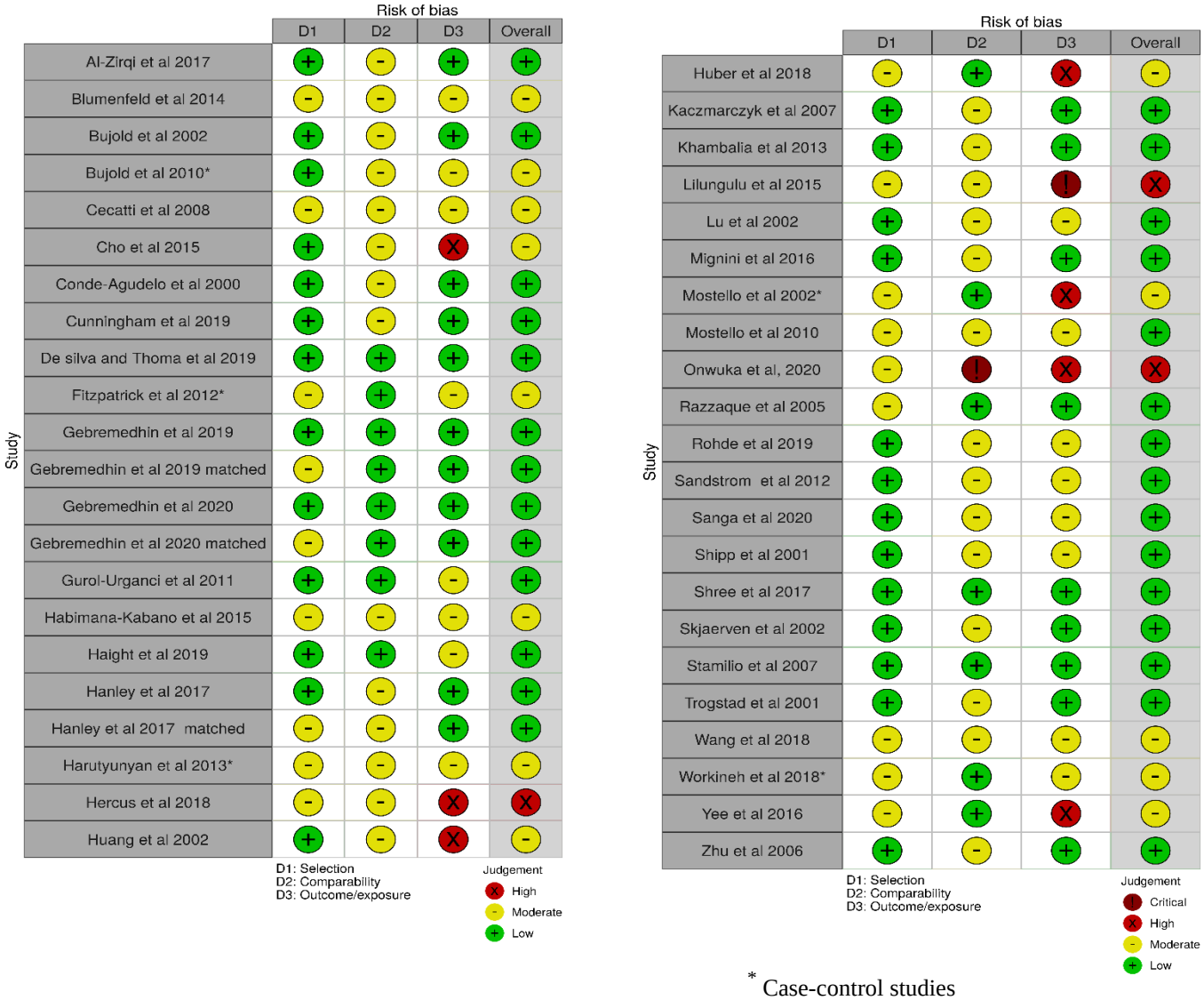
Author, Year	Maternal age	SES	Household size	Previous pregnancy complication	Gestational age	Maternal country of birth	Race/ethnicity	Paternal change	Maternal education	Maternal occupation	Plurality	Maternal conditions	Maternal height	Maternal BMI	Gravidity	Parity/Birth order	Prenatal care	Smoking	Alcohol use	Marital/cohabitation status	Obstetric history	Infant sex	Birth year/month	Previous perinatal outcome
Low- & Middle-Income Countries																								
Cecatti *et al.*, 2008	●											●		●		●	●	●		●	●			●
Conde-Agudelo *et al.*, 2000	●			●					●			●		●			●	●		●			●	●
Habimana-Kabano *et al*, 2015	●	●				●				●		●												●
Harutyunyan, 2013	●	●		●								●		●										
Lilungulu *et al.*, 2015									●	●						●				●				
Mignini *et al.*, 2015	●			●							●	●				●					●			●
Onwuka *et al.*, 2020	●	●					●									●								
Razzaque *et al.*, 2005	●		●						●						●									●
Sanga *et al.*, 2020	●			●						●		●							●					
Workneh *et al.*, 2018		●		●													●	●						
High-Income Countries																								
Al Zirqi *et al.*, 2017	●																							●

Author, Year	Maternal age	SES	Household size	Previous pregnancy complication	Gestational age	Maternal country of birth	Race/ethnicity	Paternal change	Maternal education	Maternal occupation	Plurality	Maternal conditions	Maternal height	Maternal BMI	Gravidity	Parity/Birth order	Prenatal care	Smoking	Alcohol use	Marital/cohabitation status	Obstetric history	Infant sex	Birth year/month	Previous perinatal outcome
Blumenfeld *et al.*, 2014	●			●								●		●										
Bujold *et al.*, 2002	●			●																	●			
Bujold *et al.*, 2010	●			●	●																●			
Cho *et al.*, 2015	●			●							●													
Cunningham *et al.*, 2019	●			●	●		●									●		●			●			
De silva and Thoma *et al*, 2019	●	●					●		●					●		●		●		●	●			
Fitzpatrick *et al.*, 2012	●			●			●							●							●			
Gebremedhin *et al.*, 2019	●	●		●			●					●		●		●				●		●	●	
Gebremedhin *et al.*, 2020	●	●					●	●				●		●		●				●		●	●	
Gurol-Urganci *et al.*, 2011	●	●		●			●																	
Haight *et al.*, 2019		●					●		●					●		●	●	●		●				
Hanley *et al.*, 2017	●			●								●						●					●	●
Hercus *et al.*, 2018																●		●			●			
Huang *et al.*, 2002				●	●		●								●						●	●		

Author, Year	Maternal age	SES	Household size	Previous pregnancy complication	Gestational age	Maternal country of birth	Race/ethnicity	Paternal change	Maternal education	Maternal occupation	Plurality	Maternal conditions	Maternal height	Maternal BMI	Gravidity	Parity/Birth order	Prenatal care	Smoking	Alcohol use	Marital/cohabitation status	Obstetric history	Infant sex	Birth year/month	Previous perinatal outcome
Huber *et al.*, 2018	●	●					●							●		●	●							
Kaczmarczyk *et al.*, 2007	●			●	●				●				●	●				●			●			
Khambalia *et al.*, 2013	●			●		●					●							●						
Lu *et al.*, 2002					●		●							●										
Mostello *et al.*, 2002	●	●		●	●		●	●				●					●							
Mostello *et al.*, 2010	●	●		●			●					●		●				●						
Rohde *et al.*, 2019	●	●		●										●				●	●					●
Sandstrom *et al.*, 2012	●				●	●			●				●	●				●			●	●		●
Shipp *et al.*, 2001	●				●																●			
Shree *et al.*, 2017	●	●					●		●					●				●						●
Skjaerven *et al.*, 2002	●			●				●															●	
Stamilio *et al.*, 2007	●	●			●		●									●		●			●			
Trogstad *et al.*, 2001	●			●				●															●	
Wang *et al.*, 2018	●								●			●		●										
Yee *et al.*, 2016	●				●		●					●									●			●

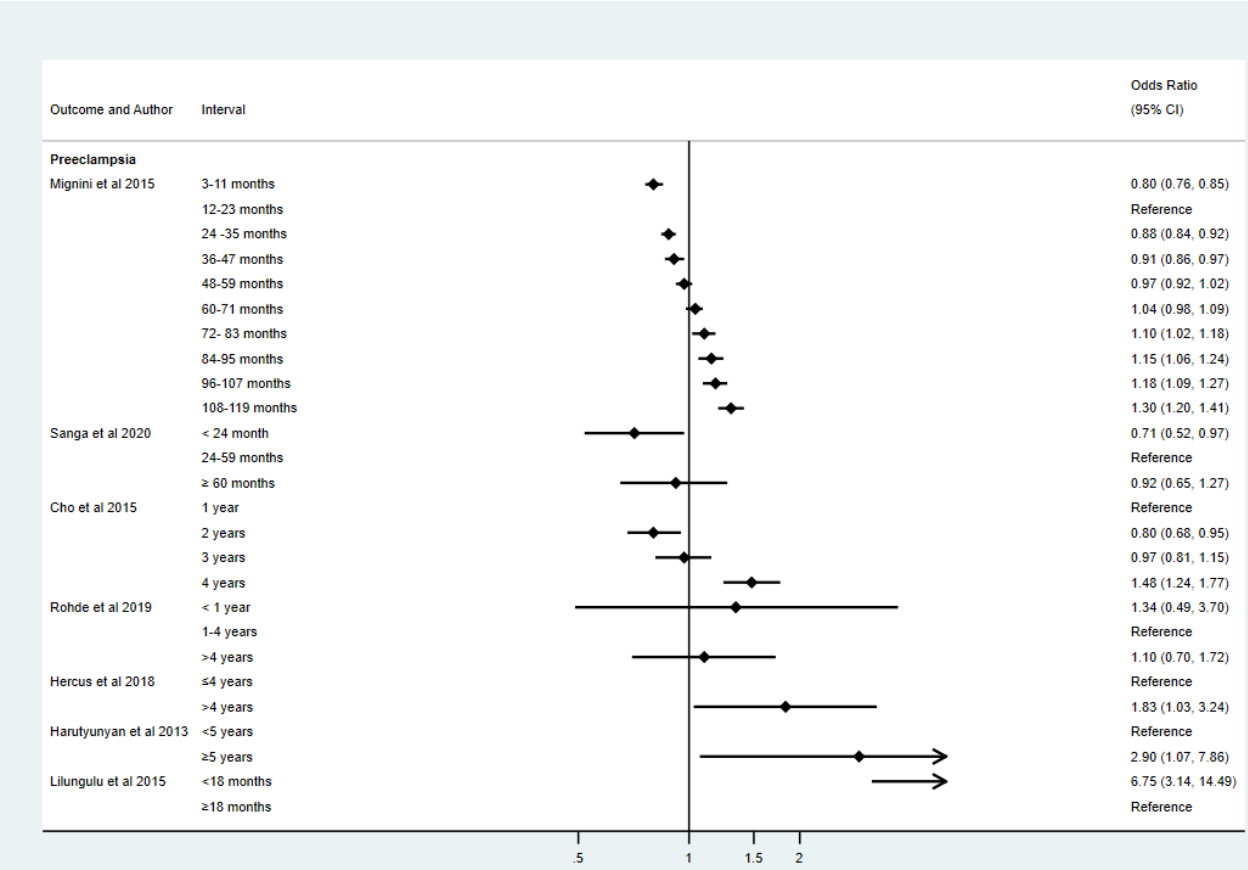
Author, Year	Maternal age	SES	Household size	Previous pregnancy complication	Gestational age	Maternal country of birth	Race/ethnicity	Paternal change	Maternal education	Maternal occupation	Plurality	Maternal conditions	Maternal height	Maternal BMI	Gravidity	Parity/Birth order	Prenatal care	Smoking	Alcohol use	Marital/cohabitation status	Obstetric history	Infant sex	Birth year/month	Previous perinatal outcome
Zhu *et al.*, 2006	●						●		●					●	●		●	●		●				●

SES: Deprivation, Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), Health insurance, source of payment, Medicaid status; Obstetric history: Type of delivery, induction of labor, use of oxytocin; Previous perinatal outcome: LBW, PTB, macrosomia, Stillbirth, miscarriage, abortion, deaths (neonatal, infant, child); Previous pregnancy complications: GDM, PE, placenta praevia, placental abruption, haemorrhage, C/S delivery; Maternal conditions: maternal medical comorbidities (hypertension, DM, HIV, anaemia); Maternal BMI includes if studies included history of obesity as covariate.

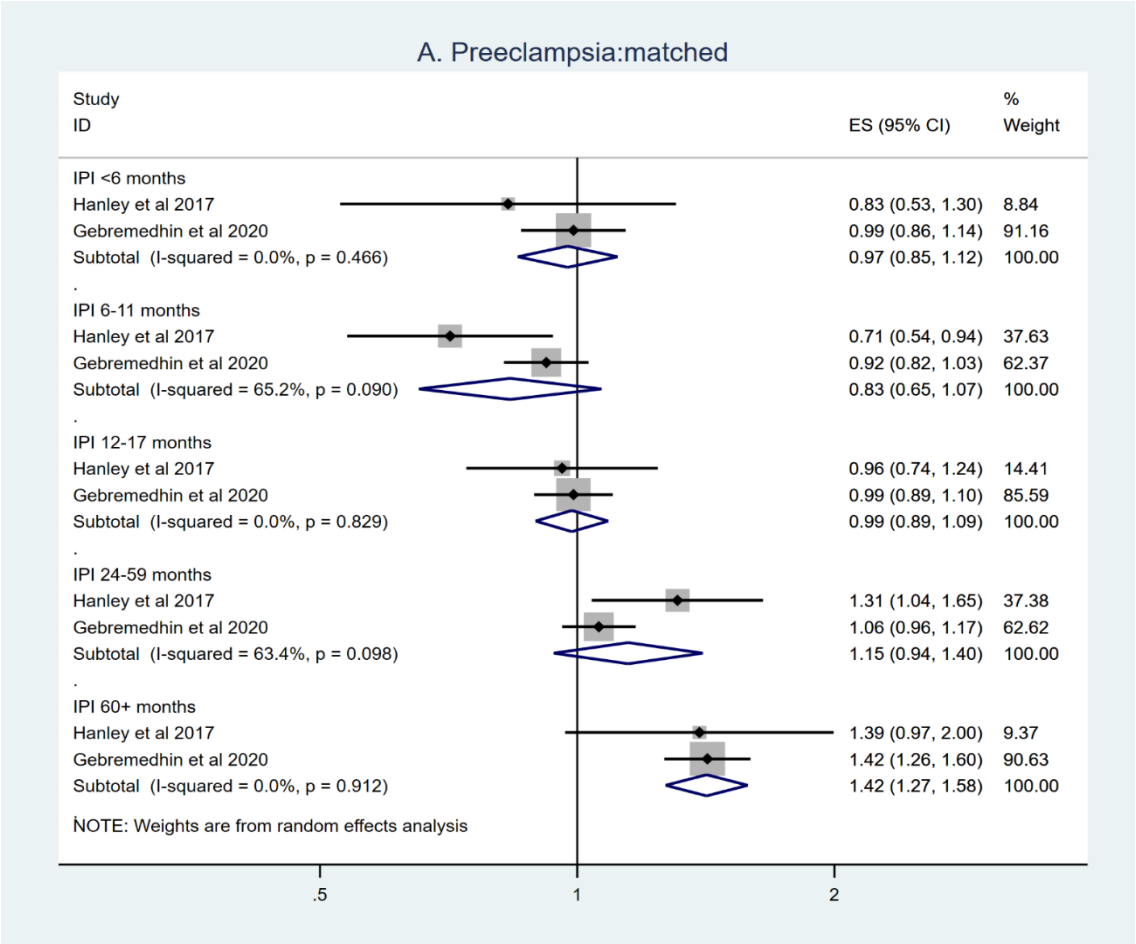


* Case-control studies

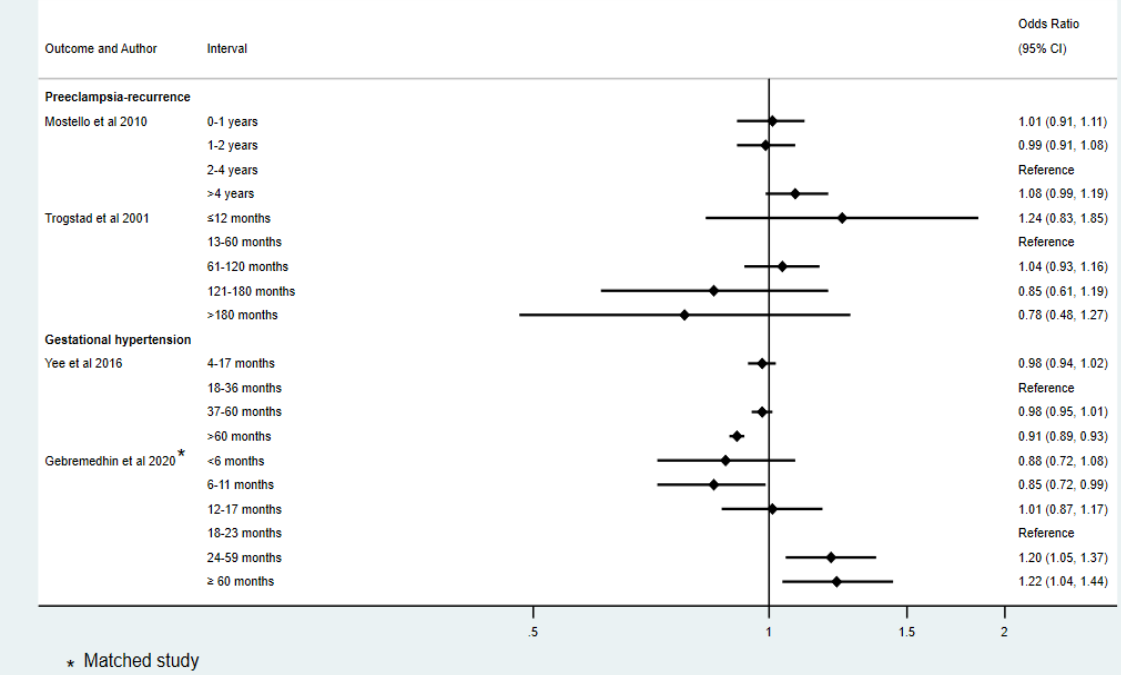
Supplemental Figure 9-1 Methodological quality of included studies according to Newcastle-Ottawa Scale criteria



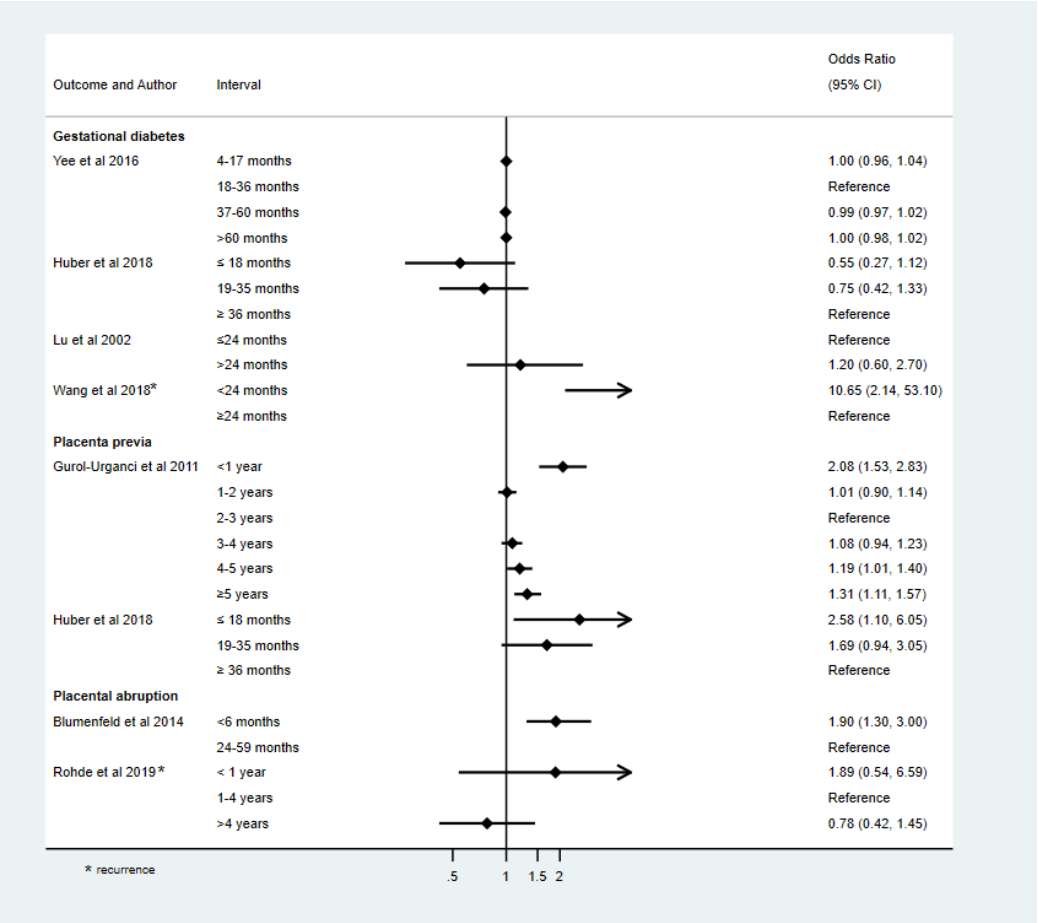
Supplemental Figure 9-2 Summary of adjusted odds ratios of preeclampsia for various IPI categories



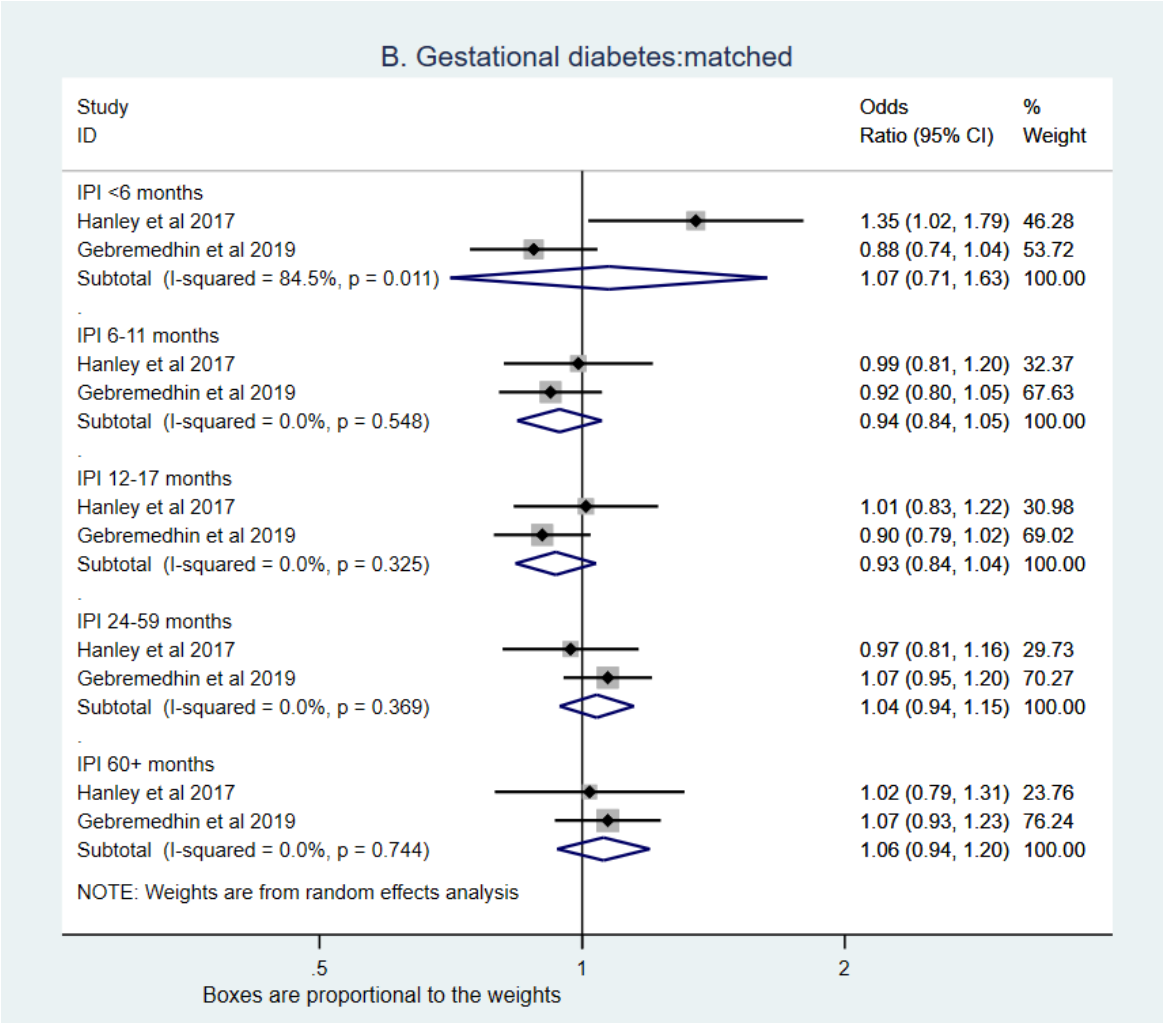
Supplemental Figure 9-3 Meta-analysis of adjusted odds ratios of preeclampsia for various IPI categories compared to IPI 18-23 months, using matched studies



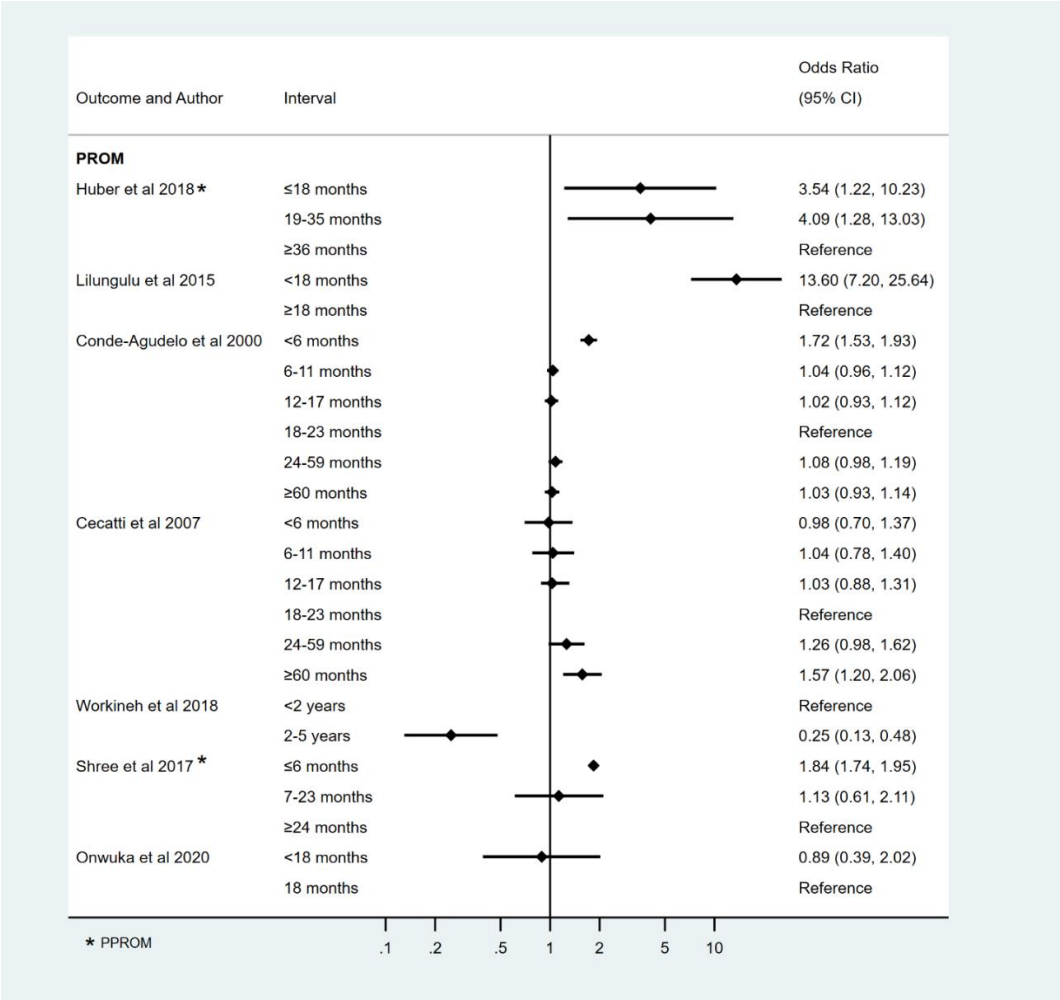
Supplemental Figure 9-4 Summary of adjusted odds ratios of preeclampsia recurrence and gestational hypertension for various IPI categories



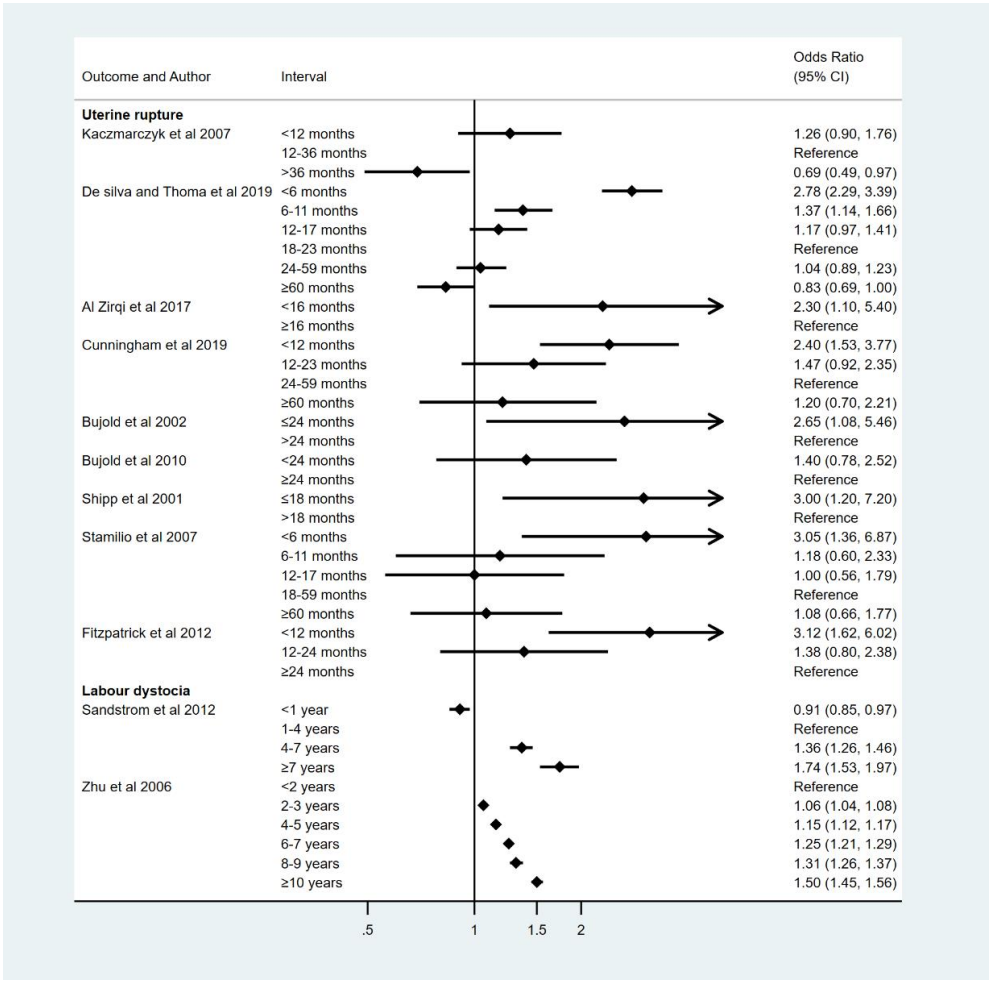
Supplemental Figure 9-5 Summary of adjusted odds ratios of gestational diabetes, placenta praevia and placental abruption for various IPI categories



Supplemental Figure 9-6 Meta-analysis of adjusted odds ratios of gestational diabetes for various IPI categories compared to IPI 18-23 months, using matched studies



Supplemental Figure 9-7 Summary of adjusted odds ratios of PROM for various IPI categories



Supplemental Figure 9-8 Summary of adjusted odds ratios of labor dystocia and uterine rupture for women attempting vaginal birth after prior caesarean delivery for various IPI categories

Chapter 10: GENERAL DISCUSSION AND CONCLUSION

Key findings, discussion, originality, implication, and conclusion

10.1 PREAMBLE

A range of factors can influence complications during pregnancy. Although inconclusive, there is growing evidence of an association between IPI and complications during pregnancy, including gestational diabetes and HDPs.[1-3] These complications are global public health concerns and significant contributors to morbidity and mortality to mothers and their babies.

This project aimed to examine the effect of IPI on pregnancy complications to inform the evidence-based IPI recommendations in high-income settings.

Using several epidemiological designs and advanced statistical modelling approaches, including matched design and negative control analyses, studies included in this thesis examined the effect of IPI on pregnancy complications and quantified the effect modifying role of maternal age and presence of previous complications.

Firstly, using the longitudinally linked perinatal and hospital records of 103,909 mothers with at least two consecutive births, we examined the association between IPI and gestational diabetes by applying a novel, within-mother design.

Secondly, using the same cohort, we further examined the causal associations between IPI and hypertensive pregnancy disorders, focusing on preeclampsia and the role of partner change in the association.

Thirdly, we evaluated the effect- modifying role of maternal age and previous complications.

We then examined the influence of previous complications on delaying the pregnancy interval using quantile regression.

Finally, we synthesised the current evidence of the association between IPI and various pregnancy complications including, PE, GDM, GH, PROM, uterine rupture and labor dystocia.

The first section of this chapter summarises each of the five primary studies' main findings and describes each study's contribution to the objectives. The results are discussed sequentially to demonstrate the links between these studies. We then included a discussion of the research findings overall, followed by the strengths and limitations of the thesis in general. The following section identifies the public health implications and directions of future research. The final section concludes the thesis by commenting more generally on the significance of the research findings to families, clinicians and policymakers in general.

10.2 MAIN FINDINGS

A summary of the major findings is provided in Table 10-1, including results related to independent associations of IPI with GDM and HDP, the effect-modifying role of maternal age and previous complications, the influence of previous complications on IPI as well as the synthesis of the current evidence of associations of IPI and pregnancy complications.

Studies One and Two used a large, population-based retrospective cohort of more than 100,000 women with at least three consecutive singleton births (n=358,046) in the year between 1980 and 2015 in WA to examine the association between IPIs and pregnancy complications (GDM and HDPs), respectively. I used a within-mother design in both studies, matching pregnancies to the same mother to control the unmeasured characterises that remained stable throughout their consecutive pregnancies. For comparison with previous studies, I also applied a conventional between-mother design. I used a prognostic score adjustment in all the matched models to minimise the multi-collinearity of time-varying confounders, such as maternal age.

Findings of within-mother and between-mother analysis from Study One (Chapter 4) do not support the hypothesis of increased risk of GDM with short intervals (<6 months). Compared to 18-23 months, lower odds of GDM were observed for mothers with IPI 6-11 months (aOR:0.89; 95% CI 0.82, 0.97) and 12-17 months (aOR:0.92; 95% CI: 0.85, 0.99). Long IPIs (≥24 months) were associated with increased risk of GDM, with the greatest adjusted effect observed for the longest IPI (≥120 months) with aOR:1.51 (95% CI: 1.33, 1.70). However, evidence of association was negligible according to the matched analyses with attenuated effect estimates for both short and long IPIs. The negative control exposure analyses in this study used post-birth IPI(as an exposure) to predict GDM on the pregnancy before the IPI, and results indicate that short post-birth IPIs (<6 months) were statistically significantly associated with higher odds of GDM in the previous pregnancy. Nevertheless, no associations were observed with long post-birth IPIs.

In study Two (Chapter 5), we expanded on findings from Study One by replicating the analyses in two common pregnancy outcomes, preeclampsia and gestational hypertension, and by examining the association separately according to partner change.

Table 10-1 Summary of major findings

Objective	Main findings
1.1 To examine the association between IPI and GDM using both within-mother and between-mother comparisons (Chapter 4).	**Unmatched analyses:** After adjustment, compared to 18-23 months, lower odds of GDM were observed for mothers with IPI 6-11 and 12-17 months. However, the risk of GDM increased with long IPIs (≥24 months). **Matched analyses:** After adjustment to time-varying factors, both short and long IPIs showed no statistically significant association with GDM. All effect estimates were attenuated after using the within-mother design. **Interpretation** Findings from both designs do not support the hypothesis that short IPI (<6 months) increases the risk of GDM
1.2 To examine the association between IPI and hypertensive pregnancy disorders using both within-mother and between-mother comparisons (Chapter 5).	**Unmatched analyses:** After adjustment, compared to 18-23 months, IPI of 6-11 months was associated with a lower risk of PE. Long IPIs (≥24 months) were associated with a higher risk of HDPs with greater effects observed IPI ≥120 months. **Matched analyses:** After adjustment to time-varying factors, no increased risk of HDPs was observed for shorter IPIs (<18-23 months). In comparison, an increased risk was observed for longer IPIs (≥24 months). **Partner change** There was a negligible difference in the association between IPI and PE for mothers who changed partners compared to those who did not change with attenuated estimates in the matched analyses. **Interpretation** There was insufficient evidence to suggest that short IPIs (<6 months increases risks of HDPs
2.1 To examine if the association between IPIs and pregnancy complications varies by maternal age (Chapter 6).	**Absolute risks (AR)** For mothers of all ages at birth prior to IPI, minimum risks were observed at 12 months for APH and PROM and six months for PE, GH, and GDM. The ARs of APH and PROM at shorter IPIs (<6 months) were greater for younger women. The risks of HDPs and GDM following long IPIs (≥36 months) were greater for older mothers (≥35 years) **Relative risks (RRs)** Risks of all complications after IPIs longer than 24-36 months were consistently higher than those of 18 months among mothers in the older age groups (30-34, ≥35 years) compared to other younger groups. No increased risk of HDPs and GDM was observed at six months of IPI compared to 18 months for mothers younger than 20 years at birth prior to IPI.

Objective	Main findings
	Interpretation An optimal IPI vary depending on maternal age and risk profile at birth prior to IPI
2.2 To examine if the association between IPI and pregnancy complications varies by previous experience with these conditions (Chapter 7).	**ARs** Cohort: First two consecutive births ARs of PE and GDM were higher for mothers with complications in the first pregnancy throughout the IPI continuum. Optimal IPIs were around 12 months for mothers with previous PE and approximately 6-12 months irrespective of previous GDM history. Cohort: First three consecutive births Predicted risks of both PE and GDM in third pregnancy were much higher for mothers with these conditions in recent or both pregnancies and lower for mothers with no complications in both first and second pregnancies. **RRs** For mothers with previous PE, there was insufficient evidence of an association between IPI and PE, with consistently lower RRs than mothers with no previous PE. Shorter IPIs of less than 18 months were associated with lower risk of GDM than at IPIs of 18 months for mothers with no previous GDM **Interpretation** Risks of IPIs on PE and GDM is modified by previous experience with these conditions, with higher ARs but lower RRs to mothers with previous complications
3.1 To ascertain whether pregnancy complications at first pregnancy influences subsequent pregnancy and whether the size of the effect varies with IPI distribution. (Chapter 8).	IPIs were longer after HDPs, but the extent of the delay was relatively small and did not differ across the IPI distribution. **Interpretation** HDPs at first pregnancy influences the subsequent interval
4.1 To synthesise the current evidence on the effect of IPI on pregnancy complications (Chapter 9).	**Pregnancy complications and short IPIs** There was insufficient evidence of harmful associations of short IPIs (<6 months) with HDPs. Short birth or interpregnancy intervals may be associated with increased risk of placenta praevia, placental abruption, and PROM. **Pregnancy complications and long IPIs** There was consistent evidence of an association between long intervals (>24 months) and pregnancy complications, mainly HDPs and labor dystocia. **Interpretation** The strength of evidence supporting associations of short intervals with pregnancy complications is low

After careful consideration of adjustment for potential confounders conceptualised using DAGs, the conventional between-mother study indicated that, compared to 18-23 months, IPI of 6-11 months was associated with a lower risk of PE (aRR:0.92; 95% CI:0.85, 0.98). In contrast, longer IPIs (≥24 months) was associated with a higher risk of HDP, with greater adjusted effects observed for IPI of ≥120 months.

After adjustment to potential time-varying confounders, the matched within-mother comparison suggested no increased risk of HDP for shorter IPIs (<18-23 months), while increased risk observed for longer IPIs (≥24 months) with a greater risk of PE observed in IPIs 60-119 (aRR:1.29, 95% CI: 1.18, 1.42), and ≥120 months (aRR:1.30, 95% CI: 1.10, 1.53) IPI categories. In the analyses to examine the role of partner change in the association between IPIs and PE, both unmatched and matched models suggested similar findings, an increased risk of PE with long IPIs, irrespective of partner change status.

The results of this thesis (Chapter 6 & Chapter 7) further demonstrated that the associations between IPIs and pregnancy complications differ by maternal age and the presence of previous complications at birth prior to IPI. These studies provided an optimal interval at which the lowest absolute risk of the outcome is observed along the IPI continuum for each modifier of interest (maternal age category or previous history of complications). RRs were also reported at selected IPIs (3, 6, 12, 24, 36, 48, and 60 months) with 18 months as reference.

For mothers of all ages at birth prior to the IPI, predicted risks (ARs) of APH and PROM were lowest at around 12 months, while predicted risks of PE, GH, and GDM were lowest at around 6 months. The ARs of APH and PROM at IPI <6 months were greater for younger women (<20 years), whereas the risks of GDM and HDP were greater for older mothers (≥35 years). Short IPI (<6 months) was associated with an increased risk of APH and PROM complications, with slightly higher estimates for younger mothers (<20 years) as compared to older (≥35 years). Longer IPIs (≥24 months) were associated with a higher risk of HDPs and GDM complications for mothers with advanced maternal age (≥35 years).

In Study Four (Chapter 7), in the cohort of mothers with two consecutive births, we found an elevated risk (ARs) of PE and GDM for mothers with complicated first pregnancy along the IPI continuum (14-16% for previous PE vs 1-2% for no previous PE; 30-45% for previous GDM vs 2-8% for no previous GDM). Risks of PE and GDM were lower at around 12 months for mothers with previous PE and approximately 6-12 months of IPI irrespective of previous GDM history. A similar pattern was observed in the cohort of mothers with three consecutive

births with elevated predicted risks for mothers with a history of complications in recent pregnancies or both pregnancies and lower ARs for mothers with no complicated pregnancy in their first and second pregnancies. We also found insufficient evidence of an association between increased risk of PE and shorter IPIs (<18 months) for mothers with previous PE, with consistently lower RRs than mothers with the absence of PE in their previous pregnancy. The association between IPI and GDM was less clear for mothers with previous GDM than mothers with no GDM in their previous pregnancy.

The fifth paper (Chapter 8) provides an insight into an area of perinatal epidemiology, especially birth-spacing research about which there is a substantial concern among researchers on whether complications at first pregnancy influence IPI and if it does, whether effects were consistent throughout the IPI continuum. I employed quantile regression analyses and adjusted for potential confounders of the association under investigation. The findings revealed insufficient evidence to suggest that associations between pregnancy complications and IPI differed by the length of the interval. Mothers with HDPs had slightly longer subsequent IPI as compared to mothers with no HDP at first pregnancy.

Finally, Study Six presented a focused synthesis and discussion of published studies on the association between IPIs and pregnancy complications, along with studies included in this thesis (Studies One and Two). In this study (Study Six), 41 articles were eligible for systematic review, and six were suitable for meta-analysis. Two studies included in this thesis (Studies One and Two) contributed to the meta-analysis for three outcomes suitable for pooling results (PE, GH, and GDM). The majority (n=35) of studies were cohort in design. Almost all studies deemed high-quality (including six studies included in the meta-analyses) were population-based cohorts. A large proportion of studies supported the adverse association between long intervals with HDPs and labor dystocia and an inconsistent but accumulating evidence of association with an increased risk of uteroplacental bleeding disorders. This study also found insufficient evidence of adverse association of short IPIs (<6 months) with HDPs. The use of different birth spacing definitions (IPI vs IBI), variations in exposure and outcome definitions, and data collection methods might have contributed to heterogeneous findings.

10.3 DISCUSSION OF MAIN FINDINGS

While there has been a growing body of literature on the relationship between IPI and pregnancy complications, clinically relevant and statistically significant associations were supported by some studies, but not all. The most consistent associations observed were

increased risk of maternal complications, mainly HDPs with long intervals and studies of uteroplacental bleeding disorders, uterine rupture, and PROM associated with short intervals (<6 or <12 months). To date, the literature is less consistent in the associations reported for an increased risk of HDPs and GDM with short intervals (<6 months). I have advanced this knowledge base by investigating the associations between IPI and pregnancy complications by matching pregnancies to the same women to achieve the best control for confounding. Findings from these analyses revealed insufficient statistical evidence supporting elevated risks of GDM and HDPs after short IPIs (<6 months), while an increased risk of HDPs with long IPIs (≥24 months). The effect estimates from the within-mother comparison were consistently lower than effect estimates obtained from between-mother comparisons. Moreover, the estimates were further attenuated with an additional adjustment for the time-variant confounders, which indicates that previous findings of the association between short IPIs and pregnancy complications using between-mother comparison may be due to confounding effects.[4-7] However, a recent study argued that the lower effect estimates in the association between short IPIs and pregnancy complications in the matched analyses might partly result from the fact that women included in those analyses were healthy enough to have at least three pregnancies- "healthy pregnant women effect".[8]

Furthermore, in the within-mother comparison, we considered two factors (birth year and maternal age at each pregnancy) as potential causal intermediates to estimate the total and direct effects and elucidate the possible causal pathway. We found attenuated effect estimates in the model that included both variables, suggesting that the association was partially explained by the pathway through maternal age or time-period. The negative control analyses further justified the findings from the matched design, as it demonstrated the possible role of confounding at shorter IPIs as an alternative explanation for the presence of association in the between-mother comparison.[9, 10] In the literature on the factors associated with preeclampsia, the relative importance of IPI and partner change has been subject to considerable debate.[11-15] Findings from this thesis addressed a significant knowledge gap in this regard, expounding that partner change did not explain the associations between long IPIs and preeclampsia. An absence of association between long post-birth IPI and GDM in the negative control exposure analyses indicates that confounding is the least explanation for the observed association in the main analyses.

The mechanism for the independent association of short IPIs with an increased risk of uteroplacental bleeding disorders (placental abruption, praevia) and PROM (Chapter 6) may

be the '*recovery time hypothesis'*.[16-19] Previous research has suggested that the *'carry-over effect'* hypothesis should also be considered,[20-22] which suggests that unresolved infections (e.g., pathohistological inflammation of placenta) from the previous birth have a potential to be carried over to the subsequent pregnancy.

As discussed in detail in Chapter 9, the findings on the elevated risks of HDPs with long IPIs (in both between-mother and within-mother comparisons including several sensitivity analyses) is consistent with previous literature.[3, 17, 23, 24] This indicates that an effect of long IPIs cannot be fully explained by persistent maternal factors, which is consistent with the 'physiologic *regression'* hypothesis whereby long intervals result in a gradual return to a higher-risk primigravid state (Chapter 2).[16] However, the observed association can still be confounded by time-varying factors that can change within-mother across pregnancies. These potential confounders may include decreasing fecundity, complications prior to IPI (e.g., HDPs) and pregnancy intention.[25-28] Some women who intend to become pregnant may have taken a long time to conceive due to factors related to decreased fecundity. While others may have waited because of a 'health selection process',[8, 29] for example, underlying issues such as severe preeclampsia in their previous pregnancy made them hesitant to conceive again. Mothers with either of these scenarios would be at higher risk of preeclampsia, without long IPI playing a causal role. We employed a quantile regression to ascertain if complication at first pregnancy influences the pregnancy interval to disentangle this. The results support the hypothesis that mothers with HDPs at first pregnancy had longer subsequent intervals. However, the extent of the delay was negligible (<2 months) [Chapter 8].

This thesis's findings advanced the existing body of evidence on optimal IPI (where IPI recommendations do not fully encompass the obstetric and socio-demographic context) by estimating the absolute risk of various complications based on socio-demographic and obstetric history. This has improved our understanding of the interval at which lowest risk (optimal) and the interval at which the highest risk is observed (harmful) based on obstetric (e.g., presence of previous complications) or socio-demographic context (e.g., maternal age at birth prior to the interval). With limited previous research on this issue,[10, 30] The current WHO recommendation suggests waiting at least 24 months before conceiving again after live births regardless of socio-demographic or obstetric context (except for intervals after spontaneous/induced abortion).[1] My study (Chapter 6 and 7) presents clinically relevant evidence-base which can assist families for an informed decision in planning future pregnancies. It can also help guide clinicians providing care and advice during postpartum

counselling and inform/revising future birth spacing guidelines. Consistent with a recent study from the US,[10] our findings demonstrated that the effect of IPI on pregnancy complications varies by maternal age. For mothers of all ages at birth prior to the interval, the optimal IPI was shorter than those recommended (6-18 months). We also found that confounding did not fully explain the observed associations between IPI and these adverse pregnancy complications. Though studies included in this thesis (Chapter 6 and 7) carefully considered various statistical adjustments, including non-linear modelling, which allowed me to observe associations across the IPI continuum.

It should be noted that causal interpretations of long IPIs association remain challenging as the possibility of residual confounding cannot be ruled out. Moreover, with a relatively small proportion of mothers in the advanced age group category (≥35 years) (Chapter 6), the stronger associations should be interpreted cautiously. It is plausible that mothers at this particular age group might have underlying subfertility (fecundability) for which this study did not account.

My findings collectively suggest that pregnancy complications (mainly HDPs and GDM) are not the result of short IPIs in themselves but are due to persistent maternal factors that are highly correlated with both IPI and the pregnancy outcomes.

10.4 ORIGINALITY

This thesis has several original contributions. Firstly, this thesis provides epidemiological evidence on the association of IPI and a wide range of pregnancy complications using the largest, high-quality, longitudinal (>35 years) population-based cohort to date. Second, although previous research has suggested an association between IPIs and pregnancy complications, most studies were from low-income settings or had various methodological limitations. This thesis applied a DAG to assist in the identification of potential confounders (for both short and long IPIs separately, Supplemental Figure 5-1, Supplemental Figure 5-2) and a quasi-experimental approach (matched design) to better control for the potential unmeasured confounders (non-time varying) that are known to bias associations. To date, few studies employed a population-based matched design demonstrating the association of IPI and pregnancy complications.[8, 17] Our matched analyses, an inference that is based purely on within-mother effects, showed that previous findings of an association between short IPIs and complications during pregnancy (HDPs and GDM) might have been introduced by confounding. Secondly, using the large population-based longitudinal cohort, this thesis was the first to examine the role of partner change in the associations between IPI and preeclampsia

using a within-mother design, which provided an insight into an area of debate for perinatal epidemiologists.

Thirdly, this thesis makes a unique contribution that addressed several of the major methodological limitations of previous studies. Most previous studies investigating the association between IPI and pregnancy complications have adjusted for maternal age as a potential confounder.[2, 3, 17, 25] However, to the best of my knowledge, no previous study has considered the effect-modifying role of maternal age in the non-linear association between IPI and pregnancy complications. I used a flexible, non-linear approach to model IPI and estimated absolute risks along the IPI continuum. This approach allowed us to present risk curves, identify the optimal IPI (at monthly scale) for each complication of interest, and estimate the optimal IPI by risk profile. These analyses demonstrated that the effect of IPI on pregnancy complications varies by obstetric and socio-demographic contexts.

Next, this thesis dispels myths related to the role of previous complications on the association between IPI and pregnancy complications. Specifically, myths associated with expecting higher RRs for mothers who experienced the complication compared to mothers with no previous complication, when in fact the RRs are lower, but ARs are higher for those mothers with previous complications across the IPI continuum. Mothers with previous complications will likely have lower RRs because the recurrence is the dominant cause, and the IPI effect on the risk of these complications is relatively small. On the contrary, the total absolute effect would have to be higher for those with previous complications because of the higher prevalence of the outcome, allowing more room to observe an effect. This thesis also confirmed that these findings were not sensitive to higher-order parity (Chapter 7).

Additionally, the quantile regression analyses included in this thesis were the first to examine if complications before the interval influence the IPI as a possible explanation for the delay of pregnancy due to the complication before the interval and whether the influence is consistent throughout the IPI continuum (Chapter 8). Thus, this thesis confirms that intervals were longer after hypertensive complications at first pregnancy. However, the results indicated that the extent of the delay was small and did not differ across the IPI continuum.

Finally, the systematic review and meta-analyses paper provided an updated synthesis with a focused discussion of studies from this thesis (Studies One and Two) in context with other studies, some of which were also recent and published by others during the course of my candidature. While previous studies reported systematic reviews examining the association

between IPI and maternal outcomes,[2, 3, 31] this study remains the only study to present a pooled result of the effects of IPI on pregnancy complications (Chapter 9).

10.5 STRENGTHS

Randomised controlled trial (RCTs) that directly randomise IPI are neither practical, feasible, nor ethical. Those that randomise interventions that might extend IPI, such as providing access to contraceptives or provision of postpartum family planning counselling, do not achieve randomisation of confounders between treatment groups and are not proxies for RCTs on IPI. For this reason, the majority of research on IPI relies on observational designs.

This research employed various epidemiological approaches to investigate the link between birth spacing and pregnancy complications, each of which has numerous strengths. First, this project was based on uniquely large, population-based administrative data, comprised of hospital separation, midwife's notification, birth registration and family connections records. IPI is not relevant for women who have only one child. While unmatched IPI studies need at least one IPI (two pregnancies), matching pregnancies to the same women require more than one IPI per mother, thereby restricting the analyses to mothers with at least two consecutive pregnancies. The 35 years study period enabled sufficient follow-up to examine the pregnancy outcomes in the same mother over time. In WA, the data linkage process is well established,[32] and is of high-quality and routinely validated.[33] The perinatal database captures >99% of births, allowing for the inclusion of all deliveries in the state during the study period.

Unlike past research, my studies examined the effects of IPI on a wide range of maternal endpoints with triangulated results utilising various quasi-experimental designs, including within-mother comparison and negative control analyses to establish a causal association. Unlike previous studies on the topic, my studies carefully considered adjustments for confounding (including the timing of adjustment) by first creating DAG to present the hypothesised relations between factors for both short and long IPIs, separately. I also included a prognostic score to adjust potential confounding factors and minimise collinearity among the factors. My study also uniquely accounted for the non-linear associations, which allowed assessment of a dose-response relationship and better clarification of optimal IPI. I also replicated results using IPI categorised with the recommended cut-offs,[3, 17, 34-36] to retain the ability to compare findings with previous studies.

Furthermore, the use of complementary epidemiological approaches employed across my studies addresses issues inherent to using conventional designs (e.g., unmatched comparison)

or matched designs alone. The latter design helped by reducing the influence of confounding, a major threat to the internal validity of causal inference.[37]Additionally, the matched design and additional statistical adjustments allowed us to present a purely within-mother effect by controlling for the unmeasured confounding factors. Thus, this study design achieves greater internal validity. Finally, using various sensitivity analyses across our studies, we addressed several limitations or assumptions in examining the link between IPI and pregnancy complications and issues related to the external generalisability of our findings.

This project also accounted for important research gaps and recommendations identified by the WHO[1], including identifying the harmful and beneficial intervals and high-quality population-based longitudinal study that considered potential confounding factors. The studies included in this thesis also carefully considered the current recommendation and good practices on birth spacing research, including clearly specifying the research questions, use of IPI opposed to IBI, considering the potential for effect modification and timing of covariate adjustment.[36]

Finally, this thesis also presents an updated and summarised synthesis of the current evidence of the association between IPI and pregnancy complications and the first to present pooled results (meta-analyses) for three outcomes, preeclampsia, gestational hypertension and gestational diabetes (Chapter 9).

10.6 LIMITATIONS

Limitations of each of the studies included in this thesis were described in detail in chapters (4-9) and summarised together in this section.

First, even though we used the largest population-based linked cohort that spans for more than three decades, some limitations should be acknowledged on the interpretation of findings from administrative data, particularly as the routinely collected data in those databases lacked certain important factors. Notable factors include breastfeeding, fecundability, contraceptive use, and information on miscarriage. Besides, data on chronic conditions and smoking were not routinely collected until 1997. Our datasets also lacked information on participants use of obstetric care during pregnancy (public vs private). As the databases capture pregnancies after >20 weeks of gestation, IPI was calculated as the time from previous birth until start of the following pregnancy that resulted in either live birth or stillbirth at or after 20 weeks' of gestation, not necessarily the subsequent pregnancy. This can lead to inaccurate measurement of the exposure, IPI.[17, 36] The intervening pregnancy can potentially influence the effects of IPI on pregnancy outcomes, as mothers with pregnancy loss likely have a longer interval.

Likewise, studies indicate that prior induced abortions or miscarriages are linked with HDPs.[12] The lack of information on fecundability and pregnancy intention may confound our results because both factors are likely to influence IPI and have reported as being associated with adverse pregnancy outcomes. Among the three main classifications of pregnancy, unintended, intended but mistimed, or intended, our exposure, IPI, is most readily modified by mothers who intend to have pregnancy.

Second, the quasi-experimental approaches applied in this thesis cannot rule out all possible confounding. For example, unmeasured factors that vary across pregnancies, such as pregnancy intention, pre-pregnancy BMI, can be causally associated with the complications and IPI.[17, 38] However, sensitivity analyses were conducted when possible when some data was available. For example, findings from our sensitivity analyses accounting for fertility treatment as a proxy for intention did not differ from the results of the primary analyses.

Third, as the matched design limited the analyses to mothers with at least three consecutive pregnancies, lack of statistical power becomes an issue, especially for rare outcomes. Additionally, the extent to which IPI-outcome association among mothers included in the matched analyses is comparable to the target population for inference (mothers who have at least one child and planning another pregnancy) is still unclear.[36, 39] Nonetheless, the characteristics of the informative strata population and the broader analytic cohort did not differ (Chapter 5).

Next, Future research would benefit from exploring the role of pregnancy complications at the mother's first birth as well as alternative analyses approach that takes time (gestational length of the second pregnancy) into account (Chapter 7).

Lastly, in the systematic review included in this thesis (Chapter 9), we were able to pool results and present meta-analyses of only six studies for three outcomes because of inconsistent exposure definition (interval type [IBI vs IPI] and category) as well as a dissimilar reference category. The most significant limitation of the meta-analysis, which reinforces the originality and contribution of this thesis, was the significantly limited number of studies on the topic. Finally, the review was restricted by language; relevant studies published in languages other than English could have been missed.

10.7 PUBLIC HEALTH IMPLICATIONS

With the growing burden of complications during pregnancy and the increasing maternal age at first birth, findings from this project have numerous public health implications for families, health care providers and policymakers.

This study's results do not support the hypothesis of a harmful association of short IPIs with HDPs and GDM in high-income settings, and previously reported associations might have been motivated by factors correlated with short IPIs, not the IPI itself. This implies that for mothers in a high-income context, short IPIs might be less important than previously assumed.[40] However, as IPI remains a strong predictor of adverse pregnancy outcomes, health care providers should consider IPI as an important indicator of a higher risk of adverse pregnancy outcomes. While modifying long IPI is challenging, it is relatively straightforward to think of policy or practice interventions to avoid short intervals such as post-partum contraception use, improve access, and integrate contraceptive counselling.[41, 42]

Our findings have also established novel associations that optimal IPIs, the interval at which the lowest risk of complications is observed, vary by maternal age and presence of pregnancy complications at birth prior to the interval and individual risk profiles. I presented absolute risks in the IPI continuum separately by maternal age categories and previous complication for each outcome of interest, which can be readily interpretable by individuals and clinicians. For example, irrespective of maternal age, this thesis's findings indicate an optimal interval of around 6-18 months, relatively shorter than those recommended. This finding might reassure mothers with advanced maternal age who must balance the delayed childbearing associated risks against the risks of having their next conception shortly after birth. However, findings from this thesis also challenge the applicability of current birth spacing recommendations, including WHO, in a high-income context such as Australia. Generally, these findings suggest that a more context-specific approach may be required for the birth spacing recommendations that take the mother's age, health status, and risk profile into consideration on top of individual/family readiness and desire to conceive again.

10.8 DIRECTIONS OF FUTURE RESEARCH

Triangulation of results using different epidemiological approaches, including the matched designs, will help researchers to address an inherent limitation in each approach. For instance, due to the intrinsic limitations of matched studies in restricting the analyses to women with three or more pregnancies, for some research questions, the study power is limited, even when

an extensive database exists.[43] For example, we did not apply the within-mother approach for two of our effect modification studies (Studies Three and Four) for this reason. Future studies will need to consider this challenge. One possibility would be to use population-based cross-jurisdiction data to increase the sample size and provide more robust results.[44]

More research is needed for the inconsistent findings on the association between IPI and pregnancy complications in high-income settings. Results should be replicated using comparative data in similar other high-income settings. Although it is challenging in terms of implementation and cost, prospective studies of a pre-pregnancy cohort or alternative natural experiment designs are needed to account for the confounding or mediating role of breastfeeding, pregnancy intention and early pregnancy loss in the association between IPI and pregnancy outcomes. Though we are not aware of any interventions that could modify the long intervals, Future work is needed to examine the effectiveness of potential practice or policy interventions that could modify short intervals, such as access to contraception, integration of contraceptive counselling to standard postpartum care. Likewise, future studies may examine specific interventions that could modify long intervals, such as avoiding teenage pregnancy, family-planning counselling. Further longitudinal studies employing a similar approach are also needed in diverse populations, particularly in a low-income context where the burden of diseases, fertility patterns, and nutritional depletion is profound.

As mothers at advanced maternal age may have issues related to infertility and possibly fertility treatment such as Artificial Reproductive Treatment (ART). It is unclear how this may influence their birth spacing patterns and whether IPI contributes differently to adverse pregnancy outcomes in mothers undergoing fertility treatment.[45] It would be worthwhile exploring these intertwined issues, as it would inform pregnancy spacing recommendations on this particular population. Additionally, examining the link between IPI and adverse pregnancy outcomes among subpopulations, including multiple gestations, mothers with previous caesarean section (e.g., uterine rupture as an outcome) may facilitate context-specific evidence-based recommendations.

10.9 CONCLUSION

Findings from this thesis have established novel pieces of evidence, some supporting previous conclusions, and others rebutting associations claimed to be causal. Our findings indicate that either short intervals are not causally associated with an elevated risk of HDPs and GDM in Australia, or the magnitude of effects is small if there is a causal association. Previous associations reported in other studies might be explained by confounding. Findings also support the conclusion that long IPIs are associated with a higher risk of HDPs. However, causal interpretation of these associations is difficult as studies on this issue, including mine, have been unable to rule out the possibility of other residual confounding. We also found that IPIs were longer after HDPs. However, the extent of the delay was relatively small and did not differ across the IPI continuum. The findings also indicate that the associations between IPIs and pregnancy complications varied by maternal age and previous compilations.

The meta-analysed results corroborated the adverse association between HDPs and long intervals but found insufficient evidence of adverse association with short intervals. These findings challenge the current one size fits all recommendation on birth spacing, including WHO, and questions their applicability to high-income settings such as Australia. Overall, our findings underscored that a more tailored— perhaps context-specific approach might be required for the birth spacing recommendations or related interventions aimed at healthy timing and spacing of pregnancy.

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APPENDICES

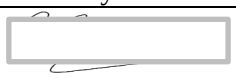
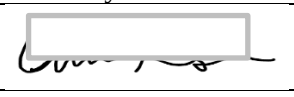
Appendix A

Authors' contributions and signatures

Statement of Authorship

Title of Paper	**Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study**		
Publication Status	Published		
Publication Details	Gebremedhin AT, Regan AK, Ball S, Betrán AP, Foo D, Gissler M, Håberg SE, Malacova E, Marinovich ML, Pereira G. Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study. Annals of epidemiology 2019;39:33-8. e3.		
Name of Principal Author (Candidate)	Amanuel Tesfay Gebremedhin		
Contribution to the Paper	Conceived and designed the study, performed data management and statistical analyses, interpreted the data, and drafted the manuscript		
Total % contribution	80%		
Certification:	This paper reports an original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreement with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/04/2021

Co-Author Contributions

Name of Co-Author	Professor Gavin Pereira		
Contribution to the Paper	Contributed to the design of the study, statistical analyses (advice), interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	04/03/2021
Name of Co-Author	Dr Annette K Regan		
Contribution to the Paper	Contributed to the design of the study, interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	03/05/2021

Name of Co-Author	Dr Stephen Ball		
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I acknowledge that these represent my contribution to the above research output			
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Name of Co-Author	Professor Mika Gissler		
Contribution to the Paper	Contributed to the interpretation of the findings, and reviewed the paper for intellectual content		
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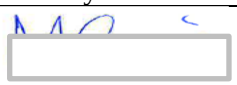
Signature		Date	04/03/2021
Name of Co-Author	Dr Siri E Håberg		
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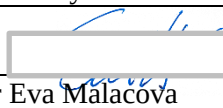
Signature		Date	March 4, 2021
Name of Co-Author	Dr Eva Malacova		
Contribution to the Paper	Contributed to the interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
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Name of Co-Author	Dr M Luke Marinovich		
Contribution to the Paper	Contributed to the interpretation of the findings, and reviewed the paper for intellectual content		
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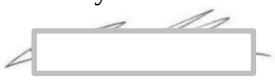
Signature		Date	04/03/2021

Statement of Authorship

Title of Paper	**Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study**		
Publication Status	Published		
Publication Details	**Gebremedhin AT**, Regan AK, Ball S, Betrán AP, Foo D, Gissler M, Håberg SE, Malacova E, Marinovich ML, Pereira G. Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study. Paediatr Perinat Epidemiol 2020. doi:10.1111/ppe.12668		
Name of Principal Author (Candidate)	Amanuel Tesfay Gebremedhin		
Contribution to the Paper	Conceived and designed the study, performed data management and statistical analyses, interpreted the data, and drafted the manuscript		
Total % contribution	80%		
Certification:	This paper reports an original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreement with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/04/2021

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Name of Co-Author	Professor Gavin Pereira		
Contribution to the Paper	Contributed to the design of the study, statistical analyses (advice), interpretation of the findings, and reviewed the paper for intellectual content		
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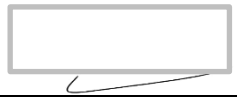
Signature		Date	04/03/2021
Name of Co-Author	Dr Annette K Regan		
Contribution to the Paper	Contributed to the design of the study, interpretation of the findings, and reviewed the paper for intellectual content		
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Signature		Date	03/05/2021
Name of Co-Author	Dr Stephen Ball		
Contribution to the Paper	Contributed to the interpretation of the findings, and reviewed the paper for intellectual content		
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Name of Co-Author	Dr Ana Pilar Betrán		
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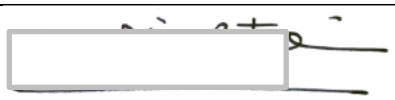
Signature		Date	04/03/2021
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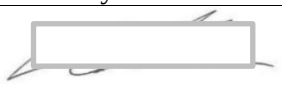
Signature		Date	04/03/2021

Statement of Authorship

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Publication Details	**Gebremedhin AT**, Tessema GA, Regan AK, Pereira G. Association between interpregnancy interval and hypertensive disorders of pregnancy: Effect modification by maternal age. *Paediatric and perinatal Epidemiology 2021*. doi:10.1111/ppe.12774		
Name of Principal Author (Candidate)	Amanuel Tesfay Gebremedhin		
Contribution to the Paper	Conceived and designed the study, performed data management and statistical analyses, interpreted the data, and drafted the manuscript		
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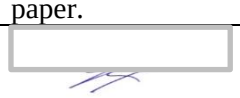
Certification:	This paper reports an original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreement with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/04/2021

Co-Author Contributions

Name of Co-Author	Professor Gavin Pereira		
Contribution to the Paper	Contributed to the design of the study, statistical analyses (advice), interpretation of the findings, and reviewed the paper for intellectual content		
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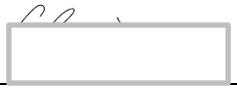
Signature		Date	04/03/2021
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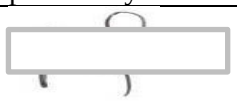
Signature		Date	30/04/2021
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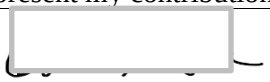
Signature		Date	03/05/2021

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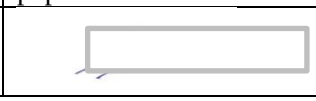
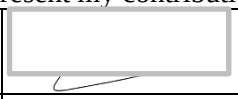
Publication Status	Submitted, Under revision		
Publication Details	This manuscript is currently under revision and awaiting editorial decision in *BMJ Open*		
Name of Principal Author (Candidate)	Amanuel Tesfay Gebremedhin		
Contribution to the Paper	Conceived and designed the study, performed data management and statistical analyses, interpreted the data, and drafted the manuscript		
Total % contribution	80%		
Certification:	This paper reports an original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreement with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/04/2021

Co-Author Contributions

Name of Co-Author	Professor Gavin Pereira		
Contribution to the Paper	Contributed to the design of the study, statistical analyses (advice), interpretation of the findings, reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	04/03/2021
Name of Co-Author	Dr Gizachew Assefa Tessema		
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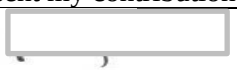
Signature		Date	30/04/2021
Name of Co-Author	Dr Annette K Regan		
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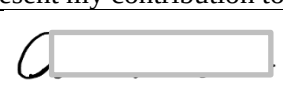
Signature		Date	03/05/2021

Statement of Authorship

Title of Paper	**The influence of pregnancy complications on interpregnancy interval: a quantile regression analysis**		
Publication Status	Unpublished and unsubmitted work written in manuscript style		
Publication Details	This manuscript is planned to be submitted after thesis submission		
Name of Principal Author (Candidate)	Amanuel Tesfay Gebremedhin		
Contribution to the Paper	Conceived and designed the study, performed data management and statistical analyses, interpreted the data, and drafted the manuscript		
Total % contribution	80%		
Certification:	This paper reports an original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreement with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/04/2021

Co-Author Contributions

Name of Co-Author	Professor Gavin Pereira		
Contribution to the Paper	Contributed to the design of the study, statistical analyses (advice), interpretation of the findings, and reviewed the paper for intellectual content		
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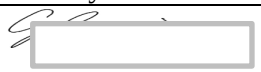
Signature		Date	04/03/2021
Name of Co-Author	Dr Annette K Regan		
Contribution to the Paper	Contributed to the design of the study, interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	03/05/2021
Name of Co-Author	Dr M Luke Marinovich		
Contribution to the Paper	Contributed to the design of the study, interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	04/03/2021
Name of Co-Author	Dr Siri E Håberg		
Contribution to the Paper	Contributed to the interpretation of the findings, and reviewed the paper for intellectual content		
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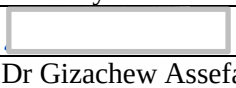
Signature		Date	04/03/2021
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Contribution to the Paper	Contributed to the interpretation of the findings, and reviewed the paper for intellectual content		
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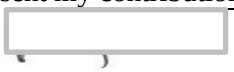
Signature		Date	30/04/2021

Statement of Authorship

Title of Paper	**Effect of interpregnancy interval on pregnancy complications: a systematic review and meta-analysis**		
Publication Status	Unpublished and unsubmitted work written in manuscript style		
Publication Details	This manuscript is planned to be submitted after thesis submission		
Name of Principal Author (Candidate)	Amanuel Tesfay Gebremedhin		
Contribution to the Paper	Conceived and designed the study, performed systematic search, data extraction and synthesis, meta analyses and drafted the manuscript		
Total % contribution	70%		
Certification:	This paper reports an original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreement with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	29/04/2021

Co-Author Contributions

Name of Co-Author	Professor Gavin Pereira		
Contribution to the Paper	Contributed to the design of the study, statistical analyses (advice), interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	04/03/2021
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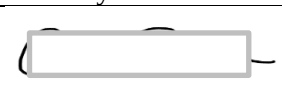
Signature		Date	03/05/2021
Name of Co-Author	Kalayu Brhane Mruts		
Contribution to the Paper	Contributed to the data extraction and quality assessment, interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	29/04/2021
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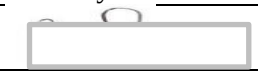
Signature		Date	30/04/2021
Name of Co-Author	Damien Foo		

Contribution to the Paper	Contributed to the screening of studies, interpretation of the findings, and reviewed the paper for intellectual content		
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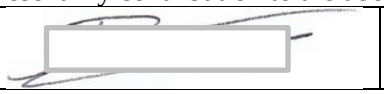
Signature		Date	04/03/2021
Name of Co-Author	Dr Stephen Ball		
Contribution to the Paper	Contributed to the interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	04/03/2021
Name of Co-Author	Dr Eva Malacova		
Contribution to the Paper	Contributed to the interpretation of the findings, and reviewed the paper for intellectual content		
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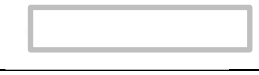
Signature		Date	04/03/2021
Name of Co-Author	Dr M Luke Marinovich		
Contribution to the Paper	Contributed to the design of the study, interpretation of the findings, and reviewed the paper for intellectual content		
I acknowledge that these represent my contribution to the above research output			
Signature		Date	04/03/2021

Appendix B-Published Articles

Appendix B1-Systematic review protocol

Open access Protocol

BMJ Open

Effects of interpregnancy interval on pregnancy complications: protocol for systematic review and meta-analysis

Amanuel Tesfay Gebremedhin,[1] Annette K Regan,[1] Eva Malacova,[1] M Luke Marinovich,[1] Stephen Ball,[2] Damien Foo,[1] Gavin Pereira[1]

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ABSTRACT

Introduction Interpregnancy interval (IPI) is the length of time between a birth and conception of the next pregnancy. Evidence suggests that both short and long IPIs are at increased risk of adverse pregnancy and perinatal outcomes. Relatively less attention has been directed towards investigating the effect of IPI on pregnancy complications, and the studies that have been conducted have shown mixed results. This systematic review will aim to provide an update to the most recent available evidence on the effect of IPI on pregnancy complications.

Method and analysis We will search electronic databases such as Ovid/MEDLINE, EMBASE, CINAHL, Scopus, Web of Science and PubMed to identify peer-reviewed articles on the effects of IPI on pregnancy complications. We will include articles published from start of indexing until 12 February 2018 without any restriction to geographic setting. We will limit the search to literature published in English language and human subjects. Two independent reviewers will screen titles and abstracts and select full-text articles that meet the eligibility criteria. The Newcastle-Ottawa tool will be used to assess quality of observational studies. Where data permit, meta-analyses will be performed for individual pregnancy complications. A subgroup analyses by country categories (high-income vs low and middle-income countries) based on World Bank income group will be performed. Where meta-analysis is not possible, we will provide a description of data without further attempt to quantitatively pool results.

Ethics and dissemination Formal ethical approval is not required as primary data will not be collected. The results will be published in peer-reviewed journals and presented at national and international conferences.

PROSPERO registration number CRD42018088578.

Strengths and limitations of this study

- ► The proposed systematic review and meta-analysis will adhere to the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines.
- ► The review aims to provide an update to the most recent available evidence on the effect of interpregnancy interval on pregnancy complications.
- ► Two independent reviewers will screen titles and abstracts, study eligibility and perform the quality assessment.
- ► This review will only include the published literature in the English language.

INTRODUCTION

The length of time between birth and the beginning of the following pregnancy (interpregnancy interval (IPI)) has been linked to an increased risk of adverse outcomes in infants and their mothers.[1–4] To reduce this risk, the WHO *and* the American College of Obstetrics and Gynaecology suggest an interval of at least 2 years and a minimum of 18 months following a live birth, respectively.[2 3] IPI is viewed as a potential modifiable risk factor for adverse maternal and perinatal outcomes for planned pregnancies.

The importance of birth spacing has been a focus for perinatal researchers and policy-makers for nearly a century.[5] Studies have revealed that both short and long IPIs are potentially associated with increased risk of adverse perinatal outcomes, including stillbirth, small for gestational age, preterm delivery and neonatal death.[1 3 4 6] Conversely, the effect of IPI on complications during pregnancy has received less attention.

There is a growing body of literature that recognises the association between short IPIs and risk of premature rupture of membrane (PROM),[7 8] placental abruption, placenta praevia,[9] uterine rupture for women who previously delivered by caesarean section[10 11] and gestational diabetes.[12] Similarly, long IPIs have long been associated with increased risk of pre-eclampsia[13 14] and labour dystocia.[4]

Although previous reviews[1 15] have suggested that IPI is associated with risk of pregnancy complications, these reviews did not identify a sufficient number of studies to evaluate the effect of IPI on pregnancy complications.

The two systematic reviews investigating the effect of IPI on maternal health/outcomes were published 10 years and 5 years ago,

respectively,[1 15] and there has since been increasing attention paid to this area and a number of publications.[12 16–19] Meanwhile, the reviews have been either limited to few maternal outcomes of interest (ie, maternal haemorrhage, PROM)[9] or not included results from studies published in the last decade.[1] A further systematic review of the effect of IPI on pregnancy complications is warranted, with a view to meta-analysis of the outcomes.

This systematic review will explore the effect of IPI on pregnancy complications. The information obtained from this review is important to inform women, their family and clinicians regarding IPI. The main purpose of the systematic review is to update, compile and critically review the evidence on the effects of IPI on pregnancy complications.

METHODS AND DESIGN

Population

The systematic review will include multiparous women with information on length of interval between two consecutive pregnancies. We will not exclude studies that implemented restrictions on age, ethnic group, parity and socioeconomic status.

Study design

This systematic review will include all observational prospective or retrospective studies that have assessed the effects of IPI with various pregnancy complications according to birth interval categories. Randomised controlled trials (RCT) are unlikely to be identified due to exposure of interest but will be included if available.

Comparator(s)/control

When assessed as a categorical variable, the reference IPI category will be 18–23 months.

Outcomes

The outcomes of interest in this review are pregnancy complications, defined as gestational diabetes, gestational hypertension, pre-eclampsia, uterine rupture, placental abruption, placenta praevia, PROM and labour dystocia.

DATA SOURCES AND SEARCH STRATEGY

We will conduct electronic searches in Ovid/MEDLINE, EMBASE, CINAHL, Scopus, Web of Science and PubMed databases, using a combination of medical subject headings (MeSH) and keywords related to IPI and pregnancy complications. We will include articles published from start of indexing until 12 February 2018 without any restriction on study type or geographic setting. A search strategy was developed (see table 1 for search criteria and online Supplementary file 1 for detailed search strategy for each database).

The search strategy will be piloted across each database to improve the effectiveness of the final search. We will also check the reference list of primary studies that will be selected for full-text evaluation for additional potentially relevant studies not identified by the electronic search. We will include studies published in peer-reviewed journals conducted with human populations and restricted to English language. Corresponding authors will be contacted to request information not presented in the manuscripts that are required for the review.

Table 1 Search criteria

	Search terms
Interpregnancy interval	Subject heading (MeSH) term: Birth interval Keywords: '*birth interval' or '*birth spacing' or '*conception interval' or '*conception spacing' or '*delivery interval' or '*delivery spacing' or '*pregnancy interval' or '*pregnancy spacing'
Pregnancy complications	Subject heading (MeSH) term: 'Pregnancy Complications' Keywords: 'obstetric complication*' or 'maternal complication*' or 'maternal morbidit*' or 'maternal outcome*'

ELIGIBILITY CRITERIA

Inclusion criteria

The studies to be included in this review are required to fulfil two criteria.

Study design criterion: all observational studies evaluating the association between IPI and pregnancy complications.

Exposure criterion: studies that investigate IPI or birth interval as the primary exposure. *IPI is* defined as the length of time between the end of a pregnancy and the start of the next pregnancy. *Birth interval* is defined as the time elapsed between the end of one pregnancy and the end of the next pregnancy.

Exclusion criteria

Studies will be excluded based on three criteria. (1) Non-primary studies: case series or reports, editorials, letters to the editor or reviews without original data. (2) Studies with insufficient information on adjusted effect (eg, unclear adjustment variable, missing CI estimates). (3) Studies that do not investigate IPI as a primary exposure.

Study selection process and software

All unique studies identified from each electronic database will be imported into an *EndNote* library. For reproducibility and to expedite a future update of the review, this library will be published as online Supplementary data. Further screening of titles and abstracts will be accomplished by two independent investigators. Results will be stored using *Covidence*, a web-based software tool that (1) allows collation of search results, (2) screen abstracts and full text articles, (3) extract data from selected articles, (4) conduct risk of bias assessment and (5) resolve disagreements and export data. In accordance with Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA), a flow diagram will be used to report the screening process. From the set of studies screened by title and abstract, two reviewers will independently screen full-text articles based on the eligibility criteria. Any discrepancies between the two reviewers for studies that have been included or excluded will be discussed first, if an agreement cannot be reached, a third investigator will be consulted for moderation. The reason for excluding each study will also be recorded.

Risk of bias (quality) assessment

The quality of included studies will be assessed by two independent reviewers using The Newcastle-Ottawa Scale for assessing quality of cohort and cross-sectional studies.[20] Any disagreement which arises between the reviewers will be resolved through discussion with a third reviewer.

Data extraction

Data will be extracted from all included studies by two independent reviewers using a specifically developed data extraction form in line with the eligibility criteria and outcomes of interest. For each study, the following data will be extracted (1) author names, (2) publication year, (3) study period, (4) geographic location, (5) World Bank income category (at the time of publication), (6) study design, (7) sample size, (8) exposure, (9) outcome measure of interest, (10) adjustment or matching variables, (11) effect size and (12) response rate (where indicated).

Data synthesis and analysis

The final review will include data presented in summary tables and a narrative synthesis to describe the variables listed in the data extraction section. Where data permit, meta-analyses will be performed for individual pregnancy complications. We will apply random effects meta-analysis using the generic inverse variance method to explore the association between IPIs and pregnancy complications.[21 22] We will calculate pooled odss ratio (OR) from all studies that provided adjusted OR or risk ratio with 95% CIs for each pregnancy complication (outcome of interest). Egger's weighted regression test will be used to assess publication bias.[23] The I^2 statistic will be reported as a measure of heterogeneity between studies.[24] Where meta-analysis is not possible, we will present data without quantitatively synthesising it. If the same data are presented in multiple studies, then those providing the most information will be considered.

Subgroup analyses

Subgroup analyses by country categories based on World Bank income group (high-income countries vs low and middle-income countries) will be performed.

Confidence in cumulative evidence

The quality of the findings on each outcome of interest across studies will be assessed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines, which are developed by the GRADE Working Group.[25] The GRADE approach will allow us to determine the quality of the evidence of each outcome. The GRADE system classifies the quality of evidence as very low (*very uncertain effect estimates*), low (*further research will likely change the effect estimate*), moderate (further research *may change the estimate and our confidence in it*) or high (further research is *very unlikely to change our confidence in the estimate of effect*).

Patient and public involvement

Members of the community *Healthy Pregnancies Consumer Reference Group* will provide community and consumer perspectives to this study. This group will provide an insight into issues that affect their pregnancy planning decisions, contextualise results and provide participant experience.

Ethics and dissemination

Formal ethical approval is not required as primary data will not be collected. This protocol adheres to the PRISMA protocols guidelines.[26] In addition, the findings of the systematic review will be reported according to the PRISMA statement.[27]

Review registration

This review has been registered with International Prospective Register for Systematic Reviews (PROSPERO) under the identification code: CRD42018088578.

Updates to study protocol

If any updates to the study protocol are required, these will be listed and included as supplementary information along with a final manuscript and updated on the PROSPERO register.

DISCUSSION

Families want to know the best time at which they conceive their next child in order to have a safer pregnancy and healthy baby. Clinicians need evidence-based recommendations to provide advice on the optimal IPI leading to fewer maternal and perinatal complications. For planned pregnancies, IPI is modifiable, and such recommendations may therefore be useful for preventing adverse maternal/pregnancy outcomes. The current WHO recommendations, which suggest that women wait at least 2 years after delivering a live birth,[2] were based on a review of observational studies predominantly in low-income and middle-income populations, which may not be generalisable to high-income countries. Context specific and updated evidence is warranted to clarify whether the evidence of studies investigated the effect of IPI on pregnancy complications is sufficient for decision-making.

This will be a comprehensive systematic review investigating the effect of IPI on pregnancy complications. Previous reviews have been limited to few maternal outcome of interest[15] or have not included results from studies published in the last 10 years.[1] A systematic review

investigating effect of IPI on pregnancy complications is now warranted. Systematic documentation and synthesising of literature on the effect of IPI on various pregnancy complications will be important to set and revise evidence-based guidelines for IPIs. By updating the current state of knowledge in IPI research, this review will provide a basis for guiding future studies and future global policies for family planning.

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Contributors ATG, AR, GP and EM conceived the idea, planned and designed the study protocol. ATG wrote the first draft. DF, SB and LM contributed to the development of the protocol and manuscript. All authors contributed to the initial question development, search strategy, study selection criteria and have approved and contributed to the final written manuscript.

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Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement Supporting data can be found at the International prospective Register of Systematic Reviews (PROSPERO) website, with registration number CRD42018088578.

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Appendix B2- PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8-9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-18

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9, Figure 5, eTbale 1, eFigure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-17
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-17, Fig 1-4, efigure3, 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

Appendix B3- Search strategy

Table B3. Systematic search of the literature related to interpregnancy interval pregnancy complications, by search engine

#	Search terms
Scopus	
#1	(((TITLE-ABS-KEY ("interpregnancy interval*")) OR (TITLE-ABS-KEY ("Birth Intervals"))) OR ((TITLE-ABS-KEY ("birth spacing")) OR ((TITLE-ABS-KEY ("inter*pregnancy interval*"))) OR (TITLE-ABS-KEY ("birth to birth interval* ")) OR (TITLE-ABS-KEY ("pregnancy spacing")) OR (TITLE-ABS-KEY ("delivery to conception interval*")) OR (TITLE-ABS-KEY ("interdelivery interval* ")) OR (TITLE-ABS-KEY ("interbirth interval* ")) OR (TITLE-ABS-KEY ("birth to conception interval*"))))
#2	((TITLE-ABS-KEY ("Pregnancy Complication*")) OR (TITLE-ABS-KEY ("obstetric complication*")) OR (TITLE-ABS-KEY ("maternal complication*")) OR (TITLE-ABS-KEY ("maternal mORbidit*")) OR (TITLE-ABS-KEY ("gestational diabetes*")) OR (TITLE-ABS-KEY (" Gestational Diabetes mellitus ")) OR (TITLE-ABS-KEY (“Pregnancy?Induced Hypertension”)) OR (TITLE-ABS-KEY (" Gestational Hypertension ")) OR (TITLE-ABS-KEY (" "pre?eclampsi*" ")) OR (TITLE-ABS-KEY (" Pregnancy Toxemia*")) OR (TITLE-ABS-KEY ("uterine rupture*")) OR (TITLE-ABS-KEY (" Placental abruption")) OR (TITLE-ABS-KEY (" Abruptio Placentae ")) OR (TITLE-ABS-KEY (" Third trimester bleeding ")) OR (TITLE-ABS-KEY (" Placenta Previa”)) OR (TITLE-ABS-KEY (" Placenta Praevia”)) OR (TITLE-ABS-KEY (" PROM")) OR (TITLE-ABS-KEY (" Premature rupture of membrane*")) OR (TITLE-ABS-KEY (" Premature Rupture of Fetal membrane*”)) OR (TITLE-ABS-KEY (" Obstetric labor Complication*")) OR (TITLE-ABS-KEY (" Obstructed labor”)) OR (TITLE-ABS-KEY (" Prolonged labOR”)) OR (TITLE-ABS-KEY (" Dystocia”)) OR (TITLE-ABS-KEY (" Labor dystocia”)) OR (TITLE-ABS-KEY (" Anemi*")) OR (TITLE-ABS-KEY (" maternal depletion”)) OR (TITLE-ABS-KEY ("maternal outcome*")))
#3	#1 AND #2
#4	#3 AND (LIMIT-TO (DOCTYPE,"ar")) AND (LIMIT-TO (LANGUAGE,"English")) AND (LIMIT-TO (SRCTYPE,"j"))
	Web of Science
#1	("interpregnancy interval*") *OR* **TOPIC:** ("Birth Intervals") *OR* **TOPIC:** ("birth spacing") *OR* **TOPIC:** ("pregnancy spacing") *OR* **TOPIC:** ("delivery to conception interval*") *OR* **TOPIC:** ("interdelivery interval* ") *OR* **TOPIC:** ("interbirth interval* ") *OR* **TOPIC:** ("birth to conception interval*") Timespan=All years Search language=English
#2	**TOPIC:** ("Diabetes, Gestational") *OR* **TOPIC:** ("gestational diabetes*") *OR* **TOPIC:** (" Gestational Diabetes mellitus") *OR* **TOPIC:** ("Hypertension, Pregnancy-Induced") *OR* **TOPIC:** ("Gestational Hypertension ") *OR* **TOPIC:** ("Pre-Eclampsia") *OR* **TOPIC:** ("pre?eclampsi*") *OR* **TOPIC:** ("Pregnancy Toxemia*") *OR* **TOPIC:** ("Uterine Rupture") *OR* **TOPIC:** ("uterine rupture*") *OR* **TOPIC:** ("Abruptio Placentae") *OR* **TOPIC:** ("Placental abruption") *OR* **TOPIC:** (" Third trimester bleeding ") *OR* **TOPIC:** ("Placenta Previa") *OR* **TOPIC:** ("Placenta Praevia") *OR* **TOPIC:** ("Fetal Membranes, Premature Rupture") *OR* **TOPIC:** ("Premature Rupture of membrane") *OR* **TOPIC:** ("Obstetric Labor Complications*") *OR* **TOPIC:** ("Obstructed labor") *OR* **TOPIC:** ("Prolonged labor") *OR* **TOPIC:** ("Dystocia") *OR* **TOPIC:** ("Labor dystocia") *OR* **TOPIC:** ("maternal Anemi*") *OR* **TOPIC:** ("maternal depletion") OR **TOPIC:** ("Pregnancy Complications") *OR* **TOPIC:** ("obstetric complication*") *OR* **TOPIC:** ("maternal complication*") *OR* **TOPIC:** ("maternal morbidit*") *OR* **TOPIC:** ("maternal outcome*") Timespan=All years Search language=English
#3	#1 AND #2
#4	**Limiters: Refined by: DOCUMENT TYPES:** (ARTICLE) AND **LANGUAGES:** (ENGLISH) AND **DOCUMENT TYPES:** (ARTICLE) AND **DOCUMENT TYPES:** (ARTICLE) AND [excluding] **DOCUMENT TYPES:** (REVIEW) Timespan=All years Search language=Auto
Pub Med	
#1	((((((((((("Birth Intervals"[MeSH Terms]) OR "Birth Intervals") OR "interpregnancy interval*") OR (("inter pregnancy interval" OR "inter pregnancy intervals"))) OR "birth spacing") OR "birth to

	birth intervals") OR "pregnancy spacing") OR "delivery to conception intervals") OR (("interdelivery interval" OR "interdelivery intervals"))) OR (("interbirth interval" OR "interbirth intervals"))) OR (("birth to conception interval" OR "birth to conception intervals"))))
#2	((((((((("pregnancy complications"[MeSH Terms]) OR "Pregnancy Complications") OR "obstetric complication") OR "maternal complication") OR "maternal morbidity") OR (("maternal morbidities" OR "maternal morbidity"))) OR "maternal outcome")) OR ((((((((((((((((((((((((((("diabetes, gestational"[MeSH Terms]) OR "gestational diabetes") OR (("gestational diabetes mellitus" OR "gestational diabetes mellitus/diabetes"))) OR "maternal hypertension") OR "Pregnancy-Induced Hypertension"[MeSH Terms]) OR "pregnancy induced hypertension") OR "gestational hypertension") OR "pre eclampsia"[MeSH Terms]) OR "pre eclampsia") OR "preeclampsia") OR "pregnancy toxemia") OR "Pregnancy Toxemia*") OR "uterine rupture"[MeSH Terms]) OR "abruptio placentae"[MeSH Terms]) OR "abruptio placentae") OR "placental abruption") OR "third trimester bleeding") OR "placenta previa") OR "placenta previa"[MeSH Terms]) OR "placenta praevia") OR "premature fetus membrane rupture") OR "fetal membranes, premature rupture"[MeSH Terms]) OR "premature rupture of membrane") OR "prom") OR "obstetric labor complications"[MeSH Terms]) OR (("labor complication" OR "labor complications"))) OR "dystocia"[MeSH Terms]) OR "obstructed labor") OR "prolonged labor") OR "maternal anemia") OR "maternal depletion"))))
#3	#1 AND #2
#4	Limiters: Filters activated: Journal Article, Full text, English
#5	Filtered to English and human
EMBASE	
1	"interpregnancy interval*".mp.
2	"inter*pregnancy interval*".mp.
3	"Birth Intervals".mp.
4	"birth spacing".mp.
5	"birth to birth interval* ".mp.
6	"pregnancy spacing".mp.
7	"delivery to conception interval".mp.
8	"interdelivery interval* ".mp.
9	"interbirth interval* ".mp.
10	"birth to conception interval*".mp.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	pregnancy diabetes mellitus/
13	"gestational diabetes*".mp.
14	" Gestational Diabetes mellitus ".mp.
15	maternal hypertension/
16	Hypertension, Pregnancy-Induced.mp.
17	" Pregnancy Induced Hypertension ".mp.
18	" Gestational Hypertension ".mp.
19	preeclampsia/
20	preeclampsia.mp.
21	"pre?eclampsi*".mp.
22	pregnancy toxemia/
23	pregnancy toxemia.mp.
24	"Pregnancy Toxemia*".mp.
25	uterus rupture/
26	Uterine Rupture.mp.
27	Abruptio Placentae/
28	Abruptio Placentae.mp.
29	"Placental abruption".mp.
30	" Third trimester bleeding ".mp.
31	placenta previa/
32	"Placenta Previa".mp.
33	" Placenta Praevia".mp.
34	premature fetus membrane rupture/
35	"Fetal Membranes, Premature Rupture".mp.
36	PROM.mp.
37	" Premature Rupture of Fetal membrane*".mp.
38	"Premature Rupture of membrane".mp.
39	"Obstetric labor Complication*".mp.

40	Obstetric Labor Complications/ or labor complication/
41	dystocia/
42	"Obstructed labor".mp.
43	"Prolonged labor".mp.
44	"Labor dystocia".mp.
45	" maternal Anemi*".mp.
46	" maternal depletion ".mp.
47	pregnancy complication/
48	"Pregnancy Complications".mp.
49	"obstetric complication*".mp.
50	"maternal complication*".mp.
51	maternal morbidity/
52	"maternal morbidit*".mp.
53	"maternal outcome*".mp.
54	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55	11 and 54
	limit 55 to (full text and human and English language)
Ovid MEDLINE	
1	"inter*pregnancy interval*".mp.
2	Birth Intervals/
3	"Birth Intervals".mp.
4	"birth spacing".mp.
5	"birth to birth interval* ".mp.
6	"pregnancy spacing".mp.
7	"delivery to conception interval".mp.
8	"interdelivery interval* ".mp.
9	"interbirth interval* ".mp.
10	"birth to conception interval*".mp.
11	"interpregnancy interval*".mp.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	"Pregnancy Complications".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14	Pregnancy Complications/
15	("obstetric complication*" or "maternal complication*" or "maternal morbidit*" or "maternal outcome*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16	Diabetes, Gestational/
17	"gestational diabetes*".mp.
18	" Gestational Diabetes mellitus ".mp.
19	Hypertension, Pregnancy-Induced/
20	" Pregnancy Induced Hypertension ".mp.
21	" Gestational Hypertension ".mp.
22	Pre-Eclampsia/
23	"pre?eclampsi*".mp.
24	"Pregnancy Toxemia*".mp.
25	Uterine Rupture/
26	"uterine rupture*".mp.
27	Abruptio Placentae/
28	" Placental abruption".mp.
29	" Third trimester bleeding ".mp.
30	Placenta Previa/
31	"Placenta Previa".mp.
32	Fetal Membranes, Premature Rupture/
33	PROM.mp.
34	" Premature Rupture of Fetal membrane*".mp.
35	"Premature Rupture of membrane".mp.

36	Obstetric Labor Complications/
37	"Obstetric labor Complication*".mp.
38	"Obstructed labor".mp.
39	"Prolonged labor".mp.
40	Dystocia/
41	"Labor dystocia".mp.
42	" maternal Anemi*".mp.
43	" maternal depletion ".mp.
44	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45	12 AND 44
46	limit 45 to (full text and human and English language)
CINAHL	
S55	Limiters - Full Text; English Language Search modes - Boolean/Phrase
S54	S12 AND S53
S53	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52
S52	" maternal depletion"
S51	" maternal Anemi*"
S50	"Prolonged labor"
S49	"Obstructed labor"
S48	(MH "Dystocia")
S47	"labor complication"
S46	(MH "Labor Complications")
S45	"Obstetric labor Complication*"
S44	"PROM"
S43	"Premature Rupture of membrane*"
S42	(MH "Fetal Membranes, Premature Rupture")
S41	"premature fetus membrane rupture"
S40	"premature fetus membrane rupture"
S39	" Placenta Praevia"
S38	(MH "Placenta Praevia")
S37	"placenta previa"
S36	" Third trimester bleeding "
S35	"Placental abruption"
S34	"Abruptio Placentae"
S33	(MH "Abruptio Placentae")
S32	"Uterine Rupture"
S31	(MH "Uterine Rupture")
S30	"pregnancy toxemia"
S29	"pre?eclampsi*"
S28	"preeclampsi"
S27	(MH "Pre-Eclampsia")
S26	"Gestational Hypertension"
S25	" Pregnancy Induced Hypertension "
S24	(MH "Pregnancy-Induced Hypertension")
S23	"maternal hypertension"
S22	." Gestational Diabetes mellitus "
S21	"gestational diabetes*"
S20	(MH "Diabetes Mellitus, Gestational")
S19	"maternal outcome*"
S18	"maternal morbidit*"
S17	"maternal morbidity"
S16	"maternal complication*"
S15	"obstetric complication*"
S14	"Pregnancy Complications"
S13	(MH "Pregnancy Complications")

S12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11	"birth to conception interval*"
S10	"interbirth interval* "
S9	"interdelivery interval* "
S8	"delivery to conception interval"
S7	"pregnancy spacing"
S6	"birth to birth interval* "
S5	"birth spacing"
S4	"inter*pregnancy interval*"
S3	"interpregnancy interval*"
S2	(MH " Birth Intervals")
S1	"Birth Intervals"

Appendix B4-Study One

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Original article

Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study

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ABSTRACT

Purpose: To examine the association between interpregnancy interval (IPI) and gestational diabetes using both within-mother and between-mother comparisons.
Methods: A retrospective cohort study of 103,909 women who delivered three or more consecutive singleton births (n = 358,046) between 1 January 1980 and 31 December 2015 in Western Australia. The association between IPI and gestational diabetes was estimated using conditional logistic regression, matching pregnancies to the same mother and adjusted for factors that vary within-mother across pregnancies. For comparison with previous studies, we also applied unmatched logistic regression (between-mother analysis).
Results: The conventional between-mother analysis resulted in adjusted odds ratios (aOR) of 1.13 (95% CI, 1.06–1.21) for intervals of 24–59 months and 1.51 (95% CI, 1.33–1.70) for intervals of 120 or more months, compared with IPI of 18–23 months. In addition, short IPIs were associated with lower odds of gestational diabetes with (aOR: 0.89; 95% CI, 0.82–0.97) for 6–11 months and (aOR: 0.92; 95% CI, 0.85–0.99) for 12–17-month. In comparison, the adjusted within-mother matched analyses showed no statistically significant association between IPIs and gestational diabetes. All effect estimates were attenuated using the within-mother matched model.
Conclusion: Our findings do not support the hypothesis that short IPI (<6 months) increases the risk of gestational diabetes and suggest that observed associations in previous research might be attributable to confounders that vary between mothers.

Disclosure of conflicts of interest: The authors have no potential conflicts of interest to disclose.

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Author contributions: ATG designed the study, performed the analysis, and drafted the manuscript; GP and AR have made a substantial contribution to the design, analysis and interpretation of the results. SB, AB, DF, MG, SEH, EM and LM contributed to the analysis and interpretation of the results. All of the authors have revised the article for important intellectual content and approved the final written manuscript.

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Introduction

Gestational diabetes is one of the major pregnancy complications that affect 6%–13% of pregnancies worldwide [1]. Pregnancies complicated by gestational diabetes have an increased risk of caesarean section, high blood pressure and greater risk of perinatal complications including perinatal death [2–5].

The length of time between previous delivery and subsequent conception (interpregnancy interval [IPI]) has been extensively evaluated with respect to its association with birth outcomes [6–9]. However, there is relatively less research on its association with pregnancy complications.

It has previously been observed that both short and long IPIs increase the risk of gestational diabetes [10–14]. However, inference was limited due to small sample sizes, reliance on hospital-based cohorts, insufficient control for important confounders (e.g., socio-economic status [SES]) and biased IPI length measurements, such as the use of birth-to-birth intervals or birth-to-outcome intervals instead of birth to conception.

The World Health Organization (WHO) and the American College of Obstetricians and Gynecologists recommend that women should wait at least two years, and at least 18 months after live birth before commencing their next pregnancy, respectively [15,16]. However, the suitability of these recommendations for mothers in high-income countries is uncertain as the recommendations emanate from studies from low-income and middle-income settings conducted prior to the early 2000's.

Several hypotheses have been postulated, including the "maternal depletion" and "physiologic regression" hypotheses [8,17,18]; however, a causal effect of IPI on pregnancy complications has not yet been elucidated. Recently, researchers have posited that the association between IPI and increased risk of adverse perinatal outcomes might be attributed to confounding factors ("systematic bias" hypothesis) [9,14,19]. It remains plausible that the previously reported associations between IPI and gestational diabetes may be explained by risk factors that tend to persist within-mothers across pregnancies and potentially vary greatly between mothers [9,14]. Complementary within-mother matched analyses offer an opportunity to account for within-mother effects.

This study aimed to examine the association between IPI and gestational diabetes employing both matched pregnancies within the same mother and unmatched between-mother comparisons in a high-income setting.

Materials and methods

Data source and study population

We conducted a retrospective cohort study using matched and unmatched approaches to examine the association between IPI and risk of gestational diabetes for all mothers who gave birth between January 1st, 1980, and December 31st, 2015 in Western Australia (WA). We sourced maternal, infant and birth information from the Midwives Notification System (MNS), a population-wide registry of all births (>99%) with at least 20 weeks' gestation or with birthweight >400 grams if the gestational length is unknown [20]. Hospitalization records were identified from Hospital Morbidity Data Collection (HMDC), which includes information on all hospitalizations in the state, with the Australian Modification of International Classification of Diseases (ICD-10-AM) coded diagnostic information and procedures performed [21]. Ethics approval was obtained from the Human Research Ethics Committee (2016/51) of the Department of Health, WA.

Our analyses included all mothers with at least three consecutive singleton births (at least two IPIs) at 20–44 weeks of gestation in WA within the study period. Of the original total of 487,297 mothers who gave birth in the study period, we sequentially excluded mothers who delivered multiples (n = 4381); mothers who delivered only once during the study period (n = 189,269); and mothers for whom parity as recorded in the birth record was discordant with the order of the birth dates of her children (n = 5902). These exclusions resulted in a sample of 287,745 mothers with ≥2 consecutive births eligible for analysis (Fig. 1). We further excluded mothers who had missing information (e.g., gestational age, SES, maternal age, negative IPI) for one or more pregnancies (n = 7109). Finally, we excluded mothers with fewer than two intervals (n = 176,727), leaving 103,909 mothers included in the final analyses.

Measures

Outcome assessment

The outcome of interest, gestational diabetes was ascertained from the MNS notifications and hospital separation codes consistent with gestational diabetes (ICD-9-AM: 648.8, ICD-10-AM: O24.4).

Exposure

The exposure, IPI, was defined as the length of time between delivery date of the previous pregnancy and the estimated conception date of the subsequent pregnancy (date of birth minus gestational age at birth). Gestational age at birth was based on dating ultrasounds, or last menstrual period when ultrasound was not available. We used IPI as a categorical variable, grouped into seven categories (<6 months, 6–11 months, 12–17 months, 18–23 months (reference), 24–59 months, 60–119 months, or 120 or more months), which is consistent with WHO recommendations and categories used in past studies [9,14,22].

Independent variables

For the within-mother matched analyses, we adjusted for factors that can vary between births to the same mother. Specifically, we adjusted for maternal age at time of each delivery (categorical variable: 14–19, 20–24, 25–29, 30–34, 35–39, or 40 years or older), parity, birth year (continuous), SES, infant sex, marital status, history of obesity, known pre-existing hypertension and gestational hypertension. SES was derived by the Australian Bureau of Statistics as the Socio-Economic Index of Areas - Index of Relative Socio-economic Disadvantage at a geographic area for the maternal residence at the time of birth [23], which we categorized into quintiles.

Statistical analysis

We summarized the socio-demographic and medical conditions of the cohort at their first pregnancy during the study period. Conditional logistic regression (accounting for matching pregnancies to the same mother) was used to estimate odds of gestational diabetes as a function of IPI categories, comparing pregnancies within-mothers. Under this approach, effect estimates also controlled for unmeasured characteristics that remained stable or strongly correlated over time for mothers throughout their consecutive pregnancies. This enables inference that is based purely on within-mother effects [7,9,14]. To estimate the total effect of IPI, we repeated our matched analyses without adjustment for maternal age at time of each delivery and birth year. In the absence of residual time-varying confounding or selection bias, we would expect similar effects of IPI on gestational diabetes in both between-mother and within-mother comparisons. It is plausible that if unmeasured persistent confounders exist, the unconditional logistic regression may result in biased estimates [9]. For comparison with previous unmatched studies, we also applied unmatched logistic regression

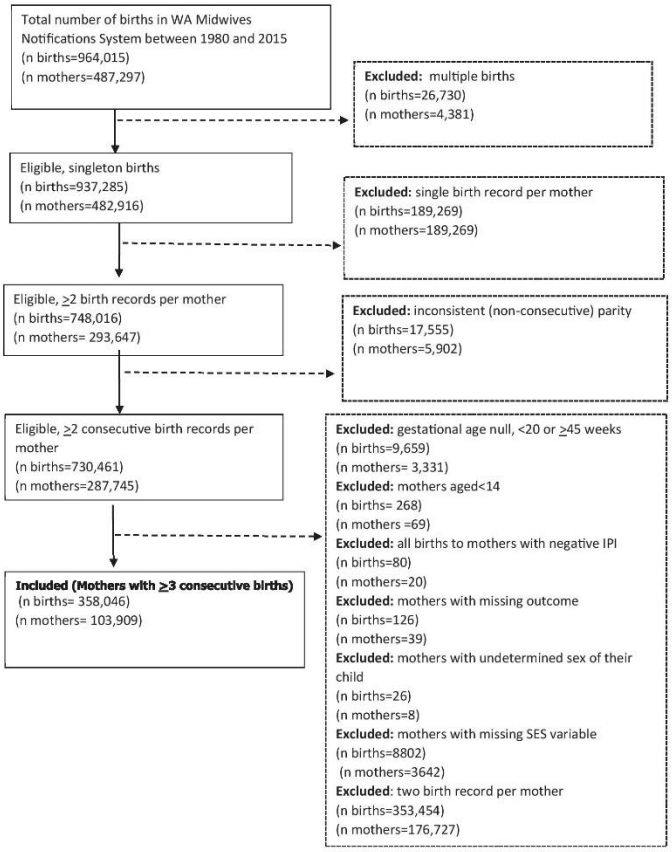

Fig. 1. Selection of eligible birth records included in this study – Western Australia, 1980–2015.

that additionally adjusted for measured covariates that vary between mothers, such as race/ethnicity. To minimize multicollinearity between time-varying covariates (such as maternal age at time of each delivery and birth year), our within-mother matched model was adjusted for a prognostic score defined as the logit of the probability of the outcome regressed on the adjustment variables from an unmatched model. This results in estimation of the direct effect of IPI and allows the whole cohort to contribute to the adjustment for the underlying risk of the outcome [24].

Supplementary analysis

We further estimated the association of gestational diabetes with post-birth IPI. In the absence of confounding factors, gestational diabetes should not be associated with the IPI that follows this birth. An observed association between gestational diabetes and this post-birth IPI indicates the presence of factors in a mother influencing both the risk of gestational diabetes and the IPI, potentially leading to bias estimates. Thus, the post-birth IPI serves as a "negative control" exposure that estimates the effect of mother-level confounding [19,25,26].

Sensitivity analysis

To ascertain the sensitivity of our results to higher-order parity, and inclusion of stillbirths, we conducted separate analyses restricted to the first three births for all mothers with births at parity 0, 1, and 2, and to mothers with at least three consecutive live births, respectively. To explore if our results are sensitive to the time period of the cohort, we restricted our further analyses to consecutive births after first of September 1997, after which smoking status and pre-existing chronic conditions were routinely recorded and ultrasound scans were more common (Appendix Table 2, Model 2a–c). Finally, we included a sensitivity analyses restricted to mothers who had no gestational diabetes in their first pregnancy, to ascertain if effect of IPI differs for those with and without gestational diabetes in the first pregnancy (Appendix Table 3).

Table 1
Socio-demographic characteristics and medical conditions of the study cohort of mothers at their first birth included during the study period (n = 103,909 mothers) in Western Australia, 1980–2015

Characteristics	Mothers, N (%)
Total number of mothers	103,909
Maternal age at first birth (y)	
<25	56,901 (54.8)
25–29	32,988 (31.7)
30–34	12,467 (12.0)
35–39	1521 (1.5)
40 or older	32 (0.03)
Marital status	
Married	83,875 (80.7)
Never married	19,221 (18.5)
Widowed, divorced, separated	618 (0.6)
Unknown	195 (0.2)
Race/ethnicity	
Caucasian	88,106 (84.8)
Aboriginal/Torres Strait Islander	8267 (7.9)
Asian*	1986 (1.9)
African	600 (0.6)
Others†	4950 (4.8)
Birth year	
1980–1984	20,264 (19.5)
1985–1989	17,681 (17.0)
1990–1994	16,811 (16.2)
1995–1999	16,053 (15.4)
2000–2004	15,538 (15.0)
2005–2009	14,448 (13.9)
2010–2015	3114 (3.0)
SES in quintiles	
<20th percentiles (most disadvantaged)	20,398 (19.6)
20–39th percentile	21,679 (20.8)
40–59th percentile	21,914 (21.1)
60–79th percentile	20,648 (19.9)
≥80th percentile (least disadvantaged)	19,270 (18.6)
Chronic conditions	
Known chronic hypertension	259 (0.3)
Known chronic diabetes	181 (0.2)
Known obesity history	237 (0.2)
Pregnancy characteristics	
Pregnancy complications	
Gestational diabetes	1716 (1.6)
Gestational hypertension	2400 (2.3)
Infant sex	
Male	54,132 (52.1)
Parity	
0	96,314 (92.7)
1	4977 (4.8)
2	1636 (1.6)
≥3	374 (1.0)

* Including Indian.
† Including Polynesian & Maori.

All analyses were performed using STATA version 15.1 (Stata Corporation, College Station, Texas). We reported unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CIs) for each model.

Results

At study entry, defined as mothers' first birth occurring during the study period, the majority of women were generally free from chronic hypertension, diabetes and obesity. There were 1716 (1.6%) mothers who had a diagnosis of gestational diabetes at study entry (Table 1). For all births included in the cohort, the incidence of gestational diabetes during the study period was 4% (Table 2). There were 16,548 (6%) births which occurred after an IPI of 0–5 months, 45,076 (18%) after 6–11 months, 50,528 (20%) after 12–17 months; 37,352 (15%), after 18–23 months; 78,909 (31%) after IPI of 24–59 months, 21,780 (9%) births after 60–119 months and 3944

Table 2
Characteristics of study population of births by gestational diabetes status for all births to mothers with at least three consecutive births during the study period (n = 254,137 births) in Western Australia, 1980–2015

Characteristics	Total	Gestational diabetes
	Births (N)	Births, N (%)*
Total number of births	254,137	10,032 (4)
Interpregnancy interval (mo)		
0–5	16,548	539 (3.3)
6–11	45,076	1261 (2.8)
12–17	50,528	1509 (3.0)
18–23	37,352	1272 (3.4)
24–59	78,909	3526 (4.5)
60–119	21,780	1499 (6.9)
120 or more	3944	426 (10.8)
Maternal age at time of each delivery (y)		
<25	53,083	915 (1.7)
25–29	83,808	2430 (2.9)
30–34	77,280	3407 (4.4)
35–39	34,138	2603 (7.6)
40 or older	5828	677 (11.6)
Race/ethnicity		
Caucasian	209,073	6803 (3.3)
Non-Caucasian	45,064	3229 (7.2)
Birth year		
1980–1984	12,277	30 (0.3)
1985–1989	35,264	238 (0.7)
1990–1994	41,065	765 (1.9)
1995–1999	40,560	1353 (3.3)
2000–2004	39,082	1613 (4.1)
2005–2009	43,408	2098 (4.8)
2010–2015	42,481	3935 (9.3)
SES in quintiles		
<20th percentiles (most disadvantaged)	51,221	2232 (4.4)
20–39th percentile	49,930	1915 (3.8)
40–59th percentile	49,689	1846 (3.7)
60–79th percentile	50,968	2027 (4.0)
≥80th percentile (least disadvantaged)	52,329	2012 (3.8)
Marital status		
Married	229,549	8873 (3.8)
Never married	19,588	887 (4.5)
Widowed, divorced, separated	4156	225 (5.4)
Unknown	844	47 (5.6)

* Row percentages.

(1.6%) of births after 120 or more months. Gestational diabetes diagnoses were more common among mothers in the older age groups, and in mothers with longer IPIs (Table 2). Moreover, mothers with shorter IPIs tended to be younger and non-Caucasian. Observation of longer IPIs was more prevalent late in the study period (1995 onwards) Appendix Table 1.

Compared to an IPI of 18–23 months, unmatched adjusted analysis showed lower odds of gestational diabetes for 6–11-month intervals (adjusted odds ratio (aOR), 0.89; 95% CI, 0.82–0.97) and 12–17-month intervals (aOR: 0.92; 95% CI, 0.85–0.99) (Table 3). However, IPI of 24 months or more was associated with greater odds of gestational diabetes. The greatest adjusted effect was observed for IPIs of 120 or more months (aOR: 1.51; 95% CI, 1.33–1.70).

Conditional logistic regression restricts analyses to births from informative (non-concordant) strata (mothers), which in this study were mothers who experienced gestational diabetes for at least one, but not all of their births. There were 18,873 births to mothers with non-concordant gestational diabetes. The unadjusted within-mother matched comparison indicated that an IPI of 24 months or longer was associated with greater odds of gestational diabetes compared to an interval of 18–23 months, with OR ranging from 1.40 (95% CI, 1.26–1.55) for 24–59 months interval, to 3.65 (95% CI, 2.95–4.52) for IPI of 120 or more months. After full adjustment for covariates including, maternal age at time of each delivery and birth year, matched analyses showed a statistically non-significant lower odd of gestational diabetes for short IPIs as compared to

Table 3
Odds Ratios (ORs) and 95% confidence intervals for the association between interpregnancy interval and gestational diabetes for births to mothers with at least three consecutive births during the study period (n = 103,909 mothers, n = 254,137 births) in Western Australia, 1980–2015

IPI in months	Unmatched		Matched			
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Informative strata, n (%)§	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡
0–5	0.95 (0.86–1.05)	1.01 (0.91–1.12)	1305 (6.9)	**0.78 (0.67–0.91)**	**0.80 (0.68–0.95)**	0.88 (0.75–1.05)
6–11	**0.81 (0.75–0.88)**	**0.89 (0.82–0.97)**	2954 (15.7)	**0.79 (0.70–0.89)**	**0.84 (0.74–0.96)**	0.92 (0.80–1.05)
12–17	**0.87 (0.80–0.94)**	**0.92 (0.85–0.99)**	3297 (17.5)	**0.83 (0.74–0.93)**	**0.86 (0.76–0.98)**	0.90 (0.79–1.02)
18–23	1.00 (reference)	1.00 (reference)	2489 (13.2)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24–59	**1.32 (1.24–1.41)**	**1.13 (1.06–1.21)**	6096 (32.3)	**1.40 (1.26–1.55)**	**1.29 (1.15–1.44)**	1.07 (0.95–1.20)
60–119	**2.09 (1.94–2.26)**	**1.32 (1.22–1.43)**	2216 (11.7)	**2.28 (2.01–2.57)**	**1.96 (1.71–2.23)**	1.08 (0.93–1.25)
120 or more	**3.42 (3.06–3.85)**	**1.51 (1.33–1.70)**	516 (2.7)	**3.65 (2.95–4.52)**	**3.02 (2.41–3.80)**	1.02 (0.77–1.34)

Bold indicates statistical significance at the 5% level.
Models adjusted for the following variables.
* Maternal age at time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, gestational hypertension and known chronic hypertension.
† Prognostic score for gestational diabetes by parity, SES, marital status, infant sex, history of obesity, gestational hypertension, and known chronic hypertension.
‡ Prognostic score for gestational diabetes by maternal age at time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, gestational hypertension and known chronic hypertension.
§ Number and percentage of informative strata of gestational diabetes for each IPI category for births to mothers with at least three consecutive births.

reference category of 18–23 months, with aOR of 0.88 (95% CI, 0.75–1.05) for IPI lower than 6 months and 0.90 (95% CI, 0.79–1.02) for IPI of 12–17 months. However, we observed a statistically non-significant increased odds of gestational diabetes for long IPI compared to an 18–23-month IPI, with aORs ranging from 1.07 (95% CI, 0.95–1.20) for IPI of 24–59 months to 1.08 (95% CI, 0.93–1.25) for IPI of 60 months or longer.

The results of our sensitivity analyses Appendix Table 2 restricted to mothers with their first three consecutive births [Model 2a], and a cohort that only included live births [Model 2b] were consistent with the effect estimates obtained from our main analyses. However, statistically significant lower odds of gestational diabetes were observed for shorter IPIs of 0–5 months and 12–17 months in the model that excluded stillbirths [Model 2b]. Additionally, we observed a negligible difference in the association between IPI and gestational diabetes when we restricted our cohort to births from September 1997 onwards, for which more information was available for adjustment, although this induced a 65% reduction in sample size [Model 2c]. We observed a little difference in the effect estimates with and without exclusion of mothers with gestational diabetes in their first pregnancy Appendix Table 3. In general, our sensitivity analyses collectively supported a weak adverse association of long IPIs and gestational diabetes, similar to those reported in the main analyses.

The adjusted model from the supplementary analyses indicated that the short post-birth IPI of 6 months or less was statistically significantly associated with gestational diabetes in the previous pregnancy (aOR: 1.25; 95% CI, 1.03–1.52). However, the long post-birth IPIs of 24 or more months were not associated with gestational diabetes in this model with aOR of 1.04 (95% CI, 0.91–1.18) for post-birth IPI of 24–59 months and 1.18 (95% CI, 0.78–1.79) for 120 or more months (Appendix Table 4).

Discussion

Principal findings

Both the between-mother adjusted model and within-mother unadjusted model indicate that IPIs of 24 months or longer were associated with greater odds of gestational diabetes compared to an interval of 18–23 months. In contrast, pregnancies that followed IPIs shorter than 18–23 months had lower odds of gestational diabetes. However, the fully adjusted within-mother matched analyses showed no statistically significant association between short and long IPIs and gestational diabetes.

Meaning of the findings

Point estimates from within-mother analyses were lower than those from between-mother analyses; and estimates from the within-mother analyses were attenuated after full adjustment for covariates, indicating that the influence of IPI could be partially explained by the pathway through time-varying confounders, most notably maternal age. Longer IPIs are inherently linked to increasing maternal age, which is a well-established risk factor for gestational diabetes [2,27]. Contrary to the findings of previous between-mother comparisons [13,14], which showed that short IPIs were statistically significantly associated with increased risk of gestational diabetes, our results did not support the existence of an adverse association between short IPIs and gestational diabetes. This finding is consistent with previous unmatched cohort studies [6,28] as well as recent case-control study [29]. However, our findings for long IPIs are consistent with findings of other studies [12,14,29].

The associations observed in the unmatched between-mother comparisons were attenuated in the within-mother matched comparisons. This suggests that the observed effects of short and long IPIs in the unmatched between-mother comparison and previous similar unmatched studies likely were influenced by factors that remain stable for mothers throughout their pregnancies (e.g., persistent lifestyle factors, SES) but vary much more between women. Our long IPI findings are consistent with those from a recent matched study of a Canadian cohort [14], which reported that matched analyses resulted in statistically non-significant associations between long IPIs and gestational diabetes. However, our findings differ for short IPIs, as the Canadian study reported greater odds of gestational diabetes for short IPIs lower than 6 months. The observed differences may be due to unmeasured confounding that could arise from the lack of adjustment for known risk factors (SES, parity) or differences in susceptibility of the study populations to IPI in the Canadian study [14]. Future research would benefit from exploring the role of pregnancy complications at mothers first birth, as it remains possible that the effect of IPI might be modified by gestational diabetes in first birth. In our cohort, there were 3906 total pregnancies among mothers who had gestational diabetes during their first pregnancy, and 1525 (39%) pregnancies were complicated by recurrent gestational diabetes.

Our supplementary analyses using post-birth IPI established the presence of confounding of the association between IPI and gestational diabetes by factors that vary between women (Appendix Table 4). Specifically, short post-birth IPIs (<6 months)

were associated with increased odds of gestational diabetes in the previous pregnancy. Intuitively, a pregnancy complication cannot be caused by an exposure that occurs after that complication. This result provides justification for the within-mother design because it demonstrates confounding at the mother-level [19,25]. The lack of association between long post-birth IPI and gestational diabetes might indicate that such confounding is less of a concern for longer intervals.

Strengths and limitations

We sourced our cohort from highly reliable population-based perinatal information ascertained from hospital separations and midwives' notifications. To our knowledge this is the largest population-based study to examine the association between IPIs and gestational diabetes among mothers with at least three consecutive births (two intervals) using within-mother comparison (matching pregnancies of the same mother). The within-mother matched design provides estimates based on a cohort of mothers who have experienced pregnancies with and without the complication of interest (gestational diabetes). The premise of this design is that it accounts to a larger extent for environmental and genetic confounders that can vary between mothers.

There were some limitations to our study. Firstly, we restricted our analyses to the outcomes of more than two births for each mother to enable matching of at least two IPIs. Thus, although our design achieves greater interval validity, there remains the possibility of selection-bias. Secondly, we attempted to control time-varying confounders but were unable to measure some variables that may have significance (e.g., pre-pregnancy weight change). However, matched analyses were statistically non-significant and adjustment for such variables would have likely attenuated effect estimates further, and our conclusions would have remained unchanged. Thirdly, it should be acknowledged that chronic conditions were not routinely collected until 1997 and without good capture until 2000. However, our sensitivity analyses suggested that the effect estimates were consistent between the main analyses, and births restricted to 1997 onwards with complete information. Finally, as with all retrospective cohort studies that use comprehensive perinatal records, we were unable to identify pregnancy loss before 20 weeks of gestation. However, gestational diabetes usually occurs later in pregnancy and if any bias is introduced by truncation of pregnancies after 20 weeks of gestation, this is likely to be limited to survivor bias. Even though, information on pregnancy loss may be relevant to consider, findings from a recent study reported insufficient evidence for differences in pregnancy losses by IPI [30].

In conclusion, there was insufficient statistical evidence for a harmful association between short IPI (<6 months) and gestational diabetes in our cohort. Our findings do not support the hypothesis that short IPI (<6 months) increases risk of gestational diabetes and suggests that observed associations in previous studies were possibly attributable to residual confounding.

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Appendix

Appendix Table 1
Characteristics of the study population of all births to mothers with at least three consecutive births during the study period (n = 254,137 births) in Western Australia, 1980–2015

Characteristics	Interpregnancy interval (months)						
	<6	6–11	12–17	18–23	24–59	60–119	120 or more
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total (n = 254,137)	16,548 (6.5)	45,076 (17.7)	50,528 (19.9)	37,352 (14.7)	78,909 (31.1)	21,780 (8.6)	3944 (1.6)
Gestational diabetes (GDM), n (%): 10,032 (4)							
Yes	539 (3.3)	1261 (2.8)	1509 (3.0)	1272 (3.4)	3526 (4.5)	1499 (6.9)	426 (10.8)
Maternal age at time of each delivery (y)							
<25	6656 (40.2)	13,032 (28.9)	11,872 (23.5)	7747 (20.7)	12,871 (16.3)	905 (4.2)	0 (0.0)
25–29	5395 (32.6)	15,905 (35.3)	17,822 (35.3)	13,023 (34.9)	25,743 (32.6)	5733 (26.3)	187 (4.7)
30–34	3220 (19.5)	11,627 (25.8)	14,883 (29.5)	11,610 (31.1)	26,394 (33.5)	8378 (38.5)	1168 (29.6)
35–39	1130 (6.8)	4024 (8.9)	5290 (10.5)	4397 (11.8)	12,040 (15.3)	5528 (25.4)	1729 (43.8)
40 or older	147 (0.9)	488 (1.1)	661 (1.3)	575 (1.5)	1861 (2.4)	1236 (5.7)	860 (21.8)
Marital status							
Married	14,263 (86.2)	41,118 (91.2)	46,825 (92.7)	34,438 (92.2)	70,892 (89.8)	18,705 (85.9)	3308 (83.9)
Never married	1948 (11.8)	3303 (7.3)	3074 (6.1)	2382 (6.4)	6312 (8.0)	2178 (10.0)	391 (9.9)
Widowed, divorced, separated	282 (1.7)	545 (1.2)	497 (1.0)	419 (1.1)	1429 (1.8)	772 (3.5)	212 (5.4)
Unknown	55 (0.3)	110 (0.2)	132 (0.3)	113 (0.3)	276 (0.4)	125 (0.6)	33 (0.8)
Race/ethnicity							
Caucasian	12,299 (74.3)	37,050 (82.2)	42,262 (83.6)	31,413 (84.1)	64,944 (82.3)	17,801 (81.7)	3304 (83.8)
Non-Caucasian	4249 (25.7)	8026 (17.8)	8266 (16.4)	5939 (15.9)	13,965 (17.7)	3979 (18.3)	640 (16.2)
Birth year							
1980–1984	1452 (8.8)	3698 (8.2)	3545 (7.0)	1973 (5.3)	1609 (2.0)	0 (0.0)	0 (0.0)
1985–1989	2460 (14.9)	7173 (15.9)	8132 (16.1)	5862 (15.7)	10,641 (13.5)	996 (4.6)	0 (0.0)
1990–1994	2569 (15.5)	7315 (16.2)	8381 (16.6)	6260 (16.8)	13,059 (16.6)	3275 (15.0)	206 (5.2)
1995–1999	2433 (14.7)	6807 (15.1)	7725 (15.3)	5787 (15.5)	13,192 (16.7)	3931 (18.1)	685 (17.4)
2000–2004	2327 (14.1)	6367 (14.1)	7201 (14.3)	5545 (14.9)	12,652 (16.0)	4125 (18.9)	865 (21.9)
2005–2009	2828 (17.1)	7398 (16.4)	8023 (15.9)	5943 (15.9)	13,443 (17.0)	4686 (21.5)	1087 (27.6)
2010–2015	2479 (15.0)	6318 (14.0)	7521 (14.9)	5982 (16.0)	14,313 (18.1)	4767 (21.9)	1101 (27.9)
SES*							
1	4602 (27.8)	9386 (20.8)	9482 (18.8)	6905 (18.5)	15,507 (19.7)	4603 (21.1)	736 (18.7)
2	3712 (22.4)	9070 (20.1)	9563 (18.9)	7096 (19.0)	15,245 (19.3)	4445 (20.4)	799 (20.3)
3	3283 (19.8)	8994 (20.0)	9909 (19.6)	7367 (19.7)	15,073 (19.1)	4276 (19.6)	787 (20.0)
4	2749 (16.6)	8938 (19.8)	10,450 (20.7)	7684 (20.6)	15,976 (20.3)	4328 (19.9)	843 (21.4)
5	2202 (13.3)	8688 (19.3)	11,124 (22.0)	8300 (22.2)	17,108 (21.7)	4128 (19.0)	779 (19.8)

* Categorized as quintiles (1 = most disadvantaged to 5 = least disadvantaged).

Appendix Table 2
Odds Ratios (OR) and 95% confidence intervals for the association between interpregnancy interval and gestational diabetes for births to (Model 2a) mothers with three consecutive births (parity 0, 1, 2); (Model 2b) mothers with at least three consecutive live births; (Model 2c) mothers with at least three consecutive births during the end of the study period (Sept 1997 onwards) in Western Australia, 1980–2015

IPI in months	Unmatched		Matched		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	Adjusted OR (95% CI)‡
Gestational diabetes					
Model 2a: (n = 96,354 mothers, n = 192,708 births)					
0–5	0.99 (0.87–1.12)	**1.14 (1.00–1.30)**	0.82 (0.66–1.03	0.83 (0.66–1.05)	0.94 (0.75–1.19)
6–11	**0.86 (0.78–0.95)**	0.97 (0.87–1.07)	0.89 (0.75–1.05)	0.93 (0.78–1.11)	1.01 (0.84–1.20)
12–17	**0.88 (0.79–0.96)**	0.94 (0.85–1.03)	**0.82 (0.70–0.96)**	**0.86 (0.73–1.01)**	0.91 (0.76–1.07)
18–23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24–59	**1.34 (1.24–1.45)**	**1.14 (1.05–1.24)**	**1.44 (1.25–1.65)**	1.37 (1.18–1.58)	1.11 (0.95–1.29)
60–119	**2.16 (1.97–2.38)**	**1.36 (1.23–1.50)**	**2.42 (2.03–2.88)**	2.22 (1.85–2.66)	1.19 (0.97–1.45)
120 or more	**3.82 (3.32–4.38)**	**1.60 (1.38–1.86)**	**3.13 (2.39–4.10)**	2.72 (2.06–3.59)	0.92 (0.65–1.30)
Model 2b: (n = 100,286 mothers, n = 244,125 births)					
0–5	0.90 (0.81–1.01)	0.96 (0.86–1.07)	**0.74 (0.63–0.88)**	**0.75 (0.62–0.90)**	**0.82 (0.68–0.98)**
6–11	**0.80 (0.74–0.87)**	**0.88 (0.81–0.96)**	**0.75 (0.66–0.85)**	**0.82 (0.71–0.94)**	0.87 (0.76–1.01)
12–17	**0.85 (0.79–0.92)**	**0.91 (0.83–0.98)**	**0.79 (0.70–0.89)**	**0.83 (0.73–0.95)**	**0.86 (0.76–0.99)**
18–23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24–59	**1.33 (1.25–1.42)**	**1.14 (1.07–1.22)**	**1.40 (1.26–1.55)**	**1.28 (1.14–1.43)**	1.10 (0.97–1.23)
60–119	**2.11 (1.95–2.29)**	**1.34 (1.23–1.45)**	**2.26 (1.99–2.56)**	**1.90 (1.65–2.18)**	1.13 (0.97–1.31)
120 or more	**3.45 (3.08–3.88)**	**1.52 (1.34–1.72)**	**3.66 (2.93–4.56)**	**2.95 (2.32–3.73)**	1.13 (0.86–1.50)
Model 2c: (n = 40,405 mothers, n = 93,716 births)					
0–5	0.91 (0.79–1.04)	1.05 (0.91–1.21)	**0.77 (0.62–0.95)**	0.83 (0.66–1.04)	0.91 (0.72–1.15)
6–11	**0.82 (0.74–0.91)**	0.93 (0.84–1.03)	**0.74 (0.63–0.87)**	0.84 (0.70–1.00)	0.90 (0.75–1.07)
12–17	0.91 (0.82–1.01)	0.97 (0.88–1.07)	**0.79 (0.67–0.92)**	0.89 (0.75–1.06)	0.92 (0.77–1.09)
18–23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24–59	**1.32 (1.20–1.44)**	**1.15 (1.07–1.27)**	**1.41 (1.22–1.62)**	**1.32 (1.13–1.54)**	1.07 (0.91–1.25)
60–119	**2.01 (1.80–2.25)**	1.33 (1.19–1.49)	**2.18 (1.81–2.63)**	**2.05 (1.67–2.51)**	1.05 (0.84–1.31)
120 or more	**2.78 (2.07–3.74)**	**1.28 (0.95–1.74)**	**1.94 (1.16–3.26)**	**2.03 (1.16–3.55)**	0.61 (0.30–1.24)

Bold indicates significance at the 5% level.
Model 2a and 2b were adjusted for the following variables.
* Maternal age at time of each delivery (categorical), birth year, parity, SES, race/ethnicity, marital status, infant sex, history of obesity; gestational hypertension and known chronic hypertension.
† Prognostic score for GDM of parity, SES, marital status, infant sex, history of obesity; gestational hypertension, and known chronic hypertension.
‡ Prognostic score for GDM of maternal age at time of each delivery (categorical), parity, birth year, SES, marital status, infant sex, history of obesity; gestational hypertension and known chronic hypertension; Model 2c: includes all variables in Model 2a plus smoking during pregnancy.

Appendix Table 3
Odds Ratios (OR) and 95% confidence intervals for the association between interpregnancy interval and gestational diabetes for births to (Model-A) mothers with at least three consecutive births during the study period (n = 103,909 mothers, n = 254,137 births); (Model-B) mothers with at least three consecutive births during the study period, excluding mothers with gestational diabetes in first pregnancy (n = 102,193 mothers, n = 250,231 births) in Western Australia, 1980–2015

IPI in months	Unmatched			
	Unadjusted OR (95% CI)		Adjusted OR (95% CI)*	
	Model A	Model B	Model A	Model B
0–5	0.95 (0.86–1.05)	0.97 (0.86–1.08)	1.01 (0.91–1.12)	1.00 (0.89–1.13)
6–11	**0.81 (0.75–0.88)**	**0.79 (0.72–0.87)**	**0.89 (0.82–0.97)**	**0.86 (0.79–0.95)**
12–17	**0.87 (0.80–0.94)**	**0.84 (0.77–0.91)**	**0.92 (0.85–0.99)**	**0.88 (0.81–0.96)**
18–23	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24–59	**1.32 (1.24–1.41)**	**1.42 (1.32–1.52)**	**1.13 (1.06–1.21)**	**1.21 (1.13–1.30)**
60–119	**2.09 (1.94–2.26)**	**2.40 (2.21–2.61)**	**1.32 (1.22–1.43)**	**1.52 (1.40–1.66)**
≥120	**3.42 (3.06–3.85)**	**4.07 (3.61–4.58)**	**1.51 (1.33–1.70)**	**1.83 (1.61–2.08)**

IPI in months	Matched							
	Informative strata, n (%)§		Unadjusted OR (95% CI)		Adjusted OR (95% CI)†		Adjusted OR (95% CI)‡	
	Model A	Model B	Model A	Model B	Model A	Model B	Model A	Model B
0–5	1305 (6.9)	1202 (6.9)	**0.78 (0.67–0.91)**	**0.77 (0.65–0.91)**	**0.80 (0.68–0.95)**	**0.79 (0.67–0.95)**	0.88 (0.75–1.05)	0.87 (0.73–1.05)
6–11	2954 (15.7)	2665 (15.3)	**0.79 (0.70–0.89)**	**0.79 (0.70–0.89)**	**0.84 (0.74–0.96)**	**0.84 (0.73–0.96)**	0.92 (0.80–1.05)	0.91 (0.79–1.05)
12–17	3297 (17.5)	3004 (17.2)	**0.83 (0.74–0.93)**	**0.82 (0.72–0.93)**	**0.86 (0.76–0.98)**	**0.84 (0.74–0.96)**	0.90 (0.79–1.02)	0.87 (0.76–1.00)
18–23	2489 (13.2)	2262 (12.9)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
24–59	6096 (32.3)	5685 (32.6)	**1.40 (1.26–1.55)**	**1.43 (1.29–1.60)**	**1.29 (1.15–1.44)**	**1.33 (1.19–1.50)**	1.07 (0.95–1.20)	1.10 (0.97–1.24)
60–119	2216 (11.7)	2128 (12.2)	**2.28 (2.01–2.57)**	**2.37 (2.08–2.69)**	**1.96 (1.71–2.23)**	**2.04 (1.77–2.34)**	1.08 (0.93–1.25)	1.11 (0.95–1.29)
≥120	516 (2.7)	504 (2.9)	**3.65 (2.95–4.52)**	**3.75 (3.02–4.67)**	**3.02 (2.41–3.80)**	**3.07 (2.43–3.88)**	1.02 (0.77–1.34)	1.01 (0.75–1.34)

Bold indicates significance at the 95% confidence level.
Models adjusted for the following variables.
* Maternal age at time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, gestational hypertension and known chronic hypertension.
† Prognostic score for gestational diabetes by parity, SES, marital status, infant sex, history of obesity, gestational hypertension, and known chronic hypertension.
‡ Prognostic score for gestational diabetes by maternal age at time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, gestational hypertension and known chronic hypertension.
§ Number and percentage of informative strata of gestational diabetes for each IPI category for births to mothers with at least three consecutive births.

Appendix Table 4
Odds Ratios (ORs) and 95% confidence intervals for the association between post-birth interpregnancy interval (interval between second and third births) and gestational diabetes in the second birth for mothers with three consecutive births during the study period (n = 96,354 births) in Western Australia, 1980–2015

IPI in months	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[†]
Gestational diabetes[*]		
0–5	**1.36 (1.13–1.65)**	**1.25 (1.03–1.52)**
6–11	**1.00 (0.86–1.16)**	0.94 (0.81–1.10)
12–17	1.05 (0.91–1.22)	1.02 (0.88–1.18)
18–23	1.00 (reference)	1.00 (reference)
24–59	0.93 (0.82–1.06)	1.04 (0.91–1.18)
60–119	**0.67 (0.55–0.81)**	0.96 (0.79–1.16)
120 or more	**0.54 (0.36–0.81)**	1.18 (0.78–1.79)

[*] Predicting gestational diabetes of second born (parity 1 births) using post-pregnancy IPI (interval between second born and third born births).
[†] Model adjusted for maternal age (categorical), birth year, parity, SES, race/ethnicity, marital status, infant sex, history of obesity, gestational hypertension and known chronic hypertension.

Appendix B5-Study Two

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ORIGINAL ARTICLE

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Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study

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Abstract

Background: Despite extensive research on risk factors and mechanisms, the extent to which interpregnancy interval (IPI) affects hypertensive disorders of pregnancy in high-income countries remains unclear.

Objectives: To examine the association between IPI and hypertensive disorders of pregnancy in a high-income country setting using both within-mother and between-mother comparisons.

Methods: A retrospective population-based cohort study was conducted among 103 909 women who delivered three or more consecutive singleton births (n = 358 046) between 1980 and 2015 in Western Australia. We used conditional Poisson regression with robust variance, matching intervals of the same mother and adjusted for factors that vary within-mother across pregnancies, to investigate the association between IPI categories (reference 18-23 months), and the risk of hypertensive disorders of pregnancy. For comparison with previous studies, we also applied unmatched Poisson regression (between-mother analysis).

Results: The incidence of preeclampsia and gestational hypertension during the study period was 4%, and 2%, respectively. For the between-mother comparison, mothers with intervals of 6-11 months had lower risk of preeclampsia with adjusted relative risk (RR) 0.92 (95% confidence interval [CI] 0.85, 0.98) compared to reference category of 18-23 months. With the within-mother matched design, we estimated a larger effect of long IPI on risk of preeclampsia (RR 1.29, 95% CI 1.18, 1.42 for 60-119 months; and RR 1.30, 95% CI 1.10, 1.53 for intervals ≥120 months)

compared to 18-23 months. Short IPIs were not associated with hypertensive disorders of pregnancy.

Conclusions: In our cohort, longer IPIs were associated with increased risk of preeclampsia. However, there was insufficient evidence to suggest that short IPIs (<6 months) increase the risks of hypertensive disorders of pregnancy.

KEYWORDS

birth spacing, hypertensive disorders of pregnancy, interpregnancy interval, pregnancy complications, within-mother

1 | BACKGROUND

Globally, hypertensive disorders of pregnancy affect 2%-10% of pregnancies and are among the most significant contributors to perinatal and maternal mortality and morbidity.[1] Hypertensive disorders of pregnancy can lead to severe complications including eclampsia, abruptio placentae, fetal growth restriction, and preterm birth.[2-5]

Interpregnancy interval (IPI) is defined as the length of time between delivery and the conception date of the subsequent pregnancy and has been evaluated extensively with respect to its association with perinatal outcomes.[6-9] However, less attention has been given towards its association with pregnancy complications.[10,11] The World Health Organization (WHO) and the American College of Obstetricians and Gynecologists suggest intervals of at least two years and at least 18 months following Livebirths, respectively.[12,13] The applicability of these recommendations for mothers in high-income countries is uncertain as they were based on large studies in low- and middle-income settings. The extent to which these recommendations are relevant for minimising effects on pregnancy complications remains unclear. Despite extensive research on risk factors and mechanisms,[14] the aetiology of hypertensive disorders of pregnancy has not been completely elucidated. Studies that examine risk factors have typically focused on preeclampsia for nulliparous mothers.[2,3,15] Among parous mothers, longer IPI,[7,16] change of partner,[17-19] and history of preeclampsia[3,20] have been associated with an increased risk of preeclampsia or gestational hypertension.

Different hypotheses have been proposed as causal effects of IPI on pregnancy complications.[21] The *maternal depletion hypothesis* proposes that mothers with closely spaced pregnancies have less time to recover from the physiological stress of their previous pregnancy.[22,23] The *physiological regression hypothesis* suggests that longer pregnancy intervals result in the gradual loss of childbearing capacities, which are developed during the preceding pregnancy, and thereby result in regression to a similar physiological state to that of primigravida.[21] However, a competing explanation posits that the increased risk of pregnancy complications might be attributed to confounding factors that are associated with both IPIs and pregnancy complications (the *systematic bias hypothesis*).[24] It remains plausible that much of the observed association between pregnancy complications and perinatal outcomes in past studies may be attributable to risk factors that vary between mothers but tend to persist between pregnancies within-mothers.[24-26] Complementary within-mother analyses offer an opportunity to investigate factors that account for these effects.

We examined the association between IPI and hypertensive disorders during pregnancy in a high-income country setting using both within-mother and between-mother comparisons.

Synopsis

Study question

Is interpregnancy interval associated with increased risk of hypertensive disorders of pregnancy?

What is already known

IPI has been extensively evaluated with respect to its association with perinatal outcomes; however, the extent to which IPI impacts pregnancy complications in high-income countries remains unclear. Previous studies have focused on between-mother comparisons, which may inadequately account for maternal risk factors.

What this study adds

This study applied a within-mother matched analysis, which enables to eliminate the effects of any confounding characteristics that remain persistent within a woman. Using this analysis, mothers with IPI ≥ 24 months had greater risk of preeclampsia and gestational hypertension in the next pregnancy, relative to IPI of 18-23 months. There was insufficient statistical evidence for harmful associations between short interpregnancy intervals (<6 months) and hypertensive disorders of pregnancy in this cohort.

2 | METHODS

2.1 | Study design

We conducted a retrospective population-based matched and unmatched cohort study on the association between IPI and the risk of hypertensive disorders of pregnancy for all mothers who gave birth within the period 1980-2015 in Western Australia (WA).

2.2 | Data sources and analytic sample

Maternal, infant, and birth information were obtained from the Midwives Notification System, which has been validated[27] and includes >99% of births in WA of at least 20 weeks' gestation or birthweight ≥400 g if the gestational length was unknown.[28] Hospitalisation records were obtained from the Hospital Morbidity Data Collection, which includes information on all hospitalisations in the state with International Classification of Diseases (ICD-9/10th revision-Australian Modification) coded diagnoses and procedures.[29] Data sources and the study protocol have been described elsewhere.[30,31] Our analyses included all mothers with at least two consecutive IPIs at 20-44 weeks of gestation in WA within the period 1980 and 2015. Of the original total of 487 297 mothers, we sequentially excluded mothers who delivered multiples; mothers who delivered only once during the study period; mothers whose children's birth years were inconsistent with parity; mothers whose IPIs were negative; and mothers who had missing gestational length, birth outcomes, age, infant sex, and socio-economic status. These exclusions resulted in 287 745 mothers with two or more consecutive births (Figure 1). Finally, we excluded mothers with fewer than two intervals, leaving 103 909 eligible women with 358 046 births. There were 254 137 births included in the analysis cohort because each of the first (parity 0) births does not have an IPI.

2.3 | Exposure

Interpregnancy interval was defined as the length of time between delivery date of the previous pregnancy and the estimated conception date of the subsequent pregnancy (date of birth minus gestational age at birth). Gestational age at birth was estimated as the best clinical estimate from dating ultrasounds, or last menstrual period when ultrasound was not available. Intervals were grouped into seven categories (<6, 6-11, 12-17, 18-23 (reference), 24-59, 60-119, and ≥120 months). These categories are consistent with the WHO recommendations and categories used in previous studies.[24,25,32,33]

2.4 | Outcomes

Midwives notifications and hospital separation codes consistent with preeclampsia (ICD-9:642.4, 642.5, 642.7, ICD-10: O14, O11) and gestational hypertension without proteinuria (ICD-9:642.3, ICD-10: O13) were used to define outcome variables. The definitions and diagnosis of hypertensive disorders of pregnancy were based on Australian Hypertension in Pregnancy Consensus Statement.[28]

2.5 | Covariates

Information on potential confounding factors including maternal age, delivery year, marital status, parity, fetal sex, race/ethnicity, and pre-existing maternal medical conditions (diabetes, hypertension, history of obesity) was also obtained from hospitalisations and midwives notifications. Race/ethnicity was classified as Caucasian versus non-Caucasian. Socio-economic status (SES) was derived by the Australian Bureau of Statistics Index of Relative Socio-economic Disadvantage at a geographic area for the maternal residence at the time of birth[34] and categorised into quintiles. We obtained the family linkages from the WA Family Connections database.

2.6 | Statistical analysis

Directed acyclic graphs (DAGs) were created based on existing literature and recent recommendations to present the potential pathway between IPI (short and long) and hypertensive disorders of pregnancy (Figure S1 & S2).[33] We used a within-mother (sibling comparison) design, matching pregnancies to the same mothers, comparing pregnancies within-mothers (to control for unmeasured characteristics that do not change over time or remain strongly correlated over time). This enables inference that is based purely on within-mother effects, minimises the need for additional adjustment, and has been successfully applied previously.[24-26] In the absence of residual time-varying confounding and selection bias, the unmatched and matched models will report similar effects of IPI. It is plausible that if unmeasured persistent confounders exist, the unmatched model may result in biased estimates.[24] A conditional Poisson regression with robust variance was used to estimate unadjusted and adjusted relative risk (RR) and 95% confidence interval (CI) for the associations between IPIs and risk of hypertensive disorders of pregnancy for the within-mother matched model.[35-38] For comparison with the unmatched design of previous studies, we also generated results by generalised linear models (GLM) fitted using a Poisson distribution with a log link function for these associations, comparing pregnancies between mothers.

For the matched analysis, we adjusted for factors that vary between births. Specifically, we adjusted for maternal age (categorised as 14-19, 20-24, 25-29, 30-34, 35-39, or ≥40 years), parity, birth year and SES (quintiles), sex, history of obesity; pre-existing diabetes, gestational diabetes, and partner change. Because time-varying adjustment variables can be proxies for IPI, which can introduce multicollinearity, we adjusted for a prognostic score, an analogue to propensity score defined as the logit of the probability of the outcome regressed on the adjustment variables from baseline cohort.[39-41] This process ensures the whole cohort is used to estimate

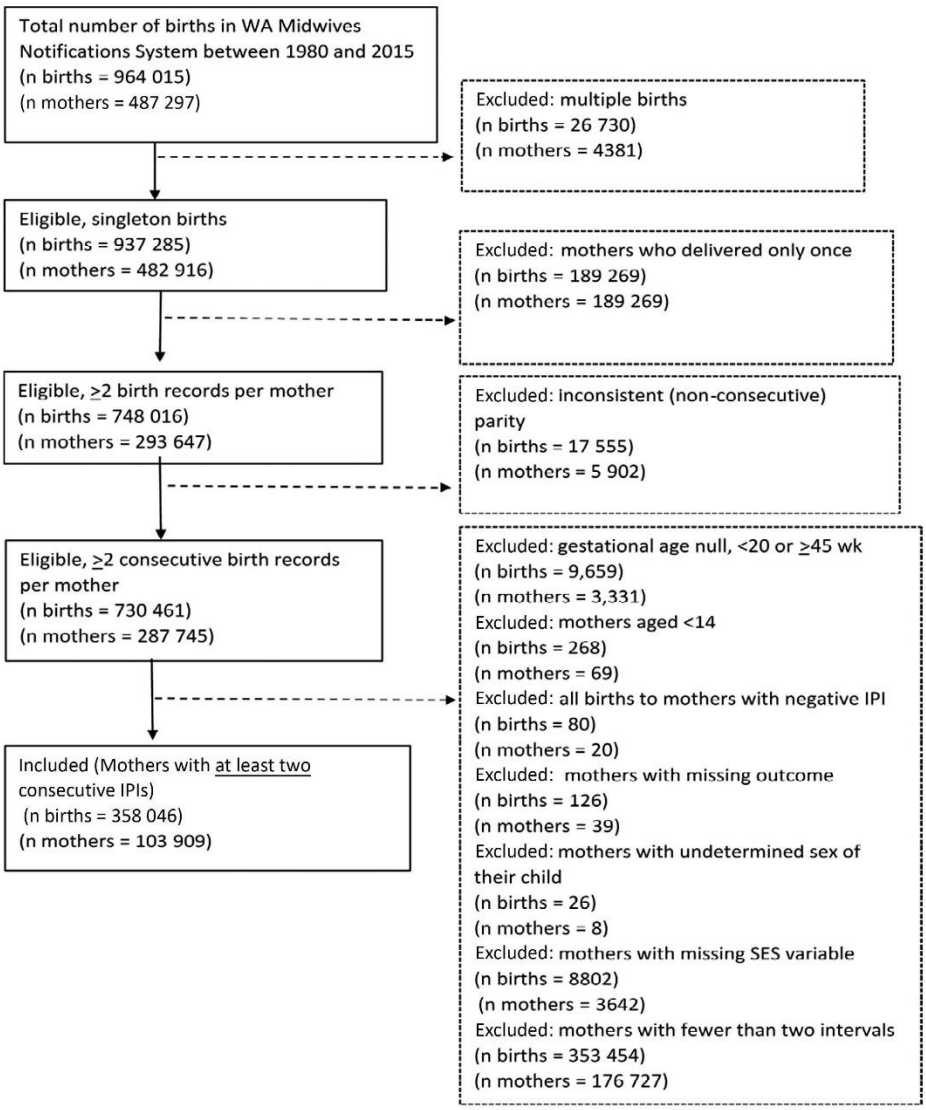

FIGURE 1 Selection of eligible birth records included in this study—Western Australia, 1980-2015

changes in underlying risk of the pregnancy complication and results in estimation of the direct effect of IPI. To estimate the total effect of IPI, we repeated analyses without adjustment for age and birth year. In the between-mother analysis, we adjusted for the same variables as we did in the within-mother analysis plus factors that can vary between mothers, such as race/ethnicity. We used STATA version 16.0 (Stata Corporation), with the *xtpoisson* command to run the matched analysis (conditional Poisson regression) and the *glm*

command to run the unmatched analysis (generalised linear models).[37] We used DAGitty v2.3 to select covariates fulfilling minimally sufficient adjustment sets.[42]

2.7 | Missing data

We undertook a complete case analysis. The proportion of missing data was small and ranged from 0.07% for maternal age to 2.6% for gestational age. Multiple imputation was not performed. Approximately 5% of the missingness was due to lack of availability of data prior to year 1997, and this bias was assessed by sensitivity analyses.

2.8 | Sensitivity analyses

To ascertain the sensitivity of our results to higher-order parity and inclusion of stillbirths, we conducted two separate supplementary analyses restricted to the first three births for all mothers with births at parity 0, 1, and 2 and analysis restricted to mothers with at least three consecutive livebirths. To explore the potential effects of measurement error/missingness, which would have occurred more commonly during the earlier years of the cohort when there was a lower likelihood that births had ultrasound-confirmed gestation as well as to investigate the potential influence of maternal smoking, which was routinely captured in the perinatal data collection from September 1997 onwards,[28] we conducted a separate analysis restricted to consecutive births after September 1997. To explore the role of partner change in the association between IPI and preeclampsia, we conducted multivariable analysis with different levels of adjustment (unadjusted, fully adjusted, adjusted for non-time-varying risk factors). To check whether characteristics of women included in the matched analyses (mothers with informative strata) differed from those mothers with non-informative strata, we presented the baseline characteristics at their first pregnancy during the study period for these groups. Furthermore, to asses generalisability of the cohort used in our within-mother analysis, we applied a conventional Poisson regression on a restricted cohort to births from mothers with informative strata obtained from within-mother analysis and compared to results of between-mother analysis obtained from the main cohort. Finally, we examined IPI as a continuous measure using restricted cubic spline with a Poisson model and conditional Poisson model for the between- and within-mother analyses, respectively. We used a spline with five knots placed at 6, 12, 18, 24, 48, 60, and 120 months of the IPI distribution (Figure S3A-B).

2.9 | Ethics approval

This research was approved by the Human Research Ethics Committee (2016/51) from the Department of Health, WA. The Ethics Committee approval was accepted on 14 September 2016.

3 | RESULTS

Study entry for each mother was defined as their first birth during the study period. At study entry, the majority of women were generally free of chronic hypertension, diabetes, and obesity (Table 1). More than half (55%) of the mothers were under 25 years, married (81%), or Caucasian (85%).

For all births included in the cohort, the incidence of preeclampsia and gestational hypertension during the study period was 4%, and 2%, respectively (Table 2). Approximately 6% of births occurred after an IPI of 0-5 months, 20% after 12-17 months, 15% after 18-23 months, and 1.5% after more than 120 months. Gestational hypertension diagnosis was more common among mothers in the older age groups, whereas preeclampsia diagnosis was more common among younger mothers (Table S1).

3.1 | IPI and risk of preeclampsia estimated by between-mother comparisons

Compared to an IPI of 18-23 months, unmatched adjusted analysis showed lower risk of preeclampsia for 6-11-month intervals (adjusted RR 0.92, 95% CI 0.85, 0.98) (Table 3).

Longer IPIs were associated with greater risk of preeclampsia after adjustment for confounders (Table 3). Compared to an IPI of 18-23 months, the greatest adjusted effects were observed for IPIs of ≥120 months. IPI of 24 months or greater remained associated with increased risk of all hypertensive disorders of pregnancy after adjustment, with greatest effects observed for preeclampsia. Mothers with shorter IPI of 6-11 had slightly lower risk of preeclampsia compared to IPI of 18-23 months.

3.2 | IPI and risk of preeclampsia estimated by within-mother comparisons

In the matched analysis after adjustment, no increased risk of preeclampsia was observed for short IPI (<17 months); while for longer IPIs, we found an increased risk of preeclampsia. Relative to 18-23-months, the two longest IPI categories had greater risk of preeclampsia. Similarly, longer IPIs were associated with greater risk of gestational hypertension (Table S2).

3.3 | Partner change and risk of preeclampsia

In our cohort, only 10% of mothers changed their partner during the study period. The proportion of mothers who changed partners ranged from two per cent for those with IPI <6 months to 63% for those with long IPIs (≥120 months) (Table 2). We observed negligible difference in risk of preeclampsia for mothers who changed partner compared to those who did not change partner (Table S6).

TABLE 1 Sociodemographic characteristics and medical conditions of the study cohort of mothers at their first birth included during the study period (n = 103 909 mothers) in WA, 1980-2015

Characteristics	Mothers, N (%)
Maternal age at first birth (years)	
<25	56 901 (54.8)
25-29	32 988 (31.7)
30-34	12 467 (12.0)
35-39	1521 (1.5)
≥40	32 (0.03)
Marital status	
Married	83 875 (80.7)
Never married	19 221 (18.5)
Widowed, divorced, separated	618 (0.6)
Unknown	195 (0.2)
Race/ethnicity	
Caucasian	88 106 (84.8)
Aboriginal/Torres Strait Islander	8267 (7.9)
Asian[a]	1986 (1.9)
African	600 (0.6)
Others[b]	4950 (4.8)
Birth year	
1980-1984	20 264 (19.5)
1985-1989	17 681 (17.0)
1990-1994	16 811 (16.2)
1995-1999	16 053 (15.4)
2000-2004	15 538 (15.0)
2005-2009	14 448 (13.9)
2010-2015	3114 (3.0)
SES in quintiles	
<20 percentiles (most disadvantaged)	20 398 (19.6)
20-39 percentile	21 679 (20.8)
40-59 percentile	21 914 (21.1)
60-79 percentile	20 648 (19.9)
≥80 percentile (least disadvantaged)	19 270 (18.6)
Chronic conditions	
Known chronic hypertension	259 (0.3)
Known chronic diabetes	181 (0.2)
Known obesity history	237 (0.2)
Pregnancy characteristics	
Pregnancy complications	
Gestational diabetes	1716 (1.6)
Preeclampsia	9928 (9.6)
Gestational hypertension	2400 (2.3)
Infant sex	
Male	54 132 (52.1)
Parity	
0	96 314 (92.7)
1	4977 (4.8)
2	1636 (1.6)
≥3	374 (1.0)

[a]Including Indian.
[b]Including Polynesian and Maori.

Among women who did not change their partner between pregnancies, compared to IPI 18-23 months, the risk of preeclampsia was associated with an increase in IPI. Similar associations were observed among mothers who did not change their partner between pregnancies. Shorter intervals were not associated with increased risk of preeclampsia. The associations were attenuated in the within-mother analysis, but the patterns of the associations were similar with the between-mother analyses (Table 4).

3.4 | Sensitivity analysis

The results from matched and unmatched models restricted to mothers with first three consecutive births were consistent with those based on mothers with at least three consecutive births (Table S3). Similarly, point estimates were consistent with those obtained after exclusion of stillbirths (Table S4). There was a negligible difference in the association between IPI and hypertensive disorders of pregnancy when the cohort was restricted to births from September 1997 onwards, for which more information was available for adjustment. Precision of the effect estimates was reduced due to a 65% reduction in the sample size (Table S5).

In the sensitivity analysis, the harmful associations with longer IPI persisted regardless of change of partner in both within and between-mother comparisons. A negligible difference in risk of preeclampsia was observed for mothers who changed partner compared to those who did not change (Table S6).

Mothers included in the within-mother analyses (mothers with informative strata) had a similar profile of characteristics at baseline, with the exception that mothers in the informative strata had higher incidence of pregnancy complications (Table S7). Moreover, the pattern of association was similar when we ran a conventional Poisson regression on the cohort restricted to informative strata obtained from within-mother analysis (Table S8). However, estimates were attenuated after this restriction.

When examined as a non-linear function, risk remained unchanged until 20 months and increased linearly thereafter for the between-mother analyses (Figure S3A). For the within-mother analyses, risk remained unchanged until 20 months, increased linearly until 80 months, and did not change thereafter (Figure S3B). In general, all other findings were very similar to those reported for the main analysis and collectively support the hypothesis of an adverse association between long IPIs and hypertensive disorders of pregnancy.

4 | COMMENT

4.1 | Principal findings

This large population-based matched study examined the association of hypertensive disorders during pregnancy with IPI in mothers with at least two intervals (three consecutive births). The results of the within-mother unadjusted model indicate that IPI of ≥60 months

TABLE 2 Characteristics of the study population of all births to mothers with at least two consecutive intervals during the study period (n = 254 137 births) in WA, 1980-2015

	Interpregnancy interval (months)						
	0-5	6-11	12-17	18-23	24-59	60-119	≥120
Characteristics	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total (n = 254 137)	16 548 (6.5)	45 076 (17.7)	50 528 (19.9)	37 352 (14.7)	78 909 (31.1)	21 780 (8.6)	3944 (1.6)
Preeclampsia, n (%): 9863 (4)							
Yes	623 (3.7)	1562 (3.5)	1805 (3.6)	1373 (3.7)	3154 (4.0)	1097 (5.0)	249 (6.3)
Gestational hypertension, n (%): 4710 (2)							
Yes	251 (1.5)	645 (1.4)	816 (1.6)	612 (1.6)	1660 (2.1)	566 (2.6)	160 (4.1)
Maternal age at time of each delivery (years)							
<25	6656 (40.2)	13 032 (28.9)	11 872 (23.5)	7747 (20.7)	12 871 (16.3)	905 (4.2)	0 (0.0)
25-29	5395 (32.6)	15 905 (35.3)	17 822 (35.3)	13 023 (34.9)	25 743 (32.6)	5733 (26.3)	187 (4.7)
30-34	3220 (19.5)	11 627 (25.8)	14 883 (29.5)	11 610 (31.1)	26 394 (33.5)	8378 (38.5)	1168 (29.6)
35-39	1130 (6.8)	4024 (8.9)	5290 (10.5)	4397 (11.8)	12 040 (15.3)	5528 (25.4)	1729 (43.8)
≥40	147 (0.9)	488 (1.1)	661 (1.3)	575 (1.5)	1861 (2.4)	1236 (5.7)	860 (21.8)
Marital status							
Married	14 263 (86.2)	41 118 (91.2)	46 825 (92.7)	34 438 (92.2)	70 892 (89.8)	18 705 (85.9)	3308 (83.9)
Never married	1948 (11.8)	3303 (7.3)	3074 (6.1)	2382 (6.4)	6312 (8.0)	2178 (10.0)	391 (9.9)
Widowed, divorced, separated	282 (1.7)	545 (1.2)	497 (1.0)	419 (1.1)	1429 (1.8)	772 (3.5)	212 (5.4)
Unknown	55 (0.3)	110 (0.2)	132 (0.3)	113 (0.3)	276 (0.4)	125 (0.6)	33 (0.8)
Race/ethnicity							
Caucasian	12 299 (74.3)	37 050 (82.2)	42 262 (83.6)	31 413 (84.1)	64 944 (82.3)	17 801 (81.7)	3304 (83.8)
Non-Caucasian	4249 (25.7)	8026 (17.8)	8266 (16.4)	5939 (15.9)	13 965 (17.7)	3979 (18.3)	640 (16.2)
Birth year							
1980-1984	1452 (8.8)	3698 (8.2)	3545 (7.0)	1973 (5.3)	1609 (2.0)	0 (0.0)	0 (0.0)
1985-1989	2460 (14.9)	7173 (15.9)	8132 (16.1)	5862 (15.7)	10 641 (13.5)	996 (4.6)	0 (0.0)
1990-1994	2569 (15.5)	7315 (16.2)	8381 (16.6)	6260 (16.8)	13 059 (16.6)	3275 (15.0)	206 (5.2)
1995-1999	2433 (14.7)	6807 (15.1)	7725 (15.3)	5787 (15.5)	13 192 (16.7)	3931 (18.1)	685 (17.4)
2000-2004	2327 (14.1)	6367 (14.1)	7201 (14.3)	5545 (14.9)	12 652 (16.0)	4125 (18.9)	865 (21.9)
2005-2009	2828 (17.1)	7398 (16.4)	8023 (15.9)	5943 (15.9)	13 443 (17.0)	4686 (21.5)	1087 (27.6)
2010-2015	2479 (15.0)	6318 (14.0)	7521 (14.9)	5982 (16.0)	14 313 (18.1)	4767 (21.9)	1101 (27.9)
SES in quintiles[a]							
1	4602 (27.8)	9386 (20.8)	9482 (18.8)	6905 (18.5)	15 507 (19.7)	4603 (21.1)	736 (18.7)
2	3712 (22.4)	9070 (20.1)	9563 (18.9)	7096 (19.0)	15 245 (19.3)	4445 (20.4)	799 (20.3)
3	3283 (19.8)	8994 (20.0)	9909 (19.6)	7367 (19.7)	15 073 (19.1)	4276 (19.6)	787 (20.0)
4	2749 (16.6)	8938 (19.8)	10 450 (20.7)	7684 (20.6)	15 976 (20.3)	4328 (19.9)	843 (21.4)
5	2202 (13.3)	8688 (19.3)	11 124 (22.0)	8300 (22.2)	17 108 (21.7)	4128 (19.0)	779 (19.8)
Partner							
Same	14 458 (87.4)	41 264 (91.5)	46 276 (91.6)	33 568 (89.9)	63 062 (79.9)	10 360 (47.6)	811 (20.6)
Different	341 (2.1)	785 (1.7)	1074 (2.1)	1279 (3.4)	8775 (11.1)	8544 (39.2)	2470 (62.6)
Unknown	1749 (10.6)	3027 (6.7)	3178 (6.3)	2505 (6.7)	7072 (8.9)	2876 (13.2)	663 (16.8)

[a]Categorised as quintiles (1 = most disadvantaged to 5 = least disadvantaged).

was associated with greater risk of hypertensive disorders of pregnancy compared to an interval of 18-23 months. Pregnancies that followed IPIs shorter than 6-11 months had lower risk of gestational hypertension. Both the within-mother and between-mother analyses showed greater risk of hypertensive disorders following long IPI (≥24 months), compared to IPI of 18-23-months. Conversely, our results do not support the existence of an adverse association between short IPI and hypertensive disorders of pregnancy.

TABLE 3 Relative Risks (RRs) and 95% confidence intervals for the association between interpregnancy interval and preeclampsia for births to mothers with at least two consecutive intervals during the study period (n = 103 909 mothers, n = 254 137 births) in WA, 1980-2015

	Unmatched			Matched		
IPI in months	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]	Informative strata, n (%)[b]	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[c]	Adjusted RR (95% CI)[d]
Preeclampsia						
0-5	1.02 (0.93, 1.12)	0.98 (0.89, 1.07)	1474 (7.0)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)	1.00 (0.90, 1.11)
6-11	0.94 (0.88, 1.01)	0.92 (0.85, 0.98)	3599 (17.1)	0.95 (0.88, 1.03)	0.95 (0.87, 1.03)	0.95 (0.87, 1.02)
12-17	0.97 (0.91, 1.04)	0.96 (0.89, 1.03)	3912 (18.6)	1.00 (0.92, 1.08)	0.99 (0.92, 1.07)	0.99 (0.92, 1.07)
18-23	1.00 (Reference)	1.00 (Reference)	2933 (13.9)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
24-59	1.09 (1.02, 1.16)	1.13 (1.06, 1.20)	6606 (31.5)	1.03 (0.96, 1.11)	1.04 (0.97, 1.12)	1.05 (0.97, 1.12)
60-119	1.37 (1.27, 1.48)	1.52 (1.40, 1.65)	2043 (9.7)	1.26 (1.15, 1.38)	1.28 (1.17, 1.41)	1.29 (1.18, 1.42)
≥120	1.72 (1.51, 1.96)	1.95 (1.68, 2.25)	440 (2.1)	1.27 (1.08, 1.49)	1.29 (1.09, 1.52)	1.30 (1.10, 1.53)

Note: Models adjusted for the following variables: [a]maternal age at time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [b]Number and percentage of informative strata of preeclampsia and gestational hypertension for each IPI category for births to mothers with at least two consecutive IPIs; [c]prognostic score for preeclampsia by parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change; [d]prognostic score for preeclampsia by maternal age at time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, gestational diabetes, and partner change.

4.2 | Strengths of the study

Our cohort drew from highly reliable sources of population-based perinatal information ascertained from hospital separations and midwives' notifications. To our knowledge, this is the largest matched study to investigate the association between hypertensive disorders of pregnancy with IPI.

4.3 | Limitations of the data

Our study has several limitations. Firstly, to facilitate the matched study our cohort was restricted to the outcomes of more than two births for each woman. Although this design achieves greater internal validity, it does so at the potential cost of external generalisability if the biological effect of IPI is different for those populations not included in our study. Secondly, as with most retrospective cohort studies that use comprehensive perinatal records, we lacked data on pregnancy loss before 20 weeks of gestation. Finally, data on chronic co-morbidities were not routinely and comprehensively collected until 1997. However, results were consistent with those after restriction to births from 1997 onwards.

4.4 | Interpretation

Point estimates from within-mother analyses were lower than those from between-mother analyses, implying that more conservative conclusions would be drawn from the results of the within-mother analyses. Estimates from the within-mother analyses were attenuated after additional adjustment for covariates, indicating that the influence of IPI was partially explained by the pathway through maternal age or time period. For example, longer IPI can result in advanced maternal age which is a well-established risk factor for hypertensive pregnancy complications.[43,44] Although it is plausible that the effect of IPI on pregnancy complications differs by outcome status (Livebirth vs stillbirth), sensitivity analysis revealed that associations did not differ after restriction to livebirths. This may be due to the small number of stillbirths in our cohort. The association between IPI and hypertensive disorders of pregnancy can vary by parity and calendar year. However, our results were not sensitive to restriction of mothers with three consecutive births, or to births from 1997 onwards.

Our finding of greater risk of hypertensive disorders during pregnancy for longer IPIs in both between-mother and within-mother comparisons, with the effect slightly smaller in the matched models, is consistent with previous studies.[6,45,46] Our results do not support the hypothesis of an adverse association between short IPI on hypertensive disorders of pregnancy, which differs from previous studies.[47,48] Our results are consistent with previous research using unmatched designs regarding the association between longer IPIs and hypertensive disorders of pregnancy,[6,7,45,49] as well as with the recent matched study conducted by Hanley *et al*[25] which reported an association between shorter IPIs (6-11 months) and lower risk of preeclampsia. However, that study reported no association between long IPI and preeclampsia/eclampsia. The differences observed between the studies may be due to the differences in the definitions of outcome variables, adjustment variables (smoking, parity, partner change), or differences in susceptibility of the study populations to IPI (selection bias).

The observation of potential protective effects for short intervals and harmful effects for longer intervals might be explained

TABLE 4 Relative Risks (RRs) and 95% confidence intervals for the association between interpregnancy interval and preeclampsia for births to mothers with at least two consecutive intervals during the study period stratified by status of partner change (n = 100 751 mothers, n = 233 068 births) in WA, 1980-2015

	Unmatched					
	Same partner (n = 209 797)			Different partner (n = 23 271)		
IPI in months	N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]	N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]
0-5	14 457 (6.9)	1.05 (0.96, 1.16)	0.99 (0.90, 1.09)	341 (1.5)	0.55 (0.24, 1.28)	0.62 (0.26, 1.45)
6-11	41 264 (19.7)	0.94 (0.87, 1.01)	0.91 (0.84, 0.98)	786 (3.4)	0.95 (0.58, 1.57)	0.99 (0.60, 1.63)
12-17	46 275 (22.1)	0.95 (0.89, 1.03)	0.94 (0.87, 1.01)	1074 (4.6)	1.19 (0.78, 1.82)	1.23 (0.81, 1.88)
18-23	33 568 (16.0)	1.00 (Reference)	1.00 (Reference)	1281 (5.5)	1.00 (Reference)	1.00 (Reference)
24-59	63 062 (30.1)	1.08 (1.01, 1.16)	1.12 (1.05, 1.20)	8775 (37.7	1.27 (0.92, 1.74)	1.26 (0.92, 1.74)
60-119	10 360 (4.9)	1.45 (1.31, 1.60)	1.57 (1.42, 1.74)	8544 (36.7)	1.41 (1.03, 1.93)	1.45 (1.04, 2.02)
≥120	811 (0.4)	1.91 (1.47, 2.46)	2.05 (1.59, 2.65)	2470 (10.6)	1.91 (1.36, 2.68)	2.14 (1.47, 3.11)
	Matched					
	Same partner (n = 209 797)			Different partner (n = 23 271)		
IPI in months	Informative strata, n (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[b]	Informative strata, n (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[b]
0-5	1104 (7.4)	1.04 (0.93, 1.17)	1.03 (0.91, 1.16)	8 (2.0)	0.44 (0.10, 1.96)	0.44 (0.10, 2.04)
6-11	2803 (18.7)	0.95 (0.87, 1.04)	0.94 (0.86, 1.03)	18 (4.4)	1.16 (0.46, 2.88)	1.12 (0.43, 2.92)
12-17	3138 (21.0)	0.98 (0.90, 1.07)	0.98 (0.90, 1.07)	26 (6.3)	1.14 (0.44, 2.92)	1.09 (0.41, 2.88)
18-23	2323 (15.5)	1.00 (Reference)	1.00 (Reference)	37 (9.0)	1.00 (Reference)	1.00 (Reference)
24-59	4576 (30.6)	1.01 (0.93, 1.09)	1.03 (0.95, 1.11)	186 (45.4)	1.67 (0.81, 3.46)	1.83 (0.92, 3.67)
≥60[c]	1016 (6.8)	1.24 (1.10, 1.40)	1.29 (1.14, 1.45)	135 (32.9)	1.83 (0.85, 3.95)	2.23 (1.05, 4.73)

Note: Total included n = 233 068 births (excluding births with unknown partner change status).

[a]Adjusted for maternal age at time of each delivery (categorical), parity, birth year, SES, race/ethnicity, marital status, infant sex, history of obesity, known chronic diabetes, and gestational diabetes.

[b]prognostic score for preeclampsia by maternal age at time of each delivery (categorical), birth year, parity, SES, marital status, infant sex, history of obesity, known chronic diabetes, and gestational diabetes.

[c]Merged IPI category as there were few observations in the >120 IPI category.

by the physiological regression hypothesis; a pathway by which multiparous mothers with long IPI return to a similar physiological state of nulliparous mothers as protective benefits of a previous birth are gradually lost over time.[21] The role of partner change across pregnancies has been debated in epidemiological studies of risk factors for preeclampsia.[16,18,19,48] In this large population-based cohort of singleton births in WA, after adjusting for smoking and other confounders, associations implied that women who changed partners between pregnancies were not at increased risk of preeclampsia in both between-mother and within-mother analyses, which is consistent with previous studies.[48,50] We also observed that long IPI is strongly associated with increased risk of preeclampsia regardless of partner change. The primipaternity (immune maladaptation) hypothesis postulates that the protective effect of multiparity is lost with partner change, which could confound the association between preeclampsia and IPI if partner change influences IPI and is associated with preeclampsia risk.[18,19,51,52] However, for our cohort there was little indication of elevated risks of preeclampsia for mothers who changed partner compared to those who did not, while effect estimates were slightly higher for mothers who changed partner. It is plausible that mothers who change partner have other risk factors that place them at elevated risk of preeclampsia. Some authors have argued that both partner change and preeclampsia may influence IPI and suggest controlling for underlying maternal conditions in addition to IPI while studying the effect of partner change on preeclampsia, to prevent collider-stratification bias.[53] To assess the magnitude of potential collider-stratification bias in the association between partner change and preeclampsia, we reported estimates for partner change with and without adjustment for IPI. The RR for partner change decreased towards unity when IPI was included, which was also found to be the case in the study by Zhang et al[53,54] However, the protective effect of partner change persisted after adjustment for maternal underlying conditions. These analyses did not include smoking status during pregnancy. However, in the sub-cohort for which smoking status was known, the associations of IPI and change of partner with the risk of preeclampsia remained relatively unchanged. Our findings

are consistent with several studies on preeclampsia,[16,48,50] and a study on placental abruption.[55] Future studies would benefit from applying complementary matched designs and exploring whether the effect of IPI on pregnancy complications is modified by previous pregnancy complications.[50,54,55]

5 | CONCLUSIONS

Longer interpregnancy intervals (≥24 months) were associated with increased risk of hypertensive pregnancy complications and that the total effect was partially attributable to advanced maternal age. There was insufficient statistical evidence to support the claim that short IPIs (<6 months) increase the risks of pregnancy complications in this cohort and suggest that these complications may not be due to IPI itself, but rather, may be due to maternal confounding factors.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Appendix B6-Study Three

Association between interpregnancy interval and hypertensive disorders of pregnancy: Effect modification by maternal age

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Compared to 18 months, the risks of hypertensive disorders of pregnancy at longer intervals (>36 months) were higher for mothers older than 35 years but not for mothers younger than 20 years.

1

Synopsis

Study Question

Does the association between interpregnancy interval (IPI) and hypertensive disorders of pregnancy vary by maternal age at the time of birth prior to the IPI?

What is already known

Short and long IPIs have been associated with an increased risk of hypertensive disorders of pregnancy. However, it is unclear whether these increased risks differ by maternal age at the time of birth prior to the IPI.

What this study adds

Using a population-based cohort of mothers, this study examined the non-linear relationship between IPI and hypertensive disorders of pregnancy for each maternal age group, modelled flexibly using restricted cubic splines, to clearly observe any dose-response relationships and better clarify optimal IPI. In this study, the risks of hypertensive pregnancy disorders following long IPIs (>36 months) were greater for mothers older than 35. There was insufficient evidence suggesting that IPI increases the risk of hypertensive disorders of pregnancy for mothers younger than 20 years. Our findings indicate that optimal IPI may vary by maternal age, and a more tailored approach to family planning counselling may be required to improve health.

ABSTRACT

Background: Short and long interpregnancy intervals (IPIs) are associated with increased risk of hypertensive disorders of pregnancy, yet whether this association is modified by maternal age remains unclear.

Objectives: To examine if the association between IPI and hypertensive disorders of pregnancy varies by maternal age at birth prior to IPI.

Methods: We conducted a population-based cohort study of all mothers who had their first two (n=169,896) consecutive births in Western Australia (WA) between 1980 and 2015. We estimated the risk of preeclampsia and gestational hypertension for 6 to 60 months of IPI according to maternal age at birth prior to IPI [<20 years, 20-24, 25-29, 30-34 and ≥35 years]. We modelled IPI using restricted cubic splines and reported adjusted relative risk (RRs) with 95% CI at 6, 12, 24, 36, 48 and 60 months, with 18 months as reference.

Results: The risk of preeclampsia was increased at longer IPIs (60 months) compared to 18 months for mothers 35 years or older (RR 2.19, 95% confidence interval (CI) 1.14, 4.18) and to a lesser extent for mothers 30-34 years old (RR 1.43, 95% CI 1.10, 1.84). The risk of preeclampsia was significantly lower at 12 months of IPI for mothers younger than 20 years as compared to 18 months (RR 0.74, 95% CI 0.57, 0.96), but not for mothers 35 years or older (RR 0.62, 95% CI 0.36, 1.07). There was insufficient evidence for increased risk of hypertensive disorders of pregnancy at shorter IPIs of <18 months for mothers of all ages.

Conclusions: Our findings challenge the "one size fits all" recommendation for an optimal IPI, and a more tailored approach to family planning counselling may be required to improve health.

Keywords: interpregnancy interval; hypertensive disorders of pregnancy; birth intervals; birth spacing; maternal age; pregnancy complications

Abstract word count: 280; **Main text word count: 3,573**

BACKGROUND

Research suggests that short and long IPIs are associated with an increased risk of perinatal[1-3] and maternal complications, including preeclampsia and gestational hypertension.[1, 4, 5] To reduce these risks, the World Health Organization (WHO) and various clinical guidelines recommend that women wait at least 18-24 months before conceiving another child. [6-8]

Maternal age at entry into parenthood, and consequential maternal age for subsequent pregnancies, has been steadily increasing in Australia[9, 10] and other high-income countries. [11, 12] Benefits that accompany advanced maternal age include improved household income, education and health care access.[10, 12] However, there is also evidence that older maternal age is associated with increased risks of hypertensive disorders of pregnancy,[1, 13, 14, 15] infertility, miscarriage, and other abnormalities, including chromosomal anomalies.[16-18] Mothers of advanced age (35 years or older) who are planning to become pregnant again may plan to have their subsequent child sooner than later to minimise the effects of diminishing fecundability.[19-21] Consequently, these closely spaced pregnancies are prone to a 'maternal depletion syndrome', which is attributable to insufficient time to recover from the physiological stress of the previous pregnancy.[22, 23] Mothers who become pregnant after long IPIs are also prone to 'physiologic regression', which is hypothesised to result in a return to a primigravida state at elevated risk of adverse pregnancy outcomes, particularly hypertensive disorders such as preeclampsia.[24] Long interval among mothers with advanced maternal age could also contribute to declining fertility. Therefore, it is plausible that both short and long IPIs have a compounding effect on older mothers who are at an already elevated risk of adverse pregnancy outcomes. Although some studies have examined the

association between IPI and birth outcomes by maternal age,[14, 20, 25, 26] there are limited studies examining these in the context of hypertensive disorders of pregnancy.[14, 20] Therefore, given the increasing number of women delaying initiation of childbearing in many high-income countries, evaluating the relationship between IPI and hypertensive disorders of pregnancy by maternal age is warranted. This study aimed to examine whether the association between IPI and hypertensive disorders of pregnancy varies by maternal age at the time of birth prior to the IPI.

METHODS

Study design

We conducted a population-based, record linked cohort study drawn from all mothers who had their first two consecutive births between 1980 and 2015 in Western Australia (WA).

Data sources and study population

Maternal, infant and birth information were derived from the Midwives Notification System, a quality-controlled database[27] and includes all registered births ≥20 weeks of gestation in WA.[28] We sourced hospitalisation records from WA Hospital Morbidity System.[29] Detailed description of data sources has been published elsewhere.[4, 30] Birth records were probabilistically linked based on maternal information to identify all births to individual women during the study period. Validation studies have established the accuracy and completeness of these databases.[27, 29, 31]

From the original total of 487,297 mothers, we sequentially excluded mothers who delivered only once during the study period; mothers whose children's birth years were inconsistent with the parity, and mothers who had missing or implausible gestational age (<20 or ≥45 weeks), missing information for pregnancy outcomes, maternal age, and

socioeconomic status (SES). These exclusions resulted in 256,047 eligible mothers who contributed 510,296 births. We further excluded subsequent pregnancies if a mother experienced the following events at the pre-interval pregnancy (first birth) : multiple gestation, intervening pregnancy loss, child death or hypertensive complications because the association between IPI and outcomes in subsequent pregnancies may be different following previous complications or perinatal loss.[32-36] Finally, we included 169,896 mothers with their first two (parity 0, 1) consecutive births in the main analytic cohort.

Exposure

Interpregnancy interval (IPI) was calculated prior to exclusions as the time between the delivery date of the first eligible birth during the study period and the estimated conception date of the subsequent pregnancy (date of birth minus gestational age at birth). Gestational age at birth was estimated using ultrasound examination; if not, information from the last menstrual period was used.

Outcomes

The outcomes of interest were ascertained from midwives notifications and hospital separation data in the state, with the International Classification of Diseases (ICD-9 through to ICD-10-AM [Australian Modification]) diagnostic codes consistent with preeclampsia (ICD-9/ICD-9-CM: 642.4, 642.5, 642.7, ICD-10-AM: O14, O11) and gestational hypertension without proteinuria (ICD-9-AM: 642.3, ICD-10-AM: O13).

Covariates

We controlled for potential confounding factors measured at the birth prior to the interval and included birth year, marital status, race/ethnicity, SES, known chronic diabetes, gestational diabetes, known obesity history and partner change status at recent birth. We

included an indicator for partner change between births in all our models to account for the potential influence of change in partner in the associations between IPI and adverse outcomes.[35, 37, 38] Race/ethnicity was classified as Caucasian versus non-Caucasian. Marital status was categorised as married, never married, widowed/divorced/ separated and unknown. SES was derived by the Australian Bureau of Statistics Index of Relative Socio-economic Disadvantage at a geographic area for the maternal residence at the time of birth,[39] and categorised into quintiles. We obtained the family linkage information from the WA Family Connections database.

Statistical analysis

We examined the association between IPI and each outcome in the overall population and stratified by maternal age categories at birth prior to the IPI (<20 years, 20 to 24 years, 25 to 29 years, 30 to 34 years and 35 years or more) using Generalised linear models (GLM) fitted using a Poisson distribution and a log link function. We first tabulated the prevalence of each outcome by IPI (categorised to <6, 6-11, 12-17, 18-23, 24-59, and ≥60 months). We modelled IPI as a continuous variable using restricted cubic splines to allow curvilinear relationship with each outcome. After considering the number of knots based on the model that minimised Akaike's Information Criterion (AIC) as recommended by Harell,[40] we chose to place the knots at the pre specified IPI lengths (i.e. 6, 12, 18, 24, 36 and 48 months) that match the thresholds commonly used to categorise IPI.[1, 32, 41] We predicted the absolute risk in 1-month increments of IPI from 6 to 60 months using post estimation calculations.[42]
For each outcome, the unadjusted model included the IPI spline terms only, and the adjusted model included the IPI spline and all the covariates listed above. All the unstratified models were also adjusted for maternal age at birth before the IPI. The predicted risks were estimated at the population average values of all covariates so that these results represent

the average risk of each outcome at the population level. Predicted risks based on risk profile (low-risk vs high-risk) are also presented (see supplementary material, eTable 7, eFigure 2, eFigure 3 for details). We then plotted the estimated absolute risks with 95% CIs at 1-month increments of IPI for the whole cohort and stratified by maternal age group to illustrate the shapes of the risk curves. For tabulated results, we presented relative risks (RRs) with 95% CIs at 6, 12, 24, 36, 48 and 60 months of IPI, with 18 months as the reference interval and performed a test for interaction for the outcome at each IPI interval.[43, 44] For evaluating effect modification with relevance to public health or clinical practice,[32, 45, 46] we calculated measure of effect modification in the additive scale (RERI: relative excess risk due to interaction) with 95% CIs for the association between IPIs (categorised to <6, 6-11, 12-17, 18-23 (reference), 24-59, and ≥60 months) and preeclampsia (yes, no) by maternal age (categorised to <20, 20 to 24, 25 to 29, 30 to 34 and ≥35 years) (eTable 2). Findings were considered significant at P <0.05 (2-sided). The term *optimal IPI* is defined in this study as the IPI at which the lowest risk was observed among women with a second pregnancy lasting >20 weeks.[47]

Missing data

Because the proportion of missing data was small (range 0.04% for maternal age to 1.2% for SES), we carried out a complete case analysis. The majority of missing data was due to lack of availability of information (e.g. SES) prior to the year 1997, and we evaluated this bias using sensitivity analyses.

Sensitivity analysis

To ascertain our results' sensitivity to higher-order parity, we conducted a separate analysis by including mothers with at least two consecutive births during the study period (eTable 3).

To assess whether our results were sensitive to the time period of the cohort,[28] we restricted our analyses to births later in the study period, after which we adjusted for additional potential confounders including paternal age, fertility treatment (assuming that these pregnancies were more likely to be intended) and smoking (eTable 4).[28] To examine the potential role of unmeasured confounding, we computed E-values, which represent the minimum strength of association on the risk ratio scale, that any unmeasured confounder would need to have with both IPI and each outcome to fully explain away the observed association, conditional on the measured covariates (eTable 5).[48] We further estimated the association between IPI and preeclampsia at first pregnancy as "negative control" (eTable 6). In the absence of unmeasured confounding, IPI should not be associated with the outcome (i.e., preeclampsia) at the preceding pregnancy.[20, 49] We finally examined the sensitivity of our results for choice of knot placement (eFigure 4). All analyses were performed using STATA version 16.1 (Stata Corporation, College Station, Texas, USA).

Ethics approval

This research was approved by the Human Research Ethics Committee (2016/51) from the Department of Health, WA.

RESULTS

Cohort description

Approximately 5% of births occurred after an IPI of <6 months, 17% after 18-23 months and 6% after 60 or more months. One-third of pregnancies were to mothers of age 25-29 years at birth prior to IPI (60,948 [36%], 27,699 (16%) were to mothers younger than 20 years, and 7,920 (5%) were to mothers older than 35 years at birth prior to IPI (Table 1).

The majority of women were Caucasian. At study entry (before the IPI), a greater proportion of mothers were socio-economically disadvantaged and married. There were also more smokers and socio-economically disadvantaged mothers in the short (<6 months) and long IPI (≥24 months) categories than other IPI categories. Non-Caucasian mothers were highly represented in the less than 6-month IPI category. We observed a decreasing trend in the intervals shorter than two years during the study period and a relatively increasing trend for intervals longer than two years (Table 1).

IPI distribution

The distribution of IPI differed by maternal age at birth prior to IPI. For mothers younger than 20 years at birth prior to IPI compared to mothers older than 35 years, short IPIs (<6 months) were more common (8% vs 5%). However, for mothers older than 35 years, long IPI (≥60 months) were less common as compared to mothers younger than 20 years at birth prior to IPI (1% vs 12%) (eFigure 1).

Prevalence of preeclampsia by IPI category

The overall prevalence of preeclampsia in this cohort was 2.2% (Table 2). Associations between IPI and preeclampsia followed a J-shaped curve (Figure 1). The lowest prevalence was observed at around 6-11 months of IPI. Prevalence was relatively higher at IPIs <6 months and ≥ 24 months across all age categories (Table 2).

IPI and risk of preeclampsia by maternal age

We found evidence of multiplicative interaction with maternal age at IPIs longer than 36 months but not at shorter intervals (<24 months) (Table 3). Associations between IPIs at 6 months with preeclampsia were not meaningfully different across maternal age groups (p of multiplicative interaction = 0.09). Similarly, there was a modest effect modification on the

additive scale of the association between long IPIs (≥60 months) and preeclampsia for mothers older than 35 years of age at birth prior to IPI with RERI 1.11 (95% CI -1.80, 4.02). In comparison to mothers younger than 20 years at index birth, we observed a negative additive interaction for all other maternal age categories at 12-17 months of IPI with RERI of -0.03 (95% CI -0.39, 0.32) for mothers 20-24 years and RERI -0.42 (95% CI -1.06, 0.22) for mothers ≥35 years (eTable 2).

Compared to 18 months, shorter IPIs (6 and 12 months) were not associated with increased risk of hypertensive disorders of pregnancy for mothers of all ages. However, we observed a significantly lower risk of preeclampsia at 12 months of IPI with RR of 0.74 (95% CI 0.57, 0.96) for mothers younger than 20 years and RR 0.82 (95% CI 0.69, 0.98) for mothers 25-29 years at birth prior to the IPI (Table 3).

Risks of hypertensive disorders of pregnancy after intervals longer than 36 months were consistently higher than those for intervals of 18 months, with some evidence of stronger associations for older mothers (30-34 years, ≥35 years) than mothers in other younger age groups (Table 3, eTable 7). We observed an increased risk of preeclampsia at 60 months compared to 18 months of IPI with RR 2.19 (95% CI 1.14, 4.18) for mothers ≥35 years, but not for mothers younger than 20 years RR 1.23 (95% CI 0.97, 1.55). Similarly, the increased risk of gestational hypertension at 60 months of IPI was more pronounced for mothers aged 30-34 years with RR 1.87 (95% CI 1.31, 2.68) than mothers aged <20 years RR 1.41 (95% CI 0.96, 2.09) (eTable 7)

Absolute risk of preeclampsia by IPI and maternal age

For mothers of all ages, predicted risks of preeclampsia were minimal at intervals of approximately 6 months. However, these estimated risks varied by maternal age prior to the IPI (Figure 1, eTable 1). For mothers older than 35 years, estimated risks were lowest for intervals between 12 and 18 months. For mothers at other ages, the intervals at which risks were lowest were less clear but appeared to be between 6 and 18 months. At all ages, estimated risks (probabilities) of hypertensive disorders of pregnancy for mothers with intervals longer than 24 months were generally as high as or higher than those for mothers with intervals at 6 months (Figure 1, eTable 1).

We estimated the absolute risk of preeclampsia according to IPI for all mothers and stratified by maternal age groups, calculated at population average values of all covariates (Figure 1 & eTable 1). These graphs can inform optimal IPI by comparing estimated risks of each outcome based on the mothers' age category. For example, the predicted risk of preeclampsia for mothers older than 35 years at prior birth and IPI of 6 months was 1.2%. These estimated risks can be compared with risks at 36 months of IPI, with predicted risks of 1.8%. A similar comparison can be made between any levels of IPI and mothers age category for each outcome examined (eTable 1, eTable 7).

Sensitivity analyses

There was a negligible difference in the effect estimates when we repeat our analyses on a cohort of mothers with at least two consecutive births (i.e., higher-order parity) (eTable 3). Sensitivity analyses examining the possible role of unmeasured or residual confounding revealed that confounding was unlikely to explain the observed associations (eTable 4, eTable 5). The E-values indicate that substantial confounding (E-value 3.8) would need to

negate the observed association of long IPIs and preeclampsia for mothers with advanced maternal age (≥35 years) (eTable 5). Additionally, the negative control analyses indicated that both short and long IPIs (interval between firstborn and second-born births were not statistically associated with an increased risk of preeclampsia at first pregnancy (outcome prior to IPI) (eTable 6), which supports our main findings. Models using quantile-based knot placement and the other predefined knots resulted in negligible difference. Consequently, we selected a model that minimised Akaike's Information Criterion (AIC) recommended by Harrell[40](eFigure 4).

COMMENT

Principal findings

In this large population-based cohort, we observed an increased risk of hypertensive disorders of pregnancy following long IPIs (>36 months), and these findings persisted after stratification by age. Compared to younger mothers at birth prior to the IPI, mothers older than 35 years had an elevated risk of hypertensive disorders of pregnancy at longer IPIs. We observed a protective association between IPIs at 12 months and preeclampsia for mothers younger than 30 years. However, associations between IPIs <12 months and preeclampsia were not meaningfully different across maternal age groups. Generally, the predicted absolute risks of hypertensive disorders of pregnancy following short or long IPIs were higher at advanced maternal age than at younger ages.

Strengths of the study

This large cohort was sourced from highly reliable population-based perinatal information spanning more than three decades. Examining the non-linear relationships between IPI and hypertensive disorders of pregnancy for each maternal age group before the interval and

presenting absolute risks, which previously have not been well studied, allowed us to observe the presence of a "dose-response" relationship and better clarification of optimal IPI. Our findings provide more clinically applicable information on the influence of different IPI values on the risk of various pregnancy complications according to maternal age.

Limitations of the data

Like other observational studies, our study was limited by the potential for unmeasured or residual confounding factors that we were unable to adjust due to lack of data availability, such as pregnancy intention and fertility issues. As we report estimated risks at each IPI based on comparing outcomes of different mothers (between-mother), our results might be biased due to unmeasured confounding. Recently, studies that have employed within-mother matched designs have reported substantially attenuated associations between IPI and hypertensive disorders of pregnancy, owing to unmeasured or residual confounding.[4, 50, 51] As we discussed in our previous paper,[4] although a within-mother matched study achieves greater internal validity, external generalisability might be limited, owing to restriction to mothers with at least three pregnancies and analyses restricted to informative strata.[32] Additionally, lack of data on pregnancy loss before 20 weeks can introduce exposure misclassification and selection bias.[32] Although our sensitivity analyses indicated that observed associations were not fully explained by unmeasured confounding (eTable 5-6), we cannot rule out the role of unmeasured confounding, and the association between long IPIs and hypertensive disorders of pregnancy should be interpreted cautiously. As ultrasound confirmed gestations were less common during the earlier periods of our birth cohort, our study may have been subject to a certain degree of misclassification. However, results from our sensitivity analysis restricted to the cohort of births later in the study

period did not meaningfully change our estimates. Due to a small number of events at extremes of IPI for mother at an advanced age, the predicted risks presented should also be interpreted cautiously. Future research would benefit from exploring the role of pregnancy complications at the mother's first birth as well as alternative analyses approach that takes time (gestational length of the second pregnancy) into account. Additionally, even though information on time to pregnancy was not available, variability in time to pregnancy would be smaller for our cohort, which consisted of mothers who had two or more births. Finally, it should be noted that this study used data that were probabilistically linked.

Interpretation

Our findings suggest that associations between short IPIs and hypertensive disorders of pregnancy were inconsistent across age groups. However, we found evidence of effect modification (on both multiplicative and additive) of the association between longer intervals (≥60 months) and preeclampsia by maternal age. Mothers older than 35 years had minimal risk at the interval between 12 and 18 months for preeclampsia and between 6 and 12 months of IPI for gestational hypertension. This finding was consistent with a recent finding from the US, which indicated a relatively shorter IPI of 12-24 months found to have a lesser risk of outcomes for women of all ages.[20] However, the observed pattern was slightly different for mothers younger than 20 years, for whom risks were lower at 6 months and started to rise up to around 12 months. The reason to explain this observation remains unclear.

Our results are supported by previous studies indicating long IPIs are associated with an elevated risk of preeclampsia and gestational hypertension.[1, 4] Unlike other studies,[1, 51] our

finding of protective associations with shorter IPIs for hypertensive disorders is consistent with a recent US study,[14] and findings of our previous work.[4]

In accordance with recent recommendations,[20, 32] we adjusted for maternal age prior to the IPI. This adjustment is most relevant for the observed associations at lower IPIs. However, the observed increased risk of hypertensive disorders of pregnancy for mothers with long IPIs can be confounded by maternal age at the time of the complication (after the IPI). Our findings indicate that as IPI exceeds one to two years, the influence of age begins to dominate the risks on the outcome. The consistent associations observed at longer IPIs (>36 months) can be explained by confounding by maternal age at the outcome of pregnancy.

Conclusions

Given the increasing trend in delayed childbearing, it is important to evaluate whether the risks of hypertensive disorders of pregnancy associated with IPI may be influenced by maternal age. For our cohort, associations between hypertensive disorders of pregnancy and IPI varied by maternal age, with optimal IPI in the range of 6-18 months, which is shorter than those recommended. The current World Health Organization (WHO) and various regional clinical guidelines suggest at least 18-24 months before conceiving another child irrespective of other maternal characteristics. Our study challenges this “one size fits all” recommendation for an optimal IPI and suggests the optimal IPI may vary depending on maternal age and risk profile of the cohort. Hence, a more tailored approach to family planning counselling may be required to improve health.

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Conflict of Interest

The authors have no potential conflicts of interest to disclose.

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Table 1. Characteristics of the study population at birth prior to IPI (first birth) for mothers with their first two consecutive births by IPI category during the study period (N=169,896 pregnancies) – Western Australia, 1980-2015

	Interpregnancy interval (months): Number (%) of pregnancies						
Characteristics [a]	All N=169,896	<6 (n=9,095)	6-11 (n=32,074)	12-17 (n=40,266)	18-23 (n=29,608)	24-59 (n=49,098)	>=60 (n=9,755)
Maternal age, y							
<20	27,699 (16.3)	2,449 (26.9)	4,846 (15.1)	4,855 (12.1)	3,630 (12.3)	8,418 (17.1)	3,501 (35.9)
20-24	38,472 (22.6)	2,443 (26.9)	7,310 (22.8)	8,577 (21.3)	6,327 (21.4)	11,002 (22.4)	2,813 (28.8)
25-29	60,948 (35.9)	2,440 (26.8)	11,269 (35.1)	15,340 (38.1)	11,494 (38.8)	17,892 (36.4)	2,513 (25.8)
30-34	34,857 (20.5)	1,319 (14.5)	6,731 (21.0)	9,291 (23.1)	6,745 (22.8)	9,920 (20.2)	851 (8.7)
≥35	7,920 (4.7)	444 (4.9)	1,918 (6.0)	2,203 (5.5)	1,412 (4.8)	1,866 (3.8)	77 (0.8)
Time period							
1980-1984	22,388 (13.2)	1,233 (13.6)	4,260 (13.3)	5,596 (13.9)	3,964 (13.4)	6,065 (12.4)	1,270 (13.0)
1985-1989	24,069 (14.2)	1,272 (14.0)	4,699 (14.7)	5,702 (14.2)	4,015 (13.6)	6,850 (14.0)	1,531 (15.7)
1990-1994	24,579 (14.5)	1,258 (13.8)	4,286 (13.4)	5,452 (13.5)	4,143 (14.0)	7,598 (15.5)	1,842 (18.9)
1995-1999	24,134 (14.2)	1,190 (13.1)	4,220 (13.2)	5,187 (12.9)	4,059 (13.7)	7,391 (15.1)	2,087 (21.4)
2000-2004	24,082 (14.2)	1,135 (12.5)	4,236 (13.2)	5,286 (13.1)	4,081 (13.8)	7,566 (15.4)	1,778 (18.2)
2005-2009	29,423 (17.3)	1,532 (16.8)	5,400 (16.8)	6,917 (17.2)	5,259 (17.8)	9,076 (18.5)	1,239 (12.7)
2010-2015	21,221 (12.5)	1,475 (16.2)	4,973 (15.5)	6,126 (15.2)	4,087 (13.8)	4,552 (9.3)	8 (0.1)
SES in quintiles							
<20th percentile (Most disadvantaged)	31,142 (18.3)	2,286 (25.1)	5,764 (18.0)	6,566 (16.3)	4,802 (16.2)	9,145 (18.6)	2,579 (26.4)
20-39th percentile	34,279 (20.2)	2,055 (22.6)	6,549 (20.4)	7,792 (19.4)	5,591 (18.9)	10,042 (20.5)	2,250 (23.1)
40-59th percentile	35,768 (21.1)	1,878 (20.6)	6,664 (20.8)	8,406 (20.9)	6,390 (21.6)	10,483 (21.4)	1,947 (20.0)
60-79th percentile	34,907 (20.5)	1,581 (17.4)	6,654 (20.7)	8,625 (21.4)	6,417 (21.7)	9,998 (20.4)	1,632 (16.7)
>=80th percentile (Least disadvantaged)	33,800 (19.9)	1,295 (14.2)	6,443 (20.1)	8,877 (22.0)	6,408 (21.6)	9,430 (19.2)	1,347 (13.8)
Marital status							
Married	22,202 (13.1)	1,634 (18.0)	3,394 (10.6)	3,663 (9.1)	2,878 (9.7)	7,281 (14.8)	3,352 (34.4)
Not married/in union	147,694 (86.9)	28,680 (82.0)	28,860 (89.4)	36,603 (90.9)	26,730 (90.3)	41,817 (85.2)	6,403 (65.6)
Race/Ethnicity							
Caucasian	146,548 (86.3)	7,184 (79.0)	27,843 (86.8)	35,649 (88.5)	26,179 (88.4)	41,562 (84.7)	8,131 (83.4)
Non-Caucasian	23,348 (13.7)	1,911 (21.0)	4,231 (13.2)	4,617 (11.5)	3,429 (11.6)	7,536 (15.3)	1,624 (16.6)
Partner							
Same	152,687 (89.9)	8,364 (92.0)	30,654 (95.6)	38,579 (95.8)	28,159 (95.1)	42,839 (87.3)	4,092 (41.9)
Different	8,148 (4.8)	78 (0.9)	235 (0.7)	385 (1.0)	440 (1.5)	3,191 (6.5)	3,819 (39.1)
Unknown	9,061 (5.3)	653 (7.2)	1,185 (3.7)	1,302 (3.2)	1,009 (3.4)	3,068 (6.2)	1,844 (18.9)
Smoking [b]	10,935 (12.8)	1,071 (22.7)	1,954 (11.8)	2,001 (9.7)	1,520 (9.9)	3,437 (14.0)	952 (23.7)

[a]Characteristics were assessed at the index (first) birth. [b]Smoking information missing for 84,166 (49.5%)

Table 2. Counts and percentages of preeclampsia by IPI categories, stratified by maternal age at birth prior to IPI during the study period (N=169,896 pregnancies) – Western Australia, 1980-2015

		Interpregnancy interval (months): Number (%) of pregnancies						
		Total	<6	6-11	12-17	18-23	24-59	>=60
	Preeclampsia	N=169,896	N=9,095	N=32,074	N=40,266	N=29,608	N=49,098	N=9,755
All mothers	Yes	3,769 (2.2)	209 (2.3)	579 (1.8)	767 (1.9)	608 (2.1)	1,203 (2.5)	403 (4.1)
	No	166,127 (97.8)	8,886 (97.7)	31,495 (98.2)	39,499 (98.1)	29,000 (97.9)	47,895 (97.5)	9,352 (95.9)
<20	Yes	702 (2.5)	55 (2.2)	90 (1.9)	117 (2.4)	87 (2.4)	214 (2.5)	139 (4.0)
	No	26,997 (97.5)	2,394 (97.8)	4,756 (98.1)	4,738 (97.6)	3,543 (97.6)	8,204 (97.5)	3,362 (96.0)
20-24	Yes	1,023 (2.7)	54 (2.2)	170 (2.3)	218 (2.5)	165 (2.6)	299 (2.7)	117 (4.2)
	No	37,449 (97.3)	2,389 (97.8)	7,140 (97.7)	8,359 (97.5)	6,162 (97.4)	10,703 (97.3)	2,696 (95.8)
25-29	Yes	1,297 (2.1)	63 (2.6)	203 (1.8)	261 (1.7)	216 (1.9)	444 (2.5)	110 (4.4)
	No	59,651 (97.9)	2,377 (97.4)	11,066 (98.2)	15,079 (98.3)	11,278 (98.1)	17,448 (97.5)	2,403 (95.6)
30-34	Yes	596 (1.7)	25 (1.9)	90 (1.3)	144 (1.5)	112 (1.7)	192 (1.9)	33 (3.9)
	No	34,261 (98.3)	1,294 (98.1)	6,641 (98.7)	9,147 (98.5)	6,633 (98.3)	9,728 (98.1)	818 (96.1)
≥35	Yes	151 (1.9)	12 (2.7)	26 (1.4)	27 (1.2)	28 (2.0)	54 (2.9)	Suppressed[a]
	No	7,769 (98.1)	432 (97.3)	1,892 (98.6)	2,176 (98.8)	1,384 (98.0)	1,812 (97.1)	73 (94.8)

[a]The No. (%) was suppressed if cell counts were less than 5, in accordance with data privacy regulations for WA Data Linkage Branch.

Table 3. Adjusted relative risk (95% confidence interval) of preeclampsia at 6, 12, 24, 36, 48, and 60 months of interpregnancy interval comparing with 18 month interval to mothers with their first two consecutive births during the study period (n=169,896 pregnancies)

Maternal age (years)	Interpregnancy interval (months)						
	6	12	18	24	36	48	60
Preeclampsia							
All mothers	1.00 (0.90-1.11)	0.85 (0.76-0.94)	1.00 (Reference)	1.07 (0.97-1.18)	1.24 (1.12-1.37)	1.35 (1.22-1.50)	1.43 (1.29-1.59)
<20	0.81 (0.63-1.05)	0.74 (0.57-0.96)	1.00 (Reference)	0.92 (0.71-1.18)	1.05 (0.82-1.35)	1.17 (0.92-1.49)	1.23 (0.97-1.55)
20-24	1.00 (0.81-1.23)	1.03 (0.84-1.26)	1.00 (Reference)	1.14 (0.94-1.37)	1.18 (0.97-1.45)	1.24 (1.01-1.53)	1.34 (1.09-1.64)
25-29	1.11 (0.92-1.34)	0.82 (0.69-0.98)	1.00 (Reference)	1.08 (0.92-1.27)	1.35 (1.14-1.60)	1.49 (1.25-1.77)	1.56 (1.31-1.86)
30-34	0.93 (0.71-1.23)	0.79 (0.61-1.01)	1.00 (Reference)	1.06 (0.85-1.32)	1.06 (0.83-1.36)	1.21 (0.94-1.56)	1.43 (1.10-1.84)
≥35	1.19 (0.71-1.98)	0.62 (0.36-1.07)	1.00 (Reference)	1.27 (0.80-2.00)	1.78 (1.06-2.96)	2.04 (1.23-3.38)	2.19 (1.14-4.18)
P value for interaction[¥]	0.09	0.71		0.11	0.03	0.02	0.05

[¥] P value for interaction comparing <20 vs ≥35 maternal age groups.

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 6, 12, 18, 24, 36, 48 months

Models were adjusted for SES, birth year, race/ethnicity, marital status, history of obesity, known chronic diabetes, gestational diabetes at birth prior to the IPI and partner change with 18-month of IPI as reference. Analyses for the overall population were additionally adjusted for maternal age

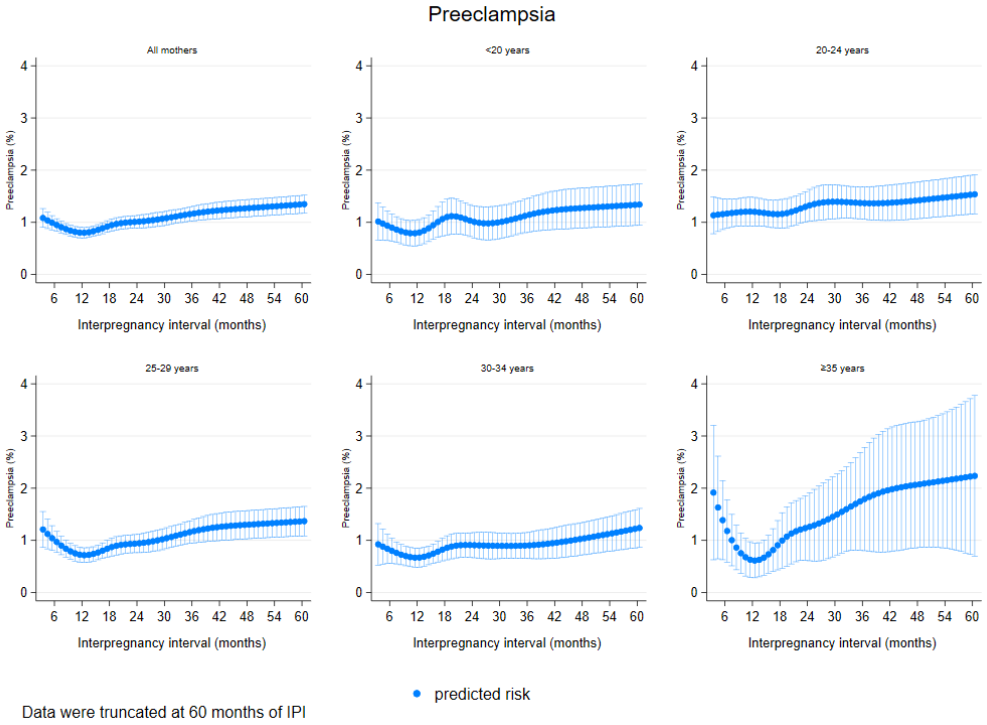


Figure 1. Predicted absolute risk of preeclampsia with 95% confidence intervals according to IPI stratified by maternal age at birth prior to the IPI

Risks are reported at population average values of all covariates: Non-Caucasian, married, no-partner change, average SES, no pre-existing conditions (diabetes, gestational diabetes, history of obesity). For the overall population in the cohort, we used average maternal age (25- 29 years) at birth prior to IPI. We choose year 2010 as birth year covariate value, which is the most recent year in the cohort

eTable 1. Predicted absolute risk of preeclampsia according to Interpregnancy interval categories, stratified by maternal age at birth prior to IPI for mothers with their first two consecutive births during the study period (n=169,896 pregnancies)

Maternal age (years)	Interpregnancy interval (months)						
	6	**12**	**18**	**24**	**36**	**48**	**60**
All mothers	0.95 (0.83, 1.07)	0.80 (0.70, 0.90)	0.95 (0.83, 1.07)	1.01 (0.89, 1.14)	1.17 (1.03, 1.31)	1.27 (1.11, 1.44)	1.35 (1.18, 1.52)
<20	0.90 (0.64, 1.16)	0.81 (0.56, 1.05)	1.10 (0.76, 1.45)	1.01 (0.70, 1.32)	1.15 (0.82, 1.47)	1.28 (0.89, 1.66)	1.34 (0.94, 1.74)
20-24	1.17 (0.89, 1.45)	1.20 (0.93, 1.48)	1.16 (0.88, 1.44)	1.33 (1.02, 1.63)	1.37 (1.06, 1.68)	1.43 (1.07, 1.78)	1.54 (1.16, 1.91)
25-29	0.97 (0.77, 1.17)	0.72 (0.58, 0.86)	0.87 (0.70, 1.04)	0.94 (0.76, 1.13)	1.18 (0.95, 1.41)	1.30 (1.03, 1.57)	1.37 (1.09, 1.65)
30-34	0.80 (0.56, 1.04)	0.67 (0.49, 0.86)	0.86 (0.63, 1.09)	0.91 (0.67, 1.15)	0.91 (0.65, 1.16)	1.04 (0.73, 1.36)	1.24 (0.86, 1.61)
≥35	1.18 (0.58, 1.78)	0.61 (0.28, 0.95)	1.00 (0.46, 1.53)	1.26 (0.61, 1.91)	1.79 (0.80, 2.78)	2.08 (0.87, 3.29)	2.24 (0.70, 3.78)

Data are predicted absolute risk (in %) (95% confidence interval); Predicted risks are reported at population average values of all covariates :Non-Caucasian, married, no-partner change, average SES, no pre-existing conditions (diabetes, gestational diabetes, history of obesity). For the overall population in the cohort, we used average maternal age (25- 29 years) at birth prior to IPI. We choose year 2010 as birth year covariate value, which is the most recent year in the cohort. Analyses restricted to those women without gestational hypertension and preeclampsia at first pregnancy.

eTable 2. Adjusted relative risks and relative excess risk due to interaction (RERI) with their 95% confidence interval of Interpregnancy interval and maternal age exposures on preeclampsia for mothers with their first two consecutive births during the study period (n=169,896 pregnancies)

Maternal age (years)	Interpregnancy interval (months)									
	18-23	<6	18-23	6-11	18-23	12-17	18-23	24-59	18-23	≥60
Preeclampsia										
<20	(Reference)	0.96 (0.68, 1.35)	(Reference)	0.76 (0.57, 1.03)	(Reference)	0.98 (0.74, 1.30)	(Reference)	1.08 (0.84, 1.40)	(Reference)	1.57 (1.17, 2.09)
20-24	1.02 (0.77, 1.36)	0.93 (0.65, 1.33)	1.01 (0.76, 1.33)	0.91 (0.69, 1.20)	1.07 (0.81, 1.42)	1.02 (0.78, 1.34)	1.05 (0.80, 1.38)	1.14 (0.89, 1.47)	1.08 (0.81, 1.42)	1.69 (1.26, 2.26)
RERI (95% CI)	-0.05 (-0.50, 0.41)		0.13 (-0.18, 0.46)		-0.03 (-0.39, 0.32)		0.01 (-0.32, 0.34)		0.05 (-0.44, 0.54)	
<20	(Reference)	0.97 (0.69, 1.36)	(Reference)	0.76 (0.56, 1.03)	(Reference)	0.99 (0.74, 1.31)	(Reference)	1.07 (0.83, 1.39)	(Reference)	1.43 (1.07, 1.91)
25-29	0.90 (0.67, 1.21)	1.26 (0.88, 1.80)	0.89 (0.67, 1.19)	0.86 (0.64, 1.14)	0.93 (0.70, 1.23)	0.84 (0.63, 1.10)	0.95 (0.72, 1.24)	1.25 (0.97, 1.61)	1.00 (0.75, 1.33)	2.05 (1.51, 2.77)
RERI (95% CI)	0.38 (-0.06, 0.84)		0.20 (-0.08, 0.49)		-0.08 (-0.41, 0.26)		0.23 (-0.06, 0.51)		0.62 (0.11, 1.12)	
<20	(Reference)	0.97 (0.69, 1.36)	(Reference)	0.75 (0.55, 1.01)	(Reference)	0.98 (0.74, 1.30)	(Reference)	1.06 (0.82, 1.36)	(Reference)	1.52 (1.13, 2.05)
30-34	0.94 (0.66, 1.32)	1.01 (0.62, 1.65)	0.91 (0.65, 1.27)	0.72 (0.51, 1.01)	1.07 (0.77, 1.47)	1.00 (0.73, 1.37)	1.06 (0.78, 1.43)	1.14 (0.86, 1.51)	1.03 (0.74, 1.43)	1.88 (1.22, 2.90)
RERI (95% CI)	0.11 (-0.44, 0.65)		0.06 (-0.28, 0.41)		-0.04 (-0.43, 0.34)		0.02 (-0.34, 0.39)		0.34 (-0.44, 1.11)	
<20	(Reference)	0.96 (0.68, 1.35)	(Reference)	0.76 (0.57, 1.03)	(Reference)	0.98 (0.74, 1.30)	(Reference)	1.06 (0.83, 1.36)	(Reference)	1.47 (1.09, 1.98)
≥35	1.06 (0.64, 1.75)	1.47 (0.76, 2.84)	1.04 (0.64, 1.70)	0.71 (0.43, 1.18)	1.18 (0.73, 1.92)	0.74 (0.45, 1.21)	1.27 (0.80, 2.01)	1.73 (1.18, 2.52)	1.23 (0.76, 1.99)	2.81 (0.98, 8.04)
RERI (95% CI)	0.45 (-0.53, 1.43)		-0.09 (-0.65, 0.47)		-0.42 (-1.06, 0.22)		0.41 (-0.30, 1.11)		1.11 (-1.80, 4.02)	

RERI: relative excess risk of preeclampsia due to interaction between interpregnancy interval and maternal age prior to IPI. RERI values different than zero indicate the presence of effect measure modification in the absolute scale. Models were adjusted for SES, birth year, race/ethnicity, marital status, history of obesity, known chronic diabetes, gestational diabetes at birth prior to the IPI and partner change with 18-23 months of IPI and <20 years of maternal age as reference.

eTable 3. Adjusted relative risk (95% confidence interval) of preeclampsia at 6, 12, 24, 36, 48, and 60 months of interpregnancy interval comparing with 18 month interval for mothers with at least two consecutive births during the study period (n=284,690 pregnancies): sensitivity analyses for higher-order parity

Maternal age (years)	Interpregnancy interval (months)						
	6	**12**	**18**	**24**	**36**	**48**	**60**
All mothers	0.86 (0.77-0.97)	0.83 (0.74-0.93)	1.00 (Reference)	1.10 (1.00-1.21)	1.49 (1.35-1.65)	1.73 (1.57-1.90)	1.88 (1.71-2.07)
<20	0.56 (0.37-0.86)	0.64 (0.42-0.98)	1.00 (Reference)	0.81 (0.54-1.19)	0.93 (0.64-1.35)	1.13 (0.79-1.60)	1.27 (0.90-1.79)
20-24	0.71 (0.54-0.93)	1.04 (0.82-1.33)	1.00 (Reference)	1.06 (0.86-1.31)	1.41 (1.13-1.75)	1.61 (1.30-2.00)	1.77 (1.44-2.19)
25-29	0.87 (0.72-1.06)	0.74 (0.62-0.89)	1.00 (Reference)	1.14 (0.98-1.32)	1.60 (1.37-1.87)	1.85 (1.59-2.15)	1.97 (1.70-2.29)
30-34	0.91 (0.72-1.16)	0.79 (0.63-1.00)	1.00 (Reference)	1.07 (0.89-1.30)	1.45 (1.19-1.77)	1.72 (1.42-2.09)	1.93 (1.59-2.34)
≥35	1.42 (0.96-2.09)	0.99 (0.66-1.47)	1.00 (Reference)	1.31 (0.93-1.85)	1.96 (1.33-2.88)	2.00 (1.37-2.94)	1.89 (1.25-2.84)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 6, 12, 18, 24, 36, 48 months of IPI. Models were adjusted for SES, nulliparity, birth year, ethnicity, marital status, history of obesity, known chronic diabetes, gestational diabetes at birth prior to the IPI and partner change with 18 months of IPI as reference. Analyses for the overall population were additionally adjusted for maternal age. Robust variance estimation was used to account for non-independence of more than two IPIs for the same women.

eTable 4. Adjusted relative risk (95% confidence interval) of preeclampsia at 6, 12, 24, 36, 48, and 60 months of interpregnancy interval comparing with 18 month interval for mothers with at least two consecutive births (n=131,839 pregnancies): sensitivity analyses restricted to cohort of births later in the study period (1997 onwards)

Maternal age (years)	Interpregnancy interval (months)						
	6	12	18	24	36	48	60
All mothers	0.88 (0.70-1.11)	0.88 (0.71-1.09)	1.00 (Reference)	1.15 (0.96-1.39)	1.54 (1.27-1.88)	1.75 (1.44-2.13)	1.89 (1.57-2.29)
<20	0.65 (0.35-1.20)	0.83 (0.44-1.56)	1.00 (Reference)	0.83 (0.47-1.44)	1.16 (0.66-2.02)	1.42 (0.84-2.39)	1.54 (0.92-2.57)
20-24	0.84 (0.48-1.47)	1.15 (0.68-1.94)	1.00 (Reference)	1.20 (0.76-1.91)	1.47 (0.91-2.38)	1.64 (1.02-2.63)	1.85 (1.16-2.94)
25-29	0.72 (0.47-1.09)	0.82 (0.58-1.17)	1.00 (Reference)	1.00 (0.73-1.37)	1.39 (1.01-1.92)	1.65 (1.21-2.25)	1.79 (1.31-2.45)
30-34	1.31 (0.83-2.06)	0.93 (0.60-1.43)	1.00 (Reference)	1.55 (1.09-2.19)	2.11 (1.43-3.11)	2.21 (1.49-3.27)	2.30 (1.53-3.44)
≥35	1.01 (0.51-2.02)	0.59 (0.29-1.22)	1.00 (Reference)	1.12 (0.59-2.12)	1.44 (0.71-2.93)	2.12 (1.07-4.19)	3.10 (1.50-6.43)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 6, 12, 18, 24, 36, 48 months of IPI. Models were adjusted for SES, birth year, ethnicity, marital status, smoking, fertility treatment at birth prior to the IPI and partner change with 18 months of IPI as reference. Analyses for the overall population were additionally adjusted for maternal age. Robust variance estimation was used to account for non-independence of more than two IPIs for the same women

Methods for sensitivity analyses

E-values

Supplemental table 5 provides e-values to quantify the minimum strength of association that confounding variables would need to have in order to fully explain the observed association in risk ratio scale.

Some of the weaker associations, such as lower risk in preeclampsia (e.g., 12 months) could be explained by confounding with E-values that ranged from 1.6 to 2.6. However, for the modest associations observed such as increased risk of hypertensive complications among older mothers at 60 months of IPI, unmeasured confounding would need to be more strongly associated with both long IPI and risk of each outcome (E values ranged from 2.5 to 3.8) (eTable 5)

Negative control analyses

We further estimated the association of hypertensive disorders of pregnancy at first pregnancy with post-birth IPI. In the absence of confounding factors, these complications should not be associated with the IPI that follows this birth. An observed association between hypertensive disorders of pregnancy at first birth and the post-birth IPI indicates the presence of factors influencing both the complications and the IPI, leading to biased estimates. Whereas, if there is no association between post-birth IPI and the prior birth outcome and a modest/strong association observed between prior IPI and consecutive outcome, it supports independent association.

In summary, the sensitivity analyses results presented in eTable 5 and eTable 6 suggest that unmeasured confounding is unlikely to fully explain the associations between IPIs and hypertensive disorders of pregnancy.

eTable 5. E-values to quantify the minimum strength of association that unmeasured confounders would need to have with both IPI and preeclampsia, conditional on the measured covariates, to fully explain the observed association between IPI and hypertensive disorders of pregnancy[¥].

	E-values for RR, (E-value for CI)						
	6	**12**	**18**	**24**	**36**	**48**	**60**
All mothers	1.00 (1.00)	1.63 (1.32)	Reference	1.34 (1.00)	1.78 (1.49)	2.04 (1.74)	2.21 (1.90)
<20	1.77 (1.00)	2.04 (1.25)	Reference	1.39 (1.00)	1.28 (1.00)	1.62 (1.00)	1.76 (1.00)
20-24	1.00 (1.00)	1.21 (1.00)	Reference	1.54 (1.00)	1.64 (1.00)	1.79 (1.11)	2.02 (1.40)
25-29	1.46 (1.00)	1.74 (1.16)	Reference	1.37 (1.00)	2.04 (1.54)	2.34 (1.81)	2.49 (1.95)
30-34	1.36 (1.00)	1.85 (1.00)	Reference	1.31 (1.00)	1.31 (1.00)	1.71 (1.00)	2.21 (1.43)
≥35	1.66 (1.00)	2.61 (1.00)	Reference	1.86 (1.00)	2.96 (1.32)	3.5 (1.76)	3.80 (1.54)

[¥] E-values are presented for relative risks (RRs) reported in Table 3

eTable 6. Adjusted relative risk (95% confidence interval) of preeclampsia at 6, 12, 24, 36, 48, and 60 months of interpregnancy interval comparing with 18 month interval to mothers with their first two consecutive births during the study period (n=169,896 pregnancies): A negative control analyses ¥

Maternal age (years)	Interpregnancy interval (months)						
	6	12	18	24	36	48	60
All mothers	0.95 (0.92-1.00)	0.98 (0.94-1.02)	1.00 (Reference)	1.04 (1.00-1.07)	0.97 (0.93-1.01)	0.95 (0.91-0.99)	0.95 (0.91-0.99)
<20	0.91 (0.82-1.01)	0.98 (0.88-1.09)	1.00 (Reference)	1.04 (0.94-1.14)	0.97 (0.88-1.08)	0.96 (0.86-1.06)	0.97 (0.87-1.07)
20-24	0.96 (0.89-1.05)	1.00 (0.93-1.09)	1.00 (Reference)	1.06 (0.99-1.14)	0.95 (0.88-1.03)	0.92 (0.85-0.99)	0.92 (0.85-1.00)
25-29	0.94 (0.87-1.01)	0.93 (0.87-0.99)	1.00 (Reference)	1.01 (0.95-1.07)	0.95 (0.89-1.02)	0.93 (0.87-0.99)	0.92 (0.86-0.98)
30-34	1.05 (0.95-1.15)	1.04 (0.95-1.13)	1.00 (Reference)	1.03 (0.95-1.12)	1.02 (0.93-1.11)	0.99 (0.90-1.08)	0.96 (0.88-1.06)
≥35	0.89 (0.74-1.06)	0.99 (0.84-1.18)	1.00 (Reference)	1.09 (0.93-1.27)	1.03 (0.86-1.24)	1.06 (0.88-1.28)	1.14 (0.95-1.37)

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 6, 12, 18, 24, 36, 48 months
Models were adjusted for SES, birth year, race/ethnicity, marital status, history of obesity, known chronic diabetes, gestational diabetes at birth prior to the IPI and partner change with 18 months of IPI as reference. Analyses for the overall population were additionally adjusted for maternal age.
¥ Predicting preeclampsia of first born (parity 0 births) using post-birth IPI (interval between first born and second born births) as negative control exposure.

eTable 7. Adjusted relative risk (95% confidence interval) of gestational hypertension at 6, 12, 24, 36, 48, and 60 months of interpregnancy interval comparing with 18 month interval to mothers with their first two consecutive births during the study period (n=169,604 pregnancies)

Maternal age (years)	Interpregnancy interval (months)						
	6	**12**	**18**	**24**	**36**	**48**	**60**
Gestational hypertension							
All mothers	0.86 (0.72-1.02)	0.80 (0.68-0.94)	1.00 (Reference)	1.08 (0.94-1.25)	1.48 (1.27-1.72)	1.75 (1.50-2.04)	1.94 (1.66-2.26)
<20	0.53 (0.33-0.85)	0.58 (0.36-0.93)	1.00 (Reference)	1.03 (0.69-1.53)	1.10 (0.72-1.67)	1.25 (0.84-1.86)	1.41 (0.96-2.09)
20-24	0.84 (0.58-1.21)	0.91 (0.64-1.29)	1.00 (Reference)	0.94 (0.68-1.30)	1.27 (0.90-1.78)	1.56 (1.12-2.19)	1.79 (1.28-2.49)
25-29	1.07 (0.80-1.44)	0.82 (0.62-1.08)	1.00 (Reference)	1.19 (0.94-1.52)	1.87 (1.46-2.41)	2.19 (1.70-2.81)	2.32 (1.80-2.99)
30-34	0.87 (0.59-1.28)	0.85 (0.62-1.18)	1.00 (Reference)	1.18 (0.88-1.60)	1.38 (0.99-1.92)	1.60 (1.14-2.24)	1.87 (1.31-2.68)
≥35	0.75 (0.41-1.37)	0.61 (0.33-1.11)	1.00 (Reference)	0.67 (0.36-1.24)	1.12 (0.58-2.15)	1.68 (0.90-3.13)	2.04 (0.97-4.27)

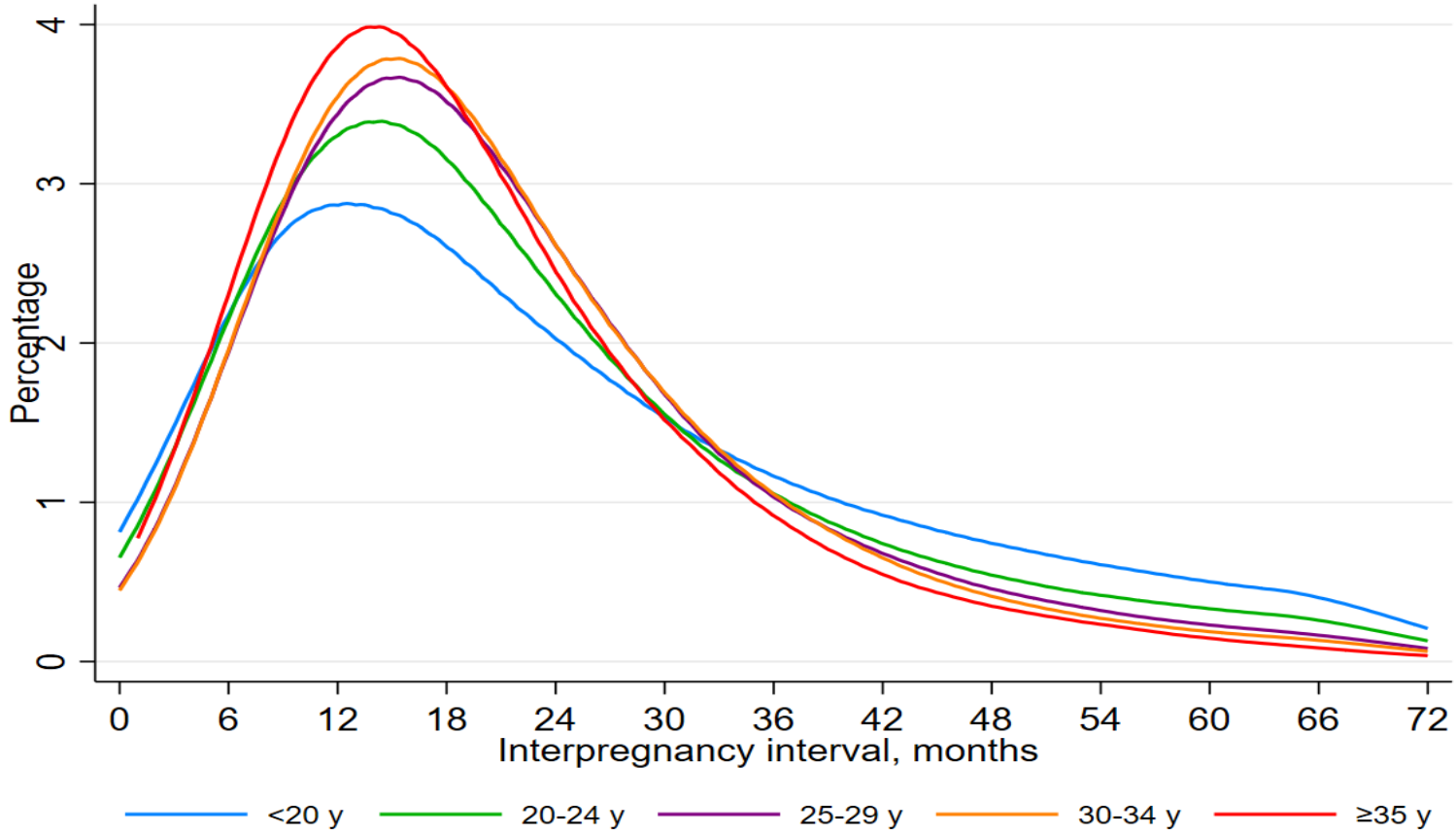
Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 6, 12, 18, 24, 36, 48 months
Models were adjusted for SES, birth year, race/ethnicity, marital status, history of obesity, known chronic diabetes, gestational diabetes at birth prior to the IPI and partner change with 18-month of IPI as reference. Analyses for the overall population were additionally adjusted for maternal age

eTable 8. Predicted absolute risk of hypertensive disorders of pregnancy according to Interpregnancy interval categories, stratified by maternal age at birth prior to IPI for mothers with their first two consecutive births during the study period (n= 169,896)

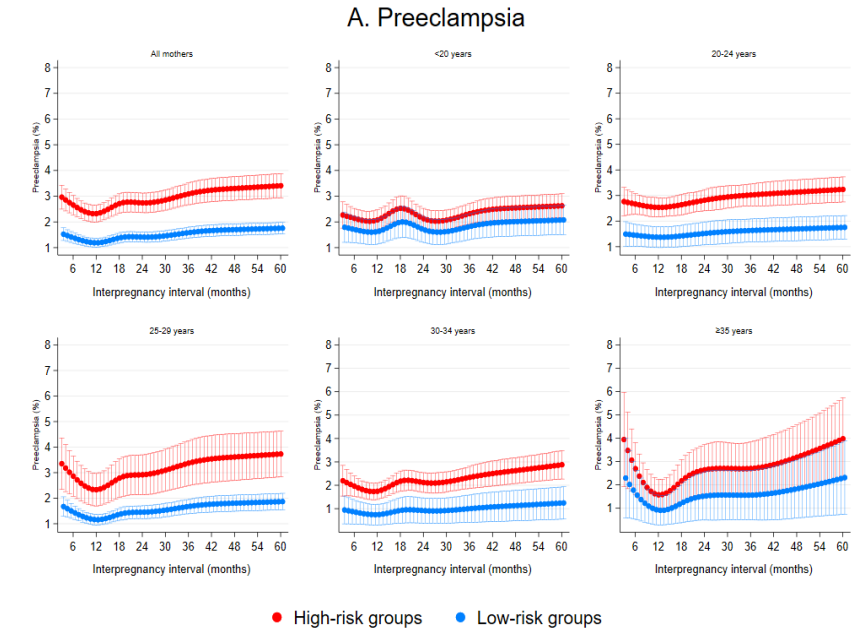
Maternal age (years)	Interpregnancy interval (months)						
	6	**12**	**18**	**24**	**36**	**48**	**60**
Preeclampsia							
Low risk group							
All mothers	1.36 (1.17, 1.56)	1.19 (1.02, 1.36)	1.39 (1.20, 1.59)	1.41 (1.21, 1.61)	1.59 (1.38, 1.80)	1.70 (1.48, 1.93)	1.76 (1.53, 1.98)
<20	1.69 (1.19, 2.19)	1.64 (1.15, 2.13)	2.00 (1.39, 2.60)	1.68 (1.18, 2.18)	1.84 (1.33, 2.34)	2.01 (1.45, 2.57)	2.08 (1.51, 2.65)
20-24	1.44 (1.01, 1.87)	1.37 (0.96, 1.78)	1.43 (1.00, 1.85)	1.52 (1.07, 1.97)	1.64 (1.19, 2.09)	1.70 (1.24, 2.16)	1.76 (1.29, 2.22)
25-29	1.43 (1.16, 1.69)	1.16 (0.95, 1.37)	1.39 (1.14, 1.63)	1.45 (1.20, 1.71)	1.68 (1.40, 1.97)	1.81 (1.49, 2.12)	1.87 (1.54, 2.19)
30-34	0.84 (0.34, 1.35)	0.75 (0.31, 1.19)	0.94 (0.38, 1.49)	0.91 (0.38, 1.45)	1.01 (0.42, 1.60)	1.14 (0.48, 1.79)	1.24 (0.55, 1.94)
≥35	1.56 (0.50, 2.62)	0.91 (0.28, 1.53)	1.25 (0.39, 2.12)	1.53 (0.49, 2.57)	1.56 (0.50, 2.63)	1.85 (0.59, 3.11)	2.31 (0.73, 3.89)
High risk group							
All mothers	2.65 (2.28, 3.03)	2.32 (2.00, 2.65)	2.71 (2.33, 3.09)	2.74 (2.36, 3.12)	3.09 (2.67, 3.51)	3.30 (2.84, 3.76)	3.41 (2.93, 3.88)
<20	2.14 (1.75, 2.53)	2.08 (1.68, 2.47)	2.53 (2.04, 3.01)	2.13 (1.73, 2.53)	2.32 (1.92, 2.72)	2.55 (2.09, 3.01)	2.63 (2.16, 3.09)
20-24	2.67 (2.26, 3.07)	2.54 (2.16, 2.91)	2.64 (2.24, 3.05)	2.82 (2.40, 3.23)	3.02 (2.59, 3.45)	3.13 (2.65, 3.61)	3.24 (2.75, 3.73)
25-29	2.86 (2.08, 3.65)	2.33 (1.70, 2.97)	2.79 (2.03, 3.54)	2.92 (2.14, 3.70)	3.37 (2.49, 4.25)	3.61 (2.70, 4.53)	3.73 (2.84, 4.63)
30-34	1.96 (1.53, 2.39)	1.75 (1.39, 2.10)	2.18 (1.74, 2.61)	2.12 (1.70, 2.54)	2.34 (1.87, 2.81)	2.63 (2.08, 3.18)	2.88 (2.27, 3.49)
≥35	2.70 (1.58, 3.81)	1.58 (0.91, 2.24)	2.17 (1.26, 3.08)	2.65 (1.57, 3.73)	2.70 (1.56, 3.84)	3.19 (1.80, 4.57)	3.98 (2.21, 5.74)
Gestational hypertension *							
Low risk group							

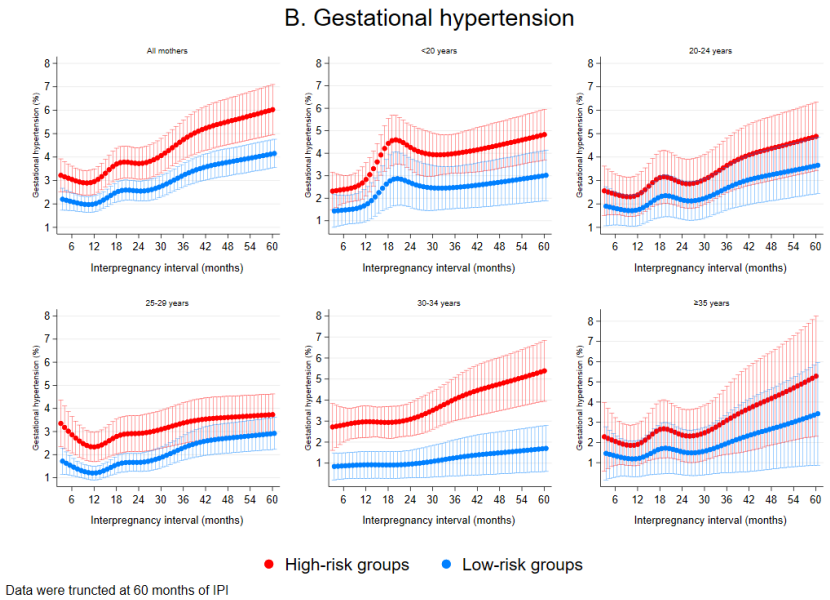
Maternal age (years)	Interpregnancy interval (months)						
	6	**12**	**18**	**24**	**36**	**48**	**60**
All mothers	2.08 (1.66, 2.39)	2.02 (1.84, 2.56)	2.53 (2.14, 2.95)	2.55 (2.25, 3.08)	3.26 (2.97, 3.98)	3.79 (3.43, 4.57)	4.15 (3.76, 4.96)
<20	1.48 (0.84, 2.12)	1.76 (0.99, 2.52)	2.77 (1.60, 3.94)	2.65 (1.57, 3.74)	2.49 (1.54, 3.43)	2.72 (1.69, 3.76)	3.02 (1.89, 4.14)
20-24	2.19 (1.43, 2.96)	2.17 (1.40, 2.93)	2.84 (1.85, 3.83)	2.62 (1.71, 3.54)	3.31 (2.28, 4.33)	3.97 (2.77, 5.17)	4.44 (3.16, 5.73)
25-29	1.46 (1.08, 1.84)	1.21 (0.91, 1.51)	1.59 (1.20, 1.98)	1.67 (1.27, 2.07)	2.33 (1.79, 2.86)	2.72 (2.08, 3.37)	2.92 (2.23, 3.61)
30-34	0.87 (0.26, 1.49)	0.92 (0.28, 1.56)	0.91 (0.28, 1.55)	0.96 (0.30, 1.63)	1.27 (0.39, 2.14)	1.50 (0.49, 2.51)	1.70 (0.60, 2.80)
≥35	1.31 (0.31, 2.32)	1.22 (0.31, 2.13)	1.70 (0.44, 2.96)	1.52 (0.39, 2.65)	1.99 (0.51, 3.47)	2.70 (0.69, 4.71)	3.42 (0.88, 5.97)
High risk group							
All mothers	3.04 (2.47, 3.61)	2.96 (2.41, 3.50)	3.70 (3.03, 4.38)	3.73 (3.05, 4.40)	4.75 (3.91, 5.58)	5.51 (4.52, 6.50)	6.02 (4.95, 7.10)
<20	2.39 (1.77, 3.01)	2.84 (2.09, 3.58)	4.44 (3.34, 5.54)	4.25 (3.25, 5.25)	3.99 (3.12, 4.87)	4.37 (3.33, 5.41)	4.83 (3.70, 5.96)
20-24	2.41 (1.54, 3.28)	2.39 (1.51, 3.26)	3.13 (2.00, 4.26)	2.89 (1.85, 3.93)	3.64 (2.47, 4.81)	4.37 (3.00, 5.73)	4.88 (3.42, 6.35)
25-29	2.86 (2.08, 3.65)	2.33 (1.70, 2.97)	2.79 (2.03, 3.54)	2.92 (2.14, 3.70)	3.37 (2.49, 4.25)	3.61 (2.70, 4.53)	3.73 (2.84, 4.63)
30-34	2.82 (2.00, 3.64)	2.97 (2.21, 3.73)	2.94 (2.18, 3.70)	3.09 (2.30, 3.89)	4.05 (3.02, 5.08)	4.77 (3.50, 6.04)	5.39 (3.94, 6.84)
≥35	2.05 (0.87, 3.23)	1.91 (0.87, 2.95)	2.65 (1.23, 4.07)	2.37 (1.07, 3.66)	3.10 (1.41, 4.78)	4.18 (1.87, 6.50)	5.28 (2.30, 8.26)

* (n=169,604); Data are predicted absolute risk (in %) (95% confidence interval); Predicted risks for low-risk group are reported at representative values of covariates :Non, Caucasian, married, least-disadvantaged SES and ,birth year in 2010 at birth prior to IPI; Predicted risks for high-risk group are reported at representative values of covariates: Caucasian, non, married, highly disadvantaged SES and birth year in 2010 at birth prior to IPI ; Change of partner between two consecutive births was included in the high- risk group for both outcomes; for the overall population in the cohort, we used average maternal age (25, 29 years) at birth prior to IPI for low-risk group while advanced maternal age (≥35 years)at birth prior to IPI for the high- risk group. we choose year 2010 as birth year covariate value during estimation for both low and high-risk groups, which is the most recent year in the cohort. Analyses restricted to those women without preexisting diabetes, hypertension, gestational diabetes, obesity or preeclampsia at first pregnancy.

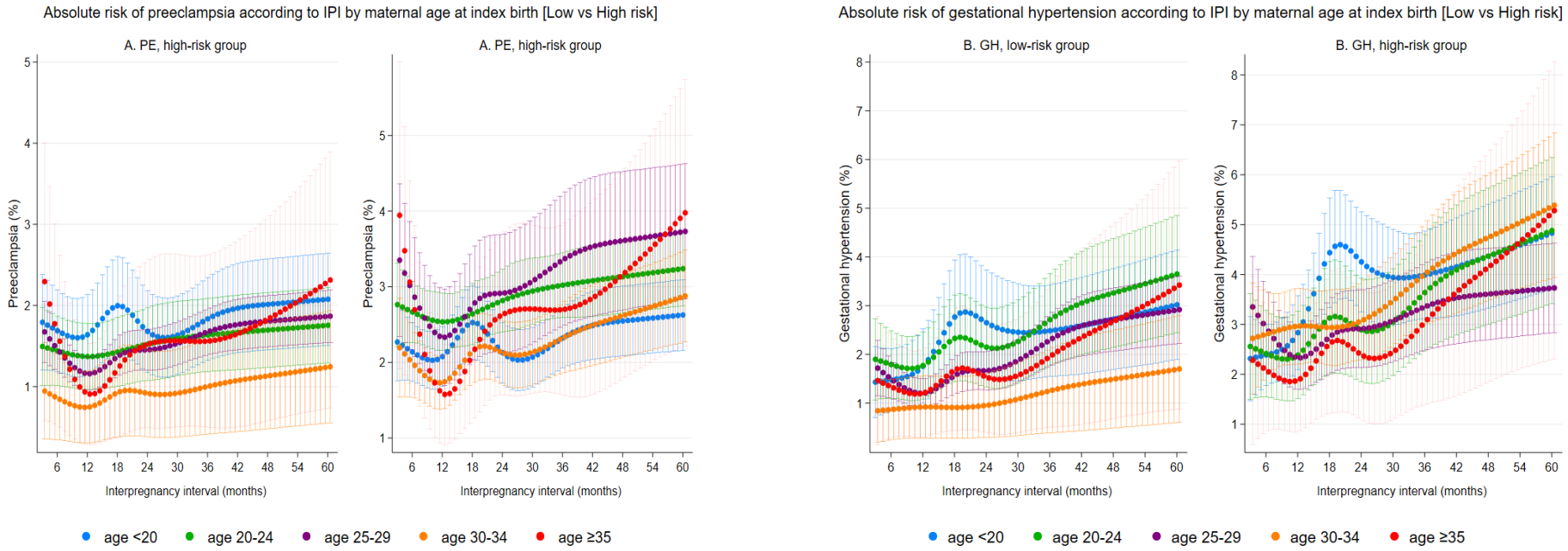


eFigure 1. Distribution of interpregnancy interval by maternal age at birth prior to IPI for mothers during the study period

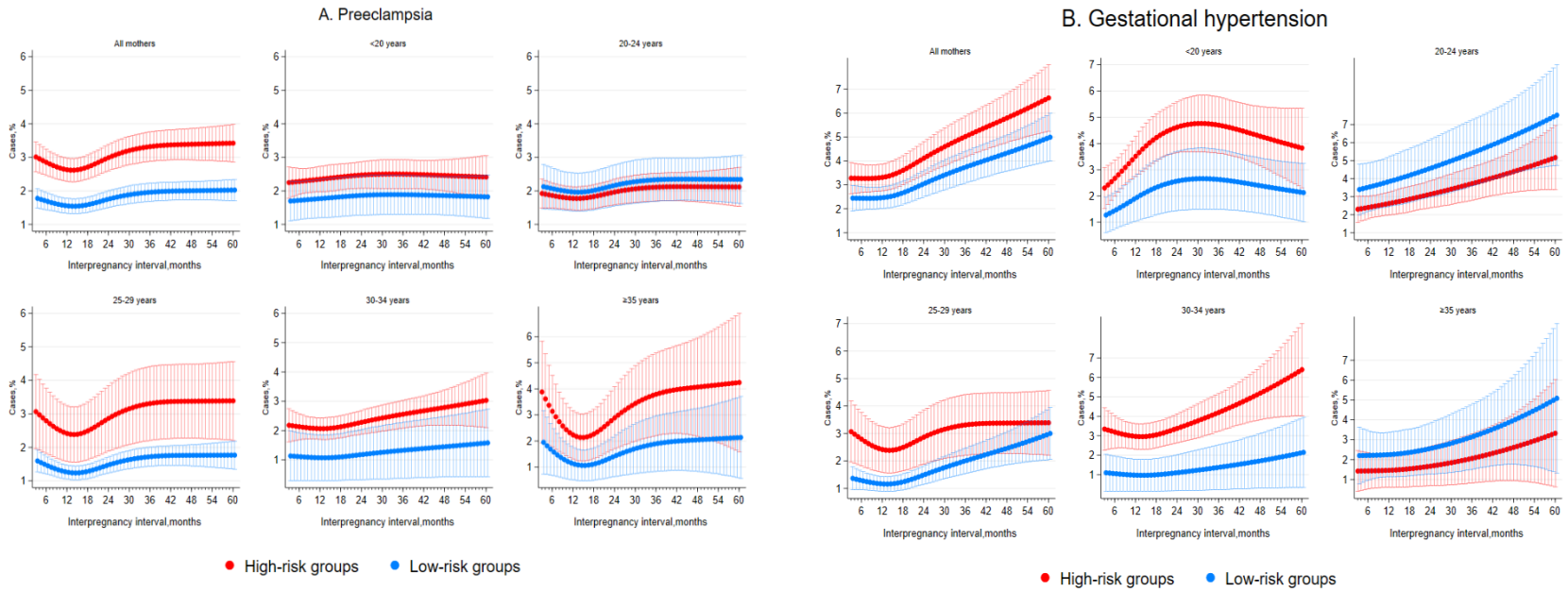




eFigure 2. Predicted absolute risk of preeclampsia (A) and gestational hypertension (B) with 95 % confidence intervals according to IPI stratified by maternal age at birth prior to the IPI IPI truncated at 60 months



eFigure 3. Predicted risk of preeclampsia and gestational hypertension at each IPI length from 6 to 60 months according to maternal age at birth prior to IPI and risk profile



eFigure 4. Predicted absolute risk of hypertensive disorders of pregnancy with 95 % confidence intervals according to IPI stratified by maternal age at birth prior to the IPI; sensitivity for knot placement

Outcomes include preeclampsia (A), gestational hypertension (B). Predicted risks for low, risk group are reported at representative values of covariates: non, Caucasian, married, least, disadvantaged SES, and birth year in 2010 at birth prior to the IPI; Predicted risks for high, risk group are reported at representative values of covariates: Caucasian, non, married, highly disadvantaged SES and birth year in 2010 at birth prior to the IPI; for the unstratified predictions (all mothers in the cohort) we used average maternal age (25, 29 years) at birth prior to the IPI for low, risk group while advanced maternal age (≥35 years) at birth prior to the IPI for the high, risk group. Change of partner between two consecutive births was included in the high, risk group for both outcomes. IPI was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles of IPI (at 5, 14, 23 and 47 months).

Appendix B7-Media release

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

NEWS AND EVENTS (HTTPS://NEWS.CURTIN.EDU.AU)

Conceiving within six months of birth does not increase risk of diabetes

MEDIA RELEASE
Wednesday 4 December 2019

Curtin University researchers have found insufficient evidence to suggest that falling pregnant again within six months of giving birth is associated with an increased risk of gestational diabetes.

The research, published in *Annals of Epidemiology,* examined data from more than 100,000 mothers in Western Australia who gave birth between January 1, 1980 and December 31, 2015 to see if they were at an increased risk of gestational diabetes if they fell pregnant again within six months.

Senior author Dr Gavin Pereira, from the School of Public Health at Curtin University, said questions had been raised regarding the length of time between giving birth and conceiving another child and the impact this may have on birth outcomes.

"The World Health Organisation (WHO) and the American College of Obstetricians and

Gynaecologists recommend that women should wait at least two years after a live birth before commencing the next pregnancy," Dr Pereira said.

"Previous research suggests that both short and long intervals between giving birth and conceiving increased the risk of gestational diabetes, which is one of the major pregnancy complications that affects six to 13 per cent of pregnancies worldwide. However, the results of these studies may have been impacted by small sample sizes, the reliance on hospital-based groups, and a lack of control for important confounders such as socio-economic status.

"In our study, we found that women who conceived a child within six months or at 24 months or longer after giving birth were at no greater risk of gestational diabetes, compared to women who fell pregnant between 18 and 23 months."

Lead author Mr Amanuel Tesfay Gebremedhin, also from Curtin's School of Public Health, said the findings had significant implications for families who were looking to conceive children in a shorter time period.

"Our findings do not support previous claims that women who conceive within six months of giving birth were at an increased risk of gestational diabetes," Mr Gebremedhin said.

"Future research would benefit from exploring whether the effects of short pregnancy spacing on future gestational diabetes are worse for women whose previous pregnancies were complicated."

The research was co-authored by researchers from the Norwegian Institute of Public Health (Norway), World Health Organisation (Switzerland), THL Finnish Institute for Health and Welfare (Finland), the Karolinska Institute (Sweden), QIMR Berghofer Institute (Queensland, Australia), and Texas A&M University (USA).

The research paper titled, '*Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study*, can be found online here (https://www.sciencedirect.com/science/article/pii/S1047279719302984?via%3Dihub).

Related Stories

Appendix C-Data variable lists

Appendix C1-MNS data variable list

Government of **Western Australia**
Department of **Health**

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Midwives Notifications Data

Please click here to select group

Every request for Midwives Notifications will be evaluated separately on its merit by the Data Custodian. To prevent potential delays it is strongly recommended applicants spend time discussing their needs with the MNS Data Custodian before submitting an application for data. See the contacts at: http://www.health.wa.gov.au/healthdata/contact/index.cfm

Further information can be found in the Guidelines for Completion of the Notification of Case Attended Health Act (Notification by Midwife) Regulations form No.2 at: http://www.health.wa.gov.au/publications/documents/Guidelines_for_Completion_of_NOCA.pdf

Request variables below by checking boxes

Request	Variable	Description
Mother's Details		
☐	Subset date of birth	MMYYYY
☐	Subset date of birth	YYYY
☐	Maternal age	
☐	State	
☐	Height	Mothers height in centimeters
☐	Weight	Available January 2012 onwards
☐	Marital status	
☐	Ethnic origin	
☐	Interpreter service required?	Available July 2016 onwards
☐	Language requiring interpreter	Available July 2016 onwards
Pregnancy Details		
☐	Previous pregnancies	
☐	Previous pregnancy outcomes	Each baby recorded separately in multiple births. Therefore this ≠ total previous pregnancies
☐	Previous pregnancy parity	Number of previous pregnancies that resulted in a birth of one or more infants at ≥20 weeks gestation Available July 2014 onwards
☐	Previous caesarean section	
☐	Number previous caesarean sections	Available January 2012 onwards
☐	Caesarean last delivery	
☐	Previous multiple birth	
☐	Expected due date	MMYYYY DDMMYYYY
☐	Date of last menstrual period	MMYYYY DDMMYYYY
☐	Is the LMP date certain?	
☐	Basis of expected due date	
☐	Gestational Age at First AN Care Visit	Available January 2010 onwards. Use with caution as antenatal care models in WA make accurate determination difficult.
☐	Number of AN Visits	Available from July 2012 onwards. Use with caution as

Last updated 30 November 2018 Module 3 Variable Lists 1

		antenatal care models in WA make accurate determination difficult.
☐	Smoking during pregnancy	Yes/no
☐	Number tobacco cigarettes smoked each day in the first 20 weeks of pregnancy	Available January 2010 onwards
☐	Number tobacco cigarettes smoked each day after the first 20 weeks of pregnancy	Available January 2010 onwards
☐	Frequency drinking alcohol	Available July 2017 onwards
☐	Number of standard alcohol drinks in a typical day	Available July 2017 onwards
☐	Screening for depression/anxiety conducted	Yes/No Available July 2017 onwards
☐	Additional followup indicated for perinatal mental health risk factors	Yes/No Available July 2017 onwards
☐	Complications of pregnancy	Tick box value supplied, not ICD code Note reportable values changed from July 2017
☐	Medical conditions	Tick box value supplied, not ICD code Note reportable values changed from July 2017
☐	Procedures/treatments	
☐	Influenza vaccination in pregnancy	Available July 2016 onwards
☐	Pertussis vaccination in pregnancy	Available July 2016 onwards
☐	Intended place of birth at onset of labour	
☐	Actual place of birth	e.g. hospital, homebirth, birth centre, other
Labour Details		
☐	Onset of labour	Method (e.g. induced)
☐	Reason for induction of labour	Available July 2016 onwards
☐	Augmentation	Method
☐	Induction	Method
☐	Analgesia (during labour)	
Delivery Details		
☐	Duration of labour 1st stage	
☐	Duration of labour 2nd stage	
☐	Anaesthesia (during delivery)	
☐	Complications of labour and delivery	Tick box value supplied, not ICD code
☐	Postnatal blood loss first 24 hours	Measured and/or estimated in mL. Available July 2014 onwards Can be provided as PPH>=500mLs to continue value reported before July 2014 or can be reported as PPH>=1000mLs etc.
☐	Perineal status	
☐	Reason for caesarean section	If requesting this field, also request 'Method of Birth' above. Available July 2014 onwards
Baby Details		
☐	Indigenous Status	Available January 2012 onwards
☐	Born before arrival	Yes/No
☐	Subset date of birth	MMYYYY
☐	Subset date of birth	YYYY
☐	Plurality	Number of babies in this birth
☐	Baby number	Order in delivery
☐	Water birth	Yes/No Available July 2015 onwards
☐	Presentation	Fetal presenting part at birth (e.g. breech)
☐	Method of birth	
☐	Accoucheur(s)	Profession of the person who delivered the baby
☐	Sex	

☐	Status of baby at birth	Alive or stillborn antenatal, stillborn intrapartum or stillborn unspecified. Breakdown for time of stillborn available from July 2011.
☐	Infant weight	
☐	Length of baby (cms)	
☐	Head circumference	
☐	Time to establish unassisted regular breathing	Recorded in minutes
☐	Resuscitation	Method used
☐	Apgar score at 1 minute	
☐	Apgar score at 5 minutes	
☐	Estimated gestation	Clinical estimation in weeks, available 1986 onwards
☐	Baby separation date	MMYYYY only
☐	Baby length of stay in days	Derived variable
☐	Mode of separation	E.g. transferred, went home
☐	Number of Days in Special Care Nursery at birth site	

Other variables		
The following variables are derived using the algorithms developed by Dr Eve Blair et al. References: (1) Blair, E.M., Liu, Y., de Klerk, N.H. & Lawrence, D.M. (2005) Optimal fetal growth for the Caucasian singleton and assessment of appropriateness of fetal growth: an analysis of a total population perinatal database. *BMC Pediatrics*, 5, 13-25. (2) Blair, E.M., Liu, Y. & Cosgrove, P. (2004) Choosing the best estimate of gestational age from routinely collected population-based perinatal data. *Paediatric and Perinatal Epidemiology*, 18, 270-276.		
☐	POBW	Percentage Optimal Birth Weight
☐	POHC	Percentage Optimal Head Circumference
☐	POL	Percentage Optimal Length
☐	Estimate of Gestational Age	Algorithmic Estimate of Gestational Age Based on LMP, EDD, baby date of birth
☐	Reporting establishment type	Derived field that indicates the type of establishment that has notified the birth. For example, tertiary or secondary site, metropolitan or rural, public, private or public provided by private
☐	Reporting establishment special care nursery	Derived field that indicates whether the reporting establishment (probably place of birth) has a Level 2 or 3 special care nursery
☐	Home birth type	Derived field that indicates if birth at home was public, private or uncontracted home birth

Geocoding

Geocoding		
Census year(s) requested: ☐ 1996 ☐ 2001 ☐ 2006 ☐ 2011 ☐ 2016		
☐	Postcode	
☐	RA	Remoteness Area
☐	Local Government Area (ABS)	1996, 2001, 2006, 2011 census
☐	Statistical Local Area (ABS)	1996, 2001, 2006 census
☐	SA2 (ABS)	2011 census
☐	SEIFA	Socioeconomic status consisting of four indices by CD, LGA, SLA and SA2: • Index of Relative Socio-Economic Disadvantage (IRSD) • Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) • Index of Education and Occupation (IEO) • Index of Economic Resources (IER).

Geocoding Information:

The Data Linkage Branch routinely processes address data from the MNS to match each record's address to a longitude and latitude. DLB also provides a "Match Quality", a coded field describing the method and specificity of the match. Information on interpreting the match score will be provided with your data. The geocoding process is dependent upon the quality of the address data, and in some cases an address may be difficult or impossible to geocode accurately, or at all.

While the latitude and longitude are not normally provided to researchers for reasons of confidentiality, corresponding geocodes are available, including Statistical Area (SA1 and SA2), Collection District (CD), Statistical Local Area (SLA) and Local Government Area (LGA). Some of these are realigned from one census to the next. The geocodes available are CD, SLA and LGA for the 1996, 2001 and 2006 censes, while SA1, SA2 and LGA are available for 2011 and 2016. Additionally, for each geocode/census combination, the Data Linkage Branch can assign Socio-Economic Indices for Area (SEIFA) and/or Remoteness Areas (RA). Please note that records with poor Match Quality will be assigned a region (e.g. an SA1) based on the centroid of a potentially large match area. This area may not overlap entirely with the assigned region. Therefore, some regions may be assigned in error. This limitation should be noted for any spatial analysis.

The boundaries, SEIFAs and RAs are developed by the Australian Bureau of Statistics (ABS), and the Data Linkage Branch uses mapping files available through the ABS website to attach them to the data. Queries about their interpretation and use should be directed to the ABS. For further information, please visit the ABS website at www.abs.gov.au.

Please note that, due to their small coverage, CD and SA1 are not usually included. Should you require these on your extract please provide written justification in the Sensitive Variables section of this document.

Sensitive Variables

All of the variables below have been determined as sensitive by the MNS Data Custodian and therefore require written justification. Please provide this in the space in the table below. Items in **bold** require DOHWA HREC approval.

Request	Variable	Description
☐	**Full date of birth of mother**	**DDMMYYYY** **Requires DOHWA HREC approval**
Enter justification here		
☐	**Full date of birth of baby**	**DDMMYYYY** **Requires DOHWA HREC approval**
Enter justification here		
☐	Collection District (ABS)	Refer to geocoding information above (1996, 2001 and 2006 census)
Enter justification here		
☐	SA1 (ABS)	Refer to geocoding information above (2011 census)
Enter justification here		
☐	**Reporting establishment**	The establishment reporting the birth, which may be the first maternity establishment to care for the woman after the birth (i.e. may not be place of birth and therefore may not match hospital code from linked HMDS records). May require approvals from the Chief Executives of the Area Health Services and/or private hospitals. **Requires DOHWA HREC approval**
Enter justification here		
☐	Home birth type	Derived field that indicates if birth at home was public, private or uncontracted home birth.
Enter justification here		
☐	**Baby transferred to**	May require approvals from the Chief Executives of the Area Health Services and/or private hospitals. If requesting this variable, also request 'mode of separation'. **Requires DOHWA HREC approval**
Enter justification here		

Comments:

Enter any extra comments here

Appendix C2-HMDS data variables

Government of **Western Australia**
Department of **Health**

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Hospital Morbidity Data

Please select group from the drop down Cohort

Every request for inpatient data will be evaluated separately on its merit by the HMDC Data Custodian. To prevent potential delays it is strongly recommended applicants spend time discussing their needs with the HMDC Data Custodian before submitting an application for data. See the contacts at:
http://ww2.health.wa.gov.au/Health-for/Health-professionals/Data-and-statistics

It is imperative applicants have referred to the online summary of HMDC data fields of the HMDC reference manual before requesting data. These documents record the changes in HMDC data collection practices/protocols over time and detail the HMDC variables. See these documents online at:
http://www.datalinkage-wa.org.au/downloads/dataset-information

For all requests, unless requested otherwise, typical exclusions include healthy newborns, boarders, organ procurements, aged care residents, funding (duplicate) hospital cases and residential aged care facilities.

Please note: Certain combinations of variables are potentially identifying and release of these combinations will be at the discretion of the HMDC Data Custodian.

Request variables below by checking boxes

Request	Variable	Description
Standard Information (provided on all HMDC data extracts)		
☑	Standard Morbidity Record Information	Admission age in years
		Sex
		Admission Status. Elective or emergency admission. Variable is unreliable from 1986-1989 and 1996-1998.
		Care Type e.g./ Acute/ Rehabilitation/ Palliative etc.
		Subset admission date - MM/YYYY
		Subset separation date - MM/YYYY
		Mode of separation - e.g. Transferred to another hospital/ deceased/ discharged etc
Patient Information		
☐	Subset date of birth	MM/YYYY
☐	Subset date of birth	YYYY
☐	Indigenous status	
☐	Marital status	Variable may be unreliable.
☐	Employment status	Variable may be unreliable; is not an indication occupation.
☐	Country/State of birth	
☐	State/Territory of residence	
☐ **OR**	Health Region of Hospital **OR (request only one)**	The WA health regions e.g./North & South Metro/ Goldfields/ South-West/ Great Southern/ Wheatbelt/ Midwest/ Pilbara/ Kimberley.

☐	Hospital Type	E.g./ Tertiary/ public metro/ private metro and rural
☐	Interpreter service	Variable may be unreliable.
☐	Language	Variable may be unreliable.
☐	Length of stay	Excludes days on leave ≠ Separation date – admission date.
☐	Source of referral-location	Available on data after July 2000
☐	Source of referral-professional	Available on data after July 2000
☐	Source of referral-transport	Available on data after July 2000
☐	Source of referral	Available on data prior to July 2000
☐	Infant weight	Available where age is less than 1 year.
☐	Funding source	E.g./ AHCA/ private insurance/ self-funded/ worker's compensation etc.
☐	Insurance status	Variable indicates if the patient has hospital (not ancillary) insurance is not an indication of a patient's method of payment
☐	Total leave days	
☐	Number of leave periods	
☐	Days of psychiatric care	
☐	Days of qualified newborn care	
☐	Days of Hospital in the Home care	
☐	Days in Intensive Care Unit - ICU	Available on data prior to July 2013
☐	Hours in ICU	Available on data after July 2013
☐	Hours of Continuous Ventilatory Support	
Diagnosis Codes		
☐	Principal diagnosis	International Classification of Diseases (ICD) codes: Jan 1970 - Dec 1978 ICD-8 Jan 1979 - Dec 1987 ICD-9 Jan 1988 - Jun 1999 ICD-9-CM (Clinical Modification; Aust.) Jul 1999 - ICD-10-AM (Australian Modification) *Be cautious when referring to ICD codes available online which may not be the same as the Australian versions.*
☐	Co-diagnosis	
☐	Additional diagnoses - up to 20	
E-Codes		
☐	External cause of injury	
☐	Activity code	
☐	Place of occurrence	
Procedure Codes		
☐	Principal procedure	Jan 1970 - Dec 1978 Code of Surgical Operations (1968) Jan 1979 - Dec 1987 International Classification of Procedures in Medicine (1978) Jan 1988 - Jun 1999 ICD-9-CM (Clinical Modification Aust.) Jul 1999 - Australian Classification of Health Interventions (ACHI) *Be cautious when referring to procedure codes available online which may not be the same as the Australian versions.*
☐	Additional procedures - up to 10	

Geocoding

Geocoding		
Census year(s) requested: ☐1996 ☐2001 ☐2006 ☐2011 ☐2016		
☐	Postcode	
☐	RA	Remoteness Area
☐	LGA (ABS)	1996, 2001, 2006, 2011, 2016 census
☐	SLA (ABS)	1996, 2001, 2006 census
☐	SA2 (ABS)	2011, 2016 census
☐	SEIFA	Socioeconomic status consisting of four indices by CD/ LGA/ SLA and SA2: • Index of Relative Socio-Economic Disadvantage (IRSD) • Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) • Index of Education and Occupation (IEO) • Index of Economic Resources (IER).

Geocoding Information:

The Data Linkage Branch routinely processes address data from the HMDC to match each record's address to a longitude and latitude. DLB also provides a "Match Quality", a coded field describing the method and specificity of the match. Information on interpreting the match score will be provided with your data. The geocoding process is dependent upon the quality of the address data, and in some cases an address may be difficult or impossible to geocode accurately, or at all.

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The boundaries, SEIFAs and RAs are developed by the Australian Bureau of Statistics (ABS), and the Data Linkage Branch uses mapping files available through the ABS website to attach them to the data. Queries about their interpretation and use should be directed to the ABS. For further information, please visit the ABS website at www.abs.gov.au.

Please note that, due to their small coverage, CD and SA1 are not usually included. Should you require these on your extract please provide written justification in the Sensitive Variables section of this document.

Other Variables

All of the variables below have been determined as sensitive and/or require written justification. Please provide this in the space in the table below.

Hospital Establishment codes are considered identifying information. Provision of these codes requires DOHWA HREC approval and/or hospital ethics approval. Approval from the Chief Executive of the Health Service Provider may also be required.

Request	Variable	Description
☐	Full date of birth	DDMMYYYY
Enter justification here		
☐	Age in days at admission	Available where age in years is less than 1 year
Enter justification here		
☐	CD (ABS)	Refer to geocoding information above (1996/ 2001 & 2006 census)
Enter justification here		
☐	SA1 (ABS)	Refer to geocoding information above (2011 and 2016 census)
Enter justification here		
☐	Admission date	DDMMYYYY
Enter justification here		
☐	Separation date	DDMMYYYY
Enter justification here		
☐	Principal procedure date	DDMMYYYY
Enter justification here		
☐	Additional procedure dates	DDMMYYYY Can be incomplete
Enter justification here		
☐	Mental health legal status	Please also select Days of Psychiatric Care
Enter justification here		

☐	*DRG*	
	Diagnostic Related Group (DRG)	Available July 1993 onwards
	Grouper version	
Enter justification here		
☐	*MDC*	
	Major Diagnostic Category (MDC)	Available July 1993 onwards
	Grouper version	
Enter justification here		
☐	Patient Identifier (UMRN)	May require Health Service/Hospital Chief Executive approval
Enter justification here		
☐	Hospital Identifier	May require Health Service/Hospital Chief Executive approval
Enter justification here		

Additional Variables
Request for variables not on this list

	Variable	Description
1		
Enter justification here		
2		
Enter justification here		
3		

Enter justification here

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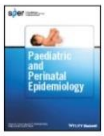

Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study

Author: Gavin Pereira, Michael Luke Marinovich, Eva Malacova, et al

Publication: Paediatric and Perinatal Epidemiology

Publisher: John Wiley and Sons

Date: Mar 19, 2020

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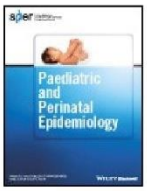

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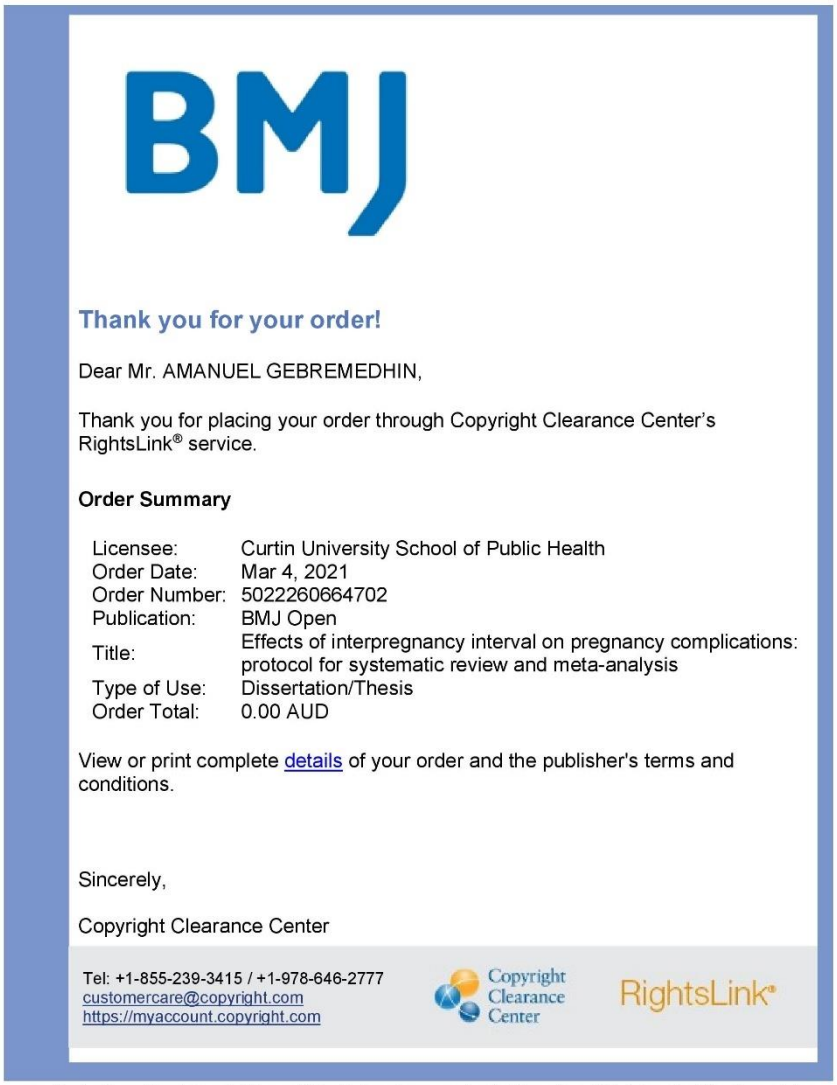

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