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Association between interpregnancy interval and pregnancy complications by previous history of complications: a population-based cohort study

Authors: Amanuel T GEBREMEDHIN [1, *], Gizachew A TESSEMA [1], Annette K REGAN [1, 2], Gavin PEREIRA [1, 3, 4]

Author Affiliations:

[1] School of Public Health, Curtin University, Perth, Western Australia, Australia

[2] School of Public Health, Texas A&M University, College Station, Texas, USA

[3] Telethon Kids Institute, WA, Australia

[4] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway

[*] **Corresponding Author:**

Amanuel Tesfay Gebremedhin

School of Public Health, Curtin University

GPO Box U1987, Perth Western Australia 6845

Email: a.gebremedhin1@postgrad.curtin.edu.au

Phone: +61 451584142

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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

ARTICLE SUMMARY

Strengths and limitations of this study

- Population-based cohort study of mothers who delivered their first two (more than 250,000) and three (96,315) consecutive singleton births in Western Australia.
- Modelling interpregnancy interval (IPI) flexibly allows for risk curve estimations and better clarification of optimal IPI.
- Findings from this study provides more clinically applicable information on the association between IPIs and risk of PE and GDM based on presence/absence of these complications.
- Data set lacks information on pregnancy loss before 20 weeks of gestation
- The possibility of the findings affected by unmeasured confounding is likely.

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 higher tendency of recurrence in subsequent pregnancies. Studies have reported a recurrence rates 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 factors 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 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.

The aim of this study was 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.

MATERIALS AND METHODS

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).

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 3 consecutive singleton births (parity 0, 1, 2) in the analytic cohort (Supplementary Figure 1).

Exposure

Interpregnancy interval (IPI) was calculated prior to exclusions as the time between 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.

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-).

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.

Statistical analysis

We examined the association between IPI and pregnancy complication (GDM and PE) stratified by 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 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 5th, 35th, 65th and 95th 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 (Supplementary Table 2). To examine the potential variability of the relationship between IPI and each outcome by 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 prior to the IPI. We then plotted the predicted risks with 95% confidence intervals (CIs) at 1-month increments of IPI for each outcome stratified by previous history of complications 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. Robust

(sandwich) variance estimation was used to account for dependence of more than one outcome per mother[23]

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) prior to year 1997, and we evaluated this bias using sensitivity analyses.

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 (Supplementary Table 2). We further included a sensitivity analysis restricted to consecutive births after 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] (Supplementary Table 3). We also performed a sensitivity analysis to examine whether our results differed by the timing of covariate adjustment (i.e., covariates at birth prior to interval versus at time of the outcome (Supplementary Table 4). All analyses were performed using STATA version 16.1 (Stata Corporation, College Station, Texas, USA).

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.

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 were similar for mothers with and without previous complications (Table 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 recurrence rate of 19.3% at second pregnancy. Risk of gestational diabetes (GDM) were 2.6% in both first and second pregnancies, with recurrence rate of 41.5% at second pregnancy (Supplementary Table 1).

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 2). For both complications, the recurrence risks were generally higher at IPIs <6 months and ≥60 months (Supplementary Table 1).

Absolute risk of pregnancy complications by IPI and previous complication status

The absolute risks of preeclampsia in the second birth was higher for mothers with previous preeclampsia than mothers with no previous preeclampsia across the IPI continuum (Table 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 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 was less clear but appeared to be around 12 months (Table 2, Figure 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 smallest at intervals approximately between 6 and 12 months for both mothers with and without previous gestational diabetes (Table 2, Figure 1, panel B).

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 3, Figure 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 history of preeclampsia in either first or second births**,** the intervals at which risks were lowest was 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 history of

preeclampsia in their recent pregnancy (12-21% for *No PE-PE* group) as 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 3, Figure 2, panel A, Supplementary Video 1).

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 (Supplementary Video 2).

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 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 were 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) as compared to mothers with no complications in their first and second pregnancies (Table 2, Figure 1, 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 complication at the immediate pervious pregnancy) were consistent with the main analyses (Supplementary Table 2). There was negligible difference in the associations between IPI and pregnancy complications when we adjusted for additional covariates including smoking and paternal age (Supplementary

Table 3). Similarly, we observed a slight difference in the association when we adjusted for variables during the time of the outcome of interest (Supplementary Table 4).

DISCUSSION

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 were associated with 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 as compared to mothers with no previous pregnancy complications, most notably when the complication was experienced for the more recent birth.

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 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 previous history of these complications.

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] Although 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 common limitation of IPI studies, including ours, is that 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.

Interpretation

We observed that mothers with previous complications had higher absolute risks for developing recurrent complications as compared to 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 risks 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 presence of previous pregnancy complications was more important than IPIs in contributing to risk of PE or GDM in subsequent pregnancies.

Previous studies have showed associations between both short and long IPIs and increased risk of pregnancy complications in subsequent pregnancy.[9,10,16,25] We showed that, for mothers with no previous complications, IPI is associated with increased risk of complications in subsequent pregnancies. Similarly, consistent with our findings, 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 (Supplementary Table 3).

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).

REFERENCES

1. Lindmark G, Lindberg B, Hogstedt S. The incidence of hypertensive disease in pregnancy. *Acta Obstetricia et Gynecologica Scandinavica.* 1983;62(118):29-32.
2. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. *Curr Diab Rep.* 2016;16(1):1-11.
3. Hernández-Díaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. *Bmj.* 2009;338:b2255.
4. McDonald S, Best C, Lam K. The recurrence risk of severe de novo pre-eclampsia in singleton pregnancies: a population-based cohort. *BJOG.* 2009;116(12):1578-1584.
5. Major CA, Deveciana M, Weeks J, Morgan MA. Recurrence of gestational diabetes: Who is at risk? *American Journal of Obstetrics and Gynecology.* 1998;179(4):1038-1042.
6. Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. *American Journal of Obstetrics and Gynecology.* 2010;203(5).
7. Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Effects of birth spacing on maternal health: a systematic review. *Am J Obstet Gynecol.* 2007;196(4):297-308.
8. Ball SJ, Pereira G, Jacoby P, de Klerk N, Stanley FJ. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. *BMJ.* 2014;349(July):g4333.
9. Gebremedhin AT, Regan AK, Ball S, et al. Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study. *Ann Epidemiol.* 2019;39:33-38.e33.
10. Gebremedhin AT, Regan AK, Ball S, et al. Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study. *Paediatric and Perinatal Epidemiology.* 2020.
11. WHO. *Report of a WHO Technical Consultation on Birth Spacing* Geneva Switzerland 13-15 June 2005: World Health Organization; 2017 Jan 05 2005.
12. Obstetricians RCo, Gynaecologists. Postpartum family planning (Best Practice Paper No. 1). *United Kingdom: RCOG.* 2015.
13. Obstetricians ACo, Gynecologists. ACOG Committee Opinion No. 736: optimizing postpartum care. *Obstet Gynecol.* 2018;131(5):e140-e150.
14. Trogstad LI, Eskild A, Magnus P, Samuelsen SO, Nesheim BI. Changing paternity and time since last pregnancy; the impact on pre-eclampsia risk. A study of 547 238 women with and without previous pre-eclampsia. *International Journal of Epidemiology.* 2001;30(6):1317-1322.

15. Basso O, Weinberg CR, Baird DD, Wilcox AJ, Olsen J. Subfecundity as a correlate of preeclampsia: a study within the Danish National Birth Cohort. *Am J Epidemiol.* 2003;157(3):195-202.
16. Mostello D, Kallogjeri D, Tungsiripat R, Leet T. Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity, and interval between births. *American Journal of Obstetrics and Gynecology.* 2008;199(1).
17. Downey F. *A validation study of the Western Australian Midwives' Notification System. 2005 data.* Perth: Department of Health, Western Australia;2007.
18. Department of Health Western Australia. Midwives Notification System. [Internet]. 2017; http://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System. Accessed 2017 Nov 28.
19. Department of Health Western Australia. *Hospital Morbdiity Data System Reference Manual.* Perth, Australia: Health Data Collections Branch, Health Information Centre;July 2004.
20. Marinovich ML, Regan AK, Gissler M, et al. Developing evidence-based recommendations for optimal interpregnancy intervals in high-income countries: protocol for an international cohort study. *BMJ open.* 2019;9(1):e027941.
21. Australian Bureau of Statistics. Socio-Economic Indexes for Areas. 2017; http://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa. Accessed 2017 Nov 28.
22. Orsini N, Greenland S. A procedure to tabulate and plot results after flexible modeling of a quantitative covariate. *The stata journal.* 2011;11(1):1-29.
23. Zou G. A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology.* 2004;159(7):702-706.
24. Hanley GE, Hutcheon JA, Kinniburgh BA, Lee L. Interpregnancy Interval and Adverse Pregnancy Outcomes: An Analysis of Successive Pregnancies. *Obstetrics and Gynecology.* 2017;129(3):408-415.
25. Basso O, Christensen K, Olsen J. Higher risk of pre-eclampsia after change of partner. An effect of longer interpregnancy intervals? *Epidemiology.* 2001;12(6):624-629.
26. Miller JE. Birth intervals and perinatal health: an investigation of three hypotheses. *Fam Plann Perspect.* 1991;23(2):62-70.
27. Hutcheon JA, Moskosky S, Ananth CV, et al. Good practices for the design, analysis, and interpretation of observational studies on birth spacing and perinatal health outcomes. *Paediatr Perinat Epidemiol.* 2019;33(1):O15-o24.

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Author contributions

ATG designed the study, performed the analysis, and drafted the manuscript; GP, GT and AR contributed to the conceptualisation, 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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Competing interests

The authors have no potential conflicts of interest to disclose.

Patient consent for publication

Not required

Ethical approval

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

Data availability statement

Data are available from the Western Australia Department of Health Data Linkage Branch with ethical approval through the Western Australia Department of Health Human Research Ethics Committee.

Figure legend

Figure 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 prior to the IPI. Abbreviations: *GDM, gestational diabetes; PE, preeclampsia*

Figure 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*

Supplementary Figure 1. Inclusion and exclusion of study cohorts

Table 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

Table 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 mo**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**
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*

Table 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 mo**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**
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)

	Interpregnancy interval, Absolute risk (95% CI)							
Outcome	**3 mo**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**
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)
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*

Figure 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

258x160mm (300 x 300 DPI)

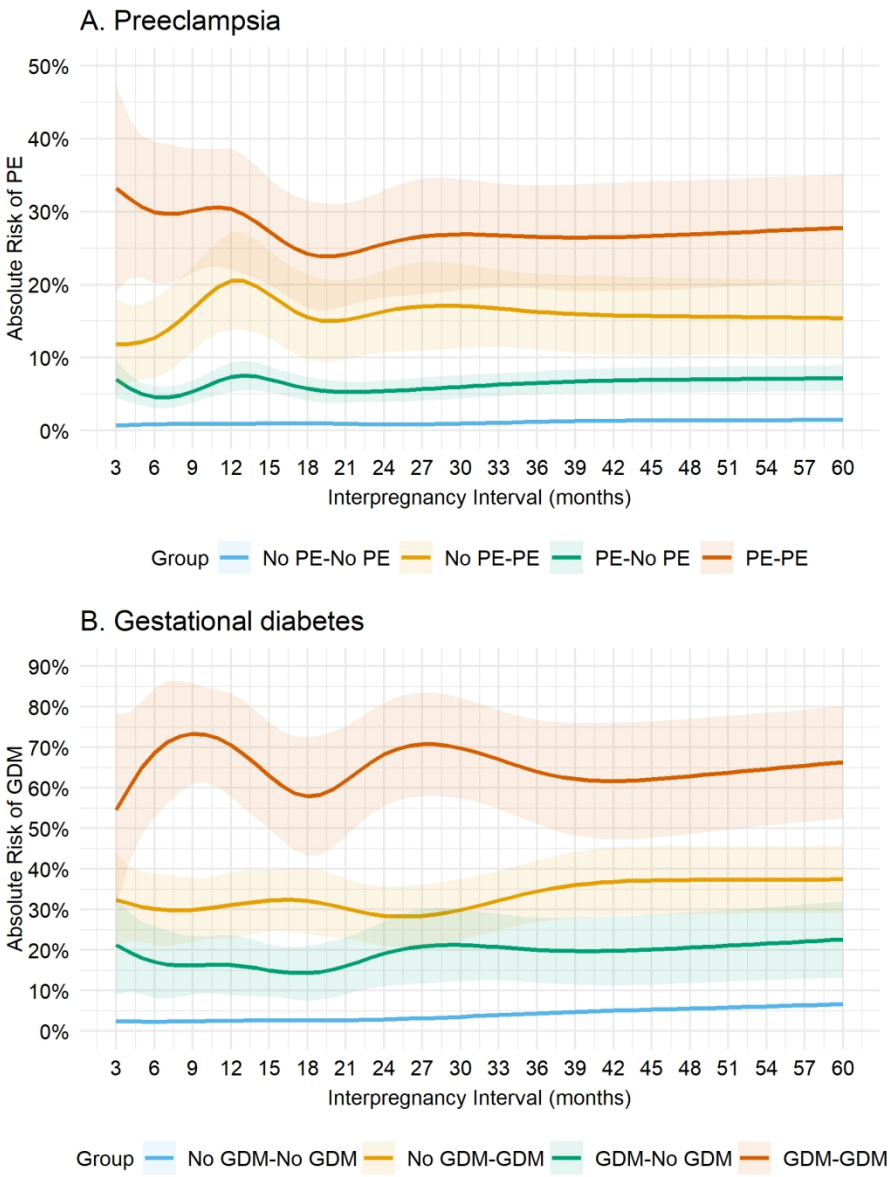
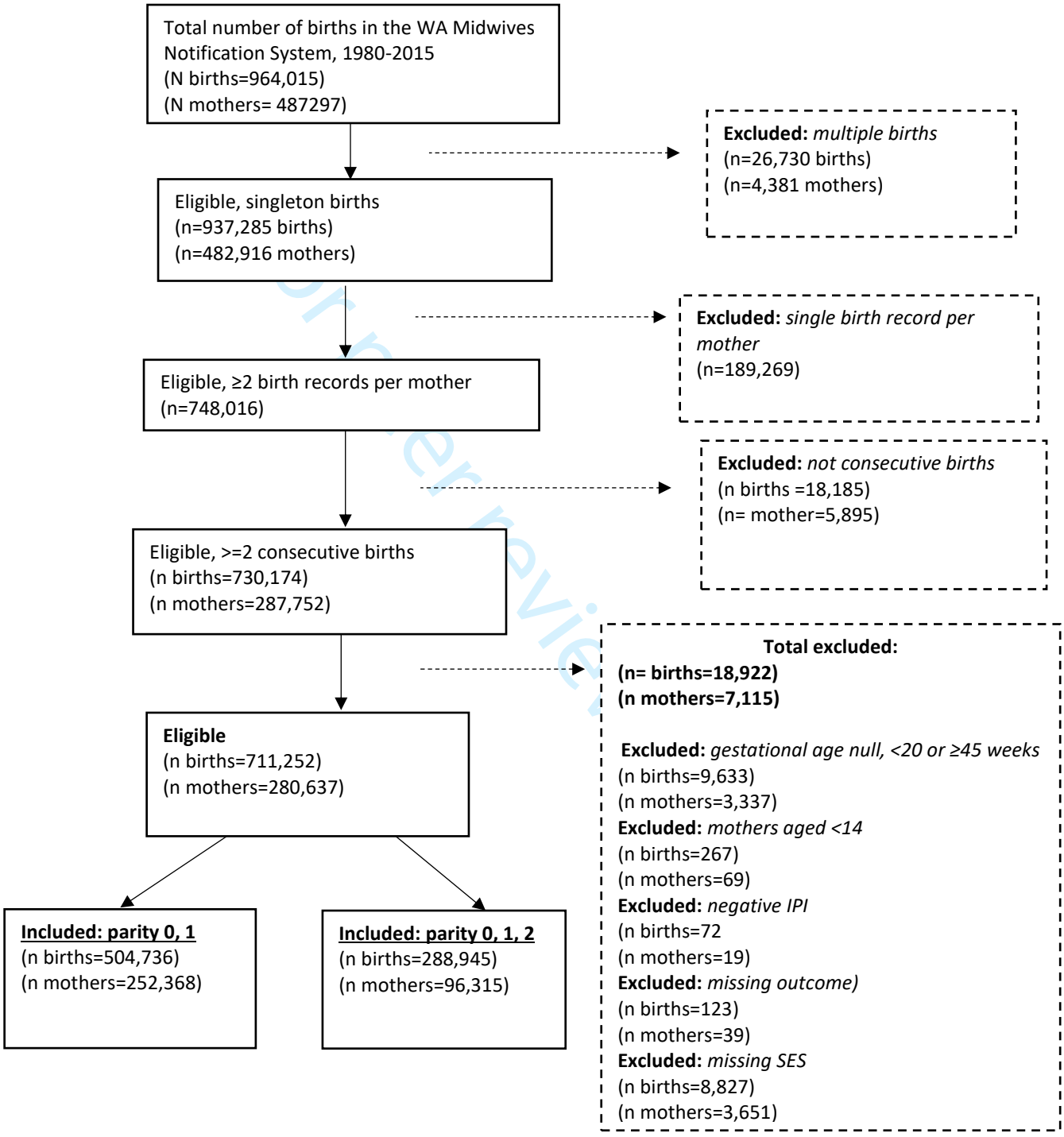


Figure 2: Predicted absolute risks (95 % CIs) at each IPI from 3 to 60 months according to previous histories for (A) preeclampsia, and (B) gestational diabetes for mothers with first three consecutive pregnancies

152x203mm (300 x 300 DPI)

SUPPLEMENTARY



Supplementary Figure 1. Inclusion and exclusion of study cohorts

Supplementary Table 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)

Supplementary Table 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 mo**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**
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*

Supplementary Table 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 mo**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**
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*

Supplementary Table 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 mo**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**
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								

	Interpregnancy interval, Absolute risk (95% CI)							
Outcome	**3 mo**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**
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*

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	NA

Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	12,14
Study size	#10	Explain how the study size was arrived at	5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8

Statistical methods	#12e	Describe any sensitivity analyses	12
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	na
Participants	#13b	Give reasons for non-participation at each stage	
Participants	#13c	Consider use of a flow diagram	eFigure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Table 1
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95%	Table 2, 3

		confidence interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2,3;
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	eTable2, 3 & 4
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13,14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	14,15
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

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Association between interpregnancy interval and pregnancy complications by previous history of complications: a population-based cohort study

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Supplementary Video 1.mp4 Supplementary Video 2.mp4	

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Association between interpregnancy interval and pregnancy complications by previous history of complications: a population-based cohort study

Authors: Amanuel T GEBREMEDHIN [1, 2 *], Gizachew A TESSEMA [1], Annette K REGAN [1, 3], Gavin PEREIRA [1, 4, 5]

Author Affiliations:

[1] Curtin School of Population Health, Curtin University, Perth, Western Australia, Australia

[2] Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, University of Western Australia, Perth, Australia

[3] School of Public Health, Texas A&M University, College Station, Texas, USA

[4] Telethon Kids Institute, WA, Australia

[5] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway

[*] **Corresponding Author:**

Amanuel Tesfay Gebremedhin

Curtin School of Population Health, Curtin University

GPO Box U1987, Perth Western Australia 6845

Email: a.gebremedhin1@postgrad.curtin.edu.au

Phone: +61 451584142

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ABSTRACT

Objective To examine if the association between interpregnancy interval (IPI) and pregnancy complications varies by presence or absence of previous complications.

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 absolute risks (AR) 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 AR 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, but lower relative risks 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

ARTICLE SUMMARY

Strengths and limitations of this study

- Population-based cohort study of mothers who delivered their first two (more than 250,000) and three (96,315) consecutive singleton births in Western Australia.
- Modelling interpregnancy interval (IPI) flexibly allows for risk curve estimations and better clarification of optimal IPI.
- Findings from this study provides more clinically applicable information on the association between IPIs and risk of PE and GDM based on presence/absence of these complications.
- Data set lacks information on pregnancy loss before 20 weeks of gestation
- The possibility of the findings affected by unmeasured confounding is likely.

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.[1-4] These complications have a higher tendency of recurrence in subsequent pregnancies. Studies have reported recurrence rates of 7 to 20% for PE and 30 to 70% for GDM, respectively.[5-8]

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.[9-12] 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.[13-15]

Recently, there has been growing literature on the association between IPIs and recurrence of pregnancy complications.[16-18] 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.

MATERIALS AND METHODS

Study design

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

Data sources and study population

We obtained maternal, infant and birth information from the Midwives Notification System, a validated database[19] 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.[20]

We sourced hospitalisation records from 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.[21] Data sources and study protocol has been published elsewhere.[12,22] Birth records were probabilistically linked based on maternal information to identify all births to individual women during the study period.

From a total of 487,297 mothers, we sequentially excluded mothers who had multiple births; 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 with at least two consecutive births 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 (Supplementary Figure 1).

Exposure

Interpregnancy interval (IPI) was calculated prior to exclusions as the time between the delivery date of the first eligible birth (that resulted in live birth or stillbirth) 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 unavailable.

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-).

Covariates

Information on potential confounding factors measured at the birth prior to the interval, and including birth year, maternal age, marital status, parity, race/ethnicity and SES were obtained from hospitalisations and perinatal records. 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 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,[23] and categorised into quintiles.

Statistical analysis

Based on existing literature and recent recommendations to represent the potential pathway between IPI and pregnancy outcomes,[24] we created a directed acyclic graph (DAG) [Supplementary Figure 2, Supplementary Figure 3]. Covariates fulfilling the minimally sufficient adjustment set were selected. 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 then 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 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.[25]

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 5th, 35th, 65th and 95th 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 (Supplementary Table 1). 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 values of the following covariates: Caucasian, married, average SES, average maternal age and birth year set to 2010 at birth prior to 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. 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. Robust (sandwich) variance estimation was used to account for non-independence of 2 or more IPIs per mother.[26]

Missing data

We carried out a complete case analysis because the proportion of missing data was small (<3%, range 0.04% for maternal age to 1.2% for SES). 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 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 (Supplementary Table 1). 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 (Supplementary Table 2).[20] We also performed a sensitivity analysis to examine whether our results differed by the timing of covariate adjustment (i.e., covariates at birth prior to interval versus at the time of the outcome (Supplementary Table

3). All analyses were performed using STATA version 16.1 (Stata Corporation, College Station, Texas, USA). The DAG was created using DAGitty version 2.3.[27]

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.

Ethical approval

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

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 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 (Supplementary Table 4).

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 2). For both complications, the recurrence risks were generally higher at IPIs <6 months and ≥60 months (Supplementary Table 4).

Absolute risk of pregnancy complications by IPI and previous complication status

The absolute risks of preeclampsia in the second birth was higher for mothers with previous preeclampsia than mothers with no previous preeclampsia across the IPI continuum (Table 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 2, Figure 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 smallest at intervals between 6 and 12 months for mothers with and without previous gestational diabetes (Table 2, Figure 1, panel B).

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 3, Figure 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) than 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 3, Figure 2, panel A, Supplementary Video 1).

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 (Supplementary Video 2).

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 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 than 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 complication (PE or GDM) compared to mothers with no complications in their first and second pregnancies (Table 2, Figure 1, 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 previous pregnancy) were consistent with the main analyses (Supplementary Table 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 (Supplementary Table 2). Similarly, we observed a slight difference in the association when we adjusted for variables at the time of the outcome of interest (Supplementary Table 3).

DISCUSSION

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. In addition, 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.

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.

Limitations of the data

In interpreting our findings, the following limitations must be considered. First, 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 used within-women (matched designs) have reported substantially attenuated associations between IPI and pregnancy complications, owing to unmeasured or residual confounding.[11,12,28] Second, 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. Third, a common limitation of IPI studies, including ours, is that the

lack of information on dates of miscarriage and gestational age at miscarriage. Additionally, 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. 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 study may have been subject to a certain degree of misclassification as ultrasound confirmed gestations were less common during the earlier periods of our birth cohort. However, results from our sensitivity analyses restricted to the cohort of births later in the study period did not meaningfully change our effect estimates. Finally, 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.

Interpretation

We observed that mothers with previous complications had higher absolute risks for developing recurrent complications as compared to 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,[8,18] 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 risks 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 presence of previous pregnancy complications was more important than IPIs in contributing to risk of PE or GDM in subsequent pregnancies.

Previous studies have showed associations between both short and long IPIs and increased risk of pregnancy complications in subsequent pregnancy.[11,12,18,29] We showed that, for mothers with no previous complications, IPI is associated with increased risk of complications in subsequent pregnancies. Similarly, consistent with our findings, risk of PE in the second pregnancy increased with increasing IPI for only mothers with no history of PE.[16] 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*,[30] 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.[30] Unmeasured variables such as changes in body mass index, pregnancy intention can also confound the association between IPI and pregnancy complications.[24] However, results from our sensitivity analysis examining the

inclusion of potential confounders (e.g smoking, paternal age, infertility status), did not change our estimates (Supplementary Table 2).

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).

REFERENCES

1. Buckley BS, Harreiter J, Damm P, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. *Diabet Med.* 2012;29(7):844-854.
2. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. *PloS one.* 2014;9(12):e113715.
3. Lawrence RL, Wall CR, Bloomfield FH. Prevalence of gestational diabetes according to commonly used data sources: an observational study. *BMC pregnancy and childbirth.* 2019;19(1):1-9.
4. Hutcheon JA, Lisonkova S, Joseph K. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best practice & research Clinical obstetrics & gynaecology.* 2011;25(4):391-403.
5. Hernández-Díaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. *Bmj.* 2009;338:b2255.
6. McDonald S, Best C, Lam K. The recurrence risk of severe de novo pre-eclampsia in singleton pregnancies: a population-based cohort. *BJOG.* 2009;116(12):1578-1584.
7. Major CA, Deveciana M, Weeks J, Morgan MA. Recurrence of gestational diabetes: Who is at risk? *American Journal of Obstetrics and Gynecology.* 1998;179(4):1038-1042.
8. Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. *American Journal of Obstetrics and Gynecology.* 2010;203(5).
9. Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Effects of birth spacing on maternal health: a systematic review. *Am J Obstet Gynecol.* 2007;196(4):297-308.
10. Ball SJ, Pereira G, Jacoby P, de Klerk N, Stanley FJ. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. *BMJ.* 2014;349(July):g4333.
11. Gebremedhin AT, Regan AK, Ball S, et al. Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study. *Ann Epidemiol.* 2019;39:33-38.e33.
12. Gebremedhin AT, Regan AK, Ball S, et al. Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study. *Paediatric and Perinatal Epidemiology.* 2020.
13. WHO. *Report of a WHO Technical Consultation on Birth Spacing* Geneva Switzerland 13-15 June 2005: World Health Organization; 2017 Jan 05 2005.

14. Royal College of Obstetricians and Gynaecologists. Postpartum family planning (Best Practice Paper No. 1). *United Kingdom: RCOG.* 2015.

15. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 736: optimizing postpartum care. *Obstet Gynecol.* 2018;131(5):e140-e150.

16. Trogstad LI, Eskild A, Magnus P, Samuelsen SO, Nesheim BI. Changing paternity and time since last pregnancy; the impact on pre-eclampsia risk. A study of 547 238 women with and without previous pre-eclampsia. *International Journal of Epidemiology.* 2001;30(6):1317-1322.

17. Basso O, Weinberg CR, Baird DD, Wilcox AJ, Olsen J. Subfecundity as a correlate of preeclampsia: a study within the Danish National Birth Cohort. *Am J Epidemiol.* 2003;157(3):195-202.

18. Mostello D, Kallogjeri D, Tungsiripat R, Leet T. Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity, and interval between births. *American Journal of Obstetrics and Gynecology.* 2008;199(1).

19. Downey F. *A validation study of the Western Australian Midwives' Notification System. 2005 data.* Perth: Department of Health, Western Australia;2007.

20. Department of Health Western Australia. Midwives Notification System. http://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System. Published 2017. Accessed 2017 Nov 28.

21. Department of Health WA. *Hospital Morbdiity Data System Reference Manual.* Perth, Australia: Health Data Collections Branch, Health Information Centre;2004.

22. Marinovich ML, Regan AK, Gissler M, et al. Developing evidence-based recommendations for optimal interpregnancy intervals in high-income countries: protocol for an international cohort study. *BMJ open.* 2019;9(1):e027941.

23. Australian Bureau of Statistics. Socio-Economic Indexes for Areas. Australian Bureau of Statistics. http://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa. Published 2017. Updated 23 September 2013. Accessed 2017 Nov 28.

24. Hutcheon JA, Moskosky S, Ananth CV, et al. Good practices for the design, analysis, and interpretation of observational studies on birth spacing and perinatal health outcomes. *Paediatr Perinat Epidemiol.* 2019;33(1):O15-o24.

25. Orsini N, Greenland S. A procedure to tabulate and plot results after flexible modeling of a quantitative covariate. *The stata journal.* 2011;11(1):1-29.

26. Zou G. A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology.* 2004;159(7):702-706.

27. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology.* 2011;22(5):745.

28. Hanley GE, Hutcheon JA, Kinniburgh BA, Lee L. Interpregnancy Interval and Adverse Pregnancy Outcomes: An Analysis of Successive Pregnancies. *Obstetrics and Gynecology.* 2017;129(3):408-415.

29. Basso O, Christensen K, Olsen J. Higher risk of pre-eclampsia after change of partner. An effect of longer interpregnancy intervals? *Epidemiology.* 2001;12(6):624-629.

30. Miller JE. Birth intervals and perinatal health: an investigation of three hypotheses. *Fam Plann Perspect.* 1991;23(2):62-70.

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Author contributions

All authors made a substantial contribution to this study. ATG designed the study, performed the analyses and drafted all sections of the manuscript. ATG, GAT, AKR, and GP contributed to the conceptualisation. All authors provided input on the methodological approach and substantive relevance, contributed to the interpretation of the findings, and reviewed the paper for intellectual content. All authors reviewed the drafts of this manuscript and approved the final version for manuscript.

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Competing interests

The authors have no potential conflicts of interest to disclose.

Patient consent for publication

Not required

Data availability statement

Data are available from the Western Australia Department of Health Data Linkage Branch with ethical approval through the Western Australia Department of Health Human Research Ethics Committee.

Figure legend

Figure 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 prior to the IPI. Abbreviations: *GDM, gestational diabetes; PE, preeclampsia*

Figure 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*

Supplementary Figure 1. Inclusion and exclusion of study cohorts

Supplementary Figure 2. Directed acyclic graph representing the association between short interpregnancy interval and preeclampsia

Supplementary Figure 3. Directed acyclic graph representing the association between long interpregnancy interval and preeclampsia

Table 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

Table 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Table 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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)

Interpregnancy interval (months): RR, AR and RD (95% CI)								
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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)
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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

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

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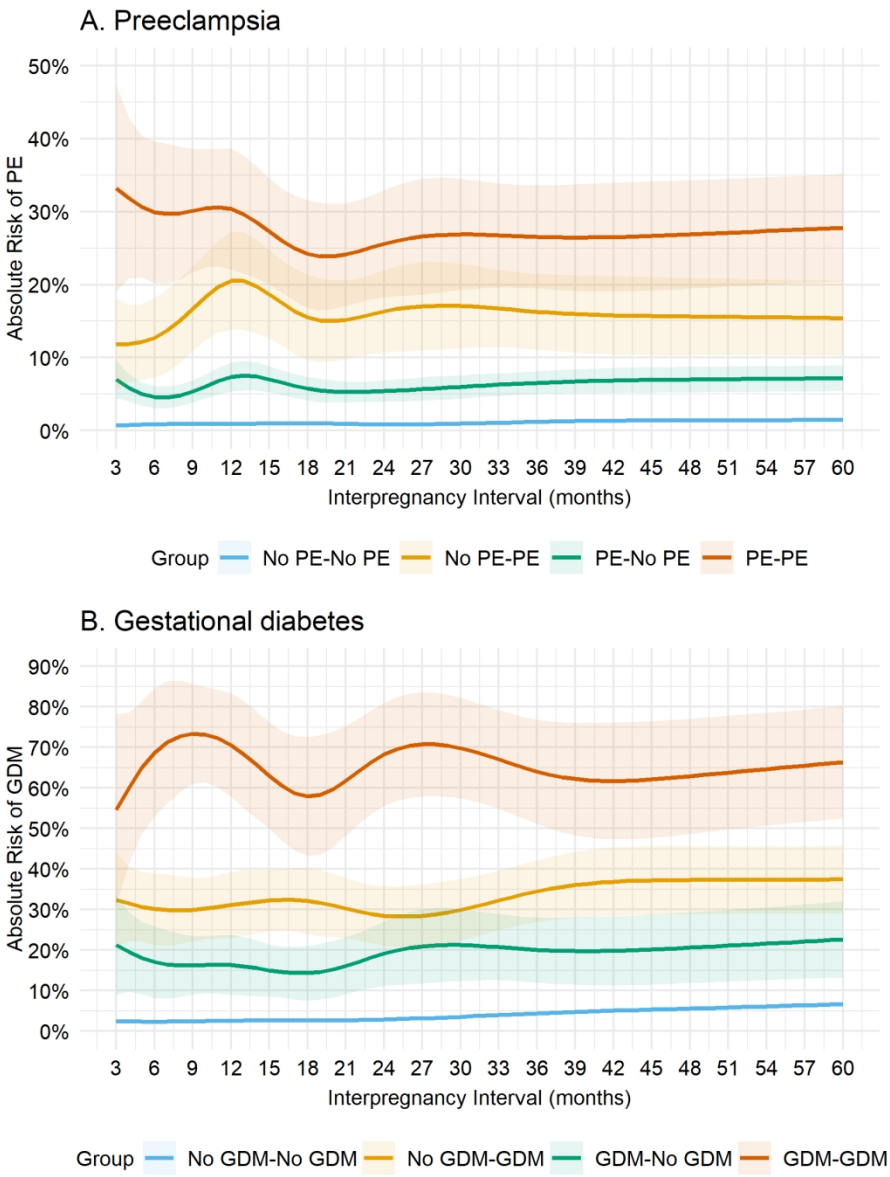
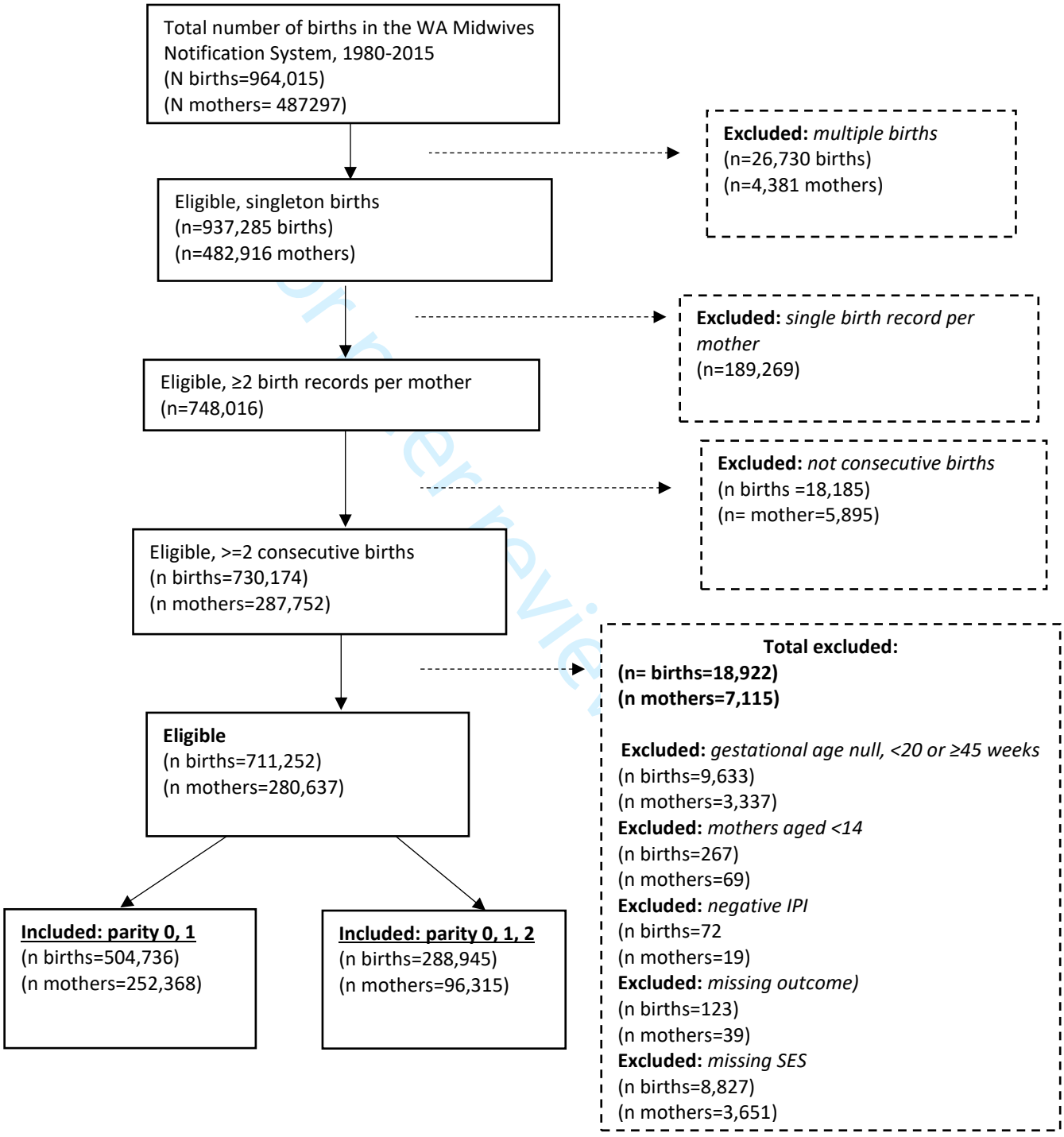


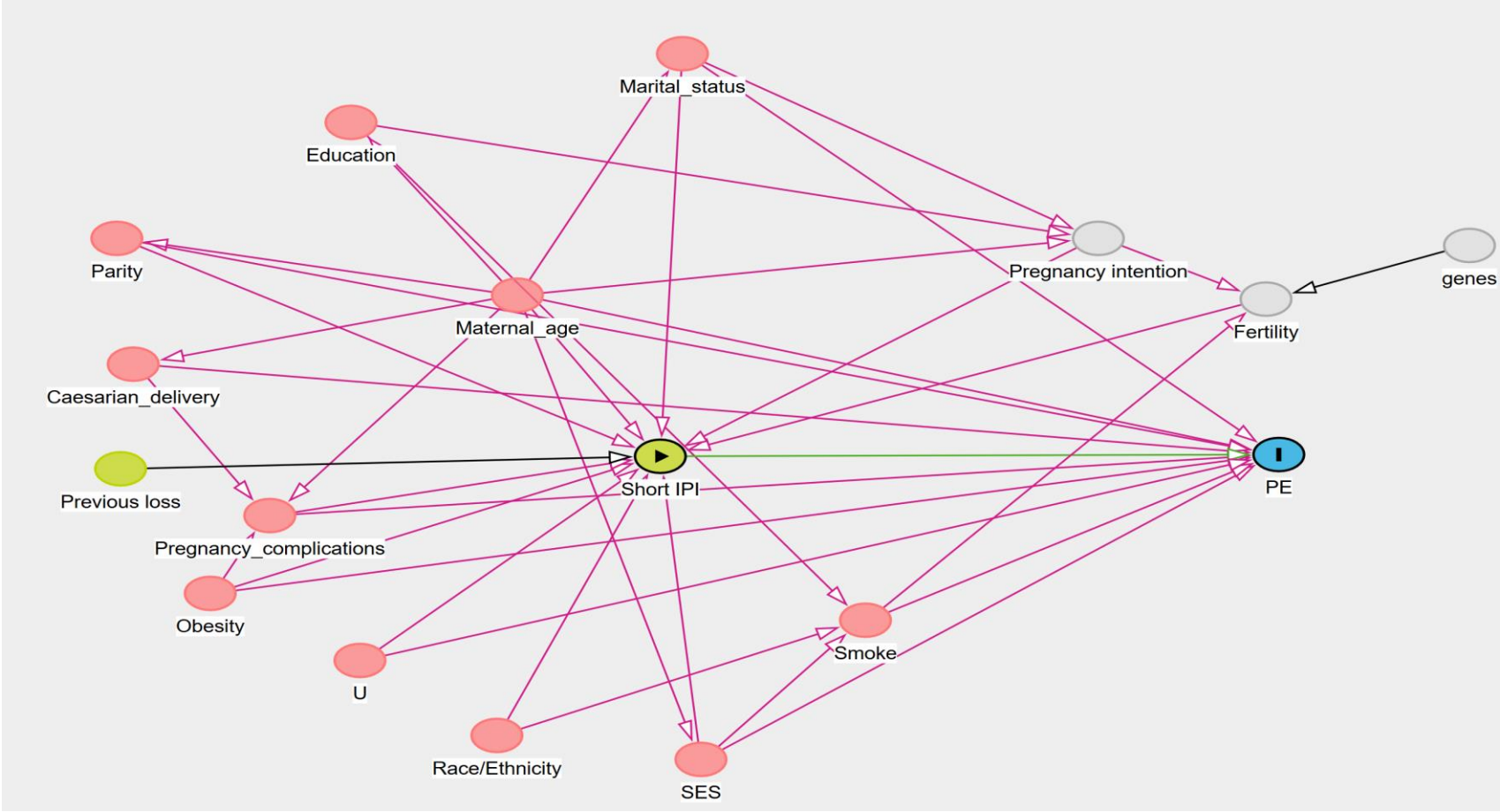
Predicted absolute risks (95 % CIs) at each IPI from 3 to 60 months according to previous histories for (A) preeclampsia, and (B) gestational diabetes for mothers with first three consecutive pregnancies

152x203mm (300 x 300 DPI)

SUPPLEMENTARY

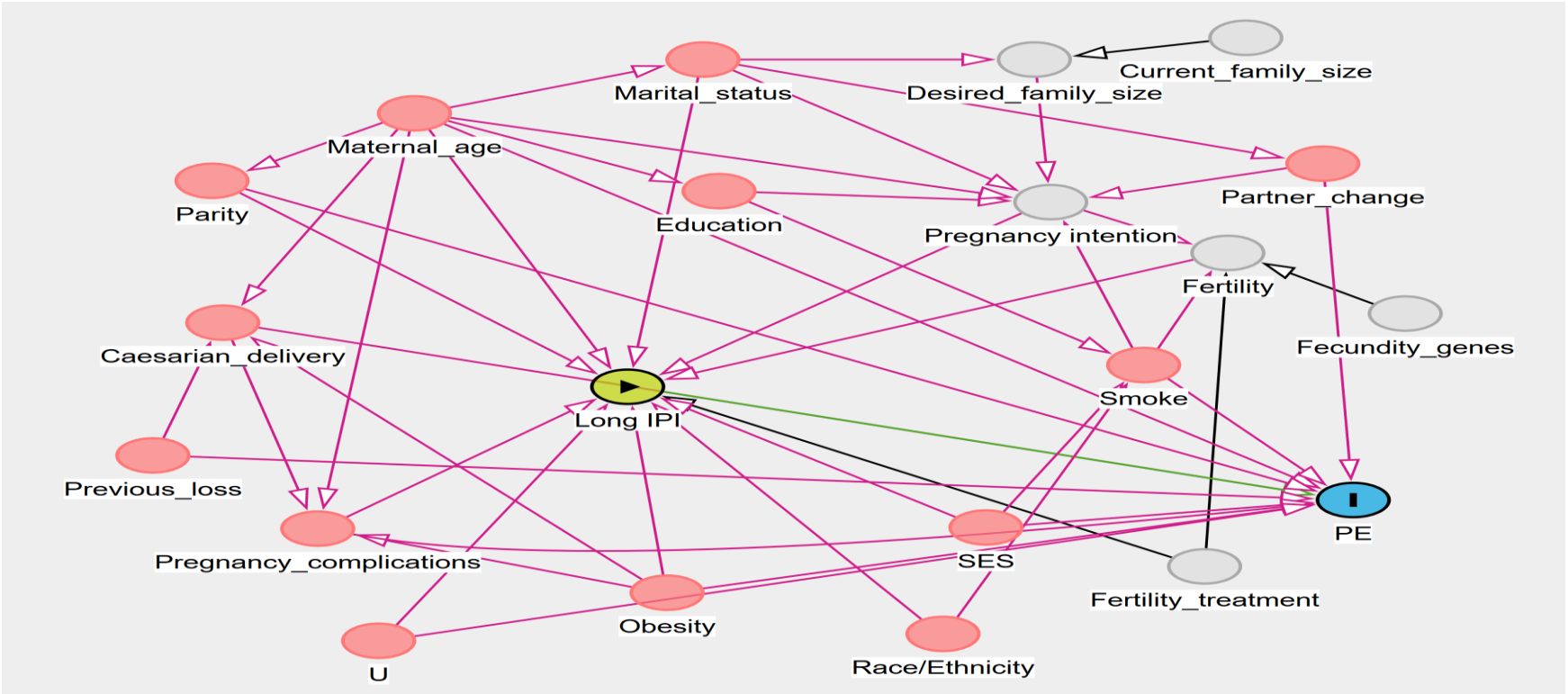


Supplementary Figure 1. Inclusion and exclusion of study cohorts



Supplementary Figure 2. Directed acyclic graph representing the association between short interpregnancy interval and preeclampsia

IPI: interpregnancy interval; PE: Preeclampsia); Outcome, exposure, measured covariates and unmeasured covariates are represented by blue, green, red and grey colours, respectively; U-unmeasured and unknown confounders; The minimal set of adjustment sets for estimating the total effect of short IPI on PE are: Marital status, maternal age, obesity, parity, pregnancy complications, SES, smoking and U. In this study, control for pregnancy complications is represented by stratification.



Supplementary Figure 3. Directed acyclic graph representing the association between long interpregnancy interval and preeclampsia

IPI: interpregnancy interval; PE: Preeclampsia); Outcome, exposure, measured covariates and unmeasured covariates are represented by blue, green, red and grey colours, respectively; U-unmeasured and unknown confounders; The minimal set of adjustment sets for estimating the total effect of long IPI on PE are: Maternal age, obesity, parity, pregnancy complications, partner change, SES, smoking and U. In this study, control for pregnancy complications is represented by stratification

Supplementary Table 1. 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Supplementary Table 2. 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Supplementary Table 3. 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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								

Interpregnancy interval (months): RR, AR and RD (95% CI)								
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Supplementary Table 4. 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)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5

Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	12,14
Study size	#10	Explain how the study size was arrived at	5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	8

Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
Statistical methods	#12e	Describe any sensitivity analyses	12
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	na
Participants	#13b	Give reasons for non-participation at each stage	
Participants	#13c	Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Table 1
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	Table 1

Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, 3
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2,3;
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Supplementary Table 2, 3 & 4
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13,14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses,	14

		results from similar studies, and other relevant evidence.	
Generalisability	#21	Discuss the generalisability (external validity) of the study results	14,15
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

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Association between interpregnancy interval and pregnancy complications by previous history of complications: a population-based cohort study

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Supplementary Video 1.mp4 Supplementary Video 2.mp4	

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Association between interpregnancy interval and pregnancy complications by previous history of complications: a population-based cohort study

Authors: Amanuel T GEBREMEDHIN [1, 2 *], Gizachew A TESSEMA [1], Annette K REGAN [1, 3], Gavin PEREIRA [1, 4, 5]

Author Affiliations:

[1] Curtin School of Population Health, Curtin University, Perth, Western Australia, Australia

[2] Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, University of Western Australia, Perth, Australia

[3] School of Public Health, Texas A&M University, College Station, Texas, USA

[4] enAble Institute, Curtin University, WA, Australia

[5] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway

[*] **Corresponding Author:**

Amanuel Tesfay Gebremedhin

Curtin School of Population Health, Curtin University

GPO Box U1987, Perth Western Australia 6845

Email: a.gebremedhin1@postgrad.curtin.edu.au

Phone: +61 451584142

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ABSTRACT

Objective To examine if the association between interpregnancy interval (IPI) and pregnancy complications varies by presence or absence of previous complications.

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 absolute risks (AR) 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 AR 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, but lower relative risks 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

ARTICLE SUMMARY

Strengths and limitations of this study

- Population-based cohort study of mothers who delivered their first two (more than 250,000) and three (96,315) consecutive singleton births in Western Australia.
- Modelling interpregnancy interval (IPI) flexibly allows for risk curve estimations and better clarification of optimal IPI.
- Findings from this study provides more clinically applicable information on the association between IPIs and risk of PE and GDM based on presence/absence of these complications.
- Data set lacks information on pregnancy loss before 20 weeks of gestation
- The possibility of the findings affected by unmeasured confounding is likely.

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.[1-4] These complications have a higher tendency of recurrence in subsequent pregnancies. Studies have reported recurrence rates of 7 to 20% for PE and 30 to 70% for GDM, respectively.[5-8]

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.[9-12] 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.[13-15]

Recently, there has been growing literature on the association between IPIs and recurrence of pregnancy complications.[16-18] 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.

MATERIALS AND METHODS

Study design

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

Data sources and study population

We obtained maternal, infant and birth information from the Midwives Notification System, a validated database[19] 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.[20]

We sourced hospitalisation records from 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.[21] Data sources and study protocol has been published elsewhere.[12,22] Birth records were probabilistically linked based on maternal information to identify all births to individual women during the study period.

From a total of 487,297 mothers, we sequentially excluded mothers who had multiple births; 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 with at least two consecutive births 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 (Supplementary Figure 1).

Exposure

Interpregnancy interval (IPI) was calculated prior to exclusions as the time between the delivery date of the first eligible birth (that resulted in live birth or stillbirth) 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 unavailable.

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-).

Covariates

Information on potential confounding factors measured at the birth prior to the interval, and including birth year, maternal age, marital status, parity, race/ethnicity and SES were obtained from hospitalisations and perinatal records. 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 was derived by the Australian Bureau of Statistics as Socio Economic Indexes for Areas (SEIFA) at a geographic area for the maternal residence at the time of birth,[23] and categorised into quintiles.

Statistical analysis

Based on existing literature and recent recommendations to represent the potential pathway between IPI and pregnancy outcomes,[24] we created a directed acyclic graph (DAG) [Supplementary Figure 2, Supplementary Figure 3]. Covariates fulfilling the minimally sufficient adjustment set were selected. 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 then 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 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.[25] Since the intraclass coefficient was considerably low and the confidence intervals of the estimates were not significantly changed in the multilevel model, the GLM model using SEIFA as a proxy for SES was utilized.

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 5th, 35th, 65th and 95th 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 (Supplementary Table 1). 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 values of the following covariates: Caucasian, married, average SES, average maternal age and birth year set to 2010 at birth prior to 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. 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. Robust (sandwich) variance estimation was used to account for non-independence of 2 or more IPIs per mother.[26]

Missing data

We carried out a complete case analysis because the proportion of missing data was small (<3%, range 0.04% for maternal age to 1.2% for SES). 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 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 (Supplementary Table 1). 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 (Supplementary Table 2).[20] We also performed a sensitivity analysis to examine whether our results differed by the timing of covariate adjustment (i.e.,

covariates at birth prior to interval versus at the time of the outcome (Supplementary Table 3). All analyses were performed using STATA version 16.1 (Stata Corporation, College Station, Texas, USA). The DAG was created using DAGitty version 2.3.[27]

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.

Ethical approval

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

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 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 (Supplementary Table 4).

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 2). For both complications, the recurrence risks were generally higher at IPIs <6 months and ≥60 months (Supplementary Table 4).

Absolute risk of pregnancy complications by IPI and previous complication status

The absolute risks of preeclampsia in the second birth was higher for mothers with previous preeclampsia than mothers with no previous preeclampsia across the IPI continuum (Table 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 2, Figure 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 smallest at intervals between 6 and 12 months for mothers with and without previous gestational diabetes (Table 2, Figure 1, panel B).

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 3, Figure 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) than 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 3, Figure 2, panel A, Supplementary Video 1).

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 (Supplementary Video 2).

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 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 than 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 complication (PE or GDM) compared to mothers with no complications in their first and second pregnancies (Table 2, Figure 1, 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 previous pregnancy) were consistent with the main analyses (Supplementary Table 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 (Supplementary Table 2). Similarly, we observed a slight difference in the association when we adjusted for variables at the time of the outcome of interest (Supplementary Table 3).

DISCUSSION

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. In addition, 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.

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.

Limitations of the data

In interpreting our findings, the following limitations must be considered. First, 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 used within-women (matched designs) have reported substantially attenuated associations between IPI and pregnancy complications, owing to unmeasured or residual confounding.[11,12,28] Second, 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. Third, a common limitation of IPI studies, including ours, is that the

lack of information on dates of miscarriage and gestational age at miscarriage. Additionally, 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. 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 study may have been subject to a certain degree of misclassification as ultrasound confirmed gestations were less common during the earlier periods of our birth cohort. However, results from our sensitivity analyses restricted to the cohort of births later in the study period did not meaningfully change our effect estimates. Finally, 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.

Interpretation

We observed that mothers with previous complications had higher absolute risks for developing recurrent complications as compared to 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,[8,18] 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 risks 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 presence of previous pregnancy complications was more important than IPIs in contributing to risk of PE or GDM in subsequent pregnancies.

Previous studies have showed associations between both short and long IPIs and increased risk of pregnancy complications in subsequent pregnancy.[11,12,18,29] We showed that, for mothers with no previous complications, IPI is associated with increased risk of complications in subsequent pregnancies. Similarly, consistent with our findings, risk of PE in the second pregnancy increased with increasing IPI for only mothers with no history of PE.[16] 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*,[30] 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.[30] Unmeasured variables such as changes in body mass index, pregnancy intention can also confound the association between IPI and pregnancy complications.[24] However, results from our sensitivity analysis examining the

inclusion of potential confounders (e.g smoking, paternal age, infertility status), did not change our estimates (Supplementary Table 2).

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).

REFERENCES

1. Buckley BS, Harreiter J, Damm P, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. *Diabet Med.* 2012;29(7):844-854.
2. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. *PloS one.* 2014;9(12):e113715.
3. Lawrence RL, Wall CR, Bloomfield FH. Prevalence of gestational diabetes according to commonly used data sources: an observational study. *BMC pregnancy and childbirth.* 2019;19(1):1-9.
4. Hutcheon JA, Lisonkova S, Joseph K. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best practice & research Clinical obstetrics & gynaecology.* 2011;25(4):391-403.
5. Hernández-Díaz S, Toh S, Cnattingius S. Risk of pre-eclampsia in first and subsequent pregnancies: prospective cohort study. *Bmj.* 2009;338:b2255.
6. McDonald S, Best C, Lam K. The recurrence risk of severe de novo pre-eclampsia in singleton pregnancies: a population-based cohort. *BJOG.* 2009;116(12):1578-1584.
7. Major CA, Deveciana M, Weeks J, Morgan MA. Recurrence of gestational diabetes: Who is at risk? *American Journal of Obstetrics and Gynecology.* 1998;179(4):1038-1042.
8. Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. *American Journal of Obstetrics and Gynecology.* 2010;203(5).
9. Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Effects of birth spacing on maternal health: a systematic review. *Am J Obstet Gynecol.* 2007;196(4):297-308.
10. Ball SJ, Pereira G, Jacoby P, de Klerk N, Stanley FJ. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. *BMJ.* 2014;349(July):g4333.
11. Gebremedhin AT, Regan AK, Ball S, et al. Effect of interpregnancy interval on gestational diabetes: a retrospective matched cohort study. *Ann Epidemiol.* 2019;39:33-38.e33.
12. Gebremedhin AT, Regan AK, Ball S, et al. Interpregnancy interval and hypertensive disorders of pregnancy: A population-based cohort study. *Paediatric and Perinatal Epidemiology.* 2020.
13. WHO. *Report of a WHO Technical Consultation on Birth Spacing* Geneva Switzerland 13-15 June 2005: World Health Organization; 2017 Jan 05 2005.

14. Royal College of Obstetricians and Gynaecologists. Postpartum family planning (Best Practice Paper No. 1). *United Kingdom: RCOG.* 2015.

15. American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 736: optimizing postpartum care. *Obstet Gynecol.* 2018;131(5):e140-e150.

16. Trogstad LI, Eskild A, Magnus P, Samuelsen SO, Nesheim BI. Changing paternity and time since last pregnancy; the impact on pre-eclampsia risk. A study of 547 238 women with and without previous pre-eclampsia. *International Journal of Epidemiology.* 2001;30(6):1317-1322.

17. Basso O, Weinberg CR, Baird DD, Wilcox AJ, Olsen J. Subfecundity as a correlate of preeclampsia: a study within the Danish National Birth Cohort. *Am J Epidemiol.* 2003;157(3):195-202.

18. Mostello D, Kallogjeri D, Tungsiripat R, Leet T. Recurrence of preeclampsia: effects of gestational age at delivery of the first pregnancy, body mass index, paternity, and interval between births. *American Journal of Obstetrics and Gynecology.* 2008;199(1).

19. Downey F. *A validation study of the Western Australian Midwives' Notification System. 2005 data.* Perth: Department of Health, Western Australia;2007.

20. Department of Health Western Australia. Midwives Notification System. http://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System. Published 2017. Accessed 2017 Nov 28.

21. Department of Health WA. *Hospital Morbdiity Data System Reference Manual.* Perth, Australia: Health Data Collections Branch, Health Information Centre;2004.

22. Marinovich ML, Regan AK, Gissler M, et al. Developing evidence-based recommendations for optimal interpregnancy intervals in high-income countries: protocol for an international cohort study. *BMJ open.* 2019;9(1):e027941.

23. Australian Bureau of Statistics. Socio-Economic Indexes for Areas. Australian Bureau of Statistics. http://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa. Published 2017. Updated 23 September 2013. Accessed 2017 Nov 28.

24. Hutcheon JA, Moskosky S, Ananth CV, et al. Good practices for the design, analysis, and interpretation of observational studies on birth spacing and perinatal health outcomes. *Paediatr Perinat Epidemiol.* 2019;33(1):O15-o24.

25. Orsini N, Greenland S. A procedure to tabulate and plot results after flexible modeling of a quantitative covariate. *The stata journal.* 2011;11(1):1-29.

26. Zou G. A modified poisson regression approach to prospective studies with binary data. *American journal of epidemiology.* 2004;159(7):702-706.

27. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology.* 2011;22(5):745.

28. Hanley GE, Hutcheon JA, Kinniburgh BA, Lee L. Interpregnancy Interval and Adverse Pregnancy Outcomes: An Analysis of Successive Pregnancies. *Obstetrics and Gynecology.* 2017;129(3):408-415.

29. Basso O, Christensen K, Olsen J. Higher risk of pre-eclampsia after change of partner. An effect of longer interpregnancy intervals? *Epidemiology.* 2001;12(6):624-629.

30. Miller JE. Birth intervals and perinatal health: an investigation of three hypotheses. *Fam Plann Perspect.* 1991;23(2):62-70.

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Author contributions

All authors made a substantial contribution to this study. ATG designed the study, performed the analyses and drafted all sections of the manuscript. ATG, GAT, AKR, and GP contributed to the conceptualisation. All authors provided input on the methodological approach and substantive relevance, contributed to the interpretation of the findings, and reviewed the paper for intellectual content. All authors reviewed the drafts of this manuscript and approved the final version for manuscript.

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Competing interests

The authors have no potential conflicts of interest to disclose.

Patient consent for publication

Not required

Data availability statement

Data are available from the Western Australia Department of Health Data Linkage Branch with ethical approval through the Western Australia Department of Health Human Research Ethics Committee.

Figure legend

Figure 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 prior to the IPI. Abbreviations: *GDM, gestational diabetes; PE, preeclampsia*

Figure 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*

Supplementary Figure 1. Inclusion and exclusion of study cohorts

Supplementary Figure 2. Directed acyclic graph representing the association between short interpregnancy interval and preeclampsia

Supplementary Figure 3. Directed acyclic graph representing the association between long interpregnancy interval and preeclampsia

Table 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

Table 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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 (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 (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 (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 (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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Table 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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 (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 (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 (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 (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 (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)

Interpregnancy interval (months): RR, AR and RD (95% CI)								
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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 (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)
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 (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 (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)	Reference	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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Figure 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

258x160mm (300 x 300 DPI)

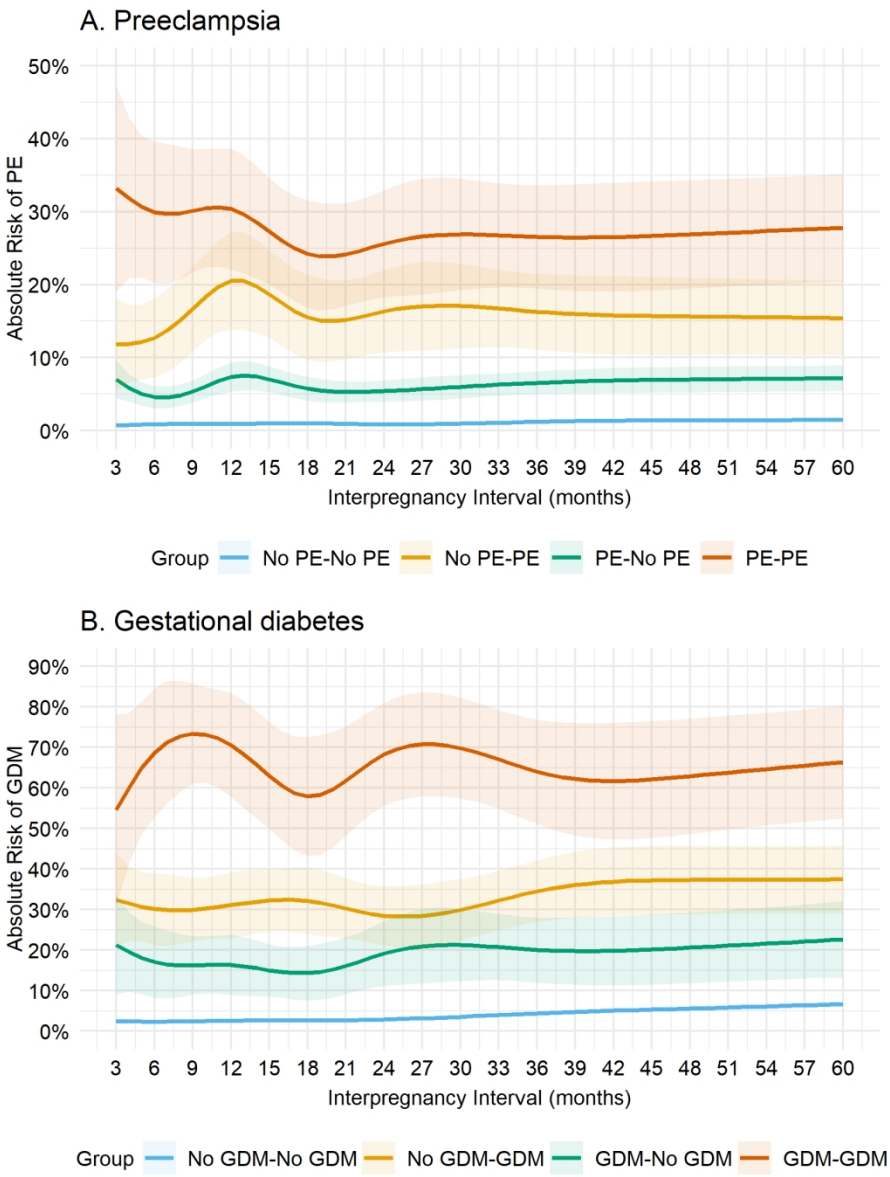
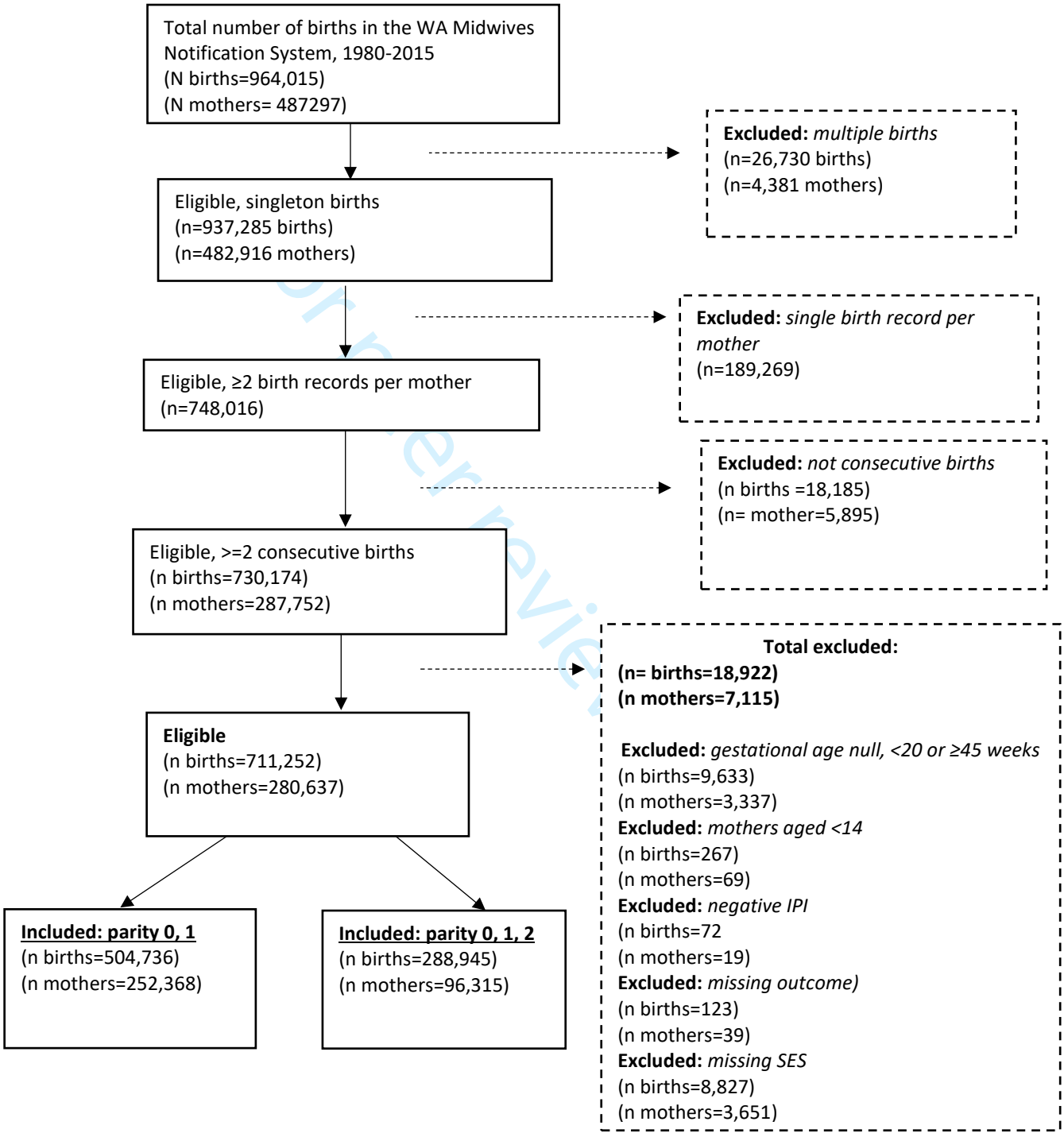


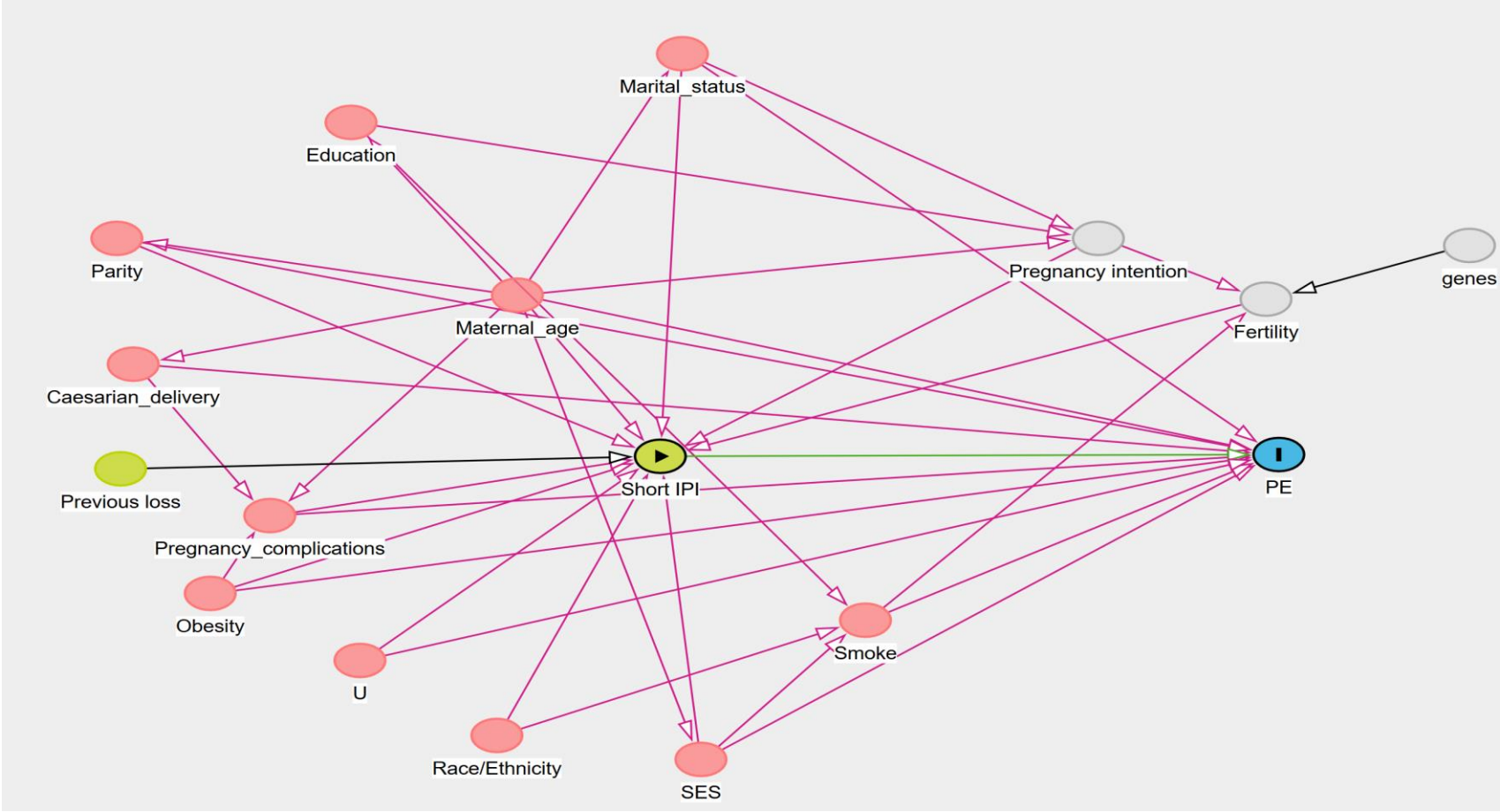
Figure 2: Predicted absolute risks (95 % CIs) at each IPI from 3 to 60 months according to previous histories for (A) preeclampsia, and (B) gestational diabetes for mothers with first three consecutive pregnancies

152x203mm (300 x 300 DPI)

SUPPLEMENTARY

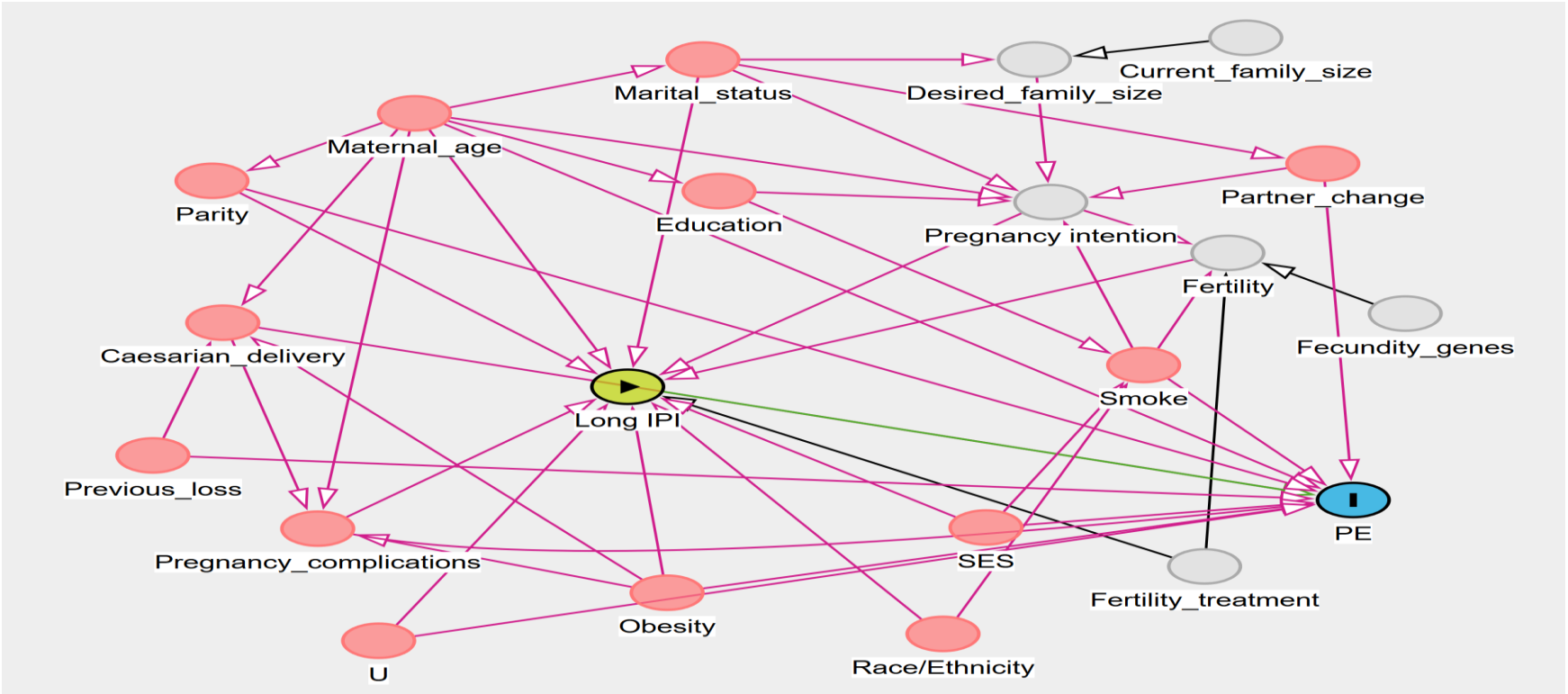


Supplementary Figure 1. Inclusion and exclusion of study cohorts



Supplementary Figure 2. Directed acyclic graph representing the association between short interpregnancy interval and preeclampsia

IPI: interpregnancy interval; PE: Preeclampsia); Outcome, exposure, measured covariates and unmeasured covariates are represented by blue, green, red and grey colours, respectively; U-unmeasured and unknown confounders; The minimal set of adjustment sets for estimating the total effect of short IPI on PE are: Marital status, maternal age, obesity, parity, pregnancy complications, SES, smoking and U. In this study, control for pregnancy complications is represented by stratification.



Supplementary Figure 3. Directed acyclic graph representing the association between long interpregnancy interval and preeclampsia

IPI: interpregnancy interval; PE: Preeclampsia); Outcome, exposure, measured covariates and unmeasured covariates are represented by blue, green, red and grey colours, respectively; U-unmeasured and unknown confounders; The minimal set of adjustment sets for estimating the total effect of long IPI on PE are: Maternal age, obesity, parity, pregnancy complications, partner change, SES, smoking and U. In this study, control for pregnancy complications is represented by stratification

Supplementary Table 1. 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Supplementary Table 2. 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Supplementary Table 3. 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 (months): RR, AR and RD (95% CI)							
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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								

Interpregnancy interval (months): RR, AR and RD (95% CI)								
Outcome	**3**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
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; RR:Relative risk; AR: Absolute risk; RD:Risk difference*

Supplementary Table 4. 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)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	5

Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5
Bias	#9	Describe any efforts to address potential sources of bias	12,14
Study size	#10	Explain how the study size was arrived at	5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	8

Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	8
Statistical methods	#12e	Describe any sensitivity analyses	12
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	na
Participants	#13b	Give reasons for non-participation at each stage	
Participants	#13c	Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Table 1
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Table 1
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	Table 1

Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	Table 1
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, 3
Main results	#16b	Report category boundaries when continuous variables were categorized	7
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 2,3;
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Supplementary Table 2, 3 & 4
Discussion			
Key results	#18	Summarise key results with reference to study objectives	13
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13,14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses,	14

		results from similar studies, and other relevant evidence.	
Generalisability	#21	Discuss the generalisability (external validity) of the study results	14,15
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19