CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

| | |
|---|---|
| Title | The impact of maternal chronic hypertension and chronic kidney disease on the risk of adverse pregnancy outcomes and long-term cardiovascular disease: a population-based epidemiology study |
| Authors | Al Khalaf, Sukainah |
| Publication date | 2022-08-31 |
| Original Citation | Al Khalaf, S. 2022. The impact of maternal chronic hypertension and chronic kidney disease on the risk of adverse pregnancy outcomes and long-term cardiovascular disease: a population-based epidemiology study. PhD Thesis, University College Cork. |
| Type of publication | Doctoral thesis |
| Rights | © 2022, Sukainah Al Khalaf. - https://creativecommons.org/licenses/by-nc-nd/4.0/ |
| Download date | 2024-07-27 16:46:59 |
| Item downloaded from | https://hdl.handle.net/10468/13729 |

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

# The Impact of Maternal Chronic Hypertension and Chronic Kidney Disease on the Risk of Adverse Pregnancy Outcomes and Long-Term Cardiovascular Disease: A Population-based Epidemiology Study

A thesis submitted to the National University of Ireland, Cork
for the degree of Doctor of Philosophy


**Thesis presented by:**

Sukainah Al Khalaf, BSN, MPH

Student number: 112220314


August 2022

**Supervisors**

Dr. Ali S. Khashan

Dr. Fergus P. McCarthy

Dr Éilis J. O'Reilly

**Head of School of Public Health**

Prof. Ivan J. Perry


School of Public Health & Irish Centre for Maternal and Child Health Research (INFANT),

University College Cork

# Table of Contents

LIST OF TABLES ..... 6
LIST OF FIGURES ..... 8
LIST OF PhD CONFERENCE PRESENTATIONS ..... 10
LIST OF PhD PEER-REVIEWED PUBLICATIONS ..... 11
LIST OF ABBREVIATIONS ..... 12
DECLARATION ..... 14
ACKNOWLEDGMENTS ..... 15
**THESIS ABSTRACT** ..... 16
**CHAPTER 1: Introduction** ..... 19
1.1 Introduction ..... 20
1.1.1 Chronic hypertension in the non-pregnant population ..... 20
1.2 Hypertension in pregnancy ..... 23
1.2.1 Increasing prevalence of chronic hypertension in the pregnant population ... 24
1.2.2 Management of women with chronic hypertension ..... 25
1.2.2.1 Pre-pregnancy care ..... 25
1.2.2.2 Management during pregnancy ..... 25
1.2.3 Chronic hypertension and adverse pregnancy outcomes ..... 29
1.2.4 Antihypertensive treatment and adverse pregnancy outcomes ..... 29
1.3 Chronic kidney disease ..... 30
1.3.1 Management of women with CKD ..... 31
1.3.1.1 Pre-pregnancy care ..... 31
1.3.1.2 Management during pregnancy ..... 32
1.3.2 Chronic kidney disease and adverse pregnancy outcomes ..... 32
1.4 Pregnancy as a stress test for future cardiovascular disease ..... 33
1.4.1 Hypertension in pregnancy and future CVD ..... 33
1.5 The need for further research ..... 34
1.6 Conceptual framework for maternal morbidity ..... 35
1.7 Overall aims and objectives ..... 38
1.8 Thesis outline ..... 39
**CHAPTER 2: Methods** ..... 41
2.1 Chapter overview ..... 42
2.2 Study design ..... 42
2.2.1 Systematic review and meta-analysis ..... 42
2.2.2 Cohort Study using Swedish National Registers ..... 44
2.2.3 Cohort Studies using data from CALIBER platform ..... 45
2.3 Data sources ..... 46
2.3.1 The Swedish National Registers ..... 46
2.3.1.1 The Medical Birth Register (MBR) ..... 47
2.3.1.2 The National Patient Register (NPR) ..... 48
2.3.1.3 The Register of Education ..... 49
2.3.1.4 Linkages between the Swedish National Registers ..... 50
2.3.2 CALIBER: A linked electronic health records platform ..... 50
2.3.2.1 Data sources in CALIBER platform ..... 50
2.3.2.1.1 Clinical Practice Research Database (CPRD) ..... 50
2.3.2.1.2 Hospital Episode Statistics (HES) ..... 52
2.3.2.1.3 Myocardial Ischaemia National Audit Project (MINAP) ..... 53
2.3.2.1.4 Office for National Statistics (ONS) ..... 54
2.3.2.1.5 Index of Multiple Deprivation (IMD) ..... 54

2.3.2.2 Data linkages between the UK EHRs ..... 55
2.4 Exposures, Outcomes and Covariates ..... 57
2.4.1 Exposures ..... 57
2.4.1.1 Chronic kidney disease ..... 57
2.4.1.2 Chronic hypertension ..... 57
2.4.1.3 Antihypertensive treatment ..... 57
2.4.1.4 Chronic hypertension and pregnancy complications ..... 58
2.4.2 Outcomes ..... 58
2.4.2.1 Adverse pregnancy outcomes ..... 58
2.4.2.2 Long-term cardiovascular disease ..... 59
2.5 Data access and ethics ..... 60
2.6 Key epidemiological considerations ..... 60
2.6.1 Validity of estimation ..... 61
2.6.2 Selection bias ..... 61
2.6.3 Information bias ..... 62
2.6.4 Confounding ..... 63
2.6.5 Random error ..... 64
2.7 Missing data ..... 65
2.7.1 Type of missing data ..... 65
2.7.2 Sources of missing data ..... 66
2.7.2.1 Sources of missing data in the Swedish national registers ..... 66
2.7.2.2 Sources of missing data in CALIBER platform ..... 67
2.7.3 Handling missing data ..... 68
2.8 Statistical modelling ..... 70
2.8.1 Meta-analysis ..... 70
2.8.1.1 Random-effects model for meta-analysis ..... 71
2.8.2 Risk difference ..... 72
2.8.3 Binary logistic regression ..... 73
2.8.3.1 Logistic regression with Propensity Score Matching ..... 74
2.8.4 Cox proportional-hazards regression ..... 76
**CHAPTER 3: The Impact of Chronic Hypertension and Antihypertensive Treatment on Adverse Perinatal Outcomes: A Systematic Review and Meta-Analysis** ..... 78
3.1 Abstract ..... 79
3.2 Introduction ..... 80
3.3 Methods ..... 81
3.4 Results ..... 84
3.5 Discussion ..... 87
3.6 Conclusion ..... 92
**CHAPTER 4: Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis** ..... 102
4.1 Abstract ..... 103
4.2 Introduction ..... 105
4.3 Methods ..... 106
4.4 Results ..... 109
4.5 Discussion ..... 114
4.6 Conclusions ..... 117
**CHAPTER 5: Pregnancy Outcomes in Women with Chronic Kidney Disease and Chronic Hypertension: A National Cohort Study** ..... 127
5.1 Abstract ..... 128
5.2 Introduction ..... 130

5.3 Methods ..... 131
5.4 Results ..... 133
5.5 Discussion ..... 135
5.6 Conclusions ..... 138
**CHAPTER 6: Role of Antihypertensive Treatment and Blood Pressure Control in The Occurrence of Adverse Pregnancy Outcomes: A Population-Based Study of Linked Electronic Health Records** ..... 146
6.1 Abstract ..... 147
6.2 Introduction ..... 148
6.3 Methods ..... 149
6.4 Results ..... 154
6.5 Discussion ..... 157
6.6 Conclusions ..... 161
**CHAPTER 7: The Association Between Chronic Hypertension and The Risk of Twelve Cardiovascular Diseases Among Parous Women: The Role of Adverse Pregnancy Outcomes** ..... 170
7.1 Abstract ..... 171
7.2 Introduction ..... 173
7.3 Methods ..... 174
7.4 Results ..... 178
7.5 Discussions ..... 180
7.6 Conclusion ..... 183
**CHAPTER 8: Discussion and Conclusions ..... 196**
8.1 Chapter overview ..... 197
8.2 Summary of main findings ..... 197
8.2.1 Findings from the systematic reviews and meta-analyses ..... 197
8.2.1.1 Systematic review and meta-analyses of chronic hypertension and antihypertensive treatment on adverse pregnancy outcomes ..... 197
8.2.1.2 Systematic review and meta-analyses of CKD and adverse pregnancy outcomes ..... 198
8.2.2 The association between CKD and chronic hypertension on adverse pregnancy outcomes in a large population-based registry ..... 200
8.2.2.1 Findings on CKD and adverse pregnancy outcomes ..... 200
8.2.2.2 Findings on chronic hypertension and adverse pregnancy outcomes ..... 201
8.2.3 Findings on the effect of antihypertensive treatment on adverse pregnancy outcomes ..... 202
8.2.4 Findings on the association between BP control and adverse pregnancy outcomes ..... 204
8.2.5 Findings on the association between pre-pregnancy hypertension and long-term CVD ..... 204
8.3 Interpretation of findings and causal inference in epidemiological research ..... 206
8.3.1 Bradford Hill's criteria for causality ..... 206
8.3.2 Bias, confounding or chance ..... 209
8.4 The impact of missing data on inferences and the likelihood of residual confounding ..... 212
8.4.1 The effect of missing data on the reported results ..... 213
8.4.1.1 The effect of missing data in the Swedish register ..... 213
8.4.1.2 The effect of missing data in the CALIBER ..... 213
8.5 Strengths and limitations of the thesis ..... 216
8.5.1 Strengths of the thesis ..... 216
8.5.2 Limitations of thesis ..... 217

8.6 Clinical and public health implications ..... 218
8.7 Recommendations for future research ..... 219
8.8 Conclusions ..... 220
**References** ..... 222
**APPENDICES** ..... 246
**Appendix 1: The impact of Chronic Hypertension and Antihypertensive Treatment on Adverse Maternal and Perinatal Outcomes: A Systematic Review and Meta-Analysis Protocol ..... 247**
**Appendix 2: Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis Protocol** ..... 250
**Appendix 3: The Impact of Chronic Hypertension And Antihypertensive Treatment on Adverse Perinatal Outcomes: A Systematic Review and Meta-Analysis (supplemental material)** ..... 253
S3.1.Supplement data on chronic hypertension meta-analysis ..... 253
*S3.1.1 Search Strategy for the association between chronic hypertension and adverse perinatal outcomes* ..... 253
*S3.1.2 Selection process and eligibility criteria* ..... 254
*S3.1.3 Data collection process and quality assessment* ..... 255
S3.2 Supplement data on antihypertensive treatment meta-analysis ..... 255
*S3.2.1 Search Strategy for the association between antihypertensive treatment and adverse perinatal outcomes* ..... 255
*S3.2.2 Selection process and eligibility criteria* ..... 257
*S3.2.3 Data collection process and quality assessment* ..... 257
S3.3 Supplementary Tables S3.1-S3.27 ..... 258
S3.4 Supplemental Figures S3.1-S3.26 ..... 299
**Appendix 4: Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis (supplemental material)** ..... 325
S4.1 Supplementary methods ..... 325
S4.2 Supplementary Tables S4.1-S4.2 ..... 327
S4.3 Supplementary Figures S4.1-S4.24 ..... 341
**Appendix 5: Pregnancy Outcomes in Women with Chronic Kidney Disease and Chronic Hypertension: A National Cohort Study (supplemental material)** ..... 358
S5.1 Supplementary Methods ..... 358
S5.2 Supplementary Results ..... 359
S5.3 Supplementary Figures (S5.1-S5.2) and Tables (S5.1-S5.6) ..... 360
**Appendix 6: The Role of Antihypertensive Treatment and Blood Pressure Control in the Occurrence of Adverse Pregnancy Outcomes: A Population-based Study of Linked Electronic Health Records (supplemental material)** ..... 370
S6.1 Supplementary Methods ..... 370
S6.2 Supplementary Figures (S6.1-S6.6) and Tables (S6.1-S6.13) ..... 371
S6.3 Results of matching: ..... 402
S6.4 Diagnostic assessment for propensity score ..... 402
**Appendix 7: The Association Between Chronic Hypertension and The Risk of Twelve Cardiovascular Diseases among Parous Women: The Role of Adverse Pregnancy Outcomes (supplemental material)** ..... 416
S7.1 Supplementary Tables S7.1-S7.3 ..... 416
**Supplementary references** ..... 427

# LIST OF TABLES

**Table 1.1** Pharmacological classes and sub-classes of antihypertensive drugs …...22

**Table 1.2** Classification of Hypertension in Pregnancy based on ISSHP categories……..……24

**Table 1.3** Guidelines for treatment of hypertension during pregnancy ……..……27

**Table 1.4** Oral antihypertensive agents for the management of chronic hypertension in pregnancy …….……28

**Table 2.1** PICO criteria used in the systematic reviews of this thesis ……..…43

**Table 2.2** Data quality standards used by CPRD …….52

**Table 3.1** Estimated odds ratios of adverse perinatal outcome for women with chronic hypertension during pregnancy compared to normotensive women……93

**Table 3.2** Estimated odds ratios of adverse perinatal outcome for women treated with antihypertensive medications during pregnancy compared to untreated women……..…….95

**Table 3.3** Estimated odds ratios of adverse perinatal outcome in treated women with chronic hypertension according to the type of antihypertensive agent during pregnancy…….……..……97

**Table 4.1** Summary results of meta-analyses of pregnancy outcomes in women with chronic kidney disease ……...…….....118

**Table 4.2** Summary results of meta-analyses of adverse pregnancy outcomes in women with CKD compared to women without CKD, according to the cause of CKD……...…….....….120

**Table 4.3** Certainty of the evidence assessed using the GRADE approach for chronic kidney disease and adverse pregnancy outcomes ……..……123

**Table 5.1** Maternal characteristics in the Swedish Medical Birth Registry..……..139

**Table 5. 2** The association between maternal chronic diseases and perinatal outcomes……..……140

**Table 5.3** The association between subtypes chronic kidney disease and perinatal outcomes …….……142

**Table 6.1** Baseline demographic characteristics for women with and without chronic hypertension during pregnancy …….…162

**Table 6.2** Chronic hypertension and adverse perinatal outcomes according to treatment status ……...……163

**Table 6.3** Antihypertensive treatment during pregnancy and adverse perinatal outcomes in women with chronic hypertension (treated vs untreated) using propensity score matched sample ……164

**Table 6.4** The effect of different antihypertensive treatment on adverse perinatal outcomes in pregnancies complicated with chronic hypertension, using propensity score matched samples ……165

**Table 6.5** The effect of less-tight versus tight control of hypertension on pregnancy outcomes in treated women with chronic hypertension ……167

**Table 7.1** Summary of maternal demographic characteristics in recorded pregnancies according to the presence of pre-pregnancy hypertension and adverse pregnancy outcomes ……184

**Table 7.2** Associations between pre-pregnancy hypertension and cardiovascular diseases according to hypertensive disorders during pregnancy and adverse pregnancy outcomes ……190

**Table 7.3** The association between pre-pregnancy hypertension and cardiovascular events (all 12 cardiovascular outcomes plus cardiovascular mortality) based on subgroup analyses ……194

**Table 7.4** Associations between pre-pregnancy hypertension and cardiovascular diseases in a subsample of non-smoking women with normal body mass index…195

**Table 8.1** Effect of smoking and body mass index on the associations between chronic hypertension and adverse pregnancy outcomes using data from the Swedish Registers ……215

**Table 8.2** Effect of smoking and body mass index on the associations between chronic hypertension and adverse pregnancy outcomes using complete-cases analysis (data from Swedish Register)……215

# LIST OF FIGURES

**Figure 1.1** Maternal morbidity measurement framework ……37

**Figure 1.2** Thesis overview including overall aim, specific objectives, corresponding chapters, and papers ……..……40

**Figure 2.1** Overview of data and shifting in ICD codes in the Swedish National Patient Register …….……49

**Figure 2.2** Data sources and linkages in CALIBER platform …….……56

**Figure 2.3** Decision process governing the choice between missing data imputation and listwise deletion …….……69

**Figure 3.1** PRISMA flow diagram of studies on the association between chronic hypertension and adverse pregnancy outcomes ……98

**Figure 3.2** PRISMA flow diagram of studies on the association between antihypertensive treatment and adverse pregnancy outcomes in women with chronic hypertension ……..……..99

**Figure 3.3** Forest plots of adjusted estimates of the association between chronic hypertension and maternal complications ……..100

**Figure 3.4** Forest plots of adjusted estimates of the association between chronic hypertension and fetal/neonatal outcomes ……..101

**Figure 4.1** PRISMA flow diagram of studies on the association between chronic kidney disease on adverse pregnancy outcome ……..……124

**Figure 4.2** Forest plots of studies of the association between chronic kidney disease and maternal complications ……125

**Figure 4.3** Forest plots of studies of the association between chronic kidney disease and fetal/neonatal outcomes ……..……..…126

**Figure 5.1** Adjusted estimates of the associations between maternal chronic disease and adverse pregnancy outcomes over time (1982-2012) ……..……145

**Figure 6.1** Predictive margins with 95% CIs of the probability of adverse perinatal outcomes by treatment across sBP levels ……...…168

**Figure 6.2** Predictive margins with 95% CIs of the probability of adverse perinatal outcomes by treatment across dBP levels ……...169

**Figure 7.1.** Study flow diagram …….…186

**Figure 7.2** Exposure variables according to pre-pregnancy hypertension, APOs, and HDP ……187

**Figure 7.3** Forest plot of adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for 12 cardiovascular outcomes, relevant composites, and the combined outcome of all cardiovascular disease including cardiovascular mortality, the exposure is pre-pregnancy hypertension …….……..…188

**Figure 7.4** Forest plot of adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for 12 cardiovascular outcomes, relevant composites, and the combined outcome of all cardiovascular disease including cardiovascular mortality, the exposures are adverse pregnancy outcomes and pre-pregnancy hypertension……..……189

**Figure 8.1** Potential mechanisms for the association between adverse pregnancy outcomes and future cardiovascular disease risk …….……208

# LIST OF PhD CONFERENCE PRESENTATIONS

## 2021

**Al Khalaf, S.Y.,** Bodunde, E., Maher, G.M., O'Reilly, É.J., McCarthy, F.P., O'Shaughnessy, M.M., O'Neill, S.M., and Khashan, A.S. Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis. *14th European Public Health Conference*. Virtual conference, November 2021. [***Oral presentation***]

**Al Khalaf, S.Y.,** Bodunde, E., Maher, G.M., O'Reilly, É.J., McCarthy, F.P., O'Shaughnessy, M.M., O'Neill, S.M., and Khashan, A.S. Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis. *7th SSNT Congress*. Virtual conference, November 2021. [***Oral presentation***]. ***Awarded investigator award for best submitted abstract***

## 2020

**Al Khalaf, S.Y.,** O'Reilly, E.J., McCarthy, F.P., Kublickas, M., Kublickiene, K. and Khashan, A.S. Cohort Study of Adverse Pregnancy Outcomes in Women with Chronic Kidney Disease. *Society for Social Medicine & Population Health*. Virtual conference, September 2020 [***Oral presentation***]

**Al Khalaf, S.Y**., O'Reilly, E.J., McCarthy, F.P., Kublickas, M., Kublickiene, K., and Khashan, A.S. Maternal Chronic Hypertension and the Risk of Adverse Maternal and Birth outcomes: A Population-based Study. *The Society for Social Medicine & Population Health*, Virtual conference, September 2020. [***Poster presentation****]*

## 2019

**Al Khalaf, S.Y.,** Barrett, P., McCarthy, F.P., O'Reilly, É.J. and Khashan, A.S. The Impact of Chronic Hypertension on Adverse Maternal and Perinatal Outcomes: A Systematic Review and Meta-Analysis. *Society for Social Medicine & European Congress of Epidemiology Joint Conference*. Cork, Ireland, September 2019. [***Oral presentation***]

**Al Khalaf, S.Y.,** Barrett, P., McCarthy, F.P., O'Reilly, É.J. and Khashan, A.S. The Impact of Chronic Hypertension on Adverse Maternal And Perinatal Outcomes: A Systematic Review and Meta-Analysis. *EuroISSHP Conference for the International Society of Hypertension in Pregnancy, Lund, Sweden, October 2019.* [***Poster presentation***]

# LIST OF PhD PEER-REVIEWED PUBLICATIONS

**2021**

Al Khalaf SY, O'Reilly ÉJ, Barrett PM, B. Leite DF, Pawley LC, McCarthy FP, Khashan AS. Impact of Chronic Hypertension and Antihypertensive Treatment on Adverse Perinatal Outcomes: Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2021 May 4;10(9):e018494.

Al Khalaf S, Bodunde E, Maher GM, O'Reilly ÉJ, McCarthy FP, O'Shaughnessy MM, O'Neill SM, Khashan AS. Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis. American Journal of Obstetrics and Gynecology. 2021 Nov 2.

Al Khalaf SY, O'Reilly ÉJ, McCarthy FP, Kublickas M, Kublickiene K, Khashan AS. Pregnancy Outcomes in Women with Chronic Kidney Disease and Chronic Hypertension: A National Cohort Study. American Journal of Obstetrics and Gynecology. 2021 Sep 1;225(3):298-e1.

**2022**

Al Khalaf S, Khashan AS, Chappell LC, O'Reilly ÉJ, McCarthy FP. Role of Antihypertensive Treatment and Blood Pressure Control in the Occurrence of Adverse Pregnancy Outcomes: A Population-Based Study of Linked Electronic Health Records. Hypertension. 2022 May 3:10-161.

# LIST OF ABBREVIATIONS

| | | | |
|---|---|---|---|
| **ACEIs** | Angiotensin-Converting Enzyme Inhibitors | **MAP** | Maternal Mean Arterial Pressure |
| **ACC** | The American College of Cardiology | **MAR** | Missing At Random |
| **ACOG** | American College of Obstetricians and Gynecologists | **MBR** | Medical Birth Register |
| **ACS** | Acute Coronary Syndrome | **MCAR** | Missing Completely At Random |
| **AHA** | American Heart Association | **mg/d** | Milligrams per day |
| **aHR** | adjusted Hazard Ratio | **MHRA** | Medicines And Healthcare Products Regulatory Agency |
| **aOR** | Adjusted Odds Ratio | **MNAR** | Missing Not At Rando |
| **APO** | Adverse Pregnancy Outcome | **MINAP** | Myocardial Ischaemia National Audit Project |
| **ARBs** | Angiotensin Receptor Blockers | **mmHg** | Millimetres of Mercury |
| **BMI** | Body Mass Index | **MR** | Modified Release |
| **BP** | Blood Pressure | **NHS** | National Health Service |
| **CALIBER** | Clinical research using Linked Bespoke studies and Electronic health Records | **NICE** | National Institute of Health and Care Excellence |
| **CCB** | Calcium Channel Blocker | **NICU** | Neonatal Intensive Care Unit |
| **CH** | Chronic Hypertension | **NOS** | Newcastle-Ottawa Scale |
| **CHIPS** | Control of Hypertension In Pregnancy Study | **NOS** | Not Otherwise Specified |
| **CI** | Confidence Interval | **NPR** | National Patient Register |
| **CKD** | Chronic Kidney Disease | **ONS** | Office For National Statistics |
| **CVD** | Cardiovascular Disease | **OPCS** | Office of Population Censuses and Surveys Classifications of Interventions and Procedures |
| **CPRD** | Clinical Practice Research Datalink | **OR** | Odds Ratio |
| **DASH** | Dietary Approaches to Stop Hypertension | **PA** | Prolonged Action |

| | | | |
|---|---|---|---|
| **DBP** | Diastolic Blood Pressure | **PbR** | payment by results |
| **eGFR** | Estimated Glomerular Filtration Rate | **PE** | Pre-Eclampsia |
| **EHRs** | Electronic Health Records | **PIN** | Personal Identification Number |
| **ESC** | European Society of Cardiology | **RCT** | Randomized Control Trial |
| **ESH** | European Society of Hypertension | **RR** | Relative Risk |
| **FGR** | fetal growth restriction | **PTB** | Preterm Birth |
| **GFR** | Glomerular Filtration Rate | **PRISMA** | Preferred Reporting Items for Systematic Review and Meta-Analysis |
| **GP** | General Practitioners | **PROSPERO** | International Prospective Register of Systematic Reviews |
| **GPRD** | General Practice Research Database | **SBP** | Systolic Blood Pressure |
| **GRADE** | Grading Of Recommendations, Assessment, Development and Evaluation | **SD** | Standard Deviation |
| **HDP** | Hypertensive Disorders of Pregnancy | **SE** | Standard Error |
| **HELLP** | Haemolysis, Elevated Liver enzyme Levels, and Low Platelet Levels | **SGA** | Small for Gestational Age |
| **HES** | Hospital Episode Statistics | **SOGC** | Society of Obstetricians and Gynaecologists of Canada |
| **HR** | Hazard Ratio | **TTP** | Trusted third party |
| **ICD** | International Classification of Diseases | **UK** | United Kingdom |
| **IMD** | Index Of Multiple Deprivation | **US** | United States |
| **ISAC** | Independent Scientific Approval Committee | **UTS** | Up To Standard |
| **ISSHP** | International Society for the Study of Hypertension in Pregnancy | **VPTB** | VERY Preterm Birth |
| **LA** | Long-Acting | **Wks.** | Weeks |
| **LBW** | Low Birthweight | **XL** | Extended Release |

## DECLARATION

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

| Signed | Date |
| --- | --- |
| Sukainah | 17/03/2022 |

# ACKNOWLEDGMENTS

The research described in this thesis was supported by a grant from the Ministry of Health (MOH), Saudi Arabia, in the form of a PhD scholarship.

I am grateful to my amazing supervisory panel, Dr. Ali Khashan, Dr. Fergus McCarthy, and Dr. Éilis O'Reilly, for the time and effort they have put into the supervision of my thesis. This thesis would not have been possible without your encouragement, insightful comments, and guidance. I would particularly like to thank Dr. Ali Khashan for always being available whenever I needed his feedback and support. I am sincerely grateful for his constant assistance and the tremendous support he provided throughout my PhD study.

I would like to acknowledge and give my warmest thanks to Dr. Michelle O'Shaughnessy (*Cork University Hospital*) and Prof. Lucy Chappell (*King's College London*), who provided invaluable insights and helped to shape some of the presented work in this thesis. Sincere thanks to my co-authors in Sweden Dr. Marius Kublickas, and Dr. Karolina Kublickiene, for their guidance and support. Thanks also to Natalie Fitzpatrick, and Dr. Arturo Gonzalez-Izquierdo (*University College London*) for their help in accessing and understanding the structure of CALIBER data. Thank you to everyone within the School of Public Health and INFANT Research Centre. A special thanks to my friend Zainab for cheering me on during the dark moments that visit me sometimes while trying to complete my PhD.

Thank you to my family for the support. In particular, many thanks to my parents, Zahra and Yousef, for supporting me throughout all my studies. They instilled in me the value and importance of hard work, education, commitment, and integrity.

Last but not least, thank you to my husband, Khaleel, who stood by me and encouraged me as I pursued another academic degree. Thanks for your patience and unending support on this journey, and beyond all else, has always believed in me. Finally, thanks to my beloved children, Abdul-Aziz and Ahmed, for your unconditional love, humour and encouragement.

**Thank you!**

# THESIS ABSTRACT

**Background and aims:** The prevalence of chronic hypertension (CH) and chronic kidney disease (CKD) have increased among pregnant women in recent decades. Given the improvement in antenatal care over the last few decades, it is still unclear whether the risk of adverse pregnancy outcomes (APOs) among women with CH and/or CKD has decreased. There is limited evidence on the association between antihypertensive treatment and APOs in women with CH. Although there is evidence that women with a history of APOs have an increased risk of cardiovascular disease (CVD), it remains unclear whether pre-pregnancy hypertension and the occurrence of APOs would influence this association. The aim of this PhD project was to investigate the impact of maternal CH and/or CKD and antihypertensive treatment on the risk of APOs and long-term CVD.

**Structure and methods:** This thesis includes eight chapters: Introduction, Methods, two systematic review articles on the impact of CH and CKD on APOs, three original research articles, and Discussion. Data from the Swedish National Registers were analysed to examine the associations between CH/CKD and the risk of APOs over the last three decades. Data from the UK CALIBER platform were used to investigate: i) the association between CH and APOs, with a focus on the role of antihypertensive treatment and control of hypertension, and ii) the associations between pre-pregnancy hypertension and subsequent diagnosis of 12 different CVDs, considering the role of APOs on these associations. Adverse pregnancy outcomes were pre-eclampsia, preterm birth, stillbirth, Caesarean section and small for gestational age (SGA). The statistical methods were done using logistic regression models for the Swedish data, logistic regression models with propensity score matching for the antihypertensive treatment analyses, while the associations between pre-pregnancy hypertension and CVD were analysed using stratified Cox models. All statistical models were adjusted for several potential confounders.

**Results:** *Systematic reviews and meta-analyses:* CH was associated with 5-fold increased odds of pre-eclampsia and approximately 2-fold increased odds of stillbirth, preterm birth, and SGA, compared to women without CH. Women with treated CH (compared to untreated normotensive women) had higher odds of APOs. However, the

results were inconsistent when outcomes were compared between treated and untreated women with CH; no increased odds of superimposed pre-eclampsia or other APOs were observed, except for 86% increased odds of SGA.

Findings from the meta-analysis suggested that women with CKD had higher odds of pre-eclampsia, Caesarean section, preterm birth, very preterm birth, and SGA. All causes of CKD were associated with increased odds of pre-eclampsia, preterm birth, and SGA, with stronger associations in women with diabetic CKD, particularly for preterm birth [adjusted odds ratio (aOR): 4.76, (95% confidence interval (CI), 3.65–6.21)] and SGA [aOR: 4.50, (95% CI, 2.92–6.94)]. The findings according to the severity of kidney disease showed that later stages of CKD were associated with a greater odds of APOs than earlier stages.

*Swedish National Registers:* The overall findings from this study suggested that the odds of APOs remain high in women with CH and/or CKD, and the odds persisted independent of parity, maternal age, and body mass index, among other potential confounders. No association was found between CKD and stillbirth. All causes of CKD were associated with higher odds of pre-eclampsia, emergency Caesarean section, and medically indicated preterm birth, and the ORs were higher in women with diabetic CKD, renovascular disease, and congenital kidney disease than other CKD subtypes.

*CALIBER studies:* The results suggested a higher odds of APOs in women with CH (treated and untreated) compared to untreated normotensive women. In women with CH, those requiring treatment (versus untreated) had 17%, 25%, and 80% increased odds of superimposed pre-eclampsia, preterm birth, and fetal growth restriction (FGR), respectively. However, these results were mainly attributable to the level of blood pressure (BP) control among the treated group; as similar results were found between the untreated and treated women with CH who achieved tight control (BP<135/85 mmHg) for all assessed outcomes except for a 59% decreased odds of superimposed pre-eclampsia and a 55% increased odds of FGR. Pregnant women with CH who were prescribed methyldopa (versus β-blockers) had 43%, 59%, and 44% increased odds of superimposed pre-eclampsia, preterm birth, and very preterm birth, but 66% lower odds of FGR. No differences in outcomes were found in women who were prescribed calcium-channel-blockers (versus β-blockers) except for 94% increased odds of preterm birth. The magnitude of the associations increased with increasing BP, and the

strongest associations were observed in women with severe hypertension (BP≥ 160/90 mmHg). In treated women with CH, less-tight (BP≥135/85 mmHg) versus tight (BP<135/85 mmHg) control was associated with almost 2-fold higher odds of superimposed pre-eclampsia, very preterm birth, and a 3-fold higher odds of severe hypertension.

During the 20-year study period, 16,499 CVD incident were observed, of which two-thirds (66%) had occurred in young women (under 40 years). Pre-pregnancy hypertension (versus no pre-pregnancy hypertension) was associated with a 2-fold higher risk of any subsequent CVD. When the results were subclassified according to the presence of APOs, the strongest associations were found in women with pre-pregnancy hypertension and APOs across the 12 CVD; with almost a 3-fold increased risk to develop any subsequent CVD, an 8-fold increased risk of coronary heart disease, and a 10-fold increased risk of heart failure, compared to those who remained normotensive without APOs.

**Conclusions:** This thesis indicated that CKD and CH were associated with a wide range of APOs than the general obstetric population. Therefore, multidisciplinary prenatal consultation and antenatal management should be provided for these women with close monitoring during pregnancy. If antihypertensive treatment is required, clinicians might consider tighter control during pregnancy as better outcomes were observed in women with tightly controlled hypertension. β-blockers might be superior in reducing APOs than methyldopa, with an exception for FGR, which was higher in the β-blockers group. Finally, the findings suggested strong associations between pre-pregnancy hypertension with subsequent CVD, with a greater risk among women who had pre-pregnancy hypertension and APOs. Pre-pregnancy hypertension should be managed adequately during pregnancy to reduce the risk of APOs and subsequently reduce the risk of CVD, which emphasizes that a history of reproductive risk factors (including APOs) should be considered in screening tools for CVD beyond the postpartum period to optimize long-term cardiometabolic health in women.

# CHAPTER 1: Introduction

## 1.1 Introduction

The majority of pregnancies are uncomplicated, resulting in a healthy child, and women recover well after delivery. However, women with pre-existing diseases, such as chronic hypertension or chronic kidney disease (CKD), are more vulnerable to pregnancy complications compared with healthy women.

In recent decades, care for women in pregnancies has improved, and subsequently, maternal health has improved. The mortality ratio has declined substantially (44%) from 385 in 1990 to 216 per 100,000 livebirths in 2015 (1). The burden of maternal mortality remains considerably high in low-income countries, particularly in sub-Saharan Africa (1). A 2014 systematic review of 23 studies (including 417 datasets from 115 countries) has reported that more than half of maternal mortality worldwide was due to indirect causes (27.5%) and the leading direct obstetric cause was haemorrhage (27.1%), while the second most common direct cause was hypertensive disorders of pregnancy (HDP) (14%) (2). Other causes included sepsis (10.7%), abortion (7.9%), embolism (3.2%), and other direct causes of death (9.6%) (2).

### 1.1.1 Chronic hypertension in the non-pregnant population

Within any population, blood pressure (BP) values occur within a continuum and are determined by mechanical, hormonal, and environmental factors. Therefore, any definition of hypertension utilises arbitrary threshold values within this continuum (3). Chronic hypertension can either be primary (essential), when a specific underlying cause of hypertension cannot be found or secondary when hypertension can be explained by a consequence of a specific abnormality or medical disorder of the renal, endocrine, immune or vascular system (3). Generally, high BP is managed using a comprehensive set of non-pharmacological and pharmacological strategies, with an emphasis on overall patient health. Non-pharmacological interventions are aimed at lifestyle changes, such as restricting salt intake, exercising regularly, and weight management. However, patients may require pharmacological intervention to maintain their BP within normal ranges (3) (antihypertensive classes are shown in **Table 1.1**).

Target BP and treatment regimens in the non-pregnant adult population differ from that in the pregnant population. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (2017) (4) and the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines (2018) (5) are

the most recent guidelines regarding prevention, assessment, and approach to treat hypertension in adults. While both updated guidelines agree on many points, there are also important differences in their recommendations. Overall, both guidelines recommend lifestyle changes, including a low-sodium diet, exercise, bodyweight reduction, low to moderate alcohol intake, and adequate potassium intake. However, the major discordance is with the level of BP defining hypertension, BP targets for treatment initiation, and the use of initial combination therapy (6).

The BP target was lowered in many guidelines following the evidence from the SPRINT (Systolic Blood Pressure Intervention Trial) study (2015), where the findings suggested that aggressive BP control (systolic blood pressure (sBP) <120 mmHg versus a standard goal of <140 mmHg) resulted in a significant reduction in cardiovascular mortality (43%) and morbidity (25%) (7). As a result, the AHA/ACC defined hypertension as BP ≥130/80 mmHg and set a target of BP ≤130/80 mmHg for all patients (4). In contrast, the ESC/ESH define hypertension as BP>140/90 mmHg, and recommend reducing BP to <140/90 mmHg, with an exception for those at high cardiovascular risk (≥10%) or in younger patients (<65 years) if the antihypertensive regime is well tolerated aiming to achieve a BP of 130/80 mmHg or lower (5).

The ESC/ESH guidelines recommend the use of initial combination therapy in a single-tablet combining at least two drugs (either angiotensin-converting enzyme inhibitors (ACEIs) or an angiotensin receptor blockers (ARBs) with either a thiazide diuretic agent or a calcium channel blocker); and to escalate to a triple combination formulation as a third step (5). The ACC/AHA Guidelines support a similar approach, which also recommends initial combination therapy. Additionally, both guidelines recommended a restriction of the use of β-blockers only to patients with comorbidities or other indications. It should be noted however, that target BP for initiation treatment and the antihypertensive regimen during pregnancy are different, and there are variations between national and international guidelines, which are illustrated below in section 1.2.

**Table 1.1** Pharmacological classes and sub-classes of antihypertensive drugs

| **Pharmacological classes (**Major classes) | **Sub-classes** | **Molecules** |
|---|---|---|
| β-blockers | Non-vasodilating with β1-selectivity | Acebutolol, atenolol, betaxolol, bisoprolol |
| | Non-vasodilating without β1-selectivity | Carteolol, esmolol, metoprolol, nadolol, oxprenolol, penbutolol, propranolol, timolol |
| | Vasodilating | Celiprolol, carvedilol, labetalol, nebivolol, pindolol |
| Diuretics | Loop diuretics | Furosemide, bumetanide, torsemide |
| | Thiazides diuretics | Bendroflumethiazide, chlorothiazide, chlortalidone, hydrochlorothiazide, indapamide, polythiazide, trichlormethiazide |
| | Potassium sparing diuretics | amiloride, eplerenone, spironolactone, triamterene |
| Angiotensin-converting enzyme inhibitors | | Benazepril, captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril, zofenopril |
| Angiotensin II receptor blockers | | Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan |
| Calcium-channel blockers | Non-dihydropyridines | Diltiazem, verapamil |
| | Dihydropyridines | Amlodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nitrendipine |
| **Other classes** | | |
| Renin inhibitors | | Aliskiren |
| Alpha-adrenergic receptor antagonists | | Doxazosin, prazosin, terazosin |
| Centrally acting agents | | Clonidine, methyldopa, rilmenidine |
| Direct acting vasodilators | | Hydralazine, minoxidine |

Source: Laurent (2017) (8).

## 1.2 Hypertension in pregnancy

Hypertension is one of the most common medical complications during pregnancy. Still, there has been a considerable debate over many aspects of the classification, diagnosis, and management of the HDP (9). Hypertension in pregnancy can be defined as chronic (predating pregnancy or diagnosed before 20 weeks' gestation) or de novo (new-onset in pregnancy, usually occurring at or after 20 weeks' gestation) (9). In general, hypertension in pregnancy is defined as sBP ≥140 and/or diastolic blood pressure (dBP) ≥90 mmHg (9).

The International Society for the Study of Hypertension in Pregnancy (ISSHP) classified HDP into chronic hypertension, white-coat hypertension, masked hypertension, gestational hypertension, transient gestational hypertension, pre-eclampsia, and pre-eclampsia superimposed on chronic hypertension (10). The definitions of each type of HDP are shown below in **Table 1.2**.

The available guidance suggested that the BP measurements should be repeated to confirm true hypertension. In practice, the diagnosis of chronic hypertension is often recognised for the first time at the first or early second trimester booking visit (9). Additionally, the diagnosis of pre-eclampsia in women with chronic hypertension can be difficult because their BP is already elevated, and proteinuria might be present before pregnancy (11). Therefore, the ISSHP has indicated that elevations in BP are not sufficient to diagnose superimposed pre-eclampsia, as such elevations are difficult to distinguish from the usual increase in BP. However, in the absence of pre-existing proteinuria, a new-onset of proteinuria in the setting of a rise in BP is sufficient to diagnose superimposed pre-eclampsia (9).

**Table 1.2** Classification of Hypertension in Pregnancy based on ISSHP categories (2021)

| ***Hypertension identified before pregnancy or before the first 20 weeks' gestation*** | |
|---|---|
| **Classification** | **definition** |
| **Chronic hypertension** | Hypertension (sBP ≥140 and/or dBP ≥90 mmHg), predating pregnancy or diagnosed before 20 weeks' gestation |
| **White-coat hypertension** | Elevated BP (sBP ≥140 and/or dBP ≥90 mmHg) when measured in the office or clinic, but normal BP (<135/85 mmHg) measured at home or work using ambulatory BP monitoring |
| **Masked hypertension** | Normal BP (<140/90 mmHg) at a clinic/office visit, but ≥135/85 mmHg at other times outside the clinic/office (usually diagnosed by 24-hour ambulatory BP monitoring) |
| ***Hypertension arising de novo of after 2o weeks of pregnancy*** | |
| **Classification** | **definition** |
| **Gestational hypertension** | Elevated BP arising at ≥ 20 weeks' gestation in the absence of proteinuria or other findings suggestive of pre-eclampsia |
| **Transient gestational hypertension** | Hypertension arising at ≥20 weeks' gestation in a clinic but then settles with repeated BP readings |
| **Pre-eclampsia** | |
| **De novo** | Pre-eclampsia (de novo) is gestational hypertension accompanied by one or more of new-onset conditions[a] at ≥ 20 weeks' gestation |
| **Superimposed on chronic hypertension** | In women with chronic hypertension, development of new proteinuria, another maternal organ dysfunction(s), or evidence of uteroplacental dysfunction[a] |

[a] These conditions include proteinuria, other maternal end-organ dysfunction, including evidence of maternal acute kidney injury, liver dysfunction, neurological complications, pulmonary oedema, hematological complications (haemolysis), or uteroplacental dysfunction (such as placental abruption or fetal growth restriction). Source: based on Magee *et al*. (10)

### 1.2.1 Increasing prevalence of chronic hypertension in the pregnant population

The prevalence of chronic hypertension in pregnant women has varied in population studies from 0.3% to 4% (12-15). A longitudinal US cohort study has reported a sustained increase by approximately 80% in the prevalence of chronic hypertension from 1995 to 2008, with 1.8% pregnancies complicated by chronic hypertension in 2007-2008 (13). Another US study has shown that during a 4-decade period (1970–2010), chronic hypertension in the pregnant population has increased by 6% per year

(16). There was a sharp increase in the prevalence with advancing maternal age even after adjustments for smoking and obesity (16). Yet this estimated prevalence is expected to continue to rise given that hypertension is associated with older age and more women are delaying childbearing, which is reflected in a statistical increase in the average of American women's age at first birth from 21.4 years in 1970 (17) to 26.8 in 2017(18). Similarly, the average age of women in the European Union at first birth has gradually increased from 28.8 years in 2013 to 29.3 years in 2018 (19). In addition, the proportion of women who had pre-pregnancy obesity [body mass index (BMI) ≥30 kg/m$^2$] has increased significantly over time, from 8% in 1989 to 16% in 2007, with one in every 1000 women giving birth in the United Kingdom being extremely obese (BMI ≥ 50 kg/m$^2$) (20, 21). Therefore, advanced maternal age, combined with other risk factors including obesity and metabolic syndrome, may contribute to the increased prevalence of chronic hypertension during pregnancy (16, 20-22).

### 1.2.2 Management of women with chronic hypertension

#### *1.2.2.1 Pre-pregnancy care*

Prenatal care for women with chronic hypertension should begin before pregnancy to provide counselling for these women about the potential risks and to optimize the antihypertensive regimens before conception (i.e., antihypertensive agent(s) may need to be changed to another class before conception) (11). Evaluation before pregnancy for secondary causes of hypertension and target-organ damage is recommended for women with chronic hypertension as such evaluation may involve radiation exposure or require surgical intervention (11, 23). Also, lifestyle modifications have been demonstrated to improve BP control in nonpregnant individuals. For example, sodium reduction, weight reduction (23), and Dietary Approaches To Stop Hypertension (DASH) diet (24) are recommended for women with chronic hypertension before pregnancy (11).

#### *1.2.2.2 Management during pregnancy*

##### *i. Blood pressure goal in pregnancy*

Overall, there are differences among national and international guidelines related to BP targets for hypertensive women during pregnancy (**Table 1.3**) (25). The ISSHP stated that antihypertensive treatment should be used to maintain BP in the range of 110-140/80-85 mmHg (9). The primary benefit of antihypertensive treatment during

pregnancy is the reduction of maternal complications, such as stroke, by minimizing the episodes of severe hypertension (26, 27).

To date, antihypertensive treatment has not been shown to reduce superimposed pre-eclampsia, fetal growth restriction, or improve neonatal outcomes (26). There is also a concern that excessive use of antihypertensive treatment during pregnancy may decrease fetoplacental perfusion and increase the risk of fetal growth restriction. For instance, an updated meta-analysis (including 34 trials; 2640 women with mild to moderate pregnancy hypertension, 2002) suggested an association between the treatment-induced mean difference in maternal mean arterial pressure (MAP) and lower mean birth weight (28). It was reported that a 10 mmHg fall in MAP was associated with a 176g decrease in birthweight, and the authors highlighted a concern that normalization of mild to moderate maternal hypertension in pregnancy may have an adverse effect on fetal growth (28).

More recent evidence from CHIPS trial (the international Control of Hypertension In Pregnancy Study) evaluated the effect of BP control on pregnancy outcomes between "tight" (target dBP 85 mmHg) and "less tight" (target dBP 100 mmHg) control, including 987 women (75% with chronic hypertension and 25% with gestational hypertension). The authors reported that "less-tight" (versus "tight") control increased the risk of maternal severe hypertension significantly [adjusted odds ratio (aOR): 1.80, (95% confidence interval (CI), 1.34–2.38)], but there was no increased risk in serious maternal complications [aOR: 1.74, (95% CI, 0.79–3.84)] (29). There were no differences between both groups in the risk of pregnancy loss [aOR: 1.14 (95% CI, 0.53–2.45)], high-level neonatal care [aOR: 1.00 (95% CI, 0.75–1.33)], or fetal growth restriction [aOR: 0.78, (95% CI, 0.56–1.08)] (29). Accordingly, four national and international practice guidelines (United Kingdom, Canada, Poland, and the ISSHP) now endorse "tight" BP control for hypertension in pregnancy (30).

**Table 1.3** Guidelines for treatment of hypertension during pregnancy

| Variable | International guidelines | | National guidelines | | |
|---|---|---|---|---|---|
| | **ISSHP, 2018** (9, 10) | **ESC, 2018** (31) | **NICE, 2019** (32) | **ACOG, 2019** (33, 34) | **SOGC, 2014** (35, 36) |
| **BP threshold for antihypertensive therapy** | ≥140/90 mmHg in clinic or office<br>≥135/85 at home | ≥150/95 mmHg, or at >140/90 mmHg in women with chronic hypertension superimposed gestational hypertension, subclinical organ damage or symptoms | ≥140/90 mmHg | ≥160/110 mmHg, or at lower BP in women with comorbidities or end-organ damage | ≥140/90 mmHg |
| Medications—first line | | | | | |
| Severe hypertension BP (≥160/110 mmHg) | IV labetalol, oral nifedipine, IV hydralazine | IV labetalol, oral nifedipine, oral methyldopa | IV labetalol, oral nifedipine, IV hydralazine, oral labetalol | IV labetalol, oral nifedipine, IV hydralazine | IV labetalol, oral nifedipine, IV hydralazine |
| Non-severe hypertension | Labetalol, methyldopa, nifedipine, oxprenolol | Labetalol, methyldopa, calcium antagonists | Labetalol, nifedipine, methyldopa | Labetalol, methyldopa, nifedipine | Labetalol, other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol), methyldopa, nifedipine |
| Medications—second line | | | | | |
| | Hydralazine, prazosin | - | - | Hydrochlorothiazide | Clonidine, hydralazine, thiazide diuretics |
| Medication to avoid during pregnancy | - | ACEIs, ARBs | ACEIs, ARBs, direct renin inhibitors, diuretics unless oliguric | ACEIs, ARBs | ACEIs, ARBs, atenolol |
| **Target BP on antihypertensive therapy** | | | | | |
| Severe hypertension | - | - | | 140–150/90–100 mmHg | < 160/110 mmHg |
| Non-severe hypertension (or unspecified) | 110–140/80–85 mmHg | - | ≤135/85 mmHg | 120 to <160/80 to <110 mmHg | dBP of 85 mmHg |

ACOG, American College of Obstetricians and Gynecologists; ACEIs, Angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; dBP, diastolic blood pressure; ESC European Society of Cardiology, NICE, National Institute for Health and Care Excellence; SOGC, Society of Obstetricians and Gynaecologists of Canada with an update on antihypertensive treatment from Hypertension Canada's 2018 guidelines

### *ii. Antihypertensive therapy*

National and international clinical practice guidelines recommend that severe hypertension be treated with antihypertensive agents, but there is disagreement regarding BP thresholds for initiating medication (**Table 1.3**) (30). First-line antihypertensive agents are labetalol, methyldopa, and nifedipine (9, 37-39). In contrast, some antihypertensive agents are contraindicated during pregnancy, such as ACEIs and ARBs, due to potential adverse effects on the fetus (30). Findings from a recent meta-analysis (2020) suggested that exposure to ACEIs/ARBs during pregnancy is associated with congenital malformations, miscarriage and stillbirth (40). More details about the first-line antihypertensive agents, including recommended doses and potential side effects for managing chronic hypertension in pregnancy, are available in **Table 1.4** below.

**Table 1.4** Oral antihypertensive agents for the management of chronic hypertension in pregnancy

| Drug | Class or mechanism of action | Usual range of dose (mg/day) | Side effect |
|---|---|---|---|
| **Labetalol** | Nonselective β-blocker | 300–1200 orally in two to three doses | Possible bronchospasm Contraindicated in severe asthma, cardiomyopathy |
| **Methyldopa** | Centrally acting alpha-agonist | 750–2250 orally in three to four doses | Transient increase in hepatic enzymes, depression |
| **Nifedipine** PA or MR | Calcium-channel blocker | 20–120 orally in two or three divided doses | Headache, flushing, peripheral edema |
| **Nifedipine** XL or LA | Calcium-channel blocker | 30–120 orally in one or two doses | Headache, flushing, peripheral edema |
| **Hydralazine** | Peripheral vasodilator | 40–300 orally in three or four divided doses | Orthostatic hypotension |

LA, long-acting; MR, modified release; PA, prolonged action; XL, extended-release

Source: based on Magee *et al*. (10), and Chahine *et al*.(41)

### 1.2.3 Chronic hypertension and adverse pregnancy outcomes

Hypertension in pregnancy has become a public health concern as previous cohort studies reported a higher risk of adverse pregnancy outcomes in women with chronic hypertension compared to normotensive women. A meta-analysis assessing pregnancy complications in women with chronic hypertension reported that chronic hypertension was associated with superimposed pre-eclampsia [risk ratio (RR=7.7), Caesarean delivery (RR=1.3), preterm delivery (RR=2.7), low birthweight (LBW) (RR=2.7), neonatal unit admission (RR=3.2) and perinatal death (RR=4.2) (42).

However, this meta-analysis did not compare the outcomes in women with chronic hypertension to those without chronic hypertension from the same population. Instead, the incidences from the US studies for women with chronic hypertension were compared with the US general population. In addition, most of the included studies in this review did not report the demographic characteristics, and the RR estimates were not adjusted for potential confounders.

Furthermore, there are inconsistencies in the reported associations between chronic hypertension and some adverse pregnancy outcomes, such as emergency Caesarean delivery (14, 43) and spontaneous preterm delivery (44, 45). Also, it remains unclear whether these associations have changed over the last few decades, given the improvement in maternal care, or whether the risks persisted independently of underlying risk factors, such as maternal age, BMI and parity. For example, the available evidence suggested that the prevalence of chronic hypertension increased sharply with advancing maternal age; adjustments for obesity and smoking did not alter this result (16). Therefore, further studies accounting for the potential confounders are warranted to estimate the magnitude of adverse pregnancy risk for women with chronic hypertension. In addition, the effect of antihypertensive treatment or hypertension control on these associations is not fully understood.

### 1.2.4 Antihypertensive treatment and adverse pregnancy outcomes

The available literature examining the effect of antihypertensive treatment on pregnant women with chronic hypertension is limited. Also, there is a lack of evidence regarding the magnitude of the effect size of adverse pregnancy outcomes relative to appropriate comparative groups. For example, previous cohort studies of women with chronic hypertension compared pregnancy outcomes in treated women with either

untreated normotensive women or untreated women with chronic hypertension. The findings suggested that women requiring antihypertensive treatment during pregnancy had a higher risk of adverse pregnancy outcomes compared to untreated normotensive women (46-50). On the other hand, the results were inconsistent when pregnancy outcomes were compared between treated and untreated women with chronic hypertension (51-54).

Findings from a meta-analysis of randomized controlled trials (RCTs) in pregnant women with chronic hypertension showed a reduced risk of severe hypertension [5 trials, 446 women; RR: 0.33, (95% CI, 0.19–0.56)] in treated women compared to no treatment or placebo (55). However, there was no effect of treatment found on other clinically important outcomes, including pre-eclampsia and small for gestational age (SGA) infants, possibly due to insufficient power in RCTs (55, 56), where enrolment of women with chronic hypertension ranged from 33 (57) to 263 (58) women with mild to moderate hypertension. In observational studies, the sample size varied widely from 169 pregnancies (156 women) in a hospital-based study (59) to 2,727 women with chronic hypertension in a population-based study (51).

Few studies have directly compared the effectiveness of different antihypertensive agents in pregnant women with chronic hypertension. A Canadian population-based study reported a higher risk of SGA infants in pregnant women exposed to β-blockers only compared to those exposed to methyldopa only (60). Data from RCTs are limited; a meta-analysis of five trials (including <300 women for each assessed outcome) comparing methyldopa versus other agents reported no differences for severe hypertension or perinatal outcomes (55). However, no data are available on whether the observed effect of adverse pregnancy outcomes is modified by control of hypertension. Thus, large population-based studies are needed to examine the impact of different antihypertensive agents and BP control on the occurrence of adverse pregnancy outcomes among women with chronic hypertension.

## 1.3 Chronic kidney disease

Chronic kidney disease is a major global public health problem and it is associated with disability, decreased quality of life, and premature mortality (61). The definitions and classifications of CKD have changed over time, with the current international guidelines defining CKD as having markers of kidney damage (e.g., albumin excretion

rate >30 mg/d) and/or a reduced estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 $m^2$ for at least 3 months duration, irrespective of the underlying cause (62, 63). The disease is further sub-classified into five stages according to the severity of the disease. Stage 1 and stage 2 are characterised by kidney damage (such as proteinuria or structural kidney abnormalities) in the presence of normal or mildly impaired kidney function, with an eGFR ≥60 mL/min/1.73$m^2$. Stages 3-5 (moderate to severe CKD) occurs when the eGFR <60 mL/min/1.73 $m^2$ (62, 63).

A global prevalence of 9.5% has been reported for CKD in women, with a higher proportion of early stages reported in women than men (61, 64). In high-income countries, CKD is estimated to affect 3% of pregnant women (65), and this prevalence is predicted to increase in parallel with increasing maternal age and obesity in this population (66).

### 1.3.1 Management of women with CKD

#### *1.3.1.1 Pre-pregnancy care*

The available guidance recommends that all women of reproductive age with CKD should be offered safe and effective contraception to allow pregnancy to be planned, with individualized and detailed risk counselling before conception (66, 67). For example, women with CKD might be taking a teratogenic medication, are within one year of renal transplantation or acute graft rejection (67). Thus, pre-pregnancy consultation is important for these women. Furthermore, data have shown that exposure to teratogenic medications such as cyclophosphamide and mycophenolate mofetil in the first trimester of pregnancy can lead to abnormalities in the developing fetus (68, 69). The first year after transplantation holds the highest risk of rejection, and women typically require management with teratogenic medications, which are associated with adverse effects on the fetus (70).

On the other hand, women with CKD considering pregnancy should be provided pre-pregnancy counselling by a multidisciplinary team to discuss the potential risk. Pre-pregnancy counselling is also important as it aims to promote optimal short and long-term health outcomes (such as minimised doses of medications, optimised BP control (<140/90 mmHg), and reduced risk of exposure to teratogenic medications) of these women and their children during and after pregnancy (67).

#### *1.3.1.2 Management during pregnancy*

Management of women with CKD during pregnancy involves substitution of known teratogens and optimization of disease control (66). It is recommended that renal function be assessed during pregnancy, and women with CKD should have additional ultrasound assessments for biometry and fetal well-being (67). Women with CKD should have specialist care of kidney disease in pregnancy, in addition to routine antenatal care. For example, they should be seen by obstetricians as well as midwives during their pregnancy, and they should have extra scans to check the growth and wellbeing of their baby (67).

Vitamin D deficiency, anaemia and hypertension are complicating comorbidities that may develop in pregnancy as a consequence of underlying CKD, which require tailored surveillance and management (66). For instance, medications to control BP may require to be adjusted before pregnancy or as soon as possible in early pregnancy, with a recommended target BP of 135/85 mmHg or less (67). Similar to pre-pregnancy management, known teratogenic and fetotoxic drugs, such as ACEIs and cyclophosphamide, should be avoided during pregnancy (66).

### 1.3.2 Chronic kidney disease and adverse pregnancy outcomes

Several studies have suggested that CKD is associated with a higher risk of adverse pregnancy outcomes (71-73). However, most of these studies are small in size and emanate from single centres, and associations with specific cause of CKD are less known. In 2015, a meta-analysis of 14 studies reported that women with CKD (compared to women without CKD) had higher odds of pre-eclampsia, Caesarean section, preterm birth, and SGA/LBW (73). However, only four out of the 14 studies accounted for potential confounders such as maternal age and other comorbidities. Many of the included studies in this review (n=8) examined adverse pregnancy outcomes among women with diabetic nephropathy as an exposed group, which makes it difficult to generalize the results to women with other underlying causes of CKD. Therefore, large-scale studies considering the underlying causes of CKD and potential confounding factors become crucial to explore these associations.

## 1.4 Pregnancy as a stress test for future cardiovascular disease

During pregnancy, the maternal body increases its activity to fulfil the demands of the developing fetus (74). Accordingly, each maternal organ adapts uniquely and works harder in order to meet the demands of the developing fetus in a different way during each trimester of pregnancy (75). If an organ or system was already vulnerable before pregnancy, gestational syndromes might develop to meet the increased physiological demands of pregnancy (75). After delivery, symptoms usually subside, though this may be transient, and due to the effect of the age-related metabolic and pro-atherogenic changes, these clinical syndromes may reappear in later life. As a result, pregnancy has been described as a medical stress test for mothers that may reveal subclinical cardiovascular phenotypes (75, 76).

Cardiovascular disease (CVD) is a class of diseases that affects blood vessels and hearts (77). Although cardiovascular mortality has decreased considerably in the last few decades, it is still the leading cause of premature death in western countries (78). In 2019, CVD was responsible for 35% of total deaths in women (79). Prior studies reported associations between chronic hypertension (pre-pregnancy hypertension) and pregnancy complications (42); however, the data are limited on the association between pre-pregnancy hypertension combined with APOs and subsequent CVD.

### 1.4.1 Hypertension in pregnancy and future CVD

Over the last few decades, there has been growing evidence that women with a history of pregnancy complications, such as pre-eclampsia, preterm birth, or fetal growth restriction, had an increased risk for later development of CVD (80-84). Several systematic reviews and meta-analyses have been performed to investigate the association between pre-eclampsia and future CVD morbidity and mortality (84-88). The most recent review was conducted by Grandi *et al*. in 2019, including 83 studies on the risk of CVD and pregnancy complications, including preeclampsia, gestational hypertension, preterm birth, stillbirth, LBW or SGA (84). The findings suggested women with a history of pre-eclampsia, gestational hypertension, preterm birth, or stillbirth are at increased risk of subsequent CVD- and cerebrovascular-related morbidity and mortality.

Moreover, a total of 46 studies examined the associations between HDP and future CVD, of which 29 examined the risk of CVD among women with all types of

HDP, while 17 studies examined the risk only in women with pre-eclampsia (84). The authors reported that preeclampsia was associated with approximately double the risk of cardiovascular-related morbidity [pooled OR: 2.24 (95% CI, 1.72–2.93)] and 75% (95% CI, 1.46–2.06) higher risk of cardiovascular-related mortality compared to women with no history of pre-eclampsia (84). However, most of the prior studies failed to adjust for important confounders (such as maternal age, BMI, and parity); the lack of adjustment may raise a concern regarding the validity of reported estimates by insufficient adjustment for the confounders (84).

In previous studies, there are inconsistencies in defining pre-eclampsia, i.e., most studies combined women with pre-eclampsia and superimposed pre-eclampsia without consideration of the potential role of the pre-existing conditions (chronic hypertension) when assessing this relationship (84-88). Few studies have examined the risk of maternal cardiovascular outcomes in relation to pre-pregnancy hypertension and HDP. Two US cohort studies reported a higher risk of future CVD among women with superimposed pre-eclampsia than those with pre-pregnancy hypertension alone (89, 90). However, data were limited on the associations between pre-pregnancy hypertension with stroke, coronary heart disease (89) and heart failure (90). In addition, these studies did not assess the impact of other pregnancy complications (such as preterm birth and fetal growth restriction) on the reported associations. Therefore, studies with large-scale datasets are needed to examine the association between chronic hypertension during pregnancy and future CVD, considering whether adverse pregnancy contributed to accelerating the risk of CVD.

## 1.5 The need for further research

As illustrated earlier in this chapter, although maternal care has improved significantly during the past few decades, it is unclear whether adverse pregnancy outcomes have decreased in women with chronic hypertension or CKD. Furthermore, previous findings on associations between CKD and adverse pregnancy outcomes were mainly driven from single-centre studies, with small sample sizes and poor methodological quality (i.e., very limited studies adjusted for potential confounders). Thus, there is a need for population-based cohort studies to examine these associations while controlling for potential confounders. Additionally, few studies investigated the effect

of a specific cause of CKD, whereas none of the prior studies investigated the associations across different CKD subtypes.

The available evidence from RCTs and observational studies reported that antihypertensive treatment reduced the risk of severe hypertension; however, its effect on other maternal, fetal and neonatal outcomes remains unclear. Therefore, there is a need for large studies to investigate the effect of different antihypertensive treatments on the occurrence of adverse maternal and perinatal outcomes.

The long-term effect of pregnancy on future CVD in women with chronic hypertension is not fully understood. As very limited data are available about the associations between chronic hypertension during pregnancy and the risk of future CVD. In addition, prior studies have been inconsistent in evaluating the exposure of interest (i.e., included superimposed pre-eclampsia and chronic hypertension with other types of HDP). The available evidence did not assess the effect of pregnancy complications on the association between chronic hypertension and future CVD. There is also a gap in the literature about the role of important potential confounders on these associations, highlighting the need for further studies investigating this relationship while considering pregnancy complications and controlling for confounding factors.

## 1.6 Conceptual framework for maternal morbidity

This thesis considers chronic maternal conditions and adverse pregnancy outcomes in the context of the conceptual framework for maternal morbidity developed by a Maternal Morbidity Working Group (91). The Maternal Morbidity Measurement Framework is a comprehensive, woman-centred, life-cycle approach that provides wide-ranging perspectives on women's health (**Figure 1.1**). For example, women with chronic hypertension and obesity might have pregnancy complications resulting in an increased risk of delivery by Caesarean sections; this provides concurrent risks of surgical intervention and requirements for anaesthesia, in line with the woman's overall health. Thus these conditions may affect not only the current pregnancy, but also future pregnancies and long-term health as chronic hypertension and obesity are risk factors for increased CVD later in life (92).

**The framework reflects the following key principles** (91)**:**

**(1) Women-centred approach:** This refers to women's perspectives on what is important to them regarding their wellbeing and long-term health. This includes any health problems that directly or indirectly influence women's lives, including adverse fetal and infant outcomes, which can lead to a negative maternal outcome.

**(2) Cyclic nature:** Maternal morbidity risks are cyclical as women can become pregnant more than once, and sequelae of a maternal condition or adverse pregnancy outcomes (such as Caesarean delivery) can occur in the subsequent pregnancies.

**(3) Lasting effect:** The effects of maternal morbidity can last a long time, beyond the pregnancy or the postpartum period (6 weeks after delivery), and there may be consequences later in life, during the post-reproductive or postmenopausal periods. For instance, women who have pre-eclampsia are more likely to have CVD later in life (80).

**(4) Socio-economic effect:** Social and economic phenomena are important for maternal health as a clinical and biological issue.

**(5) Environmental effect:** Environment influences the lived experience of morbidity, as living in a supportive environment can lead to better maternal health outcomes.

**(6) Groupings of maternal morbidity:** The framework has a meaningful grouping of maternal morbidity. Thus the occurrence of any factors that may affect maternal morbidity (such as adverse pregnancy outcomes) should be grouped in a meaningful way, consistent with the International Classification of Diseases.

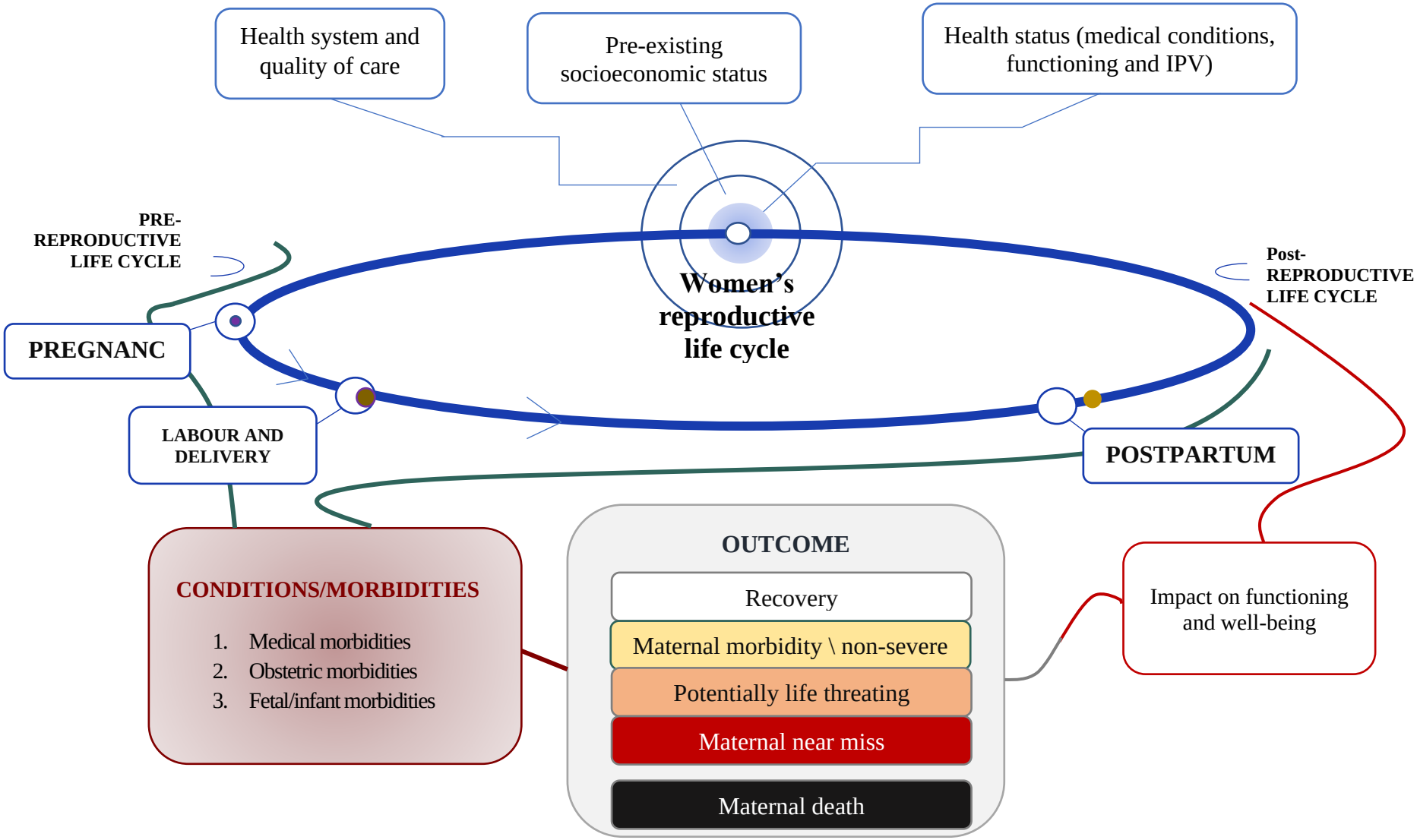



**Figure 1.1** Maternal morbidity measurement framework

Source: Based on Filippi *et al.* (91)

## 1.7 Overall aims and objectives

The overall aim of this thesis was to examine the impact of maternal chronic hypertension and CKD on the risk of adverse pregnancy outcomes and long-term cardiovascular disease.

In particular, the objectives of the current thesis were as follow:

1. To synthesise the available published literature investigating the effect of chronic hypertension and antihypertensive treatment on the risk of adverse pregnancy outcomes in the form of two systematic reviews and meta-analyses.

2. To synthesise the evidence from published literature on the association between CKD and adverse pregnancy outcomes in a form of a systematic review and meta-analysis.

3. To investigate the risk of adverse pregnancy outcomes among women with chronic hypertension and/or CKD over the last three decades using data from Swedish National Registers, controlling for several important confounders (such as obesity and smoking during pregnancy).

4. To investigate the effect of chronic hypertension and antihypertensive treatment on adverse pregnancy outcomes and examine the impact of different antihypertensive agents and hypertension control on these associations using data from the UK CALIBER platform.

5. To evaluate the impact of chronic hypertension during pregnancy on the risk of 12 cardiovascular disorders, considering whether adverse pregnancy outcomes contribute to the accelerated risk of CVD.

The thesis aims and objectives are also presented in **Figure 1.2**.

## 1.8 Thesis outline

This thesis is comprised of a number of peer-reviewed papers (or manuscripts under review) investigating the associations between maternal chronic disease (hypertension and CKD) and a range of adverse pregnancy outcomes and the effect of antihypertensive treatment on these outcomes. It also assessed the impact of chronic hypertension during pregnancy on long-term maternal CVD, considering whether adverse pregnancy outcomes are associated with the risk of CVD (**Figure 1.2**).

The thesis is outlined as follow:

***Chapter 1***: Introduction, conceptual framework, aims and objectives.

***Chapter 2***: A detailed methods chapter outlining the study designs, populations studied, data sources, and statistical methods used.

***Chapter 3***: Literature review consists of two systematic reviews and meta-analyses on the impact of chronic hypertension and antihypertensive treatment on the risk of adverse pregnancy outcomes (**paper 1**).

***Chapter 4***: Literature review, comprising a systematic review and meta-analysis on the impact of CKD on the risk of adverse pregnancy outcome (**paper 2**).

***Chapter 5***: Original population-based cohort study investigating the impact of chronic hypertension and CKD (including CKD subtypes) on the risk of adverse pregnancy outcomes; and assessing whether these associations have changed over the last three decades (**paper 3**).

***Chapter 6:*** Original population-based cohort study investigating the effect of chronic hypertension and antihypertensive treatment on adverse pregnancy outcomes. This study also assessed the impact of different antihypertensive agents and whether observed effects were modified by the level of hypertension control (**paper 4**).

***Chapter 7:*** Original population-based cohort study investigating the associations between chronic hypertension during pregnancy and future CVD, and if the occurrence of adverse pregnancy outcomes accelerated the risks (**paper 5**).

***Chapter 8:*** Discussion of the main findings, including the overall interpretation, strengths and limitations of the thesis, and conclusions.

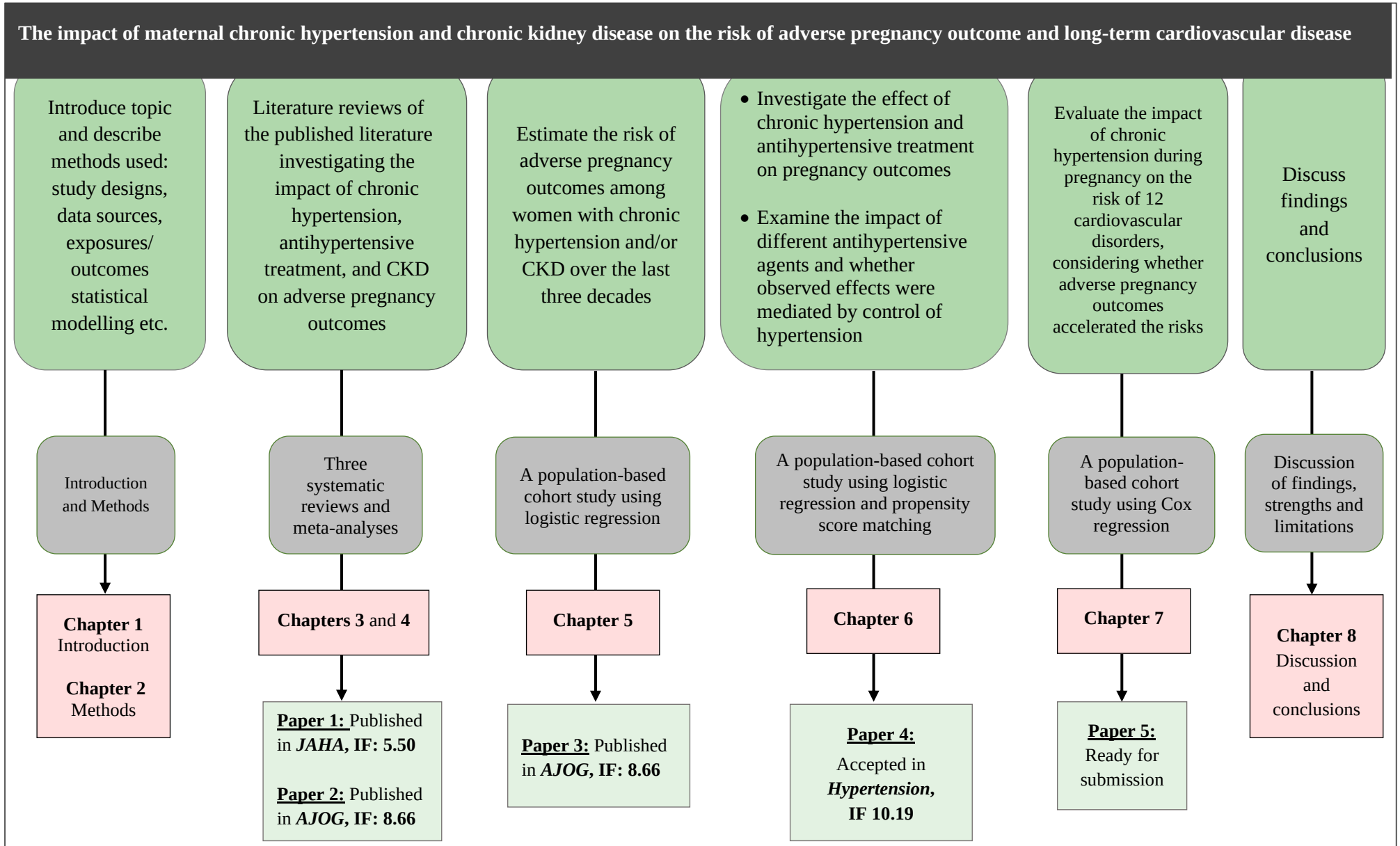



**Figure 1.2 Thesis overview including overall aim, specific objectives, corresponding chapters, and papers**

# CHAPTER 2: Methods

## 2.1 Chapter overview

This chapter is comprised of a detailed description of the methods undertaken in this PhD thesis. First, the study designs used to answer the research questions are described and justified. Second, the various data sources used, including the Swedish registers and data from the CALIBER platform, are presented with information on how the linkages were done. Also, a brief summary of the available evidence on the quality and validity of these datasets is provided. Third, the definitions of the main exposure and outcome variables are presented. Fourth, information on how the ethical approvals were obtained for the use of the data. Next, epidemiological considerations are described, including the threats to the internal and external validity. The final section in the methods chapter details the statistical methods.

## 2.2 Study design

### 2.2.1 Systematic review and meta-analysis

Chapters 3 and 4 are comprised of three systematic reviews and meta-analyses. The first two reviews synthesised the published literature on the impact of chronic hypertension and antihypertensive treatment on adverse pregnancy outcomes and are presented in Chapter 3. The first review included studies on the associations between chronic hypertension and adverse pregnancy outcomes, while the second one focused mainly on the effect of antihypertensive treatment. The third systematic review synthesised the published literature on the association between CKD and adverse pregnancy outcomes and it is presented in Chapter 4. The protocols of these reviews are available in **Appendices 1 and 2,** respectively, and were registered in PROSPERO, the International Prospective Register of Systematic Reviews (93, 94). The PICO criteria for these reviews are illustrated below in **Table 2.1**.

**Table 2.1** PICO criteria used in the systematic reviews of this thesis

| **PICO criteria used in systematic reviews on chronic hypertension and antihypertensive treatment** | |
|---|---|
| **P**opulation | Pregnant women |
| **I**ntervention/exposure | 1) Pregnant women with chronic hypertension<br>2) Pregnant women with chronic hypertension on antihypertensive treatment |
| **C**omparison | 1) Pregnant women without chronic hypertension<br>2) Untreated pregnant women (normotensive or with chronic hypertension), each group was handled separately in the analysis stage |
| **O**utcomes | Maternal outcomes: pre-eclampsia, Caesarean section, postpartum haemorrhage, haemolysis, elevated liver enzyme levels, and low platelet levels (HELLP syndrome), and maternal mortality<br>Fetal and neonatal outcomes: miscarriage, stillbirth, preterm birth (<37 weeks), very preterm birth (<34 weeks), small-for-gestational-age, low birthweight, neonatal intensive care unit admission, neonatal death, and perinatal death |
| **PICO criteria used in systematic reviews on chronic kidney disease (CKD)** | |
| **P**opulation | Pregnant women |
| **I**ntervention/exposure | 1) Pregnant women with CKD<br>2) Pregnant women with late stages of CKD |
| **C**omparison | 1) Pregnant women without CKD<br>2) Pregnant women with early stages of CKD |
| **O**utcomes | Primary outcomes: pre-eclampsia, Caesarean section, preterm birth (<37 weeks), and small-for-gestational-age<br>Secondary outcomes: maternal death, very preterm birth (<34 weeks), low birthweight, neonatal intensive care unit admission, stillbirth, neonatal death, and perinatal death |

### 2.2.2 Cohort Study using Swedish National Registers

Chapter 5 is comprised of a population-based cohort study, using data from The Swedish National Registers. In this study, we attempted to fill in some of the gaps in the literature, which were identified from the systematic reviews in Chapters 3 and 4, such as assessing the impact of BMI and parity on the reported associations, and examining the associations across CKD subtypes in a population-based study. Hence, this study aimed to assess the association between maternal chronic disease (chronic hypertension, CKD or both conditions) and adverse pregnancy outcomes over the last three decades with an emphasis on the effect of parity, maternal age, and BMI on these associations. We further investigated the associations based on the underlying cause of CKD.

The core focus of observational studies is to estimate the magnitude of risk for a specific condition (outcome) in relation to a considered exposure factor (95). Advantages of using observational studies include the use of "real-world" situations; however, residual and unmeasured confounding can remain (95). Two potential observational designs could address the research questions of this thesis (in Chapter 5): case-control and cohort studies, both of which have strengths and limitations.

In case-control studies, two groups are retrospectively compared, one group with the outcome (case); and another group without the outcome (control). The advantages of case-control studies are that they are more affordable to perform compared to cohort studies, they can be performed more quickly because they are generally retrospective (95), less expensive than cohorts, and effective for assessing rare outcomes and multiple exposures, in particular exposures that are well recalled. However, this design is vulnerable to recall/information bias in detailing exposure as investigators focus on the outcome and "move back" toward the exposure factor. In addition, disease incidence and prevalence cannot be estimated using a case-control design, except for certain circumstances. Considering that the original studies in this thesis were based on existing secondary data, case-control studies were not needed, and instead, a population-based cohort study design was used.

Population-based cohort studies are a specific category of epidemiological studies, where a sample, or even the entirety, of a defined population, is followed up and observed longitudinally to assess exposure and outcome relationships (96). Population-

based cohorts can be constructed via data linkage from several administrative and medical sources (e.g., hospital records, death certificates) using unique individual identifiers. The key advantage of a well-designed population-based cohort studies is their external validity–the applicability of their results to a defined population when constructed from a representative sample (96). Other advantages include the ability to estimate the incidence and prevalence of relevant variables in the defined population and compare distributions of measured risk factors at baseline with future distributions to assess risk factor trends over time. However, limitations of population-based cohort include high cost and logistic complexities, missing data, and lack of information on potential confounders (96).

In Chapter 5, a population-based cohort design was used to address the research questions. This design was selected for many reasons. First, using an available dataset (The Swedish National Registers) includes data on both exposures and outcomes of interest, saving resources such as large financial costs and time associated with collecting primary data. Second, the Swedish registers can be linked using unique personal identifiers. Third, these registers contain data on a wide range of sociodemographic and perinatal factors, allowing investigators to adjust for a vast number of potential confounders. Fourth, the Swedish Birth Register (MBR) has a national coverage (>99%) (97), which provided a representative, large sample size with sufficient power. This allowed us to do subgroup analysis based on important effect modifiers and confounding factors such as parity, maternal age, and BMI.

### 2.2.3 Cohort Studies using data from CALIBER platform

Chapters 6 and 7 are comprised of a population-based cohort study using linked electronic health records (EHRs) from the CALIBER platform. Chapter 6 includes four main objectives: 1) compared adverse pregnancy outcomes in women with chronic hypertension and women without chronic hypertension; 2) investigated the effect of antihypertensive treatment in women with chronic hypertension (treated vs untreated); 3) investigated the effect of different antihypertensive agents; and 4) assessed pregnancy outcomes according to BP levels. The Swedish Registry data could not be used to answer these research questions because we did not have access to the Swedish Prescribed Drug Register, which was established in 2005 (98).

Although RCTs are generally considered to be the gold standard for generating clinical evidence, specifically when evaluating the effect of treatment (i.e., antihypertensive medications), it is suggested that using "real-world" evidence in medical research presents opportunities to supplement or replace some clinical trials (99). As a result, the use of EHRs in post-marketing pharmaco-epidemiological research is gaining considerable interest, given that linked EHRs provide data on a large number of patients with detailed information on sociodemographic, clinical data (such as diagnoses and medications) and events. Rarer and long-term effects of pharmaceuticals, and the beneficial and harmful effects in populations less likely to participate in trials are often revealed in surveillance data.

Furthermore, previous RCTs assessing the effect of antihypertensive treatment during pregnancy in women with chronic hypertension were small and lacked the statistical power to detect treatment effects on perinatal outcomes (55, 100), although they were powered for the primary outcomes (mostly severe hypertension). Therefore, the scale of EHRs data offers a sufficient sample size to investigate the effect of antihypertensive treatment on perinatal outcomes while adjusting for potential confounding factors. Thus, we used a population-based study design to address the research questions (in Chapter 5) regarding the effect of using antihypertensive treatment during pregnancy on adverse pregnancy outcomes.

Chapter 7 examines the association between chronic hypertension during pregnancy and future risk of CVD, and whether the occurrence of adverse pregnancy outcomes accelerated the risks of cardiovascular events. Given that CALIBER has detailed data on 12 cardiovascular disorders, it is ideal to answer this research question.

## 2.3 Data sources

### 2.3.1 The Swedish National Registers

The National Board of Health and Welfare in Sweden had established a number of national registers for various purposes, such as to facilitate analysing data for the development of Swedish healthcare and social services. Four registers with specific information are available:1) the MBR, 2) the National Patient Register (NPR), 3) the Swedish Cancer Register, and 4) the Swedish Prescribed Drug Register. Data from the Swedish registers can be linked using Personal Identification Number (PIN). This thesis used data from two registers: the Swedish MBR and the NPR.

#### *2.3.1.1 The Medical Birth Register (MBR)*

The Swedish MBR was established in 1973 as a source of data on perinatal epidemiology, and it contains information approximately on all births in Sweden (101). All healthcare providers are required to report to the register; as a result, only 1–5% of all infants records are missing completely (97).

This register comprises information on prenatal, delivery, and neonatal care (101). Information from prenatal care includes maternal age, smoking status and information on previous pregnancies, such as maternal medical history. Information from the delivery includes data on maternal diagnoses, mode of delivery, fetal presentation, analgesia and anaesthesia and hospital code. Finally, information from neonatal care contains data about the infant's birthweight, gestational age, body length and head circumference, type of pregnancy (single or multiple births), Apgar score, infant diagnoses and whether the birth was live birth/stillbirth.

The basic structure of the register has remained unchanged since 1973, but there have been some modifications to the content and methods of data collection (97). From 1973 to 1982, the secretaries at obstetric clinics summarised documents called "Medical Birth Reports" on a standard form. These were then sent to the National Board of Health and Welfare in Sweden for computerisation. In 1982, a revised procedure was used, where the content of the register was retrieved directly from the three medical records, preventing possible discrepancies during data transfer (97). At the same time (1982), additional variables were added, including smoking status, height, and pre-pregnancy weight. Finally, the content of the register was also modified in 1990, 1994 and 1998 to include details on social factors (such as parents' nationality, mother's county of birth, year of immigration, and induction of delivery) (97).

The validity of the Swedish MBR has been established, as previous studies reported a sufficient degree of coverage of data for most variables in this register (97, 102). However, it was highlighted that in 1986, 10% of the pregnancy diagnosis had not been entered in the MBR, which includes chronic hypertension, multiple sclerosis, and epilepsy (102). Therefore, in this thesis, recorded data in the MBR on maternal chronic hypertension, CKD and other comorbidities were supplemented by data from NPR.

The importance of the MBR in the Scandinavian countries was summed up by Allen Wilcox in his paper about the Norway Medical Birth Register as he stated, “This prodigious scientific productivity is a credit to the researchers of Norway, and most especially to the founders of the Medical Birth Registry. The founders had faith that the seeds they planted would contribute to the health of the Norwegian people. What the founders could not have foreseen was the benefits that the Registry would provide to the world at large” (103).

This thesis included data on births recorded from 1982 onwards as data were better recorded, particularly for BMI and smoking status, which are considered important risk factors in the current study (Chapter 5). This way, we were able to capture the full reproductive history of the women by including women who had their first birth from 1982 onwards and by excluding women who had at least one birth between 1973 and 1982. Chronic hypertension and CKD are recorded in the MBR; these variables were supplemented by data from the NPR to capture pregnant women with chronic hypertension and CKD.

#### *2.3.1.2 The National Patient Register (NPR)*

The NPR contains information on all inpatients and outpatients in Sweden. In the 1960s, the National Board of Health and Welfare started to record inpatients data in public hospitals. Accordingly, the Swedish National Inpatient Register was launched in 1964. It initially contained data on all patients treated in psychiatric care and covered 6 of the 26 county councils in Sweden, with national coverage of only 16%, and this increased gradually to 50% in 1970 and 85% by 1983. Then, in 1984 the Ministry of Health and Welfare, together with the Federation of County Councils, decided mandatory participation for all county councils. As a result, national coverage of all inpatient admissions in Sweden was achieved in 1987 (104, 105). In addition, the register was expanded in 2001 to cover outpatient data, including day surgery and psychiatric care from both private and public hospitals (104, 105).

The type of data in NPR can be divided into four main categories. First, *patient-related data* includes personal registration number, gender, age, and place of residence. Second, information on the *caregiver* (geographical data) includes county council, hospital/clinic, and department. Third, *administrative data* contains information on admission date, length of stay (for inpatient), discharge date, and whether the admission

was planned/unplanned. The fourth category on *medical data* includes information on the primary diagnosis, secondary diagnosis and procedures (105). The diagnoses in the NPR are coded according to the Swedish international classification of disease (ICD) system (**Figure 2.1**).

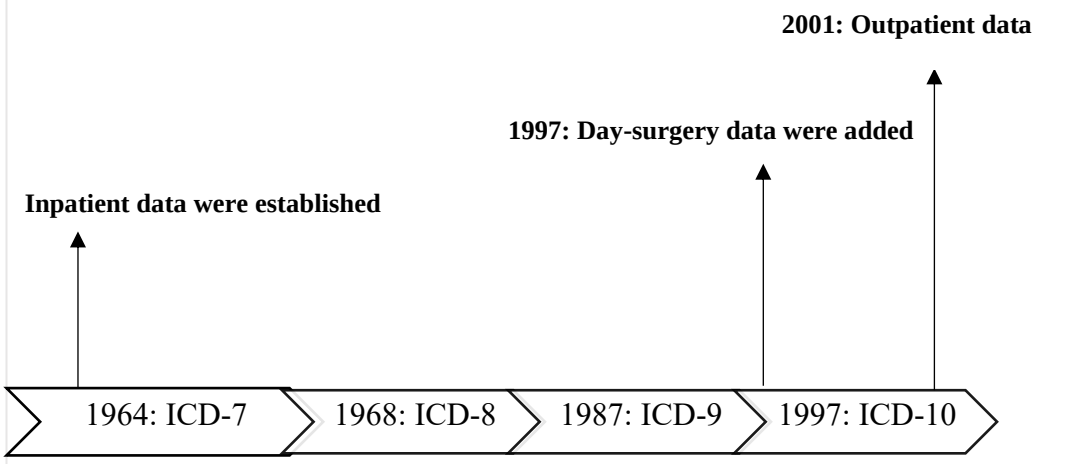



**Figure 2.1** Overview of data and shifting in ICD codes in the Swedish National Patient

The quality of the Swedish Inpatient Register has been validated in many studies. A systematic review of 132 papers reported a variation in the positive predictive value between diagnoses from inpatient data, and it generally ranged from 85-95% (104). Moreover, evidence has shown that inpatient data provide limited information on hypertension diagnosis (106), whereas this was largely captured by outpatient data (107). Consequently, it was suggested that inpatient and outpatient data should be combined (for epidemiological analyses) to provide a more comprehensive estimate of the burden of disease (106). Based on this, in this thesis (Chapter 5), inpatient and outpatient data were combined to identify pregnant women with chronic hypertension and CKD diagnoses, in addition to the recorded variables in MBR.

#### *2.3.1.3 The Register of Education*

The Swedish Register of Education was established in 1985, and it comprises the population aged 16–74 years old registered as residents in Sweden. The register contains data on education and graduation, such as the highest education level and completion year. This covers primary and secondary school education, undergraduate

and postgraduate education. In addition, information on demographics (e.g., age and sex), PIN, and the municipality of residence are recorded in this register. In 1990, the Population and Housing Census data was used to update and improve the quality of the Education Register (108).

#### *2.3.1.4 Linkages between the Swedish National Registers*

The Swedish national health registers depend on a unique identifier (PIN), which was introduced in 1947 (109). Since then, every individual that has resided in Sweden has been assigned a PIN which consisted of three parts: date of birth, a three-digit birth number, and a check digit. The three-digit birth number is sex-specific, whereas the check digit was added in 1967 to the three-digit number to verify that the first two parts (data of birth and the three-digit number) are correct. The PIN serves as a unique identifier, particularly in Swedish health care, and it is a vital component of large register linkages, including the MBR and the NPR (109).

### 2.3.2 CALIBER: A linked electronic health records platform

The CALIBER (Clinical research using Linked Bespoke studies and Electronic health Records) platform is a series of linkages between UK EHRs which consisted of four constituent data sources: 1) a longitudinal primary care electronic patient records from the Clinical Practice Research Datalink (CPRD); 2) data on hospital admissions and procedures from the Hospital Episodes Statistics (HES); 3) a national acute coronary disease registry from Myocardial Ischaemia National Audit Project (MINAP); and 4) data on cause-specific mortality records from the Office for National Statistics (ONS), in addition to social deprivation data (110). Each of these data sources is further described below.

#### 2.3.2.1 Data sources in CALIBER platform

##### *2.3.2.1.1 Clinical Practice Research Database (CPRD)*

The CPRD is one of the largest databases of longitudinal medical records from primary care in the world. It was established in 1987 as the Value Added Medical Products (VAMP) database, which was evolved into the General Practice Research Database (GPRD) in 1993. The GPRD was then expanded, with an emphasis on data linkage with other anonymised EHRs in 2012 to become the CPRD (111, 112). The CPRD is a governmental research service that collects anonymised electronic longitudinal

primary care data on a large and representative sample covering over 11.3 million patients (with 4.4 million active patients) from 674 general practitioners covering approximately 7 per cent of the UK population (111).

The CPRD provides information about patients, including socio-demographics, clinical diagnoses, laboratory tests, signs and symptoms, prescribing of drugs and devices, procedures, immunisations, health behaviours, cause and date of patient death (111). The UK general practice computer systems use Read terms, a hierarchical clinical coding system which was developed by Dr James Read and eventually acquired by the National Health Service (NHS) (113). During a 'consultation', general practitioners (GPs) or other practice staff enter a number of Read codes to describe a patient's condition (e.g. lifestyle measures such as smoking status, symptoms, diagnoses, clinical tests performed, and therapies offered) (111). Additionally, the CPRD has developed another coding system, 'medcode', which is simply a numeric equivalent of the Read code.

The CPRD uses measures to identify acceptable data for research purposes across two aspects: i) at the patient level and ii) at the primary care practice level. At the patient-level, data are used only on patients who were marked as "acceptable for research" by the CPRD. Patients are labelled as acceptable following an algorithm process, where patients with noncontinuous follow-up or patients with poor data are identified and excluded (114) (the reasons for excluding patients are illustrated in **Table 2.2**). The second measure is the overall quality of the data recorded in a primary care practice, where recording is assessed against practice-based standards (the standards are outlined in **Table 2.2**). If a practice meets these standards, they are labelled "up-to-standard (UTS)" date (115). The UTS date is determined for each participating practice as the date at which individual practice's data met the minimum standards and considered to have continuous, high-quality data fit for use in research (111, 115). In this thesis, we included data from English general practices with UTS date.

Although the CPRD covers a small proportion of the UK population, the dataset has been found to be representative of that population (116, 117) and with high validity (118). Completeness of BMI data in CPRD varies over time from 37% in 1990–1994 to 77% in 2005–2011, and recording was higher among females, older age groups and with comorbidities. However, a substantial number of patients (33–47% across years) did not have recent measures (≤3 years) of BMI records (117).

**Table 2.2** Data quality standards used by CPRD

| **Acceptable Patients**[a] | **Practice-level quality standards: Up to standard (UTS)** |
|---|---|
| • An empty or invalid first registration date[b]<br>• An empty or invalid current registration date<br>• Absence of a record for a year of birth<br>• A first registration date prior to their birth year<br>• A current registration date prior to their birth year<br>• A transferred out[c] reason with no transferred out date<br>• A transferred-out date with no transferred out reason<br>• A transferred-out date prior to their first registration date<br>• A transferred-out date prior to their current registration date<br>• A current registration date prior to their first registration date<br>• A gender other than Female/Male/Indeterminate<br>• An age of greater than 115 at end of follow up<br>• Recorded health care episodes in years prior to birth year<br>• All recorded health care episodes have empty or invalid event dates<br>• Registration status of temporary patients | • The percentage of 'acceptable' patients<br>• The monthly prescription rate comparable to other practices<br>• Percentage of prescriptions with a medical indication<br>• Death rates comparable to other practices<br>• Recording of cause of death<br>• Recording outcome of pregnancy<br>• Referral rate comparable to other practices<br>• Percentage of referrals with recorded clinical speciality |

[a] If any of these conditions are true, the patient is labelled 'unacceptable' and is not recommended for use in research; [b] Registration date refers to the date when first registered with the general practice; [c] Transferred out refers to when patient leave practice. Source: Wood *et al.* (115)

In contrast, data on prescribed medication from CPRD is well documented and has been used extensively in drug safety research (119). The GP uses the computer to generate prescriptions, and these are automatically recorded in the database; therefore, the therapy file is complete, except for prescriptions issued in secondary care and for medications that are purchased over the counter (119). Although the CPRD recorded medication prescriptions, it does not measure adherence to treatment (whether medications are taken). Nevertheless, the available evidence of data on the requesting of repeat prescriptions suggested that medication is being taken (119).

#### *2.3.2.1.2 Hospital Episode Statistics (HES)*

The HES was established in the 1980s by the Department of Health working group with the purpose of national data collection on hospital-based activity to inform management and planning of health services (120). It contains admitted patient care data since 1989 and outpatient attendance data since 2003 (121). The HES is a database

comprising detailed information of all admissions at NHS hospitals in England. In addition, the HES also covers admissions to independent sector providers funded by the NHS (122). The NHS is estimated to fund 98–99% of hospitals in England (123) and almost all births in NHS hospitals (representing approximately 97% of all births in England) (124).

During a hospital admission, data on all administrative records (such as dates and methods of admission and discharge), including inpatients, outpatients, critical care, maternity and emergency are collected (123). All clinical diagnoses are recorded using the International Classification of Diseases and Health-Related Problems, 10th Reversion (ICD-10) codes (125). Other interventions and procedures are coded using the Office of Population Censuses and Surveys Classifications of Interventions and Procedures (OPCS), Version 4 (126).

In 2004, the NHS switched the funding for hospitals from block contracts to payment by results (PbR), in which hospitals were paid for each admission record, grouped into broad reimbursement bands. As a result, the introduction of PbR led to an improvement in diagnosis accuracy (127). A systematic review of 32 studies assessed the quality of the HES data, reported a median diagnostic accuracy of 80% (IQR: 63.3–94.1%), whereas the accuracy of procedure coding was 84.2% (IQR: 68.7–88.7%) (127). Since the introduction of PbR, the accuracy for primary diagnosis has improved from 73.8% (IQR: 59.3–92.1%) to 96.0% (IQR: 89.3–96.3). The authors concluded that accuracy rates are improving and suggested that routinely collected data are sufficiently robust to support their use for research (127).

#### *2.3.2.1.3 Myocardial Ischaemia National Audit Project (MINAP)*

The MINAP is a national registry of patients attending hospitals with Acute Coronary Syndrome (ACS) events in England and Wales, and participation is mandated in all hospitals. The MINAP was established in 1998, and data collection began in 2000 (128), reached near national coverage by 2003, and covered all NHS hospitals (242 hospitals) in England and Wales since 2009. Each MINAP record contains data on patient demographic characteristics, medical history, clinical features and investigations, drug treatment (pre-, during and post-admission) and final diagnosis (110). A comparison between CPRD, HES, and MINAP found a similar prevalence of cardiovascular risk factors and comorbidities across the three data sources. However,

it was reported that each data source missed a substantial proportion (25-50%) of myocardial infarction events (129). Thus, combining data from the three sources provided a comprehensive estimate of the event.

#### *2.3.2.1.4 Office for National Statistics (ONS)*

The Office for Population Censuses and Surveys, now known as "ONS", was established in 1974. The ONS contains data on cause-specific mortality for all residents in the UK. By law, any death occurring in England and Wales must be registered within five days of the death and accompanied by a medical certificate of the cause of death, except in limited cases where deaths require further investigations (autopsy) to certify the cause of death. Hence, data on mortality is representative of the whole population of England and Wales, including those in non-private households and all age groups. However, the ONS does not include mortality data for resident people in the UK who die abroad. Data on cause-specific mortality are extracted from death certificates and recorded using I-CD8 (1971–1981), ICD-9 (1981–2000) or ICD-10 (2000 onwards) (130, 131).

Although EHRs sources are considered complementary to each other by providing a different aspect of a patient's disease status, for mortality, the ONS date of death is used as the "gold standard" (114). A study of 118,571 deaths in England reported a discrepancy in recorded death dates between primary care records (from CPRD data) and ONS national data in almost a quarter (23%) of cases (132). In the majority of cases of discrepancy, the variation was mainly due to delay in recording the date of death by the GPs (CPRD data), as the date of death recorded by the GPs comes after that recorded by ONS (132). Therefore, in line with previous literature, we used the ONS as the "gold standard" for determining mortality in this thesis.

#### *2.3.2.1.5 Index of Multiple Deprivation (IMD)*

The indices of deprivation are a tool for identifying the most deprived area in England, which policymakers and communities can use for effective targeting of resources (133). Individual practice score was calculated by the ONS, using patients' postcodes (134). The overall practice's deprivation score derived from the IMD measure, which is a set of deprivation in a small area (Lower-layer Super Output Area) in seven distinct domains: income deprivation, employment deprivation, education, skills and training deprivation, health deprivation and disability, crime, barriers to housing and services,

and living environment deprivation (133, 134). Data are not available for individual measures on deprivation, so we used the IMD as a measure of deprivation at an area level in this thesis.

#### 2.3.2.2 Data linkages between the UK EHRs

Each patient in the UK has a unique identifier (the NHS number) which enables linkages between different datasets. The NHS number was introduced with the inception of the NHS in 1984 based on the national registration number. A modern style of a ten-digit NHS number was introduced in 1996, replacing the previous system, nine digits to uniquely identify individuals, with the 10$^{th}$ digit being a check digit to confirm the validity of the other nine. Any individuals who registered with a GP can obtain the NHS number from the GP practice, and from October 2002, all babies born in England and Wales have been issued NHS numbers from birth. In addition to NHS numbers, the UK datasets can also be linked using other information on patient identifiers, such as date of birth, sex, and postcode. The NHS number is a reliable identifier for record linkage that enables the identification of patients in a unique way while preserving patient confidentiality (110).

In CALIBER research platform, data linkages are performed by a trusted third party (TTP) using the NHS number, date of birth, gender, and postcode; 96% of patients with valid NHS numbers were successfully linked (114). Additionally, around 45% of the 592 CPRD practices in the UK consented to linkage of their registered patients (110). This thesis included women in practices that consented to linkages between CPRD, and HES records (**Figure 2.2**).

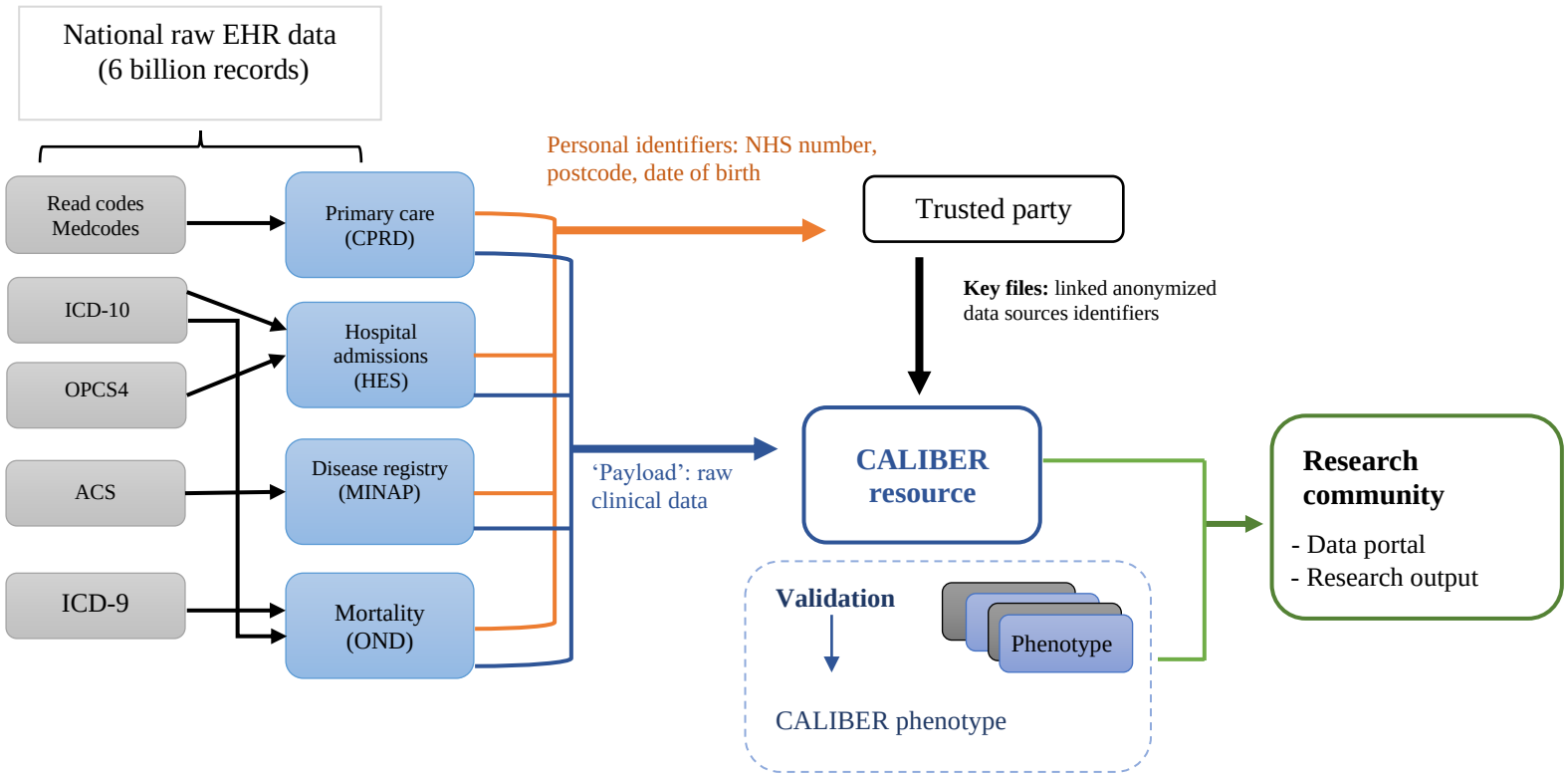



**Figure 2.2** Data sources and linkages in CALIBER platform

Source: based on Denaxas *et al.* (114).

## 2.4 Exposures, Outcomes and Covariates

### 2.4.1 Exposures

#### *2.4.1.1 Chronic kidney disease*

In the Swedish data study (Chapter 5), data on the diagnosis of CKD were obtained from the MBR and NPR using ICD-8 (through 1986), ICD-9 (1987–1996) and ICD-10 codes (1997–2012). Similarly, we used ICD codes (from the two registers) to identify the specific underlying cause of CKD, and that included: tubulointerstitial CKD, glomerular/proteinuric CKD, diabetic nephropathy, renovascular disease, congenital/malformation kidney disease, and unspecified CKD.

#### *2.4.1.2 Chronic hypertension*

In the Swedish data study (Chapter 5), data on the diagnosis of chronic hypertension were obtained from the MBR and NPR using ICD-8 (through 1986), ICD-9 (1987–1996) and ICD-10 codes (1997–2012).

In CALIBER studies (Chapters 6 and 7), data on chronic hypertension were obtained from the validated CALIBER phenotype (135), in which chronic hypertension record was classified as either *inferred* or *diagnosed*. A *diagnosed hypertension* refers to a recorded diagnosis of hypertension during a consultation in primary care or during hospitalisation. An *inferred hypertension* refers to patients who received repeat prescriptions (at least two prescriptions within 6 months) of BP lowering-medication or based on BP readings. In this thesis, pregnant women were considered to have chronic hypertension if the diagnosis date or prescription date (using the phenotype variable) was either before pregnancy or before 20 weeks' gestation.

In Chapter 6, available data on BP readings that were measured during pregnancy were used in the statistical analysis. Data on BP readings were obtained from primary care (CPRD); if a pregnant woman had more than one BP measurement, the average readings of sBP and dBP were calculated. The BP readings were categorised into (<115, 115–129, 130–139, 140–159, 160–179 and ≥180 mmHg) for sBP, and (<75, 75–84, 85–89, 90–94, 95–99 and ≥100 mmHg) for dBP.

#### *2.4.1.3 Antihypertensive treatment*

In CALIBER studies (Chapters 6 and 7), data on antihypertensive medication was identified from the CPRD. Treated women were defined as women with chronic hypertension who were *dispensed* at least one prescription for an antihypertensive

treatment during pregnancy. On the other hand, untreated groups refer to women who did not have a prescription for an antihypertensive treatment during pregnancy, and they were divided into (1) untreated normotensive women and (2) untreated women with chronic hypertension.

#### *2.4.1.4 Chronic hypertension and pregnancy complications*

In the CALIBER study (Chapter 7), data on chronic hypertension were obtained from the validated CALIBER phenotype variable (135), as illustrated above in **section 2.4.1.2**. Each pregnancy record was first classified as either (1) no pre-pregnancy hypertension or (2) pre-pregnancy hypertension (chronic hypertension). Then we sub-classified these two groups according to the presence of adverse pregnancy outcomes into: (1) neither pre-pregnancy hypertension nor adverse pregnancy outcomes, (2) no pre-pregnancy hypertension with adverse pregnancy outcomes, 3) pre-pregnancy hypertension without adverse pregnancy outcomes, and 4) pre-pregnancy hypertension with adverse pregnancy outcomes. Data on pregnancy complications include pre-eclampsia, stillbirth, preterm birth (<37 weeks), and fetal growth restriction. Data on stillbirth and preterm birth were obtained from recorded variables in the CPRD Pregnancy Register and HES Maternity File. Data on pre-eclampsia and fetal growth restriction were obtained from primary care (CPRD) and hospital care (HES) using Read or ICD-10 codes, respectively.

### 2.4.2 Outcomes

#### *2.4.2.1 Adverse pregnancy outcomes*

The original study in Chapter 5 examined the associations between maternal chronic disease (chronic hypertension and CKD) and adverse pregnancy outcomes using data from the Swedish Registers. Data on adverse pregnancy outcomes were obtained from the Swedish MBR, including pre-eclampsia, Caesarean section, preterm birth, stillbirth and SGA.

Pre-eclampsia was defined as at least 2 dBP measurements of ≥90 mmHg, combined with proteinuria (≥0.3 g/day or ≥1+ on a urine dipstick), and this was obtained from primary and secondary maternal diagnoses in the MBR using ICD codes. Caesarean section was further sub-classified into pre-labour Caesarean section (before onset of labour) and in-labour Caesarean section (after onset of labour).

Preterm birth was categorised as spontaneous preterm birth (<37 weeks' gestation) and medically indicated preterm birth (<37 weeks' gestation). Additionally, preterm birth

was classified into extreme preterm (<28 weeks), severe preterm (28–31 weeks), moderated preterm (32–33 weeks), and near term (34–36 weeks) delivery (136). Stillbirth (antepartum or intrapartum fetal death) was defined as fetal loss after 28 completed weeks (until June 2008), but that was changed to fetal loss after 22 completed weeks since July 2008 (137). Small-for-gestational-age was defined as a birthweight below two standard deviations (SDs) of the mean birthweight of the sex-specific and gestational age distributions.

In CALIBER study (Chapter 6), data on adverse pregnancy outcomes were obtained from primary care (CPRD) and secondary care (HES). The primary outcomes included a diagnosis of pre-eclampsia, fetal growth restriction, preterm birth (<37 weeks' gestation), or very preterm birth (<32 weeks' gestation). Secondary outcomes included stillbirth, emergency Caesarean section, elective Caesarean section, and severe hypertension (BP≥160/110 mmHg). The Read and ICD-10 codes were used to identify pre-eclampsia and fetal growth restriction, whereas data on preterm birth, stillbirth and Caesarean delivery were obtained from recorded variables in the CPRD Pregnancy Register and HES Maternity File.

#### *2.4.2.2 Long-term cardiovascular disease*

In Chapter 7 (using data from CALIBER), the outcome of interest included the first fatal or non-fatal occurrence of 12 cardiovascular disorders (ischemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, stroke not otherwise specified (NOS), myocardial infarction, stable angina, unstable angina, coronary heart disease NOS, peripheral arterial disease, abdominal aortic aneurysm, atrial fibrillation, and heart failure) and the composite outcome of CVD (the first event of any of the 12 cardiovascular outcomes plus any recorded cardiovascular mortality). Data on the 12 phenotypes were defined using *inferred* or *diagnosed* cases of the validated CALIBER phenotypes (110, 129), and these definitions are regularly used in studies from CALIBER on CVD (80, 135). In addition, data on CVD mortality were obtained from death certificates based on ICD-9 and ICD-10 codes.

Composite outcomes were created according to the following groupings: all stroke (ischemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage, stroke NOS), all peripheral disease (peripheral arterial disease, abdominal aortic aneurysm), and

cardiac atherosclerotic (myocardial infarction, stable angina, coronary heart disease NOS).

## 2.5 Data access and ethics

Ethical approval is not specifically required for the cohort studies undertaken for this PhD thesis as only anonymised data were used, and ethical approval for the data sources exists. However, ethical approvals were obtained to use the data from Swedish National Registers and CALIBER platform and locally from University College Cork.

In the Swedish registers, investigators can access only anonymised personal data if they apply to use data for research purposes. The Swedish Ethics Review Board allowed PIN-based register-linkages, then the PINs of the merged data are removed and replaced by unique serial numbers (lpnr) by the National Board of Health and Welfare before data are delivered to the researchers (109). The researchers are obliged to secure storage of the dataset and never back-track the identity of patients in the anonymised dataset. These precautionary measures were suggested to be sufficient to protect the integrity of patients (109). Additionally, informed consent was unnecessary and would not be feasible when performing large register-based research using the Swedish registers (138).

Ethical approval for the use of data from the Swedish registers was obtained from the Swedish Ethical Review Authority in Stockholm, Sweden (Regionala Etikprovningsnamnden Stockholm). Another ethical approval was granted from the Social Research and Ethics Committee, University College Cork (reference number 2019-214).

For CALIBER studies, the Independent Scientific Approval Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (MHRA) requests submission of the study protocol and information on investigators. The protocol was approved by the ISAC for MHRA Database Research (ISAC protocol number 16_280R).

## 2.6 Key epidemiological considerations

Most epidemiological studies aim to establish a causal association between a predictor factor (exposure) and an outcome of interest. Until now, there is no agreement among epidemiologists on a set of casual criteria (139), but there are three potential explanations for finding associations in epidemiological research when a true association does not exist: bias, confounding, and chance. Trying to minimize the impact of these factors in

design and analysis is crucial in observational studies for estimation accuracy, which might improve the potential for a causal claim.

### 2.6.1 Validity of estimation

Obtaining a valid and precise estimate of the effect of exposure on the occurrence of an outcome is the first step in epidemiological research (139). Another key point is to obtain an estimate that can be generalisable to the relevant population.

Overall, the validity of a study is divided into two types: internal and external. Internal validity implies that the study estimated unbiasedly what it claimed to, and external validity refers to the ability to generalise the study results beyond the study population (140). External validity is not a concern in this thesis, as a population-based design was used to address the research questions. However, internal validity is considered as a prerequisite for external validity, and the most violations of internal validity are selection bias, information bias and confounding (139). Each of these components is described in more detail below.

### 2.6.2 Selection bias

Selection biases are distortions that occur from procedures used to select subjects and from factors that influence study participation (139). In other words, it is an error in choosing the study group or group within the study (particularly in case-control design) and can affect the internal validity of the study (140). If the way in selecting the exposed and unexposed individuals resulted in an apparent association (even if the exposure and outcome are not related), in that case, the apparent association is a result of selection bias (140). Sources of selection bias include nonresponse of potential study subjects, as people who do not respond in a study differ from those who do (140). Other sources of selection bias include self-selection, exclusion bias (applying different eligibility criteria for selecting the exposed/case and unexposed/control groups) (139, 140).

Cohort studies enrol subjects who have not yet developed the outcomes of interest; therefore, selection bias due to enrolment procedures is rare but can occur. Selection bias in cohort studies occurs if a selection of either exposed or unexposed subjects is somehow related to the outcome or due to differential retention during follow up (141).

While selection bias in registries is rare, it is possible that poorly defined phenotype or lacks of comprehensiveness leads to selection bias and reduces the validity of effect

estimates (142). In Chapter 5, we used data from the Swedish National Registers and data were routinely collected on all patients as part of health care delivery. Similarly, in Chapters 6 and 7, we used data from CALIBER platform, which involves longitudinal, routinely collected data from primary care and secondary care. However, selection bias in registries might occur due to incomplete recruitment, i.e., if a woman had home birth. In Sweden and the UK almost all births take place in a hospital; the percentage of women planned to have home birth was 0.1% in Sweden and 2% in the UK (143, 144). Thus, this small percentage of home births is unlikely to affect our results on adverse pregnancy outcomes as almost all births in Sweden and the UK take place in hospitals. In addition, data on diagnoses of chronic hypertension and CKD in Chapter 5 were obtained from the Swedish MBR and NPR to better capture women with these conditions. Similarly, data on diagnoses of chronic hypertension and CVD (Chapters 6 and 7) were collected from different sources, including CPRD and HES, which provided a comprehensive estimate of the exposure and outcome of interest (129). Therefore, selection bias in this research is minimized.

### 2.6.3 Information bias

Information bias is a distortion in the measure of association caused by a lack of accurate measurements of key study variables (145). Accordingly, bias in estimating an effect can be caused by measurement errors in the needed information. Researchers may misclassify subjects due to inaccuracies in methods of data acquisition and thereby introduce a misclassification bias, which is further subclassified into differential and non-differential (140). The direction and magnitude of the estimates vary depending on the distribution of errors (139).

Differential misclassification occurs when misclassification of exposure/outcome is not equal between exposed and unexposed subjects, and the results can be biased in either direction towards or away from the null. The non-differential misclassification occurs if there is equal misclassification of exposure/outcome between exposed and unexposed subjects, this type of misclassification is not related to exposure or outcome (145). It results from inaccuracy of the data collection method and is shifting the results toward the null, leading potentially to underestimating the true effect size (140).

All types of studies can be subject to information bias, particularly those relying on self-report data collection. Missing data can also cause information bias, as certain groups

are more likely to have missing data (146). For instance, a UK study has reported that smoking status is generally well recorded in primary care, but misclassification of ex-smokers as never-smokers is likely to occur in those quitting smoking at an early age and/or a long time ago (147). Patients with no record of smoking status are more likely to be ex-smokers or never-smokers than current smokers (147).

Among the included studies in this thesis, women with chronic hypertension might be misclassified with gestational hypertension, as evidence has shown that the diagnosis of chronic hypertension is often identified at the first or early second-trimester appointment (9). Thus, if a pregnant woman had an unrecorded diagnosis of chronic hypertension and did not attend antenatal care in early pregnancy, she might be diagnosed (misclassified) with gestational hypertension. This may underestimate the true effect size of the association between chronic hypertension and outcomes of interest. Other sources of information bias in this thesis could be the missing data on covariates, including smoking status and BMI from CALIBER platform. However, this was handled separately in the analysis stages using an indicator variable, which allowed us to use the entire cohort while adjusting for a potential source of bias.

### 2.6.4 Confounding

Confounding is a type of systematic error in many epidemiologic studies. It refers to a distortion of the association between an exposure and an outcome by an extraneous (third variable) (148). Confounding occurs if the extraneous effect becomes mixed with the effect under study (139). The extraneous variable responsible for differences in the occurrence of outcome frequency between the exposed and unexposed is known as a confounder. There are three criteria for a variable to be a confounder; it must be: (1) associated with the outcome of interest and independent of exposure, (2) associated with the exposure of interest, and (3) it should not be caused by the exposure (not on the causal pathway) or the outcome (139).

The issue of confounding can be addressed in several ways, either in the design or analysis phase of the study. In the design phase, confounding can be controlled by randomisation, restriction, and matching. Randomisation is a method of controlling for known and unknown factors (confounders) between the study groups. However, this method can be applied to RCTs only and cannot be performed in cohort studies. Matching is a common method to handle confounding, where investigators match the

exposed to the unexposed for the factors they suspect could be a potential confounder. Restriction eliminates variation in a confounder by limiting the study to subjects with particular characteristics.

In this thesis, we addressed confounding in the design stage as we chose to restrict our database from the Swedish MBR (Chapter 5) to recorded deliveries from 1982 onwards, as data on important confounding factors (smoking and BMI) were poorly recorded before 1982. We additionally restricted the analyses in Chapter 5 to singleton babies. In Chapter 6, matching was used to adjust for baseline covariates among women with chronic hypertension (treated versus untreated). In Chapter 7, we restricted the analyses to women without a history of pre-pregnancy diabetes, CKD or unspecified hypertension during pregnancy.

Additionally, confounding can be handled in the analysis phase by adjustment or stratification (140). Stratification involves evaluating the associations between the exposure and the outcome within each stratum of the confounder. For example, results may be stratified by maternal age (old versus young). The multivariable analysis is a statistical modelling that can handle multiple confounders simultaneously. The confounding issue in the current thesis was addressed during the analysis stage by performing stratification (Chapters 5, 6 and 7) and adjustment in multivariable models (Chapters 5–7). Residual confounding can remain if there are missing data in the confounder, the confounder is not sufficiently granular, or is modelled incorrectly. In addition, there is a possibility of confounding in observational studies due to unknown or unmeasured confounders, which should be considered when interpreting results (139).

### 2.6.5 Random error

Random error is often equated with chance or random variation, and it occurs when the measured association is different from the true association in a population. Sources of random errors in the epidemiologic study include sampling variation and unexplained variation in occurrence measures (139).

Random error is commonly reduced in an epidemiologic estimate by increasing the size of the study and minimising measurement errors (139). Statistical methods can also be used to avoid reporting estimated associations that may be occurring due to chance alone. Confidence intervals (CI) reflect the amount of random error that is present in the sample and contain a range of possible values of the point estimate, with a specified level of

confidence. In epidemiological studies, the estimates are commonly reported with 95% CI. This implies that if samples of the same size were repeatedly drawn from the population and their 95% CI constructed, 95% of the CI would be expected to include the true population estimate (149), assuming there was no systematic error (bias or confounding). Hence, if the 95% CI does not include a null value, it is considered to be "statistically significant", and the association is unlikely to have occurred by chance alone. In all analyses that conducted as a part of this thesis, the effect estimates were reported with 95% CI.

## 2.7 Missing data

Missing data are a pervasive challenge in epidemiologic research, and the impact of missing data on inference can vary greatly based on the type and magnitude of missing data (150). This problem can be found even in a well-designed study. Missing data is defined as the data value that is not stored for a variable in the observation of interest (151). If the characteristics of subjects with missing data differ from those with complete data, this may introduce a serious type of bias, leading potentially to reduced statistical power, inaccurate effect estimates, and invalid conclusions (151).

### 2.7.1 Type of missing data

Missing data can be categorised as missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). Data are MCAR when the probability of having a variable with missing data does not depend on any observed or missing variables. For instance, a blood sample might be damaged in the lab; although this might be not completely random, the missing data is not related to the subject of the missing data. This is considered an unrealistic assumption in typical epidemiologic studies (150). Instead, MAR—the probability that an observation is missing depends on the set of observed responses of observed variables for this subject— is generally a more realistic assumption in epidemiologic studies (150, 151). In MAR, the reason for missingness depends on other observed characteristics of the subject, e.g., a registry examining BMI may encounter MAR data if female participants were less likely to complete a survey about their weight than male participants. Data are MNAR if the missingness pattern depends on the values of unobserved variables (150), i.e. the missing value of the variable is related to the reason it is missing. For example, a registry examining depression may encounter data that are MNAR if participants with severe

depression are more likely to refuse to complete the survey about depression severity (152).

### 2.7.2 Sources of missing data

#### *2.7.2.1 Sources of missing data in the Swedish national registers*

Data on disease diagnoses may be incomplete in the Swedish MBR. Since 1982, information on pre-existing conditions, such as chronic hypertension and CKD, has been collected by midwives using a check-box method at the first antenatal visit (97). However, this method has been reported to be inaccurate as it may lead to underestimating the true proportion of disease among the pregnant population (97). Thus, we chose to additionally obtain data on exposures (chronic hypertension and CKD) and other comorbidities from the NPR, which was established in 1964 and achieved national coverage since 1987 (104).

Data on smoking and maternal weight were first collected from 1982 onwards (97), and because we aimed to examine the role of BMI on the associations between maternal chronic diseases and adverse pregnancy outcomes, we restricted our cohort to women with first recorded deliveries from 1982 onwards. Approximately 4–9% of data were missing on smoking status during early pregnancy between 1982–2003, with some available data on maternal smoking at 30–32 weeks of pregnancy (97). In this thesis, smoking status was included as smoking at any stage of pregnancy, and those with missing data represent pregnant women with no record of smoking status at any stage of pregnancy.

Overall, data from the Swedish MBR contains missing values on smoking status (174,685, 6.3%) and BMI (634,633, 22.8%). For the years 1990–1991, no data were available for weight at first antenatal-care visit (1), accounting for approximately a third of the total missing values for BMI (215 495, 33.9%). When excluding births in 1990 and 1991, the missing data on BMI were 419,138 (16.3%). Data missing in a given year can be considered MAR. The missing smoking and remaining missing BMI can be assumed to be MAR because there is no significant differences in the frequency or distribution of the exposures and outcomes in women for whom data were available or missing. For example, the prevalence of chronic hypertension was 0.54% among women who had complete data; 0.36% among women who were missing smoking; and 0.45%

among women who were missing BMI [and 0.45% for births in years other than 1990-91].

#### *2.7.2.2 Sources of missing data in CALIBER platform*

Missingness is a common issue with EHRs based research. In this thesis, data from the UK EHRs, namely, CPRD and HES, contain missing data for ethnicity (75,485, 4.0%), smoking status (1,357,646, 71.7%), BMI (1,251,554, 66.1%), and parity (338,610, 17.9%). There was less (but still substantial) missingness on smoking status and BMI in women who had chronic hypertension 51.3% and 37.8%, respectively. The missingness was noticeably lower among the treated women with chronic hypertension, with a proportion of 31% for smoking and 21% for BMI.

Recording of BMI and smoking status are unlikely to be independent of the value of variables themselves, suggesting that data are more likely to be MNAR. For example, the record of weight and BMI from the CPRD and the UK EHRs varied based on patients' characteristics, and it was more likely to be recorded in females with higher BMI, older age, and with comorbidities (117, 153). It was also reported that former smoking is under-reported in CPRD compared with UK national survey data (154), suggesting that those with unknown smoking status may be more likely to be former smokers. The pattern of missing data in our cohort emphasises that data on lifestyle factors, such as smoking and BMI, were more likely to be recorded among women with older age and comorbidities.

Data on ethnicity from CPRD has been shown to be valid for 90%, whereas this was 77% for HES records (155). Therefore, in the current thesis, we used data from CPRD on ethnicity, supplemented with HES data where missing from CPRD and available in HES records. As a result, ethnicity was available for 96%.

#### *2.7.2.2.1 The amount of missing data in the CALIBER compared to other UK studies*

The amount of missing data in our studies is similar to what was reported in a recent CALIBER study of pregnant women, which used a similar approach to assess smoking status and BMI. The authors reported a substantial level of missingness in the UK EHRs of maternal BMI (71%) and smoking (~61%) (80). These findings confirm that many variables, such as lifestyle factors, are recorded mainly for their clinical relevance in primary and secondary care databases. For example, women with comorbidities (i.e., chronic hypertension) are more likely to have health indicators recorded compared to the rest of the general obstetric population.

In this thesis, we used the most recent records of smoking and BMI (≤2 years of pregnancy start date) from the UK EHRs. The available literature demonstrated that the completeness of BMI in CPRD increased over calendar time from 37% in 1990–1994 to 77% in 2005–2011 (117). It was also reported that the most recent BMIs (recorded ≤3 years) reflected a closer estimate to HES records, but restriction to patients with a recent BMI record resulted in excluding a large proportion (between 33% and 47% across years) of patients (117). The proportion of missingness in our dataset is also in line with a summary of QRESEARCH database (UK primary care database containing health records from approximately 4 million patients registered with over 530 EMIS practices), which reported that 58% of registered patients aged 16+ had BMI records in the past 5 years in 2007 (156).

### 2.7.3 Handling missing data

There are several approaches to handle missing data; each has strengths and limitations. The appropriateness of a missing data handling method is contextual and depends on the missing data mechanism (157) (see **Figure 2.3** below). For example, under the MAR assumption, complete-case analysis is an appropriate option if the proportion of missingness is small. This includes ignoring missing observations, where analysis is restricted to records with complete data for the analysis model, also known as listwise deletion. Evidence from a recent systematic review of pharmacoepidemiologic studies that used ≥2 distinct databases reported that a complete-case analysis (68%) was the most used method to handle missing data (158).

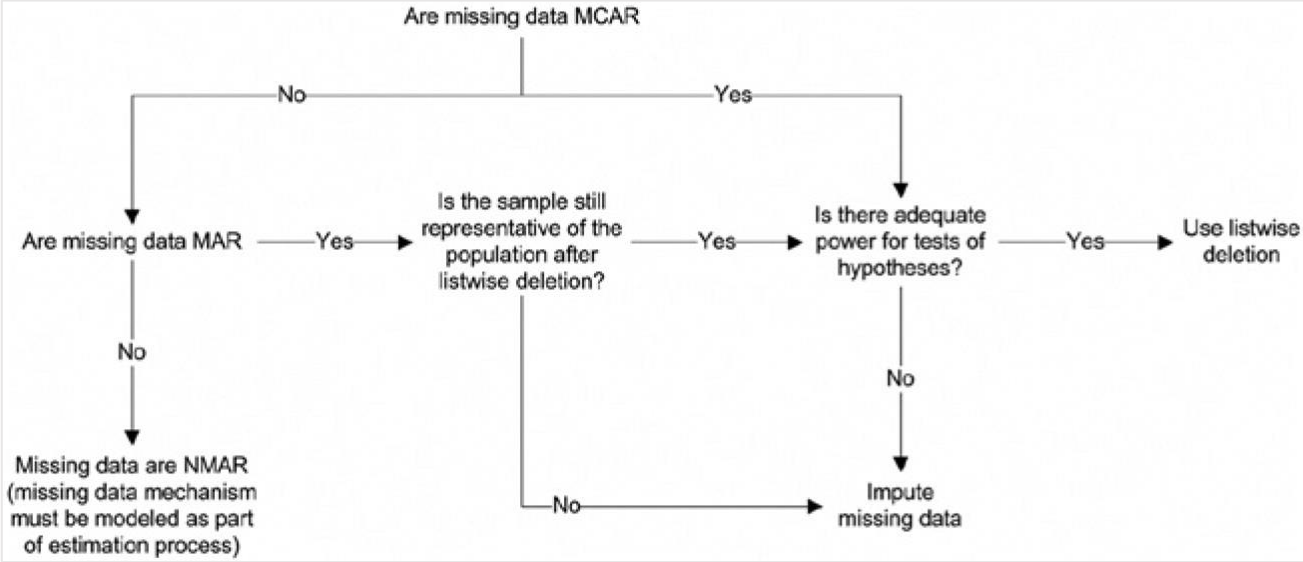



**Figure 2.3** Decision process governing the choice between missing data imputation and listwise deletion (Source: Cheema, 2014 (157))

In medical literature, the missing-indicator method is one of the most used approaches to handle missing data, where researchers use a dummy variable in the statistical model to indicate whether the value for that variable is missing, and all missing values are set to the same value (159). Hence, all observations can be included in the analysis, reducing the loss of statistical power (159). A similar approach to this is the "missingness as category", in which researchers use an extra category to handle missing data. Despite biases that may be observed in some of the regression coefficients using this method, it can improve the ability of a model to predict outcomes (160).

Missing data can also be managed using imputation-based methods. These methods involve replacing missing values with new values (using their imputed counterparts), which has become increasingly popular (157, 161). There are different types of imputation, such as mean imputation, regression imputation, single random imputation, and multiple imputation. Moreover, multiple imputation may not always provide a preferable method of handling missing data (157), and it may not be a straightforward approach, particularly in CALIBER data (with missingness from the EHRs) because the patterns of missingness are complex (111). In addition, data on smoking and BMI are unlikely to be MAR, i.e., the assumption required for multiple imputation to be valid.

When data are MCAR, it is possible to use a statistical test to identify whether the mechanism underlying missing data was MCAR using Little's test (162). However, it is

more challenging to make an assumption and handle data that are MNAR. This could be because the pattern of missing data in longitudinal studies might be complex and depend on other variables. Available literature suggested using complete-case analysis if missingness is MNAR when the probability of a variable record being missing is independent of the outcome (163).

In this thesis, where a variable had missing data, the data were added as a separate category in categorical variables in the regression models to handle missing data on BMI, smoking status, ethnicity and parity. The main advantage of this method is that all cases are included in the analyses, which is important in this thesis considering the large amount of missingness on these two variables. Moreover, given the high proportion of missing data on smoking and BMI in the UK cohort, we conducted a sensitivity analysis using the Swedish cohort to quantify the effect of BMI and smoking on the associations between chronic hypertension and adverse pregnancy outcomes. Given the large sample size and the small proportion of missing data on these particular variables [smoking (6 %) and BMI (~23%)] in the Swedish register, exploring the impact of these variables on the effect estimates were appropriate. Additionally, we performed a complete-case analysis (listwise deletion), excluding those with missingness on BMI and smoking, to better assessed their impacts on the effect estimates. The results of the sensitivity analyses are shown in Chapter 8.

## 2.8 Statistical modelling

### 2.8.1 Meta-analysis

Meta-analysis is the statistical combination of effect estimates from two or more separate studies that assessed the same associations, and it is widely used in medical research (164, 165). Meta-analysis involves a two-stage process. In the first stage, a summary statistic is extracted or calculated for each study (effect estimate to describe the observed association). This summary statistic may be a risk ratio (RR), odds ratio (OR), prevalence ratio (PR), or hazard ratio (HR), if the outcome data are dichotomous and analysed on the multiplicative scale. In the second stage, a pooled effect estimate is calculated as a weighted average of the exposure/intervention effects in the individual studies (164).

Fixed-effects and random-effects models are the most commonly used statistical models for meta-analysis. The fixed-effects model assumes that all studies included in a meta-

analysis are estimating a single true underlying effect, and it is the appropriate statistical model for meta-analysis when the number of studies is small (166). By contrast, the random-effects model is appropriate to use when it cannot be assumed that true homogeneity exists, and it is the appropriate model when the number of studies is large (i.e., to support generalization inferences beyond the included studies) (166). Therefore, in this thesis, random-effects models were used, which allows for variation in effect size across the included studies.

#### *2.8.1.1 Random-effects model for meta-analysis*

In Chapters 3 and 4, the random-effects method was used to calculate pooled effect estimates of the impact of chronic hypertension, antihypertensive treatment (Chapter 3) and CKD (Chapter 4) on adverse pregnancy outcomes. In particular, we used DerSimonian and Laird method with the inverse-variance approach for random-effects meta-analysis (167). The inverse-variance approach applies an adjustment to the study weights according to the extent of variation among the varying intervention effects (164, 168). The inverse-variance method is so-called because the weight given to each study is the inverse of the variance of the effect estimate, where larger studies (with small standard errors [SEs]) are generally given more weight than smaller studies (large SEs) (164, 169). The choice of weight in this approach minimises the imprecision (variability) of the pooled effect estimate (168). The weight used is presented in formula [1]. Then the weighted average is combined to provide a pooled estimate of the exposure effect from individual studies using formula [2]; both equations are shown below (168, 169).

$$\boldsymbol{W_i} = \frac{\mathbf{1}}{(\mathbf{SE}\{\boldsymbol{\theta}\})^{\mathbf{2}}} \qquad [\mathbf{1}]$$

$$\boldsymbol{\theta_{IV}} = \frac{\boldsymbol{sum\ of}(\mathbf{weight} \times \boldsymbol{estimate})}{\boldsymbol{sum\ of\ weights}} = \frac{\sum \boldsymbol{W_i}\,\boldsymbol{\theta_i}}{\sum \boldsymbol{W_i}} \qquad [\mathbf{2}]$$

Where $W_i$ is the weight given to the i study, SE is the standard error of estimate, and θ is the log of the measurement of association. The SE of the pooled log(OR) in inverse-variance method ($\theta_{IV}$) is calculated as follow (168, 169):

$$\boldsymbol{SE(\theta_{IV}) = \frac{1}{\sqrt{\sum W_i}}} \qquad [3]$$

The meta-analyses (in Chapters 3 and 4) included studies with different populations in different settings and at different time frames. Thus, the true effect of the exposure on adverse pregnancy outcomes might vary from study to study (170). Therefore, the random-effects models were selected, which accounts for both random variability and the variability in effect estimates among the included studies (164, 167). The effect estimates (RR or OR) of the included studies and their SEs (calculated from the 95% CI) were meta-analysed on the log OR scale. Then combined results of effect estimates were presented as a pooled OR with 95% CI.

### 2.8.2 Risk difference

The risk differences were calculated in Chapter 4 for the associations between CKD and adverse pregnancy outcomes. We used GRADEpro to estimate the risk difference, where the event risk in the unexposed group, the pooled RR and 95% CI are used to generate the absolute risk (171). As we calculated the pooled ORs in Chapter 4, two steps are needed to estimate the risk difference. First, the OR is converted into RR (using formula **[4]**), the corresponding risk is then calculated from RR (using formula **[5]**) (172). Both equations are shown below.

$$\boldsymbol{RR = \frac{OR}{1 - CER \times (1 - \mathrm{OR})}} \qquad [4]$$

$$\boldsymbol{RD\ (per\ 1000\ people) = 1000 \times CER \times |1 - RR|} \qquad [5]$$

Where RR is the risk ratio, OR is the odds ratio, and CER is the number of people with events in the unexposed group.

### 2.8.3 Binary logistic regression

Binary logistic regression is a commonly used statistical model in epidemiology that examines the association between an exposure and an outcome when the outcome of interest is dichotomous (e.g., alive/dead, healthy/sick). The regression model is used to determine the OR of an association between one binary outcome variable (dependent variable) and one or more predictors (exposures/independent variables). The outcome in this model is often coded as '0' or '1', where '1' indicates that the outcome is present, and '0' indicates that the outcome of interest is absent. Multivariable logistic regression models are widely used to investigate the associations between the exposures and outcomes while adjusting for potential confounding factors. The multivariable logistic regression can be modelled using the following equations:

$$\boldsymbol{P} = \frac{\mathbf{exp}\left(\boldsymbol{\beta_0} + \boldsymbol{\beta_1\chi_1} + \boldsymbol{\beta_2\chi_2} + \cdots + \boldsymbol{\beta_\rho\chi_\rho}\right)}{\mathbf{1} + \mathbf{exp}\left(\boldsymbol{\beta_0} + \boldsymbol{\beta_1\chi_1} + \boldsymbol{\beta_2\chi_2} + \cdots + \boldsymbol{\beta_\rho\chi_\rho}\right)} \qquad [\mathbf{6}]$$

Where $P$ is the expected probability of the outcome, $X_1$ through $X_p$ are a set of predictors (independent variables), and $\beta_0$ through $\beta_p$ are the regression coefficients **[6]**.

The multivariable logistic regression model can also be written differently using a logit equation:

$$\boldsymbol{logit}(\boldsymbol{P}) = \mathbf{ln}\left(\frac{\mathbf{P}}{\mathbf{1} - \mathbf{P}}\right) = \boldsymbol{\beta_0} + \boldsymbol{\beta_1\chi_1} + \boldsymbol{\beta_2\chi_2} + \cdots + \boldsymbol{\beta_\rho\chi_\rho} \qquad [\mathbf{7}]$$

Where the outcome is the log of the odds (i.e., the probability of the outcome is happening (P) to probabilities of the outcome not happening (1 - P). The coefficients derived from the model (e.g., $\beta_1$) indicate the change in the expected log-odds relative to a one unit change in $X_1$, holding all other predictors constant (173).

In Chapters 5 and 6, binary logistic regression was used to assess the associations between maternal chronic disease (chronic hypertension, CKD or both conditions) and adverse pregnancy outcomes; and evaluate the effect of antihypertensive treatment and hypertension control on these associations. As the outcome of interest includes only two possible categories (present/absent), binary logistic regression was considered as an appropriate method of statistical analysis.

#### *2.8.3.1 Logistic regression with Propensity Score Matching*

In CALIBER study (Chapter 6), we further used logistic regression with propensity score matching to examine the effect of antihypertensive treatment on the risk of adverse pregnancy outcomes in women with chronic hypertension. Propensity score, also known as conditional probability of treatment analysis, is one of the most commonly used parametric methods for causal inference (174). In which the probability of receiving treatment is conditional on observed baseline covariates (P [$Z_i$ = 1 | $X_i$ ]) (175, 176). In other words, it is a balancing score of the distribution of measured baseline covariates ($X_i$) to ensure they are similar between the treated/exposed and untreated/unexposed subjects (175). Thus, in a set of subjects with the same propensity score, the distribution of observed baseline covariates will be similar between the treated/exposed and untreated/unexposed. In observational studies, propensity score matching is used to reduce confounding of treatment effect estimates by matching treated/exposed and untreated/unexposed groups to be as similar as possible on the observed background characteristics (176).

In RCTs, the random allocation of treatment ensures that treatment status will not be influenced by either measured or unmeasured baseline characteristics. In ideal RCT (no loss to follow up, full adherence to exposure, blind assignment) (177), half of the individuals are assigned to treatment [$Z_i$=1], in which the propensity score is [P ($X_i$=0.5)] for all individuals (174). Therefore, the effect of treatment on outcomes can be estimated by comparing outcomes directly between treated and untreated subjects.

On the other hand, in observational studies, some individuals may be more likely to receive treatment than others, as treatment allocation is beyond the control of the investigators. Thus, the true propensity score [P ($X_i$)] is unknown and therefore needs to be estimated from the data (174). Firstly, investigators estimated the propensity scores, and then these scores are used to estimate causal effects using one of the following

methods: stratification, standardisation, and matching (174). Three main points are required for an association to be considered as causation: exchangeability, positivity, and consistency. Exchangeability assumes that treated/exposed and untreated/unexposed groups would have a similar distribution of outcomes, e.g. the treated and the untreated groups would have experienced the same risk of death if they had received the same treatment level (174, 177). Positivity in propensity score analysis implies that no individual has a propensity score equal to either 1 or 0 within levels of the covariates (174). The association measures in the matched population are consistent estimates (consistency) of effect measures, e.g., the associational RR in the matched population consistently estimates the causal RR in the matched population (174).

In the absence of randomisation (i.e. in observational studies), there is no guarantee that conditional exchangeability is true, and investigators cannot check their assumption of conditional exchangeability (177). However, conditional exchangeability is the weakest condition required for causal inference from observational data (177). It was proved that exchangeability and positivity based on the variables ($X_i$) imply exchangeability and positivity based on a balancing score (174). It should be noted that propensity score balances only the measured covariates, which does not prevent residual confounding by known unmeasured factors and unknown factors. The propensity score matching method allows researchers to design and analyse an observational study to mimic some of the particular characteristics of RCT (175). Moreover, it is used in observational studies to reduce confounding of treatment effect estimates by matching treatment and comparison groups to be as similar as possible on the measured background characteristics (176).

The method of propensity score matching analysis used in this thesis is explained in more detail under the statistical analysis in Chapter 6 and **Appendix 6**. In brief, propensity scores of being treated were estimated using logit model, with the following covariates: age, ethnicity, smoking, BMI, pre-pregnancy diabetes, parity and IMD. Then treatment and comparison subjects were matched using 1:1 nearest-neighbour (178). Next, the overlap and balance of propensity score distributions were assessed across treatment and comparison groups. Finally, the balance of covariates (included in the propensity score estimation model) was assessed after matching, with values $< 0.1$ of standardised differences indicating good balance and a negligible difference between both groups for the covariates (179).

### 2.8.4 Cox proportional-hazards regression

Cox regression for survival analysis is a method that measures associations in longitudinal data, examining the time (survival time) it takes for events to occur. This method is widely used in regression modelling of survival data. It estimates the hazard ($h$) or instantaneous risk of the outcome at any given follow-up time ($t$) given their prognostic variables. This is modelled using the following equation:

$$\boldsymbol{h(t) = h_0(t)\, exp\left(\beta_1\chi_1 + \beta_2\chi_2 + \cdots + \beta_\rho\chi_\rho\right)} \qquad [\mathbf{8}]$$

Where $h(t)$ is the expected hazard at time $t$, $h_0(t)$ is the baseline hazard (represents the hazard when all predictors [$X_1$ through $X_p$] are equal to zero). The Cox regression model is used to estimate the HR, which is the ratio of the two expected hazards (180), and it is proportional over time. HR can be interpreted in the same way as a relative risk, where values of HRs<1 indicates lower risk in the exposed compared to the unexposed group, and if the HR is >1, then this suggests a greater hazard (risk) among the exposed group compared to the unexposed group. Multivariable Cox regression models are commonly used to investigate the associations between the exposure and outcome of interest while adjusting for potential confounding factors. This method was used in Chapter 7 to estimate the adjusted HRs.

There are three main assumptions that should be checked when using Cox regression models. Firstly, the proportional-hazards assumption, where the ratio of hazards in the exposed compared to the unexposed group remains constant over time. This can be assessed using several methods, including graphical methods (where plotted curves should be parallel) or test based on Schoenfeld residuals (180). Secondly, independence of survival times between distinct individuals in the cohort. Thirdly, censoring should be 'noninformative'; in other words, the reason individuals are being censored should be not related to the exposure or outcome of interest. Informative censoring may occur when patients withdraw from a study because of drug toxicity or worsening clinical condition (181).

In Chapter 7 of this thesis, Cox regression was used to evaluate the association between chronic hypertension in pregnancy and the risk of future CVD, considering whether adverse pregnancy outcomes contribute to accelerating the risk of cardiovascular events. In this model, participants were followed-up from the first recoded delivery until they

developed an outcome of interest (i.e., CVD) or until they were censored. Possible reasons for censoring may include death (due to other causes rather than CVD), the study period ends (where participants may not have experienced the event by the end of the study), or loss to follow-up.

Following this, each woman's entry date in the study was the date of her first recorded birth. Participants were followed up from the date of entry until the/ date of CVD diagnosis, death, or study end date (31 December 2016), whichever was earliest. Hypertension and other covariates were presented as time-varying variables, except for maternal ethnicity, multiple deprivation, and family history of CVD were time-fixed variables. In addition, the assumptions for the proportionality was assessed using graphical methods, "log–log" plots.

More details about each statistical method used in the current thesis are outlined in Chapters 3–7 under the statistical section.

# CHAPTER 3: The Impact of Chronic Hypertension and Antihypertensive Treatment on Adverse Perinatal Outcomes: A Systematic Review and Meta-Analysis

**Sukainah Y. Al Khalaf**[1,2], Éilis J. O'Reilly[1,3], Peter M. Barrett[1, 2], Debora F. Leite[4], Lauren C. Pawley[5], Fergus P. McCarthy[2,6], Ali S. Khashan[1, 2]

[1] *School of Public Health, University College Cork, Cork, Ireland*

[2] *INFANT Research Centre, University College Cork, Ireland*

[3] *Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

[4] *Federal University of Pernambuco, Recife, Brazil*

[5] *Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland*

[6] *Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland*

**Published in:** *Journal of the American Heart Association*, April 2021

Doi:10.1161/JAHA.120.018494

**(Paper 1)**

## 3.1 Abstract

**Background:** Maternal chronic hypertension is associated with adverse pregnancy outcomes. Previous studies examined the association between either chronic hypertension or antihypertensive treatment and adverse pregnancy outcomes. We aimed to synthesize the evidence on the effect of chronic hypertension/antihypertensive treatment on a wide range of adverse pregnancy outcomes.

**Methods and Results:** Medline/PubMed, EMBASE, and Web of Science were searched; we included observational studies and assessed the effect of ethnicity, where possible, following a registered protocol (CRD42019120088). Random-effects meta-analyses were used. A total of 81 studies were identified on chronic hypertension, and a total of 16 studies were identified on antihypertensive treatment. Chronic hypertension was associated with higher odds of pre-eclampsia [adjusted odds ratio (aOR): 5.43 (95% confidence interval (CI), 3.85–7.65)]; Caesarean section [aOR: 1.87, (95% CI, 1.61–2.16)]; maternal mortality [aOR: 4.80, (3.04–7.58)]; preterm birth [aOR: 2.23, (95% CI, 1.96–2.53)]; stillbirth [aOR: 2.32, (2.22–2.42)]; and small for gestational age (SGA), [aOR: 1.96, (95% CI, 1.61–2.40)]. Subgroup analyses indicated that maternal ethnicity does not influence the observed associations. Women with chronic hypertension on antihypertensive treatment (versus untreated) had higher odds of SGA [aOR: 1.86, (95% CI, 1.38–2.50)].

**Conclusions:** chronic hypertension is associated with adverse pregnancy outcomes and these associations appear to be independent of maternal ethnicity. In women with chronic hypertension, those on treatment had a higher risk of SGA, although the number of studies was limited. This could result from a direct effect of the treatment or because severe hypertension during pregnancy is a risk factor for SGA and women with severe hypertension are more likely to be treated. The effect of antihypertensive treatment on SGA needs to be further tested with large randomized controlled trials.

## 3.2 Introduction

Chronic hypertension refers to high blood pressure predating pregnancy or recognized before 20 weeks' gestation (9), and is estimated to affect 1-5% of pregnancies (13, 182-184). The prevalence of chronic hypertension in pregnancy increases with increasing maternal age, obesity, diabetes and medical co-morbidities in pregnancy (16, 17, 20, 21, 185), and has nearly doubled in the USA from 1990 to 2009, especially among Black women (13, 186).

Chronic hypertension has previously been associated with an increased risk of adverse pregnancy outcomes. A systematic review and meta-analysis that included 55 studies reported an increase in the pooled incidence of adverse pregnancy outcomes among women with chronic hypertension (42). However, this review did not make a direct comparison between hypertensive and normotensive women from available literature; instead, the pooled incidences of adverse pregnancy outcomes among women with chronic hypertension were compared to the US general population. This review also did not examine the role of antihypertensive treatment or ethnic origin.

Minimizing episodes of severe hypertension during pregnancy is critical to reduce the risk of associated maternal complications, including stroke (187). Whether certain antihypertensive agents may reduce the risk of adverse pregnancy outcomes in addition to controlling maternal hypertension is unclear (39). A small number of antihypertensive agents are used to treat hypertension in pregnancy and in the postpartum period. Others are contra-indicated due to potential teratogenicity (184, 188). First-line agents for the treatment of hypertension in pregnancy include labetalol, methyldopa, or nifedipine, but there is limited evidence to suggest whether any agent performs better in reducing the occurrence of adverse pregnancy outcomes (184, 188, 189).

Previous reviews investigated either the effect of chronic hypertension or antihypertensive treatment, whereas we synthesized the evidence of both on longer list of adverse pregnancy outcomes in finer details, e.g. we looked at subtypes of preterm birth (spontaneous, indicated or not-specified). Also, as part of this review, we aimed to summarize the gaps and limitations in previous literature. Therefore, we conducted this systematic review and meta-analysis of observational studies to estimate the effect of chronic hypertension/antihypertensive treatment on maternal, fetal, and neonatal outcomes taking into account, where possible, whether maternal ethnicity or type of antihypertensive agent modified these associations.

## 3.3 Methods

### 3.3.1 Registration and reporting

The protocol for this review was registered on The International Prospective Register of Systematic Reviews (identifier: CRD42019120088) (93). We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines for all procedures and reporting (190).

### 3.3.2 Information sources and search strategy

This systematic review and meta-analysis comprised two separate comprehensive searches of the same databases. Electronic search was conducted through PubMed/ Medline, Embase and Web of Science. Additionally, the bibliographies of previous systematic reviews and all identified studies were searched for further potentially relevant articles.

***Search 1: Identifying studies on chronic hypertension***

The first search focused mainly on identifying studies assessing the association between maternal chronic hypertension and adverse perinatal outcomes. We searched the databases from inception through January 2019. We used a combination of subject headings and MESH terms, and key words related to (1) pregnant women with chronic hypertension (exposed group); (2) normotensive pregnant women (non-exposed group) and 3) maternal, fetal, and neonatal complications (outcomes). The search terms we used for retrieving relevant papers are shown in **Appendix 3**.

***Search 2: Identifying studies on antihypertensive treatment***

Similarly, we searched the same databases from inception through May 2019. The search strategy captured: (1) pregnant women with chronic hypertension on antihypertensive treatment (exposed group); (2) untreated pregnant women (non-exposed group) and (3) maternal, fetal, and neonatal complications (outcomes). The search strategy we used are shown in **Appendix 3**. We did not restrict the second search to women with chronic hypertension when assessing the effect of antihypertensive treatment because some studies of treatment effect used normotensive women as the comparison group, but in the analysis, we grouped studies that reported the effect of treatment for chronic hypertension separately.

### 3.3.3 Outcome measures

The maternal outcomes were pre-eclampsia (PE), Caesarean section (CS), post-partum haemorrhage (PPH), HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet levels) and maternal mortality. Fetal and neonatal outcomes were miscarriage, stillbirth, preterm birth (PTB) <37 weeks' gestation, very PTB (VPTB) <34 weeks' gestation, small for gestational age (SGA), low birthweight (LBW), neonatal intensive care unit (NICU) admission, neonatal death and perinatal death.

### 3.3.4 Selection process and eligibility criteria

Two investigators (S.A and P.B) independently screened titles and abstracts, excluding studies that clearly did not meet the predefined criteria. Then the full texts of potentially eligible studies were obtained. We included cohort and case-control studies and excluded randomized control trials (RCTs), case reports, case series, editorials, reviews, conference abstracts, book chapters and animal/in vitro studies. When two or more studies included the same cohort, we included the one with the largest population. We excluded studies that by design enrolled women with chronic hypertension and additional comorbidities and studies with participant numbers <25 pregnant women with chronic hypertension.

### 3.3.5 Data collection process and quality assessment

An electronic standardized data extraction form was developed and pilot-tested on seven studies before beginning data extraction. One investigator (S.A) extracted the data for all included studies, and two investigators (F.MC and D.L) extracted the data independently for more than 50% of the included studies, selected randomly, to ensure the validity of extracted data. We extracted data on year of publication, country, setting, sample size and eligibility criteria, source of data, exposures and outcomes definitions, reported effect measures (if not reported, we use raw data to calculate odds ratios [ORs]), statistical tests or models, and confounder adjusted for, if any. We used the Newcastle-Ottawa Scale (NOS) to assess the study quality, as recommended by recent guidelines to evaluate the quality of cohort and case-control studies (191). The NOS uses a "star system", in which stars are assigned to show higher quality based on three criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure and/or outcome of interest (the total score ranged from 0 to 9 where 0 is the lowest). The quality assessments were performed independently by two investigators

(S.A) and (L.P). In addition, a third investigator (A.S.K) resolved any inconsistencies between the two investigators about included articles, data extraction, and quality assessment (more details about the methods are available in **Appendix 3**.

### 3.3.6 Statistical analysis

First, we assessed the effect of chronic hypertension, compared to normotensive women (reference group), on the previously mentioned adverse maternal, fetal, and neonatal outcomes.

Then, we conducted separate meta-analyses that included studies that stratified the associations by maternal ethnicity to assess effect modification. The subgroup meta-analysis calculates the effects within each subgroup level and then compares the pooled effect estimates for each subgroup. The *P* value from the Cochran's Q test, test for interaction, was used to determine whether the magnitude of the effect of chronic hypertension differs according to maternal ethnicity. Sensitivity analyses were performed by study design (case-control/ cohort), study location (North America/Europe/Australia/and other) and decade of publication (1990-1999/ 2000-2009/and 2010-2019).

Second, we assessed the effect of antihypertensive treatment on the same outcomes. The comparative groups in these analyses were divided into two categories: (1) untreated normotensive women; and (2) untreated women with chronic hypertension. Sensitivity analyses were performed to assess the effect of different types of antihypertensive agents, including women who were exposed to beta-blockers only versus untreated women; women exposed to centrally acting anti-adrenergic agent only versus untreated women.

In these meta-analyses, we included studies with different populations in different countries and at different time frames; thus, the true impact of chronic hypertension/antihypertensive treatment on adverse pregnancy outcomes might differ from study to study. Therefore, random-effects models were selected, which accounts for both random variability and the variability in effects among the studies, to account for any remaining heterogeneity in the estimates across studies (170). The study estimates, both crude and adjusted OR (aOR), and their standard errors (calculated from confidence intervals [CI]) were meta-analyzed on the log OR scale. The weight given to each study is the inverse of the variance of the effect estimate, where larger studies are

given more weight than smaller studies (167, 192). Combined results were presented as a pooled OR with 95% CI; and for adjusted estimates, we followed the authors' definitions of adjustment.

Heterogeneity among studies was measured using the $I^2$ statistic and categorized as either low ($I^2$<25%), medium ($I^2$=25%-50%) or high ($I^2$>50%), while publication bias was assessed using Begg's funnel plot and Egger's test when there were 10 studies or more in a meta-analysis (193, 194). A statistically significant *P* value was based on a threshold of <0.05. Data were analyzed using Review Manager Software (version 5.3) (195) and Stata/MP software (version 16) for Egger's test.

## 3.4 Results

### 3.4.1 Search results and study characteristics

This systematic review and meta-analysis summarized information from 94 studies. The selection process for the first (chronic hypertension) and second (antihypertensive treatment) reviews are illustrated in **Figures 3.1** & **3.2**. For chronic hypertension, the initial search identified 9,739 studies, of which 81 articles were included (12-15, 43-47, 51, 196-266). For antihypertensive treatment, 8,629 citations were identified initially, and a total of 16 articles were included (46-54, 59, 60, 267-271). Three studies reported data on both exposures (chronic hypertension and antihypertensive treatment) (46, 47, 51). Of the 94 studies, eighty were cohort, and 14 were case-control studies.

Among studies that reported antihypertensive treatment as an exposure, six out of 16 studies examined the effect of treatment among women with chronic hypertension compared with untreated normotensive women (46-50, 271). Eight studies compared the outcomes in women with chronic hypertension (treated versus untreated) (51-54, 59, 267-269), whereas the remaining two studies compared the effect of different antihypertensive agents among women with chronic hypertension (60, 270).

Details about individual studies, including exposures and outcomes definitions, are presented in **Appendix 3** (**Tables S3.1** through **S3.27** and **Figures S3.1** through **S3.26**). Moreover, the definitions for outcomes varied across the included studies. For example, 19 studies defined SGA as birthweight <10$^{th}$ percentile for gestational age; five studies as birthweight<5$^{th}$ percentile for gestational age; three studies did not report the

definitions used; and another three studies used the International Classification of Diseases, Ninth Revision (ICD-9), codes (**Appendix 3**, **Table S3.9**).

### 3.4.2 Level of agreement, publication bias and quality assessment

The level of agreement was high (>80%) between investigators in the selection process, data extraction and quality assessment. For publication bias, the results indicated that bias may not be a substantial problem as funnel plots [for PE (**Figure S3.1b**); CS (**Figure S3.3c**); PTB (**Figure S3.6c**); stillbirth (**Figure S3.8c**); SGA (**Figure S3.9b**); and LBW (**Figure S3.10b**) in **Appendix 3**] show approximately symmetric distributions, and the results of Egger test were non-significant (*P* values= 0.65; 0.92; 0.14; 0.47; 0.29 and 0.09, respectively), suggesting that the published literature does not have publication bias. The total scores for studies' quality of Newcastle-Ottawa grading ranged from 4 to 9, with poorer quality among studies examining the effect of antihypertensive treatment.

### 3.4.3 Results of Meta-analysis

#### The impact of maternal chronic hypertension compared with normotensive women

The prevalence of chronic hypertension among cohort participants ranged from 0.3% (12) to 4.3% (15) across studies. Maternal chronic hypertension was associated with higher adjusted odds of PE [aOR: 5.43, (95% CI, 3.85–7.65)]; HELLP syndrome [aOR: 3.08, (95% CI, 1.79–5.30)]; CS [aOR: 1.87, (95% CI, 1.61–2.16]; PPH [aOR: 1.46, (95% CI, 1.17–1.81)], maternal mortality [aOR: 4.80, (95% CI, 3.04–7.58)], VPTB [aOR: 1.92, (95% CI, 1.09–3.38)]; and PTB [aOR: 2.23, (95% CI, 1.96–2.53)] (**Table 3.1** & **Figure 3.3**). We further divided the PTB into unspecified, spontaneous, and medically indicated; both crude and adjusted analyses showed four times greater odds of medically indicated PTB [aOR: 4.67, (95% CI, 3.55–6.14)]. Conversely, we found no statistically significant association between chronic hypertension and spontaneous PTB [aOR: 1.44, (95% CI, 0.74–2.80)] (**Appendix 3**, **Figures S3.8a** & **S3.8b**). We additionally excluded studies with multiple pregnancies and that did not affect the results for PTB and VPTB. We found higher odds of SGA [aOR: 1.96, (95% CI, 1.61–2.40)] and LBW [aOR: 3.05 (95% CI, 2.24, 4.15)] among mothers with chronic hypertension (**Figure 3.4**). Similarly, stillbirth [aOR: 2.32, (95% CI, 2.22–2.42)], neonatal death [aOR: 2.29, (2.02–2.59)] and perinatal death [aOR: 1.87, (95% CI, 1.33–2.63)] were associated with maternal chronic hypertension. One study on miscarriage [aOR: 1.33 (95% CI, 0.90–1.97)] and another

on NICU admission [aOR: 1.37, (95% CI, 1.05–1.79)] supported an association with chronic hypertension.

The results of subgroup analyses regarding chronic hypertension and adverse outcomes by maternal ethnicity showed that the odds of PTB among Black women with chronic hypertension [aOR: 1.84, (95% CI, 1.28–2.65)], and White women with chronic hypertension [aOR: 1.64, (95% CI, 1.29–2.07)] were higher when compared with their normotensive counterparts. Similar results were found for stillbirth, LBW and SGA when assessed by maternal ethnicity (**Table 3.1**; **Appendix 3**: **Figures S3.15-S3.18**). Yet, the test for subgroup differences indicated that maternal ethnicity does not significantly modify the effect of chronic hypertension for PTB ($P$=0.59), stillbirth ($P$=0.35), SGA ($P$=0.13) and LBW ($P$=0.18). The results of other sensitivity analyses by location or by year of publication did not change the results materially, but we found an increase in odds of maternal mortality over time among US studies (**Appendix 3**). Even though there was a high level of heterogeneity between studies, almost all estimates from forest plots consistently supported associations in the same direction. This suggests that the significant heterogeneity was an artefact of relatively large study sizes and small variance around the study-specific effect estimates (272) (see **Figures 3.3** & **3.4**, and **Appendix 3**, **Figures S3.1-S3.18**).

**The effect of antihypertensive treatment**

***Treated women with chronic hypertension versus untreated normotensive women***

The results of the association between antihypertensive treatment and adverse pregnancy outcomes are shown in **Table 3.2.** Pregnant women who were treated with antihypertensive agents had higher odds of PE [aOR: 6.57, (95% CI, 1.75–24.7)]; PTB [aOR: 2.78, (95% CI, 1.80–4.29)]; SGA [aOR: 2.21, (95% CI, 1.18–4.15)]; LBW [aOR: 3.45, (95% CI, 2.26–5.26)]; and perinatal death [aOR: 1.80, (95% CI, 1.07–3.01)]. One study reported the adjusted estimates for the effect of antihypertensive on miscarriage, elective termination of pregnancy and stillbirth, and that showed a non-significant association. Heterogeneity was low for stillbirth and perinatal death, but it was moderate to high between studies examining the effect of PE, PTB, SGA and LBW. The included studies are large with precise estimates reflected in tight CIs, which can inflate heterogeneity as overlap between studies' CIs is limited (167).

***Treated women with chronic hypertension versus untreated women with chronic hypertension***

The data suggested that antihypertensive treatment for women with chronic hypertension did not reduce the risk of adverse perinatal outcomes (**Table 3.2**). There were no significant differences in the odds of superimposed pre-eclampsia [aOR: 0.92, (95% CI, 0.27–3.11)] or other adverse outcomes, with the exception of SGA, where the odds was higher for treated women [aOR: 1.86, (95% CI, 1.38–2.50)] compared to untreated women. Moreover, there was no strong evidence that the type of antihypertensive treatment influenced the results (**Table 3.3**). For women who were on beta-blockers only, an association was observed for PTB, [aOR: 2.74, (95% CI, 1.40–5.36]; two studies); and SGA [aOR: 1.84, (95% CI, 1.20–2.82]; three studies), although these findings were based on a small number of studies. For women who were on a centrally acting anti-adrenergic agent only, increased odds were also observed, but weaker than the effect of beta-blockers, for SGA [aOR: 1.62, (95% CI, 1.09–2.42)]. Additionally, one study compared the effect of two agents (beta-blockers versus methyldopa) reported an increased risk of SGA in women with chronic hypertension on beta-blockers [aOR: 1.95 (95% CI, 1.213.15)]. Heterogeneity was observed for most outcomes and may be an artefact of precision of study estimates (167). However, for PTB estimates varied from OR: 0.44, (95% CI, 0.26–0.74) (267) to OR:6.25 (95% CI, 4.37–8.94) (52), which warrants caution in the interpretation of the pooled effect (**Appendix 3, Figures S3.23b**).

## 3.5 Discussion

This comprehensive systematic review and meta-analysis, including 94 studies, examining the effects of maternal chronic hypertension and/or antihypertensive treatment on a broad range of adverse perinatal outcomes demonstrated a significant burden of adverse pregnancy outcomes associated with chronic hypertension. Overall, there was higher odds of maternal, fetal and neonatal adverse outcomes in women with chronic hypertension, many of which are known to have life-long implications for mothers and their babies, such as increased risks of cardiovascular disease (273-275). We found no evidence to suggest that the association between chronic hypertension and adverse pregnancy outcomes differs across ethnicity.

Although antihypertensive treatment might have a potential benefit for mothers, such as preventing severe hypertension and stroke (26, 55, 56), the comparison with

normotensive women demonstrated that antihypertensive treatment did not ameliorate the risk of adverse pregnancy outcomes. Moreover, the use of antihypertensive agents for the treatment of chronic hypertension did not reduce the occurrence of adverse perinatal outcomes compared to untreated hypertensive women. Potential differences were observed in the risk of PTB and SGA depending on the agent, whereas women on multiple antihypertensive agents, likely a reflection of the severity of their hypertension, had increased odds of SGA. These findings warrant further investigation through population-based studies and large randomized trials such as the two ongoing trials of antihypertensive treatment. One examining the effect of nifedipine vs labetalol (Giant PANDA [Pregnancy Antihypertensive Drugs: Which Agent is Best?], NIHR128721), whereas the other one is evaluating whether a blood pressure treatment strategy "only when blood pressure is severe" during pregnancy is effective and safe (CHAP [Chronic Hypertension and Pregnancy], NCT02299414).

**Strengths and limitations**

This review summarized the literature for 14 maternal, fetal, or neonatal outcomes based on predefined rigorous strategies. Moreover, unlike previous reviews, which focused either on the effect of chronic hypertension or antihypertensive treatment, this meta-analysis investigated the impact of both exposures with a special consideration to the comparative groups (i.e., untreated normotensive women and untreated women with chronic hypertension). That enables us to assess if antihypertensive treatment neutralizes the risk of adverse pregnancy outcome among treated women compared to normotensive untreated women. Additionally, we were able to compare the effect of different agents among women with chronic hypertension.

As we included observational studies only, potential residual confounding is a concern. Some studies did not adjust for important confounders such as maternal BMI, smoking, other chronic diseases, and maternal ethnicity. However, we conducted sensitivity analysis for studies that stratified the associations by maternal ethnicity to better understand its effect on the adverse outcomes. Selection bias may have been an issue for studies that used data from teratology centres to obtain data about antihypertensive treatment (50). We cannot eliminate the possibility of misclassification of women with white-coat hypertension as chronic hypertension, which could decrease the magnitude of the pooled estimates. Additionally, outcome definitions vary across studies,

specifically for superimposed pre-eclampsia, and this heterogeneity might be a limitation in previous literature.

Adherence to treatment is another limitation in the current literature, as included studies failed to assess the level of adherence. Most of these studies did not report the severity of hypertension nor the gestational age when treatment was initiated. Contamination by superimposed pre-eclampsia among women with chronic hypertension is another limitation of the literature since these women could potentially lead to an overestimation of the effect. However, the data suggest similar incidences of superimposed pre-eclampsia among treated (25%) and untreated (22%) women with chronic hypertension.

A previous systematic review that assessed the effect of chronic hypertension on pregnancy outcomes concluded that chronic hypertension was associated with a high incidence of adverse pregnancy outcomes compared to the US general obstetric population (42). Our study reinforces these previous findings by including more studies from different settings and analyzing 14 adverse perinatal outcomes between women with chronic hypertension and normotensive women. In contrast to the previous review, we considered different types of PTB, and we found that women with chronic hypertension were approximately five times more likely to deliver preterm due to obstetric intervention, which can contribute to the higher risk of NICU admission and perinatal death. The risk of PE and HELLP syndrome was higher among women with chronic hypertension and may have resulted in higher incidence of medical intervention and preterm delivery.

Previous studies have yielded conflicting results on the modifying effect of maternal ethnicity on the association between chronic hypertension and adverse pregnancy outcomes. Some reported increased risk of adverse pregnancy outcomes among Black women (44, 257), others reported no differences (256, 276), whereas some studies reported increased risk among White women (215, 221). Our results suggested that maternal ethnicity does not modify the association between chronic hypertension and adverse pregnancy outcomes. Though there was a variation in the pooled estimates of adverse pregnancy outcomes by maternal ethnicity, the risk of adverse outcomes was consistently higher in women with chronic hypertension when compared with their normotensive counterparts of the same ethnicity.

Although data from RCTs represent the best evidence when examining an intervention such as treatment, previous meta-analyses of RCTs investigating the effect of using antihypertensive treatment among women with chronic hypertension, compared to no treatment, concluded that treatment decreased their risk of developing severe episodes of hypertension (26, 55, 56). Yet the effects of antihypertensive treatment on other clinically important outcomes such as PE and SGA remain unclear, possibly due to a lack of statistical power in existing trials, most of which have been of a small scale and with moderate to poor quality as authors of meta-analyses stated (26, 55, 56).

Moreover, the most recent trial of 894 women by Easterling *et al*. (2019), which compared the effect of three antihypertensive agents (labetalol, nifedipine and methyldopa) for the management of severe hypertension in pregnancy, reported that the three oral antihypertensive agents reduced blood pressure to the reference range (277). On the other hand, more neonates born to women assigned to the nifedipine were admitted to NICU, while the effects of antihypertensive treatment on other obstetric outcomes remained uncertain due to a lack of statistical power. The trial was powered based on blood pressure as the primary outcome and not for neonatal outcomes. Therefore, including only observational studies can be justified because RCTs have been designed and powered to focus mainly on controlling maternal blood pressure rather than comparing adverse maternal and neonatal outcomes. Our findings, therefore, complement previous meta-analyses of RCTs.

A systematic review of six trials and 495 hypertensive participants reported that lowering maternal blood pressure to the normal reference range had no significant effect on the risk of SGA or PE (56). Similarly, we did not find an association between antihypertensive treatment and PE. However, the effect of treatment with antihypertensives was consistent with an increased risk of SGA in our review, and this is in agreement with findings from a recent network meta-analysis which reported a higher risk of SGA in women with chronic hypertension who were on beta-blockers or methyldopa during pregnancy (278). This could result from a direct effect of the treatment or because severe hypertension at any time during pregnancy is a risk factor for SGA, and women with severe hypertension are more likely to be treated. Although the Control of Hypertension In Pregnancy Study (CHIPS) trial found no significant differences in the risk of perinatal mortality and morbidity between less-tight (target diastolic blood pressure DBP 100 mmHg) versus tight (target DBP 85 mmHg) groups, a

higher incidence of severe hypertension was noticed in the less-tight group (29). Another findings from CHIPS study demonstrated that women with severe hypertension (whether in less tight or tight group) had higher risk of adverse pregnancy outcomes, including SGA (279). However, 75% of included women in CHIPS trial had chronic hypertension, whereas the remaining had gestational hypertension.

Pregnancies complicated with chronic hypertension appear to be at increased risk of significant morbidity and mortality. The MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries) Perinatal Mortality Surveillance Report highlighted the need to reduce stillbirth and adverse outcomes, particularly in Black women who are disproportionately affected by chronic hypertension (280). Although rates of maternal mortality have decreased in many countries, the United States was recently listed by WHO as one of the eight countries with a rising rate of maternal mortality (281). In the United Kingdom, fewer than nine mothers per 100,000 live births died from complications related to pregnancy or child birth; in Canada, the rate was fewer than seven; whereas in the United States, it increased from 23 in 2005 to 25 in 2015 (281-283). Although our findings (including 4 US studies) suggested an increase in odds of maternal mortality over time among the US mothers with chronic hypertension compared to normotensive, only two out of four studies adjusted for ethnicity during the analysis stage (**Appendix 3**). Moreover, the Confidential Enquiries into Maternal Deaths and Morbidity 2014-2016 demanded urgent research to investigate why maternal mortality is disproportionately high among Black women and among those with multiple health problems or other vulnerabilities (280).

Our study supports previous recommendations that women with chronic hypertension should be assessed before conception and monitored closely for the potential development of adverse complications during pregnancy (33, 38). Furthermore, the importance of preconceptual counselling for high-risk women is highlighted by the finding that some hypertensive women were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers during pregnancy, and these may have teratogenic effects or result in termination of pregnancy. We found little or no effect of antihypertensive treatment in preventing superimposed pre-eclampsia, stillbirth, or other adverse perinatal outcomes. Although the lack of data on chronic hypertension severity is an important limitation in the existing literature, our findings should not discourage practitioners from prescribing antihypertensive treatment when clinically indicated.

Future research should consider the severity of hypertension and other confounding factors such as body mass index, smoking and use of antihypertensive treatment when assessing the association between chronic hypertension and adverse perinatal outcomes. Moreover, population-based studies and large multicentre trials are needed to assess the efficacy and safety of different antihypertensive agents during pregnancy on perinatal outcomes to ensure that healthcare practitioners have sufficient information to determine whether the benefits of treating women with mild-moderate hypertension in pregnancy outweigh potential harms.

## 3.6 Conclusion

Maternal chronic hypertension is associated with adverse maternal, fetal, and neonatal outcomes, including maternal and perinatal mortality, compared with normotensive women. These associations appear to be independent of maternal ethnicity. Treatment with antihypertensive agents did not eliminate the risk of adverse pregnancy outcomes and may increase the risk of SGA. However, various classes of antihypertensive treatment may differently influence the risk of adverse pregnancy outcomes. Further RCTs are needed to examine the effect of antihypertensive treatment on SGA and other adverse pregnancy outcomes.

**Table 3.1** Estimated odds ratios of adverse perinatal outcome for women with chronic hypertension during pregnancy compared to normotensive women

| Maternal Outcomes | No. of studies (estimates) | population | Overall crude OR [95% CI] | $I^2$, % | No. of studies (estimates) | population | Overall adjusted OR [95% CI]* | $I^2$, % |
|---|---|---|---|---|---|---|---|---|
| **PE** | 18 | 11,721,514 | 7.11 [5.01, 10.09] | 100 | 21 | 24,312,773 | 5.43 [3.85, 7.65] | 100 |
| **HELLP** | 3 | 4,744,404 | 3.60 [2.36, 5.50] | 73 | 3 | 4,744,404 | 3.08 [1.79, 5.30] | 81 |
| **CS** | 17 (19) | 6,232,257 | 2.30 [2.02, 2.63] | 95 | 9 (10) | 18,701,513 | 1.87 [1.61, 2.16] | 98 |
| **PPH** | 6 | 5,786,367 | 1.57 [1.23, 2.00] | 85 | 4 | 5,446,006 | 1.46 [1.17, 1.81] | 72 |
| **Maternal mortality** | 3 | 39,725,224 | 8.43 [6.17, 11.50] | 65 | 4 | 52,672,224 | 4.80 [3.04, 7.58] | 71 |
| **Fetal, neonatal outcomes** | | | | | | | | |
| **Miscarriage** | 2 | 110,269 | 2.48 [1.78, 3.45] | 0 | 1 | 109,932 | 1.33 [0.90, 1.97] | - |
| **Stillbirth** | 18 | 38,345,766 | 3.00 [2.69, 3.35] | 80 | 18 | 51,197,315 | 2.32 [2.22, 2.42] | 0 |
| Black women | - | | - | - | 2 | 3,283,628 | 2.27 [2.00, 2.58] | 0 |
| White women | - | | - | - | 2 | 18,357,481 | 2.92 [1.75, 4.88] | 85 |
| VPTB<34 wks. | 9 | 2,278,003 | 2.29 [1.47, 3.57] | 96 | 6 | 2,029,558 | 1.92 [1.09, 3.38] | 98 |
| **PTB<37 wks.** | **28 (35)** | **7,930,708** | **2.57 [2.22, 2.97]** | **97** | **25 (30)** | **18,713,632** | **2.23 [1.96, 2.53]** | **97** |
| Non-specified | 23 (28) | | 2.43 [2.10, 2.83] | 97 | 20 (22) | | 2.14 [1.83, 2.51] | 97 |
| Spontaneous | 3 | | 1.32 [0.97, 1.79] | 75 | 4 | | 1.44 [0.74, 2.80] | 97 |
| Medically indicated | 4 | | 6.66 [5.85, 7.58] | 11 | 4 | | 4.67 [3.55, 6.14] | 62 |
| **PTB<37 wks.** | | | | | | | | |
| Black women | - | | - | - | 5 | 135,917 | 1.84 [1.28, 2.65] | 80 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| White women | - | | - | - | 4 | 155,729 | 1.64 [1.29, 2.07] | 95 |
| **SGA** | 29 | 8,356,964 | 1.99 [1.58, 2.52] | 98 | 24 | 21,251,640 | 1.96 [1.61, 2.40] | 99 |
| Black women | - | | - | - | 2 | 16,867 | 1.30 [1.11, 1.54] | 0 |
| White women | - | | - | - | 2 | 33,673 | 1.80 [1.22, 2.65] | 62 |
| **LBW** | 14 | 4,725,825 | 2.92 [2.22, 3.84] | 98 | 11 | 4,605,536 | 3.05 [2.24, 4.15] | 98 |
| Black women | - | | - | - | 5 | 118,757 | 2.44 [1.94, 3.06] | 67 |
| White women | - | | - | - | 4 | 130,240 | 3.06 [2.39, 3.91] | 85 |
| **NICU** | 7 | 342,254 | 2.12 [1.66, 2.70] | 85 | 1 | 35,135 | 1.37 [1.05, 1.79] | - |
| **Neonatal death** | 4 | 5,196,085 | 3.11 [2.35, 4.11] | 39 | 4 | 5,301,824 | 2.29 [2.02, 2.59] | 0 |
| **Perinatal death** | 10 | 3,289,474 | 2.46 [1.70, 3.55] | 73 | 6 | 3,261,503 | 1.87 [1.33, 2.63] | 75 |

CS, caesarean section; HELLP, hemolysis, elevated liver enzyme levels, and low platelet levels; LBW, low birthweight; NICU, neonatal intensive care unit; PE, pre-eclampsia; PPH, post-partum haemorrhage; PTB, preterm birth; SGA, small for gestational age; VPTB, very preterm birth; *Authors' definitions of adjustment.

**Table 3.2** Estimated odds ratios of adverse perinatal outcomes for women treated with antihypertensive medications during pregnancy compared to untreated women

| Maternal/fetal, neonatal outcomes | No. of studies | Population | Overall crude OR [95% CI] | $I^2$, % | No. of studies | Population | Overall adjusted OR [95% CI]* | $I^2$, % |
|---|---|---|---|---|---|---|---|---|
| **Pre-eclampsia** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 2 | 99,347 | 8.78 [3.32, 23.1] | 93 | 2 | 99,347 | 6.57 [1.75, 24.7] | 96 |
| Treated CH vs untreated CH [b] | 5 | 1,532 | 0.81 [0.45, 1.45] | 93 | 2 | 641 | 0.92 [0.27, 3.11] | 90 |
| **Cesarean section** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 1 | 787 | 2.26 [1.59, 3.22] | - | - | - | - | - |
| Treated CH vs untreated CH [b] | 1 | 222 | 1.42 [0.82, 2.4] | - | 1 | 222 | 0.89 [0.58, 1.35 ] | - |
| **Preterm birth (<37 wks.)** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 5 | 1,168,383 | 2.95 [1.93, 4.52] | 95 | 5 | 1,168,383 | 2.78 [1.80, 4.29] | 95 |
| Treated CH vs untreated CH [b] | 4 | 3,763 | 1.35 [0.36, 4.97] | 97 | 3 | 3,532 | 1.88 [0.61, 5.74] | 97 |
| **Small for gestational age** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 4 | 1,135,723 | 1.84 [0.79, 4.29] | 96 | 4 | 1,135,723 | 2.21 [1.18, 4.15] | 87 |
| Treated CH vs untreated CH [b] | 6 | 4,611 | 2.21 [1.45, 3.35] | 76 | 5 | 4,442 | 1.86 [1.38, 2.50] | 53 |
| **Low birthweight** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 3 | 1,166,502 | 3.16 [2.03, 4.93] | 95 | 3 | 1,166,502 | 3.45 [2.26, 5.26] | 92 |
| Treated CH vs untreated CH [b] | 2 | 2,958 | 1.36 [0.63, 2.93] | 84 | 1 | 2,727 | 1.96 [1.44, 2.67] | - |
| **Miscarriage** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Treated CH vs untreated normotensive [a] | 1 | 787 | 1.61 [0.90, 2.88] | - | 1 | 787 | 1.44 [0.74, 2.81] | - |
| Treated CH vs untreated CH [b] | 1 | 491 | 0.42 [0.16, 1.14] | - | - | | - | - |
| **Elective termination of pregnancy** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 1 | 787 | 0.24 [0.06, 1.00] | - | 1 | 787 | 0.35 [0.07, 1.70] | - |
| Treated CH vs untreated CH [b] | - | | | | | | | |
| **Stillbirth** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 2 | 1,881 | 2.31 [0.96, 5.60] | - | 1 | 1.094 | 2.20 [0.84, 5.76] | - |
| Treated CH vs untreated CH [b] | 2 | 713 | 1.11 [0.54, 2.30] | 0 | 1 | 222 | 1.13 [0.32, 3.99] | - |
| **Neonatal intensive care unit admission** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | - | - | - | - | - | - | - | |
| Treated CH vs untreated CH [b] | 2 | 271 | 0.30 [0.17, 0.53] | 0 | 1 | 222 | 0.43 [0.25, 0.74] | - |
| **Perinatal death** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 2 | 99,347 | 1.77 [1.07, 2.93] | 0 | 2 | 99,347 | 1.80 [1.07, 3.01] | 0 |
| Treated CH vs untreated CH [b] | 1 | 169 | 3.90 [0.43, 35.68] | - | - | - | - | - |

CH: chronic hypertension. *Authors' definitions of adjustment; [a] the comparative group was untreated normotensive women; [b] all women with chronic hypertension (treated vs untreated)

**Table 3.3** Estimated odds ratios of adverse perinatal outcome in treated women with chronic hypertension according to the type of antihypertensive agent during pregnancy

| Outcomes | No. of studies | Population | Overall crude OR [95% CI] | $I^2$, % | No. of studies | Population | Overall adjusted OR [95% CI]* | $I^2$, % |
|---|---|---|---|---|---|---|---|---|
| **PTB<37 weeks' gestation/ exposed to ββ agent only** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 1 | 97,927 | 2.32 [1.40, 3.84] | - | 1 | 97,927 | 2.68 [1.57, 4.57] | - |
| Treated CH vs untreated CH [b] | 2 | 1,811 | 3.00 [1.34, 6.72] | 84 | 2 | 1,811 | 2.74 [1.40, 5.36] | 77 |
| **SGA/ exposed to ββ agent only** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 1 | 97,927 | 3.35 [1.47, 7.64] | - | 1 | 97,927 | 4.80 [2.07, 11.1] | - |
| Treated CH vs untreated CH [b] | 3 | 2,040 | 2.21 [1.28, 3.82] | 70 | 3 | 2,040 | 1.84 [1.20, 2.82] | 41 |
| **SGA/ exposed to centrally acting antiadrenergic agent only** | | | | | | | | |
| Treated CH vs untreated normotensive [a] | 1 | 98,160 | 1.36 [0.67, 2.76] | - | 1 | 98,160 | 1.01 [1.00, 1.02] | - |
| Treated CH vs untreated CH [b] | 3 | 1,545 | 1.95 [1.12, 3.40] | 56 | 2 | 1,409 | 1.62 [1.09, 2.42] | 32 |
| **SGA (single/multiple agents vs untreated women with CH‡)** | | | | | | | | |
| Single agent | - | - | - | - | 3 | 2,103 | 2.03 [1.20, 3.43] | 56 |
| Multiple agents | - | - | - | - | 3 | 1,733 | 2.55 [1.64, 3.95] | 30 |
| **SGA (centrally acting antiadrenergic vs other agents in women with CH)** | | | | | | | | |
| Treated women with CH | 5 | 2,190 | 0.82 [0.51, 1.32] | 61 | - | - | - | - |
| **SGA (ββ agent vs methyldopa in women with CH)** | | | | | | | | |
| Treated women with CH | 3 | 2,126 | 1.40 [0.70, 2.79] | 78 | 1 | | 1.95 [1.21, 3.15] | - |

ββ, beta-blockers; CH, chronic hypertension; PTB, preterm birth; SGA, small for gestaional age. *Authors' definitions of adjustment; [a] the comparative group was untreated normotensive women; [b] all women with chronic hypertension (treated vs untreated)

**Figure 3.1** PRISMA flow diagram of studies on the association between chronic hypertension and adverse pregnancy outcomes

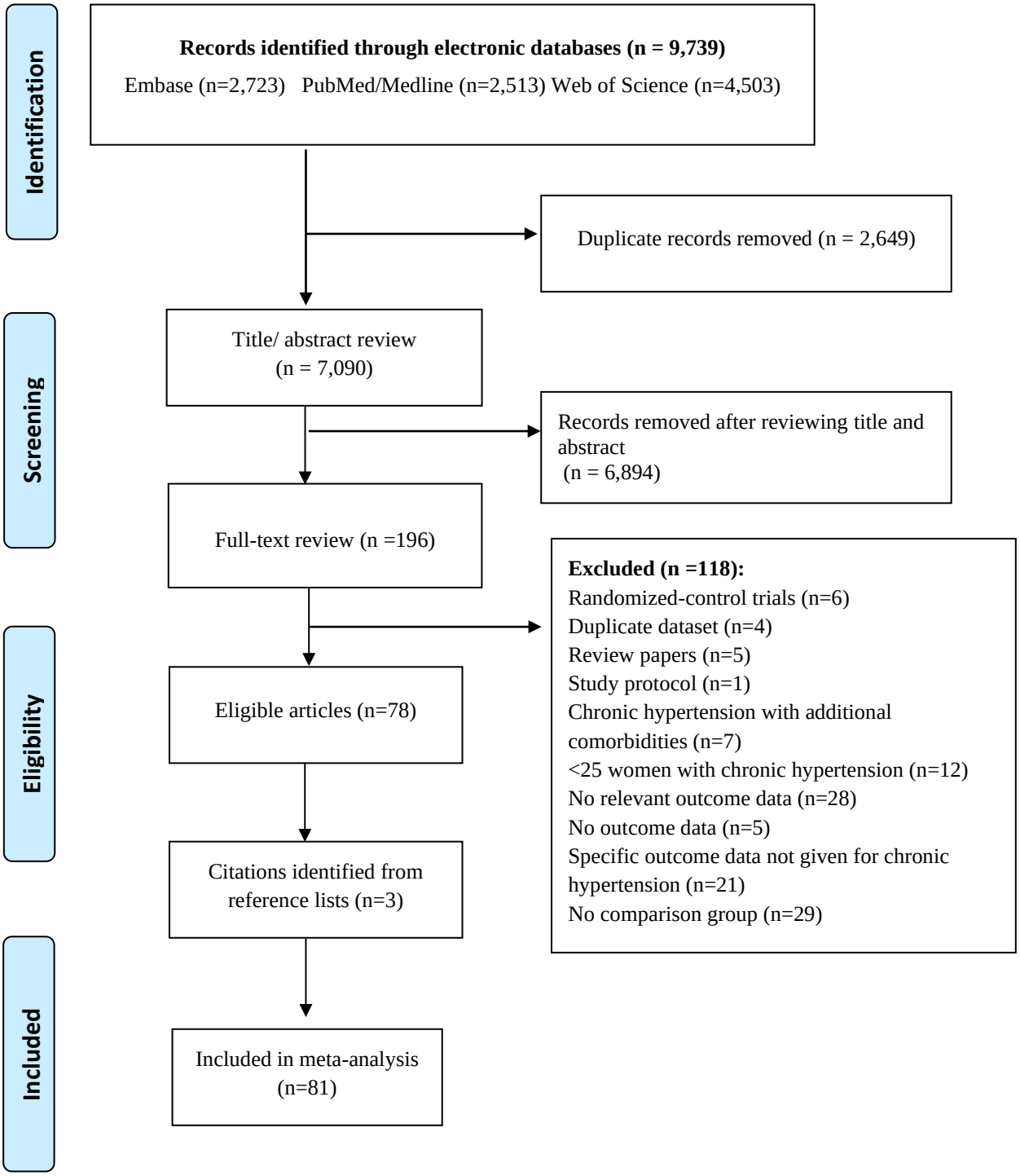
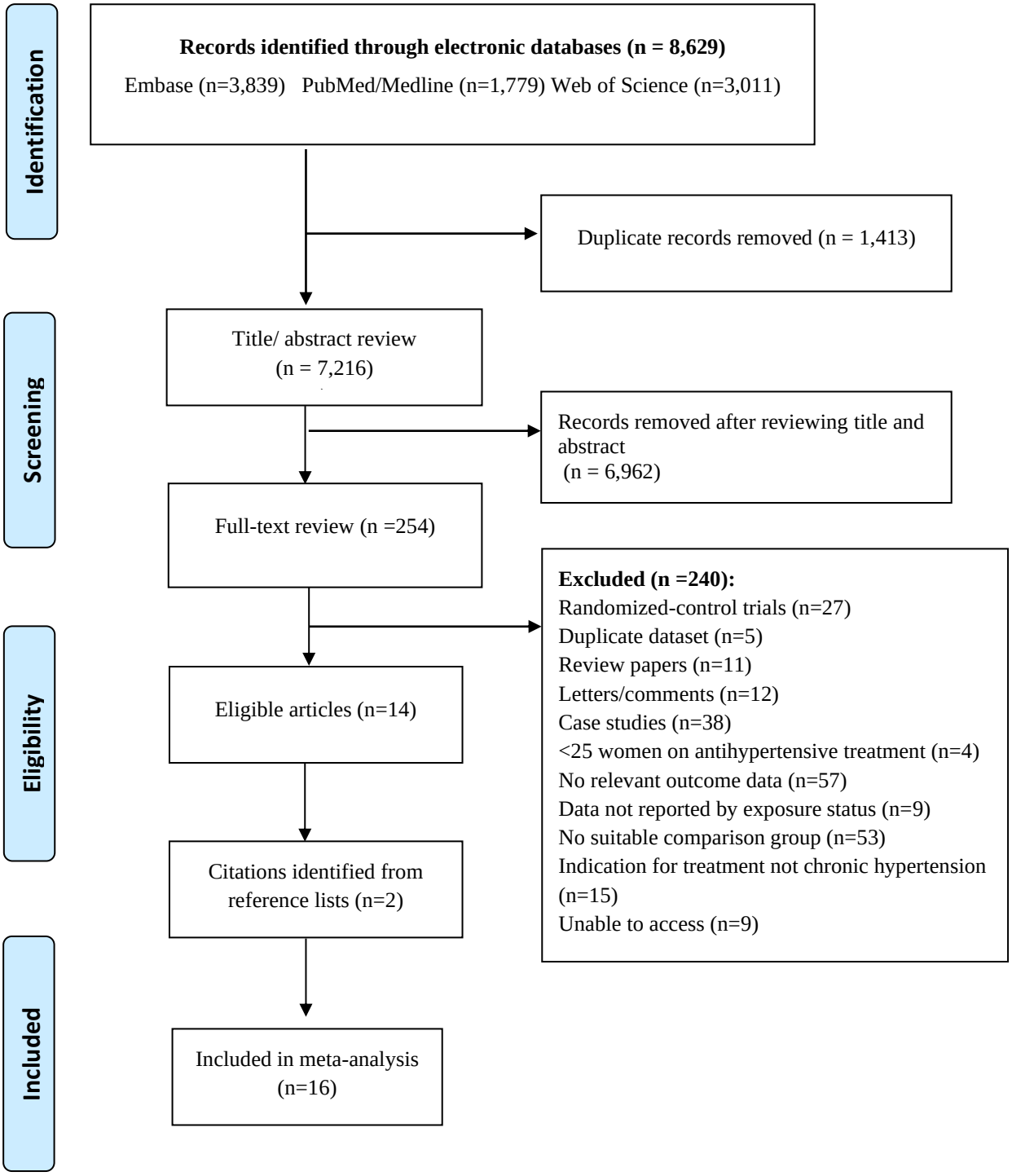


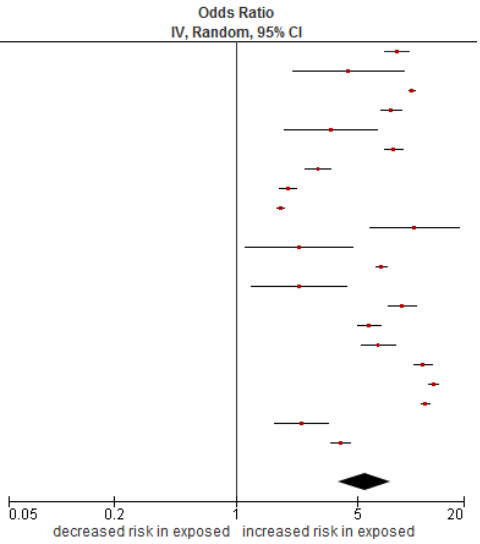
**Figure 3.2** PRISMA flow diagram of studies on the association between antihypertensive treatment and adverse pregnancy outcomes in women with chronic hypertension



**Pre-eclampsia**

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Abalos, 2014 | 2.1187 | 0.0788 | 4.9% | 8.32 [7.13, 9.71] |
| Aksornphusitaphong, 2013 | 1.4816 | 0.3774 | 4.0% | 4.40 [2.10, 9.22] |
| Bateman, 2012 | 2.3204 | 0.021 | 5.0% | 10.18 [9.77, 10.61] |
| Bilano, 2014 | 2.0477 | 0.069 | 4.9% | 7.75 [6.77, 8.87] |
| Block-Abraham, 2014 | 1.2528 | 0.3117 | 4.3% | 3.50 [1.90, 6.45] |
| Broekhuijsen, 2015 | 2.0794 | 0.0609 | 5.0% | 8.00 [7.10, 9.01] |
| Catov, 2007 | 1.0818 | 0.0844 | 4.9% | 2.95 [2.50, 3.48] |
| Conde-Agudelo, 2000 | 0.6881 | 0.0569 | 5.0% | 1.99 [1.78, 2.22] |
| Gilbert, 2007 | 0.5878 | 0.0262 | 5.0% | 1.80 [1.71, 1.89] |
| Guerrier, 2013 | 2.3514 | 0.3028 | 4.3% | 10.50 [5.80, 19.01] |
| Kiondo, 2012 | 0.8286 | 0.3649 | 4.1% | 2.29 [1.12, 4.68] |
| Lisonkova, 2013 | 1.9169 | 0.0357 | 5.0% | 6.80 [6.34, 7.29] |
| Mostello, 2002 | 0.8329 | 0.3192 | 4.3% | 2.30 [1.23, 4.30] |
| Orbach, 2013 | 2.1883 | 0.0939 | 4.9% | 8.92 [7.42, 10.72] |
| Panaitescu, 2017 | 1.7509 | 0.0794 | 4.9% | 5.76 [4.93, 6.73] |
| Rey, 1994 | 1.8718 | 0.1139 | 4.9% | 6.50 [5.20, 8.13] |
| Samadi, 2001 | 2.4604 | 0.0615 | 5.0% | 11.71 [10.38, 13.21] |
| Yanit, 2012 | 2.6027 | 0.0352 | 5.0% | 13.50 [12.60, 14.46] |
| You, 2018 | 2.4965 | 0.0276 | 5.0% | 12.14 [11.50, 12.81] |
| Youngstorm, 2018 | 0.8671 | 0.1808 | 4.7% | 2.38 [1.67, 3.39] |
| Zetterstorm, 2005 | 1.3788 | 0.0643 | 4.9% | 3.97 [3.50, 4.50] |
| **Total (95% CI)** | | | **100.0%** | **5.43 [3.85, 7.65]** |

Heterogeneity: Tau² = 0.61; Chi² = 4565.53, df = 20 (P < 0.00001); I² = 100%
Test for overall effect: Z = 9.68 (P < 0.00001)




**Maternal mortality**

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Bateman, 2012 | 1.7029 | 0.3813 | 18.5% | 5.49 [2.60, 11.59] |
| Compbell, 2013 | 2.0412 | 0.2519 | 25.5% | 7.70 [4.70, 12.62] |
| Gilbert, 2007 | 1.5748 | 0.2329 | 26.7% | 4.83 [3.06, 7.62] |
| Kuklina, 2009 | 1.0647 | 0.1896 | 29.3% | 2.90 [2.00, 4.21] |
| **Total (95% CI)** | | | **100.0%** | **4.80 [3.04, 7.58]** |

Heterogeneity: Tau² = 0.15; Chi² = 10.26, df = 3 (P = 0.02); I² = 71%
Test for overall effect: Z = 6.72 (P < 0.00001)

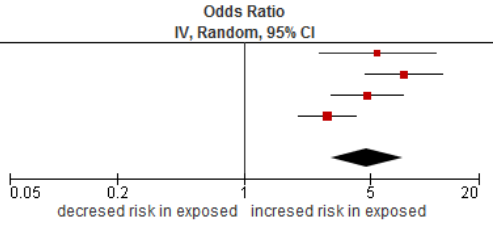
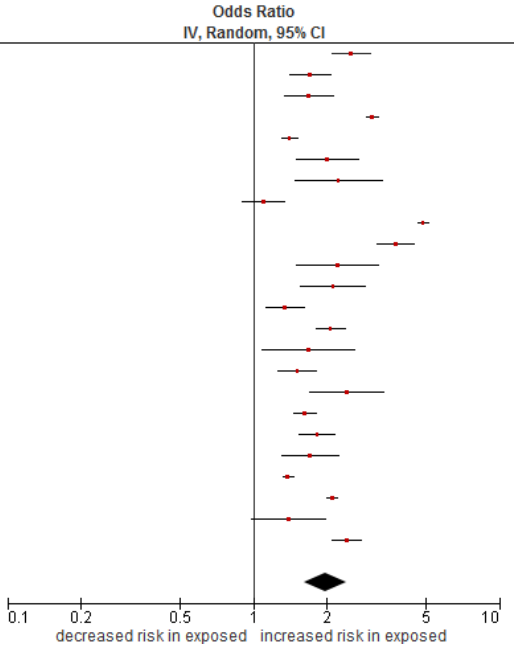



**Figure 3.3** Forest plots of adjusted estimates of the association between chronic hypertension and maternal complications

**Small for gestational age**

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Allen, 2004 | 0.9163 | 0.089 | 4.3% | 2.50 [2.10, 2.98] |
| Ananth, 1995b | 0.5306 | 0.0991 | 4.2% | 1.70 [1.40, 2.06] |
| Anderson, 2013 | 0.5188 | 0.1154 | 4.2% | 1.68 [1.34, 2.11] |
| Bateman, 2012 | 1.1151 | 0.031 | 4.4% | 3.05 [2.87, 3.24] |
| Broekhuijsen, 2015 | 0.3365 | 0.0378 | 4.4% | 1.40 [1.30, 1.51] |
| Catov, 2008 | 0.6931 | 0.1468 | 4.0% | 2.00 [1.50, 2.67] |
| Compbell, 2018 | 0.7975 | 0.2069 | 3.7% | 2.22 [1.48, 3.33] |
| Cruz, 2011 | 0.0953 | 0.1024 | 4.2% | 1.10 [0.90, 1.34] |
| Gilbert, 2007 | 1.5892 | 0.0256 | 4.4% | 4.90 [4.66, 5.15] |
| Jain, 1997 | 1.335 | 0.0877 | 4.3% | 3.80 [3.20, 4.51] |
| Odibo, 2006 | 0.7885 | 0.1954 | 3.8% | 2.20 [1.50, 3.23] |
| Orbach, 2013 | 0.7467 | 0.1541 | 4.0% | 2.11 [1.56, 2.85] |
| Ota, 2014 | 0.2927 | 0.0915 | 4.3% | 1.34 [1.12, 1.60] |
| Panaitescu, 2017 | 0.7227 | 0.0717 | 4.3% | 2.06 [1.79, 2.37] |
| Poon, 2011 | 0.5188 | 0.2207 | 3.7% | 1.68 [1.09, 2.59] |
| Rasmussen, 2006 | 0.4121 | 0.0923 | 4.3% | 1.51 [1.26, 1.81] |
| Rey, 1994 | 0.8755 | 0.1759 | 3.9% | 2.40 [1.70, 3.39] |
| Su, 2013 | 0.4824 | 0.0566 | 4.3% | 1.62 [1.45, 1.81] |
| Tuuli, 2011 | 0.5988 | 0.0852 | 4.3% | 1.82 [1.54, 2.15] |
| Venek, 2004 | 0.5306 | 0.1369 | 4.1% | 1.70 [1.30, 2.22] |
| Xaverius, 2014 | 0.3221 | 0.0252 | 4.4% | 1.38 [1.31, 1.45] |
| Yanit, 2012 | 0.7419 | 0.0249 | 4.4% | 2.10 [2.00, 2.20] |
| Youngstorm, 2018 | 0.3293 | 0.1783 | 3.9% | 1.39 [0.98, 1.97] |
| Zetterstorm, 2006 | 0.8755 | 0.0681 | 4.3% | 2.40 [2.10, 2.74] |
| **Total (95% CI)** | | | **100.0%** | **1.96 [1.61, 2.40]** |

Heterogeneity: Tau² = 0.24; Chi² = 1769.50, df = 23 (P < 0.00001); I² = 99%
Test for overall effect: Z = 6.55 (P < 0.00001)




**Low birthweight**

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Ananth, 1995b | 0.6575 | 0.0769 | 10.3% | 1.93 [1.66, 2.24] |
| Compbell, 2018 | 1.1569 | 0.2315 | 8.6% | 3.18 [2.02, 5.01] |
| Gilbert, 2007 | 1.6771 | 0.0155 | 10.5% | 5.35 [5.19, 5.52] |
| Graham, 2007 | 0.9439 | 0.0457 | 10.4% | 2.57 [2.35, 2.81] |
| Hailu, 2018 | 0.207 | 0.513 | 5.0% | 1.23 [0.45, 3.36] |
| Harvey, 2017 | 0.9282 | 0.3597 | 6.8% | 2.53 [1.25, 5.12] |
| Lydakis, 1998 | 1.3635 | 0.1369 | 9.8% | 3.91 [2.99, 5.11] |
| Odell, 2006 | 1.3481 | 0.1359 | 9.8% | 3.85 [2.95, 5.03] |
| Su, 2013 | 0.8286 | 0.082 | 10.2% | 2.29 [1.95, 2.69] |
| Vahadinia, 2008 | 1.3083 | 0.2538 | 8.3% | 3.70 [2.25, 6.08] |
| Velentgas, 1994 | 1.361 | 0.07 | 10.3% | 3.90 [3.40, 4.47] |
| **Total (95% CI)** | | | **100.0%** | **3.05 [2.24, 4.15]** |

Heterogeneity: Tau² = 0.23; Chi² = 478.34, df = 10 (P < 0.00001); I² = 98%
Test for overall effect: Z = 7.08 (P < 0.00001)

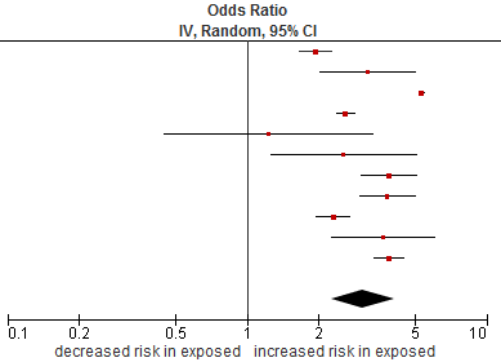



**Figure 3.4** Forest plots of adjusted estimates of the association between chronic hypertension and fatal/neonatal outcomes

# CHAPTER 4: Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-Analysis

**Sukainah Y. Al Khalaf**[1,2], Elizabeth Bodunde[1], Gillian M. Maher[1,2], Éilis J. O'Reilly[1,3], Fergus P. McCarthy[2,4], Michelle M. O'Shaughnessy[5], Sinéad M. O'Neill[6], Ali S. Khashan[1, 2]

[1] *School of Public Health, University College Cork, Cork, Ireland*

[2] *INFANT Research Centre, University College Cork, Ireland*

[3] *Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

[4] *Department of Obstetrics and Gynaecology, Cork University Hospital, Cork, Ireland*

[5] *Department of Renal Medicine, Cork University Hospital, Cork, Ireland*

[6] *School of Public Health Alumna, Cork, Ireland*

**Published in:** *American Journal of Obstetrics and Gynecology*, November 2021

Doi: 10.1016/j.ajog.2021.10.037

**(Paper 2)**

## 4.1 Abstract

**Objective:** Limited evidence exists on the role that the cause of CKD plays in determining pregnancy outcomes. The aim of this systematic review and meta-analysis was to examine the association between CKD and adverse pregnancy outcomes, by cause and severity of CKD where reported. The protocol was registered on the International Prospective Register of Systematic Reviews (CRD:42020211925).

**Data sources:** PubMed, Embase, and Web of Science were searched until May 24, 2021, supplemented with reference list checking.

**Study eligibility criteria:** Studies that compared pregnancy outcomes in women with or without CKD were included. Two reviewers independently screened titles, abstracts, and full-text articles according to *a priori* defined inclusion criteria.

**Study appraisal and synthesis methods:** Data extraction and quality appraisal were performed independently by three reviewers. The GRADE approach was used to assess the overall certainty of the evidence. Random-effects meta-analyses were used to calculate pooled estimates using the generic inverse variance method. Primary outcomes included pre-eclampsia, Caesarean section (CS), preterm birth (PTB) [<37 weeks' gestation] and small for gestational age (SGA) babies.

**Results:** Of 4,076 citations, 31 studies were included. Pre-pregnancy CKD was associated significantly with a higher risk of pre-eclampsia [pooled crude odds ratio (OR): 8.13, (95% confidence interval (CI), 4.41–15), and adjusted OR (aOR): 2.58, (1.33–5.01)], CS [aOR: 1.65, (1.21–2.25)], PTB [aOR: 1.73, (1.31–2.27)] and SGA [aOR: 1.93, (1.06–3.52)]. The association with stillbirth was not statistically significant [aOR: 1.67, (0.96–2.92)]. Subgroup analyses indicated that different causes of CKD might confer different risks and that severity of CKD is associated with risk for adverse pregnancy outcomes, as pregnancies with later stages CKD, compared to earlier stages, had higher odds of pre-eclampsia, PTB and SGA. The GRADE certainty of the evidence was 'very low'.

**Conclusions:** This meta-analysis quantified associations between pre-pregnancy CKD, overall and according to cause and severity, and adverse pregnancy outcomes. These findings might support clinicians aiming to counsel women with CKD, by allowing

them to tailor their advice according to the cause and severity of CKD. We identified gaps in the literature, and further studies examining the effect of specific kidney diseases and other clinical characteristics (e.g. proteinuria, hypertension) on adverse pregnancy outcomes are warranted.

## 4.2 Introduction

Chronic kidney disease (CKD) is a major global public health problem associated with excess morbidity, decreased quality of life, and premature mortality (61). Definitions and classifications of CKD have changed over time, with the current international guidelines defining CKD as having markers of kidney damage (e.g., albumin excretion rate >30 mg/d) and/or a reduced glomerular filtration rate (GFR)<60 mL/min/1.73 $m^2$ for at least three months duration, irrespective of the underlying cause (62, 63). The disease is then sub-classified into five stages according to the level of kidney function, stages 1-2 (mild CKD with an eGFR≥60 mL/min/1.73 $m^2$ but with other evidence of kidney damage, such as proteinuria or structural kidney abnormalities), and stages 3-5 (moderate to severe CKD, with GFR<60 mL/min/1.73 $m^2$) (62, 63). A global prevalence of 9.5% has been reported for CKD in women overall, with a higher proportion of early stages of the disease reported in women than men (61, 64). In women aged 20-39 years, the prevalence of stages 1-2 and stages 3-5 CKD are estimated to be 3% and 0.67%, respectively (71, 284).

Prior reports, many of them small in size and emanating from single centres, have shown associations between CKD and adverse pregnancy outcomes (71-73). However, associations of adverse pregnancy outcomes with the cause of CKD are less known. The most recent meta-analysis assessing the association between CKD and adverse pregnancy outcomes included 14 studies published between 1979 and 2013 (73). Investigators reported higher odds of pre-eclampsia, caesarean section (CS), preterm birth (PTB), and small for gestational age (SGA) or low birthweight (LBW) in women with CKD compared to women without CKD (73). However, eight of the 14 studies examined adverse pregnancy outcomes among women with diabetes (diabetic nephropathy as an exposed group), which makes it difficult to generalize the results to women with other underlying causes of CKD. Additionally, crude estimates were reported in this review without consideration for potential confounding factors.

Previous studies evaluating pregnancy outcomes in women with advanced stages of CKD have reported worse outcomes than those with earlier stages, although the results were inconsistent, and the magnitude of risk estimates differ across individual studies (285-287). These estimates are derived from small and single-centre cohorts, and we could not identify any systematic review of published data comparing risks for adverse pregnancy outcomes in women with advanced versus earlier stages of CKD. Moreover,

associations between the cause of CKD and pregnancy outcomes are less studied: although the pregnancy outcomes are noted to be particularly poor in certain women with lupus nephritis, the data for other forms of glomerular and non-glomerular kidney diseases are scant (288).

Thus, we conducted this systematic review and meta-analysis to synthesize the available published literature with respect to the associations between CKD and adverse pregnancy outcomes, and to evaluate, where possible, the extent to which the severity and cause of CKD modify these associations.

## 4.3 Methods

### 4.3.1 Protocol registration and reporting

The protocol for this systematic review was prospectively registered on the International Register of Systematic Reviews (identifier: CRD42020211925) (94). An additional question on CKD severity was added after registration. We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis checklist in the reporting of this systematic review (190).

### 4.3.2 Research Questions

1) Do pregnant women with CKD compared to pregnant women without CKD have a higher risk of adverse pregnancy outcomes?
2) Do pregnant women with late stages of CKD compared to early stages have a higher risk of adverse pregnancy outcomes?
3) Do specific causes of CKD associate with higher risks of adverse pregnancy outcomes?

**Population, intervention, comparison, and outcome**

The population, intervention, comparison, and outcome (PICO) approach specific to this systematic review and meta-analysis is detailed below:

***Population of interest:*** All pregnant women

***Intervention/exposure group:*** a) Pregnant women with CKD
b) Pregnant women with late stages of CKD

***Comparison group:*** a) Pregnant women without CKD
b) Pregnant women with early stages of CKD

***Outcomes:*** Primary (pre-eclampsia, CS, PTB [<37 weeks' gestation], and SGA). Secondary (maternal death, very preterm birth [VPTB, <34 weeks' gestation], LBW, neonatal intensive care unit [NICU] admission, stillbirth, neonatal death, and perinatal death).

### 4.3.3 Eligibility criteria

Observational studies (prospective cohort, retrospective cohort, or case-control designs) published in the English language were considered for inclusion if they met the PICO criteria. Reviews, case reports, editorial letters, expert opinions, and animal studies were not eligible for inclusion.

### 4.3.4 Information sources and search strategy

A systematic search of PubMed, Embase, and Web of Science was undertaken from the inception of the databases until November 12, 2020, using a detailed search strategy and key terms including CKD and pregnancy outcomes. We also conducted a pre-submission updated search on May 24, 2021. Please see **Appendix 4** for the full search strategy that was used in each database. We additionally searched the bibliographies of previous systematic reviews of the same topic and searched the reference lists of all identified studies for further potentially relevant studies.

### 4.3.5 Study selection

Two reviewers (S.A and E.B) independently screened titles and abstracts, excluding studies that clearly did not meet the predefined inclusion criteria. Full texts of potentially eligible studies were obtained and screened independently by the same two reviewers, and where consensus could not be reached, a third reviewer was consulted. Where a duplicate publication of the same data (study population) existed, we only included the largest study. The process of study selection is outlined in **Figure 4.1**.

### 4.3.6 Data extraction and quality assessment

Three reviewers performed the data extraction (E.B, G.M, and S.A) independently using a standardized data extraction form. The following information was extracted: study author, year, country, study design, sample size, exposure and outcome definitions, statistical method used, reported effect measures (if not reported, we used raw data to calculate odds ratios [(ORs) and 95% confidence intervals (CI)], and factors adjusted for, if any.

Quality assessment of the included studies was performed independently by three reviewers (S.A, G.M, and E.B) using the Newcastle-Ottawa Scale. This scale uses a "star system", in which stars are assigned to show higher quality on the basis of the following three criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure and/or outcome of interest (the total score ranged from 0 to 9) (289). We considered 0–3 stars as low quality, 4–6 stars as moderate quality and 7–9 stars as high quality. Any discrepancies on screening, extraction and quality assessment were resolved through discussion and consensus involving the three reviewers (S.A, E.B, and G.M) and the lead investigator (A.K).

### 4.3.7 GRADE Certainty of the Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to evaluate the certainty of the evidence for primary outcomes by two reviewers independently (S.A and G.M). The certainty of the evidence was assessed using GRADEpro software based on the following domains: study design, risk of bias, imprecision, inconsistency, indirectness, and publication bias (290). Given the nature of the research questions specific to this systematic review (the exposure "CKD" is a medical condition), randomized control trials are not feasible. As a result, the certainty of the evidence for the included studies was assessed based on modifications of the traditional GRADE approach (291, 292). Thus, the included observational studies started as high quality and were downgraded accordingly based on the GRADE domains.

### 4.3.7 Statistical analysis

Random-effects meta-analyses using the generic inverse variance method were performed to calculate crude and adjusted pooled ORs of the associations between CKD and outcomes of interest. Forest plots were used to display crude and adjusted pooled ORs with 95% CIs. The risk difference (RD) estimates were calculated using GRADEpro, based on the event risk in the unexposed group, the pooled OR and 95% CI.

The statistical heterogeneity between studies was assessed using the $I^2$ statistics, and values ≥75% were considered high heterogeneity (293). Publication bias was evaluated using Egger's test and funnel plots. Subgroup analyses were performed according to the cause of CKD (glomerulonephritis, diabetic CKD, polycystic kidney disease (PKD)

or unspecified CKD), study location (Asia, Australia, Europe, North America, or South America,) and the publication year (≤2010 or >2010). The subgroup meta-analysis calculates the effects within each subgroup level and then compares the pooled effect estimates for each subgroup. The *P* value from the Cochran Q test—a test for interaction—was used to determine whether the magnitude of the effect of CKD differs according to causes of CKD, location, or year of publication. Studies with "zero" event in either group were excluded from analyses.

We also conducted a post-hoc analysis excluding a study that by design included women with CKD and superimposed acute kidney disease (4% had acute kidney disease) (294) to assess if that had an influence on the reported results. A statistically significant *P* value was based on a threshold of <0.05. All analyses were performed using Review Manager version 5.3, GRADEpro was used to estimate RDs, and Stata 16 for the Egger test.

## 4.4 Results

### 4.4.1 Search results and study characteristics

The initial search yielded 4,076 unique studies after the removal of duplicates (**Figure 4.1**). After screening the titles and abstracts, 143 full-text articles were reviewed. Of these, 113 articles not meeting inclusion criteria were excluded, leaving 30 articles for inclusion from this search. Reviewing reference lists of the included articles identified one additional article. A total of 31 unique articles were included in this review; 17 studies reported pregnancy outcomes in women with CKD vs those without (294-310), 10 studies reported results for early vs late stages of CKD (285-287, 311-317), and four studies reported results for both comparisons (318-321).

Of the 31 included cohort studies, the sample size ranged widely, from 12,524,119 participants in a population-based study (298) to 31 in a single-centre hospital-based study (315). The studies were published between 1988 and 2021. Eleven studies were conducted in Europe (287, 301, 303, 304, 306, 310, 314, 316, 318-320), ten in North America (285, 286, 294, 297-299, 305, 308, 309, 315), six in Asia (295, 296, 311-313, 317), two in Australia (307, 321), and two in South America (300, 302). Thirty studies reported definitions for CKD: nine defined CKD according to the National Kidney Foundation "Kidney Disease Outcomes Quality Initiative" guidelines (285, 295, 296, 299, 300, 312, 313, 320, 321), eleven used serum creatinine or proteinuria (287, 301-

309, 315), six used eGFR (286, 311, 314, 316, 317, 319), four used medical coding (294, 297, 298, 310), and one study did not report the definition of CKD (318).

All studies scored between four and eight on the Newcastle-Ottawa Scale (**Appendix 4**, **Tables S4.1-S4.2**). The studies were rated as either moderate quality (n=16) or high quality (n=15); almost all studies with moderate quality did not adjust for confounding factors. More details about the characteristics of the studies, the definitions of CKD and outcomes from each included study are shown in (**Tables S4.1-S4.2**). Additionally, forest plots of all analyses are provided in **Appendix 4** (**Figures S4.1-S4.24**).

### 4.4.2 Results of the Meta-analyses

***The effect of CKD on adverse pregnancy outcomes (CKD compared to no CKD)***

The summary results of all meta-analyses that investigated the association between CKD and adverse pregnancy outcomes are presented in **Table 4.1**. Of the 21 studies that compared adverse pregnancy outcomes in women with CKD vs those without, 14 studies had healthy women (general obstetric population) as the unexposed group. The remaining seven studies had women with other underlying medical conditions (diabetic in six studies (301, 303-307)), but with normal kidney function as the unexposed group (301, 303-308). Six studies reported adjusted effect estimates and that included demographic characteristics, such as maternal age, smoking, parity, body mass index and other comorbidities.

Fifteen studies reported effect estimates of pre-eclampsia: the crude pooled OR was 8.13 (95% CI, 4.41–15) (**Figure 4.2**), and the RD was 16% (95% CI, 8.4– 27). Four studies provided adjusted estimates for pre-eclampsia, which attenuated the OR to 2.58 (95% CI, 1.33–5.01) and RD to 4.1% (95% CI, 0.9–9.7). Ten studies reported effect estimates for CS: the pooled crude OR was 1.66 (95% CI, 1.34–2.06), and the RD was 6.4% (95% CI, 3.4–9.8). Three studies reported adjusted OR (aOR) for CS and that showed similar results to the unadjusted estimate, aOR: 1.65 (95% CI, 1.21–2.25), and the RD was 6.3% (95% CI. 2.1–11.4). Fifteen studies reported effect estimates for PTB: the pooled crude OR was 3.07 (95% CI, 2.27–4.16) (**Figure 4.3**), and the RD was 9.2% (95% CI, 5.9–15.3). Four studies reported adjusted estimates for PTB, lowering the OR to 1.73 (95% CI, 1.31–2.27) and RD to 3.4% (95% CI, 1.5–5.8). Similarly, a higher risk of VPTB (<34 wk.) was observed in women with CKD from both crude estimates

[ten studies, OR=4.85 (95% CI, 3.01–7.80), RD=3.1% (95% CI, 1.6–5.4)] and adjusted estimates [four studies, aOR: 2.18 (95% CI, 1.61–2.95), RD=1% (95% CI, 0.5–1.6)].

Ten studies reported effect estimates for SGA: the crude OR was 2.69 (95% CI, 1.70–4.24), RD=4% (95% CI, 1.7–7.5), and the aOR (three studies) was 1.93 (95% CI, 1.06–3.52), RD=2.3% (95% CI, 0.1–5.9). Few studies reported effect estimates for miscarriage, stillbirth, and perinatal death, and both adjusted and unadjusted results were non–significant (**Table 4.1**). Additionally, the combined outcome of pregnancy loss showed an insignificant association with CKD [four studies, pooled aOR: 1.58 (95% CI, 0.92–2.73), RD=0.2% (95% CI, 0.0–0.7].

***Assessment of heterogeneity and publication bias***

Heterogeneity between studies was low for perinatal death ($I^2$=0%), moderate for CS ($I^2$=56%), and high for other outcomes. Although heterogeneity was high for most outcomes in this comparison, most effect estimates of studies examining the effect of pre-eclampsia and PTB (**Figures 4.2** & **4.3**) are in the same direction suggesting an association with CKD, which may indicate that heterogeneity between studies was because of poor overlapping between studies' 95% CIs (192). This was also explored more in subgroup analyses based on the cause of CKD, study location and year of publication. For publication bias, funnel plots of pre-eclampsia (**Figure S4.1**), CS (**Figure S4.2**), PTB (**Figure S4.3**), VPTB (**Figure S4.4c**) and SGA (**Figure S4.5**) show approximately symmetric distributions, and the results of the Egger test were nonsignificant for all outcomes (*P*-values=0.38; 0.47; 0.17; 0.10; and 0.44 respectively), indicating that publication bias was unlikely to be a substantial problem.

***The effect of CKD severity on adverse pregnancy outcomes (advanced stages compared to early stages of CKD)***

A summary of the results of the included studies that report adverse pregnancy outcomes based on the severity of kidney disease are available in **Table 4.1**. Of the 14 studies, eight compared the outcomes in women with earlier stage (stages 1 or 1-2) CKD vs later stage (stages 2-5 or 3-5) CKD (285, 311-313, 319-321). Four studies included women with stages 1-3 vs 4-5 (286, 314, 316, 317). One study defined CKD severity using creatinine level (<125 vs >125 umol/L) (287), and another study defined the severity of kidney disease according to urine protein level (315), whereas one study did not report the CKD definition (318). Only three studies in this comparison adjusted

for potential confounders, all of them adjusted for proteinuria, and two of these adjusted for hypertension as well.

The results suggest that later stages of CKD, compared to earlier stages, were associated with higher odds of pre-eclampsia [10 studies; crude OR=2.77 (95% CI, 1.73–4.44), RD=24% (95% CI, 12–35)], CS [10 studies; crude OR=1.53 (95% CI, 1.02–2.30), RD=10% (95% CI, 0.5–19)], PTB [12 studies; crude OR=4.21 (95% CI, 2.99–5.92), RD=34% (95% CI, 26.4–42)], and VPTB [eight studies; crude OR=3.11 (95% CI, 2.06–4.69), RD=19% (95% CI, 11–29)]. Eleven studies showed an association between CKD severity and SGA [crude OR=2.43 (95% CI, 1.33–4.46), RD=18% (95% CI, 5.2–33)], but this association was no longer statistically significant after adjustment for proteinuria and hypertension [three studies, aOR: 2.42 (95% CI, 0.82–7.15), RD=17% (95% CI, –2.8–43)].

The risks of LBW [three studies; crude OR=3.17 (95% CI, 1.05–9.62), RD=22% (95% CI, 0.7–49)] and NICU admission [three studies; crude OR=2.94 (95% CI, 1.05–9.62.08), RD=26% (95% CI, 11–39)] were higher in women with advanced stages of CKD. We also observed a higher risk of stillbirth, neonatal death, and perinatal death in later stages of CKD compared to earlier stages (**Table 4.1**). The combined outcome of pregnancy loss also supported a higher risk in women with advanced stages of CKD [9 studies; crude OR=4.39 (95% CI, 2.40–8.02), RD=13% (95% CI, 6–24)]. Few studies reported adjusted effect estimates (adjusted for proteinuria and hypertension), and these reported a significant risk of pre-eclampsia (n=1) and VPTB (n=2) (**Table 4.1**).

***Assessment of heterogeneity and publication bias***

Heterogeneity among studies was low in studies that assessed the outcomes including stillbirth, neonatal death, perinatal death, pregnancy loss, PTB, VPTB, NICU admission ($I^2$=0%) and CS ($I^2$=21%). A moderate level of heterogeneity was observed between studies examining the effect of pre-eclampsia ($I^2$=31%), LBW ($I^2$=58%) and SGA ($I^2$=59% and 56% in the adjusted model). This level of moderate heterogeneity might be due to poor overlapping of 95% CIs for effect estimates of individual studies. The tests for funnel asymmetry were nonsignificant for pre-eclampsia ($P$=0.14), CS ($P$=0.50), and SGA ($P$=0.61), suggesting that publication bias is not a concern (**Appendix 4, Figures S4.9b**; **S4.10b**; and **S4.13c**, respectively). However, there was little evidence for small-study effects for PTB ($P$=0.032, **Figure S4.11b**).

**The effect of the cause of CKD on adverse pregnancy outcomes**

When we investigated risks based on the cause of CKD, we determined that all causes were associated with a higher risk of pre-eclampsia, PTB, and SGA (**Table 4.2** & **Figures S4.19**, **S4.11** & **S4.13**). Adjustment for confounding factors in this analysis refers mainly to maternal demographic characteristics and other comorbidities.

The magnitude of risk of pre-eclampsia appears higher in women with glomerulonephritis and diabetic CKD [crude OR=6.52 (95% CI, 2.02–21.1), and 9.19 (95% CI, 6.05–14.0), respectively] than in women with PKD [OR=4.36 (95% CI, 3.32–5.71)]. However, adjusted estimates showed similar risks across different subgroups [glomerulonephritis: aOR=2.13 (95% CI, 1.84–2.47); diabetic CKD: aOR=2.80 (95% CI, 1.55–5.05); and PKD: aOR=3.98 (95% CI, 2.98–5.32)]. Women with diabetic CKD were more likely to have PTB [crude OR=4.71 (95% CI, 1.46–15.2), aOR=4.76 (3.65–6.21] and CS [crude OR=3.08 (95% CI, 0.71–13.30), aOR=3.75 (95% CI, 2.76–5.10)] than other CKD groups. There was effect modification by cause of CKD, which suggested that different CKD causes had differing risks of pre-eclampsia ($P$=0.03), VPTB ($P$<0.00001) and SGA ($P$=0.008). In addition, one study reported the effect estimate for women with renovascular CKD, compared to normotensive women without CKD, which suggested a higher odds of pre-eclampsia [aOR=3.64 (95% CI, 2.18–6.09)], indicated PTB [aOR=8.09 (95% CI, 5.73–11.4)], and SGA [aOR=328 (95% CI, 2.06–5.20)] (310).

Heterogeneity was moderate to high for all meta-analyses, and that was explained by causes of CKD, particularly for VPTB and SGA (**Appendix 4, Figures S4.22** & **S4.23**). When this was further investigated, a high level of heterogeneity for PTB in the diabetic CKD subgroup (n=6, $I^2$=96%) was owing to two studies with outlying effect estimates (301, 310). When these studies were excluded, the pooled crude OR for PTB in this subgroup was changed to 4.18 (95% CI, 2.86–6.11; $I^2$= 0%). Similarly, excluding these studies from the pre-eclampsia analysis decreased heterogeneity. The explanation for outlier results in these studies might be explained by studies inclusion criteria, as one study included women with microalbuminuria without reduced eGFR (301), whereas the other study compared outcomes to the general obstetric population and not mainly diabetic women without CKD (310), which was used as the reference group in other studies examining the risk of pregnancy outcomes in women with diabetic CKD.

***Sensitivity analyses by study location and year of publication***

The results of subgroup analyses by publication year (≤2010 vs >2010) showed a significant decreased risk over time for CS ($P$=0.02) and SGA ($P$<0.0001) and also explained some of the heterogeneity among the studies. However, no differences were found by study location (**Appendix 4**, **Table S4.3**).

### 4.4.3 GRADE Certainty of the Evidence

Considering that our review included observational studies, the certainty of the evidence was judged to be "low" for pre-eclampsia, PTB and VPTB, and "very low" for SGA and CS. Therefore, the certainty of the evidence overall across all outcomes was judged to be very low. The evidence was downgraded (depending on the outcome of interest) due to a serious risk of bias in the included studies (studies included were observational, most studies reported crude estimates and confounding was judged to be a serious concern); serious imprecision (the included studies had very wide 95% CIs); and inconsistency (due to a moderate level of heterogeneity that was not explained by subgroup analyses, as well as effect estimates in varying directions and crossing the line of no effect). Details about the GRADE evaluation are provided in **Table 4.3**.

## 4.5 Discussion

This systematic review and meta-analysis of 31 international studies over the last four decades examined associations between pre-pregnancy CKD and risk of adverse pregnancy outcomes. We identified three main findings. First, we confirmed that CKD is a strong risk factor for adverse pregnancy outcomes. For example, the odds for pre-eclampsia were 8-fold higher in women with CKD compared to women without CKD and remained approximately 3-fold higher after adjusting for factors including maternal age, smoking, body mass index, parity, and other comorbidities. Second, we confirmed that later stages of CKD are associated with greater risk than earlier stages, supporting findings from individual studies that have not been evaluated in a contemporary meta-analysis. Finally, we determined that the risk associated with CKD differs depending on the cause of CKD: specifically, risks were higher amongst women with diabetic CKD, particularly for CS, PTB, and SGA.

Our review reinforces previous findings on the occurrence of adverse pregnancy outcomes in women with CKD, compared to those without CKD, by including more studies from different settings (72, 73). In contrast to the previous reviews (72, 73), we

considered the cause of CKD when adverse pregnancy outcomes were compared between women with and without CKD. We also investigated the risk of adverse pregnancy outcomes among pregnant women with late stages of CKD compared to early stages. Additionally, a previous review reported high quality of the evidence for pre-eclampsia and PTB and low for SGA/LBW (73), but our GRADE evaluation showed low and very low quality of evidence for these outcomes, respectively.

There is limited research on the risk of adverse pregnancy outcomes among women with specific types of kidney diseases. In our review, most studies (n=19) combined a variety of kidney disease aetiologies in their analyses when examining the risk of adverse pregnancy outcomes. Of these, 14 reported percentages of specific diagnoses, and glomerulonephritis was the most common diagnosis in pregnant women (285, 286, 310, 312-314, 316-318, 321). Proteinuria has been found to be an important predictor of outcome in immunoglobulin A(IgA) nephropathy, which is the most common primary glomerulonephritis in pregnant women (288).

The available literature suggests that proteinuria (316, 322) and chronic hypertension (310, 316, 322) are strong determinants of adverse pregnancy outcomes in women with CKD. However, an Italian cohort study aimed to investigate whether adverse pregnancy outcomes in women with stage 1 CKD were due to hypertension, proteinuria, presence of systemic disease, or other factors associated with CKD and indicated that any persistent kidney damage (even with preserved kidney function) in the absence of hypertension, significant proteinuria or systemic disease, was associated with a higher risk for adverse pregnancy outcomes (322). Our findings from the subgroup analysis, including studies that specified the CKD subtypes, suggested a higher risk of adverse pregnancy outcomes in pregnant women with glomerulonephritis. Furthermore, we found that pregnancies in women with diabetic CKD had poor pregnancy outcomes, particularly for preeclampsia, CS and SGA, and the magnitude of effect estimates varies among included studies based on albuminuria level (microalbuminuria/macroalbuminuria). The pregnancy outcomes among pregnant women with PKD were reported in two studies, and they showed an association with pre-eclampsia, CS, PTB, SGA and stillbirth. We did not include pregnant women with lupus nephritis in our review as this particular group was studied in a recent meta-analysis that reported an association between lupus nephritis and pre-eclampsia (OR=2.84), PTB (OR=1.92), and fetal growth restriction (OR=1.43) (323).

Overall, the finding of associations between adverse pregnancy outcomes and different CKD causes confirms previous research (66). However, direct comparisons of pregnancy outcomes between women with a specific cause of CKD vs a comparator cause of CKD are lacking.

**Strengths and Limitations**

The strengths of this meta-analysis include the development and use of a comprehensive search strategy, a prospectively registered protocol, the additional comparison of pregnancy outcomes across CKD stages, subgroup analyses by cause of CKD, and inclusion of studies from multiple geographic regions spanning four decades. In addition, each process of the systematic review was carried out by at least two independent reviewers using standardized data extraction forms and validated quality appraisal tools. However, several limitations should be noted. The review was limited to English language studies only, and the grey literature was not searched. Although we estimated the crude and adjusted estimates that highlighted significant confounding when comparing the crude and adjusted estimates, most of the included studies reported crude estimates only, were performed in a single centre and were of small sample size. Nevertheless, by pooling the results of these individual studies, we aimed to better estimate the true magnitude of risk. Confounding factors were addressed in nine studies only (285, 294, 298, 299, 301, 309, 310, 316, 320), and that may attenuate the reported estimates between CKD and adverse pregnancy outcomes. Therefore, future studies should be designed to account for potential confounding to improve our understanding of these associations and the role of potential confounding.

These studies were also susceptible to other limitations of observational research, and the overall certainty of the evidence across all outcomes was judged to be “very low” using the GRADE approach (certainty was downgraded due to concerns regarding bias [incomplete adjustment for confounding] and imprecision [most studies of small sample size with very wide CIs)] and inconsistency. We cannot eliminate the possibility of under- or over- diagnosis of pre-eclampsia in some women with CKD, who had hypertension and/or proteinuria before pregnancy. Further, CKD definitions varied across the included studies, including the threshold at which a patient was considered to have early vs late CKD. Finally, we lacked sufficient data on proteinuria and blood pressure control before and during pregnancy, which are known to be strong risk factors for adverse pregnancy outcomes in women with CKD (322). Accordingly,

we could not determine whether associations with the cause of CKD were mediated by these (potentially modifiable) factors. Additionally, data on pre-eclampsia were not detailed enough to investigate whether the magnitude of risk associated with CKD varied by pre-eclampsia severity (severe vs mild or term vs preterm). Similarly, data on CS were reported as overall deliveries in most studies without distinguishing between elective or emergency CS.

Women with CKD are considered a high-risk group during pregnancy and should be offered preconception counselling by a multidisciplinary team, with close monitoring during pregnancy, delivery and in the postnatal period. However, not all women with CKD are the same. By quantifying risk differences depending on severity and cause of CKD, this systematic review will enable clinicians to better tailor care and counselling to individual patient risk. Future studies examining associations between CKD and adverse pregnancy outcomes need to account not only for the severity of CKD but also for the cause of CKD and factors (proteinuria, hypertension, immunosuppressive therapies, and disease activity) that might mediate this risk.

## 4.6 Conclusions

The results of this meta-analysis confirmed an association between pre-pregnancy CKD and adverse pregnancy outcomes, with different risks according to the cause and the severity of CKD. We hope that these findings might support clinicians aiming to counsel women with CKD considering pregnancy. However, we acknowledge that most of the included observational studies had significant limitations, which highlights the need for more robust research in the future. In particular, we advocate for the development of an international pregnancy registry of women with CKD, which would comprehensively characterize women with CKD in early pregnancy and prospectively collect data on a core set of standardized pregnancy outcomes. Such an initiative would accurately quantify absolute risks, and identify risk factors, for adverse pregnancy outcomes in women with CKD, enabling pregnancy counselling to be better tailored to individual patient risk and generating hypotheses to be tested in future interventional studies.

**Table 4.1** Summary results of meta-analyses of pregnancy outcomes in women with chronic kidney disease

| Maternal/fetal outcome | *Crude estimates* | | | | | *Adjusted Estimates* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | No. of participants | Pooled OR (95% CI) | RD (95% CI) | $I^2$, % | No. of studies | No. of participants | Pooled OR (95% CI)[a] | RD (95% CI) | $I^2$, % |
| **Women with CKD compared to women without CKD** | | | | | | | | | | |
| Pre-eclampsia | 15 | 2,782,133 | 8.13 [4.41, 15] | 16% [8.4, 27] | 93 | 4 | 2,777,209 | 2.58 [1.33, 5.01] | 4.1% [0.9, 9.7] | 93 |
| Caesarean section | 10 | 2,780,815 | 1.66 [1.34, 2.06] | 6.4% [3.4, 9.8] | 56 | 3 | 2,776,363 | 1.65 [1.21, 2.25] | 6.3% [2.1, 11.4] | 84 |
| Maternal death | – | – | – | – | – | 1 | 1,556 | 1.13 [0.44, 2.92] | 0.1% [–0.6, 1.9] | – |
| Preterm birth (<37 wk.) | 15 | 2,837,905 | 3.07 [2.27, 4.16] | 9.2% [5.9, 13.3] | 92 | 4 | 2,831,929 | 1.73 [1.31, 2.27] | 3.4% [1.5, 5.8] | 92 |
| Very preterm birth (<34 wk.) | 10 | 2,833,576 | 4.85 [3.01, 7.80] | 3.1% [1.6, 5.4] | 87 | 4 | 2,832,177 | 2.18 [1.61, 2.95] | 1.0% [0.5, 1.6] | 65 |
| Small for gestational age | 10 | 2,780,942 | 2.69 [1.70, 4.24] | 4.0% [1.7, 7.5] | 78 | 3 | 2,776,363 | 1.93 [1.06, 3.52] | 2.3% [0.1, 5.9] | 89 |
| Low birthweight | 1 | 43 | 4.00 [0.80, 20.1] | 24% [–2.2, 62] | – | 1 | 1,556 | 2.38 [1.64, 3.44] | 7.2% [3.5, 12] | – |
| Neonatal intensive unit admission | 1 | 144 | 2.40 [1.40, 4.11] | - | – | 1 | 1,556 | 1.80 [1.22, 2.66] | 4.0% [1.1, 7.9] | – |
| Miscarriage | 3 | 809 | 2.71 [0.76, 9.62] | 11% [–1.8, 37] | 75 | – | – | – | – | – |
| Stillbirth | 3 | 15,354,062 | 2.47 [0.72, 8.47] | 0.6% [–0.1, 2.8] | 99 | 3 | 15,354,062 | 1.67 [0.96, 2.92] | 0.3% [0.0, 0.7] | 94 |
| Perinatal death | 2 | 422 | 4.07 [1.02, 16.2] | 4.3% [0, 18] | 0 | 1 | 1,556 | 0.50 [0.05, 5.53] | –0.1% [–0.2, 1.1] | – |
| Pregnancy loss[b] | 8 | 15,355,293 | 2.74 [1.22, 6.16] | 0.7% [0.1, 2.0] | 96 | 4 | 15,355,618 | 1.58 [0.92, 2.73] | 0.2% [0, 0.7] | 91 |

| **Late stages compared to early stages of CKD** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pre-eclampsia | 10 | 833 | 2.77 [1.73, 4.44] | 24% [12, 35] [b] | 31 | 1 | 126 | 4.50 [1.29, 15.7] | 35% [4.9, 59] | – |
| Cesarean section | 10 | 811 | 1.53 [1.02, 2.30] | 10% [0.5, 19] | 21 | – | – | – | – | – |
| Preterm birth (<37 wk.) | 12 | 1,279 | 4.21 [2.99, 5.92] | 34% [26.4, 42] [b] | 0 | 1 | 126 | 2.03 [0.89, 4.63] | 17% [–2.5, 37] | – |
| Very preterm birth (<34 wk.) | 8 | 716 | 3.11 [2.06, 4.69] | 19% [11, 29] [b] | 0 | 2 | 207 | 3.10 [1.38, 6.95] | 18% [4, 38] | 0 |
| Small for gestational age | 11 | 729 | 2.43 [1.33, 4.46] | 18% [5.2, 33] | 59 | 3 | 301 | 2.42 [0.82, 7.15] | 17% [–2.8, 43] | 56 |
| Low birthweight | 3 | 323 | 3.17 [1.05, 9.62] | 22% [0.7, 49] | 58 | – | – | – | – | – |
| Neonatal intensive unit admission | 3 | 233 | 2.94 [1.65, 5.24] | 26% [11, 39] [b] | 0 | – | – | – | – | – |
| Miscarriage | 1 | 35 | 1.33 [0.19, 9.31] | 3.6% [–10.3, 45] | – | – | – | – | – | – |
| Stillbirth | 5 | 279 | 3.10 [1.32, 7.29] | 12% [2, 28] | 0 | – | – | – | – | – |
| Neonatal death | 3 | 223 | 6.74 [2.54, 17.9] | 22% [6.9, 43] | | 1 | 81 | 2.90 [0.10, 84] | 8.4% [–4.6, 77] | – |
| Perinatal death | 3 | 360 | 5.81 [2.27, 14.9] | 12% [3.6, 29] | 0 | – | – | – | – | – |
| Pregnancy loss[c] | 9 | 654 | 4.39 [2.40, 8.02] | 13% [6, 24] [b] | 0 | 1 | 81 | 2.90 [0.10, 84] | 8.4% [–4.6, 77] | – |

CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; RD, risk difference. [a] For adjusted estimates, we followed the author's definition: a study comparing adverse outcomes in CKD vs no CKD adjusted for factors including maternal age, smoking, body mass index, race, income, educational level, parity, and other comorbidities. Whereas the three studies comparing early vs late stages CKD adjusted for proteinuria and two of them adjusted for hypertension. [b] One study (Seah, 2020) did not report the number of events in each group for these outcomes; therefore, it was not added to the study event rates; [c] pregnancy loss included miscarriage, stillbirth, neonatal death and/or perinatal death effect estimates.

**Table 4.2** Summary results of meta-analyses of adverse pregnancy outcomes in women with CKD compared to women without CKD, according to the cause of CKD

| Maternal/fetal outcome | *Crude estimates* | | | | | *Adjusted Estimates* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | No. of participants | Pooled OR (95% CI) | RD (95% CI) | $I^2$, % | No. of studies | No. of participants | Pooled OR (95% CI)[a] | RD (95% CI) | $I^2$, % |
| **Pre-eclampsia** | | | | | | | | | | |
| Glomerulonephritis CKD | 4 | 2,758,078 | 6.52 [2.02, 21.1] | 13% [2.7, 34] | 88 | 1 | 2,756,102 | 2.13 [1.84, 2.47] | 2.9% [2.2, 3.8] | – |
| Diabetic CKD | 7 | 2,753,496 | 9.19 [6.05, 14.0] | 18% [12, 26][b] | 57 | 2 | 2,752,847 | 2.80 [1.55, 5.05] | 4.6% [1.5, 9.8] | 67 |
| PKD | 2 | 2,752,680 | 4.36 [3.32, 5.71] | 8.3 [5.9, 11] | 0 | 1 | 2,752,269 | 3.98 [2.98, 5.32] | 7.4% [5, 10] | – |
| Unspecified CKD | 5 | 2,778,417 | 5.30 [2.02, 13.9] | 19% [5.5., 42] | 95 | 3 | 2,776,363 | 2.27 [1.06, 4.87] | 3.3% [0.2, 9.5] | 94 |
| **Caesarean section** | | | | | | | | | | |
| Glomerulonephritis CKD | 3 | 2,758,033 | 1.45 [1.15, 1.85] | 4.5% [1.5, 8.1] | 45 | 1 | 2,756,102 | 1.52 [1.38, 1.67] | 5.1% [3.8, 6.5] | – |
| Diabetic CKD | 4 | 2,752,369 | 3.08 [0.71, 13.3] | 17% [–3.1, 52] | 93 | 1 | 2,752,001 | 3.75 [2.76, 5.10] | 22% [15, 29] | – |
| PKD | 2 | 2,752,680 | 1.97 [1.03, 3.77] | 9.1% [0.3, 22] | 72 | 1 | 2,751,735 | 2.67 [2.14, 3.33] | 15% [11, 19] | – |
| Unspecified CKD | 4 | 2,778,105 | 1.98 [1.37, 2.86] | 9.2%. [3.7, 16] | 81 | 3 | 2,776,363 | 1.65 [1.21, 2.25] | 6.3% [2.1, 11] | 84 |
| **Preterm birth <37 wk.** | | | | | | | | | | |
| Glomerulonephritis CKD | 4 | 2.758,147 | 5.98 [2.20, 16.3] | 19% [5.5, 42] | 95 | 1 | 2,756,102 | 2.20 [1.98, 2.44] | 5.5% [4.5, 6.5] | – |
| Diabetic CKD | 6 | 2,753,510 | 4.71 [1.46, 15.2] | 17% [2.5, 43][b] | 96 | 1 | 2,752,001 | 4.76 [3.65, 6.21] | 15% [11, 20] | – |
| PKD | 2 | 2,752,680 | 2.12 [1.04, 4.30] | 5.1% [0.2, 14] | 71 | 1 | 2,752,269 | 2.55 [1.94, 3.35] | 7% [4.4, 10] | – |
| Unspecified CKD | 6 | 2,834,297 | 2.17 [1.62, 2.90] | 5.4% [2.9, 8.5] | 90 | 4 | 2,776.286 | 1.73 [1.31, 2.27] | 3.4% [1.5, 5.8] | 92 |
| **Very preterm birth <34 wk.** | | | | | | | | | | |
| Glomerulonephritis CKD | 2 | 1,931 | 19.2 [10.4, 35.5] | 15% [8.4, 25] | 0 | – | – | – | – | – |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Diabetic CKD | 5 | 1,558 | 4.28 [2.45, 7.47] | 16% [7.6, 26][b] | 50 | 1 | 846 | 1.60 [0.64, 4.00] | 3.2% [–2, 1.4] | – |
| PKD | – | – | – | – | – | – | – | – | – | – |
| Unspecified CKD | 3 | 2,830,087 | 2.15 [1.67, 2.76] | 0.9% [0.6, 1.4] | 53 | 3 | 2,831,885 | 2.28 [1.62, 3.21] | 1.1% [0.5, 1.8] | 76 |
| **Small for gestational age** | | | | | | | | | | |
| Glomerulonephritis CKD | 2 | 2,757,646 | 1.77 [1.52, 2.07] | 1.9% [1.3, 2.6] | 0 | 1 | 2,756,102 | 1.54 [1.31, 1.81] | 1.3% [0.8, 2] | – |
| Diabetic CKD | 4 | 2,752,560 | 5.14 [2.52, 10.5] | 9.3% [3.6, 19] | 45 | 1 | 2,752,001 | 4.50 [2.92, 6.94] | 8% [4.6, 13] | – |
| PKD | 2 | 2,752,680 | 2.59 [1.84, 3.64] | 3.8% [2, 6.1] | 0 | 1 | 2,752,269 | 2.45 [1.66, 3.62] | 3.5% [1.5, 6.1] | – |
| Unspecified CKD | 5 | 2,778,428 | 2.49 [1.34, 4.61] | 3.6%. [0.8, 8.2] | 84 | 3 | 2,776,363 | 1.93 [1.06, 3.52] | 2.3% [0.1, 5.9] | 89 |
| **Low birthweight** | | | | | | | | | | |
| Glomerulonephritis CKD | – | – | – | – | – | – | – | – | – | – |
| Diabetic CKD | 1 | 43 | 4.00 [0.80, 20.1] | 24% [–2.2, 62] | – | – | – | – | – | – |
| PKD | – | – | – | – | – | – | – | – | – | – |
| Unspecified CKD | – | – | – | – | – | 1 | 1,556 | 2.38 [1.64, 3.44] | 7.2% [3.5, 12] | – |
| **Neonatal intensive unit admission** | | | | | | | | | | |
| Glomerulonephritis CKD | – | – | – | – | – | – | – | – | – | – |
| Diabetic CKD | 1 | 144 | 2.40 [1.40, 4.11] | -[b] | – | – | – | – | – | – |
| PKD | – | – | – | – | – | – | – | – | – | – |
| Unspecified CKD | – | – | – | – | – | 1 | 1,556 | 1.80 [1.22, 2.66] | 4% [1.1, 7.9] | – |
| **Stillbirth** | | | | | | | | | | |
| Glomerulonephritis CKD | 1 | 2,756,102 | 1.31 [0.82, 2.09] | 0.1% [–0.1, 0.4] | – | 1 | 2,756,102 | 1.12 [0.70, 1.79] | 0.0% [–0.1, 0.3] | – |
| Diabetic CKD | 1 | 2,752,001 | 5.75 [2.40, 13.8] | 1.5% [0.5, 4.1] | – | 1 | 2,752,001 | 1.55 [0.64, 3.75] | 0.2% [–0.1, 0.9] | – |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| PKD | 1 | 2,752,269 | 2.84 [1.18, 6.84] | 0.6% [0.1, 1.9] | – | 1 | 2,752,269 | 2.73 [1.13, 6.60] | 0.6% [0, 1.8] | – |
| Unspecified CKD | 3 | 15,354,062 | 2.47 [0.72, 8.47] | 0.6% [–0.1, 2.8] | 99 | 3 | 15,354,062 | 1.67 [0.96, 2.92] | 0.3% [0, 1.8] | 94 |
| **Perinatal death** | | | | | | | | | | |
| Glomerulonephritis CKD | – | – | – | – | – | – | – | – | – | – |
| Diabetic CKD | 2 | 422 | 4.07 [1.02, 16.2] | 4.3% [0, 18] | 0 | – | – | – | – | – |
| PKD | – | – | – | – | – | – | – | – | – | – |
| Unspecified CKD | – | – | – | – | – | 1 | 1,556 | 0.50 [0.05, 5.53] | –0.1% [–0.2, 1.1] | – |

CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; PKD, polycystic kidney disease; RD, risk difference. [a] For adjusted estimates, we followed the author's definition: these studies adjusted for factors including maternal age, smoking, body mass index, race, income, educational level, parity, and other comorbidities. [b] One study (Seah, 2020) did not report the number of events in each group for these outcomes; therefore, it was not added to the study event rates.

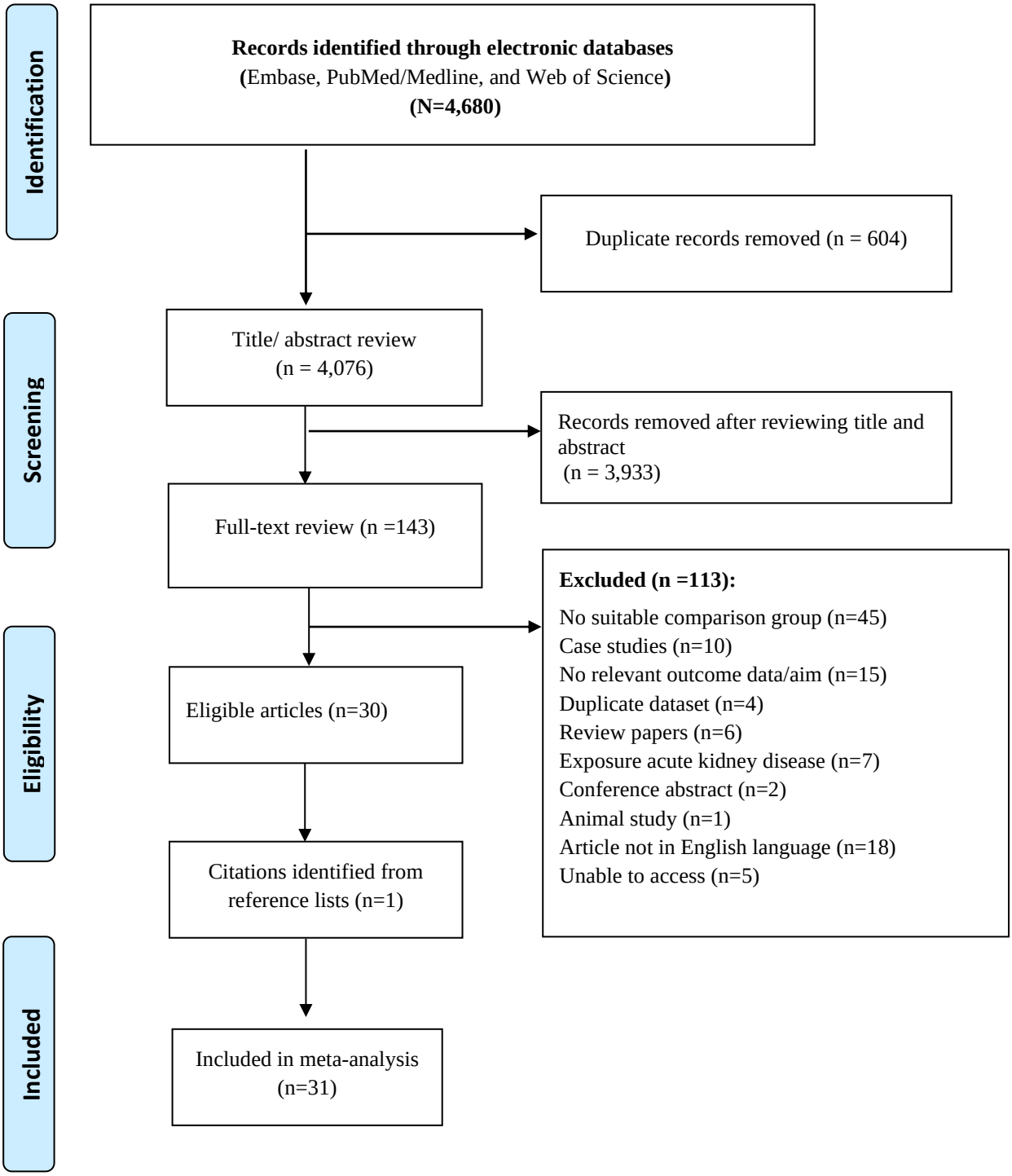
**Table 4.3** Certainty of the evidence assessed using the GRADE approach for chronic kidney disease and adverse pregnancy outcomes

| Outcome | № of studies | Certainty assessment | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Overall certainty of evidence | *Study event rates (%)* | | *Relative effect (95% CI)[a]* | *Anticipated absolute effects* | |
| | | | | | | | No CKD | CKD | | Risk with no CKD | Risk difference with CKD |
| Pre-eclampsia[b] | 16 | Serious [c] | Not serious | Not serious | Serious [d] | ⊕⊕◯◯ LOW | 76290/2759512 (2.8%) | 1299/24033 (5.4%) | **OR** 6.79 (3.93, 11.8) | 28 per 1,000 | **134 more per 1,000** (from 73 more to 222 more) |
| Preterm birth [b] | 16 | Serious [c] | Not serious [e] | Not serious | Serious [d] | ⊕⊕◯◯ LOW | 145725/2812368 (5.2%) | 2612/26949 (9.7%) | **OR 2.88** (2.16, 3.83) | 52 per 1,000 | **84 more per 1,000** (from 54 more to 121 more) |
| Small for gestational age | 11 | Serious [c] | Serious [f] | Not serious | Serious [d] | ⊕◯◯◯ VERY LOW | 70589/2758432 (2.6%) | 929/23966 (3.9%) | **OR 2.36** (1.61, 3.47) | 26 per 1,000 | **33 more per 1,000** (from 15 more to 58 more) |
| Caesarean section | 11 | Serious [c] | Serious [g] | Not serious | Serious [d] | ⊕◯◯◯ VERY LOW | 327224/2758410 (11.9%) | 4460/23961 (18.6%) | **OR 1.58** (1.32, 1.88) | 119 per 1,000 | **57 more per 1,000** (from 32 more to 83 more) |
| Very Preterm birth [b] | 11 | Serious [c] | Not serious | Not serious | Serious [d] | ⊕⊕◯◯ LOW | 23648/2808571 (0.8%) | 708/26417 (2.7%) | **OR 4.70** (2.92, 7.57) | 8 per 1,000 | **30 more per 1,000** (from 16 more to 52 more) |

**Explanations**

[a] Pooled odds ratios presented are a combination of adjusted (when reported by included studies) and crude effect estimates; [b] One study (Seah, 2020) did not report the number of events in each group for these outcomes; therefore, it was not added to the study event rates. Contact with the author proved for this information proved unsuccessful; [c] Downgraded one level for risk of bias (included studies were observational, few studies reported adjusted effect estimates and confounding was judged to be a serious concern); [d] Downgraded one level for imprecision (included studies had very wide 95% confidence intervals); [e] Although heterogeneity levels between studies was high ($I^2$=92), almost all estimates from forest plots consistently supported associations in the same direction; [f] Downgraded one level for inconsistency (due to a moderate level of heterogeneity that was not explained by subgroup analysis, as well as effect estimates in varying directions and crossing the line of no effect); [g] Downgraded one level for inconsistency (due to varying directions of effect estimates and some estimates crossing the line of no effect. Although heterogeneity was high, but that was mainly due to different causes of CKD)

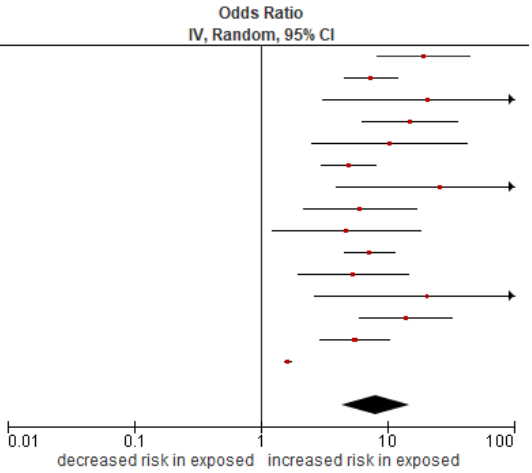
**Figure 4.1** PRISMA flow diagram of studies on the association between chronic kidney disease and adverse pregnancy outcome



**A** **Pre-eclampsia** (crude estimates)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Miodovnik,1996 | 2.964 | 0.4327 | 7.2% | 19.38 [8.30, 45.24] | 1996 |
| Fink, 1998 | 2.0005 | 0.2476 | 7.9% | 7.39 [4.55, 12.01] | 1998 |
| Biesenbach, 2000 | 3.0445 | 0.9759 | 4.6% | 21.00 [3.10, 142.20] | 2000 |
| Ekbom, 2001 | 2.7133 | 0.4436 | 7.1% | 15.08 [6.32, 35.97] | 2001 |
| Trevisan, 2004 | 2.3461 | 0.722 | 5.8% | 10.44 [2.54, 43.00] | 2004 |
| Jensen,2010 | 1.5998 | 0.2485 | 7.9% | 4.95 [3.04, 8.06] | 2010 |
| Young, 2011 | 3.2677 | 0.9624 | 4.6% | 26.25 [3.98, 173.12] | 2011 |
| Wiles, 2015 | 1.7993 | 0.5227 | 6.7% | 6.05 [2.17, 16.84] | 2015 |
| Wu, 2016 | 1.5602 | 0.6904 | 5.9% | 4.76 [1.23, 18.42] | 2016 |
| Tsuchiyama, 2017 | 1.979 | 0.2345 | 8.0% | 7.24 [4.57, 11.46] | 2017 |
| Piccoli, 2017 | 1.6785 | 0.5099 | 6.8% | 5.36 [1.97, 14.55] | 2017 |
| Li, 2018 | 3.0296 | 1.0465 | 4.3% | 20.69 [2.66, 160.89] | 2018 |
| Madej, 2020 | 2.6391 | 0.4262 | 7.2% | 14.00 [6.07, 32.28] | 2020 |
| Seah, 2020 | 1.7156 | 0.3234 | 7.6% | 5.56 [2.95, 10.48] | 2020 |
| Al Khalaf, 2021 | 0.4947 | 0.0354 | 8.3% | 1.64 [1.53, 1.76] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **8.13 [4.41, 14.97]** | |

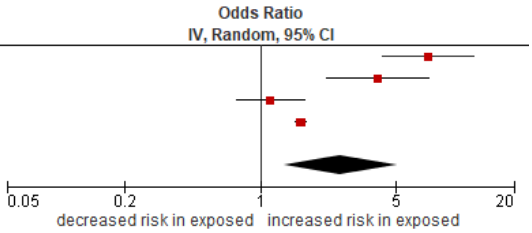
Heterogeneity: Tau² = 1.17; Chi² = 213.34, df = 14 (P < 0.00001); I² = 93%
Test for overall effect: Z = 6.72 (P < 0.00001)




**B** **Pre-eclampsia** (adjusted estimates)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Fink, 1998 | 1.9804 | 0.2782 | 23.6% | 7.25 [4.20, 12.50] | 1998 |
| Jensen,2010 | 1.3863 | 0.305 | 22.9% | 4.00 [2.20, 7.27] | 2010 |
| Kendrick, 2015 | 0.1222 | 0.2024 | 25.5% | 1.13 [0.76, 1.68] | 2015 |
| Al Khalaf, 2021 | 0.4762 | 0.0327 | 28.0% | 1.61 [1.51, 1.72] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **2.58 [1.33, 5.01]** | |

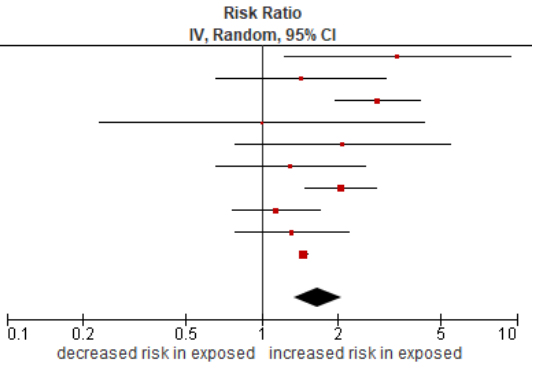
Heterogeneity: Tau² = 0.41; Chi² = 40.77, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.81 (P = 0.005)




**C** **Caserean section** (crude estimates)

| Study or Subgroup | log[Risk Ratio] | SE | Weight | Risk Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Kimmerle,1995 | 1.2254 | 0.5215 | 3.7% | 3.41 [1.23, 9.46] | 1995 |
| Miodovnik,1996 | 0.3518 | 0.3923 | 5.9% | 1.42 [0.66, 3.07] | 1996 |
| Fink, 1998 | 1.0458 | 0.195 | 13.8% | 2.85 [1.94, 4.17] | 1998 |
| Biesenbach, 2000 | 0 | 0.7454 | 2.0% | 1.00 [0.23, 4.31] | 2000 |
| Trevisan, 2004 | 0.7307 | 0.4972 | 4.0% | 2.08 [0.78, 5.50] | 2004 |
| Wu, 2016 | 0.2585 | 0.3432 | 7.1% | 1.29 [0.66, 2.54] | 2016 |
| Tsuchiyama, 2017 | 0.712 | 0.1654 | 15.7% | 2.04 [1.47, 2.82] | 2017 |
| Piccoli, 2017 | 0.1308 | 0.2046 | 13.2% | 1.14 [0.76, 1.70] | 2017 |
| Madej, 2020 | 0.2711 | 0.262 | 10.2% | 1.31 [0.78, 2.19] | 2020 |
| Al Khalaf, 2021 | 0.3784 | 0.0214 | 24.5% | 1.46 [1.40, 1.52] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **1.66 [1.34, 2.06]** | |

Heterogeneity: Tau² = 0.05; Chi² = 20.67, df = 9 (P = 0.01); I² = 56%
Test for overall effect: Z = 4.66 (P < 0.00001)




**D** **Caserean section** (adjusted estimates)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Fink, 1998 | 1.1314 | 0.2236 | 23.1% | 3.10 [2.00, 4.80] | 1998 |
| Kendrick, 2015 | 0.2852 | 0.1158 | 34.7% | 1.33 [1.06, 1.67] | 2015 |
| Al Khalaf, 2021 | 0.3365 | 0.0223 | 42.2% | 1.40 [1.34, 1.46] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **1.65 [1.21, 2.25]** | |

Heterogeneity: Tau² = 0.06; Chi² = 12.77, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 3.16 (P = 0.002)

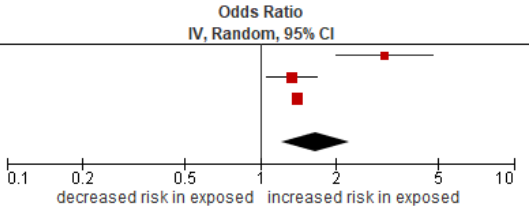
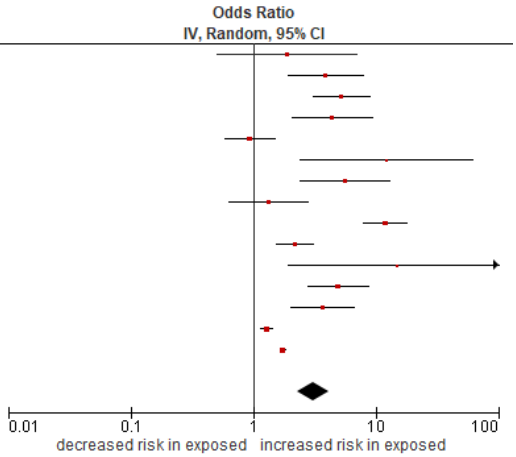



**Figure 4.2** Forest plots of studies of the association between chronic kidney disease and maternal complications

**A** **Preterm birth (<37 wk.)** (crude estimates)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Holley, 1996 | 0.6397 | 0.668 | 3.5% | 1.90 [0.51, 7.02] | 1996 |
| Miodovnik,1996 | 1.361 | 0.3573 | 6.5% | 3.90 [1.94, 7.86] | 1996 |
| Fink, 1998 | 1.6529 | 0.2747 | 7.6% | 5.22 [3.05, 8.95] | 1998 |
| Ekbom, 2001 | 1.4803 | 0.3886 | 6.1% | 4.39 [2.05, 9.41] | 2001 |
| Jensen,2010 | -0.0672 | 0.2397 | 8.1% | 0.94 [0.58, 1.50] | 2010 |
| Young, 2011 | 2.5055 | 0.8238 | 2.6% | 12.25 [2.44, 61.57] | 2011 |
| Wiles, 2015 | 1.7205 | 0.4291 | 5.7% | 5.59 [2.41, 12.96] | 2015 |
| Wu, 2016 | 0.2936 | 0.3795 | 6.3% | 1.34 [0.64, 2.82] | 2016 |
| Piccoli, 2017 | 2.4804 | 0.2101 | 8.5% | 11.95 [7.91, 18.03] | 2017 |
| Tsuchiyama, 2017 | 0.7841 | 0.1744 | 8.9% | 2.19 [1.56, 3.08] | 2017 |
| Li, 2018 | 2.7081 | 1.0524 | 1.8% | 15.00 [1.91, 118.01] | 2018 |
| Madej, 2020 | 1.5914 | 0.2929 | 7.4% | 4.91 [2.77, 8.72] | 2020 |
| Seah, 2020 | 1.3002 | 0.3063 | 7.2% | 3.67 [2.01, 6.69] | 2020 |
| Harel, 2020 | 0.2469 | 0.0591 | 9.9% | 1.28 [1.14, 1.44] | 2020 |
| Al Khalaf, 2021 | 0.5539 | 0.0271 | 10.0% | 1.74 [1.65, 1.83] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **3.07 [2.27, 4.16]** | |

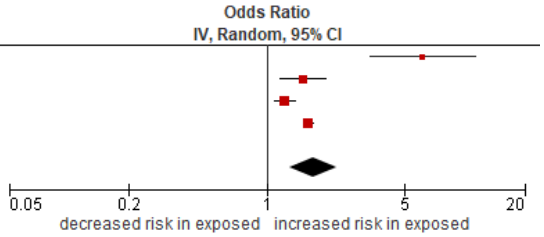
Heterogeneity: Tau² = 0.24; Chi² = 182.43, df = 14 (P < 0.00001); I² = 92%
Test for overall effect: Z = 7.25 (P < 0.00001)




**B** **Preterm birth (<37 wk.)** (adjusted estimates)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Fink, 1998 | 1.8083 | 0.3135 | 12.3% | 6.10 [3.30, 11.28] | 1998 |
| Kendrick, 2015 | 0.4187 | 0.1379 | 24.7% | 1.52 [1.16, 1.99] | 2015 |
| Harel, 2020 | 0.207 | 0.0617 | 30.7% | 1.23 [1.09, 1.39] | 2020 |
| Al Khalaf, 2021 | 0.4824 | 0.0258 | 32.3% | 1.62 [1.54, 1.70] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **1.73 [1.31, 2.27]** | |

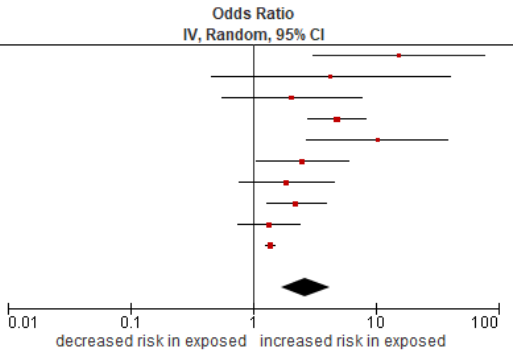
Heterogeneity: Tau² = 0.06; Chi² = 35.91, df = 3 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.91 (P < 0.0001)




**C** **Small for gestational age** (crude estimates)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Kimmerle,1995 | 2.7362 | 0.8185 | 5.5% | 15.43 [3.10, 76.74] | 1995 |
| Holley, 1996 | 1.4604 | 1.1399 | 3.4% | 4.31 [0.46, 40.23] | 1996 |
| Miodovnik,1996 | 0.7244 | 0.6695 | 7.0% | 2.06 [0.56, 7.66] | 1996 |
| Fink, 1998 | 1.5781 | 0.2809 | 13.5% | 4.85 [2.79, 8.40] | 1998 |
| Ekbom, 2001 | 2.336 | 0.6764 | 7.0% | 10.34 [2.75, 38.93] | 2001 |
| Wiles, 2015 | 0.9297 | 0.4478 | 10.4% | 2.53 [1.05, 6.09] | 2015 |
| Wu, 2016 | 0.6286 | 0.4596 | 10.2% | 1.87 [0.76, 4.62] | 2016 |
| Tsuchiyama, 2017 | 0.8069 | 0.2851 | 13.4% | 2.24 [1.28, 3.92] | 2017 |
| Piccoli, 2017 | 0.3016 | 0.2991 | 13.1% | 1.35 [0.75, 2.43] | 2017 |
| Al Khalaf, 2021 | 0.3293 | 0.0421 | 16.6% | 1.39 [1.28, 1.51] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **2.69 [1.70, 4.24]** | |

Heterogeneity: Tau² = 0.33; Chi² = 41.54, df = 9 (P < 0.00001); I² = 78%
Test for overall effect: Z = 4.23 (P < 0.0001)




**D** **Small for gestational age** (adjusted estimates)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Fink, 1998 | 1.6677 | 0.3256 | 27.1% | 5.30 [2.80, 10.03] | 1998 |
| Kendrick, 2015 | 0.3148 | 0.1922 | 33.9% | 1.37 [0.94, 2.00] | 2015 |
| Al Khalaf, 2021 | 0.2546 | 0.0412 | 38.9% | 1.29 [1.19, 1.40] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **1.93 [1.06, 3.52]** | |

Heterogeneity: Tau² = 0.24; Chi² = 18.58, df = 2 (P < 0.0001); I² = 89%
Test for overall effect: Z = 2.15 (P = 0.03)

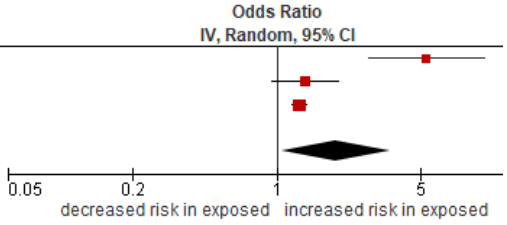



**Figure 4.3** Forest plots of studies of the association between chronic kidney disease and fetal/neonatal outcomes

# CHAPTER 5: Pregnancy Outcomes in Women with Chronic Kidney Disease and Chronic Hypertension: A National Cohort Study

**Sukainah Y. Al Khalaf**[1,2], Éilis J. O'Reilly[1,3], Fergus P. McCarthy[2,4], Marius Kublickas[5], Karolina Kublickiene[6], Ali S. Khashan[1, 2]

[1] *School of Public Health, University College Cork, Cork, Ireland*

[2] *INFANT Research Centre, University College Cork, Ireland*

[3] *Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

[4] *Department of Obstetrics and Gynaecology, Cork University Hospital, Cork, Ireland*

[5] *Department of Obstetrics and Gynaecology, Karolinska Institutet and Karolinska University hospital Stockholm, Sweden*

[6] *Renal Medicine, Department of Clinical intervention, Science and Technology (CLINTEC), Karolinska Institutet and Karolinska University hospital, Stockholm, Sweden*

**Published in:** *American Journal of Obstetrics and Gynecology*, September 2021

Doi:org/10.1016/j.ajog.2021.03.045

**(Paper 3)**

## 5.1 Abstract

***Background:*** Maternal chronic kidney disease (CKD) and chronic hypertension (CH) have been linked with adverse pregnancy outcomes. We aimed to examine the association between these conditions and adverse pregnancy outcomes over the last three decades.

***Objective:*** We conducted this national cohort study to assess the association between maternal chronic disease (CH, CKD or both conditions) and adverse pregnancy outcomes with an emphasis on the effect of parity, maternal age, and body mass index (BMI) on these associations over the last three decades. We further investigated whether different subtypes of CKD had differing effects.

***Methods:*** We used data from the Swedish Medical Birth Register (MBR), including 2,788,490 singleton births between 1982 and 2012. Women with CKD and/or CH were identified from the MBR and National Patient Register. Logistic regression models were performed to assess the associations between maternal chronic disease (CH, CKD, or both conditions) on pregnancy outcomes, including pre-eclampsia (PE), emergency and elective Caesarean sections (CS), preterm birth (PTB), small for gestational age (SGA) and stillbirth.

***Results:*** During the 30-year study period, 22,397 (0.8%) babies were born to women with CKD, 13,279 (0.48%) to women with CH and 1,079 (0.04%) to women with both conditions. Associations with CH were strongest for PE [adjusted odd ratio (aOR): 4.57, (95% confidence interval (CI), 4.33–4.84)], stillbirth [aOR: 1.65 (95% CI, 1.35–2.03)], and weakest for spontaneous PTB [aOR: 1.07, (95% CI, 0.96–1.20)]. The effect of CKD varied from [aOR: 2.05, (95% CI, 1.92–2.19)] for indicated PTB to no effect for stillbirth [aOR: 1.16, (95% CI, 0.95–1.43)] . Women with both conditions had the strongest associations for emergency CS [aOR: 1.86, (95% CI, 1.49–2.32)], elective CS [aOR: 2.68, (95% CI, 2.18–3.28)], indicated PTB [aOR: 9.09, (95% CI, 7.61–10.7)], and SGA [aOR: 4.52, (95% CI, 3.68–5.57)].

The results remained constant over the last three decades. Stratified analyses of the associations by parity, maternal age and BMI showed that adverse outcomes remained

independently higher in women with these conditions, with worse outcomes in multiparous women. All CKD subtypes were associated with higher odds of PE, emergency CS and medically indicated PTB. Different subtypes of CKD had differing risks, strongest associations of PE [aOR: 3.98, (95% CI, 2.98–5.31)] and stillbirth [aOR: 2.73, (95% CI, 1.13–6.59)] were observed in women with congenital kidney disease. Whereas women with diabetic nephropathy had the most pronounced increase odds of emergency CS [aOR: 3.54, (95% CI, 2.06–6.09)], elective CS [aOR: 7.50, (95% CI, 4.74–11.9)], and SGA [aOR: 4.50, (95% CI, 2.92–6.94)]. Additionally, Women with renovascular disease had the highest increased risk of preterm birth, both spontaneous PTB [aOR: 3.01, (95% CI, 1.57–5.76)] and indicated PTB [aOR: 8.09, (95% CI, 5.73–11.4)].

**Conclusion:** Women with CH, CKD or with both conditions are at increased risk of adverse pregnancy outcomes which were independent of maternal age, BMI, and parity. Multidisciplinary management should be provided with intensive clinical follow-up to support these women during pregnancy, particularly multiparous women. Further research is needed to evaluate the effect of disease severity on adverse pregnancy outcomes.

## 5.2 Introduction

Chronic kidney disease (CKD) affects up to 3% of pregnant women in developed countries (324). This estimated prevalence is expected to rise due to increasing maternal age and obesity rates. Previous reports from a meta-analysis (72, 73) and cohort studies (322, 325, 326) demonstrate that women with CKD have an increased risk of maternal and perinatal complications. A meta-analysis of 14 studies reported greater odds of pre-eclampsia (PE), caesarean section (CS), preterm birth (PTB), and small for gestational age (SGA)/ low birthweight in women with CKD than women without CKD (73). However, only four out of the 14 studies accounted for potential confounders such as maternal age and other comorbidities; and only six studies compared women with CKD with healthy pregnant women. The remaining eight studies enrolled patients with comorbidities of diabetes (diabetic nephropathy as an exposed group), which make it difficult to extend the results to the general population of women with other underlying causes of CKD. Moreover, most of the previous studies on CKD represent small, retrospective case series studies that were performed in a single centre and were of low methodological quality (72). Additionally, the effect size estimates of adverse outcomes vary between cohort studies (294, 301, 303), and this heterogeneity might be a result of lumping together different causes of CKD. However, limited studies have focused on pregnancy outcomes in women with specific subtypes of CKD.

Similarly, a substantial number of pregnancies (0.6-3%) are complicated by chronic hypertension (CH) (14, 16). Previous systematic review (42) and observational studies (14, 43-45, 204, 224, 230) have linked maternal CH with adverse perinatal outcomes. A recent UK cohort study reported an increased risk of PE, elective CS, indicated PTB, stillbirth and SGA in women with CH compared to normotensive women (14). Some adverse perinatal outcomes, such as fetal growth restriction and PTB, are the most important contributors to increased perinatal morbidity and mortality (327-329). However, inconsistency exists among studies that investigated the association between CH and the risk of emergency CS (14, 43) and spontaneous PTB (44, 45). Despite the reported associations between maternal CH and CKD on the risk of adverse pregnancy outcomes, it is not clear whether these outcomes have improved over the last decades. Piccoli *et al.* (2015), reported that CH affects 22–54% of pregnant women with CKD, depending on the severity of kidney disease (322). Although previous studies have

assessed the effect of maternal CH and CKD on adverse pregnancy outcomes, the evidence is limited on the combined effect of CKD and CH on adverse pregnancy outcomes and on the effect of CKD subtypes on adverse pregnancy outcomes. The role of maternal age, parity, and obesity in the associations between CKD and CH on adverse pregnancy outcomes is also unclear and requires further exploration in terms of potential confounding and effect modification. We conducted this national cohort study to assess the association between maternal chronic disease (CH, CKD or both conditions) and adverse perinatal outcomes with an emphasis on the effect of parity, maternal age, and BMI on these associations over the last three decades. We further investigated the associations among women with CKD subtypes.

## 5.3 Methods

### 5.3.1 Study design, data source and participants

This nationwide cohort study used data from the Swedish Medical Birth Registry (MBR), which contains prenatal and birth information for nearly all births (>99%) in Sweden since 1973 (102). Data were gathered prospectively from the first antenatal visit, including demographic information, reproductive history, pregnancy outcomes and complication during pregnancy, delivery and antenatal period. All disease and complications during pregnancy and/or delivery are classified according to the Swedish version of the International Classification of Diseases (ICD), using the eighth revision (ICD-8) until 1986, the ninth revision (ICD-9) from 1987 until 1996 and the tenth revision (ICD-10) since 1997.

The study cohort consisted of all registered births to women who had their first recorded delivery between January 1982 and December 2012. We excluded multiple births to improve internal comparability as multiple gestations have an increased risk of obstetric complications, including intrauterine growth restriction and preterm birth (330). We also excluded births before 1982 because data were poorly recorded, such as lack of information on maternal smoking and BMI, and to be able to adjust for maternal reproductive history (e.g. parity). We also used hospitalization data from the Swedish National Patient Register (NPR), that included inpatient data from 1964 and outpatient data from 2000 onwards, to identify women with CH or CKD (109). Data from MBR and NPR registers were linked using the anonymized unique national identification number. Ethical approval was obtained from the Swedish Ethical Review

Authority in Stockholm in, Sweden (Regionala Etikprovningsnamnden Stockholm) and the Social Research and Ethics Committee, University College Cork (#2019-214).

### 5.3.2 Exposures

Data on diagnoses of CH and CKD were obtained from the MBR and NPR using ICD codes. Similarly, we further identified the following CKD subtypes diagnoses tubulointerstitial, glomerular/proteinuric, diabetic nephropathy, renovascular disease, congenital/malformation kidney disease (women with Congenital Abnormalities of the Kidney and Urinary Tract (CAKUT)) and unspecified CKD using ICD codes from MBR and NPR (**Appendix 5, Table S5.1**).

### 5.3.3 Outcome measures

Pre-eclampsia was defined as at least two diastolic blood pressure measurements of ≥90 mmHg, combined with proteinuria (≥0.3 g/day or ≥1+ on a urine dipstick), and this was obtained from primary and secondary maternal diagnoses in the MBR using ICD-codes. Elective and emergency CS were defined as pre-labor and in-labor CS, respectively.

Preterm birth was categorized as spontaneous PTB (<37 weeks' gestation) and medically indicated PTB (<37 weeks' gestation). We further classified PTB into extreme preterm (<28 weeks), severe preterm (28-31 weeks), moderated preterm (32-33 weeks), and near term (34-36 weeks) delivery (136). Stillbirth (antepartum and intrapartum fetal death) was defined as fetal loss after 28 completed weeks (until June 2008), but that was changed to fetal loss after 22 completed weeks since July 2008 (137). SGA was defined as a birthweight below two standard deviations of the mean birthweight of the sex-specific and gestational age distributions.

### 5.3.4 Potential confounders

The following potential confounders were considered in the analysis: maternal age, smoking, BMI, parity, country of origin, asthma, diabetes, cardiovascular disease, and highest education level.

### 5.3.5 Statistical analysis

Data on the maternal and fetal characteristics are presented according to CH and CKD status using frequency and percentages for categorical variables and mean with standard deviation (SD) for continuous variables. Crude and adjusted logistic

regression models were performed to calculate the odds ratios (OR) with 95% confidence intervals (CIs) for the association between maternal CKD and CH and each of the adverse pregnancy outcomes.

The exposure variable was represented in the models as a four-category variable: (1) normotensive women without CKD (reference group); (2) women with CH; (3) women with CKD; and (4) women with CH and CKD. We performed a separate analysis to investigate the effect of different subtypes of CKD on adverse pregnancy outcomes with the same reference group. In this analysis, separate categories were created for women with CH and for those without information on specific subtypes CKD.

The potential confounders were included in the models as categorical variables as presented in **Table 5.1**, in addition to offspring year of birth. Where there were missing data on smoking during pregnancy and maternal BMI, we added a missing data category in the variable. All analyses of PTB were compared to term babies. For elective and emergency CS, we analyzed each outcome separately compared to spontaneous birth.

We conducted stratified analyses to investigate the associations over five-year periods from 1982 to 2012 to assess whether the associations changed over time (for sensitivity and subgroup analyses, see **Appendix 5**). All analyses were performed using Stata/MP 16.1, and a p-value <0.05 was considered to be statistically significant.

## 5.4 Results

This study consisted of 2,788,490 singleton births from 1,420,846 women born between 1982–2012 (972,136 women had more than one birth during the study period); the flow diagram of participants is shown in **Appendix 5** (**Figure S5.1**). During the study period, 22,397 (0.80%) babies were born to women with CKD; 13,279 (0.48%) were born to women with CH and 1,079 (0.04%) babies were born to women with both conditions (CKD and CH). The prevalence of pregnant women with CH and CKD have increased over the last three decades (**Appendix 5**, **Figure S5.2**).

The socio-demographic characteristics of the women are presented in **Table 5.1**. Women with CKD, CH or with both conditions were older on average and had higher BMI and were more likely to have diabetes, cardiovascular disease and asthma, with the highest percentage of comorbidities among women with both conditions. Women with CKD were more likely to be smokers (20%), whereas similar percentages of non-

smokers were found for women with CH and those with a combination of both conditions (84% and 81%, respectively).

***Adverse perinatal outcomes among women with CH, CKD, or with both conditions***

Table 5.2 shows the ORs for perinatal outcomes. After controlling for confounding factors, CH, CKD, or both conditions remained significantly associated with adverse perinatal outcomes. Women with CH had higher odds of PE [4.57, (95% CI, 4.85–6.46)], emergency CS [1.70, (95% CI, 1.60–1.80)], elective CS [1.73, (95% CI, 1.62–1.84)], indicated PTB [aOR: 3.90, (95% CI, 3.66–4.15)]. However, no association was found between maternal CH and spontaneous PTB [aOR: 1.07, (95% CI, 0.96, 1.20). When we further explored the impact of CH on different categories of PTB, extreme, severe, and moderate PTB were also considerably higher among women with CH compared to normotensive women. Stillbirth and SGA were associated with CH [aOR: 1.65, (95% CI,1.35–2.03), aOR: 3.55, (95% CI, 3.31–3.80) respectively].

Women with CKD in pregnancy had higher odds of PE [aOR: 1.61 (95% CI, 1.51–1.73)], emergency CS [aOR: 1.36, (95% CI, 1.29–1.43)] and elective CS [aOR: 1.60, (95% CI, 1.52–1.69)], compared to normotensive women without CKD. Maternal CKD was associated with both spontaneous PTB [aOR: 1.24, (95% CI, 1.15–1.33)] and indicated PTB [aOR: 2.05, (95% CI, 1.92–2.19)]. Additionally, mothers with CKD had almost double the odds of extreme, severe, and moderate preterm delivery compared to normotensive women (**Table 5.2**). Maternal CKD was also associated with higher odds of SGA [aOR: 1.29 (95% CI, 1.19–1.39)]. However, the association with stillbirth did not reach a significant level in the adjusted model [aOR: 1.16, (95% CI, 0.95–1.43)].

Stronger associations were found in women with both conditions (**Table 5.2**). Women with both conditions (CH and CKD) had approximately a four-fold increased odds of PE [aOR: 4.16 (95% CI, 3.40–5.09)] compared to normotensive women without CKD. Similarly, women with both conditions had higher odds of emergency and elective CS [aOR: 1.86 (1.49–2.32), aOR: 2.68 (2.18–3.28), respectively], medically indicated PTB [aOR: 9.09, (95% CI, 7.61–10.7)], and extreme PTB (<28 wk.), [aOR: 14.7, (95% CI, 10.1–21.3)]. The adjusted estimates for severe and moderate PTB were also significantly higher among women with both conditions than other groups (**Table 5.2**). Mothers with both conditions were more likely to have SGA babies [aOR: 4.52, (95%

CI, 3.68–5.57)]. Nevertheless, no effect was found for both conditions on spontaneous PTB and stillbirth. Additionally, the strength of associations between both conditions and adverse pregnancy outcomes were attenuated after adjusting for diabetes, and that might reflect the high percentage of diabetes among these women (26%).

***Adverse maternal and perinatal outcomes among women with subtypes CKD***

Table 5.3 shows the incidence and the associations between CKD subtypes and adverse perinatal outcomes. All CKD subtypes were associated with higher odds of PE, emergency CS and medically indicated PTB. Women with diabetic nephropathy had noticeable higher odds for adverse outcomes. However, after adjusting for potential confounders, women with diabetic nephropathy had the strongest associations for emergency CS [aOR: 3.54 (95% CI, 2.06–6.09)], elective CS [aOR: 7.50, (95% CI, 4.74–11.9)], and SGA [aOR: 4.50, (95% CI, 2.92–6.94)]. While women with congenital kidney disease had the most pronounced increase odds of PE [aOR: 3.98, (95% CI, 2.98–5.31)] and stillbirth [aOR: 2.73, (95% CI, 1.13–6.59)]. The associations of preterm birth were stronger in women with renovascular disease [spontaneous PTB, aOR: 3.01. (95% CI, 1.57–5.76), and indicated PTB, aOR: 8.09, (95% CI, 5.73–11.4)].

***Adverse perinatal outcomes among women with CH, CKD or with both conditions over the last three decades***

When we assessed the association between maternal CH, CKD, and a combination of both conditions over five-year periods, there were no clear patterns of these associations over time (**Figure 5.1** & **Appendix 5**, **Table S5.2**). However, a noticeable reduction in the odds of elective CS and PTB were observed in the last five year (2007–2012) in women with CH, CKD and in those with both conditions. The results of the subgroup and sensitivity analyses are presented in **Appendix 5** (**Tables S5.3-S5.6**).

## 5.5 Discussion

This large cohort study demonstrated that maternal and fetal complications remain high in women with CKD, CH or with both conditions, and these higher risks persisted independently of parity, maternal age, and BMI. Multiparous women with these conditions had worse outcomes than nulliparous women. This study adds significantly to the literature as we used a large cohort, which allowed us to undertake further analyses and investigate the effect of different subtypes of CKD. Our findings suggest that the risk of adverse pregnancy outcomes were higher in women with diabetic

nephropathy, renovascular disease and in those with congenital kidney disease than other CKD subtypes.

Our findings on the association between maternal CH and adverse perinatal outcomes are consistent with previous population-based studies on PE (12, 14, 201, 211), stillbirth (13, 14, 253), medically indicated PTB (14, 44, 218, 231), and SGA (14, 51, 235). However, two studies reported adjusted results for elective CS; a recent UK cohort study suggested an association (14), whereas a Netherlands study did not find an association between CH and elective CS (12). Interestingly, we found a lack of relationship between CH and spontaneous PTB, and this was consistent with the findings from two previous cohort studies (14, 44). Few previous reports evaluated the effects of maternal age and other characteristics on the associations between CH and adverse pregnancy outcomes. A Canadian cohort study, including 134,088 women, reported higher prevalence of CS (without specifying its type) among older women with CH (258), and that similar to our results for elective and emergency CS.

We have conducted the largest study of pregnancy outcomes in women with CKD from the last three decades. In consistent with our findings, previous studies have reported an association between CKD and adverse pregnancy outcomes (72, 73). Moreover, in our study, the adjusted odds of PE in patients with CKD was 1.61, which is lower than the reported pooled estimate in a meta-analysis of nine studies on PE (OR=10.36) (73). However, only three out of the nine studies adjusted for confounding variables (294, 301, 303), whereas six of these studies included patients with diabetic nephropathy. Our results of PE in women with diabetic nephropathy were similar with an odds ratio of 8.45, but that decreased to 2.17 after adjustment for confounders. Although pregnancy complications were higher in women with CKD, the live birth rate was high as we found a non-significant relationship between maternal CKD and stillbirth. Previous US study, including 502,186 singleton births, reported higher rate of stillbirth in women with CKD (6.4%) versus those without (0.3%) (326), but they did not report adjusted estimate. The result from a meta-analysis suggested an association between pregnancy failure with maternal CKD; however, the outcome was a composite of stillbirth, fetal death, and neonatal death together (73). None of the previous studies on CKD have evaluated the effect of maternal socio-demographic factors on adverse perinatal outcomes.

There is also limited research on the risk of adverse pregnancy outcomes among women with specific kidney disease. Our study is the first to demonstrate the adverse pregnancy outcomes in women with congenital kidney disease. A previous case series of 37 pregnancies in 20 patients, evaluating the effect of congenital urinary tract abnormality and reconstruction on pregnancy, reported a higher rate of PE and CS than the general obstetric population, whereas no adverse infants outcomes were reported (331). A recent retrospective cohort study by Li et al. (2018), in pregnancies with chronic glomerulonephritis, reported higher rates of premature delivery, low birth weights, and intrauterine growth restriction compared to pregnancy without CKD (332). Although our results in women with glomerular CKD are similar to this study, adjusted estimates were not reported, and it used data from a single centre with a small sample size (N=114).

Women with CH, CKD or with both conditions should be monitored carefully during pregnancy and delivery, specifically multiparous women and women with diabetic nephropathy, congenital kidney disease or renovascular disease. Multidisciplinary antenatal management, including nephrologists and obstetricians, should be provided with intensive clinical follow-up to support women with CKD during pregnancy and importantly in the postnatal period. Although Kidney Disease Outcomes Quality Initiative and National Institute of Health and Care Excellence (NICE) have not provided specific guidance on the management of kidney disease during pregnancy, the available guidance recommended that women with CKD should be offered preconception counselling by a multidisciplinary team and blood pressure should be optimized before pregnancy (67, 333). Additionally, a blood pressure goal of less than 140/90 mmHg has been recommended with close surveillance during pregnancy for women with CKD (67, 333). Similarly, the available guidance from NICE and The American College of Obstetricians & Gynecologists (ACOG) recommend that women with CH should be assessed before conception and monitored closely for the potential development of adverse complications during pregnancy (33, 38).

Future research should consider severity of maternal disease (CH and CKD) when assessing the association with adverse perinatal outcomes. Moreover, more population-based studies are needed to evaluate the impact of specific kidney disease on adverse

perinatal outcomes as well as therapeutic interventions to improve maternal and fetal outcomes.

**Strengths and limitations**

Our study has several strengths. First, unlike most of the previous studies focusing on the effects of CH or CKD, we performed three groups based on the existence of each chronic condition alone or a combination of both. Second, we used data from MBR which contains data on approximately all births in Sweden, and that increases the generalizability of our findings and eliminate selection bias. Third, prospective collection of data from MBR on maternal and fetal characteristics. Forth, detailed information on maternal characteristics and a wide range of well-defined adverse pregnancy outcomes enabled us to control for risk factors associated with adverse perinatal outcomes. Fifth, we used data over 30 years, and that allowed us to assess the associations over time. Sixth, the large number of participants allowed us to stratify the associations by maternal characteristics.

This study has some limitations need to be addressed. The observational nature of our study introduces a potential issue of residual confounder. However, we adjusted for a vast number of important confounders. We also conducted stratified analyses according to maternal characteristics (maternal age, BMI, and parity) to further understand their effects on the associations. Other limitations refer to missing values for smoking during pregnancy, and BMI of the study cohort. However, as mentioned in the method section, an indicator category was created for missing values to adjust for this issue in the analysis phase. In the current study, we did not evaluate the effect of disease severity on adverse outcome, but these is beyond the scope of this investigation.

## 5.6 Conclusions

Our findings showed that adverse pregnancy outcomes increase in women with CH, CKD or with both conditions and that was independent of maternal age, BMI, and parity. Multiparous women with these conditions had worse adverse perinatal outcomes. Women with these conditions should be monitored carefully during pregnancy and delivery. Larger prospective studies are needed to assess the effect of disease severity and specific kidney disease on adverse pregnancy outcomes.

**Table 5.1** Maternal characteristics in the Swedish Medical Birth Registry 1982– 2012 (including singleton pregnancies 1982-2012**,** N= 2,788,490)

| | **Normotensive N= 2,751,735*** | **Chronic hypertension (CH) N=13,279** | **Chronic kidney disease (CKD) N= 22,397** | **Women with CH & CKD N=1,079** |
|---|---|---|---|---|
| **Maternal age** | n (%) | n (%) | n (%) | n (%) |
| <20 | 70,097 (2.6) | 60 (0.5) | 586 (2.6) | 24 (2.2) |
| 20-24 | 523,437 (19) | 1,134 (8.5) | 4,106 (18) | 149 (14) |
| 25-29 | 954,962 (35) | 3,323 (25) | 7,173 (32) | 277 (26) |
| 30-34 | 807,727 (29) | 4,508 (34) | 6,651 (30) | 318 (29) |
| 35-39 | 334,592 (12) | 3,189 (24) | 3,213 (14) | 254 (23.5) |
| ≥40 | 60,920 (2.2) | 1,065 (8.0) | 668 (3) | 57 (5.3) |
| ***Mean (SD)*** | 28.8 (5.2) | 31.8 (5.3) | 29.2 (5.4) | 30.7 (5.7) |
| **Smoking** | | | | |
| No | 2,185,536 (79) | 11,225 (84) | 16,779 (75) | 876 (81) |
| 1-9 cigarettes/day | 261,543 (9.5) | 950 (7.2) | 2,851 (12.7) | 114 (11) |
| ≥10 cigarettes/day | 131,733 (4.8) | 521 (3.9) | 1,636 (7.3) | 41 (3.8) |
| Missing | 172,923 (6.3) | 583 (4.4) | 1,131 (5.1) | 48 (4.6) |
| **Body mass index, kg/m$^2$**[a] | | | | |
| Underweight | 78,868 (2.9) | 137 (1.0) | 703 (3.1) | 26 (2.4) |
| Normal | 1,403,343 (51) | 4,380 (33) | 11,322 (51) | 466 (43) |
| Overweight | 459,262 (17) | 3,210 (24) | 4,198 (19) | 216 (20) |
| Obese | 182,752 (6.6) | 2,889 (22) | 1,919 (8.6) | 166 (15) |
| Missing | 627,510 (23) | 2,663 (20) | 4,255 (19) | 205 (19) |
| **Parity** | | | | |
| 1 | 1,306,244 (47) | 5,429 (41) | 9,789 (44) | 510 (47) |
| 2 | 986,445 (36) | 4,836 (36) | 7,901 (35) | 384 (36) |
| 3 or more | 459,046 (17) | 3,014 (23) | 4,707 (21) | 185 (17) |
| **Country of Origin** | | | | |
| Sweden | 2,267,401 (83) | 11,412 (86) | 18,401 (82) | 890 (83) |
| Other Scandinavian | 79,440 (2.9) | 537 (4) | 521 (2.3) | 31 (2.9) |
| Elsewhere | 392,907 (14) | 1,306 (9.8) | 3,405 (15) | 154 (14) |
| Missing | 11,987 (0.4) | 24 (0.2) | 70 (0.3) | 4 (0.4) |
| **DM** | 17,475 (0.64) | 720 (5.5) | 541 (2.4) | 280 (26) |
| **CVD** | 3,059 (0.11) | 98 (0.74) | 71 (0.32) | 22 (2.04) |
| **Asthma** | 124,003 (4.5) | 1,007 (7.6) | 1,853 (8.3) | 186 (17) |

DM, diabetes mellitus; CVD, cardiovascular disease. *Normotensive women refer to women without hypertension and chronic kidney disease. [a] Underweight (BMI<18.5 kg/m$^2$); Normal (BMI≥18.5 to <25 kg/m$^2$); Overweight (BMI ≥25 to <30 kg/m$^2$); and Obese (BMI ≥30 kg/m$^2$)

**Table 5. 2** The association between maternal chronic diseases and perinatal outcomes (singleton pregnancies 1982–2012)

| Outcome | Pregnancies of normotensive women N= 2,751,735 | Chronic hypertension (CH) N=13,279 | Chronic kidney disease (CKD) N= 22,397 | CH & CKD N=1,079 |
|---|---|---|---|---|
| **Pre-eclampsia, n (%)** | 75,931 (2.76) | 1,938 (14.6) | 979 (4.37) | 175 (16.2) |
| Crude OR (95% CI)* | Reference | 6.15 (5.85, 6.46) | 1.64 (1.53, 1.76) | 7.01 (5.93, 8.29) |
| Adjusted OR (95% CI)[a] | Reference | 4.57 (4.33, 4.84) | 1.61 (1.51, 1.73) | 4.16 (3.40, 5.09) |
| **Emergency CS, n (%)** | 176,081 (7.89) | 1,706 (17.8) | 1,919 (11.3) | 179 (24.6) |
| Crude OR (95% CI)* | Reference | 2.30 (2.18, 2.43) | 1.37 (1.30, 1.44) | 3.27 (2.73, 3.91) |
| Adjusted OR (95% CI)[b] | Reference | 1.70 (1.60, 1.80) | 1.36 (1.29, 1.43) | 1.86 (1.49, 2.32) |
| **Elective CS, n (%)** | 149,199 (6.77) | 1,559 (16.6) | 1,978 (11.7) | 213 (27.9) |
| Crude OR (95% CI)* | Reference | 2.73 (2.58, 2.89) | 1.82 (1.72, 1.92) | 5.36 (4.53, 6.33) |
| Adjusted OR (95% CI)[b] | Reference | 1.73 (1.62, 1.84) | 1.60 (1.52, 1.69) | 2.68 (2.18, 3.28) |
| **Spontaneous PTB (<37wk.), n (%)** | 67,792 (2.53) | 369 (3.10) | 749 (3.52) | 40 (4.94) |
| Crude OR (95% CI)* | Reference | 1.12 (1.00, 1.24) | 1.29 (1.20, 1.40) | 1.73 (1.23, 2.43) |
| Adjusted OR (95% CI)[b] | Reference | 1.07 (0.96, 1.20) | 1.24 (1.15, 1.33) | 1.18 (0.83, 1.69) |
| **Medically indicated PTB(<37wk.), n (%)** | 72,935 (2.72) | 1,362 (10.6) | 1,146 (5.29) | 269 (25.9) |
| Crude OR (95% CI)* | Reference | 4.89 (4.60, 5.20) | 2.27 (2.13, 2.42) | 15.6 (13.4, 18.3) |

| | | | | |
|---|---|---|---|---|
| Adjusted OR (95% CI)[b] | Reference | 3.90 (3.66, 4.15) | 2.05 (1.92, 2.19) | 9.09 (7.61, 10.7) |
| **Extreme preterm (<28 wk.), n (%)** | 6,091 (0.23) | 119 (1.02) | 114 (0.55) | 33 (4.11) |
| Adjusted OR (95% CI)[b] | Reference | 3.72 (3.08, 4.49) | 2.16 (1.77, 2.764 | 14.7 (10.1, 21.3) |
| **Severe preterm (28-31 wk.), n (%)** | 13,749 (0.52) | 301 (2.54) | 207 (1.0) | 50 (6.10) |
| Adjusted OR (95% CI)[b] | Reference | 4.22 (3.74, 4.77) | 1.82 (1.59, 2.09) | 8.50 (6.20, 11.6) |
| **Moderated preterm (32-33 wk.), n(%)** | 16,955 (0.65) | 280 (2.37) | 256 (1.23) | 54 (6.55) |
| Adjusted OR (95% CI)[b] | Reference | 3.28 (2.89, 3.72) | 1.81 (1.59, 2.06) | 6.44 (4.72, 8.79) |
| **Near term (34-36 wk.), n (%)** | 103,932 (3.83) | 1,031 (8.2) | 1,318 (6.04) | 172 (18.3) |
| Adjusted OR (95% CI)[b] | Reference | 1.99 (1.86, 2.12) | 1.54 (1.45, 1.63) | 3.43 (2.84, 4.14) |
| **Stillbirth, n (%)** | 9,135 (0.33) | 98 (0.74) | 94 (0.42) | 7 (0.65) |
| Crude OR (95% CI)[*] | Reference | 2.23 (1.83, 2.73) | 1.27 (1.03, 155) | 1.96 (0.93, 4,12) |
| Adjusted OR (95% CI)[b] | Reference | 1.65 (1.35, 2.03) | 1.16 (0.95, 1.43) | 1.15 (0.55, 2.41) |
| **Small for gestational age, n (%)** | 70,202 (2.55) | 1,047 (7.88) | 755 (3.37) | 111 (10.3) |
| Crude OR (95% CI)[*] | Reference | 3.42 (3.20, 3.65) | 1.39 (1.28, 1.50) | 4.65 (3.81, 5.67) |
| Adjusted OR (95% CI)[b] | Reference | 3.55 (3.31, 3.80) | 1.29 (1.19, 1.39) | 4.52 (3.68, 5.57) |

CH, chronic hypertension; CKD, chronic kidney disease; CS, Caesarean section.*All crude and adjusted estimates cluster on mothers' id and adjusted for year of birth; [a] adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes, cardiovascular disease, asthma), birth year and child's gender; [b] adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes, cardiovascular disease, asthma) and birth year

**Table 5.3** The association between subtypes chronic kidney disease and perinatal outcomes (singleton pregnancies 1982–2012)

| Exposure \ Outcome | Pre-eclampsia | | |
|---|---|---|---|
| | Cases, n (%) | Crude OR (95% CI)* | Adjusted OR (95% CI)[a] |
| Normotensive without CKD (n= 2,751,735) | 75,931 (2.8) | Reference | Reference |
| Tubulointerstitial (n=1,784) | 73 (4.1) | 1.63 (1.27, 2.10) | 1.55 (1.20, 2.03) |
| Glomerular (n= 4,367) | 247 (5.7) | 2.18 (1.89, 2.52) | 2.13 (1.84, 2.47) |
| Diabetic nephropathy (n=266) | 52 (20) | 8.45 (6.12, 11.7) | 2.17 (1.54, 3.04) |
| Renovascular disease (n=220) | 25 (11) | 4.33 (2.74, 6.85) | 3.64 (2.18, 6.09) |
| CAKUT (n=534) | 58 (11) | 4.34 (3.29, 5.72) | 3.98 (2.98, 5.31) |
| Other/unspecified CKD (n=6,431) | 277 (4.3) | 1.59 (1.40, 1.82) | 1.59 (1.39, 1.81) |
| | **Emergency Cesarean section** | | |
| | Cases, n (%) | Crude OR (95% CI)* | Adjusted OR (95% CI)[b] |
| Normotensive without CKD (n= 2,231,697) | 176,081 (7.9) | Reference | Reference |
| Tubulointerstitial (n=1,435) | 193 (13) | 1.23 (1.04, 1.45) | 1.29 (1.09, 1.53) |
| Glomerular (n= 3,349) | 432 (13) | 1.48 (1.32, 1.66) | 1.43 (1.27, 1.61) |
| Diabetic nephropathy (n=109) | 62 (57) | 15.4 (9.57, 24.7) | 3.54 (2.06, 6.09) |
| Renovascular (n=161) | 27 (17) | 3.10 (2.08, 4.64) | 2.73 (1.78, 4.18) |
| CAKUT (n=355) | 55 (16) | 1.99 (1.45, 2.72) | 1.99 (1.44, 2.75) |
| Other/unspecified CKD (n=5,045) | 540 (11) | 1.35 (1.23, 1.49) | 1.40 (1.27, 1.55) |
| | **Elective Cesarean section** | | |
| | Cases, n (%) | Crude OR (95% CI)* | Adjusted OR (95% CI)[b] |
| Normotensive without CKD (n= 2,204,815) | 149,199 (6.8) | Reference | Reference |

| | | | |
|---|---|---|---|
| Tubulointerstitial (n=1,372) | 130 (9.5) | 1.44 (1.18, 1.76) | 1.15 (0.94, 1.42) |
| Glomerular (n= 3,356) | 439 (13) | 2.07 (1.84, 2.33) | 1.68 (1.48, 1.90) |
| Diabetic nephropathy (n=152) | 105 (69) | 30.8 (20.6, 45.8) | 7.50 (4.74, 11.9) |
| Renovascular disease (n=169) | 35 (21) | 3.60 (2.45, 5.30) | 4.02 (2.66, 6.08) |
| CAKUT (n=386) | 86 (22) | 3.95 (3.05, 5.11) | 4.19 (3.19, 5.49) |
| Other/unspecified CKD (n=5,058) | 553 (11) | 1.69 (1.52, 1.88) | 1.55 (1.39, 1.72) |
| | **Spontaneous preterm birth (<37 wk.)** | | |
| | Cases, n (%) | Crude OR (95% CI)* | Adjusted OR (95% CI)[a] |
| Normotensive without CKD (n= 2,678,800) | 67,792 (2.5) | Reference | Reference |
| Tubulointerstitial (n=1,705) | 55 (3.2) | 0.89 (0.67, 1.18) | 0.82 (0.62, 1.09) |
| Glomerular (n= 4,063) | 196 (4.8) | 1.71 (1.46, 2.01) | 1.60 (1.37, 1.89) |
| Diabetic nephropathy (n=142) | 8 (5.6) | 2.22 (1.08, 4.57) | 0.90 (0.43, 1.89) |
| Renovascular disease (n=165) | 10 (6.1) | 3.25 (1.69, 6.23) | 3.01 (1.57, 5.76) |
| CAKUT (n=483) | 19 (3.9) | 1.45 (0.90 2.36) | 1.33 (0.82, 2.16) |
| Other/unspecified CKD (n=6,024) | 174 (2.9) | 1.11 (0.95, 1.30) | 1.08 (0.93, 1.27) |
| | **medically indicated preterm birth** | | |
| | Cases, n (%) | Crude OR (95% CI)* | Adjusted OR (95% CI) [b] |
| Normotensive without CKD (n= 2,683,943) | 72,935 (2.7) | Reference | Reference |
| Tubulointerstitial (n=1,729) | 79 (4.6) | 3.11 (2.43, 3.97) | 2.74 (2.15, 3.50) |
| Glomerular (n= 4,171) | 304 (7.3) | 3.62 (3.17, 4.12) | 3.10 (2.71, 3.53) |
| Diabetic nephropathy (n=258) | 124 (48) | 32.9 (25.1, 43.1) | 6.52 (4.94, 8.6) |
| Renovascular disease (n=210) | 55 (26) | 9.94 (7.05, 14.0) | 8.09 (5.73, 11.4) |

| | | | |
|---|---|---|---|
| CAKUT (n=515) | 51 (10) | 4.11 (3.02, 5.60) | 3.73 (2.72, 5.11) |
| Other/unspecified CKD (n=6,257) | 407 (6.5) | 2.57 (2.29, 2.87) | 2.38 (2.13, 2.67) |
| | **Stillbirth** | | |
| | Cases, n (%) | Crude OR (95% CI)* | Adjusted OR (95% CI)[b] |
| Normotensive without CKD (n= 2,751,735) | 9,135 (0.33) | Reference | Reference |
| Tubulointerstitial (n=1,784) | 8 (0.45) | 1.36 (0.68, 2.71) | 1.28 (0.64, 2.56) |
| Glomerular (n= 4,367) | 19 (0.44) | 1.31 (0.82, 2.11) | 1.12 (0.70, 1.79) |
| Diabetic nephropathy (n=266) | 5 (1.88) | 5.75 (2.40, 13.8) | 1.55 (0.64, 3.76) |
| Renovascular disease (n=220) | 2 (0.91) | - | - |
| CAKUT (n=534) | 5 (0.94) | 2.84 (1.18, 6.82) | 2.73 (1.13, 6.59) |
| Other/unspecified CKD (n=6,431) | 18 (0.28) | 0.84 (0.53, 1.34) | 0.80 (0.50, 1.26) |
| | **Small for gestational age** | | |
| | Cases, n (%) | Crude OR (95% CI)* | Adjusted OR (95% CI)[b] |
| Normotensive without CKD (n= 2,751,735) | 70,202 (2.6) | Reference | Reference |
| Tubulointerstitial (n=1,784) | 54 (3.0) | 1.43 (1.09, 1.87) | 1.25 (0.94, 1.65) |
| Glomerular (n= 4,367) | 184 (4.2) | 1.81 (1.54, 2.12) | 1.54 (1.31, 1.81) |
| Diabetic nephropathy (n=266) | 26 (9.8) | 4.01 (2.65, 6.08) | 4.50 (2.92, 6.94) |
| Renovascular disease (n=220) | 24 (11) | 4.28 (2.77, 6.60) | 3.28 (2.06, 5.20) |
| CAKUT (n=534) | 35 (6.6) | 2.73 (1.89, 3.95) | 2.45 (1.66, 3.60) |
| Other/unspecified CKD (n=6,431) | 223 (3.5) | 1.39 (1.20, 1.60) | 1.35 (1.17, 1.56) |

CAKUT, Congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease. * All crude estimates cluster on mothers' id and adjusted for year of birth; [a] adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes, cardiovascular disease, asthma), birth year and child's gender; [b] adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes, cardiovascular disease, asthma) and birth year.

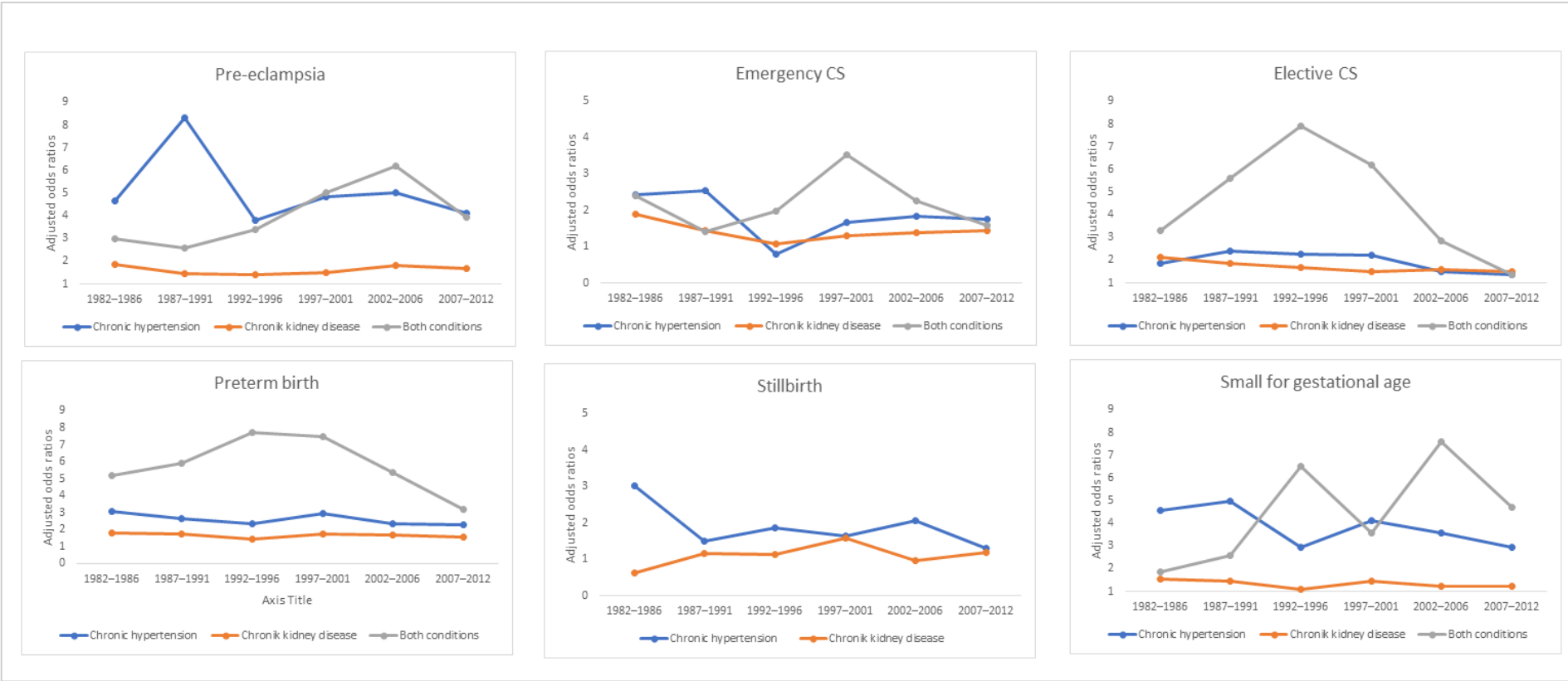



**Figure 5.1** Adjusted estimates of the associations between maternal chronic disease and adverse pregnancy outcomes over time (1982-2012)

University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Al Khalaf, S. 2022. The impact of maternal chronic hypertension and chronic kidney disease on the risk of adverse pregnancy outcomes and long-term cardiovascular disease: a population-based epidemiology study. PhD Thesis, University College Cork.

Please note that Chapters 6 & 7 (pp. 146-195) are unavailable due to a request by the author.

**CORA Cork Open Research Archive http://cora.ucc.ie**

# CHAPTER 8: Discussion and Conclusions

## 8.1 Chapter overview

The overall aim of this thesis was to examine the impact of maternal chronic hypertension and/or CKD on the risk of adverse pregnancy outcomes and long-term CVD. In particular, this work includes three systematic reviews (two papers) of the current published literature and two original studies on the impact of CKD, chronic hypertension, antihypertensive treatment on adverse pregnancy outcomes. Also, this thesis contains an original study on the associations between pre-pregnancy hypertension and future CVD. In this chapter, the main findings of this thesis are summarised, and the overall strengths and limitations, as well as the implications for clinical practice, are discussed with recommendations for future research, and overall conclusions.

## 8.2 Summary of main findings

### 8.2.1 Findings from the systematic reviews and meta-analyses

#### *8.2.1.1 Systematic review and meta-analyses of chronic hypertension and antihypertensive treatment on adverse pregnancy outcomes*

Two systematic reviews and meta-analyses were conducted separately to synthesise the available published literature on the impact of (1) chronic hypertension, and (2) antihypertensive treatment on adverse pregnancy outcomes (Chapter 3). Both reviews were based on a registered protocol (**Appendix 1**). Comprehensive searches were conducted, and studies published until January 2019 were included for the effect of chronic hypertension, and until May 2019 for the effect of antihypertensive treatment.

The systematic review on chronic hypertension and adverse pregnancy outcomes included a total of 81 studies that had reported associations between chronic hypertension and a range of adverse pregnancy outcomes. The pooled adjusted estimates suggested that women with chronic hypertension during pregnancy had a higher odds of adverse pregnancy outcomes. The adjusted pooled estimates showed a 5-fold higher odds of pre-eclampsia and approximately a 2-fold higher odds of stillbirth, preterm birth, and SGA infants in women with chronic hypertension compared to those without chronic hypertension.

The second systematic review focused on the effect of antihypertensive treatment on adverse pregnancy outcomes and included a total of 16 studies. Six studies compared

the adverse pregnancy outcomes in treated women with chronic hypertension to untreated normotensive women, whereas eight studies compared the outcomes in treated women with chronic hypertension to untreated women with chronic hypertension. The results suggested an association between treated chronic hypertension (compared to untreated normotensive women) and pre-eclampsia [aOR: 6.57, (95% CI, 1.75–24.7)]; preterm birth [aOR: 2.78, (95% CI, 1.80–4.29)]; SGA [aOR: 2.21, (95% CI, 1.18–4.15)]; LBW [aOR: 3.45, (95% CI, 2.26–5.26)]; and perinatal death [aOR: 1.80, (95% CI, 1.07–3.01)]. However, results were inconsistent when outcomes were compared between treated and untreated women with chronic hypertension; the pooled estimates were not different for these groups in relation to superimposed pre-eclampsia [aOR: 0.92, (95% CI, 0.27–3.11)], preterm birth [aOR: 1.88, (95% CI, 0.61–5.74)] or other adverse outcomes, except for a higher odds of SGA [aOR: 1.86, (95% CI, 1.38–2.50)].

Few studies reported associations by antihypertensive agent. For example, compared to untreated chronic hypertension, those treated with β-blockers only, had higher odds of preterm birth [aOR: 2.74, (95% CI, 1.40–5.36); 2 studies] and SGA [aOR: 1.84, (95% CI, 1.20–2.82; 3 studies)]. Women exposed to centrally acting antiadrenergic agent only (versus untreated hypertensive women) also had a higher odds of SGA [aOR: 1.62, (95% CI, 1.09–2.42)].

Overall, there was a scarcity of evidence from observational studies investigating the impact of antihypertensive treatment on adverse perinatal outcomes in women with chronic hypertension. In particular, the effect of different antihypertensive agents remains poorly understood. Therefore, more robust and large-scale studies were needed to address some of the literature gaps and draw more definitive conclusions on the impact of chronic hypertension and antihypertensive treatment on adverse perinatal outcomes.

#### *8.2.1.2 Systematic review and meta-analyses of CKD and adverse pregnancy outcomes*

A third systematic review and meta-analysis was conducted to summarise the published literature on the associations between CKD, its specific causes, and the risk of adverse pregnancy outcomes (Chapter 4). In addition, we synthesised the evidence that compared pregnancy outcomes between women with early and late stages of

CKD. The systematic review was based on a registered protocol (**Appendix 2**) and included a total of 31 studies published until May 2021.

The findings indicated that CKD is a strong risk factor for adverse pregnancy outcomes. When adjusted estimates were pooled, women with CKD compared to women without CKD had approximately three times higher odds of pre-eclampsia and almost double the odds for Caesarean section, preterm birth, very preterm birth, and SGA. However, associations with miscarriage, stillbirth, and perinatal death were reported in a small number of studies and did not appear to be associated with CKD. When we combined these outcomes as "pregnancy loss", there was no association with CKD [aOR:1.58, (95% CI, 0.92–2.73)].

The findings on the risk of adverse pregnancy outcomes according to the severity of kidney disease rely mainly on crude estimates because only three studies adjusted for potential confounders. The data indicated that later stages of CKD were associated with a greater odds of pregnancy complications than earlier stages. Unadjusted estimates suggested approximately 3-fold higher odds of pre-eclampsia, very preterm birth, LBW and NICU admission for women with late stages of CKD compared to those with early stages. Similarly, the crude pooled estimate for SGA was elevated for women with later stages of CKD compared to those with earlier stages [crude OR: 2.43, (95% CI, 1.33–4.46)]; however, the pooled OR remained almost unchanged but less precise when adjusted for proteinuria and hypertension [aOR: 2.42, (95% CI, 0.82–7.15)].

When CKD was stratified by cause, each of the individual causes was associated with higher odds of pre-eclampsia, preterm birth, and SGA. Nevertheless, the magnitude of the odds ratios varied depending on the cause of CKD; particularly, the odds were higher amongst women with diabetic CKD for preterm birth [aOR: 4.76, (95% CI, 3.65–6.21)] and SGA [aOR: 4.50, (95% CI, 2.92–6.94)] compared to women without CKD.

Most of the studies included in this systematic review examining the relationship between CKD and adverse pregnancy outcomes were mostly performed in a single centre and had a small sample size. In addition, the majority of the included studies had significant limitations, including a lack of adjustment for important confounders;

only nine of the 31 studies adjusted for confounding. Therefore, confounding cannot be excluded as partly explaining the reported associations between CKD and adverse pregnancy outcomes. For instance, from the pooled crude estimated OR was 8.13 for pre-eclampsia in women with CKD (compared to women without CKD); however, the pooled adjusted estimate was attenuated to 2.58. Also, limited studies have investigated the associations in women with specific kidney disease, as the majority of previous studies combined a variety of kidney diseases aetiologies in the analyses. Thus, further investigations examining associations between CKD and adverse pregnancy outcomes were needed to account for cause of CKD and potential confounding.

### 8.2.2 The association between CKD and chronic hypertension on adverse pregnancy outcomes in a large population-based registry

In Chapter 5, we assessed the associations between CKD, chronic hypertension and adverse pregnancy outcomes over the last three decades using data from the Swedish National Registers. Overall, the findings from this large population-based cohort study suggested that maternal and fetal complications are high in women with CKD and chronic hypertension, and the risks persisted independent of parity, maternal age, and BMI, among other potential confounders. In addition, we found that multiparous women with these conditions had worse adverse perinatal outcomes than primiparous women.

#### *8.2.2.1 Findings on CKD and adverse pregnancy outcomes*

After controlling for sociodemographic factors, obstetric history, and other comorbidities, CKD was associated with a higher odds of adverse pregnancy outcomes in Swedish women from 1982 to 2012. The estimates of the associations varied from [aOR: 2.05, (95% CI, 1.92–2.19)] for medically indicated preterm birth to no effect for stillbirth [aOR: 1.16, (95% CI, 0.95–1.43)]. Analysis by subtypes of CKD suggested that all causes of CKD were associated with higher odds of pre-eclampsia, emergency Caesarean section, and medically indicated preterm birth. These findings are consistent with our findings from the meta-analysis (Chapter 4), which suggested that CKD was associated with pre-eclampsia and preterm birth. The magnitude of the odds of adverse pregnancy outcomes varied according to the cause of CKD; the ORs were higher in women with diabetic nephropathy, renovascular disease, and congenital

kidney disease than other CKD subtypes compared to normotensive women without CKD.

On the other hand, women with both CKD and chronic hypertension had higher odds of adverse pregnancy outcomes than CKD or chronic hypertension alone. After controlling for potential confounders, women with both conditions (CKD and chronic hypertension) had four times higher odds of pre-eclampsia and approximately five times higher odds of SGA infants compared to normotensive women without CKD. The effect estimates for other outcomes varied from [aOR: 9.09, (95% CI, 7.61–10.7)] for medically indicated preterm birth to almost no effect for stillbirth [aOR: 1.15, (95% CI, 0.55–2.41)].

#### *8.2.2.2 Findings on chronic hypertension and adverse pregnancy outcomes*

The impact of chronic hypertension was assessed in two large cohort studies, the Swedish National Registers (Chapter 5) and the linked EHRs from the UK (Chapter 6). Similar patterns of associations were found between the two studies. The findings consistently suggested a higher odds of all assessed outcomes in pregnant women with chronic hypertension (compared to women without chronic hypertension), except for spontaneous preterm birth in the Swedish study where no association was found [aOR: 1.07, (95% CI, 0.96–1.20).

The findings from our first study using the Swedish registers showed that women with chronic hypertension during pregnancy (compared to women without chronic hypertension) had around five times higher odds of pre-eclampsia [aOR: 4.57, (95% CI, 4.85–6.46)], four times higher odds of SGA [aOR: 3.55, (95% CI, 3.31–3.80)], and three times higher odds of preterm birth [aOR: 2.82, (95% CI, 2.68–2.98)]. Findings from the UK were similar: OR for pre-eclampsia [aOR: 5.74, (95% CI, 5.44–6.07)], fetal growth restriction [aOR: 2.51, (95% CI, 2.31–2.72)], and preterm birth [aOR: 2.53, (95% CI, 2.39–2.67)]. A probable explanation for the differences in fetal growth restriction effect estimates between the two cohorts is the difference in the definition of fetal growth restriction in each dataset. Fetal growth restriction in the UK study was defined using Read and ICD-10 codes, whereas it was defined as birthweight below 2 SDs of the mean birthweight of the sex-specific and gestational age distributions in the Swedish study.

As mentioned earlier in this thesis, we did not have access to the Swedish Prescribed Drug Register to assess the effect of antihypertensive treatment on the reported associations. However, the role of antihypertensive treatment and BP control on the reported associations between chronic hypertension and adverse pregnancy outcomes was explored using data from the UK CALIBER platform (see Sections **8.2.3** and **8.2.4** below).

### 8.2.3 Findings on the effect of antihypertensive treatment on adverse pregnancy outcomes

Our findings from the CALIBER study (Chapter 6) confirm a high burden of adverse outcomes in pregnant women with chronic hypertension. Treatment with antihypertensive agents and control of hypertension appear to ameliorate some but not all of the deleterious effects of chronic hypertension. We examined the effect of antihypertensive treatment amongst women with chronic hypertension in three comparisons: 1) treated versus untreated normotensive women, 2) treated versus untreated women with chronic hypertension, and 3) one antihypertensive agent versus another different agent in women with chronic hypertension.

Our findings suggested a higher odds of adverse pregnancy outcomes in women with chronic hypertension who required antihypertensive treatment compared with untreated normotensive women. These findings were consistent with the results from our meta-analysis (Chapter 3), which suggested a higher odds of adverse pregnancy outcomes in treated women compared to normotensive women. The data presented indicated that both treated and untreated chronic hypertension were associated with a greater risk of adverse pregnancy outcomes when compared to women without chronic hypertension.

When outcomes were compared in women with chronic hypertension, those requiring treatment (versus untreated) had higher odds of superimposed pre-eclampsia [aOR: 1.17, (95% CI, 1.05–1.30)], preterm birth [aOR: 1.25, (95% CI, 1.12–1.39)], and fetal growth restriction [aOR: 1.80 (95% CI, 1.51–2.14)], but no differences were found for stillbirth and Caesarean deliveries. The measured baseline characteristics were adjusted for (using propensity score matching); however, a potential explanation for these findings is that women requiring treatment might differ from those not, particularly because antihypertensive therapy is usually initiated at a certain BP

threshold (see **Table 1.3**). In an additional analysis, we compared women with chronic hypertension who were untreated to women who were treated with tight control (BP<135/85 mmHg) and to women treated but with less-tight control (BP≥135/85 mmHg) separately to examine the impact of BP control. The results indicated that women who achieved tight control (versus untreated) had a lower odds of pre-eclampsia [aOR: 0.59, (95% CI, 0.46, 0.76)], while no differences were found for other outcomes, except for a higher odds of fetal growth restrictions [aOR: 1.55 (95% CI, 1.14–2.12)]. In contrast, women who were prescribed antihypertensive treatment but did not achieve a tight control had higher odds of all assessed outcomes compared to untreated with chronic hypertension, suggesting that increased odds of adverse perinatal outcomes in the treated group was mainly attributable to the level of BP control.

Furthermore, our investigations included active comparisons, in which one antihypertensive agent was compared to another agent; this could minimise some sources of confounding by indication as both groups were treated and had the same treatment indication (chronic hypertension) (343, 344). The results implied that different antihypertensive treatments had varying associations with adverse pregnancy outcomes; methyldopa (versus β-blockers) was associated with higher odds of severe hypertension [aOR: 1.58, (95% CI, 1.20–2.10)], superimposed pre-eclampsia [aOR: 1.43, (95% CI, 1.19–1.73)], and preterm birth [aOR: 1.44, (95% CI, 1.05–1.97)], but a lower odds of fetal growth restriction [aOR: 0.66, (95% CI, 0.48–0.90)]. We found similar effects on pregnancy outcomes when comparing outcomes in women who were prescribed calcium channel blockers versus β-blockers, except for preterm birth [aOR: 1.94, (95% CI, 1.15–3.27)]. Nonetheless, this particular analysis may lack adequate statistical power due to the small number of women who were prescribed calcium channel blockers (n=289).

We further compared the outcomes in pregnant women who were prescribed more than one antihypertensive agent versus those who were prescribed monotherapies; the results suggested that polytherapy was associated with a greater odds of maternal and perinatal complications. This could result from the fact that requiring polytherapy is a surrogate marker of chronic hypertension severity and thus a marker of adverse outcomes (342). For instance, when we excluded women with severe hypertension

from this analysis, a statistically significant association was found only for fetal growth restriction [aOR: 1.66 (95% CI, 1.29–2.15)].

### 8.2.4 Findings on the association between BP control and adverse pregnancy outcomes

In a subset sample of women with available BP readings (n=475,851), the adjusted effect estimates showed a dose-response relationship with BP levels where the odds of pregnancy complications increased with increasing BP levels. When the results of BP levels were stratified by antihypertensive treatment in women with chronic hypertension (treated and untreated separately), the magnitude of the associations with adverse pregnancy outcomes were highest in women with severe hypertension (sBP≥160 mmHg). Suggesting that, despite treatment, women with high uncontrolled BP had worse pregnancy outcomes compared to those with controlled BP. This was further investigated amongst the treated women with chronic hypertension, in which we compared pregnancy outcomes in less-tight (BP≥135/85 mmHg) versus tight (BP<135/85 mmHg) control. The adjusted effect estimates suggested approximately a 2-fold higher odds of superimposed pre-eclampsia and very preterm birth and a 3-fold higher odds of severe hypertension in women with less-tight control. However, no differences were found for fetal growth restriction [aOR: 1.83, (95% CI, 0.77, 4.31)] and stillbirth [aOR: 1.31, (95% CI, 0.96, 1.78)]; this could be due to inadequate statistical power for these outcomes.

The overall findings in this section suggested that β-blockers might be superior in reducing adverse maternal and perinatal outcomes than methyldopa, with an exception for fetal growth restriction, which was higher in the β-blockers group. In addition, the findings suggested that tight control, regardless of treatment, was associated with better pregnancy outcomes.

### 8.2.5 Findings on the association between pre-pregnancy hypertension and long-term CVD

The final population-based cohort study in this thesis focused on the associations between pre-pregnancy hypertension (chronic hypertension) and future CVD (Chapter 7). Overall, women who had pre-pregnancy hypertension had doubled the risk of developing CVD [aHR: 2.22, (95% CI, 2.03–2.42)], compared to those without pre-

pregnancy hypertension. Among the included 12 cardiovascular disorders, approximately a four-time higher risk was observed for ischemic stroke, intracerebral haemorrhage, coronary heart disease NOS, abdominal aortic aneurysm, and heart failure compared to those without pre-pregnancy hypertension. The HR for other cardiovascular phenotypes in women with pre-pregnancy hypertension (versus those without pre-pregnancy hypertension) varied from [aHR: 4.63, (95% CI, 2.75–7.81)] for unspecified stroke to no effect for peripheral arterial disease [aHR: 1.62, (95% CI, 0.96–2.91)].

When women were stratified according to the occurrence of adverse pregnancy outcomes, the results indicated a greater risk of all cardiovascular outcomes in women who experienced adverse pregnancy outcomes, with or without pre-pregnancy hypertension, compared to women who remained normotensive without pregnancy complications. In women with pre-pregnancy hypertension, the risk was larger in those with adverse pregnancy outcomes across the 12 cardiovascular disorders, except for subarachnoid haemorrhage and atrial fibrillation. For example, women with pre-pregnancy hypertension who had pregnancy complications had approximately doubled the risk of coronary heart disease [aHR: 8.33, (95% CI, 5.57–12.5)] than pregnant women with pre-pregnancy hypertension alone [aHR: 4.00, (95% CI, 3.03–5.30)], compared to those who remained normotensive without pregnancy complications. Also, stronger associations were found in women with pre-pregnancy hypertension who had pregnancy complications for heart failure [aHR: 9.65, (95% CI, 5.96–15.6)] than those with pre-pregnancy hypertension alone [aHR: 2.65, (95% CI, 1.68–4.17)].

We further evaluated whether the association between pre-pregnancy hypertension and the risk of any subsequent cardiovascular event varied by maternal ethnicity or the number of pregnancies. Using interaction terms between these variables (ethnicity and number of pregnancies) and the exposure of interest (pre-pregnancy hypertension) indicated that the risk of developing CVD did not differ.

This study provides important information to the existing evidence for the associations between chronic hypertension in pregnancy and future CVD. Women with pre-pregnancy hypertension (without pregnancy complications) had equivalent risk to those without pre-pregnancy hypertension (with pregnancy complications) for stable

angina, unstable angina, peripheral diseases, and heart failure. These findings indicated that adverse pregnancy outcomes might act as an early risk marker for maternal CVD in later life. Thus, postpartum screening for pregnancy complications, specifically pre-eclampsia, preterm birth, stillbirth, and fetal growth restriction, may reduce the burden of CVD among women with chronic hypertension during pregnancy.

## 8.3 Interpretation of findings and causal inference in epidemiological research

### 8.3.1 Bradford Hill's criteria for causality

When trying to establish a causal relationship between a cause (exposure) and an observed effect (outcome of interest), the Hill's casual criteria can be considered. The Hill's criteria for causation have been widely used in public health research to establish a causal relationship in epidemiologic evidence between a presumed cause and an observed effect. These nine criteria are: 1) strength, 2) consistency, 3) specificity, 4) temporality, 5) biologic gradient, 6) plausibility, 7) coherence, 8) experimental evidence, and 9) analogy (362).

Hill's first criterion for causation is '*strength'*, whereby the larger an association between an exposure and an outcome, the more likely it is to be causal, whereas a weaker association can be attributed to some unmeasured confounders. Recently, with advances in statistical methodology, statistical significance—not the magnitude of association—is the accepted standard for judging the strength of an observed association; and thus its potential causality (363). In the current thesis, the effect estimates were statistically significant in almost all reported outcomes, and strong associations were observed, specifically for the association between chronic hypertension and adverse pregnancy outcomes.

Consistency (reproducibility) is the repeated observation of an association in different populations. For instance, if consistent findings were observed using a variety of locations, populations, and methods, that strengthens the likelihood of an effect. In this thesis, we used data from different populations and locations (Sweden and the UK), and the findings were *'consistent'*, suggesting an association between chronic hypertension and adverse pregnancy outcomes, supporting a potentially causal

relationship. Although the results on CKD and adverse pregnancy outcomes have been varied across previous studies owing largely to methodological deficiencies, most studies reported that CKD is a risk factor for pregnancy complications which is consistent with our findings (73). Similarly, in line with our results, the available evidence from a different population suggested an association between pre-pregnancy hypertension and future CVD (89, 90).

Specificity means that the association is limited to a specific reason, with no other likely explanation, meaning the exposure causes only one disease (362). In this research, '*specificity'* was applied when comparing the effect of different antihypertensive agents, in which an agent was considered if a pregnant woman was prescribed merely one specific type of antihypertensive treatment. However, other associations evaluated in this thesis might be deemed to be a result of a multitude of causes, in which specificity might be difficult to measure. In addition, *'specificity'* is widely considered weak from an epidemiologic standpoint (363). Temporal relationship of the association means that for an exposure-outcome relationship to be causal, exposure must precede the onset of the outcome. Temporality in this research is clear as data were collected prospectively in both datasets used in the current work.

Biological gradient, the presence of a dose-response relationship, supports the causal association between an exposure and an outcome of interest. In this thesis, we were able to assess the dose-response relationship for the association between chronic hypertension and adverse pregnancy outcomes, in which we observed a dose-response relationship between increasing BP levels and adverse pregnancy outcomes. However, the dose-response relationship was not assessed according to the stage of CKD, as data were poorly recorded on CKD stages in the Swedish MBR and NPR. Plausibility refers to the existing biological or social models that explain the association of interest, although this might depend on the current body of knowledge. In this thesis, we followed the maternal morbidity measurement framework, a woman-centred, life-cycle approach that provides wide-ranging perspectives on women's health (see Chapter 1, **Figure 1.1**). In addition, several possible biological mechanisms were established that may explain the link between adverse pregnancy outcomes and subsequent CVD (See **Figure 8.1**) (360). Coherence has been viewed as being similar to biological plausibility in which the cause-and-effect relationship should make sense with available knowledge (363).

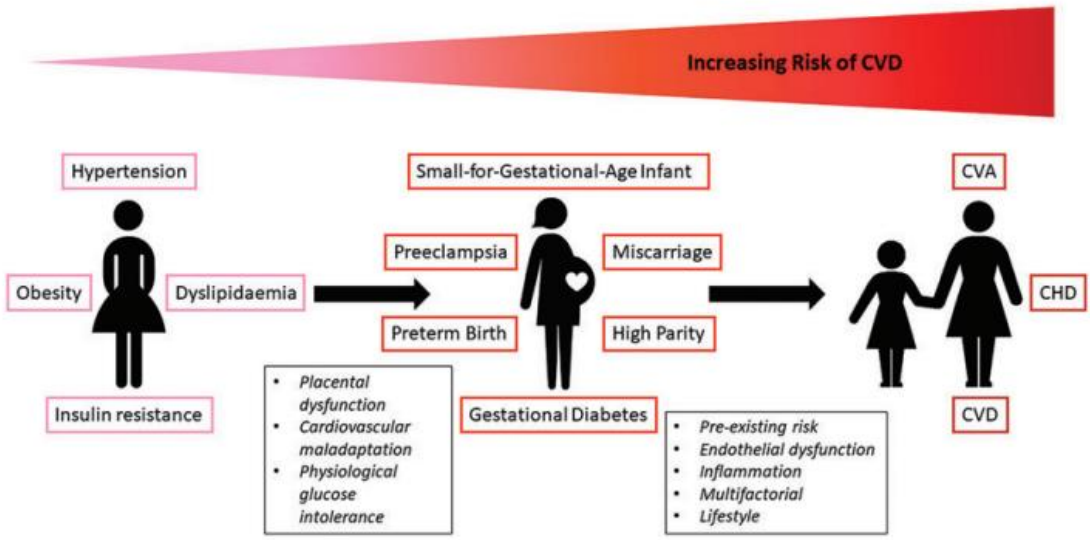



**Figure 8.1** Potential mechanisms for the association between adverse pregnancy outcomes and future cardiovascular disease risk. CHD, coronary heart disease; CVA, cerebrovascular accident; CVD, cardiovascular disease Source: Wu *et al*. (360)

Experimental evidence is drawn from experimental manipulation, such as clinical trials, where frequency of outcomes changes following an exposure/intervention or cessation of exposure/intervention, and this may lead to the strongest support for causal inference (362, 363). Nevertheless, it should be noted that many diseases result from multifaceted exposures and follow complex progression pathways; thus, multiple risk factors, such as smoking, obesity, and genetic predisposition, can contribute to disease onset and progression (363). In this thesis, conducting an RCT was not feasible when examining the effect of chronic conditions (hypertension or CKD). Multiple trials were analysed for the impact of antihypertensive treatment on adverse perinatal outcomes, yet they did not draw definitive conclusions on the effect of antihypertensive treatment. Propensity score matching was used in some analyses, in which the exposed and the unexposed groups were matched based on measured baseline characteristics, when assessing the effect on antihypertensive treatment, in order to closely replicate the design feature of an RCT of balance between the exposed

and unexposed. For the risk of developing CVD, it is possible that the combination of different risk factors may culminate in disease; thus, experimental manipulation of a single factor (exposure) may or may not result in observable decreases in disease incidence (363). The last criterion is *'analogy'* which means that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some way (364). Although this may refer to hypothesis formation rather than causal inference, it also accepted that '*analogy'* might best be subsumed under the criterion of coherence (364).

### 8.3.2 Bias, confounding or chance

Before causality can be established, it is vital to rule out the effect of other factors, namely, bias, confounding and chance. The overall results of this thesis indicated that women with chronic hypertension and CKD had a higher risk of adverse pregnancy outcomes. Our findings also suggested that tight control is associated with better pregnancy outcomes in women with chronic hypertension, particularly in those requiring antihypertensive treatment during pregnancy. Finally, this work indicates that pre-pregnancy hypertension is associated with a greater risk of future CVD, and the risk was higher when pre-pregnancy hypertension was combined with pregnancy complications. However, the possibility of alternative explanations of causality must be considered before any observed associations can be claimed to be true.

Selection bias is unlikely to affect the magnitude of the reported results, as the risk of selection bias was minimised through the use of large representative cohorts. The Swedish MBR included almost all births in Sweden (97). Similarly, data from the CPRD have been reported to be representative of the population (116, 117), and data from HES contains data on all admissions at NHS hospitals in England (122). Also, participants in the Swedish registers and the CALIBER platform were included by default when they were receiving care, as universal health coverage is provided in Sweden (365) and the UK (366). Therefore, Berkson's bias is unlikely to have influenced our results since the samples are representative of the populations of interest (367).

The data used in this thesis were collected prospectively; thereby, the possibility of recall bias can be eliminated. The occurrence of adverse pregnancy outcomes might differ according to maternal characteristics, such as age, BMI and parity, and this was

handled in subgroup analyses based on these factors. When assessing the risk of future CVD, we also used time-dependent covariates to allow for changes in exposure status and risk factors which minimize measurement error and misclassification.

It is likely that CKD was under-diagnosed in the Swedish national registers, particularly the milder forms of CKD. Although we identify women with CKD from the MBR and NPR (which has achieved nationwide coverage since 1987 (104)), outpatient data were available from 2001 onward. Therefore, it is possible that the women with CKD were severe cases who potentially required hospitalization. The observed associations between CKD and adverse pregnancy outcomes may have been attenuated to the null if women with milder forms of CKD have been categorised as unexposed.

With any longitudinal study, missing data can be an issue that could potentially affect estimates by creating selection bias and/or the loss of statistical power and precision (i.e., with complete case analysis when missing data are removed) and residual confounding. Missingness is also an issue with EHR-based research, although EHRs are a rich data source for research investigations. Multiple imputation to handle missing data is becoming the approach of choice for dealing with missingness; however, it is computationally very intense and needs to include sufficient information about the reason for missingness to avoid bias (368). In addition, most imputation techniques assume that data are missing at random (368).

A study of a UK primary care data base suggests that some data, such as BP, are MAR; other variables, specifically, smoking and drinking habits, are MNAR (369), rendering multiple imputation inappropriate for at least the smoking variable. This thesis did not undertake multiple imputation for missingness in EHRs for two main reasons. First, we had a substantial level of missingness on BMI and smoking. Second, there is evidence that data recorded on at least one risk factor (smoking) are not missing at random (369), limiting the suitability and validity of using multiple imputation.

Confounding provides an alternative explanation for any reported association in observational studies. However, detailed obstetric and demographic information was available from the Swedish national registers and CALIBER data, which allowed for the rigorous control of potential confounders throughout the thesis. For example, multivariable regression models and subgroup analyses were performed to assess the

effect of confounding factors on the observed associations. We also excluded women with pre-pregnancy diseases (e.g., diabetes mellitus and CKD) from the analyses when examining the association between pre-pregnancy hypertension and future CVD. Nevertheless, as in any observational study, some sources of unmeasured and residual confounding may remain.

The last factor to consider before an attempt to establish causality is chance. It is unlikely that the findings in this thesis were due to random error. The reported 95% confidence intervals of the main analyses were narrow, except for some subgroup and sensitivity analyses that included a small sample size with a few event rates, specifically for stillbirth outcome. Findings were replicated in two distinct groups of pregnant women and were in agreement with prior research. Thus, it is highly unlikely that the observed results arose by chance alone.

The use of a large sample size in the included studies of this thesis provided sufficient power to detect the relationship between the exposures and outcomes of interest, particularly for the effect of antihypertensive treatment on perinatal outcomes. For instance, given the current parameter estimates in our CALIBER study (Chapter 6), a minimum sample size of 4,710 (2,355 in each group, using 5% two-sided alpha and 90% power) would be required to detect an association between antihypertensive treatment and fetal growth restriction in women with chronic hypertension. As illustrated earlier in Chapter 1, the largest RCT investigated the effect of antihypertensive treatment (treated versus untreated with mild hypertension) in women with chronic hypertension included 263 women (58), whereas the largest observational study included 2,727 women in a population-based study (51). Hence, RCT needs to be conducted in multicentre over several years to enrol the required number of participants to assess such associations, which can be a complex, expensive and time-consuming study. In this thesis, we linked longitudinal records from primary and secondary care data to examine the impact of antihypertensive treatment on adverse maternal and perinatal outcomes, demonstrating the value of linked EHRs of real-world data for research investigations, especially in the absence of powered RCTs. In conclusion, causality is difficult to prove in epidemiological studies due to uncertainty of the effect of unmeasured confounders.

## 8.4 The impact of missing data on inferences and the likelihood of residual confounding

Missing data is a common problem in all types of research and that could influence the analyses and results. Strategies to handle missingness vary depending on the type of missing data; more details about the type of missing data and how to handle them are presented in Chapter 2.

As mentioned in Chapter 2, the multiple imputation method for handling missing data in the analyses of maternal chronic hypertension and adverse pregnancy outcome; and pre-pregnancy hypertension and long-term CVD (Chapters 6 and 7, respectively) was unsuitable due to the large proportion of missing data on smoking status and BMI and because data are unlikely to be MAR—an assumption that is violated. Instead, data are likely to be MNAR (e.g., missingness may vary by patient characteristics); therefore, missing data, particularly for smoking and BMI, present a limitation to our analysis for some models and thus interpretation of our results.

An alternative strategy to address this issue includes a complete-case analysis, but this will result in excluding a large number of observations, limiting the suitability of using this method as a primary analysis plan. However, it has been outlined in the literature that complete-case analysis could be unbiased for estimating a correctly specified exposure-outcome relationship if the missingness is unrelated to the outcome, even when data are MNAR (370). Therefore, we used this method as a post-hoc analysis because we assume that missing data on BMI and smoking are unlikely to be related to the outcomes of interest.

In this thesis, in the primary analyses, missing data were handled using a missing category for categorical variables, which is a straightforward and very common approach. Although this approach was deemed suitable to apply for the Swedish data as few missing values were observed, it could be insufficient for the UK data because we have a substantial amount of missing data on BMI and smoking status. Considering the huge amount of missing data in the UK cohort, we might not account fully for these variables (BMI and smoking status) when comparing pregnancy outcomes between women with chronic hypertension and those without; thus, residual confounding cannot be ruled out. Additionally, it is difficult to replicate our findings using RCTs, but these findings can be replicated using primary care data.

### 8.4.1 The effect of missing data on the reported results

#### *8.4.1.1 The effect of missing data in the Swedish register*

In the Swedish MBR, the proportion of missing data was 6% and 22% on smoking status and BMI, respectively. Therefore, using the missing category was acceptable for smoking, and the amount of missingness is unlikely to affect the reported results.

The proportion of missingness for BMI was high and if BMI was an important confounder, then there could be substantial residual confounding when using the missing indicator method. To examine the influence of missing BMI, we conducted a complete-case analysis (results are not shown) with respect to BMI and smoking status, and found results similar to the reported effect estimates using the missing indicator method.

#### *8.4.1.2 The effect of missing data in the CALIBER*

Although the amount of missing data was large for smoking status (71.7%) and BMI (66.1%) in the UK cohort, this was lower (smoking: 51.3%; BMI: 37.8%) among the exposed group (i.e., pregnant women with chronic hypertension), and even lower in the treated group (smoking: 31.4%; BMI: 21.2%). Meaning that our results from the first comparison in Chapter 6, comparing pregnancy outcomes between women with chronic hypertension and those without, could be the most affected results by the potentiality of residual confounding. Similarly, this could affect the reported results in Chapter 7 when we compared the risk of future CVD in women with pre-pregnancy hypertension versus those without. This huge amount of missingness might change the direction of effect estimates in either direction (away or toward the null) depending on the values of missing data.

As stated earlier, data on BMI and smoking status in the UK primary care data are unlikely to be MAR, limiting the suitability of using multiple imputation. Although data are more likely to fit the assumption required for complete-case analysis, performing the complete-case analysis (with respect to BMI and smoking status) resulted in excluding more than half of the study population. The results of the post-hoc analysis (using the complete-case analysis method) showed similar results to the reported results when pregnancy outcomes were compared between women with

chronic hypertension and those without (N=341,053); and when the overall risk of CVD was compared in women who had chronic hypertension in pregnancy and those without (N=363,360).

### 8.4.2 Quantifying the effect of missing data on the reported results

To further explore the impact of smoking and BMI on the associations between chronic hypertension and adverse pregnancy outcomes, we used the Swedish cohort to quantify the associations, adjusting for these variables (one at a time) to assess how this would change the effect estimates.

In the Swedish MBR, the proportion of missing data was 6% and 22% on smoking status and BMI, respectively. Therefore, we assessed the impact of these particular variables on the results by quantifying the impact of BMI and smoking on the association between chronic hypertension and adverse pregnancy outcomes. First, we analysed the full dataset using the missing indicator method (N=2,788,490). The results of this analysis are illustrated in Table 8.1. Given the large sample size, we repeated the analysis using a complete-case analysis, where observations with missing values on smoking and BMI were excluded from this analysis (n=690,273; Table 8.2). Overall, we found that adjustment for these particular variables did not change the effect estimates largely, although BMI attenuated the estimates slightly more than smoking status. In addition to this, the findings from our systematic review and meta-analysis (Chapter 3) reinforced these findings, as chronic hypertension was associated with almost all assessed outcomes in the adjusted meta-analyses.

It is well-established that raised and low pre-pregnancy BMI (versus normal BMI) and smoking during pregnancy are associated with a higher risk of adverse pregnancy outcomes (371-373). However, adjusting for these variables did not have a huge impact on the associations between chronic hypertension and adverse pregnancy outcome (Tables 8.1 & 8.2).

On the other hand, our results on the association between pre-pregnancy hypertension and future risk of CVD might also be affected by residual confounding due to the large proportion of missing data on BMI and smoking. However, when we conducted a complete-case analysis (N=363,360) that did not alter our main findings, as the risk of any subsequent CVD event was two times higher in women with pre-pregnancy

hypertension [aHR: 2.16 (95% CI, 1.87–2.50)] compared to those without. Similarly, a recent US study examining the risk of CVD, particularly heart failure, in women with pre-pregnancy hypertension, adjusting for several confounding factors, including pre-pregnancy smoking and BMI, reported a higher risk in women with pre-pregnancy hypertension than those without (90).

**Table 8.1** Effect of smoking and body mass index on the associations between chronic hypertension and adverse pregnancy outcomes using data from the Swedish Registers (N=2,788,490)

| **Outcome** | **Model 1[a]** | **Model 2[b]** | **Model 3[c]** | **Model 4[d]** |
|---|---|---|---|---|
| | **OR (95% CI)** | **aOR (95% CI)** | **aOR (95% CI)** | **aOR (95% CI)** |
| Pre-eclampsia | 6.05 (5.76, 6.34) | 5.04 (4.80, 5.30) | 6.02 (5.74, 6.31) | 5.02 (4.78, 5.27) |
| Emergency Caesarean section | 2.60 (2.47, 2.75) | 2.21 (2.10, 2.33) | 2.59 (2.46, 2.74) | 2.21 (2.10, 2.33) |
| Elective Caesarean section | 2.87 (2.72, 3.03) | 2.54 (2.40, 2.68) | 2.86 (2.71, 3.02) | 2.53 (2.39, 2.68) |
| Preterm birth (<37 week) | 3.02 (2.87, 3.18) | 2.96 (2.81, 3.11) | 3.10 (2.94, 3.26) | 3.01 (2.86, 3.17) |
| Stillbirth | 2.20 (1.81, 2.67) | 1.92 (1.59, 2.34) | 2.27 (1.87, 2.76) | 1.97 (1.62, 2.39) |
| Small for gestational age | 3.32 (3.12, 3.54) | 3.49 (3.28, 3.72) | 3.49 (3.28, 3.72) | 3.65 (3.42, 3.88) |

aOR, adjusted odds ratio. In these models, the exposure was chronic hypertension (n=14,253) compared to those without; approximately 6% of records had missing data on smoking and 22% on body mass index. [a] Model 1 shows the crude associations between chronic hypertension and adverse pregnancy outcomes; [b] Model 2 was adjusted for body mass index only; [c] Model 3 was adjusted for smoking only; [d] Model 4 was adjusted for body mass index and smoking.

**Table 8.2** Effect of smoking and body mass index on the associations between chronic hypertension and adverse pregnancy outcomes using complete-cases analysis (data from the Swedish Registers, N=2,089,217)

| **Outcome** | **Model 1[a]** | **Model 2[b]** | **Model 3[c]** | **Model 4[d]** |
|---|---|---|---|---|
| | **OR (95% CI)** | **aOR (95% CI)** | **aOR (95% CI)** | **aOR (95% CI)** |
| Pre-eclampsia | 5.88 (5.57, 6.20) | 4.71 (4.46, 4.98) | 5.83 (5.52, 6.15) | 4.67 (4.42, 4.93) |
| Emergency Caesarean section | 2.61 (2.46, 2.76) | 2.17 (2.05, 2.30) | 2.60 (2.45, 2.75) | 2.16 (2.04, 2.29) |
| Elective Caesarean section | 2.70 (2.54, 2.87) | 2.33 (2.19, 2.48) | 2.68 (2.52, 2.86) | 2.32 (2.18, 2.47) |
| Preterm birth (<37 week) | 3.10 (2.93, 3.29) | 2.97 (2.81, 3.15) | 3.14 (2.97, 3.32) | 3.01 (2.84, 3.18) |
| Stillbirth | 2.36 (1.89, 2.95) | 1.94 (1.56, 2.43) | 2.39 (1.91, 2.99) | 1.97 (1.58, 2.46) |
| Small for gestational age | 3.23 (3.01, 3.48) | 3.40 (3.16, 3.66) | 3.38 (3.14, 3.63) | 3.56 (3.31, 3.83) |

aOR, adjusted odds ratio. In these models, we conducted a complete-case analysis (listwise deletion) where records with missing values on smoking and body mass index were dropped (n=690,273). The exposure was chronic hypertension (n=11,187) compared to those without. [a] Model 1 shows the crude associations between chronic hypertension and adverse pregnancy outcomes; [b] Model 2 was adjusted for body mass index only; [c] Model 3 was adjusted for smoking only; [d] Model 4 was adjusted for body mass index and smoking.

## 8.5 Strengths and limitations of the thesis

### 8.5.1 Strengths of the thesis

This thesis includes comprehensive systematic reviews and meta-analyses of the published studies examining the impact of chronic hypertension and antihypertensive treatment on adverse pregnancy outcomes. It also includes a systematic review and meta-analysis of epidemiological evidence examining the associations between CKD and adverse pregnancy outcomes. The general strength of this thesis is the use of large population-based cohorts of pregnant women, with prospectively collected data that minimised the possibility of selection bias and recall bias and included women with a range of exposure and demography. Also, we had access to several potential confounding factors in both cohorts, and using data from two countries allowed us to assess the consistency of the results. Additionally, the validity of data from both: the Swedish National Registers (97, 102, 104) and the CALIBER platform (110, 114, 118, 127) have been established previously.

In the current thesis, we addressed some of the limitations of previous literature, which were identified from the systematic reviews, using large datasets from the Swedish National Registers to assess the associations between maternal chronic diseases (chronic hypertension and CKD) and adverse pregnancy outcomes. It is also strengthened by the use of data on maternal chronic disease from different sources (i.e., MBR and NPR), which increase the validity of the recorded variables. The Medical Birth Register contains detailed information on pregnancy, covering a woman's obstetric history and several potential confounding factors over the last three decades (1982-2012), allowing us to control for a wide range of confounding variables. To the best of our knowledge, we conducted the largest study investigating the impact of different subtypes of CKD in the occurrence of adverse pregnancy outcomes. In addition, the available evidence suggested that the risk of adverse pregnancy outcomes differ based on maternal age, BMI and parity; therefore, the use of a large sample size allowed us to conduct several a priori subgroup and sensitivity analyses in an attempt to examine the independent role of maternal chronic diseases (chronic hypertension and CKD) in the observed associations.

Furthermore, this work involved one of the most comprehensive investigations on the relationship between chronic hypertension, with a focus on the effect of

antihypertensive treatment, and adverse pregnancy outcomes using information from primary and secondary care in England. The data from the CALIBER platform are representative of the population in England, and all data were recorded prospectively, reducing the possibility of selection bias and recall bias. We also conducted a propensity-score matching when examining the effect of antihypertensive treatment, which minimized the variation in measured baseline characteristics (176).

Other strengths of this thesis included access to unique data on medications and BP readings during pregnancy. Another strength is the comparison of pregnancy outcomes across different antihypertensive agents, as evidence is limited in pregnant women with chronic hypertension (374). While previous RCTs lacked the statistical power to detect the effects of antihypertensive treatment on perinatal outcomes, our study was powered to detect the effect on clinically important outcomes, such as pre-eclampsia and fetal growth restriction. We additionally assessed the impact of BP control (less-tight versus tight control) on the occurrence of adverse pregnancy outcomes. Finally, this thesis includes one of the first studies examining the associations between pre-pregnancy hypertension and the role of pregnancy complications, and future CVD in finer detail, as data from the CALIBER platform was used to assess the risk of 12 cardiovascular disorders.

### 8.5.2 Limitations of thesis

The systematic review and meta-analysis included published studies, and English-language studies only for CKD meta-analysis (Chapter 4), so it is possible that unpublished literature and non-English studies on these topics were missed. Data on CKD stages were poorly recorded in the Swedish MBR; therefore, we have not assessed the associations according to the stage of CKD. Although we conducted a national study using data from the Swedish National Registers, we did not have access to the Prescribed Drug Register, which limited our analyses to examine the effect of antihypertensive treatment on adverse pregnancy outcomes, specifically in women with chronic hypertension. However, we investigated the impact of antihypertensive treatment using data from the CALIBER platform.

This thesis included population-based studies based on existing data, so controlling for confounding factors is limited to the data available in various datasets; therefore, residual confounding cannot be ruled out, in particular where there is substantial

missingness. While we used propensity score matching when examining the effect of antihypertensive treatment, this method can only control for the measured background characteristics (176); thus, we cannot rule out the possibility of unmeasured confounding factors in these analyses either. Data on antihypertensive treatment included prescriptions from the CPRD; therefore, it is possible that women may receive additional prescriptions from secondary care settings. As we rely on 'real-world' data, we were unable to assess adherence to prescribed antihypertensive treatment. However, accurate data on adherence is often scarce even in trials too (375). It is also possible that misclassifications of chronic hypertension as gestational hypertension may lead to misclassification bias and subsequently underestimate the reported effect estimates.

## 8.6 Clinical and public health implications

The findings of this thesis will be of interest to health care providers and women with chronic hypertension or CKD of childbearing age. As the prevalence of hypertension and CKD is increasing, more women of childbearing age will enter pregnancy with these conditions. For example, we quantified the risk of adverse pregnancy outcomes among women with chronic hypertension and CKD in a form of systematic reviews and meta-analyses, in addition to population-based studies. These findings will inform obstetricians in their discussion with, and advice they give to, women, including the potential risks of pregnancy complications when they counsel women with these conditions.

Until now, it is uncertain which antihypertensive treatment in pregnancy is associated with optimal maternal and perinatal outcomes, particularly in women with mild to moderate hypertension (374). In addition, the choice of antihypertensive drug in pregnancy remains largely determined by local practice rather than a strong evidence base. In addition, the choice of first-line antihypertensive treatment is based on licensed status and cost, which may vary by country or region (374). A Cochrane systematic review published in 2018 reported that β-blockers and calcium channel blockers were more effective than the methyldopa for preventing severe hypertension; however, the review was underpowered, due to small sample sizes, to provide definitive evidence on clinical outcomes (such as preterm birth and fetal growth restriction) (26). These findings are in line with our results in this thesis (Chapter 6)

which suggested that β-blockers might be more effective than methyldopa in preventing severe hypertension, superimposed pre-eclampsia and preterm delivery. Our findings on specific antihypertensive agent might help obstetricians to discuss the benefits and risks of the most commonly used antihypertensive agents during pregnancy.

There has been much debate about the best approach for the management of hypertension during pregnancy. Our findings from the CALIBER reinforced the findings from the CHIPS trial that less-tight control is associated with more severe hypertension (29). We also add to the literature that other pregnancy complications such as pre-eclampsia and preterm birth are associated with less-tight control. While severe hypertension might be a risk marker for adverse maternal and perinatal outcomes (29), excluding severe hypertension from the analysis did not alter the statistically significant associations between superimposed pre-eclampsia and preterm birth. Furthermore, a study has shown that the mean cost per woman–infant dyad managed by a policy of less-tight (versus tight) BP control is not significantly different with regard to overall services and hospital ward costs incurred from as early as 14 weeks of gestation up to 305 days after delivery (376). However, less-tight control was implicated in significantly more morbidity among women (29, 376). This meant that tight treatment approach may have clinical benefit for women, with no increased risk to neonates and without additional cost to the healthcare system (376).

The last part of this thesis evaluated the risk of future CVD in women with pre-pregnancy hypertension. The findings highlighted the need to consider women's obstetric history when assessing the risk of CVD in relation to pre-pregnancy hypertension and the importance of initiating postpartum cardiovascular risk screening and management (such as lifestyle modifications and pharmacological interventions) to reduce the risk of future CVD (84).

## 8.7 Recommendations for future research

Large multicentre trials and population-based studies with real-world data from other countries are needed to compare one antihypertensive agent with another, particularly the first-line antihypertensive treatments. This will help to identify whether a specific agent confers a lower risk of maternal and perinatal outcomes. Studies should focus

on the role of BP control in relation to antihypertensive treatment, to examine the consistency of the findings across countries. Such studies may be done in Scandanavian countries, Canada and Taiwan, for example, where population-based data with prescription registries are available. In addition, in the absence of clinical trials due to cost and feasibility, a large population-based cohort study is the optimal study design to estimate how many cardiovascular events could be prevented by implementing interventions such as weight loss and BP control in women with pre-pregnancy hypertension who had experienced pregnancy complications.

Future research is needed to examine the association between CKD and adverse pregnancy outcomes, adjusting for important risk factors, such as proteinuria, hypertension, antihypertensive treatment, and immunosuppressive. Available evidence over the last three decades demonstrated an increase in the live birth rate of babies born to women with CKD on dialysis, although the findings suggested a high prevalence of preterm birth and LBW (377). In the current thesis, we did not assess the impact of dialysis and stages of CKD on the reported associations because data were poorly recorded in Swedish MBR and NPR on these factors. Further work is required to estimate the effect of these factors when assessing the relationship between CKD and pregnancy complications.

## 8.8 Conclusions

The data in this thesis indicated that CKD and chronic hypertension were associated with a wide range of adverse pregnancy outcomes, including pre-eclampsia, preterm birth, and SGA. These associations persisted after adjustment for several potential confounders in large population-based cohorts. The findings suggested that multiparous women with these conditions had worse adverse perinatal outcomes than primiparous women. In women with CKD, the risks of adverse pregnancy outcomes were higher in women with diabetic nephropathy, renovascular disease and in those with congenital kidney disease than other CKD subtypes.

In women with chronic hypertension, those requiring treatment (versus untreated) had higher odds of pre-eclampsia, preterm birth, and fetal growth restriction, but no differences were found for stillbirth and Caesarean deliveries. The findings showed that different antihypertensive agents might have varying impacts on pregnancy

outcomes; β-blockers (versus methyldopa) were associated with lower odds of severe hypertension, pre-eclampsia, and preterm birth, but a higher odds of fetal growth restriction. We also found that the occurrence of adverse pregnancy outcomes varies according to control of BP, with better outcomes observed in treated women with tighter control during pregnancy.

The data in this thesis suggested that pre-pregnancy hypertension was associated with increased risk of future CVD, and maternal exposure to adverse pregnancy outcomes was consistently associated with a greater risk than pre-pregnancy hypertension alone. Adjusting for confounding factors, including family history of CVD, did not attenuate this association with the 12 most common cardiovascular disorders.

While antenatal care for pregnant women has improved over the last few decades, the overall conclusion of this thesis suggested that the risk of adverse pregnancy outcomes is higher in women with chronic hypertension and/or CKD than the general obstetric population. Therefore, multidisciplinary antenatal management should be provided for these women with intensive care. Importantly, if antihypertensive treatment is required, clinicians might consider tighter control during pregnancy as better outcomes were observed in women with tightly controlled hypertension. Finally, the findings of this thesis highlighted the need to use pregnancy complications as a naturally occurring screening tool to detect women at high risk of cardiovascular events.

## References


1. Alkema L, Chou D, Hogan D, Zhang S, Moller A-B, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. The lancet. 2016;387(10017):462-74.
2. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. The Lancet global health. 2014;2(6):e323-e33.
3. Ralston SH, Penman ID, Strachan MW, Hobson R. Davidson's Principles and Practice of Medicine E-Book: Elsevier Health Sciences; 2018.
4. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.
5. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESHGuidelines for themanagement of arterial hypertension. J Hypertens. 2018;36(10):1956-2041.
6. Bakris G, Ali W, Parati G. ACC/AHA Versus ESC/ESH on Hypertension Guidelines: JACC Guideline Comparison. J Am Coll Cardiol. 2019;73(23):3018-26.
7. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373(22):2103-16.
8. Laurent S. Antihypertensive drugs. Pharmacol Res. 2017;124:116-25.
9. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72(1):24-43.
10. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The Hypertensive Disorders of Pregnancy: The 2021 International Society for the Study of Hypertesion in Pregnancy Classification, Diagnosis & Management Recommendations for International Practice. Pregnancy Hypertens. 2021.
11. Seely EW, Ecker J. Chronic hypertension in pregnancy. Circulation. 2014;129(11):1254-61.
12. Broekhuijsen K, Ravelli AC, Langenveld J, van Pampus MG, van den Berg PP, Mol BW, et al. Maternal and neonatal outcomes of pregnancy in women with chronic hypertension: a retrospective analysis of a national register. Acta Obstetricia et Gynecologica Scandinavica. 2015;94(12):1337-45.
13. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina EV. Prevalence, trends, and outcomes of chronic hypertension: a nationwide sample of delivery admissions. American Journal of Obstetrics & Gynecology. 2012;206(2):134.e1-8.
14. Panaitescu AM, Syngelaki A, Prodan N, Akolekar R, Nicolaides KH. Chronic hypertension and adverse pregnancy outcome: a cohort study. Ultrasound Obstet Gynecol. 2017;50(2):228-35.

15. Hartikainen AL, Aliharmi RH, Rantakallio PT. A cohort study of epidemiological associations and outcomes of pregnancies with hypertensive disorders. Hypertens. 1998;17(1):31-41.
16. Ananth CV, Duzyj CM, Yadava S, Schwebel M, Tita ATN, Joseph KS. Changes in the Prevalence of Chronic Hypertension in Pregnancy, United States, 1970 to 2010. Hypertension. 2019;74(5):1089-95.
17. Matthews TJ, Hamilton BE. Delayed childbearing: more women are having their first child later in life. NCHS data brief. 2009(21):1-8.
18. Guzzo KB, Payne KK. Average age at first birth, 1970-2017. Family Profiles. 2018;25.
19. Gūtmane S. THE DISCOURSE ON THE SITUATION OF YOUTH IN THE EUROPEAN UNION IN THE CONTEXT OF POLICIES AND RESEARCH. Bridges/Tiltai. 2020;84(1).
20. Heslehurst N, Rankin J, Wilkinson JR, Summerbell CD. A nationally representative study of maternal obesity in England, UK: trends in incidence and demographic inequalities in 619 323 births, 1989–2007. International journal of obesity. 2010;34(3):420-8.
21. Knight M, Kurinczuk JJ, Spark P, Brocklehurst P. Extreme obesity in pregnancy in the United Kingdom. Obstetrics & Gynecology. 2010;115(5):989-97.
22. Norman JE, Reynolds R. The consequences of obesity and excess weight gain in pregnancy. Proc Nutr Soc. 2011;70(4):450-6.
23. Lu Y, Chen RF, Cai JJ, Huang ZJ, Yuan H. The management of hypertension in women planning for pregnancy. British Medical Bulletin. 2018;128(1):75-84.
24. Filippou CD, Tsioufis CP, Thomopoulos CG, Mihas CC, Dimitriadis KS, Sotiropoulou LI, et al. Dietary approaches to stop hypertension (DASH) diet and blood pressure reduction in adults with and without hypertension: a systematic review and meta-analysis of randomized controlled trials. Advances in Nutrition. 2020;11(5):1150-60.
25. Sinkey RG, Battarbee AN, Bello NA, Ives CW, Oparil S, Tita AT. Prevention, diagnosis, and management of hypertensive disorders of pregnancy: a comparison of international guidelines. Curr Hypertens Rep. 2020;22(9):1-10.
26. Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database of Systematic Reviews. 2018(10).
27. Sibai BM. Treatment of hypertension in pregnant women. N Engl J Med. 1996;335(4):257-65.
28. von Dadelszen P, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: an updated metaregression analysis. J Obstet Gynaecol Can. 2002;24(12):941-5.
29. Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, et al. Less-Tight versus Tight Control of Hypertension in Pregnancy. New England Journal of Medicine. 2015;372(5):407-17.
30. Scott G, Gillon TE, Anouk P, von Dadelszen P, Magee LA. GUIDELINES–SIMILARITIES/DISSIMILARITIES. A SYSTEMATIC REVIEW OF INTERNATIONAL CLINICAL PRACTICE GUIDELINES FOR PREGNANCY HYPERTENSION. American Journal of Obstetrics. 2020.
31. Regitz-Zagrosek V R-HJ, Bauersachs J, Blomström-LundqvisCt, Cífková R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P, Lang IM, et al. . 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: The Task Force for the Management of Cardiovascular Diseases during Pregnancy

of the European Society of Cardiology (ESC). European Heart Journal. 2018 39(34):3165–241.
32. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management (NG133). 2019 [cited 18 January 2022]. Available from: https://www.nice.org.uk/guidance/ng133/resources/hypertension-in-pregnancy-diagnosis-and-management-pdf-66141717671365.
33. The American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. Obstetrics and gynecology. 2019;133(1):e26-e50.
34. ACOG Committee Opinion No. 767: Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period. Obstet Gynecol. 2019;133(2):e174-e80.
35. Magee LA, Pels A, Helewa M, Rey E, Von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens. 2014;4(2):105-45.
36. Butalia S, Audibert F, Cote AM, Firoz T, Logan AG, Magee LA, et al. Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy. Can J Cardiol. 2018;34(5):526-31.
37. Gillon TER, 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).
38. Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. Bmj. 2019;366:l5119.
39. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127-e248.
40. Buawangpong N, Teekachunhatean S, Koonrungsesomboon N. Adverse pregnancy outcomes associated with first-trimester exposure to angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers: A systematic review and meta-analysis. Pharmacology research perspectives. 2020;8(5):e00644.
41. Chahine KM, Sibai BM. Chronic Hypertension in Pregnancy: New Concepts for Classification and Management. American Journal of Perinatology. 2019;36(2):161-8.
42. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. Bmj. 2014;348:g2301.
43. Lydakis C, Beevers DG, Beevers M, Lip GY. Obstetric and neonatal outcome following chronic hypertension in pregnancy among different ethnic groups. QJM: monthly journal of the Association of Physicians. 1998;91(12):837-44.
44. Premkumar A, Henry DE, Moghadassi M, Nakagawa S, Norton ME. The interaction between maternal race/ethnicity and chronic hypertension on preterm birth. American Journal of Obstetrics & Gynecology. 2016;215(6):787.e1-.e8.
45. Samadi AR, Mayberry RM. Maternal hypertension and spontaneous preterm births among black women. Obstet Gynecol. 1998;91(6):899-904.

46. Orbach H, Matok I, Gorodischer R, Sheiner E, Daniel S, Wiznitzer A, et al. Hypertension and antihypertensive drugs in pregnancy and perinatal outcomes. American Journal of Obstetrics & Gynecology. 2013;208(4):301.e1-6.
47. Youngstrom M, Tita A, Grant J, Szychowski JM, Harper LM. Perinatal Outcomes in Women With a History of Chronic Hypertension but Normal Blood Pressures Before 20 Weeks of Gestation. Obstetrics and Gynecology. 2018;131(5):827-34.
48. Lennestål R, Olausson PO, Källén B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. European journal of clinical pharmacology. 2009;65(6):615-25.
49. Bánhidy F, Cs N, Puhó EH, Czeizel AE. The efficacy of antihypertensive treatment in pregnant women with chronic and gestational hypertension: A population-based study. Hypertens Res. 2010;33(5):460-6.
50. Hoeltzenbein M, Beck E, Fietz AK, Wernicke J, Zinke S, Kayser A, et al. Pregnancy Outcome After First Trimester Use of Methyldopa: A Prospective Cohort Study. Hypertension. 2017;70(1):201-8.
51. Su CY, Lin HC, Cheng HC, Yen AM, Chen YH, Kao S. Pregnancy outcomes of anti-hypertensives for women with chronic hypertension: a population-based study. PLoS One. 2013;8(2):e53844.
52. Ray JG, Vermeulen MJ, Burrows EA, Burrows RF. Use of antihypertension medications in pregnancy and the risk of adverse perinatal outcomes: McMaster Outcome Study of Hypertension In Pregnancy 2 (MOS HIP 2). BMC Pregnancy and Childbirth. 2001;1.
53. Bayliss H, Churchill D, Beevers M, Beevers DG. Anti-hypertensive drugs in pregnancy and fetal growth: evidence for "pharmacological programming" in the first trimester? Hypertens. 2002;21(2):161-74.
54. Nzelu D, Dumitrascu-Biris D, Nicolaides KH, Kametas NA. Chronic hypertension: first-trimester blood pressure control and likelihood of severe hypertension, preeclampsia, and small for gestational age. American Journal of Obstetrics & Gynecology. 2018;218(3):337.e1-.e7.
55. Webster LM, Conti-Ramsden F, Seed PT, Webb AJ, Nelson-Piercy C, Chappell LC. Impact of Antihypertensive Treatment on Maternal and Perinatal Outcomes in Pregnancy Complicated by Chronic Hypertension: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2017;6(5):17.
56. Panaitescu AM, Roberge S, Nicolaides KH. Chronic hypertension: effect of blood pressure control on pregnancy outcome. J Matern-Fetal Neonatal Med. 2019;32(5):857-63.
57. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. British Medical Journal. 1990;301(6752):587-9.
58. Sibai BM, Mabie WC, Shamsa F, Villar MA, Anderson GD. A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. Am J Obstet Gynecol. 1990;162(4):960-6;.
59. Mabie WC, Pernoll ML, Biswas MK. Chronic hypertension in pregnancy. Obstet Gynecol. 1986;67(2):197-205.
60. Xie RH, Guo Y, Krewski D, Mattison D, Walker MC, Nerenberg K, et al. Beta-blockers increase the risk of being born small for gestational age or of being institutionalised during infancy. An International Journal of Obstetrics & Gynaecology. 2014;121(9):1090-6.

61. Bikbov B, Purcell CA, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2020;395(10225):709-33.
62. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837-46.
63. Levey AS, De Jong PE, Coresh J, Nahas ME, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17-28.
64. Bikbov B, Perico N, Remuzzi G. Disparities in chronic kidney disease prevalence among males and females in 195 countries: analysis of the global burden of disease 2016 study. Nephron. 2018;139:313-8.
65. Piccoli GB, Attini R, Vasario E, Conijn A, Biolcati M, D'Amico F, et al. Pregnancy and chronic kidney disease: A challenge in all CKD stages. Clin J Am Soc Nephrol. 2010;5(5):844-55.
66. Wiles KS, Nelson-Piercy C, Bramham K. Reproductive health and pregnancy in women with chronic kidney disease. Nat Rev Nephrol. 2018;14(3):165-84.
67. Wiles K, Chappell L, Clark K, Elman L, Hall M, Lightstone L, et al. Clinical practice guideline on pregnancy and renal disease. BMC nephrology. 2019;20(1):401.
68. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G. Fetal outcome after in utero exposure to cancer chemotherapy. Arch Intern Med. 1992;152(3):573-6.
69. Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT. Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation. 2006;82(12):1698-702.
70. Deshpande N, James N, Kucirka L, Boyarsky B, Garonzik-Wang J, Montgomery R, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. American Journal of Transplantation. 2011;11(11):2388-404.
71. Williams D, Davison J. Chronic kidney disease in pregnancy. Bmj. 2008;336(7637):211-5.
72. Nevis IF, Reitsma A, Dominic A, McDonald S, Thabane L, Akl EA, et al. Pregnancy Outcomes in Women with Chronic Kidney Disease: A Systematic Review. Clinical Journal of the American Society of Nephrology. 2011;6(11):2587-98.
73. Zhang JJ, Ma XX, Hao L, Liu LJ, Lv JC, Zhang H. A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy. Clinical Journal of the American Society of Nephrology. 2015;10(11):1964-78.
74. Williams D. Physiology of healthy pregnancy. Oxford textbook of medicine. 4th ed. ed: Oxford University Press, Oxford; 2003. p. 383–5.
75. Williams D. Pregnancy: a stress test for life. Curr Opin Obstet Gynecol. 2003;15(6):465-71.
76. Panaitescu AM, Popescu MR, Ciobanu AM, Gica N, Cimpoca-Raptis BA. Pregnancy Complications Can Foreshadow Future Disease—Long-Term Outcomes of a Complicated Pregnancy. Medicina. 2021;57(12):1320.
77. Hajar R. Framingham contribution to cardiovascular disease. Heart views: the official journal of the Gulf Heart Association. 2016;17(2):78.

78. Kesteloot H, Sans S, Kromhout D. Dynamics of cardiovascular and all-cause mortality in Western and Eastern Europe between 1970 and 2000. European heart journal. 2006;27(1):107-13.
79. Vogel B, Acevedo M, Appelman Y, Merz CNB, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. The Lancet. 2021;397(10292):2385-438.
80. Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D, Casas JP, et al. Preeclampsia and Cardiovascular Disease in a Large UK Pregnancy Cohort of Linked Electronic Health Records A CALIBER Study. Circulation. 2019;140(13):1050-60.
81. Robbins CL, Hutchings Y, Dietz PM, Kuklina EV, Callaghan WM. History of preterm birth and subsequent cardiovascular disease: a systematic review. American journal of obstetrics gynecology. 2014;210(4):285-97.
82. Wu P, Gulati M, Kwok CS, Wong CW, Narain A, O'Brien S, et al. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. J Am Heart Assoc. 2018;7(2):e007809.
83. Ngo AD, Roberts CL, Chen JS, Figtree G. Delivery of a small-for-gestational-age infant and risk of maternal cardiovascular disease–a population-based record linkage study. Heart, Lung and Circulation. 2015;24(7):696-704.
84. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications: systematic review and meta-analysis. Circulation. 2019;139(8):1069-79.
85. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux P. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. American heart journal. 2008;156(5):918-30.
86. Bellamy L, Casas J-P, Hingorani AD, Williams D. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. Bmj. 2007;335(7627):974.
87. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013;28(1):1-19.
88. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circulation: Cardiovascular Quality and Outcomes. 2017;10(2):e003497.
89. Malek AM, Wilson DA, Turan TN, Mateus J, Lackland DT, Hunt KJ. Maternal Coronary Heart Disease, Stroke, and Mortality Within 1, 3, and 5 Years of Delivery Among Women With Hypertensive Disorders of Pregnancy and Pre-Pregnancy Hypertension. J Am Heart Assoc. 2021;10(5):e018155.
90. Malek AM, Wilson DA, Turan TN, Mateus J, Lackland DT, Hunt KJ. Incident heart failure within the first and fifth year after delivery among women with hypertensive disorders of pregnancy and prepregnancy hypertension in a diverse population. J Am Heart Assoc. 2021;10(17):e021616.
91. Filippi V, Chou D, Barreix M, Say L, Group WMMW, Barbour K, et al. A new conceptual framework for maternal morbidity. International Journal of Gynecology Obstetrics. 2018;141:4-9.
92. Hussein J. Non-communicable diseases during pregnancy in low and middle income countries. Obstet Med. 2017;10(1):26-9.

93. The impact of chronic hypertension and antihypertensive treatment on adverse maternal and perinatal outcomes [Internet]. PROSPERO. 2019. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=120088
94. Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis. [Internet]. PROSPERO. 2020. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020211925.
95. Song JW, Chung KC. Observational studies: cohort and case-control studies. Plastic reconstructive surgery. 2010;126(6):2234.
96. Szklo M. Population-based cohort studies. Epidemiol Rev. 1998;20(1):81-90.
97. Swedish National Board of Health and Welfare. The Swedish Medical Birth Register-A summary of content and quality. 2003. Report No.: 2003-112-3.
98. National Board of Health and Welfare (Socialstyrelsen). The Swedish Prescribed Drug Register. 2020 [cited 23 October 2021]. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-swedish-prescribed-drug-register/.
99. Bartlett VL, Dhruva SS, Shah ND, Ryan P, Ross JS. Feasibility of using real-world data to replicate clinical trial evidence. JAMA Netw Open. 2019;2(10):e1912869-e.
100. Webster LM, Myers JE, Nelson-Piercy C, Harding K, Cruickshank JK, Watt-Coote I, et al. Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A Randomized Controlled Trial. Hypertension. 2017;70(5):915-22.
101. National Board of Health and Welfare (Socialstyrelsen). The Swedish Medical Birth Register–In English 2019 [cited 21 October 2021]. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-swedish-medical-birth-register/.
102. Cnattingius S, Ericson A, Gunnarskog J, Källén B. A quality study of a medical birth registry. Scandinavian journal of social medicine. 1990;18(2):143-8.
103. Wilcox AJ. The Medical Birth Registry of Norway – An international perspective. Norsk epidemiologi. 2009;17(2).
104. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011;11(1):1-16.
105. National Board of Health and Welfare (Socialstyrelsen). The Swedish National Patient Register–In English 2020 [cited 25 October 2021]. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-national-patient-register/.
106. Elo SL, Karlberg I. Validity and utilization of epidemiological data: a study of ischaemic heart disease and coronary risk factors in a local population. Public Health. 2009;123(1):52-7.
107. Wiréhn A-BE, Karlsson HM, Carstensen JM. Estimating disease prevalence using a population-based administrative healthcare database. Scandinavian journal of public health. 2007;35(4):424-31.
108. Statistics Sweden. Swedish Register of education 2021 [cited 24 October 2021]. Available from: https://www.jpi-dataproject.eu/Home/Database/348?topicId=4.
109. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology. 2009;24(11):659-67.

110. Denaxas SC, George J, Herrett E, Shah AD, Kalra D, Hingorani AD, et al. Data resource profile: cardiovascular disease research using linked bespoke studies and electronic health records (CALIBER). International journal of epidemiology. 2012;41(6):1625-38.
111. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data resource profile: clinical practice research datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.
112. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Therapeutic advances in drug safety. 2012;3(2):89-99.
113. Chisholm JJBBMJ. The Read clinical classification. 1990;300(6732):1092.
114. Denaxas S, Gonzalez-Izquierdo A, Direk K, Fitzpatrick NK, Fatemifar G, Banerjee A, et al. UK phenomics platform for developing and validating electronic health record phenotypes: CALIBER. Journal of the American Medical Informatics Association. 2019;26(12):1545-59.
115. Wood L, Martinez C. The general practice research database. Drug safety. 2004;27(12):871-81.
116. George J, Mathur R, Shah AD, Pujades-Rodriguez M, Denaxas S, Smeeth L, et al. Ethnicity and the first diagnosis of a wide range of cardiovascular diseases: associations in a linked electronic health record cohort of 1 million patients. PloS one. 2017;12(6):e0178945.
117. Bhaskaran K, Forbes HJ, Douglas I, Leon DA, Smeeth L. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). Bmj. 2013;3(9):e003389.
118. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall A. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. British journal of clinical pharmacology. 2010;69(1):4-14.
119. Jick SS, Kaye JA, Vasilakis-Scaramozza C, Rodríguez LAG, Ruigómez A, Meier CR, et al. Validity of the general practice research database. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2003;23(5):686-9.
120. Black D. Data for management: the Körner Report. British Medical Journal. 1982;285(6350):1227.
121. Department of Health. A Simple Guide to Payment by Results [updated 2011. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213150/PbR-Simple-Guide-FINAL.pdf.
122. NHS Digital. Hospital Episode Statistics (HES) 2021 [cited 11 November 2021]. Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics.
123. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data resource profile: hospital episode statistics admitted patient care (HES APC). International journal of epidemiology. 2017;46(4):1093-i.
124. Office for National Statistics. Characteristics of Birth 2, England and Wales. 2014 [cited 11 November 2021]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/characteristicsofbirth2/2014-11-17.
125. WHO. International Classification of Diseases (ICD). [cited 8 November 2021]. Available from: https://www.who.int/classifications/classification-of-diseases.

126. NHS Digital. Clinical Classifications 2008 [cited 8 November 2021]. Available from: https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/dcb0084-opcs-classification-of-interventions-and-procedures.
127. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. Journal of public health. 2012;34(1):138-48.
128. Herrett E, Smeeth L, Walker L, Weston C, Group MA. The myocardial ischaemia national audit project (MINAP). Heart. 2010;96(16):1264-7.
129. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. Bmj. 2013;346.
130. Office for National Statistics. Changing trends in mortality in England and Wales: 1990 to 2018 [cited 9 November 2021]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/changingtrendsinmortalityinenglandandwales1990to2017/1990to2018.
131. Shelton N, Marshall CE, Stuchbury R, Grundy E, Dennett A, Tomlinson J, et al. Cohort profile: the office for national statistics longitudinal study (the LS). International journal of epidemiology. 2019;48(2):383-4g.
132. Harshfield A, Abel GA, Barclay S, Payne RA, care p. Do GPs accurately record date of death? A UK observational analysis. BMJ supportive. 2020;10(3):e24-e.
133. Smith T, Noble M, Noble S, Wright G, McLennan D, Plunkett E, et al. The English indices of deprivation 2015. London: Department for Communities. 2015.
134. Levene LS, Baker R, Bankart J, Walker N, Wilson A. Socioeconomic deprivation scores as predictors of variations in NHS practice payments: a longitudinal study of English general practices 2013–2017. Br J Gen Pract. 2019;69(685):e546-e54.
135. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1· 25 million people. The Lancet. 2014;383(9932):1899-911.
136. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. The Lancet. 2008;371(9606):75-84.
137. Pasternak B, Wintzell V, Furu K, Engeland A, Neovius M, Stephansson OJJ. Oral fluconazole in pregnancy and risk of stillbirth and neonatal death. 2018;319(22):2333-5.
138. Ludvigsson JF, Håberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, et al. Ethical aspects of registry-based research in the Nordic countries. Clinical epidemiology. 2015;7:491.
139. Rothman KJ, Greenland S, Lash TL. Modern epidemiology: Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia; 2008.
140. Gordis L. Epidemiology. 3rd ed: Elsevier; 2004.
141. Boston University School of Public Health. Selection Bias in Cohort Studies and Clinical Trials 2021 [cited 3 March 2022]. Available from: https://sphweb.bumc.bu.edu/otlt/MPH-Modules/PH717-QuantCore/PH717-Module10-Bias/PH717-Module10-Bias4.html

142. Ferreira-González I, Marsal JR, Mitjavila F, Parada A, Ribera A, Cascant P, et al. Patient registries of acute coronary syndrome: assessing or biasing the clinical real world data? Circulation: Cardiovascular Quality and Outcomes. 2009;2(6):540-7.
143. Zielinski R, Ackerson K, Low LK. Planned home birth: benefits, risks, and opportunities. International journal of women's health. 2015;7:361.
144. Office for National Statistics. Birth characteristics in England and Wales: 2014 [cited 3 March 2022]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthcharacteristicsinenglandandwales/2015-10-08.
145. Alexander LK, Lopes B, Ricchetti-Masterson K, Yeatts KB. Sources of systematic error or bias: Information bias. 2nd ed. ed: Chapel Hill : The University of North Carolina at Chapel Hill; 2015.
146. Catalogue of bias collaboration. Bankhead CR SE, Nunan D. Information bias. In: Sackett Catalogue Of Biases. 2019.
147. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, White IR, et al. Smoker, ex-smoker or non-smoker? The validity of routinely recorded smoking status in UK primary care: a cross-sectional study. BMJ Open. 2014;4(4):e004958.
148. Alexander LK, Lopes B, Ricchetti-Masterson K, Yeatts KB. Confounding Bias, Part I. 2nd ed. ed: Chapel Hill : The University of North Carolina at Chapel Hill J ERIC Notebook.; 2015.
149. O'Brien SF, Yi QL. How do I interpret a confidence interval? Transfusion. 2016;56(7):1680-3.
150. Perkins NJ, Cole SR, Harel O, Tchetgen Tchetgen EJ, Sun B, Mitchell EM, et al. Principled approaches to missing data in epidemiologic studies. American journal of epidemiology. 2018;187(3):568-75.
151. Kang H. The prevention and handling of the missing data. Korean journal of anesthesiology. 2013;64(5):402.
152. Mack C, Su Z, Westreich D. Managing missing data in patient registries: addendum to registries for evaluating patient outcomes: a user's guide. 2018.
153. Nicholson B, Aveyard P, Bankhead C, Hamilton W, Hobbs F, Lay-Flurrie S. Determinants and extent of weight recording in UK primary care: an analysis of 5 million adults' electronic health records from 2000 to 2017. BMC medicine. 2019;17(1):1-11.
154. Booth HP, Prevost AT, Gulliford MC. Validity of smoking prevalence estimates from primary care electronic health records compared with national population survey data for England, 2007 to 2011. Pharmacoepidemiology drug safety. 2013;22(12):1357-61.
155. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. 2014;36(4):684-92.
156. NHS Digital. A Summary of Public Health Indicators Using Electronic Data from Primary Care - 2001-2007 2008 [cited 6 June 2022]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/a-summary-of-public-health-indicators-using-electronic-data-from-primary-care/2001-2007.
157. Cheema JR. A review of missing data handling methods in education research. Review of Educational Research. 2014;84(4):487-508.
158. Hunt NB, Gardarsdottir H, Bazelier MT, Klungel OH, Pajouheshnia R. A systematic review of how missing data are handled and reported in multi-database pharmacoepidemiologic studies. Pharmacoepidemiol Drug Saf. 2021;30(7):819-26.

159. Groenwold RH, White IR, Donders AR, Carpenter JR, Altman DG, Moons KG. Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis. Cmaj. 2012;184(11):1265-9.
160. Norris CM, Ghali WA, Knudtson ML, Naylor CD, Saunders LD. Dealing with missing data in observational health care outcome analyses. J Clin Epidemiol. 2000;53(4):377-83.
161. Bennett DA. How can I deal with missing data in my study? Australian and New Zealand journal of public health. 2001;25(5):464-9.
162. Little RJ. A test of missing completely at random for multivariate data with missing values. Journal of the American statistical Association. 1988;83(404):1198-202.
163. Hughes RA, Heron J, Sterne JA, Tilling K. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. International journal of epidemiology. 2019;48(4):1294-304.
164. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2. (updated February 2021). 2021.
165. Jackson D, Bowden J, Baker R. How does the DerSimonian and Laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? Journal of Statistical Planning and Inference. 2010;140(4):961-70.
166. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. International journal of evidence-based healthcare. 2015;13(3):196-207.
167. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled clinical trials. 1986;7(3):177-88.
168. Egger M, Davey Smith G, Altman D. Systematic Reviews in Health Care : Meta-Analysis in Context. New York, UNITED KINGDOM: John Wiley & Sons, Incorporated; 2001.
169. Deeks JJ, Higgins JP. Statistical algorithms in review manager 5. Statistical Methods Group of The Cochrane Collaboration. 2010;1(11).
170. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research synthesis methods. 2010;1(2):97-111.
171. GRADEpro Guideline Development Tool [Software]. [Internet]. McMaster University and Evidence Prime. 2021. Available from: gradepro.org.
172. Schünemann H BJ, Guyatt G, Oxman A, editors.,. GRADE handbook2009.
173. Peng C-YJ, Lee KL, Ingersoll GM. An introduction to logistic regression analysis and reporting. The journal of educational research. 2002;96(1):3-14.
174. Hernán MA RJ. Causal Inference: What If: Boca Raton: Chapman & Hall/CRC; 2020.
175. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate behavioral research. 2011;46(3):399-424.
176. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41-55.
177. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. Journal of Epidemiology Community Health. 2006;60(7):578-86.

178. Lunt M. Selecting an appropriate caliper can be essential for achieving good balance with propensity score matching. American journal of epidemiology. 2014;179(2):226-35.
179. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Statistics in medicine. 2007;26(4):734-53.
180. Cleves M, Gould WW, Marchenko Y. An introduction to survival analysis using Stata. Revised Third Edition ed: Stata press; 2016.
181. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. British journal of cancer. 2003;89(2):232-8.
182. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. Hypertens Res. 2017;40(3):213-20.
183. Roberts CL, Bell JC, Ford JB, Hadfield RM, Algert CS, Morris JM. The accuracy of reporting of the hypertensive disorders of pregnancy in population health data. Hypertension in Pregnancy. 2008;27(3):285-97.
184. American College of Obstetricians Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on hypertension in pregnancy. Obstetrics and gynecology. 2013;122(5):1122.
185. Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. The Lancet Diabetes & Endocrinology. 2016;4(12):1025-36.
186. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Wilson EC, Mathews T. Births: final data for 2009. 2012.
187. Sibai BM. Chronic hypertension in pregnancy. Obstetrics and Gynecology. 2002;100(2):369-77.
188. National Clinical Guideline Centre (UK). Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. National Institute for Health and Clinical Excellence: Guidance. 2011.
189. James PR, Nelson-Piercy C. Management of hypertension before, during, and after pregnancy. Heart. 2004;90(12):1499-504.
190. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.
191. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. Journal of evidence-based medicine. 2015;8(1):2-10.
192. Deeks JJ HJ, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors): Cochrane, 2019; [cited 7 June 2021]. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane, 2019. ]. Available from: https://training.cochrane.org/handbook/current/chapter-10.
193. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. Journal of the american statistical association. 2000;95(449):89-98.
194. Lin L, Chu H, Murad MH, Hong C, Qu Z, Cole SR, et al. Empirical comparison of publication bias tests in meta-analysis. J Gen Intern Med. 2018;33(8):1260-7.

195. The Cochrane Collaboration. Review Manager (RevMan) [Computer program], version 5.3. The Nordic Cochrane Centre, Copenhagen, Denmark. 2014.
196. Rey E, Couturier A. The prognosis of pregnancy in women with chronic hypertension. American Journal of Obstetrics & Gynecology. 1994;171(2):410-6.
197. Conde-Agudelo A, Belizan JM. Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women. An International Journal of Obstetrics & Gynaecology. 2000;107(1):75-83.
198. Samadi AR, Mayberry RM, Reed JW. Preeclampsia associated with chronic hypertension among African-American and White women. Ethn Dis. 2001;11(2):192-200.
199. Mostello D, Catlin TK, Roman L, Holcomb WL, Jr., Leet T. Preeclampsia in the parous woman: who is at risk? American Journal of Obstetrics & Gynecology. 2002;187(2):425-9.
200. Zetterstrom K, Lindeberg SN, Haglund B, Hanson U. Maternal complications in women with chronic hypertension: a population-based cohort study. Acta Obstet Gynecol Scand. 2005;84(5):419-24.
201. Catov JM, Ness RB, Kip KE, Olsen J. Risk of early or severe preeclampsia related to pre-existing conditions. International Journal of Epidemiology. 2007;36(2):412-9.
202. Gilbert WM, Young AL, Danielsen B. Pregnancy outcomes in women with chronic hypertension: a population-based study. J Reprod Med. 2007;52(11):1046-51.
203. Kiondo P, Wamuyu-Maina G, Bimenya GS, Tumwesigye NM, Wandabwa J, Okong P. Risk factors for pre-eclampsia in Mulago Hospital, Kampala, Uganda. Tropical Medicine & International Health. 2012;17(4):480-7.
204. Yanit KE, Snowden JM, Cheng YW, Caughey AB. The impact of chronic hypertension and pregestational diabetes on pregnancy outcomes. American Journal of Obstetrics & Gynecology. 2012;207(4):333.e1-6.
205. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. American Journal of Obstetrics & Gynecology. 2013;209(6):544.e1-.e12.
206. Guerrier G, Oluyide B, Keramarou M, Grais R. Factors associated with severe preeclampsia and eclampsia in Jahun, Nigeria. International Journal of Women's Health. 2013.
207. Aksornphusitaphong A, Phupong V. Risk factors of early and late onset pre-eclampsia. Journal of Obstetrics & Gynaecology Research. 2013;39(3):627-31.
208. Block-Abraham DM, Turan OM, Doyle LE, Kopelman JN, Atlas RO, Jenkins CB, et al. First-trimester risk factors for preeclampsia development in women initiating aspirin by 16 weeks of gestation. Obstet Gynecol. 2014;123(3):611-7.
209. Bilano VL, Ota E, Ganchimeg T, Mori R, Souza JP. Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low- and middle-income countries: a WHO secondary analysis. PLoS One. 2014;9(3):e91198.
210. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG: An International Journal of Obstetrics & Gynaecology. 2014;121 Suppl 1:14-24.

211. You SH, Cheng PJ, Chung TT, Kuo CF, Wu HM, Chu PH. Population-based trends and risk factors of early- and late-onset preeclampsia in Taiwan 2001-2014. BMC Pregnancy and Childbirth. 2018;18(1).
212. Fitzpatrick KE, Hinshaw K, Kurinczuk JJ, Knight M. Risk factors, management, and outcomes of hemolysis, elevated liver enzymes, and low platelets syndrome and elevated liver enzymes, low platelets syndrome. Obstet Gynecol. 2014;123(3):618-27.
213. Malmstrom O, Morken NH. HELLP syndrome, risk factors in first and second pregnancy: a population-based cohort study. Acta Obstetricia Et Gynecologica Scandinavica. 2018;97(6):709-16.
214. Acien P, Lloret G, Lloret M. Perinatal morbidity and mortality in pregnancy hypertensive disorders: prognostic value of the clinical and laboratory findings. International Journal of Gynaecology & Obstetrics. 1990;32(3):229-35.
215. Ananth CV, Peedicayil A, Savitz DA. Effect of hypertensive diseases in pregnancy on birthweight, gestational duration, and small-for-gestational-age births. Epidemiology. 1995;6(4):391-5.
216. McCowan LM, Buist RG, North RA, Gamble G. Perinatal morbidity in chronic hypertension. British Journal of Obstetrics & Gynaecology. 1996;103(2):123-9.
217. Jain L. Effect of pregnancy-induced and chronic hypertension on pregnancy outcome. J Perinatol. 1997;17(6):425-7.
218. Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, et al. The preterm prediction study: Risk factors for indicated preterm births. Am J Obstet Gynecol. 1998;178(3):562-7.
219. Lydakis C, Beevers M, Beevers DC, Gyh Lip MD. The prevalence of pre-eclampsia and obstetric outcome in pregnancies of normotensive and hypertensive women attending a hospital specialist clinic. International Journal of Clinical Practice. 2001;55(6):361-7.
220. Roberts CL, Algert CS, Morris JM, Ford JB, Henderson-Smart DJ. Hypertensive disorders in pregnancy: a population-based study. Med J Aust. 2005;182(7):332-5.
221. Graham J, Zhang L, Schwalberg R. Association of maternal chronic disease and negative birth outcomes in a non-Hispanic Black-White Mississippi birth cohort. Public Health Nursing. 2007;24(4):311-7.
222. Carter MF, Fowler S, Holden A, Xenakis E, Dudley D. The late preterm birth rate and its association with comorbidities in a population-based study. Am J Perinatol. 2011;28(9):703-7.
223. Ferrazzani S, Luciano R, Garofalo S, D'Andrea V, De Carolis S, De Carolis MP, et al. Neonatal outcome in hypertensive disorders of pregnancy. Early Hum Dev. 2011;87(6):445-9.
224. Tuuli MG, Rampersad R, Stamilio D, Macones G, Odibo AO. Perinatal outcomes in women with preeclampsia and superimposed preeclampsia: do they differ? American Journal of Obstetrics & Gynecology. 2011;204(6):508.e1-7.
225. Morisaki N, Togoobaatar G, Vogel JP, Souza JP, Hogue CJR, Jayaratne K, et al. Risk factors for spontaneous and provider- initiated preterm delivery in high and low Human Development Index countries: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. An International Journal of Obstetrics and Gynaecology. 2014;121:101-9.

226. Ye C, Ruan Y, Zou L, Li G, Li C, Chen Y, et al. The 2011 survey on hypertensive disorders of pregnancy (HDP) in China: prevalence, risk factors, complications, pregnancy and perinatal outcomes. PLoS One. 2014;9(6):e100180.
227. Arora CP, Kacerovsky M, Zinner B, Ertl T, Ceausu I, Rusnak I, et al. Disparities and relative risk ratio of preterm birth in six Central and Eastern European centers. Croatian Medical Journal. 2015;56(2):119-27.
228. Derakhshi B, Esmailnasab N, Ghaderi E, Hemmatpour S. Risk Factor of Preterm Labor in the West of Iran: A Case-Control Study. Iranian Journal of Public Health. 2014;43(4):499-506.
229. Tucker CM, Berrien K, Menard MK, Herring AH, Daniels J, Rowley DL, et al. Predicting Preterm Birth Among Women Screened by North Carolina's Pregnancy Medical Home Program. Maternal and child health journal. 2015;19(11):2438-52.
230. Yang Y, He Y, Li Q, Wang YY, Peng ZQ, Xu JH, et al. Preconception blood pressure and risk of preterm birth: a large historical cohort study in a Chinese rural population. Fertil Steril. 2015;104(1):124-30.
231. Souza RT, Cecatti JG, Passini R, Tedesco RP, Lajos GJ, Nomura ML, et al. The burden of provider-initiated preterm birth and associated factors: Evidence from the Brazilian Multicenter study on preterm birth (EMIP). PLoS One. 2016;11(2).
232. Campbell EE, Gilliland J, Dworatzek PDN, De Vrijer B, Penava D, Seabrook JA. Socioeconomic Status and Adverse Birth Outcomes: A Population-Based Canadian Sample. Journal of Biosocial Science. 2018;50(1):102-13.
233. Sass N, Moron AF, el-Kadre D, Camano L, de Almeida PA. [Study of pregnancy with chronic hypertension]. Revista Paulista de Medicina. 1990;108(6):261-6.
234. Haelterman E, Breart G, ParisLlado J, Dramaix M, Tchobroutsky C. Effect of uncomplicated chronic hypertension on the risk of small-for-gestational age birth. Am J Epidemiol. 1997;145(8):689-95.
235. Allen VM, Joseph KS, Murphy KE, Magee LA, Ohlsson A. The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: A population based study. BMC Pregnancy and Childbirth. 2004;4.
236. Vanek M, Sheiner E, Levy A, Mazor M. Chronic hypertension and the risk for adverse pregnancy outcome after superimposed pre-eclampsia. International Journal of Gynaecology & Obstetrics. 2004;86(1):7-11.
237. Odibo AO, Nelson D, Stamilio DM, Sehdev HM, Macones GA. Advanced maternal age is an independent risk factor for intrauterine growth restriction. Am J Perinatol. 2006;23(5):325-8.
238. Rasmussen S, Irgens LM. The effects of smoking and hypertensive disorders on fetal growth. BMC Pregnancy and Childbirth. 2006;6.
239. Zetterstrom K, Lindeberg SN, Haglund B, Hanson U. Chronic hypertension as a risk factor for offspring to be born small for gestational age. Acta Obstet Gynecol Scand. 2006;85(9):1046-50.
240. Catov JM, Nohr EA, Olsen J, Ness RB. Chronic hypertension related to risk for preterm and term small for gestational age births. Obstet Gynecol. 2008;112(2 Pt 1):290-6.
241. Cruz MO, Gao WH, Hibbard JU. Obstetrical and perinatal outcomes among women with gestational hypertension, mild preeclampsia, and mild chronic hypertension. Am J Obstet Gynecol. 2011;205(3):9.

242. Poon LCY, Karagiannis G, Staboulidou I, Shafiei A, Nicolaides KH. Reference range of birth weight with gestation and first-trimester prediction of small-for-gestation neonates. Prenatal Diagnosis. 2011;31(1):58-65.
243. Madi JM, Araujo BF, Zatti H, Rombaldi RL, Madi SRC, de Zorzi P, et al. Chronic Hypertension and Pregnancy at a Tertiary-Care and University Hospital. Hypertens. 2012;31(3):350-6.
244. Anderson NH, Sadler LC, Stewart AW, Fyfe EM, McCowan LM. Independent risk factors for infants who are small for gestational age by customised birthweight centiles in a multi-ethnic New Zealand population. Aust N Z J Obstet Gynaecol. 2013;53(2):136-42.
245. Ota E, Ganchimeg T, Morisaki N, Vogel JP, Pileggi C, Ortiz-Panozo E, et al. Risk factors and adverse perinatal outcomes among term and preterm infants born small-for-gestational-age: Secondary analyses of the WHO multi-country survey on maternal and newborn health. PLoS One. 2014;9(8).
246. Xaverius PK, Salas J, Woolfolk CL, Leung F, Yuan J, Chang JJ. Predictors of size for gestational age in St. Louis City and County. BioMed Research International. 2014;2014:515827.
247. Velentgas P, Benga-De E, Williams MA. Chronic hypertension, pregnancy-induced hypertension, and low birthweight. Epidemiology. 1994;5(3):345-8.
248. Odell CD, Kotelchuck M, Chetty VK, Fowler J, Stubblefield PG, Orejuela M, et al. Maternal hypertension as a risk factor for low birth weight infants: comparison of Haitian and African-American women. Maternal & Child Health Journal. 2006;10(1):39-46.
249. Vahdaninia M, Tavafian SS, Montazeri A. Correlates of low birth weight in term pregnancies: A retrospective study from Iran. BMC Pregnancy and Childbirth. 2008;8.
250. Harvey EM, Strobino D, Sherrod L, Webb MC, Anderson C, White JA, et al. Community-Academic Partnership to Investigate Low Birth Weight Deliveries and Improve Maternal and Infant Outcomes at a Baltimore City Hospital. Maternal & Child Health Journal. 2017;21(2):260-6.
251. Hailu LD, Kebede DL. Determinants of low birth weight among deliveries at a Referral Hospital in Northern Ethiopia. BioMed Research International. 2018;2018.
252. Zetterstrom K, Lindeberg SN, Haglund B, Hanson U. The association of maternal chronic hypertension with perinatal death in male and female offspring: a record linkage study of 866,188 women. An International Journal of Obstetrics & Gynaecology. 2008;115(11):1436-42.
253. Ahmad AS, Samuelsen SO. Hypertensive disorders in pregnancy and fetal death at different gestational lengths: a population study of 2 121 371 pregnancies. An International Journal of Obstetrics & Gynaecology. 2012;119(12):1521-8.
254. Hjertberg R, Belfrage P, Hanson U. Conservative treatment of mild and moderate hypertension in pregnancy. Acta Obstetricia et Gynecologica Scandinavica. 1992;71(6):439-46.
255. Ananth CV, Savitz DA, Bowes Jr WA. Hypertensive disorders of pregnancy and stillbirth in North Carolina, 1988 to 1991. Acta Obstet Gynecol Scand. 1995;74(10):788-93.
256. Canterino JC, Ananth CV, Smulian J, Harrigan JT, Vintzileos AM. Maternal age and risk of fetal death in singleton gestations: USA, 1995-2000. Journal of Maternal-Fetal and Neonatal Medicine. 2004;15(3):193-7.

257. Rey E. Preeclampsia and neonatal outcomes in chronic hypertension: comparison between white and black women. Ethn Dis. 1997;7(1):5-11.
258. Janoudi G, Kelly S, Yasseen A, Hamam H, Moretti F, Walker M. Factors Associated With Increased Rates of Caesarean Section in Women of Advanced Maternal Age. Journal of Obstetrics & Gynaecology Canada. 2015;37(6):517-26.
259. Kuklina EV, Ayala C, Callaghan WM. Hypertensive disorders and severe obstetric morbidity in the United States. Obstetrics & Gynecology,. 2009;113(6):1299-306.
260. Campbell KH, Savitz D, Werner EF, Pettker CM, Goffman D, Chazotte C, et al. Maternal morbidity and risk of death at delivery hospitalization. Obstet Gynecol. 2013;122(3):627-33.
261. Copper RL, Goldenberg RL, DuBard MB, Davis RO. Risk factors for fetal death in white, black and Hispanic women. Obstetrics and Gynecology. 1994;84(4 I):490-5.
262. Conde-Agudelo A, Belizan JM, Diaz-Rossello JL. Epidemiology of fetal death in Latin America. Acta Obstetricia et Gynecologica Scandinavica. 2000;79(5):371-8.
263. Aagaard-Tillery KM, Holmgren C, Lacoursiere DY, Houssain S, Bloebaum L, Satterfield R, et al. Factors associated with nonanomalous stillbirths: the Utah Stillbirth Database 1992-2002. American Journal of Obstetrics & Gynecology. 2006;194(3):849-54.
264. Reddy UM, Laughon SK, Sun L, Troendle J, Willinger M, Zhang J. Prepregnancy risk factors for antepartum stillbirth in the United States. Obstet Gynecol. 2010;116(5):1119-26.
265. Yerlikaya G, Akolekar R, McPherson K, Syngelaki A, Nicolaides KH. Prediction of stillbirth from maternal demographic and pregnancy characteristics. Ultrasound Obstet Gynecol. 2016;48(5):607-12.
266. Xiong T, Mu Y, Liang J, Zhu J, Li X, Li J, et al. Hypertensive disorders in pregnancy and stillbirth rates: A facility-based study in China. Bulletin of the World Health Organization. 2018;96(8):531-9.
267. Rezk M, Ellakwa H, Gamal A, Emara M. Maternal and fetal morbidity following discontinuation of antihypertensive drugs in mild to moderate chronic hypertension: A 4-year observational study. Pregnancy Hypertension. 2016;6(4):291-4.
268. Helou A, Walker S, Stewart K, George J. Management of pregnancies complicated by hypertensive disorders of pregnancy: Could we do better? Aust N Z J Obstet Gynaecol. 2017;57(3):253-9.
269. Mito A, Murashima A, Wada Y, Miyasato-Isoda M, Kamiya CA, Waguri M, et al. Safety of amlodipine in early pregnancy. 2019;8(15):e012093.
270. Ahmed B, Tran DT, Zoega H, Kennedy SE, Jorm LR, Havard A. Maternal and perinatal outcomes associated with the use of renin-angiotensin system (RAS) blockers for chronic hypertension in early pregnancy. Pregnancy Hypertension. 2018;14:156-61.
271. Fisher SC, Van Zutphen AR, Werler MM, Romitti PA, Cunniff C, Browne ML. Maternal antihypertensive medication use and selected birth defects in the National Birth Defects Prevention Study. Birth Defects Research. 2018;110(19):1433-42.
272. Fletcher J. What is heterogeneity and is it important? Bmj. 2007;334(7584):94-6.

273. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. Bmj. 2003;326(7394):845.
274. Palmsten K, Buka SL, Michels KB. Maternal pregnancy-related hypertension and risk for hypertension in offspring later in life. Obstet Gynecol. 2010;116(4):858-64.
275. Phillips DI, Walker BR, Reynolds RM, Flanagan DE, Wood PJ, Osmond C, et al. Low birth weight predicts elevated plasma cortisol concentrations in adults from 3 populations. Hypertension. 2000;35(6):1301-6.
276. Sibai BM, Lindheimer M, Hauth J, Caritis S, VanDorsten P, Klebanoff M, et al. Risk factors for preeclampsia, abruptio placentae, and adverse neonatal outcomes among women with chronic hypertension. New England Journal of Medicine. 1998;339(10):667-71.
277. Easterling T, Mundle S, Bracken H, Parvekar S, Mool S, Magee LA, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. The Lancet. 2019;394(10203):1011-21.
278. Bellos I, Pergialiotis V, Papapanagiotou A, Loutradis D, Daskalakis G. Comparative efficacy and safety of oral antihypertensive agents in pregnant women with chronic hypertension: a network meta-analysis. Am J Obstet Gynecol. 2020.
279. Magee LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S, et al. The CHIPS Randomized Controlled Trial (Control of Hypertension in Pregnancy Study): Is Severe Hypertension Just an Elevated Blood Pressure? Hypertension. 2016;68(5):1153-9.
280. Knight M BK, Tuffnell D, Jayakody H, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ (Eds.),. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2014-16. 2018.
281. World Health Organization. Trends in maternal mortality: 1990-2015: estimates from WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division: executive summary. World Health Organization; 2015.
282. Creanga AA, Berg CJ, Syverson C, Seed K, Bruce FC, Callaghan WM. Pregnancy-related mortality in the United States, 2006-2010. Obstet Gynecol. 2015;125(1):5-12.
283. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-Related Mortality in the United States, 2011-2013. Obstet Gynecol. 2017;130(2):366-73.
284. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. Jama. 2007;298(17):2038-47.
285. Leaños-Miranda A, Campos-Galicia I, Ramírez-Valenzuela KL, Berumen-Lechuga MG, Isordia-Salas I, Molina-Pérez CJ. Urinary IgM excretion: a reliable marker for adverse pregnancy outcomes in women with chronic kidney disease. Journal of Nephrology. 2019;32(2):241-51.
286. Feng Z, Minard C, Raghavan R. Pregnancy outcomes in advanced kidney disease. Clin Nephrol. 2015;83(5):272-8.
287. Bramham K, Briley AL, Seed P, Poston L, Shennan AH, Chappell LC. Adverse maternal and perinatal outcomes in women with previous preeclampsia: A prospective study. American Journal of Obstetrics and Gynecology. 2011;204(6):512.e1-.e9.

288. Blom K, Odutayo A, Bramham K, Hladunewich MA. Pregnancy and glomerular disease: a systematic review of the literature with management guidelines. American Society of Nephrology. 2017;12(11):1862-72.
289. Wells GA, Shea B, O'Connell Da, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford; 2000.
290. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology. 2011;64(4):401-6.
291. Huguet A, Hayden JA, Stinson J, McGrath PJ, Chambers CT, Tougas ME, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Systematic reviews. 2013;2(1):1-12.
292. Iorio A, Spencer FA, Falavigna M, Alba C, Lang E, Burnand B, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. Bmj. 2015;350.
293. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.
294. Fink JC, Schwartz SM, Benedetti TJ, Stehman-Breen CO. Increased risk of adverse maternal and infant outcomes among women with renal disease. Paediatric and Perinatal Epidemiology. 1998;12(3):277-87.
295. Tanz LJ, Stuart JJ, Williams PL, Missmer SA, Rimm EB, James-Todd TM, et al. Preterm Delivery and Maternal Cardiovascular Disease Risk Factors: The Nurses' Health Study II. J Womens Health. 2018:9.
296. Tsuchiyama F, Makino Y, Hirasawa K, Nagata S, Matsui H. Cerebral Palsy and Intellectual Disability in the Children of Women With Chronic Kidney Disease. Pediatr Neurol. 2017;73:71-7.
297. Wu M, Wang D, Zand L, Harris PC, White WM, Garovic VD, et al. Pregnancy outcomes in autosomal dominant polycystic kidney disease: A case-control study. Journal of Maternal-Fetal and Neonatal Medicine. 2016;29(5):807-12.
298. Patel EM, Goodnight WH, James AH, Grotegut CA. Temporal trends in maternal medical conditions and stillbirth. American Journal of Obstetrics and Gynecology. 2015;212(5):673.e1-.e11.
299. Kendrick J, Sharma S, Holmen J, Palit S, Nuccio E, Chonchol M. Kidney disease and maternal and fetal outcomes in pregnancy. Am J Kidney Dis. 2015;66(1):55-9.
300. Young EC, Pires ML, Marques LP, de Oliveira JE, Zajdenverg L. Effects of pregnancy on the onset and progression of diabetic nephropathy and of diabetic nephropathy on pregnancy outcomes. Diabetes Metab Syndr. 2011;5(3):137-42.
301. Jensen DM, Damm P, Ovesen PER, Mølsted-Pedersen L, Beck-Nielsen H, Westergaard JG, et al. Microalbuminuria, preeclampsia, and preterm delivery in pregnant women with type 1 diabetes: Results from a nationwide Danish study. Diabetes Care. 2010;33(1):90-4.
302. Trevisan G, Ramos JGL, Martins-Costa S, Barros EJG. Pregnancy in patients with chronic renal insufficiency at Hospital de Clinicas of Porto Alegre, Brazil. Ren Fail. 2004;26(1):29-34.
303. Ekbom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Mølvig J, Mathiesen ER. Pregnancy outcome in type 1 diabetic women with microalbuminuria. Diabetes care. 2001;24(10):1739-44.

304. Biesenbach G, Grafinger P, Zazgornik J, Stöger H. Perinatal complications and three-year follow up of infants of diabetic mothers with diabetic nephropathy stage IV. Renal Failure. 2000;22(5):573-80.
305. Miodovnik M, Rosenn BM, Khoury JC, Grigsby JL, Siddiqi TA. Does pregnancy increase the risk for development and progression of diabetic nephropathy? Am J Obstet Gynecol. 1996;174(4):1180-9; discussion 9-91.
306. Kimmerle R, Zass RP, Cupisti S, Somville T, Bender R, Pawlowski B, et al. Pregnancies in women with diabetic nephropathy: long-term outcome for mother and child. Diabetologia. 1995;38(2):227-35.
307. Seah JM, Kam NM, Wong L, Tanner C, MacIsaac RJ, Shub A, et al. The association between maternal renal function and pregnancy outcomes in type 1 and type 2 diabetes. Diabetes Res Clin Pract. 2020;165.
308. Holley JL, Bernardini J, Quadri KHM, Greenberg A, Laifer SA. Pregnancy outcomes in a prospective matched control study of pregnancy and renal disease. Clin Nephrol. 1996;45(2):77-82.
309. Harel Z, Park AL, McArthur E, Hladunewich M, Dirk JS, Wald R, et al. Prepregnancy renal function and risk of preterm birth and related outcomes. Can Med Assoc J. 2020;192(30):E851-E7.
310. Al Khalaf SY, O'Reilly EJ, McCarthy FP, Kublickas M, Kublickiene K, Khashan AS. Pregnancy outcomes in women with chronic kidney disease and chronic hypertension: a National cohort study. Am J Obstet Gynecol. 2021;225(3):298 e1- e20.
311. He YD, Liu J, Cai QQ, Lv JC, Yu F, Chen Q, et al. The pregnancy outcomes in patients with stage 3-4 chronic kidney disease and the effects of pregnancy in the long-term kidney function. J Nephrol. 2018;31(6):953-60.
312. Bharti J, Vatsa R, Singhal S, Roy KK, Kumar S, Perumal V, et al. Pregnancy with chronic kidney disease: maternal and fetal outcome. Eur J Obstet Gynecol Reprod Biol. 2016;204:83-7.
313. Singh R, Prasad N, Banka A, Gupta A, Bhadauria D, Sharma R, et al. Pregnancy in patients with chronic kidney disease: Maternal and fetal outcomes. Indian Journal of Nephrology. 2015;25(4):194-9.
314. Imbasciati E, Gregorini G, Cabiddu G, Gammaro L, Ambroso G, Del Giudice A, et al. Pregnancy in CKD stages 3 to 5: Fetal and maternal outcomes. Am J Kidney Dis. 2007;49(6):753-62.
315. Reece EA, Coustan DR, Hayslett JP, Holford T, Coulehan J, O'Connor TZ, et al. Diabetic nephropathy: Pregnancy performance and fetomaternal outcome. American Journal of Obstetrics and Gynecology. 1988;159(1):56-66.
316. Wiles K, Webster P, Seed PT, Bennett-Richards K, Bramham K, Brunskill N, et al. The impact of chronic kidney disease Stages 3-5 on pregnancy outcomes. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2020.
317. Madazlı R, Kaymak D, Alpay V, Mahmudova A, Seyahi N. Evaluation of obstetric outcomes and prognostic factors in pregnancies with chronic kidney disease. Hypertension in Pregnancy. 2021;40(1):75-80.
318. Wiles KS, Bramham K, Vais A, Harding KR, Chowdhury P, Taylor CJ, et al. Pre-pregnancy counselling for women with chronic kidney disease: A retrospective analysis of nine years' experience. BMC Nephrol. 2015;16(1).
319. Madej A, Mazanowska N, Cyganek A, Pazik J, Pietrzak B. Neonatal and Maternal Outcomes among Women with Glomerulonephritis. Am J Nephrol. 2020;51(7):534-41.

320. Piccoli GB, Attini R, Cabiddu G, Kooij I, Fassio F, Gerbino M, et al. Maternal-foetal outcomes in pregnant women with glomerulonephritides. Are all glomerulonephritides alike in pregnancy? J Autoimmun. 2017;79:91-8.
321. Davidson NL, Wolski P, Callaway LK, Barrett HL, Fagermo N, Lust K, et al. Chronic kidney disease in pregnancy: Maternal and fetal outcomes and progression of kidney disease. Obstetric Medicine. 2015;8(2):92-8.
322. Piccoli GB, Cabiddu G, Attini R, Vigotti FN, Maxia S, Lepori N, et al. Risk of adverse pregnancy outcomes in women with CKD. Journal of the American Society of Nephrology. 2015;26(8):2011-22.
323. Wu J, Ma J, Zhang W-H, Di W. Management and outcomes of pregnancy with or without lupus nephritis: a systematic review and meta-analysis. Therapeutics Clinical Risk Management. 2018;14:885.
324. Hussain A, Karovitch A, Carson MP. Blood Pressure Goals and Treatment in Pregnant Patients With Chronic Kidney Disease. Advances in Chronic Kidney Disease. 2015;22(2):165-9.
325. Bramham K, Poli-de-Figueiredo CE, Seed PT, Briley AL, Poston L, Shennan AH, et al. Association of proteinuria threshold in pre-eclampsia with maternal and perinatal outcomes: a nested case control cohort of high risk women. PLoS One. 2013;8(10):e76083.
326. Farwell J, Emerson J, Wyatt S, Rueda J, Cheng Y, Caughey A. 346: Outcomes of pregnancies complicated by chronic kidney disease. American Journal of Obstetrics & Gynecology. 2013;208(1):S153-S4.
327. Kramer MS, Demissie K, Yang H, Platt RW, Sauvé R, Liston R, et al. The contribution of mild and moderate preterm birth to infant mortality. Jama. 2000;284(7):843-9.
328. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A, Network VO. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. American journal of obstetrics and gynecology. 2000;182(1):198-206.
329. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks J, et al. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol. 2013;42(4):400-8.
330. Corsello G, Piro E. The world of twins: an update. The Journal of Maternal-Fetal & Neonatal Medicine. 2010;23(sup3):59-62.
331. Greenwell T, Venn S, Creighton S, Leaver R, Woodhouse C. Pregnancy after lower urinary tract reconstruction for congenital abnormalities. BJU international. 2003;92(7):773-7.
332. Li Y, Wang W, Wang Y, Chen Q. Fetal risks and maternal renal complications in pregnancy with preexisting chronic glomerulonephritis. Medical Science Monitor. 2018;24:1008-16.
333. Hui D, Hladunewich MA. Chronic Kidney Disease and Pregnancy. Obstetrics and Gynecology. 2019;133(6):1182-94.
334. Al Khalaf SY, O'Reilly ÉJ, Barrett PM, B. Leite DF, Pawley LC, McCarthy FP, et al. Impact of Chronic Hypertension and Antihypertensive Treatment on Adverse Perinatal Outcomes: Systematic Review and Meta-Analysis. J Am Heart Assoc. 2021:e018494.
335. 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.

336. Buis M. POSTRCSPLINE: Stata module containing post-estimation commands for models using a restricted cubic spline. 2013.
337. Langan SM, Schmidt SA, Wing K, Ehrenstein V, Nicholls SG, Filion KB, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). Bmj. 2018;363.
338. Cea Soriano L, Bateman BT, García Rodríguez LA, Hernández-Díaz S. Prescription of antihypertensive medications during pregnancy in the UK. Pharmacoepidemiol Drug Saf. 2014;23(10):1051-8.
339. Bateman BT, Hernandez-Diaz S, Huybrechts KF, Palmsten K, Mogun H, Ecker JL, et al. Patterns of outpatient antihypertensive medication use during pregnancy in a medicaid population. Hypertension. 2012;60(4):913-20.
340. Ishikawa T, Obara T, Nishigori H, Miyakoda K, Ishikuro M, Metoki H, et al. Antihypertensives prescribed for pregnant women in Japan: Prevalence and timing determined from a database of health insurance claims. Pharmacoepidemiol Drug Saf. 2018;27(12):1325-34.
341. Magee LA, Singer J, Lee T, McManus RJ, Lay-Flurrie S, Rey E, et al. Are blood pressure level and variability related to pregnancy outcome? Analysis of control of hypertension in pregnancy study data. Pregnancy Hypertens. 2020;19:87-93.
342. Allen SE, Tita A, Anderson S, Biggio JR, Harper DL. Is use of multiple antihypertensive agents to achieve blood pressure control associated with adverse pregnancy outcomes? J Perinatol. 2017;37(4):340-4.
343. Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. Nature Reviews Rheumatology. 2015;11(7):437-41.
344. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Current epidemiology reports. 2015;2(4):221-8.
345. Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. The Lancet. 2021;398(10304):957-80.
346. Public Health England. Health matters: combating high blood pressure. 2017.
347. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. Journal of the American College of Cardiology. 2020;76(25):2982-3021.
348. Jagannathan R, Patel SA, Ali MK, Narayan K. Global updates on cardiovascular disease mortality trends and attribution of traditional risk factors. Curr Diab Rep. 2019;19(7):1-12.
349. Lopez AD, Adair T. Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics. International journal of epidemiology. 2019;48(6):1815-23.
350. UK Health Security Agency. 2019. [15 February 2022]. Available from: https://ukhsa.blog.gov.uk/2019/02/14/health-matters-preventing-cardiovascular-disease/.
351. Office for National Statistics. Childbearing for women born in different years, England and Wales: 2019. 2020.
352. Parikh NI, Gonzalez JM, Anderson CA, Judd SE, Rexrode KM, Hlatky MA, et al. Adverse pregnancy outcomes and cardiovascular disease risk: unique

opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. Circulation. 2021;143(18):e902-e16.
353. Ezekowitz JA, Kaul P, Bakal JA, Quan H, McAlister FA. Trends in heart failure care: has the incident diagnosis of heart failure shifted from the hospital to the emergency department and outpatient clinics? European journal of heart failure. 2011;13(2):142-7.
354. Crump C, Sundquist J, Howell EA, McLaughlin MA, Stroustrup A, Sundquist K. Pre-term delivery and risk of ischemic heart disease in women. J Am Coll Cardiol. 2020;76(1):57-67.
355. Brown HL, Warner JJ, Gianos E, Gulati M, Hill AJ, Hollier LM, et al. Promoting risk identification and reduction of cardiovascular disease in women through collaboration with obstetricians and gynecologists: a presidential advisory from the American Heart Association and the American College of Obstetricians and Gynecologists. Circulation. 2018;137(24):e843-e52.
356. Gynecologists. ACoO. ACOG practice bulletin no. 212: pregnancy and heart disease. Obstet Gynecol. 2019;133(5):e320-e56.
357. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. Circulation. 2011;123(11):1243-62.
358. Gamble DT, Brikinns B, Myint PK, Bhattacharya S. Hypertensive Disorders of Pregnancy and Subsequent Cardiovascular Disease: Current National and International Guidelines and the Need for Future Research. Front Cardiovasc Med. 2019;6:55.
359. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. Circulation. 2014;130(12):1003-8.
360. Wu P, Mamas MA, Gulati M. Pregnancy as a predictor of maternal cardiovascular disease: the era of CardioObstetrics. Journal of Women's Health. 2019;28(8):1037-50.
361. Al Khalaf S, Khashan AS, Chappell LC, O'Reilly É J, McCarthy FP. Role of Antihypertensive Treatment and Blood Pressure Control in the Occurrence of Adverse Pregnancy Outcomes: a Population-Based Study of Linked Electronic Health Records. Hypertension. 2022:101161hypertensionaha12218920.
362. Hill AB. The environment and disease: association or causation? : Sage Publications; 1965.
363. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerging themes in epidemiology. 2015;12(1):1-9.
364. Susser M. What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epidemiol. 1991;133(7):635-48.
365. OECD/European Observatory on Health Systems and Policies. Sweden: Country Health Profile 2021, State of Health in the EU, OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels. 2021.
366. Hiam L, Orcutt M, Yates R. Universal health coverage in the UK. Bmj. 2019;367.
367. Westreich D. Berkson’s bias, selection bias, and missing data. Epidemiology. 2012;23(1):159.
368. Little RJA, Rubin DB. Statistical Analysis with Missing Data. Newy York: John Wiley & Sons, Incorporated; 2002.

369. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, Petersen I. Issues in multiple imputation of missing data for large general practice clinical databases. Pharmacoepidemiology drug safety. 2010;19(6):618-26.
370. Lee KJ, Tilling KM, Cornish RP, Little RJ, Bell ML, Goetghebeur E, et al. Framework for the treatment and reporting of missing data in observational studies: The Treatment And Reporting of Missing data in Observational Studies framework. J Clin Epidemiol. 2021;134:79-88.
371. Liu L, Ma Y, Wang N, Lin W, Liu Y, Wen D. Maternal body mass index and risk of neonatal adverse outcomes in China: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2019;19(1):105.
372. Marchi J, Berg M, Dencker A, Olander EK, Begley C. Risks associated with obesity in pregnancy, for the mother and baby: a systematic review of reviews. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2015;16(8):621-38.
373. Avşar TS, McLeod H, Jackson L. Health outcomes of smoking during pregnancy and the postpartum period: an umbrella review. BMC Pregnancy Childbirth. 2021;21(1):254.
374. Ashworth D, Battersby C, Green M, Hardy P, McManus RJ, Cluver C, et al. Which antihypertensive treatment is better for mild to moderate hypertension in pregnancy? Bmj. 2022;376:e066333.
375. Herbert RD, Kasza J, Bø K. Analysis of randomised trials with long-term follow-up. BMC Medical Research Methodology. 2018;18(1):1-9.
376. Ahmed RJ, Gafni A, Hutton EK, Hu ZJ, Pullenayegum E, Von Dadelszen P, et al. The Cost Implications of Less Tight Versus Tight Control of Hypertension in Pregnancy (CHIPS Trial). Hypertension. 2016;68(4):1049-55.
377. Wiles K, de Oliveira L. Dialysis in pregnancy. Best Practice & Research Clinical & Obstetrics Gynaecology. 2019;57:33-46.

# APPENDICES

# Appendix 1: The impact of Chronic Hypertension and Antihypertensive Treatment on Adverse Maternal and Perinatal Outcomes: A Systematic Review and Meta-Analysis Protocol

***Sukainah Al Khalaf***, *Éilis J O'Reilly, Peter Barrett, Fergus McCarthy, Ali Khashan*

**Objectives**

• To conduct a systematic review and meta-analysis of adverse maternal and perinatal outcomes among pregnant women with chronic hypertension compared with normotensive women.

• To investigate whether using antihypertensive medications during pregnancy has beneficial or harmful effects on the risk of specific maternal and perinatal outcomes.

• To compare the effect of different types of antihypertensive medications on the risk of adverse pregnancy and perinatal outcomes.

**Review Questions:**

1. What are the pooled estimates from existing literature assessing the effect of chronic hypertension during pregnancy on the risk of adverse maternal and perinatal outcomes?

2. In women with hypertension during pregnancy, does the use of antihypertensive medication reduce the risk of adverse maternal or perinatal outcomes?

3. Which antihypertensive agent is associated with the lowest risk of adverse maternal and perinatal outcomes?

**Searches**

A comprehensive electronic search of PubMed/ MEDLINE, Embase and Web of Science will be performed using a combination of medical subject heading (MeSH) terms and keywords related to chronic hypertension, use of antihypertensive treatment during pregnancy and maternal/perinatal outcomes, without any restrictions on time period.

The bibliographies of previous systematic reviews, and all included studies will be searched for further potentially relevant articles. In addition, the searches will be repeated before finalizing the results in order to identify any potentially eligible studies that have been published after the initial search

**Types of study to be included**

We will include observational studies: cohort and case-control studies.

**Condition or domain being studied**

Adverse maternal and perinatal outcomes.

**Participants/population**

Studies will be included if participants are pregnant women.

**Intervention(s), exposure(s)**

1) Chronic hypertension that predated pregnancy or was diagnosed before 20 weeks' gestation.

2) Any antihypertensive drugs used during pregnancy.

**Comparator(s)/control**

1) Normotensive women who completed their pregnancy without history or clinical diagnosis of chronic hypertension or other HDP.

2) Normotensive women, or women with hypertension, but not on antihypertensive treatment during pregnancy

**Main outcome(s)**

- Superimposed pre-eclampsia
- Small for gestational age (SGA)
- Preterm birth (<37 weeks' gestation)
- Caesarean section (elective or emergency CS)
- Neonatal intensive care unit admission
- Severe hypertension (for studies focusing on specific antihypertensive medications, defined as SBP ≥160 mm Hg and/or DBP ≥110 mm Hg).
- Neonatal death
- Stillbirth (fetal death
- Low birth weight (<2500g)
- Birth defects

**Additional outcome(s)**

- Post-partum haemorrhage
- Miscarriage (loss of an embryo or fetus< 20 weeks' gestation)
- Hemolysis, elevated liver enzyme levels, and low platelet levels (HELLP syndrome)
- Maternal death
- Neonatal death (death within the first 28 days of life)

**Data extraction (selection and coding)**

A data extraction form will be developed based on recommendations provided in the Cochrane Non Randomized Studies Methods Group. Two investigators (S.A) and (F.M) will extract the data independently from the included studies. If inadequate information is found in one of the studies relating to study design, population, intervention, or outcomes, contact will be made via email with the authors to obtain the required missing data. The following details will be extracted from each study: source of data, authors' name, study design, study period, population characteristics (sample size, appropriateness of case and control recruitment, inclusion and exclusion criteria, age and other potential confounders), definition of exposure used (chronic hypertension/using antihypertensive agents), outcome measures

(maternal/perinatal outcomes), crude and adjusted estimates. Disagreement about the extracted data will be resolved by the third investigator (A.K), if necessary.

**Risk of bias (quality) assessment**

We will assess the study quality using the Newcastle-Ottawa Scale (NOS) as recommended by the recent guidelines to evaluate the quality of cohort and case-control studies. The NOS uses a 'star system', in which stars are assigned to show higher quality based on three criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure and/or outcome of interest. The quality assessment of all included studies in this review will be assessed independently by two investigators (S.A) and (A.K). If there are any inconsistencies between the two investigators regarding the appraisal of the quality of included studies, a third investigator (E.O) will be involved to resolve the disagreement.

**Strategy for data synthesis**

We aim to perform meta-analyses to examine the association between chronic hypertension and adverse pregnancy outcomes and meta-analyses for antihypertensive medication use and adverse pregnancy outcomes separately. A meta-analysis will be performed for each exposure-outcome association, when the data allow. Both the crude and adjusted estimates for predefined outcomes along with 95% confidence intervals (CI) will be extracted as appropriate. Risk ratios (RR) and odds ratios (OR) will be extracted for dichotomous outcomes, and mean differences will be calculated for continuous outcomes.

For antihypertensive medications, we will 1) group the women as either exposed to any treatment agent versus non-exposed group; 2) group the treated women with any type of HDP versus normotensive women; 3) group the women with any type of HDP (treated vs untreated); and 4) sub-group analysis including women with chronic hypertension only (treated vs untreated). Moreover, if studies allow, we will group the exposure according to medication groups (e.g. methyldopa, vs other agents or beta-blockers vs other agents). Additionally, when data allow, we will calculate the number needed to treat for each outcome in relation to antihypertensive medication. Heterogeneity among studies will be assessed using a Cochrane Q statistic and the Higgins $I^2$ test. Random effect models will be applied for pooling the crude and then adjusted estimates.

**Analysis of subgroups or subsets**

Sensitivity analysis will be performed by study design (case-control/ cohort), according to income level of the country (low/middle/ high), study location (Europe/USA/Asia), decade of publication, and according to study quality (low/high). Publication bias will be assessed using Begg's funnel plot and Egger's test when there are 10 studies or more in a meta-analysis (18). Data will be analysed using Review Manager 5.3 and Stata/MP 14.2 for Egger's test.

# Appendix 2: Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis Protocol

***Sukainah Al Khalaf**, Elizabeth Bodunde, Gillian Maher, Éilis J O'Reilly, Fergus McCarthy, Ali Khashan*

**Review question**

Is chronic kidney disease during pregnancy associated with an increased risk of adverse perinatal outcomes?

Are specific chronic kidney disease subtypes associated with a higher risk of adverse pregnancy outcomes?

**Searches**

We will conduct a comprehensive systematic search of the literature in the following electronic databases: PubMed/ MEDLINE, Embase and Web of Science.

We will use a combination of Medical Subject Headings (MeSH) terms and keywords related to chronic kidney disease and maternal/perinatal outcomes.

Searches will be restricted to the English language only, peer-reviews literature and human studies, whereas no restrictions will be applied on time period.

The bibliographies of previous systematic reviews, and all included studies will be searched for further potentially relevant articles.

**Types of study to be included**

Inclusion criteria: we will include randomized control trial, cohort, case-control, or cross-sectional studies in which a diagnosis of chronic kidney disease during pregnancy and at least one of the outcomes of interest have been reported.

Exclusion criteria: we will exclude reviews, case reports, editorial letters, expert opinions, animal studies and duplicate publication of the same data (in these cases, we will use the largest cohort or the one that reported more outcomes of interest)

**Condition or domain being studied**

Adverse perinatal outcomes.

**Participants/population**

Studies will be included if participants are pregnant women.

**Intervention(s), exposure(s)**

Diagnosis of chronic kidney disease before or during pregnancy.

**Comparator(s)/control**

Pregnant women without chronic kidney disease.

**Main outcome(s)**

- Pre-eclampsia
- Preterm birth (<37 weeks' gestation)
- Caesarean section (elective or emergency)
- Small for gestational age

**Additional outcome(s)**

- Maternal death
- Stillbirth
- Perinatal death
- Neonatal intensive care unit admission
- Miscarriage (loss of an embryo or fetus)
- Low birth weight
- Neonatal death

**Data extraction (selection and coding)**

Two investigators (SAK and EB) will independently screen titles and abstracts, excluding studies that clearly do not meet the predefined criteria. Then the full texts of potentially eligible studies will be obtained.

A standardised data extraction form will be developed, and two investigators (EB and GM) will extract the data independently from the included studies. If inadequate information is found in one of the studies, contact will be made via email with the authors to obtain the required missing data. The following details will be extracted from each study: author and year of publication, the study design, population characteristics (sample size, inclusion and exclusion criteria), the definition of exposure used, outcome measures (maternal/perinatal outcomes), crude and adjusted estimates and confounders adjusted for, if any. Disagreement about the extracted data will be resolved by the third investigator (AK), if necessary.

**Risk of bias (quality) assessment**

Quality assessment of the included studies will be performed independently by two investigators (EB and GM) using the Newcastle-Ottawa Scale (NOS). This scale uses a 'star system', in which stars are assigned to show higher quality based on three criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure and/or outcome of interest. If there are any inconsistencies between the two investigators regarding the appraisal of the quality of included studies, a third investigator (AK) will be involved to resolve the disagreement.

**Measures of effect**

Relative risks and/or odds ratios will be abstracted or calculated (when raw data were provided) to calculate the pooled estimates for each outcome.

**Strategy for data synthesis**

We will conduct meta-analyses to assess the association between maternal chronic kidney disease and adverse pregnancy outcomes. Random effects meta-analyses using the generic inverse variance method will be performed to calculate the crude and adjusted pooled estimates for each exposure-outcome. Forest plots will be used to display crude and adjusted pooled odds ratios (OR) with 95% confidence intervals (CI).

Heterogeneity between studies will be measured using the $I^2$ statistic and categorized as either low ($I^2$<25%), medium ($I^2$=25%-50%) or high ($I^2$>50%). Publication bias will be evaluated by Begg's funnel plot when we have 10 or more studies in the meta-analysis and by using Egger test. A statistically significant p-value will be based on a threshold of <0.05. Data will be analysed using Review Manager 5.3 and Stata/MP (version 16.1) for Egger's test.

**Analysis of subgroups or subsets**

Subgroup analyses will be performed by subtypes chronic kidney disease, study design (cohort vs case-control vs cross-sectional), study location (for example: Europe vs USA vs Asia) and by decade of publication. Any additional analyses will be clearly highlighted as post-hoc analyses.

# Appendix 3: The Impact of Chronic Hypertension and Antihypertensive Treatment on Adverse Perinatal Outcomes: A Systematic Review and Meta-Analysis (supplemental material)

## S3.1.Supplement data on chronic hypertension meta-analysis

### *S3.1.1 Search Strategy for the association between chronic hypertension and adverse perinatal outcomes*

*A) Search strategy for Web of Science*

1.Pregnancy outcome* or obstetric outcome* or birth outcome* or pregnancy complication* or gestational complication*/or obstetric complication/ or birth complication* or labor complication* or uterine complication* or normal birth* or live birth* or pre-term deliver* or preterm deliver* or pre-term birth*or preterm birth* or preterm labor* or pre-term labor* or premature deliver* or premature birth* or premature labor* or prematurity or cesarean* or cesarean section* or csection* or c section* or spontaneous abortion* or miscarriage* or miscarry or stillbirth* or still birth* or intrauterine death* or intra-uterine death* or fetal death* or fetal mortality or neonatal mortalit* or neonatal death* or neo-natal death or neo-natal mortalit* or newborn death* or newborn mortalit* or new born death* or new born mortalit* or perinatal mortalit* or perinatal death* or infant mortalit* or infant death* or postneonatal mortalit* or post-neonatal mortalit* or postneonatal death* or post-neonatal death* or preeclampsia or pre eclampsia or preeclamptic or pre eclamptic or preeclamptic or pre-eclamptic toxemia* or preeclamptic toxemia* or PET or pregnancy toxemia* or toxemia* or EPH toxemia* or EPH gestosis or hypertension-edema-proteinuria gestosis or hypertension edema proteinuria gestosis/ or proteinuria-edemahypertension gestosis/ or proteinuria edema hypertension gestosis or edema proteinuria hypertension gestosis or edema-proteinuria-hypertension gestosis/ or eclampsia/ or eclamptic or HELLP or hemolysis elevated liver enzymes low platelet count/ or hemolysis-elevated liver enzymes-low platelet count or antenatal hemorrage* or antepartum hemorrage* or postnatal hemorrage* or postpartum hemorrage* or postpartum complication* or postnatal complication* or post birth complication* or post labor complication* or maternal outcome* or maternal complication* or fetal outcome* or fetal complication* or neonate complication* or neonatal complication*or newborn complication*/ or gestational age/ or special care baby unit admission* or SCBU admission* or NICU admission* or neonatal intensive care unit admission* or small for gestational age* or SGA* or IUGR* or intrauterine growth restriction* or LBW*or low birth weight* or VLBW* or very low birth weight* or neonatal intraventricular haemorrhage*or Intraventricular haemorrhage of newborn*
*2. Essential hypertensi* or chronic hypertensi* or chronic hypertension in pregnanc**

3. Search 1 and 2 were then combined (1 'AND' 2)

*B) Search strategy for Embase (via OVID)*

1. ('pregnancy outcome' OR 'pregnancy complications' OR 'high risk pregnancy' OR 'labor' OR 'delivery' OR 'fetus outcome' OR 'live birth' OR 'premature labor' OR 'immature and premature labor' OR 'prematurity' OR 'cesarean section' OR 'spontaneous abortion' OR 'stillbirth' OR 'fetus death' OR 'infant mortality' OR 'fetus mortality' OR 'maternal mortality' OR 'perinatal mortality' OR 'preeclampsia' OR 'eclampsia' OR 'eclampsia and preeclampsia' OR 'hellp' OR 'disseminated intravascular coagulation' OR 'magnesium sulfate' OR 'newborn death' OR 'gestational age' OR 'infant low birth weight' OR 'low birth weight' OR 'very low birth weight' OR 'extremely low birth weight' OR 'apgar score' OR 'newborn intensive care' OR 'small for date infant' OR 'pregnancy outcome*' OR 'maternal outcome*' OR 'pregnancy complication*' OR 'obstetric outcome*' OR 'obstetric complication*' OR 'normal birth*' OR 'live birth*' OR 'premature birth*' OR 'preterm

birth*' OR 'preterm deliver*' OR 'born preterm' OR 'cesarean*' OR 'csection*' OR 'miscarriage*' OR 'stillbirth*' OR 'intrauterine death*' OR 'antenatal haemorrhage*' OR 'antenatal haemorrhage*' OR 'antepartum haemorrhage*' OR 'antepartum haemorrhage*' OR 'postpartum haemorrhage*' OR 'postpartum haemorrhage*' OR 'postnatal haemorrhage*' OR 'postnatal haemorrhage*' OR 'postpartum complication*' OR 'postnatal complication*' OR 'special care baby unit admission*' OR 'scbu admission*' OR 'neonatal intensive care unit admission*' OR 'nicu admission*' OR 'sga' OR 'iugr' OR 'neonatal intraventricular haemorrhage' OR 'neonatal intraventricular haemorrhage' OR 'lbw' OR 'vlbw' OR 'fetus outcome*' OR 'high risk pregnan*')
2. Essential hypertensi*/ or chronic hypertensi*/ or chronic hypertension in pregnan*

3. Search 1 and 2 were then combined (1 'AND' 2)

*C) Search strategy for Medline (via OVID platform)*

1. pregnancy outcome* or pregnancy complication* obstetric complication* or obstetric labor complications/ or pregnancy, high-risk/ or delivery, obstetric or labor or live birth or obstetric labor, premature or premature birth or premature birth* or preterm birth* preterm deliver* or born preterm or caesarean section cesarean* or c-section or caesarean* or abortion, spontaneous or stillbirth or fetal death/ or infant mortality or maternal mortality or perinatal mortality or pre-eclampsia or eclampsia/ or HELLP/ or gestational age/ or infant, low birth weight/ or pregnancy/or or obstetric outcome* or normal birth* or live birth* or miscarriage* or stillbirth* or intrauterine death* or neonatal death*or antenatal haemorrhage* or postpartum haemorrhage* or antenatal haemorrhage* or postpartum hemorrage* or antepartum hemorrage* or antepartum haemorrhage* or postpartum complication*/ or special care baby unit admission* or SCBU admission* or neonatal intensive care unit admission* or NICU admission* or small for gestationa age or SGA or intrauterine growth restriction or IUGR or neonatal intraventricular hemorrage* or neonatal intraventricular haemorrhage*
2. Essential hypertensi* or chronic hypertensi* or chronic hypertension in pregnan*

3. Searches 1 and 2 were then combined (1 'AND' 2)

### *S3.1.2 Selection process and eligibility criteria*

Two of us (SA and PB) independently reviewed the titles and abstracts of all articles, studies that clearly not meeting the predefined criteria excluded, then the full text of potentially eligible studies obtained. Following that, both investigators independently screened the full text articles to define the included studies, and a third investigator (ASK) resolved any inconsistencies about included or excluded articles between the two investigators. In addition, PRISMA flow chart was used to illustrate the process for selecting the included studies with the number of references at each phase of this review.

We included cohort and case-control studies in which chronic hypertension was reported as an exposure (compared to normotensive women); and the outcomes of interest were adverse maternal, fetal, or neonatal outcomes. We excluded study designs other than observational studies, along with case reports, case series, editorials, reviews, conference abstracts, book chapters and animal/in vitro studies. When two or more studies included the same cohort, we included the one with largest population or with more relevant outcomes. Also, studies with additional comorbidities were also excluded. Moreover, as pre-eclampsia associated with

higher risk of adverse outcomes and this review focuses on the impact of chronic hypertension; we included women with chronic hypertension without superimposed pre-eclampsia, when possible. Additionally, when studies reported results for both groups separately, we used the group without pre-eclampsia as it is one of the outcomes of interest.

#### *S3.1.3 Data collection process and quality assessment*

An electronic standardised data extraction form was developed, and pilot-tested on seven studies. One of us (SA extracted the data for all included studies, and two obstetricians (FMC and DF) extracted the data independently for more than 50% of the included studies to ensure the validity of extracted data. The following details were extracted from each study: source of data, authors' name, study design, study period, population characteristics (sample size, appropriateness of case and control recruitment, inclusion/exclusion criteria, and definition of exposure, measures, and definitions of outcomes (maternal, fetal and neonatal), appropriateness of analyses, confounders adjusted for (if any), crude and adjusted estimates. Any disagreement about the extracted data was resolved by the third investigator (ASK).

We used the Newcastle-Ottawa Scale (NOS) to assess the study quality. The NOS has a version for case-control studies and one for cohort studies, and it uses a 'star system', in which stars are assigned to show higher quality based on three criteria: selection of the study groups; comparability of the groups; and the ascertainment of the exposure and/or outcome of interest. The quality assessment was assessed independently by two investigators (SAK) and (LP). Any inconsistency between the two investigators was resolved by a third investigator (ASK).

## S3.2 Supplement data on antihypertensive treatment meta-analysis

#### *S3.2.1 Search Strategy for the association between antihypertensive treatment and adverse perinatal outcomes*

*A) Search strategy for Web of Science*

1. Anti hypertensive agent*/ or / Antihypertensive agent* Anti-hypertensive agent* / or /Cardiovascular Agent*/ or /anti-hypertensive drug*/ or /antihypertensive drug*/ or /antihypertensive/ or /anti hypertensive drug*/ or /antihypertensive agents therap*/ or /anti hypertensive agents therap*/ or/ anti-hypertensive agents therap*/ or /antihypertensive agents pharmacol*/ or /anti hypertensive agents pharmacol*/ or / anti-hypertensive agents pharmacol*/ or / calcium channel blocker/ OR /beta blocker/ OR /ACEi/ OR /adrenergic receptor antagonist/ or / adrenergic receptor blocker/ OR /alpha-2 adrenergic receptor agonist/ OR /angiotensin ii receptor/ OR /hydralazine/ OR /sodium nitroprusside/ OR /clonidine hydrochloride/ OR /moxonidine/ OR /renin inhibitor/ OR /thiazide/ OR /loop diuretic/ OR /potassium sparing diuretic
2. hypertensi*
3. Pregnancy outcome* or obstetric outcome* or birth outcome* or pregnancy complication* or gestational complication*/or obstetric complication/ or birth complication* or labor complication* or uterine complication* or normal birth* or live birth* or pre-term deliver* or preterm deliver* or pre-term birth*or preterm birth* or preterm labor* or pre-term labor* or premature deliver* or premature

birth* or premature labor* or prematurity or cesarean* or cesarean section* or csection* or c section* or spontaneous abortion* or miscarriage* or miscarry or stillbirth* or still birth* or intrauterine death* or intra-uterine death* or fetal death* or fetal mortality or neonatal mortalit* or neonatal death* or neo-natal death or neo-natal mortalit* or newborn death* or newborn mortalit* or new born death* or new born mortalit* or perinatal mortalit* or perinatal death* or infant mortalit* or infant death* or postneonatal mortalit* or post-neonatal mortalit* or postneonatal death* or post-neonatal death* or preeclampsia or pre eclampsia or preeclamptic or pre eclamptic or preeclamptic or pre-eclamptic toxemia* or preeclamptic toxemia* or PET or pregnancy toxemia* or toxemia* or EPH toxemia* or EPH gestosis or hypertension-edema-proteinuria gestosis or hypertension edema proteinuria gestosis/ or proteinuria-edemahypertension gestosis/ or proteinuria edema hypertension gestosis or edema proteinuria hypertension gestosis or edema-proteinuria-hypertension gestosis/ or eclampsia/ or eclamptic or HELLP or hemolysis elevated liver enzymes low platelet count/ or hemolysis-elevated liver enzymes-low platelet count or antenatal hemorrage* or antepartum hemorrage* or postnatal hemorrage* or postpartum hemorrage* or postpartum complication* or postnatal complication* or post birth complication* or post labor complication* or maternal outcome* or maternal complication* or fetal outcome* or fetal complication* or neonate complication* or neonatal complication*or newborn complication*/ or gestational age/ or special care baby unit admission* or SCBU admission* or NICU admission* or neonatal intensive care unit admission* or small for gestational age* or SGA* or IUGR* or intrauterine growth restriction* or LBW*or low birth weight* or VLBW* or very low birth weight* or neonatal intraventricular haemorrhage*or Intraventricular haemorrhage of newborn*
Search 1 AND 2 AND 3

*B) Search strategy for Embase (via OVID platform)*

1. ('pregnancy outcome' OR 'pregnancy complications' OR 'high risk pregnancy' OR 'labor' OR 'delivery' OR 'fetus outcome' OR 'live birth' OR 'premature labor' OR 'immature and premature labor' OR 'prematurity' OR 'cesarean section' OR 'spontaneous abortion' OR 'stillbirth' OR 'fetus death' OR 'infant mortality' OR 'fetus mortality' OR 'maternal mortality' OR 'perinatal mortality' OR 'preeclampsia' OR 'eclampsia' OR 'eclampsia and preeclampsia' OR 'hellp' OR 'disseminated intravascular coagulation' OR 'magnesium sulfate' OR 'newborn death' OR 'gestational age' OR 'infant low birth weight' OR 'low birth weight' OR 'very low birth weight' OR 'extremely low birth weight' OR 'apgar score' OR 'newborn intensive care' OR 'small for date infant' OR 'pregnancy outcome*' OR 'maternal outcome*' OR 'pregnancy complication*' OR 'obstetric outcome*' OR 'obstetric complication*' OR 'normal birth*' OR 'live birth*' OR 'premature birth*' OR 'preterm birth*' OR 'preterm deliver*' OR 'born preterm' OR 'cesarean*' OR 'csection*' OR 'miscarriage*' OR 'stillbirth*' OR 'intrauterine death*' OR 'antenatal haemorrhage*' OR 'antenatal haemorrhage*' OR 'antepartum haemorrhage*' OR 'antepartum haemorrhage*' OR 'postpartum haemorrhage*' OR 'postpartum haemorrhage*' OR 'postnatal haemorrhage*' OR 'postnatal haemorrhage*' OR 'postpartum complication*' OR 'postnatal complication*' OR 'special care baby unit admission*' OR 'scbu admission*' OR 'neonatal intensive care unit admission*' OR 'nicu admission*' OR 'sga' OR 'iugr' OR 'neonatal intraventricular haemorrhage' OR 'neonatal intraventricular haemorrhage' OR 'lbw' OR 'vlbw' OR 'fetus outcome*' OR 'high risk pregnan*')
2. ('calcium channel blocker' OR 'beta blocker' OR 'acei' OR 'adrenergic receptor antagonist/blocker' OR 'alpha-2 adrenergic receptor agonist' OR 'angiotensin ii receptor' OR 'antihypertensive' OR 'hydralazine' OR 'sodium nitroprusside' OR 'clonidine hydrochloride' OR 'moxonidine' OR 'renin inhibitor' OR 'thiazide' OR 'loop diuretic' OR 'potassium sparing diuretic')
3. Hypertension

Search 1 AND 2 AND 3

*C) Search strategy for Medline (via OVID platform)*

1. Anti hypertensive agent*/ or / Antihypertensive agent* Anti-hypertensive agent* / or /Cardiovascular Agent*/ or /anti-hypertensive drug*/ or /antihypertensive drug*/ or /antihypertensive/ or /anti hypertensive drug*/ or /antihypertensive agents therap*/ or /anti hypertensive agents therap*/

or/ anti-hypertensive agents therap*/ or /antihypertensive agents pharmacol*/ or /anti hypertensive agents pharmacol*/ or / anti-hypertensive agents pharmacol*/ or / calcium channel blocker/ OR /beta blocker/ OR /ACEi/ OR /adrenergic receptor antagonist/ or / adrenergic receptor blocker/ OR /alpha-2 adrenergic receptor agonist/ OR /angiotensin ii receptor/ OR /hydralazine/ OR / nitroprusside/ OR /clonidine / OR /thiazide/ OR /loop diuretic/ OR /potassium sparing diuretic
2. Hyperten*

3. pregnancy outcome* or pregnancy complication* obstetric complication* or obstetric labor complications/ or pregnancy, high-risk/ or delivery, obstetric or labor or live birth or obstetric labor, premature or premature birth or premature birth* or preterm birth* preterm deliver* or born preterm or caesarean section cesarean* or c-section or caesarean* or abortion, spontaneous or stillbirth or fetal death/ or infant mortality or maternal mortality or perinatal mortality or pre-eclampsia or eclampsia/ or HELLP/ or gestational age/ or infant, low birth weight/ or pregnancy/or or obstetric outcome* or normal birth* or live birth* or miscarriage* or stillbirth* or intrauterine death* or neonatal death*or antenatal haemorrhage* or postpartum haemorrhage* or antenatal haemorrhage* or postpartum hemorrage* or antepartum hemorrage* or antepartum haemorrhage* or postpartum complication*/ or special care baby unit admission* or SCBU admission* or neonatal intensive care unit admission* or NICU admission* or small for gestationa age or SGA or intrauterine growth restriction or IUGR or neonatal intraventricular hemorrage* or neonatal intraventricular haemorrhage*
Search 1 AND 2 AND 3

### *S3.2.2 Selection process and eligibility criteria*

We used similar to the previously mentioned method, but the exposure is antihypertensive treatment, while the comparative groups divided into 1) untreated normotensive women and 2) untreated women with chronic hypertension. One of us (SA) reviewed the titles and abstracts of all articles, studies not meeting the including criteria excluded. Then out of 254 articles, two reviewers (SA and PB) independently reviewed these studies to decide about including studies.

### *S3.2.3 Data collection process and quality assessment*

Similarly, one investigator (SA) extracted the data for all included studies (n=16), and the second investigator (DF) extracted the data independently for more than 50% of the included studies to ensure the validity of extracted data. The following details were extracted from each study: source of data, authors' name, study design, study period, population characteristics (sample size, appropriateness of case and control recruitment, inclusion/exclusion criteria, and definition of exposure (type of antihypertensive agent / dose/ initiation of treatment), types of hypertension being treated, definitions of outcomes (maternal/fetal and neonatal), appropriateness of analyses, confounders adjusted for (if any), crude and adjusted estimates. Moreover, Newcastle-Ottawa Scale (NOS) was used to assess the study quality, and that was done independently by two investigators (SAK) and (LP). Any inconsistency between the two investigators resolved by a third investigator (ASK).

## S3.3 Supplementary Tables S3.1-S3.27

**Table S3.1** Characteristics of studies for pre-eclampsia (PE) outcome

| *Author, year published* | *Country (ies)* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Rey, 1994 | Canada | Cohort (hospital-based) | 20,375 women | 1987 to 1991 | Blood pressure (BP) >140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery | Superimposed PE: increase in SBP or DPB compared with the first trimester of 30 mm Hg and 15 mm Hg, respectively, with the appearance of protein excretion of >300 mg/day in a 24-hour collection, de novo thrombocytopenia, liver enzymes elevation, or coagulation disorders | 6 |
| Conde-Agudelo, 2000a | Latin America and the Caribbean* | Cohort, multicountry | 878,680 pregnancies | 1985 to 1997 | Chronic hypertension diagnosed using ICD-10 codes | DBP≥90 mmHg on two or more consecutive occasions 24 hours apart or a DBP≥10 mmHg on any one occasion plus proteinuria (one 24-hour urine collection with a total protein excretion of > 300 mg or ≥1+ on a urine dipstick) (ICD-10 codes) | 7 |
| Samadi, 2001 | USA | Case control (national-based) | 182687 women | 1988 to 1996 | Chronic hypertension diagnosed using ICD-9 codes | ICD-9 codes | 7 |
| Mostello, 2002 | USA | Case control (population-based) | 4702 women | 1989 to 1997 | History of chronic hypertension | NR (outcome includes PE and eclampsia) | 7 |
| Zetterstrom, 2005¥ | Sweden | Cohort (population-based) | 681,515 women | 1992 to 1998 | BP≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation using (ICD-9 and ICD-10 codes) | Preeclampsia: DBP≥90 combined with proteinuria > 300 mg/day or ≥1+ on a urine dipstick. | 8 |
| Catov, 2007 | Denmark | Cohort (national-based) | 69007 women | 1997 to 2003 | Hypertension reported before pregnancy or at the first interview (16weeks), and/or reported taking antihypertensive medication | BP >140/90mmHg on at least three occasions) in combination with proteinuria of ≥300 mg/l. | 8 |
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | ICD-9 codes | 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Kiondo, 2012 | Uganda | Case control (hospital-based) | 559 women | 2008 to 2009 | History of chronic hypertension before pregnancy or at booking | BP≥160/110 mmHg or two measurements of ≥140/90 mmHg with one 24-hour urine collection with a total protein excretion of > 300 mg or ≥1+ on a urine dipstick | 6 |
| Bateman, 2012 | USA | Cohort (population-based) | 12,947,000 | 2007 to 2008 | Chronic hypertension was defined as hypertension without comorbidities using ICD-9 codes | PE diagnosed using ICD-9 codes | 8 |
| Yanit, 2012 | USA | Cohort (population-based) | 527,937 mother-infant pairs | 2006 | Chronic hypertension diagnosed using ICD-9 codes | PE diagnosed using ICD-9 codes | 8 |
| Orbach, 2013‡ | Israel | Cohort (population-based) | 100,029 births | 1998 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | PE diagnosed using ICD-9 codes | 8 |
| Lisonkova, 2013 | USA | Cohort (population-based) | 456,668 mother-infant pairs | 2003 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | PE diagnosed using ICD-9 codes | 8 |
| Guerrier, 2013 | Nigeria | Case control (hospital-based) | 1676 women | 2010 to 2011 | History of chronic hypertension | Preeclampsia was defined as new hypertension with BP≥160/110 after 20 weeks of gestation in a woman who was normotensive before 20 weeks gestation, associated with proteinuria (≥2+ on a urine dipstick). Eclampsia was defined as occurrence of seizure and/or altered level of consciousness not caused by epilepsy or other convulsive disorders, with signs of severe preeclampsia | 6 |
| Aksornphusitaphong, 2013 | Thailand | Case control (hospital-based) | 898 women | 2005 to 2010 | History of chronic hypertension | Superimposed preeclampsia was defined as a new onset of proteinuria of at least 300 mg/24 h in hypertensive women but no proteinuria prior to 20 weeks' gestation, or a sudden increase in proteinuria or blood pressure in women with hypertension and proteinuria before 20 weeks' gestation. | 6 |
| Block-Abraham, 2014 | USA | Cohort (hospital-based) | 614 women | 2007 to 2010 | hypertension as SBP>140 mm Hg or DBP>90 mm Hg or both | new-onset or worsening proteinuria and maternal systolic blood pressure 140 mm Hg or greater or diastolic blood pressure 90 mm Hg or greater on two separate occasions, 6 or more hours apart, after 20 weeks of gestation. Preeclampsia superimposed on chronic hypertension was defined as worsening blood | 6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | pressure and increasing proteinuria after 20 weeks of gestation | |
| Bilano, 2014 | 23 countries** | Cohort (International, multicountry) | 276,103 women | (2004-2005 in Africa and Latin America), (2007-2008 in Asia) | Hypertension diagnosed before pregnancy, or before 20 weeks' gestation | high blood pressure (≥140 mmHg systolic or ≥90 mmHg diastolic or increases of 30 mmHg systolic or 15 mmHg diastolic from the baseline on at least two occasions six or more hours apart) that develops from the 20th, and proteinuria. | 7 |
| Abalos, 2014 | 29 countries*** | Cohort (International, multicountry) | 312,115 pregnancies | 2004 to 2008 | BP >140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation | presence of hypertension (blood pressure >140/90 mmHg) associated with proteinuria | 6 |
| Broekhuijsen, 2015 | Netherlands | Cohort (population-based) | 988,389 mother-infant pairs | 2002 to 2007 | BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation | Preeclampsia is defined as at least one diastolic blood pressure measurement of at least 90mmHg combined with proteinuria of at least 300 mg/day or 1þ on a urine dipstick. Mild preeclampsia is defined as a diastolic blood pressure from 90 to 109mmHg combined with proteinuria of <500mg/day or 1þ or 2þ on a urine dipstick. Severe preeclampsia is defined as preeclampsia with either a diastolic blood pressure of at least 110mmHg or albuminuria of at least 500mg/day or both | 8 |
| Panaitescu, 2017 | UK | Cohort (hospital-based) | 109,932 pregnancies | March 2006 and July 2015/ February 2007 and November 2015 | History of chronic hypertension | Superimposed on PE was diagnosed according to the guidelines of the ISSHP: as development of significant proteinuria after 20 weeks' gestation in a previously non-proteinuric woman | 8 |
| You S-H, 2018 | Taiwan | Cohort (population-based) | 2,884,347 | 2001 to 2014 | Chronic hypertension was diagnosed using (ICD-9 codes) | Two occasions of ≥ 140/90 mmHg after 20 weeks of gestation accompanied by proteinuria > 300 mg/day or ≥1+ on dipstick based (using ICD-9 codes) | 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Youngstrom, 2018‡ | USA | Cohort (hospital-based) | 1,306 mother-infant pairs | 2000 to 2014 | History of hypertension **or** the use of antihypertensive medication before pregnancy | BP ≥140/90 with either proteinuria (protein excretion ≥300 mg in 24 hours or protein-to-creatinine ratio≥0.3), thrombocytopenia (less than 100,000/mL), transaminases (aspartate aminotransferase > twice the upper limit of normal), or elevated creatinine≥1.2 mg/dL | 8 |

* Uruguay, Argentina, Peru, Colombia, Honduras, Paraguay, Salvador, Chile , Bolivia, Costa Rica, Panama, Dominican Republic, Nicaragua, Brazil, Ecuador, Mexico, Bahamas, and Venezuela; **23 countries; Algeria, Angola, Democratic Republic of Congo, Niger, Nigeria, Kenya, and Uganda from Africa; Argentina, Brazil, Cuba, Ecuador, Mexico, Nicaragua, Paraguay, and Peru from Latin America; and Cambodia, China, India, Nepal, Philippines, Sri Lanka, Thailand, and Vietnam from Asia; ***29 countries, African Region (Angola, DR Congo, Kenya, Niger, Nigeria and Uganda); Region of the Americas (Argentina, Brazil, Ecuador, Mexico, Nicaragua, Paraguay and Peru); Eastern Mediterranean Region (Afghanistan, Jordan, Lebanon, occupied Palestinian territory, Palestine, Pakistan and Qatar); South-East Asia Region (India, Nepal, Sri Lanka and Thailand); Western Pacific Region (Cambodia, China, Japan, Mongolia, Philippines and Vietnam); ¥ We combined the odds ratios for mild and severe pre-eclampsia;‡ The odds ratios (ORs) from these studies were combined for treated and untreated women with chronic hypertension.

**Table S3.2** Characteristics of studies for hemolysis, elevated liver enzyme levels, and low platelet levels (HEELP) syndrome outcome

| ***Author, year published*** | ***Country*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of chronic hypertension*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | HELLP syndrome diagnosed using ICD-9 codes | 8 |
| Fitzpatrick, 2014 | UK | Case-control (national-based | 605 women | 2011-2012 | NR | Elevated liver enzymes: (Serum aspartate aminotransferase ≥70 international units/L OR Gammaglutamy l transferase ≥70 international units/L OR Alanine aminotransferase ≥70 international units/L or greater) AND Low platelets, defined as platelet count< 1003109/L AND Hemolysis, defined by abnormal (fragmented or contracted red cells) peripheral blood smear or serum lactate dehydrogenase levels≥600 international units/L or total bilirubin ≥20.5 micromole/L OR BP≥140/90 mm Hg OR Proteinuria (≥1+ 0.3 g/L on dipstick testing, a protein:creatinine ratio ≥30 mg/mmol on a random sample, or a urine protein excretion ≥300 mg /24 h") | 7 |
| Malmstrom, 2018 | Norway | Cohort (population-based) | 418,897 pregnancies | 1999 to 2014 | Clinical definitions based on Norwegian Society | HELLP syndrome diagnosed based on Norwegian Society of Obstetricians and Gynaecologists | 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | of Obstetricians and Gynaecologists | | |

**Table S3.3** Characteristics of studies for cesarean section (CS) outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Sass, 1990 | Brazil | Case control (hospital-based) | 337 births | 1985 to 1986 | DBP ≥90mmHg before pregnancy or up to 20 weeks of pregnancy or hypertension at 10 weeks postpartum (for those whose antenatal care was not at that hospital) | CS (not specified) | 4 |
| Hjertberg, 1992 | Sweden | Cohort (hospital-based) | 2593 births | 1986 to 1987 | Chronic hypertension before pregnancy before 24weeks' gestation | CS (not specified) | 6 |
| Rey, 1994 | Canada | Cohort (hospital-based) | 20,375 mothers | 1987 to 1991 | BP >140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery | CS (not specified) | 6 |
| Jain, 1997 | USA | Cohort (hospital-based) | 109,428 mother-infant pairs | 1982 to 1987 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation. | CS (not specified) | 7 |
| Lydakis, 1998 | UK | Cohort (hospital-based) | 3,729 births | 1980 to 1997 | Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery | Emergency CS | 6 |
| Hartikainen, 1998 | Finland | Cohort (hospital-based) | 8,050 mother-infant pairs | 1985 to 1986 | Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/or antihypertensive medication, each<20 weeks' gestation | CS (not specified) | 6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Lydakis, 2001 | UK | Cohort (hospital-based) | 238 births | 1980 to 1997 | Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery | Elective CS | 6 |
| Vanek, 2004 | Israel | Cohort (hospital-based) | 114,963 mother-infant pairs | 1988 to 1999 | BP≥140/90 mmHg that measured at least twice at least 4 h apart that preceded pregnancy, or hypertension present before 20 weeks' gestation or that persists longer than the usual postpartum period (12 weeks post-delivery) | CS (not specified) | 6 |
| Roberts, 2005 | Australia | Cohort (population-based) | 227,067 women and 231,811 infants | 2000 to 2002 | Chronic hypertension diagnosed ICD-10 codes | Emergency and elective CS | 7 |
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | CS (not specified) | 8 |
| Cruz, 2011 | USA | Cohort (multicentre hospital-based) | 17,752 births | 2002 and 2008 | Hypertension reported before pregnancy, or SBP≥140 mm Hg or DBP ≥90 mm Hg before 20 weeks' gestation | CS (not specified) | 7 |
| Tuuli, 2011 | USA | Cohort (hospital-based) | 58,135 mother-infant pairs | 1990 to 2008 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation | CS (not specified) | 8 |
| Madi, 2012 | Brazil | Cohort (hospital-based) | 3,689 mother-infant pairs | 1998 to 2009. | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | CS (not specified) | 7 |
| Bateman, 2012 | USA | Cohort (population-based) | 12,947,000 pregnancies | 2007 to 2008 | Chronic hypertension was defined as hypertension without comorbidities using ICD-9 codes | CS (not specified) | 8 |
| Ye, 2014 | China | Cohort (population-based) | 108,550 Pregnancies from | 2011 to 2011 | BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of | CS (not specified) | 7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | 106, 869 women | | gestation and continued for 12 weeks of postpartum | | |
| Janoudi, 2015 | Canada | Cohort (hospital-based) | 134,088 births | 2011to 2012 | NR | CS (not specified) | 8 |
| Broekhuijsen, 2015 | Netherlands | Cohort (population-based) | 988,389 mother-infant pairs | 2002 to 2007 | BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation | Elective CS | 8 |
| Panaitescu, 2017 | UK | Cohort (hospital-based) | 109,932 pregnancies | March 2006 and July 2015/ February 2007 and November 2015 | History of chronic hypertension | Emergency and elective CS | 8 |

**Table S3.4** Characteristics of studies for post-partum haemorrhage (PPH) outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Vanek, 2004 | Israel | Cohort (hospital-based) | 114,963 mother-infant pairs | 1988 to 1999 | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | Postpartum haemorrhage | 6 |
| Roberts, 2005 | Australia | Cohort (population-based) | 227,067 women and 231,811 infants | 2000 to 2002 | ICD-10 codes | Postpartum haemorrhage | 7 |
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | Diagnosed using ICD-9 codes | 8 |
| Cruz, 2011 | USA | Cohort (multicentre hospital-based) | 17,752 | 2002 and 2008 | Hypertension reported before pregnancy, or SBP≥140 mm Hg or DBP ≥90 mm Hg before 20 weeks' gestation | Postpartum haemorrhage | 7 |
| Ye, 2014 | China | Cohort (population-based) | 108,550 Pregnancies from 106, 869 women | 2011 to 2011 | BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum | Postpartum haemorrhage | 7 |
| Broekhuijsen, 2015 | Netherlands | Cohort (population-based) | 988,389 mother-infant pairs | 2002 to 2007 | BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation | Postpartum haemorrhage | 8 |

**Table S3.5** Characteristics of studies for maternal mortality outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | Maternal in hospital death | 8 |
| Kuklina, 2009 | USA | Cohort (population-based) | 34,321,769 births | 1998 to 2006 | Chronic hypertension diagnosed using ICD-9 codes | Maternal death | 8 |
| Bateman, 2012 | USA | Cohort (population-based) | 12,947,000 pregnancies | 2007 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | Maternal death | 8 |
| Campbell, 2013 | USA | Cohort (population-based) | 1,078,553 | 1995 to 2003 | Chronic hypertension diagnosed using ICD-9 codes | Maternal death considered present if it was identified in the discharge diagnosis codes, if it was noted on the birth certificate, or if it was present on both when possible | 8 |

**Table S3.6** Characteristics of studies for stillbirth outcome

| *Author, year published* | *Country (ies)* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Copper, 1994 | USA | Cohort (population-based) | 34,350 births | 1982-1986 | NR | Birth of a fetus at 20 weeks' gestation or later with an APGAR score of 0 at 1 and 5 minutes | 7 |
| Ananth, 1995a | USA | Cohort (population-based) | 371,123 mother-infant pairs | 1988 and 1991 | NR | Fetal death (early≤20 weeks and late>28 weeks) and further defined into antepartum and intrapartum death | 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Jain, 1997 | USA | Cohort (hospital-based) | 109,428 mother-infant pairs | 1982 to 1987 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation | ***NR*** | 7 |
| Lydakis, 1998 | UK | Cohort (hospital-based) | 3,729 births | 1980 to 1997 | Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery | Intrauterine fetal death at >24 weeks' gestation with an Apgar score 0 at 1 min | 6 |
| Conde-Agudelo, 2000b | Latin America and the Caribbean* | Cohort (multicountry) | 837,232 births | 1985 to 1997 | History of chronic hypertension using ICD-10 codes | Fetal death at≥20 weeks' gestation | 7 |
| Allen, 2004 | Canada | Cohort (population-based) | 123,160 births | 1988 to 2000 | Hypertension reported before pregnancy, or prior to 20 weeks' gestation | Fetal death at≥20 weeks' gestation and birthweight ≥ 500 grams | 9 |
| Canterino, 2004 | USA | Cohort (population-based) | 21,610,873 mother-infant pairs | 1995 to 2000 | Hypertension before pregnancy or before 20 weeks' gestation | Fetal death at≥24 weeks' gestation | 7 |
| Roberts, 2005 | Australia | Cohort (population-based) | 227,067 women and 231,811 infants | 2000 to 2002 | Chronic hypertension diagnosed using ICD-10 codes | Fetal death at≥20 weeks' gestation | 7 |
| Aagaard-Tillery, 2006 | USA | Case control (population-based) | 4306 | 1992 to 2002 | NR | Fetal death at≥20 weeks' gestation or weighing ≥400g | 6 |
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | ICD-9 –CM codes | 8 |
| Zetterstrom, 2008 | Sweden | Cohort (population-based) | 866,188 mother-infant pairs | 1992 to 2004 | BP≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation using (ICD-9 and ICD-10 codes) | Intrauterine fetal death at ≥28 weeks' gestation | 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Reddy, 2010 | USA | Cohort (population-based) | 160,954 | 2002 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | Antepartum stillbirth defined as fetus having no signs of life before labor with an Apgar scores of 0 and 0 at 1 minute and 5 minutes | 7 |
| Tuuli, 2011 | USA | Cohort (hospital- based) | 58,135 mother-infant pairs | 1990 to 2008 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation | Fetal death at≥20 weeks' gestation | 8 |
| Yanit, 2012 | USA | Cohort (population-based) | 527,937 mother-infant pairs | 2006 | Chronic hypertension diagnosed using ICD-9 codes | NR | 8 |
| Bateman, 2012 | USA | Cohort (population-based) | 12,947,000 pregnancies | 2007 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | ICD-9 codes | 8 |
| Ahmad, 2012 | Norway | Cohort (population-based) | 2,027,042 mother-infant pairs | 1967 to 2006 | SBP≥ 140 mmHg or a DBP≥90 mmHg before 20 weeks' gestation (ICD-8 and ICD-10 codes) | Fetal death ≥20 weeks' gestation | 7 |
| Madi, 2012 | Brazil | Cohort (hospital- based) | 3,689 mother-infant pairs | 1998 to 2009. | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | Fetal death | 7 |
| Yerlikaya, 2016 | UK | Cohort (hospital- based) | 113,415 mother-infant pairs | 2006 to 2015 | History of chronic hypertension | Fetal death ≥24 weeks' gestation | 8 |
| Panaitescu, 2017 | UK | Cohort (hospital-based) | 109,932 pregnancies | March 2006 and July 2015/ February 2007 and November 2015 | History of chronic hypertension | Fatal death ≥24 weeks | 8 |
| Xiong, 2018 | China | Cohort (population-based) | 6,970,032 births | 2012 to 2016 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation. | Stillbirth defined according to WHO of 3rd trimester stillbirth definition | 8 |
| Youngstrom, 2018‡ | USA | Cohort (hospital- based) | 1,306 mother-infant pairs | 2000 to 2014 | History of hypertension or the use of antihypertensive medication before pregnancy | NR | 8 |

*Uruguay, Argentina, Peru, Colombia, Honduras, Paraguay, Salvador, Chile , Bolivia, Costa Rica, Panama, Dominican Republic, Nicaragua, Brazil, Ecuador, Mexico, Bahamas, and Venezuela. ‡ Odds ratios from this study was combined for treated and untreated women with chronic hypertension.

**Table S3.7** Characteristics of studies for very preterm birth (VPTB) outcome

| ***Author, year published*** | ***Country*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of chronic hypertension*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|
| Ananth, 1995b | USA | Cohort (population-based) | 276,876 | 1988 and 1990 | Chronic hypertension obtained from medical records; no further details provided | <33 weeks' gestation | 8 |
| McCowan, 1996 | New Zealand | Cohort (hospital-based) | 20,224 mother-infant pairs | 1991 to 1993 | DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy | <32 weeks' gestation | 6 |
| Roberts, 2005 | Australia | Cohort (population-based) | 227,067 women and 231,811 infants | 2000 to 2002 | chronic hypertension diagnosed using ICD-10 codes | 28-32 weeks' gestation | ***7*** |
| Tuuli, 2011 | USA | Cohort (hospital-based) | 58,135 mother-infant pairs | 1990 to 2008 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation | <32 weeks' gestation | *8* |
| Ferrazzani, 2011 | Italy | Cohort (hospital-based) | 1,154 Women | 1986 and 1995 | Hypertension diagnosed before pregnancy and/or DBP ≥90 mm Hg and/or on antihypertensive medication, each before 20 weeks' gestation uncomplicated by de novo proteinuria | <32 weeks' gestation | 6 |
| Yanit, 2012 | USA | Cohort (population-based) | 527,937 mother-infant pairs | 2006 | Chronic hypertension diagnosed using ICD-9 codes | <32 weeks' gestation | 8 |
| Broekhuijsen, 2015 | Netherlands | Cohort (population-based) | 988,389 mother-infant pairs | 2002 to 2007 | BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation | <32 weeks' gestation | 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Yang, 2015 | China | Cohort (national-based) | 344,929 | 2010 and 2013 | SBP≥ 140 mmHg or a DBP≥90 mmHg on a single occasion after participants rested for ≥10 minutes | <32 weeks' gestation, but after 28 weeks | 6 |
| Panaitescu, 2017 | UK | Cohort (hospital-based) | 109,932 pregnancies | March 2006 and July 2015/ February 2007 and November 2015 | History of chronic hypertension | <34 weeks' gestation (medically indicated and spontaneous) * | 8 |

**we combined the estimates for both medically indicated and spontaneous as it was the only study reported that for VPTB*

**Table S3.8** Characteristics of studies for preterm birth (PTB) outcome

| ***Author, year published*** | ***Country (ies)*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of chronic hypertension*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|
| Acien,1990 | Spain | Cohort (hospital-based) | 236 pregnancies and 238 newborns | 1979 and 1986 | NR | 33-36 weeks' gestation | 4 |
| Rey, 1994 | Canada | Cohort (hospital-based) | 20,375 mothers | 1987 to 1991 | BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery | NR | 6 |
| Velentgas, 1994 | USA | Cohort (population-based) | 14,562 mother-infant pairs | 1984-1990 | NR | <37 weeks' gestation | 6 |
| Ananth, 1995b | USA | Cohort (population-based) | 276,876 | 1988 and 1990 | Chronic hypertension obtained from medical records; no further details provided | <37 weeks' gestation | 8 |
| McCowan, 1996 | New Zealand | Cohort (hospital-based) | 20,224 mother-infant pairs | 1991 to 1993 | DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy | <37 weeks' gestation | 6 |
| Jain, 1997 | USA | Cohort (hospital-based) | 109,428 mother-infant pairs | 1982 to 1987 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation. | NR | 7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hartikainen, 1998 | Finland | Cohort (hospital-based) | 8,050 mother-infant pairs | 1985 to 1986 | Hypertension diagnosed before pregnancy and/or DBP >90 mm Hg and/ or antihypertensive medication, each<20 weeks' gestation | <37 weeks' gestation | 6 |
| Meis, 1998 | USA | Cohort (multi-centres) | 2929 Women | 1992 to 1994 | BP≥140/90 mmHg before 20 weeks' gestation | <37 weeks' gestation (<259 days') gestation, (medically indicated) | 7 |
| Samadi, 1998 | USA | Case control (hospital-based) | 25,060 | 1988 and 1993 | Chronic hypertension diagnosed using ICD-9 codes | <37 weeks' gestation (spontaneous) | 7 |
| Lydakis, 2001 | UK | Cohort (hospital-based) | 238 births | 1980 to 1997 | Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery | <37 weeks' gestation | 6 |
| Roberts, 2005 | Australia | Cohort (population-based) | 227,067 women and 231,811 infants | 2000 to 2002 | Chronic hypertension diagnosed using ICD-10 codes | 33-36 weeks' gestation | 7 |
| Graham, 2007 | USA | Cohort (population-based) | 202,931 mother-infant pairs | 1999 to 2003 | Hypertension diagnosed before pregnancy | <37 weeks' gestation | 7 |
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | <37 weeks' gestation | 8 |
| Carter, 2011 | USA | Cohort (population-based) | 259,576 Births | 2000 to 2008 | NR | <37 weeks' gestation | 6 |
| Ferrazzani, 2011 | Italy | Cohort (hospital-based) | 1,154 Women | 1986 and 1995 | Hypertension diagnosed before pregnancy and/or DBP ≥90 mm Hg and/or on antihypertensive medication, each before 20 weeks' gestation uncomplicated by de novo proteinuria | <37 weeks' gestation | 6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Tuuli, 2011 | USA | Cohort (hospital-based) | 58,135 mother-infant pairs | 1990 to 2008 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation | <37 weeks' gestation | 8 |
| Bateman, 2012 | USA | Cohort (population-based) | 12,947,000 pregnancies | 2007 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | <37 weeks' gestation (spontaneous) | 8 |
| Yanit, 2012 | USA | Cohort (population-based) | 527,937 mother-infant pairs | 2006 | Chronic hypertension diagnosed using ICD-9 codes | <37 weeks' gestation | 8 |
| Orbach, 2013‡ | Israel | Cohort (population-based) | 100,029 births | 1998 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | <37 weeks' gestation | 8 |
| Su, 2013 | Taiwan | Cohort (population-based) | 10,908 mother-infant pairs | 2005 to 2005 | Chronic hypertension diagnosed using ICD-9-CM codes | <37 weeks' gestation | 8 |
| Morisaki, 2014 | 29 countries* | Cohort, multicountry | 299,878 women | 2010 to 2011 | NR | <37 weeks' gestation | 7 |
| Ye, 2014 | China | Cohort (population-based) | 108,550 Pregnancies from 106, 869 women | 2011 to 2011 | BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum | <37 weeks' gestation (after 20 weeks and before 37) | 7 |
| Arora, 2015 | 5 countries** | Cohort, multicountry | 37 661 births | 2007 to 2009 | History of chronic hypertension | <37 weeks' gestation | 6 |
| Broekhuijsen, 2015 | Netherlands | Cohort (population-based) | 988,389 mother-infant pairs | 2002 to 2007 | BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation | <37 weeks' gestation | 8 |
| Derakhshi, 2014 | Iran | Case control (hospital-based) | 600 births | 2012 | NR | <37 weeks' gestation | 5 |
| Tucker, 2015 | USA | Cohort (Medicaid patients) | 15,428 women | 2011 to 2012 | NR | 24–36 weeks' gestation | 7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Yang, 2015 | China | Cohort (national-based) | 344,929 | 2010 and 2013 | SBP≥ 140 mmHg or a DBP≥90 mmHg on a single occasion after participants rested for ≥10 minutes | <37 weeks' gestation | 6 |
| Premkumar, 2016 | USA | Cohort (hospital-based) | 23,425 women | 2002 to 2015 | SBP> 140 mm Hg or DBP> 90 mm Hg recorded on at least 2 separate occasions >6 hours apart before 20 weeks' gestation | <37 weeks' gestation< 37 weeks' gestation ( medically indicated and spontaneous) | 9 |
| Souza, 2016 | Brazil | Case control (multicentre) | 2614 Births | 2011 to 2012 | NR | <37 weeks' gestation | 6 |
| Panaitescu, 2017 | UK | Cohort (hospital-based) | 109,932 pregnancies | March 2006 and July 2015/ February 2007 and November 2015 | History of chronic hypertension | <37 weeks' gestation (medically indicated and spontaneous) | 8 |
| Campbell, 2018 | Canada | Cohort (population-based) | 26,654 live births | 2009 to 2014 | NR | <37 weeks' gestation (live births) | 6 |
| Youngstrom, 2018‡ | USA | Cohort (hospital-based) | 1,306 mother-infant pairs | 2000 to 2014 | History of hypertension or the use of antihypertensive medication before pregnancy | <37 weeks' gestation | 8 |

*29 countries: African Region (Angola, DR Congo, Kenya, Niger, Nigeria and Uganda); Region of the Americas (Argentina, Brazil, Ecuador, Mexico, Nicaragua, Paraguay and Peru); Eastern Mediterranean Region (Afghanistan, Jordan, Lebanon, occupied Palestinian territory, Palestine, Pakistan and Qatar); South-East Asia Region (India, Nepal, Sri Lanka and Thailand); Western Pacific Region (Cambodia, China, Japan, Mongolia, Philippines and Vietnam); ** Czech Republic, Hungary, Romania, Slovakia, and Ukraine; ‡ The ORs from these studies were combined for treated and untreated women with chronic hypertension.

**Table S3.9** Characteristics of studies for small for gestational age (SGA) outcome

| *Author, year published* | *Country (ies)* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Sass, 1990 | Brazil | Case control (hospital-based) | 337 Births | 1985 to 1986 | DBP ≥90mmHg before pregnancy or up to 20 weeks' gestation or hypertension at 10 weeks postpartum (for those whose antenatal care was not at that hospital). | birthweight <10$^{th}$ percentile for gestational age | 4 |
| Acien,1990 | Spain | Cohort (hospital-based) | 236 pregnancies and 238 newborns | 1979 and 1986 | NR | birthweight <10$^{th}$ percentile for gestational age | 4 |
| Rey, 1994 | Canada | Cohort (hospital-based) | 20,375 mothers | 1987 to 1991 | BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery | birthweight <10$^{th}$ percentile for gestational age | 6 |
| Ananth, 1995b | USA | Cohort (population-based) | 276,876 | 1988 and 1990 | Chronic hypertension obtained from medical records; no further details provided | birthweight <10$^{th}$ percentile for gestational age | 8 |
| McCowan, 1996 | New Zealand | Cohort (hospital-based) | 20,224 mother-infant pairs | 1991 to 1993 | DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy | birthweight <5$^{th}$ percentile for gestational age | 6 |
| Haelterman, 1997 | France | Cohort (multicentre) | 1938 mother-infant pairs | 1991 to 1993 | DBP ≥90 mmHg on two or more consecutive occasions at least 4 h apart or SBP>160 mmHg before 21 weeks' gestation OR women with a prior history of hypertension and were on antihypertensive treatment. | birthweight <5$^{th}$ percentile for gestational age | 6 |
| Jain, 1997 | USA | Cohort (hospital-based) | 109,428 mother-infant pairs | 1982 to 1987 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation. | Intrauterine growth restriction (NR) | 7 |
| Hartikainen, 1998 | Finland | Cohort (hospital-based) | 8,050 | 1985 to 1986 | Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/ or | birthweight <10$^{th}$ percentile for gestational age | 6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | mother-infant pairs | | antihypertensive medication, each<20th week | | |
| Lydakis, 2001 | UK | Cohort (hospital-based) | 238 births | 1980 to 1997 | Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20th week of pregnancy in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery. | birthweight <5th percentile for gestational age | 6 |
| Allen, 2004 | Canada | Cohort (population-based) | 123,160 births | 1988 to 2000 | Hypertension reported before pregnancy, or before to 20 weeks' gestation | birthweight <5th percentile for gestational age | 9 |
| Vanek, 2004 | Israel | Cohort (hospital-based) | 114,963 mother-infant pairs | 1988 to 1999 | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | NR | 6 |
| Roberts, 2005 | Australia | Cohort (population-based) | 227,067 women and 231,811 infants | 2000 to 2002 | chronic hypertension diagnosed using ICD-10 codes | birthweight <10th percentile for gestational age | 7 |
| Odibo, 2006 | USA | Case control (hospital-based) | 2472 | 1997 to 2004 | NR | birthweight <10th percentile for gestational age | 7 |
| Rasmussen, 2006 | Norway | Cohort (population-based) | 404,400 mother-infant pairs | 1999 to 2002 | NR | birthweight <10th percentile for gestational age | 6 |
| Zetterstrom, 2006 | Sweden | Cohort (population-based) | 560,188 mother-infant pairs | 1992 to 1998 | BP≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation using (ICD-9 and ICD-10 codes) | <2 standard deviations below the mean birth weight adjusted for gestational age and sex | 8 |
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | ICD-9 codes | 8 |
| Catov, 2008 | Denmark | Cohort (national-based) | 81,008 mother-infant pairs | 1996 to 2002 | Hypertension reported before pregnancy or at the first interview (16 weeks), and/or reported taking antihypertensive medication | <2 standard deviations below the mean birth weight | 8 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cruz, 2011 | USA | Cohort (multicentre hospital- based) | 17,752 | 2002 and 2008 | Hypertension reported before pregnancy, or SBP≥140 mm Hg or DBP ≥90 mm Hg before 20 weeks' gestation | birthweight <10th percentile for gestational age | 7 |
| Poon, 2011 | UK | Cohort (hospital-based) | 33,602 pregnancies | 2006 to 2009 | History of chronic hypertension | birthweight <5th percentile for gestational age | 6 |
| Tuuli, 2011 | USA | Cohort (hospital-based) | 58,135 mother-infant pairs | 1990 to 2008 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation | birthweight <10th percentile for gestational age | 8 |
| Bateman, 2012 | USA | Cohort (population-based) | 12,947,000 pregnancies | 2007 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | ICD-9 codes | 8 |
| Madi, 2012 | Brazil | Cohort (hospital-based) | 3,689 mother-infant pairs | 1998 to 2009. | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | NR | 7 |
| Yanit, 2012 | USA | Cohort (population-based) | 527,937 mother-infant pairs | 2006 | Chronic hypertension diagnosed using ICD-9 codes | birthweight <10th percentile for gestational age | 8 |
| Anderson, 2013 | New Zealand | Cohort (population-based) | 24,434 mother-infant pairs | 2006 to 2009 | Chronic hypertension diagnosed based on the International Society for the Study of Hypertension in Pregnancy guidelines | birthweight <10th percentile for gestational age | 8 |
| Orbach, 2013‡ | Israel | Cohort (population-based) | 100,029 births | 1998 to 2008 | Chronic hypertension diagnosed using ICD-9 codes | ICD-9 codes | 8 |
| Su, 2013 | Taiwan | Cohort (population-based) | 10,908 mother-infant pairs | 2005 to 2005 | Chronic hypertension diagnosed using ICD-9 CM codes | birthweight <10th percentile for gestational age | 8 |
| Ota, 2014 | 29 countries* | Cohort (international, multicountry) | 245,773 mother-infant pairs | 2010 to 2011 | NR | birthweight <10th percentile for gestational age | 7 |
| Xaverius, 2014 | USA | Cohort (population-based) | 142,017 mother-infant pairs | 2000-2009 | History of chronic hypertension | birthweight <10th percentile for gestational age | 7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Broekhuijsen, 2015 | Netherlands | Cohort (population-based) | 988,389 mother-infant pairs | 2002 to 2007 | BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation | birthweight <10th percentile for gestational age | 8 |
| Panaitescu, 2017 | UK | Cohort (hospital-based) | 109,932 pregnancies | March 2006 and July 2015/ February 2007 and November 2015 | History of chronic hypertension | birthweight <10th percentile for gestational age | 8 |
| Campbell, 2018 | Canada | Cohort (population-based) | 26,654 live births | 2009 to 2014 | NR | birthweight <10th percentile for gestational age | 6 |
| Youngstrom, 2018‡ | USA | Cohort (hospital-based) | 1,306 mother-infant pairs | 2000 to 2014 | History of hypertension or the use of antihypertensive medication before pregnancy | birthweight <10th percentile for gestational age | 8 |

*29 countries: African Region (Angola, DR Congo, Kenya, Niger, Nigeria and Uganda); Region of the Americas (Argentina, Brazil, Ecuador, Mexico, Nicaragua, Paraguay and Peru); Eastern Mediterranean Region (Afghanistan, Jordan, Lebanon, occupied Palestinian territory, Palestine, Pakistan and Qatar); South-East Asia Region (India, Nepal, Sri Lanka and Thailand); Western Pacific Region (Cambodia, China, Japan, Mongolia, Philippines and Vietnam); ‡ The ORs from these studies were combined for treated and untreated women with chronic hypertension

**Table S3.10** Characteristics of studies for low birth weight (LBW) outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Velentgas, 1994 | USA | Cohort (population-based) | 14,562 mother-infant pairs | 1984-1990 | NR | birth weight of <2500 grams | 6 |
| Ananth, 1995b | USA | Cohort (population-based) | 276,876 | 1988 and 1990 | Chronic hypertension obtained from medical records; no further details provided | birth weight of <2500 grams‡ | 8 |
| Hartikainen, 1998 | Finland | Cohort (hospital-based) | 8,050 mother-infant pairs | 1985 to 1986 | Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/or antihypertensive medication, each<20 weeks' gestation | birth weight of <2500 grams | 6 |
| Lydakis, 1998 | UK | Cohort (hospital-based) | 3,729 births | 1980 to 1997 | Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery | birth weight of <2000 grams | 6 |
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | birth weight of ≤2500 grams | 8 |
| Graham, 2007 | USA | Population-based | 202,931 mother-infant pairs | 1999 to 2003 | Hypertension diagnosed before pregnancy | birth weight of <2500 grams | 7 |
| Odell, 2006 | USA | Population-based (Black women only) | 16,578 | 1996 to 2000 | History of chronic hypertension diagnosed using ICD 9 codes | birth weight of <2500 grams | 7 |
| Vahdaninia, 2008 | Iran | Cohort (hospital-based) | 3733 mother-infant pairs | 2005 | NR | birth weight of <2500 grams | 7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Madi, 2012 | Brazil | Cohort (hospital-based) | 3,689 mother-infant pairs | 1998 to 2009. | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | birth weight of ≤2500 grams | 7 |
| Su, 2013 | Taiwan | Cohort (population-based) | 10,908 mother-infant pairs | 2005 to 2005 | Chronic hypertension diagnosed using ICD-9 CM codes | birth weight of <2500 grams | 8 |
| Ye, 2014 | China | Cohort (population-based) | 108,550 Pregnancies from 106, 869 women | 2011 to 2011 | BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum | birth weight of <2500 grams | 7 |
| Harvey, 2017 | USA | Case control (hospital-based) | 862 births | 2010 to 2011 | NR | birth weight of <2500 grams | 8 |
| Campbell, 2018 | Canada | Cohort (population-based) | 26,654 live births | 2009 to 2014 | NR | birth weight of <2500 grams | 6 |
| Hailu,2018 | Ethiopia | Case control (hospital-based) | 441 births | 2016 | NR | birth weight of <2500 grams | 6 |

‡ We combined the ORs for birthweight < 1,499 g and birthweight (1,500-2,499 g)

**Table S3.11** Characteristics of studies for neonatal death outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Jain, 1997 | USA | Cohort (hospital-based) | 109,428 mother-infant pairs | 1982 to 1987 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation. | NR | 7 |
| Gilbert, 2007 | USA | Cohort (population-based) | 4,324,902 pregnancies | 1991 to 2001 | Chronic hypertension diagnosed using ICD-9 codes | ICD-9 –CM codes | 8 |
| Zetterstrom, 2008 | Sweden | Cohort (population-based) | 866,188 mother-infant pairs | 1992 to 2004 | BP≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation using (ICD-9 and ICD-10 codes) | Neonatal death of an infant born live at any week of gestation, within 27 days of birth | 8 |
| Madi, 2012 | Brazil | Cohort (hospital-based) | 3,689 mother-infant pairs | 1998 to 2009. | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | Neonatal mortality | 7 |
| Youngstrom, 2018‡ | USA | Cohort (hospital-based) | 1,306 mother-infant pairs | 2000 to 2014 | History of hypertension or the use of antihypertensive medication before pregnancy | NR | 8 |

‡ The ORs from this study was combined for treated and untreated women with chronic hypertension.

**Table S3.12** Characteristics of studies for perinatal death outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Acien,1990 | Spain | Cohort (hospital-based) | 236 pregnancies and 238 newborns | 1979 and 1986 | NR | Late fetal death with a birth weight≥1000 g, and early neonatal death<less 7 days | 4 |
| Sass, 1990 | Brazil | Case control (hospital-based) | 337 Births | 1985 to 1986 | DBP ≥90mmHg before pregnancy or up to 20 weeks of pregnancy or hypertension at 10w postpartum (for those whose antenatal care was NOT at that hospital). | NR | 4 |
| Rey, 1994 | Canada | Cohort (hospital-based) | 20,375 mothers | 1987 to 1991 | BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery | NR | 6 |
| McCowan, 1996 | New Zealand | Cohort (hospital-based) | 20,224 mother-infant pairs | 1991 to 1993 | DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy | Fetal deaths after 20 weeks, early and late neonatal deaths per 1000 total births | 6 |
| Jain, 1997 | USA | Cohort (hospital-based) | 109,428 mother-infant pairs | 1982 to 1987 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation. | NR | 7 |
| Hartikainen, 1998 | Finland | Cohort (hospital-based) | 8,050 mother-infant pairs | 1985 to 1986 | Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/or antihypertensive medication, each<20 weeks' gestation | Fetal death with a birth weight≥ 500 g, and/or gestational age≥ 24 completed weeks, and neonatal death<less 7 days | 6 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vanek, 2004 | Israel | Cohort (hospital-based) | 114,963 mother-infant pairs | 1988 to 1999 | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | NR | 6 |
| Ahmad, 2012 | Norway | Cohort (population-based) | 2,027,042 mother-infant pairs | 1967 to 2006 | SBP≥ 140 mmHg or a DBP≥90 mmHg before 20 weeks' gestation using (ICD-8 and ICD-10 codes) | Fetal death with a birth weight≥ 500 g, and/or gestational age≥22 weeks (154 days) and neonatal death<less 7 days | 7 |
| Ye, 2014 | China | Cohort (population-based | 108,550 Pregnancies from 106, 869 women | 2011 to 2011 | BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation or developed hypertension after 20 weeks of gestation and continued for 12 weeks of postpartum | Fetuses and neonates who were born dead, or died in the first 28 days after delivery | 7 |
| Broekhuijsen, 2015 | Netherlands | Cohort (population-based) | 988,389 mother-infant pairs | 2002 to 2007 | BP ≥140/90 mmHg diagnosed before pregnancy, or before 20 weeks' gestation | Fetal death or neonatal death within 7 days after birth | 8 |
| Youngstrom, 2018‡ | USA | Cohort (hospital-based) | 1,306 mother-infant pairs | 2000 to 2014 | History of hypertension or the use of antihypertensive medication before pregnancy | NR | 8 |

‡ The ORs from this study was combined for treated and untreated women with chronic hypertension

**Table S3.13** Characteristics of studies for neonatal intensive care unit (NICU) admission outcome

| ***Author, year published*** | ***Country*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of chronic hypertension*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|
| Hjertberg, 1992 | Sweden | Cohort (hospital-based) | 2593 | 1986 to 1987 | Chronic hypertension before pregnancy and/or before 24 weeks' gestation | Admission to NICU | *6* |
| McCowan, 1996 | New Zealand | Cohort (hospital-based) | 20,224 mother-infant pairs | 1991 to 1993 | DBP>90 mmHg before 20 weeks gestation, pre-existing history of essential hypertension and/or on antihypertensive medication before the pregnancy | Admission to NICU | 6 |
| Hartikainen, 1998 | Finland | Cohort (hospital-based) | 8,050 mother-infant pairs | 1985 to 1986 | Hypertension diagnosed before pregnancy and/or DBP > 90 mm Hg and/or antihypertensive medication, each<20 weeks' gestation | Admission to NICU | 6 |
| Roberts, 2005 | Australia | Cohort (population-based) | 227,067 women and 231,811 infants | 2000 to 2002 | Chronic hypertension diagnosed using ICD-10 codes | Admission to NICU | *7* |
| Tuuli, 2011 | USA | Cohort (hospital-based) | 58,135 mother-infant pairs | 1990 to 2008 | SBP≥ 140 mmHg or a DBP≥90 mmHg before pregnancy or before 20 weeks' gestation | Admission to NICU | *8* |
| Cruz, 2011 | USA | Cohort (Multicentre hospital- based) | 17,752 | 2002 and 2008 | Hypertension reported before pregnancy, or SBP≥140 mm Hg or DBP ≥90 mm Hg before 20 weeks' gestation | Admission to NICU | *7* |
| Madi, 2012 | Brazil | Cohort (hospital-based) | 3,689 mother-infant pairs | 1998 to 2009. | BP≥140/90 mmHg that measured at least twice, before 20 weeks' gestation, or persisting for ≥12 weeks post-delivery | Admission to NICU | *7* |

**Table S3.14** Characteristics of studies for miscarriage outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Sass, 1990 | Brazil | Case control (hospital-based) | 337 Births | 1985 to 1986 | DBP ≥90mmHg before pregnancy or up to 20 weeks of pregnancy or hypertension at 10w postpartum (for those whose antenatal care was NOT at that hospital). | NR | 4 |
| Panaitescu, 2017 | UK | Cohort (hospital-based) | 109,932 pregnancies | March 2006 and July 2015/ February 2007 and November 2015 | History of chronic hypertension | Late miscarriage included spontaneous delivery or fetal death at 16 + 0 to 23 + 6 weeks' gestation | 8 |

**Table S13.5** Characteristics of studies for stillbirth stratified by maternal ethnicity

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Ananth, 1995a | USA | Cohort (population-based) | Black:14,417<br>White:15,819 | 1988 and 1990 | Chronic hypertension obtained from medical records; no further details provided | Fetal death at≥20 weeks' gestation | 8 |
| Canterino, 2004 | USA | Cohort (population-based) | Black:3,269,211<br>White:18,341,662 | 1995 to 2000 | Hypertension before pregnancy or before 20 weeks' gestation | Fetal death at≥24 weeks' gestation | 7 |

**Table S3.16** Characteristics of studies for PTB stratified by maternal ethnicity

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Ananth, 1995b | USA | Cohort (population-based) | Black:14,417 White:15,819 | 1988 and 1990 | Chronic hypertension obtained from medical records; no further details provided | <37 weeks' gestation | 8 |
| Rey, 1997 | Canada | Cohort (hospital-based) | Black:2,450 White:17,854 | 1987 to 1991 | BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery | Prematurity/NR | 6 |
| Samadi, 1998 | USA | Case control (hospital-based) | Black:25,060 White: none | 1988 and 1993 | Chronic hypertension diagnosed using ICD-9 codes | <37 weeks' gestation | 7 |
| Graham, 2007 | USA | Cohort (population-based) | Black:91,718 White:111,213 | 1999 to 2003 | Hypertension diagnosed before pregnancy | <37 weeks' gestation | 7 |
| Premkumar, 2016 | USA | Cohort (hospital-based) | Black:2,272 White:10,843 | 2002 to 2015 | SBP> 140 mm Hg or DBP> 90 mm Hg recorded on at least 2 separate occasions >6 hours apart before 20 weeks' gestation | <37 weeks' gestation | 9 |

**Table S3.17** Characteristics of studies for SGA stratified by maternal ethnicity

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Rey, 1997 | Canada | Cohort (hospital-based) | Black:2,450 White:17,854 | 1987 to 1991 | BP>140/90 mm Hg with a diagnosed before pregnancy or hypertension in at least two measurements<20 weeks of pregnancy and/or 6 weeks after delivery | Prematurity/NR | 6 |
| Ananth, 1995b | USA | Cohort (population-based) | Black:14,417 White:15,819 | 1988 and 1990 | Chronic hypertension obtained from medical records; no further details provided | <37 weeks' gestation | 8 |

**Table S3.18** Characteristics of studies for LBW stratified by maternal ethnicity

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of chronic hypertension* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|
| Velentgas, 1994 | USA | Cohort (population-based) | Black:285<br>White:3,144 | 1984-1990 | NR | birth weight of <2500 grams | 6 |
| Ananth, 1995b | USA | Cohort (population-based) | Black:14,417<br>White:15,819 | 1988 and 1990 | Chronic hypertension obtained from medical records, no further details provided | birth weight of <2500 grams‡ | 8 |
| Lydakis, 1998 | UK | Cohort (hospital-based) | Black:79<br>White:64 | 1980 to 1997 | Hypertension (DBP ≥110 mmHg OR DBP >90 mmHg on two or more occasions ≥4 h apart) at the first booking visit before the 20 weeks' gestation in the absence of trophoblastic disease, OR hypertension at any stage of pregnancy that continued for more than 6 weeks after delivery | birth weight of <2000 grams | 6 |
| Graham, 2007 | USA | Cohort (population-based) | Black:91,718<br>White:111,213 | 1999 to 2003 | Hypertension diagnosed before pregnancy | birth weight of <2500 grams | 7 |
| Odell, 2006 | USA | Population-based (Black women only) | Black:12,258<br>White: None | 1996 to 2000 | History of chronic hypertension diagnosed using ICD 9 codes | birth weight of <2500 grams | 7 |

‡ We combined the ORs for birthweight < 1,499 g and birthweight (1,500-2,499 g).

**Table S3.19** Characteristics of studies for pre-eclampsia outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Mabie, 1986† | USA | Cohort (hospital-based) | 169 pregnancies in 156 women | 1980 to 1984 | Women with CH who were on antihypertensive treatment | Untreated women with CH | Superimposed preeclampsia: worsening hypertension (30 mmHg SBP or 15 mmHg DBP) plus either nondependent edema or proteinuria of +1 or greater by dipstick. | 6 |
| Bayliss, 2002‡ | UK | Cohort (hospital-based) | 491 pregnancies | 1980 to 1999 | Women with CH who were on antihypertensive treatment | Untreated women with CH | The onset of significant levels of proteinuria after 20 weeks gestation | 6 |
| Orbach, 2013 | Israel | Cohort (population- based) | 98,253 births | 1998 to 2008 | Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the 1st trimester | Untreated normotensive women | Proteinuria diagnosed using ICD-9 codes | 8 |
| Rezk, 2016 | Egypt | Cohort (hospital-based) | 222 women | 2012 to 2016 | Women with CH who were taking Methyldopa | Untreated women with CH | Superimposed preeclampsia: a new onset proteinuria with 0.3 g of protein or more in a 24-h urine specimen after 20 weeks' gestation), eclampsia (generalized convulsions) | 4 |
| Nzelu, 2018 | UK | Cohort (hospital-based) | 419 | 2011 to 2016 | women with CH on antihypertensive treatment | Untreated women with CH | Superimposed pre-eclampsia: hypertension, with at least 1 of the following problems: renal involvement (proteinuria 300 mg/24 h and/or creatinine 90 mmol/L or 1 mg/dL), liver impairment (transaminases >70 IU/L), neurologic complications (eg, eclampsia), thrombocytopenia (platelet count <150,000/mL). | 7 |
| Youngstrom, 2018 | USA | Cohort (hospital-based) | 1,094 mother-infant pairs | 2000 to 2014 | women with CH on antihypertensive treatment | Untreated normotensive women | BP ≥140/90 with either proteinuria (protein excretion ≥300 mg in 24 hours or protein-to-creatinine ratio≥0.3), thrombocytopenia (less than 100,000/mL), transaminases (aspartate aminotransferase > twice the upper limit of normal), or elevated creatinine≥1.2 mg/dL | 8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Mito, 2019§ | Japan | Cohort (population-based) | 231 women | 2008 to 2016 | women with CH on antihypertensive treatment at the first trimester | Untreated women with CH | Superimposed pre-eclampsia diagnosed if a woman developed new-onset proteinuria in the with a rise in blood pressure or a sudden increase in pre-existing proteinuria. | 7 |

BP, blood pressure; CH, Chronic hypertension; †The raw data for this study include women on methyldopa, other monotherapy, or multiple drug treatment vs untreated women. ‡The odds ratios of this study were combined for different agents. §The raw data for this study include women on amlodipine or other antihypertensive drug treatment vs untreated women

**Table S3.20** Characteristics of studies for cesarean section (CS) outcome

| ***Author, year published*** | ***Country (ies)*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of exposure*** | ***Comparative group*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|---|
| Rezk, 2016 | Egypt | Cohort (hospital-based) | 222 women | 2012 to 2016 | Women with CH who were taking Methyldopa | Untreated women with CH | Caesarean section (not specified) | 4 |
| Hoeltzenbei, 2017 | Germany | Cohort | 787 pregnancies | 2000 to 2014 | pregnancies with methyldopa exposure at least during the first trimester, but no longer than 20 weeks' gestation | Untreated normotensive women | Caesarean section (not specified) | 5 |

CH, Chronic hypertension

**Table S3.21** Characteristics of studies for miscarriage outcome

| *Author, year published* | *Country (ies)* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Bayliss, 2002 | UK | Cohort (hospital-based) | 491 pregnancies | 1980 to 1999 | Women with CH who were on antihypertensive treatment | Untreated women with CH | miscarriages | 6 |
| Hoeltzenbei, 2017 | Germany | Cohort | 787 pregnancies | 2000 to 2014 | pregnancies with methyldopa exposure at least during the first trimester, but no longer than 20 weeks' gestation | Untreated normotensive women | Spontaneous pregnancy loss of a fetus <500 g or in case of unknown weight <24 completed weeks after last menstrual period | 5 |

CH, Chronic hypertension

**Table S3.22** Characteristics of studies for stillbirth outcome

| *Author, year published* | *Country (ies)* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Bayliss, 2002 | UK | Cohort (hospital-based) | 491 pregnancies | 1980 to 1999 | Women with CH who were on antihypertensive treatment | Untreated women with CH | Stillbirth | 6 |
| Hoeltzenbei, 2017 | Germany | Cohort | 787 pregnancies | 2000 to 2014 | pregnancies with methyldopa exposure at least during the first trimester, but no longer than 20 weeks' gestation | Untreated normotensive women | Stillbirth | 5 |
| Rezk, 2016 | Egypt | Cohort (hospital-based) | 222 women | 2012 to 2016 | Women with CH who were taking Methyldopa | Untreated women with CH | Intrauterine fetal death | 4 |
| Youngstrom, 2018 | USA | Cohort (hospital-based) | 1,094 mother-infant pairs | 2000 to 2014 | women with CH on antihypertensive treatment | Untreated normotensive women | Stillbirth | 8 |

CH, Chronic hypertension

**Table S3.23a** Characteristics of studies for Preterm birth outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Ray, 2001† | Canada | Cohort (hospital-based) | 583 mother-infant pairs | 1986 to 1995 | women with CH on antihypertensive treatment | Untreated women with CH | <37 weeks' gestation | 6 |
| Lennestål, 2009 | Sweden | Cohort (population-based) | 1,032,094 pregnancies | 1995 to 2006 | Women who reported using antihypertensive treatment in early pregnancy, and with a delivery diagnosis of CH for women who were on beta-blocking drug | Untreated normotensive women | <37 weeks' gestation | 8 |
| Banhidy, 2010 | Hungary | Case control (population based) | 36,155 births | 1980 to 1996 | Women with CH on antihypertensive treatment | Untreated normotensive women | <37 weeks' gestation | 6 |
| Su, 2013§ | Taiwan | Cohort (population-based) | 2,727 mother-infant pairs | 2005 | women with CH on antihypertensive treatment | Untreated women with CH | <37 weeks' gestation | 8 |
| Orbach, 2013 | Israel | Cohort (population-based) | 98,253 births | 1998 to 2008 | Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the 1st trimester | Untreated normotensive women | <37 weeks' gestation | 8 |
| Rezk, 2016 | Egypt | Cohort (hospital-based) | 222 women | 2012 to 2016 | Women with CH who were taking methyldopa | Untreated women with CH | <37 weeks' gestation | 4 |
| Hoeltzenbei, 2017 | Germany | Cohort | 787 pregnancies | 2000 to 2014 | pregnancies with methyldopa exposure at least during the first trimester, but no longer than 20 weeks' gestation | Untreated normotensive women | <37 weeks' gestation | 5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Youngstrom, 2018 | USA | Cohort (hospital-based) | 1,094 mother-infant pairs | 2000 to 2014 | women with CH on antihypertensive treatment | Untreated normotensive women | <37 weeks' gestation | 8 |
| Mito, 2019‡ | Japan | Cohort (population-based) | 231 women | 2008 to 2016 | women with CH on antihypertensive treatment at the first trimester | Untreated women with CH | <37 weeks' gestation | 7 |

CH, Chronic hypertension; †We combined odds ratios from this study for women using beta-blockers or other agents; §The odds ratios of these studies were combined for different agents; ‡The raw data for this study include women on amlodipine or other antihypertensive drug treatment vs untreated women

**Table S3.23b** Characteristics for preterm birth outcome: (exposed to beta-blockers vs untreated)

| ***Author, year published*** | ***Country*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of exposure*** | ***Comparative group*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|---|
| Ray, 2001 | Canada | Cohort (hospital-based) | 391mother-infant pairs | 1986 to 1995 | women with CH on β-blocker treatment | Untreated women with CH | <37 weeks' gestation | 6 |
| Su, 2013 | Taiwan | Cohort (population-based) | 1,420 mother-infant pairs | 2005 | Pregnant women with CH who were exposed to β-blockers | Untreated women with CH | <37 weeks' gestation | 8 |
| Orbach, 2013 | Israel | Cohort (population-based) | 97,927 births | 1998 to 2008 | Pregnant women with CH who were exposed to atenolol | Untreated normotensive women | <37 weeks' gestation | 8 |

**Table S3.24a** Characteristics of studies for small for gestational age (SGA) outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Mabie, 1986† | USA | Cohort (hospital-based) | 169 pregnancies in 156 women | 1980 to 1984 | Women with CH who were on antihypertensive treatment | Untreated women with CH | Birthweight <10th percentile | 6 |
| Ray, 2001* | Canada | Cohort (hospital-based) | 583 mother-infant pairs | 1986 to 1995 | women with CH on antihypertensive treatment | Untreated women with CH | Birthweight <10th percentile | 6 |
| Bayliss, 2002* | UK | Cohort (hospital-based) | 491 pregnancies | 1980 to 1999 | Women with CH who were on antihypertensive treatment | Untreated women with CH | Birthweight <10th percentile | 6 |
| Lennestål, 2009 | Sweden | Cohort (population-based) | 1,032,094 pregnancies | 1995 to 2006 | Women who reported using antihypertensive treatment in early pregnancy, and with a delivery diagnosis of chronic hypertension for women who were on beta-blocking drug | Untreated normotensive women | Birthweight < -2SD | 8 |
| Su, 2013* | Taiwan | Cohort (population-based) | 2,727 mother-infant pairs | 2005 | women with CH on antihypertensive treatment | Untreated women with CH | Birthweight <10th percentile | 8 |
| Orbach, 2013 | Israel | Cohort (population-based) | 98,253 births | 1998 to 2008 | Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the 1st trimester | Untreated normotensive women | SGA diagnosed using ICD-9 | 8 |
| Rezk, 2016 | Egypt | Cohort (hospital-based) | 222 women | 2012 to 2016 | Women with CH who were taking Methyldopa | Untreated women with CH | Birthweight <10th percentile | 4 |
| Nzelu, 2018 | UK | Cohort (hospital-based) | 419 | 2011 to 2016 | women with CH on antihypertensive treatment | Untreated women with CH | Birthweight <5th percentile | 7 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Fisher, 2018 | USA | Cohort (population-based) | 4,282 mother-infant pairs | 2006 to 2011 | Women with CH on antihypertensive treatment | Untreated normotensive women | Birthweight <10th percentile | 6 |
| Youngstrom, 2018 | USA | Cohort (hospital-based) | 1,094 mother-infant pairs | 2000 to 2014 | women with CH on antihypertensive treatment | Untreated normotensive women | Birthweight <10th percentile | 8 |

CH, Chronic hypertension; SD, stab]ndard deviation. * Odds ratios from these studies were combined for different agents. †The raw data for this study include women on methyldopa, other monotherapy, or multiple drug treatment vs untreated women.

**Table S3.24b** Characteristics of studies for SGA outcome: (beta blockers vs untreated women)

| ***Author, year published*** | ***Country*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of exposure*** | ***Comparative group*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|---|
| Ray, 2001 | Canada | Cohort (hospital-based) | 391 mother-infant pairs | 1986 to 1995 | Pregnant women with CH who were exposed to β-blockers | Untreated women with CH | Birth weight<10th percentile | 6 |
| Bayliss, 2002 | UK | Cohort (hospital-based) | 229 pregnancies | 1980 to 1999 | Pregnant women with CH who were exposed to atenolol<15 weeks' gestation | Untreated women with CH | Birth weight<10th percentile | 6 |
| Su, 2013 | Taiwan | Cohort (population-based) | 1,420 mother-infant pairs | 2005 | Pregnant women with CH who were exposed to β-blockers | Untreated women with CH | Birth weight<10th percentile | 8 |
| Orbach, 2013 | Israel | Cohort (population-based) | 97,927 births | 1998 to 2008 | Pregnant women with CH who were exposed to atenolol | Untreated normotensive women | SGA diagnosed using ICD-9 | 8 |

CH, Chronic hypertension; β-blockers, beta blockers

**Table S3.24c** Characteristics of studies for SGA outcome: (single agent/multiple agents vs untreated women)

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Ray, 2001 | Canada | Cohort (hospital-based) | 500 mother-infant pairs (untreated. n=247, sing. n=144 multi. n=109) | 1986 to 1995 | women with CH who were on single agent (βB), or on multiple agents | Untreated women with CH | Birthweight<10$^{th}$ percentile | 6 |
| Bayliss, 2002 | UK | Cohort (hospital-based) | 268 pregnancies (sing. n=229, multi. n=243) | 1980 to 1999 | Women with CH who were on single agent (atenolol), or on multiple agents | Untreated women with CH | Birthweight<10$^{th}$ percentile | 6 |
| Su, 2013 | Taiwan | Cohort (population-based) | 1,543 mother-infant pairs (untreated n=1,006, sing. n=144, multi. n=123) | 2005 | women with CH who were on single agent (βB), or on multiple agents | Untreated women with CH | Birthweight <10$^{th}$ percentile | 8 |

βB, beta-blockers; CH, Chronic hypertension

**Table S3.24d** Characteristics of studies for SGA outcome: (centrally acting antiadrenergic vs untreated women)

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Mabie, 1986 | USA | Cohort (hospital-based) | 136 pregnancies | 1980 to 1984 | Pregnant women who were exposed to methyldopa | Untreated women with CH | Birthweight<10$^{th}$ percentile | 6 |
| Su, 2013 | Taiwan | Cohort (population-based) | 1,187 mother-infant pairs | 2005 | Pregnant women who were exposed to centrally acting antiadrenergic | Untreated women with CH | Birthweight<10$^{th}$ percentile | 8 |
| Orbach, 2013 | Israel | Cohort (population-based) | 98,160 births | 1998 to 2008 | Pregnant women who were exposed to methyldopa | Untreated normotensive women | SGA diagnosed using ICD-9 | 8 |
| Rezk, 2016 | Egypt | Cohort (hospital-based) | 222 women | 2012 to 2016 | Pregnant women who were exposed to methyldopa | Untreated women with CH | Birthweight<10$^{th}$ percentile | 4 |

CH, Chronic hypertension.

**Table S3.24e** Characteristics of studies for SGA outcome: (methyldopa vs other agents)

| ***Author, year published*** | ***Country*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of exposure*** | ***Comparative group*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|---|
| Mabie, 1986 | USA | Cohort (hospital-based) | 64 pregnancies | 1980 to 1984 | Pregnant women with CH who were exposed to methyldopa | Pregnant women with CH on hydrochlorothiazide | Birthweight<10$^{th}$ percentile | 6 |
| Su, 2013 | Taiwan | Cohort (population-based) | 595 mother-infant pairs | 2005 | Pregnant women who were exposed to centrally acting antiadrenergic | Pregnant women with CH on β-blockers | Birthweight<10$^{th}$ percentile | 8 |
| Orbach, 2013 | Israel | Cohort (population-based) | 447 births | 1998 to 2008 | Pregnant women with CH who were exposed to methyldopa | Pregnant women with CH who were exposed to atenolol | SGA diagnosed using ICD-9 | 8 |
| Xie,2014 | Canada | Cohort (population-based) | 628 Women with CH | 1980 to 1987 or 1990 to 2005 | Pregnant women with CH who were exposed to methyldopa | Pregnant women with CH on β-blockers | Birthweight<10$^{th}$ percentile | 7 |
| Ahmed, 2018 | Australia | Cohort (population-based) | 456 pregnancies | 2005 and 2012 | Pregnant women with CH who were exposed to methyldopa | Pregnancies with CH on ARBs exposure at first trimester | Birthweight<10$^{th}$ percentile | 7 |

ARB, angiotensin-receptor blockers; CH, Chronic hypertension

**Table S3.24f** Characteristics of studies for SGA outcome: (beta blockers vs methyldopa)

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Su, 2013 | Taiwan | Cohort (population-based) | 595 mother-infant pairs | 2005 | Pregnant women with CH on β-blockers | Pregnant women who were exposed to centrally acting antiadrenergic | Birthweight<10$^{th}$ percentile | 8 |
| Orbach, 2013 | Israel | Cohort (population-based) | 447 births | 1998 to 2008 | Pregnant women with CH who were exposed to atenolol | Pregnant women with CH who were exposed to methyldopa | SGA diagnosed using ICD-9 | 8 |
| Xie,2014 | Canada | Cohort (population-based) | 628 Women with CH | 1980 to 1987 or 1990 to 2005 | Pregnant women with CH on β-blockers | Pregnant women with CH who were exposed to methyldopa | Birthweight<10$^{th}$ percentile | 7 |

CH, Chronic hypertension.

**Table S3.25** Characteristics of studies for low birth weight (LBW) outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Lennestål, 2009 | Sweden | Cohort (population-based) | 1,032,094 pregnancies | 1995 to 2006 | Women who reported using antihypertensive treatment in early pregnancy, and with a delivery diagnosis of chronic hypertension for women who were on beta-blocking drug | Untreated normotensive women | Birthweight < 2,500g | 8 |
| Banhidy, 2010 | Hungary | Case control (population based) | 36,155 births | 1980 to 1996 | Women with CH on antihypertensive treatment | Untreated normotensive women | Birthweight < 2,500g | 6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Su, 2013§ | Taiwan | Cohort (population-based) | 2,727 mother-infant pairs | 2005 | women with CH on antihypertensive treatment | Untreated women with CH | Birthweight < 2,500g | 8 |
| Orbach, 2013 | Israel | Cohort (population-based) | 98,253 births | 1998 to 2008 | Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the 1st trimester | Untreated normotensive women | Birthweight < 2,500g | 8 |
| Mito, 2019† | Japan | Cohort (population-based) | 231 women | 2008 to 2016 | women with CH on antihypertensive treatment at the first trimester | Untreated women with CH | Birthweight < 2,500g | 7 |

CH, Chronic hypertension. §The ORs of these studies were combined for different agents. †The raw data for this study include women on amlodipine or other antihypertensive drug treatment vs untreated women.

**Table S3.26** Characteristics of studies for neonatal intensive care unit (NICU) admission outcome

| ***Author, year published*** | ***Country*** | ***Design*** | ***Sample size*** | ***Study duration*** | ***Definition of exposure*** | ***Comparative group*** | ***Definition of outcome*** | ***Newcastle-Ottawa grade*** |
|---|---|---|---|---|---|---|---|---|
| Rezk, 2016 | Egypt | Cohort (hospital-based) | 222 women | 2012 to 2016 | Women with CH who were taking Methyldopa | Untreated women with CH | Admission to NICU | 4 |
| Helou, 2017 | Australia | Cohort (hospital-based) | 49 women | 2010 | Women with CH on antihypertensive treatment | Untreated women with CH | Admission to NICU or SCN | 6 |

CH, Chronic hypertension; SCN: Special care nursery.

**Table S3.27** Characteristics of studies for perinatal death outcome

| *Author, year published* | *Country* | *Design* | *Sample size* | *Study duration* | *Definition of exposure* | *Comparative group* | *Definition of outcome* | *Newcastle-Ottawa grade* |
|---|---|---|---|---|---|---|---|---|
| Mabie, 1986† | USA | Cohort (hospital-based) | 169 pregnancies in 156 women | 1980 to 1984 | Women with CH who were on antihypertensive treatment | Untreated women with CH | Not reported | 6 |
| Ray, 2001* | Canada | Cohort (hospital-based) | 1,948 mother-infant pairs | 1986 to 1995 | women with CH or other HDP on antihypertensive treatment | Untreated women with CH or HDP | Perinatal death after 20 weeks gestation and up to 30 days after birth | 6 |
| Orbach, 2013 | Israel | Cohort (population- based) | 98,253 births | 1998 to 2008 | Women with CH who were on antihypertensive treatment (methyldopa or atenolol) dispensed during the first trimester | Untreated normotensive women | Not reported | 8 |
| Youngstrom, 2018 | USA | Cohort (hospital-based) | 1,094 mother-infant pairs | 2000 to 2014 | women with CH on antihypertensive treatment | Untreated normotensive women | Stillbirth and neonatal death | 8 |

CH, Chronic hypertension. †The raw data for this study include women on methyldopa, other monotherapy, or multiple drug treatment vs untreated women.
*We combined odds ratios from this study for women using beta-blockers or other agents

## S3.4 Supplemental Figures S3.1-S3.26

**Figure S3.1a** Forest plot of crude estimates of the association between chronic hypertension and PE

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Abalos, 2014 | 2.8462 | 0.0653 | 5.7% | 17.22 [15.15, 19.57] |
| Bilano, 2014 | 2.3175 | 0.0474 | 5.7% | 10.15 [9.25, 11.14] |
| Block-Abraham, 2014 | 1.0026 | 0.3083 | 4.9% | 2.73 [1.49, 4.99] |
| Broekhuijsen, 2015 | 2.0669 | 0.0617 | 5.7% | 7.90 [7.00, 8.92] |
| Catov, 2007 | 1.6233 | 0.0961 | 5.7% | 5.07 [4.20, 6.12] |
| Conde-Agudelo, 2000 | 1.6824 | 0.023 | 5.8% | 5.38 [5.14, 5.63] |
| Gilbert, 2007 | 0.8084 | 0.0249 | 5.8% | 2.24 [2.14, 2.36] |
| Guerrier, 2013 | 2.1633 | 0.1896 | 5.4% | 8.70 [6.00, 12.62] |
| Kiondo, 2012 | 0.8329 | 0.3319 | 4.8% | 2.30 [1.20, 4.41] |
| Lisonkova, 2013 | 2.0656 | 0.0341 | 5.8% | 7.89 [7.38, 8.44] |
| Mostello, 2002 | 1.7317 | 0.2901 | 5.0% | 5.65 [3.20, 9.98] |
| Panaitescu, 2017 | 2.4849 | 0.0681 | 5.7% | 12.00 [10.50, 13.71] |
| Rey, 1994 | 2.432 | 0.1495 | 5.5% | 11.38 [8.49, 15.26] |
| Samadi, 2001 | 2.4534 | 0.0614 | 5.7% | 11.63 [10.31, 13.11] |
| Yanit, 2012 | 2.6748 | 0.0308 | 5.8% | 14.51 [13.66, 15.41] |
| You, 2018 | 2.7408 | 0.0236 | 5.8% | 15.50 [14.80, 16.23] |
| Youngstorm, 2018 | 1.4907 | 0.2052 | 5.4% | 4.44 [2.97, 6.64] |
| Zetterstorm, 2005 | 1.5369 | 0.0544 | 5.7% | 4.65 [4.18, 5.17] |
| **Total (95% CI)** | | | **100.0%** | **7.11 [5.01, 10.09]** |

Heterogeneity: Tau² = 0.55; Chi² = 4395.53, df = 17 (P < 0.00001); I² = 100%
Test for overall effect: Z = 10.98 (P < 0.00001)

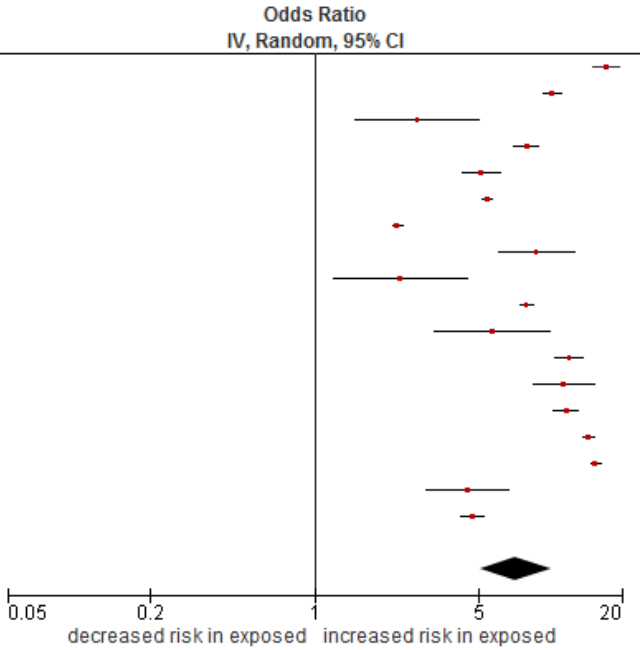



**Figure S3.1b** Funnel plot for adjusted estimates of PE (chronic hypertension versus normotensive)

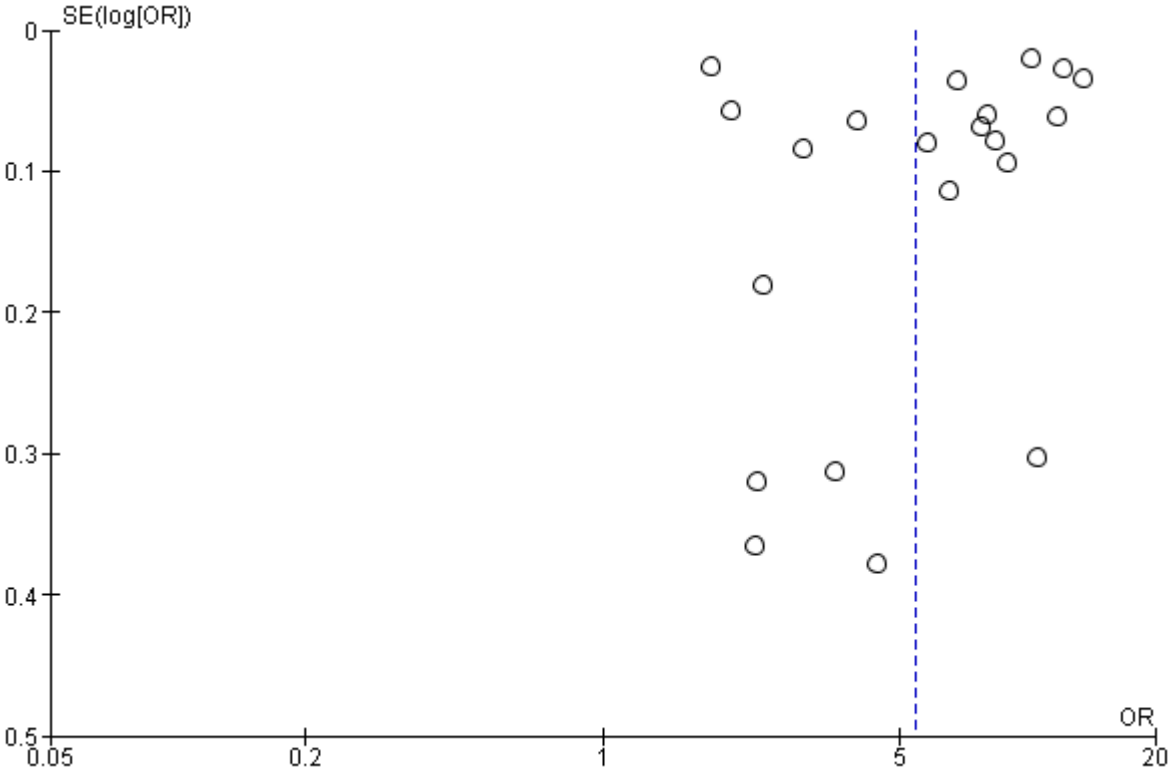


**Figure S3.2a** Forest plot of crude estimates of the association between chronic hypertension and HEELP syndrome

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Fitzpatrick, 2014 | 0.703 | 0.3863 | 19.1% | 2.02 [0.95, 4.31] |
| Gilbert, 2007 | 1.2113 | 0.1068 | 44.1% | 3.36 [2.72, 4.14] |
| Malmstorm, 2018 | 1.6677 | 0.1792 | 36.8% | 5.30 [3.73, 7.53] |
| **Total (95% CI)** | | | **100.0%** | **3.60 [2.36, 5.50]** |

Heterogeneity: Tau² = 0.09; Chi² = 7.29, df = 2 (P = 0.03); I² = 73%
Test for overall effect: Z = 5.95 (P < 0.00001)

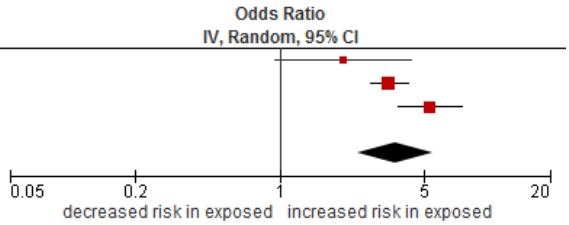



**Figure S3.2b** Forest plot of adjusted estimates of the association between chronic hypertension and HEELP syndrome

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Fitzpatrick, 2014 | 0.5247 | 0.4497 | 20.6% | 1.69 [0.70, 4.08] |
| Gilbert, 2007 | 0.9783 | 0.111 | 42.1% | 2.66 [2.14, 3.31] |
| Malmstorm, 2018 | 1.6214 | 0.1895 | 37.3% | 5.06 [3.49, 7.34] |
| **Total (95% CI)** | | | **100.0%** | **3.08 [1.79, 5.30]** |

Heterogeneity: Tau² = 0.17; Chi² = 10.38, df = 2 (P = 0.006); I² = 81%
Test for overall effect: Z = 4.05 (P < 0.0001)

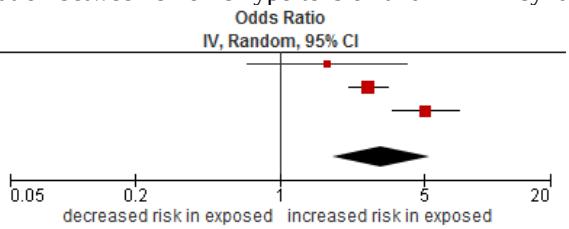



**Figure S3.3a** Forest plot of crude estimates of the association between chronic hypertension and CS

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **1.7.1 not specified** | | | | |
| Cruz, 2011 | 1.3083 | 0.0431 | 6.2% | 3.70 [3.40, 4.03] |
| Gilbert, 2007 | 1.127 | 0.0117 | 6.4% | 3.09 [3.02, 3.16] |
| Hartikainen, 1998 | 0.7668 | 0.125 | 5.2% | 2.15 [1.69, 2.75] |
| Hjertberg, 1992 | 0.6914 | 0.3635 | 2.2% | 2.00 [0.98, 4.07] |
| Jain, 1997 | 0.842 | 0.0465 | 6.2% | 2.32 [2.12, 2.54] |
| Janoudi, 2015 | 0.9731 | 0.0622 | 6.0% | 2.65 [2.34, 2.99] |
| Madi, 2012 | 0.9812 | 0.0792 | 5.8% | 2.67 [2.28, 3.12] |
| Rey, 1994 | 0.8664 | 0.1203 | 5.3% | 2.38 [1.88, 3.01] |
| Sass, 1990 | 0.7502 | 0.2117 | 3.9% | 2.12 [1.40, 3.21] |
| Tuuli, 2011 | 0.6981 | 0.0678 | 6.0% | 2.01 [1.76, 2.30] |
| Venek, 2004 | 1.0986 | 0.0538 | 6.1% | 3.00 [2.70, 3.33] |
| Ye, 2014 | 0.7074 | 0.1163 | 5.3% | 2.03 [1.62, 2.55] |
| **Subtotal (95% CI)** | | | **64.6%** | **2.56 [2.28, 2.87]** |
| Heterogeneity: Tau² = 0.03; Chi² = 127.21, df = 11 (P < 0.00001); I² = 91% | | | | |
| Test for overall effect: Z = 16.18 (P < 0.00001) | | | | |
| **1.7.2 Planned CS** | | | | |
| Broekhuijsen, 2015 | 0.1823 | 0.093 | 5.7% | 1.20 [1.00, 1.44] |
| Lydakis, 2001 | 0.7768 | 0.5085 | 1.4% | 2.17 [0.80, 5.89] |
| Panaitescu, 2017 | 1.1184 | 0.0658 | 6.0% | 3.06 [2.69, 3.48] |
| Roberts, 2005 | 0.7062 | 0.0646 | 6.0% | 2.03 [1.79, 2.30] |
| **Subtotal (95% CI)** | | | **19.0%** | **1.98 [1.27, 3.11]** |
| Heterogeneity: Tau² = 0.17; Chi² = 68.93, df = 3 (P < 0.00001); I² = 96% | | | | |
| Test for overall effect: Z = 2.99 (P = 0.003) | | | | |
| **1.7.3 Emergency CS** | | | | |
| Lydakis, 1998 | 1.1656 | 0.1678 | 4.5% | 3.21 [2.31, 4.46] |
| Panaitescu, 2017 | 0.5653 | 0.0715 | 5.9% | 1.76 [1.53, 2.02] |
| Roberts, 2005 | 0.347 | 0.0787 | 5.9% | 1.41 [1.21, 1.65] |
| **Subtotal (95% CI)** | | | **16.3%** | **1.93 [1.37, 2.72]** |
| Heterogeneity: Tau² = 0.08; Chi² = 20.00, df = 2 (P < 0.0001); I² = 90% | | | | |
| Test for overall effect: Z = 3.76 (P = 0.0002) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.30 [2.02, 2.63]** |

Heterogeneity: Tau² = 0.07; Chi² = 390.80, df = 18 (P < 0.00001); I² = 95%
Test for overall effect: Z = 12.51 (P < 0.00001)
Test for subgroup differences: Chi² = 3.25, df = 2 (P = 0.20), I² = 38.4%

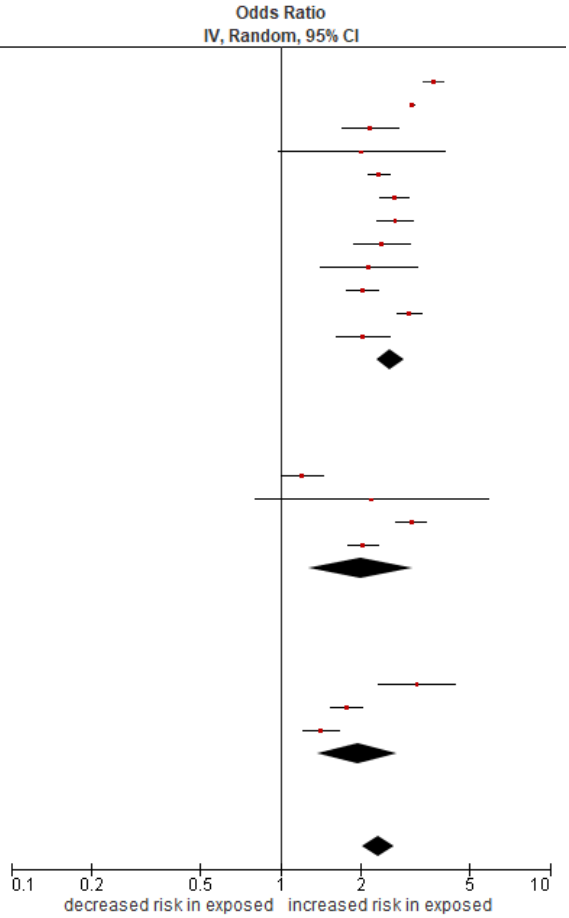


**Figure S3.3b** Forest plot of adjusted estimates of the association between chronic hypertension and CS

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **1.8.1 not specified** | | | | |
| Bateman, 2012 | 0.8713 | 0.0174 | 10.7% | 2.39 [2.31, 2.47] |
| Gilbert, 2007 | 0.8459 | 0.0133 | 10.8% | 2.33 [2.27, 2.39] |
| Janoudi, 2015 | 0.6043 | 0.0316 | 10.6% | 1.83 [1.72, 1.95] |
| Rey, 1994 | 0.5878 | 0.0601 | 10.1% | 1.80 [1.60, 2.03] |
| Tuuli, 2011 | 0.7178 | 0.0692 | 9.9% | 2.05 [1.79, 2.35] |
| Venek, 2004 | 0.9933 | 0.0601 | 10.1% | 2.70 [2.40, 3.04] |
| **Subtotal (95% CI)** | | | **62.3%** | **2.17 [1.97, 2.38]** |
| Heterogeneity: Tau² = 0.01; Chi² = 84.14, df = 5 (P < 0.00001); I² = 94% | | | | |
| Test for overall effect: Z = 16.01 (P < 0.00001) | | | | |
| **1.8.2 Planned CS** | | | | |
| Broekhuijsen, 2015 | 0.0953 | 0.0486 | 10.3% | 1.10 [1.00, 1.21] |
| Panaitescu, 2017 | 0.5822 | 0.0834 | 9.6% | 1.79 [1.52, 2.11] |
| **Subtotal (95% CI)** | | | **19.9%** | **1.40 [0.87, 2.25]** |
| Heterogeneity: Tau² = 0.11; Chi² = 25.44, df = 1 (P < 0.00001); I² = 96% | | | | |
| Test for overall effect: Z = 1.37 (P = 0.17) | | | | |
| **1.8.3 Emergency CS** | | | | |
| Lydakis, 1998 | 0.9783 | 0.1329 | 8.1% | 2.66 [2.05, 3.45] |
| Panaitescu, 2017 | -0.0101 | 0.0778 | 9.7% | 0.99 [0.85, 1.15] |
| **Subtotal (95% CI)** | | | **17.8%** | **1.61 [0.61, 4.25]** |
| Heterogeneity: Tau² = 0.48; Chi² = 41.19, df = 1 (P < 0.00001); I² = 98% | | | | |
| Test for overall effect: Z = 0.97 (P = 0.33) | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.87 [1.61, 2.16]** |
| Heterogeneity: Tau² = 0.05; Chi² = 415.85, df = 9 (P < 0.00001); I² = 98% | | | | |
| Test for overall effect: Z = 8.23 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 3.44, df = 2 (P = 0.18), I² = 41.9% | | | | |

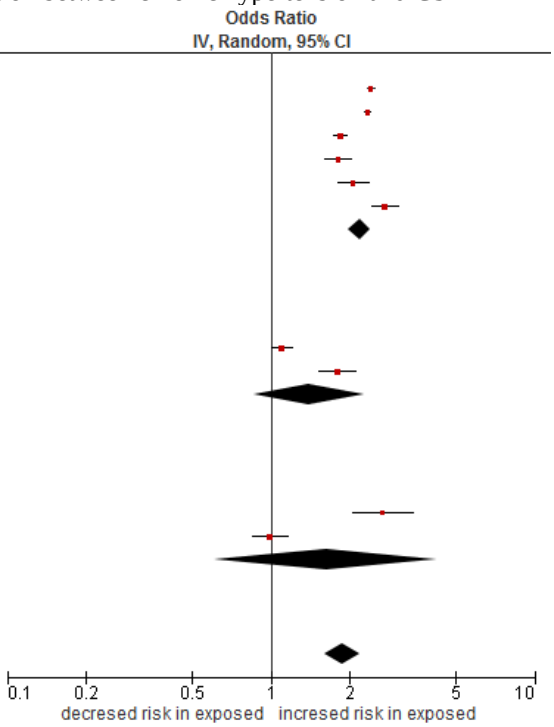



**Figure S3.3c** Funnel plot for adjusted estimates of CS (chronic hypertension versus normotensive)

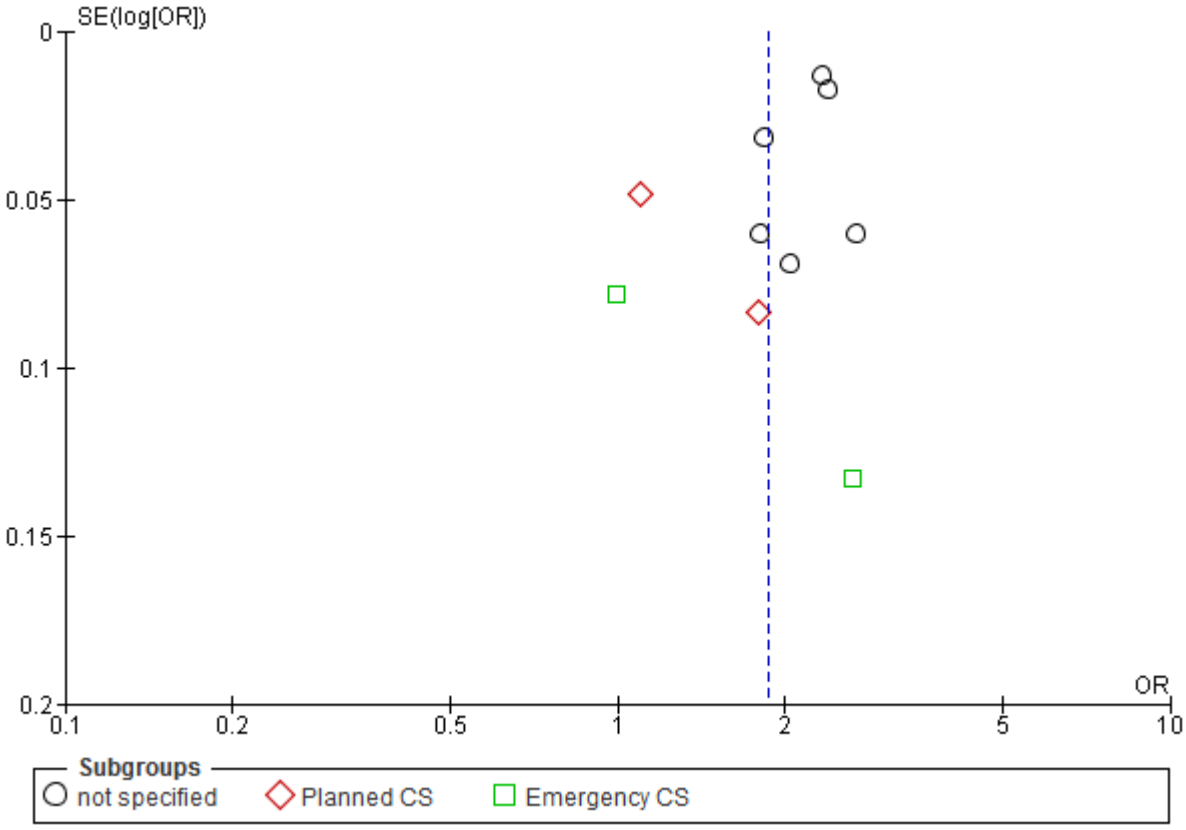


**Figure S3.4a** Forest plot of crude estimates of the association between chronic hypertension and PPH

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Broekhuijsen, 2015 | 0.0953 | 0.1024 | 19.5% | 1.10 [0.90, 1.34] |
| Cruz, 2011 | 0.5878 | 0.2069 | 13.8% | 1.80 [1.20, 2.70] |
| Gilbert, 2007 | 0.4681 | 0.0297 | 22.3% | 1.60 [1.51, 1.69] |
| Roberts, 2005 | 0.0711 | 0.1099 | 19.1% | 1.07 [0.87, 1.33] |
| Venek, 2004 | 0.8755 | 0.275 | 10.6% | 2.40 [1.40, 4.11] |
| Ye, 2014 | 0.9538 | 0.1888 | 14.7% | 2.60 [1.79, 3.76] |
| **Total (95% CI)** | | | **100.0%** | **1.57 [1.23, 2.00]** |

Heterogeneity: Tau² = 0.07; Chi² = 33.87, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 3.66 (P = 0.0002)

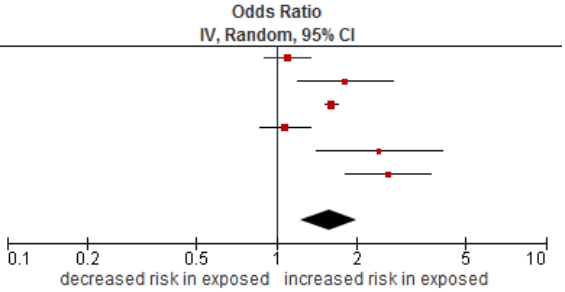



**Figure S3.4b** Forest plot of adjusted estimates of the association between chronic hypertension and PPH

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Broekhuijsen, 2015 | 0.0953 | 0.1024 | 29.6% | 1.10 [0.90, 1.34] |
| Cruz, 2011 | 0.5306 | 0.1968 | 17.6% | 1.70 [1.16, 2.50] |
| Gilbert, 2007 | 0.3646 | 0.0329 | 38.2% | 1.44 [1.35, 1.54] |
| Venek, 2004 | 0.7885 | 0.2306 | 14.6% | 2.20 [1.40, 3.46] |
| **Total (95% CI)** | | | **100.0%** | **1.46 [1.17, 1.81]** |

Heterogeneity: Tau² = 0.03; Chi² = 10.84, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 3.39 (P = 0.0007)

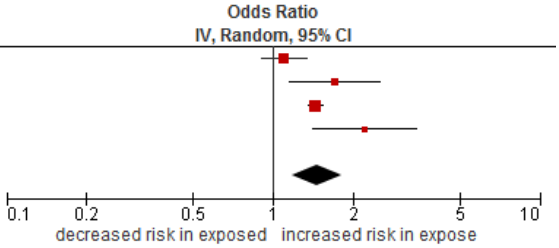



**Figure S3.5** Forest plot of crude estimates of the association between chronic hypertension and maternal mortality

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Compbell, 2013 | 2.4336 | 0.2274 | 25.1% | 11.40 [7.30, 17.80] |
| Gilbert, 2007 | 2.2022 | 0.1985 | 28.6% | 9.04 [6.13, 13.35] |
| Kuklina, 2009 | 1.9244 | 0.074 | 46.4% | 6.85 [5.93, 7.92] |
| **Total (95% CI)** | | | **100.0%** | **8.43 [6.17, 11.50]** |

Heterogeneity: Tau² = 0.05; Chi² = 5.72, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 13.43 (P < 0.00001)

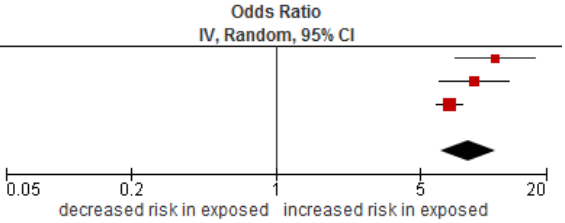



**Figure S3.6a** Forest plot of crude estimates of the association between chronic hypertension and stillbirth

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Aagord-Tittery, 2006 | 1.2442 | 0.3551 | 2.0% | 3.47 [1.73, 6.96] |
| Ahmed, 2012 | 0.8074 | 0.111 | 7.6% | 2.24 [1.80, 2.79] |
| Allen, 2004 | 1.1632 | 0.266 | 3.1% | 3.20 [1.90, 5.39] |
| Ananth, 1995 | 1.1741 | 0.12 | 7.2% | 3.24 [2.56, 4.09] |
| Canterino, 2004 | 1.2981 | 0.031 | 10.6% | 3.66 [3.45, 3.89] |
| Conde-Agudelo, 2000b | 0.9859 | 0.0448 | 10.2% | 2.68 [2.45, 2.93] |
| Gilbert, 2007 | 1.1878 | 0.0354 | 10.5% | 3.28 [3.06, 3.52] |
| Lydakis, 1998 | 1.5602 | 0.3645 | 1.9% | 4.76 [2.33, 9.72] |
| Madi, 2012 | 1.8358 | 0.3198 | 2.4% | 6.27 [3.35, 11.74] |
| Panaitescu, 2017 | 1.3987 | 0.2203 | 4.0% | 4.05 [2.63, 6.24] |
| Reddy, 2010 | 0.9858 | 0.1519 | 6.0% | 2.68 [1.99, 3.61] |
| Roberts, 2005 | 0.8116 | 0.2325 | 3.7% | 2.25 [1.43, 3.55] |
| Tuuli, 2011 | 0.8796 | 0.2154 | 4.1% | 2.41 [1.58, 3.68] |
| Xiong, 2018 | 0.9026 | 0.0565 | 9.8% | 2.47 [2.21, 2.75] |
| Yanit, 2012 | 0.9977 | 0.1518 | 6.0% | 2.71 [2.01, 3.65] |
| Yerlikaya, 2016 | 1.5173 | 0.2205 | 4.0% | 4.56 [2.96, 7.02] |
| Youngstorm, 2018 | 0.7575 | 0.4642 | 1.3% | 2.13 [0.86, 5.30] |
| Zetterstorm, 2006 | 0.9959 | 0.1641 | 5.6% | 2.71 [1.96, 3.73] |
| **Total (95% CI)** | | | **100.0%** | **3.00 [2.69, 3.35]** |

Heterogeneity: Tau² = 0.03; Chi² = 83.53, df = 17 (P < 0.00001); I² = 80%
Test for overall effect: Z = 19.82 (P < 0.00001)

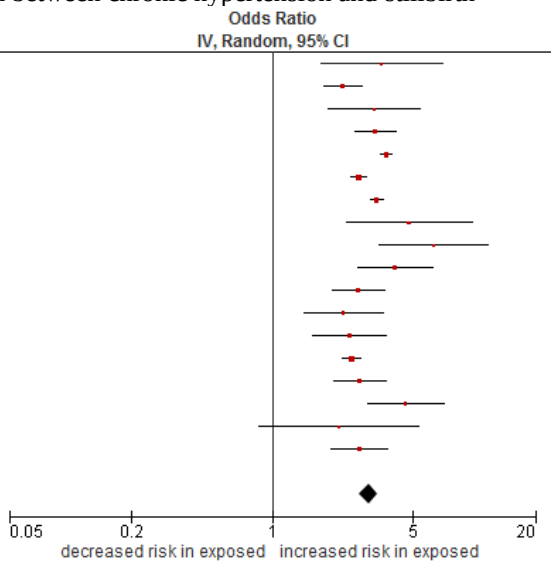


**Figure S3.6b** Forest plot of adjusted estimates of the association between chronic hypertension and stillbirth

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Aagord-Tittery, 2006 | 1.2413 | 0.5665 | 0.2% | 3.46 [1.14, 10.50] |
| Ahmed, 2012 | 0.7514 | 0.1097 | 4.0% | 2.12 [1.71, 2.63] |
| Allen, 2004 | 1.1632 | 0.266 | 0.7% | 3.20 [1.90, 5.39] |
| Ananth, 1995 | 1.0367 | 0.1221 | 3.2% | 2.82 [2.22, 3.58] |
| Bateman, 2012 | 0.802 | 0.0505 | 18.9% | 2.23 [2.02, 2.46] |
| Canterino, 2004 | 0.8587 | 0.0475 | 21.4% | 2.36 [2.15, 2.59] |
| Conde-Agudelo, 2000b | 0.8109 | 0.0678 | 10.5% | 2.25 [1.97, 2.57] |
| Copper, 1994 | 0.5306 | 0.3189 | 0.5% | 1.70 [0.91, 3.18] |
| Gilbert, 2007 | 0.8587 | 0.0428 | 26.4% | 2.36 [2.17, 2.57] |
| Jain, 1997 | 1.0986 | 0.1582 | 1.9% | 3.00 [2.20, 4.09] |
| Panaitescu, 2017 | 0.8671 | 0.2321 | 0.9% | 2.38 [1.51, 3.75] |
| Reddy, 2010 | 0.6931 | 0.1468 | 2.2% | 2.00 [1.50, 2.67] |
| Tuuli, 2011 | 0.6259 | 0.2221 | 1.0% | 1.87 [1.21, 2.89] |
| Xiong, 2018 | 0.8416 | 0.11 | 4.0% | 2.32 [1.87, 2.88] |
| Yanit, 2012 | 0.9163 | 0.1968 | 1.2% | 2.50 [1.70, 3.68] |
| Yerlikaya, 2016 | 0.9632 | 0.2328 | 0.9% | 2.62 [1.66, 4.13] |
| Youngstorm, 2018 | 0.6575 | 0.4007 | 0.3% | 1.93 [0.88, 4.23] |
| Zetterstorm, 2006 | 0.7129 | 0.1637 | 1.8% | 2.04 [1.48, 2.81] |
| **Total (95% CI)** | | | **100.0%** | **2.32 [2.22, 2.42]** |

Heterogeneity: Tau² = 0.00; Chi² = 13.11, df = 17 (P = 0.73); I² = 0%
Test for overall effect: Z = 38.32 (P < 0.00001)

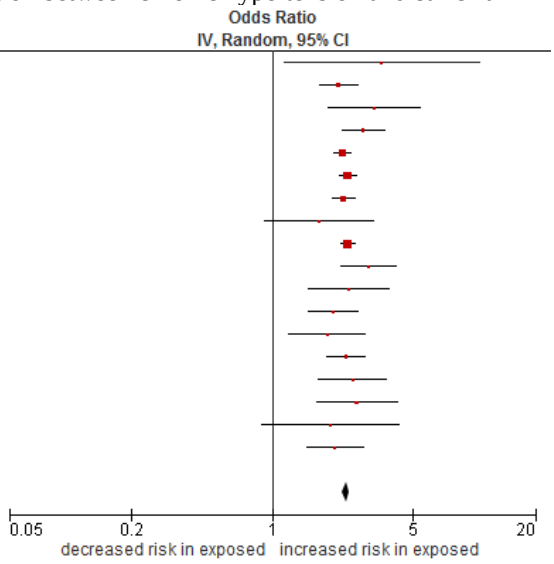



**Figure S3.6c** Funnel plot for adjusted estimates of stillbirth (chronic hypertension versus normotensive)

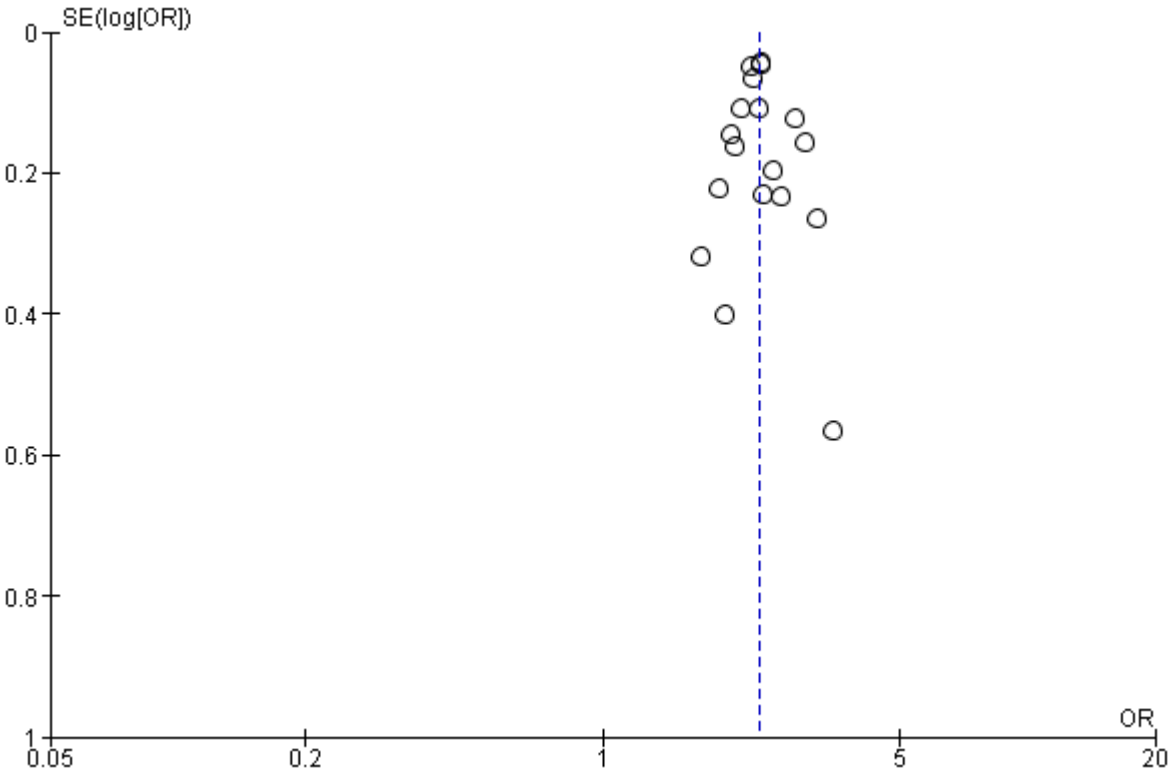


**Figure S3.7a** Forest plot of crude estimates of the association between chronic hypertension and VPTB

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Ananth, 1995b | 0.5515 | 0.1095 | 13.0% | 1.74 [1.40, 2.15] |
| Broekhuijsen, 2015 | 0.3365 | 0.123 | 12.9% | 1.40 [1.10, 1.78] |
| Ferrazzani, 2011 | 1.9399 | 0.418 | 9.2% | 6.96 [3.07, 15.79] |
| McCowan, 1996 | 0.47 | 0.5004 | 8.1% | 1.60 [0.60, 4.27] |
| Panaitescu, 2017 | 1.411 | 0.7461 | 5.5% | 4.10 [0.95, 17.70] |
| Roberts, 2005 | 0.7212 | 0.1654 | 12.5% | 2.06 [1.49, 2.84] |
| Tuuli, 2011 | 0.8459 | 0.146 | 12.7% | 2.33 [1.75, 3.10] |
| Yang, 2015 | 0.2196 | 0.0961 | 13.1% | 1.25 [1.03, 1.50] |
| Yanit, 2012 | 1.4693 | 0.0551 | 13.3% | 4.35 [3.90, 4.84] |
| **Total (95% CI)** | | | **100.0%** | **2.29 [1.47, 3.57]** |

Heterogeneity: Tau² = 0.38; Chi² = 193.91, df = 8 (P < 0.00001); I² = 96%
Test for overall effect: Z = 3.66 (P = 0.0003)

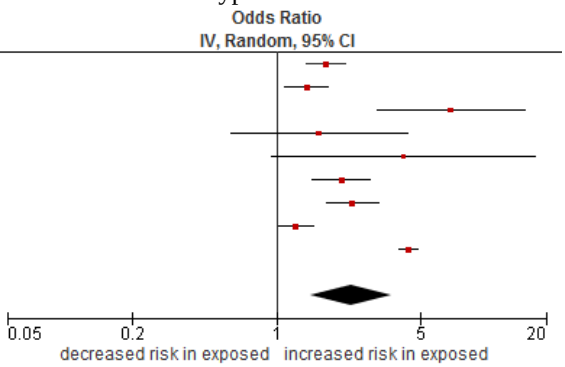



**Figure S3.7b** Forest plot of adjusted estimates of the association between chronic hypertension and VPTB

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Ananth, 1995b | 0.3365 | 0.0786 | 18.2% | 1.40 [1.20, 1.63] |
| Broekhuijsen, 2015 | 0.4055 | 0.1582 | 17.4% | 1.50 [1.10, 2.05] |
| Panaitescu, 2017 | 0.892 | 0.5819 | 10.6% | 2.44 [0.78, 7.63] |
| Tuuli, 2011 | 0.6575 | 0.1459 | 17.6% | 1.93 [1.45, 2.57] |
| Yang, 2015 | 0.2231 | 0.1037 | 18.0% | 1.25 [1.02, 1.53] |
| Yanit, 2012 | 1.4693 | 0.0551 | 18.3% | 4.35 [3.90, 4.84] |
| **Total (95% CI)** | | | **100.0%** | **1.92 [1.09, 3.38]** |

Heterogeneity: Tau² = 0.46; Chi² = 213.28, df = 5 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.24 (P = 0.02)

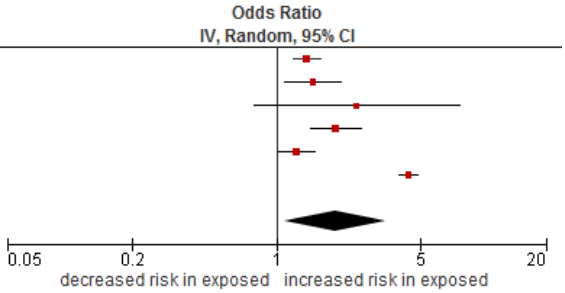


**Figure S3.8a** Forest plot of crude estimates of the association between chronic hypertension and PTB

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **1.14.1 PTB<37 weeks Not specified** | | | | |
| Acien, 1990 | 1.2344 | 0.5442 | 1.2% | 3.44 [1.18, 9.98] |
| Ananth, 1995b | 0.3294 | 0.0665 | 3.3% | 1.39 [1.22, 1.58] |
| Arora, 2015a | 0.3698 | 0.3294 | 2.0% | 1.45 [0.76, 2.76] |
| Arora, 2015b | 0.7702 | 0.2657 | 2.3% | 2.16 [1.28, 3.64] |
| Arora, 2015c | 0.4854 | 0.2996 | 2.2% | 1.62 [0.90, 2.92] |
| Arora, 2015d | -0.0695 | 0.2207 | 2.6% | 0.93 [0.61, 1.44] |
| Arora, 2015e | 1.6117 | 0.2765 | 2.3% | 5.01 [2.91, 8.62] |
| Arora, 2015f | 1.7713 | 0.2892 | 2.2% | 5.88 [3.34, 10.36] |
| Broekhuijsen, 2015 | 0.5878 | 0.0601 | 3.3% | 1.80 [1.60, 2.03] |
| Carter, 2011 | 0.8713 | 0.04 | 3.3% | 2.39 [2.21, 2.58] |
| Compbell, 2018 | 0.6168 | 0.1324 | 3.0% | 1.85 [1.43, 2.40] |
| Derakhshi, 2014 | 0.9594 | 0.2402 | 2.5% | 2.61 [1.63, 4.18] |
| Ferrazzani, 2011 | 1.8535 | 0.2104 | 2.6% | 6.38 [4.23, 9.64] |
| Gilbert, 2007 | 1.231 | 0.0129 | 3.4% | 3.42 [3.34, 3.51] |
| Graham, 2007 | 0.7063 | 0.0407 | 3.3% | 2.03 [1.87, 2.19] |
| Hartikainen, 1998 | 0.9801 | 0.1829 | 2.8% | 2.66 [1.86, 3.81] |
| Lydakis, 2001 | 1.0107 | 0.1751 | 2.8% | 2.75 [1.95, 3.87] |
| McCowan, 1996 | 0.4872 | 0.2615 | 2.4% | 1.63 [0.97, 2.72] |
| Morisaki, 2014 | 1.6134 | 0.0673 | 3.3% | 5.02 [4.40, 5.73] |
| Rey, 1994 | 1.0962 | 0.1234 | 3.1% | 2.99 [2.35, 3.81] |
| Roberts, 2005 | 0.3808 | 0.1056 | 3.1% | 1.46 [1.19, 1.80] |
| Su, 2013 | 0.8154 | 0.0701 | 3.3% | 2.26 [1.97, 2.59] |
| Tucker, 2015 | 1.0716 | 0.1108 | 3.1% | 2.92 [2.35, 3.63] |
| Tuuli, 2011 | 0.8502 | 0.0827 | 3.2% | 2.34 [1.99, 2.75] |
| Yang, 2015 | 0.3171 | 0.0479 | 3.3% | 1.37 [1.25, 1.51] |
| Yanit, 2012 | 1.2056 | 0.0311 | 3.3% | 3.34 [3.14, 3.55] |
| Ye, 2014 | 0.8643 | 0.1507 | 2.9% | 2.37 [1.77, 3.19] |
| Youngstorm, 2018 | 1.1694 | 0.123 | 3.1% | 3.22 [2.53, 4.10] |
| **Subtotal (95% CI)** | | | **79.3%** | **2.43 [2.10, 2.83]** |
| Heterogeneity: Tau² = 0.13; Chi² = 922.21, df = 27 (P < 0.00001); I² = 97% | | | | |
| Test for overall effect: Z = 11.65 (P < 0.00001) | | | | |
| **1.14.2 Spontaneous PTB<37 week** | | | | |
| Panaitescu, 2017 | 0.1906 | 0.1398 | 3.0% | 1.21 [0.92, 1.59] |
| Premkumar, 2016 | 0.0583 | 0.1436 | 3.0% | 1.06 [0.80, 1.40] |
| Samadi, 1998 | 0.5624 | 0.125 | 3.1% | 1.75 [1.37, 2.24] |
| **Subtotal (95% CI)** | | | **9.0%** | **1.32 [0.97, 1.79]** |
| Heterogeneity: Tau² = 0.05; Chi² = 7.85, df = 2 (P = 0.02); I² = 75% | | | | |
| Test for overall effect: Z = 1.78 (P = 0.08) | | | | |
| **1.14.3 Iatrogenic PTB<37week** | | | | |
| Meis, 1998 | 1.5872 | 0.2164 | 2.6% | 4.89 [3.20, 7.47] |
| Panaitescu, 2017 | 1.9228 | 0.0868 | 3.2% | 6.84 [5.77, 8.11] |
| Premkumar, 2016 | 1.9824 | 0.1015 | 3.2% | 7.26 [5.95, 8.86] |
| Souza, 2016 | 1.7504 | 0.2001 | 2.7% | 5.76 [3.89, 8.52] |
| **Subtotal (95% CI)** | | | **11.7%** | **6.66 [5.85, 7.58]** |
| Heterogeneity: Tau² = 0.00; Chi² = 3.38, df = 3 (P = 0.34); I² = 11% | | | | |
| Test for overall effect: Z = 28.60 (P < 0.00001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.57 [2.22, 2.97]** |
| Heterogeneity: Tau² = 0.16; Chi² = 1220.38, df = 34 (P < 0.00001); I² = 97% | | | | |
| Test for overall effect: Z = 12.75 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 151.84, df = 2 (P < 0.00001), I² = 98.7% | | | | |

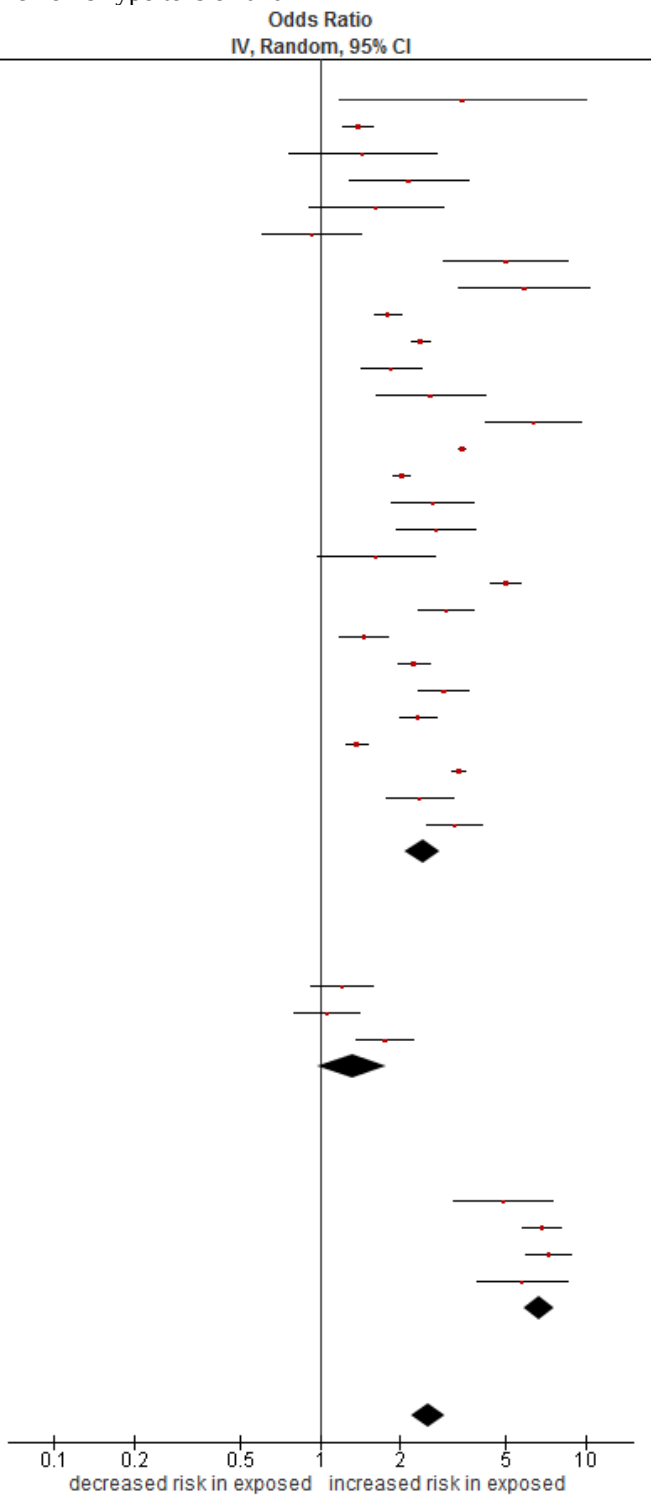


**Figure S3.8b** Forest plot of adjusted estimates of the association between chronic hypertension and PTB

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **1.13.1 PTB<37 weeks Not specified** | | | | |
| Ananth, 1995b | 0.1823 | 0.0786 | 3.8% | 1.20 [1.03, 1.40] |
| Arora, 2015a | 1.0647 | 0.3716 | 1.7% | 2.90 [1.40, 6.01] |
| Arora, 2015e | 1.5041 | 0.3424 | 1.9% | 4.50 [2.30, 8.80] |
| Arora, 2015f | 1.4351 | 0.4047 | 1.6% | 4.20 [1.90, 9.28] |
| Broekhuijsen, 2015 | 0.5878 | 0.0601 | 3.9% | 1.80 [1.60, 2.03] |
| Carter, 2011 | 1.1474 | 0.0656 | 3.9% | 3.15 [2.77, 3.58] |
| Compbell, 2018 | -0.5276 | 0.2245 | 2.7% | 0.59 [0.38, 0.92] |
| Derakhshi, 2014 | 0.9042 | 0.3434 | 1.9% | 2.47 [1.26, 4.84] |
| Gilbert, 2007 | 1.1725 | 0.0144 | 4.1% | 3.23 [3.14, 3.32] |
| Graham, 2007 | 0.6313 | 0.0424 | 4.0% | 1.88 [1.73, 2.04] |
| Jain, 1997 | 1.0986 | 0.1582 | 3.3% | 3.00 [2.20, 4.09] |
| Lydakis, 2001 | 0.8329 | 0.1251 | 3.5% | 2.30 [1.80, 2.94] |
| Morisaki, 2014 | 0.8329 | 0.0975 | 3.7% | 2.30 [1.90, 2.78] |
| Orbach, 2013 | 0.8329 | 0.0713 | 3.9% | 2.30 [2.00, 2.64] |
| Rey, 1994 | 0.47 | 0.0681 | 3.9% | 1.60 [1.40, 1.83] |
| Su, 2013 | 0.7793 | 0.0728 | 3.9% | 2.18 [1.89, 2.51] |
| Tucker, 2015 | 0.8502 | 0.1282 | 3.5% | 2.34 [1.82, 3.01] |
| Tuuli, 2011 | 0.7561 | 0.0831 | 3.8% | 2.13 [1.81, 2.51] |
| Velentgas, 1994 | 0.5878 | 0.0601 | 3.9% | 1.80 [1.60, 2.03] |
| Yang, 2015 | 0.3507 | 0.053 | 4.0% | 1.42 [1.28, 1.58] |
| Yanit, 2012 | 1.1632 | 0.0329 | 4.0% | 3.20 [3.00, 3.41] |
| Youngstorm, 2018 | 0.7419 | 0.1387 | 3.4% | 2.10 [1.60, 2.76] |
| **Subtotal (95% CI)** | | | **74.4%** | **2.14 [1.83, 2.51]** |
| Heterogeneity: Tau² = 0.12; Chi² = 744.07, df = 21 (P < 0.00001); I² = 97% | | | | |
| Test for overall effect: Z = 9.37 (P < 0.00001) | | | | |
| **1.13.2 Spontaneous PTB<37 week** | | | | |
| Bateman, 2012 | 1.0613 | 0.0216 | 4.0% | 2.89 [2.77, 3.02] |
| Panaitescu, 2017 | 0.0296 | 0.1418 | 3.4% | 1.03 [0.78, 1.36] |
| Premkumar, 2016 | -0.1393 | 0.1647 | 3.2% | 0.87 [0.63, 1.20] |
| Samadi, 1998 | 0.47 | 0.1468 | 3.4% | 1.60 [1.20, 2.13] |
| **Subtotal (95% CI)** | | | **14.0%** | **1.44 [0.74, 2.80]** |
| Heterogeneity: Tau² = 0.44; Chi² = 115.65, df = 3 (P < 0.00001); I² = 97% | | | | |
| Test for overall effect: Z = 1.08 (P = 0.28) | | | | |
| **1.13.3 Iatrogenic PTB<37week** | | | | |
| Meis, 1998 | 1.4012 | 0.2922 | 2.2% | 4.06 [2.29, 7.20] |
| Panaitescu, 2017 | 1.3164 | 0.0994 | 3.7% | 3.73 [3.07, 4.53] |
| Premkumar, 2016 | 1.6582 | 0.1175 | 3.6% | 5.25 [4.17, 6.61] |
| Souza, 2016 | 2.0109 | 0.3161 | 2.1% | 7.47 [4.02, 13.88] |
| **Subtotal (95% CI)** | | | **11.6%** | **4.67 [3.55, 6.14]** |
| Heterogeneity: Tau² = 0.04; Chi² = 7.90, df = 3 (P = 0.05); I² = 62% | | | | |
| Test for overall effect: Z = 11.07 (P < 0.00001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.23 [1.96, 2.53]** |
| Heterogeneity: Tau² = 0.10; Chi² = 913.98, df = 29 (P < 0.00001); I² = 97% | | | | |
| Test for overall effect: Z = 12.36 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 26.33, df = 2 (P < 0.00001), I² = 92.4% | | | | |

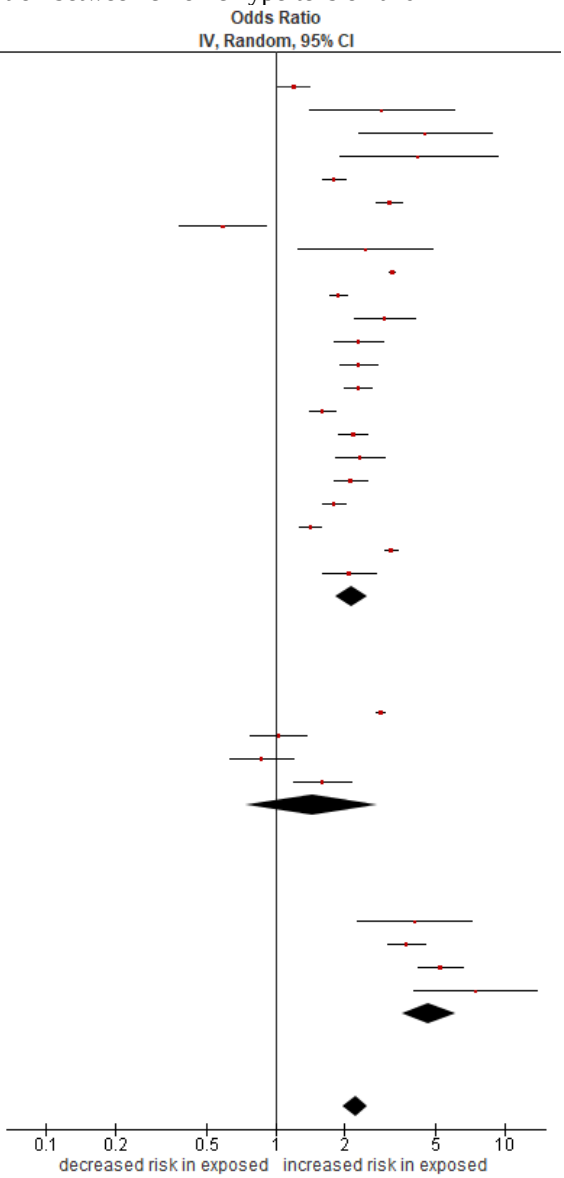


**Figure S3.8c** Funnel plot for adjusted estimates of PTB (chronic hypertension versus normotensive)

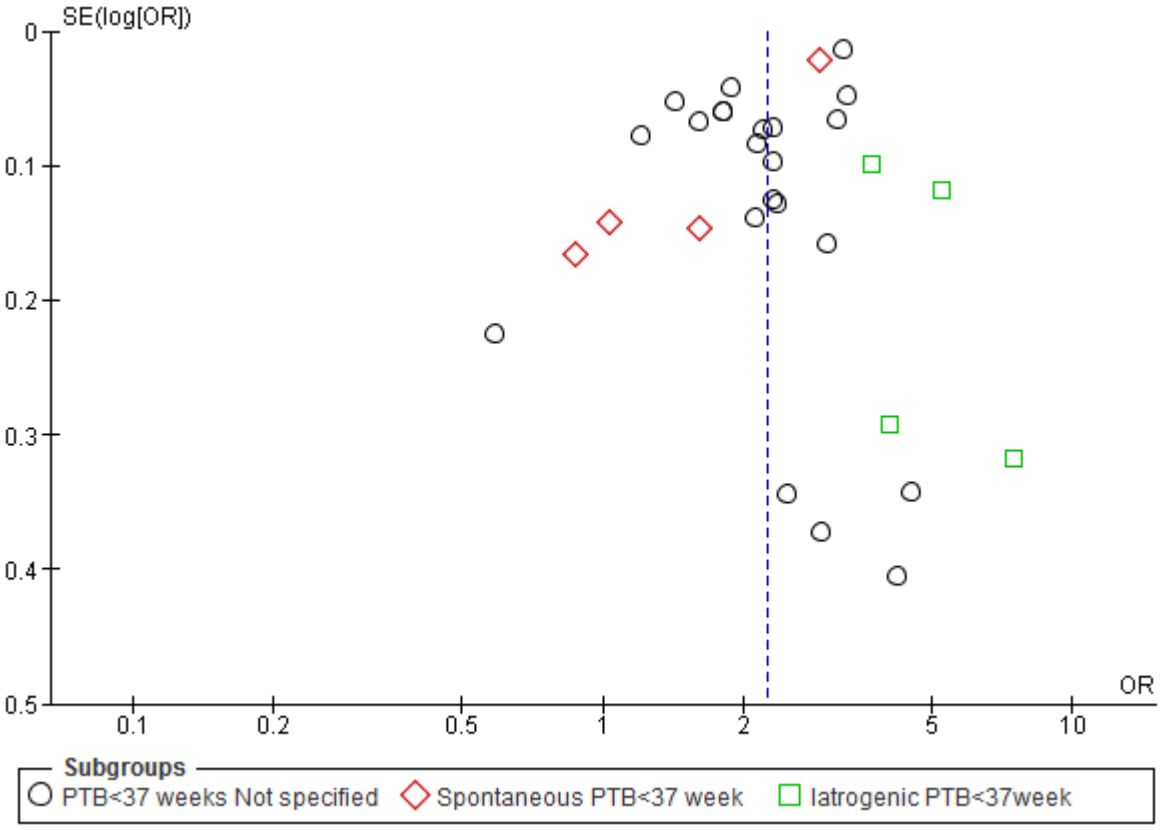



**Figure S3.9a** Forest plot of crude estimates of the association between chronic hypertension and SGA

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Acien, 1990 | 0.0878 | 0.5257 | 2.2% | 1.09 [0.39, 3.06] |
| Allen, 2004 | 0.5306 | 0.0639 | 3.7% | 1.70 [1.50, 1.93] |
| Ananth, 1995b | 0.6455 | 0.0667 | 3.7% | 1.91 [1.67, 2.17] |
| Anderson, 2013 | 0.5653 | 0.1095 | 3.7% | 1.76 [1.42, 2.18] |
| Broekhuijsen, 2015 | 0.3016 | 0.0515 | 3.7% | 1.35 [1.22, 1.50] |
| Catov, 2008 | 0.7129 | 0.1603 | 3.5% | 2.04 [1.49, 2.79] |
| Compbell, 2018 | 0.5598 | 0.1735 | 3.5% | 1.75 [1.25, 2.46] |
| Cruz, 2011 | 0.4698 | 0.078 | 3.7% | 1.60 [1.37, 1.86] |
| Gilbert, 2007 | 1.7751 | 0.0245 | 3.8% | 5.90 [5.62, 6.19] |
| Haeltermann, 1997 | 0.6931 | 0.4074 | 2.6% | 2.00 [0.90, 4.44] |
| Hartikainen, 1998 | 0.4695 | 0.1543 | 3.5% | 1.60 [1.18, 2.16] |
| Lydakis, 2001 | 0.8488 | 0.3974 | 2.7% | 2.34 [1.07, 5.09] |
| Madi, 2012 | 0.9917 | 0.138 | 3.6% | 2.70 [2.06, 3.53] |
| McCowan, 1996 | 1.0647 | 0.3034 | 3.0% | 2.90 [1.60, 5.26] |
| Odibo, 2006 | 0.9933 | 0.1876 | 3.4% | 2.70 [1.87, 3.90] |
| Ota, 2014 | 0.6575 | 0.0738 | 3.7% | 1.93 [1.67, 2.23] |
| Panaitescu, 2017 | 0.6627 | 0.0674 | 3.7% | 1.94 [1.70, 2.21] |
| Poon, 2011 | 0.5469 | 0.2099 | 3.4% | 1.73 [1.15, 2.61] |
| Rasmussen, 2006 | 0.3934 | 0.0977 | 3.7% | 1.48 [1.22, 1.79] |
| Rey, 1994 | 0.9986 | 0.1629 | 3.5% | 2.71 [1.97, 3.74] |
| Roberts, 2005 | -0.0037 | 0.0907 | 3.7% | 1.00 [0.83, 1.19] |
| Sass, 1990 | 2.4071 | 0.5398 | 2.1% | 11.10 [3.85, 31.98] |
| Su, 2013 | 0.4886 | 0.0527 | 3.7% | 1.63 [1.47, 1.81] |
| Tuuli, 2011 | 0.6098 | 0.0842 | 3.7% | 1.84 [1.56, 2.17] |
| Venek, 2004 | 0.7419 | 0.1387 | 3.6% | 2.10 [1.60, 2.76] |
| Xaverius, 2014 | 0.5048 | 0.0572 | 3.7% | 1.66 [1.48, 1.85] |
| Yanit, 2012 | 0.6906 | 0.035 | 3.8% | 1.99 [1.86, 2.14] |
| Youngstorm, 2018 | 0.0677 | 0.1548 | 3.5% | 1.07 [0.79, 1.45] |
| Zetterstorm, 2006 | 1.0986 | 0.073 | 3.7% | 3.00 [2.60, 3.46] |
| **Total (95% CI)** | | | **100.0%** | **1.99 [1.58, 2.52]** |

Heterogeneity: Tau² = 0.38; Chi² = 1861.68, df = 28 (P < 0.00001); I² = 98%
Test for overall effect: Z = 5.77 (P < 0.00001)

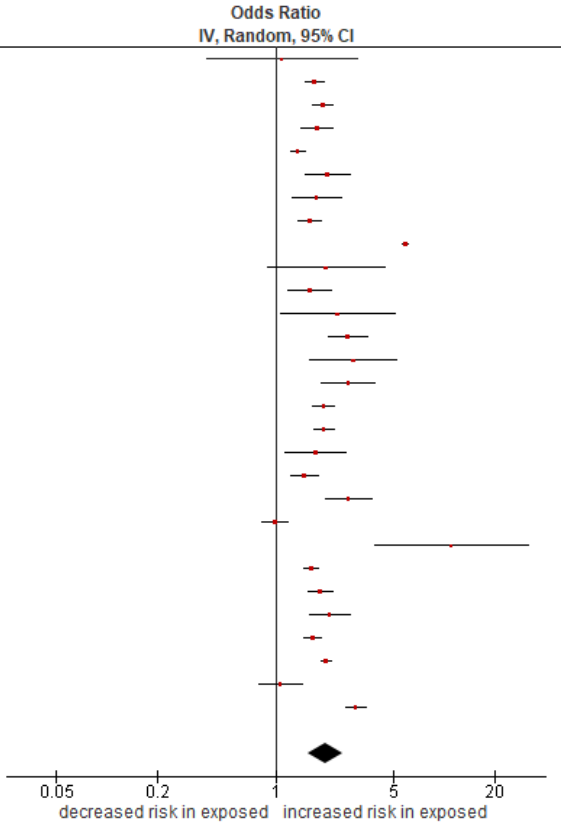


**Figure S3.9b** Funnel plot for adjusted estimates of SGA (chronic hypertension versus normotensive)

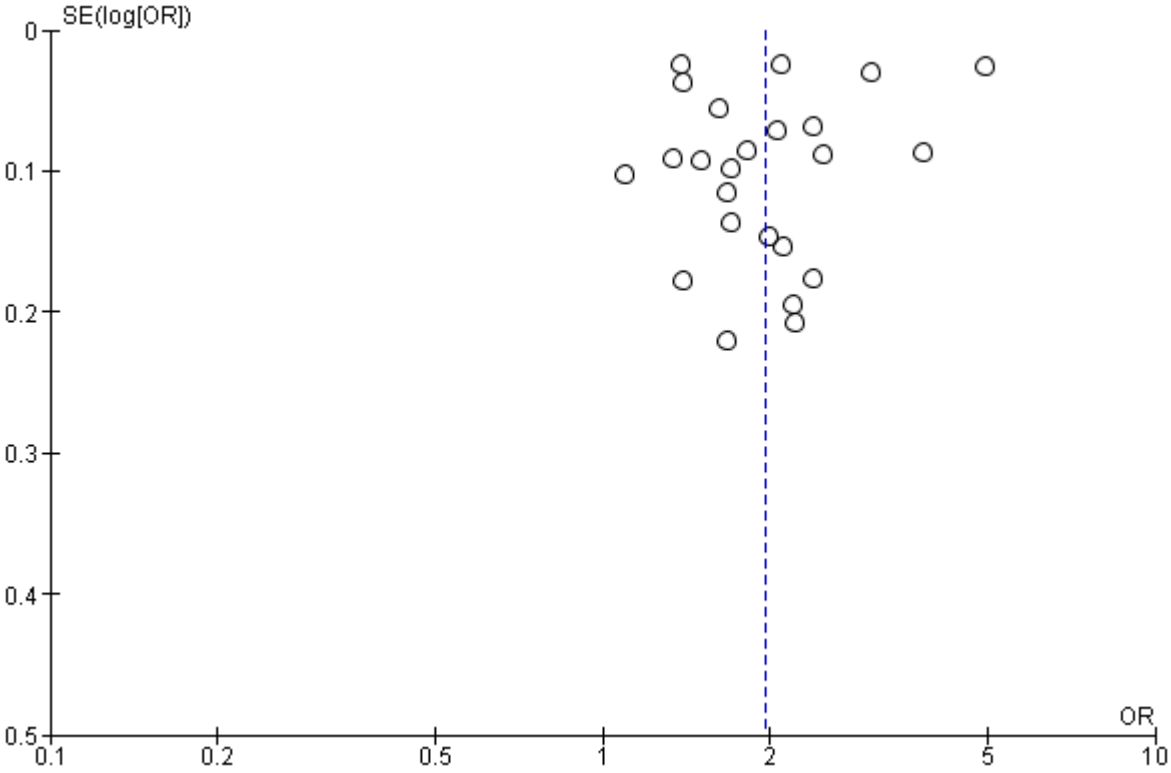



**Figure S3.10a** Forest plot of crude estimates of the association between chronic hypertension and LBW

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Ananth, 1995b | 0.7722 | 0.0631 | 7.7% | 2.16 [1.91, 2.45] |
| Compbell, 2018 | 0.9218 | 0.1331 | 7.3% | 2.51 [1.94, 3.26] |
| Gilbert, 2007 | 1.7153 | 0.0135 | 7.8% | 5.56 [5.41, 5.71] |
| Graham, 2007 | 1.0213 | 0.0438 | 7.8% | 2.78 [2.55, 3.03] |
| Hailu, 2018 | 0.0677 | 0.2543 | 6.2% | 1.07 [0.65, 1.76] |
| Hartikainen, 1998 | 1.3593 | 0.2001 | 6.7% | 3.89 [2.63, 5.76] |
| Harvey, 2017 | 0.9123 | 0.2938 | 5.8% | 2.49 [1.40, 4.43] |
| Lydakis, 1998 | 1.5728 | 0.1721 | 7.0% | 4.82 [3.44, 6.75] |
| Madi, 2012 | 1.1076 | 0.0982 | 7.5% | 3.03 [2.50, 3.67] |
| Odell, 2006 | 1.4095 | 0.1172 | 7.4% | 4.09 [3.25, 5.15] |
| Su, 2013 | 0.8629 | 0.079 | 7.6% | 2.37 [2.03, 2.77] |
| Vahadinia, 2008 | 1.1346 | 0.2434 | 6.3% | 3.11 [1.93, 5.01] |
| Velentgas, 1994 | 1.2411 | 0.0817 | 7.6% | 3.46 [2.95, 4.06] |
| Ye, 2014 | 0.7328 | 0.1683 | 7.0% | 2.08 [1.50, 2.89] |
| **Total (95% CI)** | | | **100.0%** | **2.92 [2.22, 3.84]** |

Heterogeneity: Tau² = 0.25; Chi² = 645.62, df = 13 (P < 0.00001); I² = 98%
Test for overall effect: Z = 7.68 (P < 0.00001)

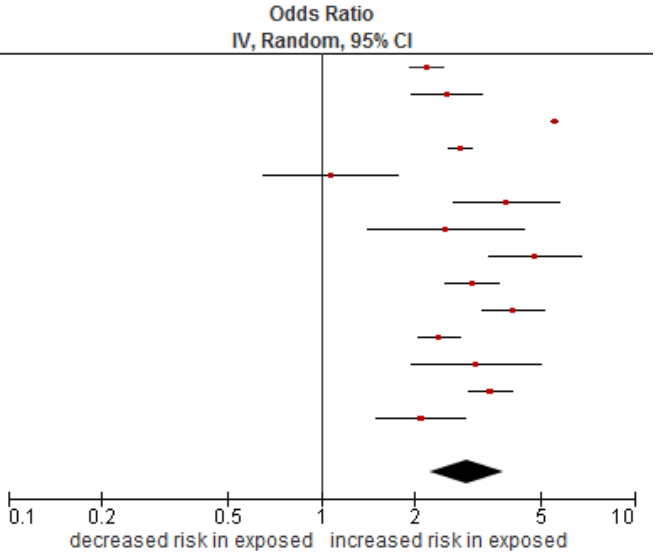


**Figure S3.10b** Funnel plot for adjusted estimates of LBW (chronic hypertension versus normotensive)

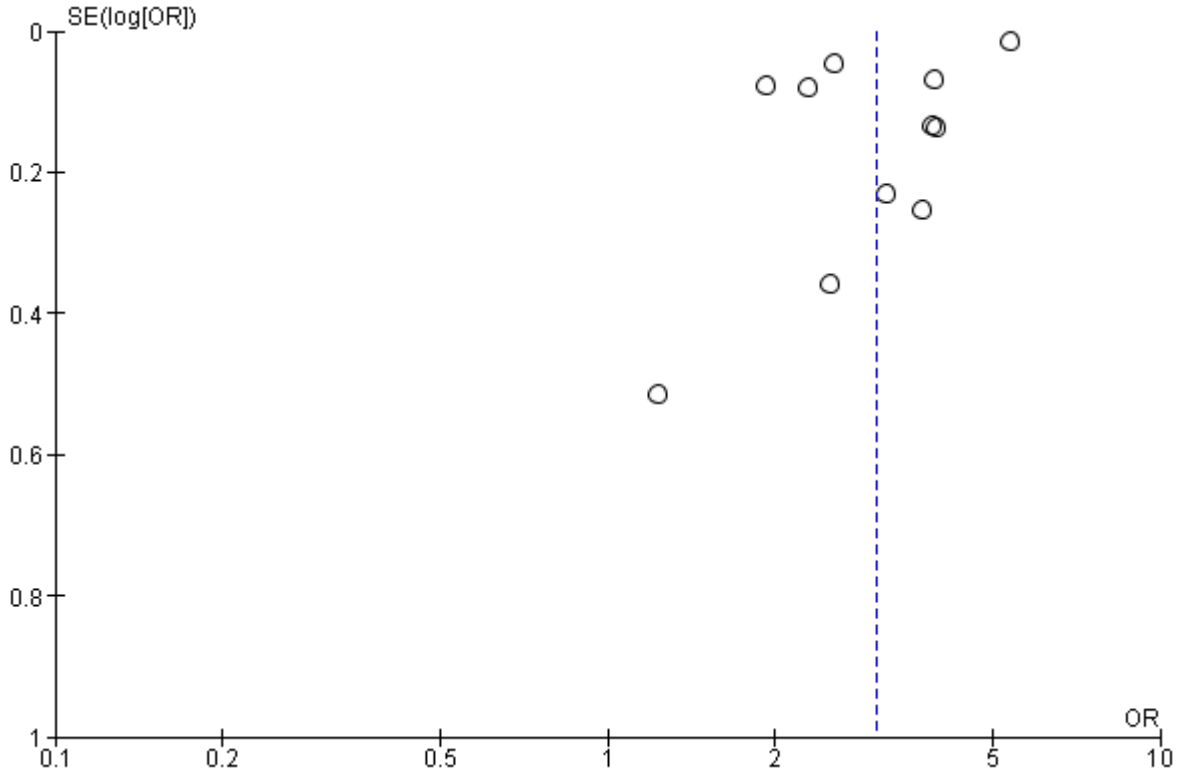



**Figure S3.11a** Forest plot of crude estimates of the association between chronic hypertension and neonatal death

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Gilbert, 2007 | 1.0335 | 0.0652 | 56.7% | 2.81 [2.47, 3.19] |
| Madi, 2012 | 1.8631 | 0.3713 | 12.0% | 6.44 [3.11, 13.34] |
| Youngstorm, 2018 | 0.8502 | 0.7927 | 3.1% | 2.34 [0.49, 11.07] |
| Zetterstorm, 2006 | 1.0613 | 0.2007 | 28.3% | 2.89 [1.95, 4.28] |
| **Total (95% CI)** | | | **100.0%** | **3.11 [2.35, 4.11]** |

Heterogeneity: Tau² = 0.03; Chi² = 4.91, df = 3 (P = 0.18); I² = 39%
Test for overall effect: Z = 7.97 (P < 0.00001)

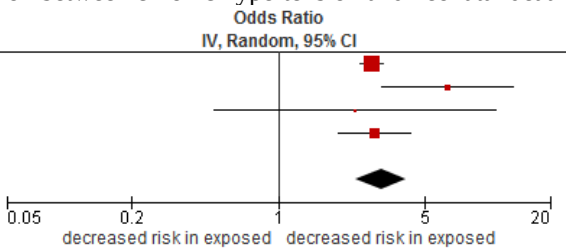



**Figure S3.11b** Forest plot of adjusted estimates of the association between chronic hypertension and neonatal death

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Gilbert, 2007 | 0.8416 | 0.0706 | 80.2% | 2.32 [2.02, 2.66] |
| Jain, 1997 | 0.5306 | 0.2221 | 8.1% | 1.70 [1.10, 2.63] |
| Youngstorm, 2018 | 1.0043 | 0.4592 | 1.9% | 2.73 [1.11, 6.71] |
| Zetterstorm, 2006 | 0.9203 | 0.2018 | 9.8% | 2.51 [1.69, 3.73] |
| **Total (95% CI)** | | | **100.0%** | **2.29 [2.02, 2.59]** |

Heterogeneity: Tau² = 0.00; Chi² = 2.19, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 13.08 (P < 0.00001)

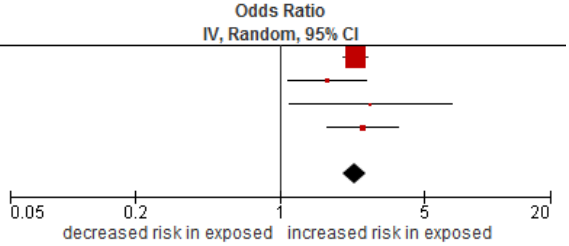


**Figure S3.12a** Forest plot of crude estimates of the association between chronic hypertension and perinatal death

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Acien, 1990 | 1.8225 | 0.7323 | 4.7% | 6.19 [1.47, 25.99] |
| Ahmed, 2012 | 0.8459 | 0.1317 | 14.9% | 2.33 [1.80, 3.02] |
| Broekhuijsen, 2015 | -0.3567 | 0.275 | 12.0% | 0.70 [0.41, 1.20] |
| Hartikainen, 1998 | 1.3371 | 0.3334 | 10.7% | 3.81 [1.98, 7.32] |
| McCowan, 1996 | 0.5306 | 0.7382 | 4.6% | 1.70 [0.40, 7.22] |
| Rey, 1994 | 1.3229 | 0.2909 | 11.6% | 3.75 [2.12, 6.64] |
| Sass, 1990 | 1.6045 | 0.5658 | 6.5% | 4.98 [1.64, 15.08] |
| Venek, 2004 | 0.5306 | 0.2221 | 13.1% | 1.70 [1.10, 2.63] |
| Ye, 2014 | 1.296 | 0.2499 | 12.5% | 3.65 [2.24, 5.96] |
| Youngstorm, 2018 | 0.7839 | 0.4 | 9.3% | 2.19 [1.00, 4.80] |
| **Total (95% CI)** | | | **100.0%** | **2.46 [1.70, 3.55]** |

Heterogeneity: Tau² = 0.22; Chi² = 33.00, df = 9 (P = 0.0001); I² = 73%
Test for overall effect: Z = 4.79 (P < 0.00001)

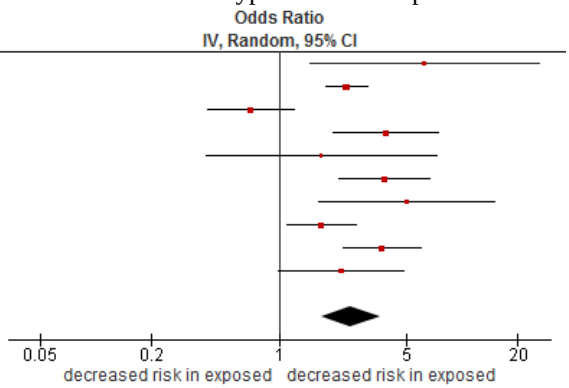



**Figure S3.12b** Forest plot of adjusted estimates of the association between chronic hypertension and perinatal death

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Ahmed, 2012 | 0.802 | 0.1325 | 20.7% | 2.23 [1.72, 2.89] |
| Broekhuijsen, 2015 | -0.2231 | 0.2398 | 16.3% | 0.80 [0.50, 1.28] |
| Jain, 1997 | 0.8755 | 0.1468 | 20.2% | 2.40 [1.80, 3.20] |
| Rey, 1994 | 1.1632 | 0.2936 | 14.1% | 3.20 [1.80, 5.69] |
| Venek, 2004 | 0.47 | 0.2398 | 16.3% | 1.60 [1.00, 2.56] |
| Youngstorm, 2018 | 0.6366 | 0.3403 | 12.4% | 1.89 [0.97, 3.68] |
| **Total (95% CI)** | | | **100.0%** | **1.87 [1.33, 2.63]** |

Heterogeneity: Tau² = 0.13; Chi² = 20.27, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 3.60 (P = 0.0003)

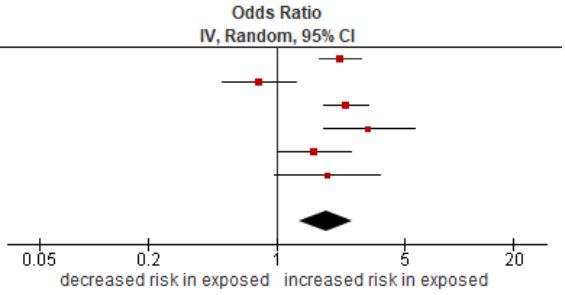



**Figure S3.13** Forest plot of crude estimates of the association between chronic hypertension and NICU admission

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Cruz, 2011 | 1.0647 | 0.0557 | 18.6% | 2.90 [2.60, 3.23] |
| Hartikainen, 1998 | 0.6678 | 0.1328 | 15.9% | 1.95 [1.50, 2.53] |
| Hjertberg, 1992 | 0.7171 | 0.4454 | 5.6% | 2.05 [0.86, 4.90] |
| Madi, 2012 | 1.1545 | 0.1013 | 17.2% | 3.17 [2.60, 3.87] |
| McCowan, 1996 | 0.2624 | 0.2477 | 11.0% | 1.30 [0.80, 2.11] |
| Roberts, 2005 | 0.6963 | 0.1277 | 16.1% | 2.01 [1.56, 2.58] |
| Tuuli, 2011 | 0.4253 | 0.1369 | 15.7% | 1.53 [1.17, 2.00] |
| **Total (95% CI)** | | | **100.0%** | **2.12 [1.66, 2.70]** |

Heterogeneity: Tau² = 0.08; Chi² = 39.08, df = 6 (P < 0.00001); I² = 85%
Test for overall effect: Z = 6.01 (P < 0.00001)

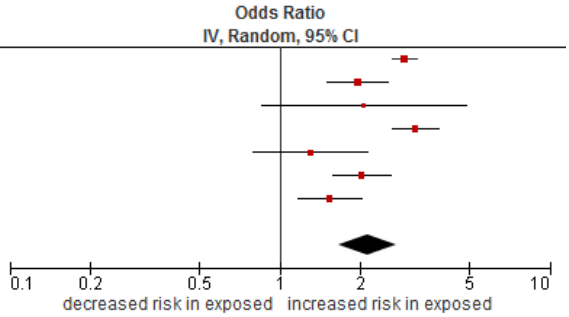



**Figure S3.14** Forest plot of crude estimates of the association between chronic hypertension and miscarriage

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Panaitescu, 2017 | 0.94 | 0.1769 | 91.5% | 2.56 [1.81, 3.62] |
| Sass, 1990 | 0.5496 | 0.5793 | 8.5% | 1.73 [0.56, 5.39] |
| **Total (95% CI)** | | | **100.0%** | **2.48 [1.78, 3.45]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 5.36 (P < 0.00001)

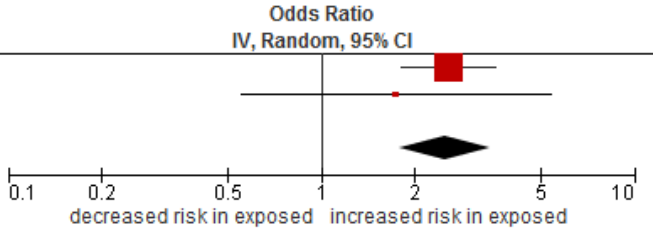


**Figure S3.15** Forest plot of adjusted estimates of the association between chronic hypertension and stillbirth by ethnicity

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **5.4.1 White** | | | | |
| Ananth, 1995 | 1.3533 | 0.1743 | 18.1% | 3.87 [2.75, 5.45] |
| Canterino, 2004 | 0.8286 | 0.1034 | 28.2% | 2.29 [1.87, 2.80] |
| **Subtotal (95% CI)** | | | **46.3%** | **2.92 [1.75, 4.88]** |
| Heterogeneity: Tau² = 0.12; Chi² = 6.70, df = 1 (P = 0.010); I² = 85% | | | | |
| Test for overall effect: Z = 4.10 (P < 0.0001) | | | | |
| **5.4.4 Black** | | | | |
| Ananth, 1995 | 0.8198 | 0.1566 | 20.2% | 2.27 [1.67, 3.09] |
| Canterino, 2004 | 0.8198 | 0.0723 | 33.5% | 2.27 [1.97, 2.62] |
| **Subtotal (95% CI)** | | | **53.7%** | **2.27 [2.00, 2.58]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0% | | | | |
| Test for overall effect: Z = 12.49 (P < 0.00001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.51 [2.06, 3.04]** |
| Heterogeneity: Tau² = 0.02; Chi² = 8.43, df = 3 (P = 0.04); I² = 64% | | | | |
| Test for overall effect: Z = 9.25 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 0.88, df = 1 (P = 0.35), I² = 0% | | | | |

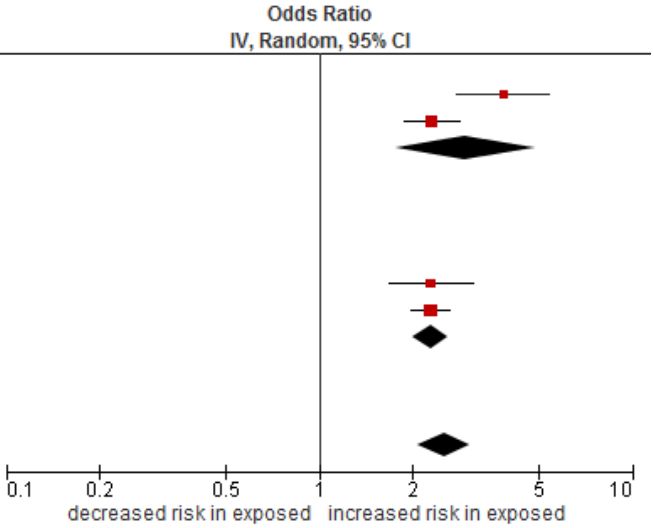



**Figure S3.16** Forest plot of adjusted estimates of the association between chronic hypertension and PTB by ethnicity

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **5.13.4 White** | | | | |
| Ananth, 1995b | 0.3365 | 0.0681 | 13.1% | 1.40 [1.23, 1.60] |
| Graham, 2007 | 0.6678 | 0.073 | 13.0% | 1.95 [1.69, 2.25] |
| Premkumar, 2016 | 0.7129 | 0.1569 | 10.8% | 2.04 [1.50, 2.77] |
| Rey, 1997 | 0.1823 | 0.2069 | 9.3% | 1.20 [0.80, 1.80] |
| **Subtotal (95% CI)** | | | **46.2%** | **1.64 [1.29, 2.07]** |
| Heterogeneity: Tau² = 0.04; Chi² = 15.23, df = 3 (P = 0.002); I² = 80% | | | | |
| Test for overall effect: Z = 4.08 (P < 0.0001) | | | | |
| **5.13.5 Black** | | | | |
| Ananth, 1995b | 0.0953 | 0.0486 | 13.5% | 1.10 [1.00, 1.21] |
| Graham, 2007 | 0.6152 | 0.0522 | 13.4% | 1.85 [1.67, 2.05] |
| Premkumar, 2016 | 1.3635 | 0.2101 | 9.2% | 3.91 [2.59, 5.90] |
| Rey, 1997 | 0.6931 | 0.305 | 6.7% | 2.00 [1.10, 3.64] |
| Samadi, 1998 | 0.47 | 0.1468 | 11.1% | 1.60 [1.20, 2.13] |
| **Subtotal (95% CI)** | | | **53.8%** | **1.84 [1.28, 2.65]** |
| Heterogeneity: Tau² = 0.15; Chi² = 77.94, df = 4 (P < 0.00001); I² = 95% | | | | |
| Test for overall effect: Z = 3.28 (P = 0.001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.72 [1.39, 2.13]** |
| Heterogeneity: Tau² = 0.09; Chi² = 97.52, df = 8 (P < 0.00001); I² = 92% | | | | |
| Test for overall effect: Z = 4.97 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0% | | | | |

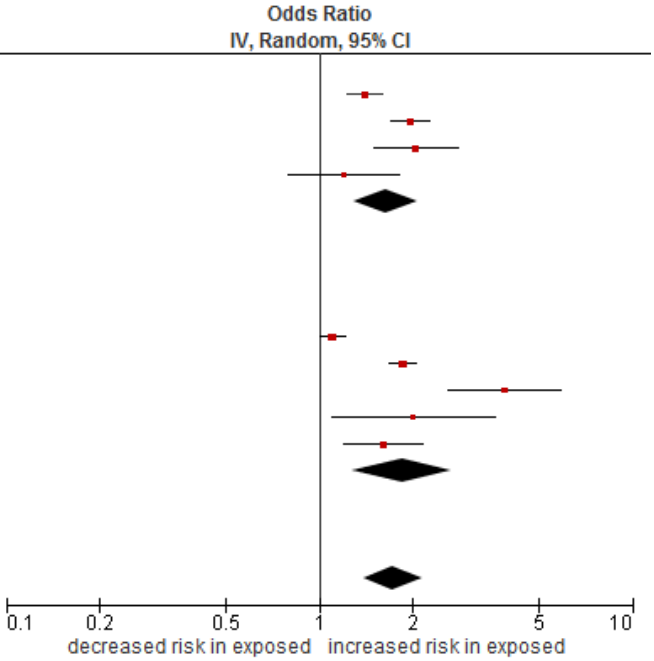


**Figure S3.17** Forest plot of adjusted estimates of the association between chronic hypertension and SGA by ethnicity

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **5.1.4 White** | | | | |
| Ananth, 1995b | 0.7419 | 0.1078 | 32.9% | 2.10 [1.70, 2.59] |
| Rey, 1997 | 0.3365 | 0.2254 | 22.0% | 1.40 [0.90, 2.18] |
| **Subtotal (95% CI)** | | | **54.9%** | **1.80 [1.22, 2.65]** |
| Heterogeneity: Tau² = 0.05; Chi² = 2.63, df = 1 (P = 0.10); I² = 62% | | | | |
| Test for overall effect: Z = 2.98 (P = 0.003) | | | | |
| **5.1.5 Black** | | | | |
| Ananth, 1995b | 0.2624 | 0.0852 | 34.9% | 1.30 [1.10, 1.54] |
| Rey, 1997 | 0.3365 | 0.4323 | 10.2% | 1.40 [0.60, 3.27] |
| **Subtotal (95% CI)** | | | **45.1%** | **1.30 [1.11, 1.54]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0% | | | | |
| Test for overall effect: Z = 3.17 (P = 0.002) | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.56 [1.14, 2.14]** |
| Heterogeneity: Tau² = 0.07; Chi² = 12.45, df = 3 (P = 0.006); I² = 76% | | | | |
| Test for overall effect: Z = 2.76 (P = 0.006) | | | | |
| Test for subgroup differences: Chi² = 2.27, df = 1 (P = 0.13), I² = 56.0% | | | | |

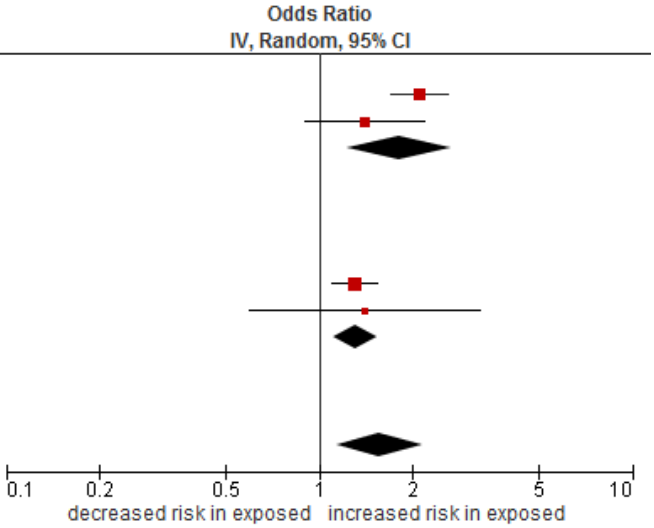
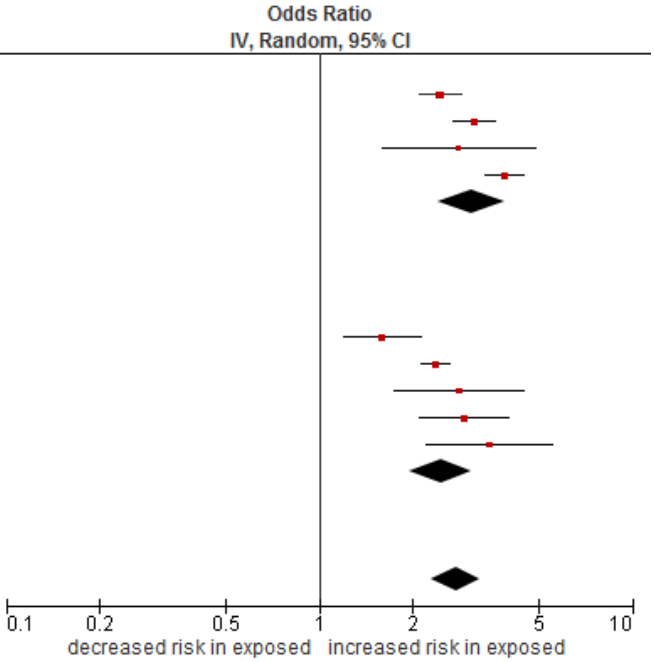



**Figure S3.18** Forest plot of adjusted estimates of the association between chronic hypertension and LBW by ethnicity

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **5.18.1 White** | | | | |
| Ananth, 1995b | 0.8879 | 0.0794 | 13.9% | 2.43 [2.08, 2.84] |
| Graham, 2007 | 1.1378 | 0.0814 | 13.9% | 3.12 [2.66, 3.66] |
| Lydakis, 1998 | 1.0296 | 0.2855 | 6.4% | 2.80 [1.60, 4.90] |
| Velentgas, 1994 | 1.361 | 0.073 | 14.1% | 3.90 [3.38, 4.50] |
| **Subtotal (95% CI)** | | | **48.3%** | **3.06 [2.39, 3.91]** |
| Heterogeneity: Tau² = 0.05; Chi² = 19.40, df = 3 (P = 0.0002); I² = 85% | | | | |
| Test for overall effect: Z = 8.93 (P < 0.00001) | | | | |
| **5.18.4 Black** | | | | |
| Ananth, 1995b | 0.4637 | 0.1479 | 11.2% | 1.59 [1.19, 2.12] |
| Graham, 2007 | 0.8544 | 0.055 | 14.7% | 2.35 [2.11, 2.62] |
| Lydakis, 1998 | 1.0296 | 0.2421 | 7.6% | 2.80 [1.74, 4.50] |
| Odell, 2006 | 1.0647 | 0.1647 | 10.5% | 2.90 [2.10, 4.00] |
| Velentgas, 1994 | 1.2528 | 0.2369 | 7.8% | 3.50 [2.20, 5.57] |
| **Subtotal (95% CI)** | | | **51.7%** | **2.44 [1.94, 3.06]** |
| Heterogeneity: Tau² = 0.04; Chi² = 11.96, df = 4 (P = 0.02); I² = 67% | | | | |
| Test for overall effect: Z = 7.66 (P < 0.00001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.73 [2.27, 3.28]** |
| Heterogeneity: Tau² = 0.06; Chi² = 50.75, df = 8 (P < 0.00001); I² = 84% | | | | |
| Test for overall effect: Z = 10.71 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 1.76, df = 1 (P = 0.18), I² = 43.2% | | | | |



Results of sensitivity analyses of adjusted estimates for adverse perinatal outcome by study location and year of publication (women with chronic hypertension vs without)

| Maternal Outcome | No. of studies (estimates) | Overall adjusted OR [95% CI] | $I^2$,% |
|---|---|---|---|
| **Pre-eclampsia** | | | |
| **Location** | | | |
| North America | 5 | 5.22 [2.87, 9.50] | 100 |
| Europe | 4 | 4.83 [3.14, 7.42] | 97 |
| Other | 8 | 6.01 [3.34, 10.79] | 99 |
| **Decades** | | | |
| 1990-1999 | 1 | 6.50 [5.20, 8.13] | - |
| 2000-2009 | 7 | 3.25 [1.74, 6.07] | 99 |
| 2010-2019 | 14 | 7.29 [6.15, 8.65] | 97 |
| **HELLP syndrome** | | | |
| **Location** | | | |
| North America | 1 | 2.66 [2.14, 3.31] | - |
| Europe | 2 | 3.15 [1.09, 9.15] | 80 |
| **Decades** | | | |
| 2000-2009 | 1 | 2.66 [2.14, 3.31] | - |
| 2010-2019 | 2 | 3.15 [1.09, 9.15] | 80 |
| **Caesarean section** | | | |
| **Location** | | | |
| North America | 5 | 2.08 [1.88, 2.31] | 95 |
| Europe | 2 | 1.11 [1.01, 1.21] | 0 |
| Other | 1 | 2.70 [2.40, 3.04] | - |
| **Decades** | | | |
| 1990-1999 | 1 | 1.80 [1.60, 2.03] | - |
| 2000-2009 | 2 | 2.48 [2.15, 2.86] | 83 |
| 2010-2019 | 5 | 1.71 [1.28, 2.30] | 98 |
| **Postpartum haemorrhage** | | | |
| **Location** | | | |
| North America | 2 | 1.45 [1.36, 1.54] | 0 |
| Europe | 1 | 1.10 [0.90, 1.34] | - |
| Other | 1 | 2.20 [1.40, 3.46] | - |
| **Decades** | | | |
| 2000-2009 | 2 | 1.67 [1.12, 2.49] | 70 |
| 2010-2019 | 2 | 1.32 [0.87, 2.02] | 74 |
| **Maternal mortality** | | | |
| **Location** | | | |
| North America | 4 | 4.80 [3.04, 7.58] | 71 |
| **Decades** | | | |
| 2000-2009 | 2 | 3.66 [2.00, 6.69] | 55 |
| 2010-2019 | 2 | 6.04 [3.82, 9.53] | 46 |
| **Fetal, neonatal outcome** | | | |
| **Stillbirth** | | | |
| **Location** | | | |
| North America | 12 | 2.37 [2.25, 2.50] | 3 |
| Europe | 4 | 2.18 [1.87, 2.55] | 0 |
| Other | 2 | 2.27 [2.03, 2.54] | 0 |
| **Decades** | | | |
| 1990-1999 | 2 | 2.89 [2.39, 3.49] | 0 |
| 2000-2009 | 7 | 2.34 [2.21, 2.47] | 0 |

| | | | |
|---|---|---|---|
| 2010-2019 | 9 | 2.26 [2.10, 2.44] | 0 |
| **Very preterm birth (<34 weeks)** | | | |
| **Location** | | | |
| North America | 3 | 2.51 [0.91, 6.92] | 99 |
| Europe | 2 | 1.55 [1.15, 2.09] | 0 |
| Other | 1 | 1.25 [1.02, 1.53] | - |
| **Decades** | | | |
| 1990-1999 | 1 | 1.40 [1.20, 1.63] | - |
| 2000-2009 | - | - | - |
| 2010-2019 | 5 | 2.06 [1.06, 3.98] | 97 |
| **Preterm birth (<37 weeks)*** | | | |
| **Location** | | | |
| North America | 16 | 2.08 [1.76, 2.46] | 96 |
| Europe | 5 | 2.56 [1.90, 3.44] | 78 |
| Other | 5 | 2.04 [1.58, 2.63] | 91 |
| **Decades** | | | |
| 1990-1999 | 5 | 1.93 [1.40, 2.66] | 90 |
| 2000-2009 | 3 | 1.90 [1.73, 2.08] | 36 |
| 2010-2019 | 18 | 2.26 [1.95, 2.61] | 94 |
| **Small for gestational age** | | | |
| **Location** | | | |
| North America | 13 | 2.18 [1.62, 2.92] | 99 |
| Europe | 6 | 1.81 [1.45, 2.27] | 92 |
| Australia | 1 | 1.68 [1.34, 2.11] | - |
| Other | 4 | 1.62 [1.39, 1.89] | 58 |
| **Decades** | | | |
| 1990-1999 | 3 | 2.50 [1.44, 4.35] | 95 |
| 2000-2009 | 7 | 2.30 [1.49, 3.56] | 98 |
| 2010-2019 | 14 | 1.73 [1.44, 2.07] | 97 |
| **Low birthweight** | | | |
| **Location** | | | |
| North America | 7 | 3.21 [2.19, 4.68] | 98 |
| Europe | 1 | 3.91 [2.99, 5.11] | - |
| Other | 3 | 2.46 [1.60, 3.77] | 59 |
| **Decades** | | | |
| 1990-1999 | 3 | 3.07 [1.85, 5.10] | 97 |
| 2000-2009 | 4 | 3.74 [2.28, 6.14] | 99 |
| 2010-2019 | 4 | 2.38 [1.95, 2.92] | 13 |
| **Perinatal mortality** | | | |
| **Location** | | | |
| North America | 3 | 2.45 [1.92, 3.11] | 0 |
| Europe | 2 | 1.36 [0.50, 3.72] | 93 |
| Other | 1 | 1.60 [1.00, 2.56] | - |
| **Decades** | | | |
| 1990-1999 | 2 | 2.54 [1.97, 3.29] | 0 |
| 2000-2009 | 1 | 1.60 [1.00, 2.56] | - |
| 2010-2019 | 3 | 1.51 [0.76, 2.99] | 86 |

*Sub-group estimates (spontaneous, iatrogenic) for two studies were combined.

**Figure S3.19a** Forest plot of crude estimates of the association between antihypertensive treatment and Pre-eclampsia

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.1.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Orbach, 2013 | 2.6561 | 0.1425 | 14.5% | 14.24 [10.77, 18.83] |
| Youngstorm, 2018 | 1.6642 | 0.2096 | 14.4% | 5.28 [3.50, 7.96] |
| **Subtotal (95% CI)** | | | **28.9%** | **8.78 [3.32, 23.19]** |
| Heterogeneity: Tau² = 0.46; Chi² = 15.32, df = 1 (P < 0.0001); I² = 93% | | | | |
| Test for overall effect: Z = 4.38 (P < 0.0001) | | | | |
| **6.1.2 Women with CH (treated vs. untreated)** | | | | |
| Bayliss, 2002 | -0.925 | 0.2213 | 14.4% | 0.40 [0.26, 0.61] |
| Mabie,1986 | 0.3317 | 0.3261 | 14.0% | 1.39 [0.74, 2.64] |
| Mito, 2019 | -0.23 | 0.2882 | 14.2% | 0.79 [0.45, 1.40] |
| Nzelua, 2018 | 0.5169 | 0.2461 | 14.3% | 1.68 [1.04, 2.72] |
| Rezk, 2016 | -0.7091 | 0.2813 | 14.2% | 0.49 [0.28, 0.85] |
| **Subtotal (95% CI)** | | | **71.1%** | **0.81 [0.45, 1.45]** |
| Heterogeneity: Tau² = 0.37; Chi² = 24.84, df = 4 (P < 0.0001); I² = 84% | | | | |
| Test for overall effect: Z = 0.71 (P = 0.48) | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.62 [0.50, 5.19]** |
| Heterogeneity: Tau² = 2.42; Chi² = 283.64, df = 6 (P < 0.00001); I² = 98% | | | | |
| Test for overall effect: Z = 0.81 (P = 0.42) | | | | |
| Test for subgroup differences: Chi² = 16.96, df = 1 (P < 0.0001), I² = 94.1% | | | | |

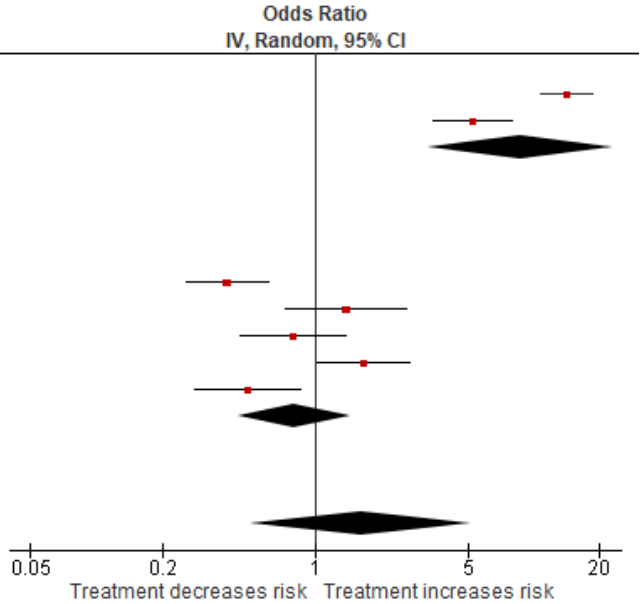



**Figure S3.19b** Forest plot of adjusted estimates of the association between antihypertensive treatment and Pre-eclampsia

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.2.1 Exposed (CH+antihypertensives) vs. normotensive non-exposed** | | | | |
| Orbach, 2013 | 2.5447 | 0.1481 | 25.4% | 12.74 [9.53, 17.03] |
| Youngstorm, 2018 | 1.1939 | 0.238 | 25.0% | 3.30 [2.07, 5.26] |
| **Subtotal (95% CI)** | | | **50.4%** | **6.57 [1.75, 24.67]** |
| Heterogeneity: Tau² = 0.87; Chi² = 23.22, df = 1 (P < 0.00001); I² = 96% | | | | |
| Test for overall effect: Z = 2.79 (P = 0.005) | | | | |
| **6.2.2 Women with CH (treated vs. untreated)** | | | | |
| Nzelua, 2018 | 0.5306 | 0.2606 | 24.9% | 1.70 [1.02, 2.83] |
| Rezk, 2016 | -0.7133 | 0.2855 | 24.7% | 0.49 [0.28, 0.86] |
| **Subtotal (95% CI)** | | | **49.6%** | **0.92 [0.27, 3.11]** |
| Heterogeneity: Tau² = 0.70; Chi² = 10.36, df = 1 (P = 0.001); I² = 90% | | | | |
| Test for overall effect: Z = 0.14 (P = 0.89) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.46 [0.59, 10.21]** |
| Heterogeneity: Tau² = 2.05; Chi² = 125.34, df = 3 (P < 0.00001); I² = 98% | | | | |
| Test for overall effect: Z = 1.24 (P = 0.21) | | | | |
| Test for subgroup differences: Chi² = 4.60, df = 1 (P = 0.03), I² = 78.2% | | | | |

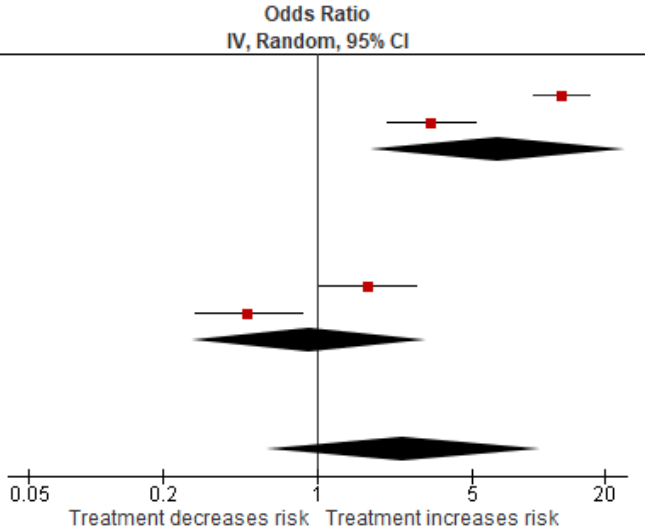


**Figure S3.20** Forest plot of crude estimates of the association between antihypertensive treatment and caesarean section

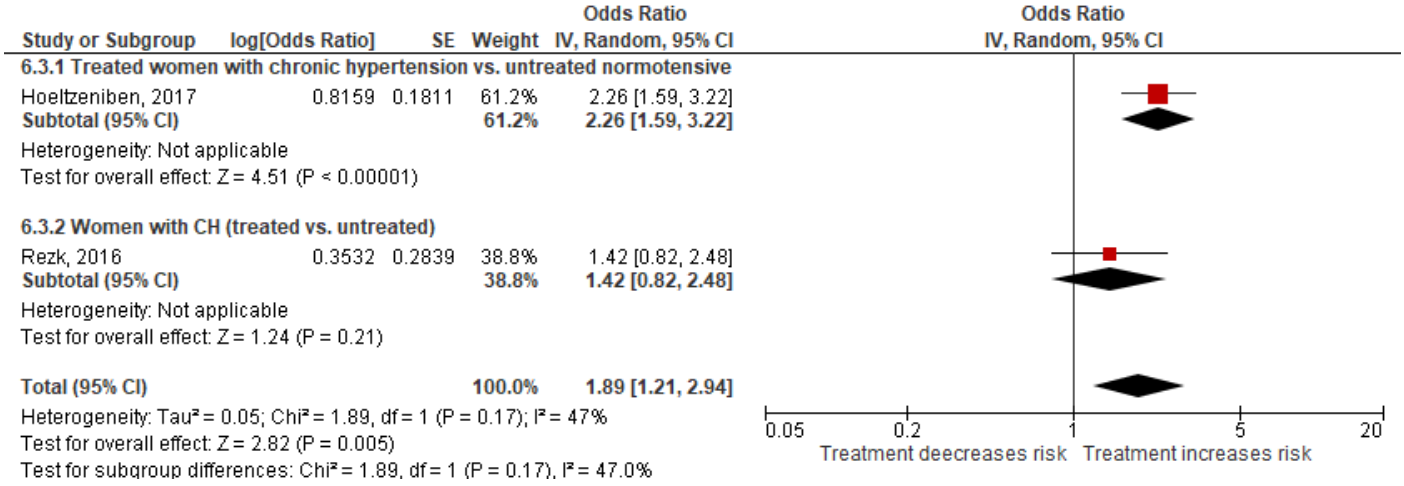



**Figure S3.21** Forest plot of crude estimates of the association between antihypertensive treatment and miscarriage

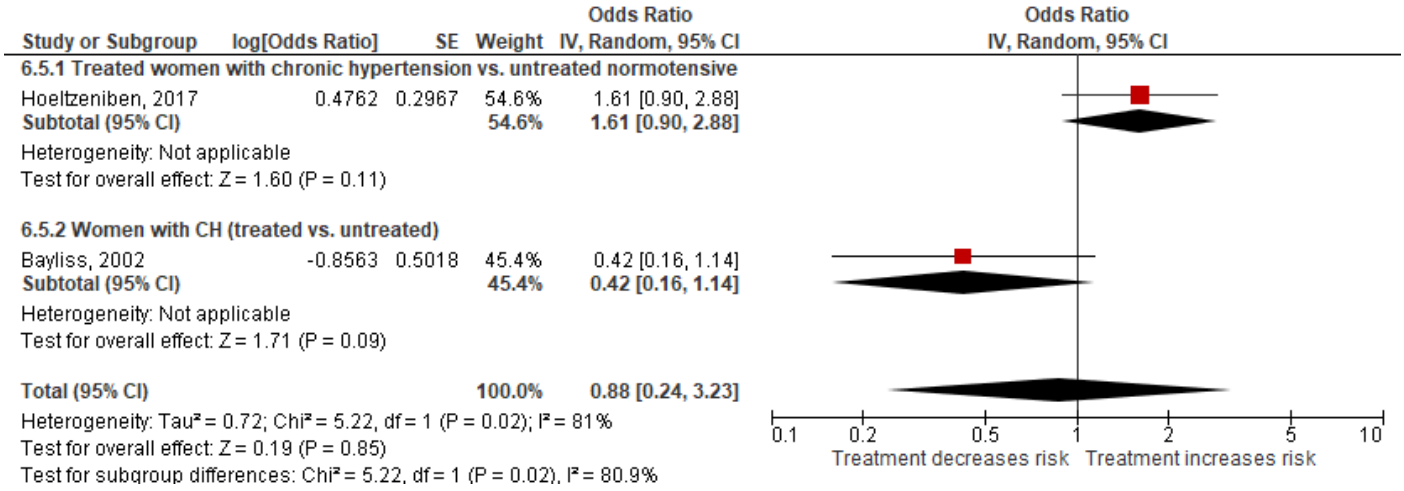


**Figure S3.22** Forest plot of crude estimates of the association between antihypertensive treatment and stillbirth

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.7.1 Exposed (CH+antihypertensives) vs. normotensive non-exposedExposed (any indication) vs. non-exposed** | | | | |
| Hoeltzeniben, 2017 | 0.7027 | 1.4162 | 4.1% | 2.02 [0.13, 32.41] |
| Youngstorm, 2018 | 0.8544 | 0.4754 | 36.3% | 2.35 [0.93, 5.97] |
| **Subtotal (95% CI)** | | | **40.4%** | **2.31 [0.96, 5.60]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0% | | | | |
| Test for overall effect: Z = 1.86 (P = 0.06) | | | | |
| **6.7.2 Women with CH (treated vs. untreated)** | | | | |
| Bayliss, 2002 | 0.0952 | 0.4532 | 40.0% | 1.10 [0.45, 2.67] |
| Rezk, 2016 | 0.1323 | 0.6473 | 19.6% | 1.14 [0.32, 4.06] |
| **Subtotal (95% CI)** | | | **59.6%** | **1.11 [0.54, 2.30]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0% | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.50 [0.85, 2.62]** |
| Heterogeneity: Tau² = 0.00; Chi² = 1.58, df = 3 (P = 0.66); I² = 0% | | | | |
| Test for overall effect: Z = 1.41 (P = 0.16) | | | | |
| Test for subgroup differences: Chi² = 1.57, df = 1 (P = 0.21), I² = 36.3% | | | | |

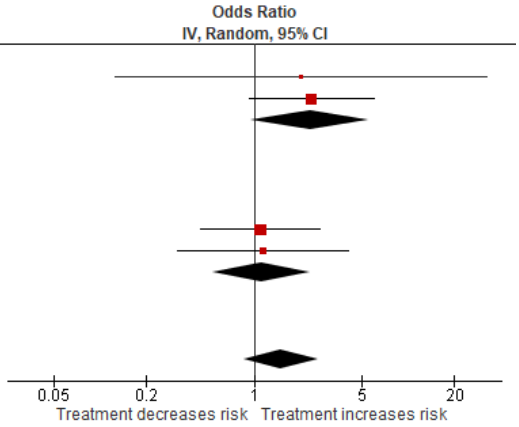



**Figure S3.23a** Forest plot of crude estimates of the association between antihypertensive treatment and preterm birth

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.11.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Banhidy,2010 | 0.4018 | 0.0788 | 11.9% | 1.49 [1.28, 1.74] |
| Hoeltzeniben, 2017 | 1.2457 | 0.2115 | 10.9% | 3.48 [2.30, 5.26] |
| Lennestal, 2009 | 1.2486 | 0.0745 | 11.9% | 3.49 [3.01, 4.03] |
| Orbach, 2013 | 1.2238 | 0.1139 | 11.7% | 3.40 [2.72, 4.25] |
| Youngstorm, 2018 | 1.3436 | 0.1555 | 11.4% | 3.83 [2.83, 5.20] |
| **Subtotal (95% CI)** | | | **57.9%** | **2.95 [1.93, 4.52]** |
| Heterogeneity: Tau² = 0.22; Chi² = 78.41, df = 4 (P < 0.00001); I² = 95% | | | | |
| Test for overall effect: Z = 5.01 (P < 0.00001) | | | | |
| **6.11.2 Women with CH (treated vs. untreated)** | | | | |
| Mito, 2019 | -0.5272 | 0.3061 | 9.8% | 0.59 [0.32, 1.08] |
| Ray,2001 | 2.1815 | 0.2233 | 10.8% | 8.86 [5.72, 13.72] |
| Rezk, 2016 | -1.3058 | 0.2969 | 9.9% | 0.27 [0.15, 0.48] |
| Su, 2013 | 0.7786 | 0.1311 | 11.6% | 2.18 [1.68, 2.82] |
| **Subtotal (95% CI)** | | | **42.1%** | **1.35 [0.36, 4.97]** |
| Heterogeneity: Tau² = 1.72; Chi² = 106.07, df = 3 (P < 0.00001); I² = 97% | | | | |
| Test for overall effect: Z = 0.45 (P = 0.66) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.17 [1.41, 3.33]** |
| Heterogeneity: Tau² = 0.40; Chi² = 191.24, df = 8 (P < 0.00001); I² = 96% | | | | |
| Test for overall effect: Z = 3.53 (P = 0.0004) | | | | |
| Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.4% | | | | |

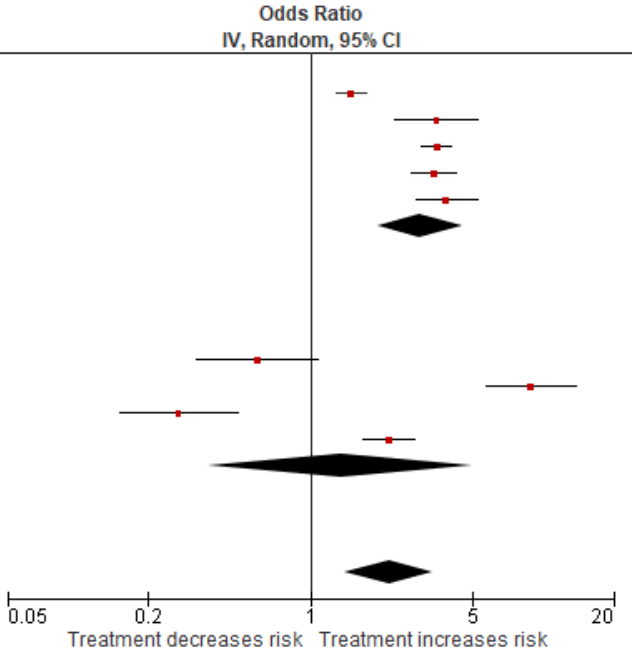


**Figure S3.23b** Forest plot of adjusted estimates of the association between antihypertensive treatment and preterm birth

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.12.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Banhidy,2010 | 0.4055 | 0.073 | 13.6% | 1.50 [1.30, 1.73] |
| Hoeltzeniben, 2017 | 1.4134 | 0.2745 | 10.8% | 4.11 [2.40, 7.04] |
| Lennestal, 2009 | 1.203 | 0.0723 | 13.6% | 3.33 [2.89, 3.84] |
| Orbach, 2013 | 1.3056 | 0.1229 | 13.1% | 3.69 [2.90, 4.69] |
| Youngstorm, 2018 | 0.8755 | 0.1759 | 12.4% | 2.40 [1.70, 3.39] |
| **Subtotal (95% CI)** | | | **63.4%** | **2.78 [1.80, 4.29]** |
| Heterogeneity: Tau² = 0.22; Chi² = 77.85, df = 4 (P < 0.00001); I² = 95% | | | | |
| Test for overall effect: Z = 4.61 (P < 0.00001) | | | | |
| **6.12.2 Women with CH (treated vs. untreated)** | | | | |
| Ray,2001 | 1.8326 | 0.1826 | 12.3% | 6.25 [4.37, 8.94] |
| Rezk, 2016 | -0.821 | 0.2684 | 10.9% | 0.44 [0.26, 0.74] |
| Su, 2013 | 0.8154 | 0.0885 | 13.4% | 2.26 [1.90, 2.69] |
| **Subtotal (95% CI)** | | | **36.6%** | **1.88 [0.61, 5.74]** |
| Heterogeneity: Tau² = 0.94; Chi² = 67.85, df = 2 (P < 0.00001); I² = 97% | | | | |
| Test for overall effect: Z = 1.10 (P = 0.27) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.45 [1.68, 3.57]** |
| Heterogeneity: Tau² = 0.27; Chi² = 145.86, df = 7 (P < 0.00001); I² = 95% | | | | |
| Test for overall effect: Z = 4.66 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0% | | | | |

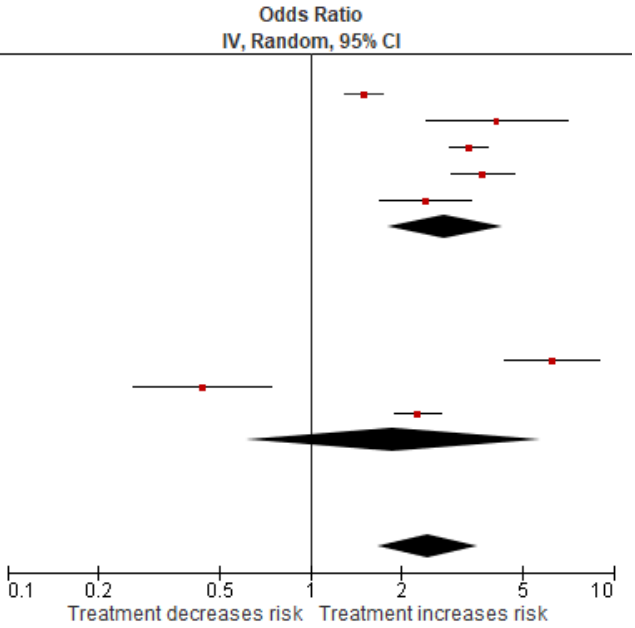



**Figure S3.23c** Forest plot of crude estimates of the association between antihypertensive treatment and preterm birth (β-blockers vs untreated)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.13.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Orbach, 2013 | 0.8416 | 0.2577 | 31.4% | 2.32 [1.40, 3.84] |
| **Subtotal (95% CI)** | | | **31.4%** | **2.32 [1.40, 3.84]** |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 3.27 (P = 0.001) | | | | |
| **6.13.2 Women with CH (treated vs. untreated)** | | | | |
| Ray,2001 | 1.5382 | 0.2739 | 30.0% | 4.66 [2.72, 7.96] |
| Su, 2013 | 0.715 | 0.1767 | 38.6% | 2.04 [1.45, 2.89] |
| **Subtotal (95% CI)** | | | **68.6%** | **3.00 [1.34, 6.72]** |
| Heterogeneity: Tau² = 0.29; Chi² = 6.38, df = 1 (P = 0.01); I² = 84% | | | | |
| Test for overall effect: Z = 2.68 (P = 0.007) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.72 [1.69, 4.39]** |
| Heterogeneity: Tau² = 0.12; Chi² = 6.53, df = 2 (P = 0.04); I² = 69% | | | | |
| Test for overall effect: Z = 4.11 (P < 0.0001) | | | | |
| Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.59), I² = 0% | | | | |

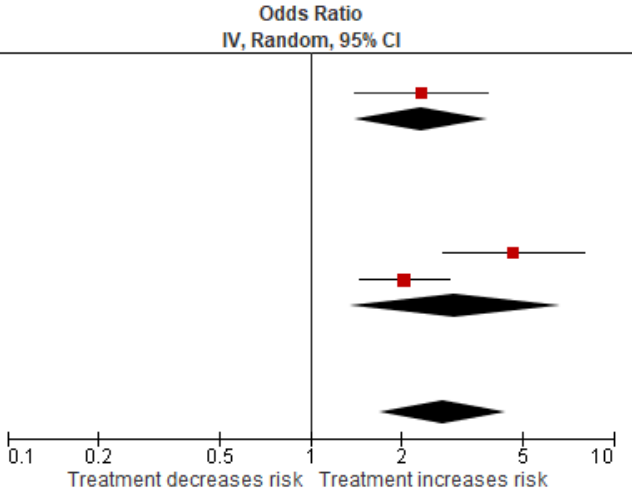


**Figure S3.23d** Forest plot of adjusted estimates of the association between antihypertensive treatment and preterm birth (β-blockers vs untreated)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.14.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Orbach, 2013 | 0.9858 | 0.2728 | 29.5% | 2.68 [1.57, 4.57] |
| **Subtotal (95% CI)** | | | **29.5%** | **2.68 [1.57, 4.57]** |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 3.61 (P = 0.0003) | | | | |
| **6.14.2 Women with CH (treated vs. untreated)** | | | | |
| Ray,2001 | 1.3863 | 0.2823 | 28.4% | 4.00 [2.30, 6.96] |
| Su, 2013 | 0.6981 | 0.1773 | 42.1% | 2.01 [1.42, 2.85] |
| **Subtotal (95% CI)** | | | **70.5%** | **2.74 [1.40, 5.36]** |
| Heterogeneity: Tau² = 0.18; Chi² = 4.26, df = 1 (P = 0.04); I² = 77% | | | | |
| Test for overall effect: Z = 2.94 (P = 0.003) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.66 [1.78, 3.98]** |
| Heterogeneity: Tau² = 0.07; Chi² = 4.35, df = 2 (P = 0.11); I² = 54% | | | | |
| Test for overall effect: Z = 4.77 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0% | | | | |

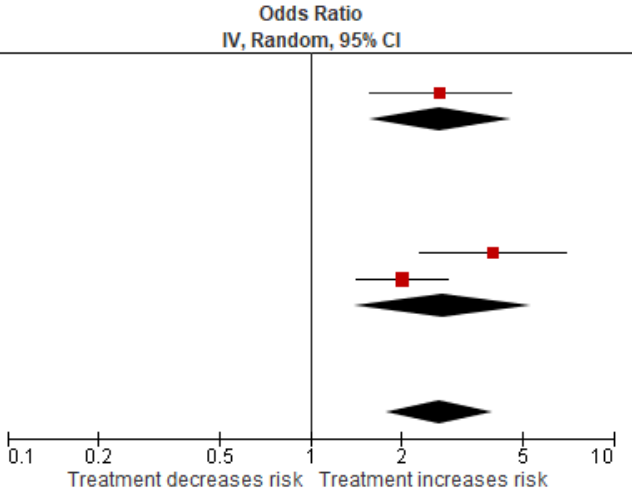



**Figure S3.24a** Forest plot of crude estimates of the association between antihypertensive treatment and small for gestational age

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.15.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Fisher, 2018 | 0.1044 | 0.4721 | 7.6% | 1.11 [0.44, 2.80] |
| Lennestal, 2009 | 1.471 | 0.0951 | 12.0% | 4.35 [3.61, 5.25] |
| Orbach, 2013 | 0.5596 | 0.2818 | 10.1% | 1.75 [1.01, 3.04] |
| Youngstorm, 2018 | 0.1823 | 0.1139 | 11.8% | 1.20 [0.96, 1.50] |
| **Subtotal (95% CI)** | | | **41.5%** | **1.84 [0.79, 4.29]** |
| Heterogeneity: Tau² = 0.67; Chi² = 80.05, df = 3 (P < 0.00001); I² = 96% | | | | |
| Test for overall effect: Z = 1.42 (P = 0.16) | | | | |
| **6.15.2 Women with CH (treated vs. untreated)** | | | | |
| Bayliss, 2002 | 1.2983 | 0.2705 | 10.2% | 3.66 [2.16, 6.22] |
| Mabie,1986 | 1.8253 | 0.5706 | 6.5% | 6.20 [2.03, 18.99] |
| Nzelua, 2018 | 0.3603 | 0.2746 | 10.2% | 1.43 [0.84, 2.46] |
| Ray,2001 | 1.1719 | 0.2799 | 10.1% | 3.23 [1.87, 5.59] |
| Rezk, 2016 | 0.2652 | 0.3134 | 9.7% | 1.30 [0.71, 2.41] |
| Su, 2013 | 0.4159 | 0.0986 | 11.9% | 1.52 [1.25, 1.84] |
| **Subtotal (95% CI)** | | | **58.5%** | **2.21 [1.45, 3.35]** |
| Heterogeneity: Tau² = 0.19; Chi² = 20.68, df = 5 (P = 0.0009); I² = 76% | | | | |
| Test for overall effect: Z = 3.71 (P = 0.0002) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.10 [1.39, 3.18]** |
| Heterogeneity: Tau² = 0.36; Chi² = 110.45, df = 9 (P < 0.00001); I² = 92% | | | | |
| Test for overall effect: Z = 3.51 (P = 0.0004) | | | | |
| Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0% | | | | |

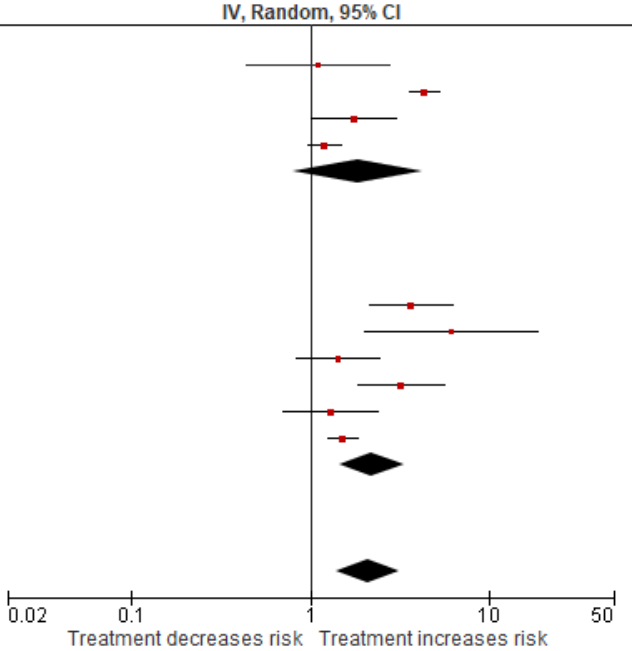


**Figure S3.24b** Forest plot of adjusted estimates of the association between antihypertensive treatment and small for gestational age

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.16.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Fisher, 2018 | -0.1744 | 0.6183 | 5.8% | 0.84 [0.25, 2.82] |
| Lennestal, 2009 | 1.4422 | 0.0894 | 13.7% | 4.23 [3.55, 5.04] |
| Orbach, 2013 | 0.802 | 0.2872 | 10.8% | 2.23 [1.27, 3.92] |
| Youngstorm, 2018 | 0.5652 | 0.2127 | 12.1% | 1.76 [1.16, 2.67] |
| **Subtotal (95% CI)** | | | **42.4%** | **2.21 [1.18, 4.15]** |
| Heterogeneity: Tau² = 0.32; Chi² = 22.73, df = 3 (P < 0.0001); I² = 87% | | | | |
| Test for overall effect: Z = 2.46 (P = 0.01) | | | | |
| **6.16.2 Women with CH (treated vs. untreated)** | | | | |
| Bayliss, 2002 | 1.2782 | 0.301 | 10.6% | 3.59 [1.99, 6.48] |
| Nzelua, 2018 | 0.5365 | 0.2345 | 11.7% | 1.71 [1.08, 2.71] |
| Ray,2001 | 0.7747 | 0.2422 | 11.6% | 2.17 [1.35, 3.49] |
| Rezk, 2016 | 0.1989 | 0.3058 | 10.5% | 1.22 [0.67, 2.22] |
| Su, 2013 | 0.4511 | 0.1371 | 13.2% | 1.57 [1.20, 2.05] |
| **Subtotal (95% CI)** | | | **57.6%** | **1.86 [1.38, 2.50]** |
| Heterogeneity: Tau² = 0.06; Chi² = 8.49, df = 4 (P = 0.08); I² = 53% | | | | |
| Test for overall effect: Z = 4.10 (P < 0.0001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.04 [1.39, 2.98]** |
| Heterogeneity: Tau² = 0.27; Chi² = 61.08, df = 8 (P < 0.00001); I² = 87% | | | | |
| Test for overall effect: Z = 3.66 (P = 0.0003) | | | | |
| Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0% | | | | |

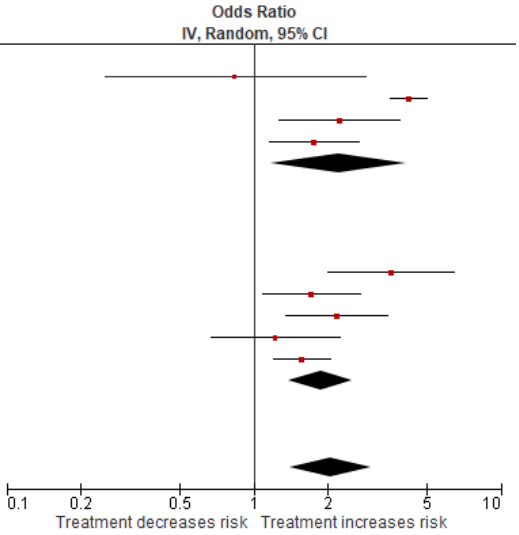



**Figure S3.24c** Forest plot of crude estimates of small for gestational age (β-blockers only vs untreated)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.17.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Orbach, 2013 | 1.209 | 0.4203 | 18.6% | 3.35 [1.47, 7.64] |
| **Subtotal (95% CI)** | | | **18.6%** | **3.35 [1.47, 7.64]** |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 2.88 (P = 0.004) | | | | |
| **6.17.2 Women with CH (treated vs. untreated)** | | | | |
| Bayliss, 2002 | 1.1299 | 0.3281 | 23.4% | 3.10 [1.63, 5.89] |
| Ray,2001 | 1.0637 | 0.3422 | 22.6% | 2.90 [1.48, 5.67] |
| Su, 2013 | 0.392 | 0.1377 | 35.3% | 1.48 [1.13, 1.94] |
| **Subtotal (95% CI)** | | | **81.4%** | **2.21 [1.28, 3.82]** |
| Heterogeneity: Tau² = 0.16; Chi² = 6.66, df = 2 (P = 0.04); I² = 70% | | | | |
| Test for overall effect: Z = 2.84 (P = 0.004) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.38 [1.46, 3.88]** |
| Heterogeneity: Tau² = 0.16; Chi² = 8.80, df = 3 (P = 0.03); I² = 66% | | | | |
| Test for overall effect: Z = 3.50 (P = 0.0005) | | | | |
| Test for subgroup differences: Chi² = 0.68, df = 1 (P = 0.41), I² = 0% | | | | |

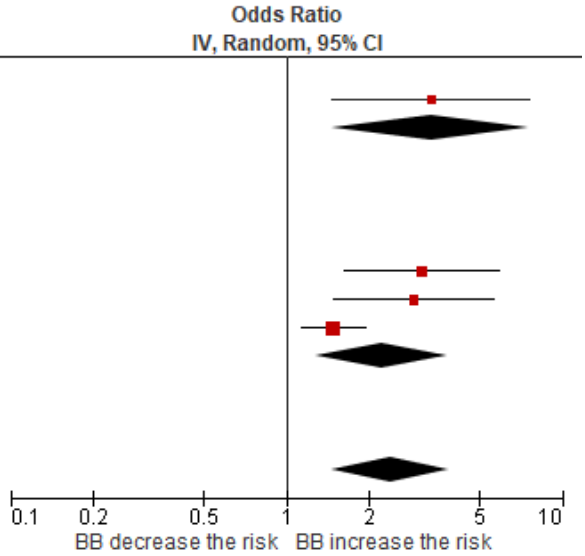


**Figure S3.24d** Forest plot of adjusted of small for gestational age (β-blockers only vs untreated)

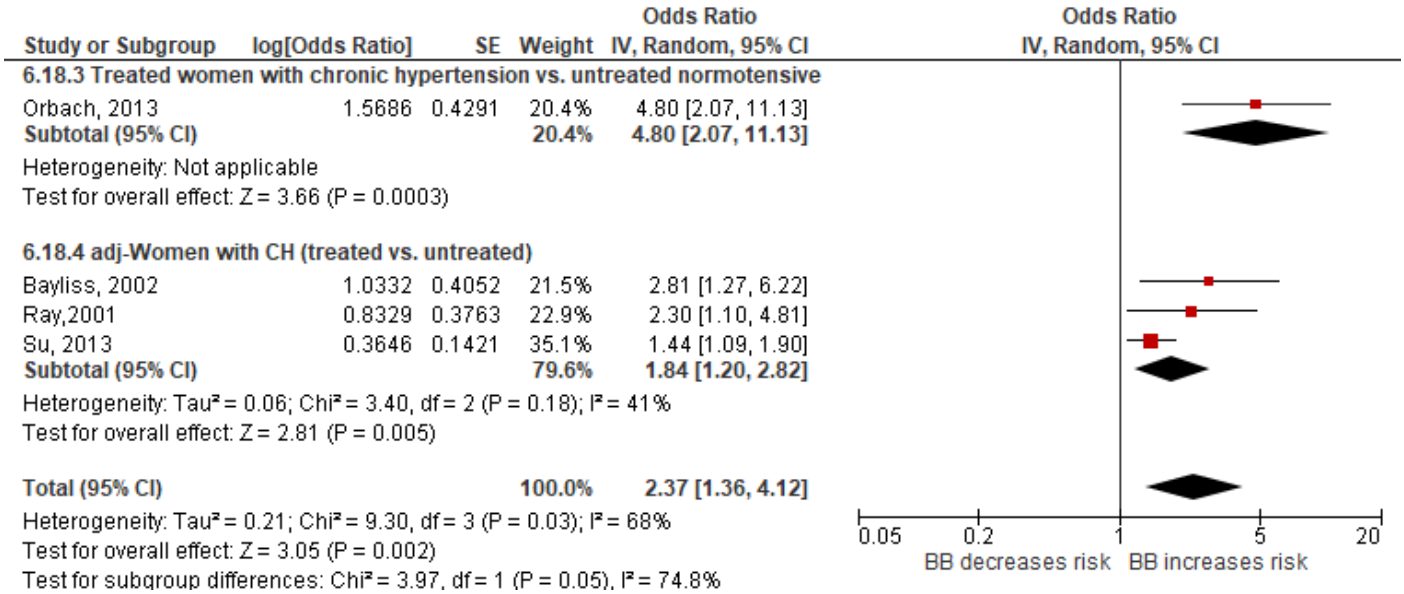



**Figure S3.24e** Forest plot of crude estimates of small for gestational age (centrally acting antiadrenergic vs untreated)

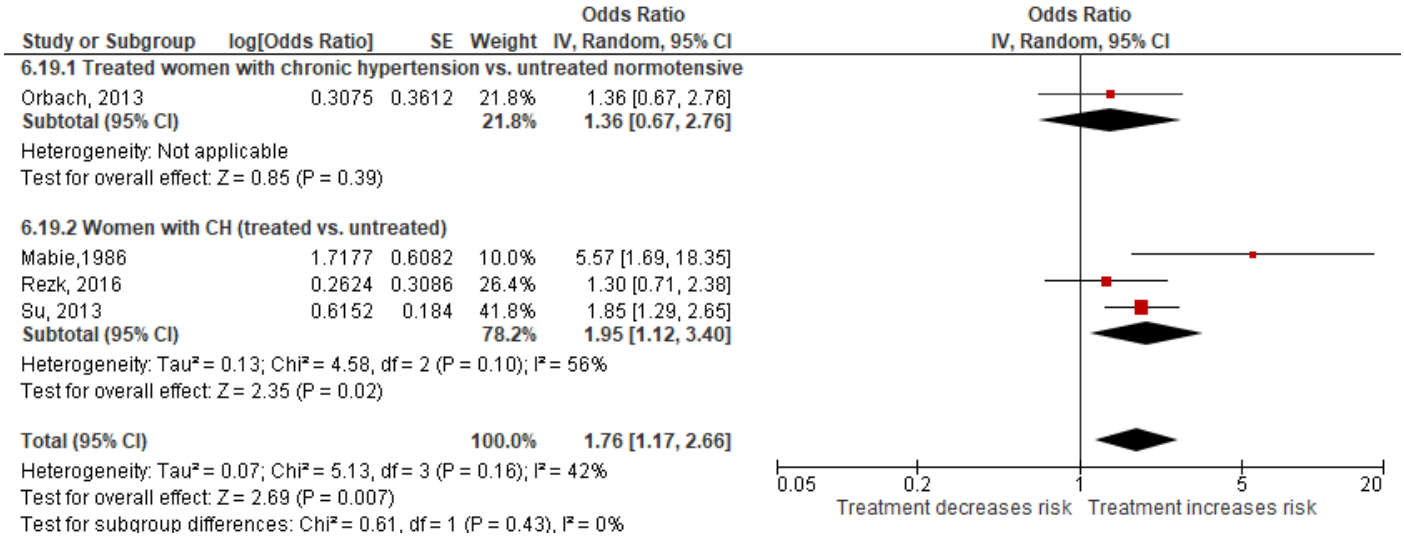


**Figure S3.24f** Forest plot of adjusted estimates of small for gestational age (centrally acting antiadrenergic vs untreated)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.21.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Orbach, 2013 | 0.01 | 0.0051 | 42.6% | 1.01 [1.00, 1.02] |
| **Subtotal (95% CI)** | | | **42.6%** | **1.01 [1.00, 1.02]** |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 1.96 (P = 0.05) | | | | |
| **6.21.2 Women with CH (treated vs. untreated)** | | | | |
| Rezk, 2016 | 0.1989 | 0.3058 | 24.1% | 1.22 [0.67, 2.22] |
| Su, 2013 | 0.6313 | 0.1843 | 33.3% | 1.88 [1.31, 2.70] |
| **Subtotal (95% CI)** | | | **57.4%** | **1.62 [1.09, 2.42]** |
| Heterogeneity: Tau² = 0.03; Chi² = 1.47, df = 1 (P = 0.23); I² = 32% | | | | |
| Test for overall effect: Z = 2.36 (P = 0.02) | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.30 [0.83, 2.03]** |
| Heterogeneity: Tau² = 0.12; Chi² = 11.74, df = 2 (P = 0.003); I² = 83% | | | | |
| Test for overall effect: Z = 1.15 (P = 0.25) | | | | |
| Test for subgroup differences: Chi² = 5.34, df = 1 (P = 0.02), I² = 81.3% | | | | |

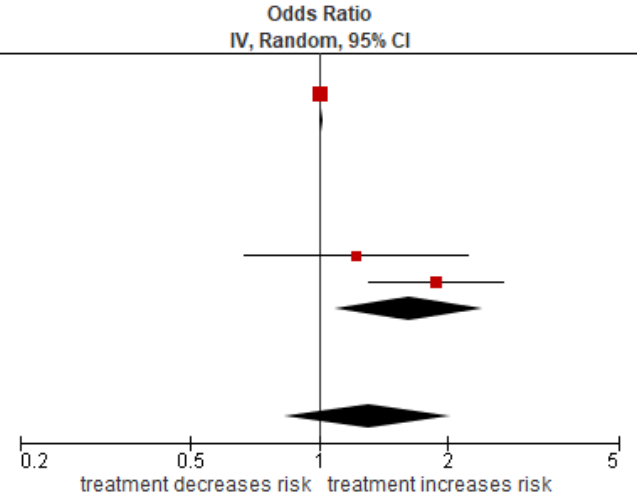



**Figure S3.24g** Forest plot of adjusted estimates of small for gestational age (single/multiple agents vs untreated)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.35.5 single agent (treated vs untreated CH)** | | | | |
| Bayliss, 2002 | 1.0332 | 0.4052 | 12.3% | 2.81 [1.27, 6.22] |
| Ray,2001 | 1.0647 | 0.4094 | 12.1% | 2.90 [1.30, 6.47] |
| Su, 2013 | 0.3646 | 0.1421 | 28.4% | 1.44 [1.09, 1.90] |
| **Subtotal (95% CI)** | | | **52.8%** | **2.03 [1.20, 3.43]** |
| Heterogeneity: Tau² = 0.12; Chi² = 4.54, df = 2 (P = 0.10); I² = 56% | | | | |
| Test for overall effect: Z = 2.63 (P = 0.009) | | | | |
| **6.35.6 multiple agents (treated vs untreated CH)** | | | | |
| Bayliss, 2002 | 1.5872 | 0.4536 | 10.6% | 4.89 [2.01, 11.90] |
| Ray,2001 | 0.8329 | 0.3763 | 13.5% | 2.30 [1.10, 4.81] |
| Su, 2013 | 0.7467 | 0.213 | 23.1% | 2.11 [1.39, 3.20] |
| **Subtotal (95% CI)** | | | **47.2%** | **2.55 [1.64, 3.95]** |
| Heterogeneity: Tau² = 0.05; Chi² = 2.84, df = 2 (P = 0.24); I² = 30% | | | | |
| Test for overall effect: Z = 4.18 (P < 0.0001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.25 [1.59, 3.18]** |
| Heterogeneity: Tau² = 0.09; Chi² = 10.65, df = 5 (P = 0.06); I² = 53% | | | | |
| Test for overall effect: Z = 4.60 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0% | | | | |

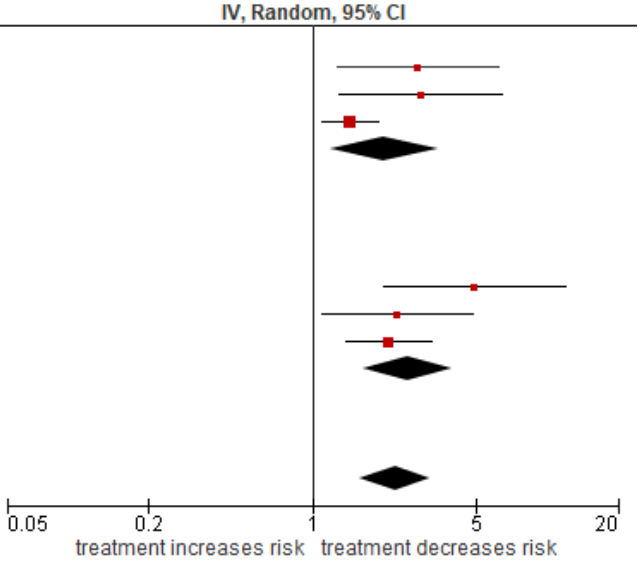


**Figure S3.24h** Forest plot of crude estimates of small for gestational age (β-blockers vs methyldopa)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.37.2 Women with CH (treated vs. untreated)** | | | | |
| Orbach, 2013 | 0.9023 | 0.5519 | 21.6% | 2.47 [0.84, 7.27] |
| Su, 2013 | -0.2233 | 0.199 | 40.0% | 0.80 [0.54, 1.18] |
| Xie, 2014 | 0.5971 | 0.2307 | 38.4% | 1.82 [1.16, 2.86] |
| **Subtotal (95% CI)** | | | **100.0%** | **1.40 [0.70, 2.79]** |
| Heterogeneity: Tau² = 0.27; Chi² = 9.09, df = 2 (P = 0.01); I² = 78% | | | | |
| Test for overall effect: Z = 0.95 (P = 0.34) | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.40 [0.70, 2.79]** |
| Heterogeneity: Tau² = 0.27; Chi² = 9.09, df = 2 (P = 0.01); I² = 78% | | | | |
| Test for overall effect: Z = 0.95 (P = 0.34) | | | | |
| Test for subgroup differences: Not applicable | | | | |

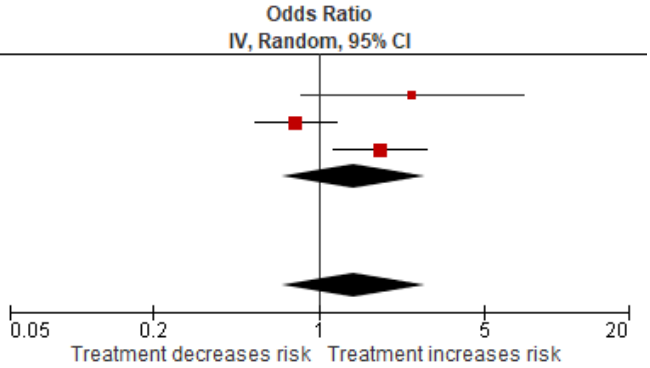



**Figure S3.24i** Forest plot of crude estimates of SGA (methyldopa vs other agents)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.36.2 Women with CH (treated vs. untreated)** | | | | |
| Ahmed, 2018 | -0.0802 | 0.2992 | 24.1% | 0.92 [0.51, 1.66] |
| Mabie,1986 | 0.9445 | 1.1037 | 4.3% | 2.57 [0.30, 22.37] |
| Orbach, 2013 | -0.9023 | 0.5519 | 12.8% | 0.41 [0.14, 1.20] |
| Su, 2013 | 0.2233 | 0.199 | 30.4% | 1.25 [0.85, 1.85] |
| Xie, 2014 | -0.5971 | 0.2307 | 28.4% | 0.55 [0.35, 0.87] |
| **Subtotal (95% CI)** | | | **100.0%** | **0.82 [0.51, 1.32]** |
| Heterogeneity: Tau² = 0.15; Chi² = 10.17, df = 4 (P = 0.04); I² = 61% | | | | |
| Test for overall effect: Z = 0.81 (P = 0.42) | | | | |
| **Total (95% CI)** | | | **100.0%** | **0.82 [0.51, 1.32]** |
| Heterogeneity: Tau² = 0.15; Chi² = 10.17, df = 4 (P = 0.04); I² = 61% | | | | |
| Test for overall effect: Z = 0.81 (P = 0.42) | | | | |
| Test for subgroup differences: Not applicable | | | | |

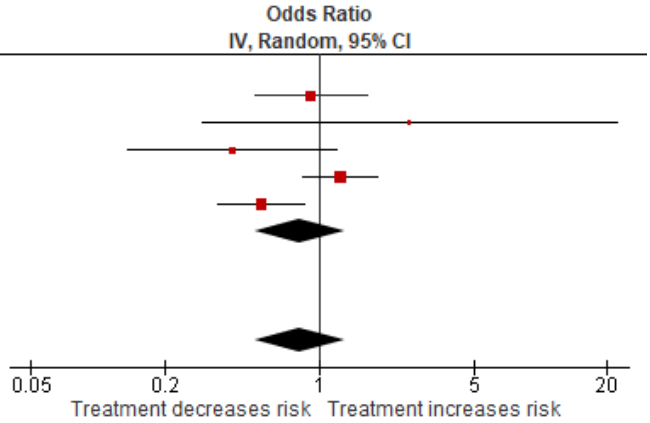



**Figure S3.25a** Forest plot of crude estimates of the association between antihypertensive treatment and low birthweight

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.23.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Banhidy,2010 | 0.8749 | 0.0825 | 21.5% | 2.40 [2.04, 2.82] |
| Lennestal, 2009 | 1.5501 | 0.0768 | 21.6% | 4.71 [4.05, 5.48] |
| Orbach, 2013 | 1.0209 | 0.113 | 20.9% | 2.78 [2.22, 3.46] |
| **Subtotal (95% CI)** | | | **63.9%** | **3.16 [2.03, 4.93]** |
| Heterogeneity: Tau² = 0.15; Chi² = 38.81, df = 2 (P < 0.00001); I² = 95% | | | | |
| Test for overall effect: Z = 5.07 (P < 0.00001) | | | | |
| **6.23.2 Women with CH (treated vs. untreated)** | | | | |
| Mito, 2019 | -0.1159 | 0.2754 | 16.2% | 0.89 [0.52, 1.53] |
| Su, 2013 | 0.6678 | 0.1547 | 19.9% | 1.95 [1.44, 2.64] |
| **Subtotal (95% CI)** | | | **36.1%** | **1.36 [0.63, 2.93]** |
| Heterogeneity: Tau² = 0.26; Chi² = 6.16, df = 1 (P = 0.01); I² = 84% | | | | |
| Test for overall effect: Z = 0.79 (P = 0.43) | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.34 [1.54, 3.55]** |
| Heterogeneity: Tau² = 0.20; Chi² = 69.56, df = 4 (P < 0.00001); I² = 94% | | | | |
| Test for overall effect: Z = 3.98 (P < 0.0001) | | | | |
| Test for subgroup differences: Chi² = 3.48, df = 1 (P = 0.06), I² = 71.2% | | | | |

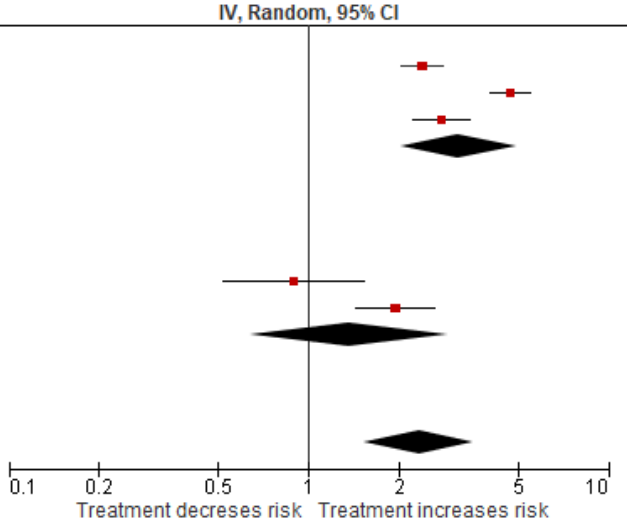


**Figure S3.25b** Forest plot of adjusted estimates of the association between antihypertensive treatment and low birthweight

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.24.1 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Banhidy,2010 | 0.8329 | 0.1251 | 24.9% | 2.30 [1.80, 2.94] |
| Lennestal, 2009 | 1.5518 | 0.0706 | 26.4% | 4.72 [4.11, 5.42] |
| Orbach, 2013 | 1.3029 | 0.1233 | 25.0% | 3.68 [2.89, 4.69] |
| **Subtotal (95% CI)** | | | **76.3%** | **3.45 [2.26, 5.26]** |
| Heterogeneity: Tau² = 0.13; Chi² = 25.34, df = 2 (P < 0.00001); I² = 92% | | | | |
| Test for overall effect: Z = 5.74 (P < 0.00001) | | | | |
| **6.24.2 Women with CH (treated vs. untreated)** | | | | |
| Su, 2013 | 0.6729 | 0.1573 | 23.7% | 1.96 [1.44, 2.67] |
| **Subtotal (95% CI)** | | | **23.7%** | **1.96 [1.44, 2.67]** |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 4.28 (P < 0.0001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **3.01 [1.98, 4.58]** |
| Heterogeneity: Tau² = 0.17; Chi² = 42.50, df = 3 (P < 0.00001); I² = 93% | | | | |
| Test for overall effect: Z = 5.15 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi² = 4.48, df = 1 (P = 0.03), I² = 77.7% | | | | |

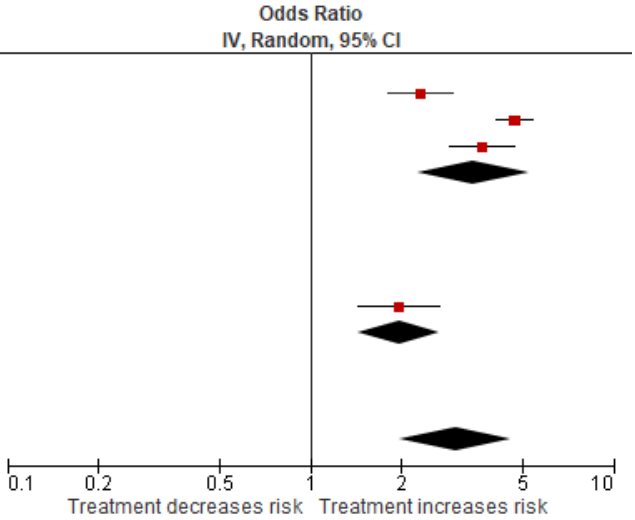
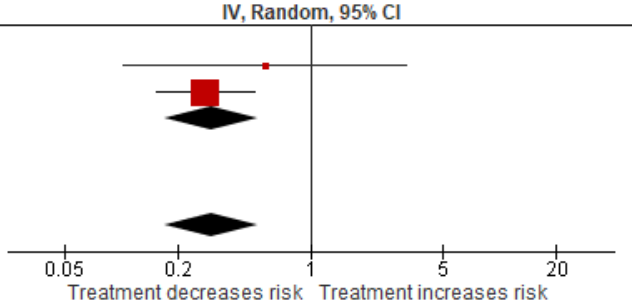



**Figure S3.26** Forest plot of crude estimates of the association between antihypertensive treatment and neonatal intensive care unit admission

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **6.25.2 Treated women with chronic hypertension vs. untreated normotensive** | | | | |
| Helou, 2017. | -0.5486 | 0.8785 | 10.6% | 0.58 [0.10, 3.23] |
| Rezk, 2016 | -1.2818 | 0.3026 | 89.4% | 0.28 [0.15, 0.50] |
| **Subtotal (95% CI)** | | | **100.0%** | **0.30 [0.17, 0.53]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0% | | | | |
| Test for overall effect: Z = 4.21 (P < 0.0001) | | | | |
| **Total (95% CI)** | | | **100.0%** | **0.30 [0.17, 0.53]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0% | | | | |
| Test for overall effect: Z = 4.21 (P < 0.0001) | | | | |
| Test for subgroup differences: Not applicable | | | | |



# Appendix 4: Chronic Kidney Disease and Adverse Pregnancy Outcomes: A Systematic Review and Meta-analysis (supplemental material)

**S4.1 Supplementary methods**

A) S*earch strategy for Web of Science*

1.Pregnancy outcome* OR obstetric outcome* OR birth outcome* OR pregnancy complication* OR gestational complication*or obstetric complication OR birth complication* OR labor complication* OR pre-term deliver* OR preterm deliver* OR pre-term birth*or preterm birth* OR preterm labor* OR pre-term labor* OR premature deliver* OR premature birth* OR premature labor* OR prematurity OR cesarean* OR cesarean section* OR csection* OR c section* OR spontaneous abortion* abortion OR pregnancy loss OR miscarriage* OR miscarry OR stillbirth* OR still birth* OR intrauterine death* OR intra-uterine death* OR fetal death* OR fetal mortalit* OR neonatal mortalit* OR neonatal death* OR newborn death* OR newborn mortalit* OR new born death* OR new born mortalit* OR perinatal mortalit* OR perinatal death* OR infant mortalit* OR infant death* preeclampsia OR preeclampsia OR pre eclampsia OR preeclamptic OR pre eclamptic OR pre-eclamptic toxemia* OR preeclamptic toxemia* OR PET OR pregnancy toxemia* OR toxemia* OR eclampsia/ OR eclamptic OR HELLP OR hemolysis elevated liver enzymes low platelet count OR hemolysis-elevated liver enzymes-low platelet count OR fetal outcome* OR fetal complication* OR neonate complication* OR neonatal complication*or newborn complication* gestational age* OR special care baby unit admission* OR SCBU admission* OR NICU admission* OR neonatal intensive care unit admission* OR small for gestational age* OR SGA* OR IUGR* OR intrauterine growth restriction* OR LBW*or low birth weight* OR VLBW* OR very low birth weight*

2.Chronic Kidney Insufficien* OR CKD OR Chronic Kidney disease OR Chronic renal disease OR Chronic renal Insufficien* OR dialysis OR kidney failure OR renal failure OR diabetic kidney disease OR diabetic chronic kidney disease OR diabetic nephropathy* OR diabetic renal disease OR congenital renal disease OR congenital kidney disease OR polycystic kidney disease OR PKD OR CAKUT OR congenital anomalies of kidney and urinary tract OR Tubulointerstitial CKD OR Glomerular CKD OR proteinuric CKD Hypertensive CKD OR hypertensive kidney disease OR renovascular disease

Searches 1 and 2 were then combined (1 ‘AND’ 2)

*B) Search strategy for Embase*

1.'pregnancy outcome' OR 'pregnancy complications' OR 'high risk pregnancy' OR 'labor' OR 'delivery' OR 'fetus outcome' OR 'parameters concerning fetus newborn pregnancy' OR 'premature labor' OR 'immature and premature labor' OR 'prematurity' OR 'cesarean section' OR 'spontaneous abortion' OR 'stillbirth' OR 'fetus death' OR 'infant mortality' OR 'fetus mortality' OR 'maternal mortality' OR 'perinatal mortality' OR 'preeclampsia' OR 'eclampsia' OR

'eclampsia and preeclampsia' OR 'hellp' OR 'disseminated intravascular coagulation' OR 'newborn death' OR 'gestational age' OR 'infant low birth weight' OR 'low birth weight' OR 'very low birth weight' OR 'extremely low birth weight' OR 'newborn intensive care' OR 'small for date infant' OR 'pregnancy outcome*' OR 'maternal outcome*' OR 'pregnancy complication*' OR 'high risk pregnanc*' OR 'obstetric outcome*' OR 'obstetric complication*' OR 'normal birth*' OR 'live birth*' OR 'premature birth*' OR 'preterm birth*' OR 'preterm deliver*' OR 'born preterm' OR 'cesarean*' OR 'csection*' OR 'miscarriage*' OR 'stillbirth*' OR 'intrauterine death*' OR 'special care baby unit admission*' OR 'scbu admission*' OR 'neonatal intensive care unit admission*' OR 'nicu admission*' OR 'sga' OR 'iugr' OR 'neonatal intraventricular haemorrhage' OR 'neonatal intraventricular haemorrhage' OR 'apgar score' OR 'lbw' OR 'vlbw'

2.'chronic Kidney Insufficien*' OR 'CKD' OR 'Chronic Kidney disease' OR 'Chronic renal disease' OR 'Chronic renal Insufficien*' OR 'dialysis or kidney failure' OR 'renal failure' OR 'diabetic kidney disease' OR 'diabetic chronic kidney disease' OR 'diabetic nephropathy' or 'diabetic renal disease' OR 'congenital renal disease' OR 'congenital kidney disease' OR 'polycystic kidney disease' OR 'PKD' OR 'CAKUT' OR 'congenital anomalies of kidney and urinary tract' OR 'Tubulointerstitial CKD' OR 'Glomerular CKD' OR 'proteinuric CKD' OR 'Hypertensive CKD' OR 'hypertensive kidney disease' OR 'renovascular disease')

3. Pregnan*

Searches 1, 2 and 3 were then combined (1 ‘AND’ 2 ‘AND’ 3)

*C) Search strategy for PubMed using MeSH term*

**1.”**Pregnancy OR "pregnancy, high risk" OR "pregnancy complications, OR "infant, low birth weight" OR "infant, extremely low birth weight" OR "infant, very low birth weight" OR "infant, small for gestational age” OR "obstetric labor, premature" OR "infant, premature" OR "infant, extremely premature" OR "Stillbirth" OR "Stillbirth" OR "abortion, spontaneous" OR "Pre-Eclampsia" OR "Eclampsia" OR "HELLP Syndrome" OR "Cesarean Section" OR "Fetal Death" OR "Pregnancy Outcome" OR "Pregnancy Complications" OR "Perinatal Mortality" OR "Infant Death" OR "Infant Mortality" OR "intensive care units, neonatal" OR "infant, newborn" OR "Intensive Care Units" OR "Fetal Growth Retardation" OR "abortion, induced"

2."Diabetic Nephropathies" OR "Fused Kidney" OR "Cakut" OR "Polycystic Kidney" OR "Renal Insufficiency, Chronic" OR "Hypertension, Renovascular" OR "Nephropathy, Chronic Tubulointerstitial"

Searches 1 and 2 were then combined (1 ‘AND’ 2)

## S4.2 Supplementary Tables S4.1-S4.2

**Table S4.1** Study characteristics (studies reported the adverse pregnancy outcomes in women with chronic kidney disease (CKD) vs those without)

| Study, Year | Country | Study design | Sample size | Definition of Chronic Kidney Disease | Study Year | Defined maternal outcomes | Defined fetal outcomes | Variable accounted for | Newcastle -Ottawa grade |
|---|---|---|---|---|---|---|---|---|---|
| Kimmerle R, 1995 | Germany | Prospectiv e cohort | 46 | DN defined as Proteinuria >400 mg/day, creatinine clearance <80 ml/min and hyper- tension in the first trimester. | 1982 – 1992 | Preeclampsia defined as acute worsening hypertension (>15% diastolic BP) in the presence of proteinuria, CS (not defined). | SGA defined as birth weight lower than 10th percentile, intrauterine/ perinatal deaths (not defined) | None | 5* |
| Holley J, 1996 | USA | Prospectiv e cohort | 86 | Proteinuria ≥150 mg/24 h, or 1st trimester Sr Cr. 0.8 mg/dl in the first trimester, or proteinuria≥300 mg/24 h, with known kidney disease. | 1991-1993 | Spontaneous abortion not defined. | Preterm birth defined as birth ≤ 36wks of gestation. IUGR, Neonatal death, Intrauterine fetal death (Not reported) | Maternal age, parity, race, and insulin dependent DM | 4* |
| Miodovnik M, 1996 | USA | Prospectiv e cohort | 182 | DN defined as total protein excretion rate: >500 mg/day, or persistent positive albuminuria (dipstick ≥2) in the absence of bacteriuria. | 1978 -1991 | Preeclampsia defined as pregnancy-induced hypertension with proteinuria >500mg/ in patient without nephropathy | Preterm birth defined as delivery before 37 complete weeks of gestation, IUGR/SGA defined as birth weight <10th percentile, Stillbirth and Neonatal mortality | None | 5-6* |
| Fink C, 1998 | USA | Retrospecti ve cohort | 675 | CKD defined according to ICD-9 codes including diabetic and hypertensive nephropathy, acute and chronic glomerulonephritis, nephrotic syndrome, acute and chronic | 1987 – 1993 | Preeclampsia, CS (outcomes not defined) | Neonatal mortality (defined as infant death within 28 days of birth), Preterm birth, SGA, Preterm birth, IUGR | Maternal age, trimester of first prenatal visit, parity, smoking and chronic hypertension | 8* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | renal failure, disorders with impaired renal function, small kidneys of unknown cause, renal agenesis, and cystic diseases. | | | | | |
| Biensanbach G, 2000 | Austria | Prospective cohort | 40 | Preconceptional persistent macroproteinuria (>0.5g protein/24h urine) without UTI and other renal diseases. | 1985 -1993 | CS, Preeclampsia (outcomes not defined) | Preterm birth defined as premature delivery (<34 week of gestation), SGA (2400g birth weight). | None | 6* |
| Ekbom P, 2001 | Denmark | Prospective cohort | 240 | Micro-albuminuria: 30-300mg/24h; or diabetic nephropathy: >300mg/ 24h. | 1996 -1999 | Miscarriage < 22wks., Preeclampsia defined BP > 140/90mmHg accompanied by proteinuria. | Preterm delivery (<37 wks. Of gestation) SGA < 10th percentile Perinatal mortality defined fetal death later than 22wks. | None | 7* |
| Trevisan G, 2004 | Brazil | Retrospective cohort | 75 | CRI defined as Sr. Cr >1.5mg/dL | 1989-1999 | Preeclampsia, CS. | Preterm birth; delivery for 28-36wks., Stillbirth (abortion; pregnancy that last for 20-28wks.) | Maternal and gestational age, time of delivery | 5* |
| Jensen D, 2010 | Denmark | Prospective Cohort | 846 | Microalbumin in early pregnancy defined as UAER between 30 and 300mg/24h or between 20 and 200ug/min | 1993 - 1999 | Preeclampsia defined as BP >140/90mmHg. | Preterm birth defined as delivery before 37 gestational wks., SGA, Birth weight. | Age, BMI, duration of diabetes, parity, pre-pregnancy insulin dose, blood pressure ≥140/90 mmHg at first visit, proliferative retinopathy, 1st/3rd trimester A1C. | 8* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Young E, 2011 | Brazil | Prospective cohort | 43 | DN defined as by the criteria of NKF | 2010 - 2011 | Preeclampsia (not defined) | Preterm birth defined as prematurity <37wks, LBW defined as <2500g or 10th percentile for gestational age, Fetal death defined as death after 22wks, Stillbirth defined as expulsion of fetus less than 500g. | None | 6* |
| Davidson N, 2015 | Australia | Retrospective cohort | 62357 | CKD defined using the KDOQI guidelines. | 2003-2010 | Preeclampsia and Hypertension in pregnancy were defined according to both SOMANZ and ISSHP guidelines | Preterm birth defined as birth in which a child is delivered before it reached the full of gestation (37 wks.). SGA defined as birth weight, length, or head circumference below the 10th percentile for gestational age. IUGR defined as birth weight below the 10th percentile for gestational age. | None | 5-6* |
| Kendrick J, 2015 | USA | Retrospective cohort | 1156 | ICD-P Code/ NKF-KDOQI, GFR <60 ml/min / 1.73 m2 for >3 months or Sr. Cr >1.2 mg/dL in first trimester | 2000-2013 | CS, Preeclampsia/, Maternal death defined as death occurring at any time. | Preterm birth defined as <37wks' gestation, LBW defined as <2500, SGA defined as <10th percentile of birth weight, NICU admission and Fetal death defined as death during hospitalization. | Age, race, history of diabetes, chronic hypertension, liver disease, connective tissue disease to women without CKD. | 8* |
| Patel E, 2015 | USA | Prospective cohort | 12,524,119 | ICD-9 coding | 2000-2010 | Maternal outcomes definition not reported | Fetal outcomes definition not reported. | Age, race/ethnicity, insurance, multiple gestation, diabetes, chronic hypertension, diabetes with chronic hypertension, cardiomyopathy, congenital heart disease, cardiac conduction disorders, systemic lupus erythematous, collagen vascular disease, HIV, thrombophilia/APS, sickle cell | 8* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | disease/trait, drug use, alcohol use, tobacco use, gestational diabetes, preeclampsia/eclampsia, fetal growth restriction, placental abruption | |
| Wiles K, 2015 | United Kingdom | Retrospective cohort | 312 | CKD definition not reported | 2003-2011 | Preeclampsia not defined; documented diagnosis in the hospital database. | Fetal growth restriction <10th percentile for gestational age. Preterm birth delivery defined as birth <37 wks. of gestation. Intrauterine death defined as death >24 wks. of gestation. Pregnancy loss defined as 2nd trimester miscarriage or intrauterine death. | None | 5* |
| Wu M, 2016 | USA | Cohort study | 146 | Diagnosis of ADPKD was determined by ultrasound using the following criteria: patients younger than 30 years: at least two cysts in one kidney or one cyst in each kidney; patients aged 30–59 years: at least two cysts in each kidney and patients aged 60 years or older: at least four cysts in each kidney | 1975-2010 | Preeclampsia defined as new onset hypertension sBP 140 mmHg or dBP 90 mmHg measured on two occasions, 6h apart) and proteinuria 300 mg in a 24-h urine specimen after 20wks. of gestation | SGA/IUGR defined as weight > 10th percentile for gestational age, Premature delivery (delivery before the 37th gestational week or 259 days from the first day of the last menstrual period). Neonatal death (death within the first month of life). Abortion defined as elective, therapeutic or spontaneous fetal loss before 20 weeks of gestation. Stillborn defined as birth of a nonviable fetus after 20 weeks of gestation. | None | 7* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Piccoli G, 2017 | Italy | Prospective cohort | 1544 | GN defined according to K-DOQI guidelines (CKD-EPI formula) | Not Reported | CS, Preeclampsia defined as hypertension accompanied by proteinuria after 20 wk. gestational in a previously normotensive, non-proteinuric woman. | Preterm birth defined as birth <37 wks., very preterm birth defined as birth <34 wks., SGA defined as birth weight below the 10th percentile. | CKD stage, age, nulliparous race, referral proteinuria, hypertension | 6-7* |
| Tsuchiyama F, 2017 | Japan | Retrospective cohort | 3206 | CKD was diagnosed. based on the K-DOQI definition of CKD | 2001-2010 | Preeclampsia defined as hypertension >140/90mmHg accompanied by proteinuria after the 20th wks. of gestation | Threatened preterm labor defined as progressive dilation of the cervix combined with regular uterine contractions that occurred between 22 and 36 wks. of gestation. SGA (below the 10th birth weight percentile for the infant's gestational age). Neonatal death defined as death within 28 days of birth. | None | 7* |
| Li Y, 2018 | China | Retrospective cohort | 114 | CGN defined according to K-DOQI guidelines. Urine protein >0.5g/d | 2018 | Preeclampsia defined by onset of BP >110mmHg | Preterm birth defined as Premature, SGA defined as birth weight below 10th percentile, LBW <2500g, IUGR fetal growth curve below 10th percentile, Fetal loss defined as abortion due to the disease. | None | 5* |
| Harel, 2020 | Canada | Population - cohort based | 55 964 | serum creatinine above the 95th percentile (i.e., > 77 µmol/L) | 2007-2016 | None | Preterm birth defined as gestational age <37 wks., very defined as gestational age <32 wks., stillbirth≥ 20 weeks' gestation. | Maternal age, rural or urban residence, residential income, region of origin, diabetes mellitus, chronic hypertension, and illicit drug or tobacco use within 4 years before the index conception date. | 8* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Madej A, 2020 | Poland | Retrospective cohort | 387 | Biopsy-proven GN. CKD stage was classified as follows: CKD1: eGFR >90; CKD2: eGFR 89–60; CKD3: eGFR 59–30, and CKD4: eGFR 15–29 mL/min/1.73 m2, according to the KDIGO | 2013-2018 | Preeclampsia defined as new-onset hypertension and proteinuria with protein excretion >0.3 g/day after 20 weeks of gestation in women without underlying hypertension and proteinuria, new onset hypertension and doubling of daily proteinuria after 20 wks. of gestation in women without hypertension but with proteinuria (with protein excretion >0.3 g/24 h at baseline), and either worsening hypertension or doubling of proteinuria in women with both hypertension and proteinuria (with protein excretion >0.3 g/24 h at baseline). | Preterm birth defined as gestational age <37 wks. Stillbirth defined as death after 21 wks. Of gestation, Neonatal death defined as live born infant dying within 28 days of delivery. | None | 7* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Seah J, 2020 | Australia | Prospective cohort | 144 | eGFR was calculated based on the CKD-EPI formula. Stages of diabetic kidney disease was defined according to the KDIGO guidelines and hyperfiltration define as an eGFR > 120 mL/min/1.73m$^2$, microalbuminuria was defined as urinary albumin excretion of 30-300 mg/day or urinary ACR of 3.5 to 35.0 mg/mmol. Macroalbuminuria was defined as urinary albumin excretion > 300 mg/day or urinary ACR > 35.0 mg/mmol. | 2004-2014 | Preeclampsia defined as the development of sBP >140mmHg ± dBP >90mmHg, and proteinuria > 300mg/24h after 20wks gestation as well as clinical diagnosis. | Preterm birth defined as delivery < 37 weeks of gestation with no separation made between iatrogenic and spontaneous. NICU (no definition reported). | None | 6* |
| Al Khalaf, 2021 | Sweden | Retrospective cohort | 2 784 490 | ICD8-ICD10 codes | 1982-2012 | Preeclampsia defined as at least 2 dBP≥90 mm Hg, combined with proteinuria (≥0.3 g/day or ≥1+ on a urine dipstick), CS. | Preterm birth defined as gestational age <37 wks., very defined as gestational age <32 wks., stillbirth defined as fetal loss >28 wk. (until June 2008) or > 22 wk. (since July 2008), SGA defied as a birthweight below 2 SDs of the mean birthweight. | Adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, other co-morbidities (diabetes mellitus, cardiovascular disease, asthma), birth year, and child's sex. | 8* |

BMI, Body Mass Index; CGN, Chronic Glomerular-nephritides; CKD, Chronic Kidney Disease; CRI, Chronic Renal Insufficiency; CKD- EPI, Chronic Kidney Disease Epidemiology Collaboration; DM, Diabetes Mellitus; DN, Diabetic Nephropathy; GFR, Glomerular Filtration Rate; Egfr, Estimated Glomerular Filtration Rate; HCPA, Hospital the Clinicas of Porto Alegre-Brazil; IUGR, Intrauterine Growth Retardation/Restriction; KDIGO, Kidney Disease Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; LBW, Low Birthweight; SGA, small for gestational age; SD: standard deviation; NICU, Neonatal Intensive Care Unit/ Need for Intensive Care Unit.

**Table S4.2** Study characteristics (studies reported the adverse pregnancy outcomes in women with late stages compared to early stages of CKD)

| Study, Year | Country | Study design | Sample size | Definition of Chronic Kidney Disease | Study Year | Defined maternal outcomes | Defined fetal outcomes | Variable accounted for | Newcastle-Ottawa grade |
|---|---|---|---|---|---|---|---|---|---|
| Reece E, 1988 | USA | Retrospective cohort | 31 | DN defined as urinary protein level was ≥300 mg/24hr before the third trimester. The severity of the proteinuria was categorized as mild (300 to 499 mg/24 hr), moderate (500 to 3000 mg/24 hr), and severe or nephrotic syndrome (>3 gm/24 hr). | 1975-1984 | Preeclampsia defined acute worsening of BP (> 15% increase in sBP or dBP or deterioration of renal function associated with multisystemic involvement, result-ting in abnormal liver function and coagulation studies, particularly elevation in the fibrin split products and thrombocytopenia. | Not reported | None | 5-6* |
| Imbasciaati E, 2007 | Italy | Cohort study | 49 | GFR was estimated using the Modification of Diet in Renal Disease 4-variable equation (based on serum creatinine level, age, sex, and race) and expressed in mm per minute per 1.73 m2 of body surface area. | 1977-2004. | CS (not reported) | Preterm delivery defined as (live birth before the 37th week), stillbirth (intrauterine death after 24 wks. of gestation), neonatal death (live infant dying within 28 days after delivery), and perinatal death (obtained as the sum of stillbirths and neonatal deaths). SGA (infants with birth weight > the 10th percentile of the Italian population according to gestational week at delivery. LBW (live-born infant weighing less than 2,500g. | None | 7* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bramham, 2011 | United Kingdom & Netherlands | Prospective cohort | 36 | Mild CKD and moderate/ severe CKD were defined as pre-pregnancy Cr < 125 mmol/L and Cr > 125 mmol/L, respectively. | 2003-2005 | Preeclampsia was defined as the new development of proteinuria in accordance with the ISSHP | SGA defined as birth weight less than 10th percentile. Preterm birth (37 wks. and <34 wks. gestation). Perinatal death (intrauterine >24wks.gestation or postnatal by 7 days). NICU (not defined). | None | 6* |
| Davidson N, 2015 | Australia | Retrospective cohort | 55 | CKD defined using the KDOQI guidelines. | 2003-2010 | Preeclampsia and Hypertension in pregnancy were defined according to both SOMANZ and ISSHP guidelines | Preterm birth defined as birth in which a child is delivered before it reached the full of gestation (37 wks.). SGA defined as birth weight, length, or head circumference below the 10th percentile for gestational age. IUGR defined as birth weight below the 10th percentile for gestational age. | None | 5-6* |
| Feng Z, 2015 | USA | Retrospective cohort | 41 | Severe CKD defined as estimated GFR (eGFR) < 30 mL/min within the first three months of pregnancy. Mild CKD defined as estimated GFR (eGFR) 45 – 100 mL/min | 2000-2012 | Pre-eclampsia defined as blood pressure > 140/90 mmHg and 2+ proteinuria on dipstick after second trimester. | Prematurity was defined as birth before 37 weeks of gestation. Perinatal death was defined as new-born death < 4 weeks of age. Low birth weight was defined as < 2,500 grams. | None | 6-7* |
| Singh N, 2015 | India | Retrospective cohort | 51 | CKD defined by K-DOQI guidelines abnormality. | 2009-2012 | Not reported | Not reported | None | 7* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Wiles K, 2015 | United Kingdom | Retrospective cohort | 35 | CKD definition not reported | 2003-2011 | Preeclampsia not defined; documented diagnosis in the hospital database. | Fetal growth restriction <10th percentile for gestational age. Preterm birth delivery defined as birth <37 wks. of gestation. Intrauterine death defined as death >24 wks. of gestation. Pregnancy loss defined as 2nd trimester miscarriage or intrauterine death. | None | 5* |
| Bharti J, 2016 | India | Retrospective cohort | 80 | CKD is defined as either kidney damage or GFR <60ml/min/1.73 m2 for ≥3 months (CKD definition according to NKF-KDOQI guidelines.) | 2005 - 2015 | Preeclampsia defined as new onset hypertension after 20 wks. Of pregnancy associated with proteinuria, CS (not defined). | SGA defined as infants < 10th percentile, Preterm birth (<37 weeks gestation), NICU, Stillbirths, | None | 7* |
| Piccoli G, 2017 | Italy | Prospective cohort | 126 | GN defined according to K-DOQI guidelines (CKD-EPI formula). | Not Reported | CS, Preeclampsia. | Preterm birth, very preterm birth, SGA, | CKD stage, age, nulliparous race, referral proteinuria, hypertension | 6-7* |
| He Y, 2018 | China | Retrospective cohort | 293 | CKD defined based on a history of CKD, clinical examination, renal function tests, 24-h urinary protein excretion, renal ultrasound, and renal biopsy. The staging of kidney diseases was based on the eGFR level. | 2005-2016 | Preeclampsia defined based on 2013 Hypertension in Pregnancy Guidelines of ACOG | Preterm birth defined as gestational age at birth of less than 34 weeks. LBW defined as neonatal birth weight ≤1500 g. | None | 6-7* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Leaños-Miranda A, 2019 | Mexico | Cohort study | 167 | CKD stage was defined according to KDIGO guidelines. GFR was calculated using the CKD-EPI formula based on preconception data or serum creatinine measured at first control in pregnancy. | 2011-2017 | Preeclampsia defined according to The American College of Obstetricians and Gynecology criteria | Preterm delivery (< 34 weeks of gestational age). Stillbirths defined as death of a fetus. Neonatal death defined as death of a new-born until hospital discharge and SGA defined as an infant whose birth weight was below the 10th percentile. | Proteinuria, urinary IgM, CKD stages, and chronic hypertension | 8* |
| Madej A, 2020 | Poland | Retrospective cohort | 72 | Biopsy-proven GN. CKD stage was classified as follows: CKD1: eGFR >90; CKD2: eGFR 89–60; CKD3: eGFR 59–30, and CKD4: eGFR 15–29 mL/min/1.73 m2, according to the KDIGO | 2013-2018 | Preeclampsia defined as new-onset hypertension and proteinuria with protein excretion >0.3 g/day after 20 weeks of gestation in women without underlying hypertension and proteinuria, new onset hypertension and doubling of daily proteinuria after 20 wks. of gestation in women without hypertension but with proteinuria (with protein excretion >0.3 g/24 h at baseline), and either worsening hypertension or doubling of proteinuria in women with both hypertension and proteinuria (with protein excretion >0.3 g/24 h at baseline). | Preterm birth defined as gestational age <37 wks. Stillbirth defined as death after 21 wks. Of gestation, Neonatal death defined as live born infant dying within 28 days of delivery. | None | 7* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Wiles K, 2020 | United Kingdom | Retrospective cohort | 178 | eGFR<60 mL/min/1.73 m2, calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. OR a creatinine >125 mmol/L prior to 20 weeks' gestation in the absence of a precipitant for kidney injury. | 2003 and 2017 | CS. | SGA defined as birthweight< 10th percentile, preterm birth (<37 weeks gestation), very preterm birth (<34 wk.) and NICU admission. | None | 6* |
| Madazli, 2021 | Turkey | Retrospective cohort | 101 | CKD defined as kidney damage (albumin-to-creatinine ratio >30 mg/ 24h two of three urine specimens, urine sediment abnormalities, tubular disorders, histologically diagnosed abnormalities, structural abnormalities detected by scanning) OR GFR<60ml/min/1.73 m2 for three months based on KDIGO guidelines | 2009 and 2019 | Preeclampsia defined according to ACOG guidelines; superimposed preeclampsia was defined as CKD with hypertension with new onset or sudden increase in proteinuria, sudden increase in BP, thrombocytopenia or deranged liver or kidney function. | stillbirth defined as fetal death after 22 wk., neonatal death that occurred < 28 days after birth, perinatal death (stillbirth + neonatal death), SGA defined as slowing of fetal growth velocity during ≥2 consecutive ultrasound with measurements ≥3 wk. apart and fetal abdominal circumference < 2 SD for gestational age) | None | 7* |

ACOG, American College of Obstetricians and Gynecologists; BP, Blood Pressure; CKD, Chronic Kidney Disease; CS, Caesarean section; DN, Diabetic Nephropathy; GFR, Glomerular Filtration Rate; eGFR, Estimated Glomerular Filtration Rate; ISSSP, International Society of Study of Hypertension in Pregnancy; IUGR, Intrauterine Growth Retardation/Restriction; KDIGO, Kidney Disease Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; LBW, Low Birthweight; MAP, Mean Arterial Pressure; MDRD, Modification of Diet in Renal Disease; NICU, Neonatal Intensive Care Unit; NKF, National Kidney Foundation; PCR, Protein Creatine Ratio; PE, Preeclampsia, SGA, Small for Gestational Age; SD, standard deviation; SOMANZ, Society of Obstetric Medicine of Australia and New Zealand; TOCOS, Torino Cagliari Observational study

**Table S4.3** Sensitivity analyses of the associations between CKD and adverse pregnancy outcomes (by location and decade of publication)

| Outcomes | Subgroup | Crude estimates | | | | Adjusted estimates* | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No of Studies | OR 95% CI | $I^2$ *(%)* | Test for subgroup differences *(P-value)* | No of Studies | OR 95% CI | $I^2$ *(%)* | Test for subgroup differences *(P- value)* |
| **Pre-eclampsia** | | | | | | | | | |
| Location | Asia | 2 | 7.61 [4.86, 11.9] | 0 | 0.63 | - | - | - | 0.88 |
| | Australia | 1 | 5.56 [2.95, 10.5] | - | | - | - | - | |
| | Europe | 7 | 6.70 [2.80, 16.0] | 93 | | 2 | 2.41 [0.99, 5.85] | 89 | |
| | North America | 3 | 9.33 [4.49, 19.4] | 57 | | 2 | 2.83 [0.46, 17.5] | 97 | |
| | South America | 2 | 14.6 [4.69, 45.2] | 0 | | - | - | - | |
| Year of Publication | Publication ≤2010 | 6 | 9.69 [5.90, 15.9] | 55 | 0.42 | 2 | 5.45 [3.05, 9.76] | 52 | <0.0001 |
| | Publication >2010 | 9 | 6.63 [3.07, 14.32] | 92 | | 2 | 1.43 [1.03, 1.98] | 66 | |
| **Caesarean Section** | | | | | | | | | |
| Location | Asia | 1 | 2.04 [1.47, 2.82] | - | 0.19 | - | - | - | 0.002 |
| | Australia | - | - | - | | - | - | - | |
| | Europe | 5 | 1.43 [1.24, 1.64] | 11 | | 1 | 1.40 [1.34, 1.46] | - | |
| | North America | 3 | 1.86 [1.06, 3.27] | 63 | | 2 | 1.99 [0.87, 4.55] | 91 | |
| | South America | 1 | 2.08 [0.78, 5.50] | - | | - | - | - | |
| Year of Publication | Publication ≤2010 | 5 | 2.33 [1.65, 3.30] | 10 | 0.02 | 1 | 3.10 [2.00, 4.80] | - | 0.0004 |
| | Publication >2010 | 5 | 1.48 [1.26, 1.73] | 31 | | 2 | 1.40 [1.34, 1.46] | 0 | |
| **Preterm birth (<37 wk.)** | | | | | | | | | |
| Location | Asia | 2 | 4.33 [0.71, 26.31] | 69 | 0.45 | - | - | - | 0.44 |
| | Australia | 1 | 3.67 [2.01, 6.69] | - | | - | - | - | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Europe | 6 | 3.58 [1.63, 7.85] | 96 | | 1 | 1.62 [1.54, 1.70] | - | |
| | North America | 5 | 2.32 [1.14, 4.71] | 88 | | 3 | 2.04 [1.14, 3.65] | 92 | |
| | South America | 1 | 12.25 [2.44, 61.57] | - | | - | - | - | |
| Year of Publication | Publication ≤2010 | 5 | 2.77 [1.25, 6.18] | 86 | 0.74 | 1 | 6.10 [3.30, 11.28] | - | <0.0001 |
| | Publication >2010 | 10 | 3.21 [2.25, 4.60] | 92 | | 3 | 1.44 [1.17, 1.78] | 88 | |
| **Very preterm birth (<34 wk.)** | | | | | | | | | |
| Location | Asia | - | - | - | 0.02 | - | - | - | 0.27 |
| | Australia | 1 | 4.18 [2.03, 8.61] | - | | - | - | - | |
| | Europe | 7 | 7.05 [2.87, 17.36] | 91 | | 2 | 1.86 [1.66, 2.08] | 0 | |
| | North America | 2 | 2.19 [1.69, 2.83] | 0 | | 2 | 4.76 [2.53, 8.97] | - | |
| | South America | - | - | - | | - | - | - | |
| Year of Publication | Publication ≤2010 | 4 | 4.49 [2.09, 9.62] | 63 | 0.80 | 1 | 1.60 [0.64, 4.00] | - | 0.48 |
| | Publication >2010 | 6 | 5.09 [2.76, 9.37] | 91 | | 3 | 2.28 [1.62, 3.21] | 76 | |
| **Small for gestational age** | | | | | | | | | |
| Location | Asia | 1 | 2.24 [1.28, 3.92] | - | 0.65 | - | - | - | 0.29 |
| | Australia | - | - | - | | - | - | - | |
| | Europe | 5 | 2.69 [1.37, 5.28] | 79 | | 1 | 1.29 [1.19, 1.40] | - | |
| | North America | 4 | 3.25 [1.87, 5.65] | 22 | | 2 | 2.63 [0.70, 9.88] | 92 | |
| | South America | - | - | - | | - | - | - | |
| Year of Publication | Publication ≤2010 | 5 | 5.37 [3.07, 9.39] | 17 | <0.0001 | 1 | 5.30 [2.80, 10.03] | - | <0.0001 |
| | Publication >2010 | 5 | 1.53 [1.25, 1.87] | 18 | | 2 | 1.29 [1.20, 1.40] | 0 | |

*For adjusted estimates we followed the author's definitions

## S4.3 Supplementary Figures S4.1-S4.24

### Forest plots and funnel plots of the association between CKD and adverse pregnancy outcomes (CKD vs no CKD comparison)

**Figure S4.1** Funnel plot of pre-eclampsia (crude estimates)

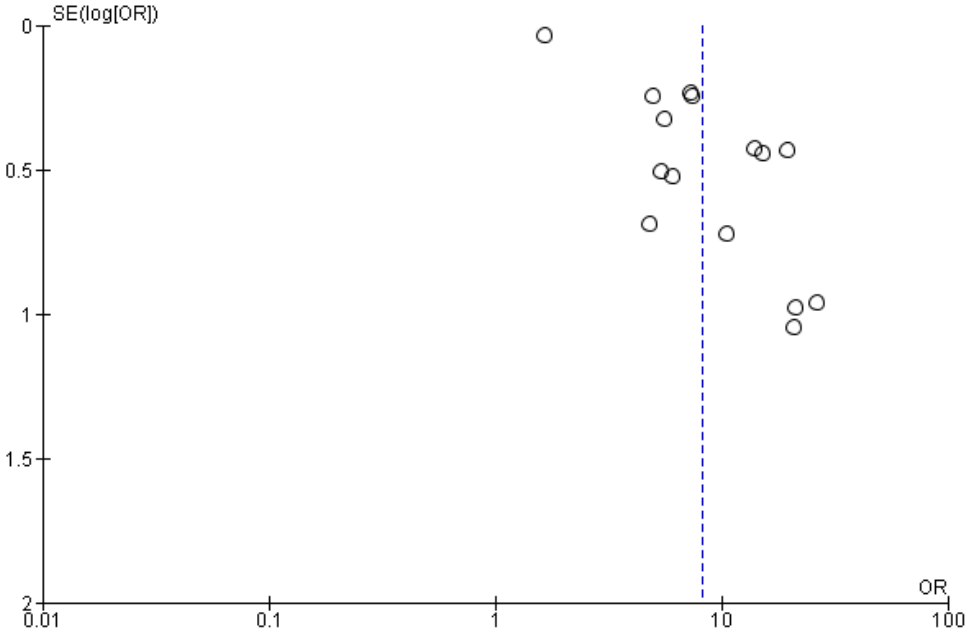



**Figure S4.2** Funnel plots of Caesarean section (crude estimates)

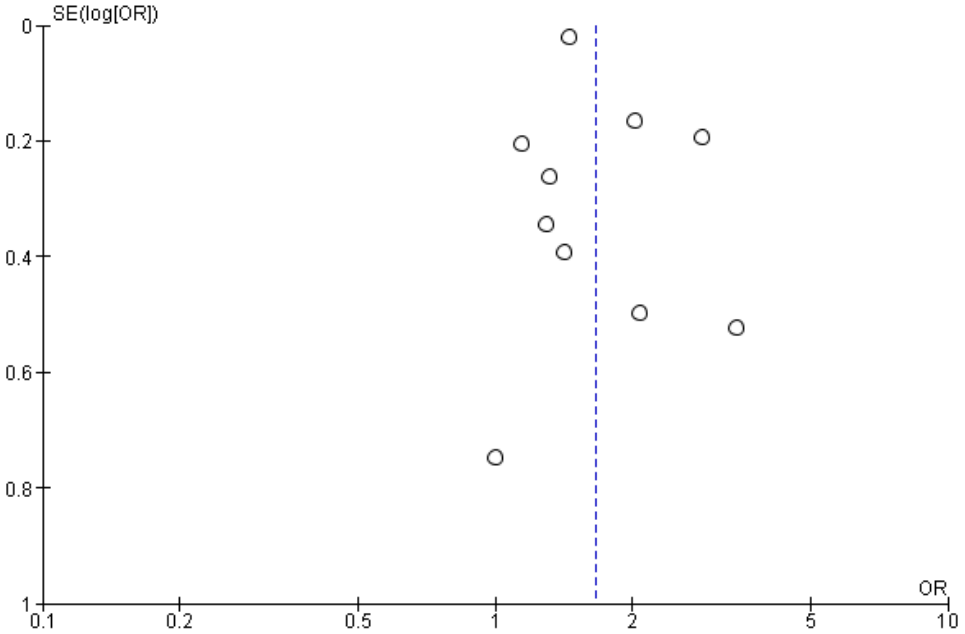


**Figure S4.3.** Funnel plot of preterm birth (crude estimates)

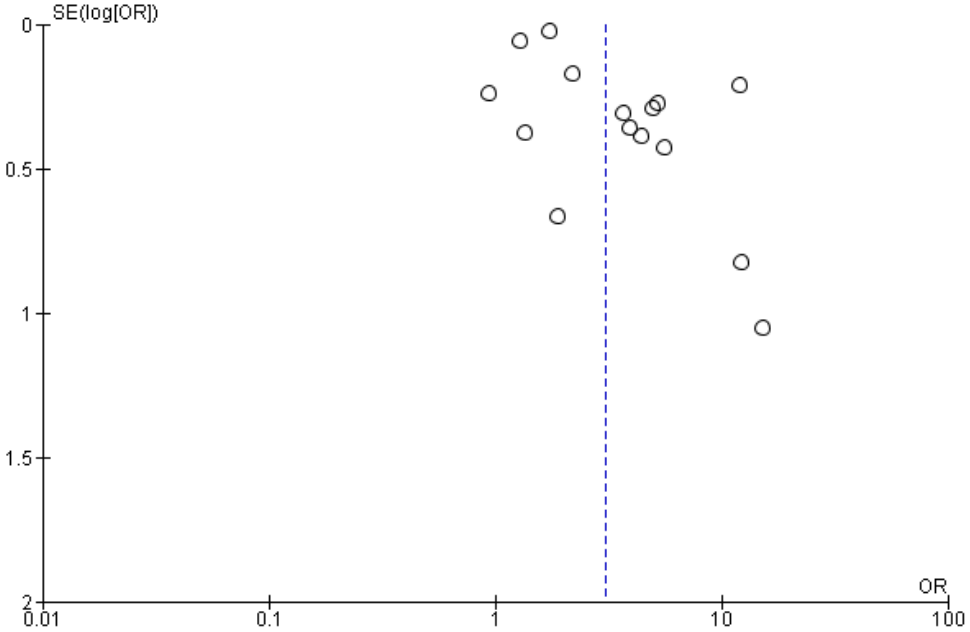



**Figure S4.4a** Forest plot of crude estimates for very preterm birth (<34 wk. gestation)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Kimmerle,1995 | 2.753 | 0.6885 | 6.7% | 15.69 [4.07, 60.49] | 1995 |
| Miodovnik,1996 | 0.967 | 0.4613 | 9.5% | 2.63 [1.06, 6.50] | 1996 |
| Ekbom, 2001 | 1.9072 | 0.4668 | 9.4% | 6.73 [2.70, 16.81] | 2001 |
| Jensen,2010 | 0.8755 | 0.3579 | 11.0% | 2.40 [1.19, 4.84] | 2010 |
| Wiles, 2015 | 2.1755 | 0.7321 | 6.2% | 8.81 [2.10, 36.98] | 2015 |
| Piccoli, 2017 | 3.0734 | 0.3671 | 10.8% | 21.62 [10.53, 44.39] | 2017 |
| Seah, 2020 | 1.4303 | 0.3685 | 10.8% | 4.18 [2.03, 8.61] | 2020 |
| Harel, 2020 | 0.7655 | 0.1382 | 13.7% | 2.15 [1.64, 2.82] | 2020 |
| Madej, 2020 | 2.6405 | 0.6004 | 7.7% | 14.02 [4.32, 45.48] | 2020 |
| Al Khalaf, 2021 | 0.6931 | 0.0595 | 14.3% | 2.00 [1.78, 2.25] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **4.85 [3.01, 7.80]** | |

Heterogeneity: Tau² = 0.41; Chi² = 71.18, df = 9 (P < 0.00001); I² = 87%
Test for overall effect: Z = 6.51 (P < 0.00001)

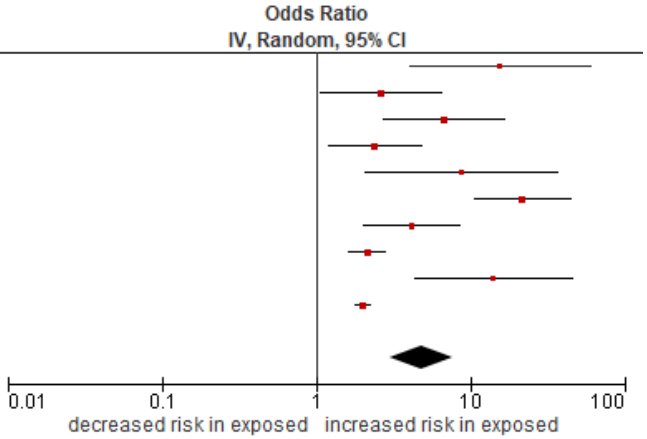



**Figure S4.4b** Forest plot of adjusted estimates for very preterm birth (<34 wk. gestation)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Jensen,2010 | 0.47 | 0.4675 | 8.8% | 1.60 [0.64, 4.00] | 2010 |
| Kendrick, 2015 | 1.5605 | 0.3233 | 15.2% | 4.76 [2.53, 8.97] | 2015 |
| Harel, 2020 | 0.7129 | 0.1435 | 32.9% | 2.04 [1.54, 2.70] | 2020 |
| Al Khalaf, 2021 | 0.6206 | 0.058 | 43.2% | 1.86 [1.66, 2.08] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **2.18 [1.61, 2.95]** | |

Heterogeneity: Tau² = 0.05; Chi² = 8.52, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 5.08 (P < 0.00001)

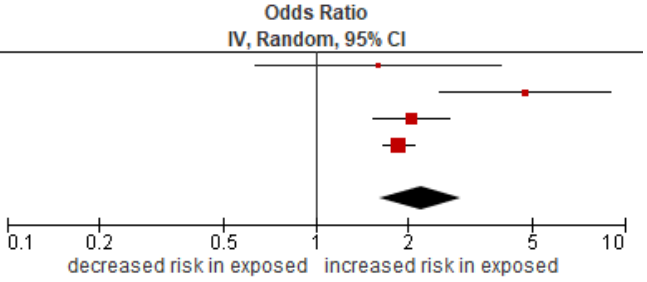


**Figure S4.4c** Funnel plot of very preterm birth (crude estimates)

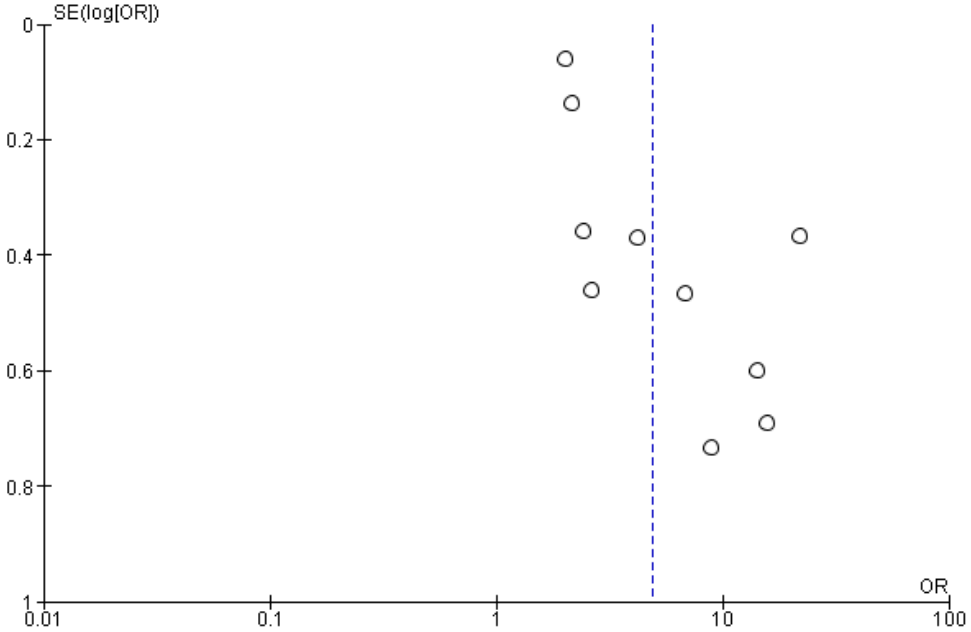



**Figure S4.5** Funnel plots of small for gestational age (crude estimates)

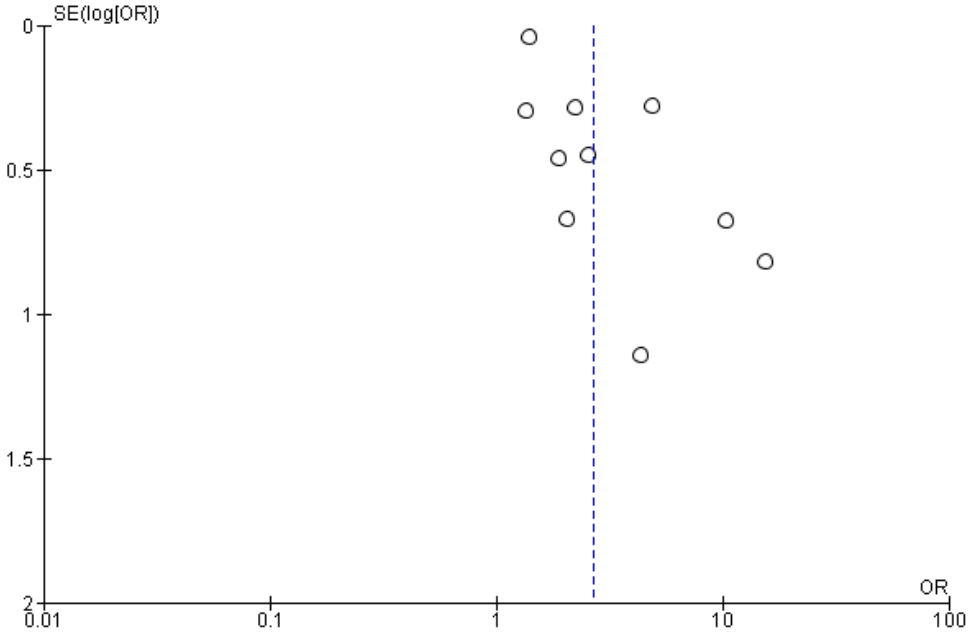


**Figure S4.6** Forest plot of crude estimates for miscarriage

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Holley, 1996 | 1.3828 | 0.8337 | 26.0% | 3.99 [0.78, 20.43] | 1996 |
| Wiles, 2015 | 1.8608 | 0.6164 | 32.3% | 6.43 [1.92, 21.52] | 2015 |
| Wu, 2016 | 0.0892 | 0.2914 | 41.8% | 1.09 [0.62, 1.94] | 2016 |
| **Total (95% CI)** | | | **100.0%** | **2.71 [0.76, 9.62]** | |

Heterogeneity: Tau² = 0.92; Chi² = 7.98, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 1.54 (P = 0.12)

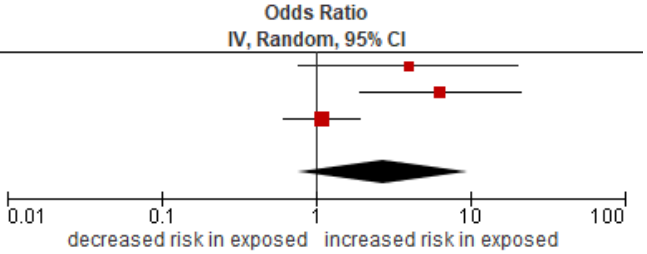



**Figure S4.7**a Forest plot of crude estimates for stillbirth death

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Patel, 2015 | 1.9315 | 0.0877 | 33.7% | 6.90 [5.81, 8.19] | 2015 |
| Harel, 2020 | 0.5247 | 0.2099 | 32.7% | 1.69 [1.12, 2.55] | 2020 |
| Al Khalaf, 2021 | 0.239 | 0.1069 | 33.6% | 1.27 [1.03, 1.57] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **2.47 [0.72, 8.47]** | |

Heterogeneity: Tau² = 1.17; Chi² = 160.66, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.43 (P = 0.15)

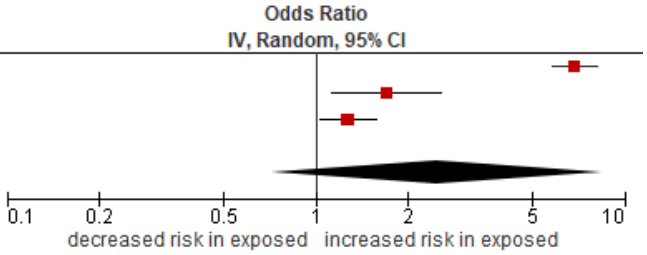



**Figure S4.7**b Forest plot of adjusted estimates for stillbirth death

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Patel, 2015 | 0.9322 | 0.0971 | 34.9% | 2.54 [2.10, 3.07] | 2015 |
| Harel, 2020 | 0.4511 | 0.2101 | 30.4% | 1.57 [1.04, 2.37] | 2020 |
| Al Khalaf, 2021 | 0.1484 | 0.1019 | 34.8% | 1.16 [0.95, 1.42] | 2021 |
| **Total (95% CI)** | | | **100.0%** | **1.67 [0.96, 2.92]** | |

Heterogeneity: Tau² = 0.22; Chi² = 31.25, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.81 (P = 0.07)

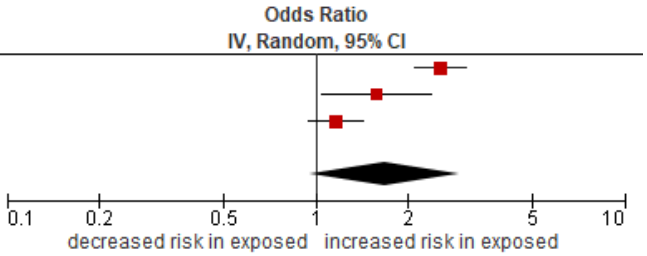
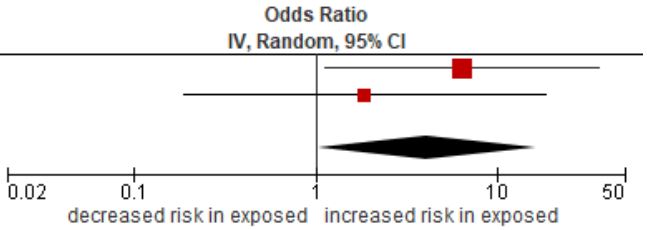



**Figure S4.8** Forest plot of crude estimates for perinatal death

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Miodovnik,1996 | 1.8533 | 0.8839 | 63.6% | 6.38 [1.13, 36.08] | 1996 |
| Ekbom, 2001 | 0.6162 | 1.1688 | 36.4% | 1.85 [0.19, 18.30] | 2001 |
| **Total (95% CI)** | | | **100.0%** | **4.07 [1.02, 16.20]** | |

Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.99 (P = 0.05)



## Forest plots of the association between CKD and adverse pregnancy outcomes (late vs early stages of CKD)

**Figure S4.9a.** Forest plot of crude estimates for pre-eclampsia

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.1.1 Glomerulonephritis** | | | | | |
| Madej, 2020 | 1.1451 | 0.6163 | 10.4% | 3.14 [0.94, 10.52] | 2020 |
| **Subtotal (95% CI)** | | | **10.4%** | **3.14 [0.94, 10.52]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 1.86 (P = 0.06) | | | | | |
| **2.1.2 Unspecified CKD** | | | | | |
| Bramham, 2011 | -0.2201 | 0.7065 | 8.6% | 0.80 [0.20, 3.20] | 2011 |
| Davidson, 2015 | 0.3857 | 0.5778 | 11.4% | 1.47 [0.47, 4.56] | 2015 |
| Wiles, 2015 | 0.4595 | 0.8643 | 6.3% | 1.58 [0.29, 8.61] | 2015 |
| Singh, 2015 | 2.1691 | 0.8715 | 6.2% | 8.75 [1.59, 48.29] | 2015 |
| Feng, 2015 | 0.1823 | 0.7958 | 7.1% | 1.20 [0.25, 5.71] | 2015 |
| Bharti, 2016 | 1.6205 | 0.5047 | 13.4% | 5.06 [1.88, 13.59] | 2016 |
| He, 2018 | 0.9471 | 0.4328 | 15.9% | 2.58 [1.10, 6.02] | 2018 |
| Leaños-Miranda, 2019 | 2.1518 | 0.5664 | 11.6% | 8.60 [2.83, 26.10] | 2019 |
| Madazli, 2021 | 0.8755 | 0.6805 | 9.1% | 2.40 [0.63, 9.11] | 2021 |
| **Subtotal (95% CI)** | | | **89.6%** | **2.71 [1.60, 4.60]** | |
| Heterogeneity: Tau² = 0.25; Chi² = 13.03, df = 8 (P = 0.11); I² = 39% | | | | | |
| Test for overall effect: Z = 3.69 (P = 0.0002) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.77 [1.73, 4.44]** | |
| Heterogeneity: Tau² = 0.18; Chi² = 13.06, df = 9 (P = 0.16); I² = 31% | | | | | |
| Test for overall effect: Z = 4.24 (P < 0.0001) | | | | | |
| Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0% | | | | | |

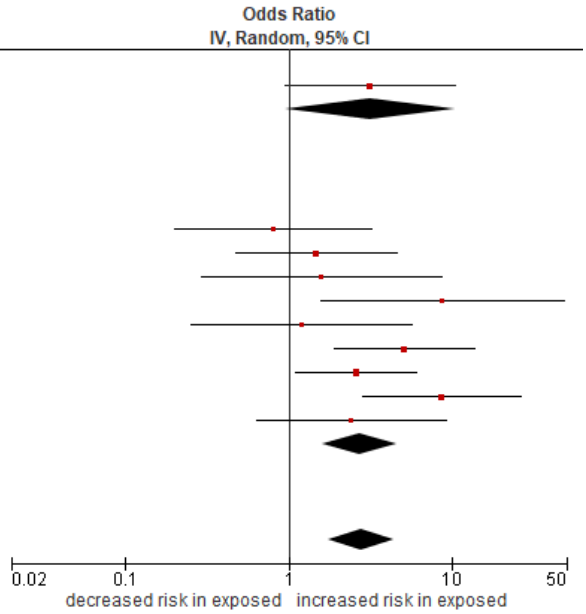



**Figure S4.9b** Funnel plot of pre-eclampsia (crude estimates)

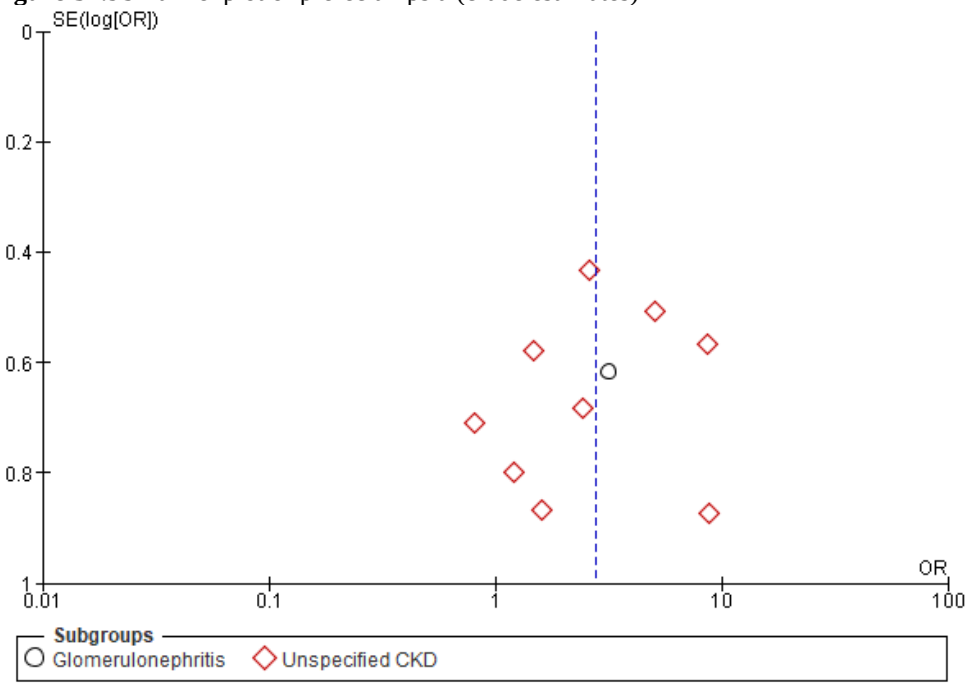


**Figure S4.10a** Forest plot of crude estimates Caesarean section

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.5.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | -0.5199 | 0.4191 | 16.3% | 0.59 [0.26, 1.35] | 2017 |
| Madej, 2020 | 0.7954 | 0.6171 | 9.2% | 2.22 [0.66, 7.43] | 2020 |
| **Subtotal (95% CI)** | | | **25.5%** | **1.06 [0.30, 3.82]** | |
| Heterogeneity: Tau² = 0.59; Chi² = 3.11, df = 1 (P = 0.08); I² = 68% | | | | | |
| Test for overall effect: Z = 0.09 (P = 0.93) | | | | | |
| **2.5.2 Diabetic CKD** | | | | | |
| Reece, 1988 | 0.2719 | 0.9338 | 4.5% | 1.31 [0.21, 8.18] | 1988 |
| **Subtotal (95% CI)** | | | **4.5%** | **1.31 [0.21, 8.18]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 0.29 (P = 0.77) | | | | | |
| **2.5.3 Unspecified CKD** | | | | | |
| Imbasciati, 2007 | 1.3815 | 0.6939 | 7.6% | 3.98 [1.02, 15.51] | 2007 |
| Bramham, 2011 | 0.4055 | 0.7032 | 7.4% | 1.50 [0.38, 5.95] | 2011 |
| Feng, 2015 | 0.098 | 0.7586 | 6.5% | 1.10 [0.25, 4.88] | 2015 |
| Davidson, 2015 | 0.5241 | 0.5601 | 10.7% | 1.69 [0.56, 5.06] | 2015 |
| Bharti, 2016 | 0.2469 | 0.4873 | 13.2% | 1.28 [0.49, 3.33] | 2016 |
| He, 2018 | 1.4823 | 0.5606 | 10.7% | 4.40 [1.47, 13.21] | 2018 |
| Wiles, 2020 | 0.2852 | 0.472 | 13.9% | 1.33 [0.53, 3.35] | 2020 |
| **Subtotal (95% CI)** | | | **70.0%** | **1.82 [1.19, 2.80]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 5.25, df = 6 (P = 0.51); I² = 0% | | | | | |
| Test for overall effect: Z = 2.75 (P = 0.006) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **1.53 [1.02, 2.30]** | |
| Heterogeneity: Tau² = 0.09; Chi² = 11.34, df = 9 (P = 0.25); I² = 21% | | | | | |
| Test for overall effect: Z = 2.06 (P = 0.04) | | | | | |
| Test for subgroup differences: Chi² = 0.70, df = 2 (P = 0.70), I² = 0% | | | | | |

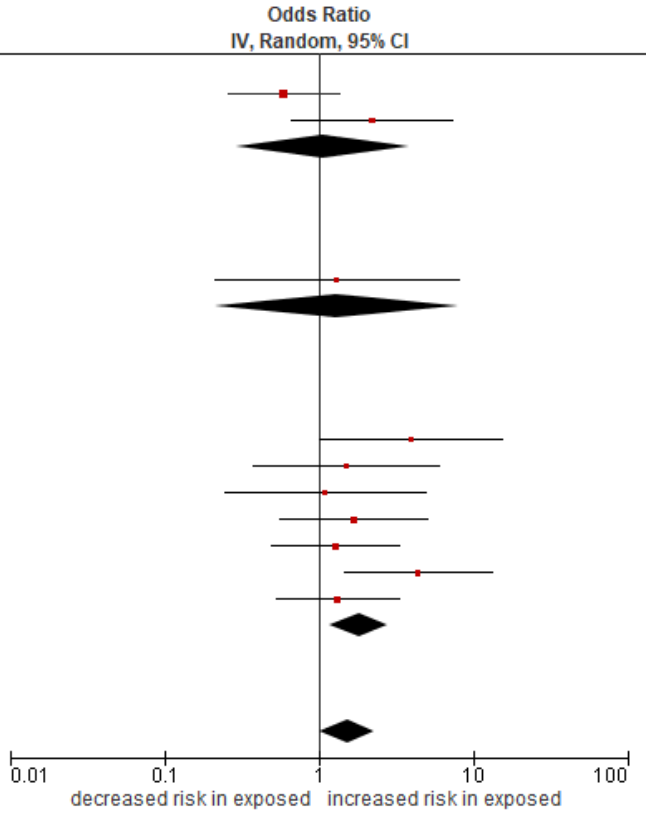



**Figure S4.10b** Funnel plot of Caesarean section (crude estimates)

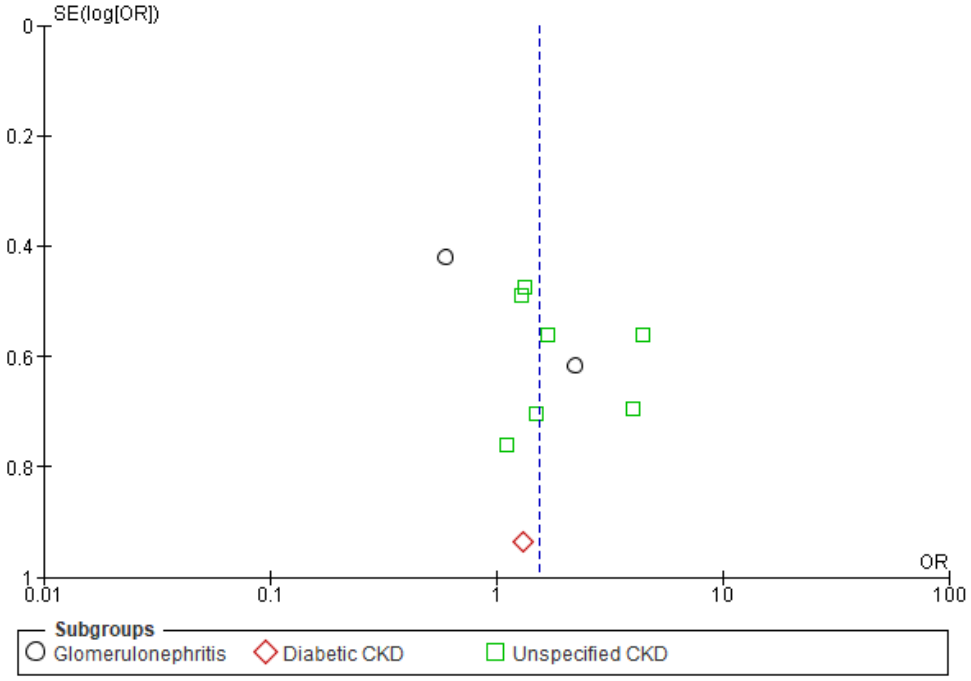


**Figure S4.11a** Forest plot of crude estimates for preterm birth (<37 wk. gestation)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.2.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | 1.204 | 0.3829 | 20.6% | 3.33 [1.57, 7.06] | 2017 |
| Madej, 2020 | 1.5581 | 0.6529 | 7.1% | 4.75 [1.32, 17.08] | 2020 |
| **Subtotal (95% CI)** | | | **27.8%** | **3.65 [1.91, 6.97]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0% | | | | | |
| Test for overall effect: Z = 3.92 (P < 0.0001) | | | | | |
| **2.2.2 Diabetic CKD** | | | | | |
| Reece, 1988 | 0.3159 | 0.8595 | 4.1% | 1.37 [0.25, 7.39] | 1988 |
| **Subtotal (95% CI)** | | | **4.1%** | **1.37 [0.25, 7.39]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 0.37 (P = 0.71) | | | | | |
| **2.2.3 Unspecified CKD** | | | | | |
| Imbasciati, 2007 | 1.0498 | 0.6121 | 8.1% | 2.86 [0.86, 9.48] | 2007 |
| Bramham, 2011 | 1.6094 | 0.8756 | 3.9% | 5.00 [0.90, 27.81] | 2011 |
| Wiles, 2015 | 1.2809 | 0.7674 | 5.1% | 3.60 [0.80, 16.20] | 2015 |
| Singh, 2015 | 0.9132 | 0.6933 | 6.3% | 2.49 [0.64, 9.70] | 2015 |
| Feng, 2015 | 2.4587 | 1.1206 | 2.4% | 11.69 [1.30, 105.11] | 2015 |
| Davidson, 2015 | 1.5686 | 0.6646 | 6.9% | 4.80 [1.30, 17.66] | 2015 |
| Bharti, 2016 | 1.441 | 0.5019 | 12.0% | 4.22 [1.58, 11.30] | 2016 |
| He, 2018 | 1.7492 | 0.4299 | 16.4% | 5.75 [2.48, 13.35] | 2018 |
| Wiles, 2020 | 2.3768 | 0.6567 | 7.0% | 10.77 [2.97, 39.01] | 2020 |
| **Subtotal (95% CI)** | | | **68.2%** | **4.77 [3.16, 7.21]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 4.14, df = 8 (P = 0.84); I² = 0% | | | | | |
| Test for overall effect: Z = 7.42 (P < 0.00001) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **4.21 [2.99, 5.92]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 6.60, df = 11 (P = 0.83); I² = 0% | | | | | |
| Test for overall effect: Z = 8.26 (P < 0.00001) | | | | | |
| Test for subgroup differences: Chi² = 2.24, df = 2 (P = 0.33), I² = 10.9% | | | | | |

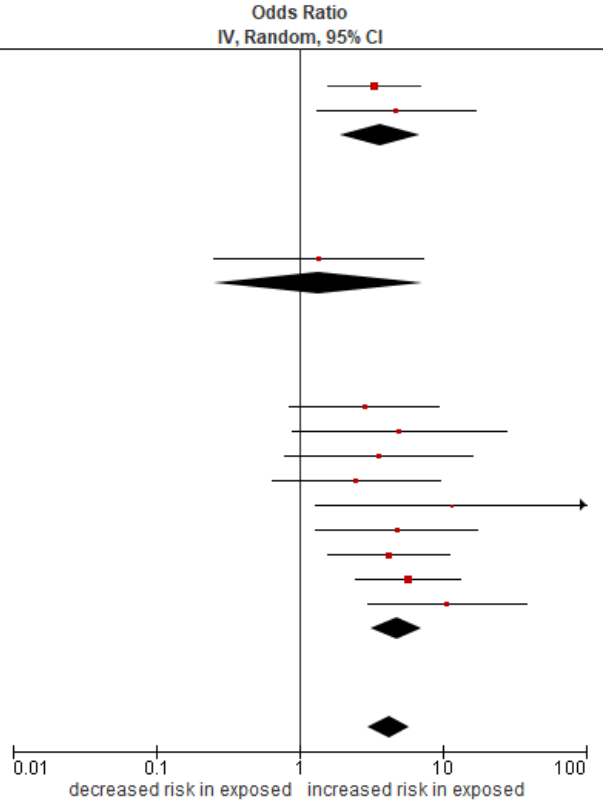



**Figure S4.11b** Funnel plot of preterm birth (<37 wk. gestation)

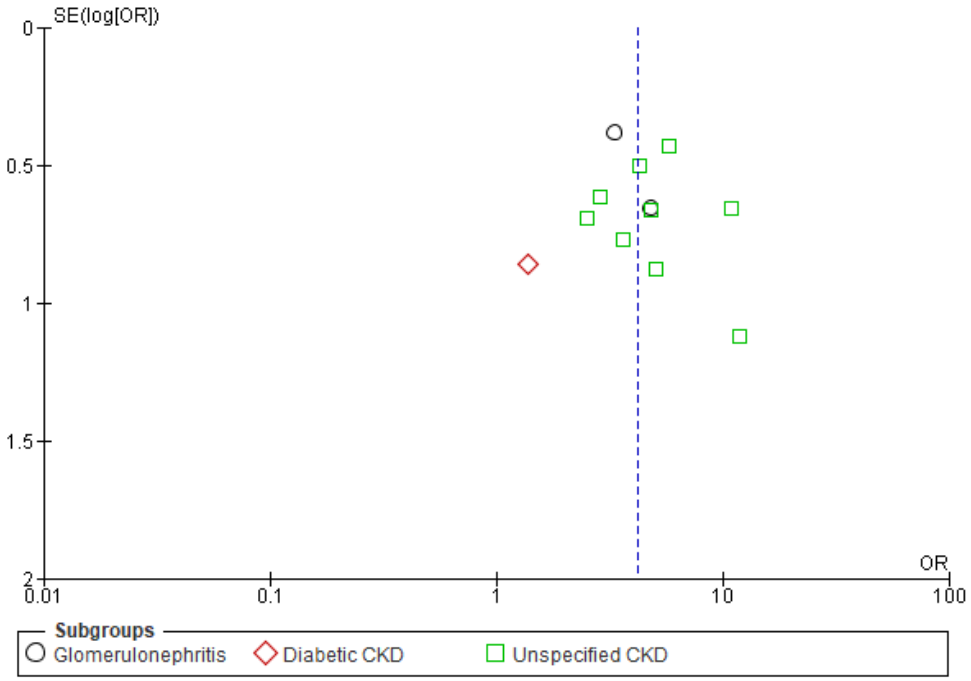


**Figure S4.12a** Forest plot of crude estimates for very preterm birth (<34 wk. gestation)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.4.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | 1.4295 | 0.5077 | 17.1% | 4.18 [1.54, 11.30] | 2017 |
| Madej, 2020 | 1.0696 | 0.7159 | 8.6% | 2.91 [0.72, 11.85] | 2020 |
| **Subtotal (95% CI)** | | | **25.7%** | **3.70 [1.64, 8.34]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0% | | | | | |
| Test for overall effect: Z = 3.16 (P = 0.002) | | | | | |
| **2.4.2 Unspecified CKD** | | | | | |
| Bramham, 2011 | 0.4745 | 0.7079 | 8.8% | 1.61 [0.40, 6.44] | 2011 |
| Wiles, 2015 | 0.7419 | 1.0713 | 3.8% | 2.10 [0.26, 17.14] | 2015 |
| Bharti, 2016 | 0.7178 | 0.594 | 12.5% | 2.05 [0.64, 6.57] | 2016 |
| He, 2018 | 1.4406 | 0.5148 | 16.6% | 4.22 [1.54, 11.58] | 2018 |
| Leaños-Miranda, 2019 | 1.5476 | 0.5498 | 14.6% | 4.70 [1.60, 13.81] | 2019 |
| Wiles, 2020 | 0.9651 | 0.495 | 18.0% | 2.63 [0.99, 6.93] | 2020 |
| **Subtotal (95% CI)** | | | **74.3%** | **2.93 [1.82, 4.72]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 2.47, df = 5 (P = 0.78); I² = 0% | | | | | |
| Test for overall effect: Z = 4.41 (P < 0.0001) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **3.11 [2.06, 4.69]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 7 (P = 0.90); I² = 0% | | | | | |
| Test for overall effect: Z = 5.41 (P < 0.00001) | | | | | |
| Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.63), I² = 0% | | | | | |

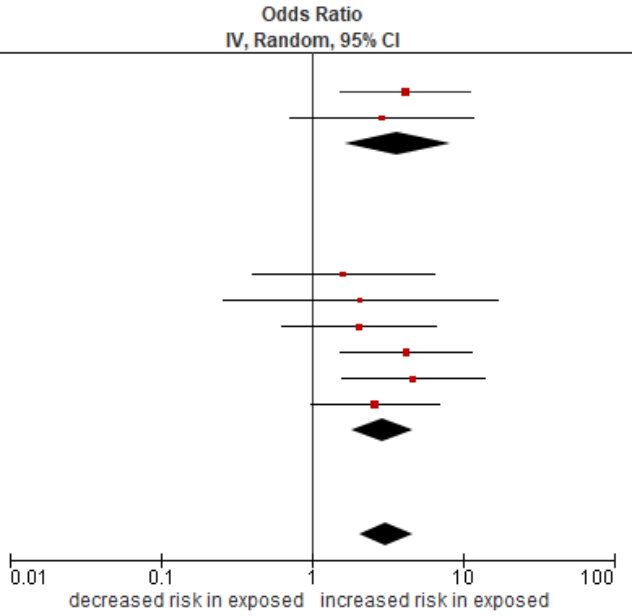



**Figure S4.12**b Forest plot of adjusted estimates for very preterm birth (<34 wk. gestation)

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.16.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | 1.1314 | 0.5475 | 56.9% | 3.10 [1.06, 9.07] | 2017 |
| **Subtotal (95% CI)** | | | **56.9%** | **3.10 [1.06, 9.07]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 2.07 (P = 0.04) | | | | | |
| **2.16.2 Unspesified CKD** | | | | | |
| Leaños-Miranda, 2019 | 1.1277 | 0.6291 | 43.1% | 3.09 [0.90, 10.60] | 2019 |
| **Subtotal (95% CI)** | | | **43.1%** | **3.09 [0.90, 10.60]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 1.79 (P = 0.07) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **3.10 [1.38, 6.95]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0% | | | | | |
| Test for overall effect: Z = 2.74 (P = 0.006) | | | | | |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0% | | | | | |

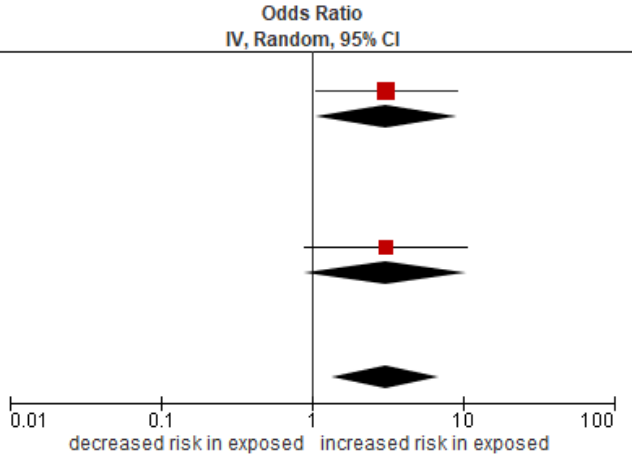


**Figure S4.13a** Forest plot of crude estimates for small for gestational age

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.3.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | -0.1149 | 0.5906 | 10.1% | 0.89 [0.28, 2.84] | 2017 |
| **Subtotal (95% CI)** | | | **10.1%** | **0.89 [0.28, 2.84]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 0.19 (P = 0.85) | | | | | |
| **2.3.2 Diabetic CKD** | | | | | |
| Reece, 1988 | 0.7985 | 1.0247 | 5.8% | 2.22 [0.30, 16.56] | 1988 |
| **Subtotal (95% CI)** | | | **5.8%** | **2.22 [0.30, 16.56]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 0.78 (P = 0.44) | | | | | |
| **2.3.3 Unspecified CKD** | | | | | |
| Imbasciati, 2007 | 0.539 | 0.5996 | 10.0% | 1.71 [0.53, 5.55] | 2007 |
| Bramham, 2011 | -0.8473 | 0.6986 | 8.8% | 0.43 [0.11, 1.69] | 2011 |
| Davidson, 2015 | 0.9067 | 0.58 | 10.2% | 2.48 [0.79, 7.72] | 2015 |
| Feng, 2015 | 2.1691 | 0.8577 | 7.2% | 8.75 [1.63, 47.00] | 2015 |
| Wiles, 2015 | -0.568 | 0.9086 | 6.7% | 0.57 [0.10, 3.36] | 2015 |
| Bharti, 2016 | 1.9148 | 0.5222 | 11.0% | 6.79 [2.44, 18.88] | 2016 |
| Leaños-Miranda, 2019 | 1.9879 | 0.5788 | 10.3% | 7.30 [2.35, 22.70] | 2019 |
| Wiles, 2020 | 1.7337 | 0.5229 | 11.0% | 5.66 [2.03, 15.78] | 2020 |
| Madazli, 2021 | 0.6785 | 0.6891 | 8.9% | 1.97 [0.51, 7.61] | 2021 |
| **Subtotal (95% CI)** | | | **84.1%** | **2.76 [1.42, 5.38]** | |
| Heterogeneity: Tau² = 0.62; Chi² = 20.30, df = 8 (P = 0.009); I² = 61% | | | | | |
| Test for overall effect: Z = 2.98 (P = 0.003) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.43 [1.33, 4.46]** | |
| Heterogeneity: Tau² = 0.60; Chi² = 24.20, df = 10 (P = 0.007); I² = 59% | | | | | |
| Test for overall effect: Z = 2.88 (P = 0.004) | | | | | |
| Test for subgroup differences: Chi² = 2.75, df = 2 (P = 0.25), I² = 27.3% | | | | | |

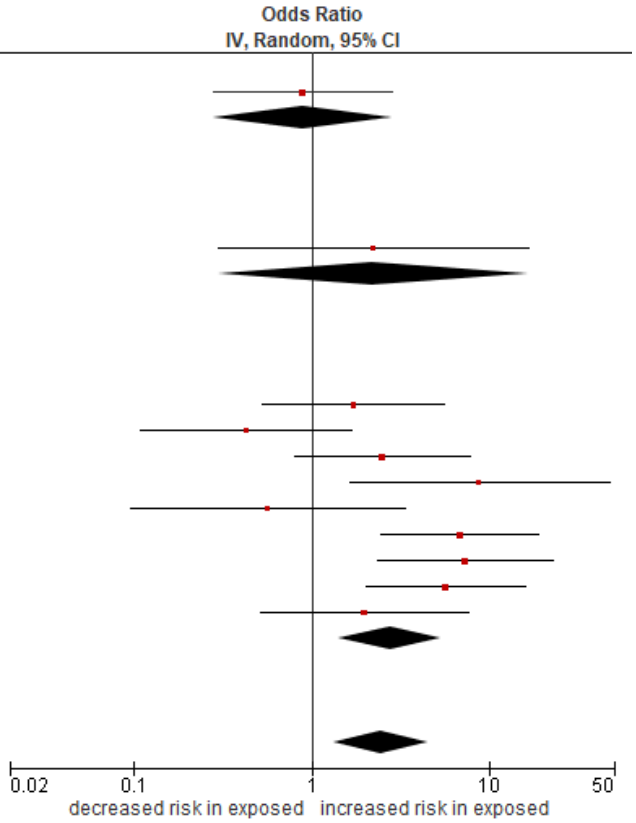



**Figure S4.13b** Forest plot of adjusted estimates for small for gestational age

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.14.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | -0.2231 | 0.636 | 33.2% | 0.80 [0.23, 2.78] | 2017 |
| **Subtotal (95% CI)** | | | **33.2%** | **0.80 [0.23, 2.78]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 0.35 (P = 0.73) | | | | | |
| **2.14.2 Unspesified CKD** | | | | | |
| Leaños-Miranda, 2019 | 1.4816 | 0.6629 | 32.0% | 4.40 [1.20, 16.13] | 2019 |
| Wiles, 2020 | 1.3938 | 0.6014 | 34.8% | 4.03 [1.24, 13.10] | 2020 |
| **Subtotal (95% CI)** | | | **66.8%** | **4.19 [1.75, 10.04]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0% | | | | | |
| Test for overall effect: Z = 3.22 (P = 0.001) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.42 [0.82, 7.15]** | |
| Heterogeneity: Tau² = 0.51; Chi² = 4.56, df = 2 (P = 0.10); I² = 56% | | | | | |
| Test for overall effect: Z = 1.60 (P = 0.11) | | | | | |
| Test for subgroup differences: Chi² = 4.55, df = 1 (P = 0.03), I² = 78.0% | | | | | |

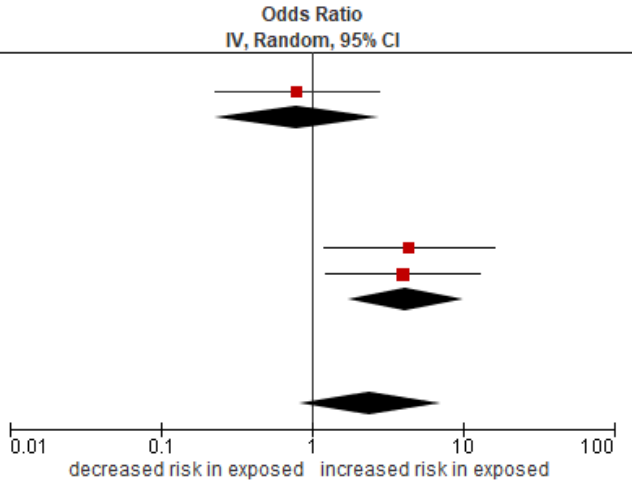


**Figure S4.13c** Funnel plots of small for gestational age

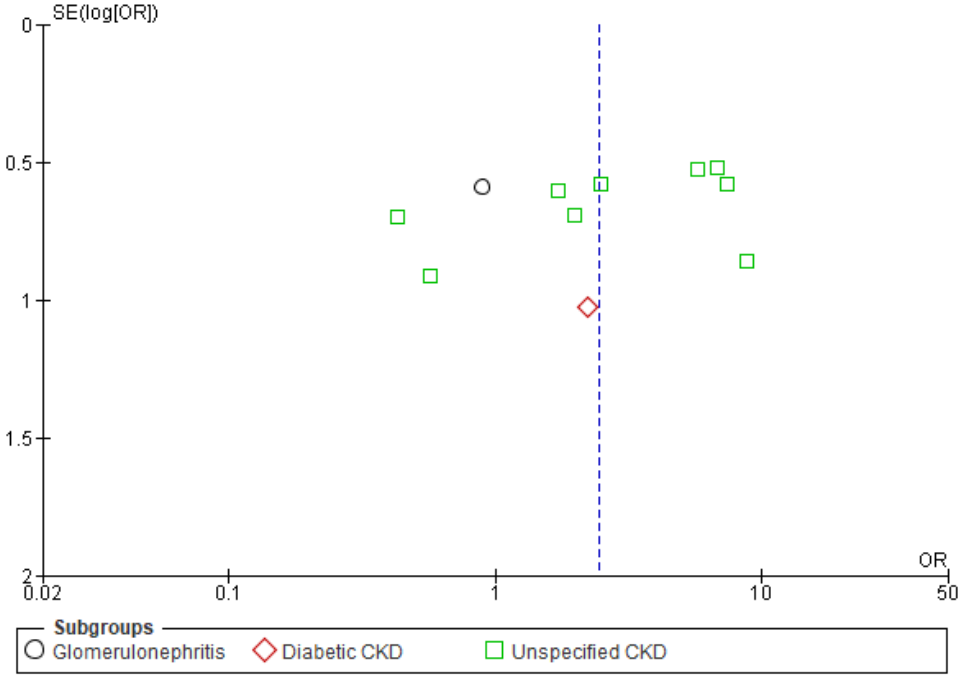
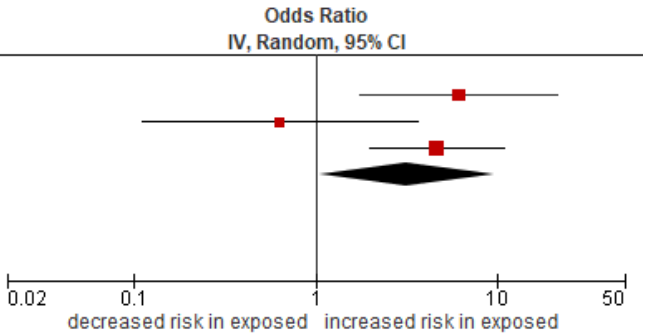



**Figure S4.14.** Forest plot of crude estimates for low birthweight

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.11.2 Unspecified CKD** | | | | | |
| Imbasciati, 2007 | 1.8124 | 0.6409 | 33.2% | 6.13 [1.74, 21.51] | 2007 |
| Singh, 2015 | -0.4537 | 0.8921 | 23.7% | 0.64 [0.11, 3.65] | 2015 |
| He, 2018 | 1.5335 | 0.4364 | 43.0% | 4.63 [1.97, 10.90] | 2018 |
| **Subtotal (95% CI)** | | | **100.0%** | **3.17 [1.05, 9.62]** | |

Heterogeneity: Tau² = 0.55; Chi² = 4.78, df = 2 (P = 0.09); I² = 58%
Test for overall effect: Z = 2.04 (P = 0.04)

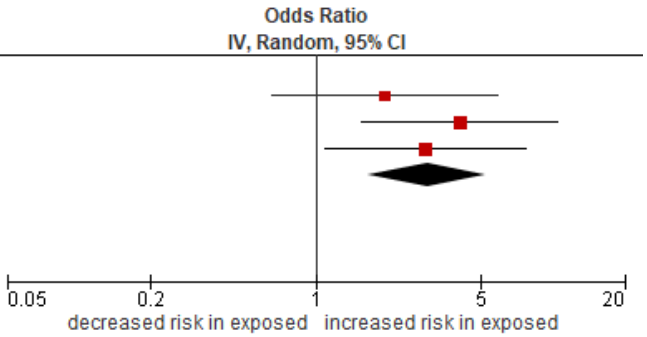



Test for subgroup differences: Not applicable

**Figure S4.15** Forest plot of crude estimates for neonatal intensive care unit admission

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.12.1 Unspecified CKD** | | | | | |
| Davidson, 2015 | 0.6731 | 0.5587 | 27.8% | 1.96 [0.66, 5.86] | 2015 |
| Bharti, 2016 | 1.3981 | 0.4839 | 37.1% | 4.05 [1.57, 10.45] | 2016 |
| Wiles, 2020 | 1.0657 | 0.4973 | 35.1% | 2.90 [1.10, 7.69] | 2020 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.94 [1.65, 5.24]** | |

Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 3.66 (P = 0.0002)




Test for subgroup differences: Not applicable

**Figure S4.16** Forest plot of crude estimates for stillbirth

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.7.1 Diabetic CKD** | | | | | |
| Reece, 1988 | 1.1451 | 1.4793 | 8.7% | 3.14 [0.17, 57.08] | 1988 |
| **Subtotal (95% CI)** | | | **8.7%** | **3.14 [0.17, 57.08]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 0.77 (P = 0.44) | | | | | |
| **2.7.2 Unspecified CKD** | | | | | |
| Singh, 2015 | 1.361 | 0.6452 | 45.7% | 3.90 [1.10, 13.81] | 2015 |
| Davidson, 2015 | 0.734 | 0.912 | 22.9% | 2.08 [0.35, 12.45] | 2015 |
| Feng, 2015 | 1.3545 | 1.4688 | 8.8% | 3.87 [0.22, 68.94] | 2015 |
| Madazli, 2021 | 0.8824 | 1.1716 | 13.9% | 2.42 [0.24, 24.02] | 2021 |
| **Subtotal (95% CI)** | | | **91.3%** | **3.10 [1.27, 7.58]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 3 (P = 0.94); I² = 0% | | | | | |
| Test for overall effect: Z = 2.48 (P = 0.01) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **3.10 [1.32, 7.29]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 4 (P = 0.98); I² = 0% | | | | | |
| Test for overall effect: Z = 2.59 (P = 0.009) | | | | | |
| Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0% | | | | | |

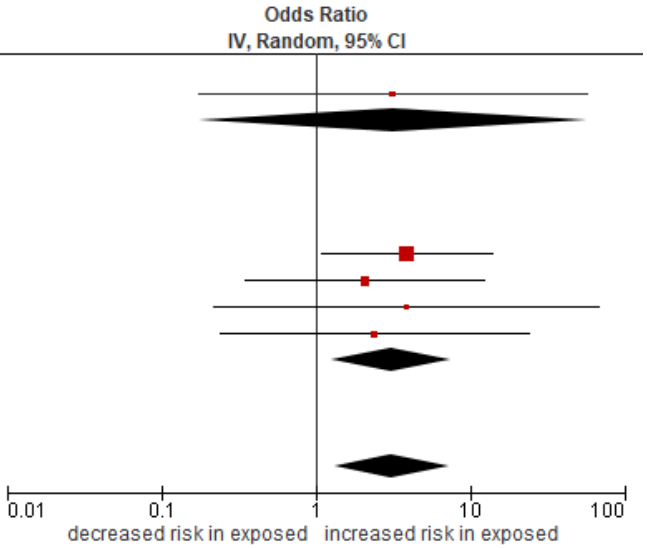



**Figure S4.17** Forest plot of crude estimates for neonatal death

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.15.2 Unspecified CKD** | | | | | |
| Feng, 2015 | 0.6286 | 1.2878 | 14.9% | 1.87 [0.15, 23.40] | 2015 |
| Leaños-Miranda, 2019 | 2.5572 | 0.7352 | 45.8% | 12.90 [3.05, 54.50] | 2019 |
| Madazli, 2021 | 1.6376 | 0.7943 | 39.3% | 5.14 [1.08, 24.40] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **6.74 [2.54, 17.88]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 2 (P = 0.39); I² = 0% | | | | | |
| Test for overall effect: Z = 3.83 (P = 0.0001) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |

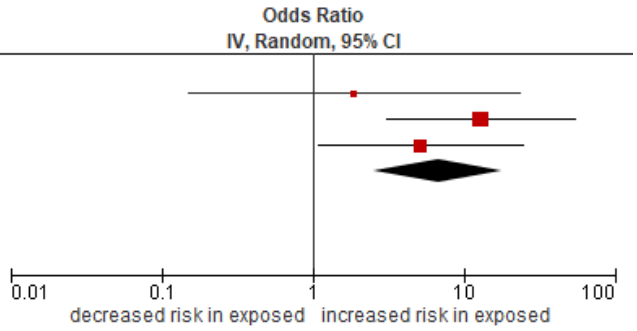
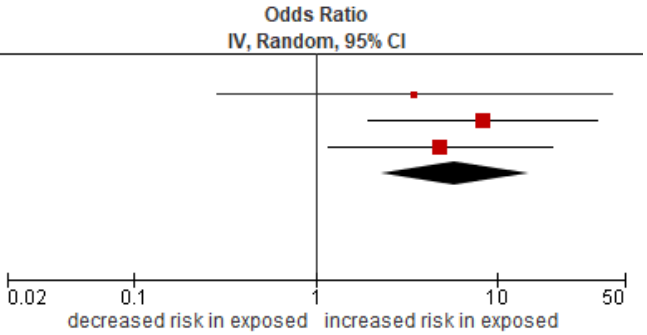



**Figure S4.18** Forest plot of crude estimates for perinatal death

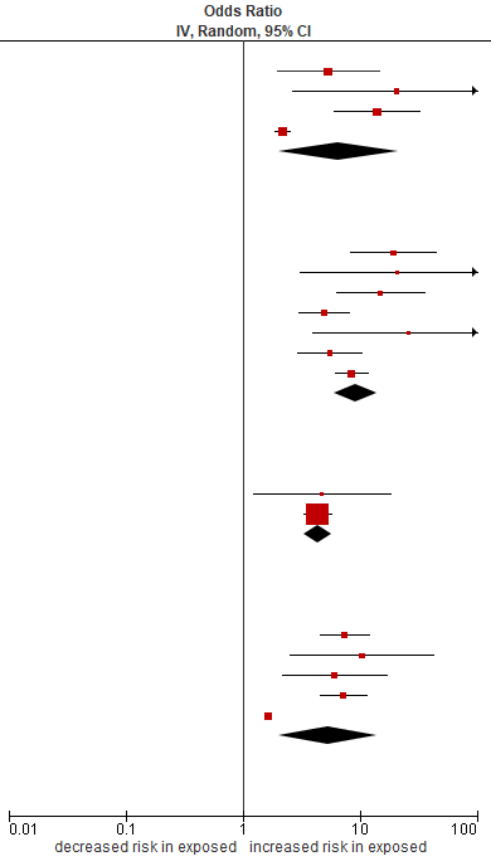
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **2.17.1 Unspecified CKD** | | | | | |
| Bramham, 2011 | 1.2528 | 1.2771 | 14.1% | 3.50 [0.29, 42.77] | 2011 |
| He, 2018 | 2.122 | 0.7407 | 41.8% | 8.35 [1.95, 35.65] | 2018 |
| Madazli, 2021 | 1.5787 | 0.7212 | 44.1% | 4.85 [1.18, 19.93] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **5.81 [2.27, 14.86]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 2 (P = 0.79); I² = 0% | | | | | |
| Test for overall effect: Z = 3.67 (P = 0.0002) | | | | | |
| Test for subgroup differences: Not applicable | | | | | |



## Forest plots of the effect of cause of CKD on adverse pregnancy outcomes (compared to no CKD)

**Figure S19.1** Forest plot of crude estimates for pre-eclampsia

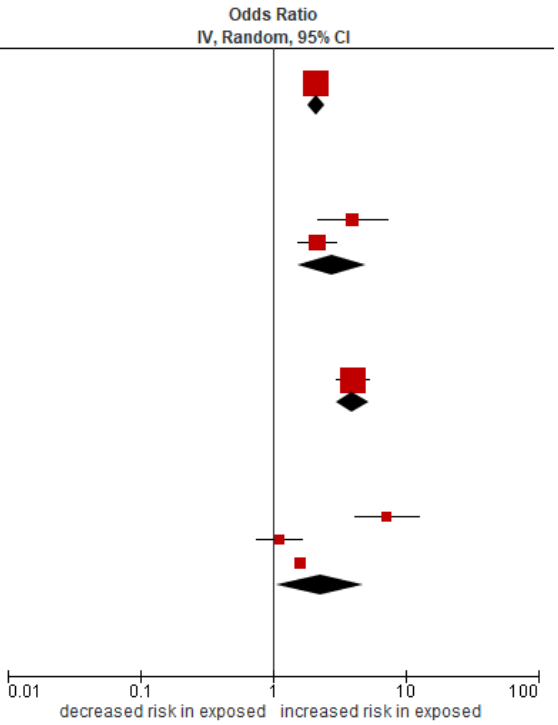
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **3.1.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | 1.6785 | 0.5099 | 25.6% | 5.36 [1.97, 14.55] | 2017 |
| Li, 2018 | 3.0296 | 1.0465 | 16.0% | 20.69 [2.66, 160.89] | 2018 |
| Madej, 2020 | 2.6391 | 0.4262 | 27.1% | 14.00 [6.07, 32.28] | 2020 |
| Al Khalaf, 2021 | 0.7793 | 0.0728 | 31.3% | 2.18 [1.89, 2.51] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **6.52 [2.02, 21.05]** | |
| Heterogeneity: Tau² = 1.14; Chi² = 25.53, df = 3 (P < 0.0001); I² = 88% | | | | | |
| Test for overall effect: Z = 3.13 (P = 0.002) | | | | | |
| **3.1.2 Diabetic CKD** | | | | | |
| Miodovnik,1996 | 2.964 | 0.4327 | 13.5% | 19.38 [8.30, 45.24] | 1996 |
| Biesenbach, 2000 | 3.0445 | 0.9759 | 4.1% | 21.00 [3.10, 142.20] | 2000 |
| Ekbom, 2001 | 2.7133 | 0.4436 | 13.1% | 15.08 [6.32, 35.97] | 2001 |
| Jensen,2010 | 1.5998 | 0.2485 | 21.5% | 4.95 [3.04, 8.06] | 2010 |
| Young, 2011 | 3.2677 | 0.9624 | 4.2% | 26.25 [3.98, 173.12] | 2011 |
| Seah, 2020 | 1.7156 | 0.3234 | 17.9% | 5.56 [2.95, 10.48] | 2020 |
| Al Khalaf, 2021 | 2.1342 | 0.1646 | 25.6% | 8.45 [6.12, 11.67] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **9.19 [6.05, 13.98]** | |
| Heterogeneity: Tau² = 0.15; Chi² = 13.81, df = 6 (P = 0.03); I² = 57% | | | | | |
| Test for overall effect: Z = 10.38 (P < 0.00001) | | | | | |
| **3.1.3 Polycystic kidney disease** | | | | | |
| Wu, 2016 | 1.5606 | 0.6906 | 4.0% | 4.76 [1.23, 18.43] | 2016 |
| Al Khalaf, 2021 | 1.4679 | 0.1413 | 96.0% | 4.34 [3.29, 5.73] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **4.36 [3.32, 5.71]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0% | | | | | |
| Test for overall effect: Z = 10.63 (P < 0.00001) | | | | | |
| **3.1.4 Any CKD** | | | | | |
| Fink, 1998 | 2.0005 | 0.2476 | 21.7% | 7.39 [4.55, 12.01] | 1998 |
| Trevisan, 2004 | 2.3461 | 0.722 | 15.4% | 10.44 [2.54, 43.00] | 2004 |
| Wiles, 2015 | 1.7993 | 0.5227 | 18.2% | 6.05 [2.17, 16.84] | 2015 |
| Tsuchiyama, 2017 | 1.979 | 0.2345 | 21.8% | 7.24 [4.57, 11.46] | 2017 |
| Al Khalaf, 2021 | 0.4947 | 0.0354 | 22.9% | 1.64 [1.53, 1.76] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **5.30 [2.02, 13.88]** | |
| Heterogeneity: Tau² = 1.05; Chi² = 85.58, df = 4 (P < 0.00001); I² = 95% | | | | | |
| Test for overall effect: Z = 3.39 (P = 0.0007) | | | | | |




Test for subgroup differences: Chi² = 8.69, df = 3 (P = 0.03), I² = 65.5%

**Figure 19.2** Forest plot of adjusted estimates for pre-eclampsia

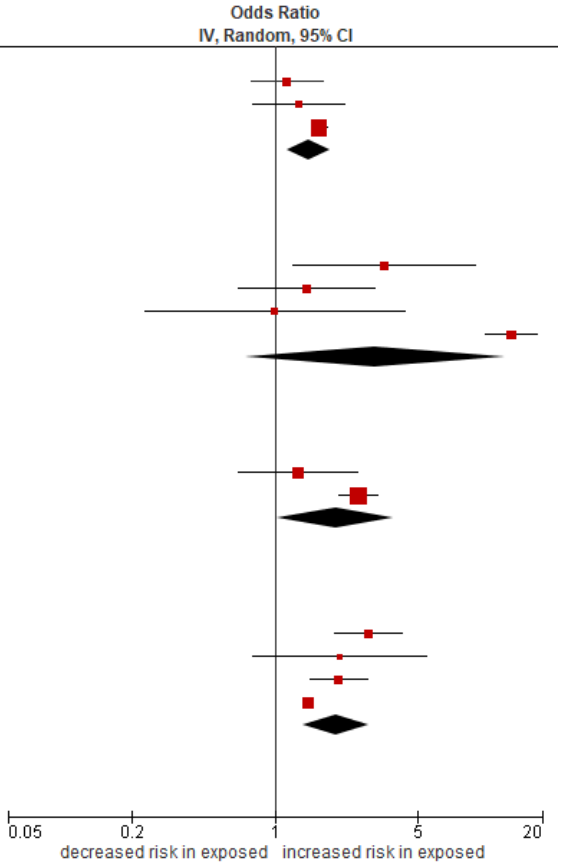
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **1.13.1 Glomerulonephritis** | | | | | |
| Al Khalaf, 2021 | 0.7561 | 0.0747 | 100.0% | 2.13 [1.84, 2.47] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.13 [1.84, 2.47]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 10.12 (P < 0.00001) | | | | | |
| **1.13.2 Diabetic CKD** | | | | | |
| Jensen,2010 | 1.3863 | 0.305 | 41.5% | 4.00 [2.20, 7.27] | 2010 |
| Al Khalaf, 2021 | 0.7747 | 0.172 | 58.5% | 2.17 [1.55, 3.04] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.80 [1.55, 5.05]** | |
| Heterogeneity: Tau² = 0.13; Chi² = 3.05, df = 1 (P = 0.08); I² = 67% | | | | | |
| Test for overall effect: Z = 3.41 (P = 0.0006) | | | | | |
| **1.13.3 Polycystic kidney disease** | | | | | |
| Al Khalaf, 2021 | 1.3813 | 0.1476 | 100.0% | 3.98 [2.98, 5.32] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **3.98 [2.98, 5.32]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 9.36 (P < 0.00001) | | | | | |
| **1.13.4 Unspecified CKD** | | | | | |
| Fink, 1998 | 1.9804 | 0.2782 | 30.7% | 7.25 [4.20, 12.50] | 1998 |
| Kendrick, 2015 | 0.1222 | 0.2024 | 33.1% | 1.13 [0.76, 1.68] | 2015 |
| Al Khalaf, 2021 | 0.4762 | 0.0327 | 36.3% | 1.61 [1.51, 1.72] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.27 [1.06, 4.87]** | |
| Heterogeneity: Tau² = 0.42; Chi² = 32.17, df = 2 (P < 0.00001); I² = 94% | | | | | |
| Test for overall effect: Z = 2.11 (P = 0.04) | | | | | |




Test for subgroup differences: Chi² = 14.54, df = 3 (P = 0.002), I² = 79.4%

**Figure S4.20a** Forest plot of crude estimates for Caesarean section

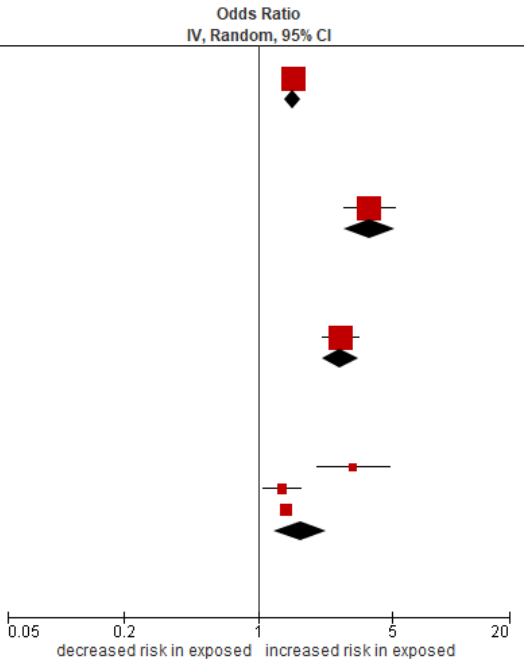
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **1.5.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | 0.1308 | 0.2046 | 23.0% | 1.14 [0.76, 1.70] | 2017 |
| Madej, 2020 | 0.2711 | 0.262 | 16.3% | 1.31 [0.78, 2.19] | 2020 |
| Al Khalaf, 2021 | 0.4947 | 0.0455 | 60.7% | 1.64 [1.50, 1.79] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **1.45 [1.15, 1.85]** | |
| Heterogeneity: Tau² = 0.02; Chi² = 3.62, df = 2 (P = 0.16); I² = 45% | | | | | |
| Test for overall effect: Z = 3.08 (P = 0.002) | | | | | |
| **1.5.2 Diabetic CKD** | | | | | |
| Kimmerle,1995 | 1.2254 | 0.5215 | 24.6% | 3.41 [1.23, 9.46] | 1995 |
| Miodovnik,1996 | 0.3518 | 0.3923 | 25.9% | 1.42 [0.66, 3.07] | 1996 |
| Biesenbach, 2000 | 0 | 0.7454 | 21.8% | 1.00 [0.23, 4.31] | 2000 |
| Al Khalaf, 2021 | 2.6532 | 0.1492 | 27.6% | 14.20 [10.60, 19.02] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **3.08 [0.71, 13.30]** | |
| Heterogeneity: Tau² = 1.99; Chi² = 43.61, df = 3 (P < 0.00001); I² = 93% | | | | | |
| Test for overall effect: Z = 1.51 (P = 0.13) | | | | | |
| **1.5.3 Polycystic kidney disease** | | | | | |
| Wu, 2016 | 0.2585 | 0.3432 | 38.6% | 1.29 [0.66, 2.54] | 2016 |
| Al Khalaf, 2021 | 0.94 | 0.1109 | 61.4% | 2.56 [2.06, 3.18] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **1.97 [1.03, 3.77]** | |
| Heterogeneity: Tau² = 0.17; Chi² = 3.57, df = 1 (P = 0.06); I² = 72% | | | | | |
| Test for overall effect: Z = 2.04 (P = 0.04) | | | | | |
| **1.5.4 Unspecified CKD** | | | | | |
| Fink, 1998 | 1.0458 | 0.195 | 25.9% | 2.85 [1.94, 4.17] | 1998 |
| Trevisan, 2004 | 0.7307 | 0.4972 | 10.2% | 2.08 [0.78, 5.50] | 2004 |
| Tsuchiyama, 2017 | 0.712 | 0.1654 | 28.1% | 2.04 [1.47, 2.82] | 2017 |
| Al Khalaf, 2021 | 0.3784 | 0.0214 | 35.8% | 1.46 [1.40, 1.52] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **1.98 [1.37, 2.86]** | |
| Heterogeneity: Tau² = 0.10; Chi² = 15.85, df = 3 (P = 0.001); I² = 81% | | | | | |
| Test for overall effect: Z = 3.63 (P = 0.0003) | | | | | |




Test for subgroup differences: Chi² = 2.98, df = 3 (P = 0.40), I² = 0%

**Figure S4.20b** Forest plot of adjusted estimates for Caesarean section

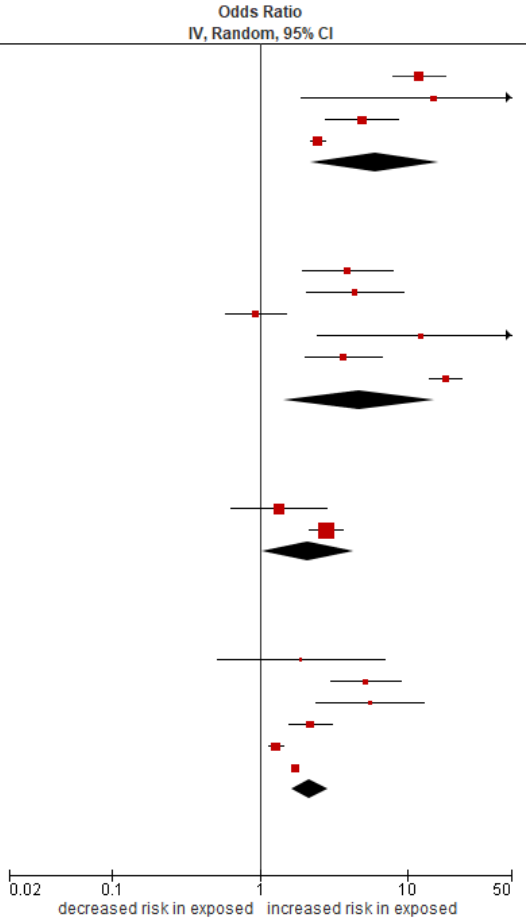
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **1.12.1 Glomerulonephritis** | | | | | |
| Al Khalaf, 2021 | 0.4187 | 0.0493 | 100.0% | 1.52 [1.38, 1.67] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **1.52 [1.38, 1.67]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 8.49 (P < 0.00001) | | | | | |
| **1.12.2 Diabetic CKD** | | | | | |
| Al Khalaf, 2021 | 1.3218 | 0.1564 | 100.0% | 3.75 [2.76, 5.10] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **3.75 [2.76, 5.10]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 8.45 (P < 0.00001) | | | | | |
| **1.12.3 Polycystic kidney disease** | | | | | |
| Al Khalaf, 2021 | 0.9821 | 0.1129 | 100.0% | 2.67 [2.14, 3.33] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.67 [2.14, 3.33]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 8.70 (P < 0.00001) | | | | | |
| **1.12.4 Unspecified CKD** | | | | | |
| Fink, 1998 | 1.1314 | 0.2236 | 23.1% | 3.10 [2.00, 4.80] | 1998 |
| Kendrick, 2015 | 0.2852 | 0.1158 | 34.7% | 1.33 [1.06, 1.67] | 2015 |
| Al Khalaf, 2021 | 0.3365 | 0.0223 | 42.2% | 1.40 [1.34, 1.46] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **1.65 [1.21, 2.25]** | |
| Heterogeneity: Tau² = 0.06; Chi² = 12.77, df = 2 (P = 0.002); I² = 84% | | | | | |
| Test for overall effect: Z = 3.16 (P = 0.002) | | | | | |




Test for subgroup differences: Chi² = 46.03, df = 3 (P < 0.00001), I² = 93.5%

**Figure S4.21a** Forest plot of crude estimates for preterm birth (<37 wk. gestation)

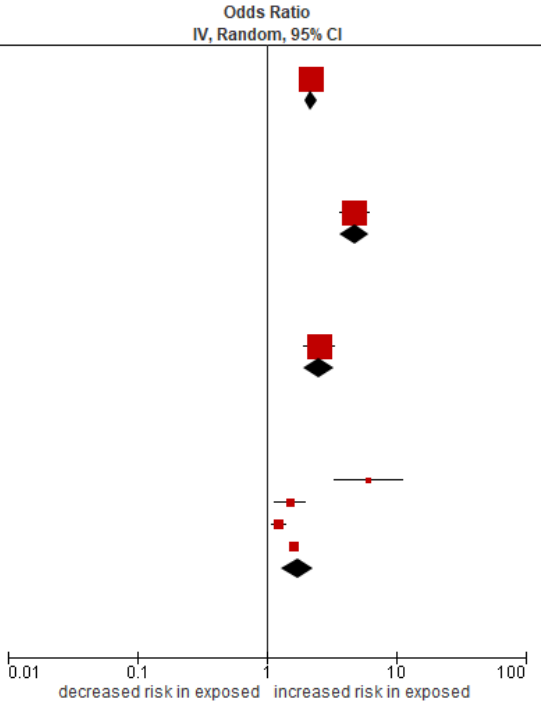
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **1.2.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | 2.4804 | 0.2101 | 28.9% | 11.95 [7.91, 18.03] | 2017 |
| Li, 2018 | 2.7081 | 1.0524 | 13.3% | 15.00 [1.91, 118.01] | 2018 |
| Madej, 2020 | 1.5914 | 0.2929 | 27.6% | 4.91 [2.77, 8.72] | 2020 |
| Al Khalaf, 2021 | 0.9042 | 0.0544 | 30.3% | 2.47 [2.22, 2.75] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **5.98 [2.20, 16.28]** | |
| Heterogeneity: Tau² = 0.86; Chi² = 59.21, df = 3 (P < 0.00001); I² = 95% | | | | | |
| Test for overall effect: Z = 3.50 (P = 0.0005) | | | | | |
| **1.2.2 Diabetic CKD** | | | | | |
| Miodovnik,1996 | 1.361 | 0.3573 | 17.0% | 3.90 [1.94, 7.86] | 1996 |
| Ekbom, 2001 | 1.4803 | 0.3886 | 16.8% | 4.39 [2.05, 9.41] | 2001 |
| Jensen,2010 | -0.0672 | 0.2397 | 17.6% | 0.94 [0.58, 1.50] | 2010 |
| Young, 2011 | 2.5055 | 0.8238 | 13.5% | 12.25 [2.44, 61.57] | 2011 |
| Seah, 2020 | 1.3002 | 0.3063 | 17.3% | 3.67 [2.01, 6.69] | 2020 |
| Al Khalaf, 2021 | 2.8959 | 0.1311 | 17.9% | 18.10 [14.00, 23.40] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **4.71 [1.46, 15.21]** | |
| Heterogeneity: Tau² = 1.98; Chi² = 131.65, df = 5 (P < 0.00001); I² = 96% | | | | | |
| Test for overall effect: Z = 2.59 (P = 0.010) | | | | | |
| **1.2.3 Polycystic kidney disease** | | | | | |
| Wu, 2016 | 0.2936 | 0.3795 | 38.6% | 1.34 [0.64, 2.82] | 2016 |
| Al Khalaf, 2021 | 1.0367 | 0.136 | 61.4% | 2.82 [2.16, 3.68] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.12 [1.04, 4.30]** | |
| Heterogeneity: Tau² = 0.19; Chi² = 3.40, df = 1 (P = 0.07); I² = 71% | | | | | |
| Test for overall effect: Z = 2.07 (P = 0.04) | | | | | |
| **1.2.4 Unspesified CKD** | | | | | |
| Holley, 1996 | 0.6397 | 0.668 | 4.2% | 1.90 [0.51, 7.02] | 1996 |
| Fink, 1998 | 1.6529 | 0.2747 | 14.1% | 5.22 [3.05, 8.95] | 1998 |
| Wiles, 2015 | 1.7205 | 0.4291 | 8.3% | 5.59 [2.41, 12.96] | 2015 |
| Tsuchiyama, 2017 | 0.7841 | 0.1744 | 19.9% | 2.19 [1.56, 3.08] | 2017 |
| Harel, 2020 | 0.2469 | 0.0591 | 26.3% | 1.28 [1.14, 1.44] | 2020 |
| Al Khalaf, 2021 | 0.5539 | 0.0271 | 27.2% | 1.74 [1.65, 1.83] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.17 [1.62, 2.90]** | |
| Heterogeneity: Tau² = 0.08; Chi² = 50.08, df = 5 (P < 0.00001); I² = 90% | | | | | |
| Test for overall effect: Z = 5.23 (P < 0.00001) | | | | | |




Test for subgroup differences: Chi² = 5.04, df = 3 (P = 0.17), I² = 40.5%

**Figure S4.21b** Forest plot of adjusted estimates for preterm birth (<37 wk. gestation)

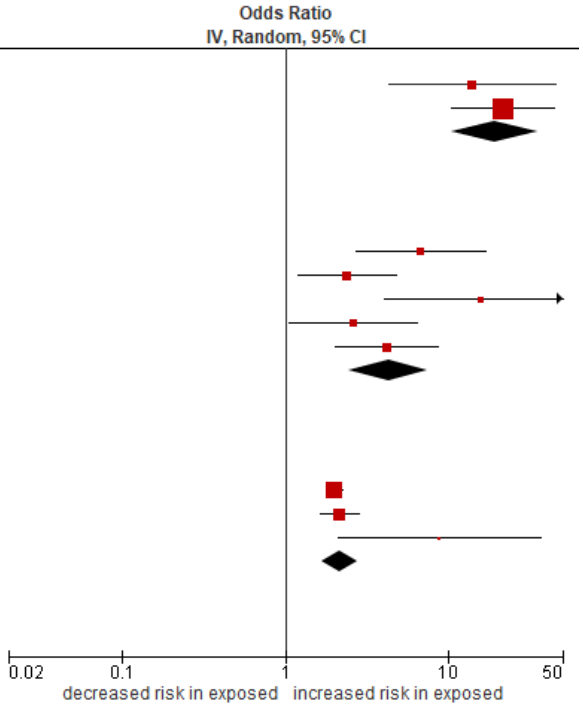
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **1.14.1 Glomerulonephritis** | | | | | |
| Al Khalaf, 2021 | 0.7885 | 0.0538 | 100.0% | 2.20 [1.98, 2.44] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.20 [1.98, 2.44]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 14.66 (P < 0.00001) | | | | | |
| **1.14.2 Diabetic CKD** | | | | | |
| Al Khalaf, 2021 | 1.5602 | 0.1355 | 100.0% | 4.76 [3.65, 6.21] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **4.76 [3.65, 6.21]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 11.51 (P < 0.00001) | | | | | |
| **1.14.3 Polycystic kidney disease** | | | | | |
| Al Khalaf, 2021 | 0.9361 | 0.1395 | 100.0% | 2.55 [1.94, 3.35] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.55 [1.94, 3.35]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 6.71 (P < 0.00001) | | | | | |
| **1.14.4 Unspecified CKD** | | | | | |
| Fink, 1998 | 1.8083 | 0.3135 | 12.3% | 6.10 [3.30, 11.28] | 1998 |
| Kendrick, 2015 | 0.4187 | 0.1379 | 24.7% | 1.52 [1.16, 1.99] | 2015 |
| Harel, 2020 | 0.207 | 0.0617 | 30.7% | 1.23 [1.09, 1.39] | 2020 |
| Al Khalaf, 2021 | 0.4824 | 0.0258 | 32.3% | 1.62 [1.54, 1.70] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **1.73 [1.31, 2.27]** | |
| Heterogeneity: Tau² = 0.06; Chi² = 35.91, df = 3 (P < 0.00001); I² = 92% | | | | | |
| Test for overall effect: Z = 3.91 (P < 0.0001) | | | | | |




Test for subgroup differences: Chi² = 33.87, df = 3 (P < 0.00001), I² = 91.1%

**Figure S4.22a** Forest plot of crude estimates for very preterm birth (<34 wk. gestation)

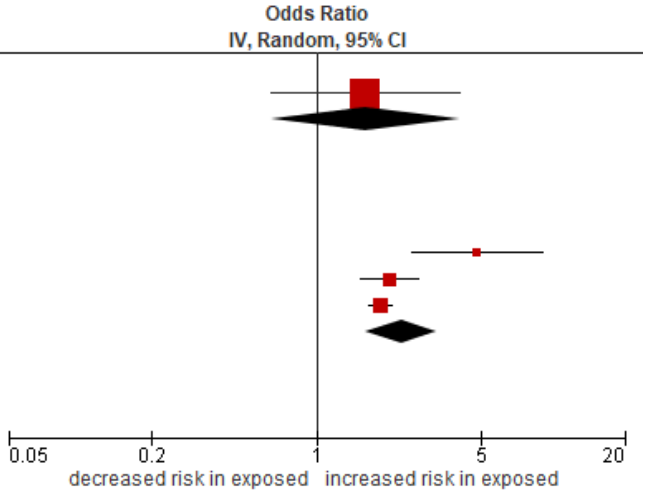
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **3.3.1 Glomerulonephritis** | | | | |
| Madej, 2020 | 2.6405 | 0.6004 | 27.2% | 14.02 [4.32, 45.48] |
| Piccoli, 2017 | 3.0734 | 0.3671 | 72.8% | 21.62 [10.53, 44.39] |
| **Subtotal (95% CI)** | | | **100.0%** | **19.21 [10.40, 35.50]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0% | | | | |
| Test for overall effect: Z = 9.44 (P < 0.00001) | | | | |
| **3.3.2 Diabetic CKD** | | | | |
| Ekbom, 2001 | 1.9072 | 0.4668 | 19.4% | 6.73 [2.70, 16.81] |
| Jensen,2010 | 0.8755 | 0.3579 | 24.7% | 2.40 [1.19, 4.84] |
| Kimmerle,1995 | 2.753 | 0.6885 | 12.0% | 15.69 [4.07, 60.49] |
| Miodovnik,1996 | 0.967 | 0.4613 | 19.7% | 2.63 [1.06, 6.50] |
| Seah, 2020 | 1.4303 | 0.3685 | 24.2% | 4.18 [2.03, 8.61] |
| **Subtotal (95% CI)** | | | **100.0%** | **4.28 [2.45, 7.47]** |
| Heterogeneity: Tau² = 0.20; Chi² = 8.06, df = 4 (P = 0.09); I² = 50% | | | | |
| Test for overall effect: Z = 5.11 (P < 0.00001) | | | | |
| **3.3.3 Unspecified CKD** | | | | |
| Al Khalaf, 2021 | 0.6931 | 0.0595 | 59.0% | 2.00 [1.78, 2.25] |
| Harel, 2020 | 0.7655 | 0.1382 | 38.0% | 2.15 [1.64, 2.82] |
| Wiles, 2015 | 2.1755 | 0.7321 | 3.0% | 8.81 [2.10, 36.98] |
| **Subtotal (95% CI)** | | | **100.0%** | **2.15 [1.67, 2.76]** |
| Heterogeneity: Tau² = 0.02; Chi² = 4.25, df = 2 (P = 0.12); I² = 53% | | | | |
| Test for overall effect: Z = 5.94 (P < 0.00001) | | | | |




Test for subgroup differences: Chi² = 43.33, df = 2 (P < 0.00001), I² = 95.4%

**Figure S4.22b** Forest plot of adjusted estimates for very preterm birth (<34 wk. gestation)

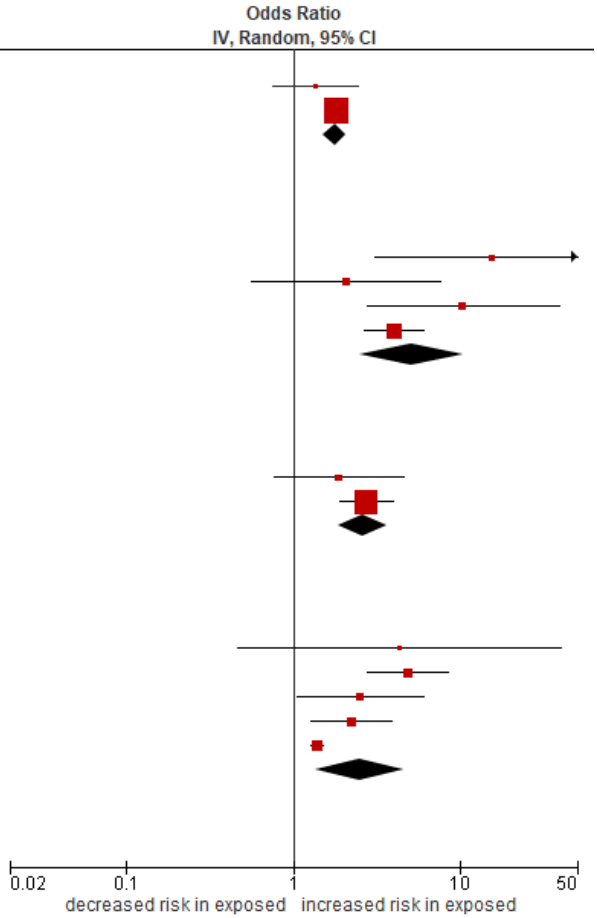
| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **3.15.1 Diabetic CKD** | | | | | |
| Jensen,2010 | 0.47 | 0.4675 | 100.0% | 1.60 [0.64, 4.00] | 2010 |
| **Subtotal (95% CI)** | | | **100.0%** | **1.60 [0.64, 4.00]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | |
| **3.15.2 Unspecified CKD** | | | | | |
| Kendrick, 2015 | 1.5605 | 0.3233 | 18.2% | 4.76 [2.53, 8.97] | 2015 |
| Harel, 2020 | 0.7129 | 0.1435 | 36.3% | 2.04 [1.54, 2.70] | 2020 |
| Al Khalaf, 2021 | 0.6206 | 0.058 | 45.6% | 1.86 [1.66, 2.08] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.28 [1.62, 3.21]** | |
| Heterogeneity: Tau² = 0.06; Chi² = 8.35, df = 2 (P = 0.02); I² = 76% | | | | | |
| Test for overall effect: Z = 4.72 (P < 0.00001) | | | | | |




Test for subgroup differences: Chi² = 0.51, df = 1 (P = 0.48), I² = 0%

**Figure S4.23a**. Forest plot of crude estimates for small for gestational age

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **1.4.1 Glomerulonephritis** | | | | | |
| Piccoli, 2017 | 0.3016 | 0.2991 | 7.1% | 1.35 [0.75, 2.43] | 2017 |
| Al Khalaf, 2021 | 0.5933 | 0.0824 | 92.9% | 1.81 [1.54, 2.13] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **1.77 [1.52, 2.07]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 1 (P = 0.35); I² = 0% | | | | | |
| Test for overall effect: Z = 7.21 (P < 0.00001) | | | | | |
| **1.4.2 Diabetic CKD** | | | | | |
| Kimmerle,1995 | 2.7362 | 0.8185 | 14.6% | 15.43 [3.10, 76.74] | 1995 |
| Miodovnik,1996 | 0.7244 | 0.6695 | 19.3% | 2.06 [0.56, 7.66] | 1996 |
| Ekbom, 2001 | 2.336 | 0.6764 | 19.1% | 10.34 [2.75, 38.93] | 2001 |
| Al Khalaf, 2021 | 1.3888 | 0.2113 | 47.0% | 4.01 [2.65, 6.07] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **5.14 [2.52, 10.51]** | |
| Heterogeneity: Tau² = 0.24; Chi² = 5.42, df = 3 (P = 0.14); I² = 45% | | | | | |
| Test for overall effect: Z = 4.50 (P < 0.00001) | | | | | |
| **1.4.3 Polycystic kidney disease** | | | | | |
| Wu, 2016 | 0.6286 | 0.4596 | 14.3% | 1.87 [0.76, 4.62] | 2016 |
| Al Khalaf, 2021 | 1.0043 | 0.1876 | 85.7% | 2.73 [1.89, 3.94] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.59 [1.84, 3.64]** | |
| Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0% | | | | | |
| Test for overall effect: Z = 5.47 (P < 0.00001) | | | | | |
| **1.4.4 Any CKD** | | | | | |
| Holley, 1996 | 1.4604 | 1.1399 | 6.0% | 4.31 [0.46, 40.23] | 1996 |
| Fink, 1998 | 1.5781 | 0.2809 | 23.5% | 4.85 [2.79, 8.40] | 1998 |
| Wiles, 2015 | 0.9297 | 0.4478 | 18.2% | 2.53 [1.05, 6.09] | 2015 |
| Tsuchiyama, 2017 | 0.8069 | 0.2851 | 23.4% | 2.24 [1.28, 3.92] | 2017 |
| Al Khalaf, 2021 | 0.3293 | 0.0421 | 28.8% | 1.39 [1.28, 1.51] | 2021 |
| **Subtotal (95% CI)** | | | **100.0%** | **2.49 [1.34, 4.61]** | |
| Heterogeneity: Tau² = 0.34; Chi² = 24.25, df = 4 (P < 0.0001); I² = 84% | | | | | |
| Test for overall effect: Z = 2.90 (P = 0.004) | | | | | |




Test for subgroup differences: Chi² = 11.70, df = 3 (P = 0.008), I² = 74.4%

**Figure S4.23b** Forest plot of adjusted estimates for small for gestational age

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| **1.16.1 Glomerulonephritis** | | | | | |
| Al Khalaf, 2021 | 0.4318 | 0.0825 | 19.7% | 1.54 [1.31, 1.81] | 2021 |
| **Subtotal (95% CI)** | | | **19.7%** | **1.54 [1.31, 1.81]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 5.23 (P < 0.00001) | | | | | |
| **1.16.2 Diabetic CKD** | | | | | |
| Al Khalaf, 2021 | 1.5041 | 0.2207 | 15.4% | 4.50 [2.92, 6.94] | 2021 |
| **Subtotal (95% CI)** | | | **15.4%** | **4.50 [2.92, 6.94]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 6.82 (P < 0.00001) | | | | | |
| **1.16.3 Polycystic kidney disease** | | | | | |
| Al Khalaf, 2021 | 0.8961 | 0.1986 | 16.2% | 2.45 [1.66, 3.62] | 2021 |
| **Subtotal (95% CI)** | | | **16.2%** | **2.45 [1.66, 3.62]** | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z = 4.51 (P < 0.00001) | | | | | |
| **1.16.4 Any CKD** | | | | | |
| Fink, 1998 | 1.6677 | 0.3256 | 11.9% | 5.30 [2.80, 10.03] | 1998 |
| Kendrick, 2015 | 0.3148 | 0.1922 | 16.4% | 1.37 [0.94, 2.00] | 2015 |
| Al Khalaf, 2021 | 0.2546 | 0.0412 | 20.4% | 1.29 [1.19, 1.40] | 2021 |
| **Subtotal (95% CI)** | | | **48.7%** | **1.93 [1.06, 3.52]** | |
| Heterogeneity: Tau² = 0.24; Chi² = 18.58, df = 2 (P < 0.0001); I² = 89% | | | | | |
| Test for overall effect: Z = 2.15 (P = 0.03) | | | | | |
| **Total (95% CI)** | | | **100.0%** | **2.15 [1.53, 3.01]** | |
| Heterogeneity: Tau² = 0.14; Chi² = 57.63, df = 5 (P < 0.00001); I² = 91% | | | | | |
| Test for overall effect: Z = 4.43 (P < 0.00001) | | | | | |
| Test for subgroup differences: Chi² = 23.18, df = 3 (P < 0.0001), I² = 87.1% | | | | | |

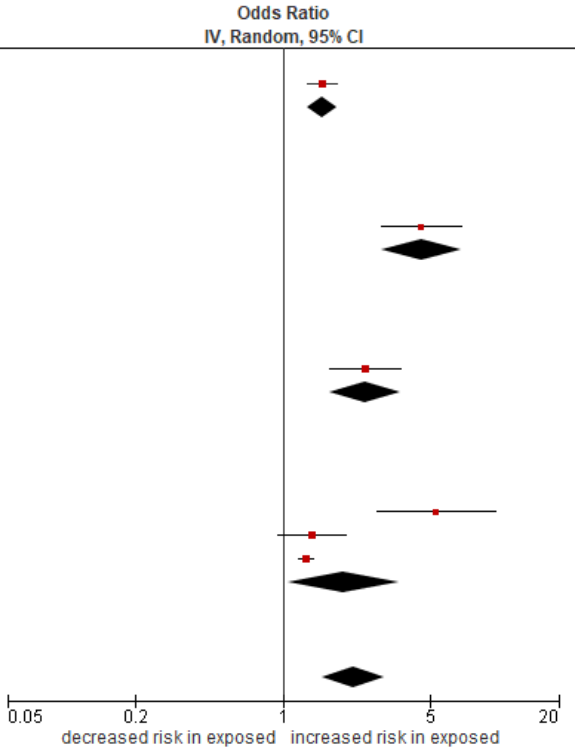


**Figure S4.24a** Forest plot of crude estimates for stillbirth

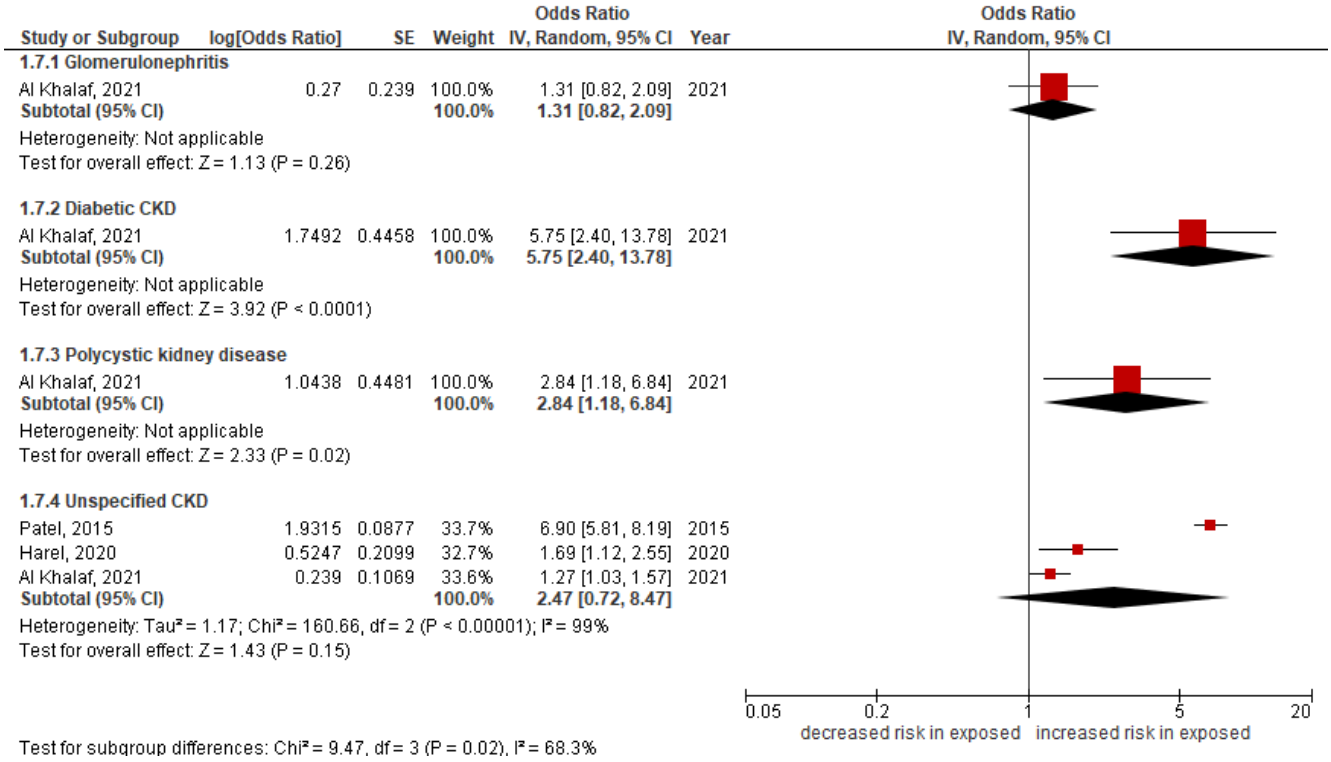
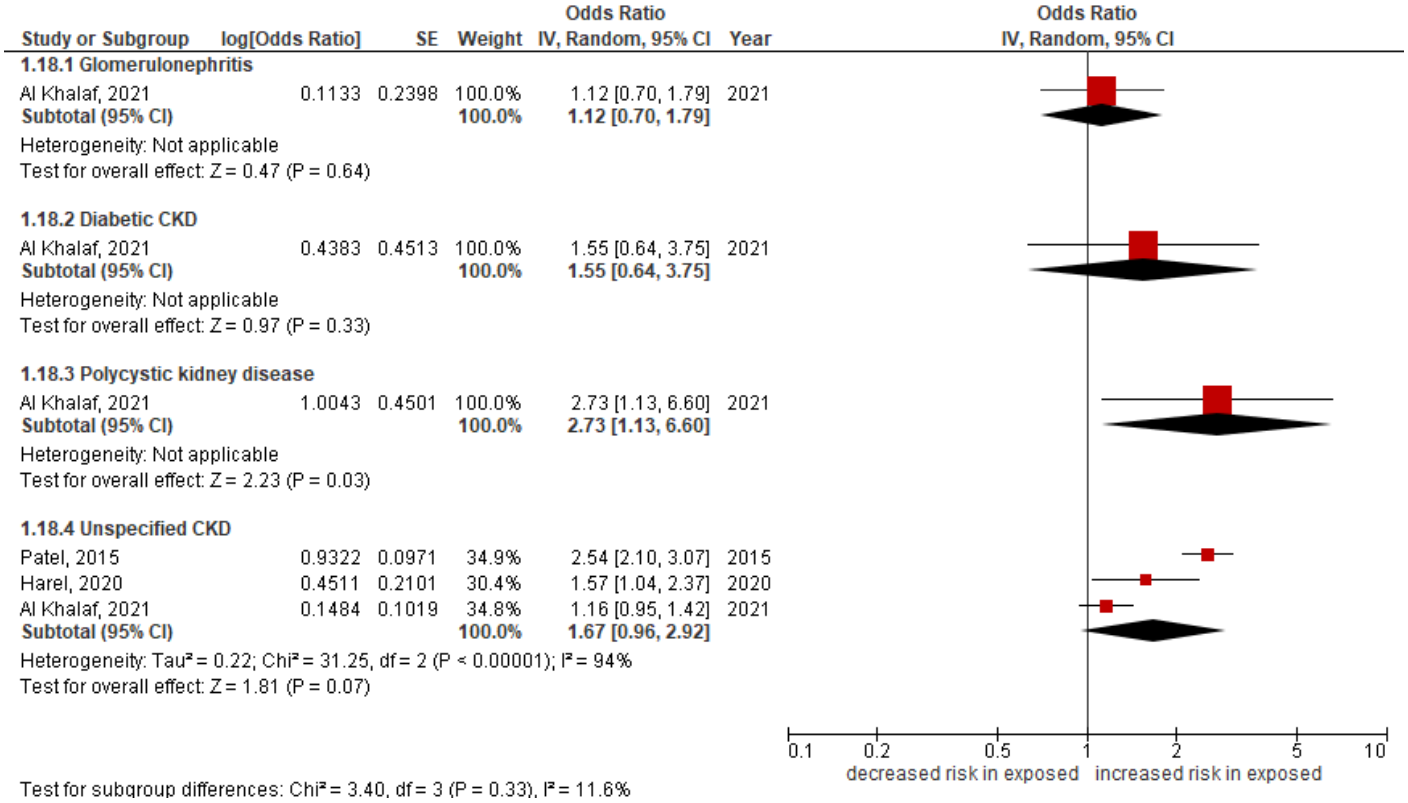



**Figure S4.24b** Forest plot of adjusted estimates for stillbirth



# Appendix 5: Pregnancy Outcomes in Women with Chronic Kidney Disease and Chronic Hypertension: A National Cohort Study (supplemental material)

## S5.1 Supplementary Methods

Potential confounders that we adjusted for included maternal demographic characteristics and comorbidities. Information about maternal age was categorized into five year categories (<20, 20-24, 25-29, 30-34, 35-39 and 40 years or older), smoking habits recorded during the 1st antenatal visit as: (non-smokers, moderate smokers "1-9 cigarettes/day" and heavy smokers "≥10 cigarettes/day"). We calculated maternal body mass index (BMI) using the women's height and pre-pregnancy weight ($kg/m^2$), and that was categorized into the following subgroups: underweight (BMI <18.5), normal (18.5 to <25), overweight (25 to <30) and obese (≥30). Parity was categorized into ("parity 1", no previous birth; "parity 2", one previous birth; and "parity 3", if a woman had two or more previous births). Country of origin and this was categorized as: Sweden, other Scandinavian countries or elsewhere. Other comorbidities included asthma, diabetes mellitus (DM), and cardiovascular disease (CVD). Data on these variables were collected from the Swedish MBR, in addition to NPR for comorbidities variables. Maternal highest educational level was obtained from the Swedish Education Register and was based on the mothers' highest level of education.

When we investigated the risk of pre-eclampsia, we adjusted for child's gender as previous studies suggested an association between fetal gender and pre-eclampsia (1, 2). We conducted sub-group analyses to examine the effect of parity (primigravida, multigravida), maternal age (<35 yrs. or ≥35 yrs.), and BMI categories on adverse perinatal outcomes. In all analyses, we accounted for the potential clustering within family. Additionally, sensitivity analyses were performed excluding women with other comorbidities including DM, CVD, and asthma.

## S5.2 Supplementary Results

***The sensitivity analyses according to maternal characteristics***

Stratified results by parity demonstrated that multiparous women with chronic hypertension (CH), chronic kidney disease (CKD) or with both conditions had worse outcomes than nulliparous women (**Table S5.3**). The adjusted estimates for pre-eclampsia, in multiparous women, were remarkably higher in women with CH [adjusted odd ratio (aOR)=6.02 (95% confidence interval (CI), 5.59–6.49)]; CKD [aOR=2.09 (95% CI, 1.88–2.32)] and in those with both conditions [aOR=7.22 (95% CI, 5.55–9.40)].

The subgroup analyses by maternal age suggested that younger women (<35 yrs.) with CH, CKD or both conditions were more likely to deliver by elective Cesarean section (CS) and to have spontaneous preterm birth (**Table S5.4**). In contrast, older women (≥35 yrs.) with CH or CKD had higher odds of medically indicated preterm birth, stillbirth and small for gestational age. Although the incidence of adverse outcomes increased with increasing BMI, the adjusted estimates of pre-eclampsia, emergency CS, elective CS, preterm birth, and small for gestational age decreased gradually with increasing BMI, in women with CH (**Table S5.5**).

The results of sensitivity analysis (excluding women with other comorbidities) are shown in **Table S5.6**. The associations for women with CH or CKD did not materially change, but it seems that most of the confounding effects were related to the confounders we excluded in this analysis (DM, CVD, and asthma). As some adjusted estimates become larger in women with both conditions, compared to normotensive women without CKD. For example, the aOR for spontaneous preterm birth became significant [aOR=1.70 (95% CI, 1.09, 2.67)]. Also, the adjusted ORs for pre-eclampsia [7.37 (95% CI, 5.93. 9.14)] and small for gestational age [5.38 (95% CI, 4.27, 6.80)] were stronger than crude estimates in women with both conditions. However, that did not change our conclusion.

**S5.3 Supplementary Figures (S5.1-S5.2) and Tables (S5.1-S5.6)**

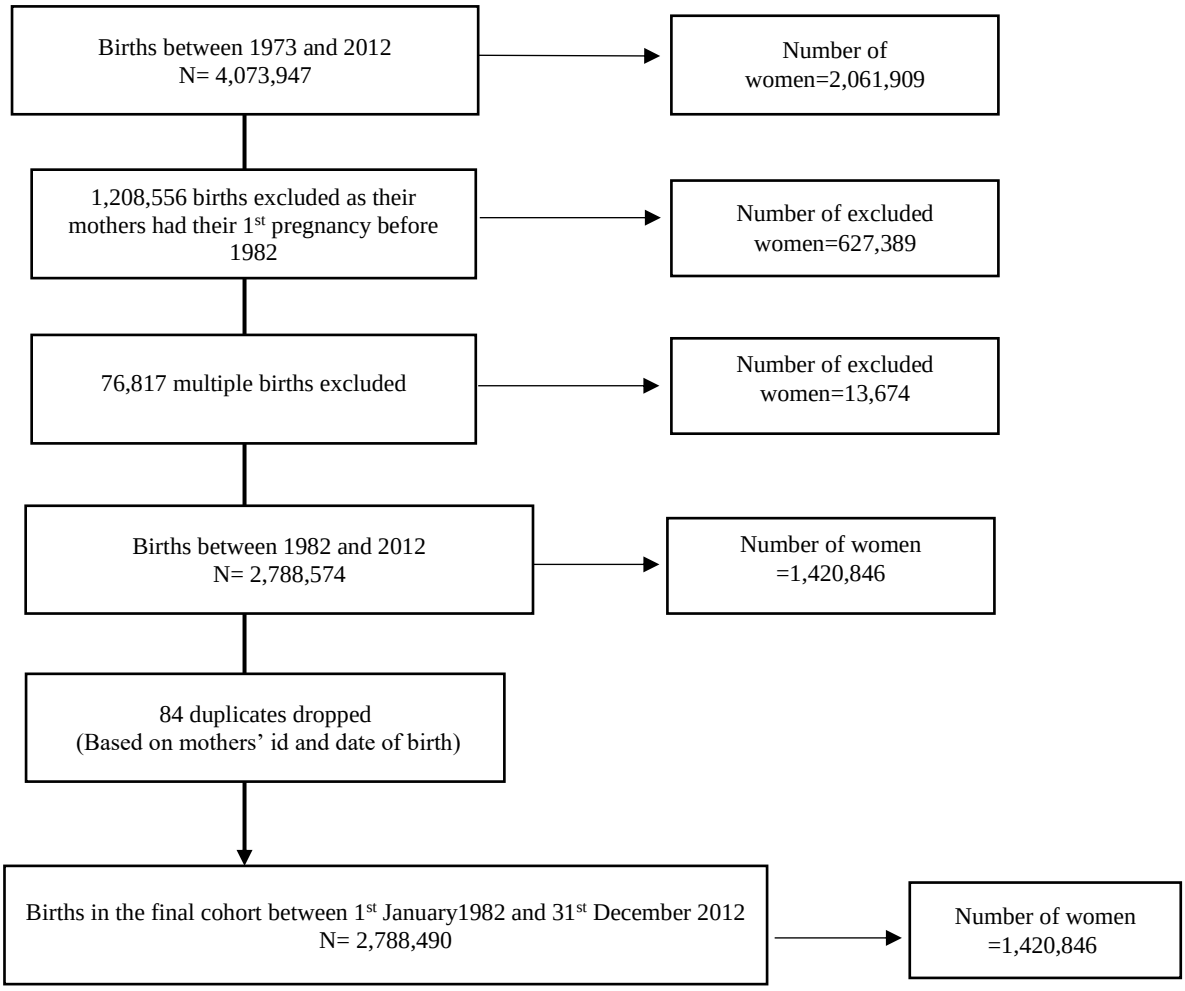



**Figure S5.1** Flowchart of the study population

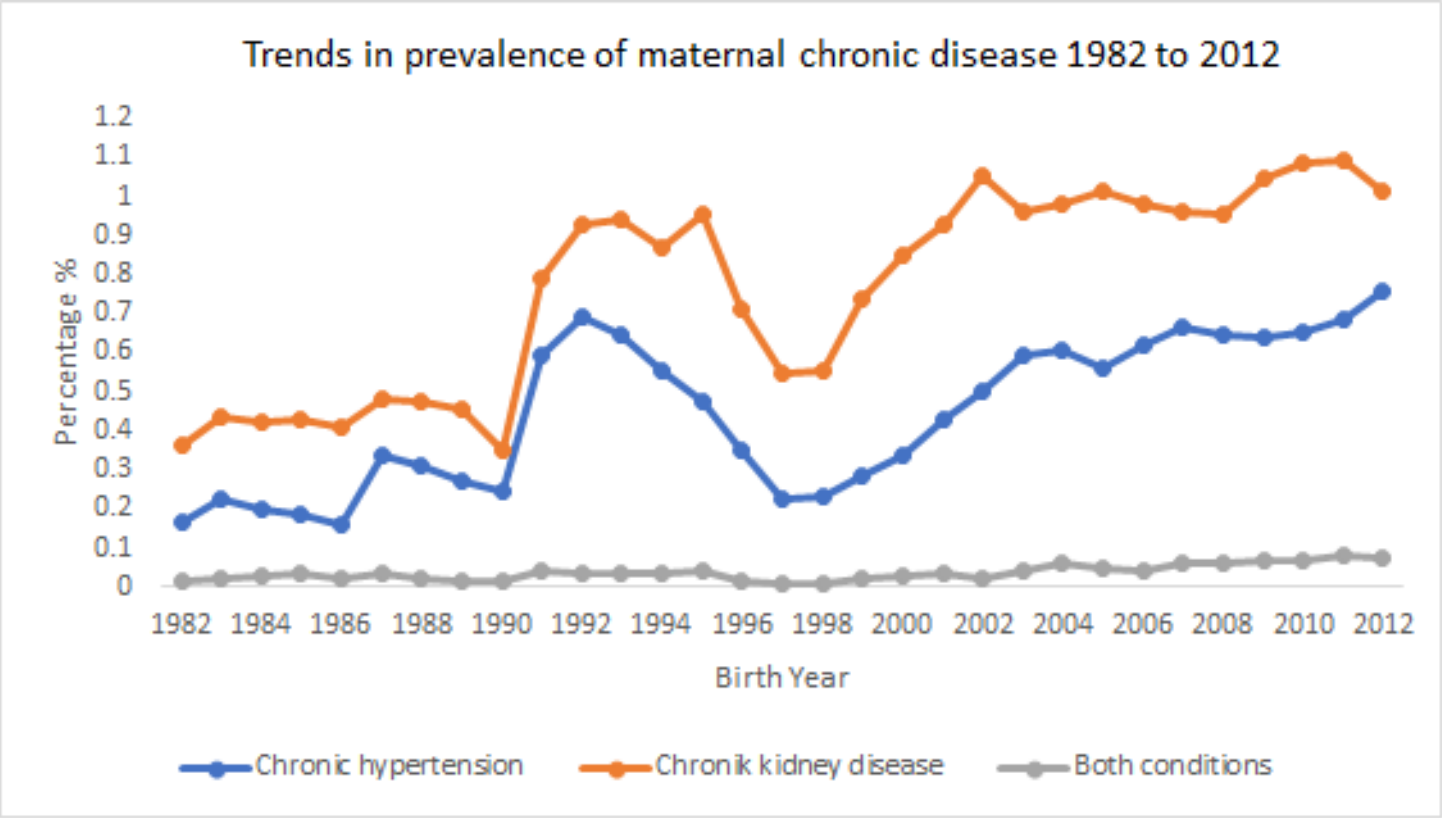



**Figure S5.2** Trends in prevalence of maternal chronic hypertension, chronic kidney disease and a combination of both conditions over the last three decades

**Table S5.1** International Classification of Diseases (ICD-codes)

| Disease | ICD-8 codes (1973-1986) | ICD-9 codes (1987-1996) | ICD-10 codes (1997-2013) |
|---|---|---|---|
| Pre-eclampsia or eclampsia | 637.00, 637.03, 637.04, 637.09, 637.10, 637.19, 637.90, 637.99 | 642E, 642F, 642G, 642H | O110, O119, O140, O141, O141A, O14.B, O141C, O141X, O142, O149, O150, O151, O152, O159 |
| Subtypes chronic kidney disease (CKD) | | | |
| Tubulointerstitial CKD | - | - | N11-N12, N15-N16 |
| Glomerular/proteinuric CKD | - | 581-583 | N01-N06, N08 |
| Diabetic nephropathy | 250,04 | 250D | E10.2, E10.2A , E10.2B, E10.2C, E10.2W, E10.2X, E11.2A , E11.2B, E11.2C, E11.2W, E11.2X, E13.2, E14.2 |
| Renovascular disease | 403-404 | 403-404 | I12.0-I13.9, I15.0, I15.1 |
| Congenital anomalies of the kidney and urinary tract | 753,00-753,99 | 753 | Q60.0-Q64.9, Q27.1, Q27.2 |
| Other/unspecified CKD | 581,00-584,99 | 585-588, V42A, V45B, V56A, V56W | N130-N139, N18-N19, Z49.0-Z49.2, Z99.2, Z94.0, T86.1 |

**Table S5.2** Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes overt time from 1982 to 2012

| Outcome | Normotensive women | | Pregnancies with CH | | Pregnancies with CKD) | | Pregnancies with CH & CKD | |
|---|---|---|---|---|---|---|---|---|
| | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) |
| **Pre-eclampsia[a]** | | | | | | | | |
| 1982–1986 | 14,181 (5.3) | Reference | 133 (27) | 4.65 (3.73, 5.80) | 111 (10) | 1.87 (1.52, 2.29) | 10 (14) | 2.98 (1.49, 5.93) |
| 1987–1991 | 9,232 (1.9) | Reference | 277 (16) | 8.30 (7.18, 9.59) | 73 (2.9) | 1.44 (1.13, 1.83) | 8 (6.5) | 2.60 (1.22, 5.51) |
| 1992–1996 | 10,210 (2.1) | Reference | 261 (9.4) | 3.81 (3.31, 4.39) | 131 (2.9) | 1.43 (1.19, 1.71) | 17 (10) | 3.41 (1.90, 6.14) |
| 1997–2001 | 12,260 (3.0) | Reference | 213 (17) | 4.84 (4.11, 5.70) | 131 (4.3) | 1.48 (1.23, 1.77) | 16 (19) | 5.04 (2.60, 9.79) |
| 2002–2006 | 12,914 (2.7) | Reference | 447 (16) | 5.01 (4.46, 5.63) | 233 (4.9) | 1.82 (1.58, 2.09) | 39 (20) | 6.19 (3.97, 9.65) |
| 2007–2012 | 17,134 (2.8) | Reference | 607 (14) | 4.12 (3.73, 4.56) | 300 (4.6) | 1.69 (1.50, 1.92) | 85 (19) | 3.95 (2.90, 5.38) |
| **Emergency cesarean section[b]** | | | | | | | | |
| 1982–1986 | 14,419 (6.4) | Reference | 72 (19) | 2.43 (1.85, 3.19) | 101 (12) | 1.89 (1.52, 2.37) | 8 (14) | 2.41 (1.09, 5.32) |
| 1987–1991 | 17,553 (4.3) | Reference | 157 (12) | 2.54 (2.12, 3.03) | 126 (6.3) | 1.43 (1.18, 1.73) | 6 (7.8) | 1.41 (0.62, 3.19) |
| 1992–1996 | 20,134 (4.9) | Reference | 93 (4.7) | 0.79 (0.64, 0.98) | 193 (5.6) | 1.08 (0.94, 1.26) | 11 (12) | 1.99 (1.03, 3.82) |
| 1997–2001 | 24,683 (7.7) | Reference | 129 (15) | 1.67 (1.37, 2.04) | 224 (9.8) | 1.30 (1.13, 1.50) | 12 (25) | 3.54 (1.69, 7.41) |
| 2002–2006 | 41,111 (11) | Reference | 481 (24) | 1.85 (1.65, 2.08) | 508 (15) | 1.38 (1.24, 1.52) | 37 (29) | 2.25 (1.44, 3.52) |
| 2007–2012 | 58,181 (12) | Reference | 774 (25) | 1.75 (1.59, 1.92) | 767 (16) | 1.43 (1.31, 1.56) | 105 (32) | 1.58 (1.15, 2.16) |
| **Elective cesarean section[b]** | | | | | | | | |
| 1982–1986 | 9,962 (4.5) | Reference | 45 (13) | 1.84 (1.30, 2.61) | 83 (9.9) | 2.11 (1.65, 2.71) | 8 (14) | 3.45 (1.62, 7.53) |
| 1987–1991 | 17,602 (4.3) | Reference | 169 (13) | 2.42 (2.03, 2.88) | 170 (8.4) | 1.86 (1.58, 2.20) | 25 (26) | 5.39 (3.29, 8.81) |
| 1992–1996 | 22,905 (5.6) | Reference | 349 (16) | 2.25 (1.99, 2.54) | 346 (9.6) | 1.67 (1.49, 1.88) | 56 (41) | 7.40 (5.09, 10.8) |
| 1997–2001 | 24,019 (7.5) | Reference | 193 (21) | 2.22 (1.88, 2.63) | 272 (12) | 1.51 (1.31, 1.73) | 24 (40) | 4.97 (2.86, 8.64) |
| 2002–2006 | 32,354 (9.0) | Reference | 317 (18) | 1.49 (1.31, 1.70) | 486 (14) | 1.59 (1.43, 1.76) | 37 (29) | 2.82 (1.83, 4.33) |
| 2007–2012 | 42,357 (8.8) | Reference | 486 (17) | 1.37 (1.23, 1.53) | 621 (13) | 1.50 (1.37, 1.65) | 63 (22) | 1.28 (0.92, 1.79) |
| **Preterm birth (<37 weeks' gestation)[b]** | | | | | | | | |
| 1982–1986 | 16,497 (6.1) | Reference | 96 (19) | 3.07 (2.43, 3.89) | 131 (12) | 1.81 (1.50, 2.19) | 20 (28) | 5.18 (3.09, 8.67) |
| 1987–1991 | 25,359 (5.3) | Reference | 237 (14) | 2.65 (2.29, 3.03) | 250 (10) | 1.77 (1.55, 2.03) | 37 (30) | 5.93 (4.00, 8.79) |
| 1992–1996 | 24,450 (4.9) | Reference | 329 (12) | 2.36 (2.10, 2.67) | 334 (12) | 1.43 (1.27, 1.61) | 58 (36) | 7.75 (5.48, 11.0) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 1997–2001 | 20,668 (5.0) | Reference | 192 (15) | 2.96 (2.51, 3.49) | 274 (9.0) | 1.75 (1.54, 1.99) | 29 (35) | 7.51 (4.56, 12.3) |
| 2002–2006 | 23,414 (5.0) | Reference | 349 (13) | 2.34 (2.08, 2.64) | 399 (8.4) | 1.67 (1.49, 1.86) | 57 (29) | 5.38 (3.76, 7.71) |
| 2007–2012 | 30,486 (4.9) | Reference | 528 (12) | 2.31 (2.09, 2.55) | 507 (7.8) | 1.54 (1.40, 1.70) | 108 (25) | 3.22 (2.48, 4.18) |
| **Stillbirth[b]** | | | | | | | | |
| 1982–1986 | 1,007 (0.37) | Reference | 7 (1.4) | 3.03 (1.40, 6.57) | 3 (0.27) | - | 1 (1.4) | - |
| 1987–1991 | 1,557 (0.33) | Reference | 10 (0.58) | 1.49 (0.79, 2.81) | 11 (0.44) | 1.15 (0.63, 2.08) | 0 | - |
| 1992–1996 | 1,498 (0.30) | Reference | 20 (0.72) | 1.86 (1.19, 2.91) | 17 (0.38) | 1.13 (0.70, 1.84) | 0 | - |
| 1997–2001 | 1,480 (0.36) | Reference | 10 (0.79) | 1.65 (0.88, 3.10) | 19 (0.62) | 1.57 (0.99, 2.47) | 1 (1.2) | - |
| 2002–2006 | 1,425 (0.30) | Reference | 23 (0.83) | 2.05 (1.34, 3.14) | 15 (0.31) | 0.97 (0.58, 1.61) | 4 (2.0) | - |
| 2007–2012 | 2,168 (0.35) | Reference | 28 (0.66) | 1.31 (0.89, 1.94) | 29 (0.45) | 1.18 (0.81, 1.72) | 1 (0.23) | - |
| **Small for gestational age[b]** | | | | | | | | |
| 1982–1986 | 9,656 (3.6) | Reference | 75 (15) | 4.59 (3.53, 5.96) | 65 (5.8) | 1.53 (1.17, 2.01) | 5 (6.9) | 1.87 (0.73, 4.75) |
| 1987–1991 | 14,014 (2.9) | Reference | 220 (13) | 4.99 (4.30, 5.80) | 118 (4.8) | 1.45 (1.20, 1.76) | 11 (8.9) | 2.59 (1.35, 4.96) |
| 1992–1996 | 12,356 (2.5) | Reference | 185 (6.6) | 2.96 (2.53, 3.46) | 136 (3.0) | 1.09 (0.91, 1.31) | 24 (15) | 6.51 (4.13, 10.2) |
| 1997–2001 | 9,614 (2.3) | Reference | 107 (8.5) | 4.13 (3.36, 5.08) | 108 (3.6) | 1.44 (1.18, 1.75) | 6 (7.2) | 3.57 (1.54, 8.30) |
| 2002–2006 | 10, 375 (2.2) | Reference | 198 (7.2) | 3.58 (3.07, 4.18) | 139 (2.9) | 1.25 (1.05, 1.48) | 27 (14) | 7.59 (4.87, 11.8) |
| 2007–2012 | 14,187 (2.3) | Reference | 262 (6.2) | 2.93 (2.57, 3.34) | 189 (2.9) | 1.21 (1.04, 1.41) | 38 (8.7) | 4.70 (3.31, 6.67) |

CH, Chronic hypertension; CKD, chronic kidney disease. [a] adjusted for maternal age, educational level, smoking, BMI, parity, country of origin, other comorbidities (diabetes, cardiovascular disease, asthma) and child's gender. [b] adjusted for maternal age, educational level, smoking, BMI, parity, country of origin, and other comorbidities (diabetes, cardiovascular disease, asthma).

**Table S5.3** Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes stratified by parity

| Outcome | Normotensive women | | Pregnancies with CH | | Pregnancies with CKD | | Pregnancies with CH & CKD | |
|---|---|---|---|---|---|---|---|---|
| | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) |
| **Pre-eclampsia[a]** | | | | | | | | |
| Primigravids | 53,339 (4.1) | Reference | 939 (17) | 3.53 (3.27, 3.81) | 563 (5.7) | 1.37 (1.25, 1.49) | 81 (16) | 2.66 (2.02, 3.51) |
| Multigravida | 22,592 (1.6) | Reference | 999 (13) | 6.02 (5.59, 6.49) | 416 (3.3) | 2.09 (1.88, 2.32) | 94 (17) | 7.22 (5.55, 9.40) |
| **Emergency cesarean section[b]** | | | | | | | | |
| Primigravids | 115,306 (11) | Reference | 948 (25) | 1.57 (1.44, 1.70) | 1,134 (16) | 1.30 (1.21, 1.38) | 95 (28) | 1.52 (1.13, 2.05) |
| Multigravida | 60,775 (5) | Reference | 758 (13) | 1.87 (1.72, 2.03) | 785 (8) | 1.41 (1.31, 1.53) | 84 (21) | 2.39 (1.78, 3.20) |
| **Elective cesarean section[b]** | | | | | | | | |
| Primigravids | 53,507 (5.6) | Reference | 505 (15) | 1.86 (1.68, 2.07) | 703 (11) | 1.76 (1.62, 1.90) | 93 (28) | 3.18 (2.34, 4.34) |
| Multigravida | 95,692 (7.6) | Reference | 1,054 (17) | 1.67 (1.55, 1.80) | 1,275 (12) | 1.52 (1.42, 1.62) | 120 (28) | 2.33 (1.80, 3.02) |
| **Spontaneous preterm birth (<37 weeks' gestation)[b]** | | | | | | | | |
| Primigravids | 38,241 (3) | Reference | 183 (3.8) | 1.06 (0.91, 1.23) | 373 (4) | 1.19 (1.07, 1.32) | 23 (6) | 1.21 (0.77, 1.90) |
| Multigravida | 29,551 (2.1) | Reference | 186 (2.6) | 1.09 (0.94, 1.27) | 376 (3.1) | 1.30 (1.17, 1.45) | 17 (3.9) | 1.17 (0.69, 1.97) |
| **Medically indicated preterm birth (<37 weeks' gestation)[b]** | | | | | | | | |
| Primigravids | 42,644 (3.4) | Reference | 649 (12) | 3.75 (3.44, 4.10) | 553 (5.9) | 1.84 (1.68, 2.01) | 137 (28) | 8.64 (6.91, 10.8) |
| Multigravida | 30,291 (2.1) | Reference | 713 (9) | 4.04 (3.71, 4.41) | 593 (4.9) | 2.28 (2.08, 2.49) | 132 (24) | 9.30 (7.37, 11.7) |
| **Stillbirth[b]** | | | | | | | | |
| Primigravids | 4,685 (0.36) | Reference | 39 (0.72) | 1.42 (1.03, 1.96) | 43 (0.44) | 1.12 (0.83, 1.52) | 2 (0.39) | - |
| Multigravida | 4,450 (0.31) | Reference | 59 (0.75) | 1.84 (1.41, 2.40) | 51 (0.40) | 1.20 (0.90, 1.59) | 5 (0.88) | 1.73 (0.73, 4.13) |
| **Small for gestational age[a]** | | | | | | | | |
| Primigravids | 46,439 (3.6) | Reference | 552 (10) | 3.07 (2.81, 3.66) | 448 (4.6) | 1.23 (1.12, 1.36) | 69 (14) | 4.26 (3.28, 5.54) |
| Multigravida | 23,763 (1.6) | Reference | 495 (6.3) | 4.24 (3.85, 4.67) | 307 (2.4) | 1.37 (1.22, 1.54) | 42 (7.4) | 4.99 (3.55, 7.01) |

Total number of primiparous women=1,321,972; multiparous women= 1,466,518

CH, chronic hypertension; CKD, chronic kidney disease. [a] adjusted for maternal age, educational level, smoking, BMI, country of origin, other comorbidities (diabetes, cardiovascular disease, asthma), birth year and child's gender. [b] adjusted for maternal age, educational level, smoking, BMI, country of origin, other comorbidities (diabetes, cardiovascular disease, asthma) and birth year.

**Table S5.4** Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes stratified by maternal age

| Outcome | Normotensive women | | Pregnancies with CH | | Pregnancies with CKD | | Pregnancies with CH & CKD | |
|---|---|---|---|---|---|---|---|---|
| | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) |
| **Pre-eclampsia[a]** | | | | | | | | |
| <35 yrs. | 64,375 (2.7) | Reference | 1,293 (14) | 4.78 (4.48, 5.12) | 779 (4.2) | 1.58 (1.46, 1.70) | 111 (14) | 3.59 (2.78, 4.63) |
| ≥35 yrs. | 11,556 (2.9) | Reference | 645 (16) | 4.48 (4.07, 4.93) | 200 (5.2) | 1.79 (1.54, 2.08) | 64 (21) | 6.17 (4.49, 8.48) |
| **Emergency cesarean section[b]** | | | | | | | | |
| <35 yrs. | 140,217 (7.3) | Reference | 1,003 (15) | 1.84 (1.71, 1.98) | 1,484 (10) | 1.37 (1.29, 1.45) | 110 (21) | 1.77 (1.36, 2.31) |
| ≥35 yrs. | 35,864 (12) | Reference | 703 (24) | 1.81 (1.64, 1.99) | 435 (16) | 1.33 (1.19, 1.49) | 69 (35) | 2.28 (1.60, 3.25) |
| **Elective cesarean section[b]** | | | | | | | | |
| <35 yrs. | 107,815 (5.7) | Reference | 828 (13) | 1.91 (1.76, 2.06) | 1,410 (10) | 1.63 (1.54, 1.74) | 136 (24) | 2.94 (2.30, 3.75) |
| ≥35 yrs. | 41,384 (13) | Reference | 731 (25) | 1.78 (1.63, 1.95) | 568 (20) | 1.51 (1.37, 1.66) | 77 (38) | 2.47 (1.78, 3.41) |
| **Spontaneous preterm birth (<37 weeks' gestation)[b]** | | | | | | | | |
| <35 yrs. | 57,372 (2.5) | Reference | 246 (3.0) | 1.08 (0.95, 1.24) | 618 (3.5) | 1.25 (1.15, 1.36) | 31 (5.3) | 1.31 (0.87, 1.96) |
| ≥35 yrs. | 10,420 (2.7) | Reference | 123 (3.3) | 1.06 (0.88, 1.27) | 131 (3.6) | 1.22 (1.02, 1.48) | 9 (4.1) | 0.88 (0.39, 1.94) |
| **Medically indicated preterm birth (<37 weeks' gestation)[b]** | | | | | | | | |
| <35 yrs. | 61,446 (2.7) | Reference | 833 (9.5) | 3.79 (3.51, 4.11) | 916 (5.1) | 2.04 (1.90, 2.20) | 179 (24) | 8.93 (7.30, 10.9) |
| ≥35 yrs. | 11,489 (3.0) | Reference | 529 (13) | 4.27 (3.86, 4.73) | 230 (6.1) | 2.08 (1.81, 2.40) | 90 (30) | 9.76 (7.38, 12.9) |
| **Stillbirth[b]** | | | | | | | | |
| <35 yrs. | 7,388 (0.31) | Reference | 60 (0.66) | 1.75 (1.35, 2.27) | 69 (0.37) | 1.10 (0.86, 1.39) | 4 (0.52) | - |
| ≥35 yrs. | 1,747 (0.44) | Reference | 38 (0.89) | 1.67 (1.20, 2.32) | 25 (0.64) | 1.39 (0.92, 2.10) | 3 (0.96) | - |
| **Small for gestational age[b]** | | | | | | | | |
| <35 yrs. | 59,502 (2.5) | Reference | 664 (7.4) | 3.61 (3.32, 3.93) | 599 (3.2) | 1.26 (1.16, 1.37) | 81 (11) | 4.92 (3.86, 6.26) |
| ≥35 yrs. | 10,700 (2.7) | Reference | 383 (9.0) | 3.77 (3.36, 4.23) | 156 (4.0) | 1.41 (1.19, 1.67) | 30 (9.7) | 3.89 (2.56, 5.89) |

Total number of pregnancies of mothers <35 years= 2,384,532; and pregnancies to mothers who were 35 years or older = 403,958.
CH, chronic hypertension; CKD, chronic kidney disease. [a] adjusted for educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes, cardiovascular disease, asthma), birth year and child's gender. [b] adjusted for educational level, smoking, BMI, country of origin, parity, other comorbidities (diabetes, cardiovascular disease, asthma) and birth year.

**Table S5.5** Adjusted estimates for the association between maternal chronic diseases and adverse pregnancy outcomes stratified by maternal BMI

| Outcome | Normotensive women | | Pregnancy with CH | | Pregnancy with CKD) | | Pregnancy with CH & CKD | |
|---|---|---|---|---|---|---|---|---|
| | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) | Cases, n (%) | OR (95% CI) |
| **Pre-eclampsia[a]** | | | | | | | | |
| Underweight[*] | 1,387 (1.8) | Reference | 16 (12) | 7.46 (4.36, 12.8) | 19 (2.7) | 1.68 (1.06, 2.67) | 1 (3.9) | - |
| Normal [ł] | 31,584 (2.3) | Reference | 553 (13) | 5.94 (5.39, 6.55) | 400 (3.5) | 1.66 (149, 1.84) | 68 (15) | 4.48 (3.21, 6.25) |
| Overweight [§] | 16,139 (3.5) | Reference | 450 (14) | 4.16 (3.73, 4.65) | 228 (5.4) | 1.65 (1.43, 1.90) | 35 (16) | 3.36 (2.14, 5.26) |
| Obese[¥] | 10,522 (5.8) | Reference | 515 (18) | 3.14 (2.82, 3.49) | 141 (7.4) | 1.38 (1.15, 1.65) | 43 (26) | 4.26 (2.85, 6.37) |
| **Emergency cesarean section[b]** | | | | | | | | |
| Underweight[*] | 3,579 (5.5) | Reference | 15 (14) | 2.43 (1.37, 4.30) | 42 (7.8) | 1.20 (0.86, 1.66) | 3 (14) | - |
| Normal [ł] | 81,779 (7.2) | Reference | 458 (14) | 1.77 (1.59, 1.97) | 855 (10) | 1.34 (1.24, 1.45) | 65 (20) | 1.44 (0.98, 2.13) |
| Overweight [§] | 37, 898 (10) | Reference | 453 (20) | 1.69 (1.50, 1.90) | 454 (14) | 1.42 (1.28, 1.58) | 47 (33) | 2.52 (1.61, 3.93) |
| Obese[¥] | 20,492 (14) | Reference | 513 (25) | 1.49 (1.33, 1.66) | 271 (19) | 1.38 (1.20, 1.60) | 42 (38) | 2.05 (1.29, 3.25) |
| **Elective cesarean section[b]** | | | | | | | | |
| Underweight[*] | 3,491 (5.3) | Reference | 8 (8.0) | 1.04 (0.50, 2.18) | 49 (8.9) | 1.50 (1.10, 2.05) | 4 (17) | - |
| Normal [ł] | 69,816 (6.2) | Reference | 428 (14) | 1.75 (1.57, 1.96) | 932 (11) | 1.66 (1.54, 1.79) | 87 (25) | 2.57 (1.87, 3.52) |
| Overweight [§] | 29,760 (8.3) | Reference | 390 (17) | 1.68 (1.45, 1.89) | 383 (12) | 1.44 (1.28, 1.62) | 48 (34) | 2.57 (1.67, 3.96) |
| Obese[¥] | 15,543 (11) | Reference | 378 (19) | 1.38 (1.21, 1.56) | 232 (17) | 1.43 (1.22, 1.67) | 31 (31) | 2.21 (1.38, 3.53) |
| **Spontaneous preterm birth (<37 weeks' gestation)[b]** | | | | | | | | |
| Underweight[*] | 2,100 (2.8) | Reference | 3 (2.5) | - | 36 (5.4) | 1.49 (1.07, 2.09) | 1 (4.4) | - |
| Normal [ł] | 33,143 (2.4) | Reference | 133 (3.3) | 1.28 (1.07, 1.53) | 349 (3.2) | 1.18 (1.06, 1.32) | 18 (5.0) | 1.12 (0.66, 1.90) |
| Overweight [§] | 12,195 (2.7) | Reference | 92 (3.2) | 1.06 (0.85, 1.31) | 130 (3.3) | 1.13 (0.93, 1.36) | 6 (3.8) | 0.74 (0.32, 1.75) |
| Obese[¥] | 5,481 (3.1) | Reference | 86 (3.4) | 0.99 (0.79, 1.24) | 80 (3.4) | 1.40 (1.11, 1.76) | 2 (1.6) | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Medically indicated preterm birth (<37 weeks' gestation)[b]** | | | | | | | | |
| Underweight* | 2,796 (3.7) | Reference | 17 (13) | 5.17 (3.05, 8.76) | 35 (5.3) | 1.70 (1.19, 2.44) | 3 (12) | - |
| Normal ł | 30,288 (2.2) | Reference | 370 (8.7) | 4.10 (3.65, 4.61) | 483 (4.4) | 2.12 (1.92, 2.32) | 103 (23) | 8.93 (6.77, 11.8) |
| Overweight § | 9,588 (2.1) | Reference | 298 (10) | 4.08 (3.58, 4.66) | 201 (4.9) | 2.27 (1.95, 2.64) | 56 (27) | 8.84 (5.93, 13.2) |
| Obese¥ | 4,997 (2.8) | Reference | 322 (11) | 3.54 (3.10, 4.04) | 103 (5.6) | 1.86 (1.52, 2.28) | 43 (26) | 7.24 (4.91, 10.7) |
| **Stillbirth[b]** | | | | | | | | |
| Underweight* | 165 (0.21) | Reference | 1 (0.73) | - | 3 (0.43) | - | 0 | - |
| Normal ł | 3,514 (0.25) | Reference | 25 (0.57) | 2.05 (1.38, 3.05) | 29 (0.26) | 0.96 (0.67, 1.39) | 2 (0.43) | - |
| Overweight § | 1,699 (0.37) | Reference | 18 (0.56) | 1.33 (0.84, 2.12) | 25 (0.60) | 1.51 (1.00, 2.28) | 0 | - |
| Obese¥ | 1,002 (0.55) | Reference | 33 (1.1) | 1.78 (1.23, 2.54) | 11 (0.57) | 0.95 (0.52, 1.72) | 2 (1.2) | - |
| **Small for gestational age[b]** | | | | | | | | |
| Underweight* | 3,719 (4.7) | Reference | 18 (13) | 3.44 (2.05, 5.79) | 40 (5.7) | 1.11 (0.80, 1.53) | 3 (12) | - |
| Normal ł | 34,134 (2.4) | Reference | 375 (8.6) | 3.91 (3.50, 4.37) | 364 (3.2) | 1.27 (1.13, 1.41) | 49 (11) | 4.53 (3.29, 6.24) |
| Overweight § | 9,451 (2.1) | Reference | 212 (6.6) | 3.52 (3.04, 4.07) | 110 (2.6) | 1.22 (1.00, 1.49) | 18 (8.3) | 5.19 (3.09, 8.70) |
| Obese¥ | 4,082 (2.2) | Reference | 176 (6.1) | 2.80 (2.37, 3.30) | 67 (3.5) | 1.55 (1.21, 1.99) | 9 (5.4) | 2.70 (1.37, 5.32) |

CH, Chronic hypertension; CKD, chronic kidney disease

* Underweight (BMI<18.5 kg/m2); ł Normal (BMI≥18.5 to<25 kg/m2); § Overweight (BMI ≥25 to <30 kg/m2), ¥ Obese (BMI: ≥30 kg/m2). [a] adjusted for maternal age, educational level, smoking, country of origin, parity, other comorbidities (diabetes, cardiovascular disease, asthma), birth year and child's gender. [b] adjusted for maternal age, educational level, smoking, country of origin, parity, other comorbidities (diabetes, cardiovascular disease, asthma) and birth year.

**Table S5.6** The association between maternal chronic diseases and perinatal outcomes after excluding women with comorbidities (singleton pregnancies 1982–2012)

| Outcome | Pregnancies of normotensive women N= 2,608,565 | Chronic hypertension (CH) N=11,550 | Chronic kidney disease (CKD) N= 20,012 | CH & CKD N= 716 |
|---|---|---|---|---|
| **Pre-eclampsia** | | | | |
| Adjusted OR (95% CI)[a] | Reference | 4.97 (4.69, 5.27) | 1.61 (1.49, 1.74) | 7.37 (5.93. 9.14) |
| **Emergency Caesarean section** | | | | |
| Adjusted OR (95% CI)[b] | Reference | 1.74 (1.63, 1.86) | 1.35 (1.27, 1.42) | 2.79 (2.20, 3.54) |
| **Elective Caesarean section** | | | | |
| Adjusted OR (95% CI)[b] | Reference | 1.76 (1.65, 1.88) | 1.57 (1.48, 1.66) | 3.76 (3.01, 4.70) |
| **Spontaneous preterm birth (<37wk.)** | | | | |
| Adjusted OR (95% CI)[b] | Reference | 1.10(0.97, 1.23) | 1.24 (1.14, 1.35) | 1.70 (1.09, 2.67) |
| **Medically indicated preterm birth (<37wk.)** | | | | |
| Adjusted OR (95% CI)[b] | Reference | 4.11 (3.85, 4.41) | 1.094 (1.81, 2.09) | 12.5 (10.22, 15.3) |
| **Stillbirth** | | | | |
| Adjusted OR (95% CI) [b] | Reference | 1.66 (1.35, 2.09) | 1.19 (0.95, 1.49) | 1.52 (0.56, 4.07) |
| **Small for gestational age** | | | | |
| Adjusted OR (95% CI)[b] | Reference | 3.62 (3.37, 3.89) | 1.25 (1.15, 1.36) | 5.38 (4.27, 6.80) |

A total of (n=147,647) records with comorbidities (DM, CVD or asthma) were deleted from these analyses. All adjusted estimates cluster on mothers' ID. [a] adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, birth year and child's gender. [b] adjusted for maternal age, educational level, smoking, BMI, country of origin, parity, and birth year.

# Appendix 6: The Role of Antihypertensive Treatment and Blood Pressure Control in the Occurrence of Adverse Pregnancy Outcomes: A Population-based Study of Linked Electronic Health Records (supplemental material)

## S6.1 Supplementary Methods

In propensity score matching, four separate comparisons were made. The first assessed adverse pregnancy outcomes in pregnancies exposed to antihypertensive treatment compared to untreated hypertensive pregnancies. In this model, the exposed group included pregnant women using any antihypertensive agent(s) (*inferred* or *diagnosed*), whereas the unexposed group included untreated pregnant women with *diagnosed* hypertension. The second comparison was of pregnancy outcomes in pregnant women with chronic hypertension using methyldopa versus β-blockers. Third, we compared pregnancy outcomes in those using calcium channel blockers versus β-blockers. Finally, we compared pregnancy outcomes in those using calcium channel blockers versus methyldopa. The propensity score algorithm was run separately for each comparison to match a record in the exposed group to the unexposed group. We used a logit model to create the propensity score for the probability of being treated, with the covariates of age (continuous), ethnicity, smoking, BMI, pre-pregnancy diabetes, parity and IMD (baseline characteristics before and after applying propensity score matching is shown in Table S6.12).

Propensity score matching analysis in this study was comprised of four steps. First, the propensity scores were estimated. Second, treatment and comparison units were matched by the closeness of their propensity scores, using 1:1 nearest-neighbour matching with a caliper width of 0.1 SDs of the logit of the propensity score (3). Third, overlap and balance of propensity score distributions (balance plots) across treatment and comparison groups were assessed through visual inspection. Fourth step was to assess the balance of covariates (included in the propensity score estimation model) after matching using standardized differences to compare all covariates, with a value $< 0.1$ indicating good balance and a negligible difference between groups for the covariates (4). Additionally, we used variance of ratios to assess the balance between the treatment and comparison groups, and kernel densities were plotted to examine balance of distributions of a continuous variable (maternal age) across matched treatment and comparison groups (5).

## S6.2 Supplementary Figures (S6.1-S6.6) and Tables (S6.1-S6.13)

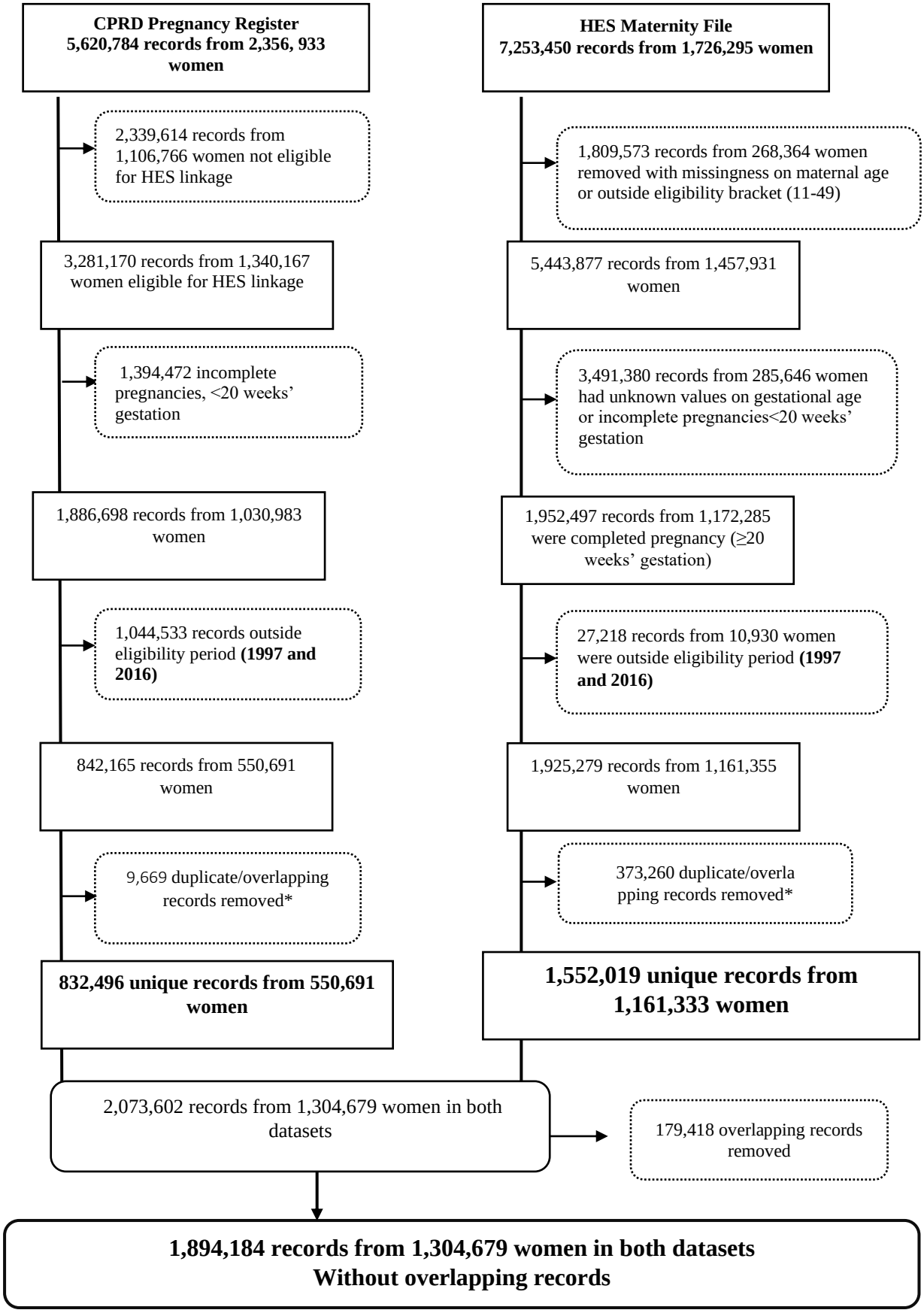



**Figure S6.1** Flow diagram of pregnancy cohort from CPRD and HES datasets

*dealing with overlapping records illustrated in **Figure S6.6**

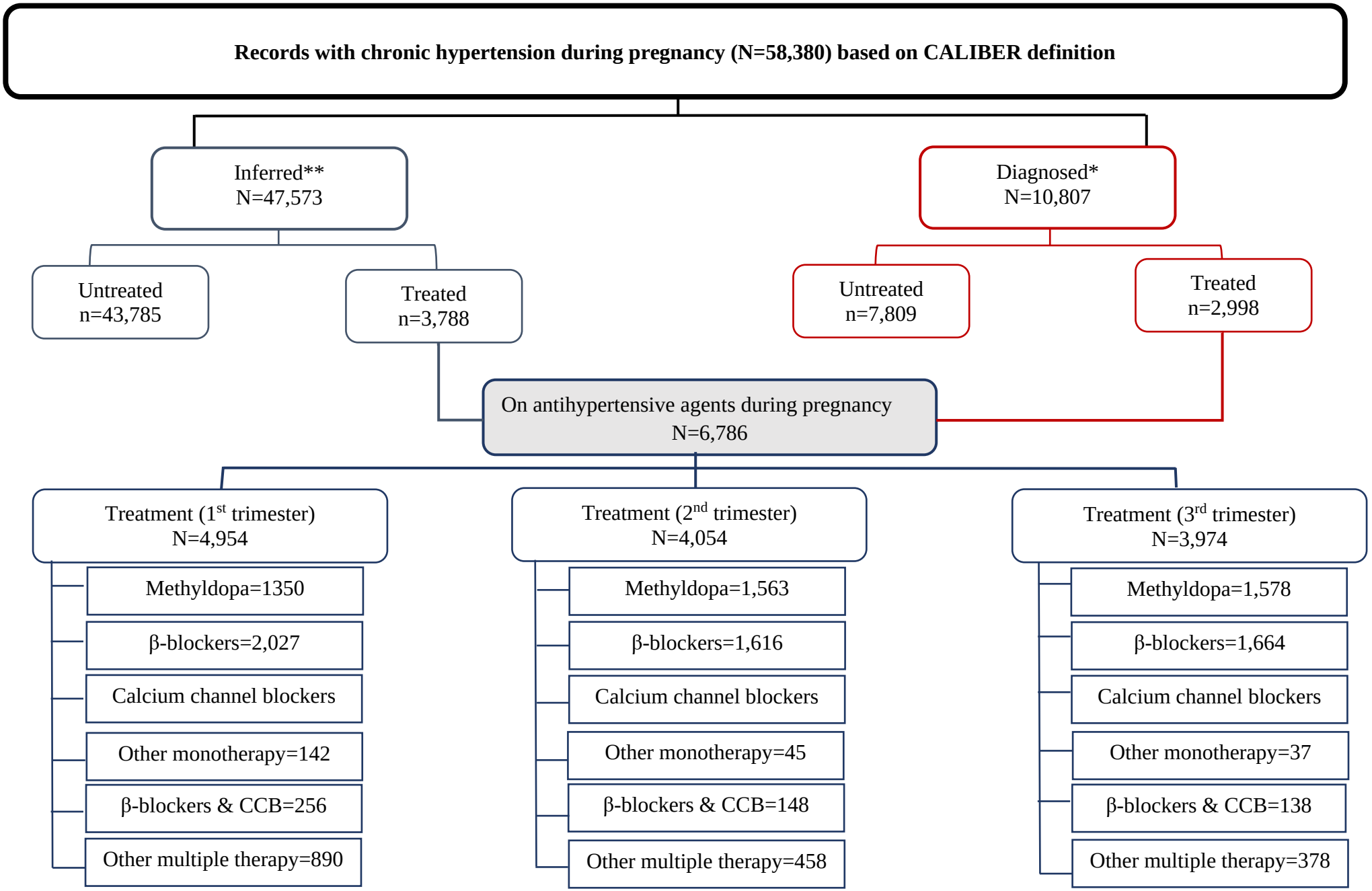



**Figure S2:** Flow diagram for women with chronic hypertension during pregnancy

*Diagnosed: Diagnosis of hypertension during a consultation in primary or secondary care; **Inferred: Based on continuous blood pressure readings or blood pressure lowering medication

**Table S6.1** Treatment patterns during the first trimester of pregnancy across women with chronic hypertension

| **SWITCHERS from 1st TRIMESTER** | **2nd TRIMESTER** | | | | |
|---|---|---|---|---|---|
| | Diuretics | β-blockers | Methyldopa | Calcium channel blockers | Polytherapy* |
| Diuretics (n=142) | NA | 4 | 9 | 0 | 2 |
| β-blockers (n=2,027) | 0 | NA | 27 | 5 | 43 |
| Methyldopa (n=1,350) | 0 | 29 | NA | 6 | 49 |
| Calcium channel blockers (n=289) | 0 | 6 | 17 | NA | 23 |
| Polytherapy (n=1,146) | 0 | 198 | 233 | 34 | NA |
| **SWITCHERS from 2nd TRIMESTER** | **3rd TRIMESTER** | | | | |
| Diuretics (n=45) | NA | 1 | 1 | 0 | 2 |
| β-blockers (n=1,616) | 0 | NA | 10 | 1 | 31 |
| Methyldopa (n=1,563) | 0 | 18 | NA | 0 | 55 |
| Calcium channel blockers (n=224) | 0 | 2 | 6 | NA | 14 |
| Polytherapy (n=606) | 0 | 65 | 75 | 9 | MA |

*Polytherapy group includes women who were exposed to more than one agent during any stage of pregnancy

**Table S6.2** Baseline demographic characteristics for normotensive and hypertensive pregnancies

| | **Normotensive untreated pregnancies* n=1,739,944** | **Diagnosed untreated hypertension n=7,809** | **Diagnosed treated hypertension n=2,998** | **Inferred untreated hypertension n=43,785** | **Inferred treated hypertension n=3,788** |
|---|---|---|---|---|---|
| **Age (years),** mean (SD) | 28.9 (6) | 32.7 (5.3) | 34.5 (5.3) | 31.4 (5.4) | 31.2 (5.9) |
| **Ethnicity, n (%)** | | | | | |
| White | 1,414,774 (81) | 6,453 (83) | 2,196 (73) | 39,767 (91) | 3,303 (87) |
| Black | 69,944 (4) | 623 (8) | 422 (14) | 1,010 (2.3) | 152 (4) |
| South Asian | 101,939 (5.9) | 241 (3.1) | 178 (5.9) | 1,226 (2.8) | 145 (3.8) |
| Other [a] | 81,695 (4.7) | 207 (2.7) | 118 (3.9) | 872 (2) | 97 (2.6) |
| Unknown | 71,592 (4.1) | 285 (3.7) | 84 (2.8) | 910 (2.1) | 91 (2.4) |
| **Smoking, n (%)** | | | | | |
| Non-smoker | 245,680 (14) | 1,394 (18) | 1,398 (47) | 9,401 (22) | 1,187 (31) |
| Ex-smoker | 89,446 (5.1) | 498 (6.4) | 425 (14) | 4,584 (11) | 525 (14) |
| Current smoker | 140,524 (8.1) | 556 (7.1) | 330 (11) | 5,919 (14) | 789 (21) |
| missing | 1,264,294 (73) | 5,361 (69) | 845 (28) | 23,881 (55) | 1,287 (34) |
| **Body mass index [b]** | | | | | |
| Underweight | 19,387 (1.1) | 38 (0.5) | 13 (0.4) | 490 (1.1) | 64 (1.7) |
| Normal | 275,769 (16) | 1,033 (13) | 502 (17) | 8,386 (19) | 949 (25) |
| Overweight | 146,769 (8.4) | 938 (12) | 652 (22) | 6,429 (15) | 723 (19) |
| Obese | 114,087 (6.6) | 1,453 (19) | 1,090 (36) | 8,571 (20) | 948 (25) |
| Severe obesity | 8,871 (0.5) | 263 (3.4) | 225 (7.5) | 1,257 (2.9) | 182 (4.8) |
| Missing | 1,175,034 (68) | 4,084 (52) | 516 (17) | 18,652 (43) | 922 (24) |
| **Pre-pregnancy diabetes, n (%)** | 5,704 (0.33) | 334 (4.3) | 193 (6.4) | 824 (1.9) | 189 (5) |
| **Chronic kidney disease, n (%)** | 713 (0.04) | 59 (0.76) | 67 (2.2) | 114 (0.26) | 26 (0.69) |
| **Parity, n (%)** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Nulliparous | 325,890 (19) | 1,312 (17) | 497 (17) | 9,728 (22) | 752 (20) |
| Multiparous | 1,106,208 (64) | 4,596 (59) | 2,033 (68) | 25,962 (59) | 2,454 (65) |
| Unknown | 307,846 (18) | 1,901 (24) | 468 (16) | 8,095 (18) | 582 (15) |
| **Maternal outcome** | | | | | |
| Pre-eclampsia | 29,859 (1.6) | 839 (11) | 490 (16) | 2,050 (4.7) | 371 (9.8) |
| Emergency Caesarean section | 172,748 (11) | 1,074 (16) | 443 (18) | 5,026 (13) | 445 (13) |
| Elective Caesarean section | 138,260 (8.8) | 1,083 (16) | 472 (18) | 4,786 (12) | 462 (14) |
| Stroke | 137 (0.01) | 3 (0.04) | - | 4 (0.01) | 4 (0.11) |
| Maternal Death | 58 | - | - | 2 | - |
| **Fetal/neonatal outcome** | | | | | |
| Stillbirth | 7,631 (0.44) | 67 (0.86) | 29 (0.97) | 269 (0.61) | 37 (0.98) |
| Gestational age (wk.), mean (SD) | 39.1 (2.6) | 38.3 (3.1) | 37.6 (3.7) | 38.7 (2.8) | 38.2 (3.2) |
| Preterm birth (<37 wk.) | 63,460 (3.7) | 677 (8.7) | 436 (15) | 2,794 (6.4) | 425 (11) |
| Very preterm birth (<32 wks.) | 17,507 (1) | 203 (2.8) | 178 (6.5) | 753 (1.8) | 140 (4) |
| Fetal growth restriction | 34,584 (2) | 270 (3.5) | 160 (5.3) | 1,304 (3) | 216 (5.7) |

* 95,860 records with either unspecified hypertension, other hypertensive disorders during pregnancy or exposed to antihypertensive agent were excluded from analyses except for pre-eclampsia investigation. [a] This category includes mixed ethnic group and another ethnic group; [b] underweight (BMI<18.5 kg/m2); Normal (BMI≥18.5 to<25 kg/m2); Overweight (BMI ≥25 to <30 kg/m2); Obese (BMI: ≥30 to <40 kg/m2); and severe obesity (BMI: ≥40 kg/m2)

**Table S6.3** Chronic hypertension and adverse perinatal outcomes compared to normotensive untreated group (based on definition/treatment of hypertension)

| Exposure / Outcome | **Chronic hypertension (**diagnosed**) vs normotensive**[a] | | | **Chronic hypertension (**inferred**) vs normotensive**[a] | | |
|---|---|---|---|---|---|---|
| | **Crude OR (95% CI)** | | | **Crude OR (95% CI)** | | |
| | Diagnosed (treated + untreated) N=10,807 | Untreated n=7,809 | Treated n=2,998 | Inferred (treated + untreated) N=53,784 | Untreated n= 43,785 | Treated n=3,788 |
| Pre-eclampsia | 8.58 (8.09, 9.09) | 7.28 (6.77, 7.82) | 11.8 (10.7, 13.2) | 3.28 (3.14, 3.42) | 2.97 (2.84, 3.11) | 6.57 (5.90, 7.31) |
| Emergency Caesarean section[b] | 1.62 (1.54, 1.71) | 1.57 (1.47, 1.68) | 1.76 (1.59, 1.95) | 1.23 (1.19, 1.26) | 1.22 (1.19, 1.26) | 1.28 (1.16, 1.41) |
| Elective Caesarean section[c] | 2.08 (1.97, 2.19) | 1.98 (1.86, 2.11) | 2.34 (2.12, 2.69) | 1.47 (1.42, 1.52) | 1.46 (1.41, 1.50) | 1.66 (1.50, 1.83) |
| Stillbirth | 2.03 (1.66, 2.49) | 1.96 (1.54, 2.50) | 2.22 (1.54, 3.20) | 1.47 (1.31, 1.64) | 1.40 (1.24, 1.59) | 2.24 (1.62, 3.10) |
| Preterm birth (<37 wk.) | 3.03 (2.85, 3.23) | 2.51 (2.32, 2.71) | 4.50 (4.06, 4.98) | 1.92 (1.84, 1.99) | 1.80 (1.73, 1.87) | 3.33 (3.02, 3.69) |
| Very preterm birth (<32 wk.)[d] | 3.76 (3.39, 4.17) | 2.73 (2.37, 3.14) | 6.65 (5.71, 7.75) | 1.93 (1.80, 2.06) | 1.76 (1.63, 1.89) | 3.99 (3.36, 4.72) |
| Fetal growth restriction | 2.04 (1.85, 2.25) | 1.77 (1.56, 1.99) | 2.78 (2.37, 3.26) | 1.62 (1.54, 1.71) | 1.51 (1.43, 1.60) | 2.98 (2.60, 3.42) |
| **Exposure / Outcome** | **Adjusted OR (95% CI)*** | | | **Adjusted OR (95% CI)*** | | |
| | **Diagnosed (treated + untreated)** | **Untreated** | **Treated** | **Diagnosed (treated + untreated)** | **Untreated** | **Treated** |
| Pre-eclampsia | 6.24 (5.87, 6.64) | 5.85 (5.43, 6.30) | 7.19 (6.49, 7.97) | 2.55 (2.44, 2.66) | 2.37 (2.26, 2.48) | 4.73 (4.23, 5.28) |
| Emergency Caesarean section[b] | 1.27 (1.20, 1.35) | 1.24 (1.16, 1.33) | 1.36 (1.22, 1.51) | 1.09 (1.06, 1.12) | 1.08 (1.05, 1.12) | 1.18 (1.07, 1.31) |
| Elective Caesarean section[c] | 1.33 (1.26, 1.41) | 1.32 (1.23, 1.41) | 1.36 (1.23, 1.51) | 1.18 (1.15, 1.22) | 1.17 (1.13, 1.21) | 1.32 (1.20, 1.47) |
| Stillbirth | 1.56 (1.27, 1.92) | 1.58 (1.24, 2.01) | 1.53 (1.06, 2.22) | 1.26 (1.12, 1.42) | 1.22 (1.08, 1.38) | 1.73 (1.25, 1.40) |
| Preterm birth (<37 wk.) | 2.48 (2.33, 2.65) | 2.13 (2.96, 2.31) | 3.43 (3.08, 3.81) | 1.65 (1.59, 1.72) | 1.75 (1.51, 1.64) | 2.57 (2.31, 2.85) |
| Very preterm birth (<32wk)[d] | 3.17 (2.85, 3.53) | 2.38 (2.07, 2.75) | 5.27 (4.50, 6.17) | 1.76 (1.64, 1.88) | 1.63 (1.51, 1.76) | 3.26 (2.74, 3.87) |
| Fetal growth restriction | 2.34 (2.12, 2.58) | 1.99 (1.76, 2.25) | 3.35 (2.85, 3.94) | 1.65 (1.56, 1.74) | 1.55 (1.46, 1.64) | 2.82 (2.46, 3.25) |

[a] The reference group refers to normotensive women who were unexposed to antihypertensive treatment during pregnancy; [b] in the analysis of emergency caesarean section, elective caesarean section was excluded; [c] in the analysis of elective caesarean section, emergency caesarean section was excluded; [d] in the analysis of very preterm birth, deliveries between 33-<37 were excluded; *Adjusted for maternal age, deprivation index (practice IMD 2015), smoking, body mass index, ethnicity, parity, and pre-pregnancy disease (diabetes, kidney disease)

**Table S6.4** Antihypertensive treatment and adverse perinatal outcomes in women with chronic hypertension (treated vs untreated) according to control level in the treated group, using propensity score matched sample

| Outcome | n (%) | Crude OR (95% CI) | Adjusted OR (95% CI)* |
|---|---|---|---|
| **Severe hypertension in 3rd trimester** | | | |
| Untreated chronic hypertension (n=6,766) | 132 (1.95) | Reference | Reference |
| Tight control[a] (n=1,076) | 20 (1.86) | 0.95 (0.59, 1.53) | 0.96 (0.59, 1.54) |
| Less-tight control[b] (n=4,287) | 257 (5.99) | 3.21 (2.59, 3.97) | 3.11 (2.50, 3.86) |
| **Pre-eclampsia** | | | |
| Untreated chronic hypertension (n=6,766) | 741 (10.9) | Reference | Reference |
| Tight control[a] (n=1,076) | 74 (6.88) | 0.60 (0.47, 0.77) | 0.59 (0.46, 0.76) |
| Less-tight control[b] (n=4,287) | 670 (15.6) | 1.51 (1.35, 1.69) | 1.47 (1.31, 1.65) |
| **Emergency Cesarean section[c]** | | | |
| Untreated chronic hypertension (n=5,923) | 893 (15.1) | Reference | Reference |
| Tight control[a] (935) | 130 (13.9) | 0.91 (0.75, 1.11) | 0.92 (0.75, 1.13) |
| Less-tight control[b] (3,654) | 622 (17.0) | 1.16 (1.03, 1.29) | 1.12 (0.99, 1.26) |
| **Elective Cesarean section[d]** | | | |
| Untreated chronic hypertension (n=5,873) | 843 (14.3) | Reference | Reference |
| Tight control[a] (n=946) | 141 (14.9) | 1.05 (0.86, 1.27) | 1.12 (0.92, 1.37) |
| Less-tight control[b] (n=3,665) | 633 (17.3) | 1.25 (1.11, 1.39) | 1.25 (1.06, 1.33) |
| **Stillbirth** | | | |
| Untreated chronic hypertension (n=6,766) | 46 (0.68) | Reference | Reference |
| Tight control[a] (n=1,076) | 6 (0.56) | 0.82 (0.35, 1.29) | 0.93 (0.39, 2.20) |
| Less-tight control[b] (n=4,287) | 49 (1.14) | 1.69 (1.13, 2.53) | 1.69 (1.11, 2.51) |
| **Preterm birth (<37 wks.)** | | | |
| Untreated chronic hypertension (n=6,766) | 700 (10.4) | Reference | Reference |
| Tight control[a] (n=1,076) | 121 (11.3) | 1.10 (0.89, 1.35) | 1.04 (0.85, 1.29) |
| Less-tight control[b] (n=4,287) | 600 (14.0) | 1.41 (1.26, 1.58) | 1.39 (1.23, 1.56) |
| **Very preterm birth (<32 wks.) [e]** | | | |
| Untreated chronic hypertension (n=6,261) | 195 (3.11) | Reference | Reference |
| Tight control[a] (n=988) | 33 (3.34) | 1.07 (0.74, 1.56) | 1.01 (0.69, 1.48) |
| Less-tight control[b] (n=3,935) | 248 (6.30) | 2.09 (1.73, 2.54) | 2.06 (1.69, 2.50) |
| **Fetal growth restriction** | | | |
| Untreated chronic hypertension (n=6,766) | 212 (3.13) | Reference | Reference |
| Tight control[a] (n=1,076) | 54 (5.02) | 1.63 (1.20, 2.21) | 1.55 (1.14, 2.12) |
| Less-tight control[b] (n=4,287) | 253 (5.90) | 1.94 (1.61, 2.34) | 1.96 (1.62, 2.37) |

* Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy disease (diabetes, kidney disease).[a] Tight control group refers to treated women with chronic hypertension whose average blood pressure in the 1st & 2nd trimesters was both <135/85 mmHg; [b] less-tight control group refers to treated women with chronic hypertension whose average blood pressure in the 1st & 2nd trimesters was either ≥135/85 mmHg. Treated women without available data on blood pressure readings were excluded (n=1430); [c] in the analysis of emergency Cesarean section, elective Cesarean section were excluded; [d] in the analysis of elective Cesarean section, emergency Cesarean section were excluded; [e] in the analysis of very preterm birth, deliveries between 33-37 were excluded

**Table S6.5** Antihypertensive treatment during pregnancy and adverse perinatal outcomes in women with chronic hypertension (treated vs untreated) using original cohort

| Treatment / Outcome | Frequency n (%) | | Treated vs untreated[a] | |
|---|---|---|---|---|
| | **Untreated (n=7,792)** | **Treated (n=6,766)** | **Crude OR (95% CI)** | **Adjusted OR (95% CI)[b]** |
| **Severe hypertension** | 235 (3) | 994 (15) | 5.54 (4.78, 6.41) | 4.13 (3.53, 4.82) |
| **Pre-eclampsia** | 836 (11) | 860 (13) | 1.21 (1.09, 1.34) | 1.17 (1.04, 1.31) |
| **Emergency Caesarean section[c]** | 1,071 (16) | 887/5,833 (15) | 0.94 (0.86, 1.04) | 0.95 (0.85, 1.07) |
| **Elective Caesarean section[d]** | 1,081 (16) | 933 /5,879(16) | 0.98 (0.89, 1.08) | 1.05 (0.94, 1.17) |
| **Stillbirth** | 67 (0.86) | 66 (0.98) | 1.14 (0.81, 1.60) | 1.31 (0.89, 1.91) |
| **Preterm birth (<37 wk.)** | 674 (8.7) | 858 (13) | 1.54 (1.38, 1.71) | 1.38 (1.23, 1.55) |
| **Very preterm birth (<32 wks.)[e]** | 201/7,319 (2.7) | 317/6,225 (5.1) | 1.90 (1.59, 2.27) | 1.66 (1.38, 2.00) |
| **Fetal growth restriction** | 269 (3.5) | 374 (5.5) | 1.64 (1.39, 1.92) | 1.45 (1.21, 1.73) |

[a] Treated women with chronic hypertension vs untreated with chronic hypertension using original cohort (N=14,558); [b] Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes; [c] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [d] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [e] in the analysis of very preterm birth, deliveries between 33-<37 were excluded

**Table S6.6** The effect of antihypertensive agents on adverse perinatal outcomes in women with chronic hypertension using original cohort

| Treatment / Outcome | **Methyldopa vs β-blockers** (unmatched sample)[a] | | **calcium channel blockers vs β-blockers** (unmatched sample)[b] | | **calcium channel blockers vs methyldopa** (unmatched sample)[c] | |
|---|---|---|---|---|---|---|
| | **Crude OR (95% CI)** | **Adjusted OR (95% CI)[d]** | **Crude OR (95% CI)** | **Adjusted OR (95% CI)[d]** | **Crude OR (95% CI)** | **Adjusted OR (95% CI)[d]** |
| **Severe hypertension (2nd trimester)** | 1.54 (1.20, 1.97) | 1.46 (1.13, 1.88) | 0.50 (0.23, 1.08) | 0.50 (0.22, 1.11) | 0.32 (0.15, 0.70) | 0.34 (0.15, 0.73) |
| **Severe hypertension (3rd trimester)** | 1.65 (1.22, 2.23) | 1.60 (1.17, 2.17) | 0.78 (0.36, 1.71) | 0.80 (0.36, 1.80) | 0.47 (0.22, 1.03) | 0.51 (0.23, 1.13) |
| **Pre-eclampsia** | 1.77 (1.49, 2.12) | 1.59 (1.32, 1.91) | 1.63 (1.15, 2.31) | 1.43 (0.98, 2.07) | 0.92 (0.65, 1.30) | 0.93 (0.65, 1.33) |
| **Emergency Caesarean section[e]** | 1.20 (1.01, 1.43) | 1.10 (0.91, 1.33) | 1.44 (1.01, 2.03) | 1.33 (0.91, 1.96) | 1.20 (0.84, 1.70) | 1.19 (0.81, 1.74) |
| **Elective Caesarean section[f]** | 0.99 (0.83, 1.18) | 0.86 (0.71, 1.03) | 1.55 (1.11, 2.14) | 1.38 (0.97, 1.97) | 1.56 (1.12, 2.18) | 1.56 (1.09, 2.23) |
| **Stillbirth** | 0.90 (0.49, 1.67) | 0.78 (0.41, 1.48) | 1.81 (0.69, 4.76) | 1.54 (0.56, 4.27) | 2.00 (0.73, 5.47) | 2.02 (0.72, 5.67) |
| **Preterm birth (<37 wk.)** | 1.65 (1.38, 1.97) | 1.55 (1.29, 1.86) | 1.96 (1.41, 2.73) | 1.88 (1.32, 2.66) | 1.19 (0.86, 1.65) | 1.14 (0.81, 1.59) |
| **Very preterm birth (<32 wks.)[g]** | 1.56 (1.17, 2.09) | 1.43 (1.06, 1.92) | 1.85 (1.08, 3.15) | 1.54 (0.87, 2.72) | 1.18 (0.69, 2.01) | 1.08 (0.63, 1.87) |
| **Fetal growth restriction** | 0.60 (0.45, 0.80) | 0.65 (0.49, 0.88) | 1.06 (0.64, 1.76) | 0.99 (0.59, 1.69) | 1.76 (1.03, 3.00) | 1.76 (1.02, 3.04) |

[a] Methyldopa vs β-blockers using unmatched sample (N=4,654); [b] Calcium channel blockers vs β-blockers using unmatched sample (N=2,991); [c] calcium channel blockers vs methyldopa using unmatched sample (N=2,241); [d] adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes; [e] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [f] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [g] in the analysis of very preterm birth, deliveries between 33-<37 were excluded

**Table S6.7** Associations between antihypertensive agents and adverse perinatal outcomes in women with chronic hypertension based on subgroup analyses

| Outcome / Treatment | **Methyldopa vs β-blockers** (matched sample)[a] | | | | **calcium channel blockers vs β-blockers** (matched sample)[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | Cases in each group | | OR (95% CI) | Interaction *p*-value | Cases in each group | | OR (95% CI) | Interaction *p*-value |
| | **β-blockers** | **Methyldopa** | | | **β-blockers** | **CCB** | | |
| **Nulliparity women (exposed vs unexposed)** | n=333 | n=354 | | | n=46 | n=53 | | |
| Severe hypertension (2nd trimester) | 13 | 23 | 1.71 (0.85, 3.43) | 0.13 | 1 | 2 | - | - |
| Severe hypertension (3rd trimester) | 13 | 20 | 1.4 7(0.72, 3.01) | 0.29 | 1 | 5 | - | - |
| Pre-eclampsia | 50 | 65 | 1.27 (0.85, 1.91) | 0.24 | 8 | 12 | 1.39 (0.51, 3.77) | 0.52 |
| Emergency Caesarean section[d] | 75/273 | 98/310 | 1.22 (0.85, 1.75) | 0.28 | 12/41 | 21/40 | 2.67 (1.07, 6.67) | 0.04 |
| Elective Caesarean section[e] | 60/258 | 44/256 | 0.68 (0.44, 1.06) | 0.09 | 5/34 | 13/32 | 3.97 (1.22, 12.9) | 0.02 |
| Stillbirth | 1 | 3 | - | - | 0 | 0 | - | - |
| Preterm birth (<37 wk.) | 41 | 46 | 1.06 (0.68, 1.67) | 0.79 | 9 | 11 | 1.08 (0.40, 2.88) | 0.88 |
| Very preterm birth (<32 wks.)[f] | 20/312 | 13/321 | 0.62 (0.30, 1.26) | 0.19 | 6/43 | 5/47 | 0.73 (0.21, 2.60) | 0.63 |
| Fetal growth restriction | 24 | 15 | 0.57 (0.29, 1.11) | 0.10 | 5 | 5 | 0.85 (0.23, 3.16) | 0.81 |
| **Child's sex, male (exposed vs unexposed)*** | n=675 | n=593 | | | n=104 | n=83 | | |
| Severe hypertension (2nd trimester) | 35 | 39 | 1.29 (0.80, 2.06) | 0.30 | 5 | 2 | - | - |
| Severe hypertension (3rd trimester) | 19 | 29 | 1.77 (0.98, 3.20) | 0.06 | 5 | 3 | - | - |
| Pre-eclampsia | 93 | 98 | 1.24 (0.91, 1.69) | 0.17 | 18 | 11 | 0.73 (0.32, 1.65) | 0.45 |
| Emergency Caesarean section[d] | 134/513 | 143/474 | 1.22 (0.93, 1.61) | 0.16 | 29/82 | 19/56 | 0.94 (0.46, 1.92) | 0.86 |
| Elective Caesarean section[e] | 162/541 | 119/450 | 0.84 (0.64, 1.11) | 0.22 | 22/75 | 27/64 | 1.76 (0.87, 3.55) | 0.12 |
| Stillbirth | 6 | 5 | 0.95 (0.29, 3.12) | 0.93 | 2 | 1 | - | - |
| Preterm birth (<37 wk.) | 94 | 94 | 1.16 (0.85, 1.59) | 0.34 | 14 | 14 | 1.30 (0.58, 2.92) | 0.52 |
| Very preterm birth (<32 wks.)[f] | 28/609 | 31/530 | 1.29 (0.76, 2.18) | 0.16 | 8/98 | 5/74 | 0.82 (0.26, 2.60) | 0.73 |
| Fetal growth restriction | 27 | 25 | 1.05 (0.61, 1.84) | 0.88 | 5 | 7 | 1.82 (0.56, 5.97) | 0.32 |
| **Child's sex, female (exposed vs unexposed)*** | N=568 | N=599 | | | n=66 | n=95 | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Severe hypertension (2nd trimester) | 26 | 34 | 1.25 (0.74, 2.12) | 0.40 | 1 | 3 | - | - |
| Severe hypertension (3rd trimester) | 15 | 27 | 1.74 (0.92, 3.31) | 0.09 | 0 | 2 | - | - |
| Pre-eclampsia | 46 | 101 | 2.30 (1.59, 3.33) | 0.00 | 9 | 14 | 1.09 (0.44, 2.70) | 0.84 |
| Emergency Caesarean section[d] | 104/449 | 123/480 | 1.14 (0.85, 1.54) | 0.38 | 12/57 | 23/72 | 1.76 (0.79, 3.94) | 0.17 |
| Elective Caesarean section[e] | 119/464 | 119/476 | 0.97 (0.72, 1.30) | 0.82 | 9/54 | 23/72 | 2.35 (0.98, 5.60) | 0.06 |
| Stillbirth | 1 | 3 | - | - | 1 | 0 | - | - |
| Preterm birth (<37 wk.) | 44 | 95 | 2.24 (1.15, 3.28) | 0.00 | 6 | 21 | 2.84 (1.08, 7.48) | 0.04 |
| Very preterm birth (<32 wks.)[f] | 17/541 | 35/539 | 2.14 (1.18, 3.87) | 0.01 | 5/65 | 9/83 | 1.46 (0.46, 4.59) | 0.52 |
| Fetal growth restriction | 40 | 25 | 0.58 (0.35, 0.97) | 0.04 | 8 | 5 | 0.40 (0.13, 1.29) | 0.13 |
| **Over five-year period/ 1998-2002** | n=294 | n=482 | | | n=43 | n=48 | | |
| Severe hypertension (2nd trimester) | 15 | 41 | - | - | 3 | 1 | - | - |
| Severe hypertension (3rd trimester) | 2 | 19 | - | - | 0 | 1 | - | - |
| Pre-eclampsia | 17 | 60 | 2.32 (1.33, 4.06) | 0.00 | 2 | 4 | - | - |
| Emergency Caesarean section[d] | 31/252 | 52/424 | 1.00 (0.62, 1.60) | 0.99 | 4/38 | 3/42 | - | - |
| Elective Caesarean section[e] | 42/263 | 57/429 | 0.81 (0.52, 1.24) | 0.33 | 5/39 | 6/45 | 1.05 (0.29, 3.74) | 0.95 |
| Stillbirth | 0 | 7 | - | - | 1 | 1 | - | - |
| Preterm birth (<37 wk.) | 21 | 44/282 | 2.10 (1.26, 3.52) | 0.01 | 3 | 11 | - | - |
| Very preterm birth (<32 wks.)[f] | 7/280 | 26/440 | 2.45 (1.05, 5.72) | 0.04 | 1/41 | 2/39 | - | - |
| Fetal growth restriction | 7 | 18 | 1.59 (0.66, 3.86) | 0.30 | 0 | 2 | - | - |
| **2003-2007 (exposed vs unexposed)** | **N=443** | **N=681** | | | n=67 | n=71 | | |
| Severe hypertension (2nd trimester) | 18 | 46 | 1.73 (0.98, 3.01) | 0.06 | 9 | 2 | - | - |
| Severe hypertension (3rd trimester) | 22 | 48 | 0.80 (0.43, 1.51) | 0.50 | 6 | 0 | - | - |
| Pre-eclampsia | 75 | 117 | 1.02 (0.74, 1.40) | 0.91 | 12 | 16 | 1.33 (0.58, 3.08) | 0.50 |
| Emergency Caesarean section[d] | 32/389 | 74/615 | 1.53 (0.99, 2.36) | 0.06 | 7/61 | 11/57 | 1.84 (0.66, 5.15) | 0.24 |
| Elective Caesarean section[e] | 54/411 | 66/607 | 0.81 (0.55, 1.18) | 0.27 | 6/60 | 14/60 | 1.38 (0.42, 4.62) | 0.60 |
| Stillbirth | 5 | 7 | 0.91 (0.29, 2.88) | 0.87 | 0 | 1 | - | - |
| Preterm birth (<37 wk.) | 35 | 107 | 2.17 (1.45, 3.25) | 0.00 | 7 | 12 | 1.74 (0.64, 4.73) | 0.28 |
| Very preterm birth (<32 wks.)[f] | 11/419 | 29/603 | 1.87 (0.93, 3.79) | 0.08 | 4/64 | 6/65 | - | - |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Fetal growth restriction | 28 | 25 | 0.56 (0.32, 0.98) | 0.04 | 10 | 4 | - | - |
| **2008-2012 (exposed vs unexposed)** | n=552 | n=508 | | | n=78 | n=93 | | |
| Severe hypertension (2nd trimester) | 22 | 36 | 1.83 (1.06, 3.16) | 0.03 | 1 | 4 | - | - |
| Severe hypertension (3rd trimester) | 17 | 23 | 1.48 (0.78, 2.82) | 0.22 | 4 | 4 | - | - |
| Pre-eclampsia | 61 | 95 | 1.85 (1.31, 2.62) | 0.00 | 14 | 16 | 0.95 (0.43, 2.09) | 0.90 |
| Emergency Caesarean section[d] | 111/475 | 96/422 | 0.97 (0.71, 1.32) | 0.83 | 14/69 | 16/77 | 1.03 (0.46, 2.30) | 0.94 |
| Elective Caesarean section[e] | 77/441 | 86/412 | 1.25 (0.89, 1.77) | 0.21 | 9/64 | 16/77 | 1.60 (0.66, 3.92) | 0.30 |
| Stillbirth | 4 | 1 | - | - | 0 | 1 | - | - |
| Preterm birth (<37 wk.) | 77 | 74 | 1.05 (0.75, 1.48) | 0.77 | 11 | 15 | 1.17 (0.50, 2.73) | 0.71 |
| Very preterm birth (<32 wks.)[f] | 32/507 | 31/465 | 1.06 (0.64, 1.77) | 0.82 | 9/76 | 9/87 | 0.86 (0.32, 2.29) | 0.76 |
| Fetal growth restriction | 27 | 19 | 0.76 (0.41, 1.38) | 0.36 | 5 | 5 | 0.83 (0.23, 2.98) | 0.77 |
| **2013-2016 (exposed vs unexposed)** | n=663 | n=282 | | | n=101 | n=77 | | |
| Severe hypertension (2nd trimester) | 33 | 16 | 1.13 (0.62, 2.11) | 0.68 | 2 | 0 | - | - |
| Severe hypertension (3rd trimester) | 15 | 7 | 1.09 (0.44, 2.71) | 0.85 | 1 | 2 | - | - |
| Pre-eclampsia | 67 | 40 | 1.47 (0.97, 2.24) | 0.07 | 8 | 7 | 1.16 (0.40, 3.36) | 0.78 |
| Emergency Caesarean section[d] | 74/549 | 51/244 | 1.70 (1.14, 2.52) | 0.01 | 18/90 | 14/61 | 1.19 (0.54, 2.62) | 0.66 |
| Elective Caesarean section[e] | 114/589 | 38/231 | 0.82 (0.55, 1.23) | 0.34 | 11/83 | 16/63 | 2.23 (0.95, 5.22) | 0.07 |
| Stillbirth | 4 | 2 | - | - | 2 | 2 | - | - |
| Preterm birth (<37 wk.) | 66 | 44 | 1.67 (1.11, 2.52) | 0.01 | 8 | 12 | 2.15 (0.83, 5.54) | 0.12 |
| Very preterm birth (<32 wks.)[f] | 24/621 | 14/252 | 1.46 (0.74, 2.88) | 0.27 | 5/98 | 0 | - | - |
| Fetal growth restriction | 44 | 9 | 0.46 (0.22, 0.96) | 0.04 | 7 | 7 | 1.34 (0.85, 4.00) | 0.60 |

CCB, calcium channel blockers; [a] Methyldopa vs β-blockers using matched sample (N=3,904); the reference group refers to women who were on β-blockers; [b] calcium channel blockers vs β-blockers using matched sample (N=578); the reference group refers to women who were on β-blockers; [c] calcium channel blockers vs methyldopa using matched sample (N=578); the reference group refers to women who were on methyldopa; [d] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [e] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [f] in the analysis of very preterm birth, deliveries between 33-<37 were excluded. *Data on child's sex was available from hospital records only

**Table S6.7** Continue from previous page; Associations between antihypertensive agents and adverse perinatal outcomes in women with chronic hypertension based on subgroup analyses

| Outcome / Treatment | **calcium channel blockers vs methyldopa** (matched sample)[c] | | | |
|---|---|---|---|---|
| | Cases in each group | | OR (95% CI) | Interaction *p*-value |
| | **Methyldopa** | **CCB** | | |
| **Nulliparity women (exposed vs unexposed)** | n=38 | n=53 | | |
| Severe hypertension (2nd trimester) | 0 | 2 | - | - |
| Severe hypertension (3rd trimester) | 1 | 5 | - | - |
| Pre-eclampsia | 8 | 12 | 1.10 (0.40, 3.02) | 0.86 |
| Emergency Caesarean section[d] | 15/34 | 21/40 | 1.40 (0.56, 3.51) | 0.47 |
| Elective Caesarean section[e] | 4/23 | 13/32 | - | - |
| Stillbirth | 0 | 0 | - | - |
| Preterm birth (<37 wk.) | 5 | 11 | 1.73 (0.55, 5.47) | 0.35 |
| Very preterm birth (<32 wks.)[f] | 2/35 | 5/47 | - | - |
| Fetal growth restriction | 3 | 5 | - | - |
| **Child's sex, male (exposed vs unexposed)*** | n=83 | n=83 | | |
| Severe hypertension (2nd trimester) | 4 | 2 | - | - |
| Severe hypertension (3rd trimester) | 2 | 3 | - | - |
| Pre-eclampsia | 16 | 11 | 0.64 (0.28, 1.48) | 0.30 |
| Emergency Caesarean section[d] | 17/63 | 19/56 | 1.39 (0.63, 3.04) | 0.41 |
| Elective Caesarean section[e] | 20/66 | 27/64 | 1.68 (0.82, 3.46) | 0.16 |
| Stillbirth | 1 | 1 | - | - |
| Preterm birth (<37 wk.) | 13 | 14 | 1.09 (0.48, 2.49) | 0.83 |
| Very preterm birth (<32 wks.)[f] | 4/74 | 5/74 | 1.27 (0.33, 4.92) | 0.73 |
| Fetal growth restriction | 2 | 7 | - | - |
| **Child's sex, female (exposed vs unexposed)*** | n=79 | n=95 | | |
| Severe hypertension (2nd trimester) | 1 | 3 | - | - |
| Severe hypertension (3rd trimester) | 2 | 2 | - | - |
| Pre-eclampsia | 13 | 14 | 0.88 (0.36, 2.00) | 0.76 |
| Emergency Caesarean section[d] | 24/61 | 23/72 | 0.72 (0.35, 1.48) | 0.37 |
| Elective Caesarean section[e] | 18/55 | 23/72 | 0.96 (0.46, 2.04) | 0.93 |
| Stillbirth | 0 | 0 | - | - |
| Preterm birth (<37 wk.) | 17 | 21 | 1.03 (0.50, 2.13) | 0.93 |
| Very preterm birth (<32 wks.)[f] | 6/86 | 9/83 | 1.27 (0.43, 3.73) | 0.68 |
| Fetal growth restriction | 7 | 5 | 0.57 (0.17, 1.88) | 0.37 |
| **Over five-year period/ 1998-2002** | n=68 | n=48 | | |
| Severe hypertension (2nd trimester) | 7 | 1 | - | - |
| Severe hypertension (3rd trimester) | 3 | 1 | - | - |
| Pre-eclampsia | 5 | 4 | - | - |
| Emergency Caesarean section[d] | 7/54 | 3/42 | - | - |
| Elective Caesarean section[e] | 14/61 | 6/45 | 0.52 (0.18, 1.47) | 0.216 |
| Stillbirth | 3 | 1 | - | - |

| | | | | |
|---|---|---|---|---|
| Preterm birth (<37 wk.) | 11 | 11 | 1.54 (0.61, 3.91) | 0.36 |
| Very preterm birth (<32 wks.)[f] | 2/59 | 2/39 | - | - |
| Fetal growth restriction | 4 | 2 | - | - |
| **2003-2007 (exposed vs unexposed)** | n=97 | n=71 | | |
| Severe hypertension (2nd trimester) | 3 | 1 | - | - |
| Severe hypertension (3rd trimester) | 5 | 0 | - | - |
| Pre-eclampsia | 17 | 16 | 1.37 (0.64, 2.94) | 0.42 |
| Emergency Caesarean section[d] | 9/87 | 11/57 | 2.07 (0.80, 5.38) | 0.13 |
| Elective Caesarean section[e] | 10/88 | 14/60 | 2.37 (0.98, 5.78) | 0.06 |
| Stillbirth | 2 | 1 | - | - |
| Preterm birth (<37 wk.) | 19 | 12 | 0.83 (0.38, 1.85) | 0.66 |
| Very preterm birth (<32 wks.)[f] | 7/85 | 6/65 | 1.13 (0.36, 3.55) | 0.83 |
| Fetal growth restriction | 3 | 4 | - | - |
| **2008-2012 (exposed vs unexposed)** | n=77 | n=93 | | |
| Severe hypertension (2nd trimester) | 3 | 4 | - | - |
| Severe hypertension (3rd trimester) | 1 | 4 | - | - |
| Pre-eclampsia | 16 | 16 | 0.79 (0.37, 1.71) | 0.55 |
| Emergency Caesarean section[d] | 12/67 | 16/77 | 1.20 (0.52, 2.76) | 0.67 |
| Elective Caesarean section[e] | 10/65 | 16/77 | 1.44 (0.60, 3.44) | 0.41 |
| Stillbirth | 0 | 1 | - | - |
| Preterm birth (<37 wk.) | 13 | 15 | 0.95 (0.42, 2.13) | 0.90 |
| Very preterm birth (<32 wks.)[f] | 8/72 | 9/87 | 0.92 (0.34, 2.53) | 0.88 |
| Fetal growth restriction | 4 | 5 | - | - |
| **2013-2016 (exposed vs unexposed)** | n=47 | n=77 | | |
| Severe hypertension (2nd trimester) | 2 | 0 | - | - |
| Severe hypertension (3rd trimester) | 1 | 2 | - | - |
| Pre-eclampsia | 6 | 7 | 0.68 (0.21, 2.17) | 0.52 |
| Emergency Caesarean section[d] | 13/40 | 14/61 | 0.62 (0.25, 1.51) | 0.29 |
| Elective Caesarean section[e] | 7/34 | 16/63 | 1.31 (0.48, 3.59) | 0.60 |
| Stillbirth | 0 | 2 | - | - |
| Preterm birth (<37 wk.) | 8 | 12 | 0.90 (0.34, 2.39) | 0.83 |
| Very preterm birth (<32 wks.)[f] | 0 | 0 | - | - |
| Fetal growth restriction | 1 | 7 | - | - |

CCB, calcium channel blockers;[a] Methyldopa vs β-blockers using matched sample (N=3,904); the reference group refers to women who were on β-blockers; [b] calcium channel blockers vs β-blockers using matched sample (N=578); the reference group refers to women who were on β-blockers; [c] calcium channel blockers vs methyldopa using matched sample (N=578); the reference group refers to women who were on methyldopa; [d] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [e] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [f] in the analysis of very preterm birth, deliveries between 33-<37 were excluded; *Data on child's sex was available from hospital records only

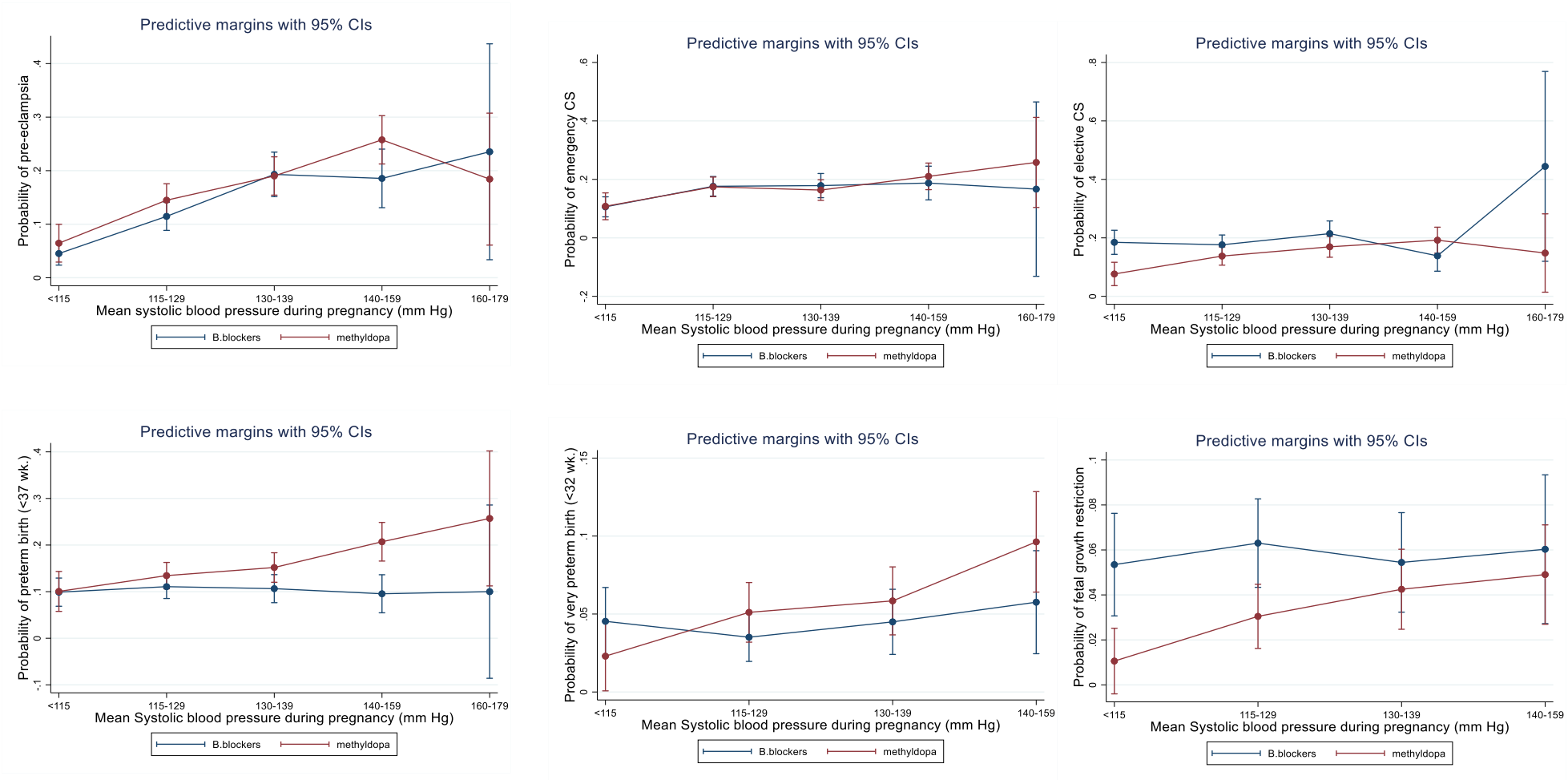



**Figure S6.3** Predictive margins with 95% CIs of the probability of adverse perinatal outcomes by type of antihypertensive agent across sBP levels. These analyses were restricted to patients with available BP readings from the propensity score matching sample (N=3,222). This model included an interaction term between antihypertensive agent and sBP levels. The large overlap in confidence intervals suggests that the probabilities of adverse outcomes is not different between both groups.

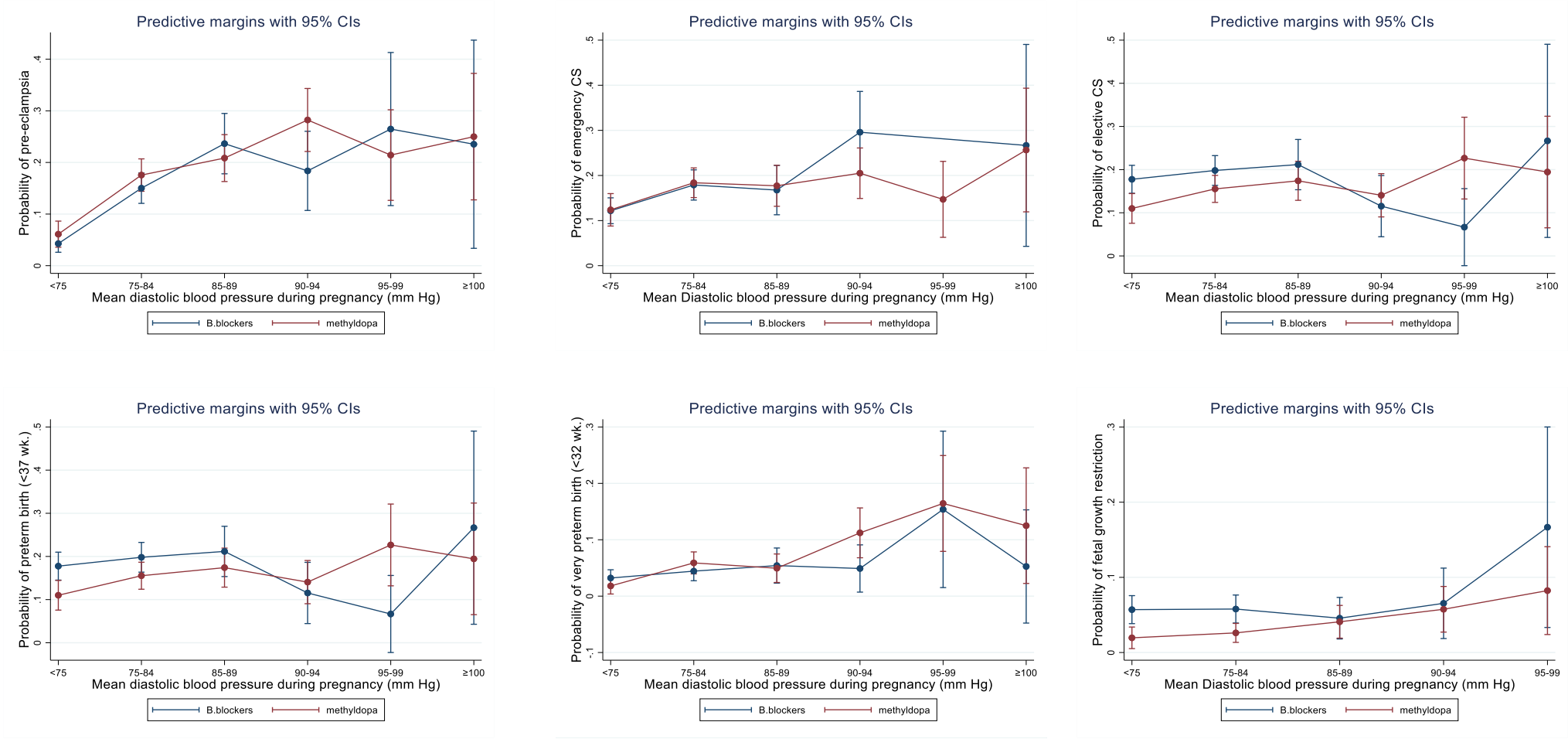



**Figure S6.4** Predictive margins with 95% CIs of the probability of adverse perinatal outcomes by type of antihypertensive agent across dBP levels. These analyses were restricted to patients with available BP readings from the propensity score matching sample (3,222). This model included an interaction term between antihypertensive agent and dBP levels. The large overlap in confidence intervals suggests that the probabilities of adverse outcomes is not different between both groups.

**Table S6.8** Antihypertensive treatment during pregnancy and adverse perinatal outcomes in women with chronic hypertension (multiple agents vs single agent)

| Outcome / Treatment | **Monotherapy (N=5,239)** | **Polytherapy (N=1,527)** | **Treated** (polytherapy vs monotherapy)[a] | | **Excluding severe hypertension[b]** (N=5,772) |
|---|---|---|---|---|---|
| | n (%) | n (%) | Crude OR (95% CI) | Adjusted OR (95% CI)* | Adjusted OR (95% CI)* |
| Severe hypertension | 674 (13) | 320 (21) | 1.80 (1.55, 2.08) | 1.53 (1.31, 1.78) | - |
| Pre-eclampsia | 645 (12) | 215 (14) | 1.17 (0.99, 1.38) | 1.03 (0.87, 1.23) | 0.97 (0.79, 1.19) |
| Emergency Caesarean section[c] | 667/4,555 (15) | 220/1,278 (17) | 1.21 (1.03, 1.43) | 1.15 (0.96, 1.38) | 1.13 (0.92, 1.39) |
| Elective Caesarean section[d] | 684/4,572 (15) | 249 (19) | 1.34 (1.14, 1.57) | 1.21 (1.02, 1.44) | 1.24 (1.03, 1.49) |
| Stillbirth | 49 (0.94) | 17 (1.1) | 1.19 (0.68, 2.08) | 1.16 (0.65, 2.05) | 1.32 (0.68, 2.54) |
| Preterm birth (<37 wk.) | 639 (12) | 219 (14) | 1.21 (1.02, 1.42) | 1.13 (0.95, 1.34) | 1.07 (0.87, 1.30) |
| Very preterm birth (<32 wks.)[e] | 223/4,823 (4.6) | 94/1,402 (6.7) | 1.48 (1.16, 1.90) | 1.33 (1.03, 1.72) | 1.34 (0.99, 1.81) |
| Fetal growth restriction | 258 (4.92) | 116 (7.6) | 1.59 (1.26, 1.99) | 1.68 (1.33, 2.13) | 1.66 (1.29, 2.15) |

[a] The reference group in these models refers women on monotherapy of antihypertensive treatment (N=6,766); [b] in this model we excluded women who had at least one event of severe hypertension ≥160/110; [c] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [d] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [e] in the analysis of very preterm birth, deliveries between 33-<37 were excluded;

**Table S6.9** Relationship between blood pressure levels and adverse perinatal outcomes including pregnancy records with available blood pressure readings

| Outcome \ SBP | <115 mm Hg | 115–129 mm Hg | 130–139 mm Hg | 140–159 mm Hg | 160–179 mm Hg | ≥180 mm Hg |
|---|---|---|---|---|---|---|
| **Pre-eclampsia[a]** | | | | | | |
| **Population (N=439,186)** | 251,115 | 150,313 | 29,101 | 8,180 | 423 | 54 |
| **Cases, (%)** | 3,720 (1.5) | 4,717 (3.1) | 1,639 (5.6) | 808 (9.9) | 52 (13) | 10 (19) |
| **Crude OR (95% CI)** | 0.46 (0.44, 0.48) | Reference | 1.84 (1.74, 1.95) | 3.38 (3.13, 3.66) | 4.33 (3.23, 5.79) | 7.02 (3.53, 13.9) |
| **Adjusted OR (95% CI)*** | 0.45 (0.49, 0.53) | Reference | 1.73 (1.63, 1.84) | 3.11 (2.87, 3.36) | 3.83 (2.85, 5.14) | 6.80 (3.38, 13.7) |
| **Emergency CS[b,**])** | | | | | | |
| **Population (N=444,391** | 353,384 | 158,294 | 25,757 | 6,585 | 326 | 46 |
| **Cases, (%)** | 21,024 (8.3) | 15,461 (9.8) | 2,857 (11) | 783 (12) | 43 (13) | 7 (15) |
| **Crude OR (95% CI)** | 0.84 (0.82, 0.85) | Reference | 1.15 (1.10, 1.20) | 1.25 (1.15, 1.35) | 1.40 (1.02, 1.94) | - |
| **Adjusted OR (95% CI)*** | 0.93 (0.91, 0.95) | Reference | 1.09 (1.04, 1.14) | 1.13 (1.05, 1.23) | 1.27 (0.91, 1.78) | - |
| **Elective CS[c,**]** | | | | | | |
| **Population (N=435,676)** | 248,992 | 154,742 | 25,107 | 6,470 | 319 | 46 |
| **Cases, (%)** | 16,632 (6.7) | 11,910 (7.7) | 2,207 (8.8) | 668 (10) | 36 (11) | 7 (15) |
| **Crude OR (95% CI)** | 0.86 (0.84, 0.88) | Reference | 1.16 (1.10, 1.21) | 1.38 (1.27, 1.52) | 1.53 (1.08, 2.16) | - |
| **Adjusted OR (95% CI)*** | 0.98 (0.96, 1.01) | Reference | 1.02 (0.97, 1.07) | 1.10 (1.01, 1.19) | 1.00 (0.70, 1.44) | - |
| **Preterm birth (<37 wk.)[d,**]** | | | | | | |
| **Population (N=475,851)** | 270,016 | 170,203 | 27,964 | 7,253 | 362 | 53 |
| **Cases, (%)** | 11,092 (4.1) | 7,246 (4.3) | 1,474 (5.3) | 551 (7.6) | 45 (12) | 6 (11) |
| **Crude OR (95% CI)** | 0.96 (0.93, 0.99) | Reference | 1.25 (1.18, 1.33) | 1.85 (1.69, 2.02) | 3.19 (2.33, 4.37) | - |
| **Adjusted OR (95% CI)*** | 0.95 (0.92, 0.98) | Reference | 1.23 (1.17, 1.31) | 1.80 (1.64, 1.97) | 3.02 (2.20, 4.15) | - |
| **Very preterm birth (<32 wk.)[e,**]** | | | | | | |
| **Population (N=460,728)** | 261,728 | 164,755 | 26,952 | 6,903 | 339 | 51 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Cases, (%)** | 2,804 (1.1) | 1,798 (1.1) | 462 (1.7) | 201 (2.9) | 22 (6.5) | 4 (7.8) |
| **Crude OR (95% CI)** | 0.98 (0.92, 1.04) | Reference | 1.59 (1.43, 1.75) | 2.72 (2.34, 3.15) | 6.29 (4.07, 9.71) | - |
| **Adjusted OR (95% CI)*** | 0.95 (0.89, 1.01) | Reference | 1.56 (1.41, 1.74) | 2.63 (2.26, 3.05) | 5.72 (3.69, 8.87) | - |
| **Stillbirth**** | | | | | | |
| **Population (N=475,851)** | 270,016 | 170,203 | 27,964 | 7,253 | 362 | 53 |
| **Cases, (%)** | 1,389 (0.51) | 957 (0.56) | 195 (0.70) | 70 (0.97) | 6 (1.7) | 1 (1.9) |
| **Crude OR (95% CI)** | 0.91 (0.84, 0.99) | Reference | 1.24 (1.06, 1.45) | 1.72 (1.35, 2.20) | - | - |
| **Adjusted OR (95% CI)*** | 0.93 (0.86, 1.01) | Reference | 1.18 (1.01, 1.38) | 1.58 (1.23, 2.01) | - | - |
| **Fetal growth restriction**** | | | | | | |
| **Population (N=475,851)** | 270,016 | 170,203 | 27,964 | 7,253 | 362 | 53 |
| **Cases, (%)** | 6,386 (2.4) | 3,276 (1.9) | 620 (2.2) | 199 (2.7) | 15 (4.1) | 2 (3.8.9) |
| **Crude OR (95% CI)** | 1.23 (1.18, 1.29) | Reference | 1.16 (1.06, 1.26) | 1.44 (1.24, 1.66) | 2.20 (1.31, 3.70) | - |
| **Adjusted OR (95% CI)*** | 1.07 (1.02, 1.12) | Reference | 1.24 (1.14, 1.35) | 1.62 (1.40, 1.87) | 2.74 (1.62, 4.61) | - |
| **DBP / Outcome** | **<75 mm Hg** | **75–84 mm Hg** | **85–89 mm Hg** | **90–94 mm Hg** | **95–99 mm Hg** | **≥100 mm Hg** |
| **Pre-eclampsia[a]** | | | | | | |
| **Population (N=439,186)** | 346,673 | 79,615 | 8,612 | 3,079 | 777 | 430 |
| **Cases, (%)** | 6,052 (1.8) | 3,602 (4.5) | 717 (8.3) | 368 (12) | 115 (15) | 92 (21) |
| **Crude OR (95% CI)** | 0.37 (0.35, 0.39) | Reference | 1.92 (1.75, 2.08) | 2.86 (2.56, 3.21) | 3.67 (3.00, 4.48) | 5.74 (4.55, 7.25) |
| **Adjusted OR (95% CI)*** | 0.42 (0.40, 0.44) | Reference | 1.84 (1.69, 2.00) | 2.73 (2.43, 3.06) | 3.45 (2.82, 4.23) | 5.59 (4.41, 7.08) |
| **Emergency CS[b,**]** | | | | | | |
| **Population (N=444,391)** | 355,701 | 77,582 | 7,451 | 2,626 | 667 | 364 |
| **Cases, (%)** | 30,609 (8.6) | 8,158 (11) | 915 (12) | 339 (13) | 96 (14) | 58 (16) |
| **Crude OR (95% CI)** | 0.80 (0.78, 0.82) | Reference | 1.19 (1.11, 1.28) | 1.26 (1.12, 1.42) | 1.43 (1.15, 1.78) | 1.61 (1.22, 2.14) |
| **Adjusted OR (95% CI)*** | 0.92 (0.90, 0.95) | Reference | 1.12 (1.03, 1.20) | 1.18 (1.04, 1.33) | 1.23 (0.98, 1.53) | 1.56 (1.16, 2.10) |
| **Elective CS[c,**]** | | | | | | |
| **Population (N=435,676)** | 349,092 | 75,730 | 7,293 | 2,565 | 646 | 350 |
| **Cases, (%)** | 24,000 (6.9) | 6,306 (8.3) | 757 (10) | 278 (11) | 75 (12) | 44 (13) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Crude OR (95% CI)** | 0.81 (0.79, 0.84) | Reference | 1.28 (1.18, 1.38) | 1.33 (1.18, 1.52) | 1.45 (1.14, 1.84) | 1.58 (1.15, 2.17) |
| **Adjusted OR (95% CI)*** | 0.99 (0.96, 1.02) | Reference | 1.12 (1.03, 1.21) | 1.10 (0.97, 1.25) | 1.09 (0.85, 1.39) | 1.20 (0.87, 1.67) |
| **Preterm birth (<37 wk.)[d,**]** | | | | | | |
| **Population (N=475,851)** | 379,701 | 83,888 | 8,208 | 2,904 | 742 | 408 |
| **Cases, (%)** | 15,544 (4.1) | 3,894 (4.6) | 548 (6.7) | 277 (9.5) | 95 (13) | 56 (14) |
| **Crude OR (95% CI)** | 0.88 (0.85, 0.91) | Reference | 1.47 (1.34, 1.61) | 2.17 (1.91, 2.46) | 3.02 (2.43, 3.75) | 3.27 (2.46, 4.34) |
| **Adjusted OR (95% CI)*** | 0.87 (0.83, 0.90) | Reference | 1.46 (1.33, 1.60) | 2.17 (1.91, 2.47) | 2.95 (2.37, 3.68) | 3.02 (2.26, 4.03) |
| **Very preterm birth (<32 wk.)[e,**]** | | | | | | |
| **Population (N=460,728)** | 368,039 | 81,061 | 7,830 | 2,729 | 691 | 378 |
| **Cases, (%)** | 3,882 (1.1) | 1,067 (1.32) | 170 (2.2) | 102 (3.7) | 44 (6.4) | 26 (6.9) |
| **Crude OR (95% CI)** | 0.80 (0.75, 0.86) | Reference | 1.66 (1.41, 1.96) | 2.91 (2.37, 3.58) | 5.10 (3.73, 6.96) | 5.54 (3.71, 8.28) |
| **Adjusted OR (95% CI)*** | 0.78 (0.72, 0.83) | Reference | 1.66 (1.41, 1.95) | 2.92 (2.37, 3.59) | 4.87 (3.55, 6.67) | 4.92 (3.27, 7.39) |
| **Stillbirth**** | | | | | | |
| **Population (N=475,851)** | 379,701 | 83,888 | 8,208 | 2,904 | 742 | 408 |
| **Cases, (%)** | 1,982 (0.52) | 535 (0.64) | 58 (0.71) | 30 (1) | 9 (1.2) | 4 (0.98) |
| **Crude OR (95% CI)** | 0.82 (0.74, 0.90) | Reference | 1.11 (0.84, 1.46) | 1.63 (1.12, 2.35) | - | - |
| **Adjusted OR (95% CI)*** | 0.85 (0.77, 0.94) | Reference | 1.07 (0.82, 1.41) | 1.52 (1.05, 2.20) | - | |
| **Fetal growth restriction**** | | | | | | |
| **Population (N=475,851)** | 397,701 | 83,888 | 8,208 | 2,904 | 742 | 408 |
| **Cases, (%)** | 8,397 (2.2) | 1,713 (2) | 225 (2.7) | 96 (3.3) | 43 (5.8) | 24 (5.9) |
| **Crude OR (95% CI)** | 1.08 (1.03, 1.10) | Reference | 1.35 (1.17, 1.59) | 1.64 (1.33, 2.12) | 2.95 (2.16, 4.17) | 3.00 (1.98, 4.21) |
| **Adjusted OR (95% CI)*** | 0.92 (0.87, 0.97) | Reference | 1.46 (1.27, 1.69) | 1.86 (1.51, 2.30) | 3.42 (2.49, 4.68) | 3.25 (2.13, 4.49) |

CS, Caesarean section; DBP, diastolic blood pressure; SBP, systolic blood pressure. [a] Data on blood pressure readings in pre-eclampsia analyses were restricted to readings from 1st and 2nd trimesters; [b] In the analysis of emergency Caesarean section, elective Caesarean section were excluded; [c] In the analysis of elective Caesarean section, emergency Caesarean section were excluded; [d] In the analysis of very preterm birth, deliveries between 33-<37 were excluded.*Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes and chronic kidney disease. **This model was restricted to records with available data on blood pressure readings, records with other hypertensive disorders of pregnancy or unspecified hypertension were excluded.

**Table S6.10** Relationship between blood pressure levels and adverse perinatal outcomes including pregnancy records with untreated chronic hypertension

| Outcome \ SBP | <115 mm Hg | 115–129 mm Hg | 130–139 mm Hg | 140–159 mm Hg | 160–179 mm Hg | ≥180 mm Hg |
|---|---|---|---|---|---|---|
| **Pre-eclampsia[a]** | | | | | | |
| **Population (N=2,508)** | 482 | 1,024 | 599 | 365 | 43 | 4 |
| **Cases, (%)** | 28 (5.8) | 83 (8.1) | 75 (13) | 48 (13) | 9 (21) | 0 |
| **Crude OR (95% CI)** | 0.70 (0.45, 1.09) | Reference | 1.62 (1.17, 2.26) | 1.76 (1.21, 2.58) | 3.00 (1.39, 6.48) | - |
| **Adjusted OR (95% CI)*** | 0.73 (0.46, 1.15) | Reference | 1.62 (1.16, 2.27) | 1.83 (1.24, 2.69) | 3.22 (1.45, 7.13) | - |
| **Emergency CS[b,**]** | | | | | | |
| **Population (N=2,512)** | 432 | 1,075 | 616 | 346 | 39 | 4 |
| **Cases, (%)** | 49 (11) | 124 (12) | 88 (14) | 48 (14) | 4 (10) | 1 (25) |
| **Crude OR (95% CI)** | 0.98 (0.69, 1.39) | Reference | 1.28 (0.95, 1.71) | 1.24 (0.86, 1.77) | - | - |
| **Adjusted OR (95% CI)*** | 1.20 (0.83, 1.75) | Reference | 1.28 (0.94, 1.74) | 1.22 (0.84, 1.78) | - | - |
| **Elective CS[c,**]** | | | | | | |
| **Population (N=2,488)** | 429 | 1,075 | 603 | 337 | 40 | 4 |
| **Cases, (%)** | 46 (11) | 124 (12) | 75 (12) | 39 (12) | 5 (13) | 1 (25) |
| **Crude OR (95% CI)** | 0.92 (0.64, 1.32) | Reference | 1.09 (0.80, 1.48) | 1.00 (0.68, 1.47) | - | - |
| **Adjusted OR (95% CI)*** | 1.13 (0.78, 1.64) | Reference | 1.90 (0.74, 1.39) | 0.93 (0.63, 1.38) | - | - |
| **Preterm birth (<37 wk.)[d,**]** | | | | | | |
| **Population (N=2,802)** | 478 | 1,199 | 691 | 385 | 44 | 5 |
| **Cases, (%)** | 24 (5) | 86 (7) | 64 (9.3) | 35 (9.1) | 6 (14) | 1 (20) |
| **Crude OR (95% CI)** | 0.68 (0.43, 1.09) | Reference | 1.32 (0.94, 1.85) | 1.29 (0.86, 1.95) | 2.04 (0.84, 4.97) | - |
| **Adjusted OR (95% CI)*** | 0.66 (0.40, 1.07) | Reference | 1.46 (1.03, 2.09) | 1.46 (0.95, 2.24) | 2.58 (1.01, 6.62) | - |
| **Very preterm birth (<32 wk.)[e,**]** | | | | | | |
| **Population (N=2,641)** | 458 | 1,132 | 649 | 357 | 40 | 5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Cases, (%)** | 4 (0.87) | 19 (1.7) | 22 (3.4) | 7 (2) | 2 (5) | 1 (20) |
| **Crude OR (95% CI)** | 0.52 (0.17, 1.53) | Reference | 2.06 (1.10, 3.83) | 1.17 (0.49, 2.81) | - | - |
| **Adjusted OR (95% CI)*** | 0.47 (0.15, 1.42) | Reference | 2.59 (1.35, 4.97) | 1.42 (0.57, 3.52) | - | - |
| **Stillbirth**** | | | | | | |
| **Population (N=2,802)** | 478 | 1,199 | 691 | 385 | 44 | 5 |
| **Cases, (%)** | 1 (0.421) | 9 (0.75) | 2 (0.29) | 4 (1) | 0 | 0 |
| **Crude OR (95% CI)** | - | - | - | - | - | - |
| **Adjusted OR (95% CI)*** | - | - | - | - | - | - |
| **Fetal growth restriction**** | | | | | | |
| **Population (N=2,802)** | 478 | 1,199 | 691 | 385 | 44 | 5 |
| **Cases, (%)** | 22 (4.6) | 27 (2.3) | 20 (2.9) | 14 (3.6) | 1 (2.3) | 1 (20) |
| **Crude OR (95% CI)** | 2.09 (1.18, 3.72) | Reference | 1.29 (0.72, 2.32) | 1.63 (0.85, 3.15) | - | - |
| **Adjusted OR (95% CI)*** | 2.12 (1.17, 3.87) | Reference | 1.40 (0.77, 2.55) | 1.91 (0.98, 3.75) | - | - |
| **DBP / Outcome** | **<75 mm Hg** | **75–84 mm Hg** | **85–89 mm Hg** | **90–94 mm Hg** | **95–99 mm Hg** | **≥100 mm Hg** |
| **Pre-eclampsia[a]** | | | | | | |
| **Population (N=2,508)** | 899 | 1,065 | 297 | 161 | 48 | 38 |
| **Cases, (%)** | 54 (6) | 102 (9.6) | 43 (16) | 26 (16) | 10 (21) | 8 (21) |
| **Crude OR (95% CI)** | 0.60 (0.43, 0.85) | Reference | 1.60 (1.09, 2.34) | 1.82 (1.14, 2.90) | 2.48 (1.20, 5.13) | 2.52 (1.12, 5.64) |
| **Adjusted OR (95% CI)*** | 0.61 (0.43, 0.87) | Reference | 1.47 (0.99, 2.18) | 1.87 (1.16, 3.03) | 2.62 (1.23, 5.54) | 2.76 (1.21, 6.32) |
| **Emergency CS[b,**]** | | | | | | |
| **Population (N=2,512)** | 890 | 1,074 | 295 | 167 | 51 | 35 |
| **Cases, (%)** | 84 (9) | 149 (14) | 46 (16) | 21 (13) | 11 (21) | 3 (9) |
| **Crude OR (95% CI)** | 0.65 (0.49, 0.86) | Reference | 1.15 (0.80, 1.64) | 0.89 (0.55, 1.46) | 1.71 (0.86, 3.41) | - |
| **Adjusted OR (95% CI)*** | 0.70 (0.52, 0.95) | Reference | 0.97 (0.67, 1.42) | 0.85 (0.51, 1.43) | 1.40 (0.67, 2.90) | - |
| **Elective CS[c,**]** | | | | | | |
| **Population (N=2,488)** | 909 | 1,049 | 282 | 165 | 45 | 38 |
| **Cases, (%)** | 103 (11) | 124 (12) | 33 (12) | 19 (12) | 5 (11) | 6 (16) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Crude OR (95% CI)** | 0.95 (0.72, 1.25) | Reference | 0.99 (0.66, 1.49) | 0.97 (0.58, 1.62) | - | - |
| **Adjusted OR (95% CI)*** | 1.08 (0.81, 1.44) | Reference | 0.90 (0.59, 1.37) | 0.93 (0.55, 1.58) | - | - |
| **Preterm birth (<37 wk.)[d,**]** | | | | | | |
| **Population (N=2,802)** | 993 | 1,198 | 328 | 186 | 56 | 41 |
| **Cases, (%)** | 49 (4.9) | 96 (8) | 33 (10) | 22 (12) | 9 (14) | 8 (14) |
| **Crude OR (95% CI)** | 0.60 (0.42, 0.85) | Reference | 1.28 (0.85, 1.95) | 1.53 (0.94, 2.52) | - | - |
| **Adjusted OR (95% CI)*** | 0.52 (0.36, 0.76) | Reference | 1.23 (0.80, 1.90) | 1.68 (1.01, 2.79) | - | - |
| **Very preterm birth (<32 wk.)[e,**]** | | | | | | |
| **Population (N=2,641)** | 951 | 1,125 | 304 | 174 | 50 | 37 |
| **Cases, (%)** | 7 (0.7) | 23 (2) | 9 (3) | 10 (5.8) | 2 (4) | 4 (11) |
| **Crude OR (95% CI)** | 0.36 (0.15, 0.83) | Reference | 1.46 (0.67, 3.19) | 2.92 (1.37, 6.24) | - | - |
| **Adjusted OR (95% CI)*** | 0.30 (0.13, 0.73) | Reference | 1.46 (0.65, 3.30) | 3.54 (1.58, 7.93) | - | - |
| **Stillbirth**** | | | | | | |
| **Population (N=2,802)** | 993 | 1,198 | 328 | 186 | 56 | 41 |
| **Cases, (%)** | 3 (0.3) | 9 (0.75) | 2 (0.61) | 1 (0.54) | 1 (1.8) | 0 |
| **Crude OR (95% CI)** | - | - | - | - | - | - |
| **Adjusted OR (95% CI)*** | - | - | - | - | - | - |
| **Fetal growth restriction**** | | | | | | |
| **Population (N=2,802)** | 993 | 1,198 | 328 | 186 | 56 | 41 |
| **Cases, (%)** | 25 (2.5) | 32 (2.7) | 14 (4.3) | 8 (4.3) | 2 (3.6) | 4 (9.8) |
| **Crude OR (95% CI)** | 0.94 (0.55, 1.60) | Reference | 1.62 (0.86, 3.08) | - | - | - |
| **Adjusted OR (95% CI)*** | 0.86 (0.48, 1.50) | Reference | 1.52 (0.79, 2.92) | - | - | - |

CS, Caesarean section; DBP, diastolic blood pressure; SBP, systolic blood pressure. [a] Data on blood pressure readings in pre-eclampsia analyses were restricted to readings from 1st and 2nd trimesters; [b] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [c] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [d] in the analysis of very preterm birth, deliveries between 33-<37 were excluded.*Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes and chronic kidney disease. **This model was restricted to records with available data on blood pressure readings, records with other hypertensive disorders of pregnancy or unspecified hypertension were excluded.

**Table S6.11** Relationship between blood pressure levels and adverse perinatal outcomes including pregnancy records with chronic hypertension and exposed to antihypertensives

| Outcome / SBP | <115 mm Hg | 115–129 mm Hg | 130–139 mm Hg | 140–159 mm Hg | 160–179 mm Hg | ≥180 mm Hg |
|---|---|---|---|---|---|---|
| **Pre-eclampsia[a]** | | | | | | |
| **Population (N=5,375)** | 1,029 | 1,835 | 1,403 | 971 | 122 | 15 |
| **Cases, (%)** | 38 (3.7) | 207 (11) | 244 (17) | 228 (23) | 25 (21) | 3 (20) |
| **Crude OR (95% CI)** | 0.30 (0.21, 0.43) | Reference | 1.66 (1.36, 2.02) | 2.41 (1.96, 2.97) | 2.03 (1.28, 3.22) | - |
| **Adjusted OR (95% CI)*** | 0.31 (0.22, 0.45) | Reference | 1.66 (1.36, 2.03) | 2.40 (1.94, 2.96) | 2.02 (1.26, 3.24) | - |
| **Emergency CS[b,**]** | | | | | | |
| **Population (N=4,892)** | 940 | 1,702 | 1,304 | 845 | 88 | 13 |
| **Cases, (%)** | 91 (9.7) | 279 (16) | 229 (18) | 172 (20) | 19 (22) | 2 (15) |
| **Crude OR (95% CI)** | 0.55 (0.43, 0.70) | Reference | 1.09 (0.90, 1.32) | 1.30 (1.06, 1.61) | 1.40 (0.83, 2.37) | - |
| **Adjusted OR (95% CI)*** | 0.63 (0.48, 0.82) | Reference | 1.07 (0.87, 1.31) | 1.36 (1.08, 1.71) | 1.37 (0.78, 2.41) | - |
| **Elective CS[c,**]** | | | | | | |
| **Population (N=4,910)** | 976 | 1,709 | 1,303 | 824 | 86 | 12 |
| **Cases, (%)** | 127 (13) | 286 (17) | 228 (18) | 151 (18) | 17 (20) | 1 (8.3) |
| **Crude OR (95% CI)** | 0.74 (0.59, 0.93) | Reference | 1.06 (0.87, 1.28) | 1.12 (0.90, 1.38) | 1.23 (0.71, 2.12) | - |
| **Adjusted OR (95% CI)*** | 0.91 (0.72, 1.16) | Reference | 0.99 (0.81, 1.21) | 1.07 (0.85, 1.34) | 1.06 (0.60, 1.86) | - |
| **Preterm birth (<37 wk.)[d,**]** | | | | | | |
| **Population (N=5,702)** | 1,067 | 1,988 | 1,532 | 996 | 105 | 14 |
| **Cases, (%)** | 127 (13) | 286 (17) | 228 (18) | 151 (18) | 17 (20) | 1 (8.3) |
| **Crude OR (95% CI)** | 0.78 (0.61, 1.00) | Reference | 1.27 (1.04, 1.55) | 1.65 (1.33, 2.04) | 2.79 (1.77, 4.40) | - |
| **Adjusted OR (95% CI)*** | 0.77 (0.59, 0.99) | Reference | 1.31 (1.07, 1.60) | 1.69 (1.36, 2.11) | 2.95 (1.85, 4.70) | - |
| **Very preterm birth (<32 wk.)[e,**]** | | | | | | |
| **Population (N=5,236)** | 1,002 | 1,838 | 1,392 | 898 | 92 | 14 |

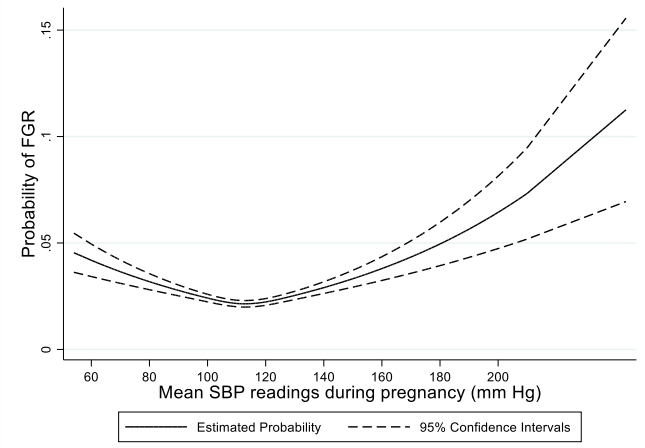
| | | | | | | |
|---|---|---|---|---|---|---|
| **Cases, (%)** | 33 (3.3) | 79 (4.3) | 78 (5.6) | 78 (8.7) | 15 (16) | 2 (14) |
| **Crude OR (95% CI)** | 0.76 (0.50, 1.15) | Reference | 1.32 (0.96, 1.82) | 2.12 (1.53, 2.93) | 4.34 (2.39, 7.88) | - |
| **Adjusted OR (95% CI)*** | 0.76 (0.49, 1.16) | Reference | 1.34 (0.97, 1.86) | 2.12 (1.52, 2.95) | 4.22 (2.28, 7.81) | - |
| **Stillbirth**** | | | | | | |
| **Population (N=5,702)** | 1,067 | 1,988 | 1,532 | 996 | 105 | 14 |
| **Cases, (%)** | 5 (0.47) | 16 (0.8) | 15 (0.78) | 18 (1.8) | 3 (2.9) | - |
| **Crude OR (95% CI)** | - | Reference | 1.22 (0.60, 2.47) | 2.27 (1.15, 4.47) | - | - |
| **Adjusted OR (95% CI)*** | - | Reference | 1.20 (0.58, 2.44) | 2.16 (1.08, 4.31) | - | - |
| **Fetal growth restriction**** | | | | | | |
| **Population (N=5,702)** | 1,067 | 1,988 | 1,532 | 996 | 105 | 14 |
| **Cases, (%)** | 51 (4.8) | 111 (5.6) | 86 (5.6) | 67 (6.7) | 7 (6.7) | - |
| **Crude OR (95% CI)** | 0.85 (0.60, 1.19) | Reference | 1.01 (0.75, 1.34) | 1.22 (0.89, 1.67) | - | - |
| **Adjusted OR (95% CI)*** | 0.70 (0.49, 1.00) | Reference | 1.14 (0.84, 1.53) | 1.42 (1.03, 1.95) | - | - |
| **DBP / Outcome** | **<75 mm Hg** | **75–84 mm Hg** | **85–89 mm Hg** | **90–94 mm Hg** | **95–99 mm Hg** | **≥100 mm Hg** |
| **Pre-eclampsia[a]** | | | | | | |
| **Population (N=5,375)** | 1,682 | 1,933 | 823 | 533 | 233 | 151 |
| **Cases, (%)** | 71 (4.2) | 269 (14) | 172 (21) | 137 (25) | 54 (23) | 42 (28) |
| **Crude OR (95% CI)** | 0.27 (0.21, 0.36) | Reference | 1.63 (1.32, 2.02) | 2.04 (1.62, 2.57) | 1.87 (1.34, 2.60) | 2.38 (1.63, 3.48) |
| **Adjusted OR (95% CI)*** | 0.27 (0.21, 0.36) | Reference | 1.62 (1.31, 2.01) | 2.05 (1.62, 2.60) | 1.88 (1.34, 2.64) | 2.29 (1.55, 3.38) |
| **Emergency CS[b,**]** | | | | | | |
| **Population (N=4,892)** | 1,556 | 1,768 | 770 | 488 | 192 | 118 |
| **Cases, (%)** | 169 (11) | 311 (18) | 149 (19) | 106 (22) | 30 (16) | 27 (23) |
| **Crude OR (95% CI)** | 0.57 (0.47, 0.70) | Reference | 1.12 (1.91, 1.40) | 1.30 (1.01, 1.67) | 0.87 (0.58, 1.31) | 1.39 (0.89, 2.17) |
| **Adjusted OR (95% CI)*** | 0.62 (0.50, 0.77) | Reference | 1.13 (0.89, 1.42) | 1.37 (1.05, 1.79) | 0.84 (0.51, 1.31) | 1.38 (0.85, 2.22) |
| **Elective CS[c,**]** | | | | | | |
| **Population (N=4,910)** | 1,622 | 1,768 | 752 | 459 | 200 | 109 |
| **Cases, (%)** | 235 (15) | 311 (18) | 131 (17) | 77 (17) | 38 (19) | 18 (17) |
| **Crude OR (95% CI)** | 0.79 (0.66, 0.95) | Reference | 0.99 (0.79, 1.24) | 0.94 (0.72, 1.24) | 1.10 (0.75, 1.60) | 0.93 (0.55, 1.56) |

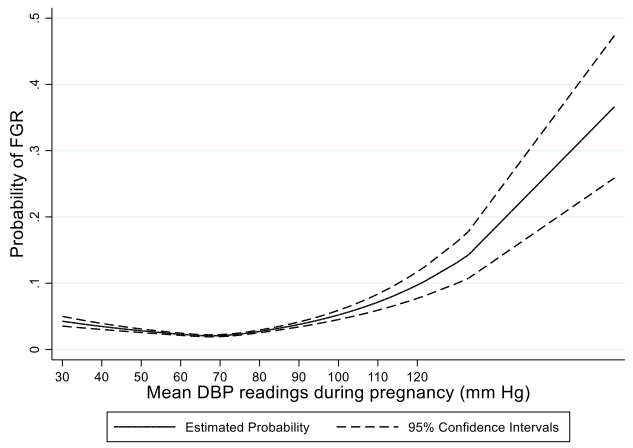
| | | | | | | |
|---|---|---|---|---|---|---|
| **Adjusted OR (95% CI)*** | 0.96 (0.79, 1.17) | Reference | 0.98 (0.77, 1.23) | 0.97 (0.73, 1.29) | 1.10 (0.74, 1.60) | 0.88 (0.52, 1.51) |
| **Preterm birth (<37 wk.)[d,**]** | | | | | | |
| **Population (N=5,702)** | 1,791 | 2,079 | 901 | 565 | 230 | 136 |
| **Cases, (%)** | 161 (9) | 259 (12) | 133 (15) | 112 (20) | 57 (25) | 29 (21) |
| **Crude OR (95% CI)** | 0.69 (0.56, 0.85) | Reference | 1.22 (0.97, 1.52) | 1.74 (1.36, 2.22) | 2.32 (1.67, 3.21) | 1.90 (1.24, 2.93) |
| **Adjusted OR (95% CI)*** | 0.67 (0.54, 0.83) | Reference | 1.27 (1.01, 1.59) | 1.86 (1.45, 2.38) | 2.51 (1.80, 3.50) | 1.88 (1.21, 2.91) |
| **Very preterm birth (<32 wk.)[e,**]** | | | | | | |
| **Population (N=5,236)** | 1,676 | 1,911 | 821 | 504 | 200 | 124 |
| **Cases, (%)** | 46 (2.7) | 91 (4.8) | 53 (6.5) | 51 (10) | 27 (14) | 17 (14) |
| **Crude OR (95% CI)** | 0.56 (0.39, 0.81) | Reference | 1.38 (0.97, 1.96) | 2.25 (1.57, 3.22) | 3.12 (1.98, 4.93) | 3.18 (1.82, 5.53) |
| **Adjusted OR (95% CI)*** | 0.56 (0.38, 0.81) | Reference | 1.44 (1.01, 2.06) | 2.35 (1.64, 3.39) | 3.25 (2.04, 5.19) | 3.19 (1.81, 5.61) |
| **Stillbirth**** | | | | | | |
| **Population (N=5,702)** | 1,791 | 2,079 | 901 | 565 | 230 | 136 |
| **Cases, (%)** | 11 (0.61) | 20 (0.96) | 10 (1.1) | 8 (1.4) | 6 (2.6) | 2 (1.5) |
| **Crude OR (95% CI)** | 0.64 (0.30, 1.33) | Reference | 1.16 (0.54, 2.48) | - | - | - |
| **Adjusted OR (95% CI)*** | 0.64 (0.30, 1.38) | Reference | 1.20 (0.56, 2.60) | - | - | - |
| **Fetal growth restriction**** | | | | | | |
| **Population (N=5,702)** | 1,791 | 2,079 | 901 | 565 | 230 | 136 |
| **Cases, (%)** | 87 (4.9) | 98 (4.7) | 57 (6.3) | 42 (7.4) | 27 (12) | 11 (8.1) |
| **Crude OR (95% CI)** | 1.03 (0.77, 1.39) | Reference | 1.37 (0.98, 1.91) | 1.63 (1.12, 2.36) | 2.69 (1.71, 4.22) | 1.78 (0.93, 3.40) |
| **Adjusted OR (95% CI)*** | 0.83 (0.61, 1.13) | Reference | 1.49 (1.06, 2.10) | 1.76 (1.21, 2.58) | 2.97 (1.87, 4.72) | 1.90 (0.98, 3.68) |

CS, Caesarean section; DBP, diastolic blood pressure; SBP, systolic blood pressure. [a] Data on blood pressure readings in pre-eclampsia analyses were restricted to readings from 1st and 2nd trimesters; [b] in the analysis of emergency Caesarean section, elective Caesarean section were excluded; [c] in the analysis of elective Caesarean section, emergency Caesarean section were excluded; [d] in the analysis of very preterm birth, deliveries between 33-<37 were excluded.*Adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes and chronic kidney disease. **This model was restricted to records with available data on blood pressure readings, records with other hypertensive disorders of pregnancy or unspecified hypertension were excluded.

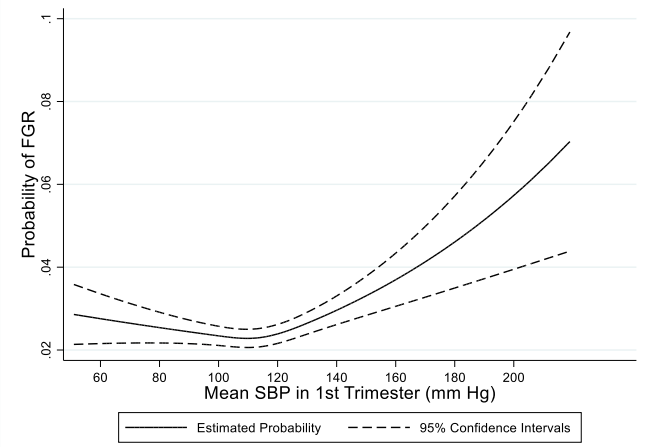
**Figure S6.5** Spline plots of the relationship between BP levels fetal growth restriction (FGR)

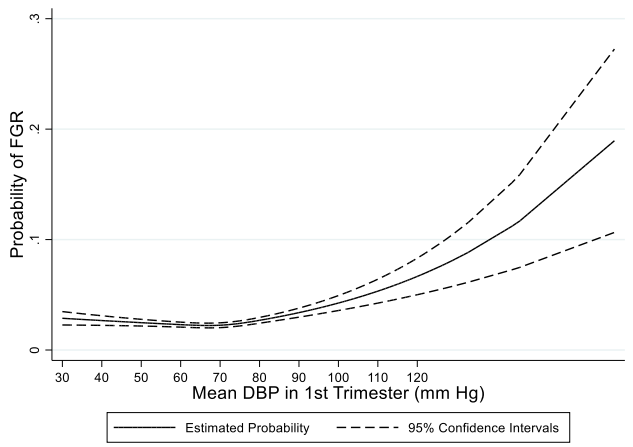
**1. Relationship between BP level and fetal growth restriction including all records with available BP readings, results from adjusted models (N=475,851) [a]**



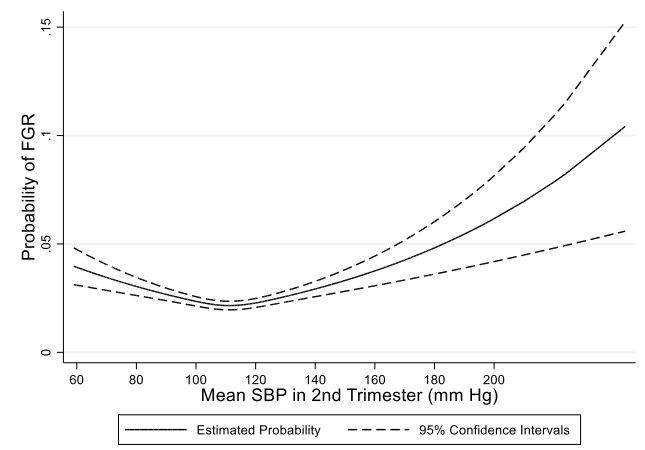



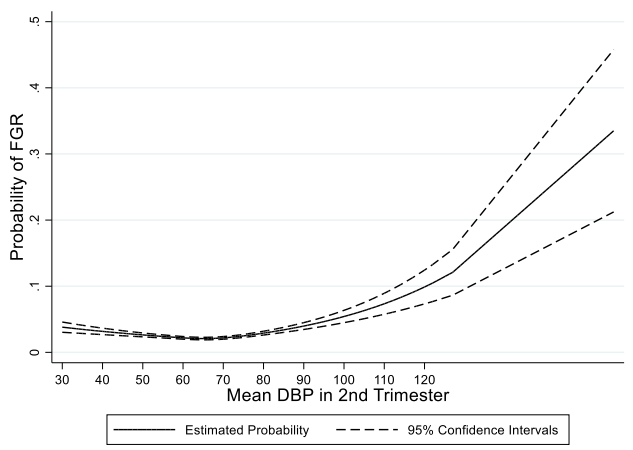

**1.1. First trimester (relationship between BP level and fetal growth restriction, (N= 264,080))**



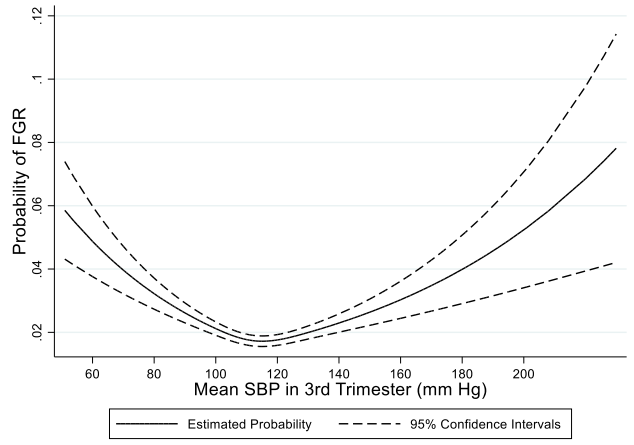



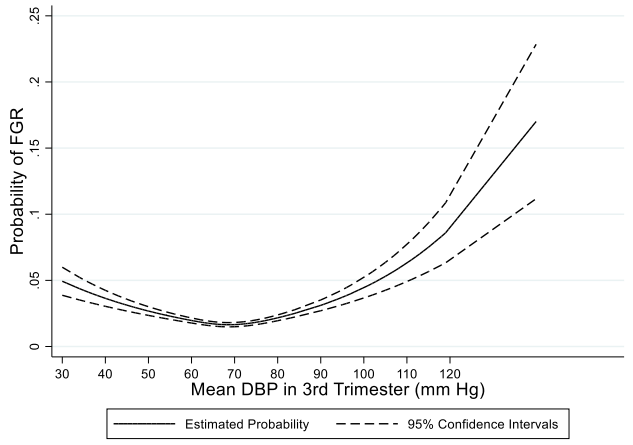

**1.2. Second trimester (relationship between BP level and fetal growth restriction, N=302,122))**



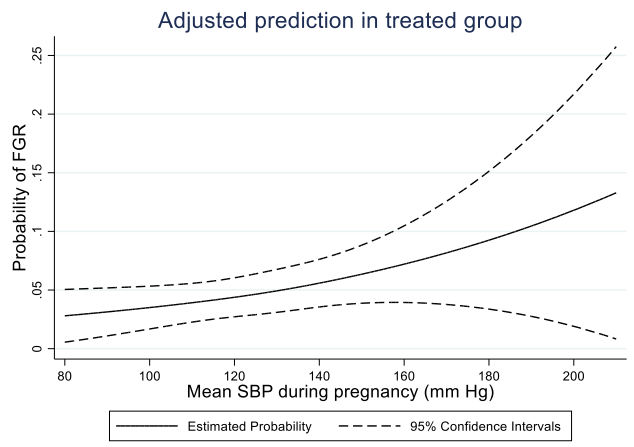



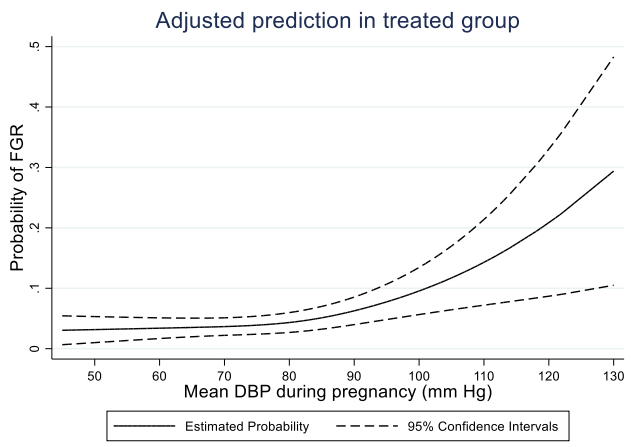
**1.3. Third trimester (relationship between BP level and fetal growth restriction, N=323,736)**



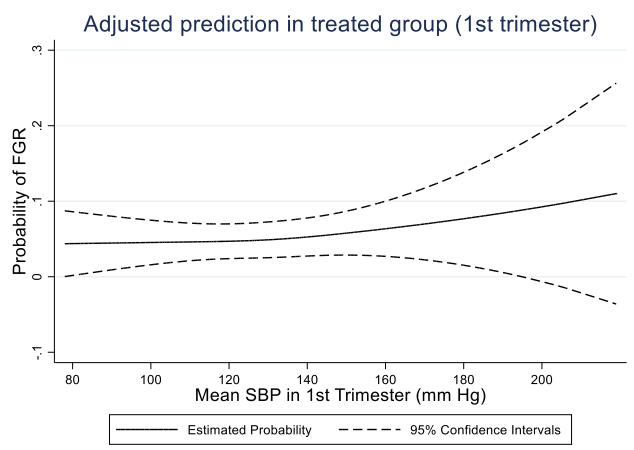



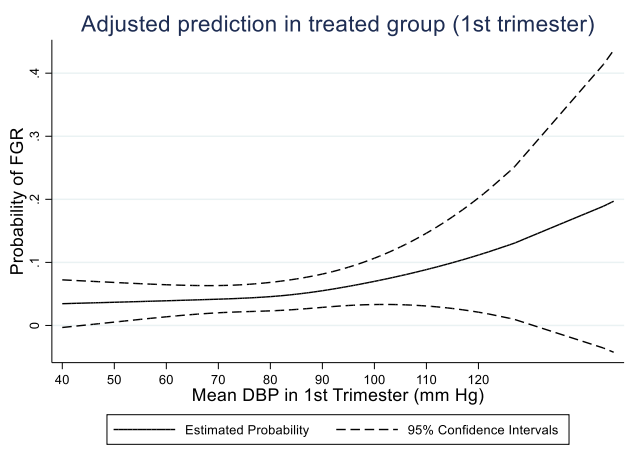

**2. Relationship between BP level and fetal growth restriction restricted to pregnancies with chronic hypertension and on antihypertensive agent(s) during pregnancy, N=5,702)**



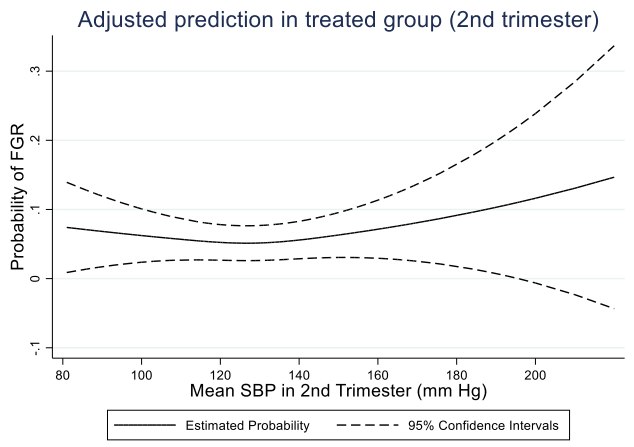



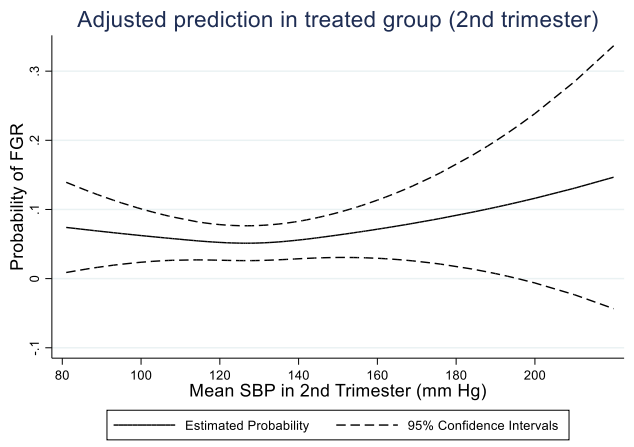

**2.1. First trimester (relationship between BP level and fetal growth restriction in treated hypertensive group, N=3,270)**



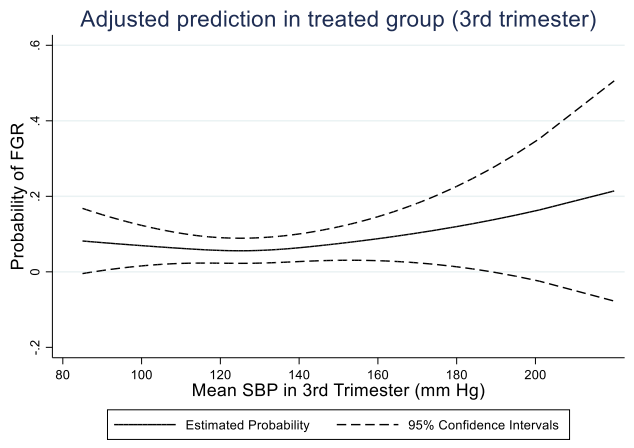



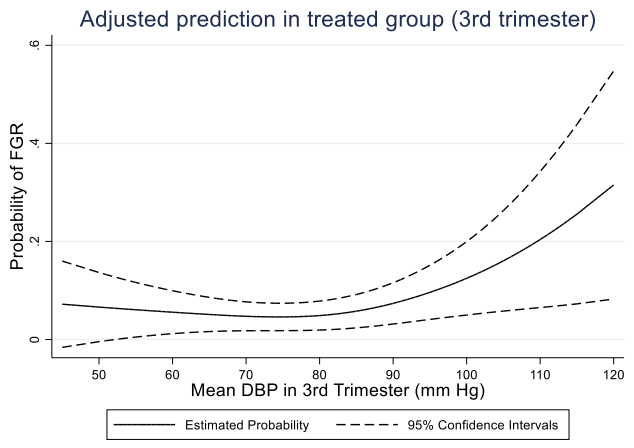
**2.2. Second trimester (relationship between BP level and fetal growth restriction in treated hypertensive group, N=2,819)**




**2.3. Third trimester (relationship between BP level and fetal growth restriction in treated hypertensive group, N=2,491)**




[a] Records with either unspecified hypertension, other hypertensive disorders during pregnancy or exposed to antihypertensive agent were excluded from these analyses. All models were generated using BP as spline variable (cubic spline with three knots) and adjusted for maternal age, deprivation index, smoking, body mass index, ethnicity, parity, and pre-pregnancy diabetes and chronic kidney disease.

**Table S6.12** Baseline demographic characteristics in the cohort and matched sample

| Study group / Covariates | Treated vs untreated | | | | Methyldopa vs β-blockers | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pre-Propensity Score Matching** (raw data) | | **Post-Propensity Score Matching[a]** | | **Pre-Propensity Score Matching** (raw data) | | **Post-Propensity Score Matching[a]** | |
| | Treated n=6,766 | Untreated n=7,792 | Treated n=6,766 | Untreated n=6,766 | Methyldopa n=1,952 | β-blockers n=2,702 | Methyldopa n=1,952 | β-blockers n=1,952 |
| **Age (years),** mean (SD) | 33 (5.8) | 33 (5.2) | 33 (5.8) | 33 (5.4) | 33 (5.7) | 32 (5.8) | 33 (5.7) | 33 (5.4) |
| **Ethnicity,** n (%) | | | | | | | | |
| White | 5,479 (81) | 6,439 (83) | 5,479 (81) | 5,641 (83) | 1,554 (80) | 2,379 (88) | 1,554 (80) | 1,596 (82) |
| Black | 574 (8.5) | 622 (8) | 574 (8.5) | 550 (8.1) | 174 (8.9) | 114 (4.2) | 174 (8.9) | 130 (6.7) |
| South Asian | 323 (4.8) | 241 (3.1) | 323 (4.8) | 229 (3.8) | 96 (4.9) | 99 (3.7) | 96 (4.9) | 97 (5) |
| Other | 215 (3.2) | 207 (3.1) | 215 (3.2) | 183 (2.7) | 70 (3.6) | 64 (2.4) | 70 (3.6) | 70 (3.6) |
| Unknown | 175 (2.6) | 283 (3.6) | 175 (2.6) | 163 (2.4) | 58 (3) | 46 (1.7) | 58 (3) | 59 (3.0) |
| **Smoking,** n (%) | | | | | | | | |
| Non-smoker | 2,578 (38) | 1,392 (18) | 2,578 (38) | 2,787 (41) | 743 (38) | 962 (36) | 743 (38) | 748 (38) |
| Ex-smoker | 949 (14) | 495 (6.4) | 949 (14) | 832 (12) | 262 (13) | 400 (15) | 262 (13) | 220 (11) |
| Current smoker | 1,112 (16) | 552 (7.1) | 1,112 (16) | 983 (15) | 282 (14) | 529 (20) | 282 (14) | 319 (16) |
| missing | 2,127 (31) | 5,353 (68) | 2,127 (31) | 2,164 (32) | 665 (34) | 811 (30) | 665 (34) | 665 (34) |
| **Body mass index[c]** | | | | | | | | |
| Underweight | 77 (1.1) | 37 (0.5) | 77 (1.1) | 59 (0.9) | 18 (0.9) | 35 (1.3) | 18 (0.9) | 12 (0.6) |
| Normal | 1,445 (21) | 1,032 (13) | 1,445 (21) | 1,482 (22) | 378 (19) | 679 (25) | 378 (19) | 515 (26) |
| Overweight | 1,374 (20) | 936 (12) | 1,374 (20) | 1,469 (22) | 400 (20) | 562 (21) | 400 (20) | 391 (20) |
| Obese | 2,035 (30) | 1,451 (19) | 2,035 (30) | 2,020 (30) | 614 (31) | 690 (26) | 614 (31) | 550 (28) |
| Severe obesity | 407 (6) | 263 (3.4) | 407 (6) | 345 (5.1) | 123 (6.3) | 127 (4.7) | 123 (6.3) | 89 (4.6) |
| Missing | 1,428 (21) | 4,073 (52) | 1,428 (21) | 1,391 (21) | 419 (21) | 609 (22) | 419 (21) | 395 (20) |
| **Diabetes**, n (%) | 381 (5.6) | 332 (4.3) | 381 (5.6) | 312 (4.6) | 175 (9) | 62 (2.3) | 175 (9) | 171 (8.8) |
| **Parity,** n (%) | | | | | | | | |
| Nulliparous | 1,240 (18) | 1,303 (17) | 1,240 (18) | 1,281 (19) | 354 (18) | 559 (21) | 354 (18) | 333 (17) |
| Multiparous | 4,477 (66) | 4,590 (59) | 4,477 (66) | 4,462 (66) | 1,282 (66) | 1,726 (64) | 1,282 (66) | 1,295 (66) |
| Unknown | 1,049 (16) | 1,899 (24) | 1,049 (16) | 1,023 (15) | 316 (16) | 417 (15) | 316 (16) | 324 (17) |

**Table S6.12** Continue from previous page: Baseline demographic characteristics in the cohort and matched sample

| Study group / Covariates | Calcium channel blockers vs. β-blockers | | | | Calcium channel blockers vs. methyldopa | | | |
|---|---|---|---|---|---|---|---|---|
| | Pre-Propensity Score Matching (raw data) | | Post-Propensity Score Matching[a] | | Pre-Propensity Score Matching (raw data) | | Post-Propensity Score Matching[b] | |
| | CCB n=289 | β-blockers n=2,702 | CCB n=289 | β-blockers n=289 | CCB n=289 | Methyldopa n=1,952 | CCB n=289 | Methyldopa n=289 |
| **Age (years),** mean (SD) | 33 (5.9) | 32 (5.8) | 33 (5.9) | 33 (5.9) | 33 (5.9) | 33 (5.7) | 33 (5.9) | 34 (5.9) |
| **Ethnicity,** n (%) | | | | | | | | |
| White | 213 (74) | 2,379 (88) | 213 (74) | 228 (79) | 213 (74) | 1,554 (80) | 213 (74) | 244 (84) |
| Black | 40 (14) | 114 (4.2) | 40 (14) | 20 (7) | 40 (14) | 174 (8.9) | 40 (14) | 15 (5.2) |
| South Asian | 20 (6.9) | 99 (3.7) | 20 (6.9) | 22 (7.6) | 20 (6.9) | 96 (4.9) | 20 (6.9) | 18 (6.2) |
| Other | 7 (2.4) | 64 (2.4) | 7 (2.4) | 11 (3.8) | 7 (2.4) | 70 (3.6) | 7 (2.4) | 10 (3.5) |
| Unknown | 9 (3.1) | 46 (1.7) | 9 (3.1) | 8 (2.8) | 9 (3.1) | 58 (3) | 9 (3.1) | 2 (0.7) |
| **Smoking,** n (%) | | | | | | | | |
| Non-smoker | 99 (34) | 962 (36) | 99 (34) | 116 (40) | 99 (34) | 743 (38) | 99 (34) | 99 (34) |
| Ex-smoker | 50 (17) | 400 (15) | 50 (17) | 42 (15) | 50 (17) | 262 (13) | 50 (17) | 39 (13) |
| Current smoker | 39 (13) | 529 (20) | 39 (13) | 41 (14) | 39 (13) | 282 (14) | 39 (13) | 52 (18) |
| missing | 101 (35) | 811 (30) | 101 (35) | 90 (31) | 101 (35) | 665 (34) | 101 (35) | 99 (34) |
| **Body mass index**[c] | | | | | | | | |
| Underweight | 7 (2.4) | 35 (1.3) | 7 (2.4) | 1 (0.4) | 7 (2.4) | 18 (0.9) | 7 (2.4) | 2 (0.7) |
| Normal | 69 (24) | 679 (25) | 69 (24) | 67 (23) | 69 (24) | 378 (19) | 69 (24) | 70 (24) |
| Overweight | 63 (21.8) | 562 (21) | 63 (21.8) | 66 (23) | 63 (22) | 400 (20) | 63 (22) | 67 (23) |
| Obese | 78 (27) | 690 (26) | 78 (27) | 99 (34) | 78 (27) | 614 (31) | 78 (27) | 93 (32) |
| Severe obesity | 18 (6.2) | 127 (4.7) | 18 (6.2) | 6 (2.1) | 18 (6.2) | 123 (6.3) | 18 (6.2) | 17 (5.8) |
| Missing | 54 (19) | 609 (22) | 54 (19) | 50 (17) | 54 (19) | 419 (21) | 54 (19) | 40 (14) |
| **Diabetes**, n (%) | 34 (12) | 62 (2.3) | 34 (12) | 39 (13) | 34 (12) | 175 (9) | 34 (12) | 39 (13) |
| **Parity,** n (%) | | | | | | | | |
| Nulliparous | 53 (18) | 559 (21) | 53 (18) | 46 (16) | 53 (18) | 354 (18) | 53 (18) | 38 (13) |
| Multiparous | 192 (66) | 1,726 (64) | 192 (66) | 194 (67) | 192 (66) | 1,282 (66) | 192 (66) | 210 (72) |
| Unknown | 44 (15) | 417 (15) | 44 (15) | 49 (17) | 44 (15) | 316 (16) | 44 (15) | 41 (14) |

CCB, Calcium channel blockers. [a] Propensity score matching was performed using nearest-neighbor with caliper (0.1) the covariates in these models are categorical (ethnicity, smoking, body mass index, diabetes parity and practice IMD 2015) except for maternal age which is continuous. [b] This model similar to that mentioned above model but the caliber was set at (0.2). [c] Underweight (BMI<18.5 kg/m2); Normal (BMI≥18.5 to<25 kg/m2); Overweight (BMI ≥25 to <30 kg/m2); Obese (BMI: ≥30 to <40 kg/m2); and severe obesity (BMI: ≥40 kg/m2)

## S6.3 Results of matching:

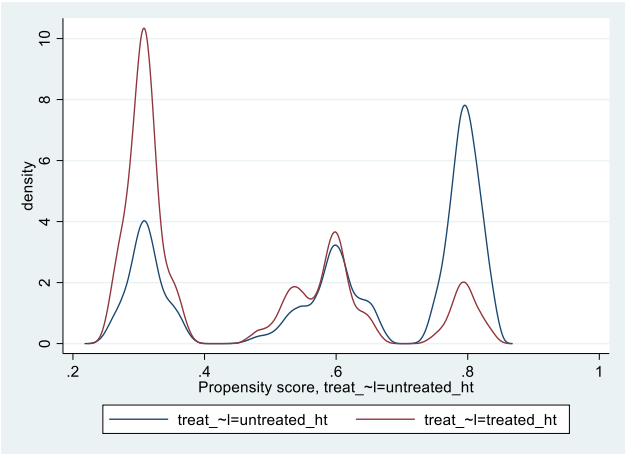
The matching method achieved balance in measured covariates across the various treatment and comparison groups (standardized differences < 0.1 in nearly all covariates). Kernel density plots for the continuous variable (maternal age) between the two groups were reasonably similar. The distributions of the propensity scores are adequately overlapped with good balance.

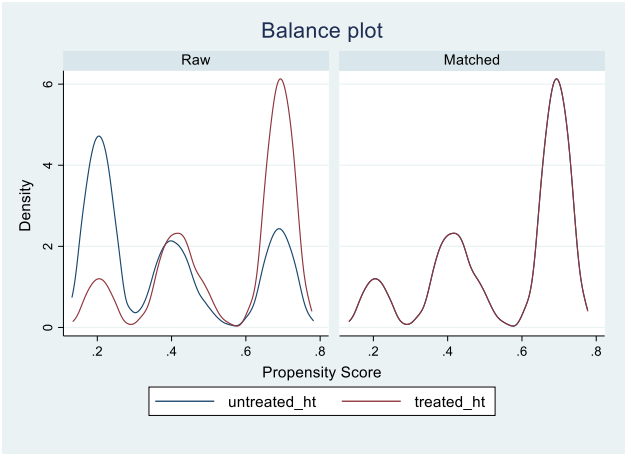
## S6.4 Diagnostic assessment for propensity score

***Diagnostic assessment for propensity score matching (treated vs untreated)***

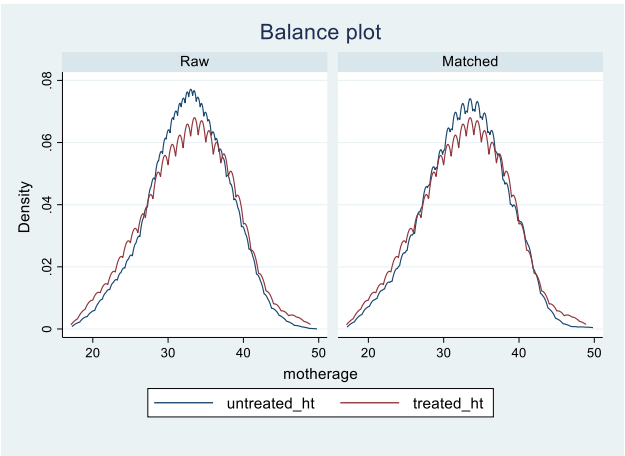
| | | |
|---|---|---|
| Number of obs = | 14,558 | 13,532 |
| Treated obs = | 6,766 | 6,766 |
| Control obs = | 7,792 | 6,766 |

| | Standardized differences | | Variance ratio | |
|---|---|---|---|---|
| | Raw | Matched | Raw | Matched |
| smoking | -.8029749 | -.0116006 | 1.002282 | .990602 |
| e2015_imd_10 | .0049165 | -.0044307 | .9244505 | .9499361 |
| ethnic_hes | .0134123 | .0593653 | .9354637 | 1.125767 |
| motherage | .0001151 | -.0057676 | 1.24921 | 1.182 |
| parity | -.1718425 | .0170241 | .8332076 | .9953997 |
| bmi | -.6833243 | .0135876 | .6674505 | 1.019405 |
| diabetes | .0632263 | .0462734 | 1.302721 | 1.208098 |




Mother age, continuous variable

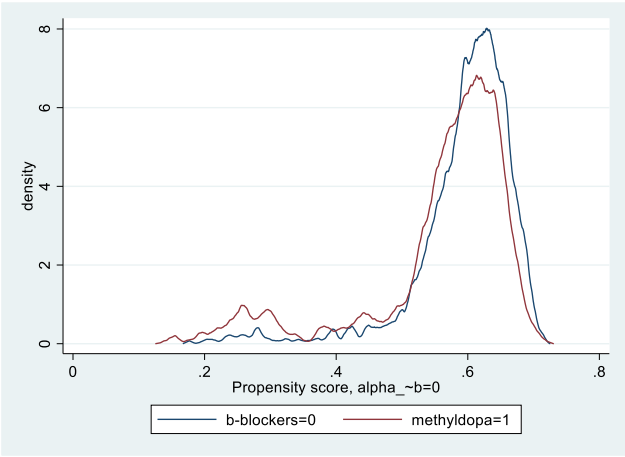


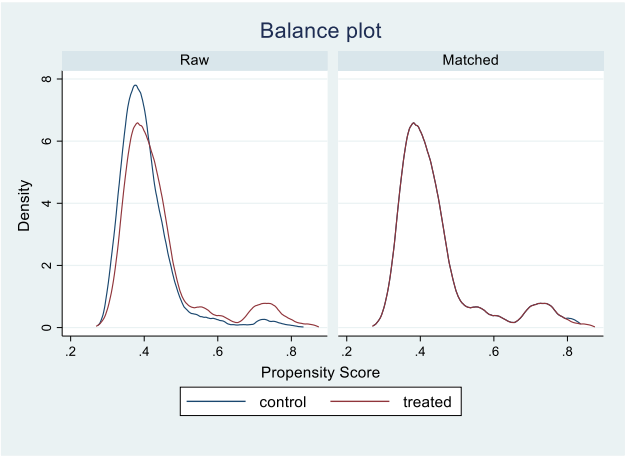
***Diagnostic assessment for propensity score matching (methyldopa vs β-blockers)***

Covariate balance summary

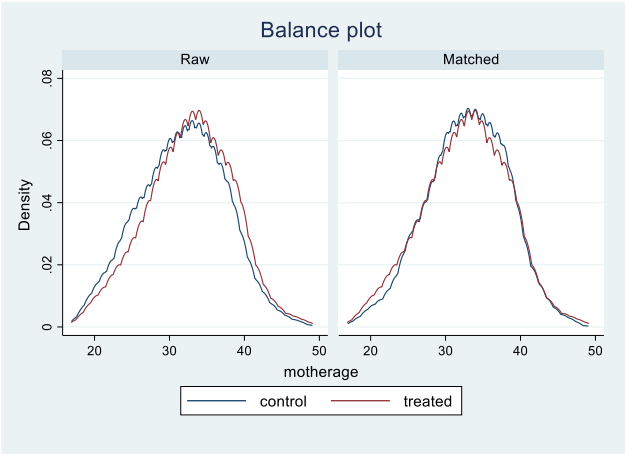
| | Raw | Matched |
|---|---|---|
| Number of obs = | 4,654 | 3,904 |
| Treated obs = | 1,952 | 1,952 |
| Control obs = | 2,702 | 1,952 |

| | Standardized differences | | Variance ratio | |
|---|---|---|---|---|
| | Raw | Matched | Raw | Matched |
| smoking | .0866368 | -.0000748 | 1.069856 | 1.000107 |
| e2015_imd_10 | .0163308 | .0132794 | .9789923 | .9807839 |
| ethnic_hes | .1825681 | .0203529 | 1.497676 | .9962426 |
| motherage | .166595 | -.0371963 | .980408 | 1.128888 |
| parity | .0558617 | -.0254832 | .9566343 | 1.018725 |
| bmi | -.0251983 | .0308687 | .964967 | 1.043757 |
| diabetes | .2924059 | .0072084 | 3.640849 | 1.021093 |




Mother age, continuous variable

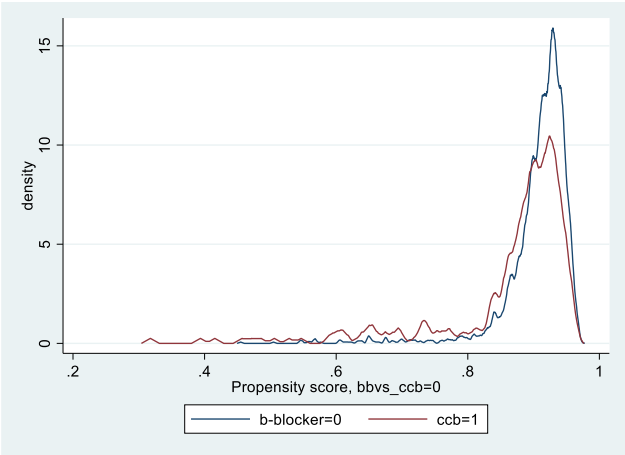


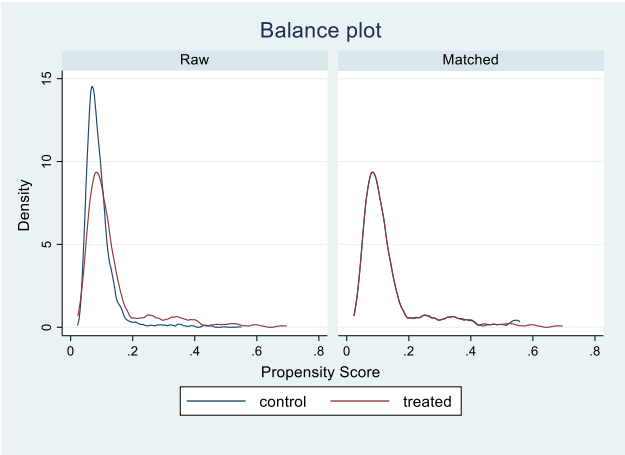
***Diagnostic assessment for propensity score matching (calcium channel blockers vs β-blockers)***

Covariate balance summary

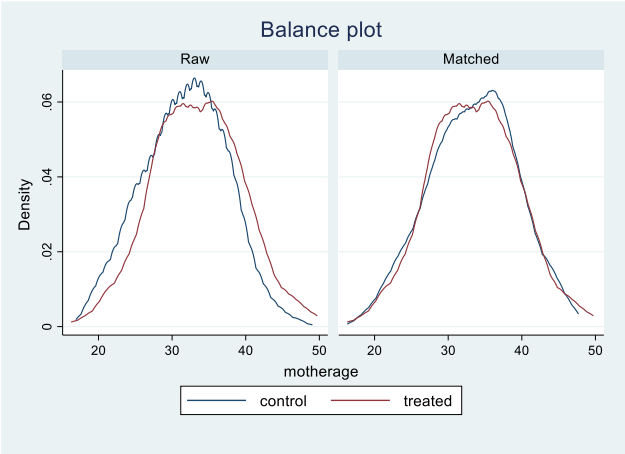
| | Raw | Matched |
|---|---|---|
| Number of obs = | 2,991 | 578 |
| Treated obs = | 289 | 289 |
| Control obs = | 2,702 | 289 |

| | Standardized differences | | Variance ratio | |
|---|---|---|---|---|
| | Raw | Matched | Raw | Matched |
| smoking | .1051499 | .0809293 | 1.085994 | 1.060063 |
| e2015_imd_10 | .2037168 | .0615079 | .9326104 | .9697613 |
| ethnic_hes | .251726 | .0286034 | 1.492381 | .9446205 |
| motherage | .2947889 | .0158528 | 1.060711 | 1.02577 |
| parity | .0363377 | -.0719775 | .9365495 | 1.018436 |
| bmi | -.0951402 | .0357488 | .8728326 | 1.062151 |
| diabetes | .3764114 | -.0520101 | 4.644544 | .8892308 |




Mother age, continuous variable

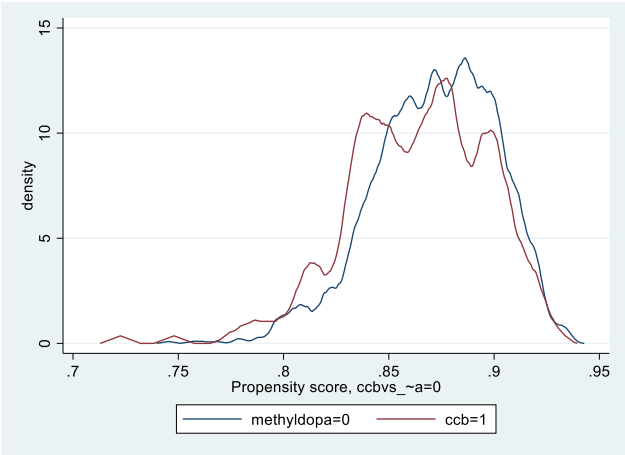


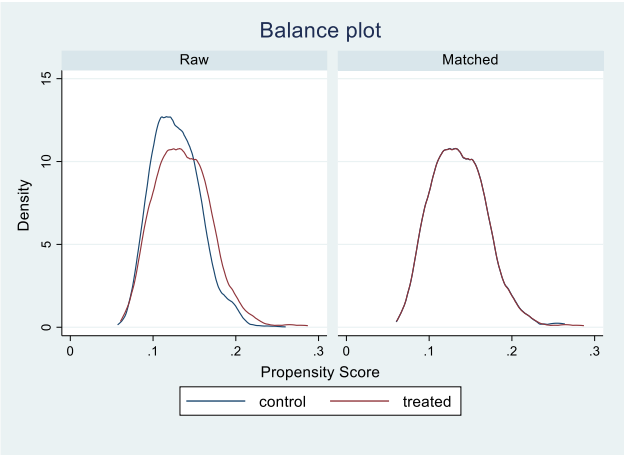
***Diagnostic assessment for propensity score matching (calcium channel blockers vs methyldopa)***

Covariate balance summary

| | Raw | Matched |
|---|---|---|
| Number of obs = | 2,241 | 578 |
| Treated obs = | 289 | 289 |
| Control obs = | 1,952 | 289 |

| | Standardized differences | | Variance ratio | |
|---|---|---|---|---|
| | Raw | Matched | Raw | Matched |
| smoking | .018541 | .014333 | 1.015084 | 1.009742 |
| e2015_imd_10 | .188217 | .0418164 | .9526228 | 1.006839 |
| ethnic_hes | .0629638 | .18925 | .9964649 | 1.443102 |
| motherage | .1321016 | -.0387607 | 1.081907 | 1.026788 |
| parity | -.0200386 | -.0751836 | .9790047 | 1.224783 |
| bmi | -.0699873 | .1309886 | .9045207 | 1.274467 |
| diabetes | .0918444 | -.0520101 | 1.275676 | .8892308 |




Mother age, continuous variable

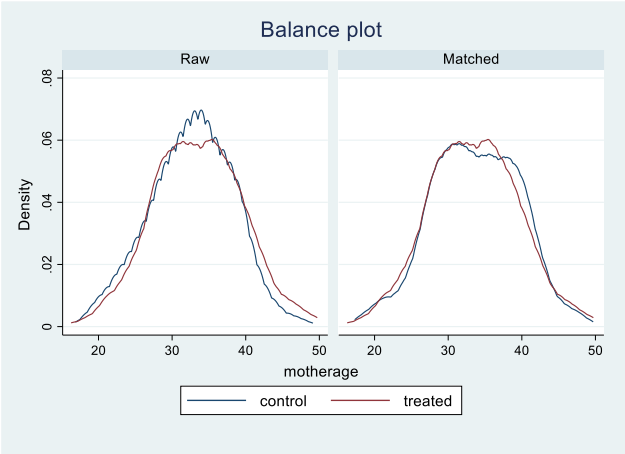


**Table S6.13** CPRD and HES codes used to identify variables

| Variable | CPRD – Read code diagnoses | HES – ICD10 Hospital diagnoses |
|---|---|---|
| Pre-eclampsia | L124.00: Mild or unspecified pre-eclampsia<br>L124.11; Mild pre-eclampsia<br>L124.12: Toxaemia NOS<br>L124000: Mild or unspecified pre-eclampsia unspecified<br>L124100: Mild or unspecified pre-eclampsia - delivered<br>L124200: Mild or unspecified pre-eclampsia - delivered with p/n comp<br>L124300: Mild or unspecified pre-eclampsia - not delivered<br>L124400: Mild or unspecified pre-eclampsia with p/n complication<br>L124500: Mild pre-eclampsia<br>L124600: Pre-eclampsia, unspecified<br>L124z00: Mild or unspecified pre-eclampsia NOS<br>L125.00: Severe pre-eclampsia<br>L125000: Severe pre-eclampsia unspecified<br>L125100: Severe pre-eclampsia - delivered<br>L125200: Severe pre-eclampsia - delivered with postnatal complication<br>L125300: Severe pre-eclampsia - not delivered<br>L125400: Severe pre-eclampsia with postnatal complication<br>L125z00: Severe pre-eclampsia NOS<br>L126.00: Eclampsia<br>L126000: Eclampsia unspecified<br>L126100: Eclampsia - delivered<br>L126200: Eclampsia - delivered with postnatal complication<br>L126300: Eclampsia - not delivered<br>L126400: Eclampsia with postnatal complication<br>L126500: Eclampsia in pregnancy<br>L126600: Eclampsia in labour<br>L126z00: Eclampsia NOS<br>L127.00: Pre-eclampsia or eclampsia with pre-existing hypertension<br>L127000: Pre-eclampsia or eclampsia with hypertension unspecified<br>L127100: Pre-eclampsia or eclampsia with hypertension - delivered<br>L127200: Pre-eclampsia or eclampsia with hypertension - del+p/n comp<br>L127300: Pre-eclampsia or eclampsia with hypertension - not delivered<br>L127400: Pre-eclampsia or eclampsia with hypertension + p/n comp<br>L127z00: Pre-eclampsia or eclampsia + pre-existing hypertension NOS<br>L129.00: Moderate pre-eclampsia<br>L12A.00: HELLP - Syndrome haemolysis, elev liver enzyme low platelets<br>L12B.00: Proteinuric hypertension of pregnancy<br>Lyu1.00: [X]Oedema,proteinuria+hypertens in pregnancy,childbrth,puerp<br>Q000.11: Fetus affected by maternal toxaemia | O14: Pre-eclampsia<br>O14.0: Mild to moderate pre-eclampsia<br>O14.1: Severe pre-eclampsia<br>O14.2: HELLP syndrome<br>O14.9: Pre-eclampsia, unspecified<br>O15: Eclampsia<br>O15.0: Eclampsia in pregnancy<br>O15.1: Eclampsia in labour<br>O15.2: Eclampsia in the puerperium<br>O15.9: Eclampsia, unspecified as to time period |
| Preterm birth | Q110.00: Very premature - less than 1000g or less than 28 weeks<br>Q111.00: Premature - weight 1000g-2499g or gestation of 28-37weeks<br>6351: Baby premature 36-38 weeks<br>6352: Baby v. premature 32-36 weeks<br>6353: Baby extremely prem.28-32 week<br>6356: Baby premature 26-28 weeks<br>6357: Baby premature 24-26 weeks<br>635..13: Premature baby<br>635A.00: Baby premature 37 weeks<br>635B.00: Baby premature 36 weeks<br>635C.00: Preterm infant status<br>635C.11: Preterm<br>L14..11: Premature labour<br>L142.11: Premature delivery<br>L143.00: Premature labour and delivery<br>L143100: Premature labour with premature delivery<br>Q11..11: Baby born premature<br>Q112.11: Extreme prematurity - less than 28 weeks<br>Q116.00: Premature infant 28-37 weeks<br>Q11z.00: Born premature NOS | O60: Preterm labour and delivery<br>O60.1: Preterm spontaneous labour with preterm delivery<br>O60.3: Preterm delivery without spontaneous labour |

| | | |
|---|---|---|
| | Qyu1100: Other preterm infants<br>Q317100: Prematurity with interstitial pulmonary fibrosis | |
| Fetal growth restriction | Q10z.00: Fetal growth retardation NOS<br>Q10z.11: Intrauterine growth retardation | O36.5: Maternal care for poor fetal growth |
| Diabetes | 6761: Diabetic pre-pregnancy counselling<br>7276: Pan retinal photocoagulation for diabetes<br>9360: Patient held diabetic record issued<br>13AB.00: Diabetic lipid lowering diet<br>13AC.00: Diabetic weight reducing diet<br>13B1.00: Diabetic diet<br>2BBF.00: Retinal abnormality - diabetes related<br>2BBk.00: O/E - right eye stable treated prolif diabetic retinopathy<br>2BBL.00: O/E - diabetic maculopathy present both eyes<br>2BBl.00: O/E - left eye stable treated prolif diabetic retinopathy<br>2BBM.00: O/E - diabetic maculopathy absent both eyes<br>2BBo.00: O/E - sight threatening diabetic retinopathy<br>2BBP.00: O/E - right eye background diabetic retinopathy<br>2BBQ.00: O/E - left eye background diabetic retinopathy<br>2BBR.00: O/E - right eye preproliferative diabetic retinopathy<br>2BBS.00: O/E - left eye preproliferative diabetic retinopathy<br>2BBT.00: O/E - right eye proliferative diabetic retinopathy<br>2BBV.00: O/E - left eye proliferative diabetic retinopathy<br>2BBW.00: O/E - right eye diabetic maculopathy<br>2BBX.00: O/E - left eye diabetic maculopathy<br>2G51000: Foot abnormality - diabetes related<br>2G5A.00: O/E - Right diabetic foot at risk<br>2G5B.00: O/E - Left diabetic foot at risk<br>2G5C.00: Foot abnormality - diabetes related<br>2G5E.00: O/E - Right diabetic foot at low risk<br>2G5F.00: O/E - Right diabetic foot at moderate risk<br>2G5G.00: O/E - Right diabetic foot at high risk<br>2G5H.00: O/E - Right diabetic foot - ulcerated<br>2G5I.00: O/E - Left diabetic foot at low risk<br>2G5J.00: O/E - Left diabetic foot at moderate risk<br>2G5K.00: O/E - Left diabetic foot at high risk<br>2G5L.00: O/E - Left diabetic foot - ulcerated<br>2G5V.00: O/E - right chronic diabetic foot ulcer<br>2G5W.00: O/E - left chronic diabetic foot ulcer<br>66A3.00: Diabetic on diet only<br>66A4.00: Diabetic on oral treatment<br>66A5.00: Diabetic on insulin<br>66A8.00: Has seen dietician - diabetes<br>66A9.00: Understands diet - diabetes<br>66Aa.00: Diabetic diet - poor compliance<br>66AA.11: Injection sites - diabetic<br>66Ab.00: Diabetic foot examination<br>66Ac.00: Diabetic peripheral neuropathy screening<br>66AD.00: Fundoscopy - diabetic check<br>66AG.00: Diabetic drug side effects<br>66Ag.00: Insulin needles changed daily<br>66AH.00: Diabetic treatment changed<br>66Ah.00: Insulin needles changed for each injection<br>66AI.00: Diabetic - good control<br>66Ai.00: Diabetic 6 month review<br>66AJ.00: Diabetic - poor control<br>66Aj.00: Insulin needles changed less than once a day<br>66AJ.11: Unstable diabetes<br>66AJ100: Brittle diabetes<br>66AJz00: Diabetic - poor control NOS<br>66AK.00: Diabetic - cooperative patient<br>66AL.00: Diabetic-uncooperative patient<br>66Am.00: Insulin dose changed | E10: Insulin-dependent diabetes mellitus<br>E11: Non-insulin-dependent diabetes mellitus<br>E13: Other specified diabetes mellitus<br>E14: Unspecified diabetes mellitus<br>G590: Diabetic mononeuropathy<br>G632: Diabetic polyneuropathy<br>H280: Diabetic cataract<br>H360: Diabetic retinopathy<br>M142: Diabetic arthropathy<br>N083: Glomerular disorders in diabetes mellitus<br>O240: Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, insulin-dependent<br>O241: Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, non-insulin-dependent<br>O243: Diabetes mellitus in pregnancy: Pre-existing diabetes mellitus, unspecified |

66An.00: Diabetes type 1 review
66AN.00: Date diabetic treatment start
66Ao.00: Diabetes type 2 review
66AO.00: Date diabetic treatment stopp.
66AP.00: Diabetes: practice programme
66Ap.00: Insulin treatment initiated
66AQ.00: Diabetes: shared care programme
66Aq.00: Diabetic foot screen
66AR.00: Diabetes management plan given
66AS.00: Diabetic annual review
66AT.00: Annual diabetic blood test
66AU.00: Diabetes care by hospital only
66AV.00: Diabetic on insulin and oral treatment
66AW.00: Diabetic foot risk assessment
66AX.00: Diabetes: shared care in pregnancy - diabetol and obstet
66AY.00: Diabetic diet - good compliance
68A7.00: Diabetic retinopathy screening
68A9.00: Diabetic retinopathy screening offered
68AB.00: Diabetic digital retinopathy screening offered
7L10000: Continuous subcutaneous infusion of insulin
7L19800: Subcutaneous injection of insulin
889A.00: Diab mellit insulin-glucose infus acute myocardial infarct
8A13.00: Diabetic stabilisation
8B3l.00: Diabetes medication review
8BL2.00: Patient on maximal tolerated therapy for diabetes
8CA4100: Pt advised re diabetic diet
8CAQ.00: Advice about blood glucose control
8CP2.00: Transition of diabetes care options discussed
8H2J.00: Admit diabetic emergency
8H3O.00: Non-urgent diabetic admission
8H7r.00: Refer to diabetic foot screener
8HBG.00: Diabetic retinopathy 12 month review
8HBH.00: Diabetic retinopathy 6 month review
8Hl1.00: Referral for diabetic retinopathy screening
8HLE.00: Diabetology D.V. done
8I3k.00: Insulin therapy declined
8I3W.00: Diabetic foot examination declined
8I3X.00: Diabetic retinopathy screening refused
8I57.00: Patient held diabetic record declined
9OLD.00: Diabetic patient unsuitable for digital retinal photography
C10..00: Diabetes mellitus
C100.00: Diabetes mellitus with no mention of complication
C100000: Diabetes mellitus, juvenile type, no mention of complication
C100011: Insulin dependent diabetes mellitus
C100100: Diabetes mellitus, adult onset, no mention of complication
C100111: Maturity onset diabetes
C100112: Non-insulin dependent diabetes mellitus
C100z00: Diabetes mellitus NOS with no mention of complication
C101.00: Diabetes mellitus with ketoacidosis
C101000: Diabetes mellitus, juvenile type, with ketoacidosis
C101100: Diabetes mellitus, adult onset, with ketoacidosis
C101y00: Other specified diabetes mellitus with ketoacidosis
C101z00: Diabetes mellitus NOS with ketoacidosis
C102.00: Diabetes mellitus with hyperosmolar coma
C102000: Diabetes mellitus, juvenile type, with hyperosmolar coma
C102100: Diabetes mellitus, adult onset, with hyperosmolar coma
C102z00: Diabetes mellitus NOS with hyperosmolar coma
C103.00: Diabetes mellitus with ketoacidotic coma
C103000: Diabetes mellitus, juvenile type, with ketoacidotic coma
C103100: Diabetes mellitus, adult onset, with ketoacidotic coma
C103y00: Other specified diabetes mellitus with coma
C103z00: Diabetes mellitus NOS with ketoacidotic coma
C104.00: Diabetes mellitus with renal manifestation
C104.11: Diabetic nephropathy

C104000: Diabetes mellitus, juvenile type, with renal manifestation
C104100: Diabetes mellitus, adult onset, with renal manifestation
C104y00: Other specified diabetes mellitus with renal complications
C104z00: Diabetes mellitis with nephropathy NOS
C105.00: Diabetes mellitus with ophthalmic manifestation
C105000: Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100: Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y00: Other specified diabetes mellitus with ophthalmic complicatn
C105z00: Diabetes mellitus NOS with ophthalmic manifestation
C106.00: Diabetes mellitus with neurological manifestation
C106.11: Diabetic amyotrophy
C106.12: Diabetes mellitus with neuropathy
C106.13: Diabetes mellitus with polyneuropathy
C106000: Diabetes mellitus, juvenile, + neurological manifestation
C106100: Diabetes mellitus, adult onset, + neurological manifestation
C106y00: Other specified diabetes mellitus with neurological comps
C106z00: Diabetes mellitus NOS with neurological manifestation
C107.00: Diabetes mellitus with peripheral circulatory disorder
C107.11: Diabetes mellitus with gangrene
C107.12: Diabetes with gangrene
C107000: Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100: Diabetes mellitus, adult, + peripheral circulatory disorder
C107200: Diabetes mellitus, adult with gangrene
C107300: IDDM with peripheral circulatory disorder
C107400: NIDDM with peripheral circulatory disorder
C107z00: Diabetes mellitus NOS with peripheral circulatory disorder
C108.00: Insulin dependent diabetes mellitus
C108.11: IDDM-Insulin dependent diabetes mellitus
C108.12: Type 1 diabetes mellitus
C108.13: Type I diabetes mellitus
C108000: Insulin-dependent diabetes mellitus with renal complications
C108011: Type I diabetes mellitus with renal complications
C108012: Type 1 diabetes mellitus with renal complications
C108100: Insulin-dependent diabetes mellitus with ophthalmic comps
C108200: Insulin-dependent diabetes mellitus with neurological comps
C108211: Type I diabetes mellitus with neurological complications
C108212: Type 1 diabetes mellitus with neurological complications
C108300: Insulin dependent diabetes mellitus with multiple complicatn
C108400: Unstable insulin dependant diabetes mellitus
C108411: Unstable type I diabetes mellitus
C108412: Unstable type 1 diabetes mellitus
C108500: Insulin dependent diabetes mellitus with ulcer
C108511: Type I diabetes mellitus with ulcer
C108512: Type 1 diabetes mellitus with ulcer
C108600: Insulin dependent diabetes mellitus with gangrene
C108700: Insulin dependent diabetes mellitus with retinopathy
C108711: Type I diabetes mellitus with retinopathy
C108712: Type 1 diabetes mellitus with retinopathy
C108800: Insulin dependant diabetes mellitus - poor control
C108811: Type I diabetes mellitus - poor control
C108812: Type 1 diabetes mellitus - poor control
C108900: Insulin dependant diabetes maturity onset
C108911: Type I diabetes mellitus maturity onset
C108912: Type 1 diabetes mellitus maturity onset
C108A00: Insulin-dependent diabetes without complication
C108A11: Type I diabetes mellitus without complication
C108B00: Insulin dependent diabetes mellitus with mononeuropathy
C108C00: Insulin dependent diabetes mellitus with polyneuropathy
C108D00: Insulin dependent diabetes mellitus with nephropathy
C108D11: Type I diabetes mellitus with nephropathy
C108E00: Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11: Type I diabetes mellitus with hypoglycaemic coma
C108E12: Type 1 diabetes mellitus with hypoglycaemic coma
C108F00: Insulin dependent diabetes mellitus with diabetic cataract

C108F11: Type I diabetes mellitus with diabetic cataract
C108G00: Insulin dependent diab mell with peripheral angiopathy
C108H00: Insulin dependent diabetes mellitus with arthropathy
C108H11: Type I diabetes mellitus with arthropathy
C108J00: Insulin dependent diab mell with neuropathic arthropathy
C108J11: Type I diabetes mellitus with neuropathic arthropathy
C108J12: Type 1 diabetes mellitus with neuropathic arthropathy
C108y00: Other specified diabetes mellitus with multiple comps
C108z00: Unspecified diabetes mellitus with multiple complications
C109.00: Non-insulin dependent diabetes mellitus
C109.11: NIDDM - Non-insulin dependent diabetes mellitus
C109.12: Type 2 diabetes mellitus
C109.13: Type II diabetes mellitus
C109000: Non-insulin-dependent diabetes mellitus with renal comps
C109011: Type II diabetes mellitus with renal complications
C109012: Type 2 diabetes mellitus with renal complications
C109100: Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111: Type II diabetes mellitus with ophthalmic complications
C109112: Type 2 diabetes mellitus with ophthalmic complications
C109200: Non-insulin-dependent diabetes mellitus with neuro comps
C109211: Type II diabetes mellitus with neurological complications
C109212: Type 2 diabetes mellitus with neurological complications
C109300: Non-insulin-dependent diabetes mellitus with multiple comps
C109400: Non-insulin dependent diabetes mellitus with ulcer
C109411: Type II diabetes mellitus with ulcer
C109412: Type 2 diabetes mellitus with ulcer
C109500: Non-insulin dependent diabetes mellitus with gangrene
C109511: Type II diabetes mellitus with gangrene
C109512: Type 2 diabetes mellitus with gangrene
C109600: Non-insulin-dependent diabetes mellitus with retinopathy
C109611: Type II diabetes mellitus with retinopathy
C109612: Type 2 diabetes mellitus with retinopathy
C109700: Non-insulin dependant diabetes mellitus - poor control
C109711: Type II diabetes mellitus - poor control
C109712: Type 2 diabetes mellitus - poor control
C109900: Non-insulin-dependent diabetes mellitus without complication
C109A00: Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11: Type II diabetes mellitus with mononeuropathy
C109B00: Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11: Type II diabetes mellitus with polyneuropathy
C109C00: Non-insulin dependent diabetes mellitus with nephropathy
C109C11: Type II diabetes mellitus with nephropathy
C109C12: Type 2 diabetes mellitus with nephropathy
C109D00: Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11: Type II diabetes mellitus with hypoglycaemic coma
C109D12: Type 2 diabetes mellitus with hypoglycaemic coma
C109E00: Non-insulin depend diabetes mellitus with diabetic cataract
C109E11: Type II diabetes mellitus with diabetic cataract
C109E12: Type 2 diabetes mellitus with diabetic cataract
C109F00: Non-insulin-dependent d m with peripheral angiopath
C109F11: Type II diabetes mellitus with peripheral angiopathy
C109F12: Type 2 diabetes mellitus with peripheral angiopathy
C109G00: Non-insulin dependent diabetes mellitus with arthropathy
C109G11: Type II diabetes mellitus with arthropathy
C109G12: Type 2 diabetes mellitus with arthropathy
C109H00: Non-insulin dependent d m with neuropathic arthropathy
C109H11: Type II diabetes mellitus with neuropathic arthropathy
C109H12: Type 2 diabetes mellitus with neuropathic arthropathy
C109J00: Insulin treated Type 2 diabetes mellitus
C109J11: Insulin treated non-insulin dependent diabetes mellitus
C109J12: Insulin treated Type II diabetes mellitus
C109K00: Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A.00: Malnutrition-related diabetes mellitus
C10A000: Malnutrition-related diabetes mellitus with coma

C10A100: Malnutrition-related diabetes mellitus with ketoacidosis
C10B.00: Diabetes mellitus induced by steroids
C10B000: Steroid induced diabetes mellitus without complication
C10C.00: Diabetes mellitus autosomal dominant
C10C.11: Maturity onset diabetes in youth
C10C.12: Maturity onset diabetes in youth type 1
C10D.00: Diabetes mellitus autosomal dominant type 2
C10D.11: Maturity onset diabetes in youth type 2
C10E.00: Type 1 diabetes mellitus
C10E.11: Type I diabetes mellitus
C10E.12: Insulin dependent diabetes mellitus
C10E000: Type 1 diabetes mellitus with renal complications
C10E100: Type 1 diabetes mellitus with ophthalmic complications
C10E112: Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200: Type 1 diabetes mellitus with neurological complications
C10E300: Type 1 diabetes mellitus with multiple complications
C10E311: Type I diabetes mellitus with multiple complications
C10E312: Insulin dependent diabetes mellitus with multiple complicat
C10E400: Unstable type 1 diabetes mellitus
C10E411: Unstable type I diabetes mellitus
C10E412: Unstable insulin dependent diabetes mellitus
C10E500: Type 1 diabetes mellitus with ulcer
C10E511: Type I diabetes mellitus with ulcer
C10E512: Insulin dependent diabetes mellitus with ulcer
C10E600: Type 1 diabetes mellitus with gangrene
C10E700: Type 1 diabetes mellitus with retinopathy
C10E711: Type I diabetes mellitus with retinopathy
C10E712: Insulin dependent diabetes mellitus with retinopathy
C10E800: Type 1 diabetes mellitus - poor control
C10E812: Insulin dependent diabetes mellitus - poor control
C10E900: Type 1 diabetes mellitus maturity onset
C10E911: Type I diabetes mellitus maturity onset
C10E912: Insulin dependent diabetes maturity onset
C10EA00: Type 1 diabetes mellitus without complication
C10EA11: Type I diabetes mellitus without complication
C10EB00: Type 1 diabetes mellitus with mononeuropathy
C10EC00: Type 1 diabetes mellitus with polyneuropathy
C10EC11: Type I diabetes mellitus with polyneuropathy
C10ED00: Type 1 diabetes mellitus with nephropathy
C10EE00: Type 1 diabetes mellitus with hypoglycaemic coma
C10EF00: Type 1 diabetes mellitus with diabetic cataract
C10EG00: Type 1 diabetes mellitus with peripheral angiopathy
C10EH00: Type 1 diabetes mellitus with arthropathy
C10EJ00: Type 1 diabetes mellitus with neuropathic arthropathy
C10EK00: Type 1 diabetes mellitus with persistent proteinuria
C10EL00: Type 1 diabetes mellitus with persistent microalbuminuria
C10EM00: Type 1 diabetes mellitus with ketoacidosis
C10EM11: Type I diabetes mellitus with ketoacidosis
C10EN00: Type 1 diabetes mellitus with ketoacidotic coma
C10EN11: Type I diabetes mellitus with ketoacidotic coma
C10EP00: Type 1 diabetes mellitus with exudative maculopathy
C10EP11: Type I diabetes mellitus with exudative maculopathy
C10EQ00: Type 1 diabetes mellitus with gastroparesis
C10ER00: Latent autoimmune diabetes mellitus in adult
C10F.00: Type 2 diabetes mellitus
C10F.11: Type II diabetes mellitus
C10F000: Type 2 diabetes mellitus with renal complications
C10F011: Type II diabetes mellitus with renal complications
C10F100: Type 2 diabetes mellitus with ophthalmic complications
C10F200: Type 2 diabetes mellitus with neurological complications
C10F211: Type II diabetes mellitus with neurological complications
C10F300: Type 2 diabetes mellitus with multiple complications
C10F311: Type II diabetes mellitus with multiple complications
C10F400: Type 2 diabetes mellitus with ulcer

C10F411: Type II diabetes mellitus with ulcer
C10F500: Type 2 diabetes mellitus with gangrene
C10F600: Type 2 diabetes mellitus with retinopathy
C10F611: Type II diabetes mellitus with retinopathy
C10F700: Type 2 diabetes mellitus - poor control
C10F711: Type II diabetes mellitus - poor control
C10F900: Type 2 diabetes mellitus without complication
C10F911: Type II diabetes mellitus without complication
C10FA00: Type 2 diabetes mellitus with mononeuropathy
C10FA11: Type II diabetes mellitus with mononeuropathy
C10FB00: Type 2 diabetes mellitus with polyneuropathy
C10FB11: Type II diabetes mellitus with polyneuropathy
C10FC00: Type 2 diabetes mellitus with nephropathy
C10FD00: Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11: Type II diabetes mellitus with hypoglycaemic coma
C10FE00: Type 2 diabetes mellitus with diabetic cataract
C10FE11: Type II diabetes mellitus with diabetic cataract
C10FF00: Type 2 diabetes mellitus with peripheral angiopathy
C10FG00: Type 2 diabetes mellitus with arthropathy
C10FH00: Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ00: Insulin treated Type 2 diabetes mellitus
C10FJ11: Insulin treated Type II diabetes mellitus
C10FK00: Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL00: Type 2 diabetes mellitus with persistent proteinuria
C10FL11: Type II diabetes mellitus with persistent proteinuria
C10FM00: Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11: Type II diabetes mellitus with persistent microalbuminuria
C10FN00: Type 2 diabetes mellitus with ketoacidosis
C10FP00: Type 2 diabetes mellitus with ketoacidotic coma
C10FQ00: Type 2 diabetes mellitus with exudative maculopathy
C10FR00: Type 2 diabetes mellitus with gastroparesis
C10M.00: Lipoatrophic diabetes mellitus
C10y.00: Diabetes mellitus with other specified manifestation
C10y100: Diabetes mellitus, adult, + other specified manifestation
C10yy00: Other specified diabetes mellitus with other spec comps
C10yz00: Diabetes mellitus NOS with other specified manifestation
C10z.00: Diabetes mellitus with unspecified complication
C10z000: Diabetes mellitus, juvenile type, + unspecified complication
C10z100: Diabetes mellitus, adult onset, + unspecified complication
C10zy00: Other specified diabetes mellitus with unspecified comps
C10zz00: Diabetes mellitus NOS with unspecified complication
C314.11: Renal diabetes
C350011: Bronzed diabetes
Cyu2.00: [X]Diabetes mellitus
Cyu2000: [X]Other specified diabetes mellitus
F171100: Autonomic neuropathy due to diabetes
F345000: Diabetic mononeuritis multiplex
F35z000: Diabetic mononeuritis NOS
F372.00: Polyneuropathy in diabetes
F372.11: Diabetic polyneuropathy
F372.12: Diabetic neuropathy
F372000: Acute painful diabetic neuropathy
F372100: Chronic painful diabetic neuropathy
F372200: Asymptomatic diabetic neuropathy
F381300: Myasthenic syndrome due to diabetic amyotrophy
F381311: Diabetic amyotrophy
F3y0.00: Diabetic mononeuropathy
F420.00: Diabetic retinopathy
F420000: Background diabetic retinopathy
F420100: Proliferative diabetic retinopathy
F420200: Preproliferative diabetic retinopathy
F420300: Advanced diabetic maculopathy
F420400: Diabetic maculopathy
F420500: Advanced diabetic retinal disease

| | |
|---|---|
| | F420600: Non proliferative diabetic retinopathy<br>F420700: High risk proliferative diabetic retinopathy<br>F420800: High risk non proliferative diabetic retinopathy<br>F420z00: Diabetic retinopathy NOS<br>F440700: Diabetic iritis<br>F464000: Diabetic cataract<br>G73y000: Diabetic peripheral angiopathy<br>K01x100: Nephrotic syndrome in diabetes mellitus<br>K01x111: Kimmelstiel - Wilson disease<br>L180500: Pre-existing diabetes mellitus, insulin-dependent<br>L180600: Pre-existing diabetes mellitus, non-insulin-dependent<br>L180X00: Pre-existing diabetes mellitus, unspecified<br>M037200: Cellulitis in diabetic foot<br>M21yC00: Insulin lipohypertrophy<br>M21yC11: Insulin site lipohypertrophy<br>M271000: Ischaemic ulcer diabetic foot<br>M271100: Neuropathic diabetic ulcer - foot<br>M271200: Mixed diabetic ulcer - foot<br>N030000: Diabetic cheiroarthropathy<br>N030011: Diabetic cheiropathy<br>N030100: Diabetic Charcot arthropathy<br>Q441.00: Neonatal diabetes mellitus<br>R054200: [D]Gangrene of toe in diabetic<br>R054300: [D]Widespread diabetic foot gangrene<br>TJ23.00: Adverse reaction to insulins and antidiabetic agents<br>TJ23z00: Adverse reaction to insulins and antidiabetic agents NOS<br>U602311: [X] Adverse reaction to insulins and antidiabetic agents<br>ZC2C800: Dietary advice for diabetes mellitus<br>ZC2C900: Dietary advice for type I diabetes<br>ZC2CA00: Dietary advice for type II diabetes<br>ZRbH.00: Perceived control of insulin-dependent diabetes<br>ZV65312: [V]Dietary counselling in diabetes mellitus |
| Chronic kidney disease | 1Z10.00: Chronic kidney disease stage 1<br>1Z17.00: Chronic kidney disease stage 1 with proteinuria<br>1Z17.11: CKD stage 1 with proteinuria<br>1Z18.00: Chronic kidney disease stage 1 without proteinuria<br>1Z11.00: Chronic kidney disease stage 2<br>1Z19.00: Chronic kidney disease stage 2 with proteinuria<br>1Z19.11: CKD stage 2 with proteinuria<br>1Z1A.00: Chronic kidney disease stage 2 without proteinuria<br>1Z1A.11: CKD stage 2 without proteinuria<br>1Z12.00: Chronic kidney disease stage 3<br>1Z15.00: Chronic kidney disease stage 3A<br>1Z16.00: Chronic kidney disease stage 3B<br>1Z1B.00: Chronic kidney disease stage 3 with proteinuria<br>1Z1B.11: CKD stage 3 with proteinuria<br>1Z1C.00: Chronic kidney disease stage 3 without proteinuria<br>1Z1C.11: CKD stage 3 without proteinuria<br>1Z1D.00: Chronic kidney disease stage 3A with proteinuria<br>1Z1D.11: CKD stage 3A with proteinuria<br>1Z1E.00: Chronic kidney disease stage 3A without proteinuria<br>1Z1E.11: CKD stage 3A without proteinuria<br>1Z1F.00: Chronic kidney disease stage 3B with proteinuria<br>1Z1F.11: CKD stage 3B with proteinuria<br>1Z1G.00: Chronic kidney disease stage 3B without proteinuria<br>1Z13.00: Chronic kidney disease stage 4<br>1Z1H.00: Chronic kidney disease stage 4 with proteinuria<br>1Z1J.00: Chronic kidney disease stage 4 without proteinuria<br>1Z1J.11: CKD stage 4 without proteinuria<br>1Z14.00: Chronic kidney disease stage 5<br>1Z1K.00: Chronic kidney disease stage 5 with proteinuria<br>1Z1L.00: Chronic kidney disease stage 5 without proteinuria<br>1Z1L.11: CKD stage 5 without proteinuria |
| HDP | |

| | |
|---|---|
| L123.00: Transient hypertension of pregnancy<br>L123000: Transient hypertension of pregnancy unspecified<br>L123100: Transient hypertension of pregnancy - delivered<br>L123300: Transient hypertension of pregnancy - not delivered<br>L123400: Transient hypertension of pregnancy + postnatal complication<br>L123500: Gestational hypertension<br>L123600: Transient hypertension of pregnancy<br>L123z00: Transient hypertension of pregnancy NOS<br>L12.00: Hypertension complicating pregnancy/childbirth/puerperium<br>L12z.00: Unspecified hypertension in pregnancy/childbirth/puerperium<br>L12z000: Unspecified hypertension in preg/childb/puerp unspecified<br>L12z100: Unspecified hypertension in preg/childb/puerp - delivered<br>L12z200: Unspecified hypertension in preg/childb/puerp -del +p/n comp<br>L12z300: Unspecified hypertension in preg/childb/puerp - not deliv<br>L12zz00: Unspecified hypertension in preg/childb/puerp NOS<br>Q000.00: Fetus or neonate affected by maternal hypertensive disease | O13; Gestational (pregnancy induced) hypertension<br>O10.9: Unspecified pre-existing hypertension complicating pregnancy, childbirth and the puerperium<br>O16: Unspecified maternal hypertension |

*Women with these codes (HDP: hypertensive disorders of pregnancy) were excluded from analyses except for pre-eclampsia analysis when comparing hypertensive with normotensive pregnancies*

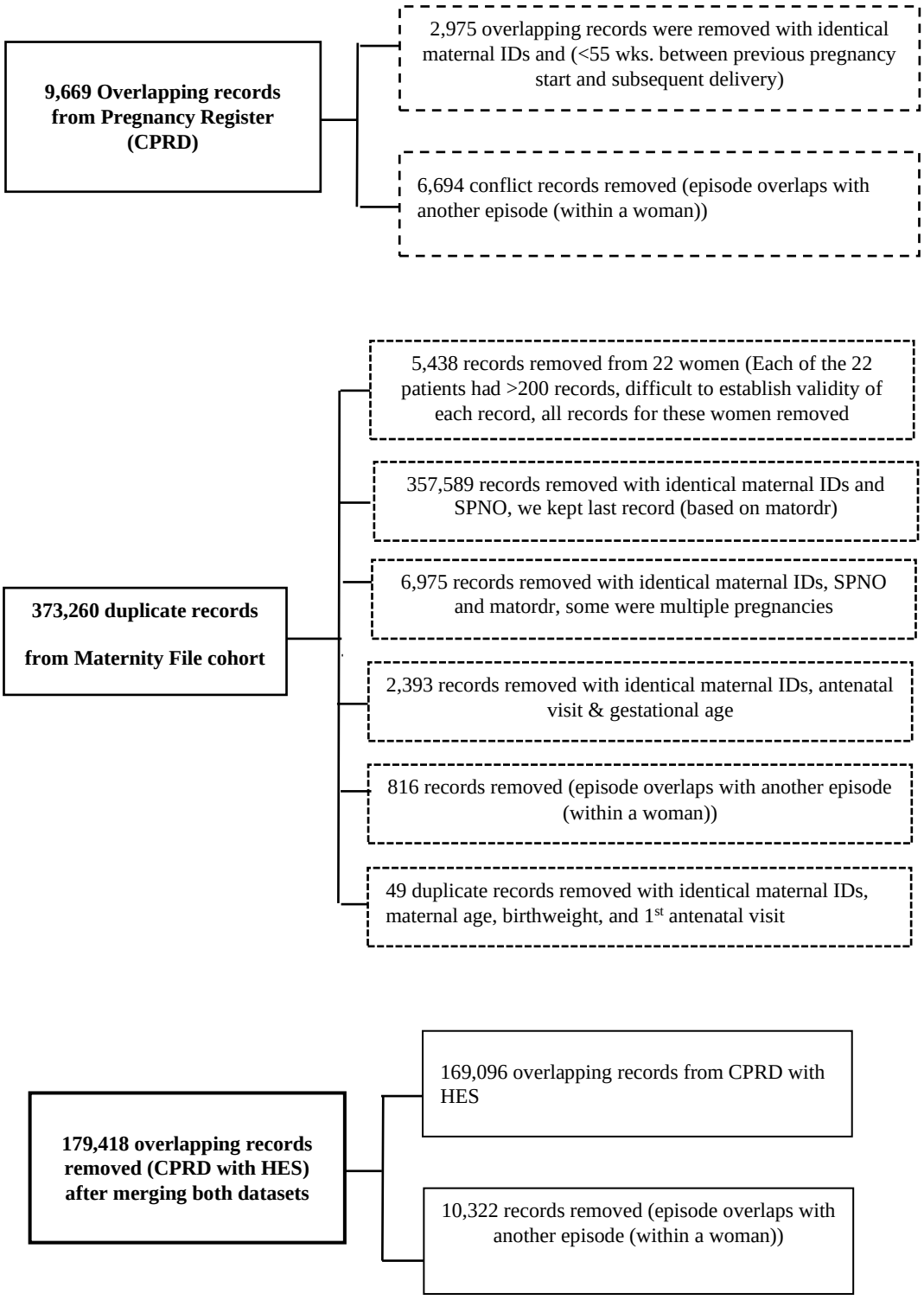



**Figure S6.6** Dealing with duplicate/overlapping records

# Appendix 7: The Association Between Chronic Hypertension and The Risk of Twelve Cardiovascular Diseases among Parous Women: The Role of Adverse Pregnancy Outcomes (supplemental material)

## S7.1 Supplementary Tables S7.1-S7.3

**Table S7.1** Associations between pre-pregnancy hypertension and cardiovascular diseases

| EVENTS | N Cases (%) | Crude HR (95% CI) | Adjusted HR (95% CI)* |
|---|---|---|---|
| Ischemic stroke | | | |
| No pre-pregnancy HTN | 665 (0.04) | Reference | Reference |
| Pre-pregnancy HTN | 30 (0.24) | 4.54 (3.14–6.58) | 4.04 (2.77–5.89) |
| Intracerebral haemorrhage | | | |
| No pre-pregnancy HTN | 317 (0.02) | Reference | Reference |
| Pre-pregnancy HTN | 11 (0.09) | 3.70 (2.02–6.78) | 4.12 (2.22–7.60) |
| Subarachnoid haemorrhage | | | |
| No pre-pregnancy HTN | 503 (0.03) | Reference | Reference |
| Pre-pregnancy HTN | 30 (0.24) | 5.40 (3.72–7.83) | 4.55 (3.11–6.64) |
| Stroke NOS | | | |
| No pre-pregnancy HTN | 251 (0.01) | Reference | Reference |
| Pre-pregnancy HTN | 16 (0.13) | 6.12 (3.67–10.2) | 4.63 (2.75–7.81) |
| All stroke | | | |
| No pre-pregnancy HTN | 1,488 (0.08) | Reference | Reference |
| Pre-pregnancy HTN | 71 (0.56) | 4.68 (3.68–5.96) | 4.22 (3.30–5.39) |
| Myocardial infarction | | | |
| No pre-pregnancy HTN | 485 (0.03) | Reference | Reference |
| Pre-pregnancy HTN | 36 (0.28) | 5.83 (4.13–8.22) | 4.53 (3.18–6.44) |
| Stable angina | | | |
| No pre-pregnancy HTN | 11,456 (0.65) | Reference | Reference |
| Pre-pregnancy HTN | 371 (2.92) | 3.13 (2.82–3.48) | 1.99 (1.80–2.22) |
| Unstable angina | | | |
| No pre-pregnancy HTN | 356 (0.02) | Reference | Reference |

| | | | |
|---|---|---|---|
| Pre-pregnancy HTN | 18 (0.14) | 3.80 (2.35–6.16) | 2.65 (1.62–4.35) |
| Coronary heart disease NOS | | | |
| No pre-pregnancy HTN | 1,102 (0.06) | Reference | Reference |
| Pre-pregnancy HTN | 83 (0.65) | 5.69 (4.53–7.15) | 4.30 (3.40–5.44) |
| Cardiac atherosclerosis | | | |
| No pre-pregnancy HTN | 12,264 (0.69) | Reference | Reference |
| Pre-pregnancy HTN | 414 (3.26) | 3.25 (2.94–3.58) | 2.09 (1.89–2.31) |
| Peripheral arterial disease | | | |
| No pre-pregnancy HTN | 630 (0.04) | Reference | Reference |
| Pre-pregnancy HTN | 12 (0.09) | 1.95 (1.10–3.46) | 1.62 (0.96–2.91) |
| Abdominal aortic aneurysm | | | |
| No pre-pregnancy HTN | 53 (0.003) | Reference | Reference |
| Pre-pregnancy HTN | 3 (0.02) | 6.30 (1.95–20.4) | 4.27 (1.30–14.0) |
| All peripheral disease | | | |
| No pre-pregnancy HTN | 683 (0.04) | Reference | Reference |
| Pre-pregnancy HTN | 14 (0.11) | 2.11 (1.24–3.60) | 1.71 (1.00–2.93) |
| Heart failure | | | |
| No pre-pregnancy HTN | 881 (0.05) | Reference | Reference |
| Pre-pregnancy HTN | 38 (0.30) | 4.38 (3.15–6.09) | 3.55 (2.53–4.98) |
| Atrial fibrillation | | | |
| No pre-pregnancy HTN | 1,489 (0.08) | Reference | Reference |
| Pre-pregnancy HTN | 69 (0.54) | 4.35 (3.41–5.55) | 3.28 (2.55–4.20) |
| All CVD** | | | |
| No pre-pregnancy HTN | 15,966 (0.9) | Reference | Reference |
| Pre-pregnancy HTN | 533 (4.2) | 3.26 (2.99–3.56) | 2.22 (2.03–2.42) |

All models were stratified by maternal age at delivery and year of birth. * Adjusted for deprivation index, smoking, body mass index, ethnicity, parity, and family history of cardiovascular disease. ** This outcome included all 12 cardiovascular disorders plus any recorded death of cardiovascular mortality.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HTN, hypertension; NOS, not otherwise specified.

**Table S7.2** Associations between pre-pregnancy hypertension and cardiovascular diseases according to adverse pregnancy outcomes

| EVENTS | N Cases (%) | Crude HR (95% CI) | Adjusted HR (95% CI)* |
|---|---|---|---|
| Ischemic stroke | | | |
| No pre-pregnancy HTN or APO | 548 (0.03) | Reference | Reference |
| No pre-pregnancy with APO | 117 (0.08) | 2.50 (2.05–2.96) | 2.40 (1.96–2.93) |
| Pre-pregnancy HTN without APO | 22 (0.22) | 4.61 (3.00–7.09) | 4.17 (2.70–6.45) |
| Pre-pregnancy HTN with APO | 8 (0.31) | 7.05 (3.41–14.2) | 6.42 (3.15–13.0) |
| Intracerebral haemorrhage | | | |
| No pre-pregnancy HTN or APO | 251 (0.02) | Reference | Reference |
| No pre-pregnancy with APO | 66 (0.04) | 3.07 (2.34–4.03) | 3.27 (2.48–4.31) |
| Pre-pregnancy HTN without APO | 6 (0.06) | 2.87 (1.27–6.47) | 3.26 (1.44–7.39) |
| Pre-pregnancy HTN with APO | 5 (0.2) | 10.7 (4.37–25.9) | 13.1 (5.33–32.2) |
| Subarachnoid haemorrhage | | | |
| No pre-pregnancy HTN or APO | 416 (0.03) | Reference | Reference |
| No pre-pregnancy with APO | 87 (0.06) | 2.47 (1.96–3.11) | 2.23 (1.77–2.82) |
| Pre-pregnancy HTN without APO | 25 (0.25) | 6.20 (4.12–9.32) | 5.25 (3.47–7.94) |
| Pre-pregnancy HTN with APO | 5 (0.20) | 5.30 (2.19–12.8) | 4.51 (1.85–11.0) |
| Stroke NOS | | | |
| No pre-pregnancy HTN or APO | 204 (0.01) | Reference | Reference |
| No pre-pregnancy with APO | 47 (0.03) | 2.69 (1.95–3.69) | 2.48 (1.80–3.42) |
| Pre-pregnancy HTN without APO | 11 (0.11) | 5.92 (3.21–10.9) | 4.55 (2.44–8.46) |
| Pre-pregnancy HTN with APO | 5 (0.20) | 11.1 (4.53–27.1) | 8.51 (3.44–21.0) |
| All stroke | | | |
| No pre-pregnancy HTN or APO | 1,218 (0.08) | Reference | Reference |
| No pre-pregnancy with APO | 270 (0.17) | 2.60 (2.28–2.97) | 2.49 (2.18–2.86) |
| Pre-pregnancy HTN without APO | 52 (0.51) | 4.76 (3.60–6.30) | 4.36 (3.28–5.78) |
| Pre-pregnancy HTN with APO | 19 (0.74) | 7.43 (4.71–11.7) | 6.93 (4.38–11.0) |
| Myocardial infarction | | | |
| No pre-pregnancy HTN or APO | 382 (0.02) | Reference | Reference |
| No pre-pregnancy with APO | 103 (0.07) | 3.38 (2.56–3.96) | 2.87 (2.23–3.47) |
| Pre-pregnancy HTN without APO | 23 (0.23) | 5.38 (3.52–8.23) | 4.23 (2.73–6.50) |

| | | | |
|---|---|---|---|
| Pre-pregnancy HTN with APO | 13 (0.51) | 13.2 (7.53–23.2) | 10.3 (5.86–18.2) |
| Stable angina | | | |
| No pre-pregnancy HTN or APO | 11,106 (0.63) | Reference | Reference |
| No pre-pregnancy with APO | 1,350 (0.87) | 1.59 (1.50–1.68) | 1.33 (1.26–1.41) |
| Pre-pregnancy HTN without APO | 276 (2.72) | 3.02 (2.68–3.41) | 1.93 (1.70–2.17) |
| Pre-pregnancy HTN with APO | 95 (3.72) | 4.35 (3.55–5.33) | 2.66 (2.17–3.26) |
| Unstable angina | | | |
| No pre-pregnancy HTN or APO | 295 (0.02) | Reference | Reference |
| No pre-pregnancy with APO | 61 (0.04) | 2.43 (1.84–3.21) | 2.10 (1.59–2.77) |
| Pre-pregnancy HTN without APO | 13 (0.13) | 3.78 (2.15–6.63) | 2.58 (1.45–4.60) |
| Pre-pregnancy HTN with APO | 5 (0.20) | 6.32 (2.57–15.5) | 4.82 (1.96–11.9) |
| Coronary heart disease NOS | | | |
| No pre-pregnancy HTN or APO | 916 (0.06) | Reference | Reference |
| No pre-pregnancy with APO | 186 (0.12) | 2.38 (2.03–2.79) | 2.08 (1.77–2.44) |
| Pre-pregnancy HTN without APO | 57 (0.56) | 5.33 (4.05–7.00) | 4.00 (3.03–5.30) |
| Pre-pregnancy HTN with APO | 26 (1.02) | 10.8 (7.23–16.1) | 8.33 (5.57–12.5) |
| Cardiac atherosclerosis | | | |
| No pre-pregnancy HTN or APO | 10,793(0.67) | Reference | Reference |
| No pre-pregnancy with APO | 1,471 (0.94) | 1.62 (1.54–1.71) | 1.36 (1.29–1.44) |
| Pre-pregnancy HTN without APO | 308 (3.04) | 3.13 (2.79–3.51) | 2.02 (1.80–2.26) |
| Pre-pregnancy HTN with APO | 106 (4.15) | 4.55 (3.75–5.52) | 2.81 (2.32–3.41) |
| Peripheral arterial disease | | | |
| No pre-pregnancy HTN or APO | 541 (0.03) | Reference | Reference |
| No pre-pregnancy with APO | 89 (0.06) | 1.87 (1.50–2.35) | 1.72 (1.37–2.16) |
| Pre-pregnancy HTN without APO | 7 (0.07) | 1.52 (0.72–3.20) | 1.26 (0.59–2.67) |
| Pre-pregnancy HTN with APO | 5 (0.20) | 4.42 (1.82–10.7) | 3.85 (1.58–9.38) |
| Abdominal aortic aneurysm | | | |
| No pre-pregnancy HTN or APO | 43 (.002) | Reference | Reference |
| No pre-pregnancy with APO | 10 (0.01) | 2.80 (1.40–5.58) | 2.43 (1.21–4.88) |
| Pre-pregnancy HTN without APO | 1 (0.01) | 2.95 (0.40–21.6) | 2.06 (0.28–15.2) |
| Pre-pregnancy HTN with APO | 2 (0.08) | 24.7 (5.92–103) | 16.9 (3.92–72.5) |
| All peripheral disease | | | |

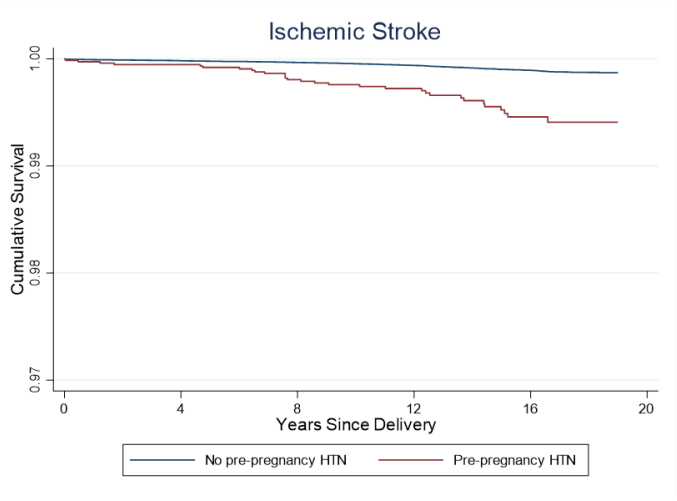
| | | | |
|---|---|---|---|
| No pre-pregnancy HTN or APO | 584 (0.04) | Reference | Reference |
| No pre-pregnancy with APO | 99 (0.06) | 1.94 (1.57–2.40) | 1.77 (1.43–2.20) |
| Pre-pregnancy HTN without APO | 8 (0.08) | 1.62 (0.80–3.25) | 1.32 (0.65–2.66) |
| Pre-pregnancy HTN with APO | 6 (0.23) | 4.60 (2.21–11.1) | 4.22 (1.87–9.51) |
| Heart failure | | | |
| No pre-pregnancy HTN or APO | 730 (0.05) | Reference | Reference |
| No pre-pregnancy with APO | 151 (0.10) | 2.38 (2.00–2.84) | 2.31 (1.93–2.76) |
| Pre-pregnancy HTN without APO | 20 (0.20) | 3.19 (2.04–5.00) | 2.65 (1.68–4.17) |
| Pre-pregnancy HTN with APO | 18 (0.70) | 11.5 (7.19–18.6) | 9.65 (5.96–15.6) |
| Atrial fibrillation | | | |
| No pre-pregnancy HTN or APO | 1,280 (0.08) | Reference | Reference |
| No pre-pregnancy with APO | 209 (0.13) | 1.91 (1.65–2.21) | 1.70 (1.46–1.97) |
| Pre-pregnancy HTN without APO | 56 (0.55) | 4.68 (3.57–6.13) | 3.55 (2.70–4.67) |
| Pre-pregnancy HTN with APO | 13 (0.51) | 4.61 (2.66–7.97) | 3.40 (1.96–5.89) |
| All CVD** | | | |
| No pre-pregnancy HTN or APO | 13,958(0.86) | Reference | |
| No pre-pregnancy with APO | 2,008 (1.3) | 1.71 (1.63–1.79) | 1.48 (1.41–1.55) |
| Pre-pregnancy HTN without APO | 399 (3.9) | 3.19 (2.88–3.53) | 2.18 (1.97–2.41) |
| Pre-pregnancy HTN with APO | 134 (5.3) | 4.52 (3.81–5.37) | 2.97 (2.50–3.52) |

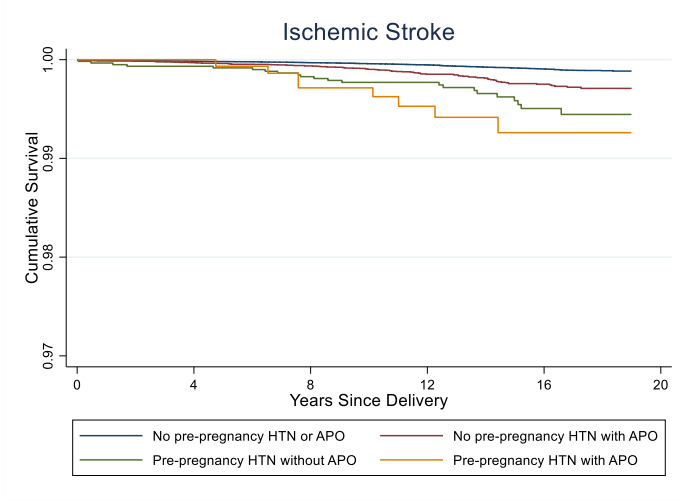
All models were stratified by maternal age at delivery and year of birth. * Adjusted for, deprivation index, smoking, body mass index, ethnicity, parity, and family history of cardiovascular disease. ** This outcome included all 12 cardiovascular disorders plus any recorded death of cardiovascular mortality. APO included hypertensive disorders during pregnancy, stillbirth, preterm birth, and fetal growth restriction
Abbreviations: APO, adverse pregnancy outcomes; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HTN, hypertension; NOS, not otherwise specified

**Table S7.3** Survival Curves for all cardiovascular outcomes according to: (A) pre-pregnancy hypertension and (B) adverse pregnancy outcomes

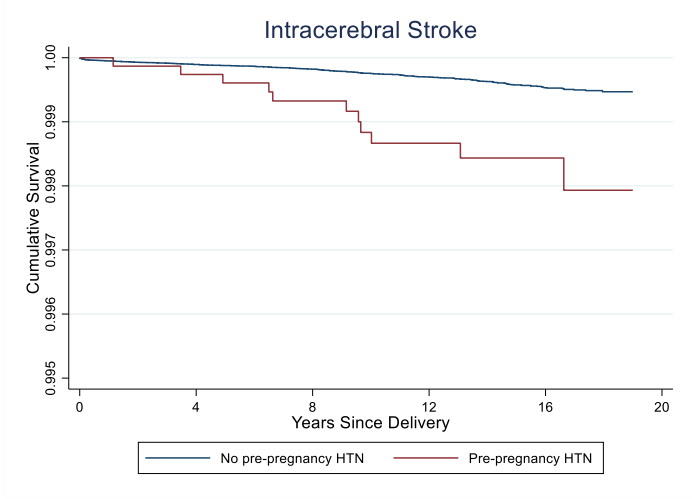
| (A) | (B) |
|---|---|

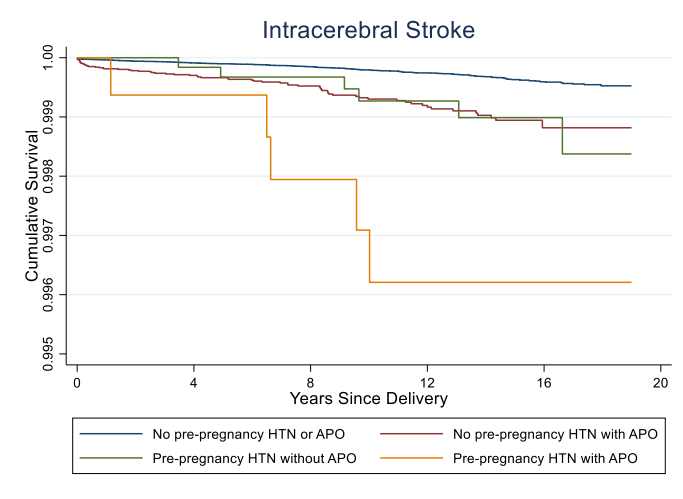
**Ischemic stroke**



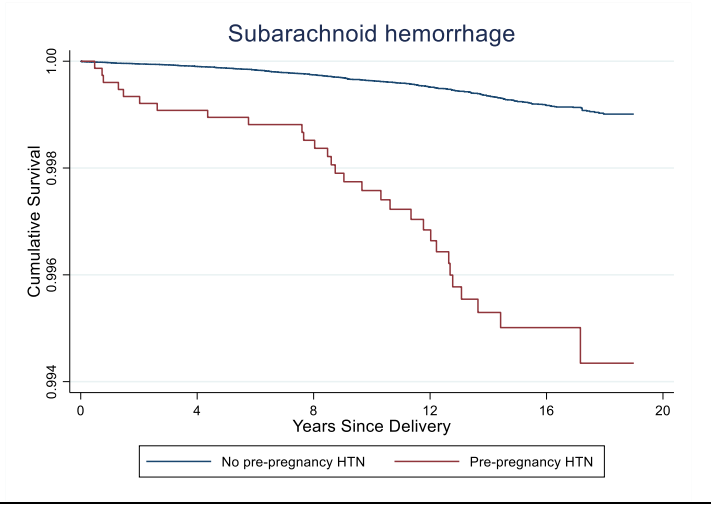



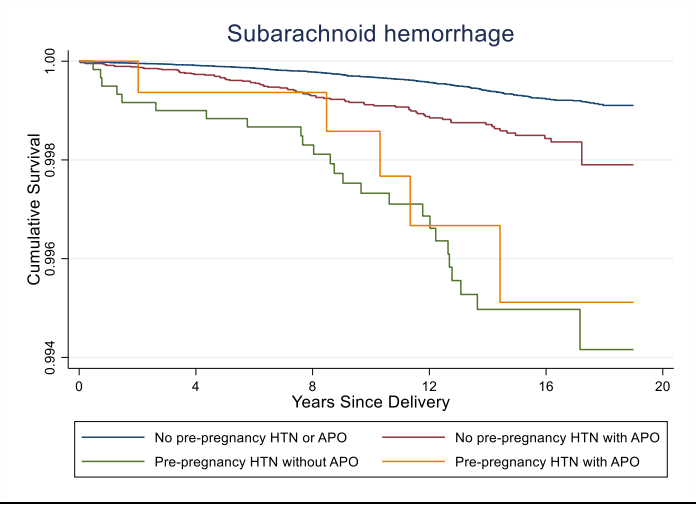

**Intracerebral haemorrhage**



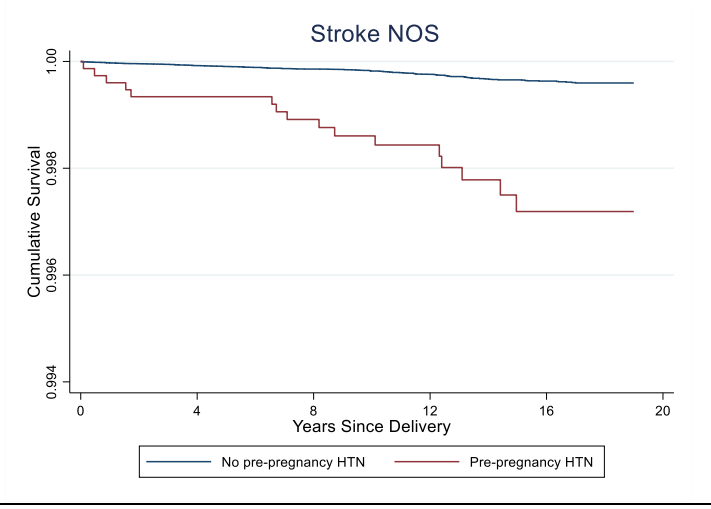



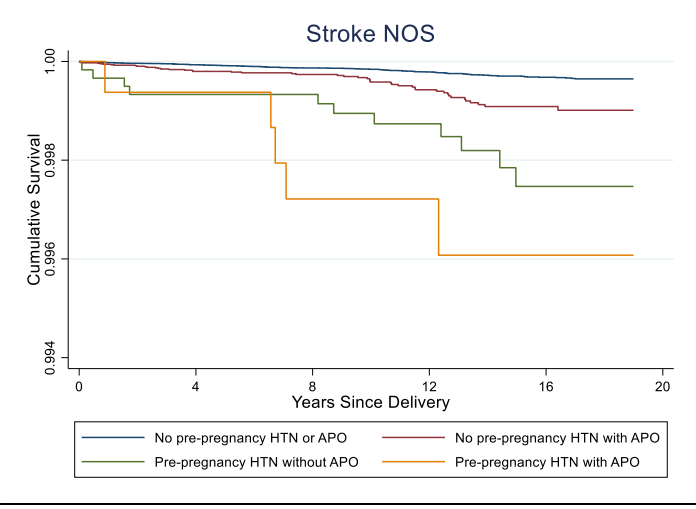
## Subarachnoid haemorrhage



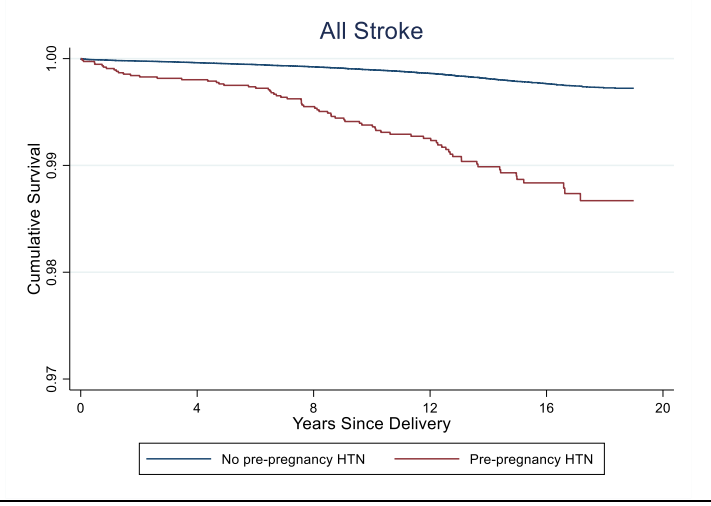



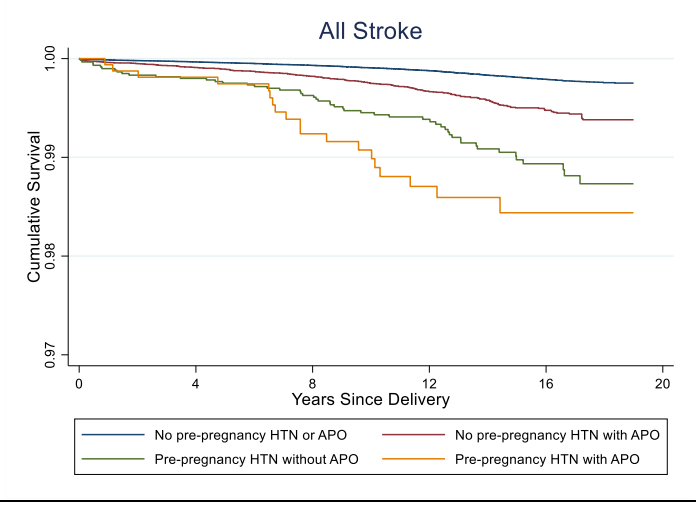

## Stroke not otherwise specified



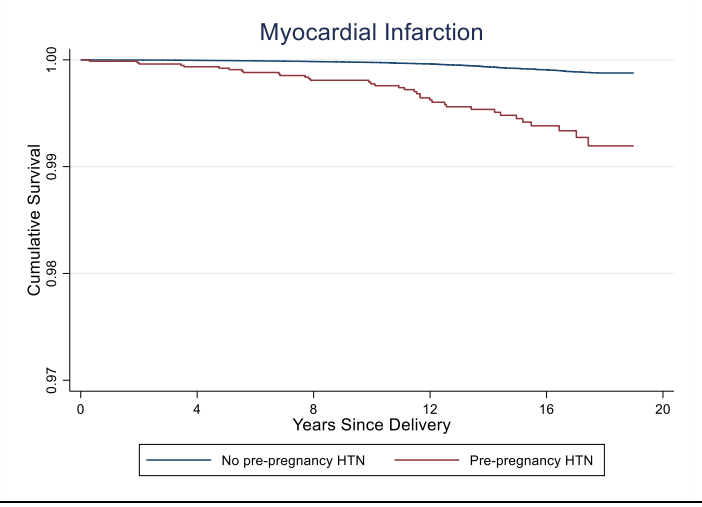



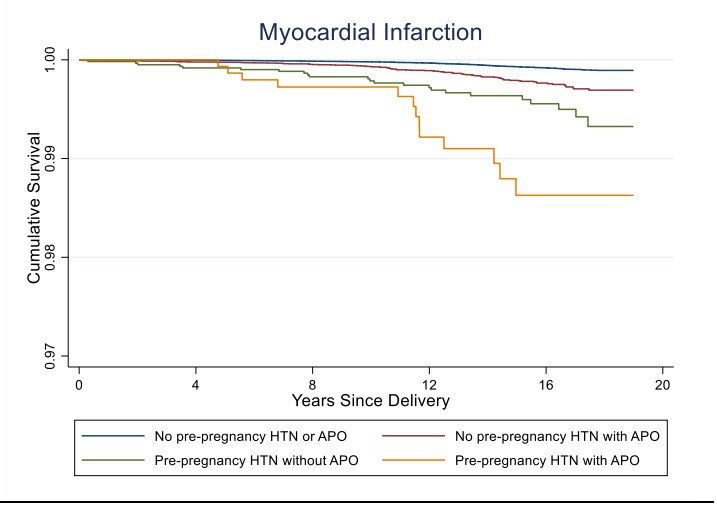

## All stoke



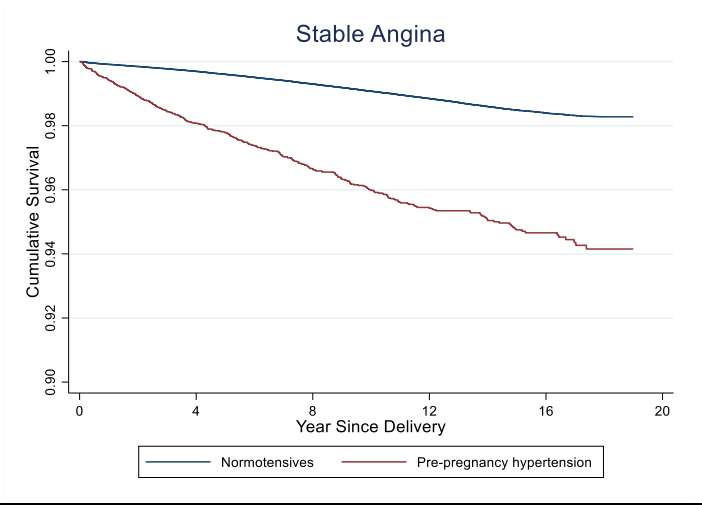



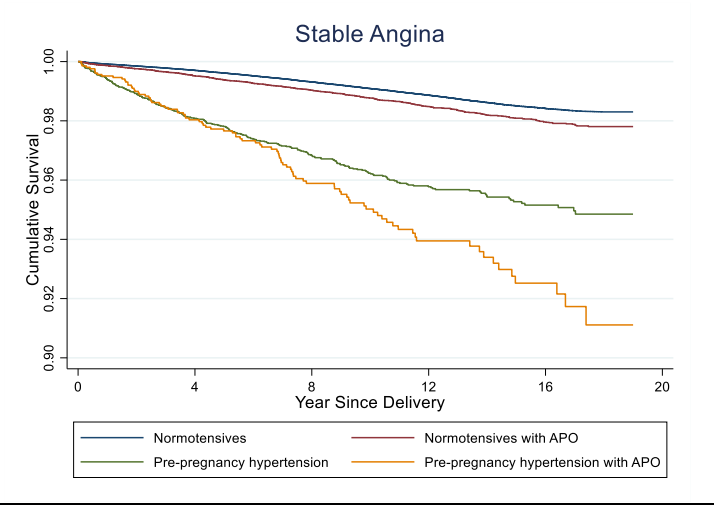
## Myocardial infarction



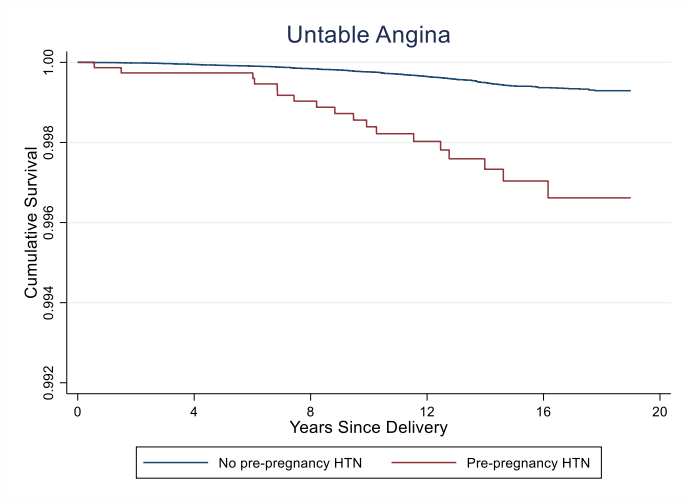



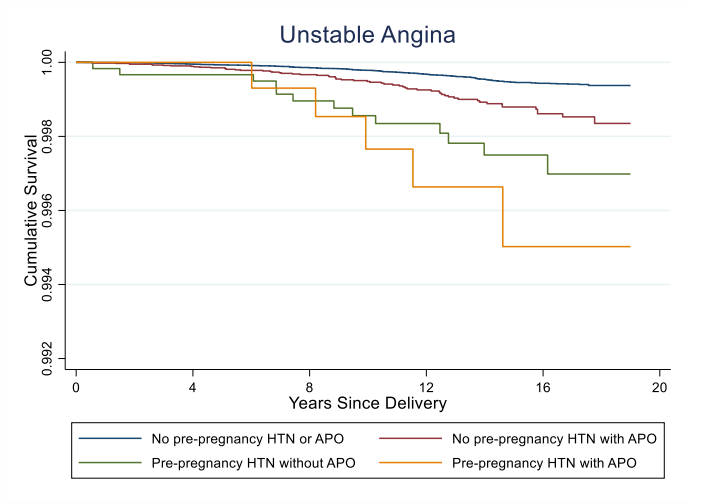

## Stable angina



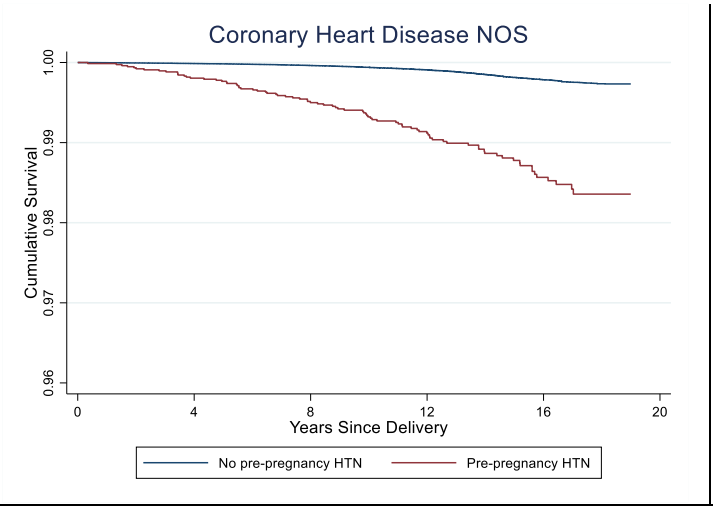



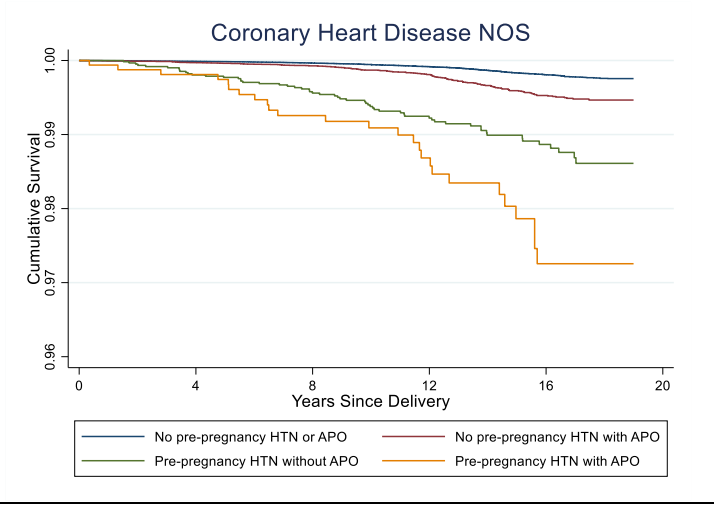

## Unstable angina



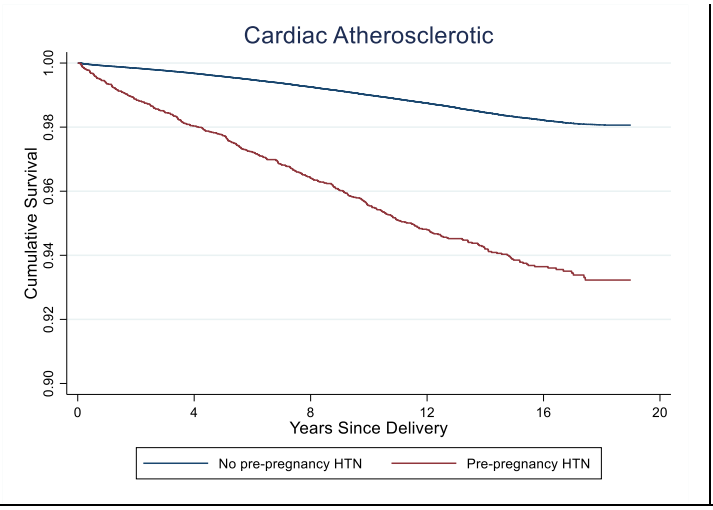



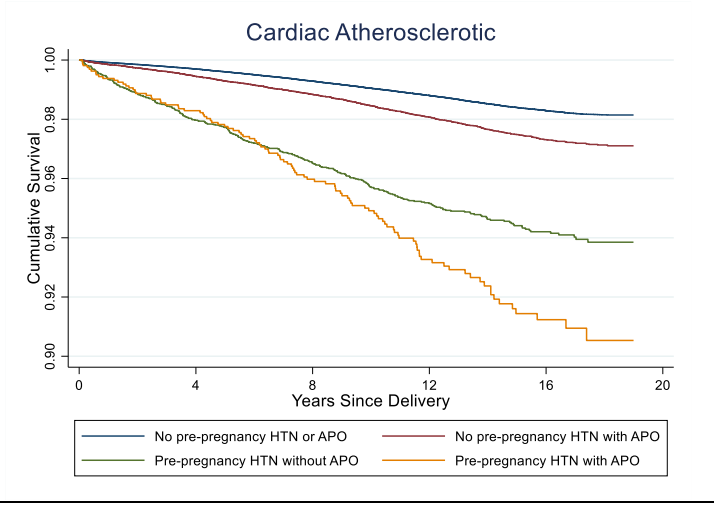
## Coronary heart disease not otherwise specified



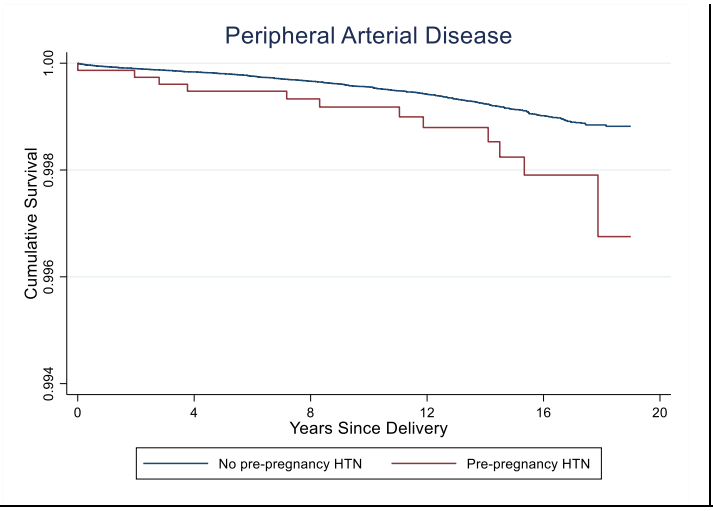



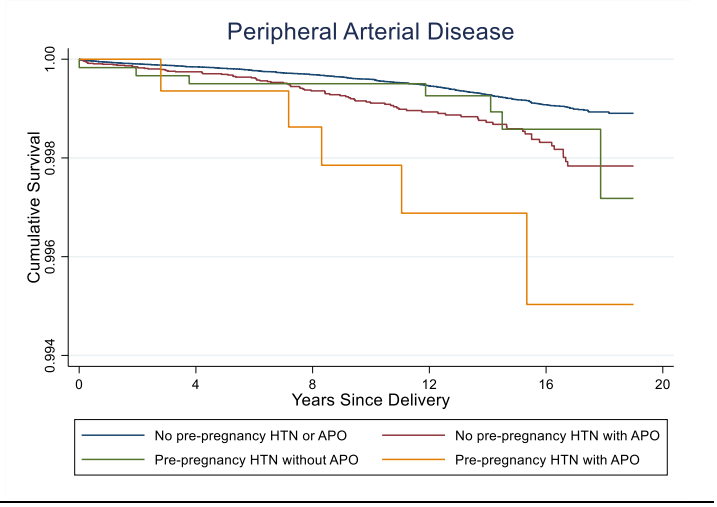

## Cardiac atherosclerosis



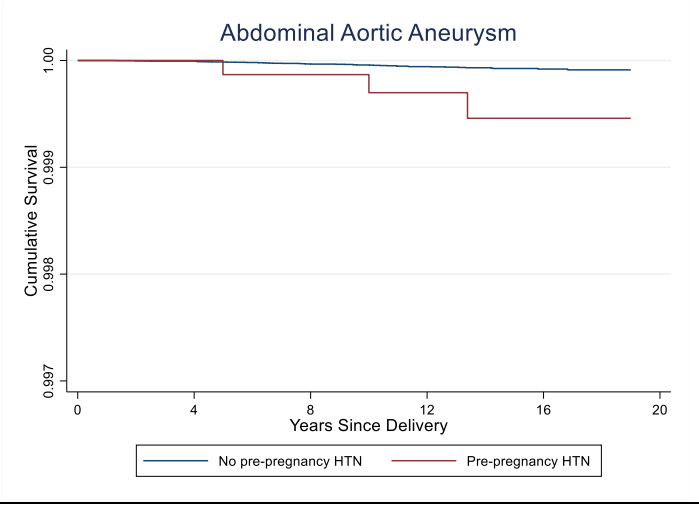



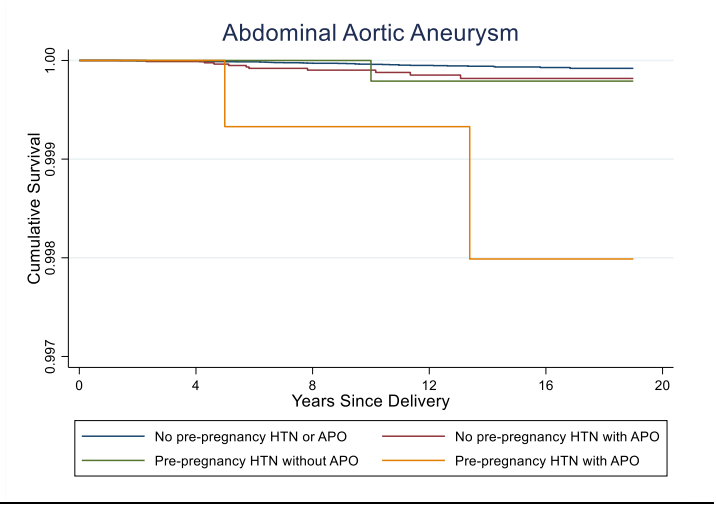

## Peripheral arterial disease



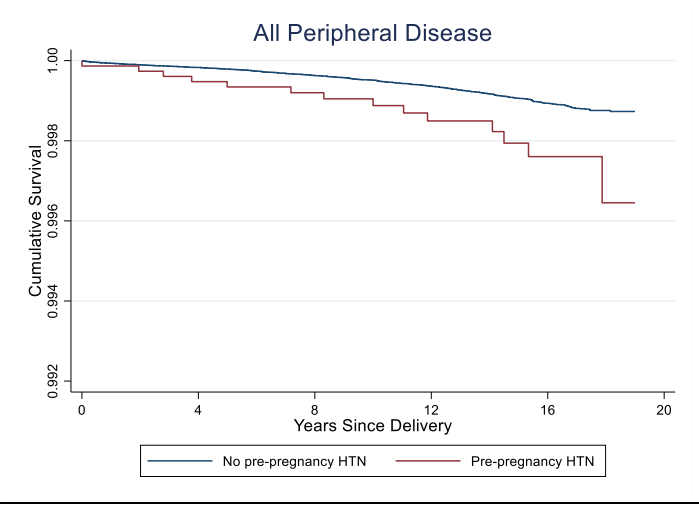



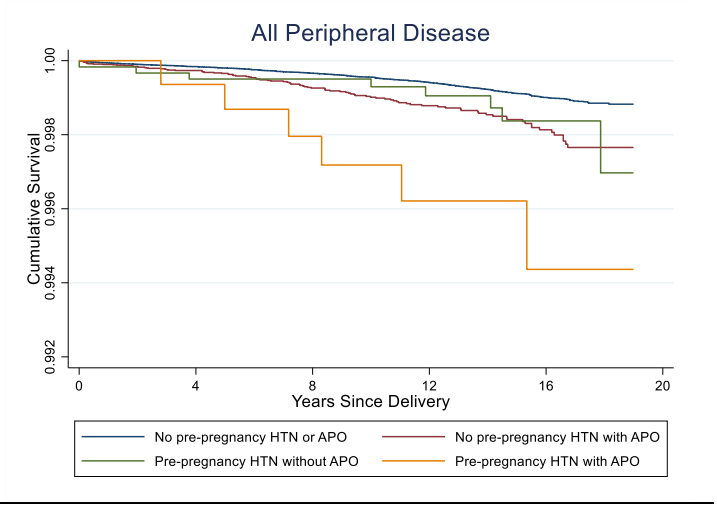
## Abdominal aortic aneurysm



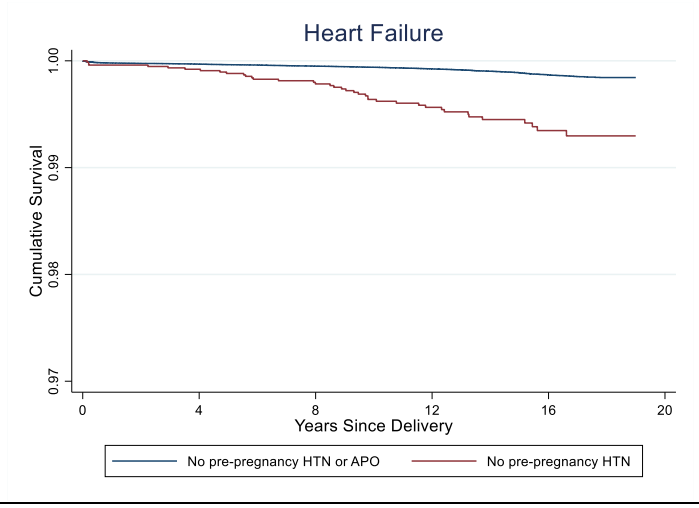



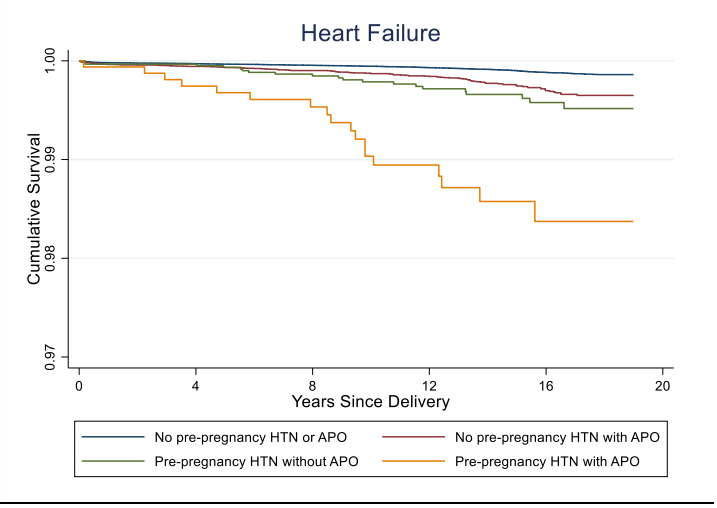

## All peripheral disease



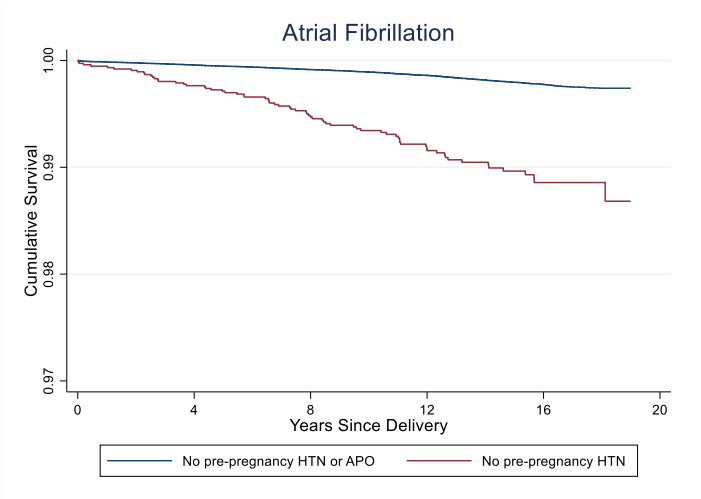



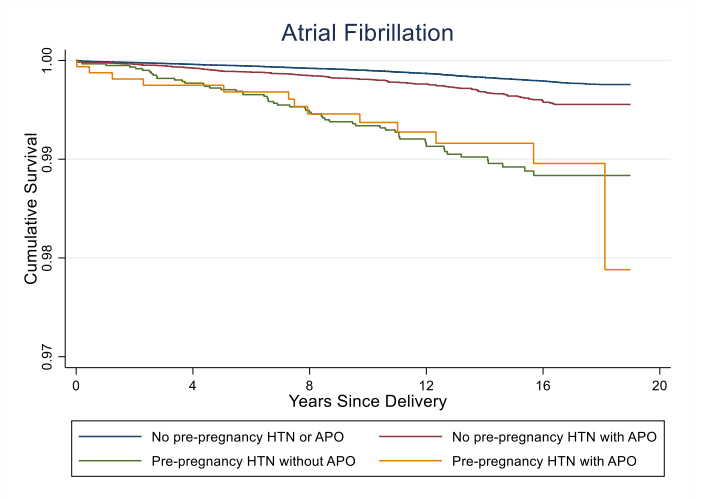

## Heart failure



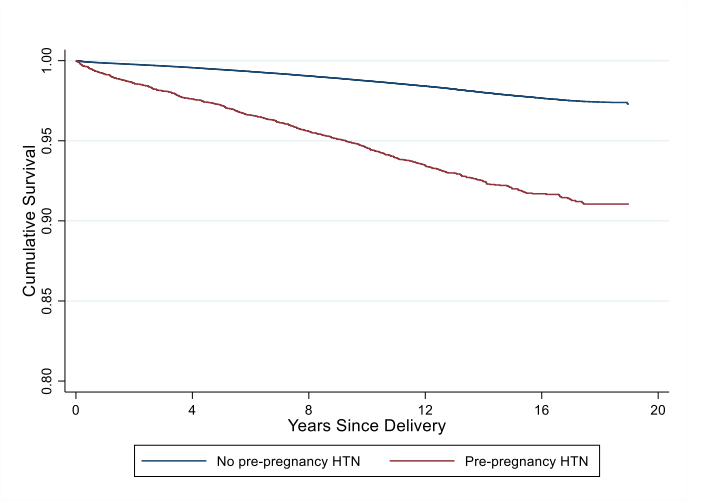



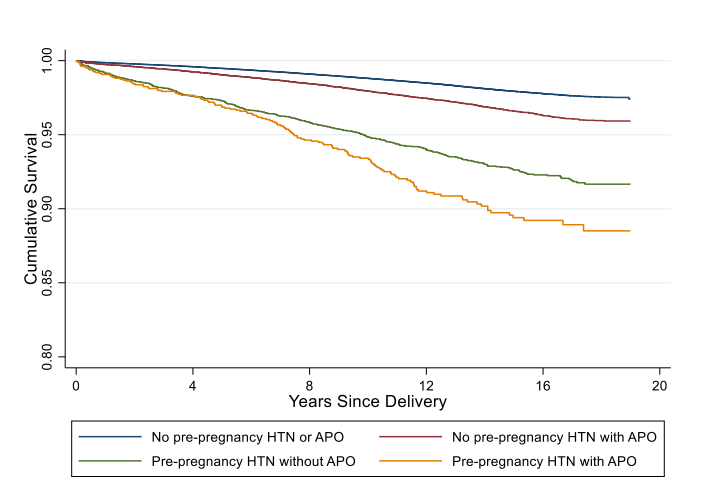
## Atrial fibrillation




## All cardiovascular disease



## Supplementary references

1. Zheng Q, Deng Y, Zhong S, Shi YJPHAIJoWsCH. Human chorionic gonadotropin, fetal sex and risk of hypertensive disorders of pregnancy: a nested case-control study. 2016;6(1):17-21.

2. Shiozaki A, Matsuda Y, Satoh S, Saito S. Impact of fetal sex in pregnancy-induced hypertension and preeclampsia in Japan. Journal of reproductive immunology. 2011;89(2):133-9.

3. Lunt M. Selecting an appropriate caliper can be essential for achieving good balance with propensity score matching. American journal of epidemiology. 2014;179(2):226-35.

4. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Statistics in medicine. 2007;26(4):734-53.

5. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS, et al. Methods for constructing and assessing propensity scores. Health Serv Res. 2014;49(5):1701-20.