CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Adverse pregnancy outcomes and the long-term risk of maternal kidney disease
Authors	Barrett, Peter M.
Publication date	2021-01-06
Original Citation	Barrett, P. M. 2021. Adverse pregnancy outcomes and the long-term risk of maternal kidney disease. PhD Thesis, University College Cork.
Type of publication	Doctoral thesis
Rights	© 2021, Peter Michael Barrett. - https://creativecommons.org/licenses/by-nc-nd/4.0/
Download date	2026-11-06 10:03:51
Item downloaded from	https://hdl.handle.net/10468/11981

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh



ucc

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Adverse pregnancy outcomes and the long-term risk of maternal kidney disease

A thesis submitted to the National University of Ireland, Cork

for the degree of Doctor of Philosophy

Thesis presented by:

Dr. Peter Michael Barrett

MB BCh BAO MSc MPhil MFPH MFPHMI PgCTLHE

Student number: 105368987

January 2021

Supervisors:

Dr. Ali S. Khashan

Dr. Fergus P. McCarthy

Assoc. Prof. Karolina Kublickiene

Head of School & Advisor

Prof. Ivan J. Perry

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

University College Cork

Contents

LIST OF TABLES 8
LIST OF FIGURES 10
LIST OF PUBLICATIONS 11
LIST OF CONFERENCE PRESENTATIONS 12
ABBREVIATIONS 14
DECLARATION 15
ACKNOWLEDGEMENTS 16
THESIS ABSTRACT 20
CHAPTER 1 Introduction 23
1.1 Introduction 23
1.1.1 Maternal health 23
1.1.2 Maternal morbidity across the life-course 24
1.1.3 Pregnancy as a stress test for future chronic disease 24
1.1.4 Adverse pregnancy outcomes and maternal kidney disease 25
1.1.5 Kidney disease as a public health problem 25
1.1.6 The need for further research 26
1.1.7 Potential biological mechanisms 27
1.2 Conceptual framework for maternal morbidity 30
1.3 Thesis outline 33
1.4 Overall aims and objectives 34
1.5 Hypothesis 35
CHAPTER 2 Literature review 37
2.1 Literature review methods 37
2.2 ADVERSE PREGNANCY OUTCOMES AND LONG-TERM RISK OF MATERNAL RENAL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS PROTOCOL 38
2.2.1 Abstract 39
2.2.2 Introduction 41
2.2.3 Methods 45
2.2.4 Discussion 50
2.2.5 Conclusion 51
2.3 ADVERSE PREGNANCY OUTCOMES AND LONG-TERM MATERNAL KIDNEY DISEASE. A SYSTEMATIC REVIEW AND META-ANALYSIS 52
2.3.1 Abstract 53
2.3.2 Introduction 56

2.3.3 Methods 57
2.3.4 Results 59
2.3.5 Discussion 62
2.3.6 Conclusions 68
CHAPTER 3 Methods 80
3.1 Chapter overview 80
3.2 Swedish health system and national registers 80
3.2.1 Swedish health system 80
3.2.2 Swedish national population registration system 82
3.2.3 Swedish personal identity number 82
3.2.4 Medical Birth Register 83
3.2.5 National Patient Register 83
3.2.6 Swedish Renal Register 84
3.2.7 Swedish Death Register 85
3.2.8 Swedish Migration Register 86
3.2.9 Swedish Register of Education 86
3.2.10 Data access and ethics 87
3.3 Study design 87
3.4 Study cohort 90
3.4.1 Timeline 90
3.4.2 Exclusions 91
3.5 Exposure and outcome variables 93
3.5.1 Main exposure variables 93
3.5.2 Main outcome variables 97
3.6 ICD coding 98
3.7 Key epidemiological considerations 99
3.7.1 Bias 100
3.7.2 Confounding 101
3.7.3 Chance findings 103
3.8 Missing data 103
3.8.1 Types of missing data 103
3.8.2 Key sources of missing data in the Swedish national registers 104
3.8.3 Handling missing data 106
3.9 Statistical methods 107
3.9.1 Cox proportional hazard regression 107
3.9.2 Time-dependent covariates 109

CHAPTER 4 RISK OF LONG-TERM RENAL DISEASE IN WOMEN WITH A HISTORY OF PRETERM DELIVERY: A POPULATION-BASED COHORT STUDY 110
4.1 Abstract 111
4.2 Introduction 113
4.3 Methods 114
4.4 Results 118
4.5 Discussion 120
4.6 Conclusions 125
CHAPTER 5 STILLBIRTH IS ASSOCIATED WITH INCREASED RISK OF LONG-TERM MATERNAL RENAL DISEASE: A NATIONWIDE COHORT STUDY 132
5.1 Abstract 133
5.2 Introduction 135
5.3 Methods 136
5.4 Results 140
5.5 Discussion 142
5.6 Conclusion 146
CHAPTER 6 HYPERTENSIVE DISORDERS OF PREGNANCY AND THE RISK OF CHRONIC KIDNEY DISEASE: A SWEDISH REGISTRY-BASED COHORT STUDY 153
6.1 Abstract 154
6.2 Introduction 156
6.3 Methods 157
6.4 Results 163
6.5 Discussion 166
6.6 Conclusion 170
CHAPTER 7 GESTATIONAL DIABETES AND THE LONG-TERM RISK OF MATERNAL KIDNEY DISEASE: A SWEDISH NATIONAL COHORT STUDY 177
7.1 Abstract 178
7.2 Background 180
7.3 Research design and methods 181
7.4 Results 186
7.5 Discussion 188
7.6 Conclusion 193
CHAPTER 8 Updated systematic review and meta-analysis 197
CHAPTER 9 Discussion 200
9.1 Summary of main findings 200
9.1.1 Findings from the systematic review and meta-analysis 200
9.1.2 Findings on preterm delivery 203

9.1.3 Findings on stillbirth 204
9.1.4 Findings on hypertensive disorders of pregnancy 206
9.1.5 Findings on gestational diabetes 209
9.1.6 Application of the conceptual framework 210
9.2 Interpretation of findings 213
9.2.1 Bias 213
9.2.2 Confounding 216
9.2.3 Chance findings 217
9.3 Strengths and limitations 218
9.3.1 Strengths 218
9.3.2 Limitations 219
9.4 Public health implications 221
9.4.1 Overview of public health considerations 221
9.4.2 Relative risk vs. absolute risk of kidney disease 221
9.4.3 Knowledge of links with chronic disease 222
9.4.4 Systematic follow-up programmes 225
9.4.5 Future research 227
CHAPTER 10. Conclusion 228
References 229
APPENDICES 245
List of appendices 245
Appendix 1. Possible biological mechanisms – preeclampsia and chronic disease 246
Appendix 2. Search strategy for systematic review 248
Appendix 3. Bias classification tool used in systematic review 251
Appendix 4. Additional files for chapter 2 - systematic review and meta-analysis 252
Appendix 5. Ethical approval documents 258
Appendix 6. Additional files for chapter 4 – preterm delivery and risk of maternal CKD/ESKD 262
Appendix 7. Additional files for chapter 5 – stillbirth and risk of maternal CKD/ESKD 264
Appendix 8. Additional files for chapter 6 – HDP and risk of maternal CKD 268
Appendix 9. Additional files for chapter 7 – GDM and risk of maternal CKD/ESKD 282
Appendix 10. Additional files for chapter 8 – updated systematic review and meta-analysis 286
Appendix 11. ADVERSE PREGNANCY OUTCOMES AND MATERNAL HEALTH: ACTION NEEDED FOR LONG-TERM BENEFIT 288
A11.1 Introduction 289

A11.2 Knowledge among healthcare professionals 289
A11.3 Screening and postpartum follow-up 290
A11.4 Clinical risk prediction 291
A11.5 Role of clinicians 292
A11.6 Future research 293
Appendix 12. ADVERSE PREGNANCY OUTCOMES – A MISSED OPPORTUNITY TO PREVENT CHRONIC DISEASE? 294
Appendix 13. Modules and workshops completed during PhD 298
Appendix 14. Awards and distinctions during PhD 299
Appendix 15. Additional publications during PhD 300

LIST OF TABLES

Table 2.1 Summary results of meta-analyses 71

Table 2.2 Characteristics of studies which investigate hypertensive disorders of pregnancy and subsequent maternal kidney disease 74

Table 2.3 Characteristics of studies which investigate preterm delivery and subsequent maternal kidney disease 77

Table 2.4 Characteristics of studies which investigate delivery of a low birth weight or small for gestational age infant and subsequent maternal kidney disease 78

Table 2.5 Characteristics of studies which investigate gestational diabetes and subsequent maternal kidney disease 79

Table 4.1 Maternal characteristics and pregnancy outcomes among women delivering between 1973 and 2012 in Sweden, stratified by exposure to preterm delivery 128

Table 4.2 Hazard ratios for maternal chronic kidney disease by history of preterm delivery, among women delivering between 1973 and 2012 in Sweden 129

Table 4.3 Hazard ratios for maternal end-stage kidney disease by history of preterm delivery, among women delivering between 1973 and 2012 in Sweden..... 130

Table 4.4 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of preterm delivery, restricted to women delivering between 1982 and 2012 in Sweden..... 131

Table 5.1 Maternal characteristics and pregnancy outcomes among women delivering between 1973 and 2012 in Sweden, stratified by exposure to at least one stillbirth..... 150

Table 5.2 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of stillbirth, among women delivering between 1973 and 2012..... 151

Table 5.3 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of stillbirth, among women delivering between 1973 and 2012 in Sweden, excluding pregnancies complicated by congenital malformations, small for gestational age, and preeclampsia..... 152

Table 6.1 Maternal characteristics and pregnancy outcomes among women who had live births between 1973 and 2012 in Sweden, stratified by exposure to preeclampsia 171

Table 6.2 Hazard ratios for maternal chronic kidney disease by history of preeclampsia and small for gestational age, among women who had live births between 1973 and 2012 in Sweden..... 172

Table 6.3 Hazard ratios for maternal chronic kidney disease by history of preeclampsia and preterm delivery, among women who had live births between 1973 and 2012 173

Table 6.4 Hazard ratios for maternal chronic kidney disease by history of recurrent preeclampsia, among women who had live births between 1973 and 2012..... 175

Table 6.5 Hazard ratios for maternal chronic kidney disease by history of preeclampsia, among women whose first live birth occurred between 1982 and 2012 in Sweden, stratified by maternal obesity 176

Table 7.1 Maternal characteristics and pregnancy outcomes among women whose first birth occurred between 1987 and 2012 in Sweden, stratified by exposure to gestational diabetes and/or type 2 diabetes..... 194

Table 7.2 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of gestational diabetes, among women whose first birth occurred between 1987 and 2012 in Sweden..... 195

Table 7.3 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of gestational diabetes and/or type 2 diabetes, among women whose first birth occurred between 1987 and 2012 in Sweden 196

Table 8.1 Comparison of pooled results between the original systematic review & meta-analysis and updated systematic review & meta-analysis 199

LIST OF FIGURES

Figure 2.1 Flow diagram of studies selected for inclusion in the systematic review 69

Figure 2.2 Forest plot for studies of the association of preeclampsia and end-stage kidney disease 70

Figure 3.1 Timeline pertaining to study design and data availability 92

Figure 4.1 Kaplan-Meier survival curves for risk of chronic kidney disease among women by exposure to moderate, very, or extremely preterm delivery 126

Figure 4.2 Kaplan-Meier survival curves for risk of chronic kidney disease among women by exposure to spontaneous or iatrogenic preterm delivery 127

Figure 5.1 Flow chart illustrating construction of study cohort 148

Figure 5.2 Kaplan-Meier survival curves for risk of chronic kidney disease among women based on their exposure to previous stillbirth 149

Figure 8.1 Updated forest plot for studies of the association of preeclampsia and chronic kidney disease. 199

Figure 9.1 Potential biological mechanisms underlying associations between preeclampsia and maternal chronic kidney disease. 208

LIST OF PUBLICATIONS

Published PhD papers

1. **Barrett PM**, McCarthy FP, Kublickiene K, Evans M, Cormican S, Judge C, et al. Adverse pregnancy outcomes and long-term risk of maternal renal disease: a systematic review and meta-analysis protocol. **BMJ Open.** 2019;9(5):e027180.

2. **Barrett PM**, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse Pregnancy Outcomes and Long-term Maternal Kidney Disease: A Systematic Review and Meta-analysis. **JAMA Network Open**. 2020;3(2):e1920964.

3. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Stillbirth is associated with increased risk of long-term maternal renal disease: a nationwide cohort study. **American Journal of Obstetrics and Gynecology.** 2020 Sep;223(3):427.e1-427.e14. doi: 10.1016/j.ajog.2020.02.031. Epub 2020 Feb 26.

4. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Risk of long-term renal disease in women with a history of preterm delivery: a population-based cohort study. **BMC Medicine.** 2020;18(1):66.

5. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Hypertensive disorders of pregnancy and the risk of chronic kidney disease: A Swedish registry-based cohort study. **PLOS Medicine.** 2020 Aug 14;17(8):e1003255. doi: 10.1371/journal.pmed.1003255. eCollection 2020 Aug.

6. **Barrett PM**, Khashan AS, McCarthy FP, Kublickiene K. Adverse pregnancy outcomes and maternal health: action needed for long-term benefit**. Acta Obstetricia et Gynecologica Scandinavica.** 2020 Jul 1. doi: 10.1111/aogs.13945. Online ahead of print.

7. **Barrett PM**. Adverse pregnancy outcomes – a missed opportunity for chronic disease prevention? **International Journal of Public Health.** 2021 Jan 25. doi: 10.3389/ijph.2021.582810. Online ahead of print.

Manuscripts submitted for peer review

8. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Gestational diabetes and the long-term risk of maternal kidney disease: a Swedish national cohort study.

LIST OF CONFERENCE PRESENTATIONS

Oral presentations

1. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Hypertensive disorders of pregnancy and the risk of chronic kidney disease: A Swedish registry-based cohort study. World Congress on Public Health, Rome, Italy (virtual conference). 12-16 October 2020.

2. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Hypertensive disorders of pregnancy and the risk of chronic kidney disease: A Swedish registry-based cohort study Society for Social Medicine and Population Health, Cambridge, UK (virtual conference). 9-11 September 2020.
   (Highly ranked abstract)

3. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Risk of long-term renal disease in women with a history of preterm delivery: a population-based cohort study. ISN World Congress of Nephrology, Abu Dhabi (virtual conference). 26-29 March 2020.
   (Winner of Best Clinical Abstract, Young Nephrologist section)

4. **Barrett PM,** McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse pregnancy outcomes and long-term maternal kidney disease: a systematic review and meta-analysis. European Public Health Conference, Marseille, France. 20-23 November 2019.

5. **Barrett PM**, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse pregnancy outcomes and the long-term risk of maternal renal disease. Gynaecology Visiting Society of UK & Ireland Annual Meeting, Cork, Ireland. 4 October 2019.
   (Invited speaker)

6. **Barrett PM**, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse pregnancy outcomes and the risk of maternal renal disease: a focus on preterm delivery and stillbirth. Institute of Obstetrics & Gynaecology Study Day, Royal College of Physicians of Ireland, Dublin, Ireland. 27 September 2019.
   (Invited speaker)

7. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Risk of long-term renal disease in women with a history of preterm delivery: a population-based cohort study. National Education Day for Doctors in Training, Royal College of Physicians of Ireland, Dublin, Ireland. 6 September 2019.
   (Winner of William Stokes Award - Highest standard of research among doctors in Higher Specialist Training)

Poster presentations

1. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Risk of long-term renal disease in women with a history of preterm delivery: a population-based cohort study. European Public Health Conference, Marseille, France. 20-23 November 2019.

2. **Barrett PM**, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Risk of long-term renal disease in women with a history of preterm delivery: a population-based cohort study. INFANT Research Day & Science Foundation Ireland Site Visit, University College Cork, Cork, Ireland. 10 October 2019.

3. **Barrett PM,** McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse pregnancy outcomes and long-term maternal kidney disease: a systematic review and meta-analysis. Society for Social Medicine and Population Health & European Congress of Epidemiology Joint Meeting, Cork, Ireland. 4-6 September 2019.

4. **Barrett PM**, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse pregnancy outcomes and long-term maternal kidney disease: a systematic review and meta-analysis. Irish Nephrology Society Annual Meeting, Dublin, Ireland. 12 April 2019.

5. **Barrett PM**, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse pregnancy outcomes and long-term maternal kidney disease: a systematic review and meta-analysis. Society for Reproductive Investigation Annual Scientific Meeting, Paris, France. 12-16 March 2019.

ABBREVIATIONS

aHR	Adjusted hazard ratio
aRR	Adjusted risk ratio
BMI	Body mass index
CH	Chronic hypertension
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
EU	European Union
FGR	Foetal growth restriction
GDM	Gestational diabetes mellitus
GDP	Gross domestic product
GH	Gestational hypertension
HDP	Hypertensive disorders of pregnancy
HELLP	Haemolysis, elevated liver enzymes, low platelets
HR	Hazard ratio
ICD	International Classification of Diseases
IUGR	Intra-uterine growth restriction
LGA	Large for gestational age
LMP	Last menstrual period
MAR	Missing at random
MBR	Medical birth register
MCAR	Missing completely at random
MICE	Multiple imputation by chained equations
MNAR	Missing not at random
MOOSE	Meta-analyses of observational studies in epidemiology
NPR	National patient register
NRF2	Nuclear factor erythroid 2–related factor 2
PE	Preeclampsia
PIN	Personal identity number
PPV	Positive predictive value
PSH	Preeclampsia superimposed on chronic hypertension
RAAS	Renin-angiotensin aldosterone system
RR	Risk ratio
RRT	Renal replacement therapy
sFLT1	Soluble fms-like tyrosine kinase-1
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
SRR	Swedish renal register
STROBE	Strengthening the reporting of observational studies in epidemiology
T2DM	Type 2 diabetes mellitus
TPR	Total population register

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.

Signed: 

Date: 23/12/2020

ACKNOWLEDGEMENTS

In 2011, just after my medical internship, I moved to Stockholm for a year to undertake a Masters in Global Health. It was during this time that I experienced the world of public health and epidemiology for the first time. Both Sweden, and this initial exposure to public health research, left a lasting impression on me. Now, almost a decade later, I am delighted to have had the opportunity to pursue PhD research using data from the country which first inspired my interest in this field.

I was honoured to be selected among the first cohort of Irish Clinical Academic Training (ICAT) Fellows in 2017, and the support I received throughout this programme has been second to none. I am sincerely grateful to the many ICAT Directors who have worked so selflessly over several years to make this initiative a reality. They have been immensely generous with their time and I have benefited enormously from their advice and feedback, and from that of the wider ICAT Steering Group.

In UCC, I was supported by Prof. Joe Eustace at the outset, and Prof. Deirdre Murray in more recent years, in dealing with a myriad of logistical and contractual challenges to facilitate my participation in ICAT. Dr. Karen Misstear, the Programme Manager, has provided tireless assistance and advice from the very beginning. It has been a pleasure getting to know her over the last few years, and I am sincerely grateful for all her help. I would like to thank the funding bodies, including the Wellcome Trust and Health Research Board, and my *almae matres* of UCC and Karolinska Institutet, for giving me this wonderful opportunity. In particular, I appreciate the kindness and camaraderie of everyone in the School of Public Health and INFANT Research Centre in UCC.

I feel privileged to have got to know the other ICAT Fellows, and I am confident that we will maintain both friendships and research links in to the future. I would especially like to thank

the other ICAT Fellows from the first cohort: Conor, David, Delia, Kapil, Liam, Róisín, and Sarah. We have been based in four different corners of the country, and we work across six very different clinical disciplines, but our shared experiences have meant that we have been able to provide each other with peer support, encouragement and practical tips throughout the PhD journey. I'm very grateful to them.

I want to express my sincere thanks to my fantastic supervisors. Before I ever heard of ICAT, I had contacted Dr. Ali Khashan expressing an interest in his research. I am delighted to have been able to work under his expert supervision. His door was always open if I wanted to discuss or debate new ideas or challenges, no matter how big or small. He gave me the opportunity to work with autonomy, and to learn through my own mistakes, but provided advice and direction whenever it was needed. He provided countless iterations of feedback on my initial ICAT application, PhD proposal, abstracts, and manuscripts, and he encouraged me to strive for excellence in my research. I feel very fortunate to have worked with him, and I look forward to continuing to do so.

I'm very grateful to Dr. Fergus McCarthy who has always been available to offer assistance and feedback on this work despite his many other commitments. I am delighted to have benefited from his guidance and encouragement over the last few years, and as an academic clinician, he has been a great role model for me. Assoc. Prof. Karolina Kublickiene always provided a valued, alternative perspective to this work. Her positive attitude has been uplifting and motivating, and I have greatly appreciated her kindness and enthusiasm along the way. She made me feel welcome and included in her own team during my research visit to Stockholm for this work. And while Covid-19 got in the way of a few follow-up visits, I very much look forward to the next time we get to meet in person.

Prof. Ivan Perry has been very generous with his time as an advisor to me during this PhD. I have appreciated the public health perspective he brought to this work at various times, and

am grateful for his mentorship and impartial words of wisdom when they were sometimes needed most. My co-authors in Sweden, Assoc. Prof. Marius Kublickas, Dr. Marie Evans, and Prof. Peter Stenvinkel, have also provided invaluable insights along the way and have helped to shape a lot of this work. *Tack så mycket*, and I hope that we can continue to work together in the years ahead.

It was only possible for me to pursue this PhD because of the unwavering support of the Faculty of Public Health Medicine in RCPI. I am particularly grateful to Dr. Mairin Boland, Prof. Elizabeth Keane, and Prof. Emer Shelley for all their advice and assistance. In my various training posts, my clinical supervisors have always accommodated my academic commitments, and for that I would like to thank Dr. Sinead Donohue, Dr. Triona McCarthy and Dr. Anne Sheahan. When the first wave of Covid-19 arose in March 2020, and I needed to return to clinical duties, I had nothing but full support from PhD supervisors, ICAT Directors and from members of the Faculty of Public Health Medicine. And when the time came for me to return to academic work again, my colleagues in the Department of Public Health HSE-South were entirely understanding and considerate of this. I look forward to working with them all again during the next phase of my career.

To my family, thank you for always encouraging me to do what I wanted to do. Mum and Dad, you have seen the ups and downs of the first decade of my career, and I am so grateful for your love and support, past and present. Although it took me a little longer than I expected to find my niche, the extra challenge or two along the way has helped me to better understand and appreciate what I enjoy most. Anything I have ever achieved has only been possible because of the lucky start you gave me in life.

Roger, Patrick, and Mary, thank you for your friendship, loyalty and encouragement at all times. I have been so proud of all of your collective achievements over the years, and am very grateful for the pride that you have taken in mine. To the newer members of the Barrett clan

– Aileen, Cillian, and Ruairí – thank you for all the fun and happiness you have brought to our family. Hopefully this thesis will provide some light bedtime reading for the boys!

To Eilís, you are my constant, day-to-day rock of support. You have been there to encourage me and to provide a listening ear every step of the way. All of my experiences are enriched by you, and my ability to pursue this PhD alongside other demands of parenthood, lockdowns, clinical work, and Covid-19 chaos, has been mainly because of your own incredible multi-tasking ability and calm perspective. I don't know how you do it all, but I appreciate it more than I can say. Lily and I are so lucky to have you in our lives, together with four wonderful parents/grandparents, to whom we are also indebted – thank you for everything Mum, Dad, Gogo and Joy.

In the first year of my PhD, just after a snowstorm in January 2019, a very small girl changed our lives in a very big way. Lily, you have brought us so much fun, love and laughter in two short years. You're the first person we want to see in the morning and the last person we want to see at night. Thank you for reminding me about what's most important in life, and for making 2020 a year to remember rather than a year to forget. We can't wait to watch you grow up and we're so excited for you to become a big sister in the spring. This thesis is dedicated to you.

THESIS ABSTRACT

Background

Adverse pregnancy outcomes, including hypertensive disorders of pregnancy (HDP), preterm delivery, foetal growth restriction, gestational diabetes (GDM), and pregnancy loss, have been associated with the risk of maternal chronic disease, particularly cardiovascular disease. Less is known about the long-term risk of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in women who have experienced pregnancy complications. This thesis aims to examine associations between adverse pregnancy outcomes and the risk of maternal CKD and ESKD in later life.

Structure and methods

This thesis begins with an introductory chapter (Chapter 1) followed by a systematic review and meta-analysis of the published literature, based on a pre-specified protocol (Chapter 2). A detailed methods chapter outlines the data sources, study design, exposure and outcome variables, and statistical approach used in each of the original observational studies conducted for this research (Chapter 3). Four population-based cohort studies are presented, and they focus on the risk of maternal kidney disease following preterm delivery (Chapter 4), stillbirth (Chapter 5), HDP (preeclampsia and gestational hypertension) (Chapter 6) and GDM (Chapter 7) respectively. In each study, data from the Swedish national registers are used, and analyses are based on Cox proportional hazard regression models with time-dependent covariates, adjusted for a wide range of medical, obstetric, and socio-demographic factors.

In Chapter 8, an updated systematic review and meta-analysis is presented to reflect newly published literature on this topic. This is followed by a discussion and interpretation of the key findings, including consideration of the public health implications arising from this work (Chapter 9). Finally, conclusions of the thesis are presented in Chapter 10.

Results

Updated systematic review and meta-analysis

Overall, the published literature on this topic was sparse and most meta-analyses were based on small numbers (<5) of original studies. HDP and preterm delivery were associated with higher risk of long-term kidney disease in parous women. Preeclampsia was associated with a strongly increased risk of ESKD (adjusted risk ratio (aRR) 4.90; 95% CI, 3.56-6.74) and a modest increased risk of CKD (aRR 1.73, 95% CI 1.42-2.12). Gestational hypertension was associated with a strongly increased risk of ESKD (aRR, 3.64, 95% CI, 2.34-5.66), and more modest increased risk of CKD (aRR 1.48, 95% CI 1.38-1.58). Preterm delivery was associated with an increased risk of ESKD (aRR 2.19, 95% CI 1.93-2.47), but there were too few studies to determine the risk of CKD, or to separate the effects of iatrogenic vs. spontaneous preterm deliveries. No significant association was observed between GDM and CKD (aRR 1.04, 95% CI 0.76-1.41), but this meta-analysis was based on pooled estimates from just two studies.

Original population-based cohort studies

Preterm delivery was associated with increased risk of both CKD and ESKD in our study. This association was strongest in women who experienced iatrogenic preterm delivery (due to preeclampsia or small for gestational age (SGA)), but the risk persisted in women who only had spontaneous preterm deliveries compared to women who delivered at term (for CKD, aHR 1.32, 95% CI 1.25-1.39; for ESKD, aHR 1.99, 95% CI 1.67-2.38). Separately, stillbirth was also

associated with an increased risk of both CKD (aHR 1.26, 95% CI 1.09–1.45) and ESKD (aHR 2.25, 95% CI 1.55-3.25) compared to women who only experienced live births. These associations persisted independent of preeclampsia, SGA or congenital malformations.

Preeclampsia was associated with a higher risk of CKD during follow-up (vs. no preeclampsia, aHR 1.92, 95% CI 1.83–2.03), but this risk differed by CKD subtype and was greater for hypertensive CKD, diabetic CKD, and glomerular/proteinuric CKD. Women who experienced preterm preeclampsia, recurrent preeclampsia, or preeclampsia complicated by antenatal obesity were at particularly high risk of CKD. There was also a modest risk of CKD among women who experienced gestational hypertension (vs. none, aHR 1.49, 95% CI 1.38–1.61).

GDM-diagnosed women were at increased risk of CKD and ESKD overall. However, when GDM was stratified according to those who developed post-pregnancy type 2 diabetes (T2DM), the associations between GDM alone (without later T2DM) and maternal kidney disease were non-significant (for CKD, 1.11, 95% CI 0.89-1.38; for ESKD, aHR 1.58, 95% CI 0.70-3.60). By contrast, strong associations were observed with CKD and ESKD in those who had GDM followed by subsequent T2DM.

Conclusion

Adverse pregnancy outcomes, specifically preeclampsia, gestational hypertension, preterm delivery and stillbirth, are associated with increased risk of maternal CKD and ESKD. These associations persisted in a nationwide cohort after controlling for a wide range of confounders. Although the relative risk of future kidney disease is highest for ESKD, associations with CKD are likely to be of greater importance from a population perspective, given the high prevalence of CKD. Women who experience adverse pregnancy outcomes may warrant systematic follow-up to prevent onset or progression of future kidney disease, but the optimal format and timing of this follow-up requires further research.

CHAPTER 1 Introduction

1.1 Introduction

1.1.1 Maternal health

Globally, maternal health has improved in recent decades. Since 2000, the maternal mortality ratio has decreased by 38% worldwide to 211 deaths per 100,000 live births (1). The burden of maternal mortality remains excessively high, particularly in lower-income countries, but fewer women now die from complications of pregnancy or childbirth than ever before. This has been largely achieved through improved antenatal care, better family planning services, more skilled birth attendance, and greater availability of advanced obstetric and postnatal care for women (1, 2).

By comparison, there has been less progress made towards reducing the global burden of maternal morbidity (3). Pregnancy and childbirth still result in a major burden of ill-health and disability among parous women (4, 5). Maternal morbidity is difficult to quantify because there is no universally accepted definition for it, but it includes “any health condition attributed to and/or complicating pregnancy and childbirth that has a negative impact on the woman's wellbeing and/or functioning” (6).

Much of the burden of maternal morbidity is related to severe, acute, or life-threatening complications of pregnancy (e.g. antepartum or postpartum haemorrhage, sepsis, obstructed labour). However, several common adverse pregnancy outcomes, which contribute to maternal morbidity, manifest more gradually. These include hypertensive disorders of pregnancy (HDP), preterm delivery (before 37 weeks gestation), foetal growth restriction, gestational diabetes mellitus (GDM), and pregnancy loss (e.g. miscarriage, stillbirth) (3).

1.1.2 Maternal morbidity across the life-course

Efforts to reduce maternal morbidity have traditionally concentrated on pregnancy, childbirth and the first six weeks postpartum. For most acute or life-threatening complications of pregnancy, their full impact will become apparent during this timeframe. However, for other adverse pregnancy outcomes (e.g. HDP, preterm delivery, GDM), a longer reference period may be required. The long-term sequelae of some pregnancy-related complications may take months or years to manifest (7).

It is increasingly recognised that a life-course approach is needed to reduce maternal morbidity (8). Women worldwide are experiencing a growing burden of chronic disease (5, 9), and an expanding body of research suggests that this may be influenced by, or related to, complications which first arise during pregnancy. This is of substantial public health importance. Every year, about 210 million women become pregnant, resulting in 140 million live births (9). Chronic disease now accounts for over 60% of disability-adjusted life years in women aged 15-49 years, and this burden rises further with increasing age (10).

1.1.3 Pregnancy as a stress test for future chronic disease

The physiological demands of pregnancy have been described as a metabolic 'stress test' for women, where underlying predisposition to chronic disease may be first unmasked (11, 12). Some women experience a transient metabolic syndrome during pregnancy, and they may be more likely to develop adverse pregnancy outcomes such as HDP or GDM. Although delivery can induce remission, these disorders may re-emerge as chronic diseases in later life when the effects of ageing diminish the limited reserves of vulnerable organ systems (13).

Associations have been clearly established between adverse pregnancy outcomes and some chronic diseases. HDP, such as preeclampsia and gestational hypertension, have been linked

with increased risk of chronic hypertension in later life (14-18). A range of adverse pregnancy outcomes (e.g. HDP, preterm delivery, GDM and pregnancy loss) have been linked to increased risk of cardiovascular disease (CVD) (14, 19, 20), and to an independent increased risk of premature CVD-related mortality (21, 22). There is also mounting evidence for associations between adverse pregnancy outcomes and cerebrovascular disease (14, 23, 24), peripheral vascular disease (14, 25) and type 2 diabetes (T2DM) (17, 26, 27) respectively.

1.1.4 Adverse pregnancy outcomes and maternal kidney disease

It is plausible that women who experience pregnancy complications may also be at increased risk of long-term kidney disease. If such associations exist, it is relevant to consider whether pregnancy-related information can be used to prevent the onset or progression of chronic kidney disease (CKD) or end-stage kidney disease (ESKD) in later life.

In 2008, a Norwegian cohort study first suggested that women who had experienced preeclampsia had three times higher risk of developing ESKD compared to women who had normotensive pregnancies (28). Since then, several studies have replicated these findings in other cohorts of women in Sweden, Canada, USA and Taiwan (29-33). However, to date, few studies have considered how non-hypertensive adverse pregnancy outcomes may affect the long-term risk of maternal ESKD. Moreover, there has been a dearth of research on the impact that pregnancy complications may have on the risk of maternal CKD more broadly, or on subtypes of kidney disease.

1.1.5 Kidney disease as a public health problem

CKD is a highly prevalent disease and a major cause of death and disability globally (34). It has a broad spectrum of severity, which depends on the stage of disease. Stage 1 and stage 2 CKD

is typically asymptomatic and often goes undiagnosed. It is characterised by kidney damage (e.g. microalbuminuria) in the presence of normal or mildly impaired kidney function, with estimated glomerular filtration rate (eGFR) above 60 mL/min/1.73m^2. CKD typically becomes symptomatic, and of greater clinical significance, from stage 3 onwards, when the eGFR drops below 60 mL/min/1.73m^2. At its most severe, CKD can progress to stage 5 where eGFR drops below 15 mL/min/1.73m^2 and treatment with dialysis or renal transplant is required (i.e. ESKD) (35).

CKD has been described as a 'neglected chronic disease' and an under-recognised public health issue (36-38). The global prevalence has increased by 29% since 1990, partly due to increases in life expectancy, coupled with rising prevalence of obesity, hypertension and diabetes. In 2017, there were about 700 million individuals recorded with CKD worldwide (34). It was the direct cause of 1.2 million deaths, and a contributory factor in a further 1.4 million CVD-related deaths (34). Its relative contribution to global disease and disability has increased over time, and in 2019, it was among the 10 leading causes of disability-adjusted life years among adults over 50 (10).

By comparison, ESKD is relatively rare, affecting fewer than 1 in 1,000 women (34). However, ESKD is a major cause of morbidity and premature mortality in those affected by it (38-40). Where renal replacement therapy (dialysis or transplant) is available, ESKD accounts for a disproportionate amount of direct healthcare expenditure and thus, prevention of ESKD is a key priority for health systems (41, 42).

1.1.6 The need for further research

The measurement of associations between pregnancy complications and chronic disease outcomes may inform if, and how, women should be monitored in the years following pregnancy. From a clinical perspective, this information can help healthcare professionals to

advise patients about their individual long-term risks, plan for targeted preventive interventions, update clinical guidelines, and develop risk prediction tools if appropriate. From a patient perspective, this information can empower women with greater knowledge about their individual risk of developing chronic diseases in later life, and it may motivate them to engage in preventive actions or influence decision-making around treatment options. By contrast, if associations are not robustly investigated, adverse pregnancy outcomes may represent a missed opportunity for primary or secondary prevention of chronic disease (43).

In order to determine whether adverse pregnancy outcomes are associated with maternal CKD or ESKD, large-scale datasets are required, with detailed information on cardiometabolic risk factors before, during and after pregnancy, as well as reliable records of specific pregnancy complications. Since pregnant women cannot be randomised to adverse pregnancy outcomes, large birth cohorts are required to undertake this research (43).

1.1.7 Potential biological mechanisms

It is unknown whether observed associations between adverse pregnancy outcomes and chronic diseases are causal. It is possible that some women's increased susceptibility to cardiometabolic disease manifests in the form of adverse pregnancy outcomes due to the transient 'stress test' of pregnancy, and that the pregnancy complications themselves do not play any causal role in chronic disease outcomes. But it is also possible that adverse pregnancy outcomes induce vascular and metabolic injury via endothelial dysfunction, inflammation, insulin resistance and accelerated atherosclerosis, and that these processes trigger the development of CVD, CKD, and other chronic diseases in later life (11, 13, 44).

This thesis will consider potential mechanisms underlying associations between adverse pregnancy outcomes and maternal CKD and ESKD, but these are complex and uncertain. It is beyond the scope of the thesis to unpack these mechanisms in detail. For example,

preeclampsia is the most widely researched adverse pregnancy outcome which has been linked to increased risk of later hypertension, CVD, cerebrovascular disease, peripheral vascular disease, T2DM and ESKD (14, 19, 27-29). However, the mechanisms underlying these associations remain unclear. Potential mechanisms are broadly summarised in Figure 1.1, and further detail on these mechanisms is available in Appendix 1 (11).

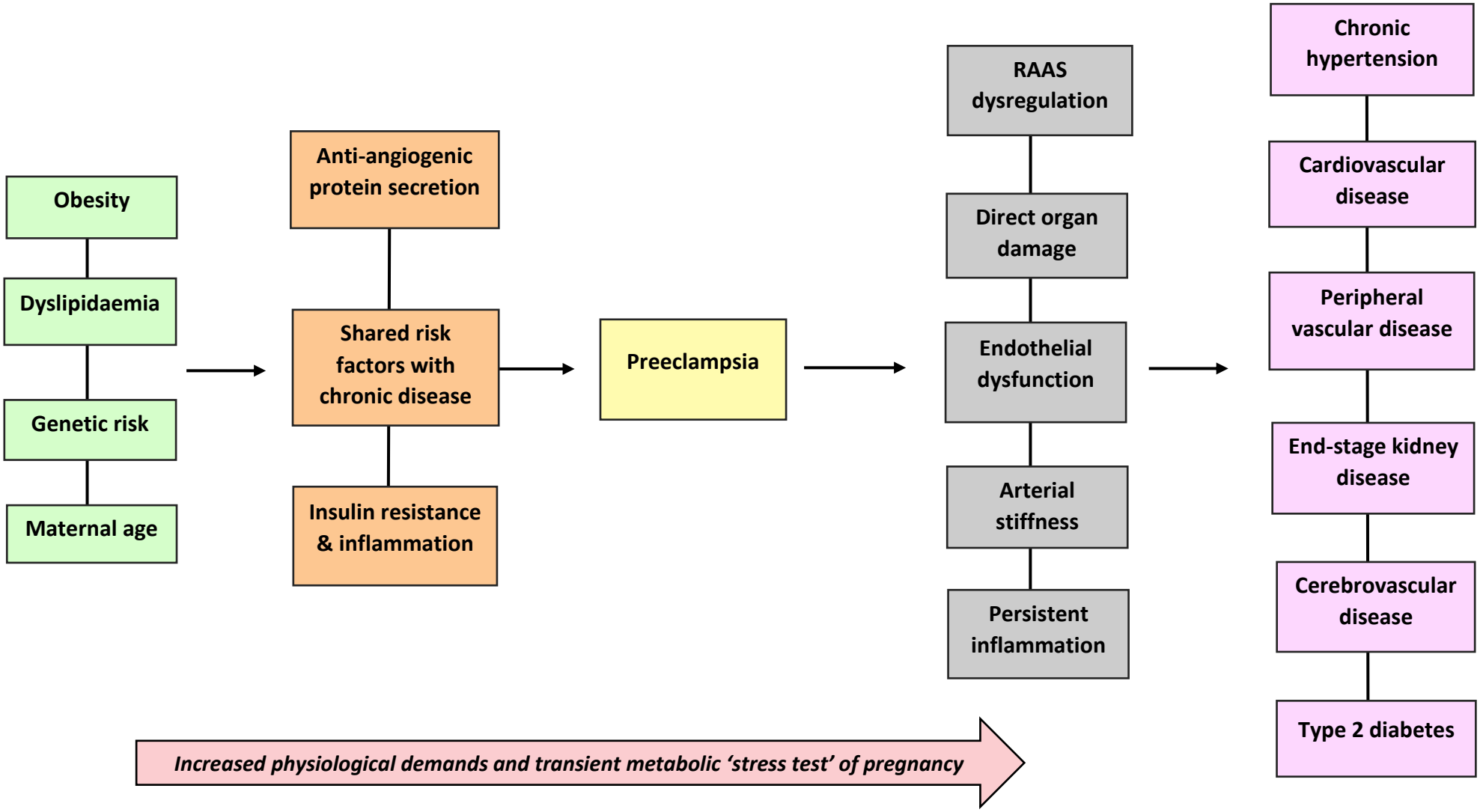


Figure 1.1 Potential biological mechanisms underlying associations between preeclampsia and maternal chronic disease outcomes.

RAAS, Renin-angiotensin aldosterone system

1.2 Conceptual framework for maternal morbidity

This thesis considers adverse pregnancy outcomes in the context of the conceptual framework for maternal morbidity developed by Filippi et al. (45). The maternal morbidity measurement framework provides a modern-day overview of the wide-ranging implications adverse pregnancy outcomes may have on maternal health outcomes, including in the years after pregnancy (Figure 1.2). This is consistent with the 2016 global strategy on women's health, published in conjunction with the Sustainable Development Goals, which highlighted the need to address maternal morbidity as an issue across the life-course (8).

The framework is underpinned by the following key principles:

(1) Woman-centred approach. The framework reflects women's perspectives on what is important to them regarding their long-term health and wellbeing. This includes any health problems that directly affect the woman herself, the foetus, or the infant.

(2) Cyclical nature. Maternal morbidity can be cyclical since women can become pregnant multiple times, and they can experience adverse pregnancy outcomes more than once. The sequelae of an adverse pregnancy outcome can also affect the woman's next pregnancy.

(3) Lasting effects. The effects of maternal morbidity are not limited to pregnancy or the immediate postpartum period. The effects can last a long time and there may be health consequences later in life, during the post-reproductive or post-menopausal years.

(4) Socio-economic influences. Maternal health is a social and economic phenomenon, and not just a clinical and biological issue.

(5) Environmental influences. Living in a supportive environment can lead to better maternal health outcomes.

(6) Groupings of maternal morbidity. Adverse pregnancy outcomes should be grouped together in a meaningful way (e.g. obstetric/medical/foetal/injuries), consistent with international classifications of diseases.

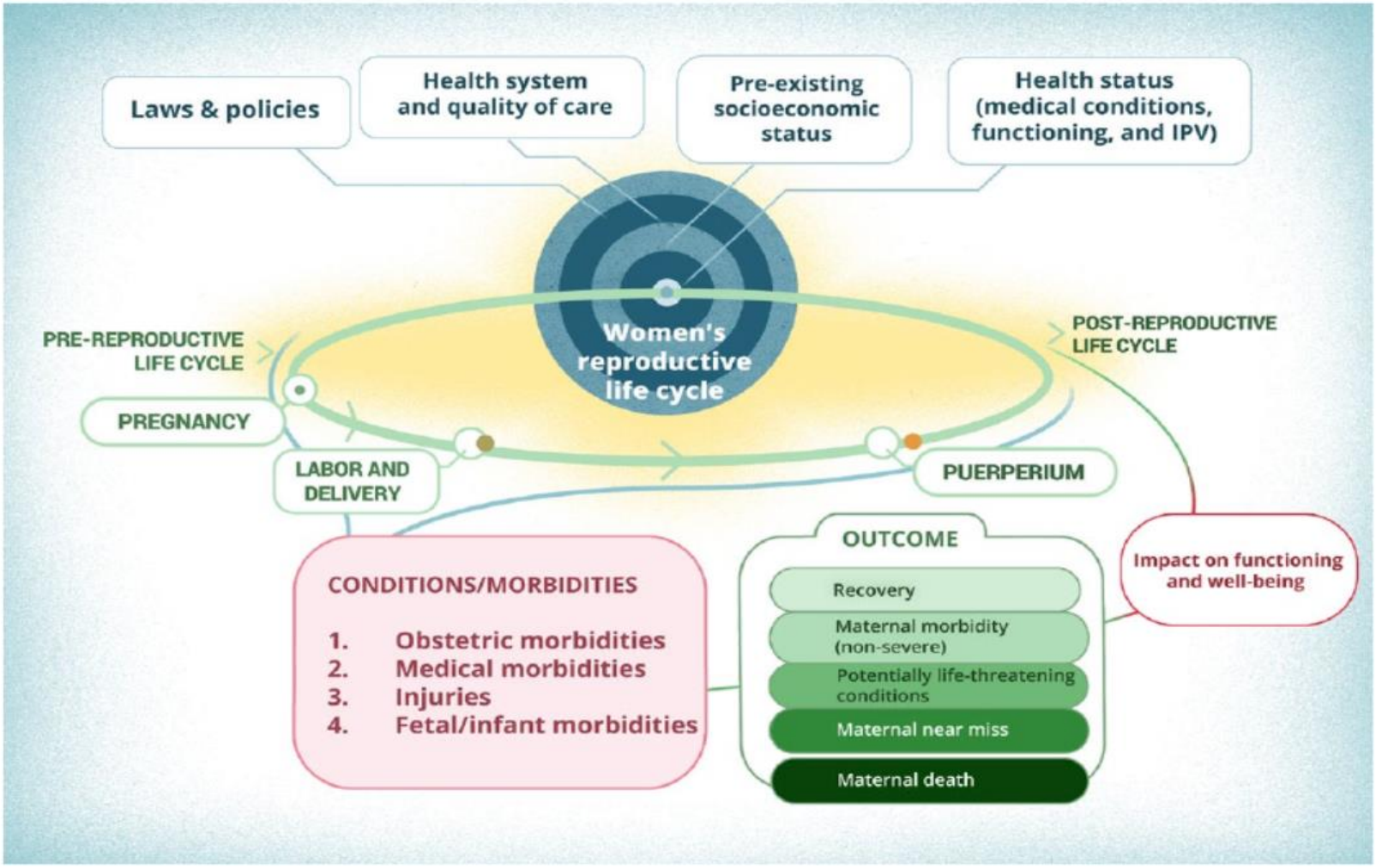


Figure 1.2 Maternal morbidity measurement framework.

Source: Filippi et al. (45)

1.3 Thesis outline

This thesis is comprised of a number of peer-reviewed papers examining associations between a range of adverse pregnancy outcomes (HDP, preterm delivery, stillbirth, GDM) and long-term risk of maternal CKD and ESKD (Figure 1.3). The thesis is outlined as follows:

Chapter 1. Introduction, aims and objectives

Chapter 2. Literature review, comprising a pre-specified systematic review protocol and subsequent systematic review and meta-analysis (**papers 1-2**)

Chapter 3. Detailed methods chapter, outlining the population studied, data sources and statistical methods used

Chapter 4. Original population-based cohort study investigating associations between preterm delivery and long-term risk of maternal CKD and ESKD (**paper 3**)

Chapter 5. Original population-based cohort study investigating associations between previous experience of stillbirth and long-term risk of maternal CKD and ESKD (**paper 4**)

Chapter 6. Original population-based cohort study investigating associations between HDP (preeclampsia and gestational hypertension) and long-term risk of maternal CKD, including CKD subtypes (**paper 5**)

Chapter 7. Original population-based cohort study investigating associations between GDM and long-term risk of maternal CKD, CKD subtypes, and ESKD (**paper 6**)

Chapter 8. Updated systematic review and meta-analysis using results from newly published studies, including studies from this thesis

Chapter 9. Discussion of the main findings, including overall interpretation, strengths and limitations of the thesis. Public health implications are presented, and these are informed by two published editorials (**papers 7-8**, presented in full in Appendix)

Chapter 10. Conclusion

1.4 Overall aims and objectives

The overall aim of this thesis is to examine whether adverse pregnancy outcomes are associated with the long-term risk of maternal kidney disease.

Specifically, the objectives are as follows:

1. Based on a pre-specified protocol, to synthesise the published literature investigating associations between adverse pregnancy outcomes and future maternal CKD and ESKD in the form of a systematic review and meta-analysis
2. To provide a detailed overview of the methods used in this research, including a description of the study population, data sources, and statistical methods applied
3. To identify whether women who experience preterm delivery have an increased risk of future CKD or ESKD, controlling for several important confounders using data from Swedish national registers
4. To measure the association between stillbirth and maternal risk of future CKD or ESKD, controlling for important confounders using data from Swedish national registers
5. To investigate whether women who experience HDP (preeclampsia and gestational hypertension) have an increased risk of future CKD, including specific subtypes of CKD
6. To determine whether women who experience GDM have an increased risk of future CKD or ESKD, including specific subtypes of CKD, independent of subsequent T2DM

7. To identify the public health implications of any observed associations between adverse pregnancy outcomes and long-term risk of maternal CKD or ESKD

The thesis objectives are also presented in Figure 1.3.

1.5 Hypothesis

The overall null hypothesis (H_0) for this research would state that there is no association between adverse pregnancy outcomes and the long-term risk of maternal kidney disease. Specifically, this would suggest that:

1. There is no association between preterm delivery and the long-term risk of maternal CKD or ESKD.
2. There is no association between previous stillbirth and the long-term risk of maternal CKD or ESKD.
3. There is no association between HDP (preeclampsia or gestational hypertension) and the long-term risk of maternal CKD, including subtypes of CKD.
4. There is no association between GDM and the long-term risk of maternal CKD or ESKD, including subtypes of CKD.

Thus, the overall null hypothesis would be rejected if associations were observed between any or all adverse pregnancy outcomes and the long-term risk of maternal CKD or ESKD.

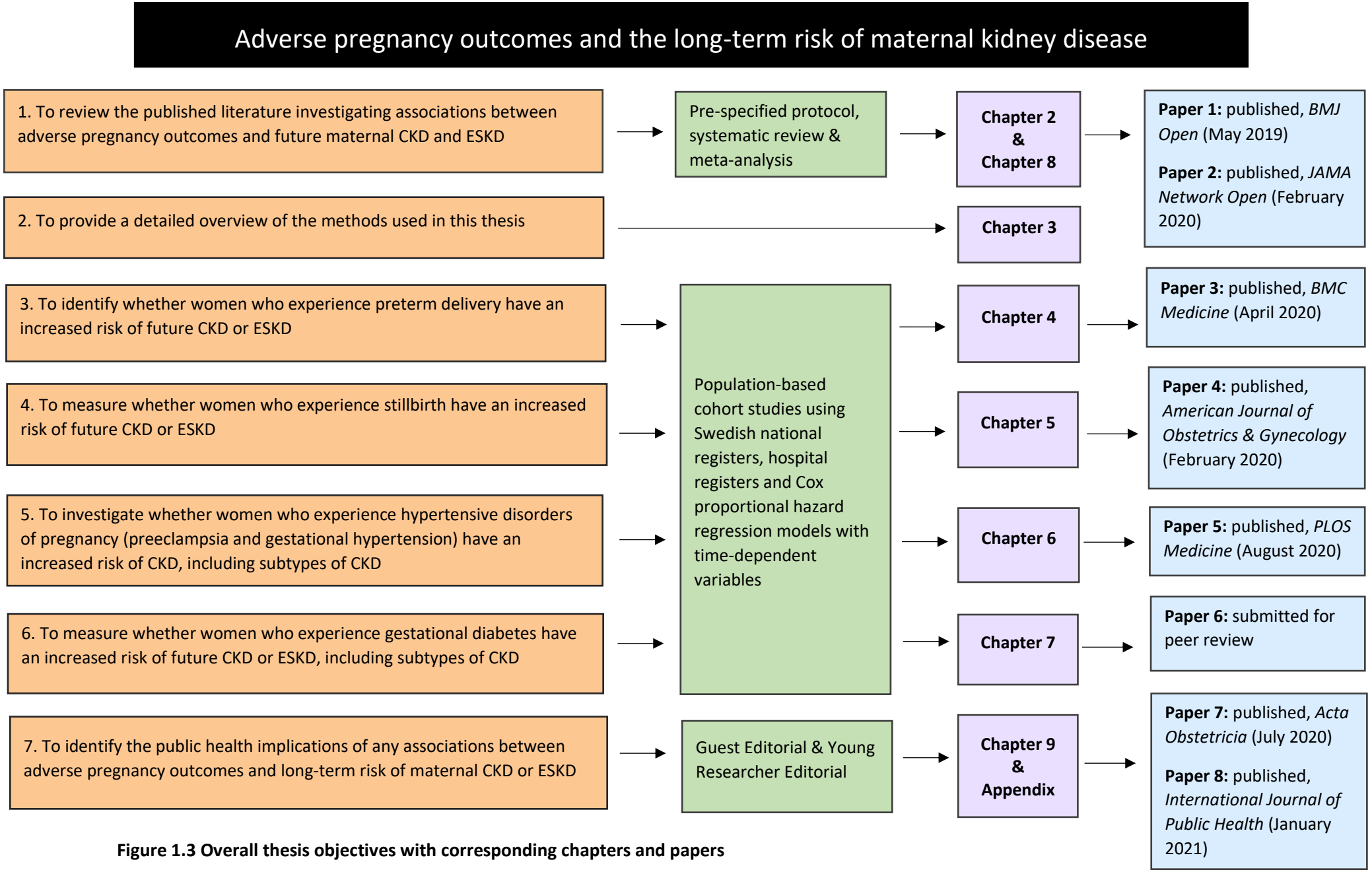


Figure 1.3 Overall thesis objectives with corresponding chapters and papers

CHAPTER 2 Literature review

2.1 Literature review methods

This literature review is comprised of a pre-specified protocol (paper 1) which was used to plan for, and conduct, a systematic review and meta-analysis on adverse pregnancy outcomes and long-term risk of maternal CKD and ESKD (paper 2).

A systematic review can be used to identify, appraise and synthesise the existing information on a specific research topic in a concise and structured way. Systematic reviews require the use of distinctive methods which help to minimise bias, and improve the validity, reliability and generalisability of scientific findings (46). Standardised checklists, such as the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist, help to improve the reporting quality of systematic reviews (47).

A meta-analysis was undertaken as part of this systematic review to ascertain pooled effect estimates for measures of association between adverse pregnancy outcomes and maternal CKD and ESKD. Meta-analyses allow the statistical combination of results from two or more studies to improve the precision of effect estimates and to resolve conflicting results which may arise from different individual studies. It is important to consider differences in study design, within-study biases, methodological diversity, and reporting biases. Thus, efforts were made to consider testing for heterogeneity, undertake sensitivity analyses, and check for publication bias from the outset (46).

2.2 ADVERSE PREGNANCY OUTCOMES AND LONG-TERM RISK OF MATERNAL RENAL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS PROTOCOL

Peter M. Barrett (1, 2), Fergus P. McCarthy (2), Karolina Kublickiene (3), Sarah Cormican (4), Conor Judge (4), Marie Evans (3), Marius Kublickas (5), Ivan J. Perry (1), Peter Stenvinkel (3), Ali S. Khashan (1, 2)

1. School of Public Health, University College Cork, Cork, Ireland
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland
3. Department of Clinical Sciences Intervention and Technology, Karolinska Institutet, Huddinge, Sweden
4. Department of Nephrology, Galway University Hospital, Galway, Ireland
5. Department of Obstetrics & Gynaecology, Karolinska Institutet, Stockholm, Sweden

Published in: *BMJ Open, May 2019*

(Paper 1)

2.2.1 Abstract

Introduction

Adverse pregnancy outcomes, such as hypertensive disorders of pregnancy (HDP), gestational diabetes (GDM) and preterm birth have been linked to maternal cardiovascular disease in later life. Pre-eclampsia (PE) is associated with an increased risk of postpartum microalbuminuria, but there is no clear consensus on whether HDP increases the risk of maternal chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Similarly, it is uncertain whether GDM, preterm birth and delivery of low birth-weight infants independently predict the risk of maternal renal disease in later life. The aims of this proposed systematic review and meta-analysis are to summarise the available evidence examining the association between adverse pregnancy outcomes (HDP, GDM, preterm birth, delivery of low birth-weight infant) and later maternal renal disease and to synthesise the results of relevant studies.

Methods and analysis

A systematic search of PubMed, EMBASE and Web of Science will be undertaken using a detailed pre-specified search strategy. Two authors will independently review the titles and abstracts of all studies, perform data extraction and appraise the quality of included studies using a bias classification tool. Original case–control and cohort studies published in English will be considered for inclusion. Primary outcomes of interest will be CKD and ESKD; secondary outcomes will be hospitalisation for renal disease and deaths from renal disease. Meta-analyses will be performed to calculate the overall pooled estimates using the generic inverse variance method. The

systematic review will follow the Meta-analyses Of Observational Studies in Epidemiology guidelines.

Ethics and dissemination

This systematic review and meta-analysis will be based on published data, and thus there is no requirement for ethics approval. The results will be shared through publication in a peer reviewed journal and through presentations at academic conferences.

PROSPERO registration number CRD42018110891

2.2.2 Introduction

Chronic kidney disease (CKD) is a major cause of premature morbidity and mortality worldwide, and its prevalence is estimated at 11%–13% among women (48). End-stage kidney disease (ESKD), although relatively rare, causes disproportionately high healthcare burden and expense (42, 49). Globally, rising levels of obesity, metabolic syndrome and advanced maternal age are resulting in increasing prevalence of adverse pregnancy outcomes, particularly hypertensive disorders of pregnancy (HDP) and gestational diabetes (GDM) (50-52). Pre-eclampsia (PE), gestational hypertension and GDM are now recognised as independent cardiovascular risk factors in women (23, 53), while preterm birth, growth restriction and gestational weight gain have also been linked to future cardiovascular disease (22, 54, 55). By comparison, relatively little is known about the long-term risk of maternal renal disease following complications of pregnancy.

There is some evidence to suggest that PE increases the risk of maternal kidney disease later in life. A meta-analysis of seven small prospective studies identified an increased risk of microalbuminuria among women who experienced PE compared with those who had normal pregnancies after a mean of 7 years follow-up (56). A large Norwegian cohort study suggested that pre-eclamptic women were at long-term risk of ESKD (28). However, the proposed association may be complicated by the strong links between PE and unmeasured cardiovascular risk factors, such as maternal obesity, which can independently increase the risk of CKD (57).

The long-term risk of CKD among these women has not been comprehensively addressed by studies to date. It is biologically plausible that PE predisposes women to higher risk of CKD; PE is associated with abnormal placental development, and subsequent development of generalised maternal endothelial dysfunction (58). PE may thus result in lasting renal endothelial damage, which may increase maternal risk of CKD and ESKD (11). PE is just one of several hypertensive disorders of pregnancy, and it is unknown if women who experience gestational hypertension, or PE superimposed on chronic hypertension, are also at increased long-term risk of maternal kidney disease.

A range of other complications of pregnancy may increase the risk of future kidney disease in women. Low birth-weight and preterm delivery have been reported to increase the risk of ESKD in women with PE (28). However, it is uncertain whether these associations persist independently, or whether birth weight and gestational age are mediators of the association with PE. In one Norwegian cohort study, preterm birth was reported to independently increase the risk of ESKD, but this study was restricted to women with pre-existing diabetes and is not generalisable to the wider population (59).

GDM is an established risk factor for type 2 diabetes (60), and may thereby increase the risk of diabetic nephropathy. However, GDM is also an independent risk factor for vascular endothelial dysfunction (61, 62), and is a plausible independent risk factor for maternal kidney disease. To date there has been limited research to examine whether GDM predicts CKD risk independent of subsequent type 2 diabetes.

Worldwide, 3%–5% of pregnancies are complicated by PE (63), 5%–18% of births are preterm (64), 11% have low birth-weight (65) and 5%–13% are complicated by GDM (66, 67). Given the high prevalence of CKD (48), any true associations between these exposures and CKD may have potentially important public health implications, particularly in resource-poor settings where adverse pregnancy outcomes are more prevalent. Women with complications of pregnancy who may be at risk of CKD, may benefit from future risk-reduction interventions or enhanced community-based follow-up care to mitigate against possible progression to renal disease. Only a minority of individuals with CKD will ever progress to ESKD, requiring dialysis or renal transplant, but they experience premature mortality (39, 40), and place a considerable economic and resource burden on health systems (41).

The aim of this systematic review and meta-analysis is to summarise the available evidence examining the association between adverse pregnancy outcomes and long-term maternal renal disease. The adverse outcomes of interest include HDP (including PE, gestational hypertension, chronic hypertension and PE superimposed on chronic hypertension), preterm birth, delivery of a low birth-weight infant and GDM.

Population

Women who have had at least one pregnancy of at least 23 weeks gestation.

Exposures

Any one of the following adverse pregnancy outcomes:

1. Diagnosis of HDP (including PE, gestational hypertension or other HDP).

2. Preterm birth.
3. Diagnosis of GDM.
4. Delivery of a low birth-weight infant (including infants who were small for gestational age).

Any of these adverse outcomes can be defined using established clinical criteria, hospital records or self-reporting of a doctor diagnosis.

Comparison

Women who never had a corresponding adverse outcome in pregnancy. For example, women who experienced a preterm birth in at least one pregnancy will be compared with women who never experienced a preterm birth.

Outcomes

Primary outcome 1: CKD.

Primary outcome 2: ESKD.

These primary outcomes can be defined either using established clinical criteria or hospital records.

Secondary outcomes: (1) hospitalisation for renal disease, (2) deaths from renal disease.

Review question

Does the presence of an adverse pregnancy outcome (ie, HDP, preterm birth, delivery of a low birth-weight infant or GDM) increase the risk of maternal kidney disease in later life?

2.2.3 Methods

This protocol was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist (68). The proposed systematic review and meta-analysis will follow the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines (47).

Search strategy

The lead author (PMB) will undertake a systematic search of the following databases: PubMed, EMBASE and Web of Science. Peer reviewed journal articles published in the English language, from inception of databases to 31 July 2019, will be included. A detailed search strategy has been compiled, and the search terms will be combined using Boolean Logic where appropriate (AND, OR). The detailed search strategy is available in Appendix 2.

The search of the electronic databases will be supplemented by hand-searching all included papers to identify any further potentially relevant studies.

Study selection

The titles and abstracts of studies retrieved from each database search will be stored in the EndNote reference manager and de-duplicated. Two review authors (PMB, SC) will screen all titles and abstracts for potentially relevant studies. The full text of the relevant studies will then be retrieved and screened for compliance with eligibility criteria by two reviewers (PMB, CJ). If consensus on eligibility cannot be achieved, a third review author will be consulted (ASK). For any articles which do not meet

the inclusion criteria, the reasons for rejection will be noted. A MOOSE flow diagram documenting the process of study selection will be completed.

Inclusion criteria

- Case–control studies and cohort studies (prospective or retrospective).
- Data provided on an adverse pregnancy outcome of interest (i.e. diagnosis of HDP, preterm birth, low birth-weight or GDM) as an exposure variable.
- Data provided on a diagnosis of either CKD or ESKD as an outcome variable.
- Provides a measure of association between one or more of the adverse pregnancy outcomes and CKD or ESKD.
- The diagnosis of maternal CKD or ESKD is made at least 3 months after pregnancy has ended.
- Data must be from an original study.
- Only English-language studies will be considered, including all years from inception of the electronic databases until July 2019.
- Peer reviewed literature only will be included.

Exclusion criteria

- Non-human studies.
- Studies that are not in English.
- Studies focused on CKD/ESKD risk in the offspring.
- Studies focused on risk of maternal acute kidney injury, without reference to subsequent CKD/ESKD.

- Case reports, case series, letters, commentaries, notes and editorials.
- Studies focused on women with pre-existing renal disease.

Data extraction

Data from all eligible studies will be extracted by two reviewers (PMB, SC) using a standardised data collection form. The information will include the author and year of publication, the study design, the exposure(s) and outcome(s) of interest, the definition used for each exposure and outcome, the stage/severity of the outcome (i.e. CKD), length of follow-up, the sample size, the confounders adjusted for (if any) and the crude and adjusted measures of association. Where necessary, corresponding authors of published studies will be contacted to obtain any information needed relating to effect estimates. Where effect estimates are not available, absolute numbers of events will be extracted, and crude measures of association will be calculated. If discrepancies arise in data extraction, these will be discussed between reviewers, and where necessary, a third reviewer will be consulted to achieve consensus (ASK).

Quality appraisal of included studies

The quality of all included studies will be independently assessed by two reviewers (PMB, CJ) using an established quality assessment tool for observational studies. This tool has been described in detail elsewhere (69). Six types of bias will be assessed: selection, exposure, outcome, analytical, attrition and confounding. For each study, each component will be assigned a risk of bias category: minimal, low, moderate,

high or not reported. For example, selection bias will be categorised as 'minimal' if the sample was from a 'consecutive unselected population', whereas selection bias will be categorised as 'high' if sample selection is unclear and if the sample is not representative of the population of interest. For each included study, the overall likelihood of bias will be assessed and reported. Where discrepancies in quality appraisal arise, a third reviewer will be consulted to achieve consensus (ASK).

Data synthesis and assessment for heterogeneity

Separate meta-analyses will be undertaken for each of the exposure variables and two primary outcomes where possible. Each meta-analysis will be undertaken to calculate the pooled estimate of the relationship between the adverse outcome of interest and subsequent development of maternal CKD or ESKD. For example, for preterm birth as the adverse outcome of interest, a meta-analysis will be undertaken to investigate the association between (1) preterm birth and CKD and (2) preterm birth and ESKD. For HDP, a meta-analysis will be undertaken to investigate the association between (1) any HDP and CKD and (2) any HDP and ESKD. Where possible, subgroup analyses will investigate the associations between PE, gestational hypertension and any other HDP with each of the primary outcomes respectively. For delivery of infants with low birth-weight, a meta-analysis will be undertaken to investigate the association between (1) low birth-weight infant and maternal CKD and (2) low birth-weight infant and maternal ESKD. Where possible, subgroup analyses will investigate the associations between infants small for their gestational age with each of the primary outcomes, respectively.

Both crude and adjusted effect estimates will be displayed using the generic inverse variance method. Adjustment will be based on the definition outlined in each of the individual studies. Heterogeneity will be explored based on I^2 values and χ^2 statistics. Random-effects models will be used if moderate or high levels of heterogeneity are observed between the studies of interest. If studies cannot be meaningfully combined in a meta-analysis, they will be presented in tabular format.

We will perform the following subgroup/sensitivity analyses, where the data allow, using RevMan version 5.3: (1) study type (case–control vs cohort study), (2) stage/severity of CKD, (3) ethnic group, (4) length of follow-up after index pregnancy, (5) number of pregnancies affected by the adverse outcome, (6) measurement of exposure and outcome data (self-reported vs medical records vs laboratory measurements), (7) study quality (minimal/low risk of bias vs moderate/high risk of bias). Furthermore, any studies which have not excluded women with pre-existing renal disease, or have not adjusted for this factor, will be considered in a separate subgroup analysis.

Where 10 or more studies are included in a meta-analysis, we will assess publication bias. The trim and fill method will be used to identify and correct for funnel plot asymmetry arising from publication bias, if appropriate (70).

Ethics and dissemination

This protocol is based on published data, and thus there is no requirement for ethics approval. The results will be disseminated through publication in a peer-reviewed journal, and through presentations at academic conferences.

Patient and public involvement

Patients were not involved in the design of this systematic review and meta-analysis. However, the authors will communicate the study findings to patient and public groups with interest in this area.

2.2.4 Discussion

Potential limitations

There are a number of limitations anticipated in this review. Publication bias may reduce the likelihood of retrieving studies which report non-significant associations between adverse pregnancy outcomes and maternal renal disease. Due to limited resources, only studies which are published in the English language will be included. Publications which only use biomarkers of renal function as outcome variables (e.g. microalbuminuria, albumin/creatinine ratio, estimated glomerular filtration rate) will not be included unless they are directly related to a diagnosis of CKD or ESKD.

A degree of heterogeneity is anticipated between studies. Differences in diagnostic methods are likely for both exposures and outcomes. The timeframe for follow-up is likely to vary considerably between studies, with women followed up for longer durations more likely to have developed renal disease. The ability to identify true associations between adverse pregnancy outcomes and future CKD or ESKD will be limited by the length of follow-up in each of the included studies. Differences in sampling frames are also likely to lead to heterogeneity. Thus, a random-effects model will be used for meta-analyses with moderate or high heterogeneity.

The presence of selection bias and residual confounding is a concern in all observational studies. Potential confounders may include maternal age, ethnic group, socio-economic status, parity, family history, hypertension, diabetes, cardiovascular disease, systemic inflammatory disease, hyperlipidaemia, obesity and smoking. Our meta-analyses will display both crude and adjusted results where possible, basing adjustment on the definition outlined in each individual study. However, given that less adjusted effect estimates may skew the overall results, a sensitivity analysis will be undertaken, where possible, to examine effect estimates which are adjusted more fully for confounders (i.e. adjusted for, at a minimum, maternal age, hypertension, diabetes, obesity, smoking, pre-existing kidney disease).

2.2.5 Conclusion

There is a lack of consensus on whether adverse pregnancy outcomes, such as HDP, preterm birth, delivery of a low birth-weight infant and GDM, independently increase the risk of maternal CKD and ESKD. This systematic review and meta-analysis will summarise the available evidence which has examined these associations, thus providing novel information on the role of pregnancy-related factors in the aetiology of maternal renal disease.

2.3 ADVERSE PREGNANCY OUTCOMES AND LONG-TERM MATERNAL KIDNEY DISEASE. A SYSTEMATIC REVIEW AND META-ANALYSIS

Peter M. Barrett (1, 2), Fergus P. McCarthy (2, 3), Karolina Kublickiene (4), Sarah Cormican (5), Conor Judge (5), Marie Evans (4), Marius Kublickas (6), Ivan J. Perry (1), Peter Stenvinkel (4), Ali S. Khashan (1, 2)

1. School of Public Health, University College Cork, Cork, Ireland
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland
3. Department of Obstetrics & Gynaecology, Cork University Maternity Hospital, Cork, Ireland
4. Department of Clinical Sciences Intervention and Technology, Karolinska Institutet, Huddinge, Sweden
5. Department of Nephrology, Galway University Hospital, Galway, Ireland
6. Department of Obstetrics & Gynaecology, Karolinska Institutet, Stockholm, Sweden

Published in: *JAMA Network Open, February 2020*

(Paper 2)

2.3.1 Abstract

Importance

Adverse pregnancy outcomes, such as hypertensive disorders of pregnancy, gestational diabetes, and preterm delivery, are associated with increased risk of maternal cardiovascular disease. Little is known about whether adverse pregnancy outcomes are associated with increased risk of maternal chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

Objective

To review and synthesise the published literature on adverse pregnancy outcomes (hypertensive disorders of pregnancy, gestational diabetes, and preterm delivery) and subsequent maternal CKD and ESKD.

Data sources

PubMed, Embase, and Web of Science were searched from inception to July 31, 2019, for cohort and case-control studies of adverse pregnancy outcomes and maternal CKD and ESKD.

Study selection

Selected studies included the following: a population of pregnant women, exposure to an adverse pregnancy outcome of interest, and at least 1 primary outcome (CKD or ESKD) or secondary outcome (hospitalisation or death due to kidney disease). Adverse pregnancy outcomes included exposure to hypertensive disorders of pregnancy (preeclampsia, gestational hypertension, or chronic hypertension), preterm delivery (<37 weeks), and gestational diabetes. Three reviewers were involved in study selection. Of 5,656 studies retrieved, 23 were eligible for inclusion.

Data extraction and synthesis

The Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines were followed throughout. Three reviewers extracted data and appraised study quality. Random-effects meta-analyses were used to calculate overall pooled estimates using the generic inverse variance method.

Main outcomes and measures

Primary outcomes included CKD and ESKD diagnosis, defined using established clinical criteria (estimated glomerular filtration rate or albuminuria values) or hospital records. The protocol for this systematic review was registered on PROSPERO (CRD42018110891).

Results

Of 23 studies included (5,769,891 participants), 5 studies reported effect estimates for more than 1 adverse pregnancy outcome. Preeclampsia was associated with significantly increased risk of CKD (pooled adjusted risk ratio [aRR], 2.11; 95% CI, 1.72-2.59), ESKD (aRR, 4.90; 95% CI, 3.56-6.74), and kidney-related hospitalisation (aRR, 2.65; 95% CI, 1.03-6.77). Gestational hypertension was associated with increased risk of CKD (aRR, 1.49; 95% CI, 1.11-2.01) and ESKD (aRR, 3.64; 95% CI, 2.34-5.66). Preterm preeclampsia was associated with increased risk of ESKD (aRR, 5.66; 95% CI, 3.06-10.48); this association with ESKD persisted for women who had preterm deliveries without preeclampsia (aRR, 2.09; 95% CI, 1.64-2.66). Gestational diabetes was associated with increased risk of CKD among black women (aRR, 1.78; 95% CI, 1.18-2.70), but not white women (aRR, 0.81; 95% CI, 0.58-1.13).

Conclusions and relevance

In this meta-analysis, exposure to adverse pregnancy outcomes, including hypertensive disorders of pregnancy, gestational diabetes, and preterm delivery, was associated with higher risk of long-term kidney disease. The risk of ESKD was highest among women who experienced

preeclampsia. A systematic approach may be warranted to identify women at increased risk of kidney disease, particularly after hypertensive disorders of pregnancy, and to optimise their long-term follow-up.

2.3.2 Introduction

Pregnancy is increasingly regarded as a metabolic stress test, which may unmask underlying vascular disease and endothelial dysfunction (11). The risk of long-term cardiovascular disease is increased among women with a history of preeclampsia, gestational hypertension, or gestational diabetes (GDM) (43, 53, 71, 72). Comparatively little is known about the long-term risk of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in women who have experienced adverse pregnancy outcomes. It is plausible that women who experience hypertensive disorders of pregnancy (HDP) have a higher risk of long-term kidney disease than women with normotensive pregnancies. Women exposed to preeclampsia have an increased risk of microalbuminuria (56, 73), and longitudinal studies have suggested that they may be at increased risk of long-term kidney disease (28, 74). It is uncertain whether gestational hypertension and chronic hypertension may have similar associations with the risk of maternal kidney disease.

Preterm delivery and delivery of a growth-restricted or low-birth-weight infant have been identified as risk factors for maternal cardiovascular disease (20, 22, 55, 75), but it is unclear whether they are independently associated with increased risk of future kidney disease. It is possible that these factors mediate the association between HDP or other pregnancy-related disorders and CKD or ESKD.

Women who develop GDM are predisposed to lasting vascular endothelial dysfunction (61, 62). It is plausible that this dysfunction may in itself increase their risk of kidney disease, even if they never develop type 2 diabetes (11). By 9 to 16 years post partum, women exposed to GDM may experience early renal damage (76), but it is uncertain whether they are at risk of clinically significant CKD.

This systematic review and meta-analysis aims to synthesise the available evidence on the associations between adverse pregnancy outcomes and long-term maternal CKD and ESKD.

2.3.3 Methods

Data Sources and Search Strategy

A systematic search of PubMed, Embase, and Web of Science was undertaken from inception of the databases until July 31, 2019. We sought studies with the following: a population of pregnant women, exposure to an adverse pregnancy outcome of interest, a comparison group of women with no corresponding adverse pregnancy outcome, and at least 1 primary outcome (CKD or ESKD) or secondary outcome (hospitalisation or death due to kidney disease). This study followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidelines (47).

The adverse pregnancy outcomes included exposure to HDP, specifically, preeclampsia, gestational hypertension, chronic hypertension, or preeclampsia superimposed on chronic hypertension (PSH), preterm delivery (<37 weeks), delivery of an infant with low birth weight (including small for gestational age and intrauterine growth restriction), and GDM. Each exposure could be defined either using established clinical criteria, hospital records, or self-reporting of a physician's diagnosis. For CKD and ESKD, they could be defined using established clinical criteria (i.e., estimated glomerular filtration rate or albuminuria values) or hospital records. The protocol for this systematic review was registered on PROSPERO (CRD42018110891) and subsequently published (77).

Study Selection

The process of study selection is outlined in Figure 2.1. Two of us (P.M.B. and S.C.) independently reviewed titles and abstracts of all studies. Peer-reviewed English-language case-control and cohort studies (prospective or retrospective) were included if they published original effect estimates of the association between at least 1 adverse pregnancy outcome of interest and a primary or secondary outcome.

Studies were excluded if maternal renal outcomes were ascertained less than 3 months postpartum to avoid misclassification with pregnancy-related acute kidney injury. Studies were also excluded if they were restricted to women with pre-pregnancy kidney disease, if they used changes in biological or laboratory markers of kidney function as the only outcome (e.g. change in estimated glomerular filtration rate or microalbuminuria) without information about CKD or ESKD diagnosis, and if they focused on renal outcomes among offspring instead of mothers.

Data Extraction and Quality Appraisal

Two investigators (P.M.B. and C.J.) extracted data independently from eligible studies. Where information was not directly available from the studies, authors were contacted to request this information, and at least 1 follow-up reminder email was sent. The bias classification tool of McDonald et al. (69) was used to assess 6 types of bias commonly associated with observational studies (selection, exposure, outcome, attrition, analytic, and confounding) (Appendix 3). For every study, the presence of each type of bias was classified as minimal, low, moderate, high, or not reported, and an overall likelihood of bias score was measured.

Statistical Analysis

Data were analysed using Review Manager software, version 5.3 (78). Random-effects meta-analyses were used to calculate overall pooled estimates of the associations between adverse pregnancy outcomes and subsequent maternal CKD or ESKD. Both crude and adjusted effect estimates were displayed using the generic inverse variance method. Post hoc analyses were also conducted using the Sidik-Jonkman method in Stata, version 15.0 (Stata Corp), given the small number of included studies in each meta-analysis (79).

Forest plots were used to display pooled estimates, with corresponding 95% CIs. Statistical heterogeneity was explored based on I^2 values and τ^2 statistics. In the meta-analyses, odds ratios, hazard ratios, and relative risks (RRs) were used as approximations of each other. Under the rare disease assumption, odds ratios and RRs are commonly used to approximate each other (80, 81), and hazard ratios may be considered as an extension of this approximation when the outcome is uncommon (81, 82).

Separate subgroup analysis by study type, follow-up time, measurement of outcome variables (self-report vs laboratory measurements vs medical records), CKD staging, and study quality were planned, but were not conducted owing to the small number of included studies. Subgroup analysis by race/ethnicity of participating women (white vs black) was possible only in the case of GDM. We planned to assess publication bias using funnel plots, but a minimum of 10 unique studies should be included in order to do so (83). We had fewer studies in each separate meta-analysis, and thus could not assess publication bias using funnel plots.

We presented adjusted effect estimates based on the definitions outlined in each individual study. However, we also conducted sensitivity analyses whereby meta-analyses were restricted to studies reporting effect estimates adjusted for important maternal comorbidities (CKD, hypertension, and diabetes).

We used the formula of Levin (84) to calculate the population-attributable fraction of preeclampsia on CKD and ESKD: $P \times (RR - 1)/P \times (RR - 1) + 1$, where P is the pooled prevalence of exposure in all cohort studies included in a given meta-analysis, and RR is the pooled adjusted RR from the meta-analysis.

2.3.4 Results

The search yielded 5,656 unique results. Of these, 23 articles were included in the systematic review, covering 14 unique study populations (5,769,891 participants). Five articles provided effect estimates for more than 1 adverse pregnancy outcome of interest.

The sample size of included studies ranged widely, from 132 participants in an American case-control study (33) to a registry-based study of 1,598,043 Canadian women (32). Ten studies were conducted in Europe (21, 28, 29, 59, 74, 85-89), 7 in Asia (30, 31, 90-94) 4 in North America (32, 33, 95, 96), and 2 in Australia (97, 98). Three studies had moderate risk of bias (89, 90, 96), but the remaining 20 studies were assessed as having minimal or low risk of bias.

The summary results of all meta-analyses are presented in Table 2.1. Detailed characteristics of the 18 articles that provided effect estimates for HDP and maternal kidney disease are presented in Table 2.2. The data relating to preterm birth are presented in Table 2.3, data relating to delivery of low-birth-weight (or small for gestational age) infants are presented in Table 2.4, and data relating to GDM are presented in Table 2.5. Nine studies provided effect estimates for any HDP and ESKD (28, 30-33, 59, 85, 86). Four of these studies were excluded from the meta-analysis, either owing to overlap of study populations or because they were restricted to women with higher baseline risk of ESKD (30, 59, 85, 86). All the remaining studies provided adjusted effect estimates for preeclampsia and ESKD, of which 2 also provided adjusted estimates for gestational hypertension, chronic hypertension, and PSH in mutually exclusive groups.

Preeclampsia

The pooled crude risk ratio for preeclampsia and ESKD was 6.16 (95% CI, 4.42-8.57) and the pooled adjusted risk ratio (aRR) was 4.90 (95% CI, 3.56-6.74) (Figure 2.2). High levels of heterogeneity were observed ($I^2 = 73\%$), owing to 1 study with outlying effect estimates

(31). When this study was excluded, the pooled aRR for preeclampsia and ESKD was attenuated to 4.32 (95% CI, 3.50-5.32; I^2 = 34%).

Three studies reported adjusted estimates for preeclampsia and CKD (pooled aRR, 2.11; 95% CI, 1.72-2.59) (Figure A4.1, Appendix 4). Four studies reported associations between preeclampsia and kidney-related hospitalisation. One study was excluded from meta-analysis owing to overlap between study populations (87). The pooled aRR for preeclampsia and kidney-related hospitalisation was 2.65 (95% CI, 1.03-6.77). The population-attributable fraction for preeclampsia on ESKD was 11.4% and for CKD was 4.0%.

Other HDP

The aRR for gestational hypertension and ESKD was 3.64 (95% CI, 2.34-5.66), but was based on only 2 effect estimates (Figure A4.2, Appendix 4). Gestational hypertension was also associated with an increased risk of CKD (aRR, 1.49; 95% CI, 1.11-2.01). Two studies reported crude estimates for chronic hypertension and ESKD or for PSH and ESKD, and the pooled estimates suggested an increased risk of ESKD (chronic hypertension: RR, 16.87; 95% CI, 11.31-25.15; and PSH: RR, 48.97; 95% CI, 26.09-91.93), but were based on small numbers of patients.

Preterm Delivery, Low Birth Weight, and GDM

Three studies reported adjusted effect estimates for preterm preeclampsia and ESKD (aRR, 5.66; 95% CI, 3.06-10.48) (Figure A4.4, Appendix 4). Four studies reported adjusted effect estimates for preterm delivery and ESKD, independent of preeclampsia, but 1 was excluded owing to overlap between study populations (85) (aRR, 2.09; 95% CI, 1.64-2.66, based on 3 effect estimates) (Figure A4.5, Appendix 4).

When we further excluded 1 study restricted to women with pre-existing diabetes (59), the association with ESKD was strengthened for both preterm preeclampsia (aRR, 7.51; 95% CI, 4.86-11.58) and preterm delivery alone (aRR, 2.24; 95% CI, 1.80-2.79).

Four studies reported associations between delivery of a low-birth-weight or growth-restricted infant (including infants who were small for gestational age or had intrauterine growth restriction) with ESKD or kidney-related hospitalisation. Three studies reported an increased adjusted risk of ESKD or kidney-related hospitalisation. However, these studies were not suitable for meta-analysis owing to excessive clinical and methodological diversity.

Three studies reported crude associations between GDM and CKD. When these effect estimates were pooled, no significant association was observed (RR, 0.99; 95% CI, 0.66-1.49). Two of these studies provided adjusted estimates of CKD that could be combined in meta-analysis (95, 96). No significant association was observed when the overall adjusted results were pooled. However, subgroup analysis showed an association with race/ethnicity: black women with GDM had a significantly higher risk of CKD (aRR, 1.78; 95% CI, 1.18-2.70), whereas white women did not (aRR, 0.81; 95% CI, 0.58-1.13) (Figure A4.6, Appendix 4).

All meta-analyses were repeated using the Sidik-Jonkman method. This method resulted in wider 95% CIs for most pooled estimates (Table A4.1, Appendix 4). The associations between preeclampsia and kidney-related hospitalisation and preeclampsia and CKD were attenuated, but the latter remained statistically significant (aRR, 1.92; 95% CI, 1.17-3.14). The results were not otherwise meaningfully different.

2.3.5 Discussion

The aim of this systematic review and meta-analysis was to synthesise the published literature on the association between adverse pregnancy outcomes and the risk of maternal CKD and

ESKD. Overall, the literature in this area was sparse, but 4 principal findings emerged. First, our adjusted pooled results indicate that HDP are associated with long-term kidney disease, particularly ESKD. The type of HDP was important; both gestational hypertension and preeclampsia were associated with increased risk of maternal ESKD, but the association was stronger for preeclampsia, particularly preterm preeclampsia. Only 1 study provided adjusted effect estimates for women exposed to chronic hypertension or PSH (31), but the risk of ESKD was particularly high in these women. Mothers exposed to HDP are at elevated risk of cardiovascular and cerebrovascular disease (23, 53), and our results suggest that their risk of long-term kidney disease is also elevated. The risk of maternal CKD after preeclampsia was lower than for ESKD, but 1 of the included studies on CKD had relatively small numbers of outcomes (88).

Second, the adjusted pooled estimates suggest that preterm delivery may be independently associated with higher risk of maternal ESKD. However, this meta-analysis was based on only 3 studies. None of these studies considered whether preterm delivery was spontaneous or obstetrically indicated, although they had adjusted for preeclampsia (28, 32, 59). Pariente et al. (94) reported that the risk of kidney-related hospitalisation was independently increased among Israeli women with preterm delivery, of whom most (70%) had spontaneous preterm delivery. When their analysis was restricted to those with indicated preterm delivery, no significant difference in kidney-related hospitalisation was observed. Further research is warranted to elucidate whether the association between preterm delivery and CKD or ESKD differs by obstetric indication.

Third, existing literature suggests that delivery of infants with low birth weight, or who are small for gestational age, may be associated with increased risk of maternal kidney disease (28, 32, 92). However, there is a paucity of research examining this association, and only 1 of

these studies controlled for maternal preeclampsia (28). It is possible that the apparent associations are confounded by unmeasured placental factors.

Fourth, it is not possible to conclude whether GDM is independently associated with an increased risk of maternal kidney disease based on the available literature. Although our meta-analysis suggests that GDM has no overall association with CKD risk, this finding was based on adjusted estimates from only 2 studies, and a subgroup analysis suggested that black women exposed to GDM have an increased risk of kidney disease. Black women have an increased risk of CKD compared with white women (99-101), and they are more likely to progress to ESKD (102). The reasons for this elevated risk remain poorly understood, but it is plausible that GDM itself may act as an independent factor associated with kidney disease. The 4 included studies on GDM differed in their treatment of subsequent type 2 diabetes; Bomback et al. (96) controlled for it by stratification and Dehmer et al. (95) treated it as a mediating factor, whereas neither of the 2 Israeli studies collected data on subsequent diabetes (91, 93).

Interpretation and Mechanisms

The mechanisms underlying observed associations in this study are uncertain, and it is plausible that some adverse pregnancy outcomes are a manifestation of underlying predisposition to chronic disease. Irrespective of causality, our results suggest that adverse pregnancy outcomes may signal future risk of CKD and ESKD, particularly after HDP.

For preeclampsia and kidney disease, pre-existing hypertension and obesity are risk factors that are common to both diseases, and these shared risk factors may partly explain this association. However, most studies in this systematic review reported strong associations even after controlling for, or excluding, women with pre-pregnancy hypertension (21, 28-33, 59, 74, 85, 86, 90) or obesity (29, 32, 87, 88, 90, 93).

Preeclampsia has been proposed as a cause of lasting vascular endothelial dysfunction, possibly associated with elevated levels of soluble fms-like tyrosine kinase-1, an antiangiogenic protein secreted by the placenta that may remain elevated post-partum (11, 103). Higher levels of soluble fms-like tyrosine kinase-1 have been linked with progression of atherosclerosis (104) and have also been observed among patients with CKD (105). Women exposed to preeclampsia may also experience arterial stiffness (106) or lasting endothelial damage (11), which may be associated with their increased risk of future renal complications (56).

The observed associations between preterm delivery or delivery of a low-birth-weight infant and maternal kidney disease may reflect subclinical disease or inflammatory processes. These associations may also be prone to residual confounding. Certain cardiovascular risk factors may be mutual to preterm delivery, growth restriction, and maternal CKD. For example, none of the studies that examined these associations had adjusted for maternal smoking, and only 1 effect estimate for preterm delivery and kidney disease was adjusted for maternal body mass index (32).

The potential mechanisms by which GDM may increase the risk of kidney disease are more intuitive, because GDM can cause persistent endothelial dysfunction (61, 62). However, smaller observational studies have examined the risk of early kidney damage in the years after pregnancy complicated by GDM, and results have been inconsistent to date (76, 107-109).

Strengths and Limitations

To our knowledge, this is the most comprehensive systematic review and meta-analysis of adverse pregnancy outcomes and their associations with maternal kidney disease to date. An independent librarian verified the search strategy, and 3 relevant databases were included, supplemented by hand searching of reference lists. Most of the included studies had large sample sizes, were longitudinal, and had low risk of bias.

We observed high levels of heterogeneity in some of the meta-analyses, as measured using I^2 and τ^2 statistics. These measures should be interpreted with caution (110), and should not be considered substitutes for assessments of clinical or methodological diversity (46). We further excluded outlying effect estimates and conducted sensitivity analyses to reduce heterogeneity (110), but some clinical and methodological diversity persisted.

For meta-analyses involving CKD as the outcome variable, variation in ascertainment of the outcome may be associated with relatively high levels of heterogeneity. For example, some studies based their definitions of CKD on clinical criteria using estimated glomerular filtration rate values with or without albumin excretion rates (87, 89, 90). Others based their definitions on *International Classification of Diseases* registry codes, which were inconsistent between different studies (30, 74, 88). We were unable to conduct meaningful subgroup analyses owing to the small number of studies in each individual meta-analysis. Similarly, we were unable to assess for publication bias, owing to small numbers of included studies in each meta-analysis.

We excluded articles that reported microalbuminuria or other markers of kidney dysfunction as the only outcome, without clear information relating to CKD or ESKD. This decision was taken to maximise probability that those who were included in the review had a clinically significant diagnosis of CKD or ESKD, and not an incidental or screening-detected finding. Our review may not capture all articles with information relating to early, asymptomatic CKD. Stage 1 CKD may be diagnosed based on microalbuminuria alone (111), but it is of lesser clinical relevance, and its inclusion may have led to further heterogeneity in meta-analyses.

Some studies reporting secondary outcomes (hospitalisation or mortality) did not clearly exclude women with pre-existing kidney disease at baseline (21, 90, 97, 98), which may have confounded associations. Furthermore, potential confounding by subclinical, undiagnosed nephropathy cannot be ruled out, even after excluding women with established kidney disease. Because the early stages of CKD are typically asymptomatic, it is possible that for some

women, pregnancy unmasks an existing predisposition to kidney disease, rather than causing this predisposition de novo.

The adjusted effect estimates in our study were based on different definitions across individual studies. We considered maternal comorbidities to be the most important confounders, and we conducted sensitivity analyses based on studies that had adjusted for these comorbidities. A large nationwide cohort study of preeclampsia and ESKD reported no difference between crude and adjusted effect estimates after controlling for other maternal factors such as body mass index, smoking, and educational level (29). However, we cannot rule out the possibility of residual confounding by these (or other) maternal factors.

Finally, we used the generic inverse variance method (DerSimonian-Laird method) for meta-analysis (46). This method may produce biased effect estimates (112), and its CIs may have below-nominal coverage (79), particularly when the number of included studies is small. However, we repeated all meta-analyses using the Sidik-Jonkman method, which has lower error rates (79), and the results were not meaningfully different.

Implications and Future Research

The findings in this systematic review may be of substantial public health relevance. The prevalence of adverse pregnancy outcomes, including HDP, has been increasing (50-52), and the worldwide prevalence of stage 3 or greater CKD is now estimated at 12% among women (48). Our study estimates that 11% of all cases of maternal ESKD and 4% of cases of CKD may be associated with preeclampsia alone.

Clinical guidelines have highlighted the need for women's obstetric history to be routinely used in their risk stratification and prevention of cardiometabolic disease (53, 113). The findings of this study may be used to inform clinical prediction tools for physicians to stratify

which women need closer follow-up for CKD. The absolute risk of clinically significant kidney disease may remain low for exposed women, but a systematic approach may be warranted to identify and advise those who are at increased relative risk, particularly after HDP. However, further robust research is needed to overcome limitations of the existing literature, and to identify effective risk reduction interventions.

2.3.6 Conclusions

Women who experience adverse pregnancy outcomes may be at increased risk of future CKD and ESKD. The associations appear to be particularly marked for women with HDP. It is unclear whether adverse pregnancy outcomes unmask an existing predisposition toward kidney disease or induce endothelial or organ damage that alters a woman's trajectory toward development of kidney disease. There is a need to optimise long-term follow-up of these women, and to implement preventive interventions that reduce their risk of developing clinically significant kidney disease.

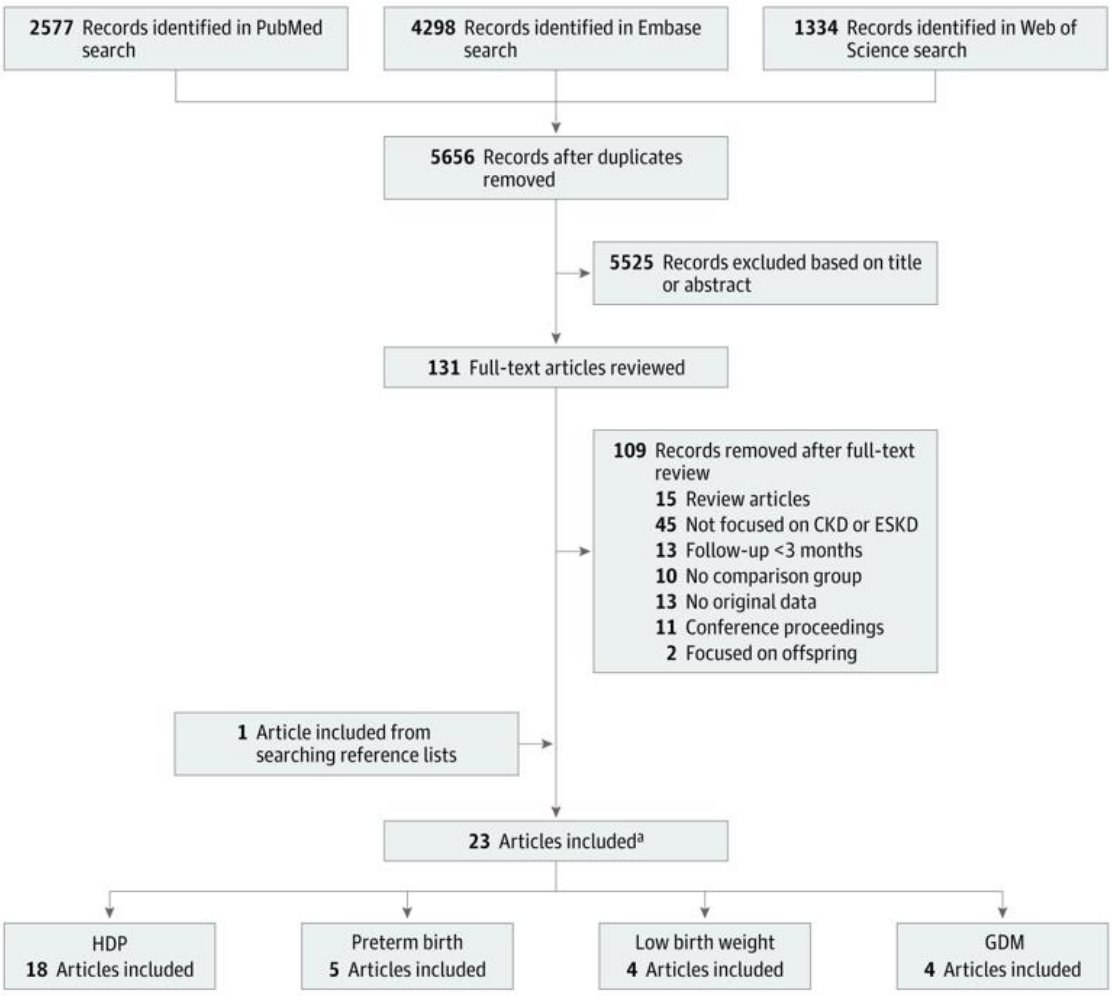


Figure 2.1 Flow diagram of studies selected for inclusion in the systematic review

CKD, indicates chronic kidney disease; ESKD, end-stage kidney disease; GDM, gestational diabetes mellitus; and HDP, hypertensive disorders of pregnancy.

[a]Five of the included studies contained effect estimates for more than 1 relevant adverse pregnancy outcome.

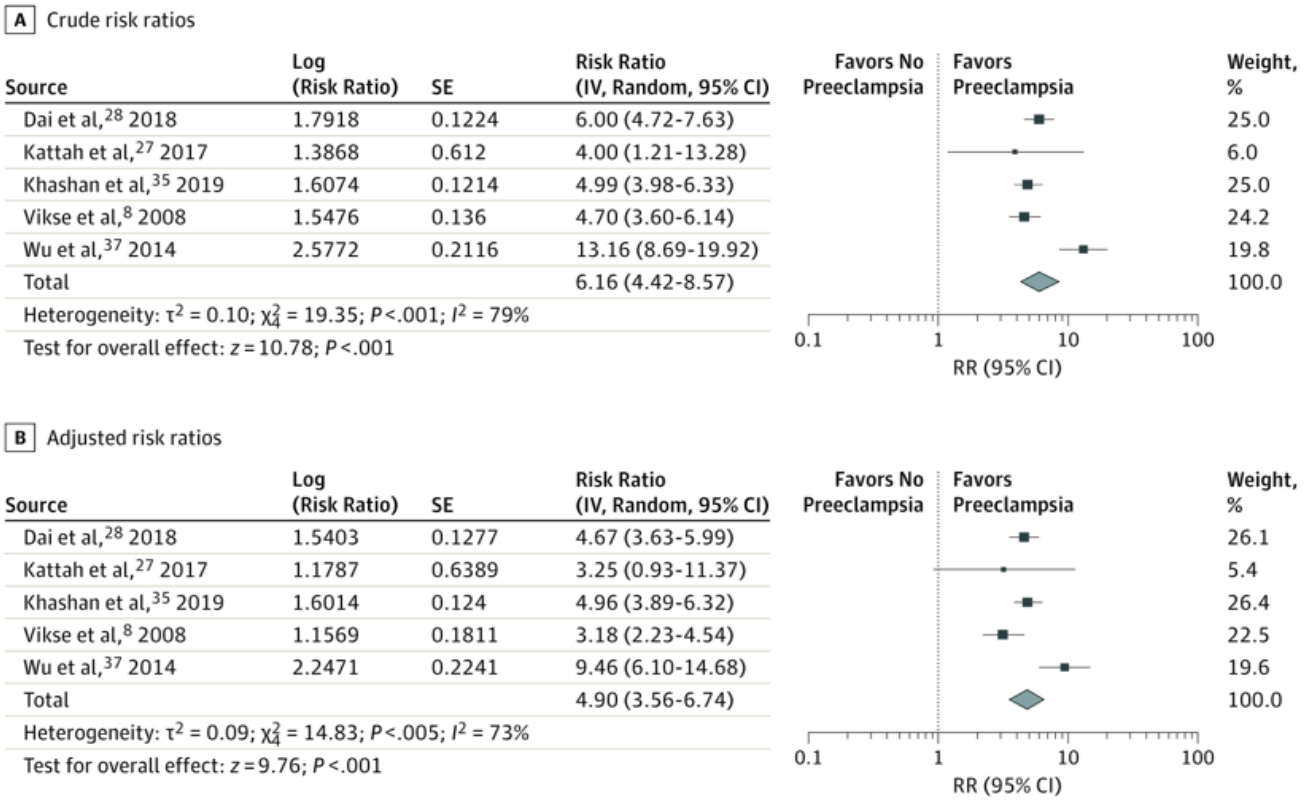


Figure 2.2 Forest plot for studies of the association of preeclampsia and end-stage kidney disease

Risk ratios (RRs) are calculated using random-effects meta-analysis. The area of the markers within the graph indicates the weight assigned to each study in the meta-analysis, while the horizontal line depicts the 95% CI. IV indicates inverse variance

Table 2.1 Summary results of meta-analyses

Exposure	Outcome	No. studies	References	Participants	No. outcomes	Pooled RR (95% CI)	I^2, %	Tau^2
Preeclampsia	**ESKD**							
	Crude	5	(28, 29, 31-33)	4,479,523	1,737	6.16 (4.42-8.57)	79%	0.10
	Adjusted (any)	5	(28, 29, 31-33)	4,479,523	1,737	4.90 (3.56-6.74)	73%	0.09
	Adjusted for comorbidities	5	(28, 29, 31-33)	4,479,523	1,737	4.90 (3.56-6.74)	73%	0.09
	CKD							
	Crude	3	(74, 87, 88)	1,097,495	4,699	2.27 (1.48-3.49)	80%	0.09
	Adjusted (any)	3	(74, 87, 88)	1,097,495	4,699	2.11 (1.72-2.59)	35%	0.01
	Adjusted for comorbidities	1	(74)	1,072,330	3,901	2.27 (2.02-2.55)	-	-
	Kidney-related hospitalisation							
	Crude	2	(21, 93)	131,224	468	1.79 (0.71-4.51)	92%	0.41
	Adjusted (any)	3	(21, 93, 98)	162,880	1,051	2.65 (1.03-6.77)	92%	0.62
	Adjusted for comorbidities	0	-	-	-	-	-	-
Gestational hypertension	**ESKD**							
	Crude	2	(31, 32)	2,542,517	806	4.37 (1.74-10.98)	67%	0.31
	Adjusted (any)	2	(31, 32)	2,542,517	806	3.64 (2.34-5.66)	7%	0.01
	Adjusted for comorbidities	2	(31, 32)	2,542,517	806	3.64 (2.34-5.66)	7%	0.01
	CKD							
	Crude	2	(87, 88)	25,165	798	1.56 (1.09-2.22)	55%	0.04
	Adjusted (any)	2	(87, 88)	25,165	798	1.49 (1.11-2.01)	40%	0.02
	Adjusted for comorbidities	0	-	-	-	-	-	-
	Kidney-related hospitalisation							
	Crude	2	(21, 87)	49,705	1,010	1.04 (0.92-1.17)	0%	0.00
	Adjusted (any)	2	(21, 98)	66,510	939	1.84 (0.60-5.67)	90%	0.60
	Adjusted for comorbidities	0	-	-	-	-	-	-
Chronic hypertension	**ESKD**							
	Crude	2	(31, 32)	2,542,517	806	16.87 (11.31-25.15)	0%	0.00
	Adjusted (any)	1	(31)	944,474	258	15.99 (5.89-43.41)	-	-
	Adjusted for comorbidities	1	(31)	944,474	258	15.99 (5.89-43.41)	-	-
	CKD							
	Crude	1	(88)	10,314	144	1.62 (0.88-3.00)-	-	-
	Adjusted (any)	1	(88)	10,314	144	1.23 (0.67-2.26)	-	-
	Adjusted for comorbidities	0	-	-	-	-	-	-

Table 2.1 (continued) Summary results of meta-analyses

Exposure	Outcome	No. studies	References	Participants	No. outcomes	Pooled RR (95% CI)	I^2, %	Tau^2
Superimposed preeclampsia	**ESKD**							
	Crude	2	(31, 32)	2,542,517	806	48.97 (26.09-91.93)	41%	0.09
	Adjusted (any)	1	(31)	944,474	258	44.72 (22.59-88.52)	-	-
	Adjusted for comorbidities	1	(31)	944,474	258	44.72 (22.59-88.52)	-	-
	CKD							
	Crude	1	(88)	10,314	144	1.56 (0.38-6.42)-	-	-
	Adjusted (any)	1	(88)	10,314	144	1.24 (0.28-5.49)	-	-
	Adjusted for comorbidities	0	-	-	-	-	-	-
Preterm delivery (no preeclampsia)	**ESKD**							
	Crude	3	(28, 32, 59)	2,169,957	1,073	3.21 (2.35-4.39)	57%	0.04
	Adjusted (any)	3	(28, 32, 59)	2,169,957	1,073	2.09 (1.64-2.66)	18%	0.01
	Adjusted for comorbidities	3	(28, 32, 59)	2,169,957	1,073	2.09 (1.64-2.66)	18%	0.01
	CKD							
	Crude	0	-	-	-	-	-	-
	Adjusted (any)	0	-	-	-	-	-	-
	Kidney-related hospitalisation							
	Crude	1	(94)	99,338	132	2.90 (2.00-4.20)	-	-
	Adjusted (any)	1	(94)	99,338	132	2.70 (1.80-3.90)	-	-
	Adjusted for comorbidities	0	-	-	-	-	-	-
Preterm preeclampsia	**ESKD**							
	Crude	3	(28, 29, 59)	1,938,355	935	7.66 (3.16-18.55)	86%	0.52
	Adjusted (any)	3	(28, 29, 59)	1,938,355	935	5.66 (3.06-10.48)	59%	0.17
	Adjusted for comorbidities	3	(28, 29, 59)	1,938,355	935	5.66 (3.06-10.48)	59%	0.17
	CKD							
	Crude	0	-	-	-	-	-	-
	Adjusted (any)	1	(74)	1,072,330	3,901	3.93 (2.90-5.33)	-	-
	Adjusted for comorbidities	1	(74)	1,072,330	3,901	3.93 (2.90-5.33)	-	-

Table 2.1 (continued) Summary results of meta-analyses

Exposure	Outcome	No. studies	References	Participants	No. outcomes	Pooled RR (95% CI)	I^2, %	Tau^2
Gestational diabetes	**ESKD**							
	Crude	0	-	-	-	-	-	-
	Adjusted (any)	0	-	-	-	-	-	-
	CKD							
	Crude	3	(91, 95, 96)	136,504	6,345	0.99 (0.66-1.49)	46%	0.06
	Adjusted (any)	2	(95, 96)	38,536	6,231	1.04 (0.76-1.41)	21%	0.01
	Adjusted for comorbidities	2	(95, 96)	38,536	6,231	1.04 (0.76-1.41)	21%	0.01
	Kidney-related hospitalisation							
	Crude	0	-	-	-	-	-	-
	Adjusted (any)	1	(93)	96,370	112	1.90 (1.10-3.20)	-	-
	Adjusted for comorbidities	0	-	-	-	-	-	-

Meta-analysis was based on the generic inverse variance (DerSimonian-Laird) method. Each study's sample risk ratio (RR) was entered in RevMan version 5.3, and the log(RR) was calculated from this. Then, based on the study's reported 95% confidence intervals (for the sample RR), RevMan calculated the standard error. RevMan uses information from the log(RR) and either the lower or upper 95% confidence interval to derive the standard error, and the value of the corresponding 95% confidence interval

Table 2.2 Characteristics of studies which investigate hypertensive disorders of pregnancy and subsequent maternal kidney disease

Author, year , *Sample size*	Country, *Follow-up*	Study design*, Data source	Exposure(s)	Outcome(s), *Measure of effect*	Exclusions	Confounders adjusted	Crude Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)
Dai, 2018 (32), *N= 1,598,043*	Canada, *median 15 years*	RC, Hospital records	HDP overall, GH, PE, CH, PE superimposed on CH, non-specific hypertension	ESKD hospitalisation, *HR*	Maternal age <15 or >44 years, multiple gestation, previous kidney disease, DM, GDM, SLE, HUS, thrombotic micro-angiopathy, hypertension secondary to kidney disease.	Maternal age, region, time period, obesity, preterm delivery, intrauterine death, foetal distress, placental disorders/abruption, oligohydramnios, prolonged pregnancy, postpartum haemorrhage, DVT, cardiac disease, blood transfusion, caesarean delivery	HDP overall, 5.8 (4.8–7.0); GH, 3.0 (1.9-4.7); PE, 6.0 (4.7-7.6); CH, 15.6 (10.1-24.2); PE superimposed on CH, 35.2 (17.5-70.8); non-specific, 5.0 (3.0-8.4)	GH, 3.27 (2.10-5.09); PE, 4.67 (3.63-5.99); non-specific, 4.60 (2.75-7.71)
Kattah, 2017 (33), *N= 132*	USA, *median 18 years*	CC, US Renal Data System	HDP overall, PE	ESKD, *OR*	Previous ESKD	Obesity, ethnicity/race, education, pre-pregnancy hypertension, DM	HDP overall, 3.34 (1.32-8.47); PE, 4.0 (1.21–13.28)	PE, 3.25 (0.93 −11.37) *(Adjusted only for obesity)*
Sandvik, 2010 (59), *N= 1,481*	Norway, *up to 37 years*	RC, Norwegian Renal Registry	PE	ESKD, *RR*	Multiple deliveries, previous kidney disease, hypertension. *All included women had pre-existing diabetes.*	Year of birth, age, marital status, stillbirth, congenital malformations of offspring, Caesarean section in first pregnancy	PE, 1.3 (0.41-4.4); Preterm PE, 2.8 (1.3-6.0)	PE, 1.3 (0.3-5.6); Preterm PE, 2.9 (1.3-6.4)
Vikse, 2008 (28), *N= 570,433*	Norway, *mean 27 years*	RC, Norwegian Renal Registry	PE	ESKD, *RR*	Multiple pregnancies, previous kidney disease, hypertension, rheumatic disease or DM	Year of delivery, maternal age, marital status, stillbirth, congenital malformation of infant	4.7 (3.6–6.1)	3.2 (2.2-4.5)
Vikse, 2010 (85), *N= 582*	Norway, *up to 16 years*	RC, Norwegian Renal Registry	PE	ESKD, *RR*	None specified. *Study restricted to women who previously underwent kidney biopsy for suspected kidney damage.*	Age, eGFR, proteinuria, diastolic blood pressure, duration of kidney disease, interstitial fibrosis and inflammation	1.2 (0.63–2.4)	1.1 (0.50–2.6)
Vikse, 2012 (86), *N= 570,675*	Norway, *mean 20 years*	RC, Norwegian Renal Registry	PE	ESKD, *RR*	Previous kidney disease, hypertension, rheumatic disease, or DM	Maternal age, marital status, number of siblings, maternal education	PE without maternal sibling with PE, 5.95 (4.37- 8.11); PE with maternal sibling with PE, 2.76 (0.88-8.63)	PE without maternal sibling with PE, 2.88 (1.69-4.90)
Wu, 2014 (31), *N= 944,474*	Taiwan, *median 9 years*	RC, National Health Insurance Research Database	HDP overall, PE, GH, CH, PE superimposed on CH	ESKD, *HR*	Previous kidney disease, DM, thrombotic micro-angiopathy, HUS, SLE, hypertension secondary to kidney disease, women with HDP in more than one pregnancy.	Maternal age, mode of delivery, number of deliveries, complications (i.e. early delivery, threatened labour, threatened premature labour)	HDP overall, 15.23 (11.07-20.95); GH 7.85 (2.92-21.1); PE, 13.16 (8.69-19.92); CH, 25.02 (9.31-67.29); PE superimposed on CH, 66.95 (34.36-130.44)	HDP overall, 10.64 (7.53-15.05); GH, 5.82 (2.15-15.77); PE, 9.46 (6.10-14.68); CH, 15.99 (5.89-43.38); PE superimposed on CH, 44.72, (22.59-88.51)

Table 2.2 (continued) Characteristics of studies which investigate hypertensive disorders of pregnancy and subsequent maternal kidney disease

Author, year, *Sample size*	Country, *Follow-up*	Study design*, Data source	Exposure(s)	Outcome(s), *Measure of effect*	Exclusions	Confounders adjusted	Crude Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)
Khashan, 2019 (29), *N= 1,366,441*	Sweden, *median 7 years*	RC, Swedish Renal Registry	PE	ESKD, *HR*	Multiple births, previous kidney disease, CVD, hypertension or DM	Maternal age, BMI, education, country of origin, smoking	Overall PE, 4.99 (3.93-6.33); Preterm PE, 9.19 (5.16-16.35)	Overall PE, 4.96 (3.89-6.32); Preterm PE, 8.76 (4.91-15.61)
Wang, 2013 (30), *N= 240,048*	Taiwan, *mean 6 years*	RC, National Health Insurance Research Database	HDP overall, PE, GH	CKD, ESKD, *HR*	Previous kidney disease, hypertension, SLE or DM	Urban status, coronary artery disease, congestive heart failure, hyperlipidemia, hypertension, DM, placental abruption	[1] For CKD - HDP overall, 10.8 (8.20–14.2) [2] For ESKD - HDP overall, 14.1 (9.76–20.3); PE, 15.9 (10.8-23.3); GH, 10.2 (5.89-17.6)	[1] For CKD - HDP overall, 9.38 (7.09–12.4) [2] For ESKD - HDP overall, 2.72 (1.76–4.22); PE, 3.19 (2.02-5.02); GH, 1.81 (0.99-3.30)
Kristensen, 2019 (74), *N= 1,072,330*	Denmark, *mean 19 years*	RC, Multiple linked national registers	PE	CKD, *HR*	Age <15 years, previous kidney disease, CVD, autoimmune disease, hypertension or DM	Maternal age, year, parity, GH, CH, gestational length, postpartum autoimmune disease, CVD, or DM.	Term PE, 3.00 (2.67-3.37)	Term PE, 2.27 (2.02-2.55); early preterm PE, 3.93 (2.90-5.33); late preterm PE, 2.81 (2.13-3.71);
Mannisto, 2013 (88), *N= 10,314*	Finland, *mean 39 years*	RC, Multiple linked national registers	PE, GH	CKD, *HR*	Missing blood pressure data, death in first year postpartum, multiple gestation, two completed pregnancies within same study year	Pre-pregnancy BMI, smoking, parity, DM, socioeconomic status. (Age used as time scale)	PE, 0.74 (0.18-3.03); GH, 2.02 (1.25-3.26); PE superimposed on CH, 1.56 (0.38-6.42); CH, 1.62 (0.88-3.00)	PE, 0.75 (0.17-3.38); GH, 1.91 (1.18-3.09); PE superimposed on CH, 1.24 (0.28-5.44); CH, 1.23 (0.67-2.24)
Oishi, 2017 (90), *N= 312*	Japan, *mean 31 years*	RC, Maternity health records	HDP	CKD, *OR*	Women with incomplete antenatal records or <5 blood pressure readings.	Maternal age, BMI, hypertension, dyslipidemia, DM, smoking	6.48 (1.60-26.30)	4.86 (1.04-22.62)
Paauw, 2018 (89), *N= 2,782*	Netherlands, *median 11 years*	PC, Participants in PREVEND cohort study	HDP	CKD, *HR*	Women unaware of their history of pregnancy disorders		1.04 (0.79-1.37)	Not reported
Ayansina, 2016 (87), *N= 14,851*	Scotland, *30-40 years*	RC, Multiple linked regional & national registers	PE, GH	CKD, Kidney-related hospitalisation, *OR*	Previous kidney disease, hypertension, multiple pregnancy, temporary residents	Maternal age, BMI, socio-economic status, smoking.	[1] For CKD - GH, 1.37 (1.15-1.64); PE, 2.02 (1.53-2.67). [2] For hospitalisation - GH, 1.08 (0.84-1.40); PE, 1.42 (0.93-2.17)	[1] For CKD - GH, 1.36 (1.14-1.63); PE, 1.92 (1.45-2.56). [2] For hospitalisation - GH, 1.02 (0.78-1.32); PE, 1.37 (0.90-2.10)

Table 2.2 (continued) Characteristics of studies which investigate hypertensive disorders of pregnancy and subsequent maternal kidney disease

Author, year, *Sample size*	Country, *Follow-up*	Study design*, Data source	Exposure(s)	Outcome(s), *Measure of effect*	Exclusions	Confounders adjusted	Crude Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)
Kessous, 2015 (93), *N= 96,370*	Israel, *mean 11 years*	RC, Clinical records at single institution	PE	Kidney-related hospitalisation, *HR*	Previous cardiovascular or kidney disease, congenital cardiac or kidney malformations, multiple pregnancy	Maternal age, parity, obesity, DM, smoking	2.93 (1.85-4.64)	3.7 (2.3-6.0)
Bhattacharya, 2012 (21), *N=34,854*	Scotland	RC, Multiple linked regional & national registers	PE, GH	Kidney-related hospitalisation, Kidney-related deaths, *OR*	Previous hypertension, multiple pregnancy	Year of birth, smoking status, social class at time of first pregnancy	(1) Hospitalisation - PE, 1.14 (0.89-1.46); GH, 1.03 (0.90-1.18) (2) Deaths - PE, 1.73 (0.52,5.81); GH, 1.71 (0.86,3.41)	(1) Hospitalisation - PE, 1.20 (0.93-1.54); GH, 1.09 (0.95-1.25) (2) Deaths - PE, 1.72 (0.51,5.79); GH, 1.81 (0.90,3.62)
Tooher, 2017 (98), *N=31,656*	Australia, *20-29 years*	RC, Regional census of all hospital admissions	HDP in 4 groups: PE, GH, CH, PE superimposed on CH	Kidney-related hospitalisation, *OR*	Women whose HDP could not be categorised in one of the 4 groups	Maternal age, gestation at delivery, parity.	Not reported	Overall HDP, 2.76 (1.98-3.84); PE, 4.74 (2.19-10.20); GH, 3.45 (1.74-6.85)
Tooher, 2016 (97), *N=31,656*	Australia, *20-29 years*	RC, Regional and national death registries	HDP in 4 groups: PE, GH, CH, PE superimposed on CH	Kidney-related deaths, *OR*	Not reported	Maternal age, gestation at delivery, parity	Overall HDP, 1.72 (0.91-3.25)	Not reported

*CC, case control; PC, prospective cohort; RC, retrospective cohort

BMI, body mass index; CH, chronic hypertension; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GDM, gestational diabetes mellitus; GH, gestational hypertension; HDP, hypertensive disorders of pregnancy; HR, hazard ratio; HUS, haemolytic uraemic syndrome; IUGR, intra-uterine growth restriction; OR, odds ratio; PE, preeclampsia; RR, risk ratio; SLE, systemic lupus erythematosus

Table 2.3 Characteristics of studies which investigate preterm delivery and subsequent maternal kidney disease

Author, year, *Sample size*	Country, *Follow-up*	Study design*, Data source	Exposure(s)	Outcome(s)	Exclusions	Confounders adjusted	Crude Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)
Dai, 2018 (32), *N= 1,598,043*	Canada, *median 15 years*	RC, Hospital records	Preterm delivery	ESKD hospitalisation	Maternal age <15 or >44 years, multiple gestation, previous kidney disease, DM, GDM, SLE, HUS, thrombotic micro-angiopathy, hypertension secondary to kidney disease.	Maternal age, region, time period, obesity, preterm delivery, intrauterine death, foetal distress, placental disorders/abruption, oligohydramnios, prolonged pregnancy, postpartum haemorrhage, DVT, cardiac disease, blood transfusion, caesarean delivery	Not reported	2.36 (1.81–3.08)
Sandvik, 2010 (59), *N=1,481*	Norway, *up to 37 years*	RC, Norwegian Renal Registry	Preterm delivery	ESKD	Multiple deliveries, previous kidney disease, hypertension. All included women had pre-existing diabetes.	Year of birth, age, marital status, stillbirth, congenital malformations of offspring, Caesarean section in first pregnancy	1.9 (1.1-3.4)	1.4 (0.71-2.6)
Vikse, 2008 (28), *N=570,433*	Norway, *mean 27 years*	RC, Norwegian Renal Registry	PE	ESKD	Multiple pregnancies, previous kidney disease, hypertension, rheumatic disease or DM	Year of delivery, maternal age, marital status, stillbirth, congenital malformation of infant	3.8 (2.9-4.9)	2.0 (1.4-3.0)
Vikse, 2010 (85), *N=582*	Norway, *up to 16 years*	RC, Norwegian Renal Registry	Preterm delivery	ESKD	None specified, but study restricted to women who underwent renal biopsy for suspected renal damage	Maternal age, eGFR, proteinuria, diastolic blood pressure, duration of renal disease, interstitial fibrosis and inflammation	2.1 (1.2–3.9)	2.4 (1.2–4.6)
Pariente, 2017 (94), *N=99,338*	Israel, *mean 11 years*	RC, Clinical records at single institution	Preterm delivery	Renal hospitalisation	Previous renal disease, congenital renal malformations	PE, DM, indicated preterm delivery (due to severe PE, severe IUGR, cord prolapse or placental abruption)	Overall preterm delivery, 2.9 (2.0-4.2); spontaneous preterm, 2.6 (1.7-3.9); induced preterm, 4.2 (2.0-9.1); indicated preterm 3.4 (1.7-6.5)	Overall preterm delivery, 2.7 (1.8-3.9); indicated preterm, 1.2 (0.7-1.9)

*RC, retrospective cohort

CI, confidence interval; DM, diabetes mellitus; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; IUGR, intra-uterine growth restriction; OR, odds ratio; PE, preeclampsia

Table 2.4 Characteristics of studies which investigate delivery of a low birth weight or small for gestational age infant and subsequent maternal kidney disease

Author, year *Sample size*	Country, *Follow-up*	Study design*, Data source	Exposure(s)	Outcome(s)	Exclusions	Confounders adjusted	Crude Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)
Vikse, 2008 (28), *N= 570,433*	Norway, *mean 27 years*	RC, Norwegian Renal Registry	Low birth weight	ESKD	Multiple pregnancies, previous kidney disease, hypertension, rheumatic disease or DM	Year of delivery, maternal age, marital status, stillbirth, congenital malformation of infant	In women with no PE, 4.0 (3.0–5.2); women with PE, 12.0 (8.2–17.6)	In women with no PE, 2.7 (1.8–3.8); women with PE, 6.8 (3.9–12.0)
Vikse, 2010 (85), *N=582*	Norway, *up to 16 years*	RC, Norwegian Renal Registry	Low birth weight	ESKD	None specified, but study restricted to women who underwent renal biopsy for suspected renal damage	Maternal age, eGFR, proteinuria, diastolic blood pressure, duration of renal disease, interstitial fibrosis and inflammation	1.7 (0.92–3.2)	1.7 (0.83–3.6)
Dai, 2018 (32), *N=1,598,043*	Canada, *median 15 years*	RC, Hospital records	IUGR	ESKD hospitalisation	Maternal age <15 or >44 years, multiple gestation, previous kidney disease, DM, GDM, SLE, HUS, thrombotic micro-angiopathy, hypertension secondary to kidney disease.	Maternal age, region, time period, obesity, preterm delivery, intrauterine foetal death, foetal distress, placenta disorders/abruption, oligohydramnios, prolonged pregnancy, postpartum haemorrhage, deep vein thrombosis and cardiac disease, blood transfusion, caesarean delivery	Not reported	1.91 (1.34–2.71)
Almasi, 2016 (92), *N= 99,342*	Israel, *mean 11 years*	RC, Clinical records at a single institution	SGA	Renal hospitalisation	Women with multiple pregnancies, pre-existing kidney disease, DM, hypertension, not engaged in antenatal care	GDM, number of pregnancies	1.6 (1.02-2.60)	1.79 (1.10-2.80)

*RC, retrospective cohort

CI, confidence interval; DM, diabetes mellitus; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GDM, gestational diabetes mellitus; IUGR, intra-uterine growth restriction; OR, odds ratio; PE, preeclampsia; SGA, small for gestational age; SLE, systemic lupus erythematosus

Table 2.5 Characteristics of studies which investigate gestational diabetes and subsequent maternal kidney disease

Author, year, *Sample size*	Country, *Follow-up*	Study design*, Data source	Exposure(s)	Outcome(s)	Exclusions	Confounders adjusted	Crude Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)
Kessous, 2015 (93), *N= 96,370*	Israel, *mean 11 years*	RC, Clinical records at single institution	GDM	Renal hospitalisation	Previous cardiovascular or renal disease, congenital cardiac or renal malformations, multiple pregnancy	Maternal age, parity, obesity, smoking. (Unclear whether adjusted for interim DM)	Not reported	3.7 (2.3-6.0)
Dehmer, 2018 (95), *N= 820*	USA, *mean 21 years*	PC, Participants in CARDIA cohort study	GDM	CKD	Previous CKD, DM, women missing measures of baseline CKD/albuminuria/ eGFR, women missing data on covariates	Maternal age, systolic blood pressure, dyslipidemia, BMI, smoking, education, eGFR, fasting glucose, physical activity level, race, family history DM. (DM treated as mediating factor)	1.46 (0.87-2.45)	For all: 1.33 (0.78-2.26) Black: 1.96 (1.04-3.67) White: 0.65 (0.23-1.83)
Beharier, 2015 (91), *N= 97,968*	Israel, *mean 11 years*	RC, Clinical records at a single institution	GDM	Renal-related hospitalisation, CKD, ESKD	Multiple pregnancies, previous kidney disease, pregnancies with missing data on key variables relating to prenatal care	Maternal age, parity. (No data on interim DM)	For total renal morbidity: 2.34 (1.4-3.7). For CKD, 0.73 (0.3-2.2). For ESKD, 1.14 (0.2-5.9)	For total renal morbidity 1.70 (1.05-2.60)
Bomback, 2010 (96), *N= 37,716*	USA	PC, Participant records from community screening programme	GDM	CKD (Stages 1-2, & stages 3-5)	Women with previous ESKD	Maternal age, race, BMI, current smoking, alcohol use, hypertension, dyslipidemia, family history of kidney disease. (Stratified by DM status)	Among those without subsequent DM: CKD stages 1-2, 1.54 (1.16–2.05); stages 3-5, 0.84 (0.65–1.09).	Among those without subsequent DM: CKD stages 1–2, 1.54 (1.16–2.05); White, 1.12 (0.68-1.84); African-American, 2.32 (1.50-3.60); CKD stages 3-5, 0.94 (0.71-1.25); White 0.83 (0.58-1.19); African-American 1.66 (0.96-2.88)

*PC, prospective cohort; RC, retrospective cohort

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GDM, gestational diabetes mellitus; OR, odds ratio; PE, preeclampsia

CHAPTER 3 Methods

3.1 Chapter overview

This chapter is comprised of a detailed description of the methods used in this research. Firstly, the Swedish health system and its national registers are described, with information given on how ethical approval was obtained for use of the data. Secondly, a description of the study population is given, including an overview of the study design and relevant exclusions. Thirdly, the definitions of exposure and outcome variables are presented, including a discussion of how variables were identified from the national registers, coded and categorised. Fourthly, key epidemiological considerations are described, including the potential impact of bias, confounding, chance findings, and missing data on each study. Finally, the statistical methods are presented, including justification for the chosen tests and assumptions associated with these methods.

3.2 Swedish health system and national registers

3.2.1 Swedish health system

Funding and structure

Sweden spends about 11.0% of GDP on health, placing it third highest among countries in the European Union (EU) for healthcare expenditure. Most of this (84%) is public expenditure, and voluntary health insurance plays only a small role in healthcare funding (114). Universal healthcare coverage is largely achieved, with full coverage provided for all legal residents, mainly funded through taxation. A small minority of Swedish citizens (6%) hold supplementary

private health insurance, mostly covered by employers to provide faster access to specialist care or elective treatment if needed.

Overall health

Overall, the health of the Swedish population is considered to be very good by international standards. The Swedish population enjoy a high life expectancy (84.1 years for women) and the highest *healthy* life expectancy of any country in the EU. The leading causes of death are CVD, stroke and dementia. The prevalence of smoking among adults is the lowest in the EU (12%) and is decreasing. Per capita alcohol consumption is the lowest in Europe. The prevalence of obesity among adults (13%) is increasing, but remains below the EU average (114). Low levels of preventable deaths in Sweden have been partially attributed to strong public health policies and public awareness campaigns spanning many years. Nonetheless, health inequalities persist, and risk factors such as smoking, obesity and alcohol consumption are more prevalent among lower-income and less educated groups.

Maternity care

Maternity care is publicly funded and free at the point of access. It is provided mainly in publicly owned facilities (115). Antenatal care is largely organised at primary care level and provided by midwives for healthy women. Those with high-risk pregnancies receive joint antenatal care from obstetricians and midwives with planned care pathways and follow-up. Midwives are responsible for most births among healthy women, but all have access to specialist obstetricians if required. Less than 1% of births are home births (115).

3.2.2 Swedish national population registration system

The Swedish national population registration system has its roots in the 17th century when the Swedish Church began recording information on its members for conscription purposes (116). In 1968, the Total Population Register (TPR) was established after a large amount of population data was computerised for the first time, and the TPR is now maintained by *Statistics Sweden* (117). The aim of the TPR is to obtain data which reflects the composition, relationships and identities of the population in order to inform national decision-making by the Swedish government and other organisations (e.g. relating to taxation). The TPR is regularly used for medical research because the data cover almost all births and deaths in Sweden and over 90% of immigrations and emigrations. The quality of data is regarded to be very high because of its high level of completeness and the ability to link individual registers together, allowing for representative population-based studies covering long periods of time (117).

It has been suggested that the main limitation of the TPR may be inaccurate coverage. Under-coverage is possible due to the temporary or unofficial status of some immigrants in the country. Over-coverage is also possible where individuals have emigrated or died abroad, if Swedish government agencies have not been informed. It is estimated that this affects <1% of the registered total population (117).

3.2.3 Swedish personal identity number

The Swedish personal identity number (PIN) was first introduced in 1947 and it is assigned to every individual upon registration of their birth or immigration in to Sweden if they are staying for at least one year. It is a unique 10-digit number, of which the first six digits are the individual's date of birth. All registers in the national population registration system use the

same PIN. This allows records to be linked across different registers and it allows individuals to be followed over time. The PIN reduces the risk of duplication errors in medical records and allows the natural course of an individual's disease to be tracked across different services (116). Immigrants who stay in Sweden for less than one year are assigned a temporary PIN, but they are not included in the TPR (117).

3.2.4 Medical Birth Register

The Medical Birth Register (MBR) was founded in 1973 and it includes data on over 96% of all births in Sweden. The MBR collects data on antenatal care, delivery, neonatal outcomes, maternal sociodemographic factors, medical and obstetric diagnoses, and lifestyle factors. It is compulsory for maternity healthcare providers to report to the MBR, but data on approximately 1-4% of births are either missing or incomplete (118).

Although there have been some modifications to the content and methods of data collection, the basic structure of the MBR and its key variables have remained largely unchanged since its inception (117). From 1973 to 1981 inclusive, medical secretaries based in obstetric clinics collected the data using standardised forms, and these were sent to the National Board of Health and Welfare in Sweden (*Socialstyrelsen*). However, from 1982 onwards the content of the MBR was retrieved directly from medical records (i.e. antenatal records, delivery records, and infant examination records respectively) to prevent possible discrepancies during data transfer. Additional variables on maternal smoking and body mass index (BMI) were also collected from this time onwards (118).

3.2.5 National Patient Register

The National Board of Health and Welfare began collecting information about in-patients in Swedish hospitals in 1964. The National Patient Register (NPR) began with only 16% national

coverage, but this gradually increased to 85% of inpatient admissions by 1983. In 1984, it became mandatory for all hospitals and governing county councils to participate and by 1987, national coverage had been achieved for all in-patient care (119, 120). The extent to which a condition has been reported and recorded in the NPR depends on a number of factors including individual care-seeking behaviour, ease of access to healthcare, and the likelihood of a physician to admit a patient (119).

For each hospital discharge, the following information is recorded: personal patient-related data (PIN, age, sex), hospital data, administrative data (admission and discharge dates), and medical information (main diagnosis, secondary diagnoses, procedures etc.). The quality of inpatient data in the NPR has been reported to be high, and under-reporting of admissions is estimated at less than 1% (119). The data have been validated in a large number of studies, and positive predictive values (PPV) of most inpatient diagnoses range from 85-95% (119).

In 2001, the NPR was expanded to cover outpatient visits to both public and private healthcare facilities. Data coverage has improved over time (120, 121), and in 2010 it was estimated that coverage from public healthcare providers was almost 100%, but coverage from private healthcare providers was lower at about 80% (119). Primary healthcare data and prescription data are not reported in the NPR.

3.2.6 Swedish Renal Register

The Swedish Renal Register (SRR) is a nationwide register of patients with CKD stages 3-5, and those on renal replacement therapy (RRT), who are followed at any nephrology clinic in Sweden (122). It was first established in 1991 and was initially restricted to patients receiving RRT. In 2007, the SRR was expanded to include those with stage 3-5 CKD (123). The register aims to monitor the underlying causes of CKD, record treatment modalities, and evaluate key

components of care for patients with CKD and ESKD. The SRR also records the progression of CKD, including the need for RRT (124).

Information is mainly recorded in the SRR on outpatient visits for patients with CKD once they reach an eGFR <30 mL/min/1.73 m^2 (i.e. stage 4-5 CKD). Nephrology units are also encouraged to include patients who are earlier in the course of their disease (eGFR 30–60 mL/min/1.73 m^2, i.e. stage 3 CKD) but this is not mandatory.

To date, more than 30,000 patients have been registered in the SRR (124). All 68 renal units in Sweden providing specialised nephrology care report to it (125), and validation studies have shown high levels of reporting of ESKD patients in particular (122, 126). The SRR contains data on over 97% of patients with renal transplant, and over 95% of dialysis patients in Sweden. However, its coverage of CKD patients is lower (123).

3.2.7 Swedish Death Register

The Swedish Death Register contains data from 1961 onwards. It includes information about deceased individuals (PIN, age, sex), their cause of death, and the date and place of their death. This information is primarily collected from death certificates filled in by physicians (127). The register has a high level of completeness, and includes virtually all deaths in Sweden. Of these, over 96% have a cause of death recorded. The remainder may have missing information either due to an incomplete or insufficiently detailed death certificate (128).

Although the quality of data in this register is high, the main source of uncertainty is the determination of the cause of death in some patients. The process for identifying the cause of death can be complex, and the physician certifying the death is required to separate any conditions that contributed to the death from any comorbidities that did not contribute. This can be especially difficult in older people who may have multiple comorbidities (127, 128).

3.2.8 Swedish Migration Register

Each year *Statistics Sweden* uses information from the TPR to produce the Migration Register. This includes information on the person's date of entry in the population registers and their country of origin (for immigrants), or date of deregistration from the national registers (for emigrants). It is estimated that the TPR contains information on 95% of immigrations and 91% of emigrations within 30 days of migrating, and these figures increase over time (117).

Individuals who leave the country for at least one year are obliged to report their move, and by doing so they become deregistered. However, knowledge about this obligation is limited and compliance is suboptimal. This can lead to under-reporting of emigration and over-coverage in the TPR (129). Underreporting of emigration data is estimated to account for up to 0.5% of the total registered population in Sweden (117).

3.2.9 Swedish Register of Education

The Register of Education contains data on educational background such as an individual's highest education level and completion year, and demographic factors including age, sex, and municipality of residence. The Register uses information from the 1970 and 1990 censuses, and is updated with graduation/examination data from more than 30 sources, including primary and secondary school systems, universities, the military academy, agriculture schools, universities outside of Sweden, and employment agency databases (130). Data on immigrants' education comes primarily from surveys targeted to new immigrants arriving in Sweden and from population and housing censuses. The Register of Education has national coverage, but the quality of data has improved since the 1990 census (131).

3.2.10 Data access and ethics

Anonymised personal data may be obtained from *Statistics Sweden* and delivered to researchers after appropriate approval by an ethical review authority. The PINs are removed from merged data and these are replaced by unique anonymous serial numbers before being delivered to researchers (119). The researchers must agree never to back-track the identity of patients in the anonymised dataset. These precautionary measures are widely accepted as being sufficient to protect patient confidentiality. Informed consent is not required, and would not be feasible, when performing population-based research using the Swedish national registers (132).

Ethical approval was granted to conduct the research in this thesis by the Swedish Ethical Review Authority in Stockholm (*Regionala Etikprövningsnämnden Stockholm*; reference number 2012/397-31/1) (Appendix 5). Merging of individual datasets was only possible using the anonymous serial number (lpnr) which had been derived from each participant's PIN before the research team received the data. Thus, no individuals were identifiable from any of the datasets.

To ensure compliance with the General Data Protection Regulation in Ireland, ethical approval was also sought from the Social Research and Ethics Committee, University College Cork, and this was granted (reference number 2019-109) (Appendix 5).

3.3 Study design

Chapters 4, 5, 6 and 7 are comprised of separate population-based cohort studies using the Swedish national registers. The studies in this thesis were informed by the systematic review undertaken in Chapter 2, which identified limitations in the existing literature and gaps in knowledge which warranted further research. These observational studies aimed to examine

whether individual adverse pregnancy outcomes (i.e. preterm delivery, stillbirth, HDP, gestational diabetes) were associated with the long-term risk of maternal CKD and ESKD respectively.

It takes several years for most people to develop CKD or ESKD, and most affected women are diagnosed a long time after pregnancy. Thus, long periods of follow-up are required to investigate these associations. Although CKD is relatively common, it is often under-diagnosed, and ESKD is considered a rare outcome.

Randomised controlled trials of adverse pregnancy outcomes are neither feasible nor ethical, and therefore the research questions in this thesis can only be answered using observational research. Cross-sectional studies provide no information on temporality, and the research hypothesis herein assumes that adverse pregnancy outcomes precede CKD/ESKD diagnosis. Population-based cohort studies and case-control studies were both considered as possible study designs, and they each have strengths and limitations.

Case-control studies are retrospective in design, where individuals with the outcome of interest are identified, suitable matched controls are sought, and past exposures are examined. Case-control studies have the advantage of being faster to conduct than prospective cohort studies, and they are less expensive, particularly when investigating associations with rare outcomes like ESKD. However, they are highly prone to selection bias, particularly when recruiting controls. Careful matching is needed to minimise confounding, and residual confounding often persists. Recall bias is another key limitation, and this can be particularly problematic if several years have elapsed between exposure (for example during pregnancy several years ago) and outcome. Furthermore, case-control studies cannot be used to measure the incidence or risk of an outcome.

Cohort studies involve recruitment of participants at baseline, where nobody has the outcome of interest. They are followed up over time to identify those who develop the outcome.

Population-based cohort studies are nationally representative, and thus selection bias is not a major concern unless there are high levels of attrition. It is possible to collect information on multiple potential confounders at baseline and during follow-up, and to adjust for these in the analysis phase of the study. Residual confounding remains a possibility, but it is less of a concern than in case-control studies. It is also possible to measure the incidence or risk of an outcome.

Prospective cohort studies tend to be very lengthy with long follow-up periods. They are expensive and generally less suited to studies with rare outcomes. By contrast, retrospective cohort studies use pre-existing data when the exposure and outcome of interest has already occurred in some individuals. Retrospective cohort studies are constrained by the fact that data on potential confounders are usually limited to the information already contained within the dataset. However, they help to overcome much of the time and cost-related barriers of prospective cohort studies.

In this thesis, each original observational study used a population-based cohort design. Although data were recorded prospectively, thereby limiting the possibility of recall bias, the studies were retrospective in nature since variables were limited to whatever was already available in the Swedish national registers.

Thus, the decision to use retrospective population-based cohort studies was based on the following: (1) Large-scale nationally representative data were available through the Swedish national registers with high levels of completeness, reducing the time and costs involved in data collection. (2) The national registers contain information on a wide range of socio-demographic, medical and obstetric factors, allowing adjustment for several potential confounders. (3) Long periods of follow-up were available, allowing sufficient time for women to have been diagnosed with CKD or ESKD. (4) A large sample size could be obtained allowing sufficient statistical power to investigate associations, particularly for rare outcomes like ESKD.

(5) The unique PIN assigned to every resident in Sweden allowed individuals' medical records to be linked across multiple separate registers, allowing for a more accurate overview of study participants and their characteristics.

3.4 Study cohort

3.4.1 Timeline

The MBR was established in 1973 and this marks the beginning of the timeframe for inclusion in this research. Data were available from the MBR until the 31st December 2012, and a minimum follow-up period of one year was sought for included women. Data from the NPR and SRR were available until the 31st December 2013. The timeline is outlined in Figure 3.1. The studies in Chapters 4, 5 and 6 considered all women who gave birth in Sweden between 1st January 1973 and 31st December 2012 eligible for inclusion.

Definitions of exposure and outcome variables were largely based on *International Classification of Disease* (ICD) coding, and the iterations of these changed over time. Further information on this is provided in section 3.5.1. The study in Chapter 7, focusing on GDM, only considered women who gave birth in Sweden between 1st January 1987 and 31st December 2012 because GDM could not be reliably ascertained from the national registers using ICD-8 coding.

Data from the NPR pre-dated the MBR because this was established in 1964. Some women appeared in the NPR with identifiable medical or obstetric comorbidities prior to their first birth in the MBR. We considered this information when applying exclusions in each study (section 3.4.2).

3.4.2 Exclusions

Women who have underlying medical conditions are more likely to be diagnosed with adverse pregnancy outcomes like preeclampsia, gestational hypertension, preterm delivery, stillbirth, or GDM. Many comorbidities are also associated with an increased risk of developing CKD or ESKD in later life. Thus, when investigating associations between individual pregnancy complications and long-term risk of CKD/ESKD, we excluded women with underlying comorbidities at baseline if they were considered potential confounders of the exposure-outcome association. The exact confounders differed for each exposure-outcome association, but all studies excluded women with pre-pregnancy CKD/ESKD, chronic hypertension, CVD, diabetes (type 1 or 2), or systemic lupus erythematosus at baseline. Women with systemic sclerosis, vasculitides, coagulopathies, and haemoglobinopathies were also excluded from the studies outlined in Chapters 5, 6 and 7.

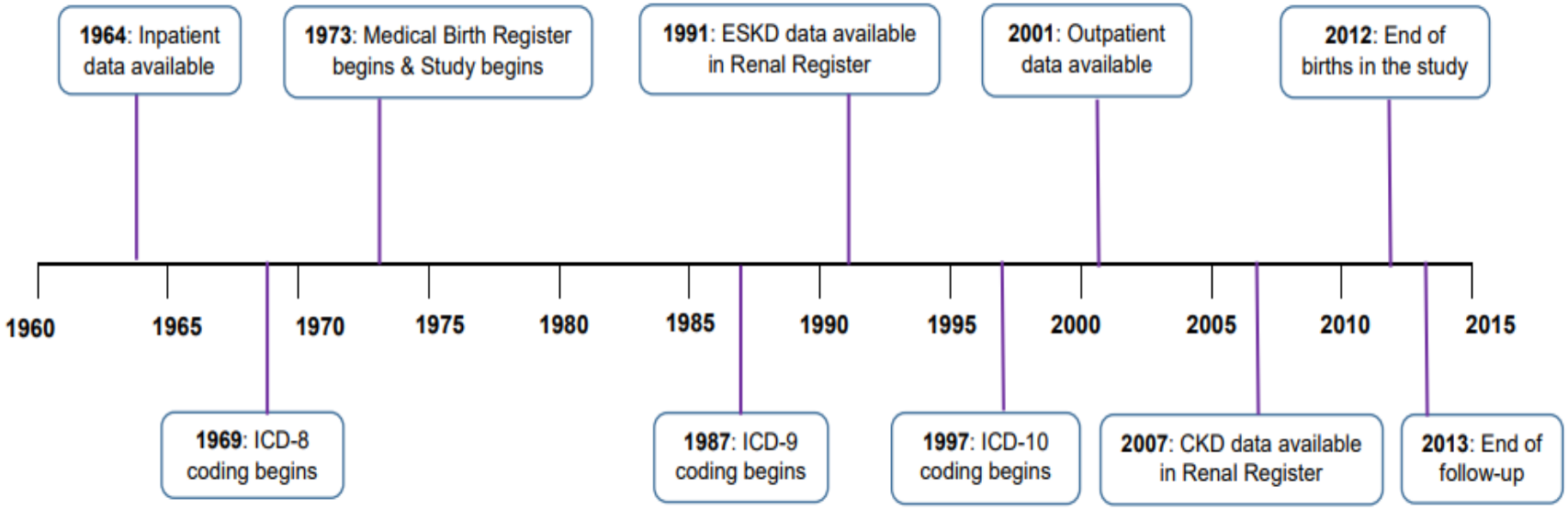


Figure 3.1 Timeline pertaining to study design and data availability

Each pregnancy was considered as a single period of potential exposure to adverse pregnancy outcomes. Women who had multiple pregnancies often had their adverse pregnancy outcome recorded multiple times in the MBR. For example, a woman who experienced preeclampsia during one pregnancy and gave birth to twins typically had two entries for preeclampsia in the MBR (one per unique child). To avoid over-counting of adverse pregnancy outcomes, we excluded multiple pregnancies from all studies at baseline. This is routine in epidemiological research using national register data, and it facilitates linkage of data using the unique PIN (28, 29, 32, 59, 87, 88, 93)

3.5 Exposure and outcome variables

3.5.1 Main exposure variables

Preeclampsia

Preeclampsia was the main exposure of interest in Chapter 6 and it was included as a covariate in all other studies. It was identified from ICD codes and was defined as a diastolic blood pressure of >90 mmHg with proteinuria (≥0.3 g/day or ≥1+ on a urine dipstick) (29). Women who developed eclampsia or Haemolysis, Elevated Liver enzymes, Low Platelets (HELLP) syndrome were included among those with preeclampsia because there were too few affected women to allow separate groups for these. However, women who developed preeclampsia superimposed on chronic hypertension were excluded from all studies, since women with pre-pregnancy hypertension were excluded at baseline.

The International Society for the Study of Hypertension in Pregnancy recommend against classifying preeclampsia as mild or severe disease (133), thus we did not do so. However,

preeclampsia was considered together with SGA and preterm delivery in Chapters 4 and 6 respectively, and these may be considered proxy markers of severity (134).

The PPV for preeclampsia diagnoses in the national registers was higher from 1987 onwards with the introduction of ICD-9 coding (118, 135), and sensitivity analyses were conducted in Chapter 6 to allow for this. Since 2014, proteinuria is no longer a requirement for a preeclampsia diagnosis (133). However, this change in definition did not affect our research because each study ended on 31st December 2013 and ICD codes were based on previous definitions of preeclampsia.

Gestational hypertension

Gestational hypertension was included as a secondary exposure variable of interest in Chapter 6. It was identified from ICD codes and defined as blood pressure of at least 140/90 mm Hg (in at least two readings at least six hours apart), without proteinuria, occurring after 20 weeks' gestation up to the date of delivery. Like preeclampsia, the PPV for gestational hypertension diagnoses in the national registers was higher from 1987 onwards (118, 135), and sensitivity analyses were conducted to allow for this (Chapter 6).

Preterm delivery

Preterm delivery was the main exposure of interest in Chapter 4, and it was also considered in detail in Chapter 6. This was broadly defined as any delivery in the MBR before 37 weeks. Gestational age at delivery was mainly estimated based on second trimester ultrasound dating, which became routinely available from 1982 onwards, but it was estimated from maternal report of last menstrual period (LMP) prior to that (118).

Preterm deliveries were categorised as moderate (32 weeks to 36+6 weeks), very (28 weeks to 31+6 weeks), or extremely preterm (<28 weeks gestation). In Chapter 4, additional categories of early term deliveries (37 weeks to 38+6 weeks) and post-term deliveries (≥ 42 weeks) were used. Early term deliveries were examined separately from those who delivered at full term (39 weeks to 41+6 weeks) since they are associated with increased risk of adverse perinatal outcomes (136, 137), and they share common risk factors with preterm deliveries (138).

Preterm deliveries were also stratified as spontaneous or iatrogenic (indicated) preterm in Chapter 4, where those deliveries complicated by preeclampsia and/or SGA were assumed to be iatrogenic preterm. The definition of SGA in the MBR was a birth weight of 2 standard deviations (SD) below the sex-specific and gestational age distributions, according to Swedish weight-based growth standards (139).

Stillbirth

Stillbirth was the main exposure variable in Chapter 5, and it was controlled for, or excluded, as a confounding factor in Chapters 4 and 6. Stillbirth was defined as foetal death after 28+0 weeks gestation between 1 January 1973 and 30 June 2008. Thereafter, the definition changed in the MBR and all foetal deaths occurring after 22+0 weeks gestation were included as stillbirths (140). The timing of stillbirth was considered in Chapter 5, and they were categorised according to whether they occurred antepartum or intrapartum.

GDM

GDM was the main exposure of interest in Chapter 7 and was based on ICD coding in the MBR or NPR. ICD coding for GDM was only available from 1987 onwards, hence the study was restricted to women whose first birth occurred after that time.

There has been lack of consensus regarding screening regimes for GDM in Sweden. Some regions apply universal screening of GDM to all pregnant women and other regions use a selective approach based on particular risk factors (e.g. previous GDM, previous stillbirth, BMI ≥30 kg/m^2, macrosomic infant >4.5kg) or random blood glucose measurements (141). Both universal and selective screening regimes stipulate the use of a 75-g oral glucose tolerance test and 2-hour value of capillary plasma glucose for diagnosis, but the diagnostic thresholds for GDM vary. The national registers do not contain information on the specific diagnostic thresholds used for individuals.

Two separate exposure variables were used for GDM in Chapter 7. The first variable was dichotomous (any GDM vs. none). The second was a categorical variable whereby GDM-diagnosed women were stratified according to whether they developed post-pregnancy T2DM during follow-up or not. This was based on new diagnoses of T2DM in the MBR and NPR.

Large for gestational age (LGA) was also considered as a proxy marker of GDM severity and control (142) and it was examined concurrently with GDM. LGA was defined in the MBR as a birth weight of 2 standard deviations (SD) above the sex-specific and gestational age distributions, according to Swedish weight-based growth standards (139).

Primary vs. secondary exposure variables

Westreich & Greenland outlined the importance of avoiding a Table 2 fallacy in observational research. This can arise when the effect estimates of secondary exposures are presented in the same manner as that for the primary exposure, and all are estimated from the same statistical model. Doing so may result in misleading effect estimates and incorrect interpretation of the relationship between a secondary exposure and outcome if this was not evaluated for possible additional confounding (143). In order to obtain valid effect estimates

for each exposure-outcome relationship, new models should be constructed with careful consideration of confounders and separate bias assessment. In this thesis, the main exposure variables of interest (HDP, preterm delivery, stillbirth, GDM) are considered in separate statistical models across four population-based cohort studies.

3.5.2 Main outcome variables

CKD

Maternal CKD was defined by a recorded diagnosis of CKD in the SRR, or based on a primary or secondary diagnosis of CKD in the NPR (using ICD codes as shown in Table A6.1, Appendix 6). The earliest date at which a woman appeared in either the SRR or the NPR was assumed to be her date of diagnosis. Only women who were diagnosed with CKD at least 3 months after their most recent pregnancy were considered, to avoid potential misclassification with acute kidney injury or transient renal dysfunction related to pregnancy. Women who had CKD due to an identifiable congenital or genetic cause were excluded from every study because their aetiology was unrelated to adverse pregnancy outcomes.

In Chapters 6 and 7, CKD was further categorised in to broad subtypes based on guidance from the National Kidney Foundation (144), prior research (29, 74), and clinical advice received from Consultant Nephrologists. The following categories were used: tubulointerstitial CKD, glomerular/proteinuric CKD, hypertensive CKD, diabetic CKD, and other/unspecified CKD. The subtype/aetiology was always based on the initial CKD diagnosis, when each woman first appeared in either the SRR or NPR.

ESKD

Maternal ESKD was defined by a recorded diagnosis of ESKD in the SRR or NPR, or by stage 5 CKD requiring dialysis or renal transplant. Women were assumed to be diagnosed on the first date they were recorded with ESKD in either the SRR or NPR. ESKD was not categorised in to subtypes because this was a rare outcome and, despite the use of national registers, there were insufficient events to allow for meaningful interrogation of ESKD subtypes.

ESKD was considered as an outcome in Chapters 4, 5, and 7. The study focusing on preeclampsia and maternal kidney disease (Chapter 6) only considered CKD as an outcome because it was clear from the existing literature (described in Chapter 2) that the association between preeclampsia and ESKD was well established. Furthermore, a study on this topic had been recently undertaken in the Swedish population (29).

3.6 ICD coding

ICD coding is widely used in the Swedish national registers. In the MBR, it is used to record pre-pregnancy comorbidities which are identified during antenatal care, as well as new pregnancy-related diseases. In the NPR, all inpatient and outpatient diagnoses are recorded using ICD codes.

During the timeframe of this research, three different iterations of ICD coding were used in Sweden, and thus different disease-specific codes were applied depending on the year of diagnosis. From 1973 to 1986, ICD-8 coding was used. In 1987, this changed to ICD-9 coding, and in 1997 this changed again to ICD-10 coding which remained in place for the remainder of the study period. For example, women with pre-pregnancy systemic lupus erythematosus were identified and excluded at baseline in each study. From 1973 to 1986, they were identified using code 73410 (ICD-8) (145). From 1987 to 1996, code 710A was used (ICD-9)

(146). Finally, from 1997 to 2013, code M32 was used (ICD-10) (147). Further information on the exact ICD codes used in each study are available in Tables A6.1, A7.1, A8.1 and A9.1 in Appendices 6-9 respectively.

There are limitations to the use of ICD codes. Mistakes in coding and in data entry can occur, and often, non-specific codes are used even when a specification is possible (119). However, the majority of ICD codes recorded in the MBR are correct when compared with medical records. In a previous Swedish validation study, diagnoses were incorrect, doubtful, or could have been replaced by a more suitable diagnosis in just 3% of cases (118). In some cases, diagnoses were omitted, possibly because a maximum of only four separate diagnoses could be coded at delivery until the end of 1998. This was expanded to 12 diagnoses from 1999 onwards.

In the NPR, the majority of ICD-coded diagnoses have high PPV but lower sensitivity. Thus, the validity of most diagnoses is high, but there is a possibility of false negatives and under-ascertainment of cases. The proportion of valid diagnoses is higher among those with more severe disease (119).

3.7 Key epidemiological considerations

In observational research, it is impossible to make definitive causal claims, even in large-scale longitudinal studies. In this thesis, cohort studies allow temporal relationships between exposure variables and maternal outcomes to be investigated, but external factors which may explain or influence measures of association need to be considered and controlled for in the design and analysis of each study. There are three potential alternative explanations for any observed associations in epidemiological research: bias, confounding, and chance. These need to be ruled out, where possible, to increase the probability that observed associations are true. The key principles of bias, confounding, and chance are considered here as they applied to the

study design. They are considered further in section 9.2 in the interpretation of findings from this research.

3.7.1 Bias

Bias refers to a systematic error in the design or analysis of a study, and it affects the accuracy of the results. It is independent of study size, and can result in a conclusion which is different from the truth. It is important to prevent or minimise systematic error in the study design phase, while also considering the possibility of bias when interpreting results.

The two principal forms of bias are selection bias and information bias. Selection bias occurs when there is a systematic difference between the characteristics of those who participate in a study and those who do not. It may result in a non-representative sample when investigating associations of interest (148). For example, in cohort studies, the characteristics of those who are lost to follow-up may be systematically different from those who remain in the study until the end date.

Information bias arises when there is systematic error in the measurement of exposure, outcome, or potential confounders. There may be a problem in how the data are collected or recorded, or they may not correctly measure what they are supposed to measure. For example, if the methods used to ascertain an outcome differ between exposed and unexposed groups, this may introduce systematic error (148).

Misclassification bias is a sub-group of information bias, and it can be differential or non-differential. Differential misclassification occurs when one group is more likely to be misclassified than another and results may be biased in either direction towards or away from the null. By contrast, non-differential misclassification is unrelated to exposure or outcome. It arises when the methods used in data collection or recording of results are inaccurate and it

results in shifting of the association towards the null. This may lead to under-estimation of the true effect size (149, 150).

3.7.2 Confounding

Confounding can have a very important influence in epidemiological studies, and can change the magnitude or direction of an association. The most common concern with confounding is that it may create the appearance of a cause-effect relationship that does not truly exist (148).

Confounding arises when another exposure exists in the study population which is associated with both the main exposure variable and the outcome of interest. This extraneous factor is typically a determinant or risk factor for the health outcome, and if it is unequally distributed between exposure subgroups, the effects of the two risk factors are not adequately separated. Consequently, the results may indicate that an association is due to one variable rather than the other, and there is distortion of the true relationship between exposure and outcome (148).

There are three general criteria for a confounder: (1) Confounders should be associated with the outcome of interest. (2) Confounders should be associated with, but independent of, the exposure of interest. (3) Confounders should not be caused by the exposure (i.e. not on the causal pathway) or caused by the outcome.

Several methods exist to control for confounding. In the study design phase, the methods used to control for confounders include randomisation, matching and restriction. Randomisation is the ideal method for ensuring that potential confounders (both known and unknown) are equally distributed between groups. However, this only applies to randomised controlled trials, and is not possible to do in cohort studies. Matching involves selecting study participants for a comparison group, which ensures that confounding variables are evenly distributed in

the groups being compared. This is commonly used in case-control studies. However, with increasing numbers of matching variables, the identification of matched subjects becomes progressively more demanding, and it does not reduce confounding by factors other than the matching variables (150). Restriction eliminates variation in a confounder by limiting the study to those who have particular characteristics, and it is feasible in cohort studies. For example, a study may be restricted to non-smokers in the design phase if smoking is deemed to be an important confounder (148). In this thesis, restriction is used to control for confounding by certain medical comorbidities (e.g. pre-pregnancy CVD, hypertension, and diabetes).

In the analysis phase, confounding can be controlled using stratification or statistical modelling methods, including multivariable adjustment. Stratification involves measuring the strength of associations in well-defined and homogeneous categories of the confounding variable (e.g. categories of gestational age). However, this cannot be used to control multiple confounders simultaneously. For this, statistical adjustment is needed and this is the main method used to control potential confounders in this thesis. It requires careful construction of multivariable models where the relationships between exposures, outcomes, and confounding factors are deemed to be biologically plausible. Where a potential confounder has not been accurately measured or accounted for, residual confounding may arise. In observational research, it is impossible to rule out the presence of residual confounding and thus, it is important to consider this when interpreting results (148, 150).

Confounding should also be distinguished from effect modification, where the magnitude of the effect of the exposure on the outcome depends on the level of another variable. For example, while diabetes may be associated with increased risk of CVD for all, this association may be stronger in women than it is in men. In this situation, sex is an effect modifier. Although confounding should be avoided wherever possible, effect modification may have biological, clinical or public health relevance, and this information may be used to define high-risk and

low-risk subgroups (150). In this thesis, checks for effect modification were used in the analysis of Chapters 5, 6 and 7.

3.7.3 Chance findings

Chance findings are caused by random error when a value of the sample measurement diverges, due to chance alone, from that of the true population value. This can result in inaccurate measures of association, particularly when subgroup analyses are over-used (151).

Random error can be reduced by increasing a study's sample size and by minimising measurement error (148). Statistical methods can also be used to estimate the probability of obtaining an estimate in a sample by chance alone. Confidence intervals reflect the amount of random error that is present in the sample, and they contain a range of likely values of the point estimate, with a specified level of confidence. Conventionally, the level used is 95%. This implies that if samples of the same size were repeatedly drawn from a population, and their 95% confidence intervals were calculated, then 95% of the confidence intervals would be expected to include the true value of the association (152). If the 95% confidence interval does not include a null association, it is deemed to be "statistically significant", and the association is unlikely to have occurred by chance alone.

3.8 Missing data

3.8.1 Types of missing data

Missing data are a pervasive challenge in observational studies. Research participants may have missing data if they refuse or forget to answer specific survey questions, if their files are lost, or when their data are not recorded properly (153). If the characteristics of those with missing data differ from who have complete data, this may represent an important source of

bias in the study. It can lead to reduced statistical power, erroneous effect estimates, and invalid study conclusions (154). The best method of handling missing data is to prevent the problem in the first place through careful planning and meticulous data collection. However, this is not always possible, even in well-designed studies.

Data may be missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). Data are MCAR when the complete cases are a random sample of the originally identified set of cases, and the probability of having a variable with missing data does not depend on any observed or missing variables. For example, this may be due to equipment failure, or destruction of data in a fire. MAR is generally more likely to hold in epidemiological studies (154). Under this assumption, the probability that an observation is missing depends on information for that subject which is present, i.e. the reason for missingness is based on other observed patient characteristics (155). Data are MNAR if the missingness pattern depends on the values of unobserved variables (154). For example, if measuring self-reported income, data may be more likely to be missing among higher earners due to unobserved participant characteristics.

3.8.2 Key sources of missing data in the Swedish national registers

Exposure variables

Overall, the Swedish national registers have a high level of completeness. The MBR contains records on over 96% of all infants, but some of these records may contain missing data from antenatal clinics. Among exposure variables, the most important sources of missing data in the MBR relate to maternal smoking in pregnancy and pre-pregnancy BMI because these were included as potential confounders in every study. These variables were first collected from 1982 onwards, and thus they were completely missing between 1973 and 1981. Between 1982

and 2003, information on smoking in early pregnancy was missing for approximately 4-9% of mothers, but some had information available on smoking status at 30-32 weeks (118). In this thesis, smokers were defined as those who reported smoking at any stage during pregnancy, and those who had missing data were women with no record of smoking status either in early pregnancy or at 30-32 weeks gestation.

Information on maternal BMI at first antenatal visit was available for approximately 65% of women between 1982 and 2003, and became more complete thereafter. There were no data on BMI available before 1982 (118). In one study (Chapter 7), a variable pertaining to gestational weight gain was derived using established criteria (156), but this was dependent on the availability of antenatal BMI in the dataset, and thus there was a considerable amount of missing data.

The other main source of data loss in the MBR relates to infant diagnoses, particularly congenital malformations (118). Where possible, the MBR should be supplemented with information from the Register of Congenital Malformations to identify these infants. This affected one study in the thesis (Chapter 5, focusing on stillbirth) because we did not have access to the Register of Congenital Malformations. Finally, since 1990, the Swedish Register of Education contains missing data on about 1.7% of those aged 25-64 years, but there are slightly higher levels of missing information before then (130). Maternal education was included as a confounder in all of the studies in this thesis.

Outcome variables

The outcome data relating to CKD and ESKD may be incomplete from the Swedish national registers. The NPR achieved national coverage for inpatient admissions and discharges in 1987. However, between 1973 and 1986, coverage was largely dependent on uptake of the register

by municipality and admitting hospital. Outpatient reviews only began to be included in the NPR in 2001, and although it has now achieved almost complete coverage for public outpatient clinics, information from private healthcare providers remains incomplete (119). This is particularly relevant for data pertaining to CKD, since many of these patients are treated on an outpatient basis.

The SRR contains over 95% complete data on ESKD, but its coverage of CKD is lower and it only began to record data on CKD patients in 2007 (123). Furthermore, many patients with milder forms of CKD will be treated in primary care and may never be recorded in the NPR or SRR, whereas those with ESKD are more likely to be captured in the national registers.

3.8.3 Handling missing data

In this thesis, three methods were used to deal with missing data. Firstly, when a categorical exposure variable had missing data, an extra category was added for the missing values and included in statistical analyses as an indicator variable. The main advantage of the indicator method is that all subjects are retained in the multivariable analysis (155), and this was used in Chapters 4, 5 and 6. However, the missing indicator method may also introduce bias because it may be only partially adjusted for confounders (155, 157).

The second method used to deal with missing data was through sensitivity analyses. When data were unavailable for specific time periods, sensitivity analyses were conducted to reduce the amount of missing values. For example, in Chapters 4, 5 and 6, all analyses were repeated from 1982 or 1987 onwards, when data on maternal smoking and BMI were more complete. This method was used to check if missing values had an impact on the overall magnitude or direction of results.

Thirdly, multiple imputation methods were used to substitute missing values with a set of plausible predicted values. Imputation techniques are based on the idea that any subject in a study sample can be replaced by a new randomly chosen subject from the same source population. The objective of multiple imputation is to analyse missing data in a way that results in valid statistical inference, rather than producing imputed values that are as close as possible to the missing values. It assumes that missing data are MAR, and it replaces them with predicted values, creating multiple imputed datasets. Multiple imputation also accounts for uncertainty from the fact that imputed values were not actually observed, but rather estimated (157). In Chapter 7, multiple imputation by chained equations (MICE) was used to impute missing values for smoking, BMI, gestational weight gain, and maternal education. MICE uses a separate conditional distribution for each imputed variable. For example, it allows a linear model to be used to impute continuous variables (e.g. BMI, gestational weight gain) and multinomial logistic models to impute categorical variables (e.g. smoking status, highest level of education). Multiple imputation results in unbiased estimates of study associations (155).

3.9 Statistical methods

3.9.1 Cox proportional hazard regression

Survival analysis is a method of measuring associations in longitudinal data which includes time to an event. It is widely used in research where individuals have experienced differing amounts of follow-up time, and one of its major advantages is that it can account for those who are lost to follow-up. In this thesis, Cox proportional hazard regression (or 'Cox regression') models are used in each epidemiological study to investigate associations between adverse pregnancy outcomes and future CKD or ESKD.

Cox regression allows individuals within a cohort to enter a study at different times depending, for example, on the date of their first delivery. Participants are followed up until they develop an outcome of interest (i.e. CKD or ESKD), or until they are censored. Censoring may arise for three main reasons. Firstly, a study participant may not have experienced the outcome (e.g. CKD or ESKD) by the time the study ends. Secondly, if a patient is lost to follow-up during the study period (for example due to emigration) it is unknown whether they may have developed the outcome. Thirdly, if a patient withdraws from a study because of a different event (e.g. death) this may make follow-up impossible.

Cox regression estimates the hazard *(h)*, or instantaneous risk of the outcome at any given follow-up time *(t)*. This is modelled using the equation: $log(h(t)) = log(h_0(t)) + \beta_1 x_1 + \ldots + \beta_p x_p$, where $h(t)$ is the hazard at time t, $h_0(t)$ is the hazard in the unexposed group at time t (baseline hazard), and β_1 to β_p is the estimated increase in the risk of the outcome, per unit increase in the value of the exposure variables x_1 to x_p, (where $x_1 = 1$ in the exposed group, and $x_1 = 0$ in the unexposed group) (158). Results from a Cox regression model are used to estimate a hazard ratio (HR) which can be interpreted in a similar way to relative risk. Multivariable-adjusted Cox regression models can be used to investigate associations between the exposure and outcome while adjusting for relevant confounders, and this method is used frequently in this thesis to estimate adjusted HRs.

In order for Cox regression models to be valid, certain conditions have to be met. Firstly, the proportional hazards assumption should hold, where the hazard ratio for the exposed compared to unexposed groups remains constant over time. This can be checked using several methods including log-log plots of survival, Kaplan-Meier vs. predicted survival plots, and using Schoenfeld residuals (159). Secondly, censoring should be non-informative, i.e. the reason individuals are censored must be unrelated to the exposure or outcome of interest (160).

3.9.2 Time-dependent covariates

A time-dependent variable is defined as any variable whose value for a given subject may differ over time *(t)*.Time-dependent covariates can be used in survival analysis to capture changes in the values of exposure variables or confounders over the follow-up period. This method is used to acknowledge that exposures and behaviours may change, and it can provide more accurate measurements of exposure-outcome associations. For example, if a longitudinal study seeks to measure the effects of smoking on cancer, time-dependent covariates could be used to capture those who become smokers after the study commences (e.g. covariate values may be updated from '0' for non-smoking at baseline to '1' for smoking during the follow-up period). This time-dependent covariate contributes more information than using smoking status at study entry alone and it more accurately reflects reality (161).

Serial measurements of the exposure variable or risk factor may be taken during follow-up, and included in a Cox regression model. In a time-dependent analysis, the follow-up time for each patient is divided into different time windows. For example, in this thesis the exposure variables contribute to time windows of varying duration reflecting time between women's consecutive deliveries (e.g. from date of first delivery until date of second delivery). Non-time-dependent variables, for example 'ethnicity', can also be used as fixed confounders or covariates for each participant across all their included time windows (162). Cox regression with time-dependent covariates was used in the original longitudinal studies outlined in Chapters 4, 5, 6 and 7.

Multivariable-adjusted logistic regression was considered as a potential alternative statistical method for the studies in this thesis. However, logistic regression cannot account for time to event data nor for censoring. Thus, survival analysis methods were preferred in all studies.

CHAPTER 4 RISK OF LONG-TERM RENAL DISEASE IN WOMEN WITH A HISTORY OF PRETERM DELIVERY: A POPULATION-BASED COHORT STUDY

Peter M. Barrett (1, 2), Fergus P. McCarthy (2, 3), Marie Evans (4), Marius Kublickas (5), Ivan J. Perry (1), Peter Stenvinkel (4), Karolina Kublickiene (4), Ali S. Khashan (1, 2)

1. School of Public Health, University College Cork, Cork, Ireland
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland
3. Department of Obstetrics & Gynaecology, Cork University Maternity Hospital, Cork, Ireland
4. Department of Clinical Sciences Intervention and Technology, Karolinska Institutet, Huddinge, Sweden
5. Department of Obstetrics & Gynaecology, Karolinska Institutet, Stockholm, Sweden

Published in: *BMC Medicine, April 2020*

(Paper 3)

4.1 Abstract

Background

Preterm delivery is an independent risk factor for maternal cardiovascular disease. Little is known about the association between preterm delivery and maternal renal function. This study aimed to examine whether women who experience preterm delivery are at increased risk of subsequent chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

Methods

Using data from the Swedish Medical Birth Register, singleton live births from 1973 to 2012 were identified and linked to data from the Swedish Renal Register and National Patient Register (up to 2013). Gestational age at delivery was the main exposure and treated as a time-dependent variable. Primary outcomes were maternal CKD or ESKD. Cox proportional hazard regression models were used for analysis.

Results

The dataset included 1,943,716 women who had 3,760,429 singleton live births. The median follow-up was 20.6 (interquartile range 9.9–30.0) years. Overall, 162,918 women (8.4%) delivered at least 1 preterm infant (< 37 weeks). Women who had any preterm delivery (< 37 weeks) were at increased risk of CKD (adjusted hazard ratio (aHR) 1.39, 95% CI 1.32–1.45) and ESKD (aHR 2.22, 95% CI 1.90–2.58) compared with women who only delivered at term (≥ 37 weeks). Women who delivered an extremely preterm infant (< 28 weeks) were at increased risk of CKD (aHR 1.84, 95% CI 1.52–2.22) and ESKD (aHR 3.61, 95% CI 2.03–6.39). The highest risk of CKD and ESKD was in women who experienced preterm delivery + preeclampsia (vs. non-preeclamptic term deliveries, for CKD, aHR 2.81, 95% CI 2.46–3.20; for ESKD, aHR 6.70, 95% CI 4.70–9.56). However, spontaneous preterm delivery was also

associated with increased risk of CKD (aHR 1.32, 95% CI 1.25–1.39) and ESKD (aHR 1.99, 95% CI 1.67–2.38) independent of preeclampsia or small for gestational age (SGA).

Conclusions

Women with history of preterm delivery are at increased risk of CKD and ESKD. The risk is higher among women who had very preterm or extremely preterm deliveries, or whose preterm delivery was medically indicated. Women who experience spontaneous preterm delivery are at increased risk of long-term renal disease independent of preeclampsia or SGA. Preterm delivery may act as a risk marker for adverse maternal renal outcomes.

4.2 Introduction

Chronic kidney disease (CKD) is a major cause of morbidity globally, with an estimated prevalence of 7–12% for stage 3 CKD or greater among women (48, 163, 164). End-stage kidney disease (ESKD), although relatively rare, has a disproportionately high healthcare burden. Preterm delivery, before 37 weeks' gestation, is recognised as a risk factor for maternal cardiovascular disease (CVD), independent of socio-demographic factors (e.g. age, ethnicity, education), obstetric history (e.g. preeclampsia, parity), and cardiometabolic factors (e.g. chronic hypertension, diabetes, body mass index (BMI)) (20, 55, 75). Although cardiovascular guidelines suggest that pregnancy-related factors, including preterm delivery, should be considered markers of future CVD risk (53, 113), little is known about the association between preterm delivery and subsequent renal disease. This information could potentially provide opportunities for risk stratification and secondary prevention of CKD in women.

Existing research on preterm delivery and the risk of maternal CKD has been limited to groups with an increased baseline risk of renal disease (59, 85), or has failed to adjust for important confounders such as maternal smoking (28, 32, 94) and obesity (28, 94). Cardiovascular risk is higher among women who experience very or extremely preterm deliveries (before 32 weeks' gestation) (20), but it is uncertain whether a similar pattern exists for future risk of CKD. It is plausible that women with earlier preterm deliveries experience greater risk of CKD or ESKD relative to women who deliver closer to full term.

Most preterm deliveries occur spontaneously, but about 30% are iatrogenic and performed for obstetric reasons, typically maternal preeclampsia or intrauterine growth restriction (IUGR) (165). Preeclampsia has been identified as a strong risk factor for ESKD (28, 31, 32), and women who experience IUGR or a small for gestational age (SGA) delivery may also be at increased risk of CKD (32, 92). Thus, the risk of maternal CKD/ESKD may differ depending on whether women experience spontaneous or iatrogenic preterm deliveries.

We aimed to examine whether women who experience preterm delivery are at increased risk of CKD and ESKD, and whether this association differs by medical indication (i.e. spontaneous or iatrogenic preterm) or across categories of gestational age.

4.3 Methods

Study population

Data from the Swedish Medical Birth Register (MBR) (established 1973) were used to identify all women who had singleton live births between January 1, 1973, and December 31, 2012. Data from the Swedish National Patient Register (NPR) (established 1964) and Swedish Renal Register (SRR) (established 1991) were linked with the MBR using anonymised unique identification numbers. Data from the NPR and SRR were used to identify women who developed CKD or ESKD during follow-up, until December 31, 2013 (study end date). Data from the Swedish Death Register and Migration Register were also available until December 31, 2013, and used for censoring.

In order to reduce potential confounding from comorbid diseases, we identified women with pre-pregnancy CKD, ESKD, CVD, hypertension, diabetes (type 1 or 2), or systemic lupus erythematosus (SLE) from the MBR, and they were excluded from the study. We also excluded all women in the NPR who were admitted to hospital with these diagnoses before their index pregnancy. Three iterations of ICD coding were used to identify pre-existing diseases in the NPR: ICD-8 coding before 1986, ICD-9 coding from 1987 to 1996, and ICD-10 coding from 1997 to 2013. New hospital admissions and outpatient reviews for preeclampsia and gestational diabetes were also identified in the NPR using ICD codes, and used to supplement information in the MBR. The ICD codes are summarised in Table A6.1, Appendix 6.

We further excluded multiple pregnancies, stillbirths, and pregnancies with implausible dates of delivery from all analyses (Figure A6.1, Appendix 6).

Preterm delivery

Maternal history of preterm delivery was the main exposure of interest. Gestational age at delivery was estimated based on second trimester ultrasound (around 17th week of pregnancy) where available, or the time from last menstrual period (LMP) to birth based on maternal report at first antenatal visit. LMP was used to estimate gestational age until 1982, but ultrasonography data became increasingly available in the MBR thereafter.

Five separate exposure variables were used to investigate the effects of gestational age, including preterm and early term delivery, on maternal CKD/ESKD risk. Each of these used different classifications of preterm delivery. For all models, time-dependent variables were used so that a woman could contribute pregnancies and person-time to both unexposed and exposed groups during follow-up. Women could contribute unexposed time if they never had a preterm delivery, or until their first preterm delivery occurred. For example, if a woman delivered at term (≥ 37 weeks) in the first pregnancy, and then had a preterm delivery (< 37 weeks) in the second pregnancy, she was considered unexposed between deliveries 1 and 2, and exposed from delivery 2 onwards irrespective of subsequent pregnancy outcomes.

For the main analysis (exposure 1), women were categorised according to any previous history of preterm delivery (ever, < 37 weeks). If women had more than one pregnancy, they were considered exposed from the date of their first preterm delivery onwards. For exposure 2, established definitions of term (≥ 37 weeks, reference group) vs. moderate (32–36 + 6 weeks)/very (28–31 + 6 weeks)/extremely (< 28 weeks) preterm were used. Maternal exposure status was always based on the earliest gestation of any previous delivery. For example, if a woman had three deliveries during follow-up, at 35 weeks, 27 weeks, and 39 weeks, respectively, she contributed exposed time to the moderate preterm category between deliveries 1 and 2, and contributed exposed time to the extremely preterm category thereafter (irrespective of her third delivery at term).

Next, for exposure 3, additional categories of early term deliveries (37–38 + 6 weeks) and post-term deliveries (≥ 42 weeks) were used together with the established categories of moderate/very/extremely preterm. The reference group for exposure 3 was those who delivered at "full term" (i.e. 39–41 + 6 weeks). Early term deliveries (37–38 + 6 weeks) were examined separately since they are associated with increased risk of adverse perinatal outcomes (136, 137), and they share common risk factors with preterm deliveries (138).

For exposure 4, preterm deliveries (< 37 weeks) were stratified by spontaneous or iatrogenic preterm, where those deliveries complicated by preeclampsia and/or SGA were assumed to be iatrogenic preterm. A series of dummy variables were included to represent non-overlapping scenarios: (i) preterm delivery alone (i.e. assumed spontaneous preterm), (ii) preterm delivery + preeclampsia, (iii) preterm delivery + SGA, and (iv) preterm delivery + preeclampsia + SGA (co-occurring). The definition of SGA in the MBR was a birth weight of 2 standard deviations (SD) below the sex-specific and gestational age distributions, according to Swedish weight-based growth standards (139).

Finally, for exposure 5, the analysis was restricted to all women in the dataset who only had two live births during the study period to examine differences in risk between none/one/two preterm deliveries (< 37 weeks).

Outcome variables

There were two main outcomes: maternal CKD and maternal ESKD. Outcome data were defined by a recorded diagnosis of CKD or ESKD in the SRR or based on a primary or secondary diagnosis of CKD or ESKD in the NPR (using ICD codes). The earliest date at which a woman appeared in either the SRR or the NPR was assumed to be her date of diagnosis for CKD/ESKD. Women who had renal disease due to an identifiable congenital or genetic cause were excluded (Table A6.1, Appendix 6).

Covariates

The following covariates were adjusted for: maternal age, year of delivery, country of origin, education level, BMI, smoking during pregnancy, gestational diabetes, preeclampsia, parity, and inter-pregnancy interval. Education level was available from the Swedish Education Register and was based on the mother's highest level of educational achievement (proxy variable for socio-economic status). Smoking status was based on any reported smoking during pregnancy, either at first antenatal visit or at 30–32 weeks' gestation. Maternal BMI was calculated based on weight and length (kg/m^2) as recorded at first antenatal visit. There were large amounts of missing data for smoking status and BMI, and these variables were only available from 1982 onwards. Missing indicator variables were created to control for this. A sensitivity analysis was also undertaken where the dataset was restricted to births between 1982 and 2012 to check for comparability with the main results.

Maternal exposure to gestational diabetes was treated as a time-dependent covariate, where women were considered exposed from their date of first delivery with gestational diabetes. Preeclampsia was also considered a time-dependent covariate and was adjusted for in all models except when exposure 4 was used, since preterm preeclamptic deliveries were already considered as a separate group. Inter-pregnancy interval was defined as the date between a woman's last live birth and her estimated date of conception for the next live birth (estimated by subtracting gestational age in days from the date of next live birth).

Statistical analysis

Data were set up for survival analysis, where entry date in the study was the date of each woman's first live birth. The association between history of preterm delivery and risk of maternal CKD was estimated using the Kaplan-Meier method. Differences in survival curves were estimated using logrank tests. We used multivariable Cox proportional hazard regression

models to estimate minimally adjusted and fully adjusted hazard ratios (aHRs) and 95% confidence intervals (CI) for the associations between preterm delivery and maternal renal disease. We followed women from date of entry until date of CKD/ESKD diagnosis, date of death, date of emigration, or study end date (31 December 2013), whichever came first. Log cumulative hazard plots were used to check the adequacy of each Cox regression model, and year of delivery was included in all minimally adjusted models to ensure the assumption of proportional hazards was met.

Two-sided *P* values were used, and $P < 0.05$ denoted statistical significance. All analyses were performed using Stata version 15 (StataCorp LLC).

4.4 Results

The study cohort consisted of 1,943,716 unique women who had 3,760,429 singleton pregnancies, followed up for a total of 42,341,527 person-years. The median follow-up was 20.6 years (interquartile range 9.9–30.0), and the maximum follow-up was 41.0 years. There were 162,918 women (8.4%) who experienced preterm delivery (< 37 weeks) at some point (Table 4.1). From 1973 to 2013, 18,001 women (0.9%) developed CKD, and 1,268 (0.07%) developed ESKD.

History of any preterm or early term delivery

Tables 4.2 and 4.3 summarise the results of the main analyses for CKD and ESKD, respectively. Women who had at least one preterm delivery (< 37 weeks) (exposure 1) were at significantly increased risk of long-term CKD (aHR 1.39, 95% CI 1.32–1.45) and ESKD (aHR 2.22, 95% CI 1.90–2.58).

Figure 4.1 shows the differences in the Kaplan-Meier curves for CKD across categories of gestational age (moderate/very/extremely preterm delivery). Relative to those who delivered at term (≥ 37 weeks), women who had at least one extremely preterm delivery (< 28 weeks) were at higher risk of CKD (aHR 1.84, 95% CI 1.52–2.22) and ESKD (aHR 3.61, 95%CI 2.03–6.39), respectively (exposure 2, Tables 4.2 and 4.3).

Women who experienced early term deliveries (37–38 + 6 weeks) were also at increased risk of CKD (aHR 1.19, 95% CI 1.15–1.24) and ESKD (aHR 1.50, 95% CI 1.31–1.73) compared to women who only had full term deliveries (39–41 + 6 weeks) (exposure 3, Tables 4.2 and 4.3).

History of spontaneous or iatrogenic preterm delivery

Figure 4.2 shows the differences in the Kaplan-Meier survival curves for CKD across categories of spontaneous vs. iatrogenic preterm delivery. Compared to women who delivered at term (≥ 37 weeks), the risk of CKD and ESKD was highest in those who experienced preterm delivery (< 37 weeks) complicated by preeclampsia (for CKD, aHR 2.81, 95% CI 2.46–3.20; for ESKD, aHR 6.70, 95% CI 4.70–9.56) (exposure 4, Tables 4.2 and 4.3). Importantly, spontaneous preterm delivery (< 37 weeks) was also associated with increased risk of both CKD (aHR 1.32, 95% CI 1.25–1.39) and ESKD (aHR 1.99, 95% CI 1.67–2.38) independent of all other factors (exposure 4, Tables 4.2 and 4.3).

Sensitivity analysis

All analyses were repeated for deliveries occurring between 1982 and 2012, when data became available on maternal BMI and smoking. No meaningful differences were observed between preterm delivery and CKD in these analyses (Table 4.4). Stronger associations were observed between extremely preterm delivery (< 28 weeks) and ESKD (aHR 5.14, 95% CI 2.81–

9.40), and for preterm delivery + SGA and ESKD (aHR 4.89, 95% CI 3.33–8.40), but these associations were based on relatively few ESKD outcomes. The 95% CIs did not differ significantly from the corresponding 95% CIs in the main analysis.

4.5 Discussion

Statement of principal findings

This study aimed to determine whether women who deliver preterm infants are at increased long-term risk of CKD and ESKD. The results suggest that preterm delivery may be considered as a marker of heightened risk of future CKD and ESKD in parous women, independent of causal mechanisms. This finding was consistent across various definitions of gestational age and was strongest in those with very/extremely preterm deliveries. Mothers exposed to early term delivery, at 37–38 + 6 weeks' gestation, were also at increased risk of future renal disease relative to women who delivered at full term (39–41 + 6 weeks).

Women who experienced iatrogenic preterm delivery were at the highest risk of subsequent CKD or ESKD, and this may be largely driven by the effects of preeclampsia or SGA, or by the cumulative effect of preterm delivery in the context of these factors. However, our results suggest that women who had spontaneous preterm delivery were also at increased risk of CKD and ESKD irrespective of obstetric comorbidities or other factors. Given that the majority of preterm deliveries are spontaneous (165), it is relevant to consider whether these women should be informed of their heightened relative risk, and whether their history of preterm deliveries should be considered as part of their overall risk profile for chronic disease.

Interpretation

There is a small body of literature which has examined independent associations between preterm delivery and maternal renal disease (77). Longitudinal studies from Canada, Israel, and Norway have each reported that preterm delivery increases the risk of maternal ESKD, but they have been limited by incomplete adjustment for confounders (28, 32, 94). Other cohort studies have been restricted to women with pre-existing diabetes (59) or renal disease (85) and cannot be generalised to wider populations. Our study builds on existing research by controlling for a broader range of covariates, including maternal smoking, BMI, and inter-pregnancy interval, and by excluding women with pre-existing medical comorbidities, which may have otherwise increased the risk of CKD. Moreover, previous studies focused on ESKD (28, 32, 59, 85) or kidney-related hospitalisation (94) as their outcome variable. To our knowledge, the current study is the first to report the association between preterm delivery and maternal CKD.

Only one previous study on this topic stratified preterm deliveries according to whether they were spontaneous or iatrogenic (94). Although spontaneous preterm delivery was independently associated with CKD and ESKD in our study, the results suggest that preeclampsia, and to a lesser extent SGA, have a greater impact on renal risk than preterm delivery. Preeclampsia has been reported to increase the risk of maternal CKD (30, 74, 87, 88) and ESKD (28, 30-32) previously.

The mechanisms underlying the independent associations between spontaneous preterm delivery and maternal CKD/ESKD are uncertain. Intuitively, it seems plausible that this is a manifestation of subclinical predisposition to renal and cardiometabolic disease. Women with a history of preterm delivery are at higher risk of developing hypertension, diabetes, and hypercholesterolaemia (166), as well as CVD (20, 55, 75), and these factors may all increase the subsequent risk of CKD and ESKD. It is also possible that inflammatory processes associated

with spontaneous preterm delivery increase the risk of endothelial dysfunction and subclinical vascular disease, which in turn increase the risk of subsequent CKD and ESKD (167, 168). Women with spontaneous preterm deliveries are considered to have a pro-inflammatory phenotype (169). They may have higher C-reactive protein (CRP) levels in pregnancy (168, 170), and CRP is a strong predictor of later CKD risk (171). Thus, inflammatory factors may underlie a woman's predisposition to deliver at earlier gestation and her later susceptibility to renal disease.

Strengths and weaknesses of the study

This study has several strengths. The use of a large national cohort of pregnant women with a 41-year follow-up period reduced the possibility of selection bias and provided statistical power to examine the effect of gestational age independently of a wide range of recognised risk factors for maternal kidney disease. The size of our cohort allowed us to provide robust effect estimates for spontaneous and iatrogenic preterm delivery. Our data were retrieved from national registers with mandatory reporting, thereby excluding the possibility of recall bias. We used time-dependent covariates which allowed for changes in exposure status over time, and are more representative of women's cumulative exposure to obstetric risks during their reproductive lifetime.

Gestational age was identified from the MBR based on maternal report of LMP in the 1970s and early 1980s, and using ultrasound estimation from 1982 onwards where available. LMP is a less accurate method of predicting a woman's delivery date than ultrasonography (172). It is possible that some term births may have been misclassified and included in earlier categories of preterm delivery. This may have led to underestimation of the observed risks, but is unlikely to have affected the overall results. When ultrasound dating is used, first trimester crown-rump length is regarded as the best parameter for determining gestational

age, and should be used where possible (173-176). In our study, the standard ultrasound method to date pregnancies was through combination of biparietal diameter and femoral length in the second trimester. Although this method has been validated previously (177), we cannot exclude the possibility of misclassification of some term or preterm births. Pregnancy dating guidelines in Sweden have been updated in recent years and recommend the use of first trimester ultrasound where possible (174), but evidence suggests ongoing variation in adherence to these guidelines (178).

Our study population was primarily Swedish/Caucasian, and this may limit generalisability of the findings. Black women have higher incidence of preterm delivery than Caucasian women (179), and the causes of preterm delivery may vary by ethnicity or change over time.

The majority of cases of CKD and ESKD were identified using ICD-coded diagnoses in the NPR. There was no specific ICD-8 code for ESKD before 1986, and although some individuals may have been captured as CKD in the NPR, ESKD cases may have been underestimated as a result. Data collection was also less comprehensive in the NPR before national coverage was achieved in 1987, and outpatient diagnoses were only recorded from 2001 onwards (119). The SRR only collected ESKD data from 1991 onwards, and CKD data from 2007 onwards; thus, we cannot exclude the possibility of immortal time bias in our study.

The SRR has almost complete coverage of ESKD cases in Sweden, but coverage of CKD cases is lower (123). There was a relatively low prevalence of CKD among women in our study, possibly due to a combination of under-ascertainment of cases from the SRR and NPR, strict exclusion criteria, and the relative youth of the cohort involved. It is likely that a considerable number of women with renal disease were never diagnosed or ascertained by either the NPR or the SRR. However, an external review has reported high positive predictive values for most diagnoses recorded in the NPR, despite lower sensitivity levels (119). Thus, it is likely that those who were diagnosed with CKD or ESKD in the dataset were valid diagnoses.

Most variables in the dataset had almost complete data, but there were large amounts of missing data on maternal BMI and smoking. Missing data can significantly affect prevalence estimates, but only have a slight impact on risk estimates assuming the lack of information is random (118). In our dataset, the availability of data on maternal BMI and smoking varied by year of delivery, because these covariates were only collected from 1982 onwards. We used missing indicator variables, and adjusted for year of delivery in all models, to control for this. We also conducted sensitivity analyses restricted to pregnancies after 1982, and most results were not substantially different.

There was no suitable ICD-8 code available for gestational diabetes in the NPR. We could not ascertain those who may have been diagnosed before 1986, although this proportion is likely to be small. Finally, we excluded women on the basis of pre-existing comorbidities at baseline, including chronic hypertension. This information came from both the birth and hospital registers, but the NPR has low sensitivity for chronic hypertension. Thus, we cannot exclude the possibility of unmeasured confounding.

Implications

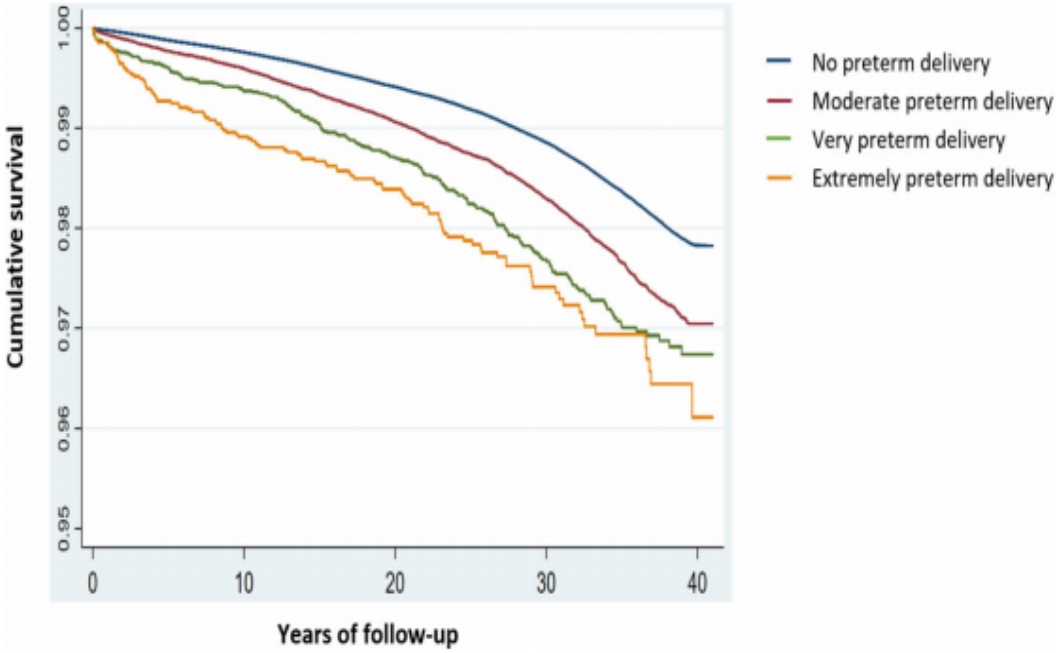
It is likely that the absolute risk of ESKD remains very low in women with a history of preterm delivery (with or without preeclampsia), despite the high relative risks observed in this study, since ESKD is a rare outcome. By contrast, modest increases in the risk of CKD in women exposed to spontaneous preterm deliveries or early term births may be important from a population perspective. Early term births (at 37–38 + 6 weeks) account for about 22% of all births in high-income countries (180), and the majority of preterm and early term births occur spontaneously (165, 181).

Obstetric history is easy to collect in the clinical setting, and it could be of potential use for renal risk stratification in women. Existing prediction models for CKD and ESKD have not taken

obstetric factors into consideration (182). Further research is warranted to elucidate whether incorporating history of spontaneous preterm delivery, and other relevant obstetric factors, adds incremental value or clinically relevant information to the overall risk of renal disease for women when other demographic and cardiometabolic risk factors have been accounted for.

4.6 Conclusions

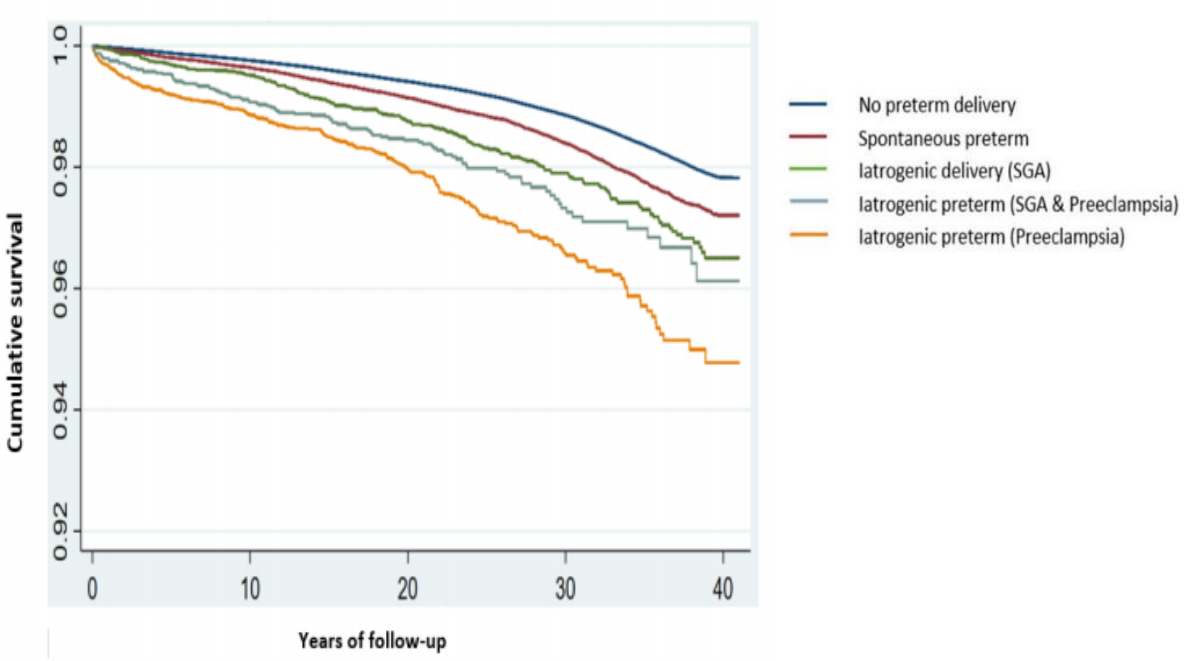
Women with a history of preterm delivery are at increased risk of maternal CKD and ESKD. The risk of renal disease is highest among women who have experienced very or extremely preterm deliveries, and those whose preterm delivery is medically indicated. Women who experience spontaneous preterm delivery are at increased risk of renal disease independently of preeclampsia and SGA. Preterm delivery may act as an important risk marker of adverse renal outcomes in the years and decades following pregnancy irrespective of causal mechanisms.



	0-10 years	10-20 years	20-30 years	30-40 years	40-41 years
No preterm delivery					
Number at risk	1,780,798	1,341,966	980,405	573,689	83,700
Number of events	3,863	4,006	4,179	3,864	2
Cumulative survival	99.8%	99.4%	98.9%	97.7%	97.7%
Moderate preterm					
Number at risk	140,318	111,427	81,078	43,282	5,346
Number of events	425	505	463	340	0
Cumulative survival	99.7%	99.1%	98.4%	97.0%	97.0%
Very preterm					
Number at risk	15,826	12,670	9,129	4,822	637
Number of events	71	71	71	31	0
Cumulative survival	99.4%	98.7%	97.5%	96.2%	96.2%
Extremely preterm					
Number at risk	6,774	5,135	3,516	1,735	220
Number of events	50	22	26	12	0
Cumulative survival	98.9%	98.3%	97.2%	95.6%	95.6%

	Chi-squared	Logrank p
No preterm delivery vs. Moderate preterm	228.6	<0.001
Moderate preterm vs. Very preterm	11.7	<0.001
Very preterm vs. Extremely preterm	2.0	0.16

Figure 4.1 Kaplan-Meier survival curves for risk of chronic kidney disease among women by exposure to moderate, very, or extremely preterm delivery between 1973 and 2012 in Sweden.



	0-10 years	10-20 years	20-30 years	30-40 years	40-41 years
No preterm delivery					
Number at risk	1,780,798	1,341,966	980,405	573,689	83,700
Number of events	3,863	4,006	4,179	3,864	2
Cumulative survival	99.8%	99.4%	98.9%	97.7%	97.7%
Spontaneous preterm					
Number at risk	134,030	106,490	78,065	42,277	5,394
Number of events	374	446	433	318	0
Cumulative survival	99.7%	99.2%	98.5%	97.2%	97.2%
Iatrogenic preterm, SGA					
Number at risk	10,917	9,104	7,034	3,998	504
Number of events	40	60	48	34	0
Cumulative survival	99.6%	98.9%	98.0%	96.5%	96.5%
Iatrogenic preterm, Preeclampsia					
Number at risk	11,302	8,558	5,319	2,206	186
Number of events	95	60	53	22	0
Cumulative survival	99.1%	98.2%	96.9%	95.1%	95.1%
Iatrogenic preterm, SGA & Preeclampsia					
Number at risk	6,669	5,080	3,305	1,358	119
Number of events	46	26	24	8	0
Cumulative survival	99.2%	98.6%	97.6%	96.6%	96.6%

	Chi-squared	Logrank p
No preterm delivery vs. Spontaneous preterm	141.7	<0.001
Spontaneous preterm vs. Iatrogenic (SGA)	11.5	<0.001
Spontaneous preterm vs. Iatrogenic (Preeclampsia)	125.5	<0.001
Iatrogenic preterm (SGA) vs. Iatrogenic preterm (Preeclampsia)	22.1	<0.001
Iatrogenic preterm (SGA + Preeclampsia) vs. Iatrogenic preterm (Preeclampsia only)	5.8	0.016

Figure 4.2 Kaplan-Meier survival curves for risk of chronic kidney disease among women by exposure to spontaneous or iatrogenic preterm delivery between 1973 and 2012 in Sweden.

Table 4.1 Maternal characteristics and pregnancy outcomes among women delivering between 1973 and 2012 in Sweden, stratified by exposure to preterm delivery

	No preterm delivery, n (%) N=1,780,798 (91.6)	**Preterm delivery, n (%)** N=162,918 (8.4)
Age in years		
<20	97,007 (5.5)	14,384 (8.8)
20-29	1,151,931 (64.7)	104,337 (64.0)
30-39	507,226 (28.5)	41,921 (25.7)
>=40	24,634 (1.4)	2,276 (1.4)
Native country		
Sweden	1,509,135 (84.7)	138,441 (85.0)
Elsewhere	271,663 (15.3)	24,477 (15.0)
Education level		
Less than Upper Secondary	233,341 (13.1)	24,540 (15.1)
Upper Secondary	800,419 (45.0)	77,826 (47.8)
Third level	709,299 (39.8)	57,702 (35.4)
Missing	37,739 (2.1)	2,850 (1.8)
Body mass index in early pregnancy (kg/m^2)		
Underweight: <18.5	41,129 (2.3)	4,830 (3.0)
Normal: 18.5-24.9	655,619 (36.8)	55,415 (34.0)
Overweight: 25-29.9	178,593 (10.0)	15,447 (9.5)
Obese: ≥30	64,011 (3.6)	6,445 (4.0)
Missing	841,446 (47.3)	80,781 (49.6)
Maternal smoking		
No	950,672 (53.4)	83,138 (51.0)
Yes	187,197 (10.5)	21,404 (13.1)
Missing	642,929 (36.1)	58,376 (35.8)
Gestational diabetes (ever)		
No	1,764,968 (99.1)	160,133 (98.3)
Yes	15,830 (0.9)	2,785 (1.7)
Preeclampsia (ever)		
No	1,709,392 (96.0)	141,702 (87.0)
Yes	71,406 (4.0)	21,216 (13.0)
Small for gestational age (SGA) (ever)		
No	1,700,028 (95.6)	140,572 (86.5)
Yes	77,671 (4.4)	22.008 (13.5)
Decade of first birth		
1973-1979	478,412 (26.9)	39,063 (24.0)
1980-1989	385,271 (21.6)	42,506 (26.1)
1990-1999	386,441 (21.7)	38,576 (23.7)
2000-2012	530,674 (29.8)	42,773 (26.3)
Parity		
1	610,494 (34.3)	38,564 (23.7)
2	793,672 (44.6)	70,936 (43.5)
3	291,217 (16.4)	35,819 (22.0)
4	64,811 (3.6)	11,970 (7.4)
5 or more	20,604 (1.2)	5,629 (3.5)

Table 4.2 Hazard ratios for maternal chronic kidney disease by history of preterm delivery, among women delivering between 1973 and 2012 in Sweden (n=1,943,716)

		Chronic kidney disease (N=18,001)	
	n	Minimally adjusted	Fully adjusted
		HR (95% CI)	HR (95% CI)
Exposure 1			
Term delivery (≥37 weeks)	15,914	1.0	1.0
Preterm delivery (<37 weeks)	2,087	1.47 (1.40-1.53)	1.39 (1.32-1.45)
Exposure 2			
Term delivery (≥37 weeks)	15,914	1.0	1.0
Moderate preterm delivery (32-36+6 weeks)	1,733	1.41 (1.34-1.48)	1.35 (1.28-1.41)
Very preterm delivery (28-31+6 weeks)	244	1.77 (1.56-2.01)	1.55 (1.36-1.76)
Extremely preterm delivery (<28 weeks)	110	2.05 (1.70-2.48)	1.84 (1.52-2.22)
Exposure 3			
Full term delivery (39-41+6 weeks)	9,134	1.0	1.0
Post-term delivery (≥42 weeks)	2,237	0.94 (0.90-0.98)	1.04 (0.99-1.09)
Early term delivery (37-38+6 weeks)	4,543	1.13 (1.09-1.17)	1.19 (1.15-1.24)
Moderate preterm delivery (32-36+6 weeks)	1,733	1.44 (1.37-1.52)	1.43 (1.36-1.51)
Very preterm delivery (28-31+6 weeks)	244	1.81 (1.60-2.06)	1.65 (1.45-1.87)
Extremely preterm delivery (<28 weeks)	110	2.11 (1.75-2.54)	1.96 (1.63-2.37)
Exposure 4			
Term delivery (≥37 weeks)	15,914	1.0	1.0
Spontaneous preterm delivery (<37 weeks)	1,571	1.32 (1.25-1.39)	1.32 (1.25-1.39)
Iatrogenic preterm delivery - Preeclampsia (<37 weeks)	230	2.82 (2.48-3.21)	2.81 (2.46-3.20)
Iatrogenic preterm delivery – SGA (<37 weeks)	182	1.74 (1.50-2.00)	1.66 (1.44-1.93)
Iatrogenic preterm delivery - Preeclampsia & SGA (<37 weeks)	104	2.11 (1.74-2.56)	2.10 (1.73-2.55)
Exposure 5			
Two term deliveries (≥37 weeks)	6,013	1.0	1.0
One preterm (<37 weeks) & one term delivery (≥37 weeks)	723	1.51 (1.40-1.63)	1.34 (1.24-1.45)
Two preterm deliveries (<37 weeks)	93	1.67 (1.36-2.05)	1.46 (1.19-1.79)

Hazard ratios represent separate Cox regression models for associations between preterm delivery and maternal chronic kidney disease. Each exposure variable (1-5) represents different categories used to define gestational age at delivery. For all categories, preterm delivery was a time-dependent variable, where exposure status was based on the earliest gestation of any previous delivery. Minimally adjusted models controlled for year of delivery. Fully adjusted models controlled for year of delivery, maternal age, country of origin, education level, parity, inter-pregnancy interval, maternal BMI, smoking in pregnancy, exposure to gestational diabetes (time-dependent) and preeclampsia (time-dependent). In the analyses involving Exposure 4 (spontaneous vs. iatrogenic preterm delivery) the models were not adjusted for preeclampsia.
Abbreviations: CI, confidence interval; HR, hazard ratio; SGA, small for gestational age

Table 4.3 Hazard ratios for maternal end-stage kidney disease by history of preterm delivery, among women delivering between 1973 and 2012 in Sweden (n=1,943,716)

		End-stage kidney disease (N=1,268)	
	n	Minimally adjusted	Fully adjusted
		HR (95% CI)	HR (95% CI)
Exposure 1			
Term delivery (≥37 weeks)	1,051	1.0	1.0
Preterm delivery (<37 weeks)	217	2.56 (2.21-2.97)	2.22 (1.90-2.58)
Exposure 2			
Term delivery (≥37 weeks)	1,051	1.0	1.0
Moderate preterm delivery (32-36+6 weeks)	174	2.36 (2.01-2.78)	2.08 (1.76-2.45)
Very preterm delivery (28-31+6 weeks)	30	3.81 (2.67-5.45)	2.90 (2.02-4.16)
Extremely preterm delivery (<28 weeks)	13	4.15 (2.35-7.33)	3.61 (2.03-6.39)
Exposure 3			
Full term delivery (39-41+6 weeks)	584	1.0	1.0
Post-term delivery (≥42 weeks)	146	0.97 (0.81-1.16)	1.13 (0.94-1.36)
Early term delivery (37-38+6 weeks)	321	1.44 (1.26-1.66)	1.50 (1.31-1.73)
Moderate preterm delivery (32-36+6 weeks)	174	2.61 (2.20-3.10)	2.40 (2.02-2.86)
Very preterm delivery (28-31+6 weeks)	30	4.22 (2.94-6.05)	3.37 (2.34-4.87)
Extremely preterm delivery (<28 weeks)	13	4.60 (2.60-8.16)	4.21 (2.37-7.49)
Exposure 4			
Term delivery (≥37 weeks)	1,051	1.0	1.0
Spontaneous preterm delivery (<37 weeks)	142	2.01 (1.68-2.39)	1.99 (1.67-2.38)
Iatrogenic preterm delivery - Preeclampsia (<37 weeks)	33	7.70 (5.41-10.97)	6.70 (4.70-9.56)
Iatrogenic preterm delivery – SGA (<37 weeks)	25	3.84 (2.58-5.71)	3.72 (2.49-5.53)
Iatrogenic preterm delivery - Preeclampsia & SGA (<37 weeks)	17	6.72 (4.15-10.86)	6.25 (3.86-10.11)
Exposure 5			
Two term deliveries (≥37 weeks)	350	1.0	1.0
One preterm (<37 weeks) & one term delivery (≥37 weeks)	75	2.71 (2.11-3.48)	2.12 (1.64-2.74)
Two preterm deliveries (<37 weeks)	8	2.61 (1.29-5.26)	2.02 (1.00-4.08)

Hazard ratios represent separate Cox regression models for associations between preterm delivery and maternal end-stage kidney disease. Each exposure variable (1-5) represents different categories used to define gestational age at delivery. For all categories, preterm delivery was a time-dependent variable, where exposure status was based on the earliest gestation of any previous delivery. Minimally adjusted models controlled for year of delivery. Fully adjusted models controlled for year of delivery, maternal age, country of origin, education level, parity, inter-pregnancy interval, maternal BMI, smoking in pregnancy, exposure to gestational diabetes (time-dependent) and preeclampsia (time-dependent). In the analyses involving Exposure 4 (spontaneous vs. iatrogenic preterm delivery) the models were not adjusted for preeclampsia.
Abbreviations: CI, confidence interval; HR, hazard ratio; SGA, small for gestational age

Table 4.4 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of preterm delivery, restricted to women delivering between 1982 and 2012 in Sweden (n=1,337,133)

	Chronic kidney disease (N=10,922)		End-stage kidney disease (N=547)	
	n	Fully adjusted HR (95% CI)	n	Fully adjusted HR (95% CI)
Exposure 1				
Term delivery (≥37 weeks)	9,428	1.0	424	1.0
Preterm delivery (<37 weeks)	1,494	1.39 (1.32-1.47)	123	2.28 (1.85-2.81)
Exposure 2				
Term delivery (≥37 weeks)	9,428	1.0	424	1.0
Moderate preterm delivery (32-36+6 weeks)	1,217	1.34 (1.26-1.42)	92	2.03 (1.61-2.56)
Very preterm delivery (28-31+6 weeks)	182	1.59 (1.37-1.84)	21	3.17 (2.015.01)
Extremely preterm delivery (<28 weeks)	95	2.05 (1.67-2.51)	10	5.14 (2.81-9.40)
Exposure 3				
Full term delivery (39-41+6 weeks)	5,032	1.0	213	1.0
Post-term delivery (≥42 weeks)	1,202	1.04 (0.97-1.11)	48	1.01 (0.74-1.39)
Early term delivery (37-38+6 weeks)	3,194	1.21 (1.15-1.26)	163	1.48 (1.20-1.82)
Moderate preterm delivery (32-36+6 weeks)	1,217	1.44 (1.35-1.53)	92	2.36 (1.83-3.04)
Very preterm delivery (28-31+6 weeks)	182	1.71 (1.47-1.98)	21	3.70 (2.32-5.90)
Extremely preterm delivery (<28 weeks)	95	2.20 (1.80-2.70)	10	5.98 (3.24-11.03)
Exposure 4				
Term delivery (≥37 weeks)	9,428	1.0	424	1.0
Spontaneous preterm delivery (<37 weeks)	1,084	1.31 (1.23-1.40)	71	1.89 (1.46-2.44)
Iatrogenic preterm delivery - Preeclampsia (<37 weeks)	188	2.76 (2.39-3.19)	22	6.52 (4.19-10.14)
Iatrogenic preterm delivery – SGA (<37 weeks)	134	1.79 (1.51-2.13)	19	4.29 (3.33-8.40)
Iatrogenic preterm delivery - Preeclampsia & SGA (<37 weeks)	88	2.18 (1.77-2.69)	11	5.91 (3.24-10.76)
Exposure 5				
Two term deliveries (≥37 weeks)	4,208	1.0	189	1.0
One preterm (<37 weeks) & one term delivery (≥37 weeks)	529	1.32 (1.21-1.45)	37	1.70 (1.18-2.44)
Two preterm deliveries (<37 weeks)	72	1.43 (1.13-1.81)	7	2.66 (1.24-5.69)

Hazard ratios represent separate Cox regression models for associations between preterm delivery and maternal chronic kidney disease. Each exposure variable (1-5) represents different categories used to define gestational age at delivery. For all categories, preterm delivery was a time-dependent variable, where exposure status was based on the earliest gestation of any previous delivery. Minimally adjusted models controlled for year of delivery. Fully adjusted models controlled for year of delivery, maternal age, country of origin, education level, parity, inter-pregnancy interval, maternal BMI, smoking in pregnancy, exposure to gestational diabetes (time-dependent) and preeclampsia (time-dependent). In the analyses involving Exposure 4 (spontaneous vs. iatrogenic preterm delivery) the models were not adjusted for preeclampsia.
Abbreviations: CI, confidence interval; HR, hazard ratio; SGA, small for gestational age

CHAPTER 5 STILLBIRTH IS ASSOCIATED WITH INCREASED RISK OF LONG-TERM MATERNAL RENAL DISEASE: A NATIONWIDE COHORT STUDY

Peter M. Barrett (1, 2), Fergus P. McCarthy (2, 3), Marie Evans (4), Marius Kublickas (5), Ivan J. Perry (1), Peter Stenvinkel (4), Ali S. Khashan (1, 2), Karolina Kublickiene (4).

1. School of Public Health, University College Cork, Cork, Ireland
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland
3. Department of Obstetrics & Gynaecology, Cork University Maternity Hospital, Cork, Ireland
4. Department of Clinical Sciences Intervention and Technology, Karolinska Institutet, Huddinge, Sweden
5. Department of Obstetrics & Gynaecology, Karolinska Institutet, Stockholm, Sweden

Published in: *American Journal of Obstetrics and Gynecology, February 2020*

(Paper 4)

5.1 Abstract

Background

Stillbirth is a devastating adverse pregnancy outcome that may occur without any obvious reason or may occur in the context of foetal growth restriction, preeclampsia, or other obstetric complications. There is increasing evidence that women who experience stillbirths are at greater risk of long-term cardiovascular disease, but little is known about their risk of chronic kidney disease and end-stage kidney disease. We conducted the largest study to date to investigate the subsequent risk of maternal chronic kidney disease and end-stage kidney disease following stillbirth.

Objective

To identify whether pregnancy complicated by stillbirth is associated with subsequent risk of maternal chronic kidney disease and end-stage kidney disease, independent of underlying medical or obstetric comorbidities.

Study Design/Methods

We conducted a population-based cohort study using nationwide data from the Swedish Medical Birth Register, National Patient Register, and Swedish Renal Register. We included all women who had live births and stillbirths from 1973 to 2012, with follow-up to 2013. Women with preexisting renal disease were excluded. Cox proportional hazard regression models were used to estimate adjusted hazard ratios and 95% confidence intervals for associations between stillbirth and maternal chronic kidney disease and end-stage kidney disease respectively. We controlled for maternal age, year of delivery, country of origin, parity, body mass index, smoking, gestational diabetes, preeclampsia, and small for gestational age deliveries. Women who had a history of medical comorbidities, which may predispose to renal disease (pre-pregnancy cardiovascular disease, hypertension, diabetes, lupus, systemic

sclerosis, haemoglobinopathy, or coagulopathy), were excluded from the main analysis and examined separately.

Results

There were 1,941,057 unique women who had 3,755,444 singleton pregnancies, followed up over 42,313,758 person-years. The median follow-up time was 20.7 years (interquartile range, 9.9–30.0 years). 13,032 women (0.7%) had at least 1 stillbirth. Women who had experienced at least 1 stillbirth had a greater risk of developing chronic kidney disease (aHR, 1.26; 95% CI, 1.09–1.45) and end-stage kidney disease (aHR, 2.25; 95% CI, 1.55–3.25) compared with women who only had live births. These associations persisted after removing all stillbirths that occurred in the context of preeclampsia, and small for gestational age or congenital malformations (for chronic kidney disease, aHR, 1.33; 95% CI, 1.13–1.57; for end-stage kidney disease, aHR, 2.95; 95% CI, CI 1.86–4.68). There was no significant association observed between stillbirth and either chronic kidney disease or end-stage kidney disease in women who had pre-existing medical comorbidities (chronic kidney disease, aHR, 1.13; 95% CI, 0.73–1.75 or end-stage kidney disease, aHR, 1.49; 95% CI, 0.78–2.85).

Conclusion

Women who have a history of stillbirth may be at increased risk of chronic kidney disease and end-stage kidney disease compared with women who have only had live births. This association persists independently of preeclampsia, small for gestational age, maternal smoking, obesity, and medical comorbidities. Further research is required to determine whether affected women would benefit from closer surveillance and follow-up for future renal disease.

5.2 Introduction

Stillbirth is a devastating adverse pregnancy outcome that affects more than 7,000 women worldwide every day, mostly in low- and middle-income countries (64, 183). Stillbirth may result from a wide range of complex pathophysiologic processes occurring in the mother, foetus, or placenta. Many stillbirth classification systems exist (184-187), but common risk factors for stillbirth include foetal growth restriction (FGR), hypertensive disorders of pregnancy, maternal obesity, infections, and congenital malformations (188, 189). Women who experience stillbirth may also be predisposed to chronic disease in later life (190), and there is increasing evidence that they are at greater risk of cardiovascular disease (CVD) (75, 191-193) and premature mortality (19, 194, 195).

Little is known about the long-term risk of chronic kidney disease (CKD) among women who experience perinatal loss. Stillbirth has been associated with renovascular hypertension (193) and mortality related to renal disease (195) in previous longitudinal studies, but existing research may be limited by relatively small numbers of stillbirths and residual confounding. The risk of subsequent CKD and end-stage kidney disease (ESKD) has not been established.

Certain obstetric factors, such as FGR and preeclampsia, have been linked to the risk of maternal renal disease previously (28, 29, 32, 77, 92). It is unclear whether any possible associations between stillbirth and maternal CKD persist independently of other obstetric complications. Furthermore, women with pre-pregnancy comorbidities such as hypertension, CVD, diabetes, autoimmune diseases, and coagulation disorders are at greater risk of stillbirth than the general population (140, 188, 189). Their baseline risk of CKD and ESKD is also elevated, and it is relevant to consider whether stillbirth has any incremental effect on the overall risk of renal disease in these women.

This study aims to identify whether women who experience stillbirth are at risk of subsequent CKD and ESKD and whether the presence of underlying medical or obstetric comorbidities influences this risk.

5.3 Methods

Study population

A population-based cohort study was undertaken using data from the Swedish Medical Birth Register (MBR, established 1973), National Patient Register (NPR, established 1964) and Swedish Renal Register (SRR, established 1991). Data from the MBR were used to identify women who had singleton live births or stillbirths between 1973 and 2012 inclusive. Data from each of these registers were linked using anonymised unique personal identification numbers. We included data on hospital admissions in the NPR from 1973 onwards and outpatient reviews from 2001 until December 31, 2013. The SRR contains information on ESKD diagnoses from 1991 onwards, and on CKD from 2007. Data from the Swedish Death Register and Migration Register were linked to the main merged dataset for follow-up censoring.

We excluded women with any diagnosis of renal disease in the NPR, MBR, or SRR before their index pregnancy. For our main analysis, we excluded women with a history of CVD, chronic hypertension, diabetes, systemic lupus erythematosus, systemic sclerosis, haemoglobinopathies, or coagulopathies at baseline. The full list of *International Classification of Diseases* (ICD) codes used are available in Table A7.1, Appendix 7. We excluded multiple pregnancies, pregnancies with implausible dates of delivery, and pregnancies with implausible birthweights for gestational age (using established thresholds) (196) from all analyses (Figure 5.1).

Stillbirth

The MBR routinely collects information on all stillbirths occurring in Sweden (118). Stillbirth was defined as foetal death after 28+0 weeks between 1 January 1973 and 30 June 2008. The definition of stillbirth was changed in Sweden on July 1, 2008, to include all foetal deaths after 22+0 weeks (140). The incidence rate of stillbirth was first calculated (per 1,000 deliveries) to examine changes over time.

Maternal history of any stillbirth was the main exposure variable. This was treated as a time-dependent variable, whereby women could contribute pregnancies and person-time to both unexposed and exposed groups during follow-up. Women were considered exposed from their first stillbirth onwards, regardless of any subsequent live births.

Most stillbirths occur before onset of labour (antepartum), but about 10% of all stillbirths in high-income countries occur during labour (intrapartum), and this rises to over 50% in some low-income settings (189). Few studies have considered whether the timing of stillbirth impacts on maternal chronic disease outcomes. Thus, stillbirths were further categorised in the MBR as occurring antepartum or intrapartum, and these categories were examined separately.

Many stillbirths occur in the context of congenital malformations, FGR, or placental insufficiency (187, 197), and these factors may confound associations between stillbirth and maternal CKD. Thus, pregnancies complicated by stillbirth and congenital malformations, FGR, or preeclampsia were sequentially excluded to identify whether associations persisted or changed. Data on congenital malformations were available as ICD-coded diagnoses in the MBR. SGA was recorded in the MBR and defined as a birth weight of 2 standard deviations below the sex-specific and gestational age distributions, per Swedish weight-based growth standards (139). Information on preeclampsia was available from ICD-coded diagnoses in the

MBR, and supplemented using information on hospital admissions or outpatient reviews from the NPR.

Outcomes

Maternal CKD and ESKD were the outcomes of interest, and these were defined by a recorded diagnosis in the SRR, or based on primary or secondary diagnosis of CKD or ESKD in the NPR (hospital admissions or outpatient reviews, using ICD-codes). ESKD was defined as stage 5 CKD, requiring dialysis or renal transplant. Women were assumed to be diagnosed with CKD or ESKD on the earliest date they were recorded in either the SRR or NPR. We excluded women who developed renal disease due to any identifiable congenital or genetic cause from all analyses (Table A7.1, Appendix 7).

Potential confounders

We adjusted for the following covariates: maternal age (continuous), year of delivery, country of origin (Sweden vs elsewhere), maternal education (highest level achieved, proxy for socioeconomic status), parity, antenatal body mass index (BMI), smoking during pregnancy, gestational diabetes, preeclampsia, and small for gestational age (SGA) delivery.

Data on maternal smoking and BMI were only collected from 1982 onwards, and they contained large amounts of missing data. We created missing indicator variables to control for this, and also conducted sensitivity analyses restricted to births from 1982 onwards. Maternal exposure to gestational diabetes, preeclampsia, and SGA delivery were included as time-dependent covariates, where women were considered exposed from the date of their first delivery with each respective adverse pregnancy outcome. Preeclampsia was defined as a diastolic blood pressure of >90 mm Hg with proteinuria (0.3 g/d or 1+ on a urine dipstick) (29),

excluding women who developed preeclampsia superimposed on chronic hypertension since women with pre-pregnancy hypertension were excluded at baseline.

Ethical considerations

Ethical approval was granted by the Swedish Ethical Review Authority in Stockholm (*Regionala Etikprövningsnämnden Stockholm*; Dnr 2012/397-31/1) and the Social Research and Ethics Committee, University College Cork (2019-109).

Statistical analysis

Data were set up for survival analysis, where entry date in the study was the date of each woman's first delivery (live birth or stillbirth). We chose survival analysis methods to allow us to quantify time to CKD/ESKD diagnosis and to capture loss to follow-up due to death or emigration. The association between history of stillbirth and risk of maternal CKD was estimated using the Kaplan-Meier method, and the difference in survival curves was estimated using the log-rank test. We used multivariable Cox proportional hazard regression models to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for associations between stillbirth and maternal CKD and ESKD respectively. We used log cumulative hazard plots and Schoenfeld residuals to check the adequacy of each Cox regression model and the proportional hazards assumption was met.

We followed up women from their date of first delivery until CKD/ESKD diagnosis, date of death, date of emigration, or study end date (December 31, 2013), whichever came first. For each association, we adjusted sequentially for maternal age (Model 1), other demographic characteristics (country of origin, maternal education, parity) (Model 2), lifestyle-related factors (pre-pregnancy BMI, smoking) or gestational diabetes (Model 3), and placental factors

(preeclampsia and SGA delivery) (Model 4). We stratified all models by year of delivery. We checked for any interactions between stillbirth and maternal age (as categorical variable), or between stillbirth and preeclampsia or SGA, in the final model. All models were performed for stillbirths overall, and for antepartum and intrapartum stillbirths separately.

We conducted 5 separate sensitivity analyses. First, we restricted the dataset to births from 1982 onwards to investigate whether missing data on maternal smoking or BMI impacted on the results. Second, we restricted the dataset to births from 1987 onwards when the NPR achieved national coverage. Third, we excluded pregnancies complicated by congenital malformations, SGA, or preeclampsia sequentially to identify whether associations with CKD or ESKD changed. Fourth, we examined women who had a pre-pregnancy history of medical comorbidities separately (ie, pre-pregnancy CVD, hypertension, diabetes, systemic lupus erythematosus, systemic sclerosis, haemoglobinopathy, or coagulopathy) to identify whether a history of stillbirth conferred any additional risk of renal disease in these women. Finally, we repeated all analyses of CKD with varying lengths of follow up at 10, 20, and 30 years following index pregnancy respectively. All analyses were performed using Stata version 15 (StataCorp LLC, College Station, TX).

5.4 Results

The study cohort consisted of 1,941,057 unique women who had 3,755,444 singleton pregnancies, followed up over 42,313,758 person-years. The median follow-up time was 20.7 years (interquartile range, 9.9-30.0 years). There were 13,032 women (0.7%) who had at least 1 stillbirth, of which 91% (n = 11,841) were antepartum. The overall incidence rate of stillbirth was 3.5 stillbirths per 1,000 deliveries between 1973 and 2012. This dropped from 5.2/1,000 deliveries in the 1970s (stillbirths occurring ≥28 weeks) to 3.1/1,000 deliveries between July

2008 and December 2012 (stillbirths occurring ≥22 weeks; or alternatively 2.7/1,000 deliveries ≥28 weeks).

The mean (standard deviation) maternal age at stillbirth was 28.9 (5.7) years. Women who had a history of stillbirth had higher parity, lower level of education, were more likely to be from outside Sweden, were more likely to smoke, and were more likely to have a history of another adverse pregnancy outcome (preeclampsia, gestational diabetes, or SGA delivery), particularly SGA (Table 5.1).

Overall, 18,017 women (0.9%) developed CKD, and 1,283 women (0.07%) developed ESKD. As shown in Figure 5.2, the risk of CKD was increased among women who had a history of stillbirth compared with women who only had live births (log-rank P<0.001). The median time to develop CKD among all women was 16.8 years (interquartile range, 7.3-26.5 years), and for ESKD was 20.2 years (11.6-27.3 years), but did not differ significantly by history of stillbirth.

Table 5.2 summarises the results of the main analysis. In age-adjusted models, women who had a history of stillbirth had significantly greater risk of CKD (vs no stillbirth, HR, 1.58; 95% CI, 1.38-1.82). After we adjusted for all other confounders, this association was attenuated, but remained statistically significant (aHR, 1.26; 95% CI, 1.09-1.45). This was largely driven by women who had antepartum stillbirths (vs no stillbirths, aHR, 1.28; 95% CI, 1.11-1.49). Stronger associations were observed for ESKD. In age-adjusted models, women with a history of any stillbirth were at greater risk of ESKD (HR, 3.51; 95% CI, 2.46-5.02) compared with women who only had live births. In fully adjusted models, this association remained strongly significant (aHR, 2.25; 95% CI, 1.55-3.25), and was largely driven by women who had antepartum stillbirths (vs no stillbirths, aHR, 2.27; 95% CI, 1.54-3.35).

The results for intrapartum stillbirth and both CKD and ESKD suggested possible non-associations (for CKD: aHR, 1.07; 95% CI, 0.67-1.69; for ESKD: aHR, 2.02; 95% CI, 0.65-6.29) but these were based on small numbers of events. There was no evidence for interactions

between stillbirth and maternal age, or between stillbirth and preeclampsia or SGA. When the dataset was restricted to women giving birth after 1982 or 1987 respectively, no meaningful differences were observed (Table A7.2, Appendix 7). When women who experienced congenital malformations, SGA, and preeclampsia were excluded from the dataset, the associations between stillbirth and maternal kidney disease were strengthened (for CKD: aHR, 1.33; 95% CI, 1.13-1.57; for ESKD: aHR, 2.95; 95%, CI, 1.86-4.68) (Table 5.3).

In total, 17,416 women with pre-pregnancy medical conditions remained in the dataset when examined separately. Of these, 863 women (5.0%) developed CKD and 270 (1.6%) developed ESKD. No significant association between stillbirth and either CKD or ESKD was observed in this group (for CKD: aHR, 1.13; 95% CI, 0.73-1.75; for ESKD: aHR, 1.49; 95% CI, 0.78-2.85) (Table A7.3, Appendix 7).

5.5 Discussion

Principal findings and interpretation

We aimed to determine whether women who experience stillbirth are at risk of long-term CKD and ESKD. We observed an overall decline in the incidence rate of stillbirth over time, a modest increased risk of future CKD in women with a history of stillbirth, and a considerably increased relative risk of ESKD. The associations between stillbirth and renal disease persisted independently of underlying medical and obstetric comorbidities, including SGA and preeclampsia. In women who were already predisposed to future renal disease due to pre-pregnancy medical comorbidities, a history of stillbirth did not appear to confer additional risk of CKD or ESKD.

There is limited prior research on the risk of long-term renal disease among women who have had stillbirths. A cohort study of Israeli women reported 5 times greater risk of mortality from renal disease in mothers who experienced stillbirth versus women in the general population,

but this study controlled for fewer pre-pregnancy comorbidities than our study and was based on much smaller numbers of stillbirths (195). A Danish registry-based study sought to describe the association between perinatal loss (stillbirths and early neonatal deaths) and maternal mortality from renal disease, but could not quantify this risk due to small numbers (190). Ranthe et al. (193) identified higher risk of renovascular hypertension among Danish women who experienced stillbirths, and this may partly explain the associations we observed with subsequent renal disease. However, to our knowledge, we are the first to identify that women with a history of stillbirth are at increased risk of being diagnosed with CKD and ESKD.

The association between stillbirth and maternal CVD has been established in previous studies (19, 75, 191-193). Thus, it is biologically plausible that stillbirth is associated with increased risk of renal disease. There are several proposed mechanisms through which this may occur: persistent endothelial dysfunction following stillbirth which may predispose women to CVD and renal disease (198); altered immune activation (199); and high homocysteine levels, which are associated with pregnancy loss and are also elevated in CKD (200, 201). Nonetheless, it seems unlikely that the observed associations between stillbirth and maternal renal disease are causal. It is possible that women who experience stillbirth have greater baseline risk of cardiometabolic disease, which also predisposes them to pregnancy loss. Stillbirth may be a manifestation of their greater risk phenotype, rather than an independent causal factor for renal disease.

Clinical and research implications

Women who experience stillbirth may warrant consideration as candidates for closer surveillance, or postpartum interventions for future hypertension and renal disease. Although associations between stillbirths and renal disease in this study were independent of other obstetric complications, the strength of associations was attenuated after adjusting for

preeclampsia or SGA delivery. Many women experience multiple adverse pregnancy outcomes, either concurrently or over the course of their reproductive lifetime, and they may be at higher risk of chronic disease than women who experience any of these in isolation. Thus, further research is warranted to determine whether obstetric factors, including stillbirth, should be considered as isolated risk markers for future maternal disease, or whether these may be more clinically useful if considered in combination with each other.

Strengths and limitations

This is the largest study to investigate the association between stillbirth and maternal CKD to date. Our sample size and long follow-up period of up to 41 years provided statistical power to examine whether stillbirth is independently associated with CKD and ESKD. All data were retrieved from national registers with mandatory reporting and high reported levels of validity (118, 119). We were able to improve on existing research by adjusting for a larger number of potential confounders. We also used time-dependent covariates, which are more representative of women's cumulative exposure to risks during their reproductive lives.

There are a number of limitations to this study. Although a large sample size was obtained, we were unable to conduct an analysis of recurrent stillbirths due to small numbers and the relative rarity of the outcomes. Few women experienced more than one stillbirth (n = 198), and it is unclear whether they may be at higher risk of long-term kidney disease.

Furthermore, intrapartum stillbirths are relatively rare in Sweden (140), and very few women experienced both intrapartum stillbirth and either CKD or ESKD. This may have reduced precision of our effect estimates, and limited our ability to draw firm conclusions on the impact of intrapartum stillbirth.

We did not have information on the underlying causes of stillbirth in this study. Although we were able to identify many stillbirths which were complicated by congenital malformations, FGR, preeclampsia, and maternal comorbidities, it is possible that these factors were incidental, or unrelated to the cause of stillbirth in some women. The underlying causes of stillbirth may be differentially associated with women's future cardiometabolic risk, and further research is needed to investigate their associations with long-term risk of renal disease

The definition of stillbirths changed during the study period, and women who had stillbirths at 22-28 weeks' gestation were not counted before 2008. It is estimated that about one third of stillbirths are excluded when high-income countries use a threshold of 28+0 weeks to define stillbirths (202). Considerably more women would have been included in the exposed group if 22+0 weeks had been used to define stillbirths from the outset (140).

Most cases of CKD and ESKD were defined using ICD-coded diagnoses in the NPR. There is a possibility of under-ascertainment of CKD from the NPR, as it only records patients who were admitted to hospital or reviewed as outpatients with a diagnosis of CKD/ ESKD (119). Many women with CKD may be undiagnosed, particularly in the early stages of disease, and the NPR will not capture those who are cared for in community settings. In addition, although the SRR has comprehensive coverage of ESKD cases in Sweden, coverage of CKD cases is lower (123). Women with pre-existing medical comorbidities may be similarly under-ascertained from the NPR. Nonetheless, high positive predictive values have been reported for other diseases in the NPR previously (119), and thus, it is likely that those who are identified as having CKD or ESKD have valid diagnoses.

Women with a history of preterm delivery may be at increased risk of CKD and ESKD (28, 77, 94, 200), and this may potentially confound the association between stillbirth and maternal renal disease. However, stillbirth often results in a preterm delivery (203), and thus, preterm birth may also mediate the association with maternal CKD/ESKD. Controlling for an

intermediate variable would introduce over-adjustment bias (204), thus we did not control for preterm delivery in our analysis. However, we included preterm delivery in fully adjusted models in a post-hoc analysis, and although results were attenuated they did not materially change.

Data on congenital malformations may be incomplete from the MBR, as these are also recorded in the Swedish Register of Congenital Malformations separately. It is possible that some births with undiagnosed malformations may have been inadvertently included in the analysis. Furthermore, residual confounding by undetected FGR is a possibility. Undetected FGR is an important contributory factor for stillbirth (205), and FGR has been linked to long-term maternal renal disease previously (32).

There was no national consensus with regard to GDM screening in Sweden during the study period (141, 206). A mix of selective and universal screening methods, and a range of diagnostic cut-off values, were used in clinical practice and this may have led to some unmeasured confounding in the study. Finally, we had large amounts of missing data on maternal BMI and smoking in our dataset, and the use of a missing indicator variable may have introduced bias. However, our sensitivity analyses were restricted to 1982 and 1987 onwards respectively, when these data were more complete, and the results were not substantially different.

5.6 Conclusion

Women who have a history of stillbirth are at increased risk of CKD and ESKD compared to women who have only had live births. This association appears to persist independently of underlying medical and obstetric comorbidities. Further research is required to better understand the underlying pathophysiology of this association, and to determine whether

affected women would benefit from closer surveillance and follow-up for future hypertension and renal disease.

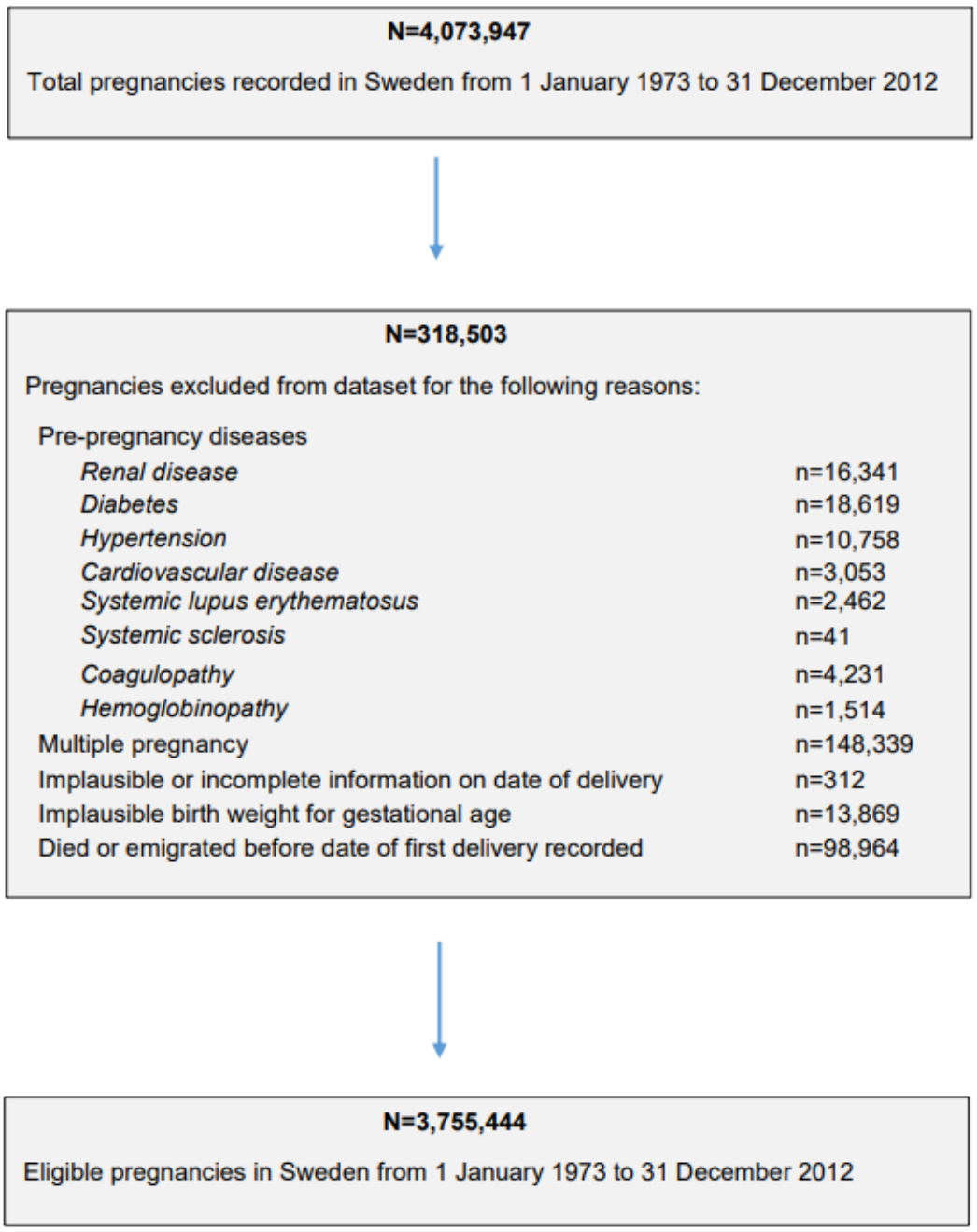
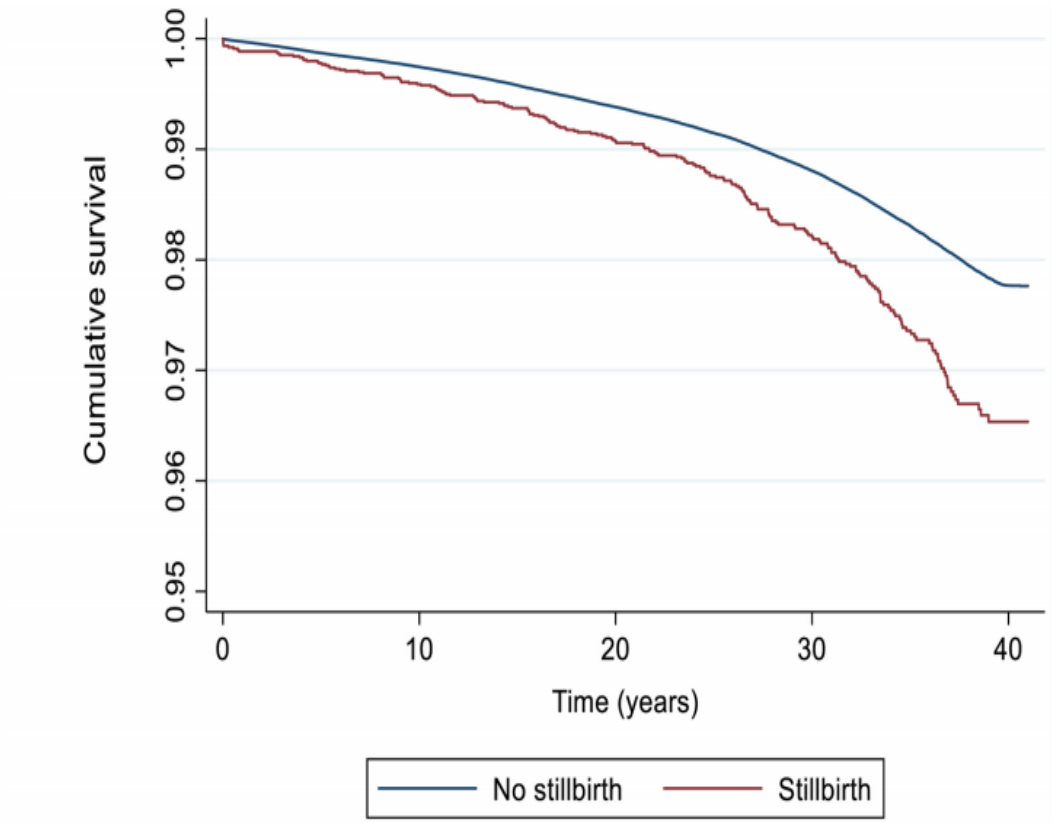


Figure 5.1 Flow chart illustrating construction of study cohort



	0-10 years	10-20 years	20-30 years	30-41 years
No history of stillbirth				
Number at risk of CKD	1,928,025	1,459,075	1,065,575	617,900
Number of CKD diagnoses	4,567	4,559	4,691	4,200
History of stillbirth				
Number at risk of CKD	13,032	10,776	8,273	5,107
Number of CKD diagnoses	38	48	56	60

Figure 5.2 Kaplan-Meier survival curves for risk of chronic kidney disease among women based on their exposure to previous stillbirth between 1973 and 2012 in Sweden

Table 5.1 Maternal characteristics and pregnancy outcomes among women delivering between 1973 and 2012 in Sweden, stratified by exposure to at least one stillbirth

	No stillbirth, n (%) N=1,928,025 (99.3)	**Stillbirth, n (%)** N=13,032 (0.7)
Age in years		
<20	110,247 (5.7)	1,006 (7.7)
20-29	1,246,167 (64.6)	8,354 (64.1)
30-39	544,976 (28.3)	3,428 (26.3)
>=40	26,635 (1.4)	244 (1.9)
Native country		
Sweden	1,634,646 (84.8)	10,489 (80.5)
Elsewhere	293,379 (15.2)	2,543 (19.5)
Education level		
Less than Upper Secondary	255,4218 (13.3)	2,259 (17.3)
Upper Secondary	871,010 (45.2)	6,237 (47.9)
Third level	761,327 (39.5)	4,250 (32.6)
Missing	40,267 (2.1)	286 (2.2)
Body mass index in early pregnancy (kg/m^2)		
Underweight: <18.5	45,620 (2.4)	233 (1.8)
Normal: 18.5-24.9	705,945 (36.6)	3,397 (26.1)
Overweight: 25-29.9	192,310 (10.0)	1,267 (9.7)
Obese: ≥30	69,543 (3.6)	641 (4.9)
Missing	914,607 (47.4)	7,494 (57.5)
Maternal smoking		
No	1,025,800 (53.2)	5,531 (42.4)
Yes	206,736 (10.7)	1,620 (12.4)
Missing	695,489 (36.1)	5,881 (45.1)
Gestational diabetes (ever)		
No	1,909,864 (99.1)	12,718 (97.6)
Yes	18,161(0.9)	314 (2.4)
Preeclampsia (ever)		
No	1,836,778 (95.3)	11,739 (90.1)
Yes	91,247 (4.7)	1,293 (9.9)
Small for gestational age (SGA) (ever)		
No	1,827,649 (94.9)	8,465 (65.1)
Yes	98,433 (5.1)	4,540 (34.9)
Decade of first birth		
1973-1979	513,507 (26.6)	4,407 (33.8)
1980-1989	423,964 (22.0)	3,121 (24.0)
1990-1999	421,561 (21.9)	2,701 (20.7)
2000-2012	568,993 (29.5)	2,803 (21.5)
Parity		
1	645,641 (33.5)	1,424 (10.9)
2	861,082 (44.7)	2,944 (22.6)
3	321,984 (16.7)	4,980 (38.2)
4	74,245 (3.9)	2,525 (19.4)
5 or more	25,073 (1.3)	1,159 (8.9)

Table 5.2 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of stillbirth, among women delivering between 1973 and 2012 in Sweden

	n	Model 1 (Age-adjusted) HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 (Fully adjusted) HR (95% CI)
Chronic kidney disease					
No stillbirth	17,815	1.0	1.0	1.0	1.0
Any stillbirth	202	1.58 (1.38-1.82)	1.44 (1.25-1.66)	1.41 (1.23-1.62)	1.26 (1.09-1.45)
No stillbirth	17,815	1.0	1.0		1.0
Antepartum stillbirth	184	1.62 (1.40-1.87)	1.47 (1.27-1.70)	1.44 (1.24-1.67)	1.28 (1.11-1.49)
Intrapartum stillbirth	18	1.29 (0.81-2.04)	1.18 (0.74-1.87)	1.17 (0.74-1.85)	1.07 (0.67-1.69)
End-stage kidney disease					
No stillbirth	1,249	1.0	1.0	1.0	1.0
Any stillbirth	34	3.51 (2.46-5.02)	3.26 (2.27-4.68)	3.11 (2.17-4.47)	2.25 (1.55-3.25)
No stillbirth	1,249	1.0	1.0	1.0	1.0
Antepartum stillbirth	30	3.62 (2.48-5.26)	3.35 (2.29-4.90)	3.19 (2.18-4.66)	2.27 (1.54-3.35)
Intrapartum stillbirth	4	2.77 (0.89-8.61)	2.61 (0.84-8.12)	2.53 (0.81-7.88)	2.02 (0.65-6.29)

Hazard ratios represent separate Cox regression models for associations between stillbirth and maternal chronic kidney disease or end-stage kidney disease. In all models, delivery of a stillbirth was a time-dependent variable, where maternal exposure status was based on the date of first stillbirth

Model 1 adjusted for maternal age, stratified by year of delivery.

Model 2 adjusted for maternal age, country of origin, maternal education and parity, stratified by year of delivery.

Model 3 adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking and maternal exposure to gestational diabetes (time-dependent covariate), stratified by year of delivery.

Model 4 adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, and maternal exposure to gestational diabetes, preeclampsia and SGA delivery (time-dependent covariates), stratified by year of delivery.

Women with pre-pregnancy history of renal disease, cardiovascular disease, hypertension, diabetes, systemic lupus erythematosus, systemic sclerosis, haemoglobinopathy or coagulopathy were excluded at baseline.

CI, confidence interval; HR, hazard ratio

Table 5.3 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of stillbirth, among women delivering between 1973 and 2012 in Sweden, excluding pregnancies complicated by congenital malformations, small for gestational age, and preeclampsia

	Chronic kidney disease			End-stage kidney disease		
	n	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)	n	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Excluding deliveries with congenital malformations						
No stillbirth	16,954	1.0	1.0	1,177	1.0	1.0
Stillbirth (any)	186	1.56 (1.35-1.80)	1.25 (1.08-1.44)	27	3.03 (2.07-4.44)	2.08 (1.41-3.10)
Further excluding SGA deliveries						
No stillbirth	16,211	1.0	1.0	1,089	1.0	1.0
Stillbirth (any)	155	1.46 (1.24-1.71)	1.29 (1.10-1.51)	21	2.77 (1.80-4.28)	2.43 (1.57-3.76)
Further excluding preeclamptic deliveries						
No stillbirth	15,370	1.0	1.0	959	1.0	1.0
Stillbirth (any)	144	1.45 (1.23-1.71)	1.33 (1.13-1.57)	19	2.94 (1.87-4.63)	2.95 (1.86-4.68)

Hazard ratios represent separate Cox regression models for associations between stillbirth and maternal chronic kidney disease or end-stage kidney disease. In all models, delivery of a stillbirth was a time-dependent variable, where maternal exposure status was based on the date of first stillbirth

Pregnancies complicated by congenital malformations, small for gestational age, or preeclampsia were sequentially excluded.

Fully adjusted models controlled for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, and maternal exposure to gestational diabetes (time-dependent covariate), stratified by year of delivery. Models were initially adjusted for preeclampsia and SGA delivery (time-dependent covariates) prior to exclusion of these deliveries from the dataset.

Women with pre-pregnancy history of renal disease, cardiovascular disease, hypertension, diabetes, systemic lupus erythematosus, systemic sclerosis, haemoglobinopathy or coagulopathy were excluded at baseline.

CI, confidence interval; HR, hazard ratio; SGA, small for gestational age

CHAPTER 6 HYPERTENSIVE DISORDERS OF PREGNANCY AND THE RISK OF CHRONIC KIDNEY DISEASE: A SWEDISH REGISTRY-BASED COHORT STUDY

Peter M. Barrett (1, 2), Fergus P. McCarthy (2, 3), Marie Evans (4), Marius Kublickas (5), Ivan J. Perry (1), Peter Stenvinkel (4), Ali S. Khashan (1, 2), Karolina Kublickiene (4).

1. School of Public Health, University College Cork, Cork, Ireland
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland
3. Department of Obstetrics & Gynaecology, Cork University Maternity Hospital, Cork, Ireland
4. Department of Clinical Sciences Intervention and Technology, Karolinska Institutet, Huddinge, Sweden
5. Department of Obstetrics & Gynaecology, Karolinska Institutet, Stockholm, Sweden

Published in: *PLOS Medicine, August 2020*

(Paper 5)

6.1 Abstract

Background

Hypertensive disorders of pregnancy (HDP) (preeclampsia, gestational hypertension) are associated with an increased risk of end-stage kidney disease (ESKD). Evidence for associations between HDP and chronic kidney disease (CKD) is more limited and inconsistent. The underlying causes of CKD are wide-ranging, and HDP may have differential associations with various aetiologies of CKD. We aimed to measure associations between HDP and maternal CKD in women who have had at least one live birth and to identify whether the risk differs by CKD aetiology.

Methods and findings

Using data from the Swedish Medical Birth Register (MBR), singleton live births from 1973 to 2012 were identified and linked to data from the Swedish Renal Register (SRR) and National Patient Register (NPR; up to 2013). Preeclampsia was the main exposure of interest and was treated as a time-dependent variable. Gestational hypertension was also investigated as a secondary exposure. The primary outcome was maternal CKD, and this was classified into 5 subtypes: hypertensive, diabetic, glomerular/proteinuric, tubulointerstitial, and other/nonspecific CKD. Cox proportional hazard regression models were used, adjusting for maternal age, country of origin, education level, antenatal BMI, smoking during pregnancy, gestational diabetes, and parity. Women with pre-pregnancy comorbidities were excluded.

The final sample consisted of 1,924,409 women who had 3,726,554 singleton live births. The mean (±SD) age of women at first delivery was 27.0 (±5.1) years. Median follow-up was 20.7 (interquartile range [IQR] 9.9–30.0) years. A total of 90,917 women (4.7%) were diagnosed with preeclampsia, 43,964 (2.3%) had gestational hypertension, and 18,477 (0.9%) developed

CKD. Preeclampsia was associated with a higher risk of developing CKD during follow-up (adjusted hazard ratio [aHR] 1.92, 95% CI 1.83–2.03, p < 0.001). This risk differed by CKD subtype and was higher for hypertensive CKD (aHR 3.72, 95% CI 3.05–4.53, p < 0.001), diabetic CKD (aHR 3.94, 95% CI 3.38–4.60, p < 0.001), and glomerular/proteinuric CKD (aHR 2.06, 95% CI 1.88–2.26, p < 0.001). More modest associations were observed between preeclampsia and tubulointerstitial CKD (aHR 1.44, 95% CI 1.24–1.68, p < 0.001) or other/nonspecific CKD (aHR 1.51, 95% CI 1.38–1.65, p < 0.001). The risk of CKD was increased after preterm preeclampsia, recurrent preeclampsia, or preeclampsia complicated by pre-pregnancy obesity. Women who had gestational hypertension also had increased risk of developing CKD (aHR 1.49, 95% CI 1.38–1.61, p < 0.001). This association was strongest for hypertensive CKD (aHR 3.13, 95% CI 2.47–3.97, p < 0.001). Limitations of the study are the possibility that cases of CKD were underdiagnosed in the national registers, and some women may have been too young to have developed symptomatic CKD despite the long follow-up time. Underreporting of postpartum hypertension is also possible.

Conclusions

In this study, we found that HDP are associated with increased risk of maternal CKD, particularly hypertensive or diabetic forms of CKD. The risk is higher after preterm preeclampsia, recurrent preeclampsia, or preeclampsia complicated by pre-pregnancy obesity. Women who experience HDP may benefit from future systematic renal monitoring.

6.2 Introduction

Preeclampsia is characterised by the development of de novo hypertension after 20 weeks' gestation, in the presence of either proteinuria, maternal organ dysfunction (including renal insufficiency), or evidence of foetal growth restriction (133). It complicates 3%–5% of pregnancies worldwide (63), and affected women are at higher risk of long-term cardiovascular disease (CVD) (53, 71, 72). Preeclampsia has also been described as a reversible kidney disease that typically self-resolves within 3 months of delivery (73). However, there is increasing evidence that some women experience sustained renal dysfunction, and large cohort studies have reported an increased risk of end-stage kidney disease (ESKD) (28-30, 32). Biological mechanisms are uncertain; this may be due to lasting vascular endothelial dysfunction related to elevated levels of anti-angiogenic proteins—such as soluble fms-like tyrosine kinase-1 (sFLT1) —or it may be due to direct glomerular damage related to underexpression of nuclear factor erythroid 2–related factor 2 (NRF2) (11, 207, 208). Other changes in the renin-angiotensin-aldosterone system, metabolic system, and factors causing endothelial dysfunction may also be involved.

Chronic kidney disease (CKD) is much more prevalent than ESKD, and although it may be considered a precursor to ESKD, the evidence for associations between preeclampsia and CKD has been inconsistent to date (73, 209). Cohort studies from Scotland and Denmark have reported increased risk of CKD following preeclampsia (74, 87), but these findings have not been replicated elsewhere (88, 210). The underlying causes of CKD are wide-ranging, and it is plausible that hypertensive disorders of pregnancy (HDP) differentially affect the risk of CKD subtypes, but few studies have considered this when investigating associations. Moreover, while the risk of ESKD is higher among women who experience preeclampsia concurrently with preterm delivery or small for gestational age (SGA) (28, 29), it is unclear whether this is also the case for CKD.

Gestational hypertension is another common hypertensive disorder that arises de novo after 20 weeks' gestation in the absence of proteinuria and is not typically accompanied by organ dysfunction or foetal growth restriction (133). Although gestational hypertension is regarded as an independent risk factor for subsequent CVD (211), few studies have investigated associations with CKD (209). The aim of this study is to investigate whether HDP (preeclampsia, gestational hypertension) are associated with the long-term risk of maternal CKD, and to identify whether the risk differs according to CKD aetiology or by concurrent preterm delivery or SGA.

6.3 Methods

Study population

Women who had singleton live births between January 1, 1973, and December 31, 2012, were identified from the Swedish Medical Birth Register (MBR; established 1973). The MBR contains detailed information on over 96% of births in Sweden (118). We used hospitalisation data from the Swedish National Patient Register (NPR; established 1964) and the Swedish Renal Register (SRR; established 1991) to identify women who developed CKD during follow-up, until December 31, 2013 (study end date). Data from all registers were linked using the anonymised unique national identification number, which is issued to all citizens of Sweden. Data from the Swedish Death Register and Migration Register were also available until December 31, 2013, and were used for censoring. We excluded multiple pregnancies (*n* = 148,339) and pregnancies with implausible dates of delivery (*n* = 312) from all analyses at baseline. We also excluded women who had stillbirths (*n* = 14,107) to avoid potential confounding since they are more likely to experience preeclampsia compared with women who only have live births, and they are at increased risk of long-term CKD (212) (Figure A8.1, Appendix 8).

We identified women with pre-pregnancy CKD, ESKD, CVD, chronic hypertension, diabetes (type 1 or 2), systemic lupus erythematosus (SLE), systemic sclerosis, coagulopathies, haemoglobinopathies, or vasculitides from the MBR, and they were excluded at baseline. We also excluded all women in the NPR who were admitted to hospital with any of those diagnoses before their first date of delivery. We used 3 iterations of *International Classification of Diseases* (ICD) coding to identify pre-existing diseases in the NPR: ICD-8 coding from 1973 to 1986, ICD-9 coding from 1987 to 1996, and ICD-10 coding from 1997 to 2013. The full list of ICD codes used in the study is summarised in Table A8.1, Appendix 8. Furthermore, we identified hospital admissions and outpatient reviews for preeclampsia and gestational diabetes in the NPR and used this information to supplement data in the MBR.

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. All data were anonymised and nonidentifiable. Ethical approval was granted by the Swedish Ethical Review Authority in Stockholm (*Regionala Etikprövningsnämnden Stockholm*) (Dnr 2012/397-31/1) and by the Social Research and Ethics Committee, University College Cork (2019–109).

Exposure variables

Preeclampsia was the main exposure of interest and was identified in the MBR and NPR using ICD codes. Preeclampsia was defined as a diastolic blood pressure of >90 mmHg with proteinuria (≥0.3 g/day or ≥1+ on a urine dipstick) (29). We included cases of eclampsia and Haemolysis, Elevated Liver enzymes, Low Platelets (HELLP) syndrome with preeclampsia because these conditions are rare in Sweden and there were too few affected women to allow for separate groups. However, we excluded women who developed preeclampsia superimposed on chronic hypertension, since women with pre-pregnancy hypertension were excluded at baseline.

Diagnoses of preeclampsia in the MBR have been validated previously and have high positive predictive value (PPV) for ICD-9 coded diagnoses when compared with medical records but lower PPV for ICD-8 coded diagnoses (135). In the current study, all analyses included women who had singleton live births with or without preeclampsia from 1973 onwards. Analyses were repeated after restricting the study population to those with a first live birth from 1987 onwards (thus restricted to ICD-9 and ICD-10 coded diagnoses alone). Since 2014, proteinuria is no longer a requirement for a preeclampsia diagnosis in Sweden (133). However, because our study ended on December 31, 2013, this did not affect our analysis.

Preeclampsia was included in statistical models as a time-dependent variable. Women were considered unexposed (i) if they never developed preeclampsia, or (ii) from the date of their index delivery (without preeclampsia) until the date of delivery of their first preeclamptic pregnancy. Women were considered 'exposed' from the date of their first preeclamptic delivery onwards, irrespective of subsequent pregnancy outcomes. For example, if a woman had 3 live births and only experienced preeclampsia in her second pregnancy, she was considered unexposed between delivery 1 and delivery 2 but was considered exposed from delivery 2 onwards (despite the non-preeclamptic third pregnancy).

In accordance with international guidelines, we did not classify preeclampsia as mild or severe disease (133). However, preeclampsia was considered together with SGA and preterm delivery respectively, and these may be considered proxy markers of severity (134). For SGA, a series of dummy variables were included to represent non-overlapping scenarios: (i) preeclampsia alone, (ii) SGA alone, or (iii) preeclampsia and SGA (co-occurring). SGA was defined in the MBR as a birth weight of 2 SDs below the sex-specific and gestational age distributions, according to Swedish weight-based growth standards (139), and was treated as a time-dependent variable.

Preterm delivery was defined as any delivery before 37 weeks' gestation. This was largely estimated based on second trimester ultrasound (from 1982 onwards) but was estimated from maternal report of last menstrual period (LMP) prior to that (118). Preterm deliveries were categorised as moderate (32 weeks to 36+6 weeks), very (28 weeks to 31+6 weeks), or extremely preterm (<28 weeks gestation). The latter two categories (very/extremely preterm) were combined in analyses due to small numbers. Maternal exposure to preterm delivery was time dependent and was allowed to change multiple times across different pregnancies, but exposure status was always based on the earliest gestation of any previous delivery.

Furthermore, we considered the effect of recurrent preeclampsia on CKD risk among women who had exactly 2 deliveries. We categorised these women as follows: (1) no preeclampsia, (2) preeclampsia in one pregnancy, and (3) preeclampsia in both pregnancies.

Gestational hypertension was a secondary exposure variable of interest and was defined as blood pressure of at least 140/90 mm Hg (in at least 2 readings 6 or more hours apart), without proteinuria, occurring after 20 weeks' gestation up to the date of delivery. It was included in statistical models as a time-dependent variable.

Outcome variables

Maternal CKD was the primary outcome. This was defined by a recorded diagnosis of CKD in the SRR or based on a primary or secondary diagnosis of CKD in the NPR (using ICD codes). The earliest date at which a woman appeared in either the SRR or NPR was taken as her date of diagnosis, and she was censored at that date irrespective of subsequent deliveries. Women who had an identifiable congenital or genetic cause of CKD were excluded at baseline. We only considered women who were diagnosed with CKD at least 3 months after the last pregnancy, to avoid any potential misclassification with acute kidney injury or any transient renal dysfunction related to preeclampsia.

We categorised CKD diagnosis in broad aetiologies; categories were selected *a priori* based on guidance from the National Kidney Foundation (144), prior research (29, 74), and clinical advice from consultant nephrologists. The following categories were used: tubulointerstitial CKD, glomerular/proteinuric CKD, hypertensive CKD, diabetic CKD, and other/unspecified CKD. The ICD codes used to define CKD in each category are shown in Table A8.1, Appendix 8. CKD subtype/aetiology was always based on the initial CKD diagnosis, when each woman first appeared in either the SRR or NPR.

Covariates

The following covariates were selected *a priori* and adjusted for: maternal age, country of origin, education level, antenatal BMI at first pregnancy, smoking during pregnancy, gestational diabetes, parity, and gestational hypertension. Information on the mother's highest level of educational achievement was available from the Swedish Education Register. Maternal smoking was based on any reported smoking during pregnancy, either at first antenatal visit or at 30–32 weeks' gestation. Maternal BMI was measured at first antenatal visit. Smoking status and BMI only became available from 1982 onwards and were more complete after 1987. Missing indicator variables were created to control for missing data on smoking and BMI.

Maternal exposure to gestational diabetes and gestational hypertension were time-dependent covariates, where women were considered exposed from their date of first delivery with gestational diabetes or gestational hypertension respectively. In the analysis of gestational hypertension and maternal CKD, we adjusted for preeclampsia as a time-dependent covariate.

Statistical analysis

Each woman's entry date in the study was the date of her first live birth. The association between preeclampsia and risk of maternal CKD was estimated using the Kaplan-Meier method. We used multivariable Cox proportional hazard regression models to estimate age-adjusted and fully adjusted hazard ratios (aHRs) and 95% CIs for the associations between preeclampsia and maternal CKD. We followed women from date of entry until date of CKD diagnosis or study end date (December 31, 2013), whichever came first. Thus, women stopped contributing person-time once they were diagnosed with CKD, and any subsequent pregnancies were not included in the analysis. Women who died or emigrated during follow-up were censored on that date. Thus, the reported HRs are the HRs that would be seen if mortality could be eliminated during the study period (213). We used log cumulative hazard plots to ensure that the proportional hazards assumption was met.

Our analysis of preeclampsia and CKD was pre-planned using 4 separate models. Model 1 explored the association between any preeclampsia and CKD (versus women who never had preeclampsia). Model 2 explored the association between preeclampsia ± SGA and CKD. Model 3 explored the association between preeclampsia ± preterm delivery and CKD. Model 4 explored the association between recurrent preeclampsia and CKD among women who had 2 live births during the study period. In each model, we considered all diagnoses of CKD collectively (overall CKD) and considered the 5 subtypes of CKD separately. Models were first adjusted for age, and then adjusted fully for all relevant covariates. In the analysis of each CKD subtype, follow-up stopped when the woman received her first diagnosis of CKD.

We conducted 3 pre-planned sensitivity analyses. Firstly, we restricted the dataset to women whose first birth occurred from 1987 onwards, when NPR coverage was more complete. The PPV for preeclampsia and gestational hypertension diagnoses was higher from this time, and information on maternal BMI and smoking was more comprehensive (118, 135). Secondly, we

categorised all births with information on maternal BMI (from 1982 onwards) according to whether mothers were obese or nonobese at the time of delivery. Thirdly, we explored the effect of excluding women who developed postpartum hypertension, to establish whether associations between preeclampsia and CKD persisted among women who remained normotensive after their last pregnancy. We undertook this analysis for all subtypes except for hypertensive CKD.

Finally, we investigated associations between gestational hypertension and CKD (versus women who never had gestational hypertension). Again, we considered all diagnoses of CKD collectively (overall CKD) and separate CKD subtypes. All analyses were performed using Stata version 15 (StataCorp, College Station, Texas).

6.4 Results

The study cohort consisted of 1,924,409 unique women who had 3,726,554 singleton live births, followed up for a total of 42,118,889 person-years. The mean age at first delivery was 27.0 (± SD 5.1) years, and median follow-up time was 20.7 years (interquartile range [IQR] 9.9–30.0 years). There were 53,265 deaths (2.8%).

There were 90,917 women (4.7%) diagnosed with preeclampsia at least once (Table 6.1). They were more likely to be native Swedes, overweight or obese, more likely to have experienced other adverse pregnancy outcomes (preterm delivery, SGA, or gestational diabetes), and less likely to be smokers compared to women who never experienced preeclampsia.

From 1973 to 2013, 18,477 women (0.9%) developed CKD, of whom 2,813 (15.2%) had tubulointerstitial CKD, 6,068 (32.8%) had glomerular/proteinuric CKD, 797 (4.3%) had hypertensive CKD, 1,226 (6.6%) had diabetic CKD, and 7,573 (41.0%) had CKD due to other/unspecified causes. The median time to CKD diagnosis after first live birth (overall) was

16.8 years (IQR 7.2–26.5). The median time to CKD diagnosis varied by aetiology: tubulointerstitial CKD: 14.6 years (IQR 5.8–24.2); glomerular/proteinuric CKD: 10.9 years (IQR 4.4–18.5); hypertensive CKD: 22.2 years (IQR 15.0–30.1); diabetic CKD: 22.1 years (IQR 12.5–29.4); and other/unspecified CKD: 22.1 years (IQR 11.5–30.0). For all CKD aetiologies, the median time to diagnosis was significantly shorter in women who had previous preeclampsia and was shortest for glomerular/proteinuric CKD (median 7.7 years; IQR 2.0–15.7) (Table A8.2, Appendix 8).

Preeclampsia

Women who had ever experienced preeclampsia were at higher risk of developing CKD compared with women who never had preeclampsia (aHR 1.92, 95% CI 1.83–2.03, $p < 0.001$). This risk differed by CKD subtype and was highest for hypertensive CKD (aHR 3.72, 95% CI 3.05–4.53, $p < 0.001$), diabetic CKD (aHR 3.94, 95% CI 3.38–4.60, $p < 0.001$), and glomerular/proteinuric CKD (aHR 2.06, 95% CI 1.88–2.26, $p < 0.001$). The risk was lower for other/unspecified CKD (aHR 1.51, 95% CI 1.38–1.65, $p < 0.001$) and tubulointerstitial CKD (aHR 1.44, 95% CI 1.24–1.68, $p < 0.001$).

There was little difference in CKD risk between preeclamptic women who experienced concurrent SGA and those who did not (Table 6.2). Hypertensive CKD risk was the exception and was more likely in women who had preeclampsia + SGA (versus neither, aHR 5.23, 95% CI 3.51–7.79, $p < 0.001$). Women who had SGA alone (without preeclampsia) were also at higher risk of CKD, but the associations were less marked than for preeclampsia. Women who had preeclampsia and who delivered at earlier gestation also had higher risk of CKD (Table 6.3). Women with at least one preeclamptic delivery before 32 weeks' gestation were at particularly high risk of CKD (versus normal term deliveries, aHR 3.19, 95% CI 2.53–4.02, $p < 0.001$).

A total of 855,095 women in the sample had only 2 births, of whom 4.4% (n = 37,322) had preeclampsia once and 0.5% (n = 4,335) had preeclampsia twice (recurrent preeclampsia). Compared with women who never had preeclampsia, those who had recurrent preeclampsia had the greatest risk of developing any form of CKD (aHR 2.64, 95% CI 2.14–3.25, p < 0.001) (Table 6.4). Again, the risk was stronger for hypertensive CKD (aHR 5.30, 95% CI 2.47–11.36, p < 0.001), diabetic CKD (aHR 6.80, 95% CI 3.96–11.68, p < 0.001), and glomerular/proteinuric CKD (aHR 3.42, 95% CI 2.44–4.78, p < 0.001).

Sensitivity analysis

When the dataset was restricted to first deliveries after 1987, some associations were strengthened. However, the overall results were not substantially different (Tables A8.3-A8.5, Appendix 8). When births were stratified by maternal obesity at index pregnancy (from 1982), the association between preeclampsia and CKD was stronger in obese women (aHR 2.27, 95% CI 1.92–2.69) than it was for nonobese women (aHR 1.71, 95 CI 1.56–1.87, *p* for interaction < 0.01) (Table 6.5). These differences persisted in analyses of preeclampsia ± SGA or preterm delivery, respectively, but not for recurrent preeclampsia. When women who developed postpartum hypertension were excluded from analyses, most associations between preeclampsia and CKD subtypes were attenuated, but not meaningfully different (Tables A8.6-A8.8, Appendix 8).

Gestational hypertension

There were 43,964 women (2.3%) diagnosed with gestational hypertension at least once. Women who had ever experienced gestational hypertension were at increased risk of developing CKD (versus no gestational hypertension, aHR 1.49, 95% CI 1.38–1.61, *p* < 0.001) (Table A8.9, Appendix 8). The association was stronger for hypertensive CKD (aHR 3.13, 95%

CI 2.47–3.97, $p < 0.001$) and diabetic CKD (aHR 1.96, 95% CI 1.56–2.47, $p < 0.001$), but did not persist for glomerular/proteinuric CKD.

When women who developed postpartum hypertension were excluded from analyses, the association with CKD was attenuated considerably (aHR 1.26, 95% CI 1.15–1.38, $p = 0.006$) (Table A8.10, Appendix 8).

6.5 Discussion

Principal findings and interpretation

This study aimed to determine whether women who experience HDP are at risk of CKD and whether this risk differs by CKD aetiology. Overall, preeclampsia was associated with significantly increased risk of CKD, and the time to CKD diagnosis was 2.7 years shorter in women who previously had preeclampsia than in those who did not. Women diagnosed with gestational hypertension were also at increased risk of CKD, but the strength of this association was less marked.

Women exposed to HDP had strongly increased risk of hypertensive CKD and diabetic CKD. These associations are consistent with previous cohort studies, which reported that preeclampsia is associated with increased risk of postpartum hypertension and type 2 diabetes (17, 27, 214, 215). Although these CKD subtypes were less commonly diagnosed in our sample than other forms of renal disease, they are likely to become predominant causes of CKD in an older cohort with longer follow-up. By contrast, we observed less marked associations between preeclampsia and tubulointerstitial CKD or nonspecific CKD.

Glomerular/proteinuric CKD accounted for one-third of all CKD cases. Preeclampsia was associated with a doubling in risk of glomerular/proteinuric CKD, and the median time to diagnosis was 3.5 years shorter. Preeclampsia may lead to glomerular endotheliosis, which

results in glomerular dysfunction, podocyte loss (216, 217) and subsequent microalbuminuria (56, 218). Notably, no significant association was observed for gestational hypertension and glomerular/proteinuric CKD. This lends support to the hypothesis that the association between preeclampsia and CKD may be mediated through persistent glomerular damage, possibly related to down-regulation of NRF2 (207, 219), and not entirely through the effects of hypertension or hyperglycaemia.

We examined whether concurrent SGA impacted on associations between preeclampsia and CKD. Previous longitudinal studies have reported an increased risk of CVD (194, 220, 221) and ESKD (28) in women who had concurrent preeclampsia and SGA, but they used relatively broad composite outcomes. In our study, co-occurring SGA appeared to add to the risk of hypertensive CKD specifically, but it made little difference to the risk of other CKD aetiologies. Women who have both SGA and preeclampsia may experience more extreme placental dysfunction (222), and it is plausible that this signals a higher risk of hypertensive disease in later life (221). Women who experienced SGA alone (without preeclampsia) were also at elevated risk of CKD, consistent with previous research (28, 32, 92), but the modest increases observed in our study suggest that this may be of limited clinical importance.

Preeclampsia was associated with higher risk of CKD in obese women compared with women whose pre-pregnancy BMI was normal. Previous studies of preeclampsia and maternal renal disease have either adjusted for obesity without considering the possibility of effect modification (87, 93) or have lacked any information on maternal BMI (28, 32, 74). It is possible that women who develop preeclampsia have different cardio-renal risk profiles depending on their pre-pregnancy BMI. Pre-pregnancy obesity has been reported to be an independent risk factor for subsequent hypertension among women who ever experienced preeclampsia (223). Furthermore, women may have elevated markers of long-term endothelial dysfunction if they were overweight before developing preeclampsia (224). Although we restricted our analysis

to women with complete information on antenatal BMI, we cannot rule out the possibility of unmeasured confounding from dyslipidaemia or recurrent preeclampsia, particularly if women with a first episode of preeclampsia received anti-hypertensive treatment or alternative cardio-protective intervention postpartum.

Our findings support the need to optimise long-term follow-up of women exposed to HDP, and particularly high-risk women who experience preterm preeclampsia or recurrent preeclampsia. We did not have information on long-term blood pressure values for women in this study. It is uncertain whether screening for hypertension would suffice in preventing CKD or enabling earlier diagnosis of CKD in women with a history of preeclampsia. The additional value of screening for albuminuria is unknown and may depend on the underlying aetiology of CKD. However, it has been estimated that the number of patients with preeclampsia who need follow-up to detect one adverse event is about 4 for overt albuminuria and 157 for CKD, and the latter is likely to be a conservative overestimate (73). Early renal damage may be masked by compensatory glomerular hyperfiltration (225), and this may also limit the ability to detect high-risk women until later in life. Thus, the optimal timing of engaging women in systematic renal and cardiovascular monitoring warrants further research. Nonetheless, 7% to 12% of all women will develop CKD in their lifetime (34, 48, 164), and the absolute risk of clinically significant disease is substantial.

Strengths and limitations

To our knowledge, this is the largest study to investigate associations between preeclampsia and CKD to date and the first to report associations between gestational hypertension and CKD subtypes. Its strengths include the use of national registry data with near-complete coverage and over 4 decades of follow-up (118); classification of CKD according to specific aetiologies; adjustment for a broader range of covariates than previous studies, including

maternal smoking and BMI; exclusion of women with a large number of relevant pre-existing comorbidities, as well as congenital and genetic forms of CKD to reduce confounding; and the use of time-dependent covariates.

However, the study is not without limitations. Although the NPR achieved national coverage for inpatients in 1987, outpatient data were only available from 2001 onwards, and the overall incidence of CKD was lower than expected. The SRR collected data on CKD from 2007 and is unlikely to be complete (123). It is possible that cases of CKD were under-diagnosed or under-ascertained in the national registers; some women may have been too young to have developed symptomatic CKD despite their long follow-up time (median 21 years), and we cannot exclude the possibility of immortal time bias in our analysis. The NPR has high PPV for most diagnoses, but its sensitivity levels tend to be lower (119), and to our knowledge these parameters have not been formally measured for CKD or its subtypes. Thus, while those who were diagnosed with CKD in our dataset are likely to have valid diagnoses, the number of undiagnosed cases is uncertain.

Hypertensive CKD and diabetic CKD were less commonly diagnosed than was anticipated, and this may have reflected lower sensitivity levels for these diagnoses or relatively short median follow-up times, or it may reflect relatively low levels of obesity and dysglycaemia among Swedish women (226, 227). The respective PPVs for ICD-8 coded diagnoses of preeclampsia and gestational hypertension were lower than for ICD-9 diagnoses (135), thus our overall results may be somewhat conservative. Our sensitivity analyses based on first deliveries after 1987 showed stronger associations between preeclampsia and CKD, but these were based on considerably fewer CKD cases, particularly when divided by CKD subtype.

Data on maternal BMI and smoking were incomplete and were only collected from 1982 onwards. We stratified by year of delivery in all our models and created a missing indicator variable to control for this. We cannot exclude the possibility of residual bias from using

missing indicator variables. However, the results of our sensitivity analyses—when data on BMI were complete—were not substantially different.

Previous studies have controlled for postpartum hypertension when investigating associations between preeclampsia and cardiometabolic disease (14, 74), and despite an inherent risk of over-adjustment bias (204), the associations appear to persist. In our sensitivity analyses, associations with CKD persisted after excluding women with postpartum hypertension. This suggests that other non-hypertensive factors also contribute to the development of maternal CKD. This analysis was limited to those diagnosed with hypertension in hospital settings during follow-up and may have missed a large number of women who were diagnosed with hypertension in community settings. Further research is required to delineate the role of mediating factors, such as postpartum hypertension, hyperglycaemia, hyperlipidaemia, and changes in maternal BMI, in the association between HDP and maternal CKD.

6.6 Conclusion

Preeclampsia is associated with an increased risk of maternal CKD in the years following pregnancy. This risk is higher after preterm preeclampsia, recurrent preeclampsia, or in preeclampsia complicated by pre-pregnancy obesity. The risk differs by CKD aetiology and is most marked for hypertensive CKD, diabetic CKD, and glomerular/proteinuric CKD. Gestational hypertension is also associated with elevated risk of CKD, although associations are more modest than for preeclampsia. Women who experience HDP may benefit from systematic renal monitoring to prevent future CKD.

Table 6.1 Maternal characteristics and pregnancy outcomes among women who had live births between 1973 and 2012 in Sweden, stratified by exposure to preeclampsia

	No preeclampsia, n (%) N=1,833,492 (95.3%)	**Preeclampsia, n (%)** N=90,917 (4.7%)	**p value**
Age at first pregnancy (years)			p<0.001
<20	103,561 (5.7)	5,971 (6.6)	
20-29	1,184,635 (64.6)	59,030 (64.9)	
30-39	520,110 (28.4)	24,424 (26.9)	
>=40	25,186 (1.4)	1,492 (1.6)	
Native country			p<0.001
Sweden	1,550,745 (84.6)	80,663 (88.7)	
Elsewhere	282,747 (15.4)	10,254 (11.3)	
Education level			p<0.001
Less than Upper Secondary	243,022 (13.3)	11,571 (12.7)	
Upper Secondary	825,165 (45.0)	44,073 (48.5)	
Third level	726,169 (39.6)	34,078 (37.5)	
Missing	39,136 (2.1)	1,195 (1.3)	
Body mass index in early pregnancy (kg/m^2)			p<0.001
Underweight: <18.5	44,069 (2.4)	1,391 (1.5)	
Normal: 18.5-24.9	676,382 (36.9)	28,187 (31.0)	
Overweight: 25-29.9	179,529 (9.8)	12,669 (13.9)	
Obese: ≥30	62,487 (3.4)	7,225 (8.0)	
Missing	871,025 (47.5)	41,445 (45.6)	
Maternal smoking			p<0.001
No	971,826 (53.0)	52,761 (58.0)	
Yes	198,463 (10.8)	7,704 (8.5)	
Missing	663,203 (36.2)	30,452 (33.5)	
Gestational diabetes (ever)			p<0.001
No	1,817,243 (99.1)	88,935 (97.8)	
Yes	16,249 (0.9)	1,982 (2.2)	
Preterm delivery (ever)			p<0.001
No	1,695,439 (92.5)	70,383 (77.4)	
Yes	138,188 (7.5)	20,581 (22.6)	
Small for gestational age (SGA) (ever)			p<0.001
No	1,747,083 (95.4)	77,094 (84.9)	
Yes	84,540 (4.6)	13,751 (15.1)	
Decade of first birth			p<0.001
1973-1979	490,813 (26.8)	21,231 (23.4)	
1980-1989	400,822 (21.9)	21,524 (23.7)	
1990-1999	399,164 (21.8)	21,950 (24.1)	
2000-2012	542,693 (29.6)	26,212 (28.8)	

Table 6.2 Hazard ratios for maternal chronic kidney disease by history of preeclampsia and small for gestational age, among women who had live births between 1973 and 2012 in Sweden (n=1,924,409)

		N, CKD	Age-adjusted, HR (95% CI)	Fully adjusted, HR (95% CI)
Overall CKD				
No preeclampsia, no SGA		15,783	1.0	1.0
Preeclampsia only		1,318	2.08 (1.96-2.20)	1.96 (1.85-2.08)
SGA only		1,150	1.45 (1.36-1.53)	1.32 (1.24-1.40)
Preeclampsia & SGA		226	2.11 (1.85-2.41)	1.95 (1.71-2.22)
1.	**Tubulointerstitial CKD**			
	No preeclampsia, no SGA	2,458	1.0	1.0
	Preeclampsia only	157	1.52 (1.29-1.78)	1.47 (1.25-1.73)
	SGA only	171	1.45 (1.24-1.70)	1.30 (1.11-1.51)
	Preeclampsia & SGA	27	1.51 (1.03-2.20)	1.41 (0.97-2.07)
2.	**Glomerular/proteinuric CKD**			
	No preeclampsia, no SGA	5,151	1.0	1.0
	Preeclampsia only	425	2.10 (1.90-2.32)	2.11 (1.90-2.33)
	SGA only	417	1.61 (1.45-1.77)	1.46 (1.32-1.62)
	Preeclampsia & SGA	75	2.22 (1.76-2.78)	2.16 (1.71-2.71)
3.	**Hypertensive CKD**			
	No preeclampsia, no SGA	610	1.0	1.0
	Preeclampsia only	104	4.43 (3.59-5.46)	3.60 (2.90-4.47)
	SGA only	57	1.76 (1.34-2.30)	1.54 (1.17-2.02)
	Preeclampsia & SGA	26	6.82 (4.60-10.11)	5.23 (3.51-7.79)
4.	**Diabetic CKD**			
	No preeclampsia, no SGA	954	1.0	1.0
	Preeclampsia only	189	5.14 (4.40-6.01)	4.03 (3.42-4.74)
	SGA only	57	1.16 (0.89-1.51)	1.05 (0.80-1.37)
	Preeclampsia & SGA	26	4.28 (2.90-6.33)	3.49 (2.36-5.16)
5.	**Other/unspecified CKD**			
	No preeclampsia, no SGA	6,611	1.0	1.0
	Preeclampsia only	443	1.65 (1.50-1.81)	1.54 (1.40-1.70)
	SGA only	448	1.34 (1.22-1.47)	1.24 (1.13-1.37)
	Preeclampsia & SGA	72	1.59 (1.26-2.00)	1.46 (1.15-1.84)

Hazard ratios represent separate Cox regression models for associations between preeclampsia and maternal chronic kidney disease. Preeclampsia was a time-dependent variable. Fully adjusted models controlled for maternal age, country of origin, education level, parity, maternal BMI, smoking in pregnancy, exposure to gestational diabetes, and exposure to gestational hypertension. Models were stratified by year of delivery. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; SGA, small for gestational age.

Table 6.3 Hazard ratios for maternal chronic kidney disease by history of preeclampsia and preterm delivery, among women who had live births between 1973 and 2012 in Sweden (n=1,924,409)

		N, CKD	Age-adjusted, HR (95% CI)	Fully adjusted, HR (95% CI)
Overall CKD				
Term delivery, no preeclampsia		15,134	1.0	1.0
Moderate preterm delivery, no preeclampsia		1,552	1.58 (1.50-1.66)	1.46 (1.39-1.54)
Very/Extremely preterm delivery, no preeclampsia		247	1.86 (1.64-2.11)	1.63 (1.44-1.85)
Term delivery + Preeclampsia		1,196	1.98 (1.87-2.10)	1.87 (1.76-1.99)
Moderate preterm delivery + Preeclampsia		276	2.65 (2.34-3.00)	2.52 (2.23-2.85)
Very/Extremely preterm delivery + Preeclampsia		72	3.34 (2.65-4.21)	3.19 (2.53-4.02)
1.	**Tubulointerstitial CKD**			
	Term delivery, no preeclampsia	2,365	1.0	1.0
	Moderate preterm delivery, no preeclampsia	220	1.38 (1.20-1.58)	1.26 (1.09-1.44)
	Very/Extremely preterm delivery, no preeclampsia	44	2.05 (1.52-2.76)	1.75 (1.30-2.36)
	Term delivery + Preeclampsia	146	1.50 (1.26-1.77)	1.45 (1.22-1.72)
	Moderate preterm delivery + Preeclampsia	24	1.39 (0.93-2.08)	1.37 (0.91-2.05)
	Very/Extremely preterm delivery + Preeclampsia	14	3.30 (1.95-5.58)	3.27 (1.93-5.54)
2.	**Glomerular/proteinuric CKD**			
	Term delivery, no preeclampsia	4,982	1.0	1.0
	Moderate preterm delivery, no preeclampsia	508	1.59 (1.45-1.74)	1.48 (1.35-1.62)
	Very/Extremely preterm delivery, no preeclampsia	78	1.83 (1.46-2.29)	1.59 (1.27-1.98)
	Term delivery + Preeclampsia	393	1.98 (1.78-2.20)	1.98 (1.78-2.20)
	Moderate preterm delivery + Preeclampsia	81	2.64 (2.12-3.29)	2.69 (2.16-3.35)
	Very/Extremely preterm delivery + Preeclampsia	26	3.87 (2.63-5.70)	3.88 (2.64-5.71)
3.	**Hypertensive CKD**			
	Term delivery, no preeclampsia	573	1.0	1.0
	Moderate preterm delivery, no preeclampsia	77	2.14 (1.68-2.71)	1.92 (1.51-2.45)
	Very/Extremely preterm delivery, no preeclampsia	17	3.50 (2.16-5.67)	2.98 (1.84-4.84)
	Term delivery + Preeclampsia	104	4.49 (3.63-5.57)	3.65 (2.92-4.55)
	Moderate preterm delivery + Preeclampsia	22	7.06 (4.60-10.83)	5.47 (3.55-8.43)
	Very/Extremely preterm delivery + Preeclampsia	*	6.94 (2.59-18.60)	5.74 (2.14-15.40)
4.	**Diabetic CKD**			
	Term delivery, no preeclampsia	839	1.0	1.0
	Moderate preterm delivery, no preeclampsia	150	2.85 (2.40-3.40)	2.54 (2.13-3.03)
	Very/Extremely preterm delivery, no preeclampsia	22	3.12 (2.04-4.76)	2.55 (1.66-3.89)
	Term delivery + Preeclampsia	155	4.62 (3.87-5.51)	3.69 (3.08-4.41)
	Moderate preterm delivery + Preeclampsia	56	11.70 (8.91-15.36)	8.80 (6.67-11.60)
	Very/Extremely preterm delivery + Preeclampsia	*	4.10 (1.53-10.96)	3.18 (1.19-8.51)

Table 6.3 (continued) Hazard ratios for maternal chronic kidney disease by history of preeclampsia and preterm delivery, among women who had live births between 1973 and 2012 in Sweden (n=1,924,409)

		N, CKD	Age-adjusted, HR (95% CI)	Fully adjusted, HR (95% CI)
5.	**Other/unspecified CKD**			
	Term delivery, no preeclampsia	6,375	1.0	1.0
	Moderate preterm delivery, no preeclampsia	597	1.43 (1.32-1.56)	1.34 (1.24-1.46)
	Very/Extremely preterm delivery, no preeclampsia	86	1.52 (1.23-1.88)	1.37 (1.10-1.69)
	Term delivery + Preeclampsia	398	1.61 (1.45-1.78)	1.50 (1.36-1.67)
	Moderate preterm delivery + Preeclampsia	93	1.78 (1.42-2.25)	1.68 (1.33-2.12)
	Very/Extremely preterm delivery + Preeclampsia	24	2.64 (1.78-3.94)	2.50 (1.68-3.74)

Hazard ratios represent separate Cox regression models for associations between preeclampsia and maternal chronic kidney disease. Preeclampsia was a time-dependent variable. Fully adjusted models controlled for maternal age, country of origin, education level, parity, maternal BMI, smoking in pregnancy, exposure to gestational diabetes, and exposure to gestational hypertension. Models were stratified by year of delivery. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; SGA, small for gestational age

*Exact number not reported as cell count ≤5

ne, not estimable

Table 6.4 Hazard ratios for maternal chronic kidney disease by history of recurrent preeclampsia, among women who had live births between 1973 and 2012 in Sweden (n=855,095)

	N, CKD	Age-adjusted, HR (95% CI)	Fully adjusted, HR (95% CI)
Overall CKD			
Two pregnancies without preeclampsia	6,326	1.0	1.0
Two pregnancies, one episode preeclampsia	551	1.90 (1.74-2.07)	1.82 (1.66-1.99)
Two pregnancies, two episodes preeclampsia	90	2.77 (2.25-3.41)	2.64 (2.14-3.25)
1. Tubulointerstitial CKD			
Two pregnancies without preeclampsia	1,054	1.0	1.0
Two pregnancies, one episode preeclampsia	78	1.59 (1.26-2.00)	1.58 (1.25-1.99)
Two pregnancies, two episodes preeclampsia	10	1.77 (0.95-3.30)	1.74 (0.93-3.25)
2. Glomerular/proteinuric CKD			
Two pregnancies without preeclampsia	2,062	1.0	1.0
Two pregnancies, one episode preeclampsia	183	1.94 (1.67-2.26)	2.02 (1.73-2.35)
Two pregnancies, two episodes preeclampsia	35	3.32 (2.38-4.64)	3.42 (2.44-4.78)
3. Hypertensive CKD			
Two pregnancies without preeclampsia	217	1.0	1.0
Two pregnancies, one episode preeclampsia	38	3.93 (2.79-5.55)	3.23 (2.25-4.63)
Two pregnancies, two episodes preeclampsia	7	6.70 (3.16-14.23)	5.30 (2.47-11.36)
4. Diabetic CKD			
Two pregnancies without preeclampsia	340	1.0	1.0
Two pregnancies, one episode preeclampsia	73	4.73 (3.67-6.10)	3.74 (2.88-4.86)
Two pregnancies, two episodes preeclampsia	14	8.44 (4.94-14.41)	6.80 (3.96-11.68)
5. Other/unspecified CKD			
Two pregnancies without preeclampsia	2,651	1.0	1.0
Two pregnancies, one episode preeclampsia	179	1.47 (1.26-1.71)	1.36 (1.16-1.58)
Two pregnancies, two episodes preeclampsia	24	1.77 (1.18-2.64)	1.64 (1.10-2.46)

Hazard ratios represent separate Cox regression models for associations between preeclampsia and maternal chronic kidney disease. Preeclampsia was a time-dependent variable. Fully adjusted models controlled for maternal age, country of origin, education level, parity, maternal BMI, smoking in pregnancy, exposure to gestational diabetes, and exposure to gestational hypertension. Models were stratified by year of delivery. Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

Table 6.5 Hazard ratios for maternal chronic kidney disease by history of preeclampsia, among women whose first live birth occurred between 1982 and 2012 in Sweden, stratified by maternal obesity (n=1,011,939)

	All women aHR (95% CI)	Women with normal BMI aHR (95% CI)	Non-obese women aHR (95% CI)	Obese women aHR (95% CI)	P value for interaction
Preeclampsia					
No preeclampsia	1.0	1.0	1.0	1.0	p<0.01
Preeclampsia (any)	1.83 (1.66-1.95)	1.62 (1.43-1.82)	1.71 (1.56-1.87)	2.27 (1.92-2.69)	
Preeclampsia and SGA					
No preeclampsia, no SGA	1.0	1.0	1.0	1.0	P<0.01
Preeclampsia only	1.85 (1.70-2.02)	1.63 (1.43-1.86)	1.75 (1.59-1.94)	2.35 (1.96-2.81)	
SGA only	1.24 (1.13-2.04)	1.19 (1.05-1.35)	1.21 (1.09-1.34)	1.58 (1.15-2.17)	
Preeclampsia & SGA	1.66 (1.35-2.04)	1.61 (1.22-2.13)	1.58 (1.25-1.98)	2.20 (1.41-3.45)	
Preeclampsia and Preterm delivery					
Term delivery, no preeclampsia	1.0	1.0	1.0	1.0	p<0.01
Moderate preterm delivery, no preeclampsia	1.38 (1.28-1.50)	1.38 (1.25-1.53)	1.35 (1.24-1.47)	1.65 (1.31-2.09)	
Very/Extremely preterm delivery, no preeclampsia	1.46 (1.18-1.79)	1.34 (1.01-1.77)	1.45 (1.16-1.81)	1.53 (0.86-2.72)	
Term delivery + Preeclampsia	1.71 (1.55-1.88)	1.52 (1.32-1.75)	1.65 (1.49-1.84)	2.05 (1.68-2.51)	
Moderate preterm delivery + Preeclampsia	2.26 (1.89-2.70)	2.05 (1.58-2.66)	2.08 (1.68-2.56)	3.15 (2.22-4.46)	
Very/Extremely preterm delivery + Preeclampsia	3.56 (2.67-4.74)	3.74 (2.48-5.63)	3.36 (2.40-4.71)	4.68 (2.70-8.12)	
Recurrent preeclampsia					
Two pregnancies without preeclampsia	1.0	1.0	1.0	1.0	p=0.469
Two pregnancies, one episode preeclampsia	1.72 (1.52-1.96)	1.46 (1.20-1.77)	1.67 (1.44-1.93)	2.09 (1.58-2.77)	
Two pregnancies, two episodes preeclampsia	2.13 (1.55-2.94)	2.13 (1.30-3.49)	2.20 (1.52-3.20)	2.11 (1.12-3.98)	

Results were based on pregnancies for which data on BMI at first antenatal visit were available. BMI was only collected from 1982 onwards in the Medical Birth Register. Analysis of recurrent preeclampsia was restricted to women who had two singleton live births from 1982 to 2012 inclusive, n=482,845. aHR, adjusted hazard ratio.

CHAPTER 7 GESTATIONAL DIABETES AND THE LONG-TERM RISK OF MATERNAL KIDNEY DISEASE: A SWEDISH NATIONAL COHORT STUDY

Peter M. Barrett (1, 2), Fergus P. McCarthy (2, 3), Marie Evans (4), Marius Kublickas (5), Ivan J. Perry (1), Peter Stenvinkel (4), Karolina Kublickiene (4), Ali S. Khashan (1, 2)

1. School of Public Health, University College Cork, Cork, Ireland
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland
3. Department of Obstetrics & Gynaecology, Cork University Maternity Hospital, Cork, Ireland
4. Department of Clinical Sciences Intervention and Technology, Karolinska Institutet, Huddinge, Sweden
5. Department of Obstetrics & Gynaecology, Karolinska Institutet, Stockholm, Sweden

Submitted for peer review

(Paper 6)

7.1 Abstract

Objective

We aimed to examine the association between gestational diabetes (GDM) and maternal chronic kidney disease (CKD) and end-stage kidney disease (ESKD) and to determine whether this depends on progression to overt T2DM.

Research design and methods

A nationwide retrospective cohort study was designed using data from the Swedish national registers. Women were included if their first delivery occurred between 1 January 1987 and 31 December 2012. Previous GDM was the main exposure variable, and this was stratified according to whether women developed T2DM after pregnancy. We estimated the risk of CKD, ESKD and different CKD subtypes (tubulointerstitial, glomerular, hypertensive, diabetic, other/non-specific). Cox-proportional hazard regression models were used.

Results

There were 1,121,633 women included, of whom 15,595 (1.4%) had GDM. Overall, GDM-diagnosed women were at increased risk of CKD (aHR 1.81, 95% CI 1.54-2.14) and ESKD (aHR 4.52, 95% CI 2.75-7.44). Associations were strongest for diabetic CKD (aHR 8.81, 95% CI 6.36-12.19) and hypertensive CKD (aHR 2.46, 95% CI 1.06-5.69). These associations were largely explained by post-pregnancy T2DM. Among women who had GDM + subsequent T2DM, strong associations were observed (CKD, aHR 21.70, 95% CI 17.17-27.42; ESKD, aHR 112.37, 95% CI 61.22-206.38). Among those who experienced GDM only, associations were non-significant (CKD, aHR 1.11, 95% CI 0.89-1.38; ESKD, aHR 1.58, 95% CI 0.70-3.60 respectively).

Conclusions

Women who experience GDM are at increased risk of CKD and ESKD if they develop T2DM. However, GDM-diagnosed women who do not develop overt T2DM have similar risk of CKD/ESKD to those with uncomplicated pregnancies.

7.2 Background

The incidence of gestational diabetes (GDM) is increasing and in 2019, it was estimated that 13% of all pregnancies worldwide were affected by GDM (228). The reasons for this are multifactorial, but they include rising maternal age, a higher prevalence of obesity among pregnant women, and lowering of diagnostic thresholds for GDM (229). Women who experience GDM are at higher risk of later cardiovascular morbidity and mortality (19), but less is known about the long-term renal sequelae following GDM. Chronic kidney disease (CKD) is a highly prevalent and preventable cause of ill-health among women, and its incidence is higher among those who experience other pregnancy-related complications (209). End-stage kidney disease (ESKD), although relatively rare, causes a disproportionate burden of morbidity and premature mortality (38). However, few studies have examined whether GDM independently increases the risk of maternal CKD or ESKD (91, 95, 96, 230).

Women who experience GDM have a 10-fold increased risk of type 2 diabetes (T2DM) (231), which in itself can cause diabetic nephropathy (229). However, it is unclear whether women who develop GDM are at long-term risk of other non-diabetic forms of CKD. About half of women with GDM will never develop T2DM, thus it is relevant to consider whether they are at increased risk of other forms of CKD in later life (229). GDM-diagnosed women are more likely to have persistent markers of endothelial dysfunction (62, 232, 233). It is possible that they may be predisposed to a range of cardiovascular and renal diseases compared to women who remained normoglycaemic in pregnancy. To date, the evidence linking prior GDM diagnosis to long-term risk of renal impairment has been conflicting (76, 93, 96, 107-109, 209).

The aim of this study was to measure the association between GDM and subsequent risk of maternal CKD and ESKD. We sought to determine whether this risk persists across a range of CKD subtypes independent of medical and obstetric comorbidities. We also sought to identify

whether this risk differs among GDM-diagnosed women according to whether they were subsequently diagnosed with T2DM, or not.

7.3 Research design and methods

Study design

We undertook a nationwide, population-based cohort study of mothers who gave birth in Sweden between 01/01/87 and 31/12/12. Data were obtained from the Swedish Medical Birth Register (MBR, established 1973) and women were included if they had their first birth on or after 01/01/87, when information on GDM diagnosis was available. The MBR was validated in 2002, and the quality of variables was deemed to be high (118).

The information from the MBR was linked to data from the Swedish National Patient Register (NPR) and Swedish Renal Register (SRR) up to 31/12/13 to identify those who developed CKD or ESKD during follow-up. The NPR contained information on inpatient admissions from 1964 onwards and outpatient reviews from 2001 onwards. The SRR contained information on ESKD diagnoses from 1991 onwards and on CKD (stage 4-5) from 2007 onwards. The registers were linked using unique anonymised serial numbers (lpnr) which were derived from each participant's personal identification number before the research team received the data. Information from the Swedish Death Register and Migration Register were also used to censor women who died or emigrated during follow-up.

Women were excluded at baseline if they had pre-pregnancy comorbidities, which may increase the risk of CKD/ESKD. We used the MBR and NPR to identify, and exclude, women who had the following comorbidities on or before the date of their first delivery: previous CKD/ESKD, cardiovascular disease (CVD), chronic hypertension, systemic lupus

erythematosus, systemic sclerosis, coagulopathies, haemoglobinopathies, or vasculitides. Women who had a diagnosis of diabetes at baseline (type 1 or type 2), defined as a diagnosis in the MBR or NPR on or before the date of their first delivery, were also excluded since those women could not, by default, develop GDM within the dataset.

We excluded women who had multiple pregnancies and births with implausible dates of delivery. We used three iterations of ICD coding to identify women who had pre-pregnancy disease; ICD-8 coding (1973-1986, used for checking previous diagnoses from the NPR and MBR at baseline), ICD-9 coding (1987-1996 inclusive) and ICD-10 coding (1997 onwards). The list of ICD codes used in the study is available in Table A9.1, Appendix 9.

Gestational diabetes

GDM was the main exposure of interest and was based on ICD diagnosis in the MBR or NPR. ICD coding for GDM was only available from 1987 onwards (ICD-9 code 648W, ICD-10 code O244), hence the study was restricted to women whose first birth occurred during or after 1987.

In Sweden, there has been lack of consensus regarding screening regimes for GDM. Antenatal care is organised across 43 different Maternal Health Care Areas (MHCAs). Some MHCAs apply universal screening of GDM to all pregnant women and other regions use a selective approach based on particular risk factors (e.g. previous GDM, previous stillbirth, body mass index (BMI) ≥30 kg/m^2, macrosomic infant >4.5kg) or random blood glucose measurements (141). Both universal and selective screening regimes stipulate the use of a 75-g oral glucose tolerance test and 2-hour value of capillary plasma glucose for diagnosis, but the diagnostic thresholds for GDM vary across MHCAs. The 2-hour plasma glucose diagnostic thresholds ranged from 9.0–11.1 mmol/L during the study period, using either capillary or venous samples. One-third

of MHCAs also used fasting glucose as a diagnostic criterion for GDM. If a fasting threshold was used, then GDM was based on fasting thresholds of 6.1-7.0 mmol/L (141, 234). We did not have information in the MBR or NPR on the specific diagnostic thresholds used for individuals.

Two separate exposure variables were used for GDM. The first variable was dichotomous (any GDM vs. none) and it was included in statistical models as a time-dependent variable. Women were considered 'exposed' from the date of their first delivery with GDM, irrespective of subsequent unaffected pregnancies. Women were considered unexposed (i) if they never developed GDM, or (ii) from the date of their first delivery (without GDM) until the date of their first GDM-affected delivery. Thus, if a woman had an unaffected pregnancy first (without GDM) and was diagnosed with GDM during a subsequent pregnancy, she would contribute both unexposed and exposed person-time during follow-up.

A second time-dependent exposure variable was created to further categorise GDM-diagnosed women according to whether they developed overt T2DM. Diagnoses of T2DM were identified from the MBR and NPR using ICD coding. The following categories were used: (i) neither GDM nor T2DM (reference group) (ii) GDM only, no subsequent T2DM (iii) T2DM only, without previous GDM (iv) GDM first + subsequent T2DM. This approach was consistent with a previous large-scale cohort study of GDM and maternal CVD (235).

Large for gestational age (LGA) was considered as a proxy marker of GDM severity if it occurred in the same pregnancy as GDM (142). LGA was defined in the MBR as a birth weight of 2 standard deviations (SD) above the sex-specific and gestational age distributions, according to Swedish weight-based growth standards (139).

Outcome variables

Maternal CKD and ESKD were the main outcomes defined by a verified diagnosis in the NPR or SRR. ESKD was defined as stage 5 CKD, requiring dialysis or renal transplant. The earliest date at which a woman appeared in either the NPR or the SRR was assumed to be her date of diagnosis for CKD/ESKD. Women were excluded if they were diagnosed with CKD/ESKD within three months of their last pregnancy to avoid potential misclassification with acute kidney injury. Women who had any form of CKD/ESKD due to an identifiable congenital or genetic cause were also excluded (Table A9.1, Appendix 9). The following subtypes/aetiologies of CKD were used: tubulointerstitial, glomerular/proteinuric, hypertensive, diabetic, other/unspecified CKD. The process for selecting these categories has been described in detail elsewhere (236).

Covariates

We adjusted for the following covariates: maternal age, country of origin (Sweden vs elsewhere), maternal education (highest level achieved), parity, antenatal BMI in first pregnancy, gestational weight gain, smoking during pregnancy and preeclampsia. All analyses were stratified by year of delivery. Information on maternal education was based on the highest educational achievement recorded in the Swedish Register of Education. Smoking status was based on any reported smoking during pregnancy, either at first antenatal visit or at 30-32 weeks' gestation. BMI was measured based on weight (kg) and height (m) at first antenatal visit. Gestational weight gain was measured by subtracting each woman's weight (kg) at first antenatal visit from her weight (kg) at the time of first delivery. This was categorised as optimal, inadequate or excessive using established criteria according to BMI category at first antenatal visit (156). Maternal exposure to preeclampsia was included as a time-dependent covariate. Preeclampsia was defined as a diastolic blood pressure of >90 mm

Hg with proteinuria (0.3 g/d or ≥1+ on a urine dipstick), but excluding women who developed preeclampsia superimposed on chronic hypertension since women with pre-pregnancy hypertension were excluded at baseline (236).

Ethical considerations

Ethical approval was obtained from the Swedish Ethical Review Authority in Stockholm (Regionala Etikprövningsnämnden Stockholm; Dnr 2012/397-31/1) and the Social Research and Ethics Committee, University College Cork (2019-109).

Statistical analysis

The association between GDM and risk of maternal CKD/ESKD was measured using the Kaplan-Meier method. The log-rank test was used to measure differences in survival curves. Multivariable Cox proportional hazard regression models were used to estimate age-adjusted and fully adjusted hazard ratios (aHRs) and 95% confidence intervals (CI). Women were followed up from the date of their first singleton birth until date of diagnosis of CKD/ESKD, study end date (31/12/13), or censoring due to death or emigration, whichever came first. Thus, women stopped contributing person-time once they were diagnosed with CKD or ESKD, and any subsequent pregnancies were not included in the analysis. Two-sided p-values were used, and $p < 0.05$ denoted statistical significance.

Firstly, we estimated the overall association between GDM and maternal CKD and ESKD respectively (vs. women who never had GDM). Secondly, we measured associations between GDM and subtypes of CKD in separate models. Thirdly, we repeated the analyses to identify whether associations differed according to whether GDM-diagnosed women developed subsequent T2DM. The following four categories were used: (i) never diagnosed with GDM or

T2DM (reference group) (ii) GDM only (iii) T2DM only, without previous GDM (iv) GDM first + subsequent T2DM. We also explored the associations between GDM +/- LGA with maternal CKD and ESKD respectively. *A priori*, we planned to assess effect modification by country of birth (Sweden vs. elsewhere) and maternal BMI (obese vs. non-obese at first antenatal visit). All analyses were performed using Stata version 15 (StataCorp LLC).

There were missing data for maternal education, smoking, BMI at first antenatal visit, and gestational weight gain (118, 237). We used multiple imputation by chained equations to address missing data, using linear models to impute BMI and gestational weight gain, and multinomial logistic models to impute maternal education and smoking status (M=20).

7.4 Results

The study cohort consisted of 1,121,633 unique women who had 2,157,330 singleton births, followed up for a total of 15,303,798 person-years. The median follow-up time was 12.2 years (interquartile range (IQR) 6.2 to 19.3 years).

There were 15,595 women (1.4%) diagnosed with GDM at least once. The incidence of GDM doubled over time, from 562 diagnoses per 100,000 births in 1987-1991, to 1,123 diagnoses per 100,000 births in 2007-2012. The demographic profile of pregnant women also changed over time from mean age 26.4 (± 4.7) years in 1987-1991, and 3.9% prevalence of obesity, to mean maternal age 30.2 (± 5.3) years in 2007-2012, and 12.1% prevalence of obesity (Table A9.2, Appendix 9).

Women who were diagnosed with GDM were more likely to be older in age at first delivery, born outside of Sweden, overweight or obese at first antenatal visit, and were less likely to have a third level education than other women (Table 7.1). Pregnancy complications (preeclampsia, LGA, stillbirth) were most prevalent among women who developed T2DM, but

were also more frequently observed among GDM-diagnosed women compared with women who remained normoglycaemic.

From 1987 to 2013, 5,879 women (0.5%) developed CKD, of whom 1,343 (22.8%) had tubulo-interstitial CKD; 1,800 (30.6%) had glomerular/proteinuric CKD; 138 (2.3%) had hypertensive CKD; 137 (2.3%) had diabetic CKD; 2,461 (41.8%) had CKD due to other/unspecified causes. Overall, 228 women (0.02%) developed ESKD during follow-up.

Gestational diabetes alone

The risk of CKD was increased among women who had a history of GDM compared with women who did not (log-rank p <0.001). After adjusting for potential confounders, women who were ever diagnosed with GDM had higher risk of developing CKD (vs. no GDM, aHR 1.81, 95% CI 1.54-2.14) (Table 7.2). This risk differed considerably by CKD subtype. The association was particularly strong for diabetic CKD (aHR 8.81, 95% CI 6.36-12.19), but was also observed for hypertensive CKD (aHR 2.46, 95% CI 1.06-5.69) and glomerular CKD (aHR 1.86, 95% CI 1.37-2.51). There was no significant association between GDM and risk of future tubulo-interstitial CKD or other/non-specific forms of CKD.

GDM was associated with increased risk of ESKD (vs. no GDM, aHR 4.52, 95% CI 2.75-7.44). However, there were too few ESKD outcomes to allow a separate analysis of ESKD subtypes. Women who experienced GDM and LGA concurrently had a higher risk of CKD (aHR 3.03, 95% CI 2.28-4.03) compared with those who experienced GDM alone (without LGA) (aHR 1.58, 95% CI 1.31-1.93). Similarly, the risk of ESKD was stronger in women who experienced GDM and LGA concurrently (aHR 8.37, 95% CI 3.64-19.23) than in women who experienced GDM alone (aHR 3.78, 95% CI 2.08-6.87) (Table A9.3, Appendix 9).

Gestational diabetes and subsequent type 2 diabetes

When the effect of subsequent T2DM was considered, the associations between GDM (only) and CKD or ESKD were attenuated to non-significance (CKD, aHR 1.11, 95% CI 0.89-1.38; ESKD, aHR 1.58, 95% CI 0.70-3.60 respectively) (Table 7.3). Women who had a history of T2DM alone had increased risk of CKD (aHR 20.70, 95% CI 18.72-22.88), ESKD (aHR 59.56, 95% CI 42.90-82.70), and each of the renal subtypes. Women who had been first diagnosed with GDM and subsequently developed overt T2DM during follow-up were at highest risk of future CKD (aHR 21.70, 95% CI 17.17-27.42) or ESKD (aHR 112.37, 95% CI 61.22-206.38).

Effect modification was observed by country of birth for associations with CKD. However, this was largely driven by differential associations between T2DM and CKD, rather than by GDM. No significant effect modification was observed by maternal BMI (Table A9.4, Appendix 9).

7.5 Discussion

We aimed to determine whether women who were diagnosed with GDM were at risk of future CKD and ESKD independent of medical and obstetric comorbidities. Women who were diagnosed with GDM were at higher risk of CKD/ESKD during follow-up, and this risk differed by CKD subtype. However, these associations were largely explained by the predisposition of GDM-diagnosed women to future T2DM. When the effects of GDM and later T2DM were separated, strong associations were observed between T2DM and CKD/ESKD. By contrast, associations between GDM and CKD/ESKD, in the absence of subsequent T2DM, were largely attenuated and became non-significant.

Previous research has reported that women with a history of GDM are more likely to have early signs of renal impairment such as elevated glomerular filtration rate (76) or microalbuminuria (96, 109) during the post-reproductive years. However, there has been

uncertainty in the published literature over whether GDM independently increases the risk of clinically significant CKD (stage 3 or greater) (209). Existing studies have been limited by incomplete adjustment for confounders like maternal obesity or pre-existing comorbidities (91, 109), use of non-specific outcome data such as renal-related hospitalisations (93), or inadequate consideration for the effects of subsequent T2DM (91, 93, 109). Our study is consistent with prospective studies from North America which reported that women who experience GDM, but who never develop overt T2DM, have an equivalent risk of clinically significant CKD/ESKD to those who remain normoglycaemic in pregnancy (96, 230). The only exception to this was the risk of glomerular CKD, where a modest association persisted among women who were exposed to GDM alone. Our study adds to previous knowledge by being the first to report associations for both CKD and ESKD separately for the same cohort of women, as well as being the first to provide detailed information on CKD subtypes.

GDM has been established as an independent risk factor for subclinical inflammation (238) and endothelial dysfunction (62), but the long-term implications of this are still emerging. GDM-diagnosed women are at higher risk of metabolic syndrome in later life, even if they remain glucose-tolerant in the years following pregnancy, and this suggests an underlying predisposition to chronic disease (239). Cardiovascular research has indicated that GDM-diagnosed women may remain at risk of future CVD irrespective of T2DM (230, 240), although the evidence for this remains inconclusive (235). Our findings suggest that GDM-diagnosed women who never develop T2DM have equivalent risk of CKD/ESKD to those who remain normoglycaemic in pregnancy. However, it is possible that GDM impacts differentially on the risk of microvascular and macrovascular outcomes (230).

Overall, the proportion of women diagnosed with GDM in this study was quite low (1.4%), and there are several possible reasons for this. The true level of GDM depends on the screening method employed (universal vs. selective), diagnostic threshold used, background

characteristics of pregnant women in the population, and uptake of screening (141). During the study period, most MHCAs in Sweden used a selective, high-risk screening approach for GDM. Diagnostic criteria for GDM were relatively strict, particularly during the earlier years of the study, and it is likely that many cases of GDM went undiagnosed. Furthermore, the prevalence of obesity was low in this study by international standards, suggesting that women of childbearing age in Sweden may be at lower risk of GDM (227). Nonetheless, we observed an increase in the incidence rate of GDM over the lifetime of this study. This is likely to have been driven by increases in maternal age at delivery, rising prevalence of obesity, sedentary lifestyle among some pregnant women, and changes to the diagnostic criteria (141, 227, 241).

We also examined whether concurrent LGA impacted on associations between GDM and CKD/ESKD. Mothers of LGA offspring tend to have less favourable anthropometric, lipid and glucose levels throughout their life course, suggesting poorer metabolic health when compared with women whose offspring are born appropriate for gestational age (242). Co-occurring GDM and LGA was associated with increases in the overall risk of future CKD/ESKD, possibly due to increased risk of progression to T2DM. The proportion of births affected by LGA is increasing, and this may be related to increases in maternal BMI, rising incidence of GDM, and decreases in maternal smoking (226). Although all GDM-diagnosed women warrant postpartum surveillance for T2DM, those who have concurrent LGA deliveries may be at particularly high risk of chronic disease and may benefit most from earlier preventive interventions.

It has been suggested that GDM-diagnosed black women may be at higher risk of CKD than GDM-diagnosed white women (209). We were only able to explore ethnicity effects in this study according to maternal country of birth (Sweden vs. elsewhere). Sweden had a predominantly white Caucasian population during the study period, and it is likely that those born outside of Sweden were of wider ethnic diversity. However, our analysis suggests that

any effect modification by ethnic origin may be driven by differential associations between T2DM and CKD, and not by GDM itself. Black women have an increased risk of T2DM compared with white women (243), and this may increase their risk of future CKD irrespective of previous GDM (99, 100).

Women who experienced T2DM with or without previous GDM were at increased risk of CKD and ESKD, including multiple subtypes of renal pathology unrelated to diabetes. The mechanisms underlying these associations are uncertain. There may be shared inflammatory or metabolic regulatory pathways which lead to CKD progression in hyperglycaemic women. For example, decreased expression or renal nuclear factor erythroid 2-related factor 2 (NRF 2) may increase the risk of a range of kidney diseases in later life (244).

Strengths and limitations

The national Swedish registers have a high level of completeness, and contain data on >96% of pregnant women (118). We were able to adjust for a wide range of covariates, and we reduced confounding by excluding women with relevant comorbidities, including pre-pregnancy diabetes and renal disease. We classified CKD according to specific subtypes to get a more detailed overview of both diabetic and non-diabetic forms of CKD, and we were able to separate the effects of GDM from T2DM depending on the timing of each diagnosis.

We only had information on ICD-coded diagnosis of GDM, and we were unable to identify which screening or diagnostic criteria had been applied to different individuals. Most MHCAs employed a selective, high-risk approach to screening and this may have introduced differential misclassification since obese women, those with LGA deliveries, and women with a prior history of GDM were more likely to have been diagnosed with GDM compared with those who appeared otherwise healthy. Many cases of GDM may have been undiagnosed and

this may have diluted the magnitude of true effect sizes (234). However, we considered the relevant screening criteria in our statistical models (e.g. obesity, LGA) and thus, the risk of CKD/ESKD is unlikely to differ substantially from that observed here. In 2015, the Swedish National Board of Health and Welfare recommended a move to standardised WHO diagnostic criteria for GDM using venous sampling (245), but this occurred after the study period.

Most cases of CKD/ESKD were identified using ICD-coded diagnoses in the NPR, with fewer cases identified from the SRR. Although it is likely that ESKD data were virtually complete, women with CKD may have been under-diagnosed or under-ascertained. . Although the NPR had achieved national coverage for all hospital admissions in Sweden by 1987, outpatient review data were only collected from 2001 onwards. The SRR began to collect ESKD data from 1991 onwards, and only collected CKD data from 2007. Some mothers may have been too young to have developed symptomatic CKD, particularly for hypertensive or diabetic subtypes which tend to develop over decades and affect women in later life. However, those who were identified as CKD/ESKD cases were likely to have valid diagnoses given that most diagnoses in the NPR have high positive predictive values (119).

Although we controlled for a wide variety of covariates, we had no information on specific treatments administered for GDM, lifestyle factors (e.g. diet, physical activity), nor biomarker data such as glucose tolerance status, glomerular filtration rate, or dyslipidaemia at follow-up. Furthermore, while we excluded women who had inherited forms of CKD at baseline, we had no information on family history of T2DM, thus we cannot exclude the possibility of some residual genetic confounding.

7.6 Conclusion

Women who experience GDM may be at increased risk of CKD or ESKD in later life, but this is largely explained by their predisposition to T2DM in the intervening years. GDM-diagnosed women who do not develop subsequent T2DM appear to have an equivalent risk of future CKD/ESKD to those who remain normoglycaemic in pregnancy. Postpartum screening for T2DM, and lifestyle or pharmacological interventions aimed at preventing onset of T2DM, are likely to reduce the burden of kidney disease among women affected by GDM.

Table 7.1 Maternal characteristics and pregnancy outcomes among women whose first birth occurred between 1987 and 2012 in Sweden, stratified by exposure to gestational diabetes and/or type 2 diabetes

	No GDM or T2DM, n (%) N=1,104,488 (98.5)	**GDM only, n (%)** N=14,751 (1.3)	**T2DM only, n (%)** N= 1,550 (0.1)	**GDM & T2DM, n (%)** N=844 (0.1)
Age at first delivery (years)				
Mean ± sd	*27.5 ± 5.1*	*28.6 ± 5.6*	*26.3 ± 4.9*	*26.5 ± 5.0*
Native country				
Sweden	916,776 (83.0)	10,188 (69.1)	1,288 (83.1)	618 (73.2)
Elsewhere	187,712 (17.0)	4,563 (30.9)	262 (16.9)	226 (26.8)
Education level				
Less than Upper Secondary	104,159 (9.4)	2,312 (15.7)	206 (13.3)	123 (14.6)
Upper Secondary	485,675 (44.0)	6,735 (45.7)	749 (48.3)	421 (49.9)
Third level	514,654 (46.6)	5,704 (38.7)	595 (38.4)	300 (35.6)
BMI in early pregnancy (kg/m^2)				
Underweight: <18.5	65,327 (5.9)	583 (4.0)	90 (5.8)	39 (4.6)
Normal: 18.5-24.9	715,438 (64.8)	6,548 (44.4)	808 (52.1)	393 (46.6)
Overweight: 25-29.9	245,523 (22.2)	4,394 (29.8)	413 (26.7)	246 (29.2)
Obese: ≥30	78,200 (7.1)	3,226 (21.9)	239 (15.4)	166 (19.7)
Gestational weight gain*				
Optimal	216,008 (19.6)	3,785 (25.7)	293 (19.0)	205 (24.4)
Inadequate	9,658 (0.9)	120 (0.8)	10 (0.6)	10 (1.2)
Excessive	877,271 (79.5)	10,817 (73.5)	1,242 (80.4)	627 (74.5)
Maternal smoking				
Yes	159,127 (14.4)	2,171 (14.7)	297 (19.2)	133 (15.8)
No	945,361 (85.6)	12,580 (85.3)	1,253 (80.8)	711 (84.2)
Preeclampsia (ever)				
Yes	52,682 (4.8)	1,610 (10.9)	230 (14.8)	118 (14.0)
No	1,051,806 (95.2)	13,141 (89.1)	1,320 (85.2)	726 (86.0)
Large for gestational age (ever)				
Yes	55,766 (5.1)	2,860 (19.4)	578 (37.3)	275 (32.6)
No	1,048,247 (94.8)	11,888 (84.6)	971 (62.7)	569 (67.4)
Small for gestational age (ever)				
Yes	48,988 (4.4)	603 (4.1)	62 (4.0)	49 (5.8)
No	1,055,025 (95.6)	14,145 (95.9)	1,487 (96.0)	795 (94.2)
Stillbirth (ever)				
Yes	3,524 (0.3)	135 (0.9)	13 (0.8)	11 (1.3)
No	1,100,964 (99.7)	14,616 (99.1)	1,537 (99.2)	833 (98.7)

BMI, body mass index; GDM, gestational diabetes; T2DM, type 2 diabetes (diagnosed after the first delivery). Women who had any diagnosis of type 1 or type 2 diabetes mellitus before or during their first pregnancy were excluded.
These results are based on multiple imputation due to missing data on maternal smoking, BMI in early pregnancy, gestational weight gain, and education level. *Categories as defined by Cedergren et al. (156)

Table 7.2 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of gestational diabetes, among women whose first birth occurred between 1987 and 2012 in Sweden (n=1,121,633)

		Chronic kidney disease (N=5,879)	
	n	**Age-adjusted, HR (95% CI)**	**Fully adjusted, HR (95% CI)**
Ever had GDM			
None	5,725	1.0	1.0
GDM	154	2.39 (2.03-2.80)	1.81 (1.54-2.14)
		Tubulo-interstitial CKD	
None	1,325	1.0	1.0
GDM	18	1.28 (0.80-2.04)	0.98 (0.62-1.57)
		Glomerular CKD	
None	1,755	1.0	1.0
GDM	45	2.47 (1.84-3.32)	1.86 (1.37-2.51)
		Hypertensive CKD	
None	132	1.0	1.0
GDM	6	3.94 (1.76-8.96)	2.46 (1.06-5.69)
		Diabetic CKD	
None	88	1.0	1.0
GDM	49	15.90 (11.71-21.59)	8.81 (6.36-12.19)
		Other/non-specific CKD	
None	2,425	1.0	1.0
GDM	36	1.30 (0.94-1.81)	1.06 (0.76-1.48)
		End-stage kidney disease (N=228)	
None	210	1.0	1.0
GDM	18	6.95 (4.29-11.26)	4.52 (2.75-7.44)

CKD, chronic kidney disease; GDM, gestational diabetes.
Hazard ratios represent separate Cox regression models for associations between GDM and maternal chronic kidney disease, subtypes of chronic kidney disease, or end-stage kidney disease respectively. In all models, GDM was a time-dependent variable, where maternal exposure status was based on the date of first affected delivery. Fully adjusted models were adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, gestational weight gain and maternal exposure to preeclampsia (time-dependent covariate), stratified by year of delivery. Women with pre-pregnancy history of renal disease, cardiovascular disease, diabetes, hypertension, systemic lupus erythematosus, coagulopathies, haemoglobinopathies and vasculitis were excluded at baseline.

Table 7.3 Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of gestational diabetes and/or type 2 diabetes, among women whose first birth occurred between 1987 and 2012 in Sweden (n=1,121,633)

		Chronic kidney disease (N=5,879)	
		Age-adjusted, HR (95% CI)	Fully adjusted, HR (95% CI)
GDM with/without T2DM		**HR (95% CI)**	**HR (95% CI)**
None	5,559	1.0	1.0
GDM only	81	1.40 (1.13-1.75)	1.11 (0.89-1.38)
T2DM only	166	24.36 (22.07-26.89)	20.70 (18.72-22.88)
GDM + T2DM	73	33.57 (26.63-42.32)	21.70 (17.17-27.42)
		Tubulo-interstitial CKD	
None	1,315	1.0	1.0
GDM only	17	1.27 (0.79-2.05)	1.00 (0.61-1.61)
T2DM only	10	5.18 (3.37-7.99)	4.55 (2.95-7.02)
GDM + T2DM	<5	ne	ne
		Glomerular CKD	
None	1,734	1.0	1.0
GDM only	36	2.10 (1.51-2.92)	1.60 (1.15-2.24)
T2DM only	21	8.20 (6.11-10.99)	6.67 (4.97-8.97)
GDM + T2DM	9	14.22 (7.38-27.41)	8.80 (4.55-17.01)
		Hypertensive CKD	
None	121	1.0	1.0
GDM only	<5	ne	ne
T2DM only	11	38.55 (22.41-66.32)	27.92 (16.02-48.68)
GDM + T2DM	5	102.81 (41.72-253.39)	56.81 (22.36-144.35)
		Other/non-specific CKD	
None	2,389	1.0	1.0
GDM only	27	1.04 (0.71-1.51)	0.86 (0.58-1.26)
T2DM only	36	7.32 (5.61-9.54)	6.42 (4.90-8.40)
GDM + T2DM	9	9.17 (4.77-17.67)	6.36 (3.30-12.27)
		End-stage kidney disease (N=228)	
None	191	1.0	1.0
GDM only	6	3.05 (1.35-6.88)	1.58 (0.70-3.60)
T2DM only	19	79.43 (57.84-109.09)	59.56 (42.90-82.70)
GDM + T2DM	12	163.37 (90.53-294.82)	112.37 (61.22-206.38)

CKD, chronic kidney disease; GDM, gestational diabetes.
Hazard ratios represent separate Cox regression models for associations between GDM and/or type 2 diabetes (diagnosed after the first delivery) and maternal CKD, subtypes of CKD, or end-stage kidney disease respectively. Diabetic CKD was excluded from this table because nobody in the reference group (i.e. never diagnosed with GDM nor T2DM) could develop the outcome which was dependent on progression to overt T2DM.
Fully adjusted models were adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, gestational weight gain and maternal exposure to preeclampsia (time-dependent covariate), stratified by year of delivery. Women with pre-pregnancy history of renal disease, cardiovascular disease, diabetes, hypertension, systemic lupus erythematosus, coagulopathies, haemoglobinopathies and vasculitis were excluded at baseline.

CHAPTER 8 Updated systematic review and meta-analysis

An updated search of the literature was conducted using similar methods to those outlined in Chapter 2 to identify new studies of adverse pregnancy outcomes and the long-term risk of maternal kidney disease. The same search terms as those used in the original systematic review (outlined in Appendix 2) were entered in to PubMed, Embase and Web of Science, and the search was restricted from 1 August 2019 through to 30 November 2020. The thesis author conducted the updated search alone, without second reviewers.

After removal of duplicates, this resulted in 538 new titles to screen for inclusion in the updated systematic review. Of these, 32 relevant abstracts were retrieved and, after full text review, four new articles met inclusion criteria (236, 237, 246, 247), including two of the studies presented in this thesis (Chapters 4 and 6). All were longitudinal studies, of which two were population-based cohort studies in Sweden (236, 237), one was a retrospective cohort study based in USA (246), and one was a prospective cohort study in Iran (247). These four articles included 10 new effect estimates which were relevant to the systematic review, including:

- 3 effect estimates for preeclampsia and CKD (236, 246, 247)
- 2 effect estimates for preterm preeclampsia and CKD (236, 237)
- 1 effect estimate for preterm preeclampsia and ESKD (237)
- 1 effect estimate for gestational hypertension and CKD (236)
- 1 effect estimate for preterm delivery and CKD (237)
- 1 effect estimate for preterm delivery and ESKD (237)
- 1 effect estimate for delivery of SGA infant and CKD (236)

Not all effect estimates were suitable for inclusion in updated meta-analyses. For example, the effect estimate for preterm delivery and CKD could not be included because it was the only effect estimate of this association. Similarly, there were no comparable studies which reported on the association between SGA delivery and maternal CKD. Moreover, two of the three updated effect estimates pertaining to preterm preeclampsia were excluded from updated meta-analyses due to potential overlap between study populations.

The updated meta-analyses included crude and adjusted estimates. Table 8.1 shows the comparison of pooled results between the original meta-analyses and updated meta-analyses where additional studies were available. Updated forest plots for crude and adjusted associations between preeclampsia and CKD are shown in Figure 8.1. All other updated forest plots are shown in Appendix 10.

When the three additional effect estimates for the preeclampsia-CKD association were added to the updated meta-analysis, the adjusted risk ratio was attenuated from 2.11 (95% CI 1.72-2.59) to 1.73 (95% CI 1.42-2.12). Although this was more modest than the original pooled estimate, it was not substantially different. The updated population-attributable fraction for preeclampsia on CKD was unchanged at 4%.

It was possible to combine two studies on preterm preeclampsia and CKD in the updated meta-analysis, whereas this had not been possible previously. The pooled effect estimate suggested that women who experience preterm preeclampsia are at considerably higher risk of CKD in later life (aRR 3.23, 95% CI 2.34-4.46).

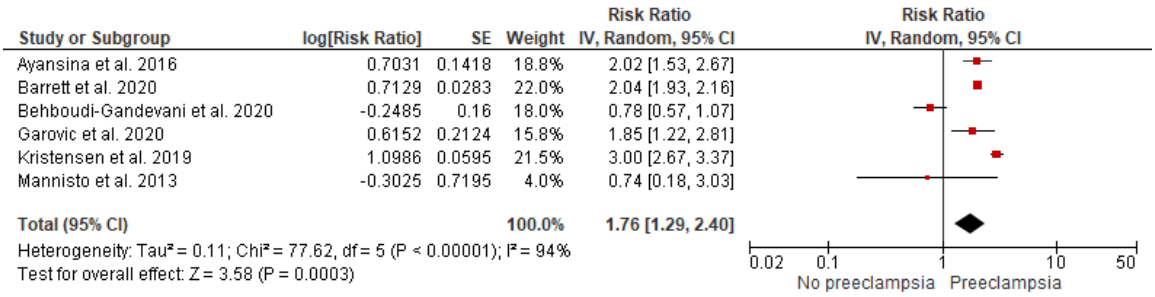
There was minimal difference in the updated pooled estimates for the gestational hypertension-CKD association. Adjusted estimates suggest that these women remain at increased risk of future CKD compared to women who have normotensive pregnancies (aRR 1.48, 95% CI 1.38-1.58). Finally, the updated pooled estimates were strengthened for the

association between preterm delivery (alone) and ESKD (aRR 2.19, 95% CI 1.93-2.47), but these were not meaningfully different from those obtained in the original meta-analysis.

Table 8.1 Comparison of pooled results between the original systematic review & meta-analysis and updated systematic review & meta-analysis

	No. studies	Original meta-analysis	No. studies	Updated meta-analysis
Crude results		**RR (95% CI)**		**RR (95% CI)**
Preeclampsia (any) + CKD	3	2.27 (1.48-3.49)	6	1.76 (1.29-2.40)
Preterm preeclampsia + CKD	0	n/a	1	n/a
Gestational hypertension + CKD	2	1.56 (1.09-2.22)	3	1.61 (1.34-1.93)
Preterm delivery + ESKD	3	3.21 (2.35-4.39)	4	2.97 (2.29-3.85)
Adjusted results		**aRR (95% CI)**		**aRR (95% CI)**
Preeclampsia (any) + CKD	3	2.11 (1.72-2.59)	6	1.73 (1.42-2.12)
Preterm preeclampsia + CKD	1	n/a	2	3.23 (2.34-4.46)
Gestational hypertension + CKD	2	1.49 (1.11-2.01)	3	1.48 (1.38-1.58)
Preterm delivery + ESKD	3	2.09 (1.64-2.66)	4	2.19 (1.93-2.47)

Crude



Adjusted

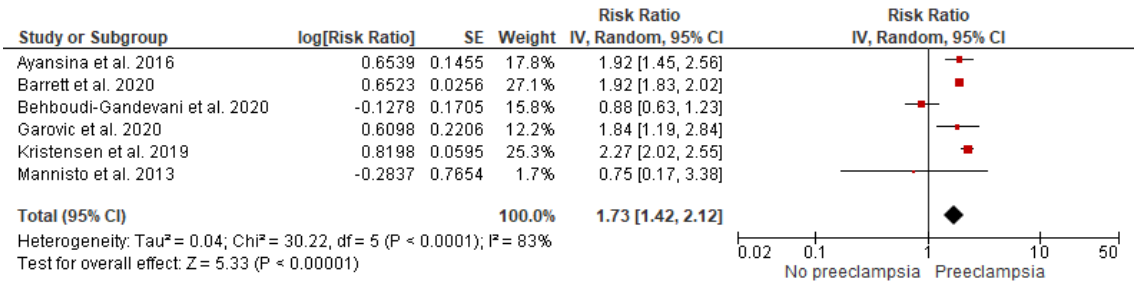


Figure 8.1 Updated forest plot for studies of the association of preeclampsia and chronic kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

CHAPTER 9 Discussion

9.1 Summary of main findings

The aim of this thesis was to rigorously investigate whether adverse pregnancy outcomes are associated with the risk of maternal CKD and ESKD. Specifically, this work includes a systematic review and meta-analysis of the current literature, and several original investigations of the impact of adverse pregnancy outcomes (preterm delivery, stillbirth, preeclampsia, gestational hypertension, and GDM) on maternal CKD, ESKD, and subtypes of renal disease. This chapter reviews the findings of these analyses, considers strengths and limitations of this work, and outlines how the results should be interpreted from a public health perspective. The implications of this work have also been considered in two published editorials (papers 7 and 8, presented in Appendix 11 and Appendix 12 respectively) which have been combined to inform the latter part of this discussion.

9.1.1 Findings from the systematic review and meta-analysis

A systematic review and meta-analysis was conducted to synthesise the available published literature on the relationship between specific adverse pregnancy outcomes and maternal CKD and ESKD (Chapter 2). The systematic review was based on a pre-specified protocol and it included studies published up until July 2019. Comprehensive search terms were used, but the literature in this area was sparse. A total of 23 studies with 5,769,891 women were included, but these studies covered a range of different associations between pregnancy-related complications and maternal kidney disease. Of these, five studies reported effect estimates for more than one adverse pregnancy outcome.

The most established evidence was available for the association between preeclampsia and future ESKD. Women who had been diagnosed with preeclampsia had a higher risk of developing ESKD during follow-up compared with women who never had preeclampsia (aRR 4.90, 95% CI 3.56-6.74). This was based on five observational studies which had low risk of bias and had adjusted comprehensively for medical and obstetric confounders (28, 29, 31-33). Using population attributable fractions, it was estimated that 11% of all cases of maternal ESKD were associated with preeclampsia alone.

Other associations linking HDP with maternal CKD or ESKD were based on weaker evidence. Three cohort studies had investigated the association between preeclampsia and CKD, and the adjusted pooled estimate suggested that women with preeclampsia had increased risk of CKD (aRR 2.11, 95% CI 1.72-2.56) (74, 87, 88). However, only one of these studies had adjusted for important pre-pregnancy comorbidities (i.e. CKD, diabetes, hypertension) (74). Gestational hypertension was associated with increased risk of CKD (aRR 1.49 95% CI, 1.11-2.01) (87, 88) and ESKD (aRR 3.64, 95% CI, 2.34-5.66) (31, 32), but pooled effect estimates were each based on just two studies.

Preterm preeclampsia was associated with a particularly high risk of future ESKD (aRR 5.66, 95% CI, 3.06-10.48) (28, 29, 59), and the literature suggested that preterm delivery alone may be associated with increased risk of ESKD independent of preeclampsia (aRR 2.09, 95% CI 1.64-2.66) (28, 32, 59). However, existing studies did not adequately address whether this risk differed by spontaneous or iatrogenic preterm delivery. Moreover, there were no studies which investigated if preterm delivery was independently associated with maternal CKD.

There was a paucity of research investigating associations between delivery of a SGA infant and future maternal CKD or ESKD. The existing literature suggested that these mothers may be at increased risk of kidney disease, but confounding from other pregnancy complications

and unmeasured placental factors was possible. For example, only one study which examined this association had controlled for maternal preeclampsia (28).

Finally, there was no clear evidence of an overall association between GDM and future CKD (aRR 1.04, 95% CI 0.76-1.41). In subgroup analyses it appeared that GDM-exposed black women were at higher risk of subsequent CKD (aRR 1.78, 95% CI 1.18-2.70), whereas GDM-exposed white women were not (aRR 0.81, 95% CI 0.58-1.13). However, these pooled effect estimates were based on just two studies with inconsistent approaches to their handling of post-pregnancy T2DM (95, 96). No studies were retrieved which had investigated the association between GDM and maternal ESKD. Further research was needed on this topic before conclusions could be drawn.

An updated systematic review was undertaken in December 2020 to identify additional research which had been published since the original systematic review (between August 2019 and November 2020 inclusive). Four additional cohort studies were retrieved, of which two were studies presented in this thesis (Chapters 4 and 6). The four additional studies included three effect estimates of the preeclampsia-CKD association. The updated meta-analysis results indicated a more modest risk of CKD among women who had been exposed to preeclampsia (aRR 1.73, 95% CI 1.42-2.12), but the population attributable fraction for preeclampsia on maternal CKD was unchanged at 4%. The risk of CKD was higher among women who experienced preterm preeclampsia (aRR 3.23, 95% CI 2.34-4.46), but this pooled estimate was based on just two studies. Updated pooled estimates for gestational hypertension and CKD (aRR 1.48, 95% CI 1.38-1.58) and for preterm delivery and ESKD (aRR 2.19, 95% CI 1.93-2.47) were not meaningfully different from those obtained in the original meta-analysis.

Thus, in this systematic review and meta-analysis, exposure to adverse pregnancy outcomes was generally associated with increased risk of long-term maternal kidney disease. However, there were a limited number of studies published on any specific associations between

pregnancy-related complications and maternal CKD or ESKD respectively. None of the meta-analyses included more than six studies, and this precluded most of the pre-planned subgroup analyses. Several of the existing studies were limited by residual confounding or the use of non-specific outcomes (such as renal hospitalisation). More robust research was needed to address some of these key limitations, and to draw more definitive conclusions on the relevance of adverse pregnancy outcomes for the risk of maternal CKD and ESKD.

9.1.2 Findings on preterm delivery

The first population-based cohort study focused on associations between preterm delivery and maternal CKD and ESKD (Chapter 4). Using data from the Swedish national registers, women who had singleton live births from 1973 to 2012 were followed for a median 20.6 years to identify those who developed CKD or ESKD in later life. Preterm delivery (<37 weeks) was the main exposure variable of interest.

Women who had any preterm delivery were at increased risk of CKD (aHR 1.39, 95% CI 1.32–1.45) and ESKD (aHR 2.22, 95% CI 1.90–2.58) compared with women who only delivered at term (≥ 37 weeks). This finding was consistent across various definitions of gestational age and was strongest in those with very/extremely preterm deliveries. For example, women who delivered at least one extremely preterm infant previously (< 28 weeks) were at significantly higher risk of CKD (aHR 1.84, 95% CI 1.52–2.22) and ESKD (aHR 3.61, 95% CI 2.03–6.39) compared to women who only delivered at term. Women who had preterm preeclampsia were particularly susceptible to future CKD (aHR 2.81, 95% CI 2.46–3.20) and ESKD (aHR 6.70, 95% CI 4.70–9.56) compared to women who had uncomplicated deliveries at term.

This study sought to investigate if the indication for preterm delivery affected associations with maternal kidney disease. Although iatrogenic preterm delivery (due to preeclampsia or

SGA) was more strongly associated with maternal CKD and ESKD, spontaneous preterm delivery was also independently associated with higher risk of maternal kidney disease. Women who had experienced spontaneous preterm delivery were at higher risk of CKD (aHR 1.32, 95% CI 1.25–1.39) and ESKD (aHR 1.99, 95% CI 1.67–2.38) compared to women who had uncomplicated deliveries at term. Given that 70% of all preterm deliveries occur spontaneously (165), this suggests that the contribution of spontaneous preterm delivery towards the burden of CKD in parous women may be substantial from a population perspective.

The mechanisms underlying the observed associations are uncertain. Women who experience preterm delivery are at higher risk of subsequent hypertension, diabetes, and hypercholesterolaemia (166), as well as CVD (20, 55, 75), and these factors may all increase the risk of future CKD or ESKD. Inflammatory processes which underlie spontaneous preterm deliveries may also increase the risk of endothelial dysfunction and subclinical vascular disease, which may in turn increase the risk of later CKD or ESKD (167, 168).

Irrespective of causal mechanisms, the findings of this study suggest that preterm delivery may act as an early risk marker for maternal kidney disease in later life. However, further research is needed to investigate how this information should be harnessed in clinical practice to prevent CKD or ESKD.

9.1.3 Findings on stillbirth

The second population-based cohort study focused on associations between stillbirth and maternal CKD and ESKD (Chapter 5). Stillbirth was not included as one of the adverse pregnancy outcomes in the systematic review for this thesis. However, on reviewing the existing literature, it became clear that while associations between stillbirth and maternal CVD

were well established (55, 191-193), there was a lack of research on stillbirth and maternal CKD or ESKD.

A considerable decline in the incidence rate of stillbirths was observed in Sweden over the study period from 5.2/1,000 deliveries (after 28 weeks) in the 1970s to 3.1/1,000 deliveries (after 22 weeks) between July 2008 and December 2012, despite using a wider definition for stillbirths in the latter years. Women who had experienced at least one stillbirth were at increased risk of developing CKD (aHR 1.26, 95% CI 1.09–1.45) or ESKD (aHR 2.25, 95% CI 1.55–3.25) during follow-up compared to women who only had live births. These associations persisted independent of maternal smoking, obesity, medical comorbidities, and obstetric factors such as SGA, preeclampsia, or congenital malformations. The associations with maternal kidney disease were largely driven by antepartum stillbirths, which made up the majority (91%) of all stillbirths in Sweden. Intrapartum stillbirths were associated with an increase in risk of ESKD, but this was not statistically significant (aHR 2.02, 95% CI 0.65-6.29). This may have been due to the small numbers of affected women, but it suggests that this finding may be of lesser clinical or public health concern.

Among women who had pre-pregnancy medical comorbidities (e.g. CVD, diabetes, hypertension), who were already predisposed to developing future kidney disease, a history of stillbirth did not appear to confer any additional risk of CKD (aHR 1.13, 95% CI 0.73-1.75) or ESKD (aHR 1.49, 95% CI 0.78-2.85). However, this analysis was also based on small numbers of events.

Like preterm delivery, the mechanisms underlying associations between stillbirth and future maternal CKD or ESKD are uncertain. It is possible that women experience endothelial dysfunction following stillbirth, and that this may increase their risk of CVD and CKD in later life (198). Women who experience stillbirths may also be predisposed to altered immune activation (199) and high homocysteine levels, which may in turn increase their risk of CKD

(200, 201). However, it seems more likely that stillbirth is a manifestation of increased baseline cardio-renal risk, rather than being causally related to CKD. The findings from this study suggest that affected women may benefit from enhanced surveillance and follow-up for future kidney disease, but the optimal format, content, and timing of this requires further investigation.

9.1.4 Findings on hypertensive disorders of pregnancy

The third population-based cohort study investigated associations between HDP, specifically preeclampsia and gestational hypertension, and the risk of maternal CKD including subtypes of CKD (Chapter 6). When the systematic review and meta-analysis was undertaken at the outset of this research (Chapter 2), it was clear that the literature on HDP and maternal CKD was sparse. By contrast, associations between preeclampsia and ESKD were well established and thus, ESKD was not included as an outcome in this particular study.

The findings indicated that, during a median 20.7 years follow-up, women who had experienced preeclampsia were at increased risk of developing any CKD (aHR 1.92, 95% CI 1.83-2.03), and their time to CKD diagnosis was 2.7 years shorter compared to women who never had preeclampsia. This risk differed considerably between CKD subtypes. The risk was highest for diabetic CKD (aHR 3.94, 95% CI 3.38–4.60), hypertensive CKD (aHR 3.72, 95% CI 3.05–4.53) and glomerular CKD (aHR 2.06, 95% CI 1.88–2.26), whereas the risk was lower for tubulointerstitial CKD (aHR 1.44, 95% CI 1.24–1.68) and other/nonspecific CKD (aHR 1.51, 95% CI 1.38–1.65).

The risk of CKD was increased among women who experienced preterm preeclampsia, recurrent preeclampsia, or preeclampsia complicated by pre-pregnancy obesity. After excluding women who developed postpartum hypertension, these associations largely

persisted, suggesting that non-hypertensive factors contribute to the development of maternal CKD. However, further research is required to elucidate the role of potential mediating factors in the associations between preeclampsia and maternal kidney disease, including postpartum hyperglycaemia, hyperlipidaemia, and changes in maternal blood pressure and BMI beyond the reproductive period.

SGA alone (without preeclampsia) was associated with a modest increase in overall risk of CKD (aHR 1.32, 95% CI 1.24-1.40). However, concurrent preeclampsia + SGA did not confer additional risk of CKD beyond those who had been diagnosed with preeclampsia alone. The only exception to this was for hypertensive CKD, where women with concurrent preeclampsia + SGA were at markedly increased risk of CKD (aHR 5.23, 95% CI 3.51–7.79). It is possible that concurrent preeclampsia + SGA signals higher risk of hypertensive disease in later life, possibly related to more extreme placental insufficiency (221, 222). However, this phenotype may not necessarily add to the risk of other subtypes of CKD.

Women who had gestational hypertension were also at increased risk of developing CKD, but this association was less marked than that observed for preeclampsia (aHR 1.49, 95% CI 1.38–1.61). The risk was greater for hypertensive CKD (aHR 3.13, 95% CI 2.47–3.97) and diabetic CKD (aHR 1.96, 95% CI 1.56–2.47).

In all studies using the Swedish national registers, under-diagnosis of CKD is a possibility, and some women may have been too young to develop symptomatic CKD despite the long follow-up time. Nonetheless, the findings indicate that women who experience preeclampsia are at higher risk of CKD in later life. Hypertensive CKD and diabetic CKD are likely to become dominant subtypes of CKD in older women, and those who experience preeclampsia appear to be at particular risk of developing these forms of CKD.

Women who experience preeclampsia secrete anti-angiogenic proteins like sFLT1 from the placenta, and it is possible that this induces endothelial injury which persists in some women.

This may result in increased risk of CKD and other chronic diseases (11). Affected women are also predisposed to a range of cardiometabolic risk factors, including hyperglycaemia and hyperlipidaemia, which increase their risk of subsequent CKD (Figure 9.1) (248). Moreover, preeclampsia may lead to glomerular endotheliosis, which accelerates podocyte loss and subsequent microalbuminuria (56, 216, 217). The biological mechanisms linking preeclampsia and maternal chronic disease are considered further in Appendix 1. But regardless of these mechanisms, the findings support the need to optimise long-term follow-up of women exposed to HDP, and especially high-risk women who have experienced preterm preeclampsia or recurrent preeclampsia in the reproductive years.

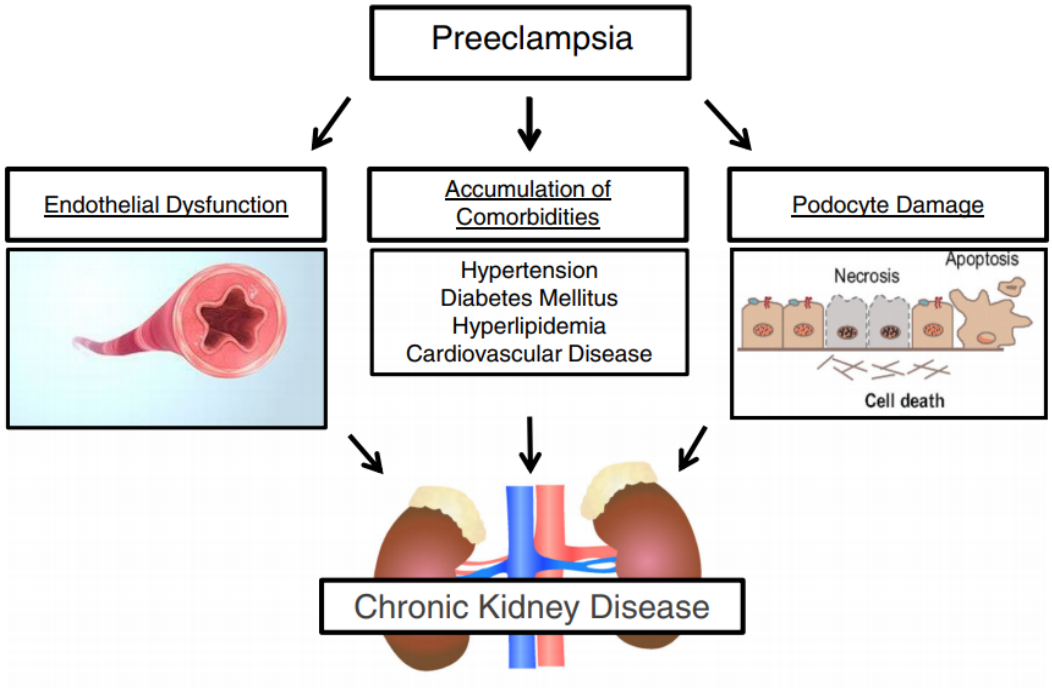


Figure 9.1 Potential biological mechanisms underlying associations between preeclampsia and maternal chronic kidney disease.

Source: Kattah et al. 2020 (248)

9.1.5 Findings on gestational diabetes

The final population-based cohort study was focused on associations between GDM and maternal CKD, ESKD, and subtypes of kidney disease (Chapter 7). This study was restricted to first deliveries occurring in Sweden between 1987 and 2012 (instead of 1973 to 2012) when ICD coding of GDM became routinely available. The incidence of GDM doubled during this time period, from 562 diagnoses per 100,000 births in 1987-1991, to 1,123 diagnoses per 100,000 births in 2007-2012. This coincided with increases in mean maternal age at first delivery from 26.4 years in 1987-1991, and 3.9% prevalence of antenatal obesity, to 30.2 years in 2007-2012, and 12.1% prevalence of obesity.

Overall, women who had experienced GDM had an increased risk of developing CKD (aHR 1.81, 95% CI 1.54-2.14) and ESKD (aHR 4.52, 95% CI 2.75-7.44) compared to women who never had GDM. This risk differed across subtypes of CKD, and was stronger for glomerular CKD (aHR 1.86, 95% CI 1.37-2.51), hypertensive CKD (aHR 2.46, 95% CI 1.06-5.69), and diabetic CKD (aHR 8.81, 95% CI 6.36-12.19), whereas no significant associations were observed with tubulointerstitial CKD or other/non-specific CKD.

When GDM was stratified according to those who did or did not develop post-pregnancy T2DM, it became clear that associations were driven by those who developed overt T2DM. Women who experienced GDM and subsequent T2DM had a higher risk of CKD (aHR 21.70, 95% CI 17.17-27.42) and ESKD (aHR 112.37, 95% CI 61.22-206.38) during follow-up (vs. those who had neither GDM nor T2DM). By contrast, there was no significant association between GDM alone (without overt T2DM) and either CKD (aHR 1.11, 95% CI 0.89-1.38) or ESKD (aHR 1.58, 95% CI 0.70-3.60).

Our systematic review (Chapter 2) had suggested the possibility of effect modification of the GDM-CKD association by maternal ethnicity. Thus, tests for interaction by maternal country of origin were undertaken. The findings indicated that there was evidence of significant effect

modification, but this was due to differential associations between T2DM and CKD, rather than GDM itself.

Most regions of Sweden had employed a selective, high-risk approach to GDM screening during the study period (141). This may have introduced some differential misclassification since obese women and those with previous LGA deliveries were more likely to be diagnosed with GDM at baseline. However, we considered the relevant screening criteria in our statistical models where possible and thus, the true risk of CKD/ESKD is unlikely to differ substantially from that observed here.

This study provides clarity to the existing evidence base for the associations between GDM and maternal kidney disease. Women who experience GDM and subsequent T2DM may be at significantly higher risk of CKD and ESKD, but women who experience GDM alone (without later T2DM) have equivalent risk of future kidney disease to those whose pregnancies were normoglycaemic. These findings suggest that postpartum screening for T2DM, and lifestyle or pharmacological interventions aimed at preventing onset of T2DM, are likely to reduce the burden of kidney disease among women who have experienced GDM.

9.1.6 Application of the conceptual framework

The maternal morbidity measurement framework (outlined in section 1.2) (45) was applied in the design and analysis of each original study of adverse pregnancy outcomes and maternal kidney disease. The following principles were adhered to:

(1) Woman-centred approach. All studies were based on maternal outcomes. Thus, analyses were focused on issues which are important for women's health throughout the life-course. The research was nationally representative, and although it captured a largely Caucasian

population, it is possible to generalise the findings herein to parous women in other high-income countries internationally.

(2) Cyclical nature. The use of time-dependent covariates meant that women could contribute unexposed and exposed person-time in each study, depending on their experiences across different pregnancies. Women were considered exposed to any given adverse pregnancy outcome from the date of their first affected delivery, irrespective of subsequent uncomplicated deliveries. The research herein also considered the possibility that women may experience adverse pregnancy outcomes multiple times. For example, in Chapter 4, a hierarchical time-dependent covariate was used for preterm delivery. Women could contribute person-time to more than one exposure category during follow-up, with her exposure status at any given time reflecting her most extreme (i.e. earliest) preterm delivery. Moreover, in Chapter 6, women with recurrent preeclampsia (across two pregnancies) were specifically considered in a separate sensitivity analysis.

(3) Lasting effects. Each study considered the lasting effects of adverse pregnancy outcomes on maternal morbidity, specifically in relation to risk of CKD or ESKD. The use of Cox regression allowed the long-term effects of adverse pregnancy outcomes to be considered beyond the reproductive years for most women, up to a maximum of 41 years follow-up.

(4) Socio-economic influences. We considered the potential influence of socio-economic factors on associations between adverse pregnancy outcomes and maternal kidney disease where possible. Although the datasets did not contain any variables on household income, occupation, or deprivation, maternal education was available as a proxy for socio-economic status and this was included as a covariate in all analyses. We also adjusted for maternal ethnicity, and while this only distinguished between native Swedes and non-natives, there are likely to be key socio-economic and cultural differences between these two categories of

participants. Furthermore, maternal migration was considered in the study design and this information was used for censoring.

(5) Environmental influences. Unlike other healthcare systems, there are very few barriers in access to healthcare in Sweden, and antenatal care is similar for all women (114). However, changes in the standards and practices of healthcare delivery were considered throughout this research. For example, in Chapter 4, a change from routine estimation of gestational age using LMP to second trimester ultrasound was the basis for a sensitivity analysis. In Chapter 5, changes to the definition of stillbirths (from 28 weeks to 22 weeks) were considered in the design and analysis. There were no variables in the datasets which provided information on area-level deprivation. However, certain lifestyle-related factors, which may be environmentally influenced, were included in all analyses where available, including maternal smoking, antenatal obesity and, in Chapter 7, gestational weight gain.

(6) Groupings of maternal morbidity. The use of ICD coding to define CKD, ESKD and all subtypes of kidney disease ensured that long-term maternal health outcomes were objectively classified. This international classification system was also used to define pre-pregnancy comorbidities and to identify adverse pregnancy outcomes in the MBR and NPR. Finally, pregnancy complications and confounding factors were categorised using widely accepted international criteria where possible. For example, in Chapter 4, preterm deliveries were classified using standard definitions for moderate/very/extremely preterm labour, and in Chapter 5, stillbirths were classified according to whether they occurred antepartum or intrapartum. In all studies, maternal obesity was classified using standard World Health Organization categories (249) and in Chapter 7, established criteria were used to categorise gestational weight gain (156).

9.2 Interpretation of findings

The results of this thesis indicate that adverse pregnancy outcomes are important risk markers for long-term maternal kidney disease. However, the possibility of alternative explanations must be considered before observed associations can be assumed to be true.

9.2.1 Bias

Selection bias

It is unlikely that selection bias had any meaningful impact on the results. This possibility was minimised through the use of a large national cohort with almost complete population coverage. The MBR included data on over 96% of births in Sweden (118), and the NPR achieved complete coverage of the population in 1987 (119). Participants were included in these registers by default if they were residing in Sweden. A long period of follow-up was used in each study, spanning up to 41 years. Universal healthcare is largely achieved in Sweden, and virtually all women enrol in antenatal care (114). Berkson's bias is unlikely to have influenced results since the sample is representative of the overall population (250).

The Swedish population was largely Caucasian during this timeframe and this may have reduced external validity of the findings. However, the TPR includes information on over 95% of immigrants in Sweden (117) and thus, it is unlikely that there were important systematic differences between participants and non-participants. Furthermore, all analyses were adjusted for maternal country of origin.

Information bias

The data in this thesis were retrieved from national registers with mandatory reporting, thereby excluding the possibility of recall bias. Exposure to some adverse pregnancy outcomes can differ between primiparous and multiparous women, but time-dependent covariates were used to allow for changes in exposure status over time rather than basing exposure on the first delivery alone. This meant that the data were more representative of women's cumulative exposure to obstetric risks during their reproductive lifetime. In addition, all analyses were adjusted for parity.

Data on maternal BMI and smoking were incomplete and were only collected from 1982 onwards. Indicator variables were used to reduce the impact of missing data in three of the population-based cohort studies. This method allowed all study participants to be retained in analysis, thereby reducing the possibility of selection bias. However, this may have resulted in some residual information bias since there may have been incomplete adjustment for confounders. Sensitivity analyses were undertaken in all studies to verify the results (e.g. from 1987 onwards when data on BMI and smoking were more complete) and these were not meaningfully different. Furthermore, in the final study of GDM and maternal kidney disease multiple imputation methods were used to reduce the possibility of bias.

It is likely that CKD was under-diagnosed in the Swedish national registers, particularly milder forms of CKD. The NPR only included outpatient data from 2001 onwards, and no primary care data were available. Thus, the CKD cases in these studies were likely to be more severe cases who required hospitalisation. The SRR only began collecting data on CKD in 2007, and while those individuals are likely to have valid diagnoses, many women with milder CKD may have been missed. Some women may have been too young to have developed symptomatic CKD despite the long follow-up time. The low incidence of hypertensive and diabetic CKD, which predominate in older age, supports this possibility. Nonetheless, it is unlikely that any

misclassification of CKD was differential, or related to exposure to any specific adverse pregnancy outcome. The results may have been shifted towards the null and thus, the associations observed in this thesis between adverse pregnancy outcomes and CKD may be somewhat conservative.

In the latter years of the study period, it is possible that healthcare professionals became more aware of the links between adverse pregnancy outcomes and CKD/ESKD, particularly after the publication of the first large cohort study in 2008, which focused on preeclampsia (28). This could have introduced surveillance bias if healthcare professionals monitored HDP-diagnosed women more closely for kidney disease than other parous women. However, the majority of follow-up time in our studies occurred before 2008, and awareness of the links between adverse pregnancy outcomes and chronic disease remains relatively low among healthcare professionals in the present day (251). Thus, this is unlikely to have strongly influenced the results.

In studies which focused on preeclampsia and GDM specifically (Chapters 6 and 7), some analyses were based on intermediate variables such as postpartum hypertension or T2DM. By controlling for these intermediate variables statistically, or by excluding them or stratifying on them, it is possible that collider bias may have been induced. This issue can arise when there is unmeasured confounding between the intermediate variable and the outcome (252). Moreover, by adjusting for intermediate variables, the possibility of over-adjustment bias cannot be excluded. The latter may have resulted in shifting of some results towards the null (204).

9.2.2 Confounding

Confounding is always a possibility in observational studies. However, considerable efforts were made to minimise this throughout the thesis. Firstly, covariate selection in each study was based on *a priori* consensus decision-making between the primary researcher and an international collaborative team of epidemiologists, obstetricians and nephrologists. Directed acyclic graphs were used to inform these discussions. Secondly, the systematic review (Chapter 2) highlighted the range of confounders which had been considered in the previous literature, and where important covariates had been overlooked. This information was used to guide decisions relating to covariate selection in each of the cohort studies. For example, all studies herein were adjusted for maternal smoking and BMI, and these had been omitted from some key studies of adverse pregnancy outcomes and maternal CKD or ESKD previously (28, 30, 74, 94).

Thirdly, women with a wide range of pre-pregnancy diseases were excluded from the analyses to reduce the possibility of confounding. These comorbidities included CKD, ESKD, CVD, diabetes, hypertension, SLE, systemic sclerosis, coagulopathies, haemoglobinopathies, and vasculitides. Moreover, women who were diagnosed with a wide range of congenital or genetic forms of CKD or ESKD were excluded from every study.

Nonetheless, some sources of residual confounding may remain. In relation to preeclampsia, one of the most challenging factors in unravelling the relationship with CKD is the role that undiagnosed, pre-existing renal impairment may play in the association. Underlying CKD, even mild and asymptomatic CKD, is associated with an increased risk of preeclampsia (248). Despite excluding those with pre-pregnancy CKD at baseline, it is still possible that observed associations are confounded by undiagnosed nephropathy.

The information available on stillbirths lacked detail, and it was not possible to determine the underlying cause of any stillbirth. Data on congenital malformations were incomplete in the MBR and unmeasured confounding by foetal growth restriction is a possibility, particularly in Chapter 5.

As mentioned above, there were no specific individual or area-level measures of deprivation available in the MBR, and maternal education had to be used as a proxy for this. Moreover, while we adjusted for antenatal BMI in every study, and we considered the potential impact of GDM and postpartum hypertension where possible, the data quality for these variables was suboptimal. There may have been residual confounding from dyslipidaemia, dysglycaemia, and other cardiometabolic or genetic risk factors.

Finally, we had no information available on the use of pharmacological or non-pharmacological interventions postpartum, and these may alter the trajectory towards the development of CKD or ESKD. However, given that the associations between adverse pregnancy outcomes and long-term risk of maternal chronic disease have been under-recognised to date (43), this is unlikely to have had a substantial impact on the results.

9.2.3 Chance findings

It is unlikely that the key findings in this thesis arose due to random error. Even after applying strict exclusion criteria at baseline, the sample size in each study was very large. The 95% confidence intervals for the main results were typically narrow, with the exception of some sensitivity analyses focused on ESKD or on less common CKD subtypes. Although a Bonferroni correction was not applied in any of the studies in this thesis, the majority of results had very small p values <0.001 (as shown in Chapter 6). Thus, it is highly improbable that these results arose by chance alone.

9.3 Strengths and limitations

9.3.1 Strengths

This thesis includes a comprehensive systematic review and meta-analysis of the epidemiological evidence examining associations between adverse pregnancy outcomes and maternal CKD and ESKD. This was planned using a pre-specified published protocol (77), and it was reported in accordance with accepted international standards (47). The search was updated towards the end of this research to include newly published studies and to provide an overview of the most recent international evidence on this topic. Findings from the systematic review were drawn upon to identify gaps in knowledge and to address key limitations of the existing literature.

Large-scale cohort studies were designed using nationally representative data from the entire parous female population in Sweden over a period of four decades. These high-quality datasets allowed a wide range of confounders to be controlled for, and multiple sensitivity analyses were undertaken in each study to validate the findings. Furthermore, a large sample size was obtained in each study, and this increased statistical power and improved accuracy of effect estimates. Several of the original cohort studies were the largest of their kind published to date in the international literature. Moreover, the classification of CKD in to specific subtypes, and the exclusion of congenital and hereditary forms of CKD at baseline, provided a more detailed overview of associations between adverse pregnancy outcomes and maternal kidney disease than most previous studies.

In order to translate the epidemiological findings from the systematic review and observational studies in to pragmatic public health messages, two editorials were published on the broader public health implications of this work (Appendix 11 and Appendix 12). These editorials consider the overall findings for CKD and ESKD in the context of previous

cardiovascular research, and what the results mean for affected women and their healthcare providers in practice.

9.3.2 Limitations

From the outset, it was clear that the literature on this research topic was sparse. In the original systematic review, only 23 studies were eligible for inclusion, and high levels of heterogeneity were observed in some of the meta-analyses. Residual confounding is likely to have affected several of the pooled effect estimates obtained in these meta-analyses, and it was not possible to assess publication bias based on the small numbers of published studies for separate adverse pregnancy outcomes. Studies which focused on biomarkers of renal dysfunction, such as microalbuminuria or reduced eGFR, were omitted. Although this was considered necessary to prevent the systematic review becoming unwieldy, it may have resulted in the exclusion of some relevant research on this topic. The scope of the systematic review may have also been narrowed because eligible articles were limited to those published in English.

Many of the inherent limitations of the original cohort studies have been considered in the preceding section, particularly in relation to bias or confounding. However, several other limitations warrant specific consideration.

Although a large amount of information was available in the Swedish national registers, there were some data gaps. For example, when investigating associations between pregnancy loss and maternal kidney disease, this had to be limited to stillbirths because the MBR only contains information on live births and stillbirths after 22 or 28 weeks respectively, depending on the year of delivery. Although women who experience recurrent miscarriage are known to be at increased risk of CVD (191, 253, 254), it was not possible to examine whether an association with CKD might also exist because this information was unavailable.

Despite the large sample size, some of the key outcome variables were rare and this may have affected the precision of some effect estimates. Fewer than 1 in 1,000 women were diagnosed with ESKD during follow-up, after relevant exclusions had been applied (e.g. exclusion of women with pre-pregnancy comorbidities), and thus it was not possible to investigate the risk of ESKD subtypes. Some key exposure variables were also uncommon. For example, in Chapter 5, the relative rarity of intrapartum stillbirths may have impacted on the accuracy of effect estimates for associations with CKD and ESKD. Similarly, it was not possible to investigate the impact of recurrent stillbirths on maternal kidney disease because too few women had experienced this.

Finally, adverse pregnancy outcomes do not arise entirely independently of each other. Although this thesis investigates the associations between specific pregnancy complications and maternal risk of CKD and ESKD, there was only limited exploration of the impact of concurrent adverse pregnancy outcomes on long-term risk. This approach was used to avoid a Table 2 fallacy, and potentially incorrect interpretation of exposure-outcome associations (143). Nonetheless, it is clear that some adverse pregnancy outcomes have a cumulative impact on the risk of maternal kidney disease (e.g. preterm preeclampsia), although this may not be the case for all (e.g. preeclampsia + SGA). Further research is required to robustly investigate the effects of multiple concurrent adverse pregnancy outcomes on the long-term risk of maternal morbidity, and to identify whether this risk differs according to whether complications arise during the same pregnancy or across the reproductive lifetime.

9.4 Public health implications

9.4.1 Overview of public health considerations

This section presents the implications of this research and provides interpretation of the findings from a public health perspective. The implications are also discussed in two published editorials (Appendix 11 and Appendix 12 respectively) which have been integrated herein. Strong associations between individual pregnancy complications and maternal CKD and ESKD were observed in this thesis. However, not all of the observed risks are of equal importance from a population perspective. Moreover, while obstetric complications offer an opportunity to provide sex-specific preventive care to women at increased risk of a range of chronic diseases, challenges remain to the use of this information in mainstream clinical practice.

9.4.2 Relative risk vs. absolute risk of kidney disease

The findings suggest that the relative risk of ESKD is high among women affected by adverse pregnancy outcomes compared to those whose pregnancies were uncomplicated. However, it is likely that the absolute risk of ESKD remains very low for affected women. ESKD is reasonably rare, affecting fewer than 1 in 1,000 women (34), and while it causes a disproportionate amount of morbidity and premature mortality (38), it is arguably of lesser public health importance than CKD.

The associations between adverse pregnancy outcomes and CKD were more modest than those observed for ESKD. For example, women who experienced preeclampsia had approximately double the relative risk of CKD compared to women with normotensive pregnancies, and those who had gestational hypertension had 49% higher risk of CKD. Women who had any spontaneous preterm delivery had 32% increased risk of CKD compared to those with term deliveries. But collectively, adverse pregnancy outcomes are very common, and the

incidence of HDP and preterm delivery has been increasing in recent years (50, 51, 64). The global prevalence of CKD is also increasing, and clinically significant CKD affects about 1 in 8 women in their lifetime (34, 48). Thus, in absolute terms, there may be substantial risk of CKD arising from these somewhat modest associations. This may support the need for a systematic programme of follow-up for affected women.

Efforts to harness information from women's obstetric history to prevent CKD may have limited impact at the individual level, but considerable impact among parous women at a population level (255). This is because of the 'prevention paradox', where interventions (or behavioural changes) can achieve large overall health gains for entire populations, despite only offering small advantages to individuals. For example, it is estimated that for every four patients with preeclampsia who are routinely followed up, one case of overt albuminuria will be detected (73). Early identification of susceptible women would help to prevent the onset or progression of CKD, and would likely reduce long-term morbidity at a population level. Additionally, it may help to reduce the burden of CVD, stroke, and other chronic diseases (256, 257).

9.4.3 Knowledge of links with chronic disease

Knowledge among healthcare professionals

If pregnancy-related information is to be used for long-term disease prevention, knowledge of associations between adverse pregnancy outcomes and CKD or other chronic diseases needs to improve. Current research suggests that healthcare professionals have relatively low levels of awareness of the long-term cardiovascular and renal risks associated with adverse pregnancy outcomes. Obstetricians tend to have greater awareness relative to other clinicians, but they are not routinely involved in the long-term aftercare of affected women (251, 258).

Only a small minority of general practitioners and internal medicine physicians appear to ask women about their pregnancy history when assessing overall CVD risk beyond the reproductive years (251, 259). Insufficient awareness of these associations may be due to 1) lack of accessible evidence-based guidelines for monitoring women with adverse pregnancy outcomes over the long-term; 2) different and competing versions of published guidelines; 3) lack of shared electronic healthcare records between obstetric and primary care services (251, 260).

Knowledge among affected women

Women who experience adverse pregnancy outcomes may also be unfamiliar with their individual risk of chronic disease (261, 262). Patients and clinicians may have different perceptions of the importance of personalised information, and this may result in communication gaps. In Canada, some doctors assumed that women who had preeclampsia did not want to know their long-term risk of CVD if women did not inquire directly about this after pregnancy (262). By contrast, in Norway, women who had experienced pregnancy complications wanted to receive more individualised information about their cardiometabolic risk by default (261). If neither healthcare providers nor patients initiate discussion about the links between adverse pregnancy outcomes and chronic disease, this prevention opportunity may be missed.

Gaps between guidelines and clinical practice

Where clear evidence-based guidelines for the aftercare of affected women are available, and known among healthcare professionals, they tend to result in improved recognition of cardiometabolic risk. Clinicians are more likely to identify risk factors for chronic disease such

as hypertension and hyperglycaemia. They are more inclined to counsel women regarding their individual risk, and this can facilitate women's own self-management (258).

At present, recommendations for post-pregnancy prevention of CKD and CVD tend to be either inconsistent or absent from national and international guidelines. A recent review of 16 international guidelines reported excessive variation in the recommended follow-up of women who had experienced HDP (260). Only eight guidelines provided any recommendations for follow-up beyond the immediate postpartum period. They typically emphasised the need to inform women and their general practitioners about the future risk of CVD and CKD. There was a lack of high-quality evidence available on long-term surveillance and risk reduction strategies, and specific follow-up actions varied considerably.

The American College of Cardiology now state that pregnancy complications should be regarded as "risk-enhancing factors" for CVD, particularly among women whose 10-year cardiovascular risk is intermediate or low (263). For example, women who have had adverse pregnancy outcomes may benefit from more intensive lifestyle modifications for primary prevention of CVD than women whose pregnancies were uncomplicated. Similarly, women at intermediate risk of CVD may benefit from earlier commencement, or higher doses, of statin therapy if they have a history of preeclampsia (263). It is unclear to what degree these guidelines are being implemented in practice.

Going forward, adverse pregnancy outcomes need to be more consistently incorporated in to a wider range of clinical guidelines, used across both community and hospital settings, to ensure that healthcare professionals and affected women are aware of their links with long-term outcomes, and to yield their full potential in disease prevention. Educational interventions for healthcare professionals also need to be designed to improve awareness of these links, and to close the 'knowledge to practice' gap (259).

9.4.4 Systematic follow-up programmes

The optimal timing, content, and format of structured follow-up programmes for women with adverse pregnancy outcomes is uncertain. Proposals have included systematic screening programmes for affected women, the inclusion of adverse pregnancy outcomes in clinical risk prediction algorithms for CKD and CVD, and the establishment of maternal health clinics to monitor women beyond the reproductive years.

Screening

It is possible that women who experience adverse pregnancy outcomes would benefit from screening for future CVD and CKD. However, there is a lack of robust evidence available on the efficacy and effectiveness of such programmes. Specific recommendations around screening eligibility, frequency of follow-up, and preventive interventions are lacking (225). Ideally, eligible women should be enrolled in a screening programme in the immediate postpartum period to detect early onset CVD or CKD, and to identify modifiable risk factors. Subclinical disease may be present, but it can be difficult to detect in the absence of sensitive and reliable biomarkers. Moreover, the presence of cardio-protective oestrogen in pre-menopausal women, and the potential masking of early renal damage by compensatory glomerular hyper-filtration, may limit the ability to detect high-risk women until later in life (225).

Any systematic public screening programme can only be justified if it facilitates earlier diagnosis or intervention, and if there is strong evidence of its clinical and cost effectiveness (264). At present, it is too premature to conclude whether the benefits of screening affected women for CVD or CKD would outweigh potential harms.

Clinical risk prediction tools

It is possible that obstetric information may add incremental value to clinical risk prediction tools for chronic disease, but the evidence for this is inconclusive to date. Recent longitudinal studies from Scandinavia suggest that HDP, preterm delivery and SGA make minimal improvements to CVD risk prediction after taking traditional risk factors in to account (265, 266), although these studies have been limited by relatively short durations of follow-up. There is a dearth of research on the use of obstetric risk factors in CKD risk prediction models to date. Larger population-based studies with longer follow-up (>10 years) are warranted to investigate whether obstetric information can enhance CVD and CKD risk prediction algorithms for women.

Postpartum health clinics

It is important that healthcare providers discuss the links between adverse pregnancy outcomes and chronic disease risk with their patients where possible. However, the provision of information may not be sufficient to achieve meaningful long-term changes for all. Some women prefer to receive structured advice or supports, and postpartum maternal health clinics may help in this regard. Such clinics allow healthcare providers and patients to agree a plan for chronic disease prevention together, either through lifestyle modifications alone or by using medical interventions and treatment.

To date, there have been few formal evaluations of these clinics, but there appears to be considerable risk of selection bias among attendees. Women with higher BMI, women from deprived backgrounds, and smokers may be less likely to attend, despite being at higher risk of chronic disease (267, 268).

9.4.5 Future research

Adverse pregnancy outcomes are a uniquely female suite of risk markers for CKD and other chronic diseases. Country and context-specific research is lacking on women's and healthcare providers' knowledge of the long-term risks following complications of pregnancy (252). Further research is needed to define the trajectory towards the development of chronic disease among affected women, including the potential role of mediating factors such as postpartum hypertension, hyperlipidaemia, albuminuria and hyperglycaemia. The relative effectiveness of preventive interventions needs to be elucidated, and the potential benefits of engaging women in screening programmes should be investigated further (225, 269). More longitudinal population-based studies are needed to determine whether adverse pregnancy outcomes offer tangible, incremental value for CVD and CKD risk prediction tools, and whether postpartum maternal health clinics offer a viable, cost-effective forum in which to counsel women about their individual risks.

CHAPTER 10. Conclusion

The data in this thesis indicate that maternal exposure to adverse pregnancy outcomes, specifically preeclampsia, gestational hypertension, preterm delivery and stillbirth, is associated with increased risk of future CKD and ESKD. These associations persisted in a large population-based cohort after controlling for a wide range of confounders including a comprehensive suite of medical and obstetric comorbidities. Although the relative risk of future disease was highest for ESKD, the associations with CKD are likely to be of greater importance from a population perspective. CKD is a highly prevalent disease in older women and thus, even modest associations between adverse pregnancy outcomes and maternal CKD are likely to have a substantial impact in absolute terms.

It is unclear whether adverse pregnancy outcomes play any causal role in associations with maternal kidney disease, but irrespective, they may be important risk markers of future chronic disease. Further research is required to investigate the role of potential mediating factors for these associations such as postpartum hypertension, hyperlipidaemia, albuminuria and hyperglycaemia.

The findings herein suggest that women who experience adverse pregnancy outcomes may warrant systematic follow-up to prevent onset or progression of maternal kidney disease. The optimal format and timing of this follow-up requires further research, and an integrated approach to CVD and CKD prevention may be most effective. Adverse pregnancy outcomes present a unique opportunity to prevent chronic disease in women and the information available in women's obstetric history should be harnessed, where possible, to improve their long-term health outcomes.

References

1. Trends in maternal mortality 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2019.
2. Kassebaum NJ, Barber RM, Dandona L, Hay SI, Larson HJ, Lim SS, et al. Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1775-812.
3. Koblinsky M, Chowdhury ME, Moran A, Ronsmans C. Maternal morbidity and disability and their consequences: neglected agenda in maternal health. J Health Popul Nutr. 2012;30(2):124-30.
4. Firoz T, Chou D, von Dadelszen P, Agrawal P, Vanderkruik R, Tuncalp O, et al. Measuring maternal health: focus on maternal morbidity. Bull World Health Organ. 2013;91(10):794-6.
5. Knaul FM, Langer A, Atun R, Rodin D, Frenk J, Bonita R. Rethinking maternal health. Lancet Glob Health. 2016;4(4):e227-8.
6. Chou D, Tuncalp O, Firoz T, Barreix M, Filippi V, von Dadelszen P, et al. Constructing maternal morbidity - towards a standard tool to measure and monitor maternal health beyond mortality. BMC Pregnancy Childbirth. 2016;16:45.
7. Black RE, Laxminarayan R, Temmerman M, Walker N, editors. Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities, 3rd Edition (Volume 2): Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2016.
8. The global strategy for women's, children's and adolescents' health (2016-2030). Survive Thrive Transform. Every Woman Every Child; 2015.
9. Graham W, Woodd S, Byass P, Filippi V, Gon G, Virgo S, et al. Diversity and divergence: the dynamic burden of poor maternal health. Lancet. 2016;388(10056):2164-75.
10. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.
11. Rangaswami J, Naranjo M, McCullough PA. Preeclampsia as a form of type 5 cardiorenal syndrome: An underrecognized entity in women's cardiovascular health. Cardiorenal Med. 2018;8(2):160-72.
12. Facca TA, Mastroianni-Kirsztajn G, Sabino ARP, Passos MT, Dos Santos LF, Fama EAB, et al. Pregnancy as an early stress test for cardiovascular and kidney disease diagnosis. Pregnancy Hypertens. 2018;12:169-73.
13. Williams D. Pregnancy: a stress test for life. Curr Opin Obstet Gynecol. 2003;15(6):465-71.
14. 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.
15. Haas DM, Parker CB, Marsh DJ, Grobman WA, Ehrenthal DB, Greenland P, et al. Association of adverse pregnancy outcomes with hypertension 2 to 7 Years postpartum. J Am Heart Assoc. 2019;8(19):e013092.
16. Behrens I, Basit S, Melbye M, Lykke JA, Wohlfahrt J, Bundgaard H, et al. Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. BMJ. 2017;358:j3078.
17. Stuart JJ, Tanz LJ, Missmer SA, Rimm EB, Spiegelman D, James-Todd TM, et al. Hypertensive disorders of pregnancy and maternal cardiovascular disease risk factor development: an observational cohort study. Ann Intern Med. 2018;169(4):224-32.

18. Egeland GM, Skurtveit S, Staff AC, Eide GE, Daltveit AK, Klungsoyr K, et al. Pregnancy-related risk factors are associated with a significant burden of treated hypertension within 10 Years of delivery: findings from a population-based Norwegian cohort. J Am Heart Assoc. 2018;7(10):e008318
19. 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. Circulation. 2019;139(8):1069-79.
20. Tanz LJ, Stuart JJ, Williams PL, Rimm EB, Missmer SA, Rexrode KM, et al. Preterm delivery and maternal cardiovascular disease in young and middle-aged adult women. Circulation. 2017;135(6):578-89.
21. Bhattacharya S, Prescott GJ, Iversen L, Campbell DM, Smith WC, Hannaford PC. Hypertensive disorders of pregnancy and future health and mortality: A record linkage study. Pregnancy Hypertens. 2012;2(1):1-7.
22. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the Child Health and Development Studies pregnancy cohort. Circulation. 2015;132(13):1234-42.
23. Bushnell C, McCullough L. Stroke prevention in women: synopsis of the 2014 American Heart Association/American Stroke Association guideline. Ann Intern Med. 2014;160(12):853-7.
24. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 practice guidelines for the management of arterial hypertension of the European society of cardiology and the European society of hypertension ESC/ESH task force for the management of arterial hypertension. J Hypertens. 2018;36(12):2284-309.
25. Wu R, Wang T, Gu R, Xing D, Ye C, Chen Y, et al. Hypertensive disorders of pregnancy and risk of cardiovascular disease-related morbidity and mortality: a systematic review and meta-analysis. Cardiology. 2020;145(10):633-647.
26. Timpka S, Markovitz A, Schyman T, Mogren I, Fraser A, Franks PW, et al. Midlife development of type 2 diabetes and hypertension in women by history of hypertensive disorders of pregnancy. Cardiovasc Diabetol. 2018;17(1):124.
27. Feig DS, Shah BR, Lipscombe LL, Wu CF, Ray JG, Lowe J, et al. Preeclampsia as a risk factor for diabetes: a population-based cohort study. PLoS Med. 2013;10(4):e1001425.
28. Vikse BE, Irgens LM, Leivestad T, Skjærven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. New Engl J Med. 2008;359(8):800-9.
29. Khashan AS, Evans M, Kublickas M, McCarthy FP, Kenny LC, Stenvinkel P, et al. Preeclampsia and risk of end stage kidney disease: a Swedish nationwide cohort study. PLoS Med. 2019;16(7):e1002875.
30. Wang IK, Muo CH, Chang YC, Liang CC, Chang CT, Lin SY, et al. Association between hypertensive disorders during pregnancy and end-stage renal disease: a population-based study. CMAJ. 2013;185(3):207-13.
31. Wu CC, Chen SH, Ho CH, Liang FW, Chu CC, Wang HY, et al. End-stage renal disease after hypertensive disorders in pregnancy. Am J Obstet Gynecol. 2014;210(2):147.e1-8.
32. Dai L, Chen Y, Sun W, Liu SL. Association between hypertensive disorders during pregnancy and the subsequent risk of end-stage renal disease: a population-based follow-up study. J Obstet Gynaecol Can. 2018;40(9):1129-38.
33. Kattah AG, Scantlebuiy DC, Agarwal S, Mielke MM, Rocca WA, Weaver AL, et al. Preeclampsia and ESRD: the role of shared risk factors. Am J Kidney Dis. 2017;69(4):498-505.
34. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020; 395(10225):709-733

35. National Kidney Foundation. Estimated glomerular filtration rate (eGFR) [Internet]. New York: National Kidney Foundation; 2020 [updated 2020, cited 2020 Dec 17]. Available from: https://www.kidney.org/atoz/content/gfr
36. National Kidney Foundation. Chronic kidney disease change package [Internet]. New York: National Kidney Foundation; 2020 [updated 2020, cited 2020 Dec 17]. Available from: https://www.kidney.org/contents/chronic-kidney-disease-change-package
37. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. Bull World Health Organ. 2018;96(6):414-22D.
38. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. J Intern Med. 2010;268(5):456-67.
39. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006;17(7):2034-47.
40. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. BMJ. 2010;341:c4986.
41. Levin A, Tonelli M, Bonventre J, Coresh J, Donner JA, Fogo AB, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet. 2017;390(10105):1888-917.
42. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. Kidney Int. 2011;80(12):1258-70.
43. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? Epidemiol Rev. 2014;36:57-70.
44. Zoet GA, Benschop L, Boersma E, Budde RPJ, Fauser B, van der Graaf Y, et al. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45- to 55-Year-Old women with a history of preeclampsia. Circulation. 2018;137(8):877-9.
45. Filippi V, Chou D, Barreix M, Say L, on behalf of the WHO Maternal Morbidity Group. A new conceptual framework for maternal morbidity. Int J Gynaecol Obstet. 2018;141:4-9.
46. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page M, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from: www.training.cochrane.org/handbook.
47. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
48. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. PloS one. 2016;11(7):e0158765.
49. Eggers PW. Has the incidence of end-stage renal disease in the USA and other countries stabilized? Curr Opin Nephrol Hypertens. 2011;20(3):241-5.
50. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. PloS one. 2014;9(12):e113715.
51. Jeyabalan A. Epidemiology of preeclampsia: impact of obesity. Nutr Rev. 2013;71 Suppl 1:S18-25.
52. Di Cianni G, Miccoli R, Volpe L, Lencioni C, Del Prato S. Intermediate metabolism in normal pregnancy and in gestational diabetes. Diabetes Metab Res Rev. 2003;19(4):259-70.
53. 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. J Am Coll Cardiol. 2011;57(12):1404-23.
54. van Kesteren F, Visser S, Hermes W, Teunissen PW, Franx A, van Pampus MG, et al. Counselling and management of cardiovascular risk factors after preeclampsia. Hypertens Pregnancy. 2016;35(1):55-61.
55. Heida KY, Velthuis BK, Oudijk MA, Reitsma JB, Bots ML, Franx A, et al. Cardiovascular disease risk in women with a history of spontaneous preterm delivery: A systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23(3):253-63.
56. McDonald SD, Han Z, Walsh MW, Gerstein HC, Devereaux PJ. Kidney disease after preeclampsia: a systematic review and meta-analysis. Am J Kidney Dis. 2010;55(6):1026-39.
57. Lastra G, Manrique C, Sowers JR. Obesity, cardiometabolic syndrome, and chronic kidney disease: the weight of the evidence. Adv Chronic Kidney Dis. 2006;13(4):365-73.
58. Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome? J Clin Invest. 1997;99(9):2152-64.
59. Sandvik MK, Iversen BM, Irgens LM, Skjaerven R, Leivestad T, Softeland E, et al. Are adverse pregnancy outcomes risk factors for development of end-stage renal disease in women with diabetes? Nephrol Dial Transplant. 2010;25(11):3600-7.
60. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009;373(9677):1773-9.
61. Knock GA, McCarthy AL, Lowy C, Poston L. Association of gestational diabetes with abnormal maternal vascular endothelial function. Br J Obstet Gynaecol. 1997;104(2):229-34.
62. Lappas M. Markers of endothelial cell dysfunction are increased in human omental adipose tissue from women with pre-existing maternal obesity and gestational diabetes. Metabolism. 2014;63(6):860-73.
63. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122-31.
64. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012;379(9832):2162-72.
65. The World Bank. Low-birthweight babies (% of births) [Internet]. Washington D.C.: The World Bank Group; 2020 [updated 2020, cited 2020 Dec 17]. Available from https://data.worldbank.org/indicator/SH.STA.BRTW.ZS
66. Eades CE, Cameron DM, Evans JMM. Prevalence of gestational diabetes mellitus in Europe: a meta-analysis. Diabetes Res Clin Pract. 2017;129:173-81.
67. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep. 2016;16(1):7.
68. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.
69. McDonald SD, Han Z, Mulla S, Murphy KE, Beyene J, Ohlsson A. Preterm birth and low birth weight among in vitro fertilization singletons: a systematic review and meta-analyses. Eur J Obstet Gynecol Reprod Biol. 2009;146(2):138-48.
70. Weinhandl ED, Duval S. Generalization of trim and fill for application in meta-regression. Res Synth Methods. 2012;3(1):51-67.
71. Valdiviezo C, Garovic VD, Ouyang P. Preeclampsia and hypertensive disease in pregnancy: their contributions to cardiovascular risk. Clin Cardiol. 2012;35(3):160-5.

72. Tooher J, Chiu CL, Yeung K, Lupton SJ, Thornton C, Makris A, et al. High blood pressure during pregnancy is associated with future cardiovascular disease: an observational cohort study. BMJ Open. 2013;3(7):e002964.
73. Covella B, Vinturache AE, Cabiddu G, Attini R, Gesualdo L, Versino E, et al. A systematic review and meta-analysis indicates long-term risk of chronic and end-stage kidney disease after preeclampsia. Kidney Int. 2019;96(3):711-27.
74. Kristensen JH, Basit S, Wohlfahrt J, Damholt MB, Boyd HA. Pre-eclampsia and risk of later kidney disease: nationwide cohort study. BMJ. 2019;365:l1516.
75. Bonamy AK, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. Circulation. 2011;124(25):2839-46.
76. Rawal S, Olsen SF, Grunnet LG, Ma RC, Hinkle SN, Granstrom C, et al. Gestational diabetes mellitus and renal function: a prospective study with 9- to 16-year follow-up after pregnancy. Diabetes Care. 2018;41(7):1378-84.
77. Barrett PM, McCarthy FP, Kublickiene K, Evans M, Cormican S, Judge C, et al. Adverse pregnancy outcomes and long-term risk of maternal renal disease: a systematic review and meta-analysis protocol. BMJ Open. 2019;9(5):e027180.
78. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
79. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25.
80. Cummings P. The relative merits of risk ratios and odds ratios. Arch Pediatr Adolesc Med. 2009;163(5):438-45.
81. Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. J Clin Epidemiol. 2002;55(9):893-9.
82. Nurminen M. To use or not to use the odds ratio in epidemiologic analyses? Eur J Epidemiol. 1995;11(4):365-71.
83. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med. 2001;20(4):641-54.
84. Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum. 1953;9(3):531-41.
85. Vikse BE, Hallan S, Bostad L, Leivestad T, Iversen BM. Previous preeclampsia and risk for progression of biopsy-verified kidney disease to end-stage renal disease. Nephrol Dial Transplant. 2010;25(10):3289-96.
86. Vikse BE, Irgens LM, Ananth Karumanchi S, Thadhani R, Reisæeter AV, Skjærven R. Familial factors in the association between preeclampsia and later ESRD. Clin J Am Soc Nephrol. 2012;7(11):1819-26.
87. Ayansina D, Black C, Hall SJ, Marks A, Millar C, Prescott GJ, et al. Long term effects of gestational hypertension and pre-eclampsia on kidney function: Record linkage study. Pregnancy Hypertens. 2016;6(4):344-9.
88. Männistö T, Mendola P, Vääräsmäki M, Järvelin MR, Hartikainen AL, Pouta A, et al. Elevated blood pressure in pregnancy and subsequent chronic disease risk. Circulation. 2013;127(6):681-90.
89. Paauw ND, van der Graaf AM, Bozoglan R, van der Ham DP, Navis G, Gansevoort RT, et al. Kidney function after a hypertensive disorder of pregnancy: a longitudinal study. Am J Kidney Dis. 2018;71(5):619-26.
90. Oishi M, Iino K, Tanaka K, Ishihara K, Yokoyama Y, Takahashi I, et al. Hypertensive disorders of pregnancy increase the risk for chronic kidney disease: A population-based retrospective study. Clin Exp Hypertens. 2017;39(4):361-5.

91. Beharier O, Shoham-Vardi I, Pariente G, Sergienko R, Kessous R, Baumfeld Y, et al. Gestational diabetes mellitus is a significant risk factor for long-term maternal renal disease. J Clin Endocrinol Metab. 2015;100(4):1412-6.
92. Almasi O, Pariente G, Kessous R, Sergienko R, Sheiner E. Association between delivery of small-for-gestational-age neonate and long-term maternal chronic kidney disease. J Matern Fetal Neonatal Med. 2016;29(17):2861-4.
93. Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Sheiner E. Long-term maternal atherosclerotic morbidity in women with pre-eclampsia. Heart. 2015;101(6):442-6.
94. Pariente G, Kessous R, Sergienko R, Sheiner E. Is preterm delivery an independent risk factor for long-term maternal kidney disease? J Matern Fetal Neonatal Med. 2017;30(9):1102-7.
95. Dehmer EW, Phadnis MA, Gunderson EP, Lewis CE, Bibbins-Domingo K, Engel SM, et al. Association between gestational diabetes and incident maternal CKD: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Kidney Dis. 2018;71(1):112-22.
96. Bomback AS, Rekhtman Y, Whaley-Connell AT, Kshirsagar AV, Sowers JR, Chen SC, et al. Gestational diabetes mellitus alone in the absence of subsequent diabetes is associated with microalbuminuria: results from the Kidney Early Evaluation Program (KEEP). Diabetes Care. 2010;33(12):2586-91.
97. Tooher J, Thornton C, Makris A, Ogle R, Korda A, Horvath J, et al. Hypertension in pregnancy and long-term cardiovascular mortality: a retrospective cohort study. Am J Obstet Gynecol. 2016;214(6):722.e1-6.
98. Tooher J, Thornton C, Makris A, Ogle R, Korda A, Hennessy A. All Hypertensive disorders of pregnancy increase the risk of future cardiovascular disease. Hypertension. 2017;70(4):798-803.
99. Barreto SM, Ladeira RM, Duncan BB, Schmidt MI, Lopes AA, Bensenor IM, et al. Chronic kidney disease among adult participants of the ELSA-Brasil cohort: association with race and socioeconomic position. J Epidemiol Community Health. 2016;70(4):380-9.
100. Bryson CL, Ross HJ, Boyko EJ, Young BA. Racial and ethnic variations in albuminuria in the US Third National Health and Nutrition Examination Survey (NHANES III) population: Associations with diabetes and level of CKD. Am J Kidney Dis. 2006;48(5):720-6.
101. Patzer RE, McClellan WM. Influence of race, ethnicity and socioeconomic status on kidney disease. Nat Rev Nephrol. 2012;8(9):533-41.
102. Lewis EF, Claggett B, Parfrey PS, Burdmann EA, McMurray JJ, Solomon SD, et al. Race and ethnicity influences on cardiovascular and renal events in patients with diabetes mellitus. Am Heart J. 2015;170(2):322-9.
103. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111(5):649-58.
104. Shin S, Lee SH, Park S, Kang SM, Chung N, Shim WH, et al. Soluble fms-like tyrosine kinase-1 and the progression of carotid intima-media thickness-24-Month follow-up study -. Circ J. 2010;74(10):2211-5.
105. Di Marco GS, Reuter S, Hillebrand U, Amler S, Konig M, Larger E, et al. The soluble VEGF receptor sFlt1 contributes to endothelial dysfunction in CKD. J Am Soc Nephrol. 2009;20(10):2235-45.
106. Hausvater AS, Giannone T, Sandoval YHG, Doonan RJ, Antonopoulos CN, Matsoukis IL, et al. The association between preeclampsia and arterial stiffness. J Hypertens. 2012;30(1):17-33.
107. Kew S, Swaminathan B, Hanley AJ, Connelly PW, Sermer M, Zinman B, et al. Postpartum microalbuminuria after gestational diabetes: the impact of current glucose tolerance status. J Clin Endocrinol Metab. 2015;100(3):1130-6.

108. Kim C, Cheng YJ, Beckles GL. Cardiovascular disease risk profiles in women with histories of gestational diabetes but without current diabetes. Obstet Gynecol. 2008;112(4):875-83.
109. Friedman S, Rabinerson D, Bar J, Erman A, Hod M, Kaplan B, et al. Microalbuminuria following gestational diabetes. Acta Obstet Gynecol Scand. 1995;74(5):356-60.
110. Hoaglin DC. Practical challenges of I(2) as a measure of heterogeneity. Res Synth Methods. 2017;8(3):254.
111. Stevens PE, Levin A, Kidney Disease: Improving global outcomes chronic kidney disease guideline development work group members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825-30.
112. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, et al. Random-effects meta-analysis of inconsistent effects: a time for change. Ann Intern Med. 2014;160(4):267-70.
113. 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. J Am Coll Cardiol. 2018;71(19):2199-269.
114. OECD/European Observatory on Health Systems and Policies. State of Health in the EU. Sweden: Country Health Profile 2017. Brussels: OECD Publishing, Paris/European Observatory on Health Systems and Policies; 2017.
115. Shaw D, Guise JM, Shah N, Gemzell-Danielsson K, Joseph KS, Levy B, et al. Drivers of maternity care in high-income countries: can health systems support woman-centred care? Lancet. 2016;388(10057):2282-95.
116. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.
117. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaelsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125-36.
118. The Swedish Medical Birth Register - A summary of content and quality. Stockholm: Centre for Epidemiology. The National Board of Health and Welfare; 2003.
119. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
120. Socialstyrelsen. The National Patient Register [Internet]. Stockholm: Socialstyrelsen; 2019 [updated 2019, cited 2020 Dec 17]. Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-national-patient-register/
121. Curran EA, Khashan AS, Dalman C, Kenny LC, Cryan JF, Dinan TG, et al. Obstetric mode of delivery and attention-deficit/hyperactivity disorder: a sibling-matched study. Int J Epidemiol. 2016;45(2):532-42.
122. Laureati P, Xu Y, Trevisan M, Schalin L, Mariani I, Bellocco R, et al. Initiation of sodium polystyrene sulphonate and the risk of gastrointestinal adverse events in advanced chronic kidney disease: a nationwide study. Nephrol Dial Transplant. 2020;35(9):1518-26.
123. Rapporteringen till nationella kvalitetsregister och hälsodataregistren. Jämförelser av täckningsgrader 2014. Stockholm: Socialstyrelsen; 2014.
124. Nationella kvalitetsregister. National Quality Registry for Renal Failure (SNR/SRR) [Internet]. Stockholm: Sveriges Kommuner och Regioner; 2020 [updated 2020, cited 2020

Dec 17] Available from: http://kvalitetsregister.se/englishpages/findaregistry/registerarkivenglish/nationalqualityregistryforrenalfailuresnrsrr.2286.html
125. Pagels AA, Stendahl M, Evans M. Patient-reported outcome measures as a new application in the Swedish Renal Registry: health-related quality of life through RAND-36. Clin Kidney J. 2019;13(3):442-9.
126. Schön S, Ekberg H, Wikström B, Odén A, Ahlmén J. Renal replacement therapy in Sweden. Scand J Urol Nephrol. 2004;38(4):332-9.
127. Sveriges officiella statistik. Dödsorsaksstatistik. Historik, produktionsmetoder och tillförlitlighet. Komplement till rapporten Dödsorsaker 2008. Stockholm: Socialstyrelsen; 2010.
128. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765-73.
129. Monti A, Drefahl S, Mussino E, Harkonen J. Over-coverage in population registers leads to bias in demographic estimates. Popul Stud (Camb). 2020;74(3):451-69.
130. Ludvigsson JF, Svedberg P, Olen O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423-37.
131. Joint Programme Initiative. More years, better lives. Swedish Register of Education [Internet]. Bonn/Berlin: Federal Ministry of Education and Research; 2020 [updated 2020, cited 2020 Dec 17] Available from: https://www.jpi-dataproject.eu/Home/Database/348
132. Ludvigsson JF, Haberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, et al. Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol. 2015;7:491-508.
133. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018;13:291-310.
134. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: World Health Organization; 2011.
135. Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. Am J Epidemiol. 1998;147(11):1062-70.
136. Brown HK, Speechley KN, Macnab J, Natale R, Campbell MK. Neonatal morbidity associated with late preterm and early term birth: the roles of gestational age and biological determinants of preterm birth. Int J Epidemiol. 2014;43(3):802-14.
137. Kirby RS, Wingate MS. Late preterm birth and neonatal outcome: is 37 weeks' gestation a threshold level or a road marker on the highway of perinatal risk? Birth. 2010;37(2):169-71.
138. Delnord M, Blondel B, Prunet C, Zeitlin J. Are risk factors for preterm and early-term live singleton birth the same? A population-based study in France. BMJ Open. 2018;8(1):e018745.
139. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr. 1996;85(7):843-8.
140. Dödfödda barn. En inventering och förslag på åtgärder. Stockholm: Socialstyrelsen; 2018.
141. Lindqvist M, Persson M, Lindkvist M, Mogren I. No consensus on gestational diabetes mellitus screening regimes in Sweden: pregnancy outcomes in relation to different screening regimes 2011 to 2012, a cross-sectional study. BMC Pregnancy Childbirth. 2014;14:185.
142. Berg M, Adlerberth A, Sultan B, Wennergren M, Wallin G. Early random capillary glucose level screening and multidisciplinary antenatal teamwork to improve outcome in gestational diabetes mellitus. Acta Obstet Gynecol Scand. 2007;86(3):283-90.

143. Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. Am J Epidemiol. 2013;177(4):292-8.
144. National Kidney Foundation. How to classify CKD 2019 [Internet]. New York: National Kidney Foundation; 2020 [updated 2020; cited 2020 Dec 17] Available from: https://www.kidney.org/professionals/explore-your-knowledge/how-to-classify-ckd
145. Klassifikation av sjukdomar m m 1968 - Systematisk förteckning. [ICD8]. Stockholm: Socialstyrelsen; 1981.
146. Klassifikation av sjukdomar 1987. Systematisk förteckning. Svensk version av International Classification of Diseases, Ninth Revision (ICD-9). Stockholm: Socialstyrelsen; 1987.

147. Internationell statistisk klassifikation av sjukdomar och relaterade hälsoproblem. Systematisk förteckning. Svensk version 2018. Svensk version av International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). Stockholm: Socialstyrelsen; 2018.
148. Bonita R, Beaglehole R, Kjellstrom T. Basic epidemiology 2nd edition. Geneva: World Health Organization; 2006.
149. Kesmodel US. Information bias in epidemiological studies with a special focus on obstetrics and gynecology. Acta Obstet Gynecol Scand. 2018;97(4):417-23.
150. Jepsen P, Johnsen SP, Gillman MW, Sorensen HT. Interpretation of observational studies. Heart. 2004;90(8):956-60.
151. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117.
152. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.
153. Pigott TD. A review of methods for missing data. Educational Research and Evaluation. 2001;7(4):353-83.
154. Perkins NJ, Cole SR, Harel O, Tchetgen Tchetgen EJ, Sun B, Mitchell EM, et al. Principled approaches to missing data in epidemiologic studies. Am J Epidemiol. 2018;187(3):568-75.
155. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59(10):1087-91.
156. Cedergren MI. Optimal gestational weight gain for body mass index categories. Obstet Gynecol. 2007;110(4):759-64.
157. 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.
158. An Introduction to Survival Analysis using Stata. Third Edition. Texas, USA: Stata Press; 2016.
159. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis Part III: multivariate data analysis -- choosing a model and assessing its adequacy and fit. Br J Cancer. 2003;89(4):605-11.
160. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part I: basic concepts and first analyses. Br J Cancer. 2003;89(2):232-8.
161. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival analysis part IV: further concepts and methods in survival analysis. Br J Cancer. 2003;89(5):781-6.
162. Dekker FW, de Mutsert R, van Dijk PC, Zoccali C, Jager KJ. Survival analysis: time-dependent effects and time-varying risk factors. Kidney Int. 2008;74(8):994-7.
163. Ji E, Kim YS. Prevalence of chronic kidney disease defined by using CKD-EPI equation and albumin-to-creatinine ratio in the Korean adult population. Korean J Intern Med. 2016;31(6):1120-30.

164. Gasparini A, Evans M, Coresh J, Grams ME, Norin O, Qureshi AR, et al. Prevalence and recognition of chronic kidney disease in Stockholm healthcare. Nephrol Dial Transplant. 2016;31(12):2086-94.
165. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
166. 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. 2019;28(5):677-85.
167. Blake GJ, Ridker PM. Novel clinical markers of vascular wall inflammation. Circ Res. 2001;89(9):763-71.
168. Pitiphat W, Gillman MW, Joshipura KJ, Williams PL, Douglass CW, Rich-Edwards JW. Plasma C-reactive protein in early pregnancy and preterm delivery. Am J Epidemiol. 2005;162(11):1108-13.
169. Sattar N. Do pregnancy complications and CVD share common antecedents? Atheroscler Suppl. 2004;5(2):3-7.
170. Moghaddam Banaem L, Mohamadi B, Asghari Jaafarabadi M, Aliyan Moghadam N. Maternal serum C-reactive protein in early pregnancy and occurrence of preterm premature rupture of membranes and preterm birth. J Obstet Gynaecol Res. 2012;38(5):780-6.
171. Kugler E, Cohen E, Goldberg E, Nardi Y, Levi A, Krause I, et al. C reactive protein and long-term risk for chronic kidney disease: a historical prospective study. J Nephrol. 2015;28(3):321-7.
172. Mongelli M, Wilcox M, Gardosi J. Estimating the date of confinement: ultrasonographic biometry versus certain menstrual dates. Am J Obstet Gynecol. 1996;174(1 Pt 1):278-81.
173. Butt K, Lim K, Diagnostic Imaging Committee. Determination of gestational age by ultrasound. J Obstet Gynaecol Can. 2014;36(2):171-81.
174. SFOG-råd. Fetometri UltraARG 2010. Stockholm: Svensk Förening för Obstetrik och Gynekologi; 2019.
175. Clinical Practice Guidelines. Pregnancy care 2019 edition. Canberra: Australian Government, Department of Health; 2018.
176. Committee Opinion No. 700 Summary: Methods for Estimating the Due Date. Obstet Gynecol. 2017;129(5):967-8.
177. Persson PH, Weldner BM. Reliability of ultrasound fetometry in estimating gestational age in the second trimester. Acta Obstet Gynecol Scand. 1986;65(5):481-3.
178. Kullinger M, Granfors M, Kieler H, Skalkidou A. Adherence to Swedish national pregnancy dating guidelines and management of discrepancies between pregnancy dating methods: a survey study. Reprod Health. 2019;16(1):95.
179. Hamilton BE, Martin JA, Osterman MJ, Curtin SC, Matthews TJ. Births: Final Data for 2014. Natl Vital Stat Rep. 2015;64(12):1-64.
180. Delnord M, Mortensen L, Hindori-Mohangoo AD, Blondel B, Gissler M, Kramer MR, et al. International variations in the gestational age distribution of births: an ecological study in 34 high-income countries. Eur J Public Health. 2018;28(2):303-9.
181. Delnord M, Zeitlin J. Epidemiology of late preterm and early term births - An international perspective. Semin Fetal Neonatal Med. 2019;24(1):3-10.
182. Collins GS, Omar O, Shanyinde M, Yu LM. A systematic review finds prediction models for chronic kidney disease were poorly reported and often developed using inappropriate methods. J Clin Epidemiol. 2013;66(3):268-77.
183. Temmerman M, Lawn JE. Stillbirths count, but it is now time to count them all. Lancet. 2018;392(10158):1602-4.
184. Wigglesworth JS. Monitoring perinatal mortality. A pathophysiological approach. Lancet. 1980;2(8196):684-6.

185. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ. 2005;331(7525):1113-7.
186. Korteweg FJ, Gordijn SJ, Timmer A, Erwich JJ, Bergman KA, Bouman K, et al. The Tulip classification of perinatal mortality: introduction and multidisciplinary inter-rater agreement. BJOG. 2006;113(4):393-401.
187. Varli IH, Petersson K, Bottinga R, Bremme K, Hofsjo A, Holm M, et al. The Stockholm classification of stillbirth. Acta Obstet Gynecol Scand. 2008;87(11):1202-12.
188. Reinebrant HE, Leisher SH, Coory M, Henry S, Wojcieszek AM, Gardener G, et al. Making stillbirths visible: a systematic review of globally reported causes of stillbirth. BJOG. 2018;125(2):212-24.
189. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587-603.
190. Hvidtjorn D, Wu C, Schendel D, Thorlund Parner E, Brink Henriksen T. Mortality in mothers after perinatal loss: a population-based follow-up study. BJOG. 2016;123(3):393-8.
191. Kharazmi E, Dossus L, Rohrmann S, Kaaks R. Pregnancy loss and risk of cardiovascular disease: a prospective population-based cohort study (EPIC-Heidelberg). Heart. 2011;97(1):49-54.
192. Parker DR, Lu B, Sands-Lincoln M, Kroenke CH, Lee CC, O'Sullivan M, et al. Risk of cardiovascular disease among postmenopausal women with prior pregnancy loss: the women's health initiative. Ann Fam Med. 2014;12(4):302-9.
193. Ranthe MF, Andersen EA, Wohlfahrt J, Bundgaard H, Melbye M, Boyd HA. Pregnancy loss and later risk of atherosclerotic disease. Circulation. 2013;127(17):1775-82.
194. Lykke JA, Langhoff-Roos J, Lockwood CJ, Triche EW, Paidas MJ. Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery. Paediatr Perinat Epidemiol. 2010;24(4):323-30.
195. Calderon-Margalit R, Friedlander Y, Yanetz R, Deutsch L, Manor O, Harlap S, et al. Late stillbirths and long-term mortality of mothers. Obstet Gynecol. 2007;109(6):1301-8.
196. Khashan AS, McNamee R, Abel KM, Pedersen MG, Webb RT, Kenny LC, et al. Reduced infant birthweight consequent upon maternal exposure to severe life events. Psychosom Med. 2008;70(6):688-94.
197. Vergani P, Cozzolino S, Pozzi E, Cuttin MS, Greco M, Ornaghi S, et al. Identifying the causes of stillbirth: a comparison of four classification systems. Am J Obstet Gynecol. 2008;199(3):319 e1-4.
198. Germain AM, Romanik MC, Guerra I, Solari S, Reyes MS, Johnson RJ, et al. Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? Hypertension. 2007;49(1):90-5.
199. Matthiesen L, Kalkunte S, Sharma S. Multiple pregnancy failures: an immunological paradigm. Am J Reprod Immunol. 2012;67(4):334-40.
200. Cohen E, Margalit I, Shochat T, Goldberg E, Krause I. The relationship between the concentration of plasma homocysteine and chronic kidney disease: a cross sectional study of a large cohort. J Nephrol. 2019;32(5):783-9.
201. Dodds L, Fell DB, Dooley KC, Armson BA, Allen AC, Nassar BA, et al. Effect of homocysteine concentration in early pregnancy on gestational hypertensive disorders and other pregnancy outcomes. Clin Chem. 2008;54(2):326-34.
202. Smith LK, Hindori-Mohangoo AD, Delnord M, Durox M, Szamotulska K, Macfarlane A, et al. Quantifying the burden of stillbirths before 28 weeks of completed gestational age in high-income countries: a population-based study of 19 European countries. Lancet. 2018;392(10158):1639-46.
203. Chakhtoura NA, Reddy UM. Management of stillbirth delivery. Semin Perinatol. 2015;39(6):501-4.

204. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology. 2009;20(4):488-95.
205. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ. 2013;346:f108.
206. Persson M, Winkvist A, Mogren I. Surprisingly low compliance to local guidelines for risk factor based screening for gestational diabetes mellitus - A population-based study. BMC Pregnancy Childbirth. 2009;9:53.
207. Ruiz S, Pergola PE, Zager RA, Vaziri ND. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int. 2013;83(6):1029-41.
208. Yu L, Wang T, Que R, Yang J, Wang Z, Jiang X, et al. The potentially protective role of ATP-binding cassette transporters in preeclampsia via Nrf2. Pregnancy Hypertens. 2019;18:21-8.
209. Barrett PM, McCarthy FP, Kublickiene K, Cormican S, Judge C, Evans M, et al. Adverse pregnancy outcomes and long-term maternal kidney disease: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(2):e1920964.
210. McDonald SD, Yusuf S, Walsh MW, Lonn E, Teo K, Anand SS, et al. Increased cardiovascular risk after pre-eclampsia in women with dysglycaemia. Diabet Med. 2013;30(1):e1-7.
211. Riise HKR, Sulo G, Tell GS, Igland J, Nygard O, Iversen AC, et al. Association between gestational hypertension and risk of cardiovascular disease among 617 589 Norwegian women. J Am Heart Assoc. 2018;7(10):e008337.
212. Barrett PM, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Stillbirth is associated with increased risk of long-term maternal renal disease: a nationwide cohort study. Am J Obstet Gynecol. 2020;223(3):427 e1- e14.
213. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016;133(6):601-9.
214. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension. 2009;53(6):944-51.
215. 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.
216. Garovic VD. The role of the podocyte in preeclampsia. Clin J Am Soc Nephrol. 2014;9(8):1337-40.
217. Ponticelli C, Moroni G. Is preeclampsia a risk for end-stage renal disease? Kidney Int. 2019;96(3):547-9.
218. Aykas F, Solak Y, Erden A, Bulut K, Dogan S, Sarli B, et al. Persistence of cardiovascular risk factors in women with previous preeclampsia: A long-term follow-up study. J Investig Med. 2015;63(4):641-5.
219. Schmidlin CJ, Dodson MB, Zhang DD. Filtering through the role of NRF2 in kidney disease. Arch Pharm Res. 2020;43(3):361-9.
220. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. Lancet. 2001;357(9273):2002-6.
221. Riise HK, Sulo G, Tell GS, Igland J, Nygard O, Vollset SE, et al. Incident coronary heart disease after preeclampsia: role of reduced fetal growth, preterm delivery, and parity. J Am Heart Assoc. 2017;6(3):e004158.
222. Burton GJ, Yung HW, Cindrova-Davies T, Charnock-Jones DS. Placental endoplasmic reticulum stress and oxidative stress in the pathophysiology of unexplained intrauterine growth restriction and early onset preeclampsia. Placenta. 2009;30 Suppl A:S43-8.

223. Cho GJ, Kim HY, Park JH, Ahn KH, Hong SC, Kim HJ, et al. Prepregnancy factors are associated with development of hypertension later in life in women with pre-eclampsia. J Womens Health. 2019;28(7):984-9.
224. Alma LJ, De Groot CJM, De Menezes RX, Hermes W, Hordijk PL, Kovacevic I. Endothelial dysfunction as a long-term effect of late onset hypertensive pregnancy disorders: High BMI is key. Eur J Obstet Gynecol Reprod Biol. 2018;225:62-9.
225. Paauw ND, Luijken K, Franx A, Verhaar MC, Lely AT. Long-term renal and cardiovascular risk after preeclampsia: towards screening and prevention. Clin Sci (Lond). 2016;130(4):239-46.
226. Surkan PJ, Hsieh CC, Johansson AL, Dickman PW, Cnattingius S. Reasons for increasing trends in large for gestational age births. Obstet Gynecol. 2004;104(4):720-6.
227. Fadl HE, Simmons D. Trends in diabetes in pregnancy in Sweden 1998-2012. BMJ Open Diabetes Res Care. 2016;4(1):e000221.
228. International Diabetes Federation. IDF Diabetes Atlas Ninth Edition 2019 [Internet]. International Diabetes Federation; 2020 [updated 2020; cited 2020 Dec 17]. Available from https://www.diabetesatlas.org/en/
229. Noctor E, Dunne FP. Type 2 diabetes after gestational diabetes: The influence of changing diagnostic criteria. World J Diabetes. 2015;6(2):234-44.
230. Retnakaran R, Shah BR. Role of type 2 diabetes in determining retinal, renal, and cardiovascular outcomes in women with previous gestational diabetes mellitus. Diabetes Care. 2017;40(1):101-8.
231. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ. 2020;369:m1361.
232. Burlina S, Dalfra MG, Chilelli NC, Lapolla A. Gestational diabetes mellitus and future cardiovascular risk: an ipdate. Int J Endocrinol. 2016;2016:2070926.
233. Gunderson EP, Chiang V, Pletcher MJ, Jacobs DR, Quesenberry CP, Sidney S, et al. History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the Coronary Artery Risk Development in Young Adults study. J Am Heart Assoc. 2014;3(2):e000490.
234. Fadl HE, Ostlund IK, Magnuson AF, Hanson US. Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. Diabet Med. 2010;27(4):436-41.
235. Tobias DK, Stuart JJ, Li S, Chavarro J, Rimm EB, Rich-Edwards J, et al. Association of history of gestational diabetes with long-term cardiovascular disease risk in a large prospective cohort of US women. JAMA Intern Med. 2017;177(12):1735-42.
236. Barrett PM, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Hypertensive disorders of pregnancy and the risk of chronic kidney disease: A Swedish registry-based cohort study. PLoS Med. 2020;17(8):e1003255.
237. Barrett PM, McCarthy FP, Evans M, Kublickas M, Perry IJ, Stenvinkel P, et al. Risk of long-term renal disease in women with a history of preterm delivery: a population-based cohort study. BMC Med. 2020;18(1):66.
238. Heitritter SM, Solomon CG, Mitchell GF, Skali-Ounis N, Seely EW. Subclinical inflammation and vascular dysfunction in women with previous gestational diabetes mellitus. J Clin Endocrinol Metab. 2005;90(7):3983-8.
239. Lauenborg J, Mathiesen E, Hansen T, Glumer C, Jorgensen T, Borch-Johnsen K, et al. The prevalence of the metabolic syndrome in a danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. J Clin Endocrinol Metab. 2005;90(7):4004-10.

240. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia. 2019;62(6):905-14.
241. Ignell C, Claesson R, Anderberg E, Berntorp K. Trends in the prevalence of gestational diabetes mellitus in southern Sweden, 2003-2012. Acta Obstet Gynecol Scand. 2014;93(4):420-4.
242. Horn J, Haug EB, Markovitz AR, Fraser A, Vatten LJ, Romundstad PR, et al. Life course trajectories of maternal cardiovascular risk factors according to offspring birthweight: The HUNT Study. Sci Rep. 2020;10(1):10436.
243. Golden SH, Yajnik C, Phatak S, Hanson RL, Knowler WC. Racial/ethnic differences in the burden of type 2 diabetes over the life course: a focus on the USA and India. Diabetologia. 2019;62(10):1751-60.
244. Martini S, Nair V, Keller BJ, Eichinger F, Hawkins JJ, Randolph A, et al. Integrative biology identifies shared transcriptional networks in CKD. J Am Soc Nephrol. 2014;25(11):2559-72.
245. Fadl H, Saeedi M, Montgomery S, Magnuson A, Schwarcz E, Berntorp K, et al. Changing diagnostic criteria for gestational diabetes in Sweden - a stepped wedge national cluster randomised controlled trial - the CDC4G study protocol. BMC Pregnancy Childbirth. 2019;19(1):398.
246. Garovic VD, White WM, Vaughan L, Saiki M, Parashuram S, Garcia-Valencia O, et al. Incidence and long-Term outcomes of hypertensive disorders of pregnancy. J Am Coll Cardiol. 2020;75(18):2323-34.
247. Behboudi-Gandevani S, Amiri M, Rahmati M, Amanollahi Soudmand S, Azizi F, Ramezani Tehrani F. Preeclampsia and the ten-year risk of incident chronic kidney disease. Cardiorenal Med. 2020;10(3):188-97.
248. Kattah A. Preeclampsia and kidney disease: deciphering cause and effect. Curr Hypertens Rep. 2020;22(11):91.
249. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. Geneva: World Health Organization; 2000.
250. Westreich D. Berkson's bias, selection bias, and missing data. Epidemiology. 2012;23(1):159-64.
251. Roth H, LeMarquand G, Henry A, Homer C. Assessing knowledge gaps of women and healthcare providers concerning cardiovascular risk after hypertensive disorders of pregnancy - a scoping review. Front Cardiovasc Med. 2019;6:178.
252. Ananth CV, Schisterman EF. Confounding, causality, and confusion: the role of intermediate variables in interpreting observational studies in obstetrics. Am J Obstet Gynecol. 2017;217(2):167-75.
253. Peters SAE, Yang L, Guo Y, Chen Y, Bian Z, Tian X, et al. Pregnancy, pregnancy loss, and the risk of cardiovascular disease in Chinese women: findings from the China Kadoorie Biobank. BMC Med. 2017;15(1):148.
254. Kessous R, Shoham-Vardi I, Pariente G, Sergienko R, Holcberg G, Sheiner E. Recurrent pregnancy loss: a risk factor for long-term maternal atherosclerotic morbidity? Am J Obstet Gynecol. 2014;211(4).
255. Rose G. Strategy of Preventive Medicine. Oxford, UK: Oxford University Press; 1992.
256. Kühn A, van der Giet M, Kuhlmann MK, Martus P, Mielke N, Ebert N, et al. Kidney function as risk factor and predictor of cardiovascular outcomes and mortality among older adults. Am J Kidney Dis. 2020;S0272-6386(20)31093-3
257. Zhao H, Jiang YF, Zhou XC, Yao L, Chen J, Wang D, et al. An effective indicator in predicting cardiovascular events: urine albumin to creatinine ratio. Eur Rev Med Pharmacol Sci. 2017;21(14):3290-5

258. Heidrich MB, Wenzel D, von Kaisenberg CS, Schippert C, von Versen-Hoynck FM. Preeclampsia and long-term risk of cardiovascular disease: what do obstetrician-gynecologists know? BMC Pregnancy Childbirth. 2013;13:61.
259. Roth H, Homer CSE, Arnott C, Roberts L, Brown M, Henry A. Assessing knowledge of healthcare providers concerning cardiovascular risk after hypertensive disorders of pregnancy: an Australian national survey. BMC Pregnancy Childbirth. 2020;20(1):717.
260. 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.
261. Sandsaeter HL, Horn J, Rich-Edwards JW, Haugdahl HS. Preeclampsia, gestational diabetes and later risk of cardiovascular disease: Women's experiences and motivation for lifestyle changes explored in focus group interviews. BMC Pregnancy Childbirth. 2019;19(1):448.
262. Hird MJ, Yoshizawa RS, Robinson S, Smith G, Walker M. Risk for cardiovascular disease after pre-eclampsia: differences in Canadian women and healthcare provider perspectives on knowledge sharing. Health Sociol Rev. 2017;26(2):128-42.
263. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082-e143.
264. Wilson JMG, Jungner G. Public health papers 34. Principles and practice of screening for disease. Geneva: World Health Organization; 1968.
265. Timpka S, Fraser A, Schyman T, Stuart JJ, Asvold BO, Mogren I, et al. The value of pregnancy complication history for 10-year cardiovascular disease risk prediction in middle-aged women. Eur J Epidemiol. 2018;33(10):1003-10.
266. Markovitz AR, Stuart JJ, Horn J, Williams PL, Rimm EB, Missmer SA, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? Findings from the HUNT study in Norway. Eur Heart J. 2019;40(14):1113-20.
267. Nowik CM, Pudwell J, Smith GN. Evaluating the postpartum maternal health clinic: how patient characteristics predict follow-up. J Obstet Gynaecol Can. 2016;38(10):930-5.
268. Cusimano MC, Pudwell J, Roddy M, Cho CK, Smith GN. The maternal health clinic: an initiative for cardiovascular risk identification in women with pregnancy-related complications. Am J Obstet Gynecol. 2014;210(5):438 e1-9.
269. Lui NA, Jeyaram G, Henry A. Postpartum interventions to reduce long-term cardiovascular disease risk in women after hypertensive disorders of pregnancy: a systematic review. Front Cardiovasc Med. 2019;6:160.
270. Hubel CA, Powers RW, Snaedal S, Gammill HS, Ness RB, Roberts JM, et al. C-reactive protein is elevated 30 years after eclamptic pregnancy. Hypertension. 2008;51(6):1499-505.
271. Freeman DJ, McManus F, Brown EA, Cherry L, Norrie J, Ramsay JE, et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. Hypertension. 2004;44(5):708-14.
272. Garovic VD, August P. Preeclampsia and the future risk of hypertension: the pregnant evidence. Curr Hypertens Rep. 2013;15(2):114-21.
273. Gyselaers W, Thilaganathan B. Preeclampsia: a gestational cardiorenal syndrome. J Physiol. 2019;597(18):4695-714.
274. Mosca L, Linfante AH, Benjamin EJ, Berra K, Hayes SN, Walsh BW, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. Circulation. 2005;111(4):499-510.

APPENDICES

List of appendices

Appendix no.

1 Possible biological mechanisms

2 Search strategy for systematic review

3 Bias classification tool used in systematic review

4 Additional files for chapter 2 - systematic review and meta-analysis

5 Ethical approval documents

6 Additional files for chapter 4 – preterm delivery and risk of maternal CKD/ESKD

7 Additional files for chapter 5 – stillbirth and risk of maternal CKD/ESKD

8 Additional files for chapter 6 – HDP and risk of maternal CKD

9 Additional files for chapter 7 – GDM and risk of maternal CKD/ESKD

10 Additional files for chapter 8 – updated systematic review and meta-analyiss

11 Guest Editorial (Paper 7). Adverse pregnancy outcomes and maternal health: action needed for long-term benefit

12 Young Researcher Editorial (Paper 8). Adverse pregnancy outcomes – a missed opportunity to prevent chronic disease?

13 Modules and workshops completed during PhD

14 Awards and distinctions during PhD

15 Additional publications during PhD

Appendix 1. Possible biological mechanisms – preeclampsia and chronic disease

The causal mechanisms underlying associations between preeclampsia and maternal chronic diseases are uncertain. Women who experience preeclampsia secrete anti-angiogenic proteins like soluble fms-like tyrosine kinase 1 (sFLT1) from the placenta. This can lead to endothelial injury which is central to the development of preeclampsia (11). Anti-angiogenic proteins persist beyond pregnancy in some women, and this may contribute to persistent endothelial dysfunction and heightened risk of chronic disease (36).

There are multiple shared risk factors between preeclampsia and chronic disease outcomes such as CVD and ESKD. These include underlying obesity, dyslipidaemia (e.g. higher triglycerides, lower levels of high density lipoprotein cholesterol), genetic predisposition and advanced maternal age (71). Women who experience preeclampsia are also more likely to have subclinical insulin resistance and inflammation before pregnancy, and this puts them at increased risk of later vascular disease and T2DM (270, 271).

Preeclampsia may also induce direct organ damage. Persistent structural cardiac changes have been observed in women following HDP, such as eccentric and concentric ventricular modelling, diastolic dysfunction and impaired contractility (11, 272). Affected women may develop glomerular endotheliosis and podocyte loss, which may increase their risk of chronic hypertension and CKD (56, 216, 217). Inflammatory biomarkers such as CRP and IL-6 are also raised, and while this may reflect an innate inflammatory susceptibility in some women, it may also arise or persist as a result of preeclampsia (271). Furthermore, women who experience preeclampsia are predisposed to persistent arterial stiffness and accelerated atherosclerosis and these factors increase the risk of CVD, ESKD, and other chronic diseases (44, 106).

Moreover, women who experience preeclampsia are more likely to develop dysregulation of the renin-angiotensin-aldosterone system, characterised by increased sensitivity to angiotensin II and increased systemic vascular resistance (11). This contributes to a higher risk of chronic hypertension in later life and predisposition to other chronic diseases.

Finally, the timing of preeclampsia onset may impact on the risk of maternal outcomes. Early preeclampsia presents with low output/high resistance circulation which may lead to an intense, acutely aggravating systemic disorder and an increased risk of cardiorenal disease. By contrast, late preeclampsia is characterised by high volume/low resistance circulation, which gradually progresses to a state of circulatory decompensation with less severe impact on future maternal outcomes (11, 273).

Appendix 2. Search strategy for systematic review

A2.1 Pre-eclampsia & gestational hypertension

H1	Antenatal
H2	Ante-natal
H3	Prenatal
H4	Pre-natal
H5	Pregnan*
H6	Gestation*
H7	H1 OR H2 OR H3 OR H4 OR H5 OR H6
H8	Pre Eclampsia
H9	Preeclampsia
H10	Pre-eclampsia
H11	Eclampsia
H12	Edema-Proteinuria-Hypertension
H13	Edema Proteinuria Hypertension
H14	Oedema-Proteinuria-Hypertension
H15	Oedema Proteinuria Hypertension
H16	EPH
H17	Toxemia*
H18	Toxaemia*
H19	Gestosis
H20	(H19 OR H7)
H21	Toxemia* OR Toxaemia* or EPH
H22	H21 AND H20
H23	Gestational hypertension
H24	Pregnancy-induced hypertension
H25	Pregnancy induced hypertension
H26	Hypertensi*
H27	Blood pressure
H28	H26 OR H27
H29	H28 AND H7
H30	H8 OR H9 OR H10 OR H11 OR H12 OR H13 OR H14 OR H15 OR H22 OR H23 OR H24 OR H25 OR H29

A2.2 Gestational diabetes

D1	Pregnancy-Induced diabetes
D2	Pregnancy Induced diabetes
D3	Gestational Diabetes
D4	diabetes in pregnancy
D5	diabetes of pregnancy
D6	Diabetes mellitus in pregnancy
D7	Diabetes mellitus of pregnancy
D8	pregnancy-related diabetes
D9	pregnancy related diabetes
D10	D1 OR D2 OR D3 OR D4 OR D5 OR D6 OR D7 OR D8 OR D9 OR D10

A2.3 Low birth weight

W1	Low Birth Weight
W2	Low-Birth-Weight
W3	Low Birth Weights
W4	Low-Birth-Weights
W5	Low Birthweight
W6	Low Birthweights
W7	Extremely Low Birth Weight
W8	Extremely-Low-Birth-Weight
W9	Extremely-Low-Birth-Weights
W10	Extremely Low Birthweight
W11	Very Low Birth Weight
W12	Very-Low-Birth-Weight
W13	Very-Low-Birth-Weights
W14	Very Low Birthweight
W15	Birth Weights
W16	Birth Weight
W17	Birthweight
W18	LBW
W19	VLBW
W20	ELBW
W21	Small for gestational age
W22	Growth restrict*
W23	IUGR
W24	W1 OR W2 OR W3 OR W4 OR W5 OR W6 OR W6 OR W7 OR W8 OR W9 OR W10 OR W11 OR W12 OR W13 OR W14 OR W15 OR W16 OR W17 OR W18 OR W19 OR W20 OR W21 OR W22 OR W23

A2.4 Preterm birth or SGA

P1	Premature Birth
P2	Preterm Birth
P3	Premature Births
P4	Preterm Births
P5	Pre-term Birth
P6	Pre-term Births
P7	Gestational age
P8	Gestational ages
P9	Fetal Age
P10	Foetal Age
P11	Fetal Ages
P12	Foetal Ages
P13	Premature Labor
P14	Preterm Labor
P15	Pre-term Labor
P16	Premature Labour
P17	Preterm Labour
P18	Pre-term Labour
P19	Premature Obstetric Labor
P20	Premature Obstetric Labour
P21	P1 OR P2 OR P3 OR P4 OR P5 OR P6 OR P7 OR P8 OR P9 OR P10 OR P11 OR P12 OR P13 OR P14 OR P15 OR P16 OR P17 OR P18 OR P19 OR P20

A2.5 Women

WO1	Woman
WO2	Women
WO3	Female*
WO4	Mother*
WO5	maternal
WO6	WO1 OR WO2 OR WO3 OR WO4 OR WO5

A2.6 Chronic or End-stage kidney disease

K1	Chronic
K2	Long-term
K3	Long term
K4	End-stage
K5	End stage
K6	K1 OR K2 OR K3 OR K4 OR K5
K7	Kidney*
K8	renal
K9	K7 OR K8
K10	Insufficien*
K11	Disease*
K12	Fail*
K13	Impair*
K14	Dysfunction*
K15	K10 OR K11 OR K12 OR K13 OR K14
K16	K6 AND K9 AND K15
K17	CKD
K18	CRD
K19	CKF
K20	CRF
K21	ESKD
K22	ESRD
K23	ESKF
K24	ESRF
K25	K17 OR K18 OR K19 OR K20 OR K21 OR K22 OR K23 OR K24
K26	K16 OR K25

A2.7 Search strategy

(H30 OR D10 OR W24 OR P21) AND WO6 AND K26

Appendix 3. Bias classification tool used in systematic review

Bias	NR	Minimal	Low	Moderate	High
Selection	☐	☐ Consectutive unselected population ☐ Sample selected from general population rather than a select group ☐ Eligibility criteria explained ☐ Rational for case and control selection explained ☐ Follow-up or assessment time explained	☐ Sample selected from large population but selection criteria not defined ☐ A select group of population (based on race, ethnicity, residence, etc.) studied	☐ Sample selection ambiguous but sample may be representative ☐ Eligibility criteria not explained ☐ Rationale for cases and controls not explained ☐ Follow-up or assessment time not explained	☐ Sample selection ambiguous and sample likely not representative ☐ Comparative groups differ in baseline characteristics ☐ A very select population studied making it difficult to generalise findings
Exposure	☐	☐ Direct questioning (interview) or completion of survey by mother at the time of exposure or close to the time of exposure ☐ Direct measurment of exposure (laboratory) ☐ Exposure from the chart	☐ Assessment of exposure from a dataset ☐ Indirect assessment (postal survey, mailed questionnaire) ☐ Recall <1 year after birth	☐ Recall 1-5 years after birth ☐ Extrapolating data from population exposure sample (with some assumptions) and not direct assessment at any time	☐ Recall >5 years after birth ☐ Indirect method of assessment (obtaining data from others and not from mother or father)
Outcome	☐	☐ Assessment from hospital record, birth certificate or from direct questionion of mothers about outcomes	☐ Assessment from administrative database	☐ Assessment from "close-ended" questions (Did you have a stillbirth or miscarriage?)	☐ Assessment from non-validated sources or generic estimate from overall population
Confounding	☐	☐ Assessed for common confounders	☐ Only certain confounders assessed	☐ Not assessed for confounders	
Analytical	☐	☐ Analyses appropriate for type of sample (if matched: paired t test, McNemar) ☐ Analytical method accounted for sampling strategy in cross-sectional study ☐ Sample size calculation performed and adequate sample studied	☐ Analyses not accounting for common statistical adjustment (e.g. multiple analyses e.g. Bonferroni) when appropriate ☐ Sample size calculation not performed, but all available eligible patients studied ☐ Sample size calculated and reasons for not meeting sample size given	☐ Sample size estimation unclear or only sub-sample of eligible patients studied	☐ Analyses inappropriate for type of sample/study
Attrition	☐	☐ None or <10% attrition and reasons for loss of follow-up explained ☐ All subjects from initiation of study to final outcome assessment were accounted for	☐ <10% attrition AND reasons for loss of follow-up not explained ☐ 11-20% attrition, reasons for loss of follow-up explained	☐ 11-20% attrition but reasons for loss of follow-up not explained ☐ >20% attrition but reasons for loss of follow-up explained ☐ All subjects from initiation of study to final outcome assessment not accounted for	☐ >20% attrition, reasons for loss of follow-up not explained

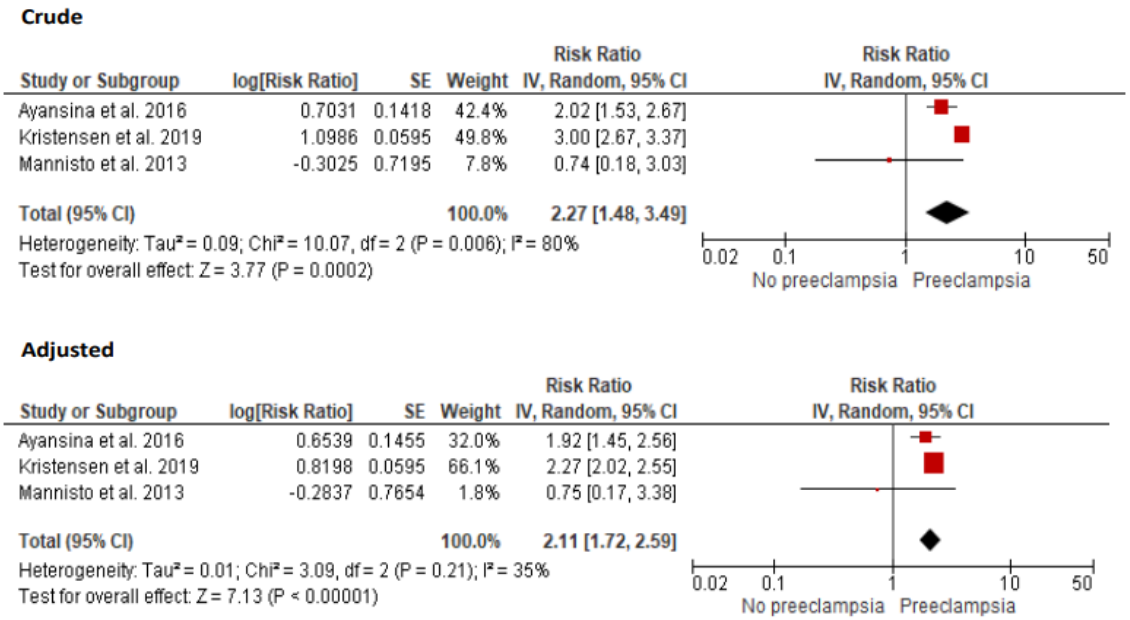


Figure A4.1. Forest plot for studies of the association of preeclampsia and chronic kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

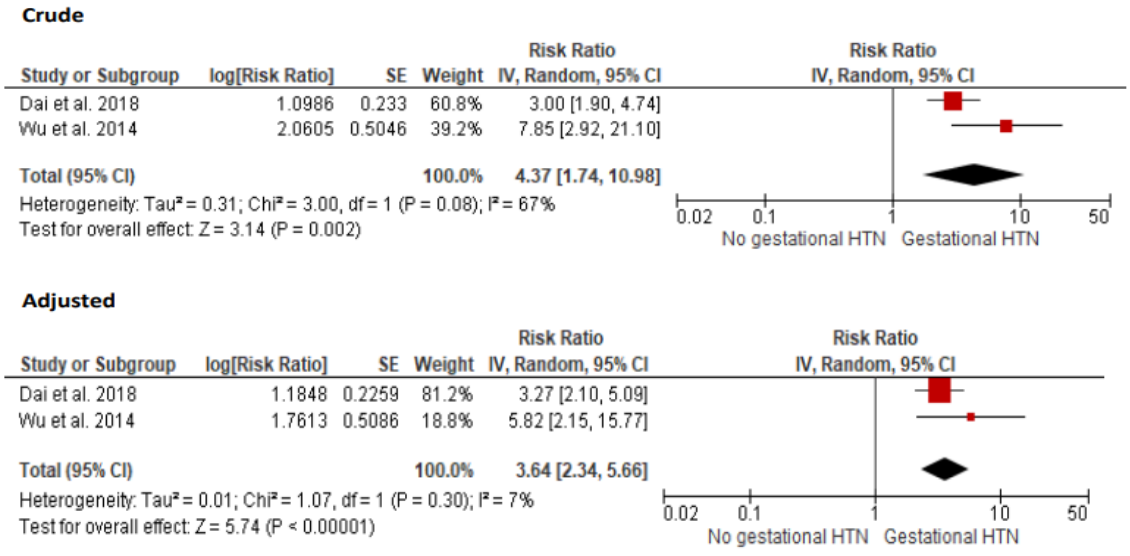


Figure A4.2. Forest plot for studies of the association of gestational hypertension and end-stage kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

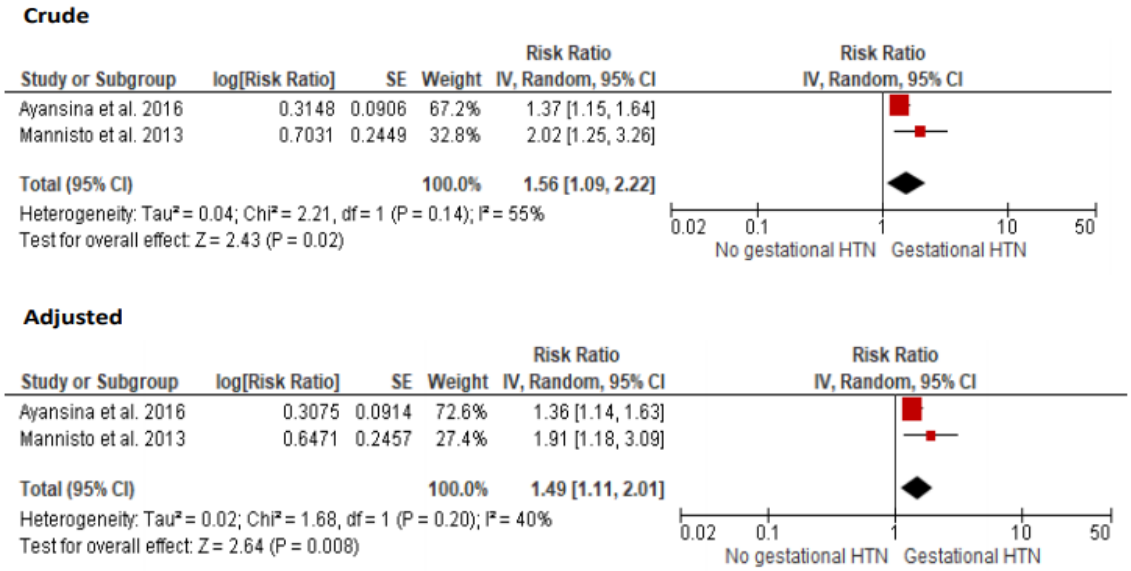


Figure A4.3. Forest plot for studies of the association of gestational hypertension and chronic kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

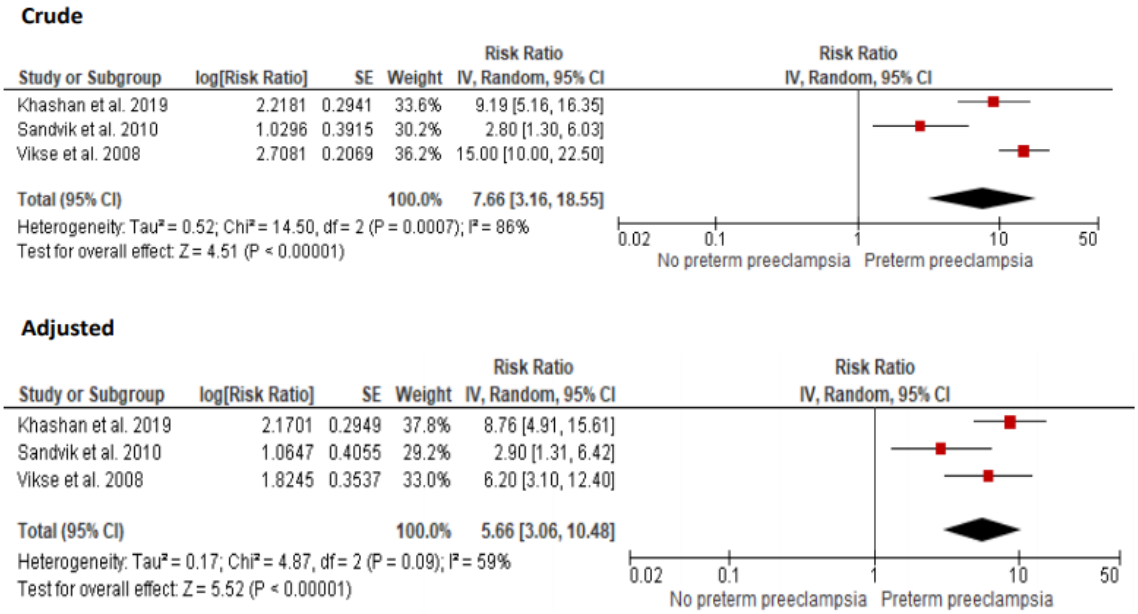


Figure A4.4. Forest plot for studies of the association of preterm preeclampsia and end-stage kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

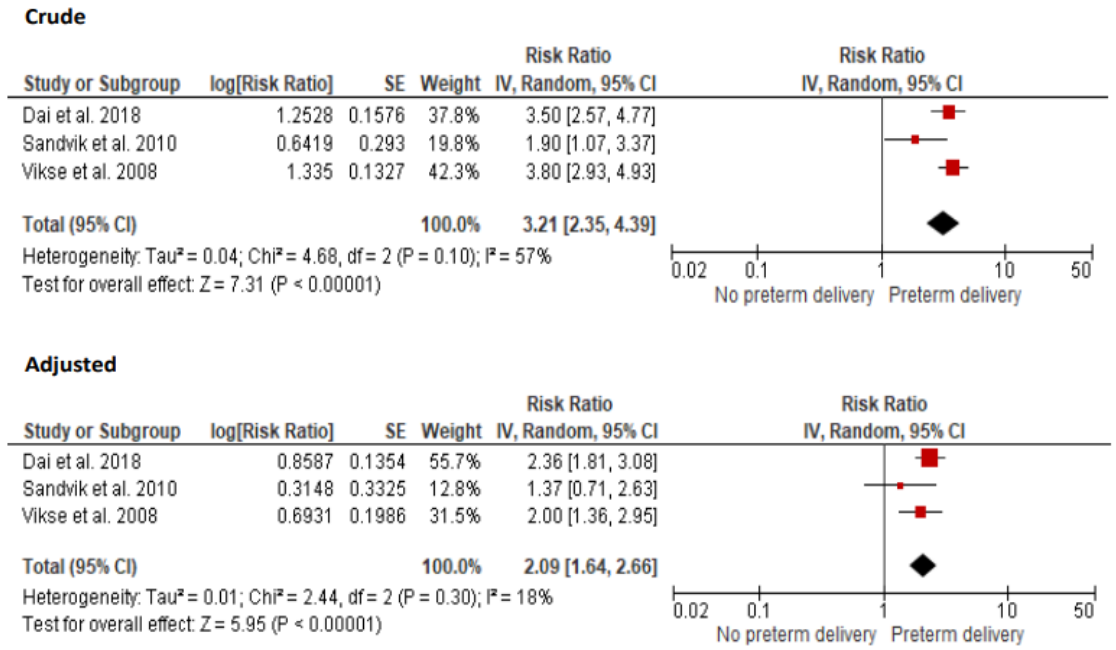


Figure A4.5. Forest plot for studies of the association of preterm delivery and end-stage kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

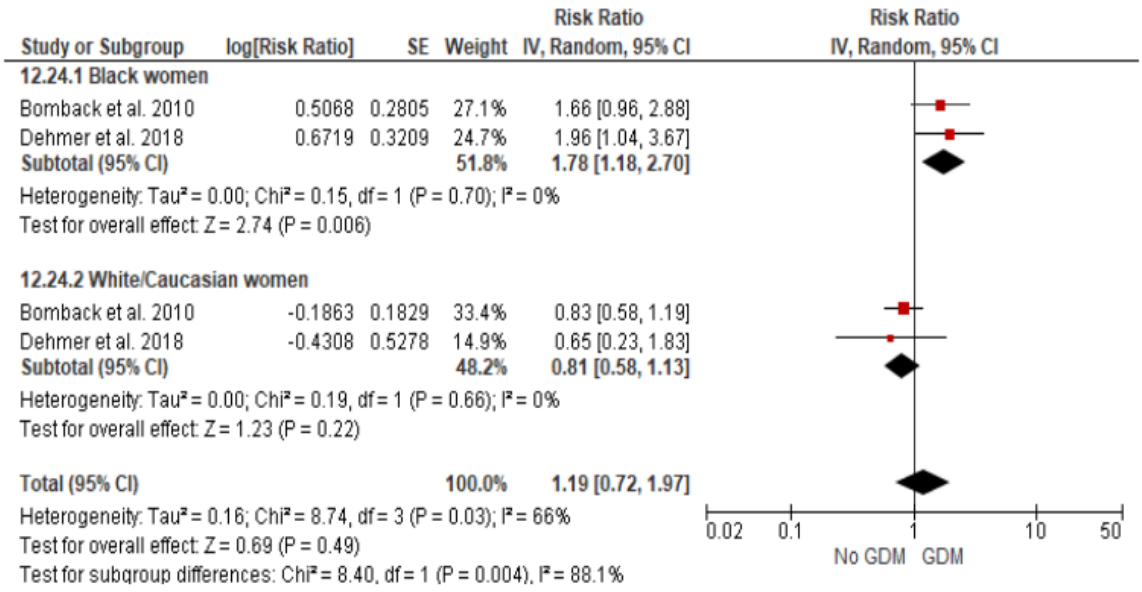


Figure A4.6. Forest plot for studies of the association of gestational diabetes and chronic kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis

Table A4.6 Summary results of meta-analyses based on Sidik-Jonkman method

Exposure	Outcome	No. studies	References	Participants	No. outcomes	Pooled RR (95% CI)	I^2, %	Tau^2
Preeclampsia	**ESKD**							
	Crude	5	(28, 29, 31-33)	4,479,523	1,737	6.17 (4.18-9.10)	85%	0.15
	Adjusted (any)	5	(28, 29, 31-33)	4,479,523	1,737	4.90 (3.44-6.98)	78%	0.11
	Adjusted for comorbidities	5	(28, 29, 31-33)	4,479,523	1,737	4.90 (3.44-6.98)	78%	0.11
	CKD							
	Crude	3	(74, 87, 88)	1,097,495	4,699	1.98 (0.88-4.45)	95%	0.41
	Adjusted (any)	3	(74, 87, 88)	1,097,495	4,699	1.92 (1.17-3.14)	84%	0.13
	Adjusted for comorbidities	1	(74)	1,072,330	3,901	2.27 (2.02-2.55)	-	-
	Kidney-related hospitalisation							
	Crude	2	(21, 93)	131,224	468	1.80 (0.64-5.02)	94%	0.52
	Adjusted (any)	3	(21, 93, 98)	162,880	1,051	2.66 (0.96-7.40)	93%	0.74
	Adjusted for comorbidities	0	-	-	-	-	-	-
Gestational hypertension	**ESKD**							
	Crude	2	(31, 32)	2,542,517	806	4.43 (1.65-11.84)	71%	0.37
	Adjusted (any)	2	(31, 32)	2,542,517	806	3.64 (2.34-5.66)	7%	0.01
	Adjusted for comorbidities	2	(31, 32)	2,542,517	806	3.64 (2.34-5.66)	7%	0.01
	CKD							
	Crude	2	(87, 88)	25,165	798	1.57 (1.07-2.29)	59%	0.05
	Adjusted (any)	2	(87, 88)	25,165	798	1.50 (1.10-2.04)	43%	0.03
	Adjusted for comorbidities	0	-	-	-	-	-	-
	Kidney-related hospitalisation							
	Crude	2	(21, 87)	49,705	1,010	1.04 (0.92-1.17)	0%	0.00
	Adjusted (any)	2	(21, 98)	66,510	939	1.88 (0.44-7.94)	94%	1.02
	Adjusted for comorbidities	0	-	-	-	-	-	-
Chronic hypertension	**ESKD**							
	Crude	2	(31, 32)	2,542,517	806	16.87 (11.31-25.15)	0%	0.00
	Adjusted (any)	1	(31)	944,474	258	15.99 (5.89-43.41)	-	-
	Adjusted for comorbidities	1	(31)	944,474	258	15.99 (5.89-43.41)	-	-
	CKD							
	Crude	1	(88)	10,314	144	1.62 (0.88-3.00)-	-	-
	Adjusted (any)	1	(88)	10,314	144	1.23 (0.67-2.26)	-	-
	Adjusted for comorbidities	0	-	-	-	-	-	-

Table A4.1 (continued) Summary results of meta-analyses based on Sidik-Jonkman method

Exposure	Outcome	No. studies	References	Participants	No. outcomes	Pooled RR (95% CI)	I^2, %	Tau^2
Superimposed preeclampsia	**ESKD**							
	Crude	2	(31, 32)	2,542,517	806	48.97 (26.09-91.94)	41%	0.09
	Adjusted (any)	1	(31)	944,474	258	44.72 (22.59-88.52)	-	-
	Adjusted for comorbidities	1	(31)	944,474	258	44.72 (22.59-88.52)	-	-
	CKD							
	Crude	1	(88)	10,314	144	1.56 (0.38-6.42)-	-	-
	Adjusted (any)	1	(88)	10,314	144	1.24 (0.28-5.49)	-	-
	Adjusted for comorbidities	0	-	-	-	-	-	-
Preterm delivery (no preeclampsia)	**ESKD**							
	Crude	3	(28, 32, 59)	2,169,957	1,073	3.11 (2.05-4.72)	76%	0.10
	Adjusted (any)	3	(28, 32, 59)	2,169,957	1,073	2.06 (1.56-2.71)	32%	0.02
	Adjusted for comorbidities	3	(28, 32, 59)	2,169,957	1,073	2.06 (1.56-2.71)	32%	0.02
	CKD							
	Crude	0	-	-	-	-	-	-
	Adjusted (any)	0	-	-	-	-	-	-
	Kidney-related hospitalisation							
	Crude	1	(94)	99,338	132	2.90 (2.00-4.20)	-	-
	Adjusted (any)	1	(94)	99,338	132	2.70 (1.80-3.90)	-	-
	Adjusted for comorbidities	0	-	-	-	-	-	-
Preterm preeclampsia	**ESKD**							
	Crude	3	(28, 29, 59)	1,938,355	935	7.56 (2.69-21.21)	90%	0.74
	Adjusted (any)	3	(28, 29, 59)	1,938,355	935	5.64 (2.99-10.67)	62%	0.19
	Adjusted for comorbidities	3	(28, 29, 59)	1,938,355	935	5.64 (2.99-10.67)	62%	0.19
	CKD							
	Crude	0	-	-	-	-	-	-
	Adjusted (any)	1	(74)	1,072,330	3,901	3.93 (2.90-5.33)	-	-
	Adjusted for comorbidities	1	(74)	1,072,330	3,901	3.93 (2.90-5.33)	-	-

Table A4.1 (continued) Summary results of meta-analyses based on Sidik-Jonkman method

Exposure	Outcome	No. studies	References	Participants	No. outcomes	Pooled RR (95% CI)	I^2, %	Tau^2
Gestational diabetes	**ESKD**							
	Crude	0	-	-	-	-	-	-
	Adjusted (any)	0	-	-	-	-	-	-
	CKD							
	Crude	3	(91, 95, 96)	136,504	6,345	0.94 (0.73-1.21)	7%	0.01
	Adjusted (any)	2	(95, 96)	38,536	6,231	1.04 (0.76-1.41)	21%	0.01
	Adjusted for comorbidities	2	(95, 96)	38,536	6,231	1.04 (0.76-1.41)	21%	0.01
	Kidney-related hospitalisation							
	Crude	0	-	-	-	-	-	-
	Adjusted (any)	1	(93)	96,370	112	1.90 (1.10-3.20)	-	-
	Adjusted for comorbidities	0	-	-	-	-	-	-

Meta-analysis was based on the Sidik-Jonkman method in Stata version 15.0. The log risk ratio (RR) and standard error for each study was entered in meta-analysis using the admetan command.

Appendix 5. Ethical approval documents

EPN

PROTOKOLL 2012/3:3
2012-03-28

Sammanträde i Stockholm

FÖR KÄNNEDOM

Avdelning 3

Ordförande
Håkan Julius

Ledamöter med vetenskaplig kompetens
Agneta Nordenskjöld *(barnkirurgi)*, t.f. vetenskaplig sekreterare
Jonas Hedlund *(infektionssjukdomar)*
Ulf Adamson *(medicin, endokrinologi)*, deltar inte i ärendena 2012/452, 2012/459-460, 2012/462 samt 2012/466
Stefan Borg *(allmän psykiatri)*
Caroline Graff *(geriatrik)*, deltar inte i ärende 2012/208
Maria Feychting *(miljömedicin, epidemiologi)*
Per-Eric Lins (*endokrinologi, invärtes medicin*)
Anne-Cathrine Mattiasson *(omvårdnad)*
Mårten Rosenqvist *(kardiologi)*, deltar inte i ärendena 2012/12, 2012/208, 2012/287 samt 2012/337
Carl Olav Stiller *(klinisk farmakologi)*

Ledamöter som företräder allmänna intressen
Inger Andersson
Bengt Gustafsson
Winston Håkanson
Ulf Uebel
Lars Åstrand
Administrativ sekreterare
Anne Manninen

§ 1 Ordföranden förklarar sammanträdet öppnat.

§ 2 Den administrativa sekreteraren anmäler att den vetenskaplige sekreteraren sedan föregående möte den 29 februari 2012 fattat beslut i 17 ärenden som avser ändring av godkännande.

§ 3 Ordföranden förordnar Agneta Nordenskjöld till vetenskaplig sekreterare.

§ 4 Ansökningar om etisk granskning av forskningsprojekt, se **Bilaga**.

§ 5 Ordföranden förklarar mötet avslutat och meddelar att nästa sammanträde i avdelning 3 äger rum onsdagen den 25 april 2012.

Håkan Julius
Ordförande

Agneta Nordenskjöld
Protokollförare, t.f. vetenskaplig sekreterare

Adress	Besöksadress	Telefon	Fax	E-post	Hemsida
FE 289 171 77 Stockholm	Nobels väg 9 171 65 Solna	08-524 800 00	08-524 866 99	kansli@stockholm.epn.se	www.epn.se

---------- Utdrag ur protokoll från sammanträde den 28 mars 2012 i avdelning 3 ----------

Dnr 2012/397-31/3
Per-Eric Lins

Sökande: Stockholms läns landsting
Behörig företrädare: Magnus Westgren
Projekt: Samband mellan graviditetskomplikationer och kronisk njursjukdom.
Forskare som genomför projektet: Marius Kublickas

BESLUT

Nämnden godkänner forskningen med påpekande att en justering sker med avseende på forskningshuvudman (Stockholms läns landsting) och behörig företrädare för forskningshuvudman (verksamhetschef).

Beslut expedierat till behörig företrädare.
Kopia för kännedom till ansvarig forskare.

Att utdraget överensstämmer med originalet intygar:

Anne Manninen, administratör

Regionala etikprövnings-
nämnden i Stockholm
Inkom: 2014 -02- 20
Dnr: 2014/334-32

Regionala Etikprövningsnämnden i Stockholm
BOX 289
171 77 Stockholm

2014-02-19

ADDENDUM

Projekt med **Dnr 2012/397-31/3** godkändes av etikkommittén den 2012-03-28.
Vi har gjort data uttag men visade sig att vi har missat ange i ansökan att vi behöver titta på högsta **inkomstnivån** före 1:a förlossning (vi har tittar på högsta utbildningsnivån, men detta räcker inte, man ska kombinera med inkomsten). Detta är viktig parameter för epidemiologisk studie.

Vi önskar därför att Ni tar ställning till denna utvidgning av data uttag från SCB.

Kopia av tidigare beslut bifogas.

2000 kr sätts på PG 950649-4

Med Vänliga Hälsningar

Marius Kublickas MD, PhD
Associate Professor
Department of Obstetrics & Gynecology
Karolinska University Hospital-Huddinge
141 86 Stockholm, Sweden
email: marius.kublickas@ki.se
Tel. 46-8-58 58 16 18
Fax. 46-8-58 58 75 75
Mobil: 46-(0)-708 49 42 21

GODKÄNNES Dat. 2014 -03- 06
Hans Glaumann
Regionala etikprövningsnämnden
i Stockholm

FW: Log 2019-109 Approved

From: Ethics Committee, Social Research
Sent: Tuesday, July 2, 2019 2:23:23 PM
To: Barrett, Peter
Cc: Khashan, Ali
Subject: Log 2019-109 Approved

Dear Peter
The Social Research and Ethics Committee has now approved your application Log 2019-109 entitled "Adverse Pregnancy Outcomes."

The committee wishes you every success with your research.
All the best
Liz

Liz Hales | Social Research Ethics Committee, University College Cork | srec@ucc.ie | Phone +353 (0)21 4903234

Independent Thinking, Shared Ambition: UCC Strategic Plan 2017-2022
Watch University College Cork: River of Life

Save our Spark. Help secure essential state funding.
Take action now www.saveourspark.ie

Appendix 6. Additional files for chapter 4 – preterm delivery and risk of maternal CKD/ESKD

Table A6.1. ICD codes used for disease definitions in study of preterm delivery and long-term risk of maternal CKD/ESKD

	ICD-8 codes (1973-1986)	ICD-9 codes (1987-1996)	ICD-10 codes (1997-2013)
Any pre-existing chronic/end-stage kidney disease, congenital or genetic causes of renal disease (for exclusion)	403-404, 580-589, 753	403-404, 580-589, 753, V42A, V45B, V56A, V56W	N00-N08, N10-N19, P960, Q271, Q272, Q60-Q63, Q878, Z49, Z992, Z940, T861
Chronic kidney disease (outcome)	403-404, 581-583, 585-588	403-404, 581-583, 585-588, V42A, V45B, V56A, V56W	N01-N06, N08, N11-N13, N15-16, N18-19, Z49, Z992, Z940, T861
End-stage kidney disease (outcome)	None	V42A, V45B, V56A, V56W	N185, Z49, Z992, Z940, T861
Cardiovascular disease	393-398 410-436	393-398 410-436	I16-I64 G45
Hypertension	401-405	401-405	I10-I15
Diabetes (type 1 or type 2)	250	250	E10-E14
Systemic lupus erythematosus	73410	710A	M32
Preeclampsia	63700, 63703, 63704, 63709, 63710, 63719, 63790, 63799	642E, 642F, 642G	O140, O141, O141A, O141B, O141C, O141X, O142, O149, O150, O151, O152, O159
Gestational diabetes	None	648W	O244

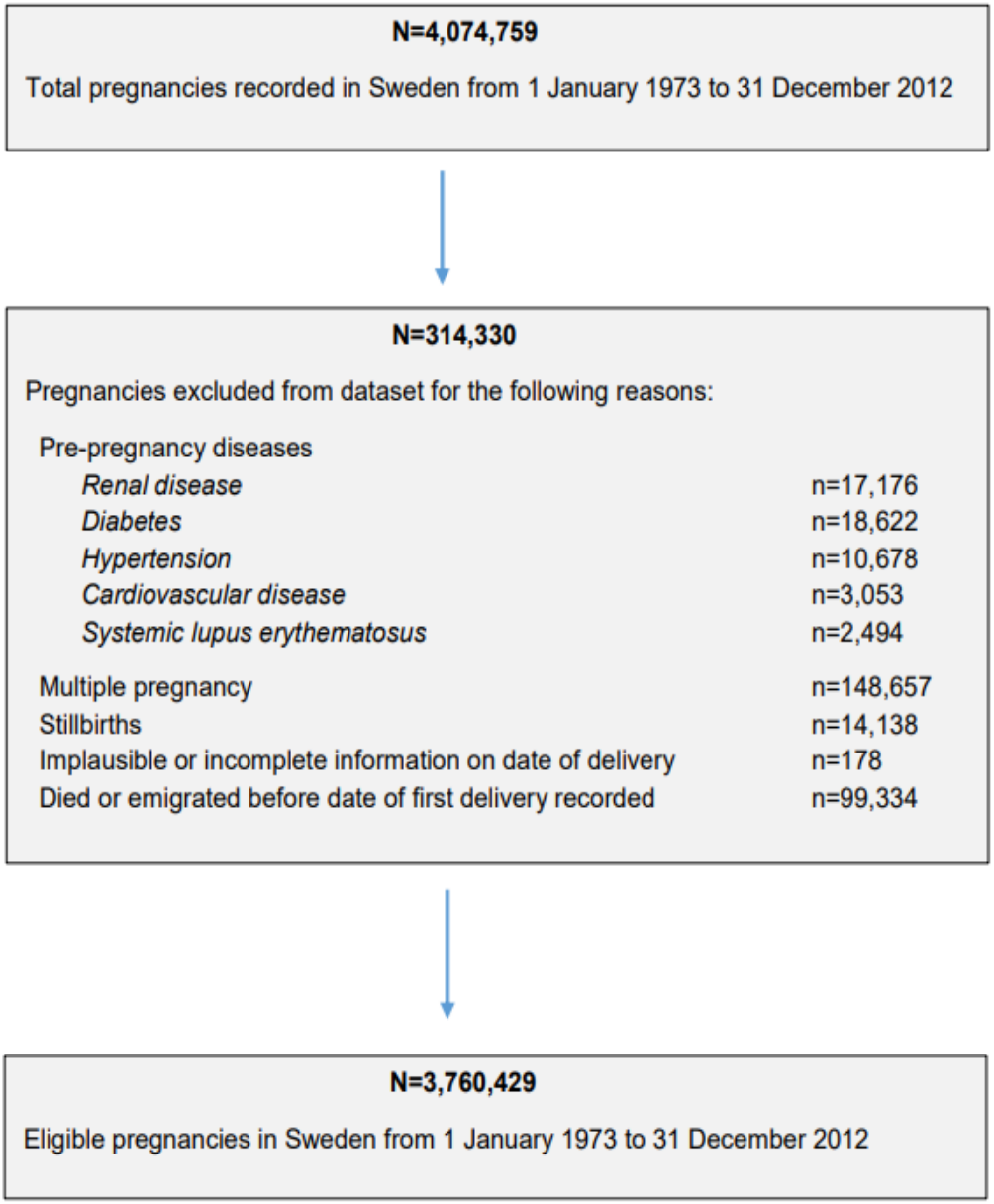


Figure A6.1. Flow chart illustrating construction of study cohort for study of preterm delivery and long-term risk of maternal CKD/ESKD

Appendix 7. Additional files for chapter 5 – stillbirth and risk of maternal CKD/ESKD

Table A7.1. ICD codes used for disease definitions in study of stillbirth and long-term risk of maternal CKD/ESKD

	ICD-8 codes (1973-1986)	ICD-9 codes (1987-1996)	ICD-10 codes (1997-2013)
Any pre-existing chronic/end-stage kidney disease, congenital or genetic causes of renal disease (for exclusion)	403-404, 580-589, 753	403-404, 580-589, 753, V42A, V45B, V56A, V56W	N00-N08, N10-N19, P960, Q271, Q272, Q60-Q63, Q878, Z49, Z992, Z940, T861
Chronic kidney disease (outcome)	403-404, 581-583, 585-588	403-404, 581-583, 585-588, V42A, V45B, V56A, V56W	N01-N06, N08, N11-N13, N15-16, N18-19, Z49, Z992, Z940, T861
End-stage kidney disease (outcome)	None	V42A, V45B, V56A, V56W	N185, Z49, Z992, Z940, T861
Cardiovascular disease	393-398 410-436	393-398 410-436	I16-I64 G45
Hypertension	401-405	401-405	I10-I15
Diabetes (type 1 or type 2)	250	250	E10-E14
Systemic lupus erythematosus	73410	710A	M32
Systemic sclerosis	73400-73409	710B	M34
Haemoglobinopathies	282-283	282-283	D56-D59
Coagulopathies	None	None	D68
Preeclampsia	63700, 63703, 63704, 63709, 63710, 63719, 63790, 63799	642E, 642F, 642G	O140, O141, O141A, O141B, O141C, O141X, O142, O149, O150, O151, O152, O159
Gestational diabetes	None	648W	O244
Congenital malformations	740-759	740-759	Q00-Q99

Table A7.2. Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of stillbirth, among women delivering after 1982 and 1987 respectively in Sweden

Sensitivity Analysis 1: All births from 1982-2012

		Chronic kidney disease (N=10,897)			
	n	**Model 1 (Age-adjusted) HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**	**Model 4 (Fully adjusted) HR (95% CI)**
No stillbirth	10,774	1.0	1.0	1.0	1.0
Any stillbirth	123	1.55 (1.29-1.85)	1.46 (1.22-1.75)	1.42 (1.18-1.69)	1.30 (1.08-1.56)
No stillbirth	10,774	1.0	1.0	1.0	1.0
Antepartum stillbirth	114	1.57 (1.31-1.89)	1.48 (1.23-1.79)	1.44 (1.19-1.73)	1.32 (1.09-1.59)
Intrapartum stillbirth	9	1.28 (0.67-2.46)	1.20 (0.62-2.31)	1.18 (0.61-2.27)	1.10 (0.57-2.11)
		End-stage kidney disease (N=547)			
	n				
No stillbirth	532	1.0	1.0	1.0	1.0
Any stillbirth	15	3.74 (2.23-6.25)	3.86 (2.28-6.51)	3.47 (2.06-5.87)	2.70 (1.59-4.60)

Sensitivity Analysis 2: All births from 1987-2012

		Chronic kidney disease (N=8,231)			
	n	**Model 1 (Age-adjusted) HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**	**Model 4 (Fully adjusted) HR (95% CI)**
No stillbirth	8,145	1.0	1.0	1.0	1.0
Any stillbirth	86	1.58 (1.28-1.95)	1.36 (1.10-1.69)	1.32 (1.06-1.63)	1.22 (0.99-1.51)
No stillbirth	8,145	1.0	1.0	1.0	1.0
Antepartum stillbirth	80	1.57 (1.26-1.96)	1.36 (1.09-1.70)	1.32 (1.06-1.65)	1.22 (0.98-1.53)
Intrapartum stillbirth	6	1.61 (0.72-3.59)	1.34 (0.60-2.99)	1.30 (0.58-2.90)	1.23 (0.55-2.74)
		End-stage kidney disease (N=359)			
	n				
No stillbirth	350	1.0	1.0	1.0	1.0
Any stillbirth	9	3.52 (1.81-6.83)	3.50 (1.78-6.88)	3.10 (1.58-6.10)	2.42 (1.22-4.80)

Hazard ratios represent separate Cox regression models for associations between stillbirth and maternal chronic kidney disease or end-stage kidney disease. In all models, delivery of a stillbirth was a time-dependent variable, where maternal exposure status was based on the date of first stillbirth
Model 1 adjusted for maternal age, stratified by year of delivery.
Model 2 adjusted for maternal age, country of origin, maternal education and parity, stratified by year of delivery.
Model 3 adjusted for maternal age, country of origin, maternal education, parity, BMI, smoking and maternal exposure to gestational diabetes (time-dependent covariate), stratified by year of delivery.
Model 4 adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, and maternal exposure to gestational diabetes, preeclampsia and SGA delivery (time-dependent covariates), stratified by year of delivery.
Women with pre-pregnancy history of renal disease, cardiovascular disease, hypertension, diabetes, systemic lupus erythematosus, systemic sclerosis, haemoglobinopathy or coagulopathy were excluded at baseline.
CI, confidence interval; HR, hazard ratio

Table A7.3. Hazard ratios for maternal chronic kidney disease and end-stage kidney disease by history of stillbirth, among women delivering between 1973 and 2012 in Sweden, restricted to women who had pre-existing medical comorbidities

	Chronic kidney disease			End-stage kidney disease		
	n	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)	n	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
No stillbirth	836	1.0	1.0	259	1.0	1.0
Stillbirth (any)	27	1.26 (0.86-1.85)	1.13 (0.73-1.75)	11	1.56 (0.85-2.86)	1.49 (0.78-2.85)

Analysis was restricted to 17,416 women with a known pre-pregnancy history of CVD, diabetes, hypertension, SLE, systemic sclerosis, haemoglobinopathy or coagulopathy. Women with pre-pregnancy renal disease were excluded.
Hazard ratios represent separate Cox regression models for associations between stillbirth and subsequent maternal chronic kidney disease and end-stage kidney disease. In all models, delivery of a stillbirth was a time-dependent variable, where maternal exposure status was based on the date of first stillbirth
Fully adjusted models controlled for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, and maternal exposure to preeclampsia, gestational diabetes, and SGA delivery (time-dependent covariates), stratified by year of delivery.
CI, confidence interval; HR, hazard ratio

Table A7.4. Hazard ratios for stillbirth and maternal chronic kidney by length of follow-up after index pregnancy

	n	Model 1 (Age-adjusted) HR (95% CI)	Model 4 (Fully adjusted) HR (95% CI)
		Chronic kidney disease after 10 years (N=6,139)	
No stillbirth	6,064	1.0	1.0
Any stillbirth	67	1.23 (0.97-1.57)	1.30 (1.01-1.66)
No stillbirth	6,064	1.0	1.0
Antepartum stillbirth	61	1.25 (0.97-1.60)	1.29 (1.00-1.67)
Intrapartum stillbirth	6	1.12 (0.50-2.53)	1.34 (0.60-3.03)
		Chronic kidney disease after 20 years (N=10,768)	
No stillbirth	10,656	1.0	1.0
Any stillbirth	112	1.33 (1.10-1.60)	1.20 (0.99-1.45)
No stillbirth	10,656	1.0	1.0
Antepartum stillbirth	103	1.38 (1.13-1.67)	1.23 (1.01-1.50)
Intrapartum stillbirth	9	0.97 (0.51-1.88)	0.90 (0.47-1.74)
		Chronic kidney disease after 30 years (N=15,100)	
No stillbirth	14,931	1.0	1.0
Any stillbirth	169	1.37 (1.18-1.60)	1.20 (1.03-1.40)
No stillbirth	14,931	1.0	1.0
Antepartum stillbirth	154	1.39 (1.18-1.63)	1.20 (1.03-1.42)
Intrapartum stillbirth	15	1.26 (0.76-2.09)	1.13 (0.68-1.87)

Hazard ratios represent separate Cox regression models for associations between stillbirth and maternal chronic kidney disease. In all models, delivery of a stillbirth was a time-dependent variable, where maternal exposure status was based on the date of first stillbirth

Model 1 adjusted for maternal age, stratified by year of delivery.

Model 2 adjusted for maternal age, country of origin, maternal education and parity, stratified by year of delivery.

Model 3 adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, and maternal exposure to gestational diabetes (time-dependent covariate), stratified by year of delivery.

Model 4 adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, and maternal exposure to gestational diabetes, preeclampsia and SGA delivery (time-dependent covariates), stratified by year of delivery.

Women with pre-pregnancy history of renal disease, cardiovascular disease, hypertension, diabetes, systemic lupus erythematosus, systemic sclerosis, haemoglobinopathy or coagulopathy were excluded at baseline.

CI, confidence interval; HR, hazard ratio

Appendix 8. Additional files for chapter 6 – HDP and risk of maternal CKD

Table A8.1. ICD codes used for disease definitions in study of preeclampsia and long-term risk of maternal CKD

	ICD-8 codes (1973-1986)	ICD-9 codes (1987-1996)	ICD-10 codes (1997-2013)
Any pre-existing chronic/end-stage kidney disease, congenital or genetic causes of renal disease (for exclusion)	403-404, 580-589, 753	403-404, 580-589, 753, V42A, V45B, V56A, V56W	N00-N08, N10-N19, P960, Q271, Q272, Q60-Q63, Q878, Z49, Z992, Z940, T861
Chronic kidney disease (CKD) (Overall outcome)	250D, 403-404, 581-583, 58499, 585-588	250D, 403-404, 581-583, 585-588, V42A, V45B, V56A, V56W	E102, E112, I12-I13, I150-I151, N01-N06, N08, N11-N13, N15-16, N18-19, Z49, Z992, Z940, T861
Tubulointerstitital CKD	-	-	N11-N12, N15-N16
Glomerular/proteinuric CKD	581-583	581-583	N01-N06, N08
Hypertensive CKD	403-404	403-404	I12-I13, I150-I151
Diabetic CKD	250D	250D	E102, E112
Other/unspecified CKD	58499, 585-588	585-588, V42A, V45B, V56A, V56W	N13, N18-N19, Z49, Z992, Z940, T861
Cardiovascular disease	393-398 410-436	393-398 410-436	I16-I64 G45
Essential hypertension	401-405	401-405	I10-I15
Diabetes (type 1 or type 2)	250	250	E10-E14
Systemic lupus erythematosus	73410	710A	M32
Systemic sclerosis	73400-73409	710B	M34
Vasculitis	446	446	M31
Haemoglobinopathies	282-283	282-283	D56-D59
Coagulopathies	None	None	D68
Preeclampsia	63700, 63703, 63704, 63709, 63710, 63719, 63790, 63799	642E, 642F, 642G	O140, O141, O141A, O141B, O141C, O141X, O142, O149, O150, O151, O152, O159
Gestational hypertension	63701	642D, 642X	O130-O139
Gestational diabetes	-	648W	O244

Table A8.2. Time to diagnosis of chronic kidney disease (CKD) subtypes among women whose first live birth occurred between 1973 and 2012 in Sweden, stratified by exposure to preeclampsia (n=1,924,409)

	n	Time to diagnosis (years)	
		Median (IQR)	Log-rank, p
Overall CKD			
No preeclampsia	16,933	16.9 (7.3-26.6)	<0.001
Exposed to preeclampsia	1,544	14.2 (4.7-24.7)	
1. Tubulointerstitial CKD			
No preeclampsia	2,629	14.7 (5.9-24.2)	<0.001
Exposed to preeclampsia	184	13.4 (5.5-20.5)	
2. Glomerular/proteinuric CKD			
No preeclampsia	5,568	11.2 (4.6-18.5)	<0.001
Exposed to preeclampsia	500	7.7 (2.0-15.7)	
3. Hypertensive CKD			
No preeclampsia	667	22.7 (15.3-30.2)	<0.001
Exposed to preeclampsia	130	20.6 (11.0-29.2)	
4. Diabetic CKD			
No preeclampsia	1,011	23.0 (13.9-30.3)	<0.001
Exposed to preeclampsia	215	15.6 (6.6-25.2)	
5. Other/unspecified CKD			
No preeclampsia	7,058	22.2 (11.6-30.1)	<0.001
Exposed to preeclampsia	515	21.3 (8.4-28.4)	

Table A8.3. Hazard ratios for maternal chronic kidney disease by history of preeclampsia and small for gestational age, among women whose first live birth occurred between 1987 and 2012 in Sweden (n=1,127,798)

		n	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Overall CKD				
No preeclampsia, no SGA		5,184	1.0	1.0
Preeclampsia only		511	2.34 (2.14-2.57)	2.29 (2.09-2.52)
SGA only		294	1.53 (1.36-1.72)	1.38 (1.22-1.55)
Preeclampsia & SGA		87	2.21 (1.79-2.74)	2.11 (1.71-2.61)
1.	**Tubulointerstitial CKD**			
	No preeclampsia, no SGA	1,192	1.0	1.0
	Preeclampsia only	84	1.65 (1.32-2.06)	1.68 (1.35-2.10)
	SGA only	56	1.30 (0.99-1.70)	1.11 (0.85-1.46)
	Preeclampsia & SGA	16	1.79 (1.09-2.94)	1.71 (1.05-2.81)
2.	**Glomerular/proteinuric CKD**			
	No preeclampsia, no SGA	1,498	1.0	1.0
	Preeclampsia only	160	2.62 (2.22-3.08)	2.61 (2.21-3.08)
	SGA only	97	1.74 (1.42-2.14)	1.58 (1.28-1.94)
	Preeclampsia & SGA	26	2.34 (1.59-3.45)	2.26 (1.53-3.33)
3.	**Hypertensive CKD**			
	No preeclampsia, no SGA	108	1.0	1.0
	Preeclampsia only	14	3.17 (1.81-5.53)	2.99 (1.70-5.29)
	SGA only	7	1.57 (0.73-3.37)	1.38 (0.64-2.97)
	Preeclampsia & SGA	8	9.18 (4.47-18.84)	8.64 (4.19-17.81)
4.	**Diabetic CKD**			
	No preeclampsia, no SGA	232	1.0	1.0
	Preeclampsia only	89	9.07 (7.10-11.59)	7.01 (5.44-9.05)
	SGA only	12	1.30 (0.73-2.33)	1.19 (0.67-2.14)
	Preeclampsia & SGA	8	4.31 (2.13-8.72)	3.80 (1.87-7.70)
5.	**Other/unspecified CKD**			
	No preeclampsia, no SGA	2,154	1.0	1.0
	Preeclampsia only	164	1.79 (1.53-2.10)	1.76 (1.50-2.07)
	SGA only	122	1.53 (1.28-1.84)	1.41 (1.18-1.70)
	Preeclampsia & SGA	29	1.76 (1.22-2.54)	1.69 (1.17-2.44)

Table A8.4. Hazard ratios for maternal chronic kidney disease by history of preeclampsia and preterm delivery, among women whose first live birth occurred between 1987 and 2012 in Sweden (n=1,127,798)

		N	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Overall CKD				
Term delivery, no preeclampsia		4,877	1.0	1.0
Moderate preterm delivery, no preeclampsia		511	1.62 (1.48-1.77)	1.49 (1.36-1.63)
Very/Extremely preterm delivery, no preeclampsia		90	2.11 (1.71-2.60)	1.82 (1.48-2.24)
Term delivery + Preeclampsia		409	2.09 (1.88-2.31)	2.04 (1.84-2.27)
Moderate preterm delivery + Preeclampsia		133	3.05 (2.56-3.62)	2.98 (2.51-3.54)
Very/Extremely preterm delivery + Preeclampsia		56	4.33 (3.33-5.63)	4.25 (3.26-5.53)
1.	**Tubulointerstitial CKD**			
	Term delivery, no preeclampsia	1,123	1.0	1.0
	Moderate preterm delivery, no preeclampsia	102	1.41 (1.15-1.73)	1.28 (1.04-1.57)
	Very/Extremely preterm delivery, no preeclampsia	23	2.38 (1.57-3.59)	2.00 (1.33-3.03)
	Term delivery + Preeclampsia	71	1.57 (1.23-2.00)	1.59 (1.25-2.04)
	Moderate preterm delivery + Preeclampsia	18	1.79 (1.12-2.85)	1.80 (1.13-2.88)
	Very/Extremely preterm delivery + Preeclampsia	11	3.69 (2.04-6.68)	3.71 (2.05-6.73)
2.	**Glomerular/proteinuric CKD**			
	Term delivery, no preeclampsia	1,435	1.0	1.0
	Moderate preterm delivery, no preeclampsia	136	1.48 (1.24-1.76)	1.37 (1.15-1.63)
	Very/Extremely preterm delivery, no preeclampsia	24	1.94 (1.29-2.90)	1.68 (1.12-2.52)
	Term delivery + Preeclampsia	129	2.23 (1.86-2.69)	2.22 (1.84-2.68)
	Moderate preterm delivery + Preeclampsia	39	3.10 (2.26-4.26)	3.09 (2.24-4.24)
	Very/Extremely preterm delivery + Preeclampsia	18	4.84 (3.04-7.71)	4.82 (3.03-7.68)
3.	**Hypertensive CKD**			
	Term delivery, no preeclampsia	97	1.0	1.0
	Moderate preterm delivery, no preeclampsia	13	1.96 (1.10-3.50)	1.82 (1.02-3.25)
	Very/Extremely preterm delivery, no preeclampsia	*	5.48 (2.23-13.47)	4.64 (1.88-11.46)
	Term delivery + Preeclampsia	12	3.29 (1.80-5.99)	3.14 (1.71-5.78)
	Moderate preterm delivery + Preeclampsia	7	7.97 (3.70-17.17)	7.61 (3.51-16.50)
	Very/Extremely preterm delivery + Preeclampsia	*	ne	ne
4.	**Diabetic CKD**			
	Term delivery, no preeclampsia	174	1.0	1.0
	Moderate preterm delivery, no preeclampsia	57	4.73 (3.51-6.37)	4.08 (3.02-5.51)
	Very/Extremely preterm delivery, no preeclampsia	13	7.91 (4.50-13.89)	5.70 (3.24-10.05)
	Term delivery + Preeclampsia	60	7.78 (5.74-10.56)	6.13 (4.49-8.37)
	Moderate preterm delivery + Preeclampsia	34	20.58 (14.26-29.71)	15.84 (10.91-22.99)
	Very/Extremely preterm delivery + Preeclampsia	*	ne	ne

5.	**Other/unspecified CKD**			
	Term delivery, no preeclampsia	2,048	1.0	1.0
	Moderate preterm delivery, no preeclampsia	203	1.43 (1.32-1.56)	1.43 (1.23-1.65)
	Very/Extremely preterm delivery, no preeclampsia	25	1.52 (1.23-1.88)	1.24 (0.83-1.84)
	Term delivery + Preeclampsia	138	1.61 (1.45-1.78)	1.70 (1.43-2.02)
	Moderate preterm delivery + Preeclampsia	35	1.78 (1.42-2.25)	1.87 (1.34-2.62)
	Very/Extremely preterm delivery + Preeclampsia	20	2.64 (1.77-3.94)	3.61 (2.32-5.61)

Hazard ratios represent separate Cox regression models for associations between preeclampsia and maternal chronic kidney disease. Preeclampsia was a time-dependent variable. Fully adjusted models controlled for maternal age, country of origin, education level, parity, maternal BMI, smoking in pregnancy, exposure to gestational diabetes, and exposure to gestational hypertension. Models were stratified by year of delivery. Abbreviations: CI, confidence interval; HR, hazard ratio; SGA, small for gestational age

*Exact number not reported as cell count ≤5

ne, not estimable

Table A8.5. Hazard ratios for maternal chronic kidney disease by history of recurrent preeclampsia, among women whose first live birth occurred between 1987 and 2012 in Sweden (n=548,621)

		N	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Overall CKD				
Two pregnancies without preeclampsia		2,583	1.0	1.0
Two pregnancies, one episode preeclampsia		258	2.14 (1.88-2.43)	2.09 (1.83-2.38)
Two pregnancies, two episodes preeclampsia		41	2.76 (2.03-3.76)	2.66 (1.95-3.63)
1.	**Tubulointerstitial CKD**			
	Two pregnancies without preeclampsia	580	1.0	
	Two pregnancies, one episode preeclampsia	42	1.52 (1.12-2.09)	1.54 (1.12-2.11)
	Two pregnancies, two episodes preeclampsia	*	1.49 (0.62-3.58)	1.47 (0.61-3.55)
2.	**Glomerular/proteinuric CKD**			
	Two pregnancies without preeclampsia	761	1.0	1.0
	Two pregnancies, one episode preeclampsia	93	2.36 (2.12-3.26)	2.68 (2.15-3.33)
	Two pregnancies, two episodes preeclampsia	15	3.45 (2.07-5.76)	3.44 (2.06-5.74)
3.	**Hypertensive CKD**			
	Two pregnancies without preeclampsia	50	1.0	1.0
	Two pregnancies, one episode preeclampsia	11	4.87 (2.53-9.36)	4.19 (2.14-8.20)
	Two pregnancies, two episodes preeclampsia	*	7.22 (1.76-29.72)	6.65 (1.60-27.57)
4.	**Diabetic CKD**			
	Two pregnancies without preeclampsia	102	1.0	1.0
	Two pregnancies, one episode preeclampsia	35	7.36 (5.01-10.81)	6.08 (4.11-9.02)
	Two pregnancies, two episodes preeclampsia	7	11.64 (5.41-25.05)	8.94 (4.11-19.43)
5.	**Other/unspecified CKD**			
	Two pregnancies without preeclampsia	1,090	1.0	1.0
	Two pregnancies, one episode preeclampsia	77	1.51 (1.20-1.91)	1.45 (1.15-1.83)
	Two pregnancies, two episodes preeclampsia	12	1.92 (1.09-3.39)	1.86 (1.05-3.29)

*Exact number not reported as cell count ≤5

Table A8.6. Hazard ratios for maternal chronic kidney disease by history of preeclampsia and small for gestational age, among women whose first live birth occurred between 1973 and 2012 in Sweden (n=1,924,409)

		n	Fully adjusted HR (95% CI)	Excluding women with postpartum hypertension HR (95% CI)
Overall CKD				
No preeclampsia, no SGA		15,783	1.0	1.0
Preeclampsia only		1,318	1.96 (1.85-2.08)	1.73 (1.62-1.85)
SGA only		1,150	1.32 (1.24-1.40)	1.33 (1.25-1.42)
Preeclampsia & SGA		226	1.95 (1.71-2.22)	1.59 (1.36-1.86)
1.	**Tubulointerstitial CKD**			
	No preeclampsia, no SGA	2,458	1.0	1.0
	Preeclampsia only	157	1.47 (1.25-1.73)	1.29 (1.08-1.54)
	SGA only	171	1.30 (1.11-1.51)	1.31 (1.11-1.53)
	Preeclampsia & SGA	27	1.41 (0.97-2.07)	1.28 (0.85-1.94)
2.	**Glomerular/proteinuric CKD**			
	No preeclampsia, no SGA	5,151	1.0	1.0
	Preeclampsia only	425	2.11 (1.90-2.33)	1.99 (1.79-2.22)
	SGA only	417	1.46 (1.32-1.62)	1.47 (1.33-1.64)
	Preeclampsia & SGA	75	2.16 (1.71-2.71)	2.09 (1.63-2.66)
3.	**Hypertensive CKD**			
	No preeclampsia, no SGA	610	1.0	-
	Preeclampsia only	104	3.60 (2.90-4.47)	-
	SGA only	57	1.54 (1.17-2.02)	-
	Preeclampsia & SGA	26	5.23 (3.51-7.79)	-
4.	**Diabetic CKD**			
	No preeclampsia, no SGA	954	1.0	1.0
	Preeclampsia only	189	4.03 (3.42-4.74)	4.31 (3.54-5.24)
	SGA only	57	1.05 (0.80-1.37)	1.04 (0.75-1.46)
	Preeclampsia & SGA	26	3.49 (2.36-5.16)	3.29 (2.00-5.42)
5.	**Other/unspecified CKD**			
	No preeclampsia, no SGA	6,611	1.0	1.0
	Preeclampsia only	443	1.54 (1.40-1.70)	1.38 (1.24-1.54)
	SGA only	448	1.24 (1.13-1.37)	1.25 (1.13-1.38)
	Preeclampsia & SGA	72	1.46 (1.15-1.84)	1.13 (0.85-1.49)

Hazard ratios represent separate Cox regression models for associations between preeclampsia and maternal chronic kidney disease. Preeclampsia was a time-dependent variable.
Fully adjusted models controlled for maternal age, country of origin, education level, parity, maternal BMI, smoking in pregnancy, exposure to gestational diabetes, and exposure to gestational hypertension. Models were stratified by year of delivery. Abbreviations: CI, confidence interval; HR, hazard ratio; SGA, small for gestational age

Table A8.7. Hazard ratios for maternal chronic kidney disease by history of preeclampsia and preterm delivery, among women whose first live birth occurred between 1973 and 2012 in Sweden (n=1,924,409)

		N	Fully adjusted HR (95% CI)	Excluding women with postpartum hypertension HR (95% CI)
Overall CKD				
Term delivery, no preeclampsia		15,134	1.0	1.0
Moderate preterm delivery, no preeclampsia		1,552	1.46 (1.39-1.54)	1.44 (1.36-1.52)
Very/Extremely preterm delivery, no preeclampsia		247	1.63 (1.44-1.85)	1.64 (1.44-1.88)
Term delivery + Preeclampsia		1,196	1.87 (1.76-1.99)	1.64 (1.52-1.75)
Moderate preterm delivery + Preeclampsia		276	2.52 (2.23-2.85)	2.15 (1.86-2.48)
Very/Extremely preterm delivery + Preeclampsia		72	3.19 (2.53-4.02)	2.66 (2.03-3.48)
1.	**Tubulointerstitial CKD**			
	Term delivery, no preeclampsia	2,365	1.0	1.0
	Moderate preterm delivery, no preeclampsia	220	1.26 (1.09-1.44)	1.25 (1.08-1.44)
	Very/Extremely preterm delivery, no preeclampsia	44	1.75 (1.30-2.36)	1.68 (1.23-2.29)
	Term delivery + Preeclampsia	146	1.45 (1.22-1.72)	1.25 (1.04-1.51)
	Moderate preterm delivery + Preeclampsia	24	1.37 (0.91-2.05)	1.20 (0.77-1.87)
	Very/Extremely preterm delivery + Preeclampsia	14	3.27 (1.93-5.54)	3.16 (1.83-5.45)
2.	**Glomerular/proteinuric CKD**			
	Term delivery, no preeclampsia	4,982	1.0	1.0
	Moderate preterm delivery, no preeclampsia	508	1.48 (1.35-1.62)	1.50 (1.36-1.65)
	Very/Extremely preterm delivery, no preeclampsia	78	1.59 (1.27-1.98)	1.66 (1.33-2.09)
	Term delivery + Preeclampsia	393	1.98 (1.78-2.20)	1.90 (1.70-2.13)
	Moderate preterm delivery + Preeclampsia	81	2.69 (2.16-3.35)	2.63 (2.08-3.32)
	Very/Extremely preterm delivery + Preeclampsia	26	3.88 (2.64-5.71)	2.93 (1.85-4.66)
3.	**Hypertensive CKD**			
	Term delivery, no preeclampsia	573	1.0	-
	Moderate preterm delivery, no preeclampsia	77	1.92 (1.51-2.45)	-
	Very/Extremely preterm delivery, no preeclampsia	17	2.98 (1.84-4.84)	-
	Term delivery + Preeclampsia	104	3.65 (2.92-4.55)	-
	Moderate preterm delivery + Preeclampsia	22	5.47 (3.55-8.43)	-
	Very/Extremely preterm delivery + Preeclampsia	*	5.74 (2.14-15.40)	-

Table A8.7 (continued). Hazard ratios for maternal chronic kidney disease by history of preeclampsia and preterm delivery, among women whose first live birth occurred between 1973 and 2012 in Sweden (n=1,924,409)

		N	Fully adjusted HR (95% CI)	Excluding women with postpartum hypertension HR (95% CI)
4.	**Diabetic CKD**			
	Term delivery, no preeclampsia	839	1.0	1.0
	Moderate preterm delivery, no preeclampsia	150	2.54 (2.13-3.03)	2.79 (2.26-3.44)
	Very/Extremely preterm delivery, no preeclampsia	22	2.55 (1.66-3.89)	3.19 (1.99-5.12)
	Term delivery + Preeclampsia	155	3.69 (3.08-4.41)	3.88 (3.11-4.84)
	Moderate preterm delivery + Preeclampsia	56	8.80 (6.67-11.60)	10.18 (7.38-14.04)
	Very/Extremely preterm delivery + Preeclampsia	*	3.18 (1.19-8.51)	ne
5.	**Other/unspecified CKD**			
	Term delivery, no preeclampsia	6,375	1.0	1.0
	Moderate preterm delivery, no preeclampsia	597	1.34 (1.24-1.46)	1.33 (1.21-1.45)
	Very/Extremely preterm delivery, no preeclampsia	86	1.37 (1.10-1.69)	1.43 (1.15-1.79)
	Term delivery + Preeclampsia	398	1.50 (1.36-1.67)	1.33 (1.18-1.49)
	Moderate preterm delivery + Preeclampsia	93	1.68 (1.33-2.12)	1.37 (1.05-1.80)
	Very/Extremely preterm delivery + Preeclampsia	24	2.50 (1.68-3.74)	2.16 (1.38-3.40)

Hazard ratios represent separate Cox regression models for associations between preeclampsia and maternal chronic kidney disease. Preeclampsia was a time-dependent variable. Fully adjusted models controlled for maternal age, country of origin, education level, parity, maternal BMI, smoking in pregnancy, exposure to gestational diabetes, and exposure to gestational hypertension. Models were stratified by year of delivery. Abbreviations: CI, confidence interval; HR, hazard ratio; SGA, small for gestational age
ne, not estimable

Table A8.8. Hazard ratios for maternal chronic kidney disease by history of recurrent preeclampsia, among women whose first live birth occurred between 1973 and 2012 in Sweden (n=1,924,409)

		N	Fully adjusted HR (95% CI)	Excluding women with postpartum hypertension HR (95% CI)
Overall CKD				
Two pregnancies without preeclampsia		6,326	1.0	1.0
Two pregnancies, one episode preeclampsia		551	1.82 (1.66-1.99)	1.61 (1.45-1.78)
Two pregnancies, two episodes preeclampsia		90	2.64 (2.14-3.25)	2.21 (1.73-2.82)
1.	**Tubulointerstitial CKD**			
	Two pregnancies without preeclampsia	1,054	1.0	1.0
	Two pregnancies, one episode preeclampsia	78	1.58 (1.25-1.99)	1.47 (1.14-1.88)
	Two pregnancies, two episodes preeclampsia	10	1.74 (0.93-3.25)	0.74 (0.28-1.98)
2.	**Glomerular/proteinuric CKD**			
	Two pregnancies without preeclampsia	2,062	1.0	1.0
	Two pregnancies, one episode preeclampsia	183	2.02 (1.73-2.35)	1.91 (1.62-2.25)
	Two pregnancies, two episodes preeclampsia	35	3.42 (2.44-4.78)	3.31 (2.32-4.72)
3.	**Hypertensive CKD**			
	Two pregnancies without preeclampsia	217	1.0	-
	Two pregnancies, one episode preeclampsia	38	3.23 (2.25-4.63)	-
	Two pregnancies, two episodes preeclampsia	7	5.30 (2.47-11.36)	-
4.	**Diabetic CKD**			
	Two pregnancies without preeclampsia	340	1.0	1.0
	Two pregnancies, one episode preeclampsia	73	3.74 (2.88-4.86)	3.56 (2.59-4.90)
	Two pregnancies, two episodes preeclampsia	14	6.80 (3.96-11.68)	7.70 (4.17-14.19)
5.	**Other/unspecified CKD**			
	Two pregnancies without preeclampsia	2,651	1.0	1.0
	Two pregnancies, one episode preeclampsia	179	1.36 (1.16-1.58)	1.21 (1.02-1.43)
	Two pregnancies, two episodes preeclampsia	24	1.64 (1.10-2.46)	1.45 (0.92-2.28)

Table A8.9. Hazard ratios for maternal chronic kidney disease by history of gestational hypertension, among women whose first live birth occurred between 1973 and 2012 in Sweden (n=1,924,409)

		n	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Overall CKD				
No gestational hypertension		17,734	1.0	1.0
Gestational hypertension		743	1.71 (1.58-1.84)	1.49 (1.38-1.61)
1.	**Tubulointerstitial CKD**			
	No gestational hypertension	2,731	1.0	1.0
	Gestational hypertension	90	1.43 (1.16-1.77)	1.34 (1.08-1.65)
2.	**Glomerular/proteinuric CKD**			
	No gestational hypertension	5,897	1.0	1.0
	Gestational hypertension	171	1.20 (1.03-1.40)	1.06 (0.91-1.24)
3.	**Hypertensive CKD**			
	No gestational hypertension	714	1.0	1.0
	Gestational hypertension	83	4.36 (3.47-5.48)	3.13 (2.47-3.97)
4.	**Diabetic CKD**			
	No gestational hypertension	1,142	1.0	1.0
	Gestational hypertension	84	3.00 (2.40-3.75)	1.96 (1.56-2.47)
5.	**Other/unspecified CKD**			
	No gestational hypertension	7,250	1.0	1.0
	Gestational hypertension	315	1.71 (1.53-1.92)	1.57 (1.40-1.76)

Hazard ratios represent separate Cox regression models for associations between preeclampsia and maternal chronic kidney disease. Gestational hypertension was a time-dependent variable.
Fully adjusted models controlled for maternal age, country of origin, education level, parity, maternal BMI, smoking in pregnancy, exposure to gestational diabetes, and exposure to preeclampsia. Models were stratified by year of delivery. Abbreviations: CI, confidence interval; HR, hazard ratio; SGA, small for gestational age

Table A8.10. Hazard ratios for maternal chronic kidney disease by history of gestational hypertension, among women whose first live birth occurred between 1973 and 2012 in Sweden (n=1,924,409)

		n	Fully adjusted HR (95% CI)	Exclude women with postpartum hypertension HR (95% CI)
Overall CKD				
No gestational hypertension		17,734	1.0	1.0
Gestational hypertension		743	1.49 (1.38-1.61)	1.26 (1.15-1.38)
1.	**Tubulointerstitial CKD**			
	No gestational hypertension	2,731	1.0	1.0
	Gestational hypertension	90	1.34 (1.08-1.65)	1.23 (0.97-1.55)
2.	**Glomerular/proteinuric CKD**			
	No gestational hypertension	5,897	1.0	1.0
	Gestational hypertension	171	1.06 (0.91-1.24)	0.93 (0.79-1.11)
3.	**Hypertensive CKD**			
	No gestational hypertension	714	1.0	-
	Gestational hypertension	83	3.13 (2.47-3.97)	-
4.	**Diabetic CKD**			
	No gestational hypertension	1,142	1.0	1.0
	Gestational hypertension	84	1.96 (1.56-2.47)	1.80 (1.34-2.43)
5.	**Other/unspecified CKD**			
	No gestational hypertension	7,250	1.0	1.0
	Gestational hypertension	315	1.57 (1.40-1.76)	1.44 (1.26-1.64)

Hazard ratios represent separate Cox regression models for associations between preeclampsia and maternal chronic kidney disease. Gestational hypertension was a time-dependent variable.
Fully adjusted models controlled for maternal age, country of origin, education level, parity, maternal BMI, smoking in pregnancy, exposure to gestational diabetes, and exposure to preeclampsia. Models were stratified by year of delivery. Abbreviations: CI, confidence interval; HR, hazard ratio; SGA, small for gestational age

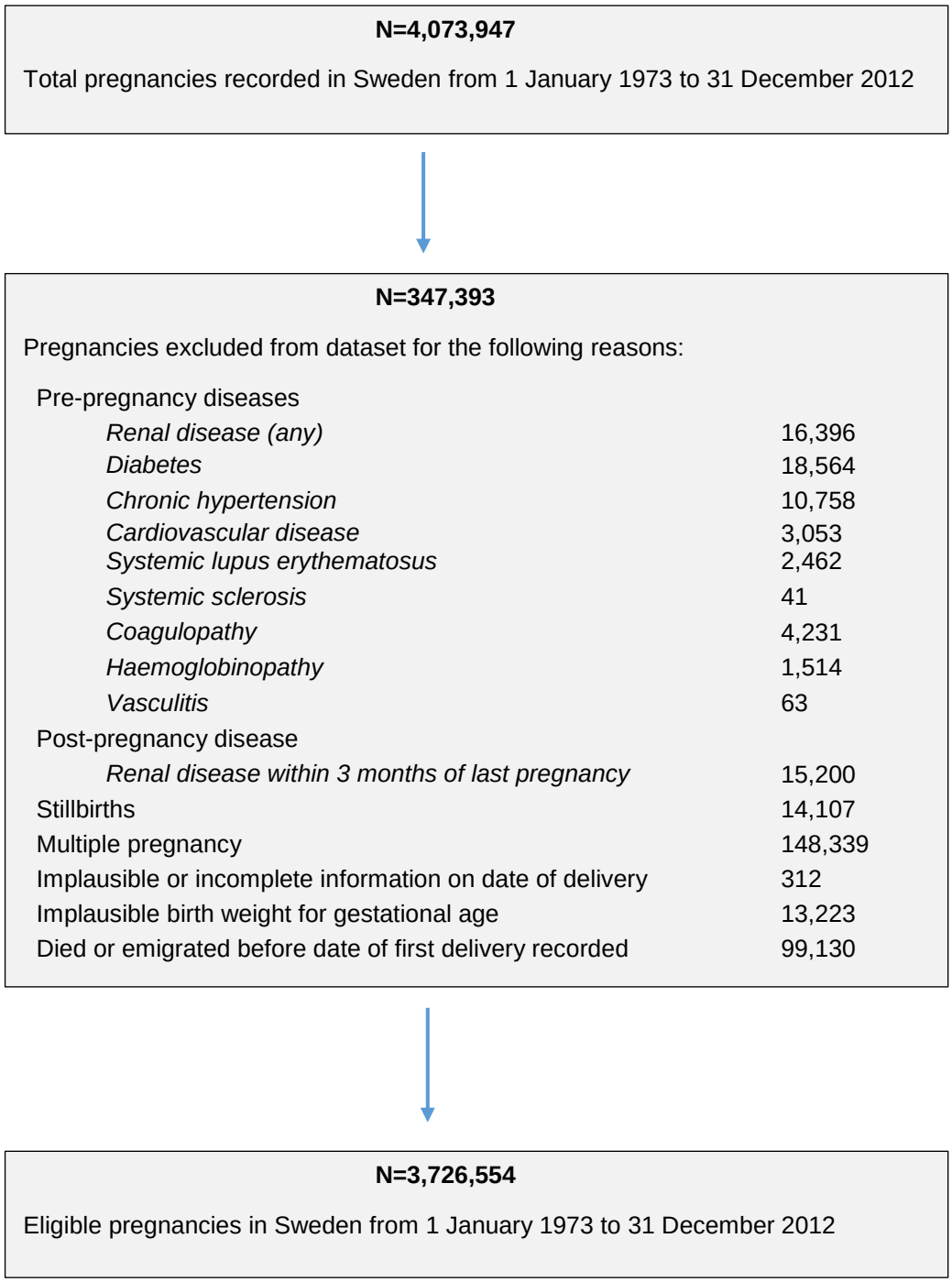
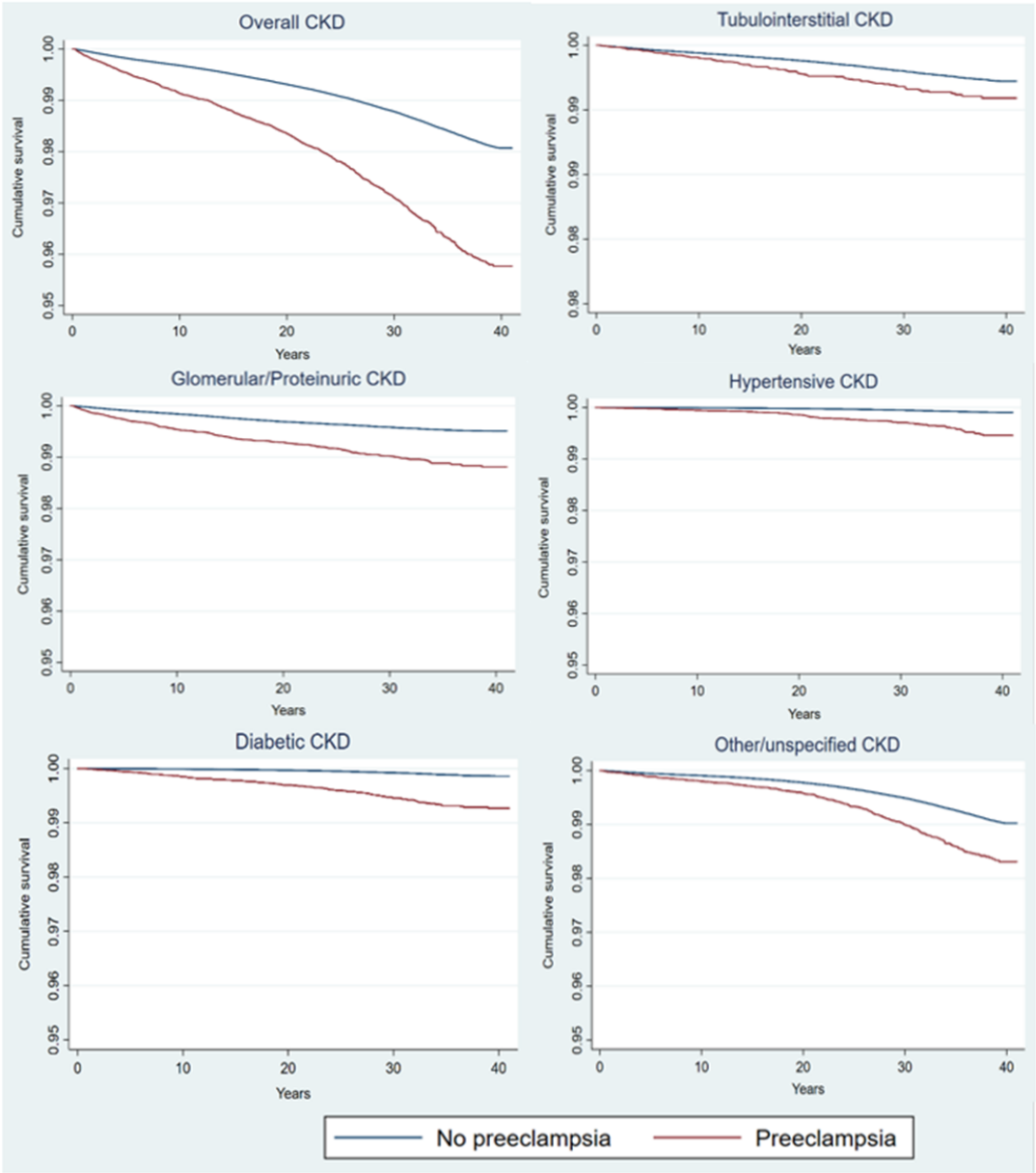


Figure A8.1. Flow chart illustrating construction of study cohort



Overall CKD	0-10 years	10-20 years	20-30 years	30-41 years
No preeclampsia				
Number at risk	1833492	1391945	1017878	591091
Number of events	5309	4447	4269	2908
Preeclampsia				
Number at risk	90917	71306	50031	27568
Number of events	601	419	347	177

Figure A8.2. Kaplan-Meier survival curves for risk of chronic kidney disease (overall and subtypes) among women whose first live birth occurred between 1973 and 2012 in Sweden, by exposure to preeclampsia.

Appendix 9. Additional files for chapter 7 – GDM and risk of maternal CKD/ESKD

Table A9.1. ICD codes used for disease definitions

	ICD-9 codes (1987-1996)	ICD-10 codes (1997-2013)
Any pre-existing chronic/end-stage kidney disease, congenital or genetic causes of renal disease (for exclusion)	403-404, 580-589, 753, V42A, V45B, V56A, V56W	N00-N08, N10-N19, P960, Q271, Q272, Q60-Q63, Q878, Z49, Z992, Z940, T861
Chronic kidney disease (CKD) (Outcome)	250D, 403-404, 581-583, 585-588, V42A, V45B, V56A, V56W	E102, E112, I12-I13, I150-I151, N01-N06, N08, N11-N13, N15-16, N18-19, Z49, Z992, Z940, T861
Tubulointerstitital CKD	-	N11-N12, N15-N16
Glomerular/proteinuric CKD	581-583	N01-N06, N08
Hypertensive CKD	403-404	I12-I13, I150-I151
Diabetic CKD	250D	E102, E112
Other/unspecified CKD	585-588, V42A, V45B, V56A, V56W	N13, N18-N19, Z49, Z992, Z940, T861
End-stage kidney disease (ESKD) (Outcome)	V42A, V45B, V56A, V56W	N185, Z49, Z992, Z940, T861
Cardiovascular disease	393-398 410-436	I16-I64 G45
Essential hypertension	401-405	I10-I15
Diabetes (type 1 or type 2)	250	E10-E14
Systemic lupus erythematosus	710A	M32
Systemic sclerosis	710B	M34
Vasculitis	446	M31
Haemoglobinopathies	282-283	D56-D59
Coagulopathies	None	D68
Preeclampsia	642E, 642F, 642G	O140, O141, O141A, O141B, O141C, O141X, O142, O149, O150, O151, O152, O159
Gestational diabetes	648W	O244

Table A9.2. Demographic changes over time among women whose first delivery occurred in Sweden between 1987 and 2012.

	Births in Sweden				
	1987-1991	1992-1996	1997-2001	2002-2006	2007-2012
Number of singleton births*	323,479	434,185	382,155	436,644	580,867
Number of births affected by GDM	1,817	3,178	3,156	3,955	6,523
Incidence rate of GDM (per 100,000 births)	562	732	826	906	1,123
Mean (± sd) age at delivery	26.4 ± 4.7	27.8 ± 4.7	29.1 ± 4.8	30.0 ± 5.0	30.2 ± 5.3
% mothers affected by antenatal obesity**	3.9	6.4	9.0	10.7	12.1
% mothers born outside of Sweden	14.4	17.3	13.2	11.2	13.5

GDM, gestational diabetes

*after exclusions applied, i.e. only women whose first birth happened during or after 1987 and excluding multiple pregnancy, pre-pregnancy medical comorbidities (renal disease, cardiovascular disease, chronic hypertension, systemic lupus erythematosus, systemic sclerosis, coagulopathies, vasculitides, haemoglobinopathies, type 1 or 2 diabetes mellitus at baseline)

**after missing data addressed using multiple imputation

Table A9.3. Hazard ratios for maternal kidney disease by history of gestational diabetes and delivery of a large for gestational age infant, among women whose first birth occurred between 1987 and 2012 in Sweden

	n	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
		Chronic kidney disease (N=5,879)	
None	5,428	1.0	1.0
GDM only	105	2.00 (1.65-2.42)	1.58 (1.31-1.93)
LGA only	297	1.60 (1.44-1.78)	1.43 (1.29-1.60)
GDM and LGA	49	4.72 (3.56-6.26)	3.03 (2.28-4.03)
		End-stage kidney disease (N=228)	
None	203	1.0	1.0
GDM only	12	5.61 (3.13-10.07)	3.78 (2.08-6.87)
LGA only	7	1.42 (0.81-2.49)	1.37 (0.78-2.42)
GDM and LGA	6	14.64 (6.49-33.02)	8.37 (3.64-19.23)

GDM, gestational diabetes; LGA, large for gestational age

Hazard ratios represent separate Cox regression models for associations between gestational diabetes and maternal chronic kidney disease or end-stage kidney disease. In all models, gestational diabetes and/or subsequent type 2 diabetes was a time-dependent variable, where maternal exposure status was based on the date of first affected delivery. Fully adjusted models were adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, gestational weight gain and maternal exposure to preeclampsia (time-dependent covariate), stratified by year of delivery. Women with pre-pregnancy history of renal disease, cardiovascular disease, diabetes, hypertension, systemic lupus erythematosus, coagulopathies, haemoglobinopathies and vasculitis were excluded at baseline.

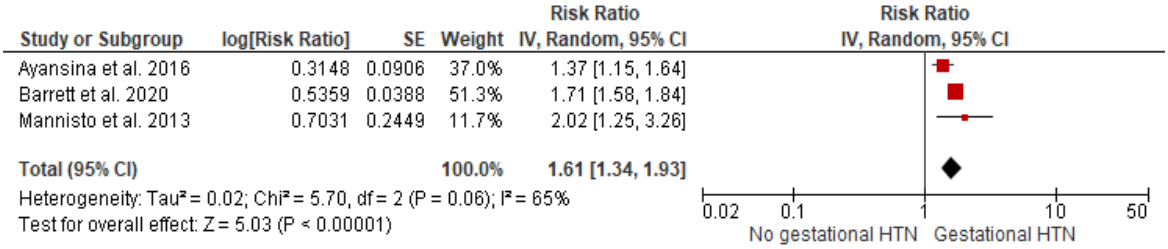
Table A9.4. Effect modification by ethnicity and antenatal obesity status of the association between gestational diabetes and/or type 2 diabetes and maternal renal disease in women whose first birth occurred between 1987 and 2012 in Sweden

	Chronic kidney disease (N=5,879)			End-stage kidney disease (N=228)		
	Age-adjusted	Fully adjusted	p interaction	Age-adjusted	Fully adjusted	p interaction
	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	
Born in Sweden						
None	1.0	1.0	0.004	1.0	1.0	0.119
GDM only	1.45 (1.12-1.86)	1.11 (0.86-1.44)		2.42 (0.77-7.60)	1.33 (0.58-4.19)	
T2DM only	23.15 (20.77-25.80)	19.84 (17.76-22.15)		93.92 (66.75-132.15)	69.90 (48.97-99.78)	
GDM + T2DM	26.82 (20.04-35.88)	14.67 (10.91-19.73)		115.01 (50.50-261.92)	82.92 (35.67-192.74)	
Born outside of Sweden						
None	1.0	1.0		1.0	1.0	
GDM only	1.22 (0.78-1.90)	1.06 (0.68-1.67)		3.19 (0.98-10.35)	2.43 (0.73-8.06)	
T2DM only	33.16 (26.08-42.15)	27.78 (21.76-35.48)		36.65 (14.29-94.02)	26.77 (10.21-70.23)	
GDM + T2DM	56.59 (38.46-83.26)	44.32 (29.87-65.75)		226.96 (93.91-548.51)	186.71 (72.48-463.41)	
Obese						
None	1.0	1.0	0.056	1.0	1.0	0.181
GDM only	0.95 (0.61-1.48)	0.78 (0.50-1.22)		5.71 (1.93-16.92)	5.27 (1.75-15.87)	
T2DM only	23.57 (18.48-30.06)	19.60 (15.31-25.09)		56.52 (20.50-155.81)	43.68 (15.27-124.98)	
GDM + T2DM	46.06 (32.26-65.76)	26.47 (18.29-38.29)		168.47 (60.85-466.42)	172.43 (57.85-513.99)	
Non-obese						
None	1.0	1.0		1.0	1.0	
GDM only	1.48 (1.15-1.91)	1.27 (0.99-1.64)		1.35 (0.33-5.46)	1.01 (0.25-4.08)	
T2DM only	23.76 (21.32-26.49)	20.82 (18.65-23.24)		82.19 (58.83-114.82)	62.27 (44.06-87.99)	
GDM + T2DM	24.66 (18.05-33.68)	18.25 (13.35-24.95)		124.60 (58.14-267.03)	89.81 (41.44-194.67)	

Hazard ratios represent separate Cox regression models for associations between gestational diabetes and maternal chronic kidney disease or end-stage kidney disease. In all models, gestational diabetes and/or subsequent type 2 diabetes was a time-dependent variable, where maternal exposure status was based on the date of first affected delivery.
Fully adjusted model adjusted for maternal age, country of origin, maternal education, parity, antenatal BMI, smoking, gestational weight gain and maternal exposure to preeclampsia (time-dependent covariate), stratified by year of delivery. Women with pre-pregnancy history of renal disease, cardiovascular disease, diabetes, hypertension, systemic lupus erythematosus, coagulopathies, haemoglobinopathies and vasculitis were excluded at baseline.

Appendix 10. Additional files for chapter 8 – updated systematic review and meta-analysis

Crude



Adjusted

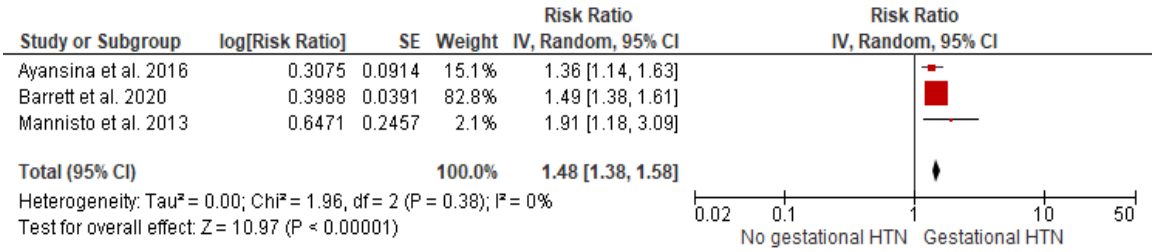


Figure A10.1. Updated forest plot for studies of the association of gestational hypertension and chronic kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

Adjusted

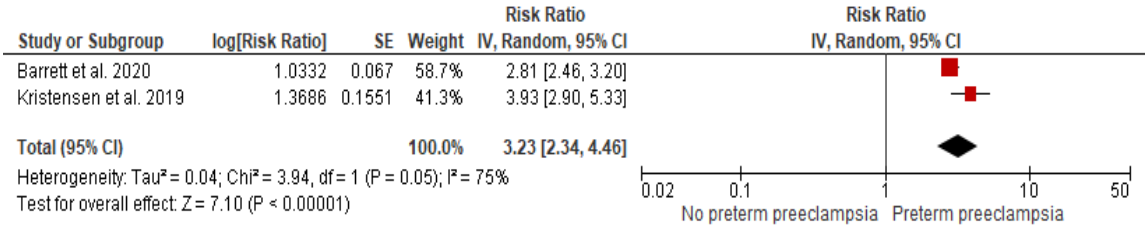
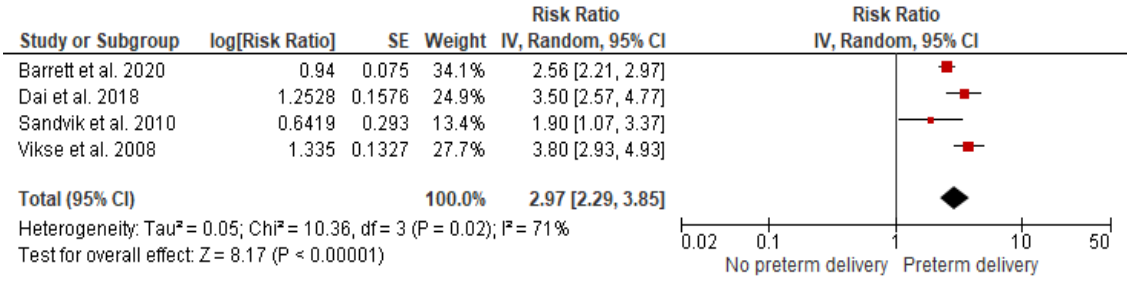


Figure A10.2. Updated forest plot for studies of the adjusted association of preterm preeclampsia and chronic kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

Crude



Adjusted

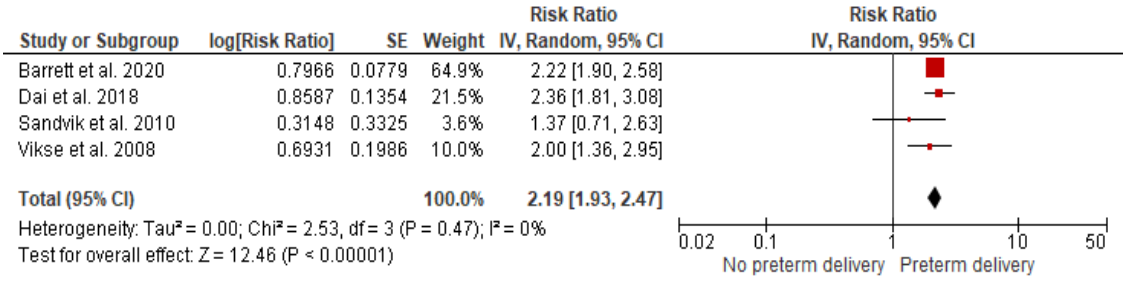


Figure A10.3. Updated forest plot for studies of the association of preterm delivery and end-stage kidney disease.

Risk ratios (RRs) are calculated using random-effects meta-analysis.

Appendix 11. ADVERSE PREGNANCY OUTCOMES AND MATERNAL HEALTH: ACTION NEEDED FOR LONG-TERM BENEFIT

Peter M. Barrett (1, 2), Ali S. Khashan (1, 2), Fergus P. McCarthy (2, 3), Karolina Kublickiene (4).

1. School of Public Health, University College Cork, Cork, Ireland
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland
3. Department of Obstetrics & Gynaecology, Cork University Maternity Hospital, Cork, Ireland
4. Department of Clinical Sciences Intervention and Technology, Karolinska Institutet, Huddinge, Sweden

Guest Editorial

Published in: *Acta Obstetricia et Gynecologica Scandinavica, July 2020*

(Paper 7)

A11.1 Introduction

In recent years, high-quality evidence has been accumulating that pregnancy complications are linked to a range of chronic diseases in later life. Pregnancy is regarded as a metabolic "stress test" which may unmask women's underlying risk of future cardiovascular disease (CVD) or chronic kidney disease (CKD). However, the potential for this information to be used in long-term cardio-renal risk reduction has not been fully realised. Women who have a history of hypertensive disorders of pregnancy, gestational diabetes, preterm delivery, intra-uterine growth restriction, or pregnancy loss are at higher risk of CVD, cerebrovascular disease, and premature mortality relative to those whose pregnancies were uncomplicated (19, 191). Similarly, elevated risks of CKD and end-stage kidney disease have been observed in women with a history of preeclampsia, gestational hypertension, preterm delivery, and stillbirth (209, 212). The causal mechanisms underlying these associations are unclear. It is possible that adverse pregnancy outcomes are simply a manifestation of subclinical predisposition to chronic disease, rather than playing any independent aetiological role. Nonetheless, these associations present an opportunity to provide sex-specific preventive care to women at risk of long-term CVD and CKD.

A11.2 Knowledge among healthcare professionals

Current research suggests that healthcare professionals have relatively low levels of knowledge of the long-term cardiovascular and renal risks associated with adverse pregnancy outcomes. Obstetricians tend to have greater awareness of this relative to other clinicians, but they are not routinely involved in the long-term aftercare of affected women. Only a small minority of GPs and internal medicine physicians appear to ask women about their pregnancy history when assessing overall CVD risk beyond the reproductive years, suggesting suboptimal knowledge among these groups (251).

Where clear evidence-based guidelines for the aftercare of affected women are available, and known among healthcare professionals, they tend to result in improved recognition of CVD and CKD risk. Clinicians are more likely to identify other risk factors for chronic disease such as hypertension and hyperglycaemia. They are also more inclined to counsel women regarding their individual long-term risk, and this can facilitate women's own self-management (251, 258).

A11.3 Screening and postpartum follow-up

It has been proposed that women who experience adverse pregnancy outcomes may benefit from screening for future CVD and CKD. However, there is a lack of robust evidence around the efficacy and effectiveness of such programmes. Specific recommendations around screening eligibility, frequency of follow-up, and preventive interventions are lacking (225). Ideally, eligible women should be enrolled in the immediate postpartum period to detect early onset CVD or renal impairment, and to identify modifiable risk factors. Subclinical disease may be present, but it can be difficult to detect in the absence of sensitive and reliable biomarkers. Moreover, the presence of cardio-protective oestrogen in pre-menopausal women, and the potential masking of early renal damage by compensatory glomerular hyper-filtration, may limit the ability to detect high-risk women until later in life (225). Any systematic public screening programme can only be justified if it facilitates earlier diagnosis or intervention, and if there is strong evidence of its clinical and cost effectiveness. At present, it is too premature to conclude whether the benefits of screening for CVD or CKD would outweigh potential harms.

The lack of evidence for screening impedes the development of clear clinical pathways for women who experience adverse pregnancy outcomes. Recommendations for cardio-renal aftercare tend to be either inconsistent or entirely absent from national and international

guidelines. A recent review of 16 international guidelines reported excessive variation in the recommended follow-up of women who had experienced hypertensive disorders of pregnancy (260). Only 8 guidelines provided any recommendations for follow-up beyond the immediate postpartum period. They typically emphasised the need to inform women and their GPs about the future risk of CVD and CKD. However, there was a lack of high-quality evidence available on long-term surveillance and risk reduction strategies, and specific follow-up actions varied considerably.

A11.4 Clinical risk prediction

It has been suggested that obstetric information may be used to add incremental value to clinical risk prediction tools for CVD or CKD, but the evidence for this is inconclusive to date. Recent longitudinal studies from Scandinavia suggest that hypertensive disorders of pregnancy, preterm delivery and small for gestational age make minimal improvements to CVD risk prediction after taking traditional risk factors in to account (265, 266), although these studies have been limited by their relatively short durations of follow-up. There is a dearth of research on the use of obstetric risk factors in renal or cerebrovascular risk prediction models to date. Larger population-based studies with longer follow-up (>10 years) are warranted to investigate whether obstetric information can be used to enhance CVD and CKD risk prediction algorithms for women.

Currently, cardiovascular guidelines from the USA suggest that adverse pregnancy outcomes may be considered as sex-specific 'risk enhancing factors' which can be applied to patients in lower or intermediate CVD risk categories (263). For women with low 10-year CVD risk, lifestyle interventions should comprise the mainstay of preventive care, but more aggressive lifestyle modifications may be recommended for women who have experienced preeclampsia since they will likely have elevated lifetime CVD risk. Additionally, information about history

of preeclampsia may be used to justify initiation or augmentation of statin therapy in those with an intermediate 10-year CVD risk.

A11.5 Role of clinicians

Despite the inherent limitations of the existing evidence base, established associations between adverse pregnancy outcomes and CVD/CKD should be communicated to affected women, and to GPs and other clinicians involved in their post-pregnancy care (251). Information about pregnancy complications may be of practical use in clinical assessment because they are easily ascertained, at minimal cost, and from an earlier stage in a woman's life than some traditional cardiovascular risk factors. Arguably, a comprehensive obstetric history should form part of any thorough evaluation of women's long-term CVD and CKD risk.

Healthcare professionals play a key role in both recognising CVD/CKD risk among women, and in promoting tailored lifestyle interventions. But while it is essential that women are informed of their cardio-renal risk profile where possible, the provision of patient information may not be sufficient to achieve meaningful long-term changes. Some women prefer to receive structured advice or supports, and postpartum maternal health clinics may help in this regard. Such clinics allow healthcare providers and patients to agree a plan for CVD and CKD prevention together, either through lifestyle modifications alone or by using medical interventions and treatment. These clinics do not offer a panacea, as there is a considerable risk of selection bias among attendees. Women with higher BMI, women from deprived backgrounds, and smokers may be less likely to attend, despite being at higher risk of chronic disease (267).

The optimal format and setting for postpartum follow-up remains uncertain, but clinicians can play a key role in agreeing joint clinical care pathways. GPs, obstetricians, internal medicine

physicians (e.g. cardiologists, nephrologists and endocrinologists) and public health physicians may be able to yield meaningful long-term clinical benefits by co-designing preventive interventions for women who experience complications of pregnancy.

A11.6 Future research

Adverse pregnancy outcomes offer a uniquely female suite of risk markers for long-term CVD and CKD. Country and context-specific research is lacking on women's and healthcare providers' knowledge of the long-term risks following complications of pregnancy (251). Further research is needed to define the trajectory towards the development of chronic disease among these women, including the role of potential mediating factors such as postpartum hypertension, hyperlipidaemia, albuminuria and hyperglycaemia. The relative effectiveness of preventive interventions needs to be elucidated, and the potential benefits of engaging women in screening programmes should be further evaluated. More longitudinal population-based studies are needed to determine whether adverse pregnancy outcomes offer tangible, incremental value for CVD and CKD risk prediction tools, and whether postpartum maternal health clinics offer a viable, cost-effective forum in which to counsel women about their individual risks. Until these research gaps can be addressed, the potential of adverse pregnancy outcomes to be used towards prevention of CVD and CKD is unlikely to be fully achieved.

Appendix 12. ADVERSE PREGNANCY OUTCOMES – A MISSED OPPORTUNITY TO PREVENT CHRONIC DISEASE?

Peter M. Barrett (1, 2, 3)

1. School of Public Health, University College Cork, Cork, Ireland
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland
3. Wellcome Trust- HRB Irish Clinical Academic Training Programme, University College Cork, Cork, Ireland

Young Researcher Editorial

Published in: *International Journal of Public Health, January 2021*

(Paper 8)

In recent years, evidence has been mounting that adverse pregnancy outcomes are associated with increased risk of maternal chronic diseases in later life. Large-scale cohort studies and comprehensive meta-analyses have linked preeclampsia, gestational hypertension, preterm delivery, and pregnancy loss with higher risk of later cardiovascular disease (CVD) and chronic kidney disease (CKD) (19, 209, 212, 237). Women who experience pregnancy complications are at greater risk of adverse cardiometabolic and renal outcomes than those who experience uncomplicated pregnancies. These associations are concerning from a population perspective. Every year, about 210 million women become pregnant, resulting in 140 million live births (9). The incidence of adverse pregnancy outcomes is rising along with maternal obesity, older age at conception, and higher prevalence of pre-pregnancy comorbidities (5, 209).

The links between adverse pregnancy outcomes and maternal CVD and CKD suggest that women's pregnancy history may include information that could help prevent chronic disease. Recent guidelines from the American College of Cardiology state that pregnancy complications may be regarded as "risk-enhancing factors" for CVD, particularly among women whose 10-year cardiovascular risk is intermediate or low (263). For example, women who have had adverse pregnancy outcomes may benefit from more intensive lifestyle modifications for primary prevention of CVD than women whose pregnancies were uncomplicated. Similarly, women at intermediate risk of CVD may benefit from earlier commencement or higher doses of statin therapy if they have a history of preeclampsia (263). Obstetric information could be used by both healthcare providers and women affected by pregnancy complications to prevent onset or progression of CVD and CKD in later life. To make use of this information, however, we must meet three key challenges.

First, current research suggests that clinicians are often unaware of the associations between adverse pregnancy outcomes and chronic disease (251, 260). Few general practitioners and internal medicine physicians report asking parous women their obstetric history when

assessing their risk of CVD beyond their reproductive years. Obstetricians are often more aware of these risks, but they do not typically follow up women after discharge from maternity services (251). Insufficient awareness might be caused by 1) lack of accessible evidence-based guidelines for monitoring women with adverse pregnancy outcomes over the long-term; 2) different and competing versions of published guidelines; 3) obstetric and primary care services may not share electronic healthcare records (251, 260). Any of these problems may make healthcare professionals uncertain about whose clinical responsibility it is to inform affected women of their long-term risk (262).

Second, women who experience adverse pregnancy outcomes may be unaware of their individual risk of chronic disease (261, 262). Patients and clinicians may have different perceptions of the importance of personalised information. In Canada, some doctors assumed that women who had preeclampsia did not want to know their long-term CVD risk if these women did not inquire directly about this after pregnancy (262). But in Norway, women who had experienced pregnancy complications wanted to be given more individualised information about their future cardiometabolic risk by default (261). If neither healthcare providers nor patients initiate discussion about the links between adverse pregnancy outcomes and chronic disease, this prevention opportunity may be missed.

Third, the optimal timing, format and content of structured follow-up programmes for women with adverse pregnancy outcomes is unclear. Some have proposed systematic screening programmes (e.g. for postpartum hypertension, albuminuria, or other markers of cardiometabolic or renal disease) to prevent or diagnose CVD and CKD early on. But we do not yet know if the long-term clinical benefits of screening outweigh harms that could arise from over-investigation. We also do not know if adverse pregnancy outcomes add incremental value to existing risk prediction tools for CVD and CKD in parous women (237). Despite these limitations, healthcare providers should be encouraged to discuss the links between adverse

pregnancy outcomes and CVD/CKD risk with their patients because this knowledge may motivate and empower women to change other modifiable risk factors for chronic disease. It may also help them make informed decisions about uptake of preventive interventions or treatment options (263).

Adverse pregnancy outcomes are a sex-specific suite of risk markers for chronic disease that offer a unique opportunity to reduce health inequities. CVD is the leading cause of mortality among women, but they are less likely than men to receive appropriate preventive care for CVD (274). CKD prevalence is higher in women than in men, affecting about 1 in 8 women over their life-course (34, 237). From a global perspective, mothers in lower-income countries disproportionately suffer from pregnancy complications and the burden of chronic disease is growing in the Global South (5, 9). If pregnancy-related information can be used to prevent CVD and CKD, this could reduce some of these disparities.

From a clinical perspective, we can now shift our focus from asking if there are associations between pregnancy complications and chronic diseases to asking how we can harness this information to increase prevention. More healthcare providers will understand these risks if adverse pregnancy outcomes are consistently incorporated into clinical guidelines for preventing CVD and CKD, and if these guidelines are accessible in both community and hospital settings (260). At the regional level, obstetricians, general practitioners, and internal medicine physicians should collaborate to ensure that affected women are told of their heightened risk of chronic disease, and to maximise opportunities for providing preventive healthcare. Finally, at the health system level, chronic disease prevention strategies should be integrated with efforts to improve maternal health across the life-course. Taking a synergistic approach could lower the burden of chronic disease and ensure more equitable health outcomes for women over the long-term (5, 9).

Appendix 13. Modules and workshops completed during PhD

Modules		**Credits**
EH6044	Systematic review and meta-analysis	5
ST6012	Survival analysis	5
PG6009	Graduate information literacy skills	5
TL6003	Theories of teaching, learning and assessment*	15
TL6004	Practice approaches to teaching, learning and assessment*	15

**Awarded Postgraduate Certificate in Teaching and Learning in Higher Education in October 2020 on completion of these two modules*

Workshops	**Location**
Media training *(September 2018)*	University College Cork
Introduction to Survival Analysis *(October 2018)*	Statistical Services Centre, Reading, UK
Improving your Stata: Data management, publication-quality outputs and automating tasks *(January 2020)*	University of Bristol, UK

Appendix 14. Awards and distinctions during PhD

Award	**Awarding body**	**Date**
Best Clinical Abstract, Young Nephrologist Section ISN World Congress of Nephrology	International Society of Nephrology	March 2020
College of Medicine & Health Doctoral Student Travel Bursary	College of Medicine & Health, University College Cork	October 2019
William Stokes Award - Best standard of research among doctors in Higher Specialist Training	Royal College of Physicians of Ireland	September 2019
Dorothy Stopford Price Medal – Best standard of research on a public health topic among doctors in Higher Specialist Training	Royal College of Physicians of Ireland	September 2019
Best Abstract, Early Career Researcher (pre-PhD) section, SSM and IEA Joint Annual Scientific Meeting	Society for Social Medicine & International Epidemiology Assocation	September 2019
Attendance Scholarship, Young Forum Gastein	European Health Forum Gastein	October 2018

Appendix 15. Additional publications during PhD

The following publications were achieved while I was registered as a PhD student, but they are unrelated to this thesis:

1. Carey C, O'Donnell K, Davoren M... **Barrett PM***. Factors associated with lower knowledge of HIV and STI transmission, testing and treatment among MSM in Ireland: findings from the MSM Internet Survey Ireland (MISI) 2015. Sex Transm Infect. 2020 Oct 26:sextrans-2020-054469. doi: 10.1136/sextrans-2020-054469. Online ahead of print.
   **Senior author and project supervisor*
2. **Barrett PM**, Mullen L, McCarthy T. Enduring psychological impact of childhood cancer on survivors and their families in Ireland: A national qualitative study. Eur J Cancer Care (Engl). 2020 Sep;29(5):e13257. doi: 10.1111/ecc.13257. Epub 2020 Jun 15.
3. **Barrett PM**, Bambury N, Kelly L, et al. Measuring the effectiveness of an automated text messaging active surveillance system for COVID-19 in the south of Ireland, March to April 2020. Euro Surveill. 2020 Jun;25(23):2000972. doi: 10.2807/1560-7917.ES.2020.25.23.2000972.
4. Cawley DT, **Barrett P**, Moran B et al. Primary appendicular soft-tissue sarcoma resection: What tumour parameters affect wound closure planning? Int Wound J. 2019 Dec;16(6):1553-1558. doi: 10.1111/iwj.13251. Epub 2019 Oct 13.
5. **Barrett P**, O'Donnell K, Fitzgerald M et al. Drug use among men-who-have-sex-with-men in Ireland; a national online survey of prevalence and associated factors. Int J Drug Policy. 2018 Dec 1;64:5-12. doi: 10.1016/j.drugpo.2018.11.011.
6. O'Donnell K, Fitzgerald M… **Barrett P**, McCartney D, Igoe D. Inequalities in HIV testing uptake and needs among men-who-have-sex-with-men living in Ireland: Findings from an internet survey. HIV Med. 2018 Nov 20. doi: 10.1111/hiv.12694.
7. O'Connor L, O'Donnell K, **Barrett P** et al. Use of geo-social networking applications is independently associated with diagnosis of sexually transmitted infection (STI) among men-who-have-sex-with-men testing for STIs in Ireland. Sex Transm Infect 2018;0:1–6. doi:10.1136/sextrans-2018-053637.
8. **Barrett P**, Cotter S, Ryan F et al. A national measles outbreak in Ireland linked to a single imported case, April to September 2016. Euro Surveill. 2018 Aug;23(31). doi: 10.2807/1560-7917.ES.2018.23.31.1700655.