Accepted: 30 January 2023 | Published Online 27 March 2023

DOI: 10.1111/1471-0528.17454

BJOG An International Journal of Obstetrics and Gynaecology

RESEARCH ARTICLE

Epidemiology

Previous pre-eclampsia, gestational diabetes mellitus and the risk of cardiovascular disease: A nested case–control study in Sweden

Karin Hildén[1] | Anders Magnuson[2] | Scott Montgomery[2,3] | Erik Schwarcz[4] | Ulf Hanson[5,6] | David Simmons[6,7] | Helena Backman[1]

[1]Department of Obstetrics and Gynaecology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

[2]Clinical Epidemiology and Biostatistics, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

[3]Clinical Epidemiology Division, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

[4]Department of Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

[5]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

[6]Faculty of Medicine, Health Örebro University, Örebro, Sweden

[7]School of Medicine, Western Sydney University, Campbelltown, Australia

Correspondence
K. Hildén, Department of Obstetrics and Gynaecology, University Hospital Örebro, SE-70385 Örebro, Sweden
Email: karin.hilden@regionorebrolan.se

Funding information
Region Örebro län, Grant/Award Number: OLL 939071 OLL 961321

Abstract

Objective: Pre-eclampsia and gestational diabetes mellitus (GDM) are two common pregnancy complications that affect birth outcomes and are associated with a long-term risk of cardiovascular disease (CVD). The aims of this study were to investigate if the pre-eclampsia association with CVD is independent of GDM and modified by body mass index (BMI) or GDM.

Design: Case–control study.

Setting: Sweden.

Population: Cases were women with a first CVD event between 1991 and 2008 and a previous pregnancy who were matched with controls without CVD (1:5) by year of birth, age and region of birth.

Methods: Conditional logistic regression was used to evaluate the associations of GDM, pre-eclampsia and maternal BMI with CVD adjusted for potential confounders and effect modifications with interaction tests.

Main outcome measures: CVD.

Results: There were 2639 cases and 13 310 controls with complete data. Pre-eclampsia and GDM were independent risk factors for CVD (adjusted odds ratio [aOR] 2.59, 95% CI 2.12–3.17 and aOR 1.47, 95% CI 1.04–2.09, respectively). After stratifying by maternal BMI, the adjusted association of pre-eclampsia with CVD did not differ notably between BMI groups: normal weight (aOR 2.65, 95% CI 1.90–3.69), overweight (aOR 2.67, 95% CI 1.52–4.68) and obesity (aOR 3.03, 95% CI 0.74–12.4). Similar findings were seen when stratifying on GDM/non-GDM.

Conclusions: Pre-eclampsia and GDM are independent risk factors for later CVD and having both during pregnancy is a major risk factor for later CVD. The association between pre-eclampsia and CVD is not modified by BMI. Effective CVD preventive programs for high-risk women are urgently needed in order to improve women's long-term health.

KEYWORDS
cardiovascular disease, gestational diabetes, hypertension, morbidity, mortality, overweight, pre-eclampsia, pregnancy, smoking

1 | INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death for women worldwide including Sweden.[1,2] Pre-eclampsia and gestational diabetes mellitus (GDM) are two common pregnancy complications that affect maternal and perinatal outcomes during pregnancy and labour; they are associated with long-term health risks[3–8] and often co-exist.

GDM increases the risk for subsequent type 2 diabetes mellitus seven- to ten-fold and women with previous GDM also have an elevated risk of later CVD.[3,5,7–10] A recent Danish study showed that GDM is a risk factor for later CVD and cardiometabolic health regardless of subsequent type 2 diabetes mellitus.[11]

Hypertensive disorders during pregnancy are also associated with an increased risk of future CVD.[6,12] There is evidence that CVD in women with hypertensive disorders during pregnancy occurs at a younger age compared with women without hypertensive disease[13] and that early hypertension during pregnancy modifies the risk.[14]

Reports on how well follow up of women with previous GDM or pre-eclampsia is implemented are limited, with only a small proportion proactively followed up in primary care[15–17] and the follow-up rates decline rapidly after 2 years.[18,19] CVD is a complication that mostly arises well beyond 2 years after delivery. With such limited follow up, there is a risk that women suffer morbidity that could possibly be prevented.

Both GDM and pre-eclampsia are associated with metabolic syndrome, a known risk factor for CVD.[20] There is a three-fold risk of metabolic syndrome in women with previous GDM, after adjusting for age and body mass index (BMI).[21] A review by Wu et al.[22] showed that women with pre-eclampsia have a two-fold risk of subsequent diabetes up to 10 years after pregnancy. One question that has arisen is whether women with both GDM and pre-eclampsia are at particularly high risk of later CVD. Pace et al. showed in their study in a Canadian population a significantly elevated risk for later CVD, in particular hypertension, if both GDM and pre-eclampsia were present. However, they were not able to adjust for maternal weight/BMI and did not assess for any effect modification by the degree of obesity.[23]

The aims of this study were to investigate if the adjusted association of pre-eclampsia with CVD is independent of GDM, and whether BMI or GDM are effect modifiers.

2 | METHODS

The population and study design in this paper have been previously described.[9] Data were obtained from Statistics Sweden and the Swedish National Board of Health and Welfare for the years 1991–2008. The data were linked using personal identification numbers issued to all residents. The Swedish Medical Birth register contains prospectively collected data on pregnancies and delivery from 1973 onwards. This register was validated in 2002 and the quality was considered high.[24] It includes data on 99% of all pregnancies with information on pregnancy, delivery and the early neonatal and postpartum period. The Patient Register started in 1964 and since 1987 has covered all of Sweden. It contains diagnoses for all discharged patients. Since 2001 it has also contained outpatient diagnoses (primary care not included). All public and private healthcare providers have been obliged to report to the register since 2001. The Cause of Death Register was used to identify death from CVD. CVD was defined as stroke, peripheral ischemic disease, atherosclerosis or ischemic heart disease including myocardial infarction. Cardiovascular disease or event was identified using the International Classification of Diseases, ninth and tenth revisions (ICD-9, ICD-10). Five controls were selected for each case. Statistics Sweden maintains the Total Population Register for information on vital status, region of residence and migration and also collects information on educational level. This register was used to collect controls.

Cases were defined as women with a pregnancy between 1991 and 2008 and a subsequent CVD event during the same period. Women with CVD before the index pregnancy were excluded. The index pregnancy was an identified pregnancy during the study period 1991–2008. Both multiparous and primiparous women were included, and the women could have pregnancies before or after this time period. Cases and controls were matched for age, but not for parity. They were also matched for year of birth and region in which they gave birth. Women with pre-gestational diabetes were excluded. A detailed description of inclusion and exclusion criteria is reported in the paper by Fadl et al.[9] Diagnosis of GDM was based on a 75-g oral glucose tolerance test with the diagnostic criteria of glucose measurements at least 6.1 mmol/L (capillary whole blood) or at least 7.0 mmol/L (plasma) (fasting) and/or a 2-hour glucose of at least 9.0 mmol/L (capillary whole blood) or at least 10.0 mmol/L (plasma). The diagnostic criteria for this period have been described in detail elsewhere.[4,25] BMI was calculated as body weight in kilogrammes divided by the square of height in meters. BMI was divided into categories according to the World Health Organization (normal weight >18.5 kg/m^2, overweight 25.0–29.99 kg/m^2, obese 30.0–34.99 kg/m^2, and severely obese ≥35.0 kg/m^2). Weight was measured at the first antenatal visit by midwives, which occurs in the first trimester; height was self-reported. At that visit the smoking status of the woman was also noted and was defined as current smoker or non-smoker in early pregnancy. Country of birth was divided into two groups; Nordic women (Sweden, Denmark, Finland, Norway and Iceland) and non-Nordic women. Pre-gestational hypertension (chronic hypertension) was defined as ICD 9 codes 642.0-2 or ICD-10 codes O10.0, O10.2, O10.4 or O 10.9. Pre-eclampsia was defined as occurrence for the first time of blood pressure of 140/90 mm Hg or higher and proteinuria of 0.3 g/day of greater after 20 weeks of gestation. Parity was divided into three categories; zero, one, or two or more previous births. Educational level was categorised into five groups; I, no education; II, compulsory school; III, post compulsory school; IV, further education; V, higher education. The information on educational level was collected as close to the index pregnancy as possible.

BJOG An International Journal of Obstetrics and Gynaecology

2.1 | Statistics

Conditional logistic regression was used to evaluate the associations of pre-eclampsia with CVD both unadjusted and adjusted for potential confounding variables; mother's BMI, parity, smoking habits, education level, chronic hypertension and country of birth (ethnicity). All independent variables were analysed on a categorical scale. The analysis strategy was as follows: (1) evaluating if the adjusted association of pre-eclampsia with CVD is independent of GDM, and (2) evaluating if the adjusted association of pre-eclampsia with CVD is modified by BMI and GDM by interaction tests. For the second strategy, stratified analysis was performed within normal weight, overweight and obese mothers but also across the combined strata of overweight/obese mothers because of data limitation in these groups and stratified by GDM. Analysis strategy (1) was also used when pre-eclampsia was categorised as mild and severe. Measure of association was odds ratio (OR) with 95% confidence intervals (CI) and A *P* value less than 0.05 was regarded as statistically significant. The statistical analyses were performed using STATA release 14 (Stata Corp, College Station, TX, USA) and IBM SPSS version 22 (IBM, Armonk, NY, USA).

3 | RESULTS

After exclusion of cases and controls with insufficient data on background characteristics or study exposures there were 2639 cases and 13 310 controls with 2614 cases and 10 160 matched controls eligible for the analysis. Among cases the majority (56.4%) had been diagnosed with ischaemic heart disease. The second most common diagnosis was ischaemic stroke (34.7%) and then peripheral ischaemic disease (7.3%) and atherosclerosis (4.5%). Mean age of included women at the time of diagnosis of CVD was 40.7 years ± 7.3 (standard deviation). Mean time interval from first pregnancy during the study period to cardiovascular event was 9.1 years ± 4.3.[9] Figure 1 shows the cumulative proportion of CVD cases after the index pregnancy for women with pre-eclampsia, GDM and women with both pre-eclampsia and GDM.

Table 1 shows the association of pre-eclampsia with CVD (unadjusted OR 2.75, 95% CI 2.28–3.32; adjusted OR 2.60, 95% CI 2.13–3.18 and OR further adjusted for GDM 2.59, 95% CI 2.12–3.17). In the last model, GDM showed an independent association with CVD (OR 1.47, 95% CI 1.04–2.09) as well as maternal BMI: overweight OR 1.31 (95% CI 1.18–1.46) and obese OR 1.90 (95% CI 1.64–2.19) compared with normal weight. No statistically significant interaction effect of BMI was found.

Stratifying by maternal BMI in Table 2, the adjusted association of pre-eclampsia with CVD did not change substantially, among normal weight (OR 2.65, 95% CI 1.90–3.69), overweight (OR 2.67, 95% CI 1.52–4.68) and obese (OR 3.03, 95% CI 0.74–12.4) women. Further adjustment for GDM showed similar findings.

Stratifying by GDM, the adjusted association of pre-eclampsia with CVD among women with GDM had an OR of 4.41 (95% CI 1.46–13.3) and for women without GDM the OR was 2.65 (95%CI 2.15–3.26).

Women with missing data for any of the variables used in the analysis did not differ by age, prevalence of GDM or ethnicity, but had a higher BMI compared with women with complete data.[9]

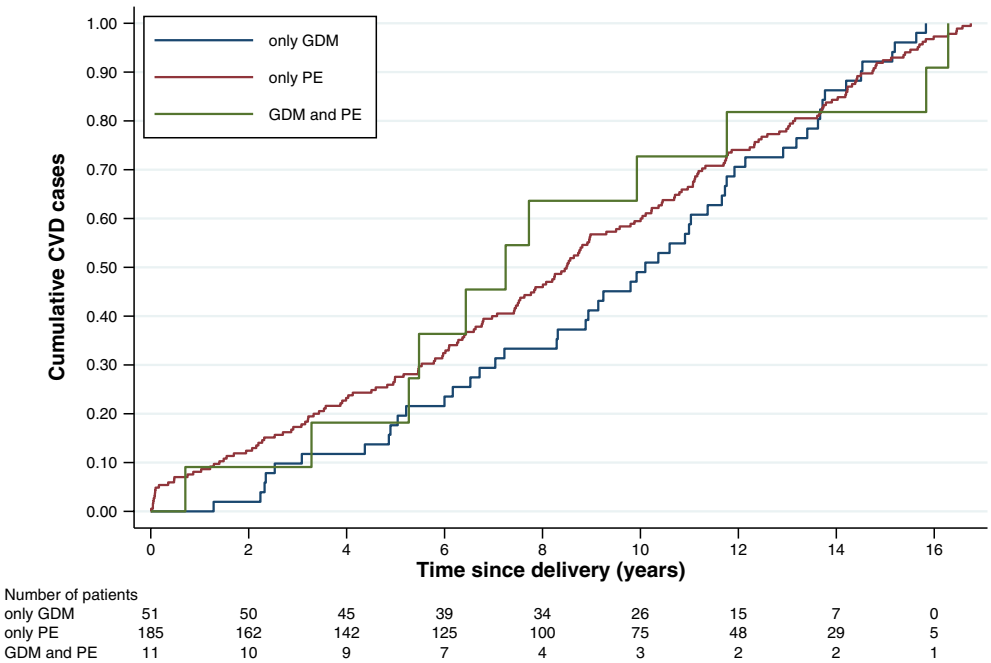

FIGURE 1 Cumulative proportion of cardiovascular disease (CVD) cases after the index pregnancy for women with pre-eclampsia (only PE), gestational diabetes mellitus (only GDM) and women with both gestational diabetes mellitus and pre-eclampsia (GDM and PE).

TABLE 1 Conditional logistic regression for pre-eclampsia associations with cardiovascular disease.

	Cases (n = 2639)	Controls (n = 13 310)	Unadjusted	Adjusted[a]	Adjusted[b]
	n (%)	n (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pre-eclampsia	196 (7.4)	364 (2.7)	2.75 (2.28–3.32)	2.60 (2.13–3.18)	2.59 (2.12–3.17)
GDM	62 (2.3)	148 (1.1)	2.19 (1.59–3.01)		1.47 (1.04–2.09)
BMI					
Under weight	62 (2.3)	336 (2.5)	1.11 (0.83–1.48)	0.98 (0.73–1.33)	0.99 (0.73–1.33)
Normal weight	1470 (55.7)	8942 (67.2)	Reference	Reference	Reference
Overweight	686 (26.0)	2981 (22.4)	1.43 (1.29–1.59)	1.31 (1.18–1.47)	1.31 (1.18–1.46)
Obese	421 (16.0)	1051 (7.9)	2.37 (2.07–2.71)	1.93 (1.67–2.23)	1.90 (1.64–2.19)
Interaction pre-eclampsia × BMI					
Pre-eclampsia × normal weight				Reference	Reference
Pre-eclampsia × overweight				0.99 (0.62–1.57)	0.99 (0.62–1.57)
Pre-eclampsia × obese				0.76 (0.45–1.29)	0.76 (0.45–1.29)
Pre-eclampsia × overweight or obese				0.94 (0.63–1.40)	0.93 (0.62–1.39)
Interaction GDM × BMI					
GDM × normal weight					Reference
GDM × overweight					4.10 (1.50–11.2)
GDM × obese					2.44 (0.93–6.37)
GDM × overweight or obese					3.43 (1.41–8.38)
Interaction pre-eclampsia × GDM					
Pre-eclampsia × non-GDM					Reference
Pre-eclampsia × GDM					1.28 (0.40–4.11)

Abbreviations: BMI, body mass index; CI confidence interval; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; OR, odds ratio.

[a]Pre-eclampsia association with CVD adjusted for BMI, chronic hypertension, smoking, ethnicity, education level and parity.

[b]Pre-eclampsia association with CVD adjusted for GDM, BMI, chronic hypertension, smoking, ethnicity, education level and parity.

4 | DISCUSSION

4.1 | Main findings

This national, nested case–control study shows that pre-eclampsia and GDM are statistically independent risk factors for later CVD. The pre-eclampsia association with CVD was present across BMI classes (except obesity, probably because of small numbers). The pre-eclampsia association with CVD was not modified by the presence of GDM. However, the number of cases and controls with both pre-eclampsia and GDM was low.

4.2 | Strengths and limitations

A strength of this study is that it is a national study using prospectively collected data from medical records that are collected in the national health registers. The registers have good coverage and are validated.[26–28] The study includes data on possible confounders, such as maternal BMI and educational level. The definition of CVD varies between studies, with inclusion of hypertension as a CVD category. It could be argued that hypertension is a mediator of CVD rather than a component of the diagnostic bundle and we therefore did not include chronic hypertension as a CVD outcome. The majority of cases with CVD in this study had a major event/condition (myocardial infarction, stroke). One limitation relates to the screening and diagnosis of GDM. Potential limitations include GDM being defined differently over the years in Sweden; and screening strategies have varied. Before the early 1990s, screening for GDM was not routine in all regions, and before introduction of the ICD-9 coding all diabetes forms during pregnancy had the same coding, making it impossible to get older reliable data on GDM pregnancies. In general, Swedish GDM criteria have used higher diagnostic thresholds, and therefore identify those with greater degrees of hyperglycaemia than many other nations. To handle any differences within Sweden between counties, the controls and cases in the same risk-set were from the same counties: this helped to eliminate confounding from differences in maternal health care and healthcare strategies in different counties. Another potential limitation is that there are several women with missing BMI in the beginning of the study period as it was not routinely measured in maternal health care at that time (routine measurements started in 1992). However, sensitivity analysis within the group with missing BMI did not reveal any major differences in the risk of CVD for these women. Another possible limitation was that women with diabetes before pregnancy were excluded.

BJOG An International Journal of Obstetrics and Gynaecology

TABLE 2 Conditional logistic regression for pre-eclampsia associations with cardiovascular disease stratified by body mass index and gestational diabetes mellitus.

Stratified by BMI					
Among normal weight (BMI 18.5 to <25 kg/m^2)					
	n (%)	*n* (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	Cases (*n* = 1470)	Controls (*n* = 8942)	Unadjusted	Adjusted[a]	Adjusted[b]
Pre-eclampsia	79 (5.4)	187 (2.1)	2.41 (1.75–3.30)	2.65 (1.90–3.69)	2.67 (1.92–3.72)
Among overweight (BMI 25 to <30 kg/m^2)					
	Cases (*n* = 686)	Controls (*n* = 2981)	Unadjusted	Adjusted[a]	Adjusted[b]
Pre-eclampsia	63 (9.2)	110 (3.7)	2.36 (1.41–3.94)	2.67 (1.52–4.68)	2.58 (1.47–4.53)
Among obese (BMI ≥30 kg/m^2)					
	Cases (*n* = 686)	Controls (*n* = 2981)	Unadjusted	Adjusted[a]	Adjusted[b]
Pre-eclampsia	52 (12.4)	63 (6.0)	4.46 (1.25–15.9)	3.03 (0.74–12.4)	3.43 (0.79–14.9)
Among overweight and obese (BMI ≥25 kg/m^2)					
	Cases (*n* = 1107)	Controls (*n* = 4032)	Unadjusted	Adjusted[a]	Adjusted[b]
Pre-eclampsia	115 (10.4)	173 (4.3)	2.48 (1.72–3.55)	2.42 (1.63–3.60)	2.38 (1.60–3.55)
Stratified by GDM					
Among GDM					
	n (%)	*n* (%)	OR (95% CI)	OR (95% CI)	
	Cases (*n* = 62)	Controls (*n* = 148)	Unadjusted	Adjusted[a,c]	
Pre-eclampsia	11 (17.7)	7 (4.7)	4.31 (1.57–11.8)	4.41 (1.46–13.3)	
Among non-GDM					
	Cases (*n* = 2577)	Controls (*n* = 13 162)	Unadjusted	Adjusted[a]	
Pre-eclampsia	185 (7.2)	357 (2.7)	2.75 (2.26–3.34)	2.65 (2.15–3.26)	

Abbreviations: BMI, body mass index; CI confidence interval; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; OR, odds ratio.

[a]Adjusted for BMI, chronic hypertension, smoking, ethnicity, education level, parity.

[b]Adjusted for BMI, chronic hypertension, smoking, ethnicity, education level, parity and GDM.

[c]No estimate due to small sample size in the matched analysis, instead unconditional logistic regression adjusted for matching variables mother's age (<20, 20–29, 30–39, ≥40 years) and year of birth (1991–95, 1996–2000, 2001–06) was used.

Type 2 diabetes in pregnancy is still uncommon in Sweden, approximately less than 0.3% of pregnancies during the time of this study.[29] It would also have been valuable to have data on family history of CVD.

4.3 | Interpretation, the interplay between GDM and pre-eclampsia

It has been shown that women with a history of GDM have vascular changes several years after pregnancy[30,31] and that pre-eclampsia is a disease primarily affecting blood vessels.[32] There are also studies that show similarities in maladaptation to pregnancy in pre-eclampsia and GDM (oxidative stress, dyslipidaemia and angiogenic imbalance), but it is not clear if these maladaptations arise from a common aetiology or are responses to different processes.[33] It has been shown in a recent study that women with GDM and women with pre-eclampsia have similar impairment in myocardial function in the third trimester.[34] Our study suggests that the relationship is independent, implying that there could be at least some different steps in the pathological processes, albeit with the same CVD end point.

A Canadian cohort study by Pace et al. studied the associations between gestational hypertension, GDM or the presence of both conditions with later CVD.[23] In that study it was concluded that the combination of gestational hypertension and GDM gave a 2.4 hazard ratio for later CVD, with the limitation that they were not able to adjust for maternal BMI.

There is evidence that women with GDM have an increased risk of developing pre-eclampsia[35] and it has previously been shown that the risk for pre-eclampsia is increased even among normal weight women with GDM.[36] Treatment of GDM reduces the risk for pre-eclampsia but whether the conditions share the same biological mechanisms is unclear.[37,38] On the other hand, there is some evidence that women with pre-eclampsia have an increased risk of GDM in a subsequent pregnancy or diabetes later in life.[39,40] In previous studies no adjustment was made for BMI, a risk factor and confounder for pre-eclampsia, GDM and CVD, leaving the possibility open that this relationship was partly due to these potential confounders.

Further work is needed to tease out how the patho-aetiological pathways to CVD differ and overlap between pre-eclampsia and GDM.

The risk of later CVD if you are exposed to pre-eclampsia during pregnancy has been shown to be elevated.[6,41–43] Whether CVD risk is mediated through hypertension after pregnancy is largely unknown and not reported in studies. Our findings suggest that the association of pre-eclampsia and later CVD is not affected in the same way by mothers' BMI in early pregnancy as is the case for GDM.[9] BMI greater than 25 kg/m^2 in early pregnancy is strongly associated with obesity and type 2 diabetes later in life.[44]

In spite of the CVD risk among women with past pre-eclampsia and/or GDM, evidence that intervention reduces this risk, or differs between these two independent CVD risk factors is limited. Furthermore, follow up of women with previous GDM appears to be limited and there are no conclusive data on when to commence screening for CVD risk factors.[18,19,45] Generally, monitoring and treatment of CVD risk factors are recommended when the 10-year risk is estimated to be approximately 10%.[46] The mean time to an event in these women was under 10 years and yet guidelines do not generally include past pre-eclampsia or past GDM as risk factors.[43,47] Besides pharmacological interventions to reduce CVD risk, prevention programmes involving lifestyle or metformin treatment have been shown to reduce or postpone type 2 diabetes mellitus incidence.[48–50]

When it comes to postpartum follow up after pre-eclampsia the situation is even worse than for women with GDM. There are few available studies on the evaluation of follow-up programmes for women with pre-eclampsia. Although there is no apparent international consensus on how prevention should be organised within healthcare systems, our data suggest that the risk is so high that standard interventions should either be tested through trials or simply put into place. These would include CVD risk factor monitoring and treatment and lifestyle programmes like the diabetes prevention programmes.[51] There is evidence that such programmes are difficult to implement because women often have wider commitments, including to their family.[52]

Ongoing efforts to reduce overweight and obesity could have an effect on the risk for GDM and subsequent type 2 diabetes mellitus, but BMI does not seem to be related to CVD events associated with pregnancies complicated by pre-eclampsia. Further studies are needed on prevention strategies to improve women's health.

5 | CONCLUSION

We have shown in this study that GDM and pre-eclampsia are statistically, independently associated with elevated risk for CVD later in life and the association of pre-eclampsia is similar in different BMI classes. In order to improve women's health, structured follow up with access to preventive healthcare postpartum and onwards through their lives, is needed.

AUTHOR CONTRIBUTIONS

KH, HB, AM, SM and UH designed the study, KH, HB and AM interpreted the data, KH, HB, DS and AM wrote the manuscript, and KH, HB, AM, SM, ES, UH and DS critically revised the manuscript.

ACKNOWLEDGEMENTS

Örebro County Council provided funding for Online Open Publication.

FUNDING INFORMATION

The study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement, research time for HB OLL-939071 and KH OLL- 961321.

CONFLICT OF INTEREST STATEMENT

Region Örebro Län payed the employer of DS to enable travels to Sweden. Completed disclosure of interests form available to view online as supporting information.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS APPROVAL

The study was approved by the regional Ethics Committee in Uppsala, Sweden, Number 2009/027, date of approval 2009-03-11.

ORCID

K. Hildén https://orcid.org/0000-0002-3707-6696
H. Backman https://orcid.org/0000-0002-2691-7525

REFERENCES

1. World Health Organization. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization; 2011. p. 176.
2. Wellfare SNBoHa. Statistics on Causes of Death 2016. 2017 Contract No.: 2017-9-11.
3. 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.
4. 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.
5. Burlina S, Dalfra MG, Chilelli NC, Lapolla A. Gestational diabetes mellitus and future cardiovascular risk: an update. Int J Endocrinol. 2016;2016:2070926.
6. 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.
7. Allen VM, Joseph K, Murphy KE, Magee LA, Ohlsson A. The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: a population based study. BMC Pregnancy Childbirth. 2004;4(1):17.
8. Roberts JM. Preeclampsia: what we know and what we do not know. Semin Perinatol. 2000;24(1):24–8.
9. Fadl H, Magnuson A, Ostlund I, Montgomery S, Hanson U, Schwarcz E. Gestational diabetes mellitus and later cardiovascular disease: a Swedish population based case-control study. BJOG. 2014;121(12):1530–6.

10. 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.
11. Christensen MH, Rubin KH, Petersen TG, Nohr EA, Vinter CA, Andersen MS, et al. Cardiovascular and metabolic morbidity in women with previous gestational diabetes mellitus: a nationwide register-based cohort study. Cardiovasc Diabetol. 2022;21(1):179.
12. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013;28(1):1–19.
13. McDonald EG, Dayan N, Pelletier R, Eisenberg MJ, Pilote L. Premature cardiovascular disease following a history of hypertensive disorder of pregnancy. Int J Cardiol. 2016;219:9–13.
14. Sharma S, Skog J, Timpka S, Ignell C. Preeclampsia and high blood pressure in early pregnancy as risk factors of severe maternal cardiovascular disease during 50-years of follow-up. Pregnancy Hypertens. 2021;26:79–85.
15. Ehrenthal DB, Maiden K, Rogers S, Ball A. Postpartum healthcare after gestational diabetes and hypertension. J Womens Health. 2014;23(9):760–4.
16. Stasenko M, Cheng YW, McLean T, Jelin AC, Rand L, Caughey AB. Postpartum follow-up for women with gestational diabetes mellitus. Am J Perinatol. 2010;27(9):737–42.
17. Olesen CR, Nielsen JH, Mortensen RN, Boggild H, Torp-Pedersen C, Overgaard C. Associations between follow-up screening after gestational diabetes and early detection of diabetes-a register based study. BMC Public Health. 2014;14:841.
18. Nijdam ME, Timmerman MR, Franx A, Bruinse HW, Numans ME, Grobbee DE, et al. Cardiovascular risk factor assessment after pre-eclampsia in primary care. BMC Fam Pract. 2009;10:77.
19. Haw JS, Galaviz KI, Straus AN, Kowalski AJ, Magee MJ, Weber MB, et al. Long-term sustainability of diabetes prevention approaches: a systematic review and meta-analysis of randomized clinical trials. JAMA Intern Med. 2017;177(12):1808–17.
20. Spaan JJ, Sep SJ, van Balen VL, Spaanderman ME, Peeters LL. Metabolic syndrome as a risk factor for hypertension after pre-eclampsia. Obstet Gynecol. 2012;120(2 Pt 1):311–7.
21. 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.
22. Wu P, Kwok CS, Haththotuwa R, Kotronias RA, Babu A, Fryer AA, et al. Pre-eclampsia is associated with a twofold increase in diabetes: a systematic review and meta-analysis. Diabetologia. 2016;59(12):2518–26.
23. Pace R, Brazeau AS, Meltzer S, Rahme E, Dasgupta K. Conjoint associations of gestational diabetes and hypertension with diabetes, hypertension, and cardiovascular disease in parents: a retrospective cohort study. Am J Epidemiol. 2017;186(10):1115–24.
24. The Swedish Medical Birth Register - A summary of content and quality. 2003 Available from: https://www.socialstyrelsen.se/register/halsodataregister/medicinskafodelseregistret/inenglish
25. Ostlund I, Hanson U. Occurrence of gestational diabetes mellitus and the value of different screening indicators for the oral glucose tolerance test. Acta Obstet Gynecol Scand. 2003;82(2):103–8.
26. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765–73.
27. 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.
28. 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.
29. Fadl HE, Simmons D. Trends in diabetes in pregnancy in Sweden 1998-2012. BMJ Open Diabetes Res Care. 2016;4(1):e000221.
30. 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.
31. Guimaraes MF, Brandao AH, Rezende CA, Cabral AC, Brum AP, Leite HV, et al. Assessment of endothelial function in pregnant women with preeclampsia and gestational diabetes mellitus by flow-mediated dilation of brachial artery. Arch Gynecol Obstet. 2014;290(3):441–7.
32. Tomimatsu T, Mimura K, Endo M, Kumasawa K, Kimura T. Pathophysiology of preeclampsia: an angiogenic imbalance and long-lasting systemic vascular dysfunction. Hypertens Res. 2017;40(4):305–10.
33. Weissgerber TL, Mudd LM. Preeclampsia and diabetes. Curr Diab Rep. 2015;15(3):9.
34. Thirunavukarasu S, Ansari F, Cubbon R, Forbes K, Chowdhary A, Jex N, et al. 137 gestational diabetes, preeclampsia and the maternal heart. Heart. 2022;108(Suppl 1):A103–A4.
35. Yogev Y, Chen R, Hod M, Coustan DR, Oats JJ, Metzger BE, et al. Hyperglycemia and adverse pregnancy outcome (HAPO) study: preeclampsia. Am J Obstet Gynecol 2010;202(3):255.e1-7.
36. Hilden K, Hanson U, Persson M, Fadl H. Overweight and obesity: a remaining problem in women treated for severe gestational diabetes. Diabet Med. 2016;33:1045–51.
37. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352(24):2477–86.
38. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009;361(14):1339–48.
39. Lee J, Ouh YT, Ahn KH, Hong SC, Oh MJ, Kim HJ, et al. Preeclampsia: a risk factor for gestational diabetes mellitus in subsequent pregnancy. PLoS One. 2017;12(5):e0178150.
40. 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.
41. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974.
42. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2):e003497.
43. Malek AM, Wilson DA, Turan TN, Mateus J, Lackland DT, Hunt KJ. Maternal coronary heart disease, stroke, and mortality within 1, 3, and 5 years of delivery among women with hypertensive disorders of pregnancy and pre-pregnancy hypertension. J Am Heart Assoc. 2021;10(5):e018155.
44. Moll U, Olsson H, Landin-Olsson M. Impact of Pregestational weight and weight gain during pregnancy on long-term risk for diseases. PLoS One. 2017;12(1):e0168543.
45. Groenhof TKJ, van Rijn BB, Franx A, Roeters van Lennep JE, Bots ML, Lely AT. Preventing cardiovascular disease after hypertensive disorders of pregnancy: searching for the how and when. Eur J Prev Cardiol. 2017;24(16):1735–45.
46. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham heart study. Circulation. 2008;117(6):743–53.
47. Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, et al. Adverse pregnancy outcomes and cardiovascular disease risk: unique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. Circulation. 2021;143(18):e902–e16.
48. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, et al. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the diabetes prevention program outcomes study 10-year follow-up. J Clin Endocrinol Metab. 2015;100(4):1646–53.

49. Lindstrom J, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aunola S, Keinanen-Kiukaanniemi S, et al. Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish diabetes prevention study (DPS). Diabetologia. 2013;56(2):284–93.
50. Diabetes Prevention Program Research Group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited Most in the diabetes prevention program and diabetes prevention program outcomes study. Diabetes Care. 2019;42(4):601–8.
51. Diabetes Prevention Program Outcomes Study Research Group, Orchard TJ, Temprosa M, Barrett-Connor E, Fowler SE, Goldberg RB, et al. Long-term effects of the diabetes prevention program interventions on cardiovascular risk factors: a report from the DPP outcomes study. Diabet Med. 2013;30(1):46–55.
52. O'Reilly SL, Dunbar JA, Versace V, Janus E, Best JD, Carter R, et al. Mothers after gestational diabetes in Australia (MAGDA): a randomised controlled trial of a postnatal diabetes prevention program. PLoS Med. 2016;13(7):e1002092.

SUPPORTING INFORMATION

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

How to cite this article: Hildén K, Magnuson A, Montgomery S, Schwarcz E, Hanson U, Simmons D, et al. Previous pre-eclampsia, gestational diabetes mellitus and the risk of cardiovascular disease: A nested case–control study in Sweden. BJOG. 2023;130(10):1209–1216. https://doi.org/10.1111/1471-0528.17454