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Original research

Severity of obstructive coronary artery stenosis after pre-eclampsia

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2022-321513).

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Received 14 June 2022
Accepted 29 September 2022
Published Online First 21 October 2022

ABSTRACT

Introduction Women with a history of pre-eclampsia are at higher risk of premature coronary artery disease. Assessment of obstructive coronary artery stenosis by invasive coronary angiography has not been evaluated after pre-eclampsia.

Methods A population-based cohort study was completed in Ontario, Canada, where there is universal healthcare and collection of angiographic data. Included were women with a live birth or stillbirth from 2002 to 2020, and without known heart disease. One birth was randomly selected per woman. The main exposure compared women with versus without pre-eclampsia. The primary outcome was angiographically established obstructive coronary artery stenosis, assessed starting 42 days after the index birth. Cause-specific hazard models accounting for competing risks generated HRs, adjusted for age, parity, income, rurality, diabetes, chronic hypertension, renal disease, substance use and dyslipidaemia.

Results Among 42 252 women ever with pre-eclampsia and 1359 122 never with pre-eclampsia, mean age was 31.1 years and 30.6 years, respectively. After 9 years of follow-up, obstructive coronary artery stenosis occurred in 186 women with pre-eclampsia (4.53 per 10 000 person-years) versus 1237 women without pre-eclampsia (0.97 per 10 000 person-years)—an unadjusted HR 4.41 (95% CI 3.78 to 5.14) and adjusted HR 2.07 (95% CI 1.77 to 2.43). Relative to those with neither, the adjusted HR for coronary stenosis was highest in women with pre-eclampsia and preterm birth (3.11, 95% CI 2.51 to 3.87), or pre-eclampsia and stillbirth (2.80, 95% CI 1.05 to 7.47).

Conclusions Pre-eclampsia is associated with a greater risk of premature-onset obstructive coronary artery stenosis, especially when it is complicated by a preterm birth or a stillbirth.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Existing research has described the onset of premature coronary artery disease in women with a history of prior pregnancy complications, including pre-eclampsia and preterm birth.
⇒ What has not been studied, however, is an objective comparison of women with and without a history of pre-eclampsia and the severity of obstructive coronary artery stenosis by invasive coronary angiography

WHAT THIS STUDY ADDS

⇒ This population-based cohort study was completed within a universal healthcare system.
⇒ Prior pre-eclampsia was associated with a doubling of the risk of obstructive coronary artery stenosis, and a near tripling of that risk following pre-eclampsia with preterm birth or stillbirth.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Among pre-eclampsia-affected women, guidelines generally recommend annual assessment and management of blood pressure, body mass index and glucose.
⇒ Whether these recommended steps can attenuate the progression to obstructive coronary artery stenosis in women with pre-eclampsia, especially those concomitantly experiencing preterm birth, stillbirth or another adverse perinatal condition, remains to be determined.

INTRODUCTION

Women with a history of pre-eclampsia, particularly those with early onset pre-eclampsia complicated by preterm delivery or a stillbirth, have a higher risk of premature coronary artery disease (CAD) and heart failure compared with non-pre-eclamptic women.[1–5] This premature risk is akin to their age-matched male counterparts, and is only partly explained by other cardiac factors, such as diabetes mellitus and chronic hypertension, with at least a doubling of risk persisting after accounting for such risk factors.[6 7] The accelerated onset of premature CAD associated with pre-eclampsia—especially pre-eclampsia coupled with a preterm birth or stillbirth[8]—is correlated with a greater number of malperfusion lesions within the maternal circulation of the placenta at the index birth.[9] A decade after their affected pregnancy, these women display a more atherogenic lipid profile, higher blood pressure and corresponding microvascular rarefaction.[9] Moreover, women with prior pre-eclampsia who later develop CAD also experience worse outcomes after coronary revascularisation.[10]

A multitude of publications describe the future risk of CAD in the years that follow a pregnancy.[1 3] Existing research has also described measures of coronary artery calcification using non-invasive coronary CT angiography (CCTA) in women with and without a history of prior

► http://dx.doi.org/10.1136/heartjnl-2022-321877

To cite: Ray JG, Austin PC, Park AL, *et al*. *Heart* 2023;**109**:449–456.

pregnancy complications.[11–13] What has not been studied, however, is an objective comparison of women with and without a history of pre-eclampsia and the severity of coronary artery stenosis by invasive coronary angiography, including multivessel disease or concomitant reduced left ventricular ejection fraction (LVEF).

The current study, completed within a real-world setting of universal healthcare access, evaluated the risk of angiographically proven stenotic CAD, CAD severity and multivessel disease with reduced LVEF, in women with prior pre-eclampsia, including pre-eclampsia necessitating preterm delivery or pre-eclampsia resulting in a stillbirth.

METHODS

This population-based cohort study was conducted in Ontario, Canada, where there is universal access to obstetrical and cardiac care on an inpatient and outpatient basis through the Ontario Health Insurance Plan (OHIP). All study data exist within administrative health data sets, detailed in online supplemental table S1 and elsewhere.[2 5 6 10] All hospital births, outpatient and inpatient encounters, and coronary angiography procedures (https://www.ices.on.ca/Research/Research-programs/Cardiovascular/CCN) are captured in these data sets, which are linked using unique encoded identifiers and analysed at ICES (https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx). Use of data is authorised under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Participants

We included all women in Ontario aged 16–50 years who had an obstetrical live birth or stillbirth at ≥20 weeks' gestation, between 1 January 2002 and 31 March 2020—the former corresponding to the adoption of the International Classification of Diseases, Tenth Revision in Canada. Women who *ever* had a pre-eclamptic pregnancy during the study period comprised the pre-eclampsia-exposed group, from which one randomly selected pregnancy was chosen as the index birth for each woman. From the unexposed non-pre-eclampsia group—namely, all other eligible women who *never* had pre-eclampsia in any pregnancy within the study period—one pregnancy was also randomly selected as the index birth. Pre-eclampsia was based on new-onset hypertension with proteinuria or another target organ effect, such as a seizure (eclampsia) or the HELLP syndrome (ie, haemolysis, elevated liver enzymes and a low platelet count). The diagnostic criteria for pre-eclampsia were largely unchanged during the study period.[14 15]

We excluded women diagnosed with any form of heart disease between 3 years prior to the index birth to 42 days after hospital discharge for the index birth, or those who had coronary angiography within that same timeframe (online supplemental table S1). Also excluded were women who died within 42 days after the index birth, and those without a valid health insurance number, to enable linkage of administrative data sets. Exclusion of those with events within 42 days after birth (the conventional postpartum period)[16] was to ensure that the need for coronary angiography was not a direct consequence of a pregnancy complication, such as a peripartum cardiomyopathy or spontaneous coronary artery dissection,[17] and that each woman survived past the postpartum period. All eligible women were followed to the earliest of their first coronary angiography, death, loss of OHIP eligibility, (eg, due to outmigration from Ontario) and end of our observation period determined by availability of data (31 December 2020).

Outcomes

Our primary study outcome was *obstructive coronary artery stenosis* identified at the time of coronary artery angiography,

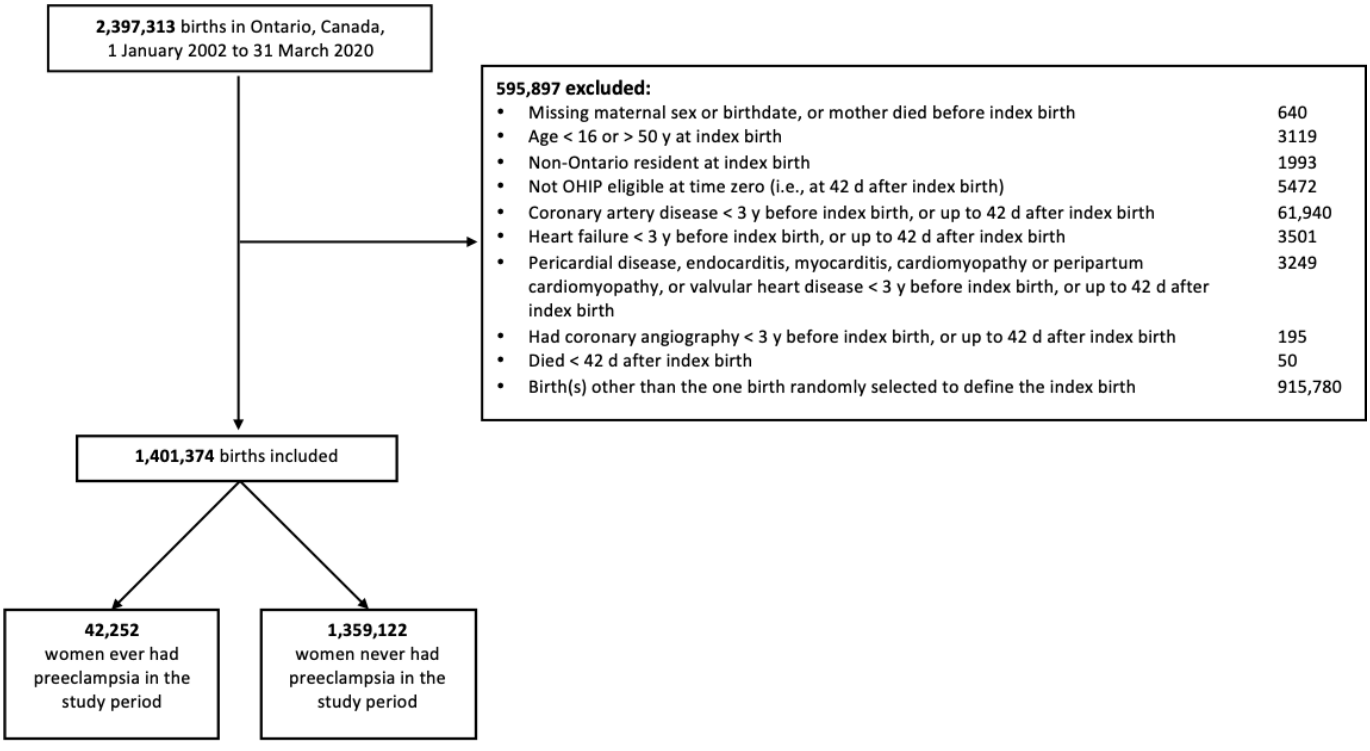


Figure 1 Study flow diagram for creation of the cohort of women with and women pre-eclampsia, between 2002 and 2020. d, days; OHIP, Ontario Health Insurance Plan; y, years.

Table 1 Characteristics of women with and without a history of pre-eclampsia during the study period of January 2002 to March 2020

Characteristic	Women with pre-eclampsia (n=42 252)	Women without pre-eclampsia (n=1 359 122)	Standardised difference between women with versus without pre-eclampsia
At the index birth			
Mean (SD) age, years	31.1 (5.7)	30.6 (5.5)	0.09
Income quintile (Q)			
Q1 (lowest)	9702 (23.0)	300 310 (22.1)	0.02
Q2	8509 (20.1)	273 950 (20.2)	0.0
Q3	8777 (20.8)	277 962 (20.5)	0.01
Q4	8556 (20.2)	278 771 (20.5)	0.01
Q5 (highest)	6465 (15.3)	223 323 (16.4)	0.03
Missing	243 (0.6)	4806 (0.4)	0.03
Rural residence	5455 (12.9)	125 209 (9.2)	0.12
Unknown residence	35 (0.1)	1281 (0.1)	0.0
Median (IQR) parity	1 (0–1)	1 (0–1)	NR
Singleton pregnancy	40 096 (94.9)	1 331 386 (98.0)	0.17
Mean (SD) prepregnancy body mass index, kg/m^2*	26.0 (6.4)	24.4 (5.1)	0.27
Conditions ≤365 days before the index date			
Prepregnancy diabetes mellitus	5526 (13.1)	105 565 (7.8)	0.17
Chronic hypertension	8377 (19.8)	35 993 (2.6)	0.57
Dyslipidaemia	387 (0.9)	10 478 (0.8)	0.02
Renal disease	774 (1.8)	4710 (0.3)	0.14
Drug dependence or tobacco use	690 (1.6)	19 774 (1.5)	0.01
Conditions at the index birth			
Preterm birth <37 weeks' gestation	11 426 (27.0)	91 354 (6.7)	0.56
Stillbirth	464 (1.1)	6440 (0.5)	0.07
Median (IQR) no. years of follow-up, from time zero	10 (4–15)	9 (4-14)	NR
Total no. person-years of follow-up, from time zero	410 259	12 754 500	NR
Total no. receiving coronary angiography during follow-up	474 (1.1)	5238 (0.4)	0.09
Median (IQR) no. years to coronary angiography, if received, from time zero	10.1 (5.8–13.5)	9.9 (6.3–13.4)	NR
Total no. deaths, from time zero	309 (0.7)	6821 (0.5)	0.03
Total no. followed to end of study of 31 December 2020	40 189 (95.1%)	1 291 538 (95.0%)	0.0
Total no. lost to follow-up before end of study of 31 December 2020	1280 (3.0%)	55 525 (4.1%)	0.06

All data are presented as number (%) unless otherwise indicated.
*Body mass index was known among 7995 women with and 286 836 women without pre-eclampsia.
NR, not reportable.

performed at least 42 days after the index delivery discharge (time zero). Coronary artery stenosis was defined as having any of the following affected coronary arteries: (1) Left main (LM) ≥50% luminal diameter stenosis, (2) Proximal, mid or distal left anterior descending (LAD) ≥70% stenosis, (3) Mid or distal LAD ≥70% stenosis, (4) Left circumflex ≥70% stenosis, or (5) Right coronary artery (RCA) ≥70% stenosis.[18 19]

A secondary outcome was coronary angiography with the presence of *multivessel obstructive coronary artery stenosis*, defined as: (1) Coronary angiography but no stenotic disease (< 50% stenosis in all coronary artery branches); (2) One-vessel disease (≥70% stenosis in one coronary artery, excluding the LM); (3) Two-vessel disease (≥70% stenosis in two coronary arteries, or ≥50% stenosis of the LM); or (4) Three-vessel disease (≥70% stenosis in three coronary arteries, or ≥50% stenosis in the LM and also ≥70% stenosis in the RCA).[20] Another secondary outcome was *stenotic CAD with reduced LVEF*, defined as the presence of obstructive coronary artery stenosis (see primary outcome description) with a LVEF <50%, estimated by contrast left ventriculography at the time of coronary artery angiography.[21] As a conservative approach, a woman without obstructive coronary artery stenosis who had reduced LVEF or did not undergo ventriculography was classified as being outcome-free.

Statistical analysis

Characteristics of women with pre-eclampsia and their non-pre-eclamptic counterparts were compared using means, proportions and standardised differences of means. Where continuous data were not normally distributed (eg, parity), we reported a median and IQR, without assessing a corresponding standardised difference. Incidence rates for outcomes were calculated as the number of eligible women experiencing the outcome per 10 000 years of follow-up. Due to low event counts, 95% CIs were calculated based on the gamma distribution.

For each study outcome, cause-specific hazard modelling was performed, which accounted for the competing risks of death, outmigration from Ontario and loss of OHIP eligibility. Cause-specific hazards models are equivalent to a Cox proportional hazards model that censors on those events that might occur before, and therefore, prevent a participant from experiencing the outcome of interest.[22] Women were censored at the earliest of receiving coronary angiography, occurrence of a competing

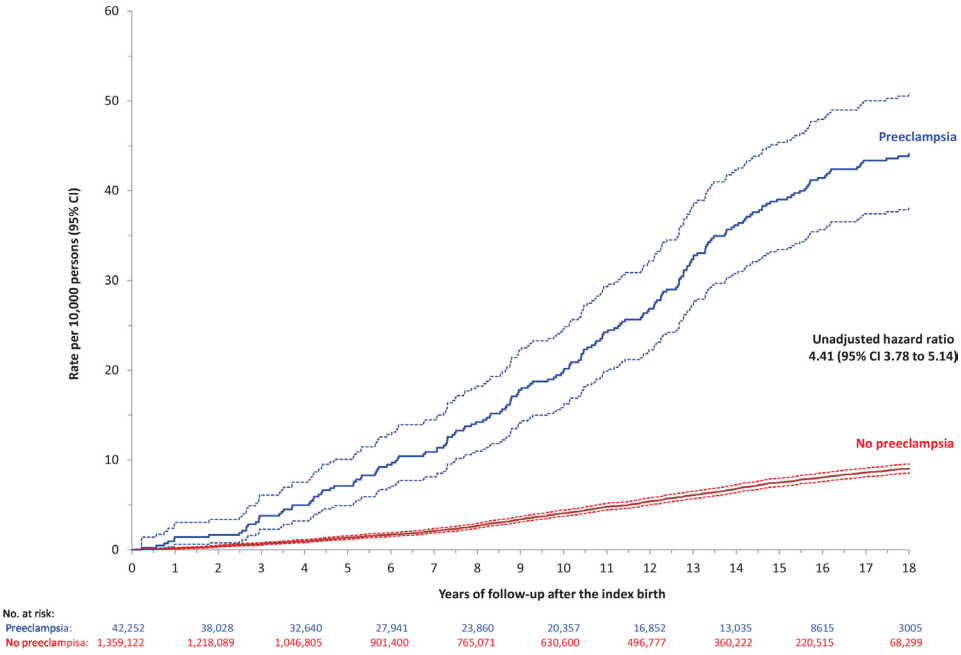


Figure 2 Rate of angiographically demonstrated obstructive coronary artery stenosis among women with versus without a history of pre-eclampsia, assessed starting 42 days after the index birth hospitalisation discharge date.

risk event or arrival at the end of the study observation period (31 December 2020).

Covariates in the first adjusted model were maternal age, parity, neighbourhood income quintile, rural residence, type 1 or type 2 diabetes mellitus, chronic hypertension, renal disease, drug dependence/tobacco use and dyslipidaemia within 365 days preceding the index date. In a second, fully adjusted model, diabetes mellitus, chronic hypertension, renal disease, drug dependence/tobacco use and dyslipidaemia were included as time-varying covariates—each assessed from the index date to the end of follow-up.

The same approach to the main model was used in comparing women with versus without a history of pre-eclampsia and a concomitant (ie, same index pregnancy) preterm live birth <37 weeks' gestation, as well as in comparing women with versus without a history of pre-eclampsia and a concomitant stillbirth.

For the secondary outcome of multivessel obstructive coronary artery stenosis among women with versus without prior pre-eclampsia, we fit separate cause-specific hazard models for each of (1) Angiography with <50% stenosis in all coronary artery branches; (2) Angiography with ≥70% stenosis in one coronary artery; (3) Angiography with ≥70% stenosis in two coronary arteries, or ≥50% stenosis of the LM; (4) Angiography with ≥70% stenosis in three coronary arteries, or ≥50% stenosis in the LM and also ≥70% stenosis in the RCA; and (5) Death. For the secondary outcome of obstructive coronary artery stenosis with reduced LVEF, modelling was like that in the main model.

As prepregnancy body mass index (BMI) was only recorded for about 20% of births, mostly in the later years of the study period, it was added to the main model, which then only comprised that smaller subset of births (additional analysis #1).

A re-analysis of the main model started with each woman's *first* birth in the study period, and assessed pre-eclampsia as a time-varying exposure (additional analysis #2a), including by the number of times pre-eclampsia occurred (0, 1 or ≥2 times) (additional analysis #2b).

All statistical analyses were performed using SAS V.9.4 for UNIX (SAS Institute). Cause-specific hazard modelling was conducted using the PROC PHREG procedure.

Patient and public involvement

No patient was consulted or involved in this study.

Did we involve patients/service users/carers/lay people in the design of this study? No.

Was the development of outcome measures informed by patients' priorities, experience and preferences? No.

Were patients/carers/laypeople involved in the recruitment to and conduct of the study? No.

How will the results be disseminated to study participants? Not applicable.

Are patients/carers/laypeople thanked in the contributorship statement/acknowledgements? Not applicable.

Was the development of the research question and outcome measures informed by patients' priorities, experience and preferences? No.

RESULTS

There were 2397313 identified births in Ontario during the study period, of which 1401374 (58.5%) were randomly selected to form the study cohort, and in which 42252 (3.1%) formed the pre-eclampsia exposed group and 1359122 (96.9%) the non-pre-eclampsia group (figure 1).

The mean (SD) age at study entry was 31.1 (5.7) years and 30.6 (5.5) years in the pre-eclampsia and non-pre-eclampsia groups, respectively, with largely similar demographic characteristics at baseline (table 1).

Contrasting women with pre-eclampsia with their non-pre-eclampsia counterparts, important standardised differences >0.10 were seen for more multifetal pregnancies, diabetes mellitus, chronic hypertension and renal disease among women with pre-eclampsia, as well as a higher rate of preterm birth before 37 weeks' gestation (table 1). The proportion of deaths

Table 2 Risk of developing obstructive coronary artery stenosis among women with versus without a history of pre-eclampsia, January 2002 to March 2020

Exposure group	Number of women with obstructive coronary artery stenosis (incidence rate per 10 000 person-years, 95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)*	Fully adjusted HR (95% CI)†
Women without pre-eclampsia (n=1 359 122)	1237 (0.97, 0.92 to 1.03)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Women with pre-eclampsia (n=42 252)	186 (4.53, 3.91 to 5.23)	4.41 (3.78 to 5.14)	2.75 (2.31 to 3.26)	2.07 (1.77 to 2.43)

The time zero index date starts 42 days after the index birth hospitalisation discharge date.
*Adjusted for maternal age, parity, neighbourhood income quintile (1 or missing, 2, 3, 4, 5), residence (rural, urban or missing) at the time of the index delivery, as well as diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use and dyslipidaemia within 365 days preceding the index date.
†Further adjusted for time-varying diabetes mellitus, chronic hypertension, renal disease, drug dependence or tobacco use, and dyslipidaemia—each arising at time zero onwards, up to the day before the coronary angiography.

after time zero did not differ between women with (0.7%) and without (0.5%) pre-eclampsia, while 95.1% and 95.0%, were followed to the end of the study period (31 December 2020), and 3.0% and 4.1% were lost to follow-up, respectively (table 1).

After a median (IQR) duration of follow-up of 9 (4–14) years, 474 women with pre-eclampsia (1.1%) and 5238 women without pre-eclampsia (0.4%) underwent coronary angiography at least 42 days after the index birth hospital discharge date. Those with pre-eclampsia underwent angiography after a median (IQR) of 10.1 (5.8–13.5) years from the index date, which was not notably different than those without pre-eclampsia (9.9 (6.3–13.4)) years.

Main outcome

New-onset angiographically proven obstructive coronary artery stenosis occurred among 186 women (4.53 per 10 000 person-years) with, and 1237 (0.97 per 10 000 person-years) without, pre-eclampsia—an unadjusted HR of 4.41 (95% CI 3.78 to 5.14) (figure 2 and table 2).

The HRs were 2.75 (95% CI 2.31 to 3.26) on adjusting for baseline covariates, and 2.07 (95% CI 1.77 to 2.43) after further including time-varying covariates. On further adjusting for maternal BMI among the 294 831 (21.0%) of births in whom BMI was available, the respective HRs were 3.30 (95% CI 1.90 to 5.72) and 1.94 (95% CI 1.17 to 3.21) (additional analysis #1, online supplemental table S2).

Relative to women without pre-eclampsia or concomitant preterm birth, the fully adjusted HR was 1.63 (95% CI 1.42 to 1.88) in those with preterm birth alone, 1.81 (95% CI 1.45 to 2.26) after pre-eclampsia alone, and 3.11 (95% CI 2.51 to 3.87) following pre-eclampsia with concomitant preterm birth (table 3).

In the analysis of women with combinations of pre-eclampsia and/or stillbirth, relative to women neither, the risk for obstructive coronary artery stenosis was highest in those with pre-eclampsia and stillbirth together (adjusted HR 2.80, 95% CI 1.05 to 7.47), although, based on a small number of events (table 4).

On starting time zero from each woman's *first* birth, and handling pre-eclampsia as a time-varying exposure, the adjusted HR for obstructive coronary artery stenosis was 1.72 (95% CI 1.40 to 2.11) (additional analysis #2 a, online supplemental table S3). The rate of obstructive coronary artery stenosis increased non-significantly by the number of pre-eclampsia-affected births, although there were only six events in women who had pre-eclampsia at least twice (additional analysis #2b, online supplemental table S3).

Secondary outcomes

Among the 5712 women who underwent coronary angiography, 1016 (18.7%) met the criteria for one-vessel disease, 272 (5.0%) for two-vessel disease and 135 (2.5%) for three-vessel stenosis (online supplemental figure S1). Relative to women without a history of pre-eclampsia, those with pre-eclampsia had an increasingly higher adjusted HR for one-vessel (1.82, 95% CI 1.49 to 2.24), two-vessel (2.61, 95% CI 1.88 to 3.61) and three-vessel (2.62, 95% CI 1.69 to 4.04) stenosis, while the competing risk of death was not elevated (adjusted HR 0.86, 95% CI 0.76 to 0.96) (online supplemental figure S1).

Left ventriculography was performed among 263 of the 474 women (55.5%) in the pre-eclampsia group who underwent coronary angiography, and 3086 of the 5238 women (58.9%) in the non-pre-eclampsia group who had coronary angiography. Comparing those with versus without a history of pre-eclampsia,

Table 3 Risk of developing obstructive coronary artery stenosis among women with versus without a history of pre-eclampsia and a concomitant preterm live birth before 37 weeks' gestation

Exposure group	Number of women with obstructive coronary artery stenosis (incidence rate per 10 000 person years, 95% CI)	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)*
Neither pre-eclampsia nor concomitant preterm birth (n=1211 021)	965 (0.85, 0.80 to 0.91)	1.00 (referent)	1.00 (referent)
No pre-eclampsia, but had a preterm birth (n=141 661)	250 (1.80, 1.58 to 2.03)	2.09 (1.82 to 2.41)	1.63 (1.42 to 1.88)
Pre-eclampsia, but no preterm birth (n=27 208)	88 (3.28, 2.63 to 4.04)	3.51 (2.82 to 4.37)	1.81 (1.45 to 2.26)
Pre-eclampsia and concomitant preterm birth (n=14 580)	95 (6.93, 5.61 to 8.48)	8.10 (6.56 to 10.01)	3.11 (2.51 to 3.87)

This analysis was limited to women with a live birth in the index pregnancy, January 2002 to March 2020. The time zero index date starts 42 days after the index birth hospitalisation discharge date.
*Adjusted for maternal age, parity, neighbourhood income quintile (1 or missing, 2, 3, 4, 5), residence (rural, urban or missing) at the time of the index delivery, as well as diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidaemia within 365 days preceding the index date, and further adjusted for time-varying diabetes mellitus, chronic hypertension, renal disease, drug dependence or tobacco use, and dyslipidaemia—each arising at time zero onward up to the day before the coronary angiography.

Table 4 Risk of developing obstructive coronary artery stenosis among women with versus without a history of pre-eclampsia and a concomitant stillbirth, January 2002 to March 2020

Exposure group	Number of women with obstructive coronary artery stenosis (incidence rate per 10 000 person years, 95% CI)	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)*
No pre-eclampsia; live birth (n=1,344,626)	1193 (0.95, 0.89 to 1.0)	1.00 (referent)	1.00 (referent)
No pre-eclampsia; stillbirth (n=14 496)	44 (3.0, 2.2 to 4.0)	2.99 (2.21 to 4.04)	1.94 (1.43 to 2.62)
Pre-eclampsia; live birth (n=41 715)	182 (4.5, 3.9 to 5.2)	4.48 (3.83 to 5.24)	2.11 (1.79 to 2.47)
Pre-eclampsia; stillbirth (n=537)	< 6 (7.2, 2.0 to 18.3)	6.96 (2.60 to 18.62)	2.80 (1.05 to 7.47)

The time zero index date starts 42 days after the index birth hospitalisation discharge date.
*Adjusted for maternal age, parity, neighbourhood income quintile (1 or missing, 2, 3, 4, 5), residence (rural, urban or missing) at the time of the index delivery, as well as diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidaemia within 365 days preceding the index date, and further adjusted for time-varying diabetes mellitus, chronic hypertension, renal disease, drug dependence or tobacco use, and dyslipidaemia—each arising at time zero onward up to the day before the coronary angiography.

Table 5 Risk of developing obstructive coronary artery stenosis with concomitant reduced left ventricular ejection fraction (LVEF) <50% among women with versus without a history of pre-eclampsia, January 2002 to March 2020*

Exposure group	Number of women with obstructive coronary artery stenosis and reduced LVEF (incidence rate per 10 000 person years, 95% CI)	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)†
Women without pre-eclampsia (n=1 358 335)	140 (0.11, 0.09 to 0.13)	1.00 (referent)	1.00 (referent)
Women with pre-eclampsia (n=42 140)	22 (0.54, 0.34 to 0.81)	4.64 (2.96 to 7.28)	2.03 (1.27 to 3.24)

The time zero index date starts 42 days after the index birth hospitalisation discharge date.
An overview of the study findings can be found in the central figure (figure 3).
*Left ventriculography was performed among 263 of the 474 women (55.5%) in the pre-eclampsia group who underwent coronary angiography, and 3086 of the 5238 women (58,9%) in the non-pre-eclampsia group who had coronary angiography.
†Adjusted for maternal age, parity, neighbourhood income quintile (1 or missing, 2, 3, 4, 5), residence (rural, urban or missing) at the time of the index delivery, as well as diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidaemia within 365 days preceding the index date, and further adjusted for time-varying diabetes mellitus, chronic hypertension, renal disease, drug dependence or tobacco use, and dyslipidaemia—each arising at time zero onwards up to the day before the coronary angiography.

the associated HR for obstructive coronary artery stenosis with an LVEF <50% was 4.64 (95% CI 2.96 to 7.28), which was only partially attenuated after adjusting for all confounders (HR 2.03, 95% CI 1.27 to 3.24) (table 5).

DISCUSSION

In this large population-based cohort study, completed within a universal healthcare system, a history of pre-eclampsia was associated with a greater risk of obstructive coronary artery stenosis, and greater disease severity characterised by multivessel CAD, and obstructive coronary artery stenosis with reduced LVEF. The risk of coronary artery stenosis was notably more pronounced in women with pre-eclampsia and preterm birth, and perhaps, with a simultaneous stillbirth (figure 3).

Strengths and limitations

In contrast to prior studies, our ability to leverage angiography testing at a province-wide level enabled us to not only evaluate for coronary artery stenosis, but also the degree of disease severity. By excluding women with pre-existing heart disease and assessing study outcomes starting at 42 days after discharge from the index birth hospitalisation, our results also avoided the described higher short-term risk of coronary artery dissection or heart failure as a direct consequence of uncontrolled blood pressure with acute pre-eclampsia.[17 23 24]

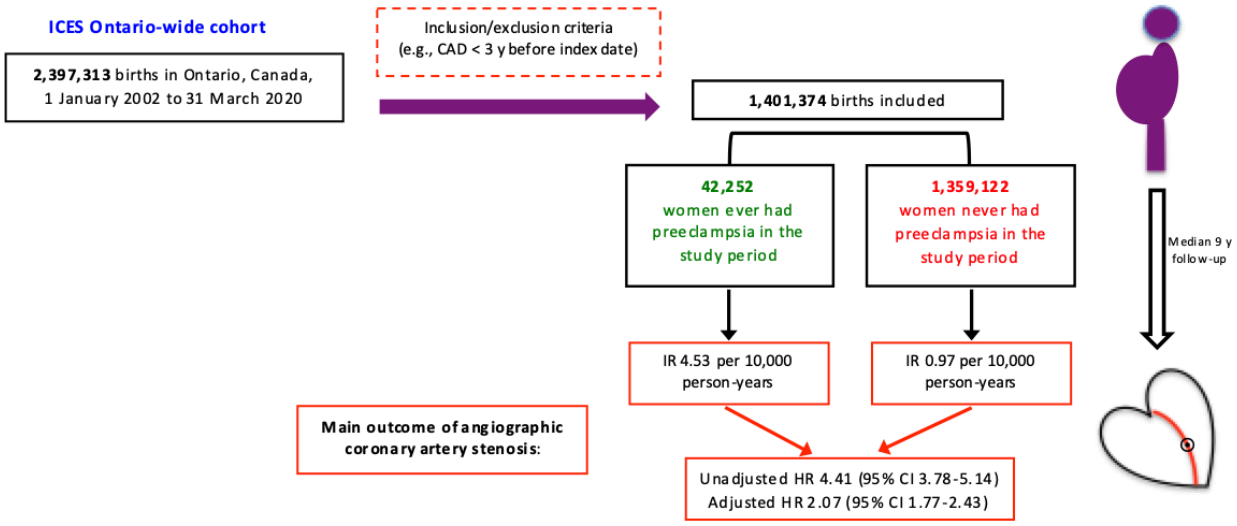
The main model considered one birth randomly selected per woman, and defined a history of pre-eclampsia exposure as that arising at any time during the study period. This was a practical consideration for the applied clinical setting, in which a clinician assessing a woman's cardiac risk would inquire about her ever having a history of pre-eclampsia, regardless of which pregnancy was affected. Since those with and without a history of pre-eclampsia had a median parity of 1, and about the same duration of follow-up (median (IQR) 10 (4–15) vs 9 (4–14) years, respectively), it is unlikely that this approach generated biased risk estimates. Moreover, HRs were only slightly attenuated by starting at the first birth, and assessing pre-eclampsia as a time-varying exposure. While we also attempted to evaluate the influence of repeat pregnancies affected by pre-eclampsia,[25 26] there were only six outcome events among women who had at least two pre-eclampsia-affected births.

We accounted for major factors that may confound the relation between pre-eclampsia and coronary artery stenosis, such as diabetes mellitus and chronic hypertension, both at baseline and in a time-varying manner. However, we did not have information on lipid concentrations, measures of blood pressure or glycaemic control, family history of heart disease, educational level attained, concurrent medications or quantity of smoking. Certainly, the low rates of drug dependence and tobacco use seen here underscore the importance of correctly capturing the latter. As maternal prepregnancy BMI was available for only 21% of births, imputing missing values was not feasible.

While a fairly large proportion of adverse pregnancy outcomes are due to pre-eclampsia and placental vascular disease,[9] we did not discern the underlying causes for either preterm birth or stillbirth, which may differentially influence a woman's risk of CAD. Including preterm births and stillbirths due to non-placental causes would likely have diminished the relation between pre-eclampsia and future CAD.

Other studies

Previously published epidemiological studies have consistently shown a higher risk of heart disease and stroke in relation to pre-eclampsia, especially pre-eclampsia necessitating preterm delivery.[2 3] However, those studies largely used administrative databases with diagnostic codes for cardiac ischaemia and/or



	Exposure group	Adjusted HR (95% CI)
Additional analysis of preeclampsia +/- preterm birth and risk of angiographic coronary artery stensosis	*No preeclampsia; no preterm birth (N = 1,211,021)*	1.00 (Referent)
	No preeclampsia; preterm birth (N = 141,661)	1.63 (1.42 to 1.88)
	Preeclampsia; no preterm birth (N = 27,208)	1.81 (1.45 to 2.26)
	Preeclampsia; preterm birth (N = 14,580)	3.11 (2.51 to 3.87)
Additional analysis of preeclampsia +/- stillbirth and risk of angiographic coronary artery stensosis	**Exposure group**	**Adjusted HR (95% CI)**
	No preeclampsia; livebirth (N = 1,344,626)	1.00 (Referent)
	No preeclampsia; stillbirth (N = 14,496)	1.94 (1.43 to 2.62)
	Preeclampsia; livebirth (N = 41,715)	2.11 (1.79 to 2.47)
	Preeclampsia; stillbirth (N = 537)	2.80 (1.05 to 7.47)

Figure 3 Summary figure showing the study design and results for eligible participants with versus without a history of pre-eclampsia. Shown are incidence rates (IR) and HRs.

heart failure, which are limited in their ability to assess, with certainty, CAD or CAD severity. The current study was able to overcome such limitations by providing direct angiographic data on obstructive coronary artery stenosis and reduced LVEF. Even so, in women with signs and symptoms of coronary ischaemia and <50% coronary artery stenosis, a self-reported remote history of an adverse pregnancy outcome, like pre-eclampsia, was associated with microvascular dysfunction (ie, lower coronary flow reserve) in other research.[27] Certainly, future work can consider measuring both coronary flow reserve and a validated angiographic score at the time of invasive coronary angiography.

Non-invasive CT has also been used to study coronary artery calcification among women with prior pre-eclampsia or preterm birth. For example, among 79 women free of overt cardiovascular disease examined an average of 35 years after their first live birth, a high CT Coronary Artery Calcification Score (CACS) was more common in those with (23%) versus without (0%) pre-eclampsia (unadjusted OR 3.54, 95% CI 1.39 to 9.02).[13] The OR remained significant even after adjusting for hypertension and BMI (2.48, 95% CI 0.86 to 7.19). Another multicentre prospective cohort study compared 164 asymptomatic women aged 45–55 years and a remote history of pre-eclampsia to 387 similarly aged women without prior pre-eclampsia.[12] Pre-eclampsia was associated with a higher relative risk of any elevated CACS (1.7, 95% CI 1.2 to 2.3) and a very high CACS (2.8, 95% CI 0.4 to 19.3).

A proportion of women who had coronary angiography in our study did not concomitantly undergo ventriculography, paralleling rates seen in another setting.[28] As echocardiography was not available here, we thus solely considered the presence of a reduced LVEF <50% as a measure of myocardial dysfunction. Nonetheless, a meta-analysis reported greater cardiac dysfunction on echocardiography among women with a history of pre-eclampsia.[29] Future research should assess the mechanisms for reduced LV performance after pre-eclampsia, in terms of microvascular dysfunction, coronary atherosclerosis and chronic hypertension.

CONCLUSION

Our findings provide objective evidence of premature-onset obstructive coronary artery stenosis in women with pre-eclampsia, supporting prior studies of the association between pre-eclampsia and a diagnosis of CAD.[1–3] We also showed that coronary artery stenosis is more severe when pre-eclampsia is complicated by preterm birth or a stillbirth, and even after accounting for known traditional cardiac risk factors. International guidelines now consider prior pre-eclampsia as a risk factor for heart disease, as recently summarised elsewhere.[30] Among pre-eclampsia-affected women, these guidelines generally recommend annual assessment and management of blood pressure, BMI and glucose. Whether these recommended steps can attenuate the progression to obstructive coronary artery stenosis and altered LV performance in women with pre-eclampsia, especially those concomitantly experiencing preterm birth, stillbirth or another adverse perinatal condition, remains to be determined.

Non-invasive coronary imaging methods, such as CCTA, may be one method to assess the progression of CAD in women with and without pre-eclampsia. Such non-invasive methods may also provide a meaningful way to evaluate the regression of CAD lesions in women with pre-eclampsia (±preterm birth or stillbirth) following aggressive lifestyle and pharmacological therapies, including antihypertensive and lipid-lowering treatments.

Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY.

Acknowledgements The authors thank Dr Rinku Sutradhar, PhD, ICES, University of Toronto, for her statistical suggestions.

Contributors JGR designed the study, drafted the manuscript, and is responsible for the overall content as guarantor and thereby accepts full responsibility for the finished work and the conduct of the study. AC performed all statistical analyses and helped draft and revise the manuscript. All authors provided substantial contributions to data interpretation and critical revisions and approved the final manuscript.

Funding This work was supported by a grant from the Canadian Institutes of Health Research (no grant number). This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. PCA is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation.

Disclaimer Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI. The authors acknowledge that the clinical registry data used in this publication is from participating hospitals through CorHealth Ontario, which serves as an advisory body to the Ministry of Health (MOH), is funded by the MOH, and is dedicated to improving the quality, efficiency, access and equity in the delivery of the continuum of adult cardiac, vascular and stroke services in Ontario, Canada. This Study is based in part on data provided by Better Outcomes Registry and Network ("BORN"), part of the Children's Hospital of Eastern Ontario. The interpretation and conclusions contained herein do not necessarily represent those of BORN Ontario.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. No additional data are available.

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Table S1. Variables used to define cohort entry and exclusion criteria, study exposures, outcomes and adjustment variables.

Assessment	Timing	Disease, procedure or measure	ICD-9 [ICD-10-CA] diagnostic codes in DAD, SDS and NACRS	CCP [CCI] procedural codes in DAD, SDS, NACRS	Diagnostic codes in OHIP	Other sources
Inclusion criteria	At the delivery	Any obstetrical hospital livebirth or stillbirth from 20 weeks' gestation onward. Only include women aged 16-50 years, with a valid health insurance number.	MOMBABY (see link at https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library=MOMBABY)	--	--	--
Exclusion criteria (any dxtype, exclude suspect diagnoses)	≤ 3 years before the index birth hospitalization discharge date, or < 42 days after the index birth hospitalization discharge date	Coronary artery disease	410, 411, 413, 414.0, 429.2 [I20, I21, I22 , I24, I25.0, I25.1, I51.3]	48 [1HZ80, 1IJ50, 1IJ54, 1IJ55, 1IJ57, 1IJ76, 1IJ80, 1IK80, 1IK87, 1IL35, 2IL70, 3IP10]	410, 412, 413, 429	--
	Same	Heart failure	428 [I50]	--	428	--
	Same	Pericardial disease, endocarditis, myocarditis, cardiomyopathy or peripartum cardiomyopathy, valvular heart disease	420-425 [I30-I43], 674.5 [O90.3], 390-392 [I00-I02, I05-I09]	--	398	--
	Same	Coronary angiography	--	--	--	CCN
	< 42 days after the index birth hospitalization discharge date	Death	--	--	--	RPDB

Assessment	Timing	Disease, procedure or measure	ICD-9 [ICD-10-CA] diagnostic codes in DAD, SDS and NACRS	CCP [CCI] procedural codes in DAD, SDS, NACRS	Diagnostic codes in OHIP	Other sources
Main study exposures	One delivery hospitalization was randomly chosen as the index birth for each woman (Main exposure)	Preeclampsia or eclampsia in the randomly selected index birth	642.4-642.7 [O11, O14, O15]	--	--	--
	First delivery hospitalization in the study period (Additional analysis #2a)	Preeclampsia or eclampsia as a time-varying exposure	Same	--	--	--
	Any delivery hospitalization in the study period, starting at the first delivery (Additional analysis #2b)	Preeclampsia or eclampsia as a time-varying exposure, assessing the number of times preeclampsia or eclampsia occurred (0, 1 or ≥ 2 times)	Same	--	--	--
Study outcomes **If multiple sequential coronary angiographies, first was used**	≥ 42 days after the index birth (delivery) discharge date ("time zero")	1) Coronary artery stenosis at coronary angiography	--	--	--	CCN - Having any of the following: a) Left main (LM) ≥ 50% stenosis, or b) Proximal left anterior descending (LAD) ≥ 70% stenosis, or c) Mid or distal LAD ≥ 70% stenosis, or d) Circumflex ≥ 70% stenosis, or e) Right coronary artery (RCA) ≥ 70% stenosis

Assessment	Timing	Disease, procedure or measure	ICD-9 [ICD-10-CA] diagnostic codes in DAD, SDS and NACRS	CCP [CCI] procedural codes in DAD, SDS, NACRS	Diagnostic codes in OHIP	Other sources
	Same	2) Multi-vessel obstructive coronary artery stenosis at coronary angiography	--	--	--	CCN - Exclusively having one of the following: a) No disease: < 50% stenosis in all coronary artery branches, or b) 1-vessel disease: ≥ 50% stenosis in one coronary artery, or c) 2-vessel disease: ≥ 50% stenosis in two coronary arteries (or ≥ 50% stenosis of the LM), or d) 3-vessel disease: ≥ 50% stenosis in three coronary arteries (or ≥ 50% stenosis in the LM and also ≥ 70% stenosis in the RCA).

Assessment	Timing	Disease, procedure or measure	ICD-9 [ICD-10-CA] diagnostic codes in DAD, SDS and NACRS	CCP [CCI] procedural codes in DAD, SDS, NACRS	Diagnostic codes in OHIP	Other sources
		3) Stenotic coronary artery disease with concomitantly reduced left ventricular function stenosis at coronary angiography	--	--	--	CCN - Having <u>any</u> of the following: a) Left main (LM) ≥ 50% stenosis, or b) Proximal left anterior descending (LAD) ≥ 70% stenosis, or c) Mid or distal LAD ≥ 70% stenosis, or d) Circumflex ≥ 70% stenosis, or e) Right coronary artery (RCA) ≥ 70% stenosis <u>and concomitantly</u> left ventricular ejection fraction < 50%
	Same	Death				RPDB
Covariates	At the index birth hospitalization discharge date	Neighbourhood income quintile (1/missing, 2, 3, 4, 5)		--	--	RPDB, Statistics Canada census data
	Same	Residence (rural, urban/missing)		--	--	RPDB, Statistics Canada census data
	< 365 d before the index birth hospitalization discharge date	Diabetes mellitus	250, 648.8 [E10, E11, E13, E14, O244]	--	250	--
	Same	Chronic hypertension	401, 405, 642.0-642.2, 642.7 [I10, I15, O10, O11]	--	401	--
	Same	Dyslipidemia	272.0, 272.1, 272.2, 272.3, 272.4, 272.5 [E78]	--	272	--

Assessment	Timing	Disease, procedure or measure	ICD-9 [ICD-10-CA] diagnostic codes in DAD, SDS and NACRS	CCP [CCI] procedural codes in DAD, SDS, NACRS	Diagnostic codes in OHIP	Other sources
	Same	Renal disease	669.3, 958.5 634.3, 635.3, 636.3, 637.3, 638.3, 639.3, 250.4x, 274.1x, 403.xx, 404.xx, 405.01, 405.11, 405.91, 440.1, 446.21, 581.xx, 582.xx, 583.xx, 584.5-584.9, 585.x, 586, 587.x, 588.0, 588.8x, 588.9, 590.0x, 593.7x, 791.0, 794.4 [O08.4, T79.5, O90.4, E10.20, E10.21, E10.23, E11.20, E11.21, E11.23, M10.39, I12, I13, I15.0, I70.1, M31.0, N01.x, N03.x, N04.x, N05.x, N06.x, N07.x, N08.x, N11.x, N12, N13.7, N13.8, N13.9, N14.x, N15.x, N16.x, N17.x, N18.x, N19.x, N25.0, N25.8, N25.9, N26, R80, R94.4]	--	403, 581, 585	--
	Same	Drug dependence or tobacco use	291, 292, 2940, 303, 304, 305, 648.3, 649.0, 6555, 980 [F10-F19, F55, G312, O354, O355, T51, T652, Z720, Z721, Z722]	--	291, 292, 303, 304, 305	--
	At the index birth	Pre-pregnancy body mass index				BORN

Assessment	Timing	Disease, procedure or measure	ICD-9 [ICD-10-CA] diagnostic codes in DAD, SDS and NACRS	CCP [CCI] procedural codes in DAD, SDS, NACRS	Diagnostic codes in OHIP	Other sources
Censoring variables	From 42 days after the index birth hospitalization discharge date	Date of outward migration or loss of OHIP eligibility	--	--	--	RPDB
	December 31, 2020	End of study	--	--	--	--
Variables for additional exposures occurring in conjunction with preeclampsia	Any delivery hospitalization	Preterm livebirth < 37 weeks' gestation	Before 2002: 644.2, 765 [O60, P07.2, P07.3] Since 2002: Gestational age < 37 completed weeks	--	--	--
	Any delivery hospitalization	Stillbirth at 20+ weeks' gestation	--	--	--	MOMBABY: m_stillbirth='T'

BORN Better Outcomes Registry and Network; CCP Canadian Classification of Diagnoses and Procedures; CCI Canadian Classification of Interventions; DAD Discharge Abstract Database; ICD-9 International Classification of Diseases, 9th Revision; ICD-10-CA International Classification of Diseases, 10th Revision, Canada; NACRS National Ambulatory Care Reporting System; OHIP Ontario Health Insurance Plan; RPDB Registered Persons Database; SDS Same Day Surgery Database; CCN Cardiac Care Network of Ontario.

Table S2 (Additional analysis #1). Risk of developing obstructive coronary artery stenosis among women with vs. without a history of preeclampsia, January 2002 to March 2020, further adjusted for pre-pregnancy body mass index (BMI). The time zero index date starts 42 days after the index birth hospitalization discharge date. This analysis is limited to 286,836 women in whom pre-pregnancy BMI was known.

Exposure group	Number of women with obstructive coronary artery stenosis (incidence rate per 10,000 person years, 95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]	Fully adjusted hazard ratio (95% CI)[b]
Women without preeclampsia (N = 278,841)	127 (0.52, 0.43 to 0.62)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Women with preeclampsia (N = 7995*)*	19 (2.72, 1.64 to 4.25)	5.28 (3.26 to 8.57)	3.30 (1.90 to 5.72)	1.94 (1.17 to 3.21)

[a]Adjusted for maternal age, parity, neighbourhood income quintile (1 or missing, 2, 3, 4, 5), residence (rural, urban or missing) at the time of the index delivery, pre-pregnancy BMI, as well as diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidemia within 365 days preceding the index date.

[b]Further adjusted for time-varying diabetes mellitus, chronic hypertension, renal disease, drug dependence or tobacco use, and dyslipidemia – each arising at time zero onward, up to the day before the coronary angiography.

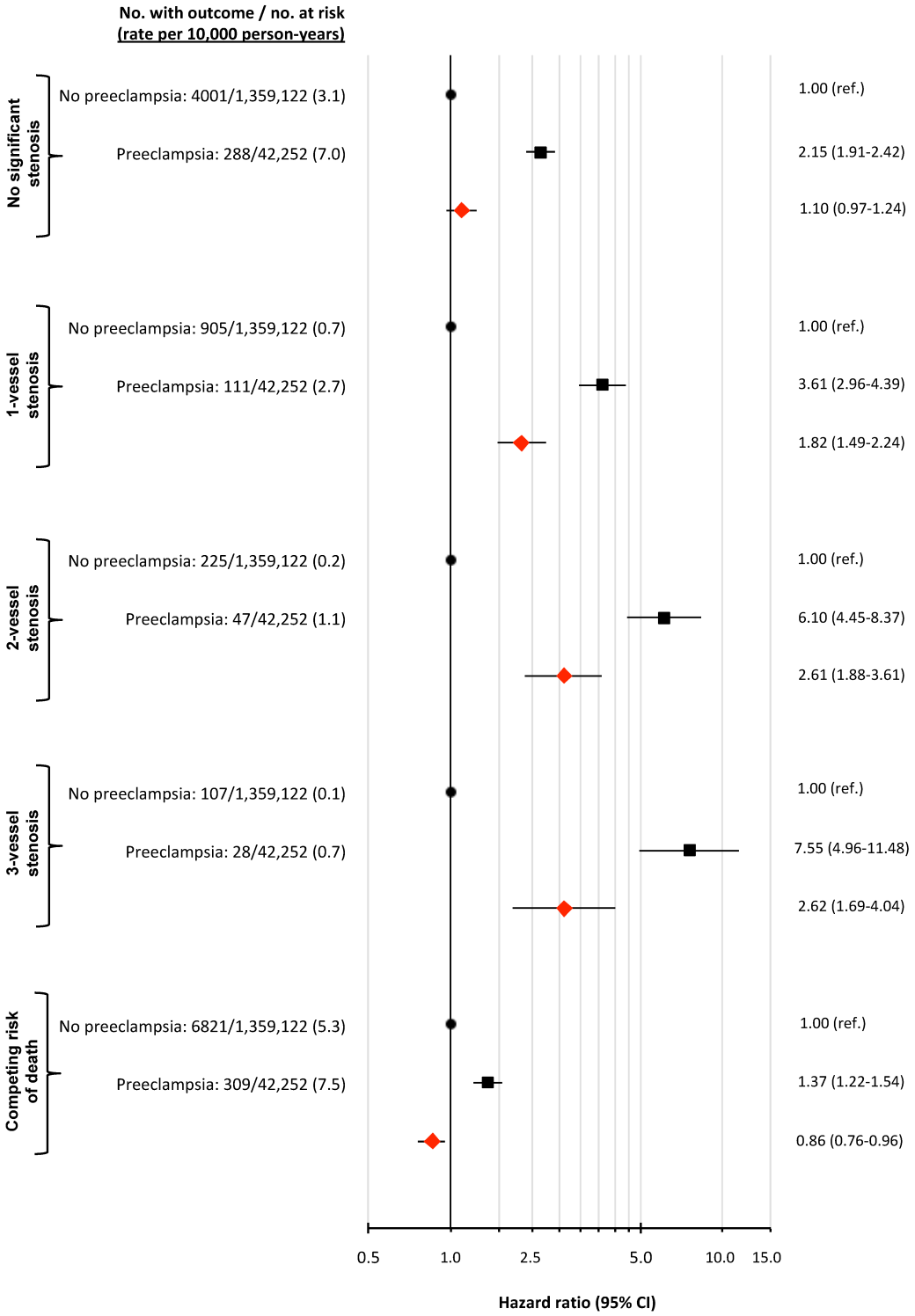
Table S3. Risk of developing obstructive coronary artery stenosis in relation to a history of preeclampsia as a time-varying exposure, starting at each woman's first birth in the study period, January 2002 to March 2020. Preeclampsia is modelled in a time-varying manner as absent or present (Additional analysis #2a [upper]), or as absent, occurring once, or occurring at least twice (Additional analysis 2b [lower]). The time zero index date starts 42 days after the first birth hospitalization discharge date.

Time-varying exposure group (number of person-years of follow-up)	Number of women with obstructive coronary artery stenosis (incidence rate per 10,000 person years, 95% CI)	Fully adjusted hazard ratio (95% CI)
Women without a history of preeclampsia (14,198,019 person-years)	1124 (0.79, 0.75 to 0.84)	1.00 (Referent)
Women with a history of preeclampsia (286,879 person-years)	108 (3.76, 3.09 to 4.55)	1.72 (1.40 to 2.11)[a]
Women without preeclampsia (14,198,019 person-years)	1124 (0.79, 0.75, 0.84)	1.00 (Referent)
Women with preeclampsia once (275,802 person-years)	102 (3.70, 3.02 to 4.49)	1.65 (1.34 to 2.04)[b]
Women with preeclampsia at least twice (11,077 person-years)	6 (5.42, 1.99 to 11.79)	1.63 (0.73 to 3.64)[b]

[a]Adjusted for maternal age, parity, neighbourhood income quintile (1 or missing, 2, 3, 4, 5), residence (rural, urban or missing) at the time of the first delivery, as well as time-varying diabetes mellitus, chronic hypertension, renal disease, drug dependence or tobacco use, and dyslipidemia – each arising at time zero onward, up to the day before the coronary angiography.

[b]Adjusted for maternal age, neighbourhood income quintile (1 or missing, 2, 3, 4, 5), residence (rural, urban or missing) at the time of the first delivery, as well as time-varying parity, diabetes mellitus, chronic hypertension, renal disease, drug dependence or tobacco use, and dyslipidemia – each arising at time zero onward, up to the day before the coronary angiography.

Figure S1. Risk of multi-vessel obstructive coronary artery stenosis[a] associated with a history of preeclampsia. Shown are unadjusted (*black squares*) and adjusted (*red diamonds*) hazard ratios[b] among women with preeclampsia, relative to those without preeclampsia (*black circles*)



[a]a) No stenotic disease: < 50% stenosis in all coronary arteries, b) 1-vessel disease: ≥ 70% stenosis in one coronary artery, excluding left main coronary artery, c) 2-vessel disease: ≥ 70% stenosis in two coronary arteries (or ≥ 50% stenosis of left main coronary artery, or d) 3-vessel disease: ≥ 70% stenosis in three coronary arteries (or ≥ 50% stenosis in left main coronary artery + ≥ 70% stenosis in right coronary artery).

[b]Hazard ratios were generated using a competing risk model, and adjusted for maternal age, parity, income quintile, urban/rural residence, diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidemia – each within 365 days preceding the index date, and further adjusted for time-varying type 1 or type 2 diabetes mellitus, chronic hypertension, renal disease, drug dependence or tobacco use, and dyslipidemia – each arising at 42 days after the index birth up to the day before the coronary angiography.