Canadian Journal of Cardiology 36 (2020) 60–68

Clinical Research

Preeclampsia Brings the Risk of Premature Cardiovascular Disease in Women Closer to That of Men

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See editorial by Dayan and Udell, pages 13–16 of this issue.

ABSTRACT

Background: It is not known if sex differences in the risk of premature cardiovascular disease (CVD) vary by whether a woman had preeclampsia or not. The current study determined whether prior preeclampsia brings a woman's risk of CVD closer to that of a male counterpart.

Methods: A population-based cohort study was completed in Ontario, Canada, from 1993 to 2017. Participants were 55,186 women with prior preeclampsia, 110,372 randomly selected age- and region-matched men, and 110,372 similarly selected women who gave birth without prior preeclampsia. The primary outcome was a CVD composite outcome of any hospitalization or revascularization for coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, and dysrhythmia.

RÉSUMÉ

Introduction : On ignore si les différences entre les sexes dans le risque de maladie cardiovasculaire (MCV) prématurée varient en fonction la présence d'antécédents ou de l'absence d'antécédents de pré-éclampsie chez les femmes. L'étude actuelle a déterminé si les antécédents de pré-éclampsie rapprochaient le risque de MCV de la femme à celui de son homologue masculin.

Méthodes : Une étude de cohorte en population générale a été réalisée en Ontario, au Canada, de 1993 à 2017. Elle était composée de 55 186 participantes ayant des antécédents de pré-éclampsie, de 110 372 hommes sélectionnés de manière aléatoire et appariés selon l'âge et la région, et de 110 372 femmes sélectionnées de façon similaire qui avaient donné naissance sans avoir eu précédemment de pré-éclampsie. Le critère de jugement principal était le critère com-

It is generally accepted that women with a history of preeclampsia, especially early-onset preeclampsia necessitating preterm delivery, are at higher risk of premature cardiovascular disease (CVD) compared with non-preeclamptic women.[1-3] Those with prior preeclampsia also have worse outcomes after coronary revascularization.[4]

Middle-aged men are at least twice as likely to develop premature CVD than same-aged female counterparts.[5-13] This was consistently observed in the United Kingdom,[14] Australia,[15] United Sates, Canada,[16] and Norway,[17] even upon adjusting for conventional CVD risk factors.[17] It is unclear how sex differences in the risk of premature CVD vary by whether a woman had preeclampsia or not.

The current study evaluated whether history of preeclampsia bring a woman's risk of premature CVD nearer to that of an age-matched male counterpart. Analyses further contrasted that risk by CVD subtypes (coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, or dysrhythmia) and in the co-presence of the more severe form of preeclampsia necessitating preterm delivery.[1-3]

Methods

A population-based cohort study was completed in Ontario, Canada, where there is universal healthcare, including obstetrical and adult inpatient and outpatient care. We used administrative health datasets, as described in Supplemental Table S1 and by others,[2-4] that were linked

Received for publication February 20, 2019. Accepted June 18, 2019.

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See page 67 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.06.028

Results: Median follow-up was approximately 16 years. Relative to women without prior preeclampsia (1193 events; 7.5 per 10,000 person-years), men had the highest risk of CVD (3706 events; 24.3 per 10,000 person-years) (adjusted hazard ratio [aHR], 2.52; 95% confidence interval [CI], 2.35-2.69). Women with a history of preeclampsia were also at higher risk (1252 events; 16.0 per 10,000 person-years) (aHR, 1.17; 95% CI, 1.08-1.28). Women with preeclampsia requiring preterm delivery were even more likely to experience CVD (21.5 per 10,000 person-years) (aHR, 1.44; 95% CI, 1.18-1.76). The absolute risk of CVD in men (22.5 per 10,000 person-years) was similar to the risk in women with preeclampsia and preterm delivery, but men had the highest aHR (2.48; 95% CI, 2.11-2.93).

Conclusions: Although men remain at significantly higher risk of CVD, a history of preeclampsia, especially with preterm birth, elevates a woman's risk closer to that of a man.

posite de MCV de toute hospitalisation ou revascularisation pour une coronaropathie, une maladie vasculaire cérébrale, une artériopathie périphérique, une insuffisance cardiaque et une dysrythmie.

Résultats : Le suivi médian était approximativement de 16 ans. Par rapport aux femmes sans antécédents de pré-éclampsie (1193 événements ; 7,5 par 10 000 personnes-années), les hommes étaient exposés à un risque plus élevé de MCV (3706 événements ; 24,3 par 10 000 personnes-années) (rapport de risque ajusté [RRa], 2,52 ; intervalle de confiance [IC] à 95 %, 2,35-2,69). Les femmes qui avaient des antécédents de pré-éclampsie étaient également exposées à un risque plus élevé (1252 événements ; 16,0 par 10 000 personnes-années) (RRa, 1,17 ; IC à 95 %, 1,08-1,28). Les femmes qui avaient eu une prééclampsie et nécessité un accouchement avant terme étaient encore plus susceptibles d'avoir une MCV (21,5 par 10 000 personnes-années) (RRa, 1,44 ; IC à 95 %, 1,18-1,76). Le risque absolu de MCV chez les hommes (22,5 par 10 000 personnes-années) était similaire chez les femmes ayant eu une prééclampsie et un accouchement avant terme, mais le RRa le plus élevé (2,48 ; IC à 95 %, 2,11-2,93) était observé chez les hommes.

Conclusions : Bien que les hommes demeurent exposés à un risque significativement plus élevé de MCV, le risque chez les femmes qui ont des antécédents de pré-éclampsie, particulièrement celles qui ont donné naissance avant terme, se rapproche du risque chez les hommes.

using unique encoded identifiers and analysed at the Institute for Clinical Evaluative Sciences. The use of data in this project was authorized under Section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Participants

The preeclampsia cohort comprised women aged 16 to 50 years who had a live birth or stillbirth hospital delivery at 20 or more weeks gestation. Excluded were women diagnosed with any cardiac, cerebrovascular, or peripheral arterial disease $\leq$ 5 years before "time zero," as described next, as well as non-Ontario residents and those without a valid Ontario Health Insurance Plan number (Supplemental Table S1). One delivery was randomly selected per preeclamptic woman, to create an index pregnancy and to simplify the data analyses, forming the exposure group of women with preeclampsia. We 2:1 matched women without preeclampsia to women with preeclampsia on maternal age, index delivery date era (1993-2001, International Classification of Diseases [ICD] 9th Revision or 2002-2017 [ICD 10th Revision Canada]), and Local Health Integration Network, the latter representing one of 14 geographical entities designed to plan, integrate, and fund local health services in Ontario. Otherwise, those without preeclampsia had the same inclusion, exclusion, and selection criteria as those with preeclampsia. An exposure group of randomly selected men was likewise 2:1 matched to the women with preeclampsia on age and Local Health Integration Network, and by the same inclusion and exclusion criteria (Supplemental Table S1). However, because a man cannot experience an obstetrical delivery, another method was needed to create a matched index date for the male cohort, as well as evidence that they had interacted with the healthcare system. Thus, it was required that any eligible male had at least 1 outpatient primary healthcare visit within $\pm$16 weeks (ie, 112 days) of the delivery date of his matched preeclamptic female counterpart (Supplemental Table S1).

Exposures and outcomes

The main exposure of interest was being a male or having a pregnancy affected by preeclampsia, which were each compared with a pregnancy without preeclampsia. During the study era, preeclampsia was based on new-onset hypertension with proteinuria or another target organ effect, such as a seizure, hemolysis, elevated liver enzymes, or low platelet count syndrome.

The primary study outcome was a CVD composite of any hospitalization or revascularization for coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, or dysrhythmia, using validated hospitalization codes and algorithms[5-7] (Supplemental Table S1). The CVD outcome was ascertained starting at 90 days after the index delivery date of the group of women with preeclampsia and their matched female counterparts without preeclampsia, or at 90 days after the index primary care visit index date among the matched male counterparts, thereby creating a common "time zero" for all 3 cohorts. Setting "time zero" at 90 days was also done to ensure that a CVD event was not a direct consequence of a pregnancy complication, such as a peripartum stroke due to preeclampsia.

Secondary outcomes included each CVD subtype within the CVD composite, namely, coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, or dysrhythmia again ascertained starting at the 90-day "time zero," as well as all-cause mortality, alone, and in combination with CVD.

All study outcomes were identified using the ICD coding system (ICD 9th Revision before 2002, and ICD 10th Revision Canada thereafter), and the Canadian Classification

of Diagnoses and Procedures (before 2002) and the Canadian Classification of Interventions (2002 onward) (Supplemental Table S1). Neighbourhood income quintile and rurality were based on Statistics Canada census data.

Statistical analysis

Standardized differences compared the characteristics of women with preeclampsia and their matched male counterparts, as well as women without preeclampsia and their matched non-preeclamptic female counterparts.

The main model assessed the primary CVD composite outcome among women with prior preeclampsia and men, each relative to the matched women without preeclampsia (the referent). Time-to-event analyses were conducted using multivariable Cox regression models, accounting for matching, to derive a hazard ratio (HR) and 95% confidence interval (CI) for each study outcome. Censoring was at death, end of Ontario Health Insurance Plan eligibility, or arrival at the end of study period at December 31, 2017, thereby allowing for a maximum follow-up of 22 years. In Model 1, HRs were adjusted for neighbourhood income quintile (1/missing, 2, 3, 4, 5), residence (rural/missing, urban), type 1 or type 2 (nongestational) diabetes mellitus, chronic hypertension, renal disease, illicit drug or tobacco use, and dyslipidemia, each considered within 365 days before or up to 90 days after the index date. Model 2 further adjusted for time-varying type 1 or type 2 diabetes mellitus, chronic hypertension, renal disease, illicit drug or tobacco use, and dyslipidemia, each arising at time zero onward. The proportional hazards assumption was assessed by a Wald test for interaction between the exposure groups and a function of survival time, which did not detect a significant departure.

The main model was then stratified by age at the index date (16-29, 30-35, and 36-50 years) (Additional Analysis 1). As a proxy for ethnicity, the main model was further adjusted for the world region of origin (Canada/long-term resident, Caribbean, East Asia/Pacific, Hispanic America, Middle East/North African, South Asia, Sub-Saharan Africa, Western Nations/Europe), using the Immigration, Refugees, and Citizenship Canada's Permanent Resident Database (Additional Analysis 2). This database contains data on country of citizenship for immigrants to Canada from 1985 onward.

The CVD composite outcome was reassessed comparing the subgroup of women with prior preeclampsia requiring preterm delivery before 37 weeks gestation and their male counterparts, each relative to the matched women without preeclampsia or preterm birth (Additional Analysis 3).

Because some CVD events are sudden and fatal, and may occur outside of a hospital setting, we re-ran the main model, but included all-cause mortality as a part of the CVD composite outcome, from 90 days after the index birth and no longer censored on death (Additional Analysis 4). Furthermore, all-cause mortality (regardless of CVD) was also evaluated (Additional Analysis 5).

Because all aforementioned analyses for CVD or death started at 90 days, early adverse events would be missed. Accordingly, an assessment of the CVD composite outcome (Additional Analysis 6) and the CVD or death composite outcome (Additional Analysis 7) was conducted, re-setting "time zero" to the index delivery date for women and the index primary care visit for men, with a maximum follow-up up to 90 days thereafter. Last, the main model for the CVD composite outcome was re-run, setting "time zero" at the index delivery date for women without the 90-day ceiling (Additional Analysis 8). All statistical analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc, Cary, NC).

Systematic review and meta-analysis of CVD risk in men vs women

In an effort to contrast the current study findings with those of prior published studies of the relative risk (RR) of CVD in men vs women, a systematic literature search was performed using PubMed and Embase. Included were English-language cohort studies that intended to compare the risk of any incident CVD in men vs women and that enabled the calculation of a RR (or HR) and a 95% CI. One author (AL) performed initial screening, and 2 authors (AL and EL) independently performed data abstraction. Further details are provided next.

A pooled RR was generated using an inverse-variance, random-effects meta-analysis (Review Manager 5.2, Cochrane, Copenhagen, Denmark). If a study included multiple age groups at entry, then selection was made on the group with the greatest number of young or middle-aged adults. If a study had more than 1 CVD subtype, then the subtype with the largest sized denominator was selected.

Results

There were 3,184,270 identified pregnancies in Ontario during the study period, of which 55,186 (1.7%) were randomly selected to form the preeclampsia cohort (Supplemental Fig. S1A). The matched cohorts comprised 110,372 randomly selected women without preeclampsia (Supplemental Fig. S1A) and 110,372 men (Supplemental Fig. S1B).

The mean age at entry in the 3 cohorts was 29.6 years (Table 1). Contrasting women with preeclampsia with their matched male counterparts, important standardized differences greater than +0.10 were seen for diabetes mellitus, chronic hypertension, and renal disease, and standardized differences greater than −0.10 were noted for dyslipidemia and illicit drug or tobacco use (Table 1). Contrasting women with and without preeclampsia, important standardized differences were seen for parity, a singleton pregnancy, diabetes mellitus, chronic hypertension, renal disease, and preterm birth < 37 weeks gestation (Table 1).

After a median duration of follow-up of approximately 16 years, new-onset premature CVD occurred in 3706 men (24.3 per 10,000 person-years), 1252 women with prior preeclampsia (16.0 per 10,000 person-years), and 1193 women without prior preeclampsia (7.5 per 10,000 person-years) (Fig. 1). Comparing men with women without preeclampsia, the crude HR for CVD was 3.30 (95% CI, 3.09-3.52), which was unchanged in the multivariable model with baseline covariates (Model 1 adjusted hazard ratio [aHR], 3.28; 95% CI, 3.07-3.50), but substantially attenuated after adjusting for time-varying comorbidities (Model 2 aHR, 2.52; 95% CI, 2.35-2.69) (Table 2). Contrasting women with vs without prior preeclampsia, the crude HR (2.14, 95% CI,

Table 1. Characteristics of women who developed preeclampsia, their matched male counterparts, and their matched female counterparts with a non-preeclamptic pregnancy

Characteristic	Women with preeclampsia (N = 55,186)	Matched men (N = 110,372)	Standardized difference	Women with preeclampsia (N = 55,186)	Matched women without preeclampsia (N = 110,372)	Standardized difference
At the index date						
Mean (SD) age, y	29.6 (5.8)	29.6 (5.8)	0.00	29.6 (5.8)	29.6 (5.8)	0.00
Age, 35-39 y	8961 (16.2)	17,922 (16.2)	0.00	8961 (16.2)	17,922 (16.2)	0.00
Age, 40-44 y	2172 (3.9)	4344 (3.9)	0.00	2172 (3.9)	4344 (3.9)	0.00
Age, 45-50 y	191 (0.3)	382 (0.3)	0.00	191 (0.3)	382 (0.3)	0.00
Income quintile (Q)						
Q1 (lowest)	12,733 (23.1)	26,032 (23.6)	−0.01	12,733 (23.1)	25,665 (23.3)	0.00
Q5 (highest)	8220 (14.9)	17,128 (15.5)	−0.02	8220 (14.9)	17,520 (15.9)	−0.03
Missing	427 (0.8)	584 (0.5)	0.03	427 (0.8)	643 (0.6)	0.02
Rural residence	7872 (14.3)	14,270 (12.9)	0.04	7872 (14.3)	14,910 (13.5)	0.02
Median (IQR) parity	0 (0-1)	–	–	0 (0-1)	0 (0-1)	−0.24
Singleton pregnancy	52,215 (94.6)	–	–	52,215 (94.6)	108,618 (98.4)	−0.21
Live birth outcome in index pregnancy	54,607 (99.0)	–	–	54,607 (99.0)	109,841 (99.5)	−0.07
Era at the index date						
1993-2001	31,007 (56.2)	62,014 (56.2)	0.00	31,007 (56.2)	62,060 (56.2)	0.00
2002-2017	24,179 (43.8)	48,358 (43.8)	0.00	24,179 (43.8)	48,312 (43.8)	0.00
Conditions ≤ 365 d before the index date						
Nongestational diabetes mellitus	5584 (10.1)	2300 (2.1)	0.34	5584 (10.1)	6052 (5.5)	0.17
Chronic hypertension	12,656 (22.9)	3962 (3.6)	0.60	12,656 (22.9)	3025 (2.7)	0.63
Dyslipidemia	505 (0.9)	3666 (3.3)	−0.17	505 (0.9)	725 (0.7)	0.03
Renal disease	690 (1.3)	269 (0.2)	0.12	690 (1.3)	168 (0.2)	0.13
Illicit drug or tobacco use	685 (1.2)	9834 (8.9)	−0.35	685 (1.2)	1275 (1.2)	0.01
Conditions at the live birth delivery						
Preterm birth < 37 wk gestation	15,055 (27.6)	–	–	15,055 (27.6)	6158 (5.6)	0.63
Median (IQR) no. of y of follow-up, from time zero	16.4 (7.6-20.6)	15.7 (6.7-20.3)	–	16.4 (7.6-20.6)	16.1 (7.7-20.8)	–
Total no. of person-y of follow-up, from time zero	783,637	1,525,531	–	783,637	1,587,125	–

All data are presented as number (%) unless otherwise indicated.
IQR, interquartile range; SD, standard deviation.

1.98-2.32) was significantly attenuated upon adjusting for baseline covariates (Model 1 aHR, 1.51; 95% CI, 1.37-1.65) and time-varying comorbidities (Model 2 aHR, 1.17; 95% CI, 1.08-1.28) (Table 2).

For the CVD subtypes, men continued to exhibit the highest associated risk for cardiac disease, followed by women with preeclampsia (Fig. 2). However, cerebrovascular disease was most common in women with preeclampsia (4.0 per 10,000 person-years), followed by men (3.0 per 10,000 person-years). Still, relative to women without preeclampsia (1.8 per 10,000 person-years), the corresponding fully aHRs for cerebrovascular disease were lower for women with preeclampsia than for men (Fig. 2).

Upon stratifying the main model by baseline age, the main findings of a higher risk of CVD in men, and in women with preeclampsia, persisted (Additional Analysis 1, Supplemental Fig. S2). Of note, the HRs were most pronounced among men aged 30 to 35 years and more than 35 years and among women aged 30 to 35 years with preeclampsia. Adding world region of origin to the main model did not appreciably change the main findings, with an aHR for CVD of 1.16 (95% CI, 1.07-1.26) for women with preeclampsia and 2.50 (95% CI, 2.33-2.67) for men, each relative to women without preeclampsia (Additional Analysis 2 [data not otherwise shown]).

Upon limiting the cohort to women with prior preeclampsia requiring preterm delivery and their matched counterparts, the Model 2 aHR for the CVD composite outcome increased to 1.44 (95% CI, 1.18-1.76) in the preeclampsia-preterm birth group and to 2.48 (95% CI, 2.11-2.93) among the men, each compared with women without preeclampsia or preterm birth (Additional Analysis 3, Table 3).

Including all-cause mortality in the CVD composite outcome generated higher event rates, especially among women without preeclampsia and among men (Additional Analysis 4, Supplemental Table S2). The corresponding aHR was 2.55 (95% CI, 2.42-2.68) for men and 1.06 (95% CI, 0.99-1.13) for women with preeclampsia. For the outcome of all-cause mortality, the respective aHRs were 3.02 (95% CI, 2.82-3.24) and 1.28 (95% CI, 1.16-1.41) (Additional Analysis 5, Supplemental Table S3).

Re-setting "time zero" to the index date of delivery for women and the primary care visit date for men, with follow-up to a maximum of 90 days thereafter, the risk for the CVD composite outcome was higher in women with preeclampsia than in women without preeclampsia, but was not elevated in men (Additional Analysis 6, Supplemental Table S4). The same was observed for the CVD or death composite outcome occurring between the index date and 90 days thereafter (Additional Analysis 7, Supplemental Table S5). Last, when the main model for the CVD composite outcome was run by re-setting "time zero" to the index date and without limiting follow-up to 90-days thereafter, the aHR was 2.36 (95% CI, 2.21-2.53) for men and 1.24 (95% CI, 1.15-1.35) for women with preeclampsia (Additional Analysis 8, Supplemental Table S6).

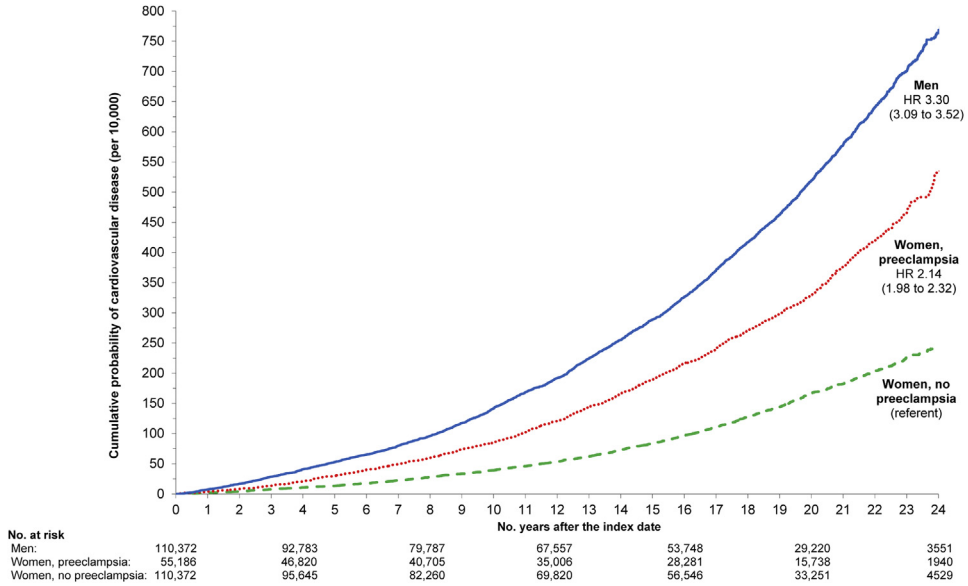

Figure 1. Cumulative probability and unadjusted hazard ratio (HR) and 95% confidence interval (CI) of the premature cardiovascular disease (CVD) composite outcome arising at ≥ 90 days after the index date (time zero) among women with prior preeclampsia (**red dotted line**) and among men (**solid blue line**), each relative to women without prior preeclampsia (**dashed green line**).

Discussion

Compared with those without preeclampsia, women with a history of preeclampsia had a heightened risk of premature CVD, approaching a rate approximately half that of same-aged men. When preeclampsia was accompanied by preterm birth, the absolute risk was nearly the same as for men.

Limitations and strengths

To match on a common index date (or narrow time window, in the case of men), the current study required that all men had least 1 outpatient primary healthcare visit. This may have led to the inclusion of men at higher risk of CVD and an overestimation of their CVD risk. In contrast, all female participants had a requisite birth, which may have led to the inclusion of healthier women capable of conceiving or carrying a pregnancy forward. Because 1 pregnancy was randomly selected per woman, the effect of repeat pregnancies with preeclampsia on CVD risk could not be evaluated. Others have shown that women with recurrent preeclampsia are at higher risk of CVD.[18,19]

CVD end points were initially restricted to those requiring a hospitalization or revascularization procedure and arising at least 90 days after the index birth for women or index primary care visit for men. Although this approach ensured that CVD outcomes were accurately captured, pre−90-day or fatal out-of-hospital CVD events would be missed. Additional Analysis 6 (Supplemental Table S4), limited to within the first 90 days after delivery, shows a higher short-term risk of CVD in women with preeclampsia. This supports the approach taken within our main model of beginning follow-up after 90 days to avoid including a peripartum stroke or cardiomyopathy that might be a direct consequence of uncontrolled blood pressure in women with acute preeclampsia. Factors that may partly explain the relation between preeclampsia and subsequent CVD were accounted for in the models, including diabetes mellitus, renal disease, and chronic hypertension.[20] Adjusting not only for baseline covariates but also for time-varying diabetes mellitus, chronic hypertension, and renal disease, for example, markedly

Table 2. Risk of the premature cardiovascular disease composite outcome of any hospitalization or revascularization for coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, or dysrhythmia arising at ≥ 90 days after the index date (time zero) among women with prior preeclampsia and among 2:1 matched men, each relative to 2:1 matched women without prior preeclampsia

Exposure group	No. of cardiovascular disease events (incidence rate per 10,000 person-years, 95% CI)	Unadjusted HR (95% CI)	Model 1 adjusted HR (95% CI)	Model 2 adjusted HR (95% CI)
Women without preeclampsia (N = 110,372)	1193 (7.5, 7.1-7.9)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Women with preeclampsia (N = 55,186)	1252 (16.0, 15.1-16.9)	2.14 (1.98-2.32)	1.51 (1.37-1.65)	1.17 (1.08-1.28)
Men (N = 110,372)	3706 (24.3, 23.5-25.1)	3.30 (3.09-3.52)	3.28 (3.07-3.50)	2.52 (2.35-2.69)

HRs in Model 1 were adjusted for neighbourhood income quintile (1/missing, 2, 3, 4, 5), residence (rural/missing, urban), diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidemia, each within 365 days before or up to 90 days after the index date. HRs in Model 2 were further adjusted for time-varying diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidemia, each arising at time zero onward.

CI, confidence interval; HR, hazard ratio.

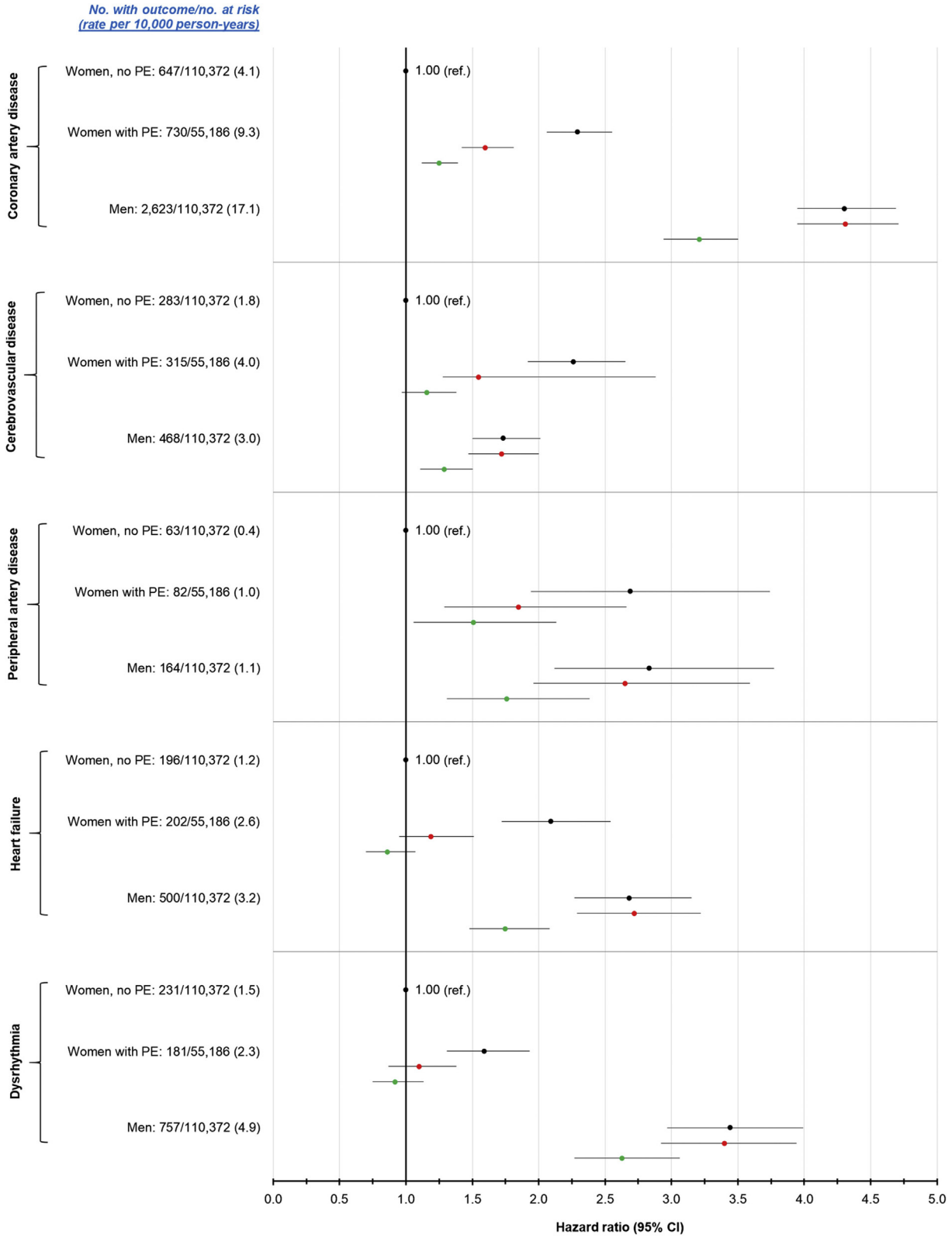

Figure 2. Risk of the premature CVD composite outcome arising at $\geq$ 90 days after the index date (time zero) among women with prior preeclampsia and 2:1 matched men, each relative to 2:1 matched women without prior preeclampsia. Unadjusted HRs are in **black circles**. HRs in Model 1 (**red circles**) were adjusted for neighbourhood income quintile (1/missing, 2, 3, 4, 5), residence (rural/missing, urban), diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidemia, each within 365 days before, or up to 90 days after, the index date. HRs in Model 2 (**green circles**) were further adjusted for time-varying diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidemia, each arising at time zero onward. CI, confidence interval; PE, preeclampsia.

Table 3. (Additional Analysis 3). **Risk of the premature cardiovascular disease composite outcome of any hospitalization or revascularization for coronary artery disease, cerebrovascular disease, peripheral artery disease, heart failure, or dysrhythmia arising at ≥ 90 days after the index date (time zero) among women with prior preeclampsia requiring preterm live birth delivery before 37 weeks gestation and among 2:1 matched men, each relative to 2:1 matched women without prior preeclampsia or preterm live birth delivery before 37 weeks gestation**

Exposure group	No. of CVD events (incidence rate per 10,000 person-years, 95% CI)	Unadjusted HR (95% CI)	Model 1 adjusted HR (95% CI)	Model 2 adjusted HR (95% CI)
Women without preeclampsia or preterm livebirth delivery at < 37 wk gestation (N = 25,096)	206 (6.9, 6.0-7.9)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Women with preeclampsia requiring preterm delivery at < 37 wk gestation (N = 12,548)	316 (21.5, 19.1-23.9)	3.17 (2.66-3.79)	2.00 (1.60-2.51)	1.44 (1.18-1.76)
Men (N = 25,096)	652 (22.5, 20.8-24.3)	3.36 (2.87-3.94)	3.29 (2.80-3.88)	2.48 (2.11-2.93)

HRs in Model 1 were adjusted for neighbourhood income quintile (1/missing, 2, 3, 4, 5), residence (rural/missing, urban), diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidemia, each within 365 days before or up to 90 days after the index date. HRs in Model 2 were further adjusted for time-varying diabetes mellitus, chronic hypertension, renal disease, illicit drug/tobacco use, and dyslipidemia, each arising at time zero onward.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

attenuated the HR for cerebrovascular disease, heart failure, and dysrhythmias among women with preeclampsia (Fig. 2). Even so, data on obesity, family history of CVD, and medication use were not collected or adjusted for and might partly explain any residual confounding.

Other studies

Systemic reviews and cohort studies have shown that women with preeclampsia and other maternal placental disorders are at higher risk of CVD than unaffected women,[2,21,22] especially when preeclampsia is co-incident with preterm delivery.[2,21] However, no prior research has evaluated the degree to which a history of preeclampsia elevates a woman's risk of premature CVD relative to that of a man of the same age.

To complement the current study, a meta-analysis was completed (Supplemental Table S7 and Supplemental Fig. S3) comprising 9 prior published studies examining CVD, largely limited to coronary artery disease (Supplemental Table S8). Among young and middle-aged adults included, the resulting pooled RR of CVD was 2.72 (95% CI, 2.06-3.59) comparing men with women (Supplemental Fig. S4). This pooled estimate is only slightly higher than the adjusted RR of 2.52 (95% CI, 2.35-2.69) seen in the current cohort study, which specifically compared men with women without preeclampsia. However, this meta-analysis was not exhaustive, in that non-English studies were excluded, as were those that did not provide a RR or that could otherwise enabled its calculation. The 9 included studies largely considered different subtypes of heart disease, potentially leading to different RRs comparing men vs women, while providing little information about the comparative risk of cerebrovascular disease, for example.

The current study observed a large attenuation in the risk of premature CVD in women with preeclampsia after adjustment for certain covariates, such as diabetes mellitus and chronic hypertension, especially conditions arising after time zero. In a Norwegian study of women who had blood pressure, lipids, and body mass index measured before and after pregnancy, the relation between preeclampsia and post-pregnancy cardiovascular risk appeared partly due to pre-pregnancy risk factors.[23] In a nested cohort study of 21 women with prior preeclampsia and 21 women who never had preeclampsia, the 10-year rate of chronic hypertension was higher among the former and their 10-year Framingham CVD risk scores were worse.[24] In another cohort study, women who remained hypertensive several years after a preeclampsia-affected pregnancy had a 10-year Framingham estimated absolute risk of CVD of 3.1%, compared with a risk of 1.5% among formerly preeclamptic women who did not have persistent hypertension.[25] A higher risk estimate was also seen for women with early-onset (1.7%) than late-onset (1.3%) preeclampsia. Classic cardiovascular risk factors seemed to behave as confounders, yet they may independently contribute to placental vascular disease (and ensuing preeclampsia), as well as premature CVD. Additionally, vascular damage experienced during preeclampsia may be permanent and further contribute to the development of CVD.[22]

Clinical relevance

On the basis of the current cumulative probability curves at 10 years, the absolute risk of CVD is approximately 39 per 10,000 in women without preeclampsia, 86 per 10,000 in women with preeclampsia, and 142 per 10,000 in men (Fig. 1). Thus, for every 10,000 young women who experience preeclampsia and are followed over 10 years, one might expect an additional 46 premature CVD events over same-aged women without preeclampsia. Moreover, for every 10,000 young men followed over 10 years, there might be an additional 103 premature CVD events compared with same-aged female counterparts without preeclampsia. How these notable estimates might influence current 10-year risk scores for CVD remains to be determined. In the current study, the median follow-up was approximately 16 years, which means that a typical participant was only 46 years old at the end of the study. Most women who had preeclampsia would still be premenopausal by the study end, and thus their risk of CVD might not yet be fully realized.

Certainly, it appears that young and middle-aged men remain at the highest overall risk of premature CVD, with the exception of the situation when a woman has preeclampsia with preterm delivery, in which case affected women have a near-equivalent risk as their same-age male counterparts. The latter is important, given the aforementioned studies that

showed a higher 10-year CVD risk score in women with early-onset preeclampsia or persistent (chronic) hypertension after preeclampsia.[24,25] In general, chronic hypertension is a foremost risk factor for stroke,[26] which supports the recommendation that blood pressure should be periodically measured after preeclampsia,[27] along with body mass index or abdominal waist circumference.[2] Given that women with preeclampsia have a notably higher risk of peripartum CVD, as further demonstrated herein, blood pressure control remains a mainstay, in keeping with current Canadian guidelines.[28]

Conclusions

Women with preeclampsia are at intermediary risk for premature CVD, higher than in non-preeclamptic women and lower than in men. When preeclampsia is of early onset, necessitating preterm delivery, the rate of CVD approaches that of men, especially for developing cerebrovascular disease. Comparing risk factors for stroke (and other CVD) in men vs women with a history of preeclampsia could lead to a better understanding of whether they develop different stroke subtypes and whether the pathogenesis of stroke and other CVD is similar.

Disclaimer

Parts of this material are based on data or information compiled and provided by the Canadian Institute for Health Information. However, the analyses, conclusions, opinions, and statements expressed in the material are those of the author(s), and not necessarily those of the Canadian Institute for Health Information.

Funding Sources

This work was supported by a grant from the Canadian Institutes of Health Research. This study was supported by the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by the Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care 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 article.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.06.028.