Maternal cardiovascular disease after twin pregnancies complicated by hypertensive disorders of pregnancy: a population-based cohort study

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Cite as: CMAJ 2021 September 20;193:E1448-58. doi: 10.1503/cmaj.202837

Abstract

Background: People whose singleton pregnancy is affected by hypertensive disorders of pregnancy (HDP) are at risk of future cardiovascular disease. It is unclear, however, whether this association can be extrapolated to twin pregnancies. We aimed to compare the association between HDP and future cardiovascular disease after twin and singleton pregnancies.

Methods: We conducted a population-based retrospective cohort study that included nulliparous people in Ontario, Canada, 1992–2017. We compared the future risk of cardiovascular disease among pregnant people from the following 4 groups: those who delivered a singleton without HDP (referent) and with HDP, and those who delivered twins either with or without HDP.

Results: The populations of the 4 groups were as follows: 1431651 pregnant people in the singleton birth without HDP group; 98631 singleton birth with HDP; 21046 twin birth without HDP; and 4283 twin birth with HDP. The median duration of follow-up was 13 (interquartile range 7–20) years. The incidence rate of cardiovascular disease was lowest among those with a singleton or twin birth without HDP (0.72 and 0.74 per 1000 person-years, respectively). Compared with people with a singleton birth without HDP, the risk of cardiovascular disease was highest among those with a singleton birth and HDP (1.47 per 1000 person-years; adjusted hazard ratio [HR] 1.81 [95% confidence interval (CI) 1.72–1.90]), followed by people with a twin pregnancy and HDP (1.07 per 1000 person-years; adjusted HR 1.36 [95% CI 1.04–1.77]). The risk of the primary outcome after a twin pregnancy with HDP was lower than that after a singleton pregnancy with HDP (adjusted HR 0.74 [95% CI 0.57–0.97]), when compared directly.

Interpretation: In a twin pregnancy, HDP are weaker risk factors for postpartum cardiovascular disease than in a singleton pregnancy.
with rates of 14% and 5%, respectively. The higher risk of HDP in twin pregnancies may be due to higher circulating sFlt1 and sEng owing to greater placental mass in twin pregnancies, and less related to the classic vascular risk factors for HDP in a singleton pregnancy. Therefore, a logical question is whether the established higher risk of future cardiovascular disease after singleton pregnancies with HDP also occurs in twin pregnancies with HDP. Limited data are available to answer this question. In the current study, we aimed to test the hypothesis that the association between HDP and future cardiovascular disease is less pronounced in twin versus singleton pregnancies.

Methods

Study design and participants
We conducted a population-based retrospective cohort study using linked administrative health databases for the province of Ontario, Canada, in which hospital and physician care is publicly funded for all residents. Eligible participants were nulliparous people aged 18–45 years who had a singleton or twin hospital live birth between Apr. 1, 1992, and Mar. 31, 2017. If a person had more than 1 pregnancy, we considered only the first.

We excluded pregnancies with invalid or missing data on gestational age, infant birth weight or infant sex; non-Ontario residents, or people not eligible for the Ontario Health Insurance Plan (OHIP) at the time of delivery; people who died or lost OHIP eligibility within 120 days after the delivery date; and a pregnancy complicated by a stillbirth of 1 or both fetuses. Furthermore, in order to avoid the inclusion of people with pre-existing cardiovascular disease before the index pregnancy, we also excluded those with any recognized form of cardiovascular disease within 2 years before the conception date of the index pregnancy. We present the list of diagnostic and billing codes used to identify cardiovascular disease before the index pregnancy in Appendix 1, Appendix A (available at www.cmaj.ca/lookup/doi/10.1503/cmaj.202837/tab-related-content). Those codes are used by caregivers at both inpatient and outpatient settings.

Data sources
We obtained data from Ontario health care administrative databases held at ICES. These databases contain data on health service utilization by residents of the province and include the Registered Persons Database, which records demographic information for all residents of Ontario, including deaths; and the Ontario Health Insurance Plan provider service claims database, which records all fee-for-service billing and shadow-billing claims submitted by Ontario physicians for inpatient or ambulatory consultations, assessments and diagnostic or therapeutic procedures. All in-hospital deliveries in Ontario are included in the ICES MOMBABY data set with 98% deterministic linkage of newborn and maternal hospital records. We obtained all hospital discharges from the Canadian Institutes of Health Information Discharge Abstract Database. We identified all emergency department records using the National Ambulatory Care Reporting System. We used Immigration, Refugees and Citizenship Canada’s Permanent Resident Database to obtain immigration information. Records from the administrative databases are deterministically linked using a patient’s encrypted health card number.

We used the International Classification of Diseases (ICD) coding system (9th Revision [ICD-9] before 2002 and the Canadian version, 10th Revision [ICD-10-CA] thereafter) to identify previously validated study exposures and outcomes. We based residential area income quintile and rurality on Statistics Canada Census data.

Exposures
The primary exposure was 1 of 4 mutually exclusive states in the index (first) pregnancy: i) singleton birth, no HDP; ii) singleton birth, with HDP; iii) twin birth, no HDP; iv) twin birth, with HDP. We defined HDP as either pre-eclampsia (ICD-9 codes 642.4 or 642.7, and ICD-10 codes O11, O14 or O15) or gestational hypertension (ICD-9 codes 642.3 or 642.9, and ICD-10 code O13) at the index birth, ascertained from the Canadian Institute for Health Information Discharge Abstract Database. For the primary analysis, we chose people with a first singleton birth without HDP as the reference group, as they provide a large sample of pregnant people who are likely representative of the population at large. For those with a twin pregnancy and HDP, we also estimated the risk of future cardiovascular disease relative to singleton pregnancies and HDP in order to provide a direct comparison between the 2 groups.

As people with pre-eclampsia may have a more pronounced risk of cardiovascular disease than those with gestational hypertension, especially when pre-eclampsia arises preterm, we further considered 2 secondary exposures: any pre-eclampsia, and pre-eclampsia with a preterm birth before 34 weeks’ gestation. As gestational age at birth is available only from April 2002 onward, we limited the analysis to births starting Apr. 1, 2002.

Outcomes
We defined the primary outcome as a cardiovascular disease composite of any future hospital admission for heart failure, cardiac dysrhythmia, coronary artery disease, cerebrovascular disease or peripheral artery disease (Appendix 1, Appendix B). Secondary study outcomes included the individual components of the primary outcome, as well as all-cause mortality. To minimize the immediate effect of HDP and other factors related to pregnancy and delivery on the risk of cardiovascular disease, we assessed study outcomes starting at 120 days after the index birth date.

Statistical analysis
We used standard descriptive statistics to present the baseline characteristics of the 4 exposure groups. We expressed time-to-event analyses for each study outcome as incidence rates per 1000 person-years, with 95% confidence intervals (CIs), starting 120 days after the index birth date. We used Cox proportional hazards models to generate unadjusted and adjusted hazard ratios (HRs), and censored on death, outmigration from the province, or reaching the end of the study period of Mar. 31, 2018. If a person had more than 1 cardiovascular disease event, we counted the first event. A priori, we adjusted HRs for the
pregnant person’s age at the index birth, neighbourhood income quintile, world region of origin, assisted reproductive technology use, and cardiovascular risk factors present before pregnancy, including diabetes mellitus, chronic hypertension, obesity, dyslipidemia, tobacco use or drug dependence, and kidney disease (Appendix 1, Appendix C). We generated time-to-event curves using the Kaplan–Meier procedure and compared exposure groups using the log-rank test.

We analyzed data using the SAS Enterprise Guide statistical software Version 6.1 (Cary, NC).

Ethics approval
The use of data in this project was authorized under section 45 of Ontario’s Personal Health Information Protection Act, in accordance with the Sunnybrook Research Ethics Board.

Results
There were 3,267,689 births during the study period. Of the 1,555,611 nulliparous people who met the study inclusion criteria, 25,329 (1.6%) had a twin gestation (Figure 1). The proportions of pregnancies complicated by HDP in the singleton and twin groups were 6.4% (98,631/1,530,282) and 16.9% (4,283/25,329), respectively (Figure 1).

The baseline characteristics of the study groups at the time of the index (first) pregnancy are presented in Table 1. Most people lived in a city and had no prepregnancy morbidity.

The median (interquartile range) duration of follow-up was 13 (7–20) years. The cumulative probability of the cardiovascular disease composite outcome was lowest among people without HDP, either in a singleton or twin pregnancy (incidence rate 0.72 and

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Figure 1: Description of the study groups. Note: HDP = hypertensive disorders of pregnancy, OHIP = Ontario Health Insurance Plan. *For the term “birth,” the unit of analysis is newborn rather than pregnancy. Thus, a delivery of twins is counted as 2 births.
Table 1: Baseline characteristics of the study groups

| Characteristic                              | No. (%)* of singleton births, no HDP | No. (%)* of singleton births, with HDP | No. (%)* of twin births, no HDP | No. (%)* of twin births, with HDP |
|--------------------------------------------|--------------------------------------|----------------------------------------|----------------------------------|----------------------------------|
| Age at delivery, mean ± SD, yr             | 28.8 ± 5.4                           | 29.2 ± 5.5                              | 30.7 ± 5.2                       | 31.1 ± 5.4                       |
| 18–24                                      | 319 126 (22.3)                       | 20 519 (20.8)                           | 2616 (12.4)                      | 485 (11.3)                       |
| 25–40                                      | 1 091 669 (76.3)                     | 75 871 (76.9)                           | 17 868 (84.9)                    | 3615 (84.4)                      |
| > 40                                       | 20 856 (1.5)                         | 2241 (2.3)                              | 562 (2.7)                        | 183 (4.3)                        |
| World region of origin                     |                                      |                                        |                                  |                                  |
| Canada                                     | 1 050 177 (73.4)                     | 80 537 (81.7)                           | 16 172 (76.8)                    | 3518 (82.1)                      |
| Africa and Middle East                     | 56 757 (4.0)                         | 2557 (2.6)                              | 926 (4.4)                        | 124 (2.9)                        |
| Americas                                   | 50 256 (3.5)                         | 3149 (3.2)                              | 623 (3.0)                        | 118 (2.8)                        |
| Asia and Pacific                           | 207 322 (14.5)                       | 8961 (9.1)                              | 2280 (10.8)                      | 362 (8.5)                        |
| Europe                                     | 60 521 (4.2)                         | 2969 (3.0)                              | 925 (4.4)                        | 139 (3.2)                        |
| United States                              | 6541 (0.5)                           | 454 (0.5)                               | 118 (0.6)                        | 22 (0.5)                         |
| Not stated                                  | 77 (0.0)                             | ≤ 5§                                    | ≤ 5§                             | ≤ 5§                             |
| Neighbourhood-level household income       |                                      |                                        |                                  |                                  |
| Quintile 1 (lowest)                        | 337 527 (23.6)                       | 22 028 (22.3)                           | 3938 (18.7)                      | 714 (16.7)                       |
| Quintile 2                                 | 299 580 (20.9)                       | 20 795 (21.1)                           | 4126 (19.6)                      | 800 (18.7)                       |
| Quintile 3                                 | 286 262 (20.0)                       | 20 576 (20.9)                           | 4226 (20.1)                      | 904 (21.1)                       |
| Quintile 4                                 | 280 197 (19.6)                       | 19 793 (20.1)                           | 4659 (22.1)                      | 963 (22.5)                       |
| Quintile 5 (highest)                       | 221 176 (15.4)                       | 14 939 (15.1)                           | 4027 (19.1)                      | 882 (20.6)                       |
| Unknown                                    | 6909 (0.5)                           | 500 (0.5)                               | 70 (0.3)                         | 20 (0.5)                         |
| Rural residence at delivery               | 78 470 (5.5)                         | 6481 (6.6)                              | 1107 (5.3)                       | 238 (5.6)                        |
| Prepregnancy morbidity                    |                                      |                                        |                                  |                                  |
| Diabetes                                   | 13 902 (1.0)                         | 2759 (2.8)                              | 280 (1.3)                        | 101 (2.4)                        |
| Chronic hypertension                       | 39 389 (2.8)                         | 9388 (9.5)                              | 702 (3.3)                        | 312 (7.3)                        |
| Tobacco use or drug dependence             | 50 694 (3.5)                         | 3767 (3.8)                              | 749 (3.6)                        | 147 (3.4)                        |
| Kidney disease                             | 4110 (0.3)                           | 622 (0.6)                               | 71 (0.3)                         | 30 (0.7)                         |
| Assisted reproductive technology           | 11 980 (0.8)                         | 1387 (1.4)                              | 2596 (12.3)                      | 613 (14.3)                       |
| Gestational age at birth, wk               |                                      |                                        |                                  |                                  |
| < 37                                       | 64 071 (4.5)                         | 13 666 (13.9)                           | 10 081 (47.9)                    | 2514 (58.7)                      |
| < 34                                       | 17 867 (1.2)                         | 5060 (5.1)                              | 4008 (19.0)                      | 594 (13.9)                       |
| Neonatal characteristics†                  |                                      |                                        |                                  |                                  |
| Female infant                              | 698 713 (48.8)                       | 47 191 (47.8)                           | 20 649 (49.1)                    | 4320 (50.4)                      |
| Birth weight, mean ± SD, g                 | 3367 ± 545                           | 3159 ± 742                              | 2358 ± 656                       | 2365 ± 543                       |
| ≤ Tenth percentile†                        | 104 987 (7.3)                        | 19 663 (19.9)                           | 27 377 (65.0)                    | 6007 (70.1)                      |
| ≤ Third percentile‡                        | 24 470 (1.7)                         | 8386 (8.5)                              | 11 975 (28.4)                    | 2308 (26.9)                      |
| Duration of follow-up of pregnant person, median (IQR), yr | 13 (7–20)                           | 13 (7–20)                              | 12 (7–18)                        | 12 (7–19)                        |

Note: HDP = hypertensive disorders of pregnancy, IQR = interquartile range, SD = standard deviation.
*Unless otherwise specified.
†The unit of analysis for neonatal characteristics is infant rather than pregnancy.
‡Based on the Canadian growth reference of Kramer and colleagues.45
§Data suppressed because of small cell size.
0.74 per 1000 person-years, respectively), highest in those with a singleton birth and HDP (1.47 per 1000 person-years), and intermediate in those with a twin birth and HDP (1.07 per 1000 person-years) (Figure 2 and Table 2). Relative to a singleton birth without HDP, the corresponding adjusted HRs were 1.81 (95% CI 1.72–1.90) in singleton pregnancies with HDP and 1.36 (95% CI 1.04–1.77) in twin pregnancies with HDP (Table 2, Figure 3). When we compared the risk of the primary outcome in the twin pregnancy with HDP group versus the singleton pregnancy with HDP group, the adjusted HR was 0.74 (95% CI 0.57–0.97) (Appendix 1, Appendix D).

Hypertensive disorders of pregnancy were associated with all the secondary outcomes in singleton pregnancies, but not in twin pregnancies (Table 3). For instance, relative to a singleton birth without HDP, the corresponding adjusted HRs for heart failure, coronary artery disease and cerebrovascular disease were 2.20 (95% CI 1.92–2.51), 1.91 (95% CI 1.80–2.03) and 2.13 (95% CI 1.88–2.42), in singleton pregnancies with HDP and 1.74 (95% CI 0.87–3.48), 1.37 (95% CI 0.98–1.91) and 1.51 (95% CI 0.76–3.04) in twin pregnancies with HDP, respectively (Table 4).

When we calculated the risk of the secondary outcomes in the twin pregnancy with HDP group using the singleton pregnancy with HDP group as the reference, the effect size ranged from 0.36 to 0.83 (indicating a lower risk of the secondary outcomes in twin pregnancy with HDP compared with the reference group), but none of these associations were statistically significant (Appendix 1, Appendix E).

In both singleton and twin gestations, the associations between either pre-eclampsia or pre-eclampsia with preterm birth before 34 weeks and the primary cardiovascular disease composite were similar in direction and magnitude to those observed for the primary exposure of HDP (Table 2; Appendix 1, Appendices D and F).

Finally, to determine whether age during pregnancy modifies the associations described above, we stratified the analysis for the primary outcome by age (Table 4). Although the incidence rates were higher among people aged 35 years or older than those younger than 35 years, the risk of the primary outcome in each of the groups in relation to the referent group (singleton pregnancies without HDP) remained similar (Table 4).

**Interpretation**

**Main findings**

In agreement with our hypothesis, we found that those with a history of HDP in a twin pregnancy were at an intermediate risk of the primary composite cardiovascular disease outcome, with

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**Figure 2:** Cumulative probability of the composite primary outcome by plurality and hypertensive disorders of pregnancy (HDP; gestational hypertension or pre-eclampsia) in a first pregnancy. Note: The cumulative probability curves of the composite cardiovascular outcome are presented for twin and singleton pregnancies with and without HDP. *n* = number at risk at each 5-year interval shown. Differences between the 4 groups were statistically significant (p < 0.001, log-rank test).
the risk being lower than in those with HDP in a singleton pregnancy, but higher than in people with a twin pregnancy without HDP. The association was not affected by the severity of hypertensive complications.

Comparison with other studies

The association of HDP with future cardiovascular disease is well established. In a recent meta-analysis, women with a history of pre-eclampsia had a relative risk of 2.5 for future coronary artery disease, 4.2 for heart failure, and 2.2 for cardiovascular death. Given the relatively high prevalence of HDP in twin pregnancies (16.9% in the current study, which is in agreement with previous reports), it is important to determine whether this association can be extrapolated to people who experienced HDP in a twin pregnancy. As previous studies were either limited to people with singleton gestations or did not differentiate between people with singleton and twin gestations, our findings add to the literature by qualifying the relationship between HDP and future cardiovascular disease among people who have a twin pregnancy. A recently published cohort study reported that pre-eclampsia in women with multifetal pregnancy was not associated with a higher risk of future cardiovascular disease. However, that study addressed only pre-eclampsia (and not gestational hypertension) as the exposure variable, and did not adjust for known cardiovascular risk factors such as diabetes mellitus and kidney disease. Our results confirm previous findings regarding the association of HDP in singleton gestations with future maternal cardiovascular disease but suggest that the magnitude of this association is lower in those who experienced HDP during a twin pregnancy. Although the adjusted hazard ratio for future cardiovascular disease in the twin pregnancy with HDP group

Table 2 (part 1 of 2): Risk of the primary composite outcome in relation to plurality and the hypertensive disorders of pregnancy using people with a singleton birth with no hypertensive disorders as the reference group

| Exposure                      | No. events | Incidence rate (per 1000 person-year, 95% CI) | Unadjusted HR (95% CI) | Adjusted HR† (95% CI) |
|-------------------------------|------------|---------------------------------------------|------------------------|-----------------------|
| Any hypertensive disorder of pregnancy | 13 076/1 431 651 | 0.72 (0.71–0.73) | 1811/98 631 | 1.47 (1.40–1.54) | 2.08 (1.98–2.18) | 1.81 (1.72–1.90) |
| Pre-eclampsia                 | 13 840/1 489 419 | 0.73 (0.72–0.75) | 1047/40 863 | 1.73 (1.63–1.84) | 2.09 (1.97–2.23) | 1.83 (1.72–1.95) |
| Preterm pre-eclampsia†        | 255/18 802 | 1.17 (1.03–1.32) | 126/4125 | 2.44 (2.05–2.91) | 1.99 (1.61–2.46) | 1.84 (1.48–2.30) |

Table 2 (part 2 of 2): Risk of the primary composite outcome in relation to plurality and the hypertensive disorders of pregnancy using people with a singleton birth with no hypertensive disorders as the reference group

| Exposure                      | No. events | Incidence rate (per 1000 person-year, 95% CI) | Unadjusted HR (95% CI) | Adjusted HR† (95% CI) |
|-------------------------------|------------|---------------------------------------------|------------------------|-----------------------|
| Any hypertensive disorder of pregnancy | 185/21 046 | 0.74 (0.64–0.85) | 55/4283 | 1.07 (0.82–1.40) | 1.56 (1.20–2.04) | 1.36 (1.04–1.77) |
| Pre-eclampsia                 | 200/22 963 | 0.74 (0.64–0.85) | 40/2366 | 1.01 (0.87–1.16) | 1.28 (0.94–1.75) | 1.65 (1.21–2.26) | 1.42 (1.04–1.93) |
| Preterm pre-eclampsia†        | 40/4180 | 0.84 (0.62–1.15) | 8/422 | 0.77 (0.55–1.07) | 1.65 (0.83–3.30) | 1.39 (0.69–2.81) | 1.10 (0.54–2.23) |

Note: CI = confidence interval, HR = hazard ratio.
*The primary outcome is defined as a composite of any future hospital admission for heart failure, cardiac dysrhythmia, coronary artery disease, cerebrovascular disease, or peripheral artery disease.
†Adjusted for age at first birth, neighbourhood income quintile, world region of origin, assisted reproductive technology, and cardiovascular risk factors present at baseline before the first pregnancy.
‡Defined as pre-eclampsia with a preterm birth < 34 weeks’ gestation.
did not differ significantly from that found in the singleton pregnancy with HDP group (as reflected by the overlapping CIs), this is likely to be due to insufficient power, given the considerable differences in the point estimates of the hazard ratios, and as demonstrated by the differences in the incidence rates and the survival curves (Figure 2) between the twin pregnancy with HDP and singleton pregnancy with HDP groups. Furthermore, the risk of the primary outcome in twin pregnancies with HDP was significantly lower than in singleton pregnancies with HDP (adjusted HR 0.74 [95% CI 0.57–0.97]).

The mechanisms underlying the association between HDP and future cardiovascular disease remain unclear. One explanation is that HDP is associated with a release of inflammatory and anti-angiogenic factors, and although these changes usually resolve postpartum, some patients experience sustained vascular damage and endothelial dysfunction, which may predispose them to future cardiovascular disease. The differences in the associations between HDP and future cardiovascular disease between twin and singleton pregnancies identified in our study argues against a direct causal relationship between HDP and future maternal cardiovascular disease, however, because the association between HDP and future cardiovascular disease would be expected to be similar in people who had delivered twins and singletons, respectively, if that was the case. Furthermore, the lack of a “dose–response” relationship between the severity of HDP and future cardiovascular disease, as we observed, further argues against a direct causal relationship between HDP and future cardiovascular disease.

A second explanation for the association between HDP and future cardiovascular disease attributes this association to the

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Figure 3: Incidence rate of cardiovascular morbidity or death by plurality and hypertensive disorders of pregnancy (HDP; gestational hypertension or pre-eclampsia) in the first pregnancy. The incidence rates of the composite cardiovascular outcome are presented for people with twin and singleton pregnancies with and without HDP. Values are presented as rate per 1000 person-years (PYs) with 95% confidence intervals (CI).
presence of underlying clinical or subclinical maternal vascular risk factors that predispose patients to both HDP and future cardiovascular disease (Appendix 1, Appendix G). Our observation of a lower association of HDP with future cardiovascular disease in people who had delivered twins compared with singletons provides support for this explanation. In people who have delivered twins, where the pathogenesis of HDP is heterogeneous and some of it likely attributed to transient factors such as increased placental

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### Table 3 (part 1 of 2): Risk of the secondary outcomes in relation to plurality and the hypertensive disorders of pregnancy using people with a singleton birth with no hypertensive disorders as the reference group

| Outcome                  | Singleton birth, no HDP (referent) | Singleton birth, with HDP |
|--------------------------|------------------------------------|----------------------------|
|                          | Incidence rate (per 1000 person-year, 95% CI) | No. events | Incidence rate (per 1000 person-year, 95% CI) | No. events | Unadjusted HR (95% CI) | Adjusted HR* (95% CI) |
| Heart failure            | 1466 0.08 (0.08–0.08)               | 266 0.21 (0.19–0.24)     | 2.70 (2.37–3.08) | 2.20 (1.92–2.51) |
| Cardiac dysrhythmia      | 1976 0.11 (0.10–0.11)               | 236 0.19 (0.17–0.22)     | 1.78 (1.55–2.03) | 1.55 (1.34–1.77) |
| Coronary artery disease  | 8139 0.45 (0.44–0.46)               | 1208 0.98 (0.92–1.03)    | 2.23 (2.10–2.37) | 1.91 (1.80–2.03) |
| Cerebrovascular disease  | 1764 0.10 (0.09–0.10)               | 290 0.23 (0.21–0.26)     | 2.45 (2.16–2.77) | 2.13 (1.88–2.42) |
| Peripheral artery disease| 1608 0.09 (0.08–0.09)               | 149 0.12 (0.10–0.14)     | 1.37 (1.16–1.62) | 1.24 (1.04–1.46) |
| All-cause mortality      | 10183 0.56 (0.55–0.57)              | 922 0.74 (0.69–0.79)     | 1.35 (1.26–1.44) | 1.23 (1.14–1.31) |

### Table 3 (part 2 of 2): Risk of the secondary outcomes in relation to plurality and the hypertensive disorders of pregnancy using people with a singleton birth with no hypertensive disorders as the reference group

| Outcome                  | Twin birth, no HDP | Twin birth, with HDP |
|--------------------------|--------------------|----------------------|
|                          | Incidence rate (per 1000 person-year, 95% CI) | No. events | Unadjusted HR (95% CI) | No. events | Unadjusted HR (95% CI) | Adjusted HR* (95% CI) |
| Heart failure            | 28 0.11 (0.08–0.16) | 1.46 (1.00–2.11)     | 1.37 (0.92–2.01) | 8 0.15 (0.08–0.31) | 2.02 (1.01–4.05) | 1.74 (0.87–3.48) |
| Cardiac dysrhythmia      | 28 0.15 (0.11–0.20) | 1.43 (1.03–1.97)     | 1.33 (0.96–1.85) | 9 0.17 (0.09–0.34) | 1.68 (0.87–3.24) | 1.44 (0.75–2.77) |
| Coronary artery disease  | 125 0.50 (0.42–0.59) | 1.19 (0.99–1.41)     | 1.11 (0.93–1.33) | 35 0.68 (0.49–0.95) | 1.61 (1.16–2.25) | 1.37 (0.98–1.91) |
| Cerebrovascular disease  | 19 0.08 (0.05–0.12) | 0.82 (0.52–1.28)     | 0.80 (0.51–1.26) | 8 0.16 (0.08–0.31) | 1.67 (0.83–3.35) | 1.51 (0.76–3.04) |
| Peripheral artery disease| 14 0.06 (0.03–0.09) | 0.64 (0.38–1.09)     | 0.63 (0.37–1.06) | ≤5† 0.04 (0.01–0.15) | 0.45 (0.11–1.80) | 0.41 (0.10–1.64) |
| All-cause mortality      | 152 0.60 (0.51–0.71) | 1.13 (0.96–1.33)     | 1.09 (0.92–1.28) | 28 0.54 (0.37–0.79) | 1.01 (0.70–1.47) | 0.93 (0.64–1.35) |

Note: CI = confidence interval, HDP = hypertensive disorders of pregnancy (pre-eclampsia or gestational hypertension), HR = hazard ratio.

*Adjusted for age at first birth, neighbourhood income quintile, world region of origin, assisted reproductive technology, and cardiovascular risk factors present at baseline before the first pregnancy.

†Data suppressed because of small cell size.

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### Table 4 (part 1 of 2): Risk of the primary composite outcome in relation to plurality and the hypertensive disorders of pregnancy using people with a singleton birth with no hypertensive disorders as the referent, stratified by age of the pregnant person at delivery*

| Exposure                                      | Singleton birth, no hypertensive complication (referent) | Singleton birth, with hypertensive complication |
|-----------------------------------------------|--------------------------------------------------------|-----------------------------------------------|
|                                               | No. events | Incidence rate (per 1000 person-year, 95% CI) | No. events | Incidence rate (per 1000 person-year, 95% CI) | Unadjusted HR (95% CI) | Adjusted HR† (95% CI) |
| Age of pregnant person ≤ 35 yr                |            |                                              |            |                                              |                        |                        |
| Any hypertensive disorder of pregnancy        | 1 275 539  | 0.65 (0.64–0.66)                             | 85 434     | 1.28 (1.22–1.35)                             | 2.00 (1.89–2.11)       | 1.77 (1.68–1.88)       |
| Pre-eclampsia                                 | 1 325 408  | 0.66 (0.65–0.68)                             | 35 565     | 1.54 (1.44–1.65)                             | 2.06 (1.92–2.21)       | 1.83 (1.70–1.96)       |
| Preterm pre-eclampsia‡                       | 15 804     | 0.99 (0.86–1.15)                             | 3400       | 2.17 (1.77–2.65)                             | 2.07 (1.61–2.65)       | 1.95 (1.51–2.52)       |
| Age of pregnant person > 35 yr                |            |                                              |            |                                              |                        |                        |
| Any hypertensive disorder of pregnancy        | 156 112    | 1.32 (1.27–1.37)                             | 13 197     | 2.80 (2.55–3.08)                             | 2.17 (1.96–2.41)       | 1.86 (1.67–2.07)       |
| Pre-eclampsia                                 | 164 011    | 1.37 (1.32–1.42)                             | 5298       | 3.16 (2.77–3.61)                             | 2.08 (1.81–2.39)       | 1.75 (1.53–2.02)       |
| Preterm pre-eclampsia‡                       | 2998       | 2.16 (1.71–2.72)                             | 725        | 3.87 (2.74–5.48)                             | 1.73 (1.14–2.63)       | 1.49 (0.95–2.34)       |

Note: CI = confidence interval, HR = hazard ratio.

*The primary outcome is defined as a composite of any future hospital admission for heart failure, cardiac dysrhythmia, coronary artery disease, cerebrovascular disease or peripheral artery disease.

†Adjusted for age at first birth, neighbourhood income quintile, world region of origin, assisted reproductive technology, and cardiovascular risk factors present at baseline before the first pregnancy.

### Table 4 (part 2 of 2): Risk of the primary composite outcome in relation to plurality and the hypertensive disorders of pregnancy using people with a singleton birth with no hypertensive disorders as the referent, stratified by age of the pregnant person at delivery*

| Exposure                                      | Twin birth, no hypertensive complication | Twin birth, with hypertensive complication |
|-----------------------------------------------|---------------------------------------|----------------------------------------|
|                                               | No. events | Incidence rate (per 1000 person-year, 95% CI) | Unadjusted HR (95% CI) | Adjusted HR† (95% CI) | No. events | Incidence rate (per 1000 person-year, 95% CI) | Unadjusted HR (95% CI) | Adjusted HR† (95% CI) |
| Age of pregnant person ≤ 35 yr                |            |                                              |                        |                        |            |                                              |                        |                        |
| Any hypertensive disorder of pregnancy        | 17 351     | 0.63 (0.53–0.75)                             | 1.01 (0.85–1.20)       | 0.97 (0.82–1.15)       | 3381       | 0.92 (0.67–1.26)                             | 1.46 (1.06–1.99)       | 1.30 (0.95–1.78)       |
| Pre-eclampsia                                 | 18 850     | 0.64 (0.55–0.76)                             | 1.01 (0.86–1.19)       | 0.98 (0.83–1.15)       | 1882       | 1.00 (0.68–1.47)                             | 1.40 (0.95–2.06)       | 1.23 (0.84–1.81)       |
| Preterm pre-eclampsia‡                       | 3529       | 0.73 (0.51–1.05)                             | 0.75 (0.51–1.10)       | 0.79 (0.54–1.17)       | 310        | 1.32 (0.55–3.17)                             | 1.27 (0.52–3.10)       | 1.06 (0.43–2.58)       |
| Age of pregnant person > 35 yr                |            |                                              |                        |                        |            |                                              |                        |                        |
| Any hypertensive disorder of pregnancy        | 3695       | 1.31 (0.99–1.72)                             | 1.09 (0.83–1.44)       | 1.09 (0.83–1.44)       | 902        | 1.76 (1.08–2.88)                             | 1.50 (0.92–2.45)       | 1.39 (0.85–2.28)       |
| Pre-eclampsia                                 | 4113       | 1.23 (0.94–1.61)                             | 1.00 (0.76–1.31)       | 1.00 (0.76–1.32)       | 484        | 2.70 (1.60–4.56)                             | 1.99 (1.18–3.37)       | 1.82 (1.08–3.08)       |
| Preterm pre-eclampsia‡                       | 651        | 1.50 (0.81–2.79)                             | 0.73 (0.38–1.42)       | 0.76 (0.39–1.50)       | 112        | 2.83 (0.91–8.78)                             | 1.42 (0.45–4.52)       | 1.24 (0.38–4.08)       |

Note: CI = confidence interval, HR = hazard ratio.

*The primary outcome is defined as a composite of any future hospital admission for heart failure, cardiac dysrhythmia, coronary artery disease, cerebrovascular disease or peripheral artery disease.

†Adjusted for age at first birth, neighbourhood income quintile, world region of origin, assisted reproductive technology, and cardiovascular risk factors present at baseline before the first pregnancy.

†Defined as pre-eclampsia with a preterm birth < 34 weeks’ gestation.
mass rather than to vascular predisposition, the association between HDP with future maternal cardiovascular disease would be expected to be weaker than in people who have delivered singletons (Appendix 1, Appendix G). This explanation is further supported by previous studies reporting that the risk of recurrence of HDP in subsequent pregnancies is greater for people with a history of HDP in a singleton gestation (where HDP is likely to reflect vascular predisposition) than for those with a history of HDP in a twin gestation (where HDP is more likely to be the result of the transient risk factor such as increased placental mass).\textsuperscript{53}

Limitations

The main limitations of our study are those inherent to the use of administrative databases that are based on diagnostic or billing codes to determine outcomes. Thus, cases with mild cardiovascular disease may not have been recorded. In addition, although we adjusted the analysis for multiple confounding variables, we could not rule out residual confounding, as data on certain cardiovascular risk factors, such as family history of cardiovascular disease and maternal body mass index, were not available. Furthermore, given the observational nature of the study, data on preventive interventions and risk reduction measures in those with a history of HDP were not available.\textsuperscript{11,12,54} Finally, despite the large sample size, the current study was underpowered to detect associations with the secondary outcomes in the twin group.

Conclusion

We found that compared with HDP in singleton pregnancies, HDP in twin pregnancies is less likely to be associated with future cardiovascular disease. This suggests that HDP in twin gestations is a weaker risk factor for future cardiovascular disease than HDP in singleton pregnancies. This has important implications for the counselling and risk stratification of cardiovascular risk, given the relatively high prevalence of HDP in twin gestations, as well as for the understanding of the mechanisms underlying HDP in twin compared with singleton pregnancies. Future studies should focus on the pathophysiology of HDP in twin compared with singleton pregnancies, and on the mechanisms underlying the association between HDP and future cardiovascular disease in these 2 groups.

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