Circulation

ORIGINAL RESEARCH ARTICLE

Risk of Incident Atrial Fibrillation in Women With a History of Hypertensive Disorders of Pregnancy: A Population-Based Retrospective Cohort Study

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BACKGROUND: Hypertensive disorders of pregnancy (HDP) are a major cause of maternal morbidity and mortality and are associated with acute cardiac events in the peripartum period, as well as cardiovascular disease later in life. Despite the robust association between hypertension and atrial fibrillation (AFib), comparatively little is known about HDP and its subtypes as sex-specific risk factors for AFib.

METHODS: A population-based retrospective cohort study was conducted, including 771 521 nulliparous women discharged for obstetrical delivery of their first live or stillborn singleton infant between 2002 and 2017 in Ontario, Canada. Data were obtained from record-level, coded, and linked population-based administrative databases housed at ICES. Using competing risks Cox proportional hazards regression, we estimated crude and multivariable-adjusted cause-specific hazard ratios and 95% CIs for associations between history of any HDP (and its 6 subtypes), and AFib before death, as well as all-cause mortality without a previous AFib diagnosis.

RESULTS: Approximately 8% of women were diagnosed with HDP during the 16-year exposure accrual period. The total person-time of follow-up was 7 380 304 person-years, during which there were 2483 (0.3%) incident AFib diagnoses and 2951 (0.4%) deaths. History of any HDP was associated with an increased cause-specific hazard ratios of incident AFib and death without a previous AFib diagnosis (adjusted cause-specific hazard ratios, 1.45 [95% CI, 1.28–1.64] and 1.31 [95% CI, 1.16–1.47], respectively). These associations were observed in relatively young women (median time to event, 7 years postpartum). Associations suggestive of a dose-response relationship were observed, with more severe HDP subtypes and prepregnancy chronic hypertension associated with a 1.5 to 2.2 times higher cause-specific rate of AFib, and a 1.4 to 2.1 times higher cause-specific rate of death compared with no hypertension in pregnancy.

CONCLUSIONS: Women exposed to HDP in their first delivery have a significantly increased cause-specific hazard ratios of incident AFib compared to their unexposed counterparts, with higher rates observed in subjects exposed to more severe de novo HDP diagnoses as well as chronic hypertension in pregnancy. These findings underscore the need to consider HDP history in risk calculation/stratification for arrhythmic and nonarrhythmic cardiovascular diseases, improve surveillance of traditional and female-specific cardiovascular disease risk factors, and develop targeted prevention strategies to reduce the occurrence and burden of HDP.

Key Words: atrial fibrillation ■ epidemiology ■ hypertension ■ preeclampsia ■ pregnancy ■ retrospective cohort

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Clinical Perspective

What Is New?

- In this population-based retrospective cohort study of 771 521 nulliparous women, a history of hypertensive disorders of pregnancy (HDP) significantly increased the cause-specific hazard of incident atrial fibrillation compared with women without HDP, even after adjustment for confounders, and this association was observed in relatively young women (median follow-up: 7 years postpartum).
- Associations suggestive of a dose-response relationship were observed, whereby subjects with more severe de novo HDP diagnoses, as well as those with prepregnancy chronic hypertension, had higher cause-specific rates of atrial fibrillation, with the highest rate observed in subjects exposed to chronic hypertension in pregnancy.

What Are the Clinical Implications?

- These findings suggest that women with a history of any HDP, especially those with prepregnancy chronic hypertension, may benefit from closer monitoring for the early detection of atrial fibrillation.
- Enhanced population-based surveillance of, and targeted strategies to prevent, HDP as a female-specific cardiovascular risk factor are needed to mitigate intermediate- and long-term cardiovascular disease risk associated with these adverse pregnancy conditions.

Nonstandard Abbreviations and Acronyms

AFib	atrial fibrillation
CIHI-DAD	Canadian Institutes for Health Information Discharge Abstract Database
csHR	cause-specific hazard ratio
CVD	cardiovascular disease
HDP	hypertensive disorders of pregnancy
ICD-10	International Classification of Diseases, Tenth Revision
ICES	Institute for Clinical Evaluative Sciences
MOMBABY	Mother-Baby database
OHIP	Ontario Health Insurance Program
RECORD	Reporting of Studies Conducted Using Observational Routinely-Collected Health Data
RPDB	Registered Persons Database

Hypertensive disorders of pregnancy (HDP), which affect 5% to 15% of all pregnancies,[1,2] are a heterogeneous group of obstetrical complications[3] representing a major cause of maternal and fetal/neonatal morbidity and mortality.[4] Several studies report associations between a history of HDP and acute cardiac events in the peripartum period, as well as cardiovascular disease (CVD) later in life.[5,6]

Most studies reporting CVD risk after HDP have focused on nonarrhythmic cardiovascular outcomes (eg, myocardial infarction/coronary artery disease, stroke, and heart failure).[7–9] Previous studies examining the association between HDP and incident atrial fibrillation (AFib)[4,10–13] either have considered AFib as part of a composite outcome[10,12] or have focused solely on preeclampsia.[12,14,15] Further, most of these studies had relatively short (median) follow-up times (eg, 1,[11] 2,[14] and 7[16] years), did not consider death as a competing risk, and failed to control for important confounders. Moreover, despite evidence that HDPs may represent distinct disease phenotypes,[7] no previous studies have examined potential dose-response associations between distinct HDP subtypes (eg, chronic hypertension in pregnancy, gestational hypertension) and incident AFib.

The global prevalence of AFib has doubled over the past 3 decades, rising from 19 million individuals in 1990 to 38 million in 2017.[17] It is now considered the cardiovascular epidemic of the 21st century, with the absolute burden of AFib projected to rise by >60% by 2025.[18] Given the rising social, economic, and public health burden of AFib,[17] and growing evidence suggesting that women are more symptomatic,[19] report lower overall quality of life, experience greater functional impairment,[20] are more susceptible to AFib with rising blood pressure,[21] and are diagnosed later in the disease course compared with men,[22] more evidence is needed on HDP and its subtypes as sex-specific risk factors for AFib.[11]

In light of the identified knowledge gaps, our primary aim was to examine the association between exposure to any HDP in a first singleton pregnancy and subsequent incident AFib using a competing risks analytic framework. Our secondary aim was to evaluate potential dose-response relationships between the severity of HDP (based on specific HDP subtypes) and incident AFib using the same analytical approach.

METHODS

This study followed published methodological guidance on assessing CVD risk in people with a history of HDP using administrative health care data.[7] We also used the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) statement[23] to guide study reporting. A copy of our completed RECORD checklist is provided in Table S1.

Data Availability Statement

The data set used in this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). Although legal data sharing agreements between ICES and

data providers prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at http://www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Study Design and Setting

This was a population-based retrospective cohort study of nulliparous women discharged from Ontario hospitals after delivery of their first live or stillborn singleton infant between April 1, 2002, and December 31, 2017 (index date of cohort entry; Figure 1). Subjects were followed until they had an incident AFib diagnosis, they had a recorded death date, they were no longer eligible for the Ontario Health Insurance Program (OHIP; ie, migrated out of Ontario), or at the end of study follow-up (December 31, 2019), whichever came first. An overarching summary of the study methodology is depicted in Figure 2. Ontario is the most populous province of Canada and provides essential medical services, in-hospital prescription drugs, and immunizations free of charge for all residents through OHIP. Data generated from the use of routine health care services are maintained at ICES. ICES is an independent, nonprofit research institute, the legal status of which, under the health information privacy law of Ontario, allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

Data Sources

We used data obtained from record-level, coded, population-based administrative databases that were linked using unique encoded identifiers and analyzed at ICES (Figure S1; details about each data set are provided in Table S2).

Demographic information at index delivery (maternal date of birth, residential postal code) was obtained from the Registered

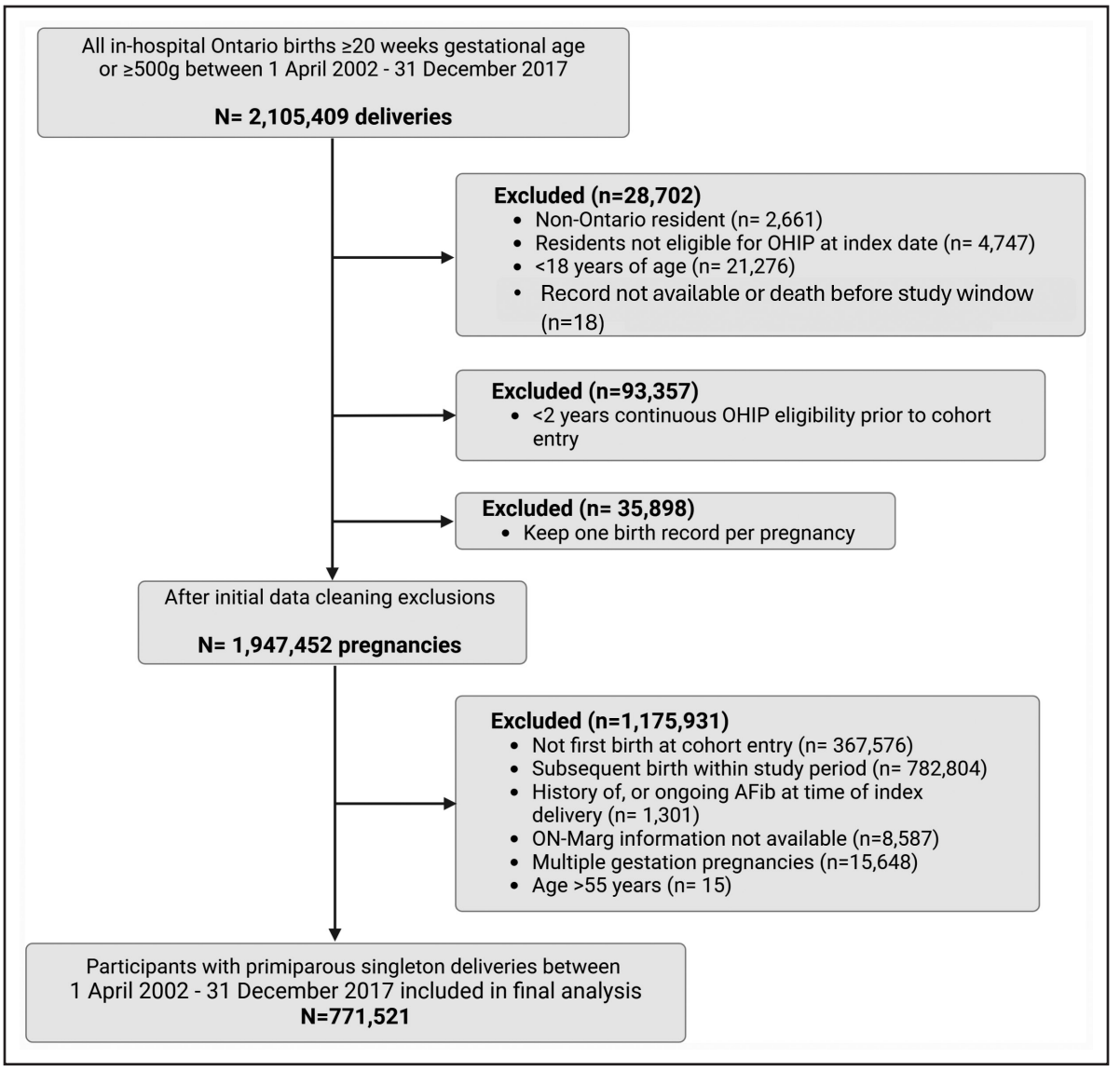

Figure 1. Flow diagram illustrating the selection of study subjects.

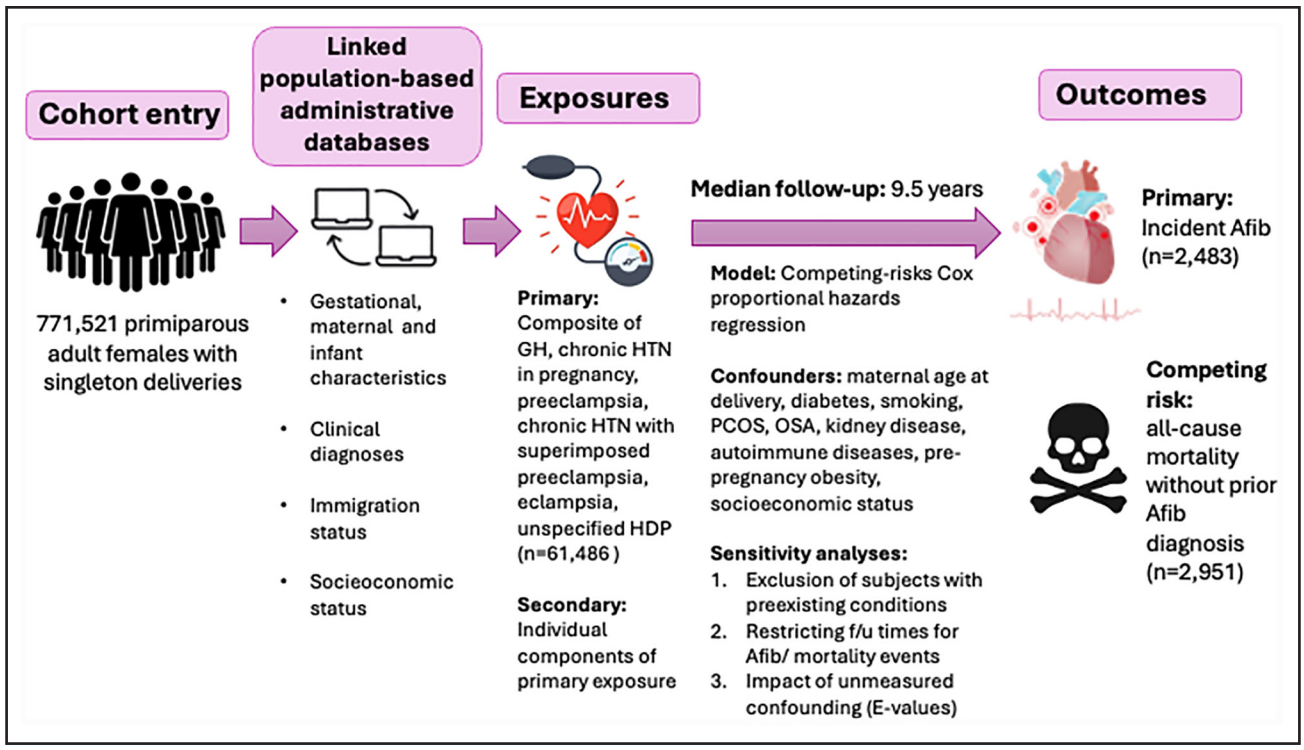

Figure 2. Summary of the study methodology.
AFib indicates atrial fibrillation; f/u, follow-up; GH, gestational hypertension; HDP, hypertensive disorders of pregnancy; HTN, hypertension; OSA, obstructive sleep apnea; and PCOS, polycystic ovarian syndrome.

Persons Database (RPDB), a population registry file of all people eligible for OHIP since 1991 that enables linkage with other data holdings at ICES. The mother-baby database (MOMBABY), which uses the Canadian Institutes for Health Information Discharge Abstract Database (CIHI-DAD) to link in-hospital maternal and infant delivery records, was used to obtain information about maternal parity as well as the baby's sex, date of birth, birthweight, and gestational age at birth. Information about diagnoses and procedures from clinical encounters was obtained from the National Ambulatory Care Reporting System, OHIP, CIHI-DAD, and the Same Day Surgery database, as well as several ICES-derived cohorts (Ontario Hypertension Dataset, Ontario Diabetes Dataset, Ontario Crohn's and Colitis Cohort, Ontario Rheumatoid Arthritis Dataset).

We used the Ontario portion of the permanent resident database of Immigration, Refugee and Citizenship Canada to ascertain immigration status. Information about area-level socioeconomic status was ascertained using the Ontario Marginalization Index (quintiles)[24] by linking residential postal codes (RPDB) with census data, and we used the Rurality Index for Ontario to determine subject rurality at index delivery. The postal code conversion file was used to convert subject postal codes to area-level quintiles.

Subject Eligibility

All adults ≥18 years of age who delivered their first live or stillborn infant at ≥20 weeks gestational age, or >500-g birthweight, between April 1, 2002, and December 31, 2017 (index date), were initially eligible for inclusion. Individuals were excluded if they were >55 years of age (n=15 with biologically implausible values), were not Ontario residents, had an invalid health card number, had a recorded death date before their index date, were not eligible for OHIP coverage, or had <2 years of continuous coverage, before cohort entry. People with a history of or ongoing AFib at the time of index delivery and those missing data required for the Ontario Marginalization Index (n=8587; 1.1%) were also excluded. During the exposure accrual period, approximately 98% of all births in Ontario occurred in-hospital.[25]

Study Variables

A directed acyclic graph illustrating the hypothesized relationships between study variables (ie, primary exposure, outcome, relevant confounders) is shown in Figure S2.

Primary and Secondary Exposures

The primary exposure was a composite "any HDP" variable defined as any diagnosis of gestational hypertension, chronic hypertension in pregnancy, preeclampsia, chronic hypertension with superimposed preeclampsia (superimposed preeclampsia), eclampsia, or unspecified HDP in subjects' first obstetrical delivery. Secondary exposures included each individual HDP within the composite HDP exposure.

No case-finding definitions/algorithms for "any HDP," or individual HDP subtypes, have been validated on Ontario population-based administrative data. As such, each HDP exposure was identified by applying the best available, and most relevant, case-finding definition validated in other jurisdictions to each subject's discharge abstract (Table S3).[7,26] We also searched for "unspecified" HDP by looking for any *International*

Classification of Diseases, Tenth Revision (*ICD-10*) code beginning with O16 in each subject's obstetrical discharge abstract.

We used a hierarchical "severity coding" approach to exposure classification whereby any subject whose discharge abstract met the case-finding definition for >1 HDP subtype had their exposure status recoded such that only their most severe diagnosis was recorded. Further details on this approach are provided in Data Supplement S4.

Outcome and Competing Risk

The primary outcome was incident AFib, which was identified using a case-finding definition previously validated in Ontario population-based administrative data (Table S4).[27] This algorithm has a reported specificity of 99%, and a positive predictive value of 71%, for the identification of incident AFib in Ontario adults ≥20 years of age.[27] We did not differentiate between AFib type (ie, paroxysmal, persistent, and long-standing). The competing risk, all-cause death, was determined by the presence of a death date in the RPDB.

Confounders

We identified several risk factors for AFib that are also associated with, but not an effect of, HDP (ie, confounders) based on input from clinical experts and evidence available from published literature. Behavioral and clinical factors identified as confounders included maternal age at delivery, preexisting diabetes, polycystic ovary syndrome, sleep apnea, smoking, kidney disease, chronic immune-mediated inflammatory conditions, and prepregnancy obesity. We used Ontario Marginalization Index material resources dimension quintiles[24] to control for potential confounding by area-level socioeconomic status.[28] All confounders were treated as time-fixed and assessed only at baseline. Table S4 provides further details on the methods used to identify these conditions.

Follow-Up for Outcome and Competing Risk

Subjects were followed until they had an incident AFib diagnosis (outcome), had a recorded death date in the RPDB (competing risk), or were no longer eligible for OHIP, or at the end of study follow-up, whichever came first. All subjects who were eligible for OHIP, were still alive, and did not fulfill the algorithm for AFib by December 31, 2019, were censored.

Statistical Methods

Descriptive Analyses

Baseline characteristics and comorbidities (ie, conditions present at any time before index delivery) are presented as medians (interquartile range) and number affected (n), with percentages (%) for categorical variables. We assessed differences in baseline characteristics between HDP exposure status using absolute standardized differences. Absolute standardized differences >10% were considered indicative of potentially meaningful differences between the exposure and characteristic being assessed.[29] We also calculated the proportion of subjects diagnosed with each HDP subtype over the study period. In accordance with ICES privacy policies, small cells (counts <6) have been suppressed or combined to reduce the risk of reidentification.

Crude and Multivariable Cause-Specific Cox Proportional Hazards Regression

Before fitting statistical models, each study variable was assessed for missingness, the presence of extreme/influential values, and possibly erroneous data (as appropriate). Phi coefficients were used to assess the strength of correlation between dichotomous variables; coefficients ≥0.2 were interpreted as at least moderately correlated variables.[30]

Cause-Specific Cox Proportional Hazards Regression

We used competing-risks Cox proportional hazards regression to compute crude and multivariable-adjusted cause-specific hazard ratios (csHRs), and accompanying 95% CIs, to assess the association between history of any HDP, and specific HDP subtypes and: (1) incident AFib in those still alive during follow-up, and (2) all-cause mortality in the absence of a previous AFib diagnosis.

We fit separate models for incident AFib and all-cause mortality, treating subjects who died, or were diagnosed with AFib, as censored in each respective model. We also tested for multiplicative interaction between HDP and material resources given known disparities in the burden of HDP and AFib according to socioeconomic status.[31] Calendar time was used as the underlying timescale in all models. To assess the robustness of our findings, we re-ran multivariable models using age as the time scale.

For each cause-specific model, we used both graphical and formal statistical tests to assess whether the effect of each variable on the cause-specific hazard ratios (csHazard) function was constant over time.[32] A 2-sided P value <0.05 was considered evidence that the variable being tested likely violated the proportional hazards assumption.[33]

After visually assessing residual plots, and considering the results of formal statistical tests, the proportional hazards assumption was considered violated for gestational hypertension (AFib model only), as well as the covariates age (both cause-specific models) and material resources (mortality models only). As such, in AFib models for subjects exposed to gestational hypertension, we performed a time-segmented analysis by restricting follow-up time to >4.5 years after delivery, as the PH assumption held for this follow-up period. In models assessing all-cause mortality, we stratified by material resources.[34] Final models included maternal age at delivery as a restricted cubic spline with five knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles.[35]

Sensitivity Analyses

We carried out 3 sensitivity analyses. Two were carried out to assess how excluding subjects with certain preexisting conditions (Table S5) and restricting follow-up times for observing AFib/mortality events affected effect estimates. A third sensitivity analysis assessed the potential impact of unmeasured confounding on the effect estimates generated (E-values). Further details are provided in Data Supplement S6.

All analyses were carried out using SAS Enterprise Guide (Version 8.3, SAS Institute, Cary, NC). Forest plots were generated using the ggplot2 package[36] in RStudio (v. 2023.12.1.402) to visualize effect estimates (95% CIs) and facilitate comparisons between HDP exposures.

Ethics Approval

The use of the data in this project is authorized under section 45 of the Ontario Personal Health Information Protection Act and does not require review by a research ethics board.

RESULTS

Selection of Study Subjects

We identified 2 105 409 women discharged from an Ontario hospital for a potentially eligible obstetrical delivery between April 1, 2002, and December 31, 2017. After excluding ineligible subjects, a total of 771 521 women were included in the study (Figure 1).

Baseline Maternal Characteristics at Study Entry

Most maternal risk factors and adverse pregnancy outcomes were more prevalent in people with a history of HDP. However, few differences were considered potentially meaningful (absolute standardized differences >10%; Table 1).

Briefly, subjects with a history of HDP in their first obstetrical delivery were older than those with no HDP, and were more likely to have preexisting diabetes and hypertension. In contrast, those with a history of HDP were less likely to be immigrants, to reside in an urban area, or to reside in neighborhoods with the highest quintile of racialized and newcomer populations (Table 1). The prevalence of preexisting cardiovascular and endocrine conditions was numerically equivalent, or marginally higher, in subjects diagnosed with HDP (Table S6). Additional details related to baseline obstetrical characteristics are provided in Table S7.

Hypertensive Disorder of Pregnancy Exposure Status and Incident Chronic Hypertension After Delivery

Approximately 8% of study subjects were diagnosed with HDP during the 16-year exposure accrual period. The most common diagnosis was gestational hypertension; the least common was eclampsia (Figure 3). Nearly 5% of study subjects (n=36 507) were diagnosed with incident chronic hypertension at some point after pregnancy during the follow-up period. It was especially prevalent in subjects diagnosed with gestational hypertension (n=6486; 16%) and preeclampsia (n=2030; 14%) in their index delivery.

Incidence Rates and Time to Event Analyses

The total person-time of follow-up was 7 380 304 person-years (median follow-up, 9.5 years), during which there were 2483 (0.3%) incident AFib diagnoses and 2951 (0.4%) deaths. Crude cause-specific incidence rates (95% CIs) for AFib and all-cause mortality for HDP, and each HDP subtype, are presented in Table 2. The median age (quartile 1 through quartile 3) of subjects with AFib was 30 years (26 to 34 years), with 68% <40 years of age at their time of diagnosis, whereas the median age of those who died was 29 years (23 to 33 years), with 67% <40 years of age at their time of death. A total of 766 087 subjects were censored (n=26 926 [3.5%] because of a lapse in OHIP coverage; n=739 161 [95.8%] at end of study).

When HDP was assessed as a composite exposure, the median time to event was nearly identical for both AFib and all-cause mortality (7.1 versus 7.0 years, respectively). However, when each HDP exposure was assessed separately, there was considerable heterogeneity with respect to median time to event for both event types (Figure S4).

Cause-Specific Cumulative Incidence Curves

Cause-specific cumulative incidence curves for incident AFib and all-cause mortality, stratified by HDP exposure status, are shown in Figure 4. Subjects with a history of any HDP in their first singleton delivery had a consistently higher incidence of AFib and all-cause mortality compared with their unexposed counterparts over the follow-up period; differences in these curves were apparent within approximately 2 years of delivery. For all-cause mortality, clear differences in these curves occurred slightly later, at approximately 3 years after delivery. Similar findings were noted for each HDP subtype (Figures S5 and S6).

Cause-Specific Hazard of AFib and All-Cause Mortality

After adjusting for confounders, we found that a history of any HDP in a first obstetrical delivery was associated with a 45% increased csHazard of incident AFib (adjusted csHR, 1.45 [95% CI, 1.28–1.64]) as well as an increased csHazard of death in subjects without a previous AFib diagnosis (adjusted csHR, 1.31 [95% CI, 1.16–1.47]; Figure 5A and 5B, respectively).

With respect to specific HDP subtypes, we found that a history of gestational hypertension, preeclampsia, and chronic hypertension in pregnancy were each associated with an increased csHazard of incident AFib (adjusted csHR, 1.49 [95% CI, 1.25–1.78], 1.53 [95% CI, 1.20–1.96], and 2.24 [95% CI, 1.55–3.23], respectively; Figure 5A). Although crude estimates indicated a significant cause-specific association between superimposed preeclampsia and incident AFib, the observed relationship was attenuated and no longer significant after multivariable adjustment (csHR, 1.70 [95% CI, 0.84–3.43]; Table S8).

Histories of preeclampsia, unspecified HDP, chronic hypertension in pregnancy, and superimposed preeclampsia were each independently associated with an increased csHazard of death in subjects without an AFib diagnosis (adjusted csHR, 1.43 [95% CI, 1.13–1.81],

Table 1. Baseline Maternal Characteristics at Study Entry

	Total	No HDP	HDP	ASD (%)*
Total No. study subjects (%)	771 521 (100)	710 035 (92.0)	61 486 (8.0)	…
Maternal characteristics				
Age at first delivery, y				
Median (Q1–Q3)	29 (25–32)	29 (25–32)	29 (26–33)	**13**
Age group				
<20 y	34 697 (4.5)	32 613 (4.6)	2084 (3.4)	5
20–24 y	132 764 (17.2)	123 448 (17.4)	9316 (15.2)	2
25–29 y	250 841 (32.5)	231 439 (32.6)	19 402 (31.6)	6
30–34 y	244 567 (31.7)	225 397 (31.7)	19 170 (31.2)	6
35–39 y	90 178 (11.7)	81 204 (11.4)	8974 (14.6)	2
40–44 y	17 258 (2.2)	14 976 (2.1)	2282 (3.7)	1
45–49 y	1117 (0.1)	889 (0.1)	228 (0.4)	9
50+ y	99 (0.01)	69 (0.01)	30 (0.05)	**10**
Comorbid conditions				
Diabetes	11 296 (1.5)	8828 (1.2)	2468 (4.0)	**17**
Polycystic ovary syndrome	26 192 (3.4)	23 229 (3.3)	2963 (4.8)	8
Sleep apnea†	15 148 (2.0)	13 102 (1.8)	2046 (3.3)	9
Ever smoker	23 730 (3.1)	21 676 (3.1)	2054 (3.3)	2
Kidney disease	18 337 (2.4)	16 060 (2.3)	2277 (3.7)	9
Chronic immune-mediated inflammatory conditions‡	16 569 (2.1)	14 942 (2.1)	1627 (2.6)	4
Obesity	2359 (0.3)	1788 (0.3)	571 (0.9)	9
Sociodemographic characteristics				
Immigrant§	159 375 (20.7)	149 546 (21.1)	9829 (16.0)	**13**
Rurality Index for Ontario‖				
Urban	579 948 (75.2)	536 410 (75.5)	43 538 (70.8)	**11**
Suburban	140 165 (18.2)	126 912 (17.9)	13 253 (21.6)	9
Rural	47 714 (6.2)	43 371 (6.1)	4343 (7.1)	4
Missing	3694 (0.5)	3342 (0.5)	352 (0.6)	1
ON-Marg dimension				
Age and labor force dimension				
Quintile 1	250 642 (32.5)	231 223 (32.6)	19 419 (31.6)	2
Quintile 5	103 732 (13.4)	94 977 (13.4)	8755 (14.2)	3
Material resources dimension				
Quintile 1	166 892 (21.6)	153 917 (21.7)	12 975 (21.1)	1
Quintile 5	158 854 (20.6)	145 886 (20.5)	12 968 (21.1)	1
Households and dwellings dimension				
Quintile 1	149 548 (19.4)	138 366 (19.5)	11 182 (18.2)	3
Quintile 5	184 498 (23.9)	170 461 (24.0)	14 037 (22.8)	3
Racialized and newcomer populations dimension				
Quintile 1	106 365 (13.8)	96 557 (13.6)	9808 (16.0)	7
Quintile 5	234 329 (30.4)	218 336 (30.8)	15 993 (26.0)	**11**
Visible minority quintile				
Quintile 1	161 174 (20.9)	146 182 (20.6)	14 992 (24.4)	9
Quintile 5	125 948 (16.3)	117 881 (16.6)	8067 (13.1)	10
Missing	3960 (0.5)	3684 (0.5)	276 (0.4)	1

Values are n (%) unless otherwise noted. An ASD >10% (bold) was interpreted as a potentially meaningful difference in a baseline characteristic between groups. ASD indicates absolute standardized difference; IRCC, Immigration, Refugee, and Citizenship Canada; OHIP, Ontario Health Insurance Program; ON-Marg, Ontario Marginalization Index; and Q, quartile.

*Although guidance varies, ASDs of approximately 20%, 50%, and 80% may indicate small, medium, and large differences between exposure groups (HDP vs no HDP) for each baseline characteristic assessed.[37] In this study, ASDs >10% were considered indicative of potentially meaningful differences; however, in line with best practices in causal inference, statistical measures such as the magnitude of ASDs should not be used to classify a variable as a confounder.[7,38]

†Proxy variable based on having ≥1 OHIP code for sleep study.

‡Composite variable that includes subjects diagnosed with ≥1 of the following conditions before cohort entry: lupus, inflammatory bowel disease, psoriatic arthritis, ankylosing spondylitis, or rheumatoid arthritis.

§Has an IRCC landing date.

‖Categorized as: urban, Rurality Index for Ontario <10; suburban, Rurality Index for Ontario 10–39; and rural, Rurality Index for Ontario ≥40.

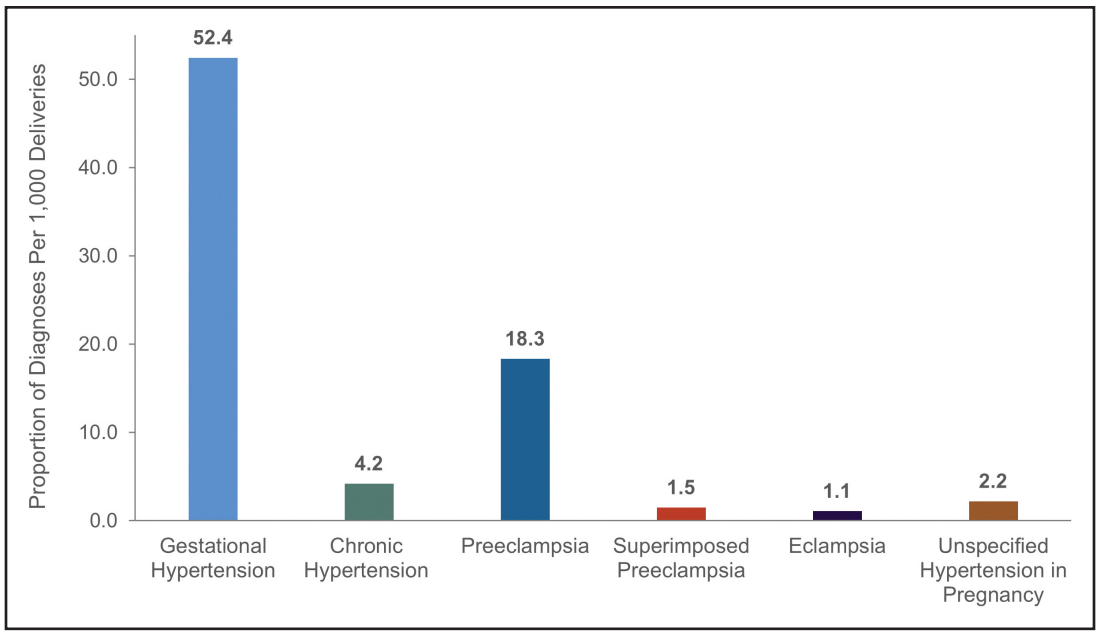

Figure 3. Proportion of study subjects (per 1000 deliveries) diagnosed with a hypertensive disorder of pregnancy during the exposure accrual period of the study, by subtype.
For each hypertensive disorders of pregnancy subtype, the numerator included the total number of subjects diagnosed with that specific subtype during the study period, and the denominator included the total number of study subjects.

1.91 [95% CI, 1.13–3.23], 2.04 [95% CI, 1.43–2.91], and 2.12 [95% CI, 1.20–3.78], respectively) (Figure 5B). Crude estimates also indicated a significant cause-specific association between both gestational hypertension and eclampsia and all-cause mortality. However, these relationships were attenuated and no longer significant after multivariable adjustment (csHR, 1.13 [95% CI, 0.97–1.31] and 1.91 [95% CI, 0.96–3.83], respectively; Table S9).

Dose-Response Relationships

We identified associations suggestive of a dose-response relationship whereby both higher severity of

Table 2. Total Number of Events, Person-Years of Follow-Up, Cause-Specific Incidence Rates, and Incidence Rate Ratios for Incident Atrial Fibrillation and All-Cause Mortality Without a Previous Atrial Fibrillation Diagnosis by Any Hypertensive Disorder of Pregnancy and Individual Subtypes

	Exposure							
	Not exposed	Any HDP	Gestational hypertension	Chronic hypertension	Preeclampsia	Superimposed preeclampsia	Eclampsia	Unspecified
Incident atrial fibrillation								
Total events	2187	<300*	178	30	65	<10*	<10*	10
Total PY of follow-up	6 797 092	583 212	393 969	29 456	123 329	10 022	9207	17 229
cs^{IR} per 10 000 PY (95% CI)	3.2 (3.1–3.3)	5.1 (4.6–5.6)	4.5 (4.0–5.1)	10.2 (7.1–13.2)	5.3 (4.2–6.4)	*	*	5.8 (2.8–8.8)
cs^{IRR} (95% CI)	Reference	1.58 (1.40–1.78)	1.40 (1.21–1.64)	3.17 (2.21–4.54)	1.64 (1.28–2.10)	*	*	1.80 (0.97–3.36)
All-cause mortality without a previous atrial fibrillation diagnosis								
Total events	2631	320	181	32	73	12	8	14
Total PY of follow-up	6 797 092	583 212	393 969	29 456	123 329	10 022	9207	17 229
$cs^{IR\ per}$ 10 000 PY (95% CI)	3.9 (3.8–4.0)	5.5 (5.0–6.0)	4.6 (4.0–5.2)	10.9 (7.7–14.0)	5.9 (4.8–7.1)	12.0 (6.3–17.7)	8.7 (3.6–13.7)	8.1 (4.6–11.7)
cs^{IRR} (95% CI)	Reference	1.42 (1.26–1.59)	1.19 (1.02–1.38)	2.81 (1.98–3.98)	1.53 (1.21–1.93)	3.09 (1.75–5.45)	2.24 (1.12–4.49)	2.10 (1.24–3.55)

All calculations made using the fmsb package (v.0.7.6)[39] in RStudio (v. 2023.12.1.402). cs indicates cause-specific; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio; and PY, person-years.

*Data suppressed because of small numbers to comply with ICES privacy requirements.

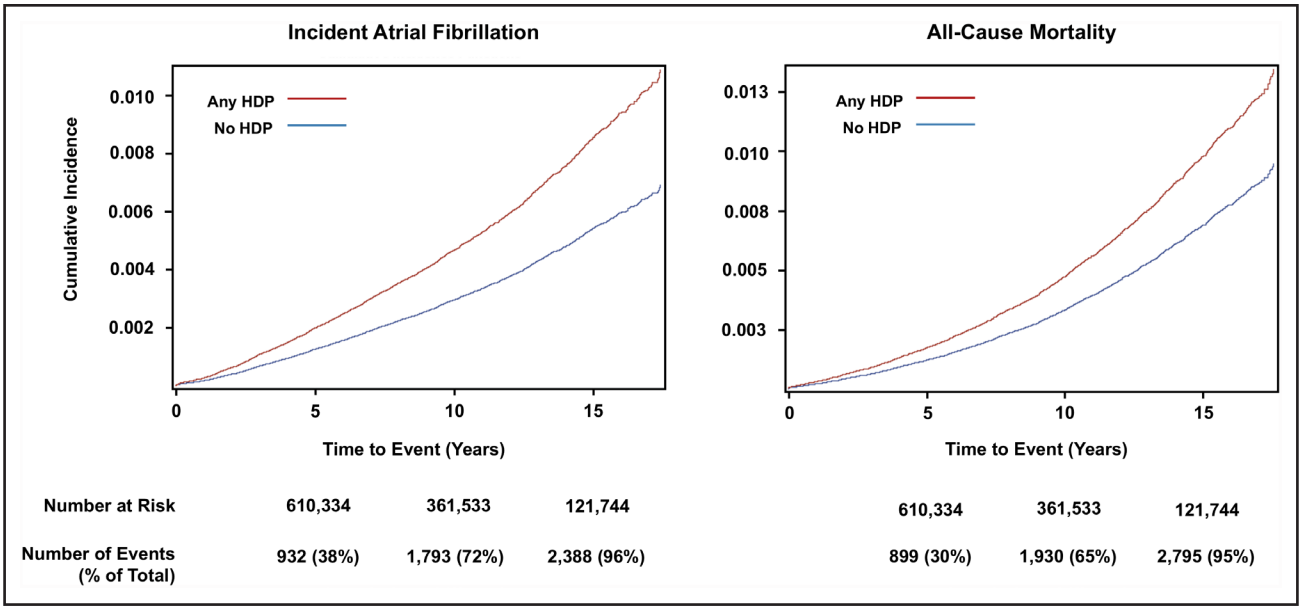

Figure 4. Cause-specific cumulative incidence curves for atrial fibrillation (outcome) and all-cause mortality (competing risk) stratified by hypertensive disorder of pregnancy exposure status (first obstetrical delivery).

de novo HDP diagnoses and exposure to prepregnancy chronic hypertension were associated with higher cause-specific rates of AFib and all-cause mortality (Table 3).

Sensitivity Analyses

When the observation period for incident AFib events and all-cause mortality was limited to >90 days after index delivery, the csHazard of AFib was attenuated slightly in those exposed to any HDP, chronic hypertension in pregnancy, and preeclampsia in their first obstetrical delivery. However, all estimates remained statistically significant. Similar results were found for estimates of death without a previous AFib diagnosis (Table S10). Estimates obtained for models limited to >120 days of follow-up were similar to those limited to >90 days of follow-up (not reported). Using age as the timescale had minimal impact on the estimates, and our conclusions remain unchanged (data not shown).

When models were re-run after excluding subjects with baseline cardiovascular and endocrine conditions, most estimates remained essentially unchanged or were minimally attenuated (Table S10). The only exception was the estimate for subjects exposed to chronic hypertension in pregnancy, in which the csHR for AFib increased slightly from 2.24 (95% CI, 1.55–3.23) to 2.42 (95% CI, 1.63–3.59) after excluding subjects with these baseline conditions. Similar results were found for all-cause mortality without a previous AFib diagnosis after subjects with these preexisting conditions were excluded from the analysis (adjusted csHR, 2.05 [95% CI, 1.43–2.92] versus 2.20 [95% CI, 1.51–3.19]).

E-values indicated that effect estimates were generally robust to unmeasured confounding (Table S11). For gestational hypertension, chronic hypertension in pregnancy, and preeclampsia, an unmeasured confounder would need to at least double the risk of AFib and be at least twice as prevalent in those with a history of these HDPs to explain away the observed associations. Similarly, for chronic hypertension in pregnancy, preeclampsia, superimposed preeclampsia, and unspecified HDP, an unmeasured confounder would need to at least double the risk of mortality before a previous AFib diagnosis and be at least twice as prevalent in those with a history of these exposures to explain away the observed associations.

DISCUSSION

This population-based retrospective cohort study of 771 521 nulliparous women has 3 novel findings. First, a history of HDP is independently associated with an increased risk of both AFib and all-cause mortality, and these associations were observed in relatively young women (median time to event, 7 years postpartum). Second, histories of gestational hypertension, preeclampsia, and chronic hypertension in pregnancy are each independently associated with an increased csHazard of incident AFib, whereas a history of preeclampsia, unspecified HDP, chronic hypertension in pregnancy, and superimposed preeclampsia are each independently associated with an increased csHazard of all-cause mortality without a previous AFib diagnosis. Third, a dose-response relationship may exist within these associations because both higher HDP severity

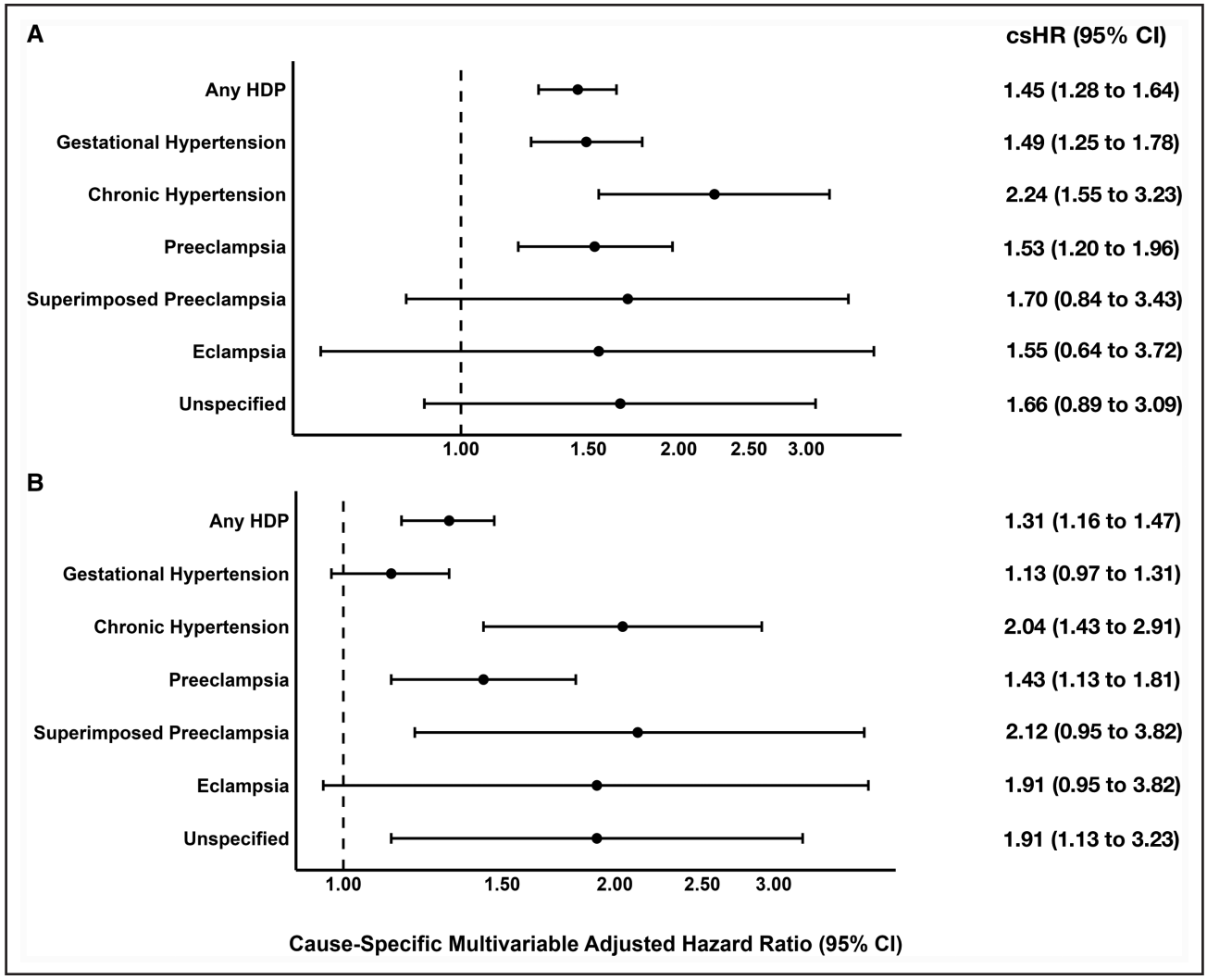

Figure 5. Case-specific adjusted hazard rations for atrial fibrillation and all-cause mortality.
Cause-specific multivariable adjusted hazard ratios and accompanying 95% CIs (log-scale) for atrial fibrillation (**A**) and all-cause mortality (**B**) by any hypertensive disorder of pregnancy and each subtype. Hazard ratios adjusted for maternal age at delivery, diabetes, polycystic ovary syndrome, sleep apnea, smoking, kidney disease, obesity, chronic immune-mediated conditions, and Ontario Marginalization Index material resources dimension (quintiles).

and the presence of prepregnancy chronic hypertension were found to be associated with higher rates of both events.

The pathophysiological mechanism(s) underlying the observed associations are complex. However, HDP and AFib share many important features,[40] such as cardiac remodeling,[41] endothelial dysfunction,[42] and inflammation,[43] which are likely central to the development of AFib in individuals with a history of HDP. This is further supported by evidence that HDP-associated inflammation and endothelial dysfunction can persist well into the postpartum period,[40,44] or become permanent,[45] resulting in extensive changes to endothelial cell function.[46] Indeed, recent work[47] also suggests that cardiovascular alterations in HDP lead to early vascular aging, which could explain the increased predisposition to AFib noted in individuals exposed to HDP in this study, especially given that AFib is typically associated with older age.

A limited number of cohort studies have reported significant associations between a history of HDP and incident AFib.[4,11,13] We found a comparatively lower rate of incident AFib than Leon et al,[13] who reported a nearly 2-fold higher risk of AFib in people exposed to HDP after 9.3 years of follow-up. In comparison, after a median 9.5 years of follow-up, we found a 1.45-fold higher adjusted csHazard of AFib and a 1.3-fold higher adjusted csHazard of all-cause mortality in those with a history of any HDP. A few factors could explain these findings.

First, although Leon et al[13] controlled for some important confounders, several others (eg, prepregnancy body mass index, tobacco use, and kidney disease) were not accounted for. Second, their data were analyzed using conventional Cox models, under the assumption of non-

Table 3. Cause-Specific Multivariable Adjusted Hazard Ratios (95% CIs) for Incident Atrial Fibrillation and All-Cause Mortality Without a Previous Atrial Fibrillation Diagnosis

	Gestational hypertension*	Preeclampsia	Eclampsia	Unspecified	Superimposed preeclampsia	Chronic hypertension in pregnancy
Incident atrial fibrillation						
Adjusted† csHR (95% CI)	**1.49 (1.25–1.78)**	**1.53 (1.20–1.96)**	1.55 (0.64–3.72)	1.66 (0.89–3.09)	1.70 (0.84–3.43)	**2.24 (1.55–3.23)**
All-cause mortality without a previous atrial fibrillation diagnosis						
Adjusted† csHR (95% CI)	1.13 (0.97–1.31)	**1.43 (1.13–1.81)**	1.91 (0.95–3.82)	**1.91 (1.13–3.23)**	**2.04 (1.43–2.91)**	**2.12 (1.20–3.78)**

*A time-segmented analysis was undertaken in these models whereby follow-up time for events was restricted to >4.5 years after index delivery, as the proportional hazards assumption held for this follow-up period.

†All cause-specific hazard ratios (csHR) adjusted for age at delivery, diabetes, polycystic ovary syndrome, sleep apnea, smoking, kidney disease, obesity, chronic immune-mediated conditions, and material resources (Ontario Marginalization Index material resources dimension quintiles). Bold estimates indicate statistical significance.

informative censoring.[48] However, in the presence of ≥1 competing risk, this assumption is violated and can result in upward-biased effect estimates.[48] In this study, we accounted for a more robust set of confounders and used cause-specific Cox models to appropriately address competing risks, which may explain our comparatively lower adjusted hazard ratios for both incident AFib and all-cause mortality.

Robust evidence suggests an association between history of HDP and risk of both CVD and mortality within the first decade after an affected pregnancy.[49] A recently published study[49] reported a 1.2-fold increased risk of all-cause death in women <50 years of age with a history of any HDP compared with their unexposed counterparts. Despite this, only one published study[11] reporting estimates of AFib risk in people exposed to HDP acknowledged the omission of mortality assessment as a study limitation.

In alignment with previous work,[49] we found that a history of any HDP in a first obstetrical delivery was associated with a 30% increased rate of death without a previous AFib diagnosis after 9.5 years of follow-up. It is important to note that the median age of subjects who died during the follow-up period was 29 years, with 67% of subjects <40 years of age when they died. Further, although both incident AFib and death were rare outcomes, death was slightly more common than AFib (2951 versus 2483, respectively). These findings underscore the importance of considering mortality as a competing risk for nonfatal CVD outcomes in this relatively young population, because failure to do so could result in artificially inflated estimates of association.

We identified associations suggestive of a dose-response relationship whereby both higher HDP severity and the presence of prepregnancy chronic hypertension were associated with higher cause-specific rates of both AFib and all-cause mortality. Although the increasing magnitude of these point estimates suggests a dose-response pattern, cautious interpretation is needed because of overlapping 95% CIs and nonsignificant estimates for specific diagnoses, likely caused at least in part by insufficient power to examine specific associations among subtypes. Further, these associations did not directly align with our "hierarchical" definition of HDP severity, which was assessed from the viewpoint of their acute clinical consequences for mother and fetus.[7] Specifically, during exposure classification, we considered chronic hypertension in pregnancy to be the second most severe HDP diagnosis. However, it was associated with the highest csHazard of AFib and second highest csHazard of mortality without a previous AFib diagnosis (adjusted csHR, 2.24 [95% CI, 1.55–3.23] and 2.04 [95% CI, 1.43–2.91], respectively). Indeed, if future studies assessing CVD risk in people with a history of HDP continue to examine HDP as a composite exposure or adopt a narrow definition of HDP severity, critical dose-response associations may remain unidentified.[7]

Despite the obvious time-varying nature of HDP and CVD risk factors, most previous work assessing CVD risk in people with a history of HDP has used a first-pregnancy, time-fixed approach to exposure ascertainment and data analysis.[50] In this study, we also defined HDP exposure status according to subjects' first delivery, and only adjusted for confounders that were assessed before cohort entry. Consequently, we were unable to account for changes in HDP exposure and confounder status over time and did not assess the cumulative effect of exposure to HDP in subsequent pregnancies on incident AFib. As such, our effect estimates may be subject to further residual confounding or other time-related bias.[51] However, previous work, discussed as follows, can provide important insight about the robustness of this approach within our context.

One recent study[12] reported that the adjusted hazard of arrhythmia for people with a history of preeclampsia in a first pregnancy was consistent with findings from a sensitivity analysis wherein preeclampsia was treated a time-dependent variable (adjusted hazard ratio, 1.37 [95% CI, 1.23–1.54] versus 1.29 (95% CI, 1.14–1.45], respectively). Additional studies[51,52] have also found minimal differences between estimates of CVD risk generated using marginal structural (time-varying) Cox

models compared with those generated using time-fixed analyses. As such, although the robustness of our findings should be assessed in models that account for the time-varying nature of HDP and confounders, previous research suggests that CVD risk may be primarily driven by HDP exposure in a first pregnancy, and time-varying confounding may have a minimal impact on effect estimates.[51]

Strengths and Limitations

Our large sample size and use of population-based data sources from the most populous ethnically and culturally diverse province in Canada enhance the generalizability of our findings. We followed established guidance on the reporting of studies carried out using routinely collected data,[23] controlled for several important confounders, and accounted for the competing risk of death, and our findings were robust to several sensitivity analyses.

Although we controlled for a robust set of confounders, we cannot rule out the possibility that residual confounding affected our results. Prepregnancy body mass index was unavailable for ≈70% of subjects; thus, we adjusted for obesity by identifying *ICD-10* codes for this diagnosis in health records. However, individuals with codes for this condition likely only represent extreme cases, so control for this factor was likely incomplete and might have resulted in spuriously inflated associations. Despite this, the results of our E-value sensitivity analysis provide some reassurance about the robustness of our findings to unmeasured confounding.

We considered incident chronic hypertension as an intermediate factor in the causal pathway between HDP and incident AFib and did not include it in multivariable models to prevent overadjustment bias.[53] However, given the strong association between chronic hypertension in pregnancy and incident AFib identified in this study, the shared pathological features of both conditions (eg, left ventricular hypertrophy or diastolic dysfunction),[41] and the fact that incident chronic hypertension after HDP was especially prevalent in subjects diagnosed with gestational hypertension (16%) and preeclampsia (14%), a formal causal mediation analysis[54] should be conducted to further elucidate the role that postpregnancy chronic hypertension might play in this association.

In the administrative data sources used for this study, medication/prescription data are only available for individuals age ≥65 years. As a result, this information was not available for most participants, whose median age was 29 years at cohort entry. This represents a limitation because we were unable to assess antihypertensive or antiarrhythmic use in our study. However, commonly prescribed antihypertensive medications do not have established antiarrhythmic effects, and substantial antiarrhythmic use is unlikely, given that participants with baseline AFib were excluded and ventricular tachycardia is rare in women <50 years of age.[55] Therefore, it is unlikely that this limitation influenced our study findings.

Finally, we identified only AFib cases that were diagnosed and documented in subjects' administrative records, which may have led to an underestimation of AFib incidence in cases of clinically silent or unsuspected arrhythmia. However, this reflects a broader challenge in AFib detection and diagnosis, rather than a limitation unique to this study or the use of administrative data.

Conclusions

Histories of gestational hypertension, preeclampsia, and chronic hypertension in pregnancy are each independently associated with a higher csHazard of incident AFib, with associations observed in relatively young women. Given its rapidly increasing global prevalence and significant morbidity and mortality burden, AFib has become one of the most substantial CVD challenges of the 21st century, particularly for women. These findings underscore the need to: (1) incorporate HDP history into risk calculation/stratification for arrhythmic and nonarrhythmic CVD, (2) enhance surveillance of traditional and female-specific CVD risk factors, and (3) develop targeted prevention strategies to reduce the occurrence and burden of HDP.

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Disclosures

When this project was initiated, D.B.F. was employed by the University of Ottawa and had an academic appointment at the Children's Hospital of Eastern Ontario Research Institute; although she continues to hold adjunct appointments in both institutions, she is now employed by Pfizer and works on an unrelated topic. The other authors report no conflicts.

Supplemental Material

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