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ORIGINAL RESEARCH

# Long-Term Cardiovascular Outcomes After Pregnancy in Women With Heart Disease

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**BACKGROUND:** Women with heart disease are at risk for pregnancy complications, but their long-term cardiovascular outcomes after pregnancy are not known.

**METHODS AND RESULTS:** We examined long-term cardiovascular outcomes after pregnancy in 1014 consecutive women with heart disease and a matched group of 2028 women without heart disease. The primary outcome was a composite of mortality, heart failure, atrial fibrillation, stroke, myocardial infarction, or arrhythmia. Secondary outcomes included cardiac procedures and new hypertension or diabetes mellitus. We compared the rates of these outcomes between women with and without heart disease and adjusted for maternal and pregnancy characteristics. We also determined if pregnancy risk prediction tools (CARPREG [Canadian Cardiac Disease in Pregnancy] and World Health Organization) could stratify long-term risks. At 20-year follow-up, a primary outcome occurred in 33.1% of women with heart disease, compared with 2.1% of women without heart disease. Thirty-one percent of women with heart disease required a cardiac procedure. The primary outcome (adjusted hazard ratio, 19.6; 95% CI, 13.8–29.0; $P<0.0001$) and new hypertension or diabetes mellitus (adjusted hazard ratio, 1.6; 95% CI, 1.4–2.0; $P<0.0001$) were more frequent in women with heart disease compared with those without. Pregnancy risk prediction tools further stratified the late cardiovascular risks in women with heart disease, a primary outcome occurring in up to 54% of women in the highest pregnancy risk category.

**CONCLUSIONS:** Following pregnancy, women with heart disease are at high risk for adverse long-term cardiovascular outcomes. Current pregnancy risk prediction tools can identify women at highest risk for long-term cardiovascular events.

**Key Words:** cardiovascular ■ heart disease ■ long-term ■ pregnancy

An increasing number of women with heart disease are undergoing pregnancy, with maternal cardiovascular disease estimated to affect 1% to 4% of pregnancies.[1,2] In the presence of maternal heart disease, the hemodynamic stress of pregnancy can lead to maternal deterioration, and many studies have shown that pregnant women with heart disease are at higher risk of adverse cardiac and obstetric outcomes compared with the pregnant women without heart disease,[1,3–8] While considerable progress has been made in predicting and treating cardiac complications in women with heart disease during pregnancy,[9–14] their long-term cardiovascular outcomes have not been systematically examined. Determining late outcomes is important in women with heart disease, as they may be at risk for both cardiovascular deterioration after pregnancy as well as the development of hypertension or diabetes mellitus, in view of the relationship between pregnancy-related complications and future adverse cardiovascular events.[13,15] Therefore, the primary purpose of this study was to examine long-term cardiovascular outcomes in women with heart disease after their pregnancy and compare these to a matched group of women without heart disease. We hypothesized that pregnant women with heart disease would have a higher rate

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## CLINICAL PERSPECTIVE

### What Is New?

- Women with heart disease are at higher risk of late postpregnancy cardiovascular complications and new hypertension/diabetes mellitus compared with women without heart disease.
- Risk prediction methods developed for assessment of pregnancy risk in women with heart disease can also be used to risk stratify long-term cardiovascular risks.

### What Are the Clinical Implications?

- Ongoing surveillance and risk factor modification in women with heart disease beyond pregnancy is important.
- Current tools for cardiovascular risk assessment during pregnancy can also be used to risk stratify for long-term cardiovascular risk after pregnancy.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CARPREG** | Canadian Cardiac Disease in Pregnancy study |
| **ICES** | Institute for Clinical Evaluative Sciences |
| **WHO** | World Health Organization |

of long-term cardiovascular outcomes than pregnant women without heart disease. We also examined whether previously validated pregnancy risk prediction tools could be useful to identify those women at highest risk for long-term cardiovascular complications.

## METHODS

### Study Design and Population

We conducted a retrospective matched-cohort study in Ontario, Canada, where >99% of births occur in hospitals and residents have universal access to hospital and physician services.[16,17] This study was designed by the authors, approved by the local research ethics committees, conducted at ICES (formerly Institute for Clinical Evaluative Sciences), and reported according to recommended guidelines (Table S1). ICES is an independent, not-for-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. The lead author (Dr Siu) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The data set from this study is held securely in coded form at ICES. While data-sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

We identified and matched pregnant women with heart disease (exposure factor) who had received care at the Mount Sinai and Toronto General Hospital's pregnancy and heart disease program, with pregnant women without heart disease identified from administrative healthcare databases at ICES. We retrieved data from the following databases: (1) demographic characteristics and vital statistics from Ontario's Registered Persons Database and (2) birth outcomes from the MOMBABY database. The MOMBABY database links the hospital record of a delivering woman with that of her newborn in pregnancies that progress beyond 20 weeks' gestation or with a newborn birth weight >500 g as recorded on the Discharge Abstract Database at the Canadian Institute for Health Information. Other baseline data were determined using other ICES databases (summaries of the databases provided in Table S2). These databases have been used extensively for healthcare research including late outcome studies of pregnant women.[15,17–30] Neighborhood-level income quintile and rural/urban residence were determined using Statistics Canada definitions.

We included consecutive pregnant women with preexisting heart disease (congenital, acquired, or cardiac arrhythmia) receiving care in the pregnancy and heart disease program who had at least 1 birth between 1994 (establishment of the program) and 2015 (to ensure minimum follow-up duration of 5 years). This program provides primary and tertiary care for pregnant women with heart disease in the Greater Toronto Metropolitan area. Patients were followed until the sixth postpartum month, after which their ongoing care and follow-up was continued by their primary physician or specialist. Details pertaining to the underlying cardiac lesion were recorded for all women at their antenatal visit.[3,4] The first pregnancy that progressed beyond 20 weeks' gestation and the corresponding birth, between 1994 and 2015, were defined as the index pregnancy and index birth, respectively. The date of the index birth was the cohort entry date. We matched the study cohort

with pregnant women, also from 1994 to 2015, without heart disease or prior cardiovascular procedures, from the general Ontario population using the MOMBABY database. In women without heart disease who had multiple births during that period, a birth was randomly selected and was designated the index birth, to enable matching with women in the heart disease group who had births before 1994.

We derived a prognostic risk score to match women with heart disease to women without heart disease.[31] To do so, we used the sample of pregnant women without heart disease to regress the hazard of all-cause mortality, heart failure, myocardial infarction, stroke, arrhythmia, or atrial fibrillation (ie, the study's primary composite outcome) on baseline variables measured at the time of the index pregnancy (comorbid conditions, fertility therapy, ethnicity, multifetal births, cesarean delivery, gestational diabetes mellitus, and site of delivery; Table S3). To create the community comparison group of women without heart disease, women without heart disease were matched to each woman with heart disease on the following: (1) prognostic risk score ±0.2 SDs, (2) age at index birth ±1 year, (3) same fiscal year of index birth, (4) any births before index birth, (5) residence in metropolitan area (Toronto), and (6) income quintile. Using these 6 factors, we matched each pregnant woman with heart disease to 2 pregnant women without heart disease with the same predicted risk of subsequently developing the composite outcome based on demographic and baseline variables. This strategy of 1:2 matching was to improve the precision of the risk estimates in the matched groups without a commensurate increase in bias.[32]

## Covariate Conditions and Pregnancy Risk

Covariate conditions and outcome were obtained using diagnostic or procedural codes from the *International Classification of Disease Ninth Revision* (*ICD-9*); *International Classification of Disease, Ninth Revision, Tenth Revision, Canada* (*ICD-10-CA*); Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; Canadian Classification of Health Interventions; and the above-mentioned ICES databases (Table S4). Covariate conditions and outcome were defined before data analysis, as per ICES policy.

In the heart disease group, antepartum cardiac variables and diagnosis were used to calculate the maternal cardiovascular risk during the index pregnancy using 3 validated risk classification methods in current use that are applicable to women with a range of cardiac conditions: the original CARPREG (Canadian Cardiac Disease in Pregnancy) risk score,[3] the expanded CARPREG II risk score,[4] and the modified World Health Organization (WHO) classification system.[14] These risk classification methods estimate the mother's baseline cardiovascular risk during pregnancy and the first 6 postpartum months (Table S5). Using each method, women in the heart disease group were classified as either low or intermediate-to-high risk for maternal cardiovascular complications during their index pregnancy.

## Outcomes

Women were followed until death or end of the follow-up period (December 31, 2019), whichever occurred earlier. The primary outcome was a composite of all-cause mortality, heart failure, myocardial infarction, stroke, arrhythmia (including cardiac arrest, ventricular and atrial tachyarrhythmia, and heart block), or atrial fibrillation. The secondary outcomes were (1) components of the composite primary outcome, (2) cardiovascular death, (3) therapeutic cardiac procedures (catheter based or surgical), and (4) incident hypertension or diabetes mellitus. For determination of outcomes, cardiovascular events that occurred during the antepartum period or within the first 6 postpartum months were considered to be pregnancy related, as changes in the maternal cardiovascular system do not fully resolve until this time has elapsed.[4,33] The validated algorithms for incident diabetes mellitus and incident hypertension exclude gestational diabetes mellitus or hypertensive disorders of pregnancy.[25,28]

## Statistical Analysis

All analyses were conducted using SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC) at ICES. Continuous variables were summarized using the median and interquartile range. To comply with ICES's privacy policy, we suppressed frequency counts between 1 and 5. We compared baseline characteristics between women in the heart disease and comparison groups using standardized differences, with a value ≥0.10 considered a potentially important difference. Unadjusted cumulative incidence curves of outcomes (which accounted for the appropriate competing risk when necessary) were generated.

We fit separate Cox regression models to compare primary and secondary outcomes between heart disease and comparison groups. When there were competing risks (mortality not included as an outcome), cause-specific regression models were used instead of Cox regression. The covariates for each model included heart disease status, any obstetric complication (ie, ante- or postpartum hemorrhage, placental abruption, placental infarction, premature delivery or rupture of membranes, gestational hypertension or preeclampsia/eclampsia, poor

fetal growth, or stillbirth) during the index pregnancy, any cardiac complication (heart failure, arrhythmia, stroke, or myocardial infarction) during the index pregnancy, fetal congenital heart defect during index pregnancy, Charlson Comorbidity Index,[34] and the baseline demographic variables used in matching (age and fiscal year of index birth, any births before index birth, residence in Toronto metropolitan area, income quintile). Covariates relating to outcome of the index pregnancy (obstetric complications, cesarean delivery, and congenital heart disease in the infant) were included because of their relationship to subsequent cardiovascular disease in the general population.[13,15,35–37] As the matching process may not balance all covariates including comorbid diagnoses, we adjusted for residual confounding by using the Charlson Index, as well as the demographic variables used in the matching process. The model also included 2 time-varying covariates for births subsequent to index pregnancy (currently pregnant; number of births after the index birth), to adjust for the possible influence of subsequent pregnancies on outcomes. If the hazard ratio associated with the variable of interest (heart disease group) did not meet the proportional hazard assumption, we computed time-specific instantaneous hazard ratios by inclusion of a time interaction term into the models. Level of significance was set at 0.05 (two sided).

Adjusted cumulative incidence curves were generated from the Cox regression (when mortality was included in the outcome) or Fine-Gray models (when mortality was not included as an outcome); time-varying covariates were not included in these models, as cumulative incidence functions cannot be estimated in the presence of time-varying covariates.[38] We repeated the above procedure by using CARPREG, CARPREG II, and WHO risk groups (low versus intermediate-to-high risk for pregnancy maternal cardiovascular complications) in place of the heart disease group variable.

Cumulative incidence curves were truncated at the time of follow-up, beyond which the total number of women at risk was ≤20% of the baseline. Ninety-five percent CIs were calculated using 1000 bootstrap samples. A robust variance estimator was used to account for the matched nature of the sample.

## RESULTS

A total of 1036 women with heart disease were eligible for matching after excluding pregnancy-associated deaths (n=1–5, exact number suppressed because of ICES's privacy policy) and applying other exclusion criteria (Figure S1). After applying the matching algorithm, 1014 women with heart disease were successfully matched to 2028 women in the comparison group. The median age at the time of the index birth was 30 years in both groups. At the time of the index birth, a higher proportion of the heart disease group had a Charlson score ≥1, delivered at a tertiary care center, had an infant born with congenital cardiac defect, or had a cardiovascular complication during pregnancy, when compared with the comparison group; the 2 groups were not significantly different with respect to other characteristics (Table 1). In the heart disease group, the most frequent maternal cardiac lesions were congenital heart defect and left-sided valvular disease.

The maximum follow-up duration was 25 years in both groups, with a total of 14 416 and 29 414 person-years' follow-up for the heart disease group and comparison group, respectively. Median follow-up duration in the heart disease (13.7 years; interquartile range, 8.6–19.8 years) and comparison group (14.0 years; interquartile range, 8.8–20.2) were similar (Table 1). Data collection was complete for all outcomes. A primary outcome occurred in 298 women in the heart disease group (25.3 events/1000 person-years) versus 32 women in the comparison group (1.1 events/1000 person-years) with an adjusted hazard ratio of 19.6 for the entire follow-up period (Table 2). The adjusted cumulative incidence of a primary outcome in the heart disease group was 20.1% at 10 years and 33.1% at 20 years of follow-up; the corresponding cumulative incidence was 2.1% in the comparison group at 20 years of follow-up (Figure 1A). There was a time dependency to this elevated hazard for the primary outcome, with the highest hazard ratios in the earlier years of follow-up after delivery (Figure 1B).

The adjusted rates for all-cause mortality, congestive heart failure, atrial fibrillation, myocardial infarction, or stroke were higher in the heart disease group compared with the comparison group (Table 2). The rate of cardiovascular death was 1.0 per 1000 person-years in women with heart disease and 0.04 per 1000 person-years in controls (crude hazard ratio, 20.3; adjusted hazard ratio not calculated because of very low rate in the comparison group). At 20 years of follow-up, the heart disease group had a higher adjusted cumulative incidence of heart failure and atrial fibrillation compared with the comparison group (Figure 2A and 2B). The heart disease group also frequently required therapeutic cardiac procedures (30.6% at 20 years) and developed new hypertension or diabetes mellitus (27.2% at 20 years), both of which were higher than in the comparison group (0.5% and 18.4%, cardiac procedures and incident hypertension/diabetes mellitus, respectively) (Figure 2C and 2D). Unadjusted cumulative incidence curves (Figures S2 and S3) showed similar trends as adjusted curves.

**Table 1. Baseline and Follow-Up Characteristics in Women With Heart Disease and Matched Comparison Group**

| | Heart Disease Group (n=1014 Women) | Community Group (n=2028 Women) | Standardized Difference |
|---|---|---|---|
| At index birth | | | |
| Median (IQR) maternal age, y | 30.0 (27.0–34.0) | 30.0 (27.0–34.0) | 0 |
| Low residential income area,* n (%) | 415 (40.9) | 830 (40.9) | 0 |
| Rural residence, n (%) | 45 (4.4) | 94 (4.6) | 0.01 |
| Residence within metropolitan area,† n (%) | 635 (62.6) | 1270 (62.6) | 0 |
| Ethnicity, n (%) | | | |
| Chinese | 47 (4.6) | 92 (4.5) | 0 |
| South Asian | 39 (3.8) | 68 (3.4) | 0.03 |
| Not Chinese or South Asian | 928 (91.5) | 1868 (92.1) | 0.02 |
| Any comorbid condition,‡ n (%) | 450 (44.4) | 846 (41.7) | 0.05 |
| Charlson Index ≥1, n (%) | 79 (7.8) | 22 (1.1) | 0.33 |
| Fertility treatment, n (%) | 38 (3.7) | 66 (3.3) | 0.03 |
| Any previous births, n (%) | 299 (29.5) | 598 (29.5) | 0 |
| Gestational diabetes mellitus, n (%) | 59 (5.8) | 155 (7.6) | 0.07 |
| Multifetal pregnancy, n (%) | 28 (2.8) | 49 (2.4) | 0.02 |
| Delivery at tertiary center, n (%) | 912 (89.9) | 1345 (66.3) | 0.6 |
| Cesarean delivery, n (%) | 295 (29.1) | 598 (29.5) | 0.01 |
| Preterm birth, n (%) | 132 (13.0) | 221 (10.9) | 0.07 |
| Stillbirth, n (%) | 0 (0.0) | 1–5 (0.1–0.2) | 0.03–0.07 |
| Obstetric complication during index pregnancy,§ n (%) | 303 (29.9) | 536 (26.4) | 0.08 |
| Cardiac complication during index pregnancy,‖ n (%) | 65 (6.4) | 0 (0.0) | 0.37 |
| Infant born with congenital cardiac lesion, n (%) | 91 (9.0) | 35 (1.7) | 0.33 |
| Primary maternal cardiac diagnosis,¶ n (%) | | | |
| Congenital | 399 (39.3) | | |
| Cardiomyopathy | 112 (11.0) | | |
| Left-sided valve disease | 312 (30.8) | | |
| Isolated arrhythmia | 118 (11.6) | | |
| Ischemic heart disease | 26 (2.6) | | |
| Other | 47 (4.6) | | |
| After index birth | | | |
| Median (IQR) follow-up, y | 13.7 (8.6–19.8) | 14.0 (8.8–20.2) | 0.05 |
| Range | 0.9–25.2 | 3.8–25.7 | |
| Number of women with subsequent births, n (%) | 493 (48.6) | 869 (42.9) | 0.12 |
| Number of subsequent pregnancies | | | |
| Median (IQR) | 0.00 (0.00–1.00) | 0.00 (0.00–1.00) | 0.13 |
| Range | 0.00–8.00 | 0.00–5.00 | |
| Median (IQR) interval between index birth and next subsequent birth, y | 2.9 (2.1–4.4) | 2.9 (2.1–4.4) | 0 |

IQR indicates interquartile range.

*Residing within the 2 lowest neighborhood income quintiles.

†Residence within Greater Toronto Metropolitan Area.

‡Any comorbid condition (hypertension, diabetes mellitus, pulmonary disease, renal disease, cancer, collagen vascular disease, thyroid disease, cerebrovascular disease, peripheral vascular disease, dyslipidemia, obesity, or substance abuse).

§Admission within 9 months before and including index birth, for ante- or postpartum hemorrhage, placental abruption, placental infarction, premature delivery or rupture of membranes, gestational hypertension or preeclampsia/eclampsia, poor fetal growth, or stillbirth.

‖Admission within 9 months before and 6 months after index birth, for heart failure, arrhythmia, stroke, or myocardial infarction.

¶In women with multiple cardiac lesions, the diagnosis that is the most hemodynamically significant was considered to be the primary diagnosis. Lesions that do not fall into the first 5 mutually exclusive categories were classified as other.

**Table 2. Frequency and Rate of Adverse Outcomes in Women With Heart Disease and Matched Comparison Group**

| | Heart Disease n=1014 Women | | Comparison n=2028 Women (Referent) | | Unadjusted HR (95% CI) | Adjusted HR (95% CI) | *P* Value for Adjusted HR |
|---|---|---|---|---|---|---|---|
| | n (%) | Rate per 1000 Person-Years (95% CI) | n (%) | Rate per 1000 Person-Years (95% CI) | | | |
| Composite outcome | 298 (29.4) | 25.4 (22.7–28.4) | 32 (1.6) | 1.1 (0.8–1.5) | 24.0 (16.6–35.0) | 19.6 (13.8–29.0)* See Figure 1B for time dependent HRs | <0.0001 |
| All-cause mortality† | 43 (4.2) | 3.0 (2.2–4.0) | 14 (0.7) | 0.5 (0.3–0.8) | 6.8 (3.6–12.7) | 5.4 (2.9–10.4)* | <0.0001 |
| Heart failure† | 117 (11.5) | 8.7 (7.2–10.4) | 1–5 | 0.2 (0.1–0.4) | 65.8 (25.4–240.1) | 45.7 (20.6–129.8)* | <0.0001 |
| Atrial fibrillation† | 205 (20.2) | 16.5 (14.4–18.9) | 9 (0.4) | 0.3 (0.2–0.6) | 61.8 (31.3–128.3) | 44.7 (24.2–94.5)* Year 1: 153.4 (39.4–597.0) Year 5: 89.2 (31.9–249.6) Year 10: 45.3 (21.7–94.8) Year 15: 23.0 (10.9–48.5) | <0.0001 |
| Arrhythmia† | 142 (14.0) | 10.8 (9.17–12.72) | 1–5 | 0.07‡ | 184.7‡ | § | |
| Myocardial infarction or stroke† | 23 (2.3) | 1.6 (1.1–2.4) | 8 (0.4) | 0.3 (0.1–0.6) | 7.0 (2.9–16.5) | 5.6 (2.5–13.6) | 0.0001 |
| Therapeutic cardiac procedures | 281 (27.7) | 24.3 (21.7–27.3) | 8 (0.4) | 0.3 (0.1–0.5) | 105.2 (50.1–245.4) | 83.7 (44.2–184.9)* Year 1: 314.0 (76.3–1292.3) Year 5: 179.8 (59.4–544.6) Year 10: 89.6 (39.7–202.2) Year 15: 44.6 (21.3–93.4) | <0.0001 |
| New diabetes mellitus or hypertension | 209 (20.6) | 17.5 (15.3–20.0) | 274 (13.5) | 10.7 (9.5–12.0) | 1.7 (1.4–2.0) | 1.6* (1.4–2.0) | <0.0001 |

HR indicates hazard ratio.

*Hazard ratio from analyses assuming constant proportional hazard between heart disease and comparison groups, instantaneous hazard ratios at 1, 5, 10, and 15 years are provided when proportional hazard assumption was not met.

†Secondary outcomes are not mutually exclusive.

‡ 95% confidence intervals not provided as per Institute for Clinical Evaluative Sciences' privacy policy for low counts.

§Time-dependent hazard ratios not calculated because of low number of events in the comparison group.

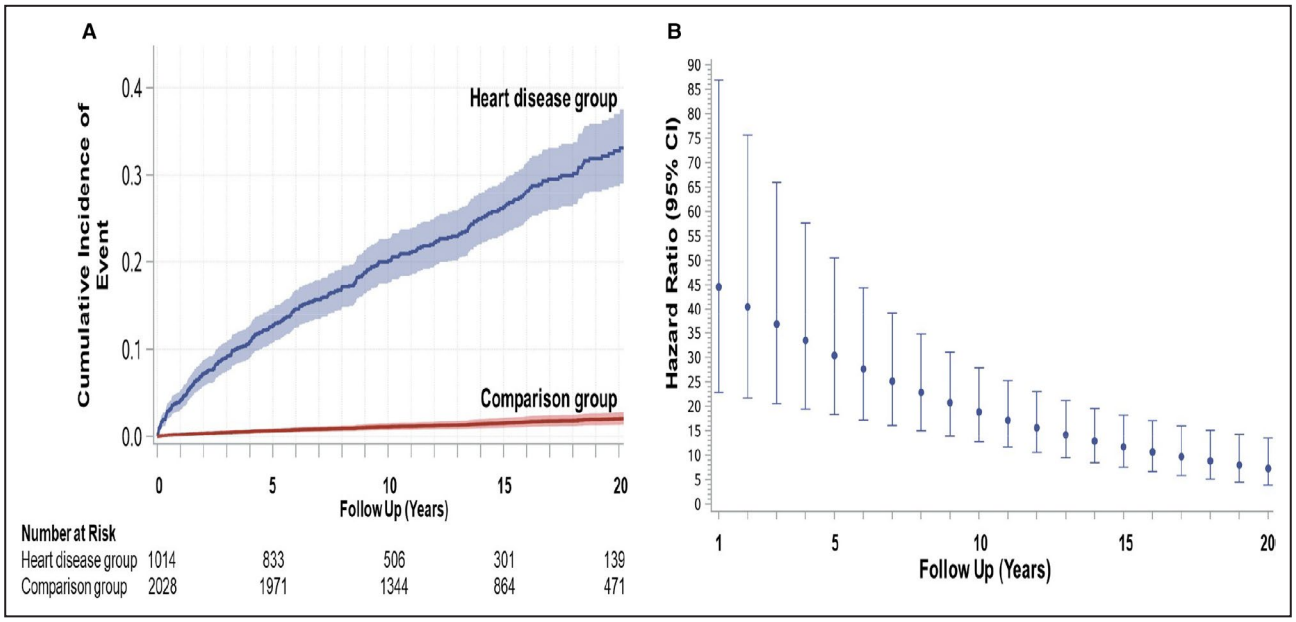


**Figure 1. Adjusted time-to-event curves for primary outcome and hazard ratios.**
**A**, Adjusted cumulative incidence of the primary outcome (all-cause mortality, heart failure, myocardial infarction, stroke, arrhythmia, or atrial fibrillation) with 95% CIs in the heart disease group and matched comparison group. Numbers at risk were obtained from unadjusted cumulative incidence curves. **B**, Instantaneous hazard ratio (point estimates and 95% CIs) of primary outcome in heart disease group (comparison group=referent) as a function of follow-up time.

In a secondary analysis, in which the cumulative incidence of primary outcomes was stratified by the occurrence of cardiac or obstetric complications during the index pregnancy (Figure S4), the unadjusted cumulative 20-year incidence of a primary outcome in women with heart disease who experienced

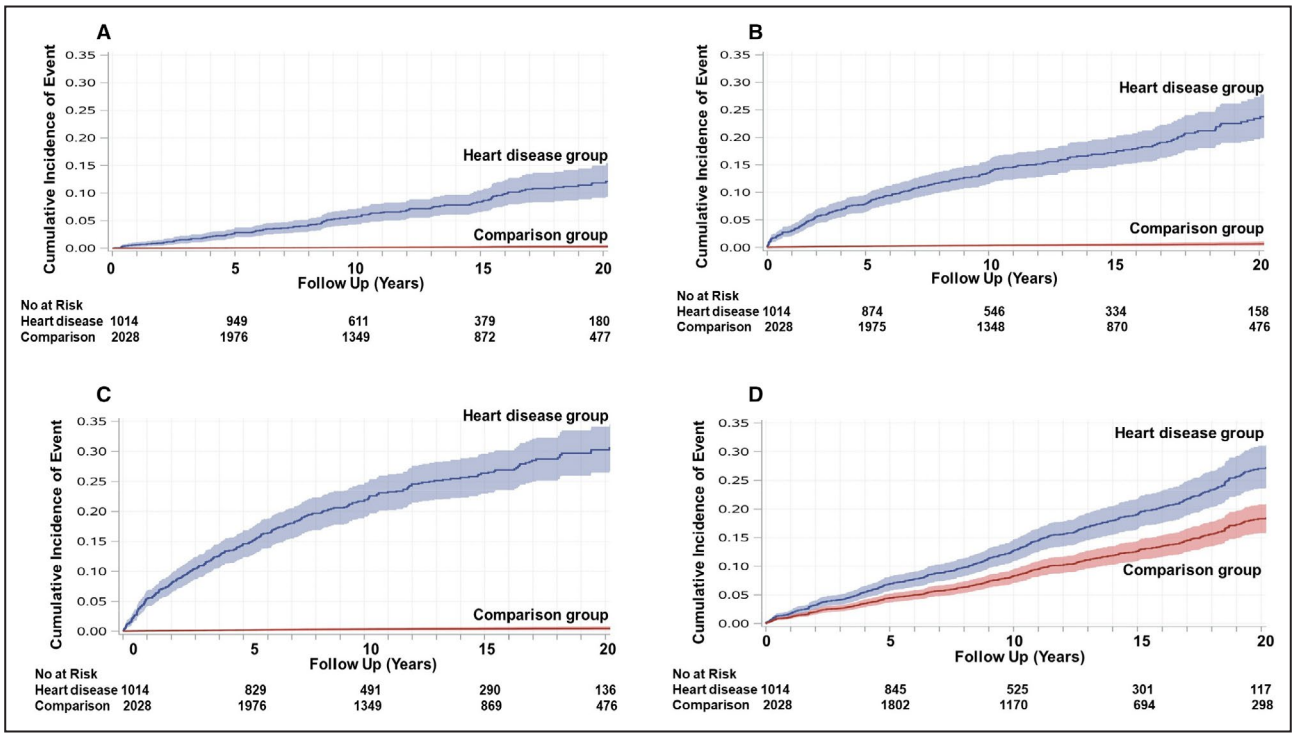


**Figure 2. Adjusted time-to-event curves for selected secondary outcomes.**
Adjusted cumulative incidence and 95% CIs for selected secondary outcomes (heart failure [**A**], atrial fibrillation [**B**], therapeutic cardiac procedures [**C**], and new hypertension or diabetes mellitus [**D**]) in heart disease group and matched comparison group. Numbers at risk were obtained from unadjusted cumulative incidence curves.

**Table 3. Adjusted Model for Primary Outcome, Cardiac Procedures, and New Hypertension/Diabetes Mellitus**

| Parameter | Primary Composite Outcome | | Cardiac Procedure | | New Hypertension or Diabetes Mellitus | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P Value* | HR (95% CI) | *P* Value | HR (95% CI) | *P Value* |
| Heart disease group (community comparison group=referent) | 19.6 (13.8–29.0)* See Figure 1B for time-dependent HRs | <0.001 | 83.7 (44.2–184.9)* See Table 2 for time-dependent HRs | <0.001 | 1.6 (1.4–2.0) | <0.001 |
| Obstetric complication during index pregnancy | 1.25 (1.0–1.6) | 0.072 | 0.9 (0.7–1.1) | 0.36 | 1.5 (1.2–1.8) | <0.001 |
| Cardiac complication during index pregnancy | 3.3 (2.3–4.6) | <0.001† | 1.9 (1.3–2.8) | <0.001 | 1.0 (0.6–1.6) | 0.98 |
| Infant born with congenital cardiac lesion | 1.3 (0.9–1.9) | 0.12 | 1.3 (0.9–1.9) | 0.15 | 1.5 (1.1–2.1) | 0.023 |
| Number of subsequent pregnancies | 1.1 (0.9–1.3) | 0.50 | 0.8 (0.6–1.0) | 0.090 | 0.9 (0.8–1.1) | 0.38 |
| Any subsequently pregnancies | 2.0 (1.3–3.0) | 0.0030† | 0.39 (0.16–0.79) | 0.020 | 0.4 (0.2–0.8) | 0.019 |
| Charlson Index score ≥1 | 1.5 (0.9–2.3) | 0.068 | 1.1 (0.7–1.8) | 0.68 | 1.4 (0.8–2.3) | 0.21 |
| Age at index birth | 1.04 (1.02–1.06) | 0.0016 | 0.99 (0.97–1.01) | 0.29 | 1.05 (1.04–1.07) | <0.0001 |
| Low residential income area | 1.0 (0.8–1.3) | 0.77 | 0.9 (0.7–1.1) | 0.42 | 1.4 (1.2–1.7) | 0.0001 |
| Greater Toronto metropolitan area residence | 1.0 (0.8–1.3) | 0.87 | 1.2 (0.9–1.5) | 0.28 | 1.2 (1.0–1.4) | 0.14 |
| Index birth is first pregnancy | 0.8 (0.7–1.1) | 0.16 | 0.9 (0.7–1.2) | 0.41 | 0.8 (0.6–0.9) | 0.014 |
| Fiscal year of index birth | 0.98 (0.96–0.99) | 0.039† | 0.97 (0.94–0.99) | 0.0033 | 0.97 (0.95–0.99) | 0.0010 |

HR indicates hazard ratio.
*hazard ratio from analyses assuming constant proportional hazard between heart disease and comparison groups.

a pregnancy complication was 48.5% compared with 32.5% in women with heart disease who did not experienced a pregnancy complication. In comparison, the cumulative incidence in women from the comparison group was 3.6% and 2.1%, with and without pregnancy complications, respectively. When atrial fibrillation and arrhythmia were excluded from analysis, the adjusted cumulative incidence of all-cause mortality, heart failure, stroke, or myocardial infarction at 20 years was 15.0% and 1.4% in the heart disease and comparison groups, respectively (Figure S5). The unadjusted rate of the primary outcome and the frequency of the component events, stratified by principal cardiac diagnosis, are provided in Table S6.

Maternal heart disease was associated with an elevated hazard for the primary composite outcome or cardiac procedure even after adjustment for the statistically significant covariates such as cardiac complications during pregnancy and maternal age (Table 3). Similarly, the elevated hazard for incident hypertension and diabetes mellitus associated with maternal heart disease was after adjustment for statistically significant covariates including obstetric complications during pregnancy, baby born with congenital heart disease, maternal age, low residential income area, and nulliparity. The inverse relationship between fiscal year of birth and outcomes can be attributed to the shorter follow-up time for women with more recent births.

After the index birth, there were additional births in 48.6% of the heart disease group and 42.9% of the comparison group, with a median time of 2.9 years between the index and subsequent birth in both groups (Table 1). There was no significant relationship between number of subsequent births and the primary outcome (Table 3). The hazard of having a primary outcome was increased during the time of subsequent pregnancy (Table 3). However, only 11.4% of the primary outcomes in the heart disease group occurred during subsequent pregnancies (none in the comparison group); these events were either heart failure, atrial fibrillation, or arrhythmia. Similarly, 2.4% of cardiac therapeutic procedures performed in the heart disease group (none in the comparison group) were in relation to subsequent pregnancies.

Table 4 provides a summary of pregnancy risk groups stratified by maternal cardiac lesions. The proportion of the heart disease group at intermediate-to-high risk for cardiovascular complications during their index pregnancy was 42%, 29%, and 30%, corresponding to CARPREG risk score >1, CARPREG II risk score ≥4, and WHO class III or IV (estimated cardiovascular pregnancy risk of ≥27%, >22%, and ≥19%, respectively). Women at intermediate-to-high pregnancy risk were also at the highest risk of experiencing a primary outcome during follow-up (Figures 3 and 4). This finding was consistent regardless of the pregnancy risk classification tool that was used (Table S7, Figures 3A, 3C, and 4A). The adjusted cumulative incidence of

**Table 4. Principal Cardiac Lesion in Heart Disease Group and Maternal Cardiovascular Risk at Time of Index Pregnancy**

| Maternal Cardiac Lesion | Total No. | Maternal Cardiovascular Risk | | | | | |
|---|---|---|---|---|---|---|---|
| | | CARPREG Risk Score* | | CARPREG II Risk Score† | | WHO Classification‡§ | |
| | | Low Risk n (%) | Intermediate-to-High Risk n (%) | Low Risk n (%) | Intermediate-to-High Risk n (%) | Low Risk n (%) | Intermediate-to-High Risk n (%) |
| Congenital | 399 | 334 (83.7) | 65 (16.3) | 365 (91.5) | 34 (8.5) | 283 (77.3) | 83 (22.7) |
| Cardiomyopathy | 112 | 36 (32.1) | 76 (67.9) | 42 (37.5) | 70 (62.5) | 47 (42.0) | 65 (58.0) |
| Left sided valve | 312 | 161 (51.6) | 151 (48.4) | 230 (73.7) | 82 (26.3) | 173 (72.4) | 66 (27.6) |
| Isolated arrhythmia | 118 | 0 | 118 (100) | 34 (28.8) | 84 (71.2) | 69 (71.9) | 27 (28.1) |
| Ischemic | 26 | 21–25‖ | 1–5‖ | 14 (53.8) | 12 (46.2) | 6–10‖ | 1–5‖ |
| Other | 47 | 35–40‖ | 10–15‖ | 40 (85.1) | 7 (14.9) | 5–10‖ | 5–10‖ |
| Total | 1014§ | 591 (58.3%) | 423 (41.7%) | 725 (71.5) | 289 (28.5) | 586 (70.2) | 249 (29.8) |

CARPREG indicates Canadian Cardiac Disease in Pregnancy study; and WHO, World Health Organization.
*CARPREG Risk Score: low risk=5%, intermediate-to-high risk = ≥25%.
†CARPREG II Risk Score: low risk=5% to 15%, intermediate to high risk = ≥22%.
‡Modified WHO: low risk=2.5% to 19% (WHO class I, II, II–III), intermediate-to-high risk = ≥19% (WHO class III or IV).
§Total patients n=835 for WHO groups as cardiac lesions in 179 patients could not be classified into a WHO risk group.
‖ Exact numbers not provided because of Institute for Clinical Evaluative Sciences' privacy policy.

a primary outcome at 20 years was 50.6%, 51.0%, and 53.6% when intermediate-to-high pregnancy risk groups were defined using CARPREG, CARPREG II, and WHO classification tools, respectively. While the risk of a primary outcome was elevated during the early years of follow-up in both pregnancy risk groups, women in the intermediate-to-high pregnancy risk group had the highest risk (Figures 3B, 3D, and 4B). When the data were reanalyzed using separate WHO classes, the results were similar to when the WHO classes were combined into high and low-to-intermediate categories. The adjusted cumulative incidence of a primary outcome in women in WHO classes III and IV was 52.8% to 54.2% at 20 years, compared with 12.5% for women in WHO class I. In contrast, the comparison group's corresponding cumulative incidence was 2.1% (Figure S6).

## DISCUSSION

In this large study of women with heart disease, adverse cardiovascular events occurred in ≈1 in 3 women during the 20 years following pregnancy, representing a 20-fold increase in risk when compared with a matched group of women without heart disease. Furthermore, many women with heart disease required therapeutic cardiac procedures during this same period. Women with heart disease were also more likely to develop new hypertension or diabetes mellitus when compared with women without heart disease. Risk stratification tools used to predict cardiovascular complications in pregnant women with heart disease, such as the CARPREG risk score or the WHO classification, were also helpful in identifying those women at highest risk of long-term cardiovascular complications.

The hemodynamic and metabolic changes associated with pregnancy are responsible for the higher frequency of maternal and feto-neonatal complications reported in pregnant women with preexisting heart disease compared with pregnant women without heart disease.[3,5–8] Whether these pregnancy changes affect long-term outcomes in women with preexisting heart disease has not been systematically examined. Prior studies examining outcomes after pregnancy in women with heart disease have been limited, reporting on only small numbers of women, following for relatively short time intervals after pregnancy, or lacking comparison groups.[39–42] Combining patient level and administrative data allowed us to match and adjust for confounding factors and capture outcome events over a prolonged period of follow-up.[13,15,35–37] The high rate of occurrence of adverse cardiovascular events in women with heart disease, when they were still relatively young (age 40–50 years), highlights the significant long-term burden of cardiovascular disease in this

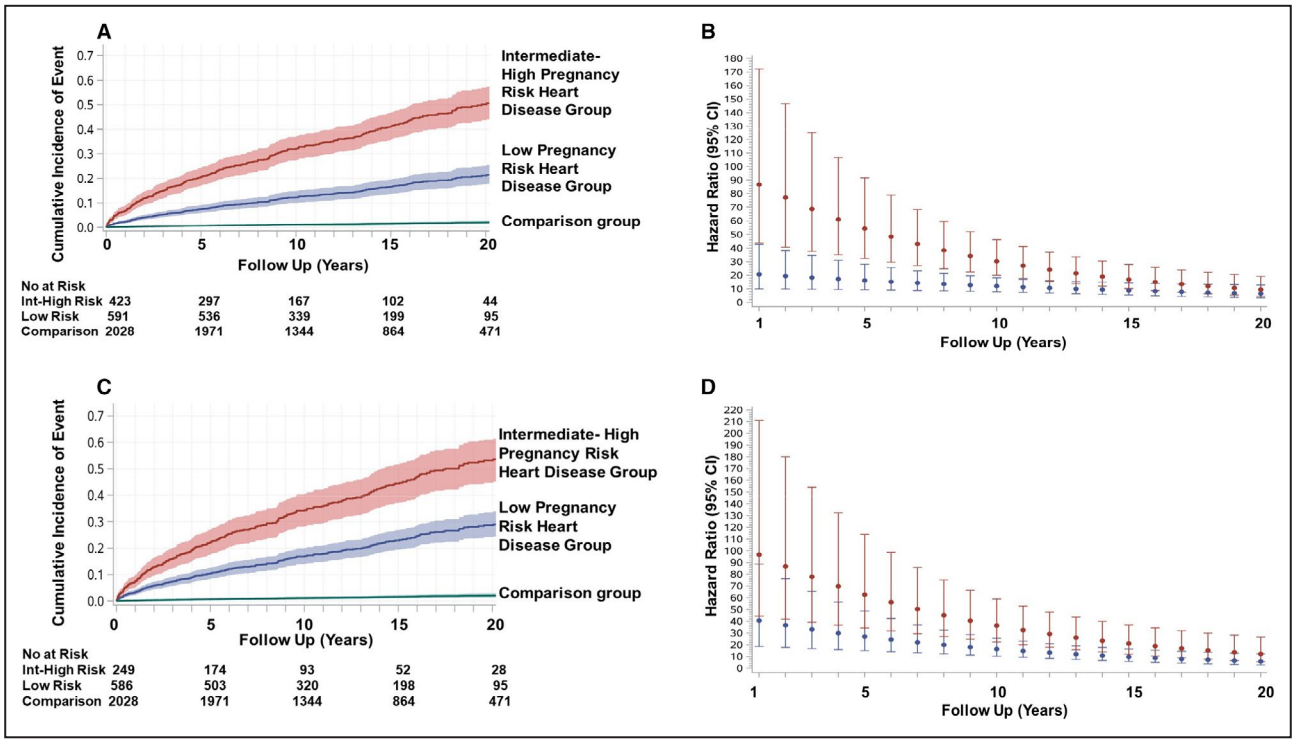


**Figure 3. Pregnancy risk groups: adjusted time-to-event curves for primary outcome and hazard ratios.**
Adjusted cumulative incidence of primary outcome and 95% CIs as a function of maternal cardiovascular risk during index pregnancy. Incidence rates are separated into low pregnancy risk heart disease group vs intermediate-to-high pregnancy risk heart disease group, as defined by the CARPREG (Canadian Cardiac Disease in Pregnancy) risk score (**A**),[3] and the modified World Health Organization classification system (**C**).[14] Numbers at risk were obtained from unadjusted cumulative incidence curves. Comparison group denotes matched community comparison group. Instantaneous hazard ratios (point estimates and 95% CIs) for the low (in blue) and intermediate-to-high (in red) pregnancy risk groups corresponding to the CARPREG risk score (**B**) and WHO (**D**) risk classification are shown (comparison group=referent).

population. The high rates of long-term cardiovascular events in these young women with heart disease may represent the natural history of their underlying cardiac disease. It is also possible that the hemodynamic stress of pregnancy adversely affects cardiac structure and function in women with preexisting heart disease differently than women without heart disease.[43] We have reported that women with heart disease have an exaggerated increase in B-type natriuretic peptide during pregnancy, likely as a result of ventricular distention.[44] Incomplete return of cardiac structure and function back to the prepregnancy state may be a partial reason for our observation that the risk of cardiac outcome was the highest in the earlier years of follow-up.

To our knowledge, this study was the first to examine long-term major cardiovascular adverse events and cardiovascular risk factors in women with preexisting heart disease. Previous population studies in women without heart disease have demonstrated the relationship between obstetric complications, such as gestational hypertension, maternal placental syndrome, cesarean delivery, and congenital heart disease in the offspring,[13,15,35–37] and subsequent long-term cardiovascular outcomes in the mother. In our current study, even after adjusting for the above-mentioned risk factors, women with heart disease were still more likely to develop new hypertension or diabetes mellitus than women without heart disease. Their higher long-term atherosclerotic risk is suggested by the higher rate of myocardial infarction or stroke in the heart disease group. Pregnancy-related hypercoagulability, inflammatory activity, insulin resistance, and dyslipidemia are more pronounced in women with gestational hypertension, with endothelial dysfunction thought to be the link between gestational hypertension, placental disorders, and late atherosclerotic events.[13,15,35–37] Since pregnant women with heart disease are already at elevated risk for noncardiac pregnancy complications,[8] it is possible that maternal heart disease may further elevate their propensity for hypertension or insulin resistance. While the mechanisms underlying our study findings will require further investigation, the combination of preexisting heart disease and increased risk for atherosclerotic risk factors is an unfavorable combination and points to the need for continuing postpartum surveillance and risk factor modification in this group of women.

We and others have derived and validated classification methods to predict the risk of maternal cardiovascular complications in pregnant women with heart disease.[9] Our study was the first to demonstrate that previously derived pregnancy risk assessment tools to predict maternal cardiovascular complications in pregnant women with heart disease,[3,4,14] can be expanded and used for risk stratification of long-term cardiovascular outcomes. When applying our study results, it is important to note that CARPREG risk scores incorporate history of heart failure, arrhythmia, and stroke before the index pregnancy and is independent of the primary outcomes, which are measured after the index pregnancy. Furthermore, in calculating the risk of primary outcomes in relationship to CARPREG and WHO risk categories, we also adjusted for cardiovascular events during pregnancy. As the long-term cardiovascular risk in low-risk groups such as WHO class I was higher than matched comparison groups, our study findings are a reminder that "low risk" does not mean "no risk." Our study findings simplify risk assessment for the clinician who can identify pregnancy-related and long-term cardiovascular risk with 1 risk assessment tool. Importantly, this ability to risk stratify long-term risk was consistently observed with the 3 different pregnancy risk classification tools that were evaluated. In addition, the above-mentioned risk assessment tools include the wide spectrum of maternal heart disease seen in women of childbearing age.

The strength of this study was the combined use of patient-level and administrative data. The use of patient-level data enabled the characterization of the pregnancy risk profile of the women with heart disease. The use of administrative healthcare databases enabled us to identify a comparable group of women without heart disease from the Ontario population, as well as determining outcomes without loss of follow-up. By using birth records from Ontario, Canada's most populous province, we were able to identify a comparison group that was similar to the heart disease group on key parameters other than maternal heart disease. As we used validated administrative databases that captured both ambulatory encounters and hospitalization, we are able to provide a more accurate determination of the frequency of late cardiovascular outcomes. This research approach also allowed for adjustment for the effects of subsequent pregnancies on outcomes. Our study was not designed to address whether pregnancy accelerates clinical or lesion progression in women with heart disease,[40–42] as it would be difficult to identify a comparable group of women with heart disease who never underwent pregnancy. A population-based study from Canada reported that 80% of women of childbearing age with congenital heart disease have at least 1 pregnancy, with absolute number and rates of pregnancy increasing with time.[2] In addition to the progressive decline in the number of women with heart disease who do not undergo pregnancy, women with heart disease who did not undergo pregnancy may differ from women with heart disease who underwent pregnancy in demographics,

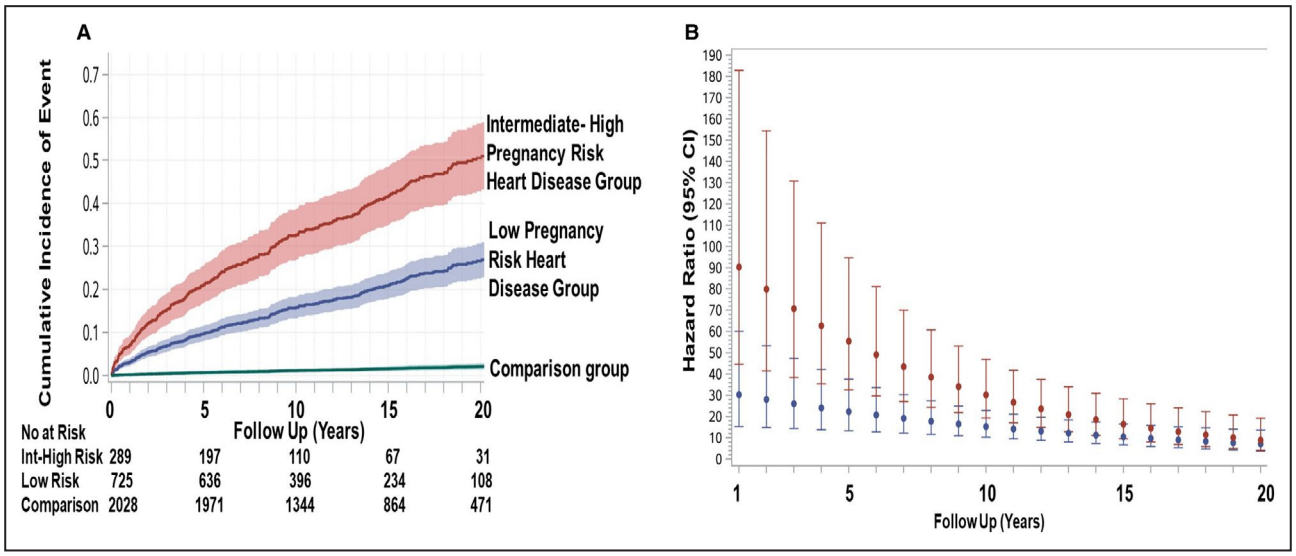


**Figure 4. CARPREG (Canadian Cardiac Disease in Pregnancy) II adjusted time-to-event curves for primary outcome and hazard ratios.**

**A**, Adjusted cumulative incidence of primary outcome (with 95% CIs) as a function of maternal cardiovascular risk during index pregnancy in the low pregnancy and intermediate-to-high (Int-High) pregnancy risk heart disease groups, as defined by the CARPREG II risk score.[4] Comparison group denotes matched community comparison group. No at risk denotes number at risk from unadjusted cumulative incidence curves. **B**, Instantaneous hazard ratios (with 95% CIs) of primary outcome (matched community group=referent) as a function of time, in the low (in blue) and intermediate-to-high (in red) risk groups corresponding to the CARPREG II risk score.

comorbidities, or prognosis. Our study results are applicable only to women with pregnancies that progress beyond 20 weeks and women who survived beyond the postpartum period. However, we have previously reported that 96% of pregnancies in women with heart disease progressed beyond 20 weeks.[4] There were <6 maternal deaths during the index pregnancy in this study. The proportion of mortality from cardiovascular causes may be underreported, as cause of death is based on certificates of death. While we were not able to determine the role of postpregnancy care in determining outcomes, our analyses adjusted for baseline demographics and socioeconomic status. However, the generalizability of our study findings was optimized by the determination of outcomes using standardized hospital admissions and ambulatory visit databases, including a large study group with a spectrum of cardiac lesions and pregnancy risks, and conducted in women who have universal access to health care.

## CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE

Following pregnancy, women with heart disease are at high risk for adverse long-term cardiovascular outcomes including new hypertension or diabetes mellitus. Our findings highlight the importance of ongoing surveillance and risk factor modification in these young women after pregnancy. Current tools for cardiovascular risk assessment during pregnancy can also be used to risk stratify for long-term cardiovascular risk after pregnancy.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplementary Material

Tables S1–S7
Figures S1–S6

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# Supplemental Material

**Table S1. STROBE Statement.**

| | Item | Recommendation | Where Reported |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Abstract |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Introduction |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Introduction |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | Methods |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Methods |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | Methods |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed | Methods |

| | | | |
|---|---|---|---|
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Methods Tables S2-S5 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Methods Table S2 |
| Bias | 9 | Describe any efforts to address potential sources of bias | Methods |
| Study size | 10 | Explain how the study size was arrived at | Methods |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Methods Tables S2-S5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Methods |
| | | (*b*) Describe any methods used to examine subgroups and interactions | Methods |
| | | (*c*) Explain how missing data were addressed | Methods |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed | N/A |
| | | (*e*) Describe any sensitivity analyses | N/A |

N/A, not applicable

**Table S2. Description of ICES Databases and Algorithms and their role in the current study.**

| Name of Data Base | Description | Type of data utilized | How the data were utilized in the study | Original Validation Measures for ICES Derived Databases |
|---|---|---|---|---|
| Canadian Institute for Health Information Discharge Abstract Database (DAD) | Hospital discharge data since 1988 | • Dates of hospitalization<br>• Procedures<br>• Diagnoses<br>• Comorbidities | • Cohort identification<br>• Baseline characteristics<br>• Outcome | Not applicable |
| Ontario Mother-Baby Linked Dataset (MOMBABY) | Linked DAD of inpatient admission of mother and baby since 1988 | Diagnostic codes | • Cohort identification<br>• Outcome | Not applicable |
| Registered Persons Database (RPDB) | Demographic data of anyone who has received Ontario health care number since 1990 | • Date of birth/death<br>• Sex<br>• Geographic information | • Cohort identification<br>• Baseline characteristics<br>• Outcome | Not applicable |

| | | | | |
|---|---|---|---|---|
| | | • Time period of insurance coverage | | |
| Ontario Health Insurance Plan (OHIP) claims database | All reimbursement claims by registered health care providers since 1991 | • Diagnostic codes<br>• Procedure codes | • Cohort identification<br>• Baseline characteristics<br>• Outcome | Not applicable |
| Ontario Registrar General (ORGD) | Cause of death (as recorded on medical certificate of death) since 1979 | Diagnostic codes | Outcome | Not applicable |
| Ontario Health care institutions (INST) | Ontario health care institutions | Index birth at acute care obstetric referral center | Baseline characteristics | Not applicable |
| Ontario Cancer Registry (OCR) | Registry of all Ontario residents diagnosed with or died from cancer except non-melanoma skin cancer since 1964 | Record of patient as being in the registry | Baseline characteristics | Not applicable |

| | | | | |
|---|---|---|---|---|
| Canadian Institute for Health Information National Ambulatory Care Reporting System (NACRS) | Individual level data for institutional-based ambulatory care including care provided in emergency departments and out-patient clinics since 2000, and day surgeries since 1988 | Diagnostic codes | • Cohort identification<br>• Baseline characteristics | Not applicable |
| Same Day Surgery (SDS) | Database of same day surgeries since 1991 | Procedural or diagnostic code | • Baseline characteristics<br>• Outcome | Not applicable |
| Ethnicity dataset (ETHNIC)[26] | Validated dataset to identify Chinese or South Asian ethnicity based on surname | Ethic Groups | Baseline characteristics | • Sensitivity 50% - 80%<br>• Specificity 100% |
| Ontario Diabetes Database (ODD)[21, 28] | Validated dataset of Ontario residents identified as having diabetes mellitus since 1991 | Record of patient as being in the dataset | • Baseline characteristics<br>• Outcome | • Sensitivity 90%<br>• Specificity 99% |

| | | | | |
|---|---|---|---|---|
| Ontario Myocardial Infarction Database (OMID)[27] | Validated dataset of Ontario residents identified as having myocardial infarction since 1992 | Record of patient as being in the dataset | • Baseline characteristics<br>• Outcome | • Sensitivity 89%<br>• Specificity 93% |
| Ontario Hypertension database (HYPER)[25] | Validated dataset of Ontario residents identified as having hypertension since 1988 | Record of patient as being in the dataset | • Baseline characteristics<br>• Outcome | • Sensitivity 72%<br>• Specificity 95% |
| Ontario Asthma database (ASTHMA)[18] | Validated dataset of Ontario residents diagnosed with asthma since 1991 | Record of patient as being in the dataset | • Baseline characteristics | • Sensitivity 81%<br>• Specificity 90% |
| Ontario Chronic obstructive pulmonary disease database (COPD)[19] | Validated dataset of Ontario residents 35 years or older diagnosed with COPD since 1991 | Record of patient as being in the dataset | Baseline characteristics | • Sensitivity 85%<br>• Specificity 95% |
| Ontario Congestive Heart Failure database (CHF)[29] | Validated dataset of Ontario residents 40 years or older diagnosed with congestive heart failure since 1988 | Record of patient as being in the dataset | • Covariate<br>• Outcome | • Sensitivity 85%<br>• Specificity 97% |

| | | | | |
|---|---|---|---|---|
| Atrial fibrillation (AF) Algorithm [30] | Any of: hospitalization or an emergency room code for AF or 4 physician billing code for AF in 1 yr | | | • Sensitivity 89%<br>• Specificity 99% |

**Table S3. Prognostic Risk Score Utilized for Matching.**

- Group in which baseline model was derived: Women from Ontario that had a recorded birth during 1994 to 2015 period
- Dependent variable: Time to the first of any event during follow up including death, heart failure, myocardial infarction, stroke, arrhythmia, or atrial fibrillation.
- Independent variable (in binary format) at index birth

i. Any comorbid condition (referent =no) : Chronic Hypertension, Diabetes mellitus, Pulmonary disease, Renal disease, Cancer, Non cancerous thyroid disease, Collagen vascular disease, Dyslipidemia, Obesity, Substance abuse, Cerebrovascular disease, or Peripheral vascular disease

ii. Fertility therapy (referent =no)

iii. Cesarean section (referent =no)

iv. Ethnic (South Asian or Chinese vs other=referent)

v. Multi fetal births (referent = no)

vi. Delivery at tertiary obstetric center (referent = no)

vii. Gestational diabetes during index pregnancy (referent = no)

**Table S4. Variables used to define the cohort entry and exclusion criteria, as well as the study exposure, outcome, and adjustment variables.**

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| **Cohort entry criterion** | April 1, 1991 - December 31, 2019 | Births | | MOMBABY*<br>Cohort entry date = date of index birth |
| **Cohort exclusion criteria** | | male, non-Ontario resident, or death within 6 months of index birth | | RPDB† |
| | Prior to cohort entry date | Cardiac Diagnosis (for community comparison group only) | 391-398,402-429, 6738, 6740, 745-7474, 48, 49, (1HZ80, 1IJ50, 1IJ54, 1IJ55, 1IJ57, 1IJ76, 1IJ80, 1IJ86, 1IK80, 1IK87, 1IL35, 2IL70, I01, I020, I05- I52, Q20- Q26, O903) | OHIP diagnostic codes‡<br>390, 391, 394, 398, 402, 410, 412, 413, 415, 426, 427, 428, 429, 745, 746, 747 |
| | Prior to cohort entry date (age at index birth) | Surgery or catheter intervention on cardiac valves, thoracic aorta, or congenital cardiac lesions, | 4702-4703, 4712- 4713, 4722- 4729, 4781 - 4784, 4791– 4794, 5034, (1HJ, 1HM80, 1HN, 1HP71 - 1HP87, 1HR, 1HS, 1HT, 1HU, 1HV, 1HX, 1IA8, 1IB8, 1IC50,1IC80) | OHIP Fee Codes‡<br>R729, R730, R736, R773, R774, R930, |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | | prior to cohort entry date (community comparison group only) | | Z461, R733, R720, R724, R772, R728 |
| | Prior to cohort entry date | Coronary revascularization (surgical or catheter; for community comparison group only) | 480-483, (1IJ50, 1IJ55, 1IJ57, 1IJ76, 1IJ80) | |
| | Prior to cohort entry date | Cardiac arrhythmia intervention (pacemaker, ablation, defibrillator) for community comparison group only) | 496, 497, 498, (1HZ53, 1HH59, 1HB53, 1HD55, 1HB55, 1HZ38, 1HZ55) | |
| | Prior to cohort entry date | Cardiac transplantation or cardiac assist device (for community comparison group only) | 456, 495, (1HY85, 1HZ85, 1HP53) | |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| **Study outcomes** | April 1, 1991 – December 31, 2019 | Death during follow up (>6 mos after index birth) | | RPDB†<br>ORGD§ |
| | April 1, 1991 – December 31, 2019 | Cardiovascular death during follow up (>6 mos after index birth) | | RPDB†<br>ORGD§ |
| | April 1, 1991 – December 31, 2019 | New congestive heart failure during follow up (>6 mos after index birth) | 428, 5184, (I50, J81) | Ontario Congestive Heart Failure database |
| | April 1, 1991 – December 31, 2019 | New myocardial infarction during follow up (>6 mos after index birth) | 410, (I21) | Ontario Myocardial Infarction Database |
| | April 1, 1991 – December 31, 2019 | New Arrhythmia (any of supraventricular or atrial tachycardia, atrial fibrillation or flutter, ventricular tachycardia, ventricular | 4260, 4270 – 4275, (I442, I46, I470 - I472, I479, I48, I490) | |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | | fibrillation, paroxysmal tachycardia, cardiac arrest, complete heart block) during follow up (>6 mos after index birth) | | |
| | April 1, 1991 – December 31, 2019 | New Atrial fibrillation during follow up (>6 mos after index birth) | | Atrial fibrillation algorithm<br>• OHIP‡<br>• Canadian Institute for Health Information<br>• National Ambulatory Care Reporting System |
| | April 1, 1991 – December 31, 2019 | New stroke (central nervous system hemorrhage, thrombosis, or embolism) | 430 – 436, 3623, (I60 - I64, H34) | |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | | during follow up (>6 months after index birth) | | |
| | April 1, 1991 – December 31, 2019 | New Diabetes mellitus during follow up (>42 days after birth) | | Ontario Diabetes Database |
| | April 1, 1991 – December 31, 2019 | New Hypertension during follow-up (>90 days after birth) | | Ontario Hypertension database |
| | April 1, 1991 – December 31, 2019 | Cardiovascular procedure during follow-up (6 months), excluding 9 months preceding subsequent births | Same codes as above (listed under exclusion criteria for comparison group) for: 1) Surgery or catheter intervention on cardiac valves, thoracic aorta, or congenital cardiac lesions; 2) Coronary revascularization; 3) Cardiac arrhythmia intervention; 4) Cardiac transplantation or cardiac assist device | |
| **Covariates** | At date of cohort entry | Age, Income quintile, Rurality, Residence within Toronto Metropolitan Area, fiscal year of cohort entry | | RPDB†; Canadian Institute for Health Information Discharge Abstract Database |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | At date of cohort entry | Ethnic group | | Ethnicity dataset |
| | Prior to date of cohort entry | Hypertension | | Ontario Hypertension database (exclude diagnosis within 150 days prior to birth) |
| | Prior to date of cohort entry | Diabetes mellitus | | Ontario Diabetes Database (exclude diagnosis within 120 days prior to birth and 90 days after birth) |
| | Prior to date of cohort entry | Cancer | | Ontario Cancer Registry |
| | Prior to date of cohort entry | Pulmonary disease | | Ontario Asthma & Chronic obstructive |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | | | | pulmonary disease databases |
| | Within 3 years prior to cohort entry date | Renal Disease | 5845- 5849, 6693, 9585, 6343, 6353, 6363, 6373, 6383, 6393, 2504, 2741, 403, 404, 405, 4401, 581- 583, 585- 588, 5900, 5937, 791, 7944, (N17, O084, T795, O904, E1020, E1120, E1121, M1039, I12, I13, I150, M310, N01, N03- N08, N11- N12, N137- N139, N14- N16) | OHIP Diagnostic Codes‡ 403, 581, 585 |
| | Within 3 years prior to cohort entry date | Non Cancer Thyroid Disease | 226, 242, 244, 245, (D34, E032- E035, E038- E039, E05- E06) | OHIP Diagnostic Codes‡ 226, 242, 244, 245 |
| | Within 3 years prior to cohort entry date | Collagen Vascular Diseases | 7100- 7104, 7108- 7109, 7140- 7144, 7149, (M313, M318, M319- M320, M32- M35, M368, M05- M07) | OHIP Diagnostic Codes‡ 710, 714, 720- 721, 739 |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | Within 3 years prior to cohort entry date | Cerebrovascular disease | 433- 434, 436- 437, 5011-5012, (G46, I63- I66, I672, I678, 1JE57, 1JW57, 1JX57, 1JW76) | OHIP Diagnostic Codes‡ 432, 436, 437 |
| | Within 3 years prior to cohort entry date | Peripheral vascular disease | 4400, 4402, 444, 5018, 5028, 5038, 5124- 5126, 5129, (1JM76, 1JX76, 1KA76, 1KE76, 1KG57, 1KT76, 1ID76, 1KG76, 1KG87, I700, I702, I74) | OHIP Diagnostic Code‡ 443 |
| | Within 3 years prior to cohort entry date | Fertility treatment | V261, V268, 8192, (Z311 - Z313, 1RM83) | OHIP Procedural code‡ G334 |
| | Within 3 years prior to cohort entry date | Dyslipidemia | 2720 -2725, (E78) | OHIP Diagnostic Code‡ 272 |
| | Within 3 years prior to cohort entry date | Obesity | 2780, (E66) | OHIP Diagnostic Code‡ 278 |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | Within 3 years prior to cohort entry date | Smoking or substance abuse | 291-292, 2940, 303 – 305, 6483, 6555, 980, (F10 - F19, F55, G312, O354 -O355, T51, T652, Z720 - Z722) | OHIP Diagnostic Codes‡ 291-292, 303 - 305 |
| | Within 3 years prior to cohort entry date | Any births (livebirths or stillbirths) prior to index birth | | MOMBABY* |
| | At cohort entry date (date of index birth) | Multi-fetal pregnancy | V311, V312, V321, V322, V341, V342, V351, V352, V361, V362, V371, V372, V272, V273, V274, V275, V276, V277, (Z372, Z373, Z374, Z375, Z376, Z377, Z3790, O30, O31) | MOMBABY*: B_Multibirth or M_Multibirth |
| | At cohort entry date (date of index birth) | Delivery at tertiary obstetric centres | | Ontario Health care institutions |
| | From start of pregnancy until 1 year post cohort | Fetus or newborn with congenital cardiac lesion | 745 – 747, (Q20 - Q26) | |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | entry date (date of index birth) | | | |
| | At cohort entry date (date of index birth) | Caesarean delivery | 86, (5MD60) | |
| | Within 9 months of cohort entry date (date of index birth), and up to 6 months after. | Cardiac event related admission (Heart failure, arrhythmia, stroke, or MI) during index pregnancy | Same as above codes for outcomes (congestive heart failure, arrhythmia, stroke, or myocardial infarction) | |
| | Within 9 months of cohort entry date including hospital stay related to index birth | Obstetric event related admission (antepartum bleed, preterm birth or rupture membrane, post partum hemorrhage, gestational hypertension/ | 6408 – 6413, 6418 – 6419, 6567, 6442, 6581, 6440, 765, 666, 6420, 6424 – 6427, 6429, 6423, 6565, 7649, 7680 - 7681, 6564, V271, V273 - V274, V276 - V277, (O2080, O2090, O365, O4381, O4410, O45, O46, O431, O43801 - O43819, O439, O60, O4201, O4211, P059, P072 | MOMBABY*<br>Stillbirth or birth <37 weeks gestation age<br>OHIP diagnostic code‡<br>642 |

| | | | Diagnostic or Procedural Codes | |
|---|---|---|---|---|
| **Assessment** | **Timing** | **Parameter** | **ICD-9 or CCP (ICD-10 or CCI)** | **Other sources** |
| | | preeclampsia, stillbirth, fetal death, abruptio placenta, placental infarction, poor fetal growth) | - P073, O72, O11, O13 - O16, P95, Z371, Z373 - Z374, Z376 -Z377, O364) | |
| | Within 9 months of cohort entry | Gestational Diabetes | 64800 – 64804, (O244, O248, O249) | |
| | After cohort entry date | Subsequent births after index birth | | MOMBABY* |

ICD-9, International Classification of Diseases, 9th revision; CCP, /Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; ICD-10, International Classification of Diseases, 10th revision; CCI, Canadian Classification of Health Interventions, * MOMBABY database; †Registered Persons Database; ‡ Ontario Health Insurance Plan; § Ontario Registrar General

**Table S5. Summary of the 3 Methods to Predict Maternal Cardiovascular Risks in Pregnant Women with Heart Disease.**

| Name | Predictors and Risk Score Point Value | Calculation of Risk Score | Risk Groups and Predicted Risk of Maternal Cardiovascular Events during Pregnancy and subsequent 6 months post delivery |
|---|---|---|---|
| CARPREG | • New York Heart Association class III or IV or cyanosis (1 point)<br>• Systemic ventricular EF <40% (1 point)<br>• Left heart obstruction (1 point)<br>• Cardiac event prior to current pregnancy (1 point) | Each predictor = 1 point<br><br>Risk score = sum of points | Score 0, event rate 5%<br>Score 1, event rate 27%<br>Score >1, event rate 75% |
| CARPREG II | • Cardiac event prior to current pregnancy (3 points)<br>• Baseline New York Heart Association III/IV or Cyanosis (3 points)<br>• Systemic ventricular EF <55% (2 points)<br>• Left heart obstruction (mitral valve area<2 $cm^2$ or aortic valve area<1.5 $cm^2$, or peak left ventricular outflow tract | Weighted risk score<br>Risk score = sum of points | Score 0 to 1, event rate 5%<br>Score 2, event rate 10%<br>Score 3, event rate 15%<br>Score 4, event rate 22%<br>Score $\geq$ 4, event rate 41% |

| | | | |
|---|---|---|---|
| | gradient>30 mmHg) or a least moderate-severe mitral regurgitation (2 points)<br>• Mechanical valve (3 points)<br>• Pulmonary hypertension (2 points)<br>• Coronary artery disease (2 points)<br>• High-risk aortopathy (2 points)<br>• No prior cardiac interventions (1 point)<br>• Late pregnancy assessment (1 point) | | |
| WHO* | <u>WHO class I *</u><br>• Small or mild pulmonary stenosis, patent ductus arteriosus, mitral valve prolapse<br>• Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous connection)<br>• Atrial or ventricular ectopic beats, isolated<br><u>WHO class II *</u><br>• Unoperated atrial or ventricular septal defect<br>• Repaired tetralogy of Fallot | | Class I, event rate 2.5% - 5%<br>Class II, event rate 5.7% - 10.5%<br>Class II–III, event rate 10% - 19%<br>Class III, event rate 19% - 27%<br>Class IV, event rate 40% - 100% |

| | | | |
|---|---|---|---|
| | • Most arrhythmias (supraventricular arrhythmias)<br>• Turner syndrome without aortic dilation<br><u>WHO class II–III *</u><br>• Mild left ventricular impairment (EF>45%)<br>• Hypertrophic cardiomyopathy<br>• Native or tissue valvular heart disease not considered WHO I or IV (mild mitral stenosis, moderate aortic stenosis)<br>• Marfan or other HTAD † syndrome without aortic dilatation<br>• Aorta <45 mm in association with bicuspid aortic valve pathology<br>• Repaired coarctation<br>Atrioventricular septal defect<br><u>WHO class III *</u><br>• Moderate left ventricular impairment (EF 30-45%)<br>• Previous peripartum cardiomyopathy without residual left ventricular impairment<br>• Mechanical valve | | |

| | | | |
|---|---|---|---|
| | • Systemic right ventricle with good or mildly decreased ventricular function<br>• Fontan circulation if otherwise well and the cardiac condition uncomplicated<br>• Unrepaired cyanotic heart disease<br>• Other complex congenital heart disease<br>• Moderate mitral stenosis<br>• Severe asymptomatic aortic stenosis<br>• Moderate aortic dilation (40–45 mm in Marfan syndrome or other HTAD, † 45–50 mm in bicuspid aortic valve, Turner syndrome with aortic size index 20-25mm/$m^2$, tetralogy of Fallot <50mm)<br>• Ventricular tachycardia<br><u>WHO class IV*</u><br>• Pulmonary arterial hypertension<br>• Severe systemic ventricular dysfunction (Ejection fraction<30% or New York Heart Association Functional class III-IV) | | |

| | | | |
|---|---|---|---|
| | • Previous peripartum cardiomyopathy with any residual left ventricular impairment<br>• Severe mitral stenosis<br>• Severe symptomatic aortic stenosis<br>• Systemic right ventricle with moderate or severely decreased ventricular function<br>• Severe aortic dilatation (>45 mm in Marfan syndrome or other HTAD, † >50 mm in bicuspid aortic valve, Turner syndrome with aortic size index >25mm/$m^2$, tetralogy of Fallot >50mm)<br>• Vascular Ehlers-Danlos<br>• Severe (re)coarctation<br>• Fontan with any complication | | |

* modified World Health Organization; † heritable thoracic aortic disease

**Table S6. Principal Cardiac Lesion in Heart Disease Group, Time to Event, and Nature of Long-Term Events.**

| Maternal Cardiac Lesion | Total No. | Frequency of Primary Composite Outcome | Unadjusted Rate (95% CI) of Primary Composite Outcome per 1000 person-years | Time to Primary Composite Outcome Yrs Median (IQR) | Frequency of Components of Primary Composite Outcome * | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Death | HF | AF | Arr | Stroke | MI |
| Congenital | 399 | 85 | 16.9 (13.7-20.8) | 6.6 (2.7-13.5) | 10 | 34 | 54 | 42 | 1-5 † | 1-5 † |
| Cardiomyopathy | 112 | 53 | 54.7 (42.1-71.1) | 4.1 (1.8-8.8) | 10 | 26 | 38 | 27 | 1-5 † | 1-5 † |
| Left sided valve | 312 | 88 | 21.4 (17.4-26.4) | 6.5 (3.5-12.0) | 14 | 43 | 66 | 43 | 12 | 1-5 † |
| Isolated arrhythmia | 118 | 53 | 58.3 (45.0-75.7) | 1.8 (0.9-4.9) | 1-5 † | 1-5 † | 41 | 23 | 0 | 0 |
| Ischemic | 26 | 8 | 29.4 (14.9-58.3) | 3.6 (2.4-4.9) | 1-5 † | 1-5 † | 1-5 † | 1-5 † | 0 | 0 |
| Other | 47 | 11 | 24.2 (13.5-43.3) | 3.0 (1.5-6.3) | 1-5 † | 7 | 1-5 † | 1-5 † | 0 | 0 |

*not mutually exclusive; † low counts suppressed as per ICES privacy policy; HF, heart failure; AF, atrial fibrillation, Arr, arrhythmia; MI, myocardial infarction

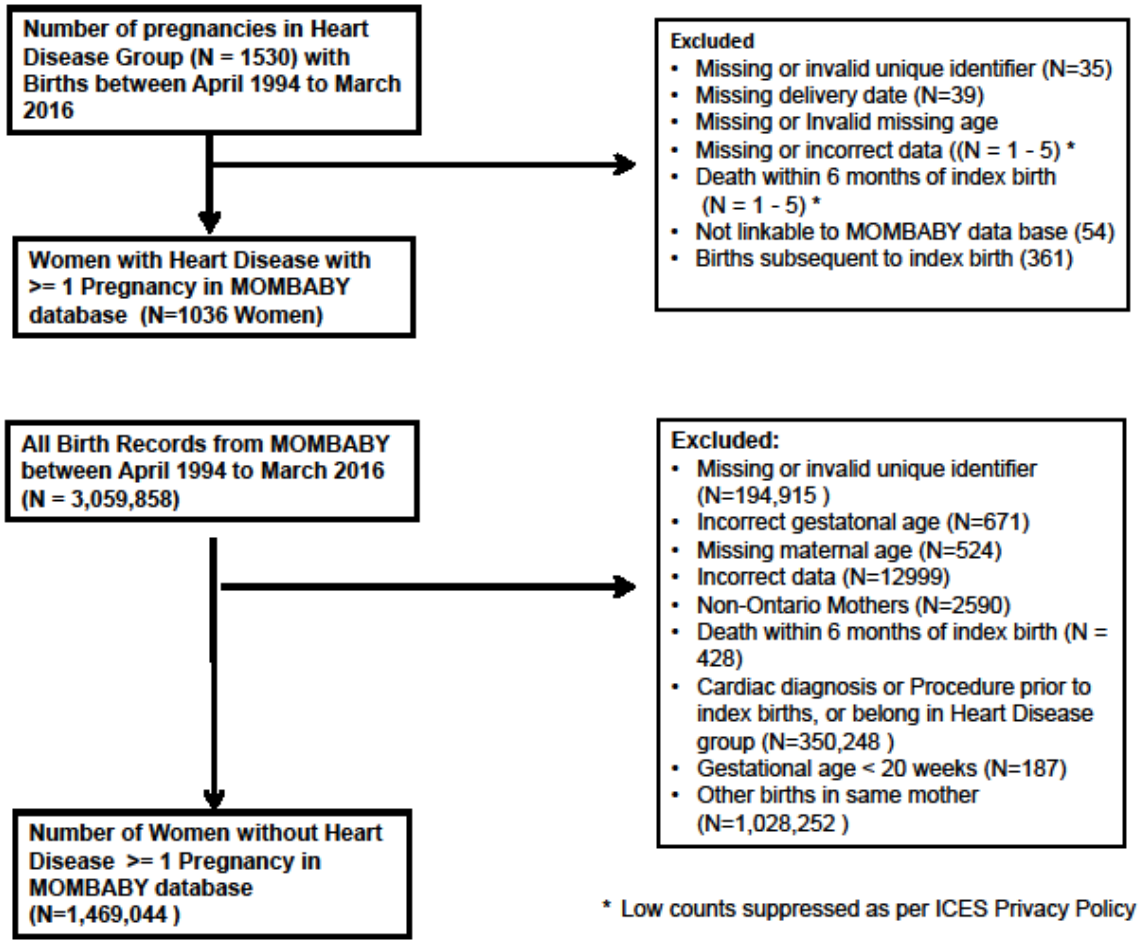
**Table S7. Adjusted Model for Primary Outcome Using Pregnancy Risk Classification Systems.**

| | **CARPREG** * | | **CARPREG II** * | | **WHO** † | |
|---|---|---|---|---|---|---|
| **Parameter** | **Hazard Ratio (95% CI)** | **P value** | **Hazard Ratio (95% CI)** | **P value** | **Hazard Ratio (95% CI)** | **P value** |
| Heart Disease Group: Low Pregnancy Risk (Community comparison group = referent) | 11.4 (7.7 - 17.3) ‡ See Figure 3B for instantaneous hazard ratios over time | **<0.001** | 15.0 (10.4 - 22.4) ‡ See Figure S4B for instantaneous hazard ratios over time | **<0.001** | 16.4 (10.9 - 25.6) ‡ See Figure 3D for instantaneous hazard ratios over time | **<0.001** |
| Heart Disease Group: Intermediate to High Pregnancy Risk (Community comparison group = referent) | 34.2 (23.7 - 51.0) ‡ See Figure 3B for instantaneous hazard ratios over time | **<0.001** | 34.7 (23.6 - 52.3) ‡ See Figure S4B for instantaneous hazard ratios over time | **<0.001** | 37.7 (24.9 - 59.4) ‡ See Figure 3D for instantaneous hazard ratios over time | **<0.001** |
| Obstetric complication during index pregnancy | 1.3 (1.0-1.6) | 0.069 | 1.2 (1.0-1.5) | 0.12 | 1.1 (0.9-1.5) | 0.32 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cardiac complication during index pregnancy | 2.4 (1.7-3.4) | **<0.001** | 2.5 (1.7-3.5) | **<0.0001** | 2.8 (2.0-4.0) | **<0.001** |
| Baby born with congenital cardiac lesion | 1.6 (1.1-2.2) | **0.017** | 1.4 (0.9-1.9) | 0.12 | 1.4 (1.0-2.0) | 0.058 |
| Number of subsequent pregnancies | 1.1 (0.9-1.3) | 0.51 | 1.1 (0.9-1.3) | 0.54 | 1.1 (0.9-1.4) | 0.43 |
| Status of subsequent pregnancy | 2.0 (1.3-3.0) | **0.0031** | 2.0 (1.3-3.0) | **0.0021** | 1.9 (1.2-2.9) | **0.011** |
| Charlson index score $\geq$ 1 | 1.7 (1.1-2.5) | **0.017** | 1.5 (1.0-2.3) | **0.047** | 1.4 (0.8-2.2) | 0.20 |
| Age at index birth | 1.04 (1.02-1.06) | **0.0021** | 1.04 (1.01-1.06) | **0.0033** | 1.04 (1.01-1.06) | **0.0086** |
| Low residential income area | 1.0 (0.8-1.3) | 0.92 | 1.04 (0.8-1.3) | 0.75 | 1.0 (0.8-1.3) | 0.72 |
| Greater Toronto Metropolitan Area residence | 1.1 (0.9-1.4) | 0.52 | 1.0 (0.8-1.3) | 0.75 | 1.1 (0.8-1.4) | 0.53 |
| Index birth is first pregnancy | 0.9 (0.7-1.1) | 0.39 | 0.9 (0.7-1.1) | 0.36 | 0.8 (0.6-1.1) | 0.20 |
| Fiscal year of index birth | 0.98 (0.96-0.99) | **0.041** | 0.98 (0.96-1.00) | 0.067 | 0.99 (0.96-1.01) | 0.25 |

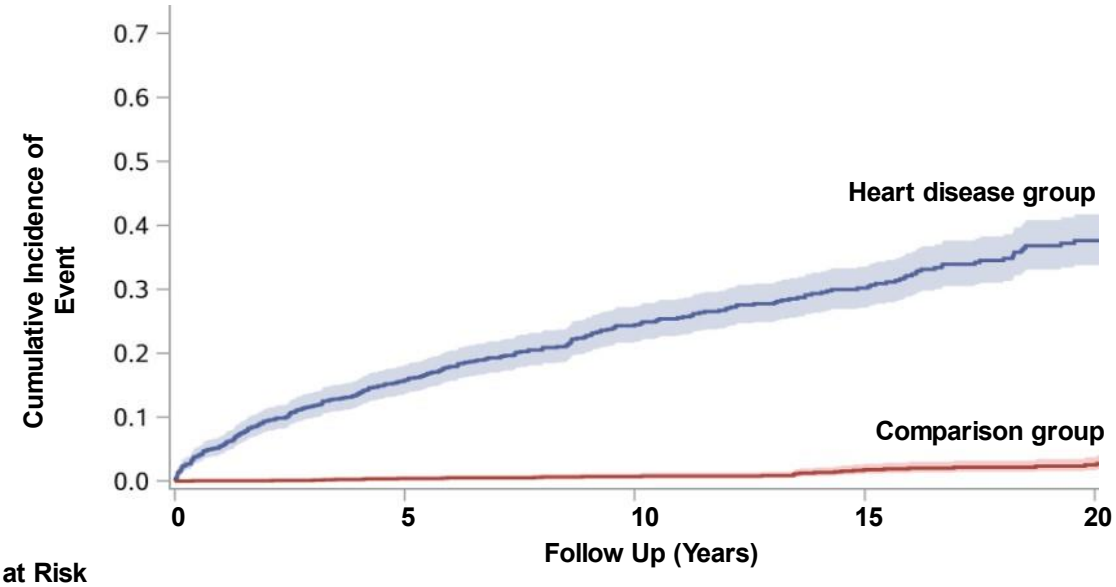
***** Canadian Cardiac Disease in Pregnancy Study; † modified World Health Organization classification; WHO; ‡ hazard ratio from analyses assuming constant proportional hazard between heart disease and comparison groups

**Figure S1. Flow Chart Showing Cohort Formation.**




Flow Chart showing formation of heart disease and community comparison groups.

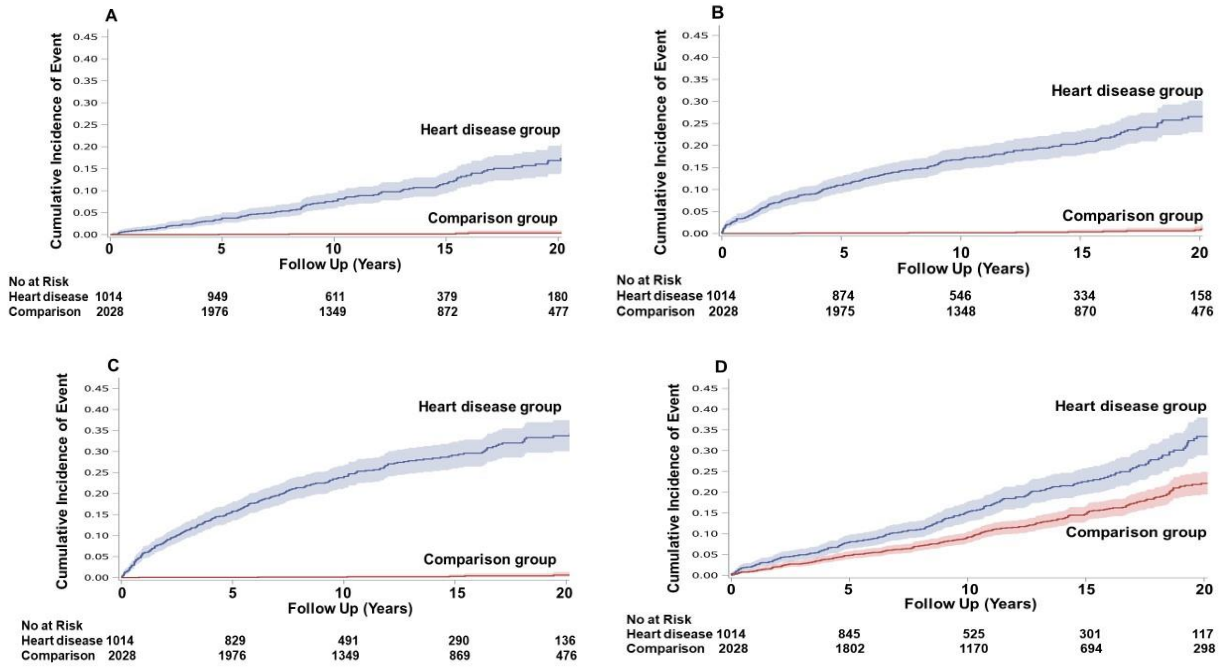
**Figure S2. Unadjusted Time-to-Event Curves for Primary Outcome.**




| Number at Risk | | | | |
|---|---|---|---|---|
| Heart disease group 1014 | 833 | 506 | 301 | 139 |
| Comparison group 2028 | 1971 | 1344 | 864 | 471 |

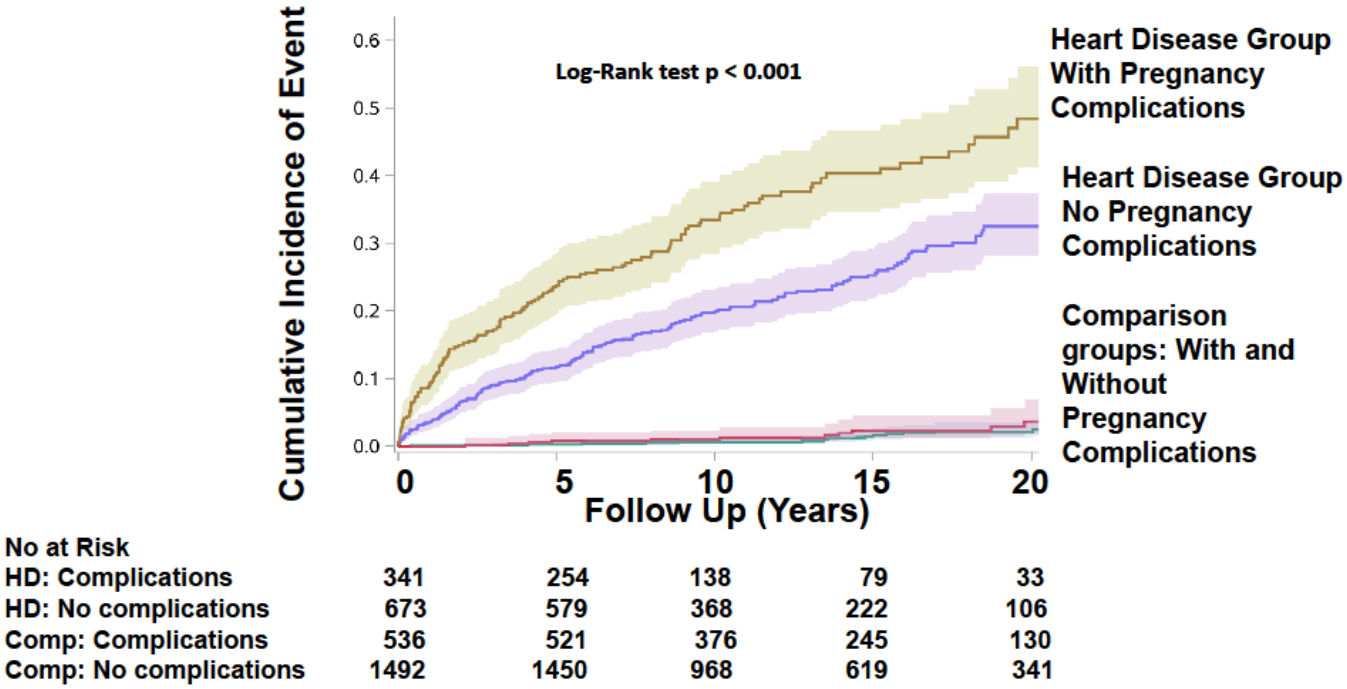
Unadjusted cumulative incidence (with 95% confidence intervals) of primary outcome in heart disease and matched community comparison group (comparison group).

**Figure S3. Unadjusted Time-to-Event Curves for Selected Secondary Outcomes.**



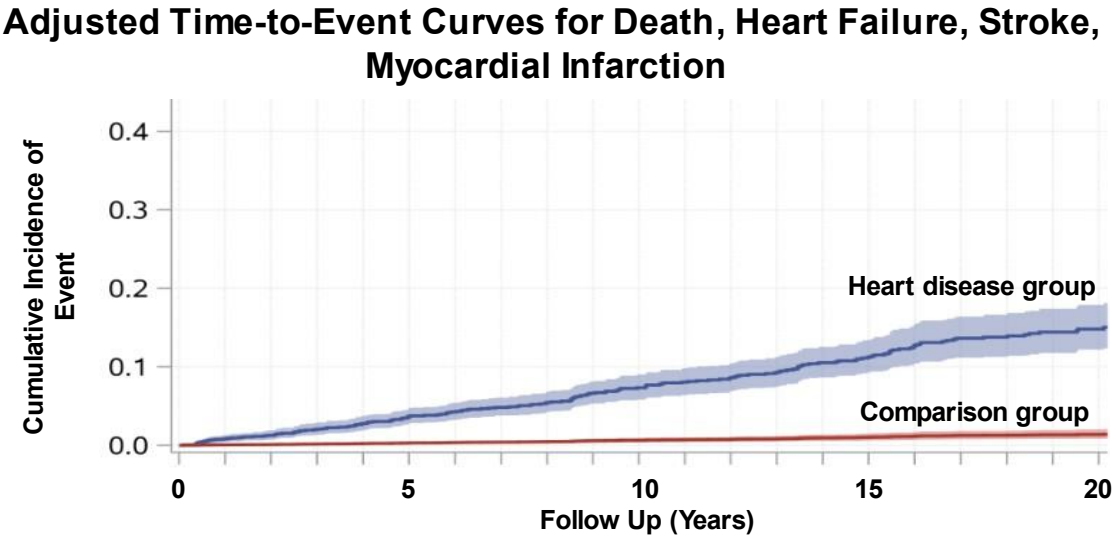

Unadjusted cumulative incidence (with 95% confidence intervals) of heart failure (A), atrial fibrillation (B), therapeutic cardiac procedures (C), and new hypertension or diabetes mellitus (D), in heart disease and matched community comparison group (comparison group).

**Figure S4. Unadjusted Time-to-Event Curves for Primary Outcome Stratified by Occurrence of Pregnancy complications.**




Unadjusted comparison of outcome in heart disease and comparison groups as stratified by whether a pregnancy complication (cardiac or obstetric) occurred during the index pregnancy. The unadjusted rate of composite primary outcome (rate per 1000 person-years, 95%) was 37.2 (31.4-44.1), 20.5 (17.6-23.8), 1.5 (0.9-2.6), and 0.9 (0.6-1.5), corresponding to heart disease group with pregnancy complications (in brown), heart disease group without pregnancy complications (in purple), comparison group with pregnancy complications (in red), and comparison group without pregnancy complications (in green).

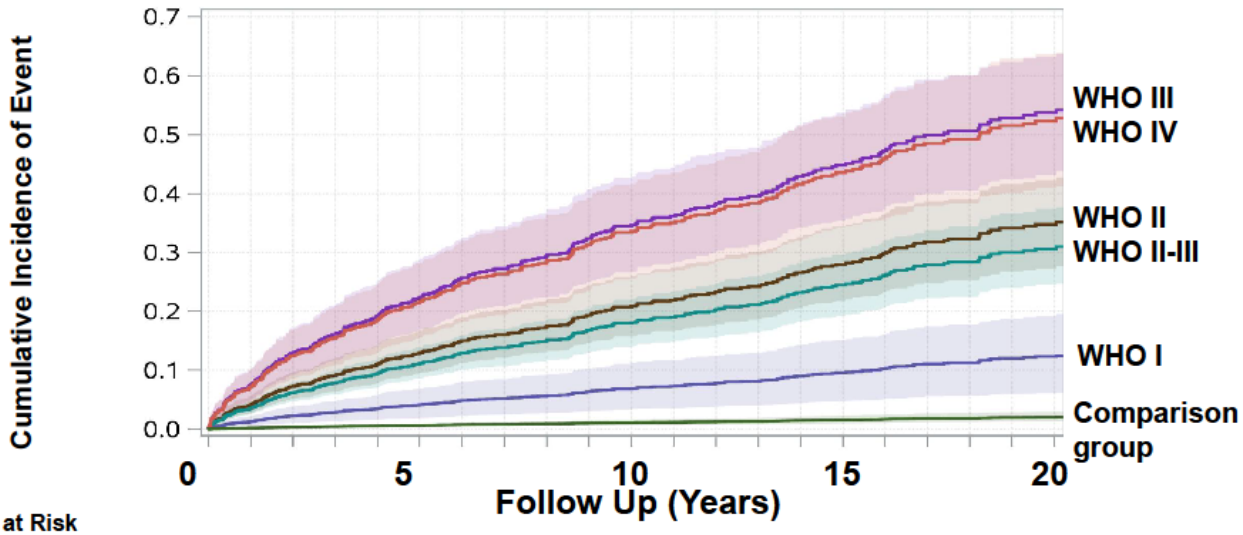
**Figure S5. Adjusted Time-to-Event Curve for Death, Heart Failure, Stroke, or myocardial infarction.**




| Number at Risk | | | | |
|---|---|---|---|---|
| Heart disease group 1014 | 942 | 600 | 369 | 174 |
| Comparison group 2028 | 1973 | 1346 | 866 | 473 |

Adjusted cumulative incidence of the primary outcome (all-cause mortality, heart failure, myocardial infarction, or stroke) with 95% confidence intervals in the heart disease group and matched comparison group. Numbers at risk were obtained from unadjusted cumulative incidence curves.

**Figure S6. Adjusted Time-to-Event Curve for Primary Outcomes separated by individual WHO Risk Groups.**




| No at Risk | | | | | |
|---|---|---|---|---|---|
| WHO IV | 89 | 66 | 38 | 23 | 12 |
| WHO III | 160 | 108 | 55 | 29 | 16 |
| WHO II-III | 264 | 228 | 147 | 90 | 41 |
| WHO II | 216 | 176 | 103 | 60 | 27 |
| WHO I | 106 | 99 | 70 | 48 | 27 |
| Comparison group | 2028 | 1971 | 1344 | 864 | 471 |

Adjusted cumulative incidence of primary outcome and 95% confidence intervals as a function of maternal cardiovascular risk during index pregnancy. Incidence rates are separated into pregnancy risk groups according to the modified World Health Organization classification system (WHO). Numbers at risk were obtained from unadjusted cumulative incidence curves. Comparison group denotes matched community comparison group.