Circulation

ORIGINAL RESEARCH ARTICLE

Long-Term Risk of Cardiovascular Disease in Women Who Have Had Infants With Heart Defects

Nathalie Auger, MD, MSc
Brian J. Potter, MDCM, SM
Marianne Bilodeau-Bertrand, MSc
Gilles Paradis, MD, MSc

BACKGROUND: The possibility that congenital heart defects signal a familial predisposition to cardiovascular disease has not been investigated. We aimed to determine whether the risk of cardiovascular disorders later in life was higher for women who have had newborns with congenital heart defects.

METHODS: We studied a cohort of 1 084 251 women who had delivered infants between 1989 and 2013 in Quebec, Canada. We identified women whose infants had critical, noncritical, or no heart defects, and tracked the women over time for future hospitalizations for cardiovascular disease, with follow-up extending up to 25 years past pregnancy. We calculated the incidence of cardiovascular hospitalization per 1000 person-years, and used Cox proportional hazards regression to estimate hazard ratios and 95% confidence intervals (CIs) for the association between infant heart defects and risk of maternal cardiovascular hospitalization. Models were adjusted for age, parity, preeclampsia, comorbidity, material deprivation, and time period.

RESULTS: Women whose infants had heart defects had a higher overall incidence of cardiovascular hospitalization. There were 3.38 cardiovascular hospitalizations per 1000 person-years for those with critical defects (95% CI, 2.67–4.27), 3.19 for noncritical defects (95% CI, 2.96–3.45), and 2.42 for no heart defects (95% CI, 2.39–2.44). In comparison with no heart defects, women whose infants had critical defects had a hazard ratio of 1.43 (95% CI, 1.13–1.82) for any cardiovascular hospitalization, and women whose infants had noncritical defects had a hazard ratio of 1.24 (95% CI, 1.15–1.34), in adjusted models. Risks of specific causes of cardiovascular hospitalization, including myocardial infarction, heart failure, and other atherosclerotic disorders, were also greater for mothers of infants with congenital heart defects than with no defects.

CONCLUSIONS: Women whose infants have congenital heart defects have a greater risk of cardiovascular hospitalization later in life. Congenital heart defects in offspring may be an early marker of predisposition to cardiovascular disease.

Key Words: cardiovascular diseases ■ cardiovascular surgical procedures ■ cohort studies ■ heart defects, congenital ■ pregnancy outcome ■ risk factors

Sources of Funding, see page xxx

http://circ.ahajournals.org

Clinical Perspective

What Is New?

- This longitudinal cohort analysis of >1 million women is the first to show that congenital heart defects in offspring are associated with increased risk of maternal cardiovascular morbidity later in life, including atherosclerotic disease, cardiac hospitalization, and cardiac transplantation.
- The association with subsequent cardiovascular morbidity risk is present for both critical and noncritical congenital heart defects.

What Are the Clinical Implications?

- Women who have given birth to offspring with congenital heart defects may benefit from earlier attention to traditional cardiovascular risk factors and more aggressive primary prevention strategies.

Cardiovascular disease is a leading cause of death in women,[1] killing >2 million worldwide in 2013 alone.[2] However, early life risk factors for cardiovascular disease are not well understood. Some studies report associations with prior pregnancy disorders,[3,4] and recently, longitudinal data suggest that women whose offspring have congenital anomalies may have a 26% greater risk of cardiovascular mortality later in life.[5] Factors such as stress from caregiving are thought to contribute to the association,[5] but the impact of specific congenital anomalies on cardiovascular disease risk has yet to be studied.

Heart defects are a particularly promising subset of congenital anomalies for their potential to explain the relationship between infant anomalies and subsequent maternal cardiovascular disease. Congenital heart defects are the most common type of birth defect with a worldwide prevalence of ≈7.7 per 1000 live births.[6] Moreover, adult cardiovascular disease and congenital heart defects share common risk factors. Diabetes mellitus, obesity, and preeclampsia, for example, are strongly related to both congenital heart defects in offspring and maternal cardiovascular disease.[4,7–9] Congenital heart defects may also reflect a familial genetic predisposition to cardiovascular pathology.[10,11] Caring for infants with critical heart defects is associated with psychosocial and financial stress,[12,13] which may increase the risk of maternal cardiovascular disease in the long term.[14] Despite supportive evidence for a link between congenital heart defects in infants and maternal cardiovascular risk, the association between the 2 has yet to be studied. We therefore assessed the long-term risk of cardiovascular disease in women whose newborns had heart defects.

METHODS

Data

This study included all women who delivered at least 1 live birth in hospitals in the province of Quebec, Canada between 1989 and 2013. In Quebec, 99% of deliveries occur in hospital.[15] Using encrypted health insurance numbers, we followed the cohort longitudinally over time beginning at the first delivery to identify any cardiovascular hospitalizations thereafter. There were 3 possible reasons for ending follow-up: (1) hospitalization for a cardiovascular disorder or procedure; (2) death; or (3) end of study on March 31, 2014. We extracted the data from discharge abstracts in the Maintenance and Use of Data for the Study of Hospital Clientele registry, which contains summary abstracts for all hospitalizations in Quebec.[16]

For each admission, we had information on up to 26 diagnostic and 20 procedural codes, and data on admission to a coronary care unit or death during hospitalization, as well. We excluded women without health insurance numbers because they could not be followed longitudinally, and 22 734 women with preexisting cardiovascular disease or congenital heart defects. Similarly, we excluded women who only had stillbirths. Data on heart defects in fetuses who were stillborn are not collected in Quebec.

Heart Defects

We identified all neonates who had heart defects documented on their discharge summary using diagnostic codes of the *International Classification of Diseases, Ninth and Tenth Revisions*, and procedure codes of the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures and the Canadian Classification of Health Interventions (Table I in the online-only Data Supplement). We categorized heart defects according to severity, including critical and noncritical. We defined critical heart defects as those requiring attention shortly after delivery to prevent sequelae in infants, in contrast to noncritical defects where treatment may be delayed or not required.[17] We included 7 critical anomalies (tetralogy of Fallot; transposition of the great vessels; truncus arteriosus; hypoplastic left heart syndrome; common ventricle; coarctation of the aorta; other critical defects including total anomalous pulmonary venous return, Ebstein anomaly, tricuspid and pulmonary atresia), and 8 noncritical anomalies (endocardial cushion defect; ventricular septum defect; atrial septum defect; valve anomaly; other anomalies of the aorta; pulmonary artery anomalies; heterotaxy; other remaining noncritical defects).[4]

Women who delivered ≥1 neonate with a heart defect were ascertained by linking the maternal discharge abstract to the neonatal abstract. The exposure was categorized as follows: (1) women who delivered at least 1 neonate with a critical heart defect; (2) women who delivered at least 1 neonate with a noncritical defect, but none with a critical defect; and (3) women whose neonates were all free of any heart defect. For analyses of specific defects in women whose infants had both critical and noncritical defects, only critical defects were considered (critical defects were given priority). Women whose infants had multiple exclusively critical or noncritical defects were included in a separate category. We analyzed exposure as a time-fixed covariate on the assumption that

the presence of a heart defect at a later pregnancy reflects a maternal predisposition to cardiovascular disease that would have been present from the time of the first live birth.

Cardiovascular Hospitalization After Pregnancy

We used diagnostic and procedure codes to identify all women who were hospitalized with a diagnosis of a cardiovascular disorder, or who underwent a cardiovascular procedure during follow-up (Table II in the online-only Data Supplement). We analyzed the first event of cardiovascular disease. We analyzed a range of maternal cardiovascular disorders, focusing on the heart (heart failure, ischemic heart disease, myocardial infarction, angina, cardiac arrest, inflammatory heart disorder, conduction disorder, valve disorder, cardiomyopathy), lungs (pulmonary embolism, pulmonary vascular disease), cerebrovascular system (ischemic stroke, hemorrhage), and other specific diseases including hypertension, other atherosclerotic disease, aortic aneurysm or dissection, aneurysm of other vessels, deep vein thrombosis, and arterial embolism. We also considered several cardiovascular interventions, including coronary angioplasty, coronary artery bypass grafting, pacemaker insertion, valve surgery, cardiac transplant, and admission to a coronary care unit. Women with >1 cardiovascular diagnosis were included in each outcome category.

Covariates

We considered several covariates as potential confounders, including maternal age at first delivery (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years), total parity (1, 2, ≥3 deliveries), preeclampsia (yes, no), comorbidity during pregnancy or subsequent admissions (obesity, diabetes mellitus, dyslipidemia, depression), material deprivation defined as the most socioeconomically deprived quintile of neighborhoods (yes, no), and the time period at first delivery (1989–1996, 1997–2004, 2005–2012). We analyzed comorbidity as a time-fixed covariate using a global metric (any versus no comorbidity). Socioeconomic deprivation was estimated from census data on employment rate, proportion of population with no high school diploma, and mean neighborhood income.[4,18] Data on material deprivation were missing for 6.2% of women, which we imputed based on maternal age, parity, preeclampsia, comorbidity, and period at first delivery.

Data Analysis

We estimated the incidence of cardiovascular hospitalization per 1000 person-years. We calculated the cumulative incidence after 25 years of follow-up for women who had critical, noncritical, or no heart defects in their offspring. To account for death as a competing outcome, we estimated the cumulative incidence using the cumulative incidence function.[19] The cumulative incidence function does not censor deaths, but rather handles them as a competing event.[19] We computed 95% confidence intervals (CIs) using the counting process method.[20]

Using accelerated failure time models with a Weibull distribution, we estimated the median number of years required to reach a cumulative incidence of 5 cardiovascular hospitalizations per 10 000 women. The Weibull distribution assumes proportional hazards and coincides with the Cox model.[21] We computed the median time using each patient's estimated survival time from the model.[21] We adjusted these models for maternal age at first delivery, parity, preeclampsia, comorbidity, material deprivation, and time period.

Using Cox proportional hazards regression, we calculated hazard ratios and 95% CIs for the association between congenital heart defects in offspring and subsequent risk of maternal cardiovascular hospitalization. We adjusted these models for the same set of covariates, and assessed the proportional hazards assumption using log (–log survival) plots. We used the number of days since the first delivery as the time scale and censored women if they were never hospitalized for cardiovascular issues by the end of the study. We used the Fine and Gray method to handle deaths, a competing risk.[20] Analyses were performed for each cardiovascular indication separately, and for all cardiovascular hospitalizations combined, as well.

We tested models with the exposure as a time-varying covariate, in the event that mechanisms linking infant heart defects with maternal cardiovascular disease began only at the first affected pregnancy. In time-varying models, women contribute follow-up to the unexposed category until the first pregnancy affected by heart defects.[22] Because the large sample size prevented convergence of time-varying models, we performed a subsample analysis comprising all women whose infants had heart defects and a 1:3 random sample of women without defects. The subsample comprised 65 600 women, including 16 400 whose infants had heart defects. Because long interpregnancy intervals are rare in Quebec, the time contributed to the exposed category in the time-varying analysis is very similar to the time in the time-fixed analysis.

In sensitivity analyses, we included 1505 women who only had stillbirths, assuming different scenarios: (1) all stillbirths had critical defects; (2) all stillbirths had noncritical defects; (3) 5% of stillbirths had critical defects, 20% had noncritical defects, and 75% had no heart defects; and (4) no stillbirths had heart defects. We also restricted the analysis to women without preeclampsia.

We performed the analyses with SAS version 9.4 (SAS Institute Inc). The study abided by ethical requirements for research involving humans in Canada, and we obtained an ethics waiver from the institutional review board of the University of Montreal Hospital Center. Informed consent was not required.

RESULTS

There were 1 084 251 women in this study, including 1516 with critical and 14 884 with noncritical heart defects in the offspring (Table 1). The incidence of cardiovascular hospitalization was higher for women whose infants had heart defects (Table 2). There were 3.38 cardiovascular hospitalizations per 1000 person-years for critical defects (95% CI, 2.67–4.27), 3.19 for noncritical defects (95% CI, 2.96–3.45), and 2.42 for no heart defects (95% CI, 2.39–2.44).

In comparison with no heart defects, women whose offspring had critical or noncritical heart defects tended to be hospitalized earlier for most cardiovascular diseases

Table 1. Maternal Characteristics According to Presence of Heart Defects in Offspring, N=1 084 251, Quebec, 1989 to 2014

	No. of Women (%)		
	Critical Defect	Noncritical Defect	No Defect
Age at first delivery, y			
<20	103 (6.8)	1247 (8.4)	62 369 (5.8)
20–24	401 (26.5)	3647 (24.5)	235 834 (22.1)
25–29	529 (34.9)	5371 (36.1)	398 436 (37.3)
30–34	352 (23.2)	3285 (22.1)	264 436 (24.8)
35–39	102 (6.7)	1097 (7.4)	90 861 (8.5)
≥40	29 (1.9)	237 (1.6)	15 915 (1.5)
Parity			
1	385 (25.4)	4178 (28.1)	485 029 (45.4)
2	592 (39.1)	6434 (43.2)	428 456 (40.1)
≥3	539 (35.6)	4272 (28.7)	154 366 (14.5)
Preeclampsia			
Yes	133 (8.8)	1434 (9.6)	59 431 (5.6)
No	1383 (91.2)	13 450 (90.4)	1 008 420 (94.4)
Comorbidity*			
Yes	120 (7.9)	1319 (8.9)	52 701 (4.9)
No	1396 (92.1)	13 565 (91.1)	1 015 150 (95.1)
Material deprivation			
Yes	336 (22.2)	3337 (22.4)	210 924 (19.8)
No	1180 (77.8)	11 547 (77.6)	856 927 (80.2)
Period of childbirth			
1989–1996	582 (38.4)	5927 (39.8)	479 065 (44.9)
1997–2004	462 (30.5)	5001 (33.6)	274 192 (25.7)
2005–2012	472 (31.1)	3956 (26.6)	314 594 (29.5)
Maternal deaths	7 (0.5)	32 (0.2)	2638 (0.2)
Total	1516	14 884	1 067 851
Person-years	20 443	207 973	15 253 959

*Obesity, diabetes mellitus, dyslipidemia, depression.

(Table 3). For myocardial infarction, women whose infants had critical defects required a median of 7.2 years to attain 5 hospitalizations per 10 000, whereas women whose offspring had no heart defects required 9.8 years. Similarly, women whose infants had critical, noncritical, or no congenital heart defects required a median of 16.8, 15.2, and 22.0 years, respectively, to attain 5 cardiac arrests per 10 000. Although this pattern was observed for most types of cardiovascular hospitalizations, the median time to various cardiovascular hospitalizations was not significantly different between women who had children with critical and noncritical defects.

The cumulative incidence of cardiovascular hospitalization began to diverge shortly after pregnancy for several outcomes (Figure). For women whose offspring had critical heart defects, the incidence of heart failure, myocardial infarction, and coronary angioplasty increased more rapidly after 10 years of follow-up in comparison with women whose infants had no heart defects, whereas the incidence of valve surgery accelerated after 18 years of follow-up. With noncritical defects, the increase in cardiovascular hospitalizations was generally steady over time.

Even after adjustment, having an offspring with a congenital heart defect was associated with a greater risk of cardiovascular hospitalization in comparison with no heart defects (Table 4). In comparison with no heart defects, women whose infants had critical defects had 1.43 times the risk of any cardiovascular hospitalization (95% CI, 1.13–1.82; P=0.003), and women whose infants had noncritical defects had 1.24 times the risk (95% CI, 1.15–1.34; P<0.0001). Specific causes of cardiovascular hospitalization were also greater for mothers of infants with congenital heart defects in comparison with no defects. Women whose infants had critical heart defects, for instance, had 2.61 times the risk of myocardial infarction (95% CI, 1.31–5.20; P=0.007), 3.04 times the risk of other atherosclerotic disease (95% CI, 1.72–5.36; P=0.0001), and 43.2 times the risk of cardiac transplant (95% CI, 6.41–291.7; P=0.0001). Women whose infants had noncritical defects had 2.08 times the risk of heart failure (95% CI, 1.53–2.82; P<0.0001), 2.52 times the risk of pulmonary vascular disease (95% CI, 1.54–4.11; P=0.0002), and 2.13 times the risk of pacemaker insertion (95% CI, 1.29–3.52; P=0.003). Associations were sometimes stronger for critical than for noncritical heart defects, although there was no statistically significant difference between the groups. There was no evidence of interaction with age at first delivery, total parity, preeclampsia, comorbidity, and material deprivation.

Results were similar when we tested models with the exposure as a time-varying covariate, although statistical power was lower because of the smaller sample size (Table 5). In time-varying models, women whose infants had critical heart defects had 1.34 times the risk of any cardiovascular disease (95% CI, 1.03–1.75), and women whose infants had noncritical heart defects had 1.33 times the risk (95% CI, 1.21–1.47).

The risk of maternal cardiovascular hospitalization also varied depending on the specific heart defect in the infant (Table 6). Relative to no heart defect, women whose infants had tetralogy of Fallot had 1.49 times the risk of any cardiovascular hospitalization (95% CI, 0.95–2.34), and women whose infants had hypoplastic left heart had 2.24 times the risk (95% CI, 1.27–3.96). Risks were also elevated for several noncritical defects. Relative to no heart defect, women whose infants had noncritical pulmonary artery defects had 1.66 times the risk of any cardiovascular hospitalization (95% CI, 1.27–2.17), and women whose infants had noncritical heterotaxy defects had 2.42 times the risk (95% CI, 1.15–5.08). Women whose infants had noncritical ven-

Table 2. Unadjusted Incidence of Any Cardiovascular Hospitalization per 1000 Person-Years According to Characteristics of Women, N=1 084 251, Quebec, 1989 to 2014

	Total No. of Women	No. of Women Hospitalized for Cardiovascular Disorder	Person-Years	Unadjusted Incidence of Any Cardiovascular Hospitalization per 1000 Person-Years (95% Confidence Interval)
Heart defect				
Yes				
Critical	1516	69	20 443	3.38 (2.67–4.27)
Noncritical	14 884	664	207 973	3.19 (2.96–3.45)
No	1 067 851	36 878	15 253 959	2.42 (2.39–2.44)
Age at first delivery, y				
<20	63 719	1762	922 609	1.91 (1.82–2.00)
20–24	239 882	7017	3 501 623	2.00 (1.96–2.05)
25–29	404 336	12 591	5 873 656	2.14 (2.11–2.18)
30–34	268 073	10 519	3 775 758	2.79 (2.73–2.84)
35–39	92 060	4710	1 217 576	3.87 (3.76–3.98)
≥40	16 181	1012	191 154	5.29 (4.98–5.63)
Total parity				
1	489 592	19 187	6 507 445	2.95 (2.91–2.99)
2	435 482	13 162	6 364 106	2.07 (2.03–2.10)
≥3	159 177	5262	2 610 824	2.02 (1.96–2.07)
Preeclampsia				
Yes	60 998	4461	759 064	5.88 (5.71–6.05)
No	1 023 253	33 150	14 723 311	2.25 (2.23–2.28)
Comorbidity*				
Yes	54 140	9612	805 036	11.94 (11.70–12.18)
No	1 030 111	27 999	14 677 339	1.91 (1.89–1.93)
Material deprivation				
Yes	214 597	8458	3 002 566	2.82 (2.76–2.88)
No	869 654	29 153	12 479 809	2.34 (2.31–2.36)
Total	1 084 251	37 611	15 482 375	2.43 (2.40–2.45)

*Obesity, diabetes mellitus, dyslipidemia, depression.

tricular septum defects had 1.17 times the risk (95% CI, 1.00–1.37) and those with atrial septum defects had 1.21 times the risk (95% CI, 1.04–1.42) of any cardiovascular hospitalization. Women whose infants had multiple noncritical defects had 1.26 times the risk (95% CI, 1.04–1.54) of any cardiovascular hospitalization. The risk was also higher for women whose infants had multiple critical defects, but the association was not statistically significant (hazard ratio, 1.17; 95% CI, 0.37–3.74). There was no evidence of statistically significant differences between specific defects.

We found little or no change in the findings when women who only had stillbirths were included in analyses. Excluding women with preeclampsia led to random variation in the results, and wider CIs for critical heart defects because of the smaller number of exposed women (Table III in the online-only Data Supplement). Nonpreeclamptic women whose infants had critical heart defects, for instance, had 1.29 times the risk of any cardiovascular disorder or intervention (95% CI, 0.98–1.69), 2.64 times the risk of myocardial infarction (95% CI, 1.26–5.50), and 43.23 times the risk of cardiac transplant (95% CI, 6.41–291.73). Associations were more stable for noncritical defects. Nonpreeclamptic women whose infants had noncritical defects had 1.24 times the risk of any cardiovascular disorder or intervention (95% CI, 1.14–1.35), 2.04 times the risk of heart failure (95% CI, 1.44–2.89), and 2.31 times the risk of pacemaker insertion (95% CI, 1.38–3.88).

DISCUSSION

In this longitudinal cohort of >1 million parous women, having a newborn with a congenital heart defect was

Table 3. Adjusted Median Time to Hospitalization for 1 084 251 Women According to Presence of Heart Defects in Offspring, Quebec, 1989 to 2014

	Median No. of Years to Reach 5 Cardiovascular Hospitalizations per 10 000 Women (Interquartile Range)*		
	Critical	Noncritical	No Defect
Any cardiovascular disorder or intervention	1.1 (0.9–1.2)	1.2 (0.9–1.3)	1.3 (1.1–1.4)
Cardiovascular disorders			
Any disorder	1.1 (0.9–1.3)	1.2 (0.9–1.4)	1.3 (1.1–1.5)
Heart			
Heart failure	7.6 (5.6–9.3)	7.8 (5.7–9.6)	11.4 (9.0–13.9)
Ischemic heart disease	6.5 (5.1–7.6)	7.4 (5.8–8.7)	7.7 (6.4–9.1)
Myocardial infarction	7.2 (5.8–8.4)	10.0 (8.3–12.0)	9.8 (8.1–11.7)
Angina	19.3 (15.9–23.3)	13.1 (10.8–15.6)	14.2 (12.0–17.0)
Cardiac arrest	16.8 (12.1–21.3)	15.2 (11.4–19.5)	22.0 (17.2–28.6)
Inflammatory heart disorder	14.0 (12.9–16.4)	12.6 (11.1–14.6)	17.0 (15.1–19.8)
Conduction disorder	1.5 (1.3–1.6)	1.8 (1.6–2.0)	2.3 (1.9–2.5)
Valve disorder	4.0 (3.1–5.1)	7.4 (5.6–9.5)	7.8 (6.0–9.9)
Cardiomyopathy	–	8.2 (6.1–10.2)	14.4 (10.9–17.4)
Lungs			
Pulmonary embolism	4.1 (3.6–4.5)	4.6 (4.1–5.1)	4.8 (4.4–5.4)
Pulmonary vascular disease	15.5 (9.5–19.6)	13.3 (8.3–16.8)	18.6 (11.5–23.5)
Cerebrovascular			
Ischemic stroke	6.3 (4.8–7.4)	5.8 (4.4–7.7)	7.4 (5.6–8.6)
Hemorrhage	6.2 (4.7–7.3)	6.8 (5.0–8.3)	8.7 (6.9–11.5)
Hypertension	3.3 (2.6–3.7)	3.5 (2.7–4.0)	3.7 (3.2–4.2)
Other atherosclerosis	7.4 (6.1–8.7)	9.9 (7.9–11.7)	10.2 (8.9–12.3)
Aortic aneurysm or dissection	–	38.2 (27.6–47.5)	44.8 (32.6–54.4)
Aneurysm of other vessels	8.2 (7.2–9.8)	10.0 (8.7–11.7)	12.0 (10.8–13.1)
Deep vein thrombosis	5.2 (4.2–7.1)	5.3 (4.3–7.5)	5.4 (3.9–7.8)
Arterial embolism	17.7 (13.5–20.7)	16.2 (13.0–19.7)	20.2 (17.0–24.5)
Interventions			
Any intervention	3.8 (3.2–4.7)	5.5 (4.6–6.7)	6.1 (5.1–7.2)
Coronary angioplasty	10.1 (8.1–11.5)	12.8 (10.4–14.7)	12.8 (10.9–14.7)
Coronary artery bypass graft	24.2 (17.1–31.3)	25.0 (18.7–35.1)	33.3 (23.8–43.6)
Pacemaker insertion	–	11.2 (9.2–13.4)	16.1 (14.4–19.5)
Valve surgery	8.5 (6.5–10.0)	37.9 (27.5–44.3)	23.4 (18.9–27.7)
Cardiac transplant	18.9 (10.4–45.8)	67.7 (40.9–177.8)	284.2 (197.7–492.5)
Coronary care unit	5.4 (4.2–6.6)	7.4 (5.6–9.0)	7.2 (5.9–9.0)

Outcomes are not mutually exclusive; women may have >1 cardiovascular disorder or intervention.

*Median number of years to reach a cumulative incidence of 5 cardiovascular hospitalizations per 10 000 women, adjusted for age at start of follow-up, total parity, preeclampsia, comorbidity, material deprivation, and time period. Median time is long for very rare outcomes, because more time is required to cumulate the required number of events.

associated with an increased risk of cardiovascular disease later in life. Women whose offspring had critical or noncritical heart defects were hospitalized for cardiovascular disease sooner, and the risks were greater for most types of cardiovascular disorders, including ischemic heart disease, other atherosclerotic disease, and cardiac transplant. Associations were stronger for critical defects such as hypoplastic left heart syndrome, but the majority of noncritical heart defects were also associated with an elevated risk of cardiovascular hospitalization. Thus, having an infant with a congenital heart defect may represent a novel risk factor for developing cardiovascular disease. Women who have a newborn with a heart defect may therefore benefit from early

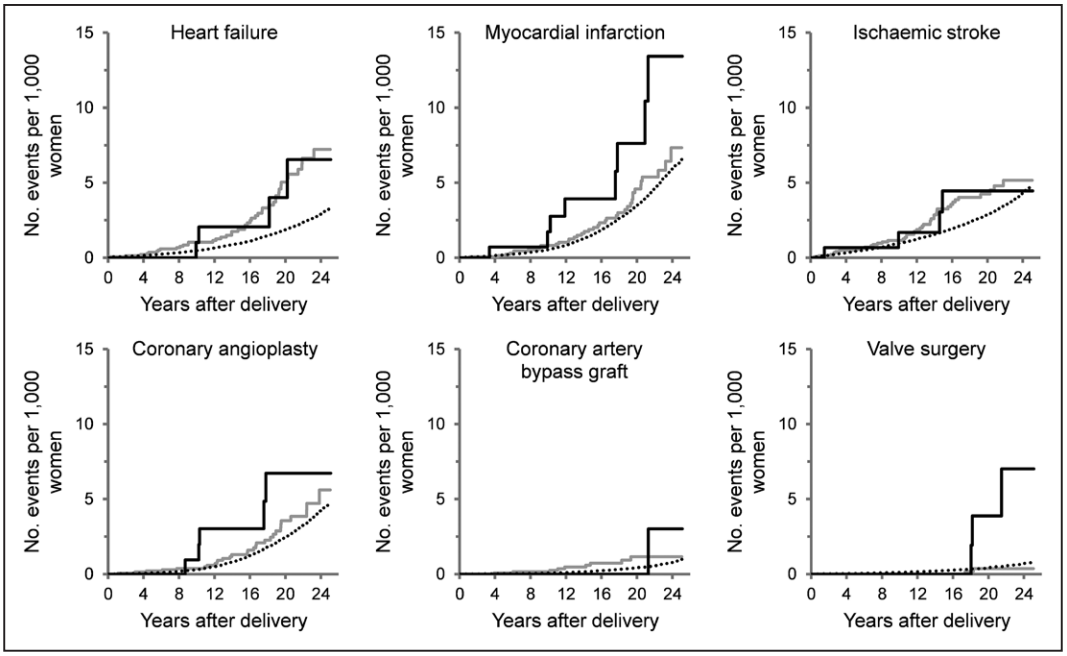

Figure. Unadjusted cumulative incidence of cardiovascular hospitalization for 1 084 251 women according to the presence of heart defects in offspring, Quebec, 1989 to 2014.
Black line indicates critical heart defects; gray line, noncritical heart defects; and dotted line, no heart defect. Gray *P* value: Heart failure <0.0001; myocardial infarction 0.01; ischemic stroke 0.04; coronary angioplasty 0.06; coronary artery bypass graft 0.04; valve surgery 0.0002. Results are shown for 6 representative outcomes reflecting the tendency for higher cumulative incidence in women whose infants have heart defects. Table IV in the online-only Data Supplement shows the number of women remaining at risk at each time point.

primary prevention and counseling to reduce their risk of cardiovascular disease.

Few studies have investigated the possibility that heart defects in offspring signal a greater propensity for heart disease in mothers. In a cohort study of 455 250 women who delivered infants between 1979 and 2010 in Denmark, the presence of any congenital anomaly in a newborn was associated with a greater risk of maternal mortality, including cardiovascular death up to 28 years later.[5] In this same study, women whose infants had any congenital anomaly had 2 times the risk of death from myocardial infarction, but there was no association with stroke mortality.[5] Although these results reflect congenital anomalies as a whole, heart defects are frequent and have the potential to account for much of the association with cardiovascular mortality.[6] Our own results suggest that the presence of a heart defect in an infant is associated with the subsequent risk of hospitalization for a range of cardiovascular disorders, including myocardial infarction and ischemic stroke, although not all associations were statistically significant. Because the cohort was relatively young, it is possible that the association with late-onset cardiovascular diseases will strengthen with longer follow-up. It is also interesting to contrast these findings with a small body of evidence suggesting no increased risk of cancer in women whose newborns had congenital anomalies.[23,24]

How congenital heart defects in infants relate to later maternal cardiovascular disease is unclear. Because we found no evidence to support a clinically meaningful difference in the results for the time-fixed versus time-varying analysis, it is possible that the relationship between congenital heart defects and maternal cardiovascular risk reflects both stress-related pathways and a maternal predisposition to cardiovascular disease present from the start of the study. Imbalance in angiogenic biomarkers such as placental growth factor and altered cytokine production, as well, have been linked with both congenital heart defects and adult cardiovascular disease.[25–28] Congenital heart defects and adult cardiovascular disease share common risk factors. For instance, preeclampsia is associated with both heart defects and cardiovascular disorders later in life.[4,9] Diabetes mellitus, and more weakly obesity, are also associated with congenital heart defects and cardiovascular disease.[7,8] Although we adjusted for several of these characteristics, it is possible that other behavioral or lifestyle factors, such as nutrition or smoking, mediate some of the associations independent of overt comorbidities. A genetic component cannot be excluded.

Furthermore, mothers of infants with heart defects have a high risk of stress, anxiety, and depression.[12] This is especially the case for severe heart defects that often involve repeated and costly hospitalizations.[13] With 85% of infants with heart defects now surviving past

Table 4. Hazard Ratio of Cardiovascular Hospitalization for 1 084 251 Women Whose Infants Had Critical or Noncritical Heart Defects Versus No Defects, Quebec, 1989 to 2014

	No. of Women			Unadjusted Hazard Ratio (95% Confidence Interval)		Adjusted Hazard Ratio (95% Confidence Interval)*	
	Critical	Noncritical	No Defect	Critical	Noncritical	Critical	Noncritical
Any cardiovascular disorder or intervention	69	664	36 878	1.47 (1.16–1.86)	1.39 (1.29–1.50)	1.43 (1.13–1.82)	1.24 (1.15–1.34)
Cardiovascular disorders							
Any disorder	68	654	36 201	1.47 (1.16–1.87)	1.40 (1.29–1.51)	1.44 (1.13–1.84)	1.24 (1.15–1.34)
Heart							
Heart failure	<5	43	1388	2.26 (0.85–6.02)	2.40 (1.77–3.25)	2.19 (0.82–5.86)	2.08 (1.53–2.82)
Ischemic heart disease	11	89	4775	1.84 (1.02–3.33)	1.48 (1.20–1.82)	1.90 (1.05–3.41)	1.36 (1.10–1.68)
Myocardial infarction	8	39	2557	2.50 (1.25–5.02)	1.21 (0.88–1.66)	2.61 (1.31–5.20)	1.13 (0.82–1.55)
Angina	<5	27	1485	0.54 (0.08–3.82)	1.44 (0.99–2.11)	0.56 (0.08–3.97)	1.33 (0.91–1.95)
Cardiac arrest	<5	12	444	1.74 (0.25–12.4)	2.07 (1.17–3.67)	1.89 (0.27–13.5)	2.01 (1.13–3.57)
Inflammatory heart disorder	<5	12	550	1.37 (0.19–9.74)	1.62 (0.91–2.87)	1.29 (0.18–9.08)	1.45 (0.82–2.57)
Conduction disorder	17	137	7317	1.76 (1.10–2.84)	1.40 (1.18–1.66)	1.74 (1.08–2.81)	1.31 (1.11–1.55)
Valve disorder	5	26	1667	2.28 (0.95–5.47)	1.17 (0.79–1.72)	2.30 (0.96–5.55)	1.10 (0.74–1.62)
Cardiomyopathy	<5	29	778	–	2.89 (2.00–4.19)	–	2.50 (1.72–3.63)
Lungs							
Pulmonary embolism	5	45	2865	1.34 (0.56–3.21)	1.19 (0.88–1.59)	1.31 (0.54–3.15)	1.09 (0.81–1.47)
Pulmonary vascular disease	<5	17	449	1.79 (0.25–12.8)	3.04 (1.87–4.92)	1.67 (0.24–11.9)	2.52 (1.54–4.11)
Cerebrovascular							
Ischemic stroke	<5	42	2200	1.40 (0.52–3.73)	1.45 (1.07–1.97)	1.46 (0.55–3.88)	1.38 (1.01–1.87)
Hemorrhage	<5	27	1374	1.67 (0.54–5.17)	1.48 (1.01–2.17)	1.83 (0.59–5.66)	1.52 (1.04–2.22)
Hypertension	39	410	20 003	1.56 (1.14–2.14)	1.62 (1.47–1.79)	1.48 (1.06–2.06)	1.35 (1.22–1.49)
Other atherosclerosis	12	63	3318	2.93 (1.66–5.17)	1.52 (1.19–1.96)	3.04 (1.72–5.36)	1.37 (1.07–1.77)
Aortic aneurysm or dissection	<5	<5	97	–	1.61 (0.40–6.54)	–	1.30 (0.31–5.43)
Aneurysm of other vessels	<5	16	849	1.82 (0.46–7.29)	1.44 (0.88–2.37)	1.88 (0.47–7.56)	1.39 (0.85–2.29)
Deep vein thrombosis	<5	30	2057	1.10 (0.36–3.42)	1.09 (0.76–1.56)	1.13 (0.36–3.51)	1.05 (0.73–1.50)
Arterial embolism	<5	12	502	1.56 (0.22–11.1)	1.85 (1.04–3.28)	1.62 (0.23–11.5)	1.70 (0.96–3.03)
Cardiovascular interventions							
Any intervention	14	77	4381	2.52 (1.49–4.25)	1.37 (1.09–1.71)	2.50 (1.49–4.20)	1.24 (0.99–1.56)
Coronary angioplasty	5	29	1772	2.28 (0.95–5.48)	1.31 (0.91–1.89)	2.39 (1.00–5.76)	1.23 (0.85–1.78)
Coronary artery bypass graft	<5	9	326	2.46 (0.35–17.5)	2.20 (1.14–4.27)	2.83 (0.40–20.0)	2.16 (1.11–4.23)
Pacemaker insertion	<5	16	559	–	2.19 (1.34–3.60)	–	2.13 (1.29–3.52)
Valve surgery	<5	<5	325	7.22 (2.32–22.5)	0.48 (0.12–1.91)	7.33 (2.37–22.7)	0.45 (0.11–1.80)
Cardiac transplant	<5	<5	23	32.6 (4.37–243.7)	6.39 (1.52–27.0)	43.2 (6.41–291.7)	7.25 (1.72–30.6)
Coronary care unit	6	39	2467	1.90 (0.85–4.21)	1.22 (0.89–1.67)	1.78 (0.80–3.94)	1.06 (0.77–1.46)

*Hazard ratios for heart defects versus no heart defect, adjusted for age at start of follow-up, total parity, preeclampsia, comorbidity, material deprivation, and time period. Outcomes are not mutually exclusive; women may have >1 cardiovascular disorder or intervention.

adolescence,[29] the psychosocial impact of congenital heart disease on caregivers may not be benign and may have a cumulative effect over the long term. We adjusted for depression in this analysis, but other stressors may explain some of the increased risk of cardiovascular disease in mothers.[14]

A number of limitations of the current analysis deserve discussion. First, we could only identify heart defects in infants who were born alive. Congenital defects in pregnancies that resulted in elective termination, miscarriage, or stillbirth were not considered. In addition, only heart defects identified at delivery were identifiable in our database. Defects discovered later in childhood were therefore not included. Similarly, the data set did not allow us to distinguish noncritical persistent defects from more benign findings that could be expected to resolve with maturity.[29] Thus, some women might be misclassified in terms of their exposure status.

Table 5. Hazard Ratio of Cardiovascular Hospitalization for 65 600 Women Whose Infants Had Critical or Noncritical Heart Defects Versus No Defects, Time-Varying Exposure, Quebec, 1989 to 2014

	Adjusted Hazard Ratio (95% Confidence Interval)*	
	Critical	Noncritical
Any cardiovascular disorder or intervention	1.34 (1.03–1.75)	1.33 (1.21–1.47)
Cardiovascular disorders		
Any disorder	1.34 (1.03–1.75)	1.34 (1.22–1.47)
Heart		
Heart failure	2.56 (0.91–7.16)	2.17 (1.43–3.29)
Ischemic heart disease	2.48 (1.34–4.60)	1.64 (1.26–2.13)
Myocardial infarction	3.35 (1.61–6.96)	1.30 (0.88–1.90)
Angina	0.72 (0.10–5.25)	1.37 (0.85–2.21)
Cardiac arrest	2.61 (0.34–20.26)	2.66 (1.24–5.73)
Inflammatory heart disorder	0.99 (0.13–7.38)	1.14 (0.56–2.33)
Conduction disorder	1.46 (0.84–2.56)	1.29 (1.04–1.60)
Valve disorder	2.43 (0.97–6.10)	1.08 (0.67–1.75)
Cardiomyopathy	–	3.11 (1.81–5.34)
Lungs		
Pulmonary embolism	1.09 (0.40–2.96)	1.13 (0.80–1.61)
Pulmonary vascular disease	1.31 (0.17–9.92)	2.17 (1.14–4.12)
Cerebrovascular		
Ischemic stroke	1.17 (0.37–3.74)	1.61 (1.11–2.35)
Hemorrhage	1.29 (0.31–5.34)	1.57 (0.98–2.52)
Hypertension	1.46 (1.03–2.07)	1.48 (1.31–1.67)
Other atherosclerosis	4.01 (2.17–7.39)	1.73 (1.26–2.39)
Aortic aneurysm or dissection	–	1.07 (0.21–5.44)
Aneurysm of other vessels	2.02 (0.48–8.56)	1.40 (0.74–2.66)
Deep vein thrombosis	0.98 (0.24–4.02)	1.39 (0.90–2.14)
Arterial embolism	3.37 (0.43–26.68)	3.59 (1.53–8.42)
Cardiovascular interventions		
Any intervention	2.79 (1.60–4.87)	1.40 (1.06–1.85)
Coronary angioplasty	3.08 (1.21–7.80)	1.37 (0.87–2.17)
Coronary artery bypass graft	3.11 (0.37–25.81)	2.60 (1.06–6.38)
Pacemaker insertion	–	2.19 (1.16–4.13)
Valve surgery	7.43 (2.03–27.12)	0.57 (0.13–2.57)
Cardiac transplant	38.71 (1.88–798.87)	5.83 (0.51–67.00)
Coronary care unit	1.80 (0.78–4.15)	1.11 (0.76–1.62)

*Hazard ratios for heart defects versus no heart defect, adjusted for age at first delivery, total parity, preeclampsia, comorbidity, material deprivation, and period at first delivery.

Table 6. Association Between Specific Heart Defects in Infants and Subsequent Risk of Any Maternal Cardiovascular Hospitalization Among 1 084 251 Women, Quebec, 1989 to 2014

	Any Cardiovascular Disorder or Procedure		
	No. of Women	Cumulative Incidence at 25 y per 1000 Women (95% Confidence Interval)	Hazard ratio (95% Confidence Interval)*
Critical or noncritical	733	107.8 (93.5–123.1)	1.25 (1.17–1.35)
Critical defect			
Any	69	99.9 (74.8–129.2)	1.43 (1.13–1.82)
Tetralogy of Fallot	19	120.3 (67.4–189.6)	1.49 (0.95–2.34)
Transposition of great vessels	9	78.0 (33.6–147.1)	1.26 (0.66–2.40)
Truncus arteriosus	<5	54.5 (17.1–124.7)	1.49 (0.53–4.23)
Hypoplastic left heart	13	114.2 (59.9–187.8)	2.24 (1.27–3.96)
Common ventricle	6	149.4 (59.0–279.0)	1.62 (0.71–3.70)
Coarctation of aorta	13	88.8 (43.8–153.5)	1.32 (0.75–2.32)
Other critical	<5	17.2 (3.3–55.9)	0.54 (0.13–2.22)
Multiple critical	<5	67.9 (12.3–192.7)	1.17 (0.37–3.74)
Noncritical			
Any	664	108.5 (93.1–125.3)	1.24 (1.15–1.34)
Endocardial cushion	13	127.7 (67.5–207.7)	1.47 (0.85–2.54)
Ventricular septum	158	92.9 (74.8–113.4)	1.17 (1.00–1.37)
Atrial septum	160	103.5 (82.9–126.7)	1.21 (1.04–1.42)
Valve	8	135.5 (42.7–281.8)	0.72 (0.37–1.39)
Aorta	<5	97.2 (8.3–321.6)	1.27 (0.32–4.99)
Pulmonary artery	53	120.3 (85.8–161.1)	1.66 (1.27–2.17)
Heterotaxy	7	113.9 (44.7–218.8)	2.42 (1.15–5.08)
Other noncritical	163	113.4 (79.2–154.2)	1.21 (1.04–1.41)
Multiple noncritical	100	111.5 (84.2–143.1)	1.26 (1.04–1.54)
No defect	36 878	80.6 (79.4–81.9)	Reference

*Hazard ratios are for heart defects versus no heart defect, adjusted for maternal age at start of follow-up, parity, preeclampsia, comorbidity, material deprivation, and time period.

However, any misclassification would be expected to attenuate the strength of the measured associations.

In terms of outcomes, we did not have data for women who were hospitalized outside Quebec or died outside hospitals. In addition, the cohort was composed of women who were relatively young at baseline, and, for many women, follow-up did not extend

past menopause, thus excluding the highest risk period for cardiovascular disease.[30] The analysis may have therefore been underpowered to detect associations with outcomes that were rare, and future studies with longer follow-up are needed. Analyses of recurrent cardiovascular events may also be merited, because this study stopped follow-up at the first cardiovascular hospitalization. We did not find evidence of interaction with preeclampsia, suggesting that preeclampsia is not a modifier. Nonetheless, future research using larger sample sizes may be useful to determine if effects differ depending on the presence of preeclampsia. We lacked information on risk factors such as smoking, body mass index, and ethnicity, and residual confounding cannot be excluded, making this an important limitation.

In this longitudinal study, women whose infants had critical or noncritical heart defects had >25% greater risk of any cardiovascular hospitalization later in life. Associations were stronger for many outcomes, and were present with both critical and noncritical heart defects. The presence of a heart defect in a woman's offspring may therefore be a novel risk factor for the development of maternal cardiovascular disease. More study is needed to determine if women whose infants with heart defects could benefit from targeted primary prevention initiatives.

ARTICLE INFORMATION

Received June 29, 2017; accepted February 5, 2018.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.117.030277/-/DC1.

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure but can be obtained from the Ministry of Health of Social Services following standard procedures for access.

Correspondence

Nathalie Auger, MD, MSc, 190 Cremazie Blvd E, Montreal, Quebec H2P 1E2, Canada. E-mail nathalie.auger@inspq.qc.ca

Affiliations

University of Montreal Hospital Research Centre, Quebec, Canada (N.A., B.J.P., M.B.-B.). Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada (N.A., G.P.). Institut national de santé publique du Québec, Montreal, Canada (N.A., M.B.-B., G.P.). Division of Cardiology, Department of Medicine, University of Montreal Hospital Centre, Quebec,Canada (B.J.P.).

Sources of Funding

This work was supported by the Canadian Institutes of Health Research (MOP-130452), Public Health Agency of Canada (6D02363004), and Fonds de recherche du Québec-Santé (career award 34695).

Disclosures

None.

REFERENCES

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385:117–171. doi: 10.1016/S0140-6736(14)61682-2.
2. Sacco RL, Roth GA, Reddy KS, Arnett DK, Bonita R, Gaziano TA, Heidenreich PA, Huffman MD, Mayosi BM, Mendis S, Murray CJ, Perel P, Piñeiro DJ, Smith SC Jr, Taubert KA, Wood DA, Zhao D, Zoghbi WA. The Heart of 25 by 25: Achieving the goal of reducing global and regional premature deaths from cardiovascular diseases and stroke: a modeling study from the American Heart Association and World Heart Federation. *Circulation*. 2016;133:e674–e690. doi: 10.1161/CIR.0000000000000395.
3. Bonamy AK, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. *Circulation*. 2011;124:2839–2846. doi: 10.1161/CIRCULATIONAHA.111.034884.
4. Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association between preeclampsia and congenital heart defects. *JAMA*. 2015;314:1588–1598. doi: 10.1001/jama.2015.12505.
5. Cohen E, Horváth-Puhó E, Ray JG, Pedersen L, Adler N, Ording AG, Wise PH, Milstein A, Toft Sørensen H. Association between the birth of an infant with major congenital anomalies and subsequent risk of mortality in their mothers. *JAMA*. 2016;316:2515–2524. doi: 10.1001/jama.2016.18425.
6. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJ. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol*. 2011;8:50–60. doi: 10.1038/nrcardio.2010.166.
7. Patel SS, Burns TL. Nongenetic risk factors and congenital heart defects. *Pediatr Cardiol*. 2013;34:1535–1555. doi: 10.1007/s00246-013-0775-4.
8. Cannon CP. Cardiovascular disease and modifiable cardiometabolic risk factors. *Clin Cornerstone*. 2008;9:24–38; discussion 39–41.
9. Auger N, Fraser WD, Schnitzer M, Leduc L, Healy-Profitós J, Paradis G. Recurrent pre-eclampsia and subsequent cardiovascular risk. *Heart*. 2017;103:235–243. doi: 10.1136/heartjnl-2016-309671.
10. Li J, Zhu X, Yu K, Jiang H, Zhang Y, Deng S, Cheng L, Liu X, Zhong J, Zhang X, He M, Chen W, Yuan J, Gao M, Bai Y, Han X, Liu B, Luo X, Mei W, He X, Sun S, Zhang L, Zeng H, Sun H, Liu C, Guo Y, Zhang B, Zhang Z, Huang J, Pan A, Yuan Y, Angileri F, Ming B, Zheng F, Zeng Q, Mao X, Peng Y, Mao Y, He P, Wang QK, Qi L, Hu FB, Liang L, Wu T. Genome-wide analysis of dna methylation and acute coronary syndrome. *Circ Res*. 2017;120:1754–1767. doi: 10.1161/CIRCRESAHA.116.310324.
11. Serra-Juhé C, Cuscó I, Homs A, Flores R, Torán N, Pérez-Jurado LA. DNA methylation abnormalities in congenital heart disease. *Epigenetics*. 2015;10:167–177. doi: 10.1080/15592294.2014.998536.
12. Wei H, Roscigno CI, Hanson CC, Swanson KM. Families of children with congenital heart disease: A literature review. *Heart Lung*. 2015;44:494–511. doi: 10.1016/j.hrtlng.2015.08.005.
13. Solberg Ø, Dale MT, Holmstrøm H, Eskedal LT, Landolt MA, Vollrath ME. Long-term symptoms of depression and anxiety in mothers of infants with congenital heart defects. *J Pediatr Psychol*. 2011;36:179–187. doi: 10.1093/jpepsy/jsq054.
14. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. *Am J Hypertens*. 2015;28:1295–1302. doi: 10.1093/ajh/hpv047.
15. Auger N, Le TU, Park AL, Luo ZC. Association between maternal comorbidity and preterm birth by severity and clinical subtype: retrospective cohort study. *BMC Pregnancy Childbirth*. 2011;11:67. doi: 10.1186/1471-2393-11-67.
16. Ministry of Health and Social Services. *Med-Echo System Normative Framework - Maintenance and use of data for the study of hospital clientele*. Quebec:Government of Quebec; 2017.
17. Eckersley L, Sadler L, Parry E, Finucane K, Gentles TL. Timing of diagnosis affects mortality in critical congenital heart disease. *Arch Dis Child*. 2016;101:516–520. doi: 10.1136/archdischild-2014-307691.
18. Pampalon R, Hamel D, Gamache P, Philibert MD, Raymond G, Simpson A. An area-based material and social deprivation index for public health in Québec and Canada. *Can J Public Health*. 2012;103(8 Suppl 2):S17–S22.
19. Lin G, So Y, Johnston G. Analyzing survival data with competing risks using SAS software. *SAS Global Forum 2012. Statistics and Data Analysis*. 2012;paper 344–2012:1–8.
20. So Y, Lin G, Johnston G. Using the PHREG Procedure to Analyze Competing-Risks Data. Cary, NC:SAS Institute Inc.; 2014.
21. George B, Seals S, Aban I. Survival analysis and regression models. *J Nucl Cardiol Off Publ Am Soc Nucl Cardiol*. 2014;**21**:686–694.
22. Allison PD. *Survival Analysis Using SAS: A Practical Guide*, 2nd ed. Cary, NC:SAS Institute Inc; 2010.

23. Sun Y, Overvad K, Zhou WJ, Zhu JL, Olsen J. Cancer risks in parents who had a child with a congenital malformation. *Birth Defects Res B Dev Reprod Toxicol*. 2013;98:154–163. doi: 10.1002/bdrb.21051.
24. Zhu JL, Basso O, Hasle H, Winther JF, Olsen JH, Olsen J. Do parents of children with congenital malformations have a higher cancer risk? A nationwide study in Denmark. *Br J Cancer*. 2002;87:524–528. doi: 10.1038/sj.bjc.6600488.
25. Llurba E, Sánchez O, Ferrer Q, Nicolaides KH, Ruíz A, Domínguez C, Sánchez-de-Toledo J, García-García B, Soro G, Arévalo S, Goya M, Suy A, Pérez-Hoyos S, Alijotas-Reig J, Carreras E, Cabero L. Maternal and foetal angiogenic imbalance in congenital heart defects. *Eur Heart J*. 2014;35:701–707. doi: 10.1093/eurheartj/eht389.
26. Carnevale D, Lembo G. Placental growth factor and cardiac inflammation. *Trends Cardiovasc Med*. 2012;22:209–212. doi: 10.1016/j.tcm.2012.07.022.
27. Blossom SJ, Rau JL, Best TH, Bornemeier RA, Hobbs CA. Increased maternal cytokine production and congenital heart defects. *J Reprod Immunol*. 2013;97:204–210. doi: 10.1016/j.jri.2012.12.004.
28. Stoner L, Lucero AA, Palmer BR, Jones LM, Young JM, Faulkner J. Inflammatory biomarkers for predicting cardiovascular disease. *Clin Biochem*. 2013;46:1353–1371. doi: 10.1016/j.clinbiochem.2013.05.070.
29. Ávila P, Mercier LA, Dore A, Marcotte F, Mongeon FP, Ibrahim R, Asgar A, Miro J, Andelfinger G, Mondésert B, de Guise P, Poirier N, Khairy P. Adult congenital heart disease: a growing epidemic. *Can J Cardiol*. 2014;30(12 suppl):S410–S419. doi: 10.1016/j.cjca.2014.07.749.
30. Lobo RA, Davis SR, De Villiers TJ, Gompel A, Henderson VW, Hodis HN, Lumsden MA, Mack WJ, Shapiro S, Baber RJ. Prevention of diseases after menopause. *Climacteric*. 2014;17:540–556. doi: 10.3109/13697137.2014.933411.

Long-Term Risk of Cardiovascular Disease in Women Who Have Had Infants With Heart Defects

Nathalie Auger, Brian J. Potter, Marianne Bilodeau-Bertrand and Gilles Paradis

Circulation. published online April 2, 2018;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Table S1 Diagnostic and procedure codes for congenital heart defects

	International Classification of Diseases, 9th revision/Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures	International Classification of Diseases, 10th revision/Canadian Classification of Health Interventions
Critical heart defect		
Any	745.0-745.3; 746.01; 746.1; 746.2; 746.7; 747.1; 747.41/47.81; 47.83	Q20.0-Q20.50; Q21.3; Q21.4; Q22.0; Q22.4; Q22.5; Q23.4; Q25.1; Q26.2/1.HP.87; 1.LA.84; 1.LD.84
Tetralogy of Fallot	745.2/47.81	Q21.3/1.HP.87; 1.LD.84
Transposition of great vessels	745.1	Q20.1-Q20.3; Q20.50
Truncus arteriosus	745.0/47.83	Q20.0; Q21.4/1.LA.84
Hypoplastic left heart	746.7	Q23.4
Common ventricle	745.3	Q20.4
Coarctation of aorta	747.1	Q25.1
Other critical	746.01; 746.1; 746.2; 747.41	Q22.0; Q22.4; Q22.5; Q26.2
Noncritical heart defect		
Any	745.4-745.9; 746.00; 746.02; 746.09; 746.3-746.6; 746.81-746.9; 747.2; 747.3; 747.40; 747.42; 747.49; 759.3/47.52-47.55; 47.62-47.64; 47.72-47.74	Q20.58-Q21.2; Q21.8; Q21.9; Q22.1-Q22.3; Q22.8-Q23.3; Q23.8-Q24.9; Q25.2-Q26.1; Q26.3-Q26.4; Q26.8-Q26.9; Q89.3/1.HN.80; 1.HR.80; 1.LC.84
Endocardial cushion	745.6/47.55; 47.64; 47.74	Q21.2/1.LC.84
Ventricular septum	745.4/47.54; 47.63; 47.73	Q21.0; Q21.8/1.HR.80
Atrial septum	745.5/47.52; 47.53; 47.62; 47.72	Q21.1/1.HN.80
Valve	746.00; 746.02; 746.09; 746.3-746.6	Q22.1-Q22.3; Q22.8-Q23.3; Q23.8; Q23.9
Aorta	747.2	Q25.2-Q25.4
Pulmonary artery	747.3	Q25.5-Q25.7
Heterotaxy	746.87; 759.3	Q20.58; Q20.6; Q24.0; Q24.1; Q89.3
Other noncritical	745.7-745.9; 746.81-746.86; 746.89-746.9; 747.40; 747.42; 747.49	Q20.8-Q20.9; Q21.9; Q24.2-Q24.9; Q25.8-Q26.1; Q26.3-Q26.4; Q26.8-Q26.9
Covariates		
Preeclampsia	642.3-642.7	O11; O13-O15
Comorbidity	249; 250; 272; 278.0; 296.2; 296.3; 300.4; 311; 649.1	E10-E14; E66; E78; F32; F33; F34.1

Table S2 Diagnostic and procedure codes for cardiovascular disorders

	International Classification of Diseases, 9th revision/Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures	International Classification of Diseases, 10th revision/Canadian Classification of Health Interventions
Cardiovascular disorders		
Any disorder	401-405; 410-422; 424-428; 429.2; 430-442; 443.2; 444-445; 451.1; 451.83; 453.4-453.5; 453.72; 453.82; 461.0	I10-I30; I33-I40; I42-I50; I60-I72; I74; I80.1-I80.3
Heart		
Heart failure	428	I50
Ischaemic heart disease	410-414	I20-I25
Myocardial infarction	410; 411.0; 412	I21-I23; I25.2
Angina	413	I20
Cardiac arrest	427.5	I46
Inflammatory heart disorder	420-422	I30; I33; I40
Conduction disorder	426-427.4; 427.6-427.9	I44-I45; I47-I49
Valve disorder	424	I34-I39
Cardiomyopathy	425	I42-I43
Lungs		
Pulmonary embolism	415.1	I26
Pulmonary vascular disease	415.0; 416-417	I27-I28
Cerebrovascular		
Ischaemic stroke	433-437.2; 437.4-438	I63-I66; I67.2-I69
Haemorrhage	430-432	I60-I62
Hypertension	401-405; 416.8; 437.2; 461.0	I10-I15; I27.0; I67.4
Other atherosclerotic	414.0; 414.3; 414.4; 429.2; 440	I25.0; I25.1; I70
Aortic aneurysm or dissection	441	I71
Aneurysm of other vessels	437.3; 442; 443.2	I67.0; I67.1; I72
Deep vein thrombosis	451.1; 451.83; 453.4-453.5; 453.72; 453.82	I80.1-I80.3
Arterial embolism	444-445	I74
Interventions		
Any intervention	45.69; 47.0-47.3; 47.96-48.3; 49.59-49.8	1.HB.55; 1.HD.55; 1.HS-1.HY.85; 1.HZ.38-1.HZ.55; 1.HZ.85; 1.IJ.50-1.IJ.80
Coronary angioplasty	48.0	1.IJ.50; 1.IJ.55; 1.IJ.57; 1.IJ.80
Coronary artery bypass graft	48.1-48.3	1.IJ.76
Pacemaker insertion	49.6-49.8	1.HB.55; 1.HD.55; 1.HZ.38; 1.HZ.53; 1.HZ.55
Valve surgery	47.0-47.3; 47.96; 47.97	1.HS; 1.HT; 1.HU; 1.HV; 1.HW; 1.HX
Cardiac transplant	45.69; 49.59	1.HY.85; 1.HZ.85

Table S3 Hazard ratio of cardiovascular hospitalization for 1,023,253 women without preeclampsia whose infants had critical or noncritical heart defects vs. no defects, Quebec, 1989-2014

	Adjusted hazard ratio (95% confidence interval)*	
	Critical	Noncritical
Any cardiovascular disorder or intervention	1.29 (0.98-1.69)	1.24 (1.14-1.35)
Cardiovascular disorders		
Any disorder	1.29 (0.98-1.70)	1.24 (1.14-1.36)
Heart		
Heart failure	2.63 (0.98-7.01)	2.04 (1.44-2.89)
Ischaemic heart disease	1.81 (0.95-3.45)	1.39 (1.10-1.76)
Myocardial infarction	2.64 (1.26-5.50)	1.09 (0.77-1.56)
Angina	0.65 (0.09-4.60)	1.51 (1.02-2.25)
Cardiac arrest	2.13 (0.30-15.21)	2.18 (1.20-3.97)
Inflammatory heart disorder	1.41 (0.20-9.94)	1.22 (0.63-2.36)
Conduction disorder	1.70 (1.02-2.83)	1.32 (1.10-1.58)
Valve disorder	2.10 (0.79-5.61)	1.05 (0.69-1.62)
Cardiomyopathy	-	2.27 (1.46-3.52)
Lungs		
Pulmonary embolism	1.15 (0.43-3.08)	1.19 (0.88-1.61)
Pulmonary vascular disease	1.96 (0.28-13.94)	2.41 (1.38-4.22)
Cerebrovascular		
Ischaemic stroke	1.28 (0.41-3.97)	1.13 (0.78-1.65)
Haemorrhage	2.07 (0.67-6.41)	1.18 (0.74-1.89)
Hypertension	1.36 (0.93-1.99)	1.35 (1.20-1.52)
Other atherosclerosis	2.99 (1.61-5.55)	1.34 (1.01-1.79)
Aortic aneurysm or dissection	-	1.87 (0.45-7.83)
Aneurysm of other vessels	2.11 (0.53-8.48)	1.31 (0.75-2.26)
Deep vein thrombosis	1.26 (0.41-3.93)	1.21 (0.85-1.74)
Arterial embolism	1.88 (0.27-13.26)	1.57 (0.81-3.05)
Interventions		
Any intervention	2.71 (1.59-4.63)	1.28 (1.00-1.64)
Coronary angioplasty	2.27 (0.85-6.04)	1.23 (0.82-1.86)
Coronary artery bypass graft	3.21 (0.45-22.67)	2.34 (1.15-4.75)
Pacemaker insertion	-	2.31 (1.38-3.88)
Valve surgery	8.82 (2.86-27.22)	0.57 (0.14-2.28)
Cardiac transplant	43.23 (6.41-291.73)	7.25 (1.72-30.61)
Coronary care unit	2.06 (0.93-4.57)	1.06 (0.74-1.50)

*Hazard ratios for heart defects versus no heart defect, adjusted for age at first delivery, total parity, comorbidity, material deprivation, and time period.

Table S4 Number of women remaining at risk at different time points according to presence of heart defects in offspring, Quebec, 1989-2014

	Number of years after index delivery						
	0	4	8	12	16	20	24
Heart failure							
Critical	1,516	1,370	1,107	859	642	398	90
Noncritical	14,884	13,670	11,555	8,997	6,493	3,959	899
No defect	1,067,851	947,957	788,324	649,442	513,524	350,148	88,785
Myocardial infarction							
Critical	1,516	1,369	1,106	857	640	396	89
Noncritical	14,884	13,672	11,559	8,996	6,493	3,958	897
No defect	1,067,851	947,942	788,257	649,237	513,062	349,490	88,469
Ischaemic stroke							
Critical	1,516	1,369	1,106	860	641	397	89
Noncritical	14,884	13,667	11,552	8,985	6,480	3,955	899
No defect	1,067,851	947,780	787,977	648,968	513,018	349,676	88,613
Coronary angioplasty							
Critical	1,516	1,370	1,107	858	641	397	90
Noncritical	14,884	13,671	11,561	8,998	6,495	3,962	897
No defect	1,067,851	948,014	788,379	649,446	513,330	349,780	88,591
Coronary artery bypass graft							
Critical	1,516	1,370	1,107	861	644	399	90
Noncritical	14,884	13,672	11,562	8,999	6,499	3,969	903
No defect	1,067,851	948,055	788,495	649,701	513,861	350,517	88,901
Valve surgery							
Critical	1,516	1,370	1,107	861	644	398	90
Noncritical	14,884	13,673	11,564	9,002	6,503	3,972	903
No defect	1,067,851	948,041	788,467	649,686	513,870	350,544	88,921

Correction

In the article by Auger et al, "Long-Term Risk of Cardiovascular Disease in Women Who Have Had Infants With Heart Defects," which published ahead of print April 2, 2018 (DOI: 10.1161/CIRCULATIONAHA.117.030277), the Sources of Funding were incorrect and should read:

"This work was supported by the Heart and Stroke Foundation of Canada (G-18-0021776), Public Health Agency of Canada (6D02363004), and Fonds de recherche du Québec-Santé (career award 34695)."