Congenital Heart Disease

Association Between Maternal Chronic Conditions and Congenital Heart Defects
A Population-Based Cohort Study

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Background—This study quantifies the association between maternal medical conditions/illnesses and congenital heart defects (CHDs) among infants.

Methods and Results—We carried out a population-based study of all mother-infant pairs (n=2 278 838) in Canada (excluding Quebec) from 2002 to 2010 using data from the Canadian Institute for Health Information. CHDs among infants were classified phenotypically through a hierarchical grouping of International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada codes. Maternal conditions such as multifetal pregnancy, diabetes mellitus, hypertension, and congenital heart disease were defined by use of diagnosis codes. The association between maternal conditions and CHDs and its subtypes was modeled using logistic regression with adjustment for maternal age, parity, residence, and other factors. There were 26 488 infants diagnosed with CHDs at birth or at rehospitalization in infancy; the overall CHD prevalence was 116.2 per 10 000 live births, of which the severe CHD rate was 22.3 per 10 000. Risk factors for CHD included maternal age ≥40 years (adjusted odds ratio [aOR], 1.48; 95% confidence interval [CI], 1.39–1.58), multifetal pregnancy (aOR, 4.53; 95% CI, 4.28–4.80), diabetes mellitus (type 1: aOR, 4.65; 95% CI, 4.13–5.24; type 2: aOR, 4.12; 95% CI, 3.69–4.60), hypertension (aOR, 1.81; 95% CI, 1.61–2.03), thyroid disorders (aOR, 1.45; 95% CI, 1.26–1.67), congenital heart disease (aOR, 9.92; 95% CI, 8.36–11.8), systemic connective tissue disorders (aOR, 3.01; 95% CI, 2.23–4.06), and epilepsy and mood disorders (aOR, 1.41; 95% CI, 1.16–1.72). Specific CHD subtypes were associated with different maternal risk factors.

Conclusions—Several chronic maternal medical conditions, including diabetes mellitus, hypertension, connective tissue disorders, and congenital heart disease, confer an increased risk of CHD in the offspring. (Circulation. 2013;128:583-589.)

Key Words: epidemiology • etiology • heart defects, congenital • maternal-fetal relations

Congenital heart defects (CHDs), defined as gross structural abnormalities of the heart or intrathoracic vessels, affect 5 to 15 per 1000 live births.1–3 CHDs constitute the most common congenital anomaly subgroup among newborns and have emerged as one of the most important causes of infant mortality.4–6 Furthermore, CHDs have a significant impact on child and adult morbidity and disability.7–11

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The last 2 decades have seen major breakthroughs in the understanding of nonmodifiable risk factors for CHD, including the identification of specific genetic abnormalities for some CHD phenotypes. However, at most, 15% of all CHD cases can be traced to a genetic cause (eg, 8%–10% have aneuploidy and 3%–5% have single-gene defects). An even smaller proportion can be attributable to known environmental factors such as maternal rubella infection, although a few studies suggest that the fraction of cases attributable to identifiable factors may be as high as 30% for some types of heart defects.12–14 Nevertheless, CHD prevention has been hampered by a limited understanding of modifiable risk factors.15–20

One important area for focus in obstetrics is prenatal diagnosis of severe CHDs. Such early diagnosis permits optimal care during pregnancy, during delivery, and in the newborn

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period (including surgical correction of the defect) and pregnancy termination for lethal and very severe heart defects. It is therefore important to identify pregnant women at higher risk for CHDs to facilitate targeted screening. It also allows targeted preconception counseling to improve reproductive outcomes and to promote primary prevention. This study was carried out to better quantify the associations between chronic conditions in pregnant women (ie, maternal illnesses such as diabetes mellitus, hypertension, thyroid disorders, CHDs, and systemic connective disorders) and CHD in offspring.

Methods
Our population-based cohort study included all live births in Canada (excluding Quebec) for the fiscal years 2002 to 2003 to 2010 to 2011. Information on study subjects was obtained from the Discharge Abstract Database of the Canadian Institute for Health Information, which contains abstracted and collated information from the medical records of all hospitalizations in Canada (excluding Quebec because comparable data from this province were not available in the Discharge Abstract Database). The hospitalization data were extracted by trained medical archivists in each hospital and coded according to a specified protocol.21 Records for the mother and the infant were deterministically linked through the use of Canadian Institute for Health Information’s common mother-infant identifiers. Included in this study were all mother-infant pairs (excluding births <22 weeks’ gestation or <500-g birth weight) who had a hospital delivery in Canada. Stillbirths were not included because a substantial fraction of stillbirths in Canada include cases that follow prenatal diagnosis and pregnancy termination22 and because stillbirths <22 weeks’ gestation or <500-g birth weight) who had a hospital delivery in Canada. Stillbirths were not included because a substantial fraction of stillbirths in Canada include cases that follow prenatal diagnosis and pregnancy termination22 and because stillbirth records could not be linked to the mothers’ records.

Chronic medical conditions affecting the mother and CHDs in offspring were identified on the basis of information in the 25 diagnostic fields of the medical record, coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10 CA). The diagnosis of CHDs was based on hospitalization records at childbirth and at rehospitalization, with the latter identified through a previously validated deterministic algorithm for linking live births and readmissions that occurred within 1 year after birth.23 Information in the Discharge Abstract Database has previously been validated and used extensively in perinatal health surveillance and research.3,21,23–25

CHDs (ICD-10 CA codes Q200-Q269 and Q893) were classified into phenotypes on the basis of the classification used by Botto et al12 and Oyen et al.1 This classification algorithm for CHDs was recently designed for etiologic studies, and infants with CHD were classified into the following 17 cardiac subtypes by grouping specific ICD-10 CA codes in hierarchical fashion: (1) heterotaxia (abnormalities in left-right cardiac asymmetry associated with intracardiac defects such as an atrioventricular septal defect [AVSD], abnormalities of systemic and pulmonary venous drainage, malposition of the great vessels, and subpulmonary or aortic obstruction); (2) conotruncal defects; (3) AVSD; (4) anomalies of pulmonary venous return; (5) left ventricular outflow tract obstruction (LVOTO); (6) right ventricular outflow tract obstruction (RVOTO); (7) isolated atrial septal defect (ASD); (8) isolated ventricular septal defect (VSD); (9) ASD and VSD; (10) complex defects; (11) conotruncal defect plus AVSD; (12) septal defect plus LVOTO; (13) septal defect plus RVOTO; (14) isolated patent ductus arteriosus (PDA) in newborns at or after term gestation (ie, ≥37 weeks); (15) isolated PDA in preterm births; (16) unspecified CHD; and (17) all other specified CHD (see the online-only Data Supplement for definitions and ICD-10 CA codes). In addition, heterotaxia, conotruncal defects, AVSD, anomalous pulmonary venous return, LVOTO, RVOTO, complex defects, and associated defects (ie, phenotypes 11–15) were categorized as severe CHDs.2,12,26,28 Determinants of interest in the mother included tobacco use (ICD-10 CA codes F17, F16.5, Z50.8, Z58.7, Z71.6, Z72.0); alcohol or substance use (F10-F16, F18, K29.2, K70, K85.2, K86, O35.4, O35.5, R78, T51, X42, X45, X62, X65, Y12, Y15, Z50.2, Z71.4, Z71.5, Z72.1, Z72.2, Z86.4); obesity (E66); preexisting diabetes mellitus (type 1: E10, O245, O240; type 2: E11, O241, O246); preexisting hypertension (I10-I15, O10, O11); thyroid disorders (E00-E07); congenital heart disease (Q20-Q28); atherosclerotic and other heart disease (I20-I25, I42, I43, O90.3, O99.4); anemia and related disorders (D50-D89); systemic connective tissue disorders (M30-M36); and epilepsy and specific mood disorders (G40, G41, G30, F31, F38, F39).

We calculated the number of cases, proportion, and prevalence rate for each of the above-described CHD subtypes and all identified severe CHDs among live births (during the childbirth admission or at rehospitalization) as described above. We then determined the prevalence of CHD (with or without PDA in preterm live births) among live-born infants within categories of the following factors: maternal age (<20, 20–24, 25–29, 30–34, 35–39, and ≥40 years), parity (0, 1, 2, 3, missing), multiple gestation, rural residence, infant sex, region (Atlantic, Ontario, West, Pacific, and North), and year of birth.

We estimated crude and adjusted odds ratios (aORs) and their 95% confidence intervals (CIs) for the association between chronic conditions in the mother and any CHD (excluding isolated PDA among preterm infants). Logistic regression models were used to obtain the independent effects of each of these conditions after adjustment for all of the determinants listed above.

We also estimated the proportion of CHD cases that would be eliminated if a particular risk factor (assumed to be causally associated with CHD) was removed from the population using the adjusted effect measure in the following equation: Pe(RR−1)/Pe(RR−1)+1, where Pe is the proportion of the population exposed to the risk factor and RR is the relative risk (OR given rare disease) associated with the risk factor.29

Separate logistic models were also created to assess the relationship between chronic medical conditions and specific severe subtypes of CHD (ie, heterotaxia, conotruncal defects, AVSD, anomalous pulmonary venous return, LVOTO, RVOTO, and multiple cardiac defects consisting of conotruncal defect plus AVSD, septal defect plus LVOTO, and septal defect plus RVOTO) and VSD and ASD. All statistical analyses were carried out with SAS version 9.2 (SAS Institute, Cary, NC).

This study was carried out by the Public Health Agency of Canada, which has a federal mandate to monitor the health of the Canadian population. The data source involved denormalized information from all hospitals in Canada (excluding Quebec); therefore, ethics review board approval was not required.

Results
Of 2278838 infants born in hospitals in Canada (excluding Quebec) between 2002 to 2003 and 2010 to 2011, 22365 were identified in live birth records and 4123 at rehospitalization as having ≥1 CHDs, yielding an overall CHD prevalence of 116.2 per 10000 live births. After exclusion of cases with isolated PDA born before 37 weeks’ gestation (n=3228), the overall CHD prevalence was 101.8 per 10000 live births. The prevalence of severe CHD was 22.3 per 10000 live births (Table 1).

The most prevalent CHD was isolated PDA with a prevalence rate of 38.1 per 10000 live births, whereas the prevalence of isolated PDA at term was 23.7 per 10000 live births. Isolated septal defects (eg, ASD alone or VSD alone), the second most prevalent cardiac defects, accounted for 27.5% of all CHDs (prevalence rate, 32.0 per 10000 live births). Other CHDs included conotruncal defects (10.4 per 10000 live births), the combined left and right heart obstructive defects (3.4 per 10000 live births), and AVSD (2.8 per 10000 live births). Other specified CHDs accounted for 15.4% of all CHD cases (prevalence, 17.9 per 10000 live births), whereas unspecified cases represented ≈5% of all CHD cases (Table 1).
CHD prevalence was higher among infants of younger mothers, older mothers, women with a parity ≥ 2, and women living in rural areas and male infants (Table 2). Multiple births had a substantially elevated prevalence of CHD (43.3 per 1000 live births). The prevalence rates of CHD declined significantly from 10.9 per 1000 live births in 2002 to 9.8 per 1000 live births in 2010 (P for trend <0.0001), and there was substantial regional variation in prevalence rates (Table 2).

Prevalence rates of CHD were significantly higher among women with chronic medical conditions. For instance, the prevalence of CHD among women with type 1 diabetes mellitus was 48.7 per 1000 live births compared with a prevalence of 10.1 per 1000 live births among women who did not have type 1 diabetes mellitus (Table 3). The aOR for CHD among women with CHDs was 9.9 (95% CI, 8.4–11.8). Women with diabetes mellitus and systemic connective tissue disorders had ≈ 3- to 5-fold higher rates of CHD. Alcohol or substance use was also significantly associated with overall CHDs (aOR, 1.9; 95% CI, 1.7–2.0) in the adjusted model. Approximately 4.8% and 2.6% of the CHD cases could be attributed to multifetal pregnancy and maternal age ≥ 35 years, respectively, at the population level. As a whole, 14% of CHD cases could be prevented if all the risk factors were eliminated from the population (Table 3).

Tables 4 and 5 show associations between chronic medical conditions in the mother and specific subtypes of CHD in the offspring. Diabetes mellitus and congenital heart disease in the mother were strong risk factors for heterotaxia, conotruncal defects, AVSD, left and right ventricular outflow obstruction, septal defects, and multiple defects.
Maternal age <20 y 4.7 1154 (10.9) 21 440 (9.9) 1.16 (1.09–1.23) 1.17 (1.10–1.25) 1.2
Maternal age 35–39 y 15.4 3801 (10.8) 19 399 (10.1) 1.13 (1.09–1.18) 1.09 (1.05–1.14) 1.2
Maternal age ≥40 y 3.1 1092 (15.4) 22 108 (10.0) 1.62 (1.51–1.72) 1.48 (1.39–1.58) 1.4
Multifetal pregnancy 1.4 1348 (43.3) 21 852 (9.7) 4.61 (4.36–4.88) 4.53 (4.28–4.80) 4.8
Tobacco use 0.5 164 (13.3) 22 2431 (10.2) 1.31 (1.13–1.53) 1.04 (0.89–1.22) 0.0
Alcohol or substance use 1.5 739 (21.2) 22 2461 (10.0) 2.15 (2.00–2.32) 1.88 (1.74–2.04) 1.3
Obesity 0.8 345 (19.3) 22 2855 (10.1) 1.93 (1.73–2.15) 1.48 (1.32–1.65) 0.4
Preexisting diabetes mellitus (type 1) 0.3 295 (48.7) 22 22905 (10.1) 5.03 (4.48–5.66) 4.65 (4.13–5.24) 0.9
Preexisting diabetes mellitus (type 2) 0.3 355 (47.9) 22 22845 (10.1) 4.96 (4.45–5.52) 4.12 (3.69–4.60) 0.9
Preexisting hypertension 0.6 319 (25.0) 22 22811 (10.1) 2.51 (2.25–2.81) 1.81 (1.61–2.03) 0.4
Thyroid disorders 0.5 2 13 (18.0) 22 22987 (10.1) 1.80 (1.65–2.17) 1.45 (1.26–1.67) 0.2
Congenital heart disease 0.1 179 (102.8) 23 2021 (10.1) 11.2 (9.61–13.1) 9.92 (8.36–11.8) 0.7
Atherosclerotic heart disease 0.3 170 (22.2) 23 20300 (10.1) 2.22 (1.91–2.59) 1.14 (0.96–1.35) 0.3
Anemia and related disorders 1.4 472 (14.9) 23 22728 (10.1) 1.48 (1.35–1.62) 1.26 (1.15–1.39) 0.3
Connective tissue disorders 0.1 46 (34.7) 23 21354 (10.2) 3.51 (2.62–4.71) 3.01 (2.23–4.06) 0.1
Epilepsy and mood disorders 0.2 117 (26.4) 23 2083 (10.1) 2.65 (2.20–3.18) 1.41 (1.16–1.72) 0.1
Any of the above 28.3 8893 (13.8) 24 14307 (8.7) 1.59 (1.55–1.63) 1.59 (1.54–1.63) 14.3

CHD indicates congenital heart defect; and CI, confidence interval.
*Adjusted odds ratios were based on a multivariate logistic model including all listed conditions plus maternal age (<20, 20–24, 25–29, 30–34, 35–39, and ≥40 years), infant sex, parity (0, 1, 2, ≥3, missing), rural residence, and region and year of birth.
†Population-attributable fraction was estimated with the adjusted odds ratios.

Discussion

Our study describes the prevalence of CHD and its phenotypes and shows a declining trend in the frequency of CHD in infants in Canada between 2002 and 2010. Our study also identified associations between a number of maternal chronic conditions and overall CHD, as well as VSD, ASD, and several severe CHD subtypes. Most associations between chronic medical conditions and CHD were specific for both maternal illness and CHD phenotype. Several maternal conditions such as multifetal pregnancy, diabetes mellitus, CHDs, and systemic connective tissue diseases were strongly associated with CHD.

Our prevalence estimates for overall CHD and most severe CHD subtypes were similar to those reported previously from other countries. However, some subtype-specific rates of CHD prevalence were different despite our use of the same grouping algorithm. For example, in contrast to the severe CHD rate of 32.3 per 10 000 live births observed in Denmark in 2000 to 2005, we observed a substantially lower rate of severe CHD in Canada (22.3 per 10 000 live births). Other differences between the 2 countries included a lower frequency of LVOTO and RVOTO (3.5 versus 10.8 per 10 000 live births) and a higher prevalence of isolated PDA at term in Canada (5.0 versus 23.7 per 10 000 live births). Possible explanations include selective termination of severe CHD cases after prenatal diagnosis, differences in CHD classification, folate acid food fortification, and potentially more complete case ascertainment of mild CHD in Canada.

A large number of isolated defects (ie, isolated VSD, ASD, and PDA) accounted for 60% of CHDs; this estimate is higher than those in previous reports. The increasing availability of echocardiography with a resultant increase in the diagnosis of minor defects in asymptomatic infants is a potential explanation. In addition, large variations were observed between regions that may reflect true differences or possibly an artifact of differences in documentation and case ascertainment.

As in previous studies, preexisting maternal diabetes mellitus (types 1 and 2) was observed to be a significant risk factor for CHD overall and for almost every CHD subtype. Numerous studies have shown that diabetes mellitus causes cardiovascular malformations before the seventh week of gestation because of a link between glycemic control during organogenesis and fetal malformations. We therefore focused on assessing the risk of preexisting diabetes mellitus in our data rather than assessing the effect of gestational diabetes mellitus. On the other hand, the elevated risk of CHD...
observed with some maternal chronic conditions (eg, epilepsy and mood disorders) may be a consequence of medication used to treat those conditions rather than the medical condition per se. Our goal, however, was to identify women at high risk for CHD regardless of whether the chronic condition or its treatment was the true cause of CHD.

Our findings of associations between maternal chronic illnesses such as congenital heart disease and systemic connective tissue disorders and CHD were also in line with previous studies. In addition, we observed that preexisting hypertension among mothers posed an elevated risk of certain subtypes of CHD. We also observed an association between maternal cigarette smoking and CHDs as in previous studies.

The strengths of our study include its size, population-based nature, standardized data extraction, and ICD-10 CA coding. The large study size allowed estimation of associations between relatively uncommon maternal illnesses and rare subtypes of severe CHD. Such large epidemiological studies of CHD prevalence and cause have not been undertaken previously at the national level in Canada or elsewhere. The inclusion of CHD cases diagnosed at birth or at rehospitalization any time in infancy was another strength of the study.

It is widely acknowledged that the systems for classifying CHD are challenging because of the wide range of known defects, differing causes, and developmental mechanisms. Infants with multiple cardiac defects may be counted multiple times in congenital anomaly surveillance. The classification algorithm used in our study, however, assigned each infant (including those with multiple cardiac defects) to a specific cardiac phenotype among a group of exhaustive and mutually exclusive categories. This classification scheme of cardiac defects was developed with an anatomic and developmental rationale and permitted the conversion of ICD-10 CA diagnosis codes to a flexible coding scheme for studying CHD.

Several limitations inherent in our study merit discussion. First, maternal illnesses and preexisting conditions recorded at childbirth hospitalization were likely underreported, especially obesity, smoking, and alcohol/substance abuse. Thus, the potential for misclassification and residual confounding exists and could potentially bias some of the associations between maternal conditions and CHD. In addition, our study cannot exclude a possible detection bias whereby mothers with a fetus or newborn with CHD may have been more likely to have detailed documentation of exposures and medical conditions in their medical records. Other limitations include our inability to assess the temporal effects of multivitamin and folic acid supplementation and universal food fortification on the occurrence of severe CHD (previously reported from Quebec). Fortification of grain products with folic acid has been mandatory in Canada since December 1998.

Similarly, we were unable to assess the effects of prenatal diagnosis and subsequent termination of pregnancy. Finally,
Table 5. Associations Between Maternal Factors, Including Age and Chronic Medical Conditions, and Specific CHDs in Offspring, Including RVOTO, VSD, and ASD, and Multiple Heart Defects, Canada (Excluding Quebec), 2002 to 2010

<table>
<thead>
<tr>
<th>Maternal Characteristic</th>
<th>RVOTO (n=243)</th>
<th>VSD (n =3691)</th>
<th>ASD (n =2888)</th>
<th>Multiple Defects† (n=622)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age &lt;20 y</td>
<td>1.18 (0.67–2.07)</td>
<td>1.16 (0.99–1.35)</td>
<td>1.43 (1.21–1.68)</td>
<td>2.07 (1.24–3.46)</td>
</tr>
<tr>
<td>Maternal age 35–39 y</td>
<td>1.04 (0.69–1.58)</td>
<td>1.05 (0.95–1.17)</td>
<td>1.25 (1.04–1.52)</td>
<td>1.35 (1.02–1.78)</td>
</tr>
<tr>
<td>Maternal age ≥40 y</td>
<td>1.04 (0.50–2.02)</td>
<td>1.41 (1.19–1.67)</td>
<td>1.27 (1.14–1.41)</td>
<td>2.06 (1.36–3.08)</td>
</tr>
<tr>
<td>Multifetal pregnancy</td>
<td>2.67 (1.37–5.21)</td>
<td>2.04 (1.68–2.49)</td>
<td>3.07 (2.54–3.69)</td>
<td>1.19 (0.61–2.30)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>2.57 (1.02–6.44)</td>
<td>1.21 (0.83–1.77)</td>
<td>1.14 (0.77–1.67)</td>
<td>0.91 (0.29–2.85)</td>
</tr>
<tr>
<td>Alcohol or substance use</td>
<td>2.61 (1.38–4.95)</td>
<td>1.97 (1.62–2.39)</td>
<td>2.45 (2.01–2.98)</td>
<td>1.68 (0.95–2.96)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.39 (0.05–2.77)</td>
<td>1.18 (0.87–1.62)</td>
<td>1.74 (1.32–2.31)</td>
<td>1.56 (0.73–3.34)</td>
</tr>
<tr>
<td>Preexisting diabetes mellitus (type 1)</td>
<td>2.93 (0.72–11.8)</td>
<td>3.01 (2.11–4.30)</td>
<td>3.69 (2.60–5.25)</td>
<td>4.36 (2.05–9.28)</td>
</tr>
<tr>
<td>Preexisting diabetes mellitus (type 2)</td>
<td>2.03 (0.50–8.29)</td>
<td>3.27 (2.42–4.44)</td>
<td>4.15 (3.12–5.52)</td>
<td>2.68 (1.18–6.09)</td>
</tr>
<tr>
<td>Preexisting hypertension</td>
<td>3.17 (1.39–7.81)</td>
<td>1.52 (1.11–2.09)</td>
<td>3.12 (2.41–4.03)</td>
<td>1.95 (0.95–3.98)</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>1.64 (0.92–3.91)</td>
<td>1.46 (1.03–2.07)</td>
<td>1.02 (0.64–1.62)</td>
<td>2.56 (1.26–5.20)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>44.9 (19.5–103.3)</td>
<td>1.62 (0.71–3.71)</td>
<td>2.12 (0.98–4.61)</td>
<td>15.2 (6.75–34.2)</td>
</tr>
<tr>
<td>Atherosclerotic heart disease</td>
<td>0.49 (0.12–2.29)</td>
<td>1.79 (1.19–2.68)</td>
<td>1.68 (1.09–2.58)</td>
<td>1.65 (0.69–3.94)</td>
</tr>
<tr>
<td>Anemia and related disorders</td>
<td>1.03 (0.45–2.31)</td>
<td>1.13 (0.89–1.44)</td>
<td>1.53 (1.19–1.95)</td>
<td>1.37 (0.73–2.57)</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td>...‡</td>
<td>2.54 (1.13–5.67)</td>
<td>2.93 (1.31–6.56)</td>
<td>...‡</td>
</tr>
<tr>
<td>Epilepsy and mood disorders</td>
<td>2.77 (0.78–9.80)</td>
<td>1.25 (0.76–2.81)</td>
<td>0.96 (0.54–1.71)</td>
<td>1.20 (0.28–5.20)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>1.48 (1.14–1.92)</td>
<td>1.31 (1.23–1.41)</td>
<td>1.49 (1.38–1.60)</td>
<td>1.51 (1.26–1.81)</td>
</tr>
</tbody>
</table>

aOR indicates adjusted odds ratio; ASD, atrial septal defect; CHD, congenital heart defect; CI, confidence interval; RVOTO, right ventricular outflow tract obstruction; and VSD, ventricular septal defect.

* aORs for each CHD subtype were based on logistic models including all listed conditions plus maternal age (<20, 20–24, 25–29, 30–34, 35–39, and ≥40 years), infant sex, parity (0, 1, 2, ≥3, missing), rural residence, and region and year of birth.

† Multiple defects include conotruncal defect plus AVSD, septal defect plus left ventricular outflow tract obstruction, and septal plus RVOTO.

‡ Odds ratios could not be computed (no cases of the specific CHD among those with the factor present).

region of residence was based on hospital of birth, and this conferred an artifactual protective effect against CHD among live births in northern regions as a result of a referral of high-risk pregnancies to hospitals in southern Canada.

Conclusions

Our study shows a declining prevalence of CHD in infants from 2002 to 2010 and a relatively low overall rate of severe CHD in Canada. Several maternal conditions/illnesses were highly associated with CHD, and different maternal conditions were associated with specific CHD subtypes. Understanding these relationships and probable causes may allow an opportunity to promote preconception health and primary prevention. Moreover, information on the proportion of CHD cases prevented prenatally based on the population-attributable fractions estimated in our study may be helpful in identifying pregnant women at higher risk for CHD to facilitate targeted screening and selective termination for lethal and very severe heart defects.

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Disclosures

None.

References


CLINICAL PERSPECTIVE
This Canadian study attempted to quantify the association between maternal medical conditions/illnesses and congenital heart defects (CHDs) among infants. The analysis was based on a large population-based cohort of 2,278,838 mother-infant pairs, including infants with CHDs diagnosed at birth or at rehospitalization any time in infancy. The prevalence of CHDs was 2,115 per 10,000 live births, and the overall trend in CHDs declined from 2002 to 010. Several maternal characteristics and conditions were strongly associated with CHDs in the offspring. Risk factors for CHDs included maternal age ≥40 years (adjusted odds ratio [aOR], 1.48; 95% confidence interval [CI], 1.39–1.58), multifetal pregnancy (aOR, 4.53; 95% CI, 4.28–4.80), diabetes mellitus (type 1: aOR, 4.65; 95% CI, 4.13–5.24; type 2: aOR, 4.12; 95% CI, 3.69–4.60), hypertension (aOR, 1.81; 95% CI, 1.61–2.03), thyroid disorders (aOR, 1.45; 95% CI, 1.26–1.67), congenital heart disease (aOR, 9.92; 95% CI, 8.36–11.8), systemic connective tissue disorders (aOR, 3.01; 95% CI, 2.23–4.06), and epilepsy and mood disorders (aOR, 1.41; 95% CI, 1.16–1.72). Approximately 4.8% and 2.6% of the CHD cases could be attributed to multifetal pregnancy and maternal age ≥35 years, respectively, at the population level. As a whole, 14% of those CHD cases could be prevented if the above-mentioned risk factors were eliminated from the population. Understanding these relationships and probable causes may provide an opportunity to promote preconception health and primary prevention and help to facilitate targeted screening for lethal and very severe heart defects.
Association Between Maternal Chronic Conditions and Congenital Heart Defects: A Population-Based Cohort Study
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SUPPLEMENTAL MATERIAL

Appendix. Definition and ICD-10 codes of cardiac phenotypes

Newborns with congenital heart defects (Q20.0 – Q26.9, Q89.3) were classified into the following 17 phenotypes by grouping specific ICD-10 codes in hierarchical fashion. For example, cases with any heterotaxia diagnosis, regardless of other heart defect codes, were allocated to the heterotaxia group. Then, all conotruncal defect codes but without AVSD were identified; by definition, because of the hierarchical nature of the classification scheme, cases with heterotaxia could not be included in the conotruncal defect group. Further, cases with AVSD but without heterotaxia or conotruncal defects, were identified, and so on. Specifically, the phenotypes were defined as follows: 1) heterotaxia with or without any other heart defect (Q24.0, Q24.1, Q89.3, Q20.6); 2) conotruncal defects [truncus arteriosus, interrupted aortic arch, d-transposition of great arteries, tetralogy of Fallot (TOF), double outlet right ventricle] without concomitant atrioventricular septal defect; conoventricular VSD without ASD or AVSD, pulmonary valve stenosis (PVS) and VSD, and pulmonary atresia and VSD without AVSD [Q20.0, Q25.1A, Q25.2, Q25.3, Q25.4, Q20.3, Q21.3, Q20.1, without Q21.1; (Q21.4, without Q21.1 or Q21.2); (Q22.1 and Q21.0, without Q21.2); (Q25.5 and Q21.0; without Q21.2]; (3) AVSD (without TOF) [(Q21.2, without Q21.3)]; (4) APVR (total and partial APVR, but without AVSD) [Q26, Q26.2, Q26.4, Q26.8, Q26.9, without Q21.2; Q26.3, without Q21.2]; (5) LVOTO [hypoplastic left heart syndrome, coarctation of aorta with intact ventricular septum, aortic stenosis] [Q23.4, Q25.1, without Q21.0), Q23.0, Q23.1A]; (6) RVOTO [PVS only, tricuspid atresia, Ebstein anomaly, pulmonary artery atresia with intact ventricular septum and without
TOF] [Q22.1 only, Q22.4, Q22.5, (Q25.5, without Q21.0 or Q21.3); isolated septal defects [(7) VSD only, (8) ASD only, (9) VSD and ASD only] [Q21.0 only, Q21.1 only, (Q21.0 and Q21.1) only; (10) complex defects (single ventricle) [Q20.4]; (11) conotruncal defects with AVSD {{[Q20.0, Q25.1A, Q25.2, Q25.3, Q25.4, Q20.3, Q21.3, Q20.1, (Q21.4 without Q21.1), (Q22.1 and Q21.0), (Q25.5 and Q21.0)] and Q21.2}; (12) septal defects with LVOTO (VSD and coarctation of aorta, VSD/ASD and aortic stenosis, VSD/ASD and coarctation of aorta) [(Q21.0 and Q25.1)]; (13) septal defects with RVOTO (ASD and PVS, VSD and PVD, VSD/ASD and PVS) [Q21.1, Q21.0 and Q22.1, (Q21.1 and Q22.1, Q21.0 and Q22.1 and Q21.0 and Q22.1)]; (14 & 15) patent ductus arteriosus (Q25.0 only); (16) unspecified [Q24.9 only]; and (17) other specified heart defects.