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Association of maternal chronic disease with risk of congenital heart disease in offspring

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Abstract

Background: Information about known risk factors for congenital heart disease is scarce. In this population-based study, we aimed to investigate the relation between maternal chronic disease and congenital heart disease in offspring.

Methods: The study cohort consisted of 1 387 650 live births from 2004 to 2010. We identified chronic disease in mothers and mild and severe forms of congenital heart disease in their offspring from Taiwan's National Health Insurance medical claims. We used multivariable logistic regression analysis to assess the associations of all cases and specific types of congenital heart disease with various maternal chronic diseases.

Results: For mothers with the following chronic diseases, the overall prevalence of congenital heart disease in their children was significantly higher than for mothers without these diseases: diabetes mellitus type 1

(adjusted odds ratio [OR] 2.32, 95% confidence interval [CI] 1.66–3.25), diabetes mellitus type 2 (adjusted OR 2.85, 95% CI 2.60–3.12), hypertension (adjusted OR 1.87, 95% CI 1.69–2.07), congenital heart defects (adjusted OR 3.05, 95% CI 2.45–3.80), anemia (adjusted OR 1.31, 95% CI 1.25–1.38), connective tissue disorders (adjusted OR 1.39, 95% CI 1.19–1.62), epilepsy (adjusted OR 1.37, 95% CI 1.08–1.74) and mood disorders (adjusted OR 1.25, 95% CI 1.11–1.41). The same pattern held for mild forms of congenital heart disease. A higher prevalence of severe congenital heart disease was seen only among offspring of mothers with congenital heart defects or type 2 diabetes.

Interpretation: The children of women with several kinds of chronic disease appear to be at risk for congenital heart disease. Preconception counselling and optimum treatment of pregnant women with chronic disease would seem prudent.

Congenital heart disease is the most common congenital disorder in newborns. Prevalence at birth ranges from 5 to 15 per 1000 live births.[1–4]

Despite advances in pediatric cardiac diagnosis and medical care, congenital heart disease remains the leading cause of perinatal and infant death due to congenital malformations.[5,6] However, little information is available about the risk factors, especially modifiable environmental and behavioural factors that may have adverse effects on fetal cardiac development; this lack of information represents a great obstacle in the prevention of congenital heart disease. One earlier study suggested that the proportion of cases attributable to these external factors might be as high as 30% for certain types of congenital heart disease.[7] Periconceptional intake of multivitamin supplements containing folic acid may reduce the risk in offspring.[8,9] Maternal lifestyle

factors, including cigarette smoking, alcohol consumption and obesity, have also been associated with risk of congenital heart disease.[10–12] It is also well established that maternal rubella infection during pregnancy can result in offspring with various congenital heart diseases.[13]

Available information about the association of maternal chronic diseases with congenital heart disease is limited. Pregnant women with congenital heart defects are at increased risk of certain congenital heart conditions in their offspring.[14] Additionally, such diseases in offspring have been associated with maternal pregestational and (less consistently) gestational diabetes.[15–17] One recent population-based study reported that a number of maternal chronic diseases, including diabetes mellitus, hypertension, connective tissue disorders and congenital heart disease, were associated with an increased risk of congenital heart disease in the offspring.[18] However, differences

in incidence and survival among different ethnic groups and geographic areas could be attributable to the variable genetic and environmental backgrounds associated with different locations.[19,20]

We conducted a nationwide population-based study in Taiwan to further evaluate the potential role of maternal chronic diseases in the risk of congenital heart disease in offspring.

Methods

Data sources

We used data from the Taiwan Maternal and Child Health Database, a nationwide population-based data set established, updated and supervised by the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan.[21] These data comprise several registration data sets, including Birth Registrations (2004–2011), Birth Notifications (2004–2011), Mortality Registrations (2004–2011) and medical claims of the National Health Insurance program (1998–2011); they cover 99% of Taiwanese residents and non-Taiwanese individuals permitted to work and study in Taiwan and can be interlinked through encrypted personal identification numbers.

Details of the Taiwan Maternal and Child Health Database have been described elsewhere.[22] Information from the database has been validated, and a high level of completeness and validity was observed for most of its components.[23] For the current study, we used all of the component data sets except Mortality Registrations. The Birth Notifications data set provides information on prenatal care and the lifestyle of pregnant women, as well as data on stillbirths and newborn characteristics recorded at birth (e.g., congenital abnormalities and Apgar scores). In Taiwan, it is a legal requirement that all live births and deaths be registered within 10 days. The Birth Registrations data set consists of the sociodemographic characteristics of live births (e.g., infant's sex, birth weight and gestational age; single v. multiple births; and birth order) and of the parents (e.g., age at delivery, education and marital status).

Taiwan's National Health Insurance program was implemented in March 1995, and up to 99% of the country's 23 million residents receive medical care through this program. More than 96% of hospitals (including more than 100 regional and tertiary care hospitals) and clinics in Taiwan are contracted to provide health care services that are reimbursed by the National Health Insurance Administration.[24] For this study, we used both inpatient and outpatient medical claims data from the National Health Insurance program, which provided information on diagnoses and procedures for each clinical visit and admission.

Study design and participants

Our study was a population-based, nationwide cohort study of live births in Taiwan between 2004 and 2010. For inclusion in the study, gestational age had to be greater than 22 weeks and birth weight had to be at least 500 g, to avoid including live births with an implausible gestational age or birth weight.[25]

Exposure variables

We identified chronic diseases diagnosed in the mothers before pregnancy from both inpatient and outpatient claims, using codes from the clinical modification of the International Classification of Diseases, 9th Revision (ICD-9-CM; see Table A1 in Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160061/-/DC1). These conditions included pregestational diabetes (both type 1 and type 2), hypertension, congenital heart defects, thyroid disorders, anemia, systemic connective tissue disorders, epilepsy and specific psychologic disorders. We considered these chronic diseases primarily because they were suspected of being associated with congenital heart disease in previous studies.[14,16–18]

Outcome variables

The outcome variables were any form of congenital heart disease in an infant, as identified by ICD-9-CM codes (see Table A2 in Appendix 1). To avoid including clinically nonsignificant forms or spontaneously resolved defects, we included only those children in whom the lesions were recorded during at least one hospital admission or during more than 3 outpatient clinic visits within 1 year after birth.[4,26] We defined 2 subgroups according to severity. Tetralogy of Fallot, transposition of the great arteries, double outlet of right ventricle, total anomalous pulmonary venous return, tricuspid atresia, congenital corrected transposition of great arteries, common truncus and common ventricles were classified as severe; all other lesions were classified as mild.

Confounders

The potential confounders considered in this study were found, in previous studies, to be potentially associated with the risk of congenital heart disease.[14,16–18] These potential confounders were classified into 3 categories: characteristics of the delivery, sociodemographic and lifestyle characteristics of the mother and characteristics of the infant.

The characteristics of delivery included the type of delivery (single or multiple births) and parity. The maternal sociodemographic and lifestyle characteristics included cigarette smoking and alcohol use, nationality, level of education, age at delivery and father's age at delivery.

According to information from Taiwan's Ministry of the Interior, Chinese individuals from mainland China accounted for the majority of non-native Taiwanese mothers (64.6%), followed by Vietnamese (21.2%) and Indonesian (4.4%) individuals.[27] The evaluated characteristics of infants included sex, year of birth and geographic location of the birth site. Adjustments for geographic locations were made to account for possible geographic variations in diagnostic techniques and frequency of screening for congenital heart disease in Taiwan.[28] These adjustments may help to reduce the effect of urban–rural differences in accessibility to medical health services in Taiwan.[29] In turn, these adjustments may help to reduce the effect of differences in ascertainment bias by geography.

Statistical analysis

We calculated the prevalence of all and specific types of congenital heart disease from 2004 to 2010 and used the Poisson regression model to test for trends in the biannual prevalence of these diseases. We assessed the prevalence values for all and specific types of congenital heart disease in association with maternal chronic diseases present before pregnancy, we adjusted for potential confounders using logistic regression models, and we reported the results as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Because a mother might have had more than one delivery during the 7-year study period and because there could be geographic clustering of infants' congenital heart diseases, we used a logistic regression model with the generalized estimating equation to account for within-participant correlations of offspring born to the same mothers and offspring residing in the same geographic area to obtain robust standard error estimates.[30]

To assess the potential effect of maternal chronic disease on risk of congenital heart disease in the offspring, we calculated the percent population attributable risk (i.e., the proportion of cases that would have been avoided in the population if the selected maternal chronic disease had been eliminated).[31] The statistical analysis was performed using SAS software, version 9.3 (SAS Institute), and a 2-tailed p value less than 0.05 was considered statistically significant.

Ethics approval

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (B-ER-102-120-t). The privacy of all patients was protected by the encryption of personal identification numbers; therefore, informed consent was not required.

Results

Risk of congenital heart disease

After excluding stillbirths and live births with gestational age less than 22 weeks or birth weight less than 500 g, we identified 1 387 650 live births (delivered by 1 059 772 mothers) in Taiwan between 2004 and 2010 (Figure 1). For a total of 27 240 live births, congenital heart disease was diagnosed during infancy, representing an overall prevalence of 19.63 per 1000 live births. After exclusion of infants with isolated patent ductus arteriosus born before 37 weeks of gestation, the overall prevalence was reduced to 16.92 per 1000 live births (Table 1). The prevalence rate of severe forms was 1.35 per 1000 live births and that of mild forms was 16.57 per 1000 live births (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160061/-/DC1). Among the severe conditions recorded, tetralogy of Fallot (0.58 per 1000 live births), transposition of great arteries (0.42 per 1000 live births) and double outlet of the right ventricle (0.23 per 1000 live births) were the 3 most numerous. Atrial septal defect (10.29 per 1000 live births), patent ductus arteriosus (5.19 per 1000 live births) and ventricular septal defect (4.92 per 1000 live births) accounted for most of the mild forms of congenital heart disease.

There was no significant secular trend in the overall prevalence of congenital heart disease during the study period (Table 1). However, the prevalence of severe forms showed a significantly declining trend (p for trend < 0.001), from 1.52 per 1000 live births in 2004–2005 to 1.11 per 1000 live births in 2010. A significant declining trend was also noted for specific types, including transposition of great arteries, common ventricle, hypoplastic left heart syndrome, common truncus and tricuspid atresia. No significant time trend was observed for the prevalence of mild congenital heart disease, but the prevalence of certain mild forms, including atrial septal defect, patent ductus arteriosus (≥ 37 wk) and pulmonary stenosis, showed significant variations over the study period.

Associations between maternal chronic disease and congenital heart disease in offspring

The prevalence and adjusted ORs for congenital heart disease in relation to parental and infant characteristics are shown in Appendix 1 (see Table A3). Several maternal chronic diseases, specifically type 1 and type 2 diabetes, hypertension, congenital heart defects, anemia, connective tissue disorders, epilepsy and mood disorders, were significantly associated with a

higher prevalence of any form of congenital heart disease in the offspring (Table 2). The maternal chronic diseases that were significantly associated with mild forms of congenital heart disease in offspring were the same as those significantly associated with all congenital heart diseases (Table 3). However, only maternal congenital heart defects (adjusted OR 6.72, 95% CI 4.06–11.12) and type 2 diabetes (adjusted OR 2.80, 95% CI 2.04–3.85) were associated with a significantly higher prevalence of severe congenital heart disease in the offspring (Table 3).

Population attributable risk for all congenital heart disease

The presence of any of the chronic diseases investigated here was associated with a population attributable risk of 5.73%. The highest population attributable risk for a specific chronic disease was noted for anemia (2.17%), followed by type 2 diabetes (1.45%) and hypertension (0.71%) (Table 2).

Interpretation

In this population-based study, we identified a decreasing trend in the prevalence of severe but not mild congenital heart disease from 2004 to 2010 in Taiwan. We also found that several maternal chronic diseases, specifically type 1 and type 2 diabetes, hypertension, congenital heart defects, anemia, connective tissue disorders, epilepsy and mood disorders, were associated with a significantly higher prevalence of overall and mild forms of congenital heart disease in offspring. Only maternal congenital heart defects and type 2 diabetes were significant predictors of severe congenital heart disease in offspring. Although some maternal diseases were associated with congenital heart disease in offspring, caution should be applied in interpreting these associations, because the population attributable risks were very low.

The prevalence of congenital heart disease among Taiwanese infants was relatively higher than the prevalence reported from other countries, which has ranged from 5 to 15 per 1000 live births.[1–4] Apart from the influence of racial disparities, the increasing utilization of echocardiography in newborns in Taiwan, to facilitate the early diagnosis of mild congenital heart disease, is a possible explanation for this difference, especially in asymptomatic infants.[4,32]

Moreover, the prevalence of congenital heart disease in our study was higher than the prevalence reported in one previous local study, by Wu and associates,[4] who used only National Health Insurance claims in their analysis. Medical visits by infants under 60 days of age may be reimbursed through National Health Insurance claims under the name of either the father or the mother; however, records for an infant's father and mother cannot be accessed simultaneously. This situation results in incomplete coverage of medical visits by infants with congenital heart disease.[33] Because such infants (especially those with severe forms) tend to
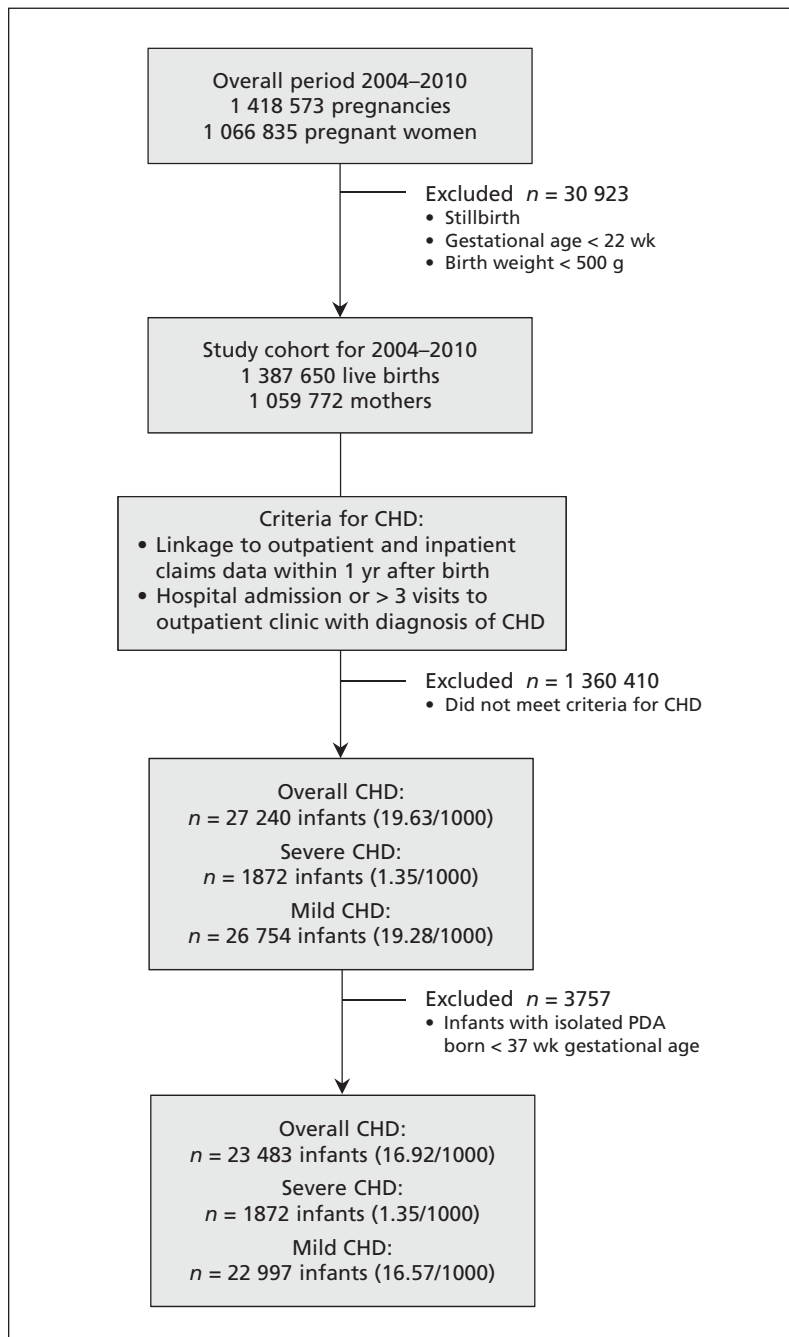

Figure 1: Flow diagram of the study cohort (2004–2010) and identification of infants with congenital heart disease (2004–2011). The overall number of infants with congenital heart disease is less than the sum of those with severe and mild forms because some infants had multiple forms of disease, both mild and severe. Note: CHD = congenital heart disease, PDA = patent ductus arteriosus.

experience a higher mortality rate in early life, incomplete coverage of all clinical visits for congenital heart disease could lead to underestimation of prevalence. The current study may not be subject to such underestimation, because we used the Taiwan Maternal and Child Health Database (specifically the Birth Registrations and Birth Notifications data sets), in addition to National Health Insurance claims; we were therefore able to obtain complete medical claims data for infants.

It was not clear why the prevalence of severe congenital heart disease showed a decreasing trend over time. One possible explanation is that more frequent utilization of antenatal diagnostic techniques, especially fetal echocardiography, led more parents to terminate pregnancies with known severe cardiac abnormalities. A previous study found that earlier diagnosis of congenital heart disease was associated with an average 1.4-fold increase in the probability of termination.[34]

In this study, maternal congenital heart defects were associated with an approximately 3-fold higher rate of congenital heart disease in offspring, consistent with reports from previous studies.[14,18] Genetic predisposition may have played an important role in this association. Many previous studies have identified significant associations between maternal pregestational type 1 and type 2 diabetes and the risk of congenital heart disease in offspring[16–18] and have shown that poor glycemic control in the first trimester of pregnancy is associated with an increased risk of congenital heart disease.[16] Additionally, researchers have postulated a genetic and environmental interaction that leads to disruption of fetal heart development due to the teratogenic impact of high blood glucose levels during the early stages of embryogenesis, especially before the seventh week of gestation.[16,35]

In one previous study, there was a 20%–30% increase in the risk of congenital heart disease in the offspring of mothers with a history of hypertension,[36] which was in accordance with our results. Chronic hypertension can result in

Table 1: Prevalence rates of overall and specific types of congenital heart disease (CHD) among live births in Taiwan, 2004 to 2010 (excluding isolated patent ductus arteriosus in preterm infants)

| Type of CHD | Total no. | Period; prevalence per 1000 live births | | | | | p for trend |
		2004–2005	2006–2007	2008–2009	2010	2004–2010	
Overall	23 483	17.24	16.82	16.33	17.75	16.92	0.4
Severe CHD	1 872	1.52	1.41	1.20	1.11	1.35	< 0.001
Tetralogy of Fallot	810	0.65	0.59	0.53	0.55	0.58	0.06
Transposition of great arteries	583	0.46	0.49	0.37	0.28	0.42	0.001
Double outlet of right ventricle	320	0.24	0.28	0.21	0.15	0.23	0.07
Total anomalous pulmonary venous return	224	0.16	0.17	0.02	0.14	0.16	0.7
Common ventricle	152	0.11	0.15	0.09	0.05	0.11	0.03
Hypoplastic left heart syndrome	142	0.12	0.13	0.08	0.06	0.10	0.008
Common truncus	129	0.11	0.11	0.08	0.05	0.09	0.01
Tricuspid atresia	118	0.13	0.06	0.07	0.06	0.09	< 0.001
Congenital corrected transposition of great arteries	34	0.03	0.02	0.03	0.02	0.03	0.6
Mild CHD	22 997	16.80	16.49	16.02	17.49	16.57	0.8
Atrial septal defect	14 284	10.34	9.99	9.88	11.89	10.29	0.009
Patent ductus arteriosus (≥ 37 wk)	7 197	5.84	5.03	4.65	5.15	5.19	< 0.001
Ventricular septal defect	6 830	4.85	5.14	4.93	4.57	4.92	0.4
Pulmonary stenosis	2 679	2.10	2.05	1.68	1.77	1.93	< 0.001
Coarctation of aorta	656	0.48	0.46	0.45	0.55	0.47	0.7
Endocardial cushion defect	325	0.26	0.23	0.24	0.20	0.23	0.2
Aortic stenosis	221	0.13	0.16	0.18	0.19	0.16	0.08
Ebstein anomaly	62	0.05	0.04	0.05	0.03	0.05	0.8
Cor triatriatum	26	0.02	0.02	0.02	0.02	0.02	0.8

uteroplacental insufficiency, which leads to compromised blood flow to the developing fetus and increases the risk of congenital heart disease if present early in the pregnancy. Moreover, mothers exposed to certain antihypertensve drugs are at increased risk of delivering infants with cardiovascular malformations.[37]

The current study also showed that maternal epilepsy and mood disorders were associated with an increased risk of congenital heart disease in infants. Previous studies have shown

that the use of certain anticonvulsants,[38] tranquilizers[39] or hypnotics[40] is associated with an increased risk of congenital heart disease in offspring. Maternal exposure to certain therapeutic drugs might therefore be a possible explanation for the increased risk among mothers with epilepsy and mood disorders.

Our study also showed that maternal anemia and connective tissue disorders were associated with an increased risk of congenital heart disease in offspring. Similar results were reported

Table 2: Prevalence rates and odds ratios for all congenital heart disease (CHD) in offspring in relation to maternal chronic diseases

Maternal chronic disease	No. of offspring with CHD (n = 23 483)	Prevalence per 1000 live births (95% CI)	OR (95% CI)		PAR, %
			Unadjusted	Adjusted*	
Diabetes mellitus, type 1					
No	23 039	16.9 (16.7–17.1)	Reference	Reference	
Yes	444	111.7 (81.1–150.1)	7.39 (5.41–10.10)	2.32 (1.66–3.25)	0.04
Diabetes mellitus, type 2					
No	22 845	16.6 (16.4–16.8)	Reference	Reference	
Yes	638	57.9 (53.5–62.6)	3.65 (3.36–3.97)	2.85 (2.60–3.12)	1.45
Hypertension					
No	23 000	16.7 (16.5–16.9)	Reference	Reference	
Yes	483	42.1 (38.4–46.0)	2.59 (2.36–2.84)	1.87 (1.69–2.07)	0.71
Thyroid disorders					
No	23 153	16.9 (16.7–17.1)	Reference	Reference	
Yes	330	19.1 (17.0–21.2)	1.13 (1.01–1.26)	1.00 (0.89–1.12)	0.01
Congenital heart defects					
No	23 380	16.9 (16.7–17.1)	Reference	Reference	
Yes	103	54.7 (44.7–66.4)	3.31 (2.69–4.08)	3.05 (2.45–3.80)	0.28
Anemia					
No	21 270	16.5 (16.3–16.7)	Reference	Reference	
Yes	2 213	22.3 (21.4–23.2)	1.35 (1.29–1.42)	1.31 (1.25–1.38)	2.17
Connective tissue disorders					
No	23 302	16.9 (16.7–17.1)	Reference	Reference	
Yes	181	25.4 (21.8–29.3)	1.52 (1.31–1.76)	1.39 (1.19–1.62)	0.20
Epilepsy					
No	23 404	16.9 (16.7–17.1)	Reference	Reference	
Yes	79	24.3 (19.2–30.2)	1.45 (1.16–1.82)	1.37 (1.08–1.74)	0.09
Mood disorders					
No	23 144	16.9 (16.6–17.1)	Reference	Reference	
Yes	339	23.8 (21.4–26.5)	1.42 (1.27–1.59)	1.25 (1.11–1.41)	0.26
Any of the above					
No	19 374	16.1 (15.8–16.3)	Reference	Reference	
Yes	4109	26.2 (25.4–27.0)	1.59 (1.54–1.65)	1.55 (1.49–1.61)	5.73

Note: CI = confidence interval, OR = odds ratio, PAR = population attributable risk.
*Estimated from a multiple logistic regression model with the generalized estimating equation, with adjustment for maternal nationality, parental age, level of parental education, birth order, single v. multiple births, sex of the infant, infant's year of birth, urbanization of the birth site, and maternal smoking and alcohol consumption.

by Liu and associates.[18] Anemia is a complex condition that must be studied carefully to determine the underlying causes and the possibility of confounding by other factors associated with inadequate multivitamin or folate supplementation, such as malnutrition. However, the specific reasons for these findings are unknown, and further research is needed. Finally, the factors underlying the association between maternal connective tissue disorders and congenital heart disease in offspring are as yet unknown. Future studies should be conducted to support or refute this finding.

Strengths and limitations

This study was based on a large sample, which allowed reliable assessment of relations between maternal chronic diseases and specific types of

Table 3: Prevalence rates and odds ratios for mild and severe congenital heart disease (CHD) in offspring in relation to maternal chronic diseases

Maternal chronic disease	Mild CHD			Severe CHD		
	Prevalence per 1000 live births (95% CI)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Prevalence per 1000 live births (95% CI)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Diabetes mellitus, type 1						
No	16.5 (16.3–16.8)	Reference	Reference	1.4 (1.3–1.4)	Reference	Reference
Yes	111.7 (81.1–149.9)	7.55 (5.52–10.32)	2.39 (1.70–3.35)	2.5 (0.1–14.1)	1.92 (0.27–13.63)	0.73 (0.10–5.32)
Diabetes mellitus, type 2						
No	16.3 (16.0–16.5)	Reference	Reference	1.3 (1.3–1.4)	Reference	Reference
Yes	56.5 (52.1–61.1)	3.63 (3.34–3.95)	2.82 (2.57–3.10)	4.0 (2.9–5.4)	3.04 (2.25–4.10)	2.80 (2.04–3.85)
Hypertension						
No	16.4 (16.2–16.6)	Reference	Reference	1.3 (1.3–1.4)	Reference	Reference
Yes	41.6 (37.9–45.5)	2.61 (2.37–2.86)	1.89 (1.70–2.09)	2.3 (1.5–3.4)	1.77 (1.21–2.59)	1.35 (0.90–2.02)
Thyroid disorders						
No	16.6 (16.3–16.8)	Reference	Reference	1.4 (1.3–1.4)	Reference	Reference
Yes	18.6 (16.6–20.7)	1.12 (1.01–1.26)	1.00 (0.89–1.12)	1.0 (0.6–1.6)	0.72 (0.45–1.17)	0.73 (0.45–1.18)
Congenital heart defects						
No	16.5 (16.3–16.7)	Reference	Reference	1.3 (1.2–1.4)	Reference	Reference
Yes	52.6 (42.8–64.0)	3.24 (2.62–4.01)	2.97 (2.37–3.71)	9.0 (5.3–14.5)	6.63 (4.06–10.83)	6.72 (4.06–11.12)
Anemia						
No	16.2 (15.9–16.4)	Reference	Reference	1.3 (1.2–1.4)	Reference	Reference
Yes	21.9 (21.0–22.8)	1.36 (1.30–1.42)	1.32 (1.26–1.38)	1.4 (1.2–1.7)	1.07 (0.90–1.27)	1.03 (0.86–1.23)
Connective tissue disorders						
No	16.5 (16.3–16.7)	Reference	Reference	1.4 (1.3–1.4)	Reference	Reference
Yes	25.4 (21.8–29.3)	1.55 (1.34–1.80)	1.42 (1.21–1.65)	1.1 (0.5–2.2)	0.83 (0.38–1.80)	0.88 (0.40–1.90)
Epilepsy						
No	16.6 (16.3–16.8)	Reference	Reference	1.4 (1.3–1.4)	Reference	Reference
Yes	24.3 (19.2–30.2)	1.48 (1.18–1.86)	1.39 (1.10–1.77)	1.8 (0.7–4.0)	1.37 (0.61–3.05)	1.18 (0.49–2.83)
Mood disorders						
No	16.5 (16.3–16.7)	Reference	Reference	1.4 (1.3–1.4)	Reference	Reference
Yes	23.4 (30.0–26.1)	1.43 (1.28–1.59)	1.26 (1.11–1.42)	1.7 (1.1–2.5)	1.25 (0.82–1.90)	1.20 (0.76–1.87)
Any of the above						
No	15.7 (15.5–15.9)	Reference	Reference	1.3 (1.3–1.4)	Reference	Reference
Yes	25.7 (24.9–26.5)	1.60 (1.54–1.66)	1.55 (1.50–1.61)	1.7 (1.5–1.9)	1.28 (1.12–1.46)	1.27 (1.10–1.46)

Note: CI = confidence interval, OR = odds ratio.
*Estimated from a multiple logistic regression model with the generalized estimating equation, with adjustment for maternal nationality, parental age, level of parental education, birth order, single v. multiple births, sex of the infant, infant's year of birth, urbanization of the birth site, and maternal smoking and alcohol consumption.

congenital heart disease. In addition, Taiwan's Birth Registrations data set was considered complete and valid in a previous study.[23]

Some limitations should be noted. We restricted the detection period to the first year of life, which may have resulted in under-identification of congenital heart disease that developed in later years. However, such under-identification would be minimal, given the high frequency of prenatal care[41] and health checkups during infancy[42] under National Health Insurance coverage in Taiwan. Although their prevalence was low, some maternal lifestyle factors, including smoking and alcohol consumption, are likely to be underreported in the Birth Notifications data set, relative to previous survey data.[43] There is also potential for residual confounding because of incomplete consideration of some essential nutritional elements associated with congenital heart disease, including folic acid and multivitamin supplementation,[8,9] These potential confounders were not available from the data source for this study. We used ICD-9-CM codes, which are not as specific as the ICD-10-CM codes;[18] this may have led to some misclassification of disease in both mothers and infants. Nonetheless, the prevalences reported here and in the study by Wu and associates,[4] who used similar criteria, were generally within the previously reported range.[44,45] Finally, the decision to exclude live births with birth weight less than 500 g or gestational age less than 22 weeks was based mainly on expert opinion. Such exclusions are expected to have little influence on our results, since a recent study from Taiwan estimated that the proportion of live births with birth weight less than 500 g was low (3.8 per 10 000).[46]

Conclusion

Maternal chronic diseases, including diabetes, hypertension, congenital heart disease, anemia, connective tissue disorders, epilepsy and mood disorders, may predispose mothers to deliver offspring with congenital heart disease. The results of the current study are of value for preconception counselling and identification of high-risk pregnant women. Women with such chronic diseases should control their disease to the extent possible before conception, to minimize the risk of congenital heart disease in their children. For pregnant women who are at high risk, more frequent prenatal screening (with fetal echocardiography) may be warranted. Early recognition of congenital heart disease also permits optimal preparation and care during pregnancy, delivery and the postnatal period.

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