

Effect of Folic Acid Food Fortification in Canada on Congenital Heart Disease Subtypes

BACKGROUND: Previous studies have yielded inconsistent results for the effects of periconceptional multivitamins containing folic acid and of folic acid food fortification on congenital heart defects (CHDs).

METHODS: We carried out a population-based cohort study (N=5 901 701) of all live births and stillbirths (including late-pregnancy terminations) delivered at ≥ 20 weeks' gestation in Canada (except Québec and Manitoba) from 1990 to 2011. CHD cases were diagnosed at birth and in infancy (n=72 591). We compared prevalence rates and temporal trends in CHD subtypes before and after 1998 (the year that fortification was mandated). An ecological study based on 22 calendar years, 14 geographic areas, and Poisson regression analysis was used to quantify the effect of folic acid food fortification on nonchromosomal CHD subtypes (n=66 980) after controlling for changes in maternal age, prepregnancy diabetes mellitus, preterm preeclampsia, multiple birth, and termination of pregnancy.

RESULTS: The overall birth prevalence rate of CHDs was 12.3 per 1000 total births. Rates of most CHD subtypes decreased between 1990 and 2011 except for atrial septal defects, which increased significantly. Folic acid food fortification was associated with lower rates of conotruncal defects (adjusted rate ratio [aRR], 0.73, 95% confidence interval [CI], 0.62–0.85), coarctation of the aorta (aRR, 0.77; 95% CI, 0.61–0.96), ventricular septal defects (aRR, 0.85; 95% CI, 0.75–0.96), and atrial septal defects (aRR, 0.82; 95% CI, 0.69–0.95) but not severe nonconotruncal heart defects (aRR, 0.81; 95% CI, 0.65–1.03) and other heart or circulatory system abnormalities (aRR, 0.98; 95% CI, 0.89–1.11).

CONCLUSIONS: The association between food fortification with folic acid and a reduction in the birth prevalence of specific CHDs provides modest evidence for additional benefit from this intervention.

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Sources of Funding, see page 653

Key Words: association ■ folic acid ■ heart defects, congenital ■ primary prevention

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Clinical Perspective

What Is New?

- Food fortification with folic acid, mandated in Canada in 1998, was aimed primarily at preventing neural tube defects, and its effect on congenital heart defects (CHDs) remains controversial.
- We studied ≈6 million Canadian births from 1990 to 2011 to quantify the effects of folic acid food fortification on the birth prevalence of specific non-chromosomal CHD subtypes after controlling for concomitant changes in maternal age, prepregnancy diabetes mellitus, preterm preeclampsia, multiple birth, and pregnancy termination.

What Are the Clinical Implications?

- Overall, there was an 11% reduction in nonchromosomal CHDs after folic acid food fortification.
- Specifically, folic acid food fortification was associated with a 27% (95% confidence interval, 15–38) reduction in conotruncal defects, a 23% (95% confidence interval, 4–39) reduction in coarctation of the aorta, a 15% (95% confidence interval, 4–25) reduction in ventricular septal defects, and an 18% (95% confidence interval, 5–31) reduction in atrial septal defects. These effects were also seen when analyses were restricted to isolated CHD cases.
- Our ecological study provides modest evidence of a protective effect of folic acid food fortification on CHDs.

Congenital heart defects (CHDs) affect ≈1% of newborns and account for approximately one-third of infant deaths associated with congenital anomalies.^{1–5} Despite extensive investigation into potential causes and risk factors, only a small percentage of cases (15%) have been definitively linked to a known cause.^{6–8} One intervention with potential for preventing CHDs is periconceptional folic acid supplementation.^{9–17} Analysis of secondary outcomes in a Hungarian randomized trial showed that the birth prevalence of congenital cardiovascular anomalies was reduced among women offered periconceptional multivitamin (including folic acid) and trace element supplementation compared with women offered supplemental trace elements only.^{9–11} However, nonexperimental studies have yielded inconsistent results for the effectiveness of periconceptional multivitamins containing folic acid and of folic acid fortification on the birth prevalence of CHDs.^{14–23}

Folic acid fortification of all types of flour, enriched pasta, and cornmeal became mandatory in Canada in November 1998. Previous studies from Canada have shown that food fortification with folic acid has resulted in a substantial reduction in the birth prevalence of neural tube defects.^{24,25} Such fortification also has been associ-

ated with a reduction in the birth prevalence of severe conotruncal CHDs but not of other less severe types of CHDs.¹⁸ However, these assessments of the effect of folic acid food fortification and periconceptional folic acid supplements did not adequately account for simultaneous changes in other known risk factors for CHDs.^{5–8,26–29} Therefore, we carried out a study to assess the effect of folic acid food fortification on CHDs using a design that accounted for temporal changes in older maternal age, prepregnancy diabetes mellitus, preterm preeclampsia, multiple birth, and prenatal diagnosis of and pregnancy termination for lethal congenital anomalies.

METHODS

Study Population

The study was based on hospital separation records obtained from the Discharge Abstract Database of the Canadian Institute for Health Information for 1990 to 2011. This database captures information from all hospitals in Canada (excluding Québec) and includes ≈98% of live births and stillbirths (ie, fetal deaths delivered at ≥20 weeks of gestation or ≥500-g birth weight).^{5,30} Information in the database includes maternal characteristics and postal code of residence, infant sex, birth weight, gestation, most responsible diagnosis, secondary and other diagnoses, and procedures performed during the hospitalization. Data for the province of Manitoba, which were not fully captured until 2003, were excluded from the study.

Case Ascertainment and Classification of CHDs

Up to fiscal year 2000 to 2001, diagnoses in the Discharge Abstract Database were coded according to the *International Classification of Diseases, Ninth Revision (ICD-9)*, with the *Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems for Diagnoses (ICD-10)* being adopted by Canadian hospitals in 2001 to 2002. The validity of information in the Discharge Abstract Database is assessed continually through abstraction and other studies.^{30,31} These studies show that the diagnosis of CHDs is accurate and that the transition of the coding system from *ICD-9* to *ICD-10* did not materially affect the coding of CHDs.^{5,18,28}

CHDs among all live births, stillbirths (including pregnancy terminations), and infants readmitted in the first year after birth were ascertained by the use of *ICD-9* codes for diagnoses from 1990 to 2001 to 2002 (745.0–747.9), after which *ICD-10* codes (Q20.0–Q26.9) were used. All CHD cases were then classified into the following 6 categories by grouping *ICD* codes in hierarchical fashion, as previously proposed^{4–6,8,18}: (1) conotruncal defects consisting of common truncus (745.0/Q20.0 and Q21.4), transposition of great vessels (745.1/Q20.1–Q20.3 and Q20.5), and tetralogy of Fallot (745.2/Q21.3); (2) nonconotruncal defects including endocardial cushion defects (745.6/Q21.2), common ventricle (745.3/Q20.4), and hypoplastic left heart syndrome (746.7/Q23.4); (3) coarctation of the aorta (747.1/Q25.1); (4) ventricular septal defect (745.4/Q21.0 and Q21.8); (5) atrial septal defect (745.5/Q21.1), and (6) other heart and circulatory system anomalies (ie, *ICD* codes for CHDs excluding the above-mentioned 5 categories). The first 3 categories made up the severe CHD

subtypes. Pregnancy terminations resulting from congenital anomalies were included among stillbirths, although they could not be identified separately until 1997 in our data source.

Food fortification with folic acid was the intervention of interest, and births from January 1999 on were considered exposed to this intervention. This time point was chosen for demarcating the onset of food fortification with folic acid because mandatory food fortification with folic acid began in November 1998. However, many food producers began fortification with folic acid well before the mandatory period.^{18,24,25,32}

Statistical Analysis

We first assessed temporal trends in the birth prevalence of all CHDs by specific CHD subtypes. Analyses also were carried out among CHD cases not associated with a chromosomal anomaly and among CHD cases associated with a chromosomal anomaly to delineate potential differences among CHD cases with a genetic pathogenesis.^{6,7,21,33} Our assessment of the effect of folic acid food fortification was designed as an ecological Poisson regression analysis with spatiotemporal variations in the incidence of specific CHD subtypes between 1990 and 2011 described as a function of maternal age, prepregnancy diabetes mellitus, preterm preeclampsia, multiple birth, termination of pregnancy, and folic acid food fortification. Food fortification with folic acid was represented in the model using a dichotomous variable (0 for the prefortification period, 1 for postfortification period).^{34,35} The maternal age distribution was modeled using the proportion of women with a maternal age of <20, 20 to 24, 30 to 34, 35 to 39, and ≥40 years. The rates of prepregnancy diabetes mellitus and multiple birth were modeled per 1000 total births. The rate of pregnancy termination for congenital anomalies was estimated with the use of a proxy variable, namely the rate of stillbirths with known birth weight <500 g per 1000 total births. This proxy variable includes a substantial and increasing fraction of late-pregnancy terminations for prenatally diagnosed congenital anomalies.^{5,26,27,36,37} Data were stratified according to geographic area of maternal residence (14 strata: 5 regions in Ontario; 2 in Alberta; 2 in British Columbia; 1 for Saskatchewan, New Brunswick, and Newfoundland each; 1 for Nova Scotia and Prince Edward Island combined; and 1 for the Northwest Territories, Yukon, and Nunavut combined) and year (9 strata from 1990–1998, 13 strata from 1999–2011), resulting in 126 strata for the prefortification period and 182 strata for the post-food fortification period. Goodness of fit of the Poisson regression model was assessed with deviance statistics and the Pearson χ^2 test, and variance estimates were corrected for overdispersion through appropriate scaling.

In secondary analyses, we examined the effect of folic acid fortification on the basis of isolated CHD subtypes (ie, excluding CHD cases with other congenital anomalies⁹). These analyses were carried out because we suspected that women whose fetuses had multiple congenital anomalies would be more likely to have a pregnancy termination and because other congenital anomalies such as neural tube defects and orofacial clefts are known to be affected by maternal multivitamin use or folic acid food fortification.^{13–15,38} All the above analyses were done with SAS version 9.2 (SAS Institute, Cary, NC).

In other analyses, we used Joinpoint regression (also known as change point analysis), which detects points of deviation

(joinpoints) from a linear slope, to assess temporal patterns.^{38,39} This analytic approach was used to identify the time point when CHD birth prevalence began to change. The regression identifies significant change points by performing several permutation tests and assessing these in terms of goodness of fit. We used the National Cancer Institute's Joinpoint Regression Program version 4.3.0.0 for the crude and fully adjusted rates of conotruncal defects from 1990 to 2011.⁴⁰

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 Québec); therefore, institutional review board approval was not required.

RESULTS

Between 1990 and 2011, the Canadian hospitalization database recorded 5 901 701 total births, with 72 591 CHD cases identified among stillbirths (8.6%), live births during the childbirth admission (69.7%), or infants during subsequent hospital readmissions (21.7%). The overall birth prevalence of CHDs was 12.3 per 1000 total births. Among all CHDs, 20% were severe CHD subtypes, and ventricular and atrial septal heart defects accounted for nearly half of the cases (47.5%; Table 1).

Overall, the prevalence of CHDs declined over the 22 years of the study, with rates of most CHD subtypes, including conotruncal heart defects, decreasing significantly, but rates of atrial septal defects increased substantially. Specifically, rates of conotruncal heart defects decreased from 13.1 per 10 000 total births in 1990 to 10.1 per 10 000 total births in 2011. On the other hand, rates of atrial septal defects increased from 18.7 per 10 000 total births in 1990 to 33.2 per 10 000 total births in 2011 (Figure). Rates of older maternal age, prepregnancy diabetes mellitus, preterm preeclampsia, multiple birth, and pregnancy termination all increased from 1990 to 2011 (Figures I and II in the online-only Data Supplement).

Table 2 shows results of 3 Poisson regression models for conotruncal defect, atrial septal defect, and chromosomal anomaly-associated CHDs. The unadjusted rate ratio expressing the association between food fortification with folic acid and conotruncal defects was 0.78 (95% confidence interval [CI], 0.72–0.84); adjustment for other covariates strengthened this inverse association slightly (rate ratio, 0.73; 95% CI, 0.62–0.85). The association between folic acid food fortification and atrial septal defects changed substantially after adjustment for other covariates (crude rate ratio, 1.21; 95% CI, 1.11–1.31; adjusted rate ratio, 0.82; 95% CI, 0.69–0.95; Table 2). The reversal in the effect of folic acid food fortification on atrial septal defects was due almost entirely to adjustment for maternal age (rate ratio for folic acid food fortification adjusted for maternal age only, 0.80; 95% CI, 0.67–0.94). Adjustment for maternal age

Table 1. Distribution and Prevalence of CHD, Canada (Excluding Québec and Manitoba), 1990 to 2011

CHD Category*	Stillbirths, n†	Live Births, n	Follow-up in Infancy, n	Total Cases, n	Frequency of CHD	
					Proportion, %	Rate per 1000 Total Births, n
Conotruncal defects	623	644	1971	7238	10.0	1.23
Severe nonconotruncal defects	428	2202	1567	4197	5.8	0.71
Coarctation of the aorta	235	2108	1041	3384	4.7	0.57
Ventricular septal defect	1660	11 867	4582	18 109	24.9	3.07
Atrial septal defect	1357	10 316	4772	16 445	22.6	2.79
Other heart and circulatory system anomalies	1931	19	1814	23 218	32.0	3.93
Total	6234 (8.6)	50 610 (69.7)	15 747 (21.7)	72 591 (100.0)	100.0	12.3

CHD indicates congenital heart defect.

*CHD cases were divided into 6 categories based on an hierarchical algorithm.

†Including pregnancy terminations at ≥ 20 wk and < 500 -g birth weight.

had a far less dramatic influence on the association with other CHD subtypes. Rates of both conotruncal defects and atrial septal defects were positively and significantly associated with the rates of preterm preeclampsia and prepregnancy diabetes mellitus in adjusted models. Chromosomal anomaly-associated CHDs were not associated with folic acid food fortification (adjusted rate ratio, 0.97; 95% CI, 0.82–1.14).

Table 3 summarizes the results of Poisson regression for the 6 specific subtypes of CHDs and for all nonchromosomal CHDs combined, presenting both the unadjusted and adjusted associations between food fortification with folic acid and each CHD subtype. The unadjusted inverse associations were all statistically significant ex-

cept for the nonsignificant association with severe nonconotruncal defects and the association between food fortification with folic acid and atrial septal defects, which was positive and statistically significant. Adjustment for maternal age, prepregnancy diabetes mellitus, preterm preeclampsia, multiple birth, and pregnancy termination showed that folic acid fortification was significantly and negatively associated with conotruncal heart defects, coarctation of the aorta, ventricular septal defects, and atrial septal defects but not nonconotruncal heart defects and other heart and circulatory system anomalies. Folic acid food fortification was associated with significantly lower rates of coarctation of the aorta (23% lower) and atrial and ventricular septal defects,

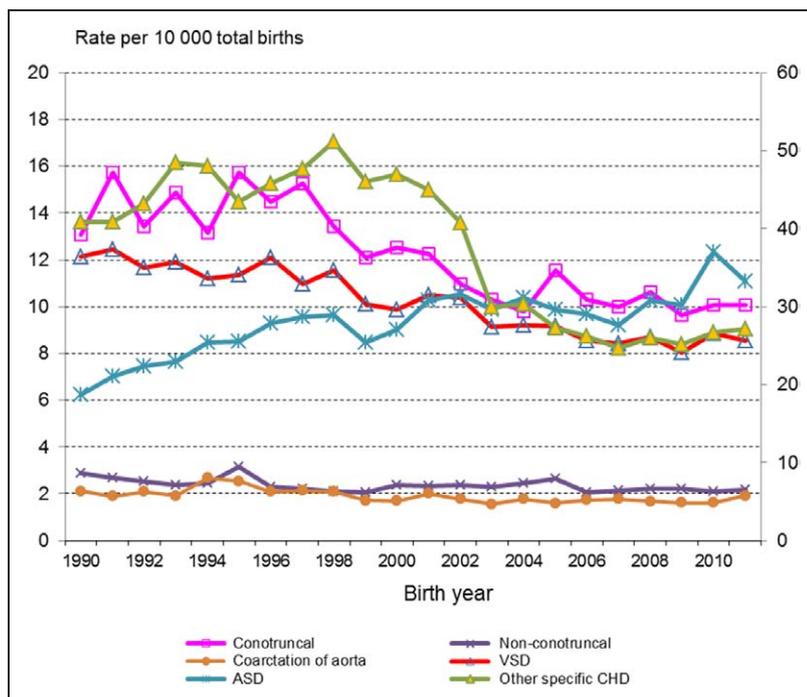


Figure. Temporal trends in congenital heart defects (CHDs) by subtype, Canada (excluding Québec and Manitoba), 1990 to 2011.

Left y axis, conotruncal defects, coarctation of aorta, and nonconotruncal defects. Right y axis, ventricular septal defect (VSD), atrial septal defect (ASD), and other heart and circulatory anomalies.

Table 2. Results of Poisson Regression Analysis Showing the Effect of Food Fortification With Folic Acid and Other Determinants on Rates of Conotruncal Heart Defects, Atrial Septal Defects, and CHD Cases With a Chromosomal Anomaly, Canada (Excluding Québec and Manitoba), 1990 to 2011

Determinant	Unadjusted Model*		Adjusted Model*	
	Rate Ratio	95% CI	Rate Ratio	95% CI
Conotruncal heart defect†				
Folic acid food fortification	0.78	0.72–0.84	0.73	0.62–0.85
Multiple birth rate	0.96	0.95–0.98	0.99	0.97–1.01
Pregnancy termination rate	0.94	0.92–0.97	1.00	0.97–1.04
Diabetes rate	1.01	0.99–1.03	1.02	1.00–1.03
Preterm preeclampsia	0.99	0.99–1.00	1.02	1.01–1.02
Atrial septal defect†				
Folic acid food fortification	1.21	1.11–1.31	0.82	0.69–0.95
Multiple birth rate	1.04	1.02–1.05	0.99	0.97–1.02
Pregnancy termination rate	1.05	1.02–1.08	1.01	0.98–1.05
Diabetes rate	1.04	1.03–1.06	1.02	1.01–1.04
Preterm preeclampsia	1.00	1.00–1.01	1.01	1.01–1.02
Chromosomal anomaly–associated CHD				
Folic acid food fortification	0.88	0.81–0.95	0.97	0.82–1.14
Multiple birth rate	0.98	0.96–0.99	0.99	0.96–1.02
Pregnancy termination rate	0.95	0.93–0.98	0.96	0.93–1.01
Diabetes rate	1.04	1.02–1.05	1.04	1.03–1.06
Preterm preeclampsia	1.00	0.98–1.02	1.02	1.01–1.04

CHD indicates congenital heart defect; and CI, confidence interval. Regression results, that is, rate ratios, represent the effect of unit change in the independent variable on the rate of conotruncal heart defects, atrial septal defects, and CHD cases with a chromosomal anomaly. Folic acid food fortification was represented with a dichotomous variable (0/1); the multiple birth, pregnancy termination, pregestational diabetes, and preterm preeclampsia rates were expressed per 1000 total births.

*Goodness of fit of the Poisson regression model was assessed with deviance statistics and the Pearson χ^2 , and variance estimates were corrected for overdispersion through appropriate scaling.

†Cases with chromosomal anomaly are not included.

which were 18% and 15% lower, respectively. Overall, food fortification with folic acid was associated with a significant 11% (95% CI, 2–18) reduction in nonchromosomal CHDs.

Secondary analyses based on isolated CHDs (ie, excluding 12.9% of CHDs that were associated with noncardiac defects) also showed that folic acid food fortification was inversely associated with CHD subtypes. Rate ratios from these regression analyses expressing the effect of folic acid food fortification on isolated CHD subtypes (Table 1 in the online-only Data Supplement) were not significantly different from the rate ratios in the primary analyses.

Crude Joinpoint analysis of rates of conotruncal defects (excluding cases with chromosomal anomalies) by year showed no change points (Figure 3Ia in the online-only Data Supplement). However, the adjusted analysis

showed that rates of conotruncal defects significantly declined by 8.2% (95% CI, 5.3–11.0) per annum from 1996 through 2003, after which the rate of decline slowed (Figure 3Ib in the online-only Data Supplement).

DISCUSSION

Our population-based study showed an inverse association between food fortification with folic acid and the overall birth prevalence of CHDs. The associations between folic acid food fortification and specific CHD subtypes varied, with relatively large reductions in the frequency of conotruncal defects and coarctation of the aorta, modest reductions in ventricular and atrial septal defects, and no change in nonconotruncal heart defects or other anomalies of the heart and circulatory system. The estimate of the effect of food fortification with folic

Table 3. Results of Poisson Regression Analysis Showing the Effect of Food Fortification With Folic Acid on Rates of Nonchromosomal CHD Subtypes, Canada (Excluding Québec and Manitoba), 1990 to 2011

Outcome	Unadjusted Model*				Adjusted Model*		
	Nonchromosomal CHDs, n	Rate Ratio	95% CI	P Value	Rate Ratio	95% CI	P Value
Conotruncal defect	6819	0.78	0.72–0.84	<0.0001	0.73	0.62–0.85	0.0002
Severe nonconotruncal defect	2957	0.93	0.83–1.03	0.157	0.81	0.65–1.03	0.086
Coarctation of the aorta	3157	0.84	0.77–0.93	0.003	0.77	0.61–0.96	0.022
Ventricular septal defect	17 075	0.79	0.75–0.84	<0.0001	0.85	0.75–0.96	0.013
Atrial septal defect	14 982	1.21	1.11–1.31	<0.0001	0.82	0.69–0.95	0.012
Other heart and circulatory anomalies	21 990	0.74	0.69–0.77	<0.0001	0.98	0.89–1.11	0.97
All nonchromosomal heart defects	66 980	0.87	0.83–0.91	<0.0001	0.89	0.82–0.98	0.031

CHD indicates congenital heart defects; and CI, confidence interval. The rate ratio expresses the effect of food fortification with folic acid. Independent variables in each of the adjusted models included food fortification with folic acid (yes/no) and the multiple birth, termination of pregnancy, prepregnancy diabetes, and preeclampsia rates (all per 1000 total births), as well as the proportion of women with a maternal age of <20, 20 to 24, 30 to 34, 35 to 39, and ≥ 40 years.

*Goodness of fit of the Poisson regression model was assessed with deviance statistics and the Pearson χ^2 , and variance estimates were corrected for overdispersion through appropriate scaling.

acid on each specific subtype of CHDs was similar in primary analyses involving all CHD cases and in secondary analyses restricted to isolated CHDs. This concordance provides further assurance that the estimated effect of folic acid food fortification excluded the influence of temporal increases in pregnancy termination for prenatally diagnosed CHDs, given the assumption that termination of pregnancy might occur more often in those cases with multiple anomalies.

The temporal trends in each congenital heart disease subtype showed a declining pattern, and unadjusted associations between folic acid food fortification and congenital heart disease subtypes were all protective except for atrial septal defects. Atrial septal defects increased over time, and the unadjusted rate ratio expressing the association between folic acid food fortification and atrial septal defects was 1.21 (95% CI, 1.11–1.31); however, adjustment for covariates, especially maternal age, changed the relationship between folic acid food fortification and atrial septal defects (adjusted rate ratio, 0.82; 95% CI, 0.69–0.95). Prepregnancy diabetes mellitus and older maternal age are well-known risk factors for atrial septal defects.^{7,8} Preterm preeclampsia was also associated with CHDs, as has recently been reported.^{28,29}

Several studies support a preventive role for folic acid in the occurrence of CHDs. A Hungarian study^{9,10} showed a 43% reduction in CHDs, whereas a population-based study from Atlanta¹⁴ showed a 24% reduction, albeit for multivitamin supplements including folic acid. The largest effects in these studies were seen in connection with ventricular septal defects and conotruncal heart defects. Similar reductions in CHDs after food for-

tification with folic acid have also been observed in studies from the Netherlands and Québec.^{18,20}

Our Poisson regression models estimated the effect of food fortification with folic acid on CHDs, assuming an effect beginning in 1999. However, the temporal pattern of reduction in the birth prevalence of conotruncal defects in the Joinpoint analyses was consistent with an effect beginning in 1996. Although this effect preceded the point when food fortification with folic acid became mandatory, it coincided with the period when food fortified with folic acid became available in Canada. The United States announced in February 1996 that folic acid fortification of food would become mandatory as of January 1, 1998, and after this announcement, such fortification of food with folic acid became permissible but not yet mandatory in Canada. White wheat flour, enriched pasta, and cornmeal products fortified with folic acid at the same levels as in the United States were sold in Canada well before 1998,^{18,24,25,32,41,42} and this was reflected in increases in blood levels of folic acid in the Canadian population well before food fortification became mandatory.^{25,32}

In our study, determinants other than food fortification with folic acid were also associated with CHDs; expected positive associations were noted between CHDs and both prepregnancy diabetes mellitus and preterm preeclampsia. Unexpectedly, we did not observe an association between multiple birth⁴³ and conotruncal defects or between pregnancy termination and conotruncal defects, the latter perhaps a consequence of our use of stillbirths <500-g birth weight as a proxy for pregnancy terminations. This proxy, although

a reasonable option for modeling late-pregnancy terminations (because stillbirths ≥ 20 weeks and < 500 g have increased substantially in recent years^{5,26,27,36,37}), cannot take into account early-pregnancy terminations. Another unexpected finding was the continued reduction in CHDs such as conotruncal defects for several years after the initiation of food fortification with folic acid. However, CHDs seem less folate sensitive than neural tube defects and may have required a longer period before population red blood cell folate levels rose to a level at which reductions in incidence were fully realized.

The underlying mechanism for the possible preventive effect of folic acid supplementation on CHDs has been explored for years. Studies show that both infant and maternal *MTHFR* C677T polymorphisms contribute to the risk of CHDs and that periconceptional folic acid supplementation reduces the risk of CHDs associated with maternal *MTHFR* C677T and related polymorphisms.⁴⁴ Recent studies also suggest that folic acid may influence the pathogenesis of CHDs through other more complex pathways, including epigenetic mechanisms that are responsible for transgenerational effects.⁴⁵ A possible implication of epigenetic mechanisms is that a beneficial effect of folic acid fortification in reducing the prevalence at birth of CHDs may take > 1 generation to become fully apparent.⁴⁵

The strengths of our study include its size, population-based provenance, and long (22 years) period of observation. CHD cases in our study included those diagnosed at birth and infants hospitalized in the year after birth. We used a pathogenesis-based grouping of CHDs^{6,8,18} rather than a severity-based grouping,²¹ which may have helped to better identify CHD subtypes amenable to prevention through folic acid food fortification.

The limitations of our study include an inability to assess the effects of temporal increases in supplementation with folic acid and multivitamins. Other limitations include potential deficiencies with our data source and the ecological design of our study (Both folic acid food fortification and CHDs were assessed in population groups, not individuals). This design is susceptible to confounding at both the ecological and individual levels. However, the consistency in results between the primary and secondary analyses, which examined non-chromosomal, chromosomal anomaly-associated, and isolated CHDs separately, and adjustment for various risk factors for CHDs provide assurance for the validity of the estimated effectiveness of food fortification with folic acid. We were not able to model the effects of maternal smoking and obesity because complete information on these risk factors was not available in our data source. According to the Canadian Community Health Survey, the prevalence of smoking among pregnant women declined by $\approx 25\%$ between 1993 to 1996 and 2009 to 2010.^{25,46}

CONCLUSIONS

Our study shows associations between food fortification with folic acid and reductions in the birth prevalence of specific CHD subtypes. The associations were stronger for conotruncal defects and coarctation of the aorta and more modest for septal defects. Older maternal age, prepregnancy diabetes mellitus, and preterm preeclampsia were also associated with population rates of CHDs. Although food fortification with folic acid was aimed primarily at reducing neural tube defects, this population-based intervention may also have had a beneficial effect on specific types of CHDs, which in aggregate are more common.

ACKNOWLEDGMENTS

We thank Robert Semenciw and Lin Xie (both with the Public Health Agency of Canada) for advice with statistical modeling and the Canadian Institute for Health Information for providing access to the Discharge Abstract Database at the Public Health Agency of Canada.

SOURCES OF FUNDING

This study was carried out under the auspices of the Canadian Perinatal Surveillance System of the Public Health Agency of Canada. Dr Joseph is supported by a chair award from the Canadian Institutes of Health Research (APR-126338) and an investigator award from the Child and Family Research Institute. Dr Little holds a Tier 1 Canada Research Chair in Human Genome Epidemiology. The views expressed in this article are those of the authors and do not represent those of the Public Health Agency of Canada or other funding bodies.

DISCLOSURES

None.

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FOOTNOTES

Received February 17, 2016; accepted June 27, 2016.

The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.022126/-/DC1>.

Circulation is available at <http://circ.ahajournals.org>.

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Effect of Folic Acid Food Fortification in Canada on Congenital Heart Disease Subtypes
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Circulation. 2016;134:647-655

doi: 10.1161/CIRCULATIONAHA.116.022126

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

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SUPPLEMENTAL MATERIAL

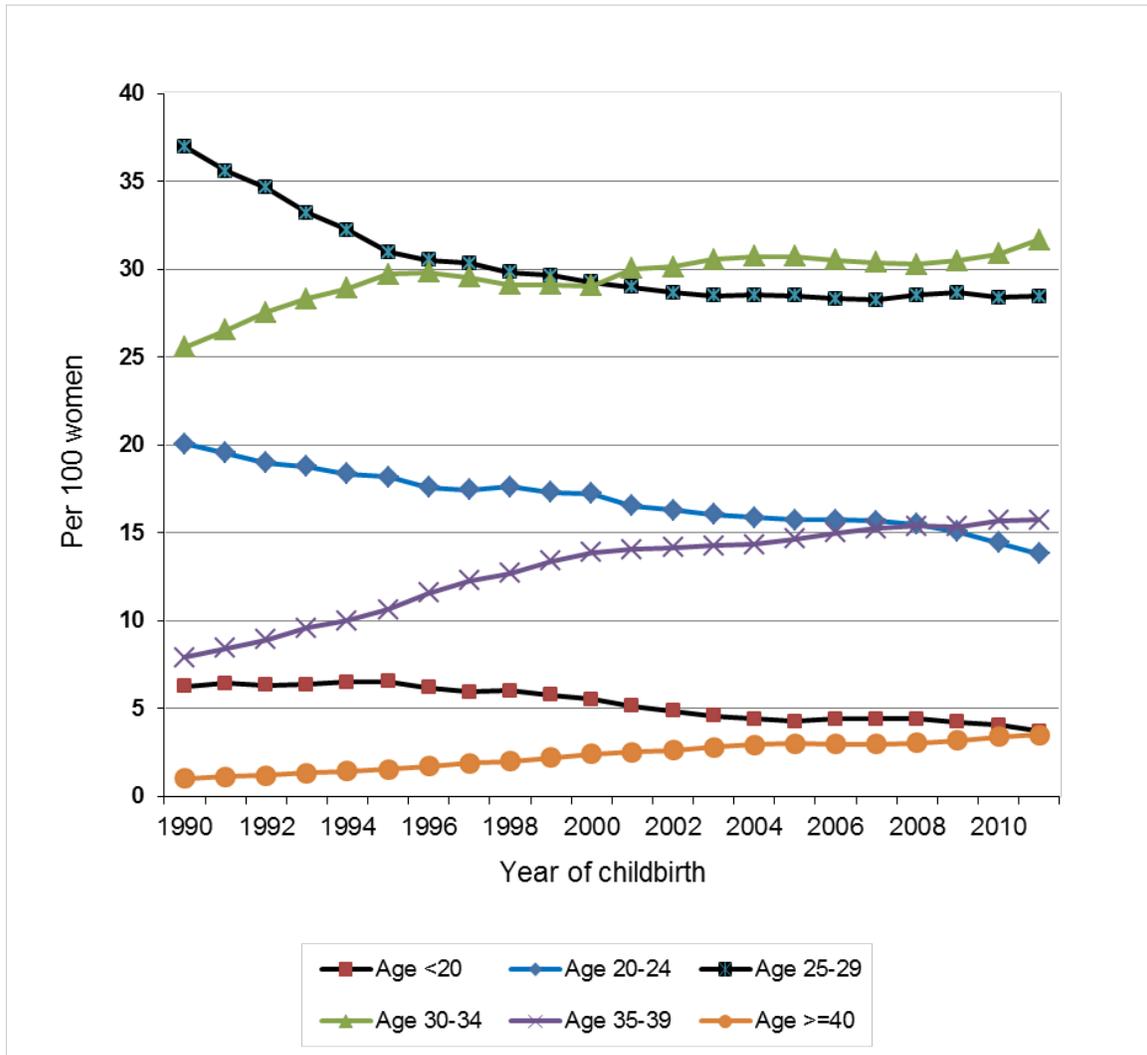
Supplemental Table. Sensitivity analysis: Results of Poisson regression analysis showing the effect of food fortification with folic acid on rates of isolated congenital heart defect subtypes (i.e., excluding any extra-cardiac anomaly), Canada (excluding Québec and Manitoba), 1990 to 2011.

Outcome	Unadjusted model *			Adjusted model *	
	Number of cases	Rate ratio	95% confidence interval	Rate ratio	95% confidence interval
Isolated conotruncal heart defect	5 839	0.76	0.70-0.82	0.71	0.60-0.85
Isolated non-conotruncal defect	2 433	0.91	0.81-1.02	0.82	0.64-1.04
Isolated coarctation of the aorta	2 333	0.82	0.73-0.91	0.77	0.64-0.97
Isolated ventricular septal defect	14 581	0.80	0.75-0.84	0.86	0.76-0.96
Isolated atrial septal defect	13 016	1.17	1.09-1.25	0.83	0.70-0.98
Other isolated CHD	19 397	0.73	0.68-0.78	1.02	0.91-1.15
Total isolated CHD	57 599	0.88	0.84-0.91	0.92	0.86-0.99
Non-isolated CHD	9 381	0.88	0.82-0.94	0.89	0.79-0.98

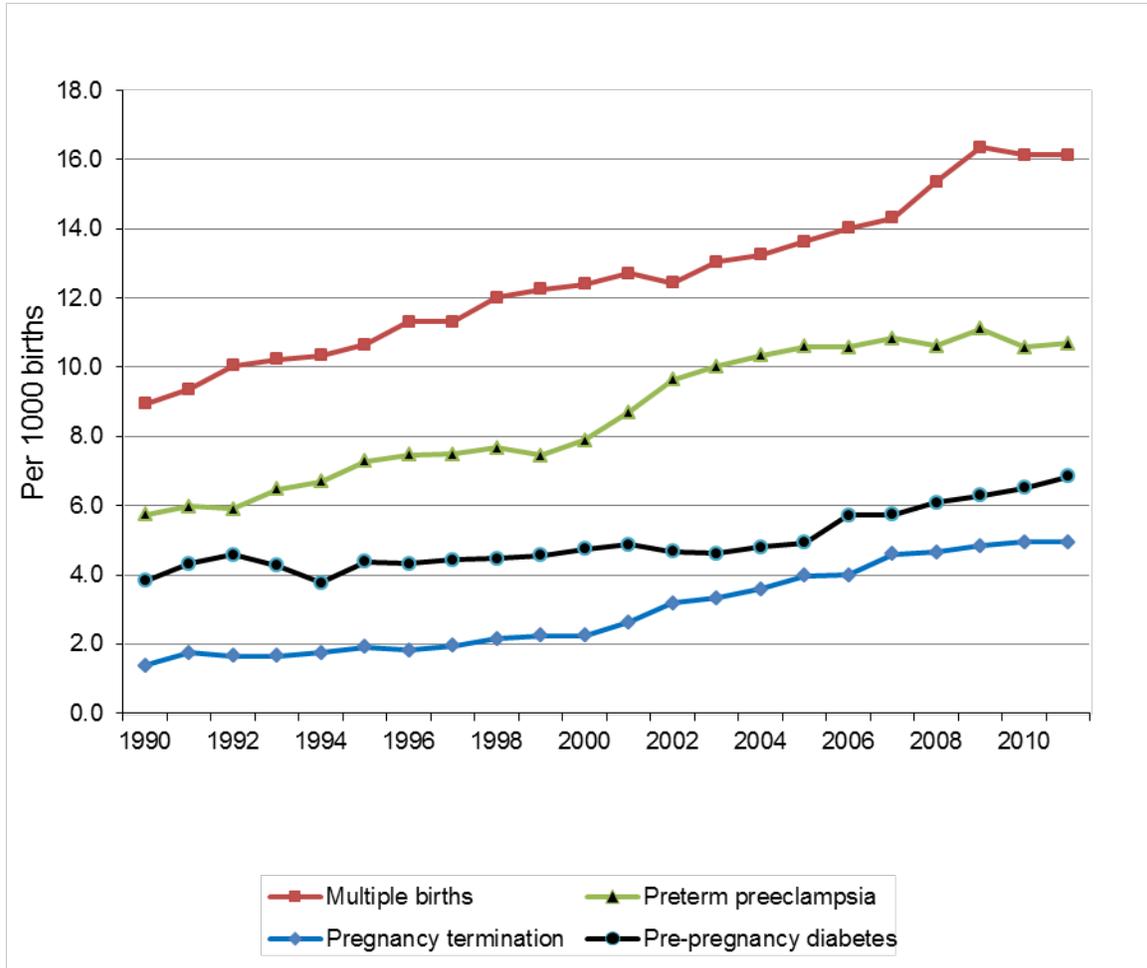
* Goodness of fit of the Poisson regression model was assessed using deviance statistics and Pearson's Chi-square and variance estimates were corrected for overdispersion through appropriate scaling.

Independent variables in each of the adjusted models included food fortification with folic acid (yes/no), the multiple birth rate, the termination of pregnancy rate, the pre-pregnancy diabetes mellitus rate, the preeclampsia rate (all per 1000 total births), the proportion of women with a maternal age <20 years, 20-24 years, 30-34 years, 35-39 years and ≥ 40 years.

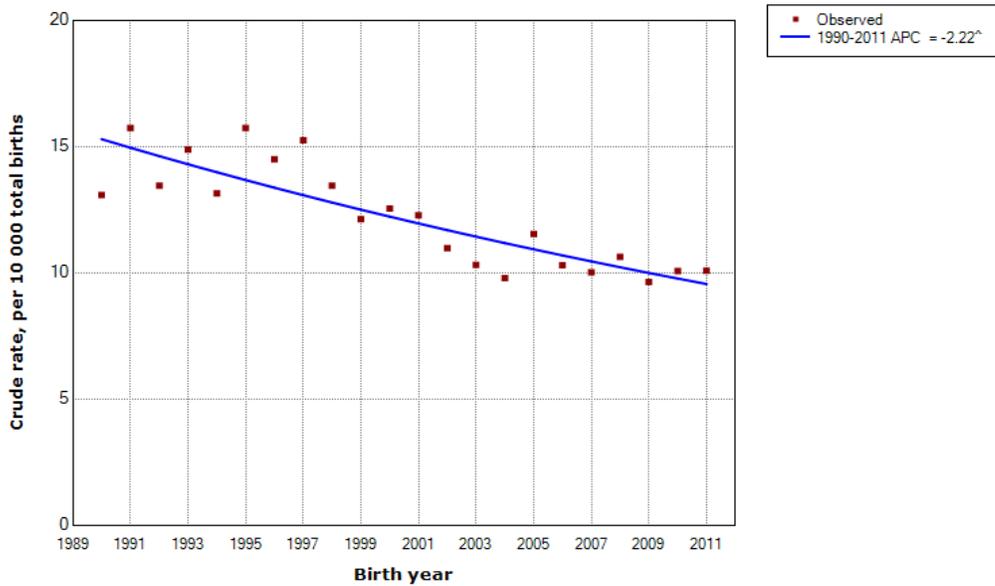
Supplemental Figure I. Temporal changes in maternal age at childbirth, Canada (excluding Québec and Manitoba), 1990-2011.



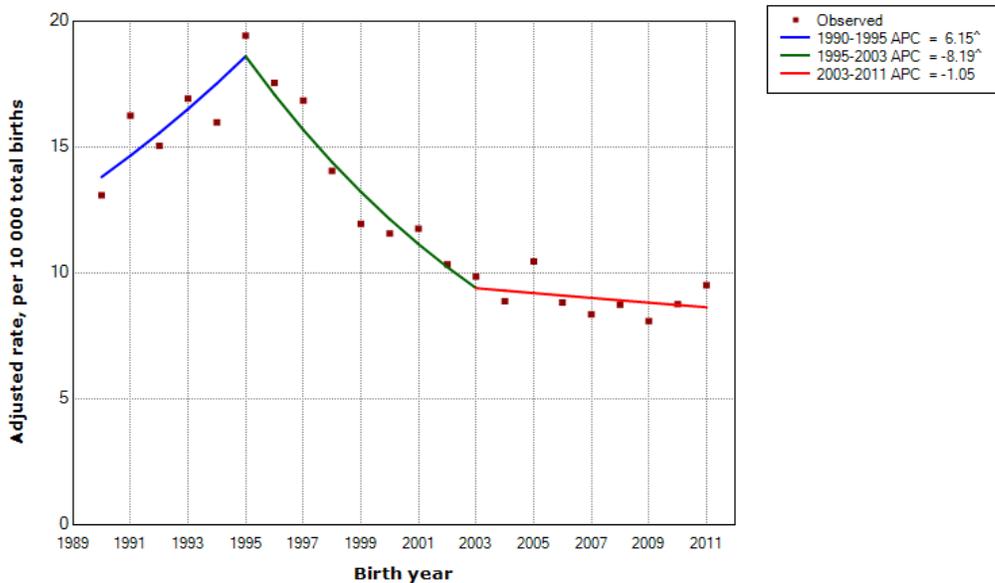
Supplemental Figure II. Temporal trends in maternal and pregnancy factors potentially associated with congenital heart defects, Canada (excluding Québec and Manitoba), 1990-2011.



Supplemental Figure III-a. Change point for the trend in birth prevalence of conotruncal defects in unadjusted model : : 0 Joinpoints



Supplemental Figure III-b. Change point for the trend in birth prevalence of conotruncal defects in adjusted model : : 2 Joinpoints



Note: a) Cases with chromosomal anomalies were excluded; b) ^ denotes that APC (Annual Percent Change) is significantly different from zero at $P < 0.05$; c) Adjusted for maternal age, preterm preeclampsia, pre-pregnancy diabetes, multiple birth and termination of pregnancy.

Supplemental Figure Legends

Supplemental Figure I. Temporal changes in maternal age at childbirth, Canada (excluding Québec and Manitoba), 1990 – 2011

Supplemental Figure II. Temporal trends in maternal and pregnancy factors potentially associated with congenital heart defects, Canada (excluding Québec and Manitoba)

Supplemental Figure III-a. Change point for the trend in birth prevalence of conotruncal defects in unadjusted model : 0 Joinpoints

Supplemental Figure III-b. Change points for the trend in birth prevalence of conotruncal defects in fully adjusted model: 2 Joinpoints