

# Analyses of trends in prevalence of congenital heart defects and folic acid supplementation

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*Provenance:* This is an invited Editorial commissioned by the Section Editor Haiyun Yuan (Department of Cardiovascular Surgery, Guangdong Provincial Cardiovascular Institute, Guangdong General Hospital, Guangzhou, China).

*Comment on:* Liu S, Joseph KS, Luo W, *et al.* Effect of Folic Acid Food Fortification in Canada on Congenital Heart Disease Subtypes. *Circulation* 2016;134:647-55.

Submitted Feb 18, 2017. Accepted for publication Mar 01, 2017.

doi: 10.21037/jtd.2017.03.16

View this article at: <http://dx.doi.org/10.21037/jtd.2017.03.16>

## Introduction

Congenital heart defects (CHDs) are of public health concern given that they occur in approximately 1% of all live births (1,2), are the leading cause of infant deaths due to birth defects (3,4), and are one of the most common reasons for use of health services among children with chronic conditions, accounting for \$5.6 billion in hospitalization costs alone in 2009–15.1% of all pediatric hospitalization costs (5). These costs extend beyond childhood as children with CHD are now surviving well into later decades in life (6). Most CHDs are thought to be multifactorial in origin, involving genetic and environmental factors (7-10). Despite notable contributions of epidemiologic research in the discovery of the etiology of these defects, the number of modifiable risk factors identified has been limited: including maternal pre-pregnancy diabetes, exposure to certain medications or maternal infections (e.g., rubella), uncontrolled maternal phenylketonuria, and possibly maternal pre-pregnancy obesity, smoking, and consanguinity (8,11). There is a need to identify modifiable risk factors to provide the evidence basis for prevention interventions.

One potential modifiable risk factor for CHD that has been the subject of several epidemiologic studies in recent years is intake of folic acid during the periconceptional period (12-23). However, the results of these studies have been inconsistent. Most recently, Liu and colleagues

in a study published in *Circulation* (24) conducted an ecologic analysis of CHD prevalence before and after the initiation of a public policy in Canada mandating folic acid fortification of food (FAFF). In this article, the authors describe trends in prevalence rates of CHD (overall), and CHD subtypes, among all live births and stillbirths/late-pregnancy terminations (>20 weeks gestation) before and after FAFF was mandated in Canada in 1998.

Liu *et al.* (24) studied approximately 6 million births between 1990 and 2011 in 14 geographic areas in Canada in an effort to quantify the effect of FAFF on non-chromosomal subtypes of CHD. They evaluated six subtypes of non-chromosomal CHD and found an overall reduction in prevalence of non-chromosomal CHDs of 11% (95% CI: 2–18) after FAFF. Evaluation of individual subtypes of CHD showed reductions in prevalence after FAFF of 27% (95% CI: 15–38) for conotruncal defects, 23% (95% CI: 4–39) for coarctation of the aorta, 15% (95% CI: 4–25) for ventricular septal defects (VSDs), and 18% (95% CI: 5–31) for atrial septal defects (ASDs). Findings from this type of ecologic analysis need to be interpreted with several methodological considerations in mind.

## Methodological considerations

One fundamental assumption of analysis of trends in

prevalence of CHD is that ascertainment and classification of CHDs in the population under study remain constant during the study period. CHDs can occur as simple (i.e., isolated/nonsyndromic) defects, while others (at least 30%) occur as complex defects (i.e., genetic, syndromic, or associations with other noncardiac defects). Some of the more complex types of CHDs may have a higher likelihood of stillbirth and/or prenatal diagnosis and elective termination (e.g., CHDs associated with chromosomal anomaly). Also, advances in prenatal echocardiography in recent decades have both allowed for earlier fetal echocardiographic screening as well as improved sensitivity and accuracy of prenatal detection and diagnosis of severe forms of CHDs (e.g., hypoplastic left heart syndrome) that may result in elective termination. If trends in prenatal diagnosis and elective termination (prior to 20 weeks gestation) of pregnancies complicated by CHD increased during the study period, then it may be difficult to assess the extent to which the observed decreasing trend in birth prevalence of CHDs is directly related to early diagnosis and elective termination versus concomitant effects of FAFF.

In the study by Liu and colleagues (24), terminations resulting from congenital anomalies were not identifiable in the dataset until 1997 (the year prior to FAFF). Therefore, terminations due to the presence of CHD were not included in the calculation of the prevalence rates for CHD in the cohort prior to FAFF for years 1990-1996 (7 of the 8 years of this cohort). If those terminations had been included, the difference in CHD prevalence detected between the two time periods/FAFF groups might have actually been much lower than shown by the study results.

The study by Liu and colleagues (24) examined the trends in prevalence of all CHD types as a group as well as for different CHD subgroups. These different CHD subgroups included conotruncal defects (common truncus, transposition of the great vessels, Tetralogy of Fallot), severe nonconotruncal defects (including endocardial cushion defects, common ventricle, and hypoplastic left heart syndrome), coarctation of the aorta, VSDs, ASDs, and “other heart and circulatory system abnormalities” (all ICD codes for congenital heart defects not included in the first 5 categories). Separate analysis of trends in prevalence for each one of these CHD subgroups comprised of anatomically similar specific CHD phenotypes allowed for a more robust assessment of trends in prevalence pre and post FAFF and to corroborate expected changes in prevalence for CHD subgroups previously reported to

show associations with folic acid intake, namely conotruncal defects and VSDs (13-15,17,20,21,23). Of interest is that the decreasing trends in prevalence for these two subgroups of CHD continued well beyond the implementation of the FAFF policy, suggesting that other factors besides FAFF may have contributed in part to the decrease in prevalence during this period.

The sudden drop in prevalence of 16/10,000 to 10/10,000 between 2000 and 2002 for the subgroup of other specific CHDs was not addressed by Liu *et al.* Such sudden changes in prevalence may occur as a result of changes in surveillance methods such as increased detection and/or reporting of cases, or improved classification of cases and non-cases.

In studies of temporal trends in prevalence of CHD in relation to changes in FAFF at the population level, it is important to consider temporal changes in prevalence of other maternal risk factors known to be associated with CHD births. In their study (24), Liu *et al.* took into account an increasing prevalence of diagnosed pregestational diabetes, increasing average maternal age, and the increase in termination rate resulting from a fetal diagnosis of CHD. However, the prevalence of other potential confounders such as prepregnancy obesity and cigarette smoking that were not taken into account may have declined during the study period and could have contributed to the observed decline in prevalence in relation to FAFF implementation and beyond.

Another limitation of the study by Liu *et al.* (24) is that there was no information provided on trends in blood folate levels for women of childbearing age in the study population, leaving the reader to assume that the decreased prevalence of CHD observed was due to an increase in maternal folate levels due to the population level change of the FAFF. However, there was no evidence provided of trends in prevalence of serum folate levels in the population of women of childbearing age to justify this assumption.

### Challenges in drawing causal inferences from ecologic analyses of environmental factors and CHDs

As pointed out in the study by Liu and colleagues (24), there are several studies in the literature supporting a preventative role for folic acid in the development of CHDs (12-22,24). These studies were reviewed and the findings demonstrated a similar trend in relation to the inverse association of outflow tract anomalies (most consistently conotruncal defects) and ventricular septal

defects with the supplementation of either isolated folic acid (by dietary fortification or pharmaceutical supplementation) or multivitamin supplementation. More precisely, there was a reduction in risk of these subtypes of cardiac defects seen in multiple studies, despite mode of supplementation with folic acid (presumed mechanism of multivitamin supplementation). The findings for outflow tract anomalies and ventricular septal defects are summarized in (Table 1). Czeizel and colleagues (15,16) reported a 43% reduction in the prevalence of CHD in their series of 2 studies which included a randomized controlled trial (RCT) in Hungary followed by a cohort controlled trial which was initiated after the RCT was stopped. In an additional study in 2015, Czeizel reported that medical documentation of maternal high-dose folic acid supplementation during the critical period of cardiac development was associated with a significant reduction in prevalence of VSDs (OR 0.57, 95% CI: 0.45–0.73), d-transposition of the great vessels (OR 0.47, 95% CI: 0.26–0.86), Tetralogy of Fallot (0.53, 95% CI: 0.17–0.94), and ASDs (OR 0.63, 95% CI: 0.4–0.98) (17).

Alternatively, Bedard *et al.*, (13) in a population in Alberta, Canada, reported no significant decline overall in isolated CHDs after FAFF but found that left ventricular outflow tract obstruction and coarctation of the aorta showed a significant decrease in prevalence. Of interest is that they did find that isolated ASDs and ASD with associated VSD both demonstrated an increased prevalence after FAFF (13).

Leirgul *et al.* (18) evaluated 517,748 non-chromosomal pregnancies in Norway and found that maternal report of regular intake of multivitamin and folic acid had no association with severe CHDs. However, these investigators did find an unexpected 20% increase in the prevalence of VSDs in those reporting regular use of folic acid in pregnancy, and an overall trend during the 10-year study period of increased folic acid intake from 1999 to 2009 and a simultaneous overall decline in CHD over the same period. There was no significant change in prevalence for severe defects over the study period (18).

When considering the findings of Liu and colleagues (24) in comparison with the above mentioned studies, Liu *et al.* (24) reported a smaller overall decrease in prevalence of CHD than Czeizel (17). However, both groups demonstrated a reduction in both conotruncal defects as well as atrial and ventricular septal defects when subtypes of CHD were evaluated. Bedard (13) showed a decrease in left sided obstructive lesions (left ventricular outflow tract obstruction and coarctation of the aorta). He detected no significant

overall decline in CHD, unlike the first two groups. He also showed an increase in the prevalence of isolated ASDs as well as ASDs with associated VSDs. Similarly, Leirgul and colleagues (18) reported an overall decline in all forms of CHD but no association with severe CHD, and surprisingly found a 20% increase in prevalence of VSDs.

Feng and colleagues (25) recently published a comprehensive meta-analysis of the literature on maternal folic acid supplementation the risk of CHDs. This meta-analysis included 18 studies, consisting of 1 randomized controlled trial, 1 cohort study, and 16 case-control studies. They found an overall significantly decreased risk of CHD with maternal folic acid supplementation (OR 0.72, 95% CI: 0.63–0.82). When CHD subtypes were considered, they found similar risk reduction for conotruncal defects (RR 0.64, 95% CI: 0.54–0.76), septal defects-isolated VSD or ASD (RR 0.64, 95% CI: 0.49–0.83), and atrioventricular septal defects (RR 0.60, 95% CI: 0.44–0.83).

The finding of decreased prevalence of conotruncal defects with maternal folic acid supplementation in several studies is encouraging, but not consistent across all studies. The difference in findings related to septal defects across the studies could be due to a number of factors including differences in clinical methods and rates of detection of septal defects as well as timing of evaluation and differences in defining ASD versus patent foramen ovale (persistent fetal structure). When considering differences across studies for each subtype, the variability of classification methods of CHD used in each case may also explain, in part, the resulting discrepancies in findings.

### **Importance of dietary intake of folic acid and additional supplementation in women of childbearing age**

Despite these methodological considerations, the results of the study by Liu and colleagues are important as they are suggestive that folic acid levels may have an impact on the reduction in prevalence of CHD. The current FAFF policy in Canada and in the US and recommendations for increased dietary intake of folic acid and additional pharmacological supplementation for all women of childbearing age to prevent neural tube defects may also contribute to the prevention of some CHDs (e.g., conotruncal defects and VSDs). The development of the cardiac system, also being completed early in gestation, stands to potentially benefit from such prevention intervention efforts, particularly among pregnancies to women with increased susceptibility

**Table 1** Risk reduction in outflow tract anomalies and ventricular septal defects with folic acid/multivitamin supplementation

CHD Phenotype	OR (95% CI)	Supplementation type	Data source	Reference
Outflow tract anomalies (conotruncal anomalies and left sided outflow tract obstruction)				
Conotruncal defects	0.73 aRR (0.62–0.85)	Folic acid fortification of food, Canada	Discharge abstract database of the Canadian Institute for Health Information, 1990–2011	Liu, 2016 <i>Circulation</i>
Conotruncal defects	0.57 (0.33–1.0)	Periconceptional MVI	Atlanta birth defects case control study, 1968–1980	Botto, 1996 <i>Pediatrics</i>
dTGA	0.36 (0.15–0.89)			
TOF	0.48 (0.17–1.35)			
Truncus	1.2 (0.37–3.96)			
Conotruncal defects	0.46 (0.24–0.86)	Periconceptional MVI	MACDP	Botto, 2000 <i>Am J of Epidemiol</i>
Conotruncal defects	0.29 (0.09–0.97)	Periconceptional MVI	Hungarian RCT	Czeizel, 1998 <i>Eur J Obstst Gynecol Reprod Biol</i>
Conotruncal defects	0.55 (0.29–0.89)	Folic acid supplementation during critical developmental period	Hungarian case control surveillance of congenital abnormalities (HCCSCA) 1980–1996.	Czeizel, 2015 <i>Eur J Obstst Gynecol Reprod Biol</i>
TOF	0.59 (0.17–0.94)			
dTGA	0.47 (0.26–0.86)			
dTGA	Highest threes quartiles of folic acid supplementation: 0.65 (0.3–1.5) 0.78 (0.4–1.7) 0.76 (0.4–1.7)	Folic acid supplementation -quartiles: I =<245 µg/day II =245–355 µg/day III =356–542 µg/day IV =>542 µg/day	BWIS	Scanlon, 1998 <i>Epidemiology</i>
Conotruncal defects	0.53 (0.34–0.85)	Any MVI use	California birth cohort 1987–1988 (CABDMP)	Shaw, 1995 <i>Am J Med Genet</i>
Conotruncal defects	0.77 (0.52–1.15)	Periconceptional folic acid	EUROCAT	Van Beynum, 2010 <i>Eur Heart Journal</i>
Coarctation of the aorta	0.77 aRR (0.61–0.96)	Folic acid fortification of food, Canada	Discharge abstract database of the canadian institute for health information, 1990–2011	Liu, 2016 <i>Circulation</i>
LVOTO	0.76 (0.61–0.94)	Folic acid fortification of food; Alberta, Canada	Alberta congenital anomalies surveillance system, Ped. Card. clinics, pathology, hospital reports	Bedard, 2013 <i>Birth Def Res A Clin Mol Teratol</i>
Coarctation of the aorta	0.55 (0.32–0.92)			
LVOTO	1.23 (0.82–1.85)	Periconceptional folic acid	EUROCAT	Van Beynum, 2010 <i>Eur Heart Journal</i>
Ventricular septal defects				
VSD	0.85 aRR (0.75–0.96)	Folic acid fortification of food, Canada	Discharge abstract database of the information, 1990–2011	Liu, 2016 <i>Circulation</i>
VSD	0.61 (0.38–0.99)	Periconceptional MVI	MACDP	Botto, 2000 <i>Am J of Epidemiol.</i>
VSD	0.57 (0.45–0.73)	Folic acid supplementation during critical developmental period	Hungarian case control surveillance of congenital abnormalities	Czeizel, 2015 <i>Eur J Obstst Gynecol Reprod Biol</i>
VSD	0.69 (0.5–0.96)	Periconceptional folic acid supplementation	EUROCAT	Van Beynum, 2010 <i>Eur Heart Journal</i>

CHD, congenital heart defect; OR, ddds ratio; aRR, adjusted rate ratio; MVI, multivitamin; MACDP, Metropolitan Atlanta Congenital Defects Program (subset of the Atlanta Birth Defects Case-Control Study); RCT, randomized controlled trial; BWIS, Baltimore Washington Infant Study; CABDMP, California Birth Defect Monitoring Program; dTGA, dextro(D)-transposition of the great arteries; TOF, Tetralogy of Fallot; LVOTO, left ventricular outflow tract obstruction; VSD, ventricular septal defect; EUROCAT, European Registry of Congenital Anomalies and Twins.

for CHDs among their offspring (e.g., women with cardiometabolic disorders). Further studies are needed to investigate the role of folic acid in the development of CHD and the potential biologic mechanisms of the presumed impact on the development of the fetal cardiovascular system.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Parnell AS, Correa A. Analyses of trends in prevalence of congenital heart defects and folic acid supplementation. *J Thorac Dis* 2017;9(3):495-500. doi: 10.21037/jtd.2017.03.16