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Maternal Food Insecurity Is Associated with Increased Risk of Certain Birth Defects,[1,2]

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Abstract

Food insecurity represents a lack of access to enough food to meet basic needs. We hypothesized that food insecurity may increase birth defect risks, because it is an indicator of increased stress or compromised nutrition, which are both implicated in birth defect etiologies. This study used population-based case-control data. Included in the analysis were 1,189 case mothers and 695 control mothers who were interviewed by telephone. We calculated a food insecurity score as the number of affirmative responses to 5 questions from a shortened instrument designed to measure food insecurity. OR for the food insecurity score specified as a linear term indicated that a higher score was associated with increased risk of cleft palate, d-transposition of the great arteries, tetralogy of Fallot, spina bifida, and anencephaly, but not with cleft lip with or without cleft palate, after adjustment for maternal race-ethnicity, education, BMI, intake of folic acid-containing supplements, dietary intake of folate and energy, neighborhood crime, and stressful life events. In addition, several models suggested effect modification by certain factors. For example, for anencephaly, among women with the worst score for neighborhood crime (i.e. 6), the OR associated with a 1-unit change in the food insecurity score was 1.57 (95% CI 1.06, 2.33), whereas among women with a low crime score (i.e. 2), the corresponding OR was 1.16 (95% CI 0.96, 1.38). This study suggests that increased risks of certain birth defects may be included among the negative consequences of food insecurity.

Introduction

Food insecurity represents a lack of access to enough food to meet basic needs (1). It is associated with decreased nutritional status, including limitations in the quality, quantity, and/or frequency of food intake (2-4) and lower serum nutrient levels (3,5). It reflects some level of financial stress (2) and 1 study reported that it was associated with increased perceived stress among pregnant women (6).

Food insecurity has been shown to affect several health outcomes. For example, it is associated with decreased self-rated health status among adults and children (2,7-9) and with depression and anxiety in mothers (6,10). Its effects on reproductive outcomes have not been well studied. These effects may be particularly important, however, given the increased nutritional requirements during pregnancy and the potential negative effects of stress and compromised nutrition on maternal and infant health (6).

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Food insecurity has not been evaluated with respect to birth defect risks. We hypothesized that food insecurity may increase risks of birth defects, because it is an indicator of increased stress or compromised nutrition, which are both implicated in the etiologies of birth defects. For example, several observational studies have reported that maternal stressful life events are associated with increased risks of neural tube defects (NTD), orofacial clefts, and conotruncal heart defects (11-20). Many studies have reported that these birth defects are associated with intake of folic acid and other nutrients (21-26). In addition, previous studies have reported that dietary quality (27,28), dieting that involves food restriction (29), and famine (30,31) are associated with increased NTD risk. This study investigated food insecurity as a risk factor for NTD, orofacial clefts, and conotruncal heart defects using recent data from a population-based case-control study in California.

Methods

This case-control study included liveborn, stillborn (fetal deaths at ≥20 wk gestation), and prenatally diagnosed, electively terminated cases that occurred to mothers residing in Los Angeles, San Francisco, and Santa Clara counties (20). The study included data on deliveries that had estimated due dates (EDD) from July, 1999 to June, 2004. Case information was abstracted from multiple hospital reports and medical records and then reviewed by a clinical geneticist. Infants diagnosed with single gene disorders or chromosomal aneusomies (based on information gathered from chart reviews) were ineligible. Each case was classified as isolated if there was no concurrent major malformation or as non-isolated if there was at least 1 accompanying major malformation. Case groups included spina bifida, anencephaly, cleft palate, cleft lip with or without cleft palate, and the conotruncal heart defects d-transposition of the great arteries and tetralogy of Fallot. Spina bifida included cases of lipomeningocele, meningomyelocele, and myelocystocele. For each conotruncal heart defect case, anatomic and physiologic features were confirmed by reviewing echocardiography, cardiac catheterization, surgery, or autopsy reports. Infants with d-transposition of the great arteries associated with an endocardial cushion defect or with double outlet right ventricle were excluded. Ascertainment of clefts and NTD ended with EDD June 30, 2003; ascertainment of the conotruncal heart defects ended with EDD June 30, 2004. Nonmalformed, liveborn controls were selected randomly from birth hospitals to represent the population from which the cases were derived. Specifically, controls were randomly selected from area hospitals in proportion to their contribution to the total population of liveborn infants (i.e. the number of eligible control infants from each hospital was in proportion to that hospital's contribution to the most recent birth cohort for which vital statistics data were available). Ascertainment of controls ended with EDD June 30, 2004.

Mothers were eligible to interview if they were the biologic mother and carried the pregnancy of the selected study subject, they were not incarcerated, and their primary language was English or Spanish. Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, no earlier than 6 wk after the infant's EDD. A variety of exposures were assessed, focusing on the periconceptional time period, which was defined as 2 mo before through 2 mo after conception.

In total, 80% of eligible case mothers (1355) and 77% of control mothers (700) were interviewed. Eleven percent of eligible case mothers and 12% of control mothers were not locatable and the remainder of the nonparticipants declined the interview. The median time between EDD and interview completion was 10 mo for cases and 8 mo for controls. Cases and controls with a family history of the selected defects in a parent or sibling, mothers who had type I or II diabetes, and mothers taking medications to prevent seizures were excluded from all analyses, given that those subjects may be different etiologically (80 cases and 5 controls). Nonisolated cleft cases were also excluded, given that a different etiology is suspected for them

(86 cases). After these exclusions, 695 controls were available for analyses (623 with EDD through June 30, 2003) and 1189 cases: 139 anencephaly, 186 spina bifida, 145 isolated cleft palate, 419 isolated cleft lip with or without cleft palate, 165 tetralogy of Fallot, and136 d-transposition of the great arteries (1 case had anencephaly and tetralogy of Fallot).

Food insecurity

To measure food insecurity, we used 5 of 6 questions about experiences and behaviors associated with having difficulty meeting basic food needs from a shortened, validated scale (1). The exact questions were: During the 2 mo before through the 2 mo after you became pregnant: 1) Did your food ever run out before you could afford to buy more? 2) Could you ever not afford to eat balanced meals? 3) Did you ever cut the size of your meals or skip meals because there wasn't enough money for food? 4) How often did this happen? (considered affirmative if the response was ~1 time per month or more frequent); and 5) Were you ever hungry but didn't eat because you couldn't afford enough food? One of the 6 questions from the original scale was excluded ("Did you ever eat less than you felt you should have because there wasn't enough money for food?") due to an erroneous skip pattern in the questionnaire format (it was originally asked as question 5). A food insecurity score was calculated by summing the number of affirmative responses to the 5 questions.

Covariates

Several known risk factors for the selected birth defects were considered as covariates: maternal race-ethnicity (US-born Hispanic, foreign-born Hispanic, non-Hispanic white, other); education (less than high school, high school, some college, 4-y college degree or more); pre-pregnancy BMI (kilograms per square meter); intake of folic acid-containing multivitamin/mineral supplements (any vs. none); and dietary intake of folate and energy (kiloJoules) during the periconceptional period. As additional measures of maternal stress, we included an index of neighborhood crime (the number of "yes" responses to 6 questions) (32) and an index of stressful life events (the number of "yes" responses to 18 questions) (20), also reported during the periconceptional period. To assess usual dietary intake of folate and energy, women answered a 107-item, modified version of the Health Habits and History Questionnaire, a well-known, semiquantitative FFQ with demonstrated reliability and validity (33,34). Participants reported their usual frequency and serving size for each food item they consumed and they answered several questions about food preparation techniques (e.g. what type of fat is usually used in preparing foods). The FFQ was modified to include ethnic foods appropriate to the diverse study population, especially Hispanics; a version with similar modifications demonstrated good validity and reliability, particularly among Hispanics (35). Analytic software developed for the survey instrument (i.e. Dietsys) was used to compute the average daily dietary intake of single nutrients. Data were recoded to missing for the following women, due to potentially invalid results: women with 4 or more missing food items (n = 23 total); women who reported eating >30 foods per day (n = 54) or fewer than 4 foods per day (n = 6 total, but 3 were retained for analysis, because the interviewer confirmed special circumstances that resulted in reduced food intake); women who reported 3 or more high frequency foods (n = 24; i.e. foods that were eaten 2 or more times per day or beverages that were consumed more than 6 times per day); and women who consumed >6000 kcal/d (i.e. 25,116 kJ, n = 35) or fewer than 500 kcal/d (i.e. 2093 kJ, n = 5). In total, these criteria resulted in missing data for 49 mothers of controls and 52 mothers of cases.

Analysis

The association of the food insecurity score with each outcome was evaluated using logistic regression to estimate OR and 95% CI. The food insecurity score was specified as continuous for most analyses, but it was also examined as a categorical variable to ensure that a continuous specification seemed appropriate. The continuous specification was preferred, because it yields the most power to detect differences, which was especially important for analyses of specific phenotypes. To determine whether the specification of the food insecurity score as a continuous variable was appropriate, we compared the goodness-of-fit of models specifying the score using a linear term with saturated models specifying the score as categorical by comparing the deviances of nested models for each phenotype. The categorical model (i.e. 5 dummy variables) is statistically equivalent to a saturated polynomial model for the score (i.e. raised to the second, third, fourth, and fifth power) so that the deviance comparison is valid (36).

Backward step-wise selection was used to derive final multivariable models that included the food insecurity score as a continuous variable. The initial models included all potential covariates listed above and all 2-way interactions of the food insecurity score with each of the covariates. In each step, the term with the highest *P*-value was removed until all terms had $P < 0.10$ (covariates with $P \geq 0.10$ were retained if their 2-way interaction remained in the model). Because of missing data on some covariates and concern about selection bias (i.e. it is possible that women who have missing data are different from women with no missing data), we compared models that were derived based on 2 scenarios: 1) including the same set of subjects throughout the backward selection procedure (i.e. subjects with complete data on all covariates); and 2) allowing the inclusion of different subjects at each stage of model selection (i.e. subjects with complete data on the covariates in each model generated during the backward selection process). We then selected the model with the best fit, which was assessed using the likelihood ratio test; for these comparisons, we included the maximum number of subjects that had complete covariate data for both models so they would be nested. All data collection was approved by the State of California, Health and Human Services Agency, Committee for the Protection of Human Subjects.

Results

Most of the mothers of case and controls were Hispanic, many had less than a high school education, a majority took a folic acid-containing supplement during the periconceptional period, a majority did not report any positive responses to the questions about neighborhood crime, and a majority reported at least 1 stressful life event (Table 1).

The percentage of mothers reporting "yes" to each food insecurity question was from 3 to 9% among the controls and from 6 to 11% among the cases. The correlations of the food insecurity questions with each other ranged from 0.35 to 0.66 among controls and 0.42 to 0.63 among cases, with the exception of the correlation between questions 3 and 4 (see above); their correlation was higher ($r = 0.93$ among controls and $r = 0.97$ among cases), because we asked question 4 only if the answer to question 3 was affirmative. Internal consistency of the revised 5-item scale was good, with Cronbach's α equal to 0.87 among controls. A total of 87% of the mothers of controls responded negatively to all 5 food insecurity questions; the corresponding percentage among the case phenotypes was slightly lower (Table 2).

For analyses of the food insecurity score as a categorical variable, certain phenotypes were grouped together due to sparse cells and instability of estimates. There was some indication that higher scores were associated with higher risk, but a clear dose-response pattern was not evident and the estimates tended to be imprecise (Table 2). The goodness-of-fit of models including the food insecurity score as continuous were then compared with models including it as categorical. All model comparisons had *P*-values ≥ 0.2, suggesting that the categorical specification did not substantially improve the fit of the model. The food insecurity score was therefore specified as a continuous variable in further analyses.

Unadjusted OR for the food insecurity score specified as continuous indicated that a higher score was associated with increased risk of all of the phenotypes (Table 3). Results were similar for all women and for the reduced set of women who were included in the final multivariable models. Among all women, the increase in risk for a 1-unit change in the food insecurity score ranged from 3 to 20% and the increase in risk for a 3-unit change ranged from 9 to 73% (the change in risk for a 3-unit change was calculated by raising the OR for a 1-unit change to the third power).

The final multivariable models included various sets of covariates and the models for spina bifida and cleft lip with or without cleft palate were the only ones that did not include any 2-way interactions (Table 4). For spina bifida, the adjusted OR (1.12) was similar to the unadjusted OR (1.15). For cleft lip with or without cleft palate, the adjusted OR (0.98) was closer to 1 than the unadjusted OR (1.07).

The association of food insecurity with risk of anencephaly was particularly strong among women who had higher scores for neighborhood crime (Table 4). For example, among women with the worst score on neighborhood crime (i.e. 6), the OR for a 1-unit change in the food insecurity score was 1.57 and the OR for a 3-unit change was 3.86.

The multivariable models for cleft palate and d-transposition of the great arteries suggested that their association with food insecurity was modified by BMI (Table 4). Adjusted OR were calculated for the median BMI value among women considered to be underweight, normal weight, overweight, and obese (37). The OR suggested that the association of food insecurity with these 2 phenotypes was particularly strong in women who were underweight; in women with a BMI of 18.9 kg/m^2, for cleft palate, the OR for a 1-unit change in the food insecurity score was 1.81, which translates to an OR of 5.9 for a 3-unit change; for d-transposition of the great arteries, the corresponding OR were 1.51 and 3.45. For cleft palate, food insecurity was associated with reduced risk among obese women (OR 0.56).

The final model for tetralogy of Fallot suggested that its association with food insecurity was modified by folic acid supplement intake (Table 4). Among women who did not take supplements, a 1-unit change in the food insecurity score was associated with increased risk (OR 1.23); among women who did take supplements, a 1-unit increase in food insecurity was not associated with increased risk (OR 0.86).

Discussion

We found that positive responses to a brief series of questions designed to measure food insecurity were associated with increased risks of certain birth defects, even after consideration of the potential confounding or modifying effects of maternal race-ethnicity, education, BMI, intake of folic acid-containing supplements, dietary intake of folate and energy, neighborhood crime, and stressful life events.

This study used 5 of 6 questions from a shortened, validated scale (1). According to the scale developers, a score of 0-1 represents food security; 2-4, food insecurity without hunger, and 5-6, food insecurity with hunger. Rather than restrict our analysis to these 3 categories, we chose an alternative analytic approach (i.e. we did not collapse responses into these predefined categories) for the following reasons: given that we included only 5 of the 6 original questions, some women with a score of 1 may have been misclassified as food secure; a positive response to any of the questions suggests potential stress or nutritional compromise; the association of these questions with health outcomes has not been examined by many previous studies; and analyzing all possible scores allowed us to maximize our exploration and use of the data, rather than losing some potentially important information. The current analysis may be considered somewhat exploratory given that we chose this analytic approach and that no previous studies to our knowledge have examined the association of food insecurity with birth defect risks.

We observed evidence for effect modification in several of the final multivariable models. Results for anencephaly were stronger among women with higher scores on neighborhood crime, results for cleft palate and d-transposition of the great arteries were stronger among women who were underweight, and results for tetralogy of Fallot were stronger among women who did not take folic acid supplements during early pregnancy. We prefer not to speculate about potential explanations for these results, given the somewhat preliminary nature of the current study, but each of these observations is in the expected direction.

National estimates suggest that ~12% of U.S. households may have experienced food insecurity in the last year (38). The current study found that 10% of control mothers had 2 or more affirmative responses to the food insecurity questions and would therefore be considered food insecure (1). However, this percentage may be an underestimate of actual food insecurity in the past year, given that we used only 5 of the 6 original questions in the scale and our estimates were only for a 4-mo time span.

We hypothesized that food insecurity may be associated with risks of birth defects, because it is an indicator of increased stress or compromised nutrition. Maternal food restriction (defined as not eating for 13 h or more) and maternal stressful life events have been shown to be associated with elevated maternal corticotropin-releasing hormone and corticosteroid levels during pregnancy (39-41). Corticosteroids are teratogenic in animal models for various organ systems (11,42,43) and they represent 1 possible explanation for observed associations of maternal stress and food restriction with risks of birth defects. Corticosteroid medication use during pregnancy has been shown to be associated with increased risk of orofacial clefts (44-51), but its association with other birth defects is less certain due to a lack of studies rather than a lack of evidence.

Strengths of this study include its comprehensive case ascertainment, detailed phenotypic review, population-based control selection, and satisfactory level of participation in maternal interviews. Given the relatively low frequency of the individual birth defects, we were limited to a retrospective study design and recall bias could have occurred. Although there is concern that mothers of malformed infants will overreport or more thoroughly report exposures than controls (52-54), several studies suggest that recall bias is likely to be minimal for many exposures (53-56), but none of them studied food insecurity. An additional concern is that the time between exposures and actual interview could have affected mothers' ability to correctly recall exposures; it is unknown whether such limitations would be different for mothers of cases or controls. Other, longer instruments to assess food insecurity would have provided more detailed information that could have been useful to the analysis; however, the shortened version has been well validated (1). Our approach of modeling the food insecurity score as a continuous variable is unique, but it is supported by statistical testing that compared the continuous approach with a more traditional, categorical approach. Given our somewhat provocative findings, as well as the limitation in our measurement of food insecurity, further studies of food insecurity and birth defects using more detailed measures of food insecurity may be useful. The current study controlled for potential confounding or modifying effects of several factors, including some aspects of stress (stressful life events, neighborhood crime), nutrition (intake of supplements and dietary intake of folic acid and energy), and socioeconomic level (maternal education), but residual confounding by unmeasured aspects of these factors may serve as an alternative explanation for our findings. Some women chose not to participate and a number of women were missing data on the studied covariates; the generalizability of our results beyond the mothers with complete data is unknown.

Food insecurity is a prevalent problem in the United States. It has negative consequences for a variety of nutritional and non-nutritional outcomes (57). This study suggests that increased risks of certain birth defects may be included among them.

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TABLE 1

Characteristics of mothers of controls (*n* = 695) and cases (*n* = 1189)

	Controls	Cases
	n (%)[1]	
Race-ethnicity		
US-born Hispanic	153 (22)	194 (17)
Foreign-born Hispanic	263 (38)	501 (43)
Non-Hispanic white	142 (21)	273 (23)
Other	127 (19)	208 (18)
Total, *n*	685	1176
Education		
Less than high school graduation	200 (29)	381 (32)
High school graduation	166 (24)	240 (20)
1-3 y college	150 (22)	276 (24)
≥4 y college	166 (24)	277 (24)
Total, *n*	682	1174
Prepregnancy BMI, *kg/m*^{2}		
Underweight (<19.8)	104 (16)	136 (13)
Normal weight (19.8-26.0)	349 (54)	579 (54)
Overweight (26.1-29.0)	79 (12)	166 (15)
Obese (>29.0 kg/m^2)	118 (18)	197 (18)
Total, *n*	650	1078
Intake of folic acid-containing supplements[2]		
No	270 (39)	515 (43)
Yes	423 (61)	672 (57)
Total, *n*	693	1187
Neighborhood crime[3]		
None	374 (55)	640 (55)
Any	303 (45)	516 (45)
Total, *n*	677	1156
Stressful life events[3]		
None	300 (44)	424 (36)
Any	388 (56)	750 (64)
Total, *n*	688	1174
Dietary folic acid intake,[4] *μg/d*	437.4 ± 189.4	420.1 ± 202.0
Total, *n*	646	1137
Dietary energy intake,[4] *kcal/d*	2690.8 ± 961.6	2614.2 ± 994.2
Total, *n*	646	1137

[1] Total number of cases is <1189 and of controls is <695 due to missing data; numbers may not add to 100% due to rounding.

[2] During the 2 mo before or the first 2 mo after conception.

[3] Indicates the percentage of women with any vs. no "yes" responses to the series of questions, during the 2 mo before through the first 2 mo after conception.

[4] Values are means ± SD; 1 kcal = 4.184 kJ.

TABLE 2

Number of affirmative responses to the food insecurity questions reported by mothers of cases and controls, from 2 mo before through 2 mo after conception, and its association with risks of birth defects

Affirmative responses	Controls	NTD[1]	Orofacial clefts	Conotruncal heart defects	NTD	Orofacial clefts	Conotruncal heart defects
n			*n* (%)[2]			OR (95% CI)	
0	597 (86)	259 (80)	469 (84)	251 (84)	Reference	Reference	Reference
1	29 (4)	14 (4)	26 (5)	16 (5)	1.0 (0.5, 1.9)	1.0 (0.6, 1.8)	1.3 (0.7, 2.5)
2	15 (2)	14 (4)	14 (3)	7 (2)	2.1 (1.0, 4.4)	1.1 (0.5, 2.4)	1.1 (0.4, 2.8)
3	15 (2)	8 (2)	17 (3)	7 (2)	1.2 (0.5, 2.8)	1.4 (0.7, 2.8)	1.1 (0.4, 2.8)
4	22 (3)	21 (6)	23 (4)	10 (3)	2.3 (1.2, 4.3)	1.4 (0.7, 2.6)	1.1 (0.5, 2.3)
5	10 (1)	8 (2)	9 (2)	7 (2)	1.6 (0.6, 4.2)	1.0 (0.4, 2.5)	1.7 (0.6, 4.4)

[1] Analyses of NTD and clefts were restricted to the 618 controls with EDD through June 30, 2003.

[2] Percentages may not add to 100% due to rounding.

TABLE 3

Unadjusted OR for food insecurity, specified as continuous, and selected birth defects, for all women and for women included in the final multivariable models

	All women			Women included in final multivariable models		
	Cases	Controls	OR (95% CI)[1]	Cases	Controls	OR (95% CI)
	n			*n*		
Spina bifida	185	618	1.15 (1.00, 1.31)	184	615	1.15 (1.00, 1.31)
Anencephaly	139	618	1.20 (1.04, 1.39)	125	567	1.21 (1.04, 1.42)
Cleft palate	143	618	1.03 (0.87, 1.22)	118	533	1.09 (0.89, 1.33)
Cleft lip with or without cleft palate	415	618	1.07 (0.96, 1.20)	374	575	1.07 (0.95, 1.21)
d-Transposition of the great arteries	135	688	1.10 (0.94, 1.29)	127	639	1.12 (0.95, 1.33)
Tetralogy of Fallot	163	688	1.03 (0.87, 1.20)	157	641	1.09 (0.93, 1.29)

[1] Reflects the OR for a 1-unit change in the food insecurity score; the OR for an *x*-unit change equals (OR for a 1-unit change)^x.

TABLE 4

Adjusted OR for the food insecurity score and birth defects, stratified by maternal characteristics

	Cases	Controls	Adjusted OR (95% CI)[1]
	n		
Spina bifida[2]	184	615	1.12 (0.97, 1.28)
Anencephaly[3]	125	567	
Neighborhood crime = 2			1.16 (0.96, 1.38)
Neighborhood crime = 4			1.35 (1.04, 1.75)
Neighborhood crime = 6			1.57 (1.06, 2.33)
Cleft palate[4]	118	533	
Underweight (BMI = 18.9 kg/m^2)			1.81 (1.17, 2.78)
Normal weight (BMI = 22.8 kg/m^2)			1.27 (1.00, 1.61)
Overweight (BMI = 27.4 kg/m^2)			0.83 (0.59, 1.19)
Obese (BMI = 32.0 kg/m^2)			0.56 (0.29, 1.06)
Cleft lip with or without cleft palate[5]	374	575	0.98 (0.85, 1.12)
d-Transposition of the great arteries[6]	127	639	
Underweight (BMI = 18.9 kg/m^2)			1.51 (1.13, 2.02)
Normal weight (BMI = 22.8 kg/m^2)			1.29 (1.07, 1.56)
Overweight (BMI = 27.4 kg/m^2)			1.07 (0.86, 1.34)
Obese (BMI = 32.0 kg/m^2)			0.89 (0.62, 1.30)
Tetralogy of Fallot[7]	157	641	
No folic acid supplement intake			1.23 (0.98, 1.53)
Folic acid supplement intake			0.86 (0.63, 1.18)

[1] Reflects the OR for a 1-unit change in the food insecurity score; the adjusted OR for an x-unit change equals (OR for a 1-unit change)x; the subsequent footnotes list the variables that remained in the phenotype-specific models after backward step-wise selection.

[2] Spina bifida OR were adjusted for race-ethnicity.

[3] Anencephaly OR were adjusted for BMI and stressful life events.

[4] Cleft palate OR were adjusted for dietary folate, neighborhood crime, and stressful life events; BMI was included as a continuous variable; the adjusted OR were calculated for the median BMI value in control mothers in each BMI category.

[5] Cleft lip with or without cleft palate OR were adjusted for race-ethnicity, folic acid supplement intake, BMI, and stressful life events.

[6] d-Transposition of the great arteries OR were adjusted for maternal education; BMI was included as a continuous variable; the adjusted OR were calculated for the median BMI value in control mothers in each BMI category.

[7] Tetralogy of Fallot OR were adjusted for race-ethnicity, dietary folate intake, and stressful life events.