Lack of Periconceptional Vitamins or Supplements Containing Folic Acid and Diabetes-associated Birth Defects

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Original Article

Title: Lack of Periconceptional Vitamins or Supplements Containing Folic Acid and Diabetes-associated Birth Defects

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Article Condensation and Short Version of Title

Offspring of pregnant women with preexisting diabetes who do not use vitamins or supplements containing folic acid during the periconceptional period may experience an increased risk for birth defects due to diabetes.

Short Title: Lack of Folic Acid Supplements and Diabetes-associated Birth Defects

ABSTRACT

OBJECTIVE: To examine the risk of birth defects in relation to lack of use of periconceptional vitamins or supplements containing folic acid and diabetes.

STUDY DESIGN: The National Birth Defects Prevention Study (1997–2004), a multicenter, population-based case-control study of birth defects (14,721 case and 5,437 control infants). Cases were categorized into 18 types of heart defects and 26 non-cardiac birth defects. We estimated odds ratios for independent and joint effects of pre-existing diabetes and lack of periconceptional use of vitamins or supplements containing folic acid.

RESULTS: The pattern of odds ratios suggested an increased risk of defects associated with diabetes in the absence versus the presence of periconceptional use of vitamins or supplements containing folic acid.

CONCLUSIONS: Lack of periconceptional use of vitamins or supplements containing folic acid may be associated with an excess risk for birth defects due to diabetes.

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Key words: birth defects, diabetes mellitus, folic acid, supplements, vitamins

Abbreviations: CDC, Centers for Disease Control and Prevention; CHD, congenital heart defect; CI, confidence interval; NBDPS, National Birth Defects Prevention Study;

OR, odds ratio; RERI, relative excess risk due to interaction

INTRODUCTION

Offspring of mothers with pre-existing diabetes (i.e., type 1 or type 2 diabetes mellitus) have a two- to fourfold increased risk for a wide spectrum of birth defects.[1-3] Human studies have shown that hyperglycemia during organogenesis is associated with an increased risk for birth defects and that this risk correlates directly with maternal glucose levels.[4-7] However, animal studies have suggested a complex pathogenetic process also involving excess concentrations of other biochemical abnormalities associated with hyperglycemia (e.g., elevated triglycerides, branched-chain amino acids, β-hydroxybutyrate, somatomedin inhibitors, and reactive oxygen species) as potential co-factors in diabetic embryopathy.[8-10]

Multidisciplinary preconception care programs focused on glucose monitoring and control during the periconceptional period have been associated with a reduction in prevalence of birth defects among offspring of pregnancies complicated by pre-existing diabetes.[11, 12] However, continuing occurrence of birth defects among offspring of pregnancies complicated by pre-existing diabetes[1, 2, 13] underscores ongoing challenges facing prevention efforts. One challenge is that about one-third of women of reproductive age with pre-existing diabetes are undiagnosed.[14] Furthermore, more than 60% of women with pre-existing diabetes have unplanned pregnancies, lack access to preconception care, or might find it difficult to comply with prescribed glycemic control regimens.[15-17]

Holding some promise for prevention efforts are reports from animal studies suggesting that high doses of certain antioxidants (e.g., vitamins C and E),[18, 19] fatty acids

(e.g., lipoic acid and arachidonic acid);[20, 21] and possibly folic acid[22, 23] can reduce the risk for birth defects among pregnancies complicated by diabetes. Human studies have demonstrated that maternal periconceptional use of folic acid or multivitamin supplements containing folic acid reduces the risk for neural tube defects.[24, 25] However, evidence of similar risk reduction for other defects has been less consistent.[26, 27]

Because offspring of women with pre-existing diabetes are at increased risk for neural tube defects, the American Diabetes Association supports the U.S. Public Health Service recommendation that women capable of becoming pregnant consume 400 micrograms (μg) of folic acid daily from all sources, and further stipulates that, during periconceptional and prenatal periods, women with pre-existing diabetes increase their folic acid intake to 600 μg daily through supplements or fortified food sources.[12, 28] However, data on efficacy of periconceptional folic acid intake in reducing the risk of birth defects among women with pre-existing diabetes are limited.[29]

We used the National Birth Defects Prevention Study (NBDPS), a population-based, case-control study of birth defects, to examine the independent and joint effects of pre-existing diabetes and the absence of periconceptional intake of vitamins or supplements containing folic acid on the occurrence of birth defects.

MATERIALS AND METHODS

Study population

The NBDPS is an ongoing study based on birth defects surveillance systems in the following states: Arkansas, California, Georgia/Centers for Disease Control and Prevention (CDC), Iowa, Massachusetts, New Jersey (through 2002), New York, North

Carolina (beginning 2003), Texas, and Utah (beginning 2003).[30] Case infants selected for the study had at least one of more than 30 eligible birth defects and were live born, stillborn, or electively terminated. Case records were reviewed systematically by clinical geneticists to exclude case infants with recognized or strongly suspected single-gene conditions or chromosomal abnormalities. Controls were live born infants without birth defects selected randomly either from birth certificates or hospital birth records. Mothers were interviewed in either English or Spanish by telephone 6 weeks to 24 months after the estimated date of delivery using a computer-based questionnaire. Interviewers obtained information on maternal demographic characteristics, exposures (e.g., nutritional, behavioral, or occupational), and medication use both before and during pregnancy. Interview participation rates were 70% among mothers of case infants and 67% among mothers of control infants. The NBDPS was approved by the institutional review boards of CDC and the participating study centers.

Clinical information on case infants was reviewed by a team of clinical geneticists and clinicians with expertise in pediatric cardiology.[31, 32] Case infants were classified as having an isolated birth defect if they had: (a) one major birth defect only; (b) one major birth defect and one or more minor birth defects; (c) one or more major birth defects affecting one organ system only; or (d) one major birth defect with a well-described sequence of related defects and no major unrelated birth defects. Case infants were classified as having multiple birth defects if they had two or more major unrelated defects in different organ systems.[31] For case infants with a congenital heart defect (CHD), an additional layer of classification was employed to denote “simple” cases as anatomically

discrete or having a well-recognized single malformation (e.g., hypoplastic left heart syndrome or tetralogy of Fallot).[32]

Definitions of exposures and covariates

All information was self-reported during the maternal telephone interviews. Mothers reported whether a physician had diagnosed them previously with pre-existing diabetes or gestational diabetes. Based on such reports, we classified case and control infants into one of four mutually exclusive categories: (1) infant of a mother with pre-existing diabetes, if the mother reported having been diagnosed with type 1 or type 2 diabetes prior to the estimated date of conception of the index infant; (2) infant of a mother with gestational diabetes, if the mother reported having been diagnosed with gestational diabetes during the index pregnancy; (3) infant of a nondiabetic mother, if the mother reported never having been diagnosed with any type of diabetes; and (4) unknown, if the response was missing or inconstant (maternal report of preexisting diabetes diagnosed during the index pregnancy). The current analyses covered only infants of mothers classified into categories 1 and 3.

Mothers were asked about their use of a multivitamin, prenatal vitamin, or single-component vitamin, including information on the product brand used, start and stop dates (and/or duration of use), and frequency of use. If exact dates of use were unknown, mothers could report less specific information, such as a pregnancy month (e.g., first month of pregnancy) or time of year (e.g., beginning of the year), which was converted into dates to determine the timing of use in relation to the pregnancy. NBDPS investigators determined whether the specific product reported contained folic acid or

not.[33] Periconceptional users of vitamins or supplements containing folic acid were identified as mothers who reported any use during the month before conception or during the first 3 months of pregnancy. Those who reported no use during the entire time period from 1 month before conception through the end of the first trimester were considered nonusers. Mothers with an unknown intake, those who began intake after the end of the first trimester, or those who began (and ended) intake before the start of month before conception were excluded from these analyses.

Several covariates were considered potential confounders. Self-reported prepregnancy height and weight were converted to metric units and maternal body mass index (BMI) was calculated as weight in kilograms divided by height in square meters (kg/m^2). Four BMI groups were formed: (1) underweight (<18.5 kg/m^2); (2) normal weight (18.5–24.9 kg/m^2); (3) overweight (25.0–29.9 kg/m^2); and (4) obese (≥30.0 kg/m^2).[34] Additional variables included: maternal age (<20, 20–24, 25–29, 30–34, and ≥35 years); maternal race or ethnicity (non-Hispanic White, non-Hispanic Black or African American, Hispanic, and other race or ethnicity); timing of entry into prenatal care (at or before 10 weeks' gestation vs. later); annual household income (≥$40,000 vs. less); and parity (first vs. subsequent live birth).

Exclusions

Case and control infants delivered during the period from October 1, 1997, through December 31, 2004, were eligible for this study. We restricted the analysis to case and control mothers with pre-existing diabetes (type 1 or type 2) with a known date of diagnosis (month and year) prior to the index pregnancy and mothers with no diabetes

of any type. Of the 16,419 case mothers and 5,958 control mothers who participated in the NBDPS, 1,313 case and 386 control mothers with gestational diabetes or with unknown or inconsistent diabetes status were excluded, as were 441 case and 147 control mothers who were neither definitive users nor nonusers of vitamins or supplements containing folic acid during the period of 1 month before pregnancy through the third month of pregnancy. Because 56 cases and 12 controls met both exclusion criteria, the final analyses comprised 14,721 case mothers and 5,437 control mothers. Control infants included in the analyses of hypospadias were restricted to male infants only.

Statistical analysis

We conducted multiple logistic regressions using the covariates described previously to estimate relative risks using adjusted odds ratios and 95% confidence intervals. We evaluated the independent and joint effects of pre-existing diabetes and the absence of periconceptional intake of vitamins or supplements containing folic acid by comparing the risk for birth defects among four mutually exclusive groupings of mothers: (1) mothers without diabetes with periconceptional intake of vitamins or supplements containing folic acid (reference group); (2) mothers without diabetes with no periconceptional intake of vitamins (the "independent" effect of no periconceptional intake); (3) mothers with pre-existing diabetes with periconceptional intake of vitamins containing folic acid (the "independent" effect of preexisting diabetes); and (4) mothers with pre-existing diabetes with no periconceptional intake of vitamins (joint effect). To assess whether there was an interaction between diabetes and lack intake of vitamins containing folic acid that departed from additivity of effects, we calculated the relative

excess risk due to interaction (RERI) and its 95% confidence interval. The confidence intervals were calculated based on Taylor expansions of the variances and covariances from the multiple logistic regression models. A Microsoft Excel spreadsheet developed by Andersson and colleagues and available at *www.epinet.se* facilitated these calculations.[35] RERI estimates greater than zero suggested superadditive effects, while estimates equal to zero suggested additive effects only.

We assessed the sensitivity of our results to certain exclusions and definitions by looking at changes in estimates associated with: (1) the inclusion or exclusion of multiple gestations and a first-degree family history of birth defects (two strong, but uncommon, risk factors); (2) changes in the definition of periconceptional intake of vitamins or supplements containing folic acid (i.e., changes in the gestational months of periconceptional use); and (3) restricting the analyses to cases of isolated birth defects only. All analyses were conducted using SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The prevalence of pre-existing diabetes was 0.5% among control mothers and 2.4% among case mothers Reported use of vitamins containing folic acid in the periconceptional period (i.e., in the month before conception or the first 3 months of pregnancy) was similar among both groups, approximately 87%. Fifty-seven case mothers (0.4%) and only two control mothers were in the hypothesized group at highest risk—those with pre-existing diabetes and without periconceptional intake of vitamins containing folic acid. Case and control mothers differed in this joint distribution. They

also differed with respect to BMI, education, parity, household income, and timing of entry into prenatal care (Table 1).

Tables 2 and 3 show the independent and joint effect estimates of the association between maternal pre-existing diabetes and lack of periconceptional intake of vitamins or supplements containing folic acid and the occurrence of CHDs and non-cardiac birth defects, respectively. RERI could be calculated for nine of thirteen specific types of CHDs. For eight of these nine specific types of CHDs (Table 2), there was suggestion of superadditive effects (RERI estimate >0); for any CHD, there was an increased point estimate for the effect of pre-existing diabetes in the absence of periconceptional intake of vitamins containing folic acid compared with the effect of pre-existing diabetes in the presence of vitamin intake containing folic acid (e.g., any congenital heart defect: No, No = 1.13; Yes, Yes = 5.51; Yes, No = 13.35). For four CHD subtypes, there were no case infants in the highest risk group and, therefore, the RERI could not be calculated. Of the eight specific CHD subtypes with RERI estimates >0, six had estimates >2.0 and a point estimate for the joint effect of pre-existing diabetes in the absence of periconceptional intake of vitamins containing folic acid approximately two or more times that of the effect of pre-existing diabetes in the presence of periconceptional intake of vitamins. However, the RERI estimates were imprecise and did not reach statistical significance for any of the types of CHDs or CHD groups.

A similar pattern was seen for non-cardiac birth defects (Table 3). Independent and joint effects could be calculated for 13 out of 21 specific types of these birth defects, for 9 of which there were suggestive synergistic effects (RERI >0). The analyses for 8 of these 13 types of birth defects yielded RERI estimates >2.0 and an estimate of the odds of

a case for the joint effect of pre-existing diabetes with no periconceptional intake of vitamins containing folic acid approximately two or more times that of the odds of a case for pre-existing diabetes with periconceptional intake of vitamins containing folic acid. A negative RERI was obtained for only one type of birth defect, anotia-microtia. Again, however, the RERI estimates were imprecise and not statistically significant.

Sensitivity analyses restricting the study sample to singletons (94% of case infants; 97% of control infants) or to case infants without a first-degree family history of the birth defect of interest (94%−100% of each case group) and control infants without a first-degree family history of any birth defect (98% of control infants) did not yield meaningfully different results. Similarly, restricting the analyses to isolated case infants (or infants with simple, isolated CHD) or using a more conservative definition of supplement use (1 month before to 1 month after the date of conception) did not change the results appreciably, but increased the confidence intervals considerably and led to less distinction in effect estimates between the exposure groups (data not shown).

COMMENT

We found evidence for an association between pre-existing diabetes and increased risk for birth defects despite use of vitamins or supplements containing folic acid. Our findings for specific birth defects were limited by small numbers of case mothers jointly exposed to pre-existing diabetes and no periconceptional use of vitamins or supplements containing folic acid. However, there was evidence to suggest that offspring of mothers with pre-existing diabetes and no periconceptional use of vitamins or supplements containing folic acid experienced at least a non-statistically significant twofold greater

risk for birth defects when compared with offspring of mothers with pre-existing diabetes who reported periconceptional use of vitamins or supplements containing folic acid.

Strengths of this study included the large representative sample and standardized procedures for case definition and classification of birth defects. The control population was a representative sample of infants without defects from the delivery cohorts that gave rise to the infants with birth defects.[30, 36] Case infants were identified by population-based surveillance systems that used multiple sources for ascertainment. In addition, interview participation rates were comparable for case and control mothers and our findings changed little with adjustment for potential confounders.

Our classification of diabetes based on maternal reports of diagnosed diabetes was similar to that used in previous population-based, case-control studies of birth defects.[1, 37] As self-reports of diabetes tend to have less than 100% sensitivity,[38, 39] underreporting of diabetes by women with a prior diagnosis of diabetes probably resulted in a lower prevalence of pre-existing diabetes in pregnancy among our study controls (0.5%) than that reported among pregnant women in the general population (0.75%) where the diagnosis of pre-existing diabetes was based on hospital discharge data.[40] Because some women with diabetes might have been undiagnosed, it is possible that a fraction of the women who reported having no diabetes actually might have had undiagnosed type 2 diabetes, resulting in further exposure misclassification. Because there was no reason to believe that the resultant misclassification of diabetes status occurred differently for case and control mothers, the net effect of such misclassification probably was of an attenuation of associations of diabetes with birth defects.

The low prevalence of reported pre-existing diabetes limited our ability to obtain reliable estimates for the joint effect of pre-existing diabetes and lack of use of vitamins or supplements containing folic acid on the risk for birth defects. For about 33% (12/35) of the specific types of birth defects, we were not able to obtain an estimate of a joint effect due to a lack of case mothers in this exposure category. However, a consistent pattern of a greater odds ratio for the joint effect of pre-existing diabetes and no periconceptional vitamin or supplement use than for the independent effect of pre-existing diabetes (in the presence of periconceptional vitamin or supplement use) for about 75% (17/23) of the specific types of birth defects examined is noteworthy and warrants corroboration.

Our assessment of the independent and joint effects of diabetes and lack of use of supplements containing folic acid was based on the assumption that the level of glycemic control was similar across groups of women with diabetes regardless of supplement use. However, it is likely that women with diabetes who used supplements also planned their pregnancies and therefore may have had better glycemic control before and early in pregnancy than women with diabetes who did not use supplements and who may not have planned their pregnancies. As timely institution of intensive glycemic control for pregnant women with insulin-dependent diabetes has been associated with rates of birth defects similar to those observed among pregnant women who did not have diabetes,[4, 6, 41] it is possible that the apparent synergistic effects of diabetes and lack of supplement use may reflect underlying differences in pregnancy planning and diabetes control rather than an effect of lack of supplement use per se. This possibility remains an important consideration given that over 50% of women with diabetes do not plan their pregnancies

and that we did not have information on the level of glycemic control among case and control mothers.

The validity of self-reported supplement intake is likely to be high,[42, 43] particularly with regard to folic acid content, given the predominant intake of prenatal supplements that have relatively standard folic acid content. The extent of error in the reported dates of intake, however, is unknown. Our definition of supplement intake (i.e., any use during the month before conception or during the first 3 months of pregnancy) was more inclusive than the ones used in other studies and may explain the higher prevalence of supplement use observed in our study. We chose a more inclusive definition of supplement use in order to provide more precise point estimates for the associations of interest albeit at risk of being biased towards the null.

Our finding of no consistent association between neural tube defects and maternal supplement use among the offspring of women without pre-existing diabetes differed from observations in studies conducted before the era of folic acid fortification (i.e., 1998), which were generally consistent regarding a protective effect of periconceptional use of folic acid against neural tube defects and formed the basis for the US Public Health Service recommendation that women capable of becoming pregnant consume 400 μg of folic acid/day.[24, 25, 28] Our findings on neural tube defects and supplement use, however, were consistent with a report of recent decreases in the prevalence of low serum (<3 nanograms per milliliter [ng/mL]) and red blood cell (<140 ng/mL) folate levels among women of childbearing age in the United States (from 20.6% to 0.6% and from 37.6% to 5.5%, respectively, from the period 1988−1994 to the period 2003−2004).[44]

Another possibility that could explain the lack of a protective effect of supplement use against neural tube defects is that some pregnancies affected by neural tube defects in the study birth cohort were terminated without being enrolled in the study.

Our finding that offspring of women with pre-existing diabetes who reported no periconceptional use of vitamins or supplements containing folic acid appeared to be associated with at greater risk for birth defects than the offspring of women with pre-existing diabetes who had reported use of vitamins or supplements containing folic acid is consistent with that of a previous epidemiologic study.[29] This observation also is consistent with results from animal studies among pregnancies complicated by diabetes showing that administration of high doses of the antioxidant vitamins E and C,[18, 45] certain fatty acids,[20, 21, 46] or folic acid can prevent diabetic embryopathy.[22, 23, 47] In our study, we had adequate information to classify supplements containing folic acid, as well as those containing vitamin E or C. However, we had no information on the concentration of micronutrients or on the dose taken. Furthermore, we found a high concordance between intake of supplements containing folic acid and supplements containing vitamins E and C, which made it difficult to evaluate the independent and joint effects of intake of these different types of micronutrients. As in a previous study, we were not able to account for potential confounding by level of glycemic control, which still remains as another possible explanation for our findings.

The risk of birth defects among women with preexisting diabetes remains very high. Prevention of the excess of birth defects to children born to women with pre-existing diabetes would make a marked improvement in the health of children. So far we have made little progress in reaching this goal. The strongest evidence we have, and we

have only observational data, is that good glucose control before and early in pregnancy is associated with a lower risk of birth defects. Until there is better evidence, we should seek to improve glucose control of all women of reproductive age who have pre-existing diabetes, especially among those planning a pregnancy. All women of reproductive age should be encouraged to consume enough folic acid. In countries such as all of Europe where there is no required folic acid fortification, all women of reproductive age should be encouraged to consume folic acid containing vitamin supplements because it is known from randomized controlled trials that such consumption will prevent spina bifida and anencephaly. In countries like the United States and Canada where there is fortification, there is uncertainty about what additional prevention may occur from consuming a multivitamin with folic acid. Our data are consistent with the idea that such consumption may, but it is far from established, decrease the risk of certain birth defects among offspring of women with pre-existing diabetes.

Authorship Contributions

Adolfo Correa was responsible for: 1) substantial contributions to (a) the concept, design, overview of analysis, and interpretation of the data and (b) drafting and revising the manuscript critically for important intellectual content; and 2) final approval of the manuscript submitted.

Suzanne Gilboa was responsible for: 1) substantial contributions to (a) design, conduct of the analysis, summarizing the results, and interpretation of the data, and (b) drafting the methods and results sections, including the tables; and 2) final approval of the manuscript submitted.

Lorenzo Botto was responsible for: 1) substantial contributions to (a) concept and design, and (b) revising the manuscript critically for important intellectual content; and 2) final approval of the manuscript submitted.

Cynthia Moore was responsible for: 1) substantial contributions to (a) concept and design, and (b) revising the manuscript critically for important intellectual content; and 2) final approval of the manuscript submitted.

Charlotte Hobbs was responsible for: 1) substantial contributions to (a) concept and design, and (b) revising the manuscript critically for important intellectual content; and 2) final approval of the manuscript submitted.

Mario Cleves was responsible for: 1) substantial contributions to (a) analysis and interpretation of the data, and (b) revising the manuscript critically for important intellectual content; and 2) final approval of the manuscript submitted.

Tiffany Riehle-Colarusso was responsible for: 1) substantial contributions to (a) concept and design, and (b) revising the manuscript critically for important intellectual content; and 2) final approval of the manuscript submitted.

D. Kim Waller was responsible for: 1) substantial contributions to (a) analysis and interpretation of the data, and (b) revising the manuscript critically for important intellectual content; and 2) final approval of the manuscript submitted.

E. Albert Reece was responsible for: 1) substantial contributions to (a) concept and design, and (b) revising the manuscript critically for important intellectual content; and 2) final approval of the manuscript submitted.

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TABLE 1

Characteristics of mothers of infants born without birth defects (control infants) and mothers of case infants with selected birth defects, National Birth Defects Prevention Study, 1997−2004

	Control infants (n = 5,437)		Case infants (n = 14,721)		
	N	**%**	**N**	**%**	***P*-value**
Characteristic					
Pre-existing diabetes	29	0.5	346	2.4	<.0001
Periconceptional[a] intake of vitamins or supplements containing folic acid	4,764	87.6	12,791	86.9	0.17
Joint distribution of pre-existing diabetes and periconceptional[a] intake of vitamins or supplements containing folic acid					<.0001
No diabetes, yes periconceptional intake	4,737	87.1	12,502	84.9	
No diabetes, no periconceptional intake	671	12.3	1,873	12.7	
Yes preexisting diabetes, yes periconceptional intake	27	0.5	289	2.0	
Yes preexisting diabetes, no periconceptional intake	2	0.0	57	0.4	
Body mass index (kg/m^2)					0.002
<18.5	306	5.6	849	5.8	
18.5−<25.0	2,993	55.0	7,760	52.7	
25.0−<30.0	1,142	21.0	3,152	21.4	
≥30.0	788	14.5	2,420	16.4	
Missing	208	3.8	540	3.7	
Age (years)					0.71
<20	616	11.3	1,730	11.8	
20−24	1,249	23.0	3,482	23.7	
25−29	1,433	26.4	3,744	25.4	
30−34	1,398	25.7	3,615	24.6	
≥35	741	13.6	2,150	14.6	

Education					0.002
<High school	890	16.4	2,575	17.5	
High school	1,329	24.4	3,820	25.9	
>High school	3,166	58.2	8,202	55.7	
Missing	124	2.3	52	0.4	
Race and ethnicity					0.65
Non-Hispanic White	3,288	60.5	8,952	60.8	
Non-Hispanic Black or African American	623	11.5	1,517	10.3	
Hispanic	1,180	21.7	3,290	22.3	
Other	329	6.1	920	6.2	
Missing	17	0.3	42	0.3	
Parity					<.0001
First livebirth	2,235	41.1	6,567	44.6	
Second or subsequent livebirth	3,201	58.9	8,148	55.3	
Missing	1	0.0	6	0.0	
Multiple gestation pregnancy	155	2.9	911	6.2	<.0001
Household income ≥$40,000/year[b]	2,122	39.0	5,596	38.0	0.009
Entry into prenatal care at or before 10 weeks' gestation[c]	3,614	66.5	9,975	67.8	0.04

[a] Any intake in the month before conception or during the first 3months of pregnancy.

[b] Household income was missing for 3.0% of control and 6.5% of case infants.

[c]Prenatal care information was missing for 0.3% of control and 1.0% of case infants.

TABLE 2

Independent and joint effect estimates for maternal pre-existing diabetes, periconceptional intake of vitamins or supplements containing folic acid, and selected congenital heart defects, National Birth Defects Prevention Study, 1997−2004

Congenital heart defect	Maternal diabetes[a]	Use of vitamins[b]	Cases:Controls	OR (95% CI)[c]	RERI (95% CI)
Any congenital heart defect	No	Yes	5206:4737	Reference	7.71 (-11.55−26.97)
	No	No	773:671	1.13 (0.99−1.30)	
	Yes	Yes	180:27	5.51 (3.60−8.42)	
	Yes	No	35:2	13.35 (3.18−55.96)	
Heterotaxia	No	Yes	128:4737	Reference	Not calculated
	No	No	34:671	1.25 (0.76−2.05)	
	Yes	Yes	9:27	11.94 (5.06−28.20)	
	Yes	No	0:2	Not calculated	
Any conotruncal defect	No	Yes	1034:4737	Reference	5.73 (-14.71−26.18)
	No	No	140:671	1.09 (0.86−1.38)	
	Yes	Yes	41:27	6.41 (3.82−10.77)	
	Yes	No	7:2	12.23 (2.3−63.93)	
Truncus arteriosus	No	Yes	43:4737	Reference	28.89 (-114.00−171.78)
	No	No	6:671	1.22 (0.40−3.69)	
	Yes	Yes	6:27	24.93 (8.99−69.13)	
	Yes	No	2:2	54.04 (3.85−759.21)	
Tetralogy of Fallot	No	Yes	460:4737	Reference	11.91 (-18.19−42.02)
	No	No	59:671	0.99 (0.70−1.41)	
	Yes	Yes	16:27	4.57 (2.28−9.16)	
	Yes	No	3:2	16.48 (2.67−101.80)	

D-Transposition of the great arteries	No	Yes	320:4737	Reference	0.81 (-18.02−19.65)
	No	No	50:671	1.51 (1.05−2.17)	
	Yes	Yes	9:27	6.16 (2.80−13.56)	
	Yes	No	2:2	7.49 (0.65−85.72)	
Atrioventricular septal defect	No	Yes	122:4737	Reference	42.49 (-71.02−156.00)
	No	No	18:671	1.26 (0.69−2.29)	
	Yes	Yes	8:27	12.24 (5.17−28.93)	
	Yes	No	2:2	54.98 (7.00−432.12)	
Total anomalous pulmonary venous return	No	Yes	122:4737	Reference	Not calculated
	No	No	16:671	0.94 (0.50−1.76)	
	Yes	Yes	3:27	4.82 (1.40−16.64)	
	Yes	No	0:2	Not calculated	
Any left ventricular outflow tract obstruction defect	No	Yes	840:4737	Reference	1.59 (-9.34−12.51)
	No	No	84:671	0.79 (0.59−1.06)	
	Yes	Yes	19:27	4.01 (2.15−7.48)	
	Yes	No	2:2	5.39 (0.75−38.93)	
Hypoplastic left heart syndrome	No	Yes	246:4737	Reference	Not calculated
	No	No	21:671	0.58 (0.32−1.05)	
	Yes	Yes	6:27	3.42 (1.27−9.22)	
	Yes	No	0:2	Not calculated	
Coarctation of the aorta	No	Yes	434:4737	Reference	4.42 (-13.18−22.03)
	No	No	52:671	0.96 (0.67−1.38)	
	Yes	Yes	10:27	4.32 (2.02−9.24)	
	Yes	No	2:2	8.70 (1.19−63.88)	

Aortic stenosis	No	Yes	191:4737	Reference	Not calculated
	No	No	13:671	0.58 (0.30−1.13)	
	Yes	Yes	5:27	5.35 (1.95−14.68)	
	Yes	No	0:2	Not calculated	
Any right ventricular outflow tract obstruction defect	No	Yes	726:4737	Reference	4.58 (-9.47−18.63)
	No	No	112:671	1.28 (0.99−1.65)	
	Yes	Yes	15:27	2.83 (1.42−5.62)	
	Yes	No	3:2	7.69 (1.25−47.18)	
Pulmonary atresia	No	Yes	107:4737	Reference	12.38 (-26.41−51.61)
	No	No	14:671	1.06 (0.56−2.00)	
	Yes	Yes	2:27	3.01 (0.68−13.25)	
	Yes	No	1:2	15.45 (1.26−189.12)	
Pulmonary valve stenosis[d]	No	Yes	569:4390	Reference	2.43 (-9.61−14.47)
	No	No	86:599	1.29 (0.97−1.72)	
	Yes	Yes	12:24	3.22 (1.53−6.78)	
	Yes	No	2:2	5.94 (0.81−43.52)	
Ventricular septal defect–perimembranous	No	Yes	928:4737	Reference	5.35 (-12.16−22.86)
	No	No	152:671	1.25 (0.99−1.57)	
	Yes	Yes	28:27	4.43 (2.51−7.82)	
	Yes	No	5:2	10.03 (1.77−56.66)	
Atrial septal defect−secundum or not otherwise specified	No	Yes	1274:4737	Reference	9.45 (-15.70−34.59)
	No	No	227:671	1.25 (1.03−1.53)	
	Yes	Yes	56:27	6.76 (4.16−10.98)	
	Yes	No	11:2	16.46 (3.61−75.07)	

OR, odds ratio; *CI*, confidence interval; *RERI*, relative excess risk due to interaction.

[a] For maternal diabetes: Yes = pree-xisting diabetes; No = no diabetes of any type.

[b] For use of vitamins: Yes = any use from the period of 1 month before pregnancy through the third month of pregnancy of a vitamin or supplement containing folic acid; No = no use during the month before conception and the first 3 months of pregnancy of a vitamin or supplement containing folic acid.

[c] Adjusted for maternal age, race and ethnicity, entry into prenatal care, prepregnancy body mass index, parity, and household income.

[d] Note different number of control infants for pulmonary valve stenosis because of limited ascertainment in California.

TABLE 3

Independent and joint effect estimates for maternal pre-existing diabetes, periconceptional intake of vitamins or supplements containing folic acid, and selected non-cardiac birth defects, National Birth Defects Prevention Study, 1997−2004

Birth defect	Maternal diabetes[a]	Use of vitamins[b]	Cases:Controls	OR (95% CI)[c]	RERI (95% CI)
Any birth defect	No	Yes	12502:4737	Reference	5.92 (-7.96−19.79)
	No	No	1873:671	1.12 (1.00−1.26)	
	Yes	Yes	289:27	3.27 (2.46−5.63)	
	Yes	No	57:2	9.77 (2.38−40.12)	
Any neural tube defect	No	Yes	787:4737	Reference	6.65 (-7.83−21.14)
	No	No	138:671	1.08 (0.84−1.38)	
	Yes	Yes	10:27	1.66 (0.73−3.74)	
	Yes	No	4:2	8.39 (1.50−46.89)	
Anencephaly	No	Yes	233:4737	Reference	29.72 (-28.54−87.99)
	No	No	32:671	1.03 (0.65−1.63)	
	Yes	Yes	2:27	1.80 (0.42−7.81)	
	Yes	No	3:2	31.56 (4.98−199.94)	
Spina bifida	No	Yes	470:4737	Reference	0.69 (-5.25−6.64)
	No	No	84:671	1.02 (0.75−1.38)	
	Yes	Yes	5:27	1.66 (0.62−4.42)	
	Yes	No	1:2	2.37 (0.21−26.68)	
Encephalocele	No	Yes	84:4737	Reference	Not calculated
	No	No	22:671	1.60 (0.88−2.92)	
	Yes	Yes	3:27	1.84 (0.24−14.13)	
	Yes	No	0:2	Not calculated	

Hydrocephaly	No	Yes	204:4737	Reference	20.03 (-26.68−66.74)
	No	No	34:671	0.97 (0.60−1.55)	
	Yes	Yes	8:27	5.63 (2.36−13.41)	
	Yes	No	3:2	25.63 (4.16−158.02)	
Holoprosencephaly	No	Yes	48:4737	Reference	Not calculated
	No	No	13:671	1.52 (0.69−3.39)	
	Yes	Yes	2:27	9.06 (1.97−41.77)	
	Yes	No	0:2	Not calculated	
Anotia-Microtia	No	Yes	263:4737	Reference	-1.51 (-16.30−13.28)
	No	No	53:671	1.01 (0.69−1.48)	
	Yes	Yes	13:27	7.07 (3.27−15.28)	
	Yes	No	1:2	5.57 (0.46−66.97)	
Choanal atresia	No	Yes	70:4737	Reference	Not calculated
	No	No	9:671	1.27 (0.55−2.95)	
	Yes	Yes	0:27	Not calculated	
	Yes	No	1:2	45.96 (3.54−597.50)	
Any oral cleft[d]	No	Yes	1835:4613	Reference	11.36 (-9.78−32.51)
	No	No	315:665	1.30 (1.09−1.55)	
	Yes	Yes	23:27	2.17 (1.20−3.93)	
	Yes	No	11:2	13.84 (3.01−63.68)	
Cleft palate[d]	No	Yes	642:4613	Reference	0.50 (-8.14−8.24)
	No	No	103:665	1.54 (1.18−2.01)	

	Yes	Yes	10:27	2.68 (1.26−5.68)	
	Yes	No	1:2	3.27 (0.29−37.13)	
Cleft lip with or without cleft palate[d]	No	Yes	1193:4613	Reference	17.30 (-12.59−47.19)
	No	No	212:665	1.20 (0.98−1.47)	
	Yes	Yes	13:27	1.83 (0.88−3.77)	
	Yes	No	10:2	19.33 (4.12−90.69)	
Esophageal atresia	No	Yes	311:4737	Reference	Not calculated
	No	No	38:671	1.03 (0.66−1.59)	
	Yes	Yes	6:27	3.25 (1.28−8.24)	
	Yes	No	0:2	Not calculated	
Ileal, jejunal, and multiple small intestinal atresias	No	Yes	182:4737	Reference	Not calculated
	No	No	34:671	1.32 (0.85−2.04)	
	Yes	Yes	0:27	Not calculated	
	Yes	No	0:2	Not calculated	
Anorecal atresia	No	Yes	422:4737	Reference	23.87 (-23.81−71.54)
	No	No	72:671	1.42 (1.03−1.95)	
	Yes	Yes	12:27	4.41 (2.08−9.38)	
	Yes	No	5:2	28.70 (5.46−150.97)	
Biliary atresia	No	Yes	73:4737	Reference	45.05 (-75.08−165.19)
	No	No	11:671	1.13 (0.55−2.33)	
	Yes	Yes	1:27	2.56 (0.33−19.53)	
	Yes	No	1:2	47.74 (3.85−592.05)	

Hypospadias[d]	No	Yes	966:2374	Reference	1.51 (-9.19−12.22)
	No	No	76:338	0.84 (0.60−1.15)	
	Yes	Yes	17:16	2.44 (1.14−5.20)	
	Yes	No	1:1	3.78 (0.23−61.46)	
Bilateral renal agenesis/hypoplasia	No	Yes	67:4737	Reference	Not calculated
	No	No	17:671	2.38 (1.25−4.51)	
	Yes	Yes	4:27	12.24 (3.94−38.07)	
	Yes	No	1:2	Not calculated	
Any limb deficiency	No	Yes	500:4737	Reference	9.86 (-17.09−36.81)
	No	No	76:671	1.00 (0.73−1.37)	
	Yes	Yes	15:27	4.87 (2.44−9.72)	
	Yes	No	3:2	14.73 (2.39−90.85)	
Longitudinal limb deficiency	No	Yes	188:4737	Reference	18.48 (-31.43−68.40)
	No	No	25:671	0.94 (0.57−1.56)	
	Yes	Yes	7:27	6.37 (2.52−16.09)	
	Yes	No	2:2	24.79 (3.34−184.23)	
Transverse limb deficiency	No	Yes	289:4737	Reference	Not calculated
	No	No	48:671	1.04 (0.69−1.55)	
	Yes	Yes	4:27	2.43 (0.83−7.15)	
	Yes	No	0:2	Not calculated	
Craniosynostosis	No	Yes	551:4737	Reference	Not calculated
	No	No	52:671	0.98 (0.70−1.37)	

	Yes	Yes	5:27	1.57 (0.59−4.21)	
	Yes	No	0:2	Not calculated	
Diaphragmatic hernia	No	Yes	355:4737	Reference	4.34 (-10.83−19.50)
	No	No	45:671	0.86 (0.57−1.29)	
	Yes	Yes	5:27	2.00 (0.69−5.86)	
	Yes	No	1:2	6.20 (0.55−70.06)	
Omphalocele	No	Yes	194:4737	Reference	Not calculated
	No	No	26:671	1.09 (0.66−1.79)	
	Yes	Yes	4:27	2.77 (0.93−8.28)	
	Yes	No	0:2	Not calculated	
Gastroschisis	No	Yes	496:4737	Reference	Not calculated
	No	No	99:671	0.93 (0.69−1.25)	
	Yes	Yes	1:27	0.41 (0.05−3.49)	
	Yes	No	0:2	Not calculated	
Sacral agenesis	No	Yes	23:4737	Reference	98.41 (-314.14−510.96)
	No	No	3:671	1.56 (0.41−5.96)	
	Yes	Yes	9:27	82.35 (26.22−258.65)	
	Yes	No	2:2	181.32 (18.16−1810.96)	

OR, odds ratio; *CI*, confidence interval; *RERI*, relative excess risk due to interaction.

[a] For maternal diabetes: Yes = pre-existing diabetes; No = no diabetes of any type.

[b] For use of vitamins: Yes = any use from the period of 1 month before pregnancy through the third month of pregnancy of a vitamin or supplement containing folic acid; No = no use during the month before conception and the first 3months of pregnancy of a vitamin or supplement containing folic acid.

[c] Adjusted for maternal age, race and ethnicity, entry into prenatal care, prepregnancy body mass index, parity, and household income.

[d] Note different number of control infants for oral clefts due to limited ascertainment in Utah, and different number of control infants for hypospadias due to restriction to males.