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Periconceptional nutrient intakes and risks of conotruncal heart defects

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Abstract

Evidence exists for an association between maternal use of a vitamin supplement with folic acid in early pregnancy and a reduced risk for offspring with conotruncal heart defects. Few inquiries about periconceptional nutrition, other than folate, and risk of heart defects have been made. Data derived from a population-based case-control study of fetuses and liveborn infants among a cohort of California births between July 1999 and June 2004. In total, 76% of eligible case mothers and 77% of eligible control mothers were interviewed. Cases included 140 with d-transposition of great arteries (dTGA), and 163 with tetralogy of Fallot (TOF). Total number of controls was 698. Self-reported use of vitamins was elicited by questionnaire for the periconceptional period. Dietary nutrient intake was elicited by a well-known food frequency questionnaire. The odds ratio for dTGA associated with supplemental vitamin use was 1.0 (95% confidence interval, 0.7-1.5) and for TOF was 0.9 (0.6-1.3). We observed increased risks associated with lower dietary intakes of linoleic acid, total carbohydrate, and fructose for dTGA, whereas decreased risks were observed for lower intakes of total protein and methionine for TOF. Lower dietary intake of several micronutrients, namely folate, niacin, riboflavin, and vitamins B₁₂, A, and E, even after simultaneous adjustment for other studied nutrients, were associated with increased risks of dTGA, but not for TOF. These associations were observed among women who did not use vitamin supplements periconceptionally. Analytic consideration of several potential confounders did not reveal alternative interpretations of the results. Our population-based case-control study attempted to extend the knowledge base on nutrition and heart defect risk and prevention.

Introduction

Congenital heart defects comprise the most common group of human malformations, affecting nearly 1 in 100 births (1,2). Despite their sizable contribution to child morbidity and infant mortality, etiologies of the majority of heart defects remain unknown. Within the overall group of heart defects those known as conotruncal defects are some of the more common phenotypes. Conotruncal defects may be associated with chromosomal abnormalities (3-7), especially 22q11 microdeletion (7,8), Mendelian disorders (9,10), and teratogens (11,12). Individually, each suspected "cause" is rare.

One promising clue to etiologies of conotruncal heart defects has been that women who use vitamins containing folic acid in early pregnancy are at approximately a 30% reduced risk to deliver offspring with these heart defects (13-17). Folic acid supplementation has been the

focus for the preponderance of inquiries about periconceptional nutrition and risks of heart defects, and birth defects more generally. There are very limited data about maternal dietary intakes of other nutrients, particularly for infants born with specific heart defect phenotypes.

In the present analysis, we investigated the previously observed association between conotruncal heart defects, specifically d-transposition of the great arteries and tetralogy of Fallot, and periconceptional vitamin use, and potential associations with numerous other dietary nutrients. These inquiries were made by analyzing data collected in a recent population-based case-control study conducted 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. The study included data on deliveries that had estimated due dates from July 1999 to June 2004. Case information was abstracted from multiple hospital reports and medical records and then reviewed by a clinical geneticist (EJL). Infants diagnosed with single gene disorders or chromosomal aneusomies (based on information gathered from chart reviews) were ineligible (8). Cases included the conotruncal heart defects d-transposition of the great arteries (dTGA) and tetralogy of Fallot (TOF). Infants with dTGA or TOF associated with an endocardial cushion defect or with double outlet right ventricle were excluded. For each case, anatomic and physiologic features were confirmed by reviewing echocardiography, cardiac catheterization, surgery, or autopsy reports. Non-malformed, 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).

Mothers were eligible for 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, and no earlier than 6 weeks after the infant's estimated date of delivery. A variety of exposures were assessed, focusing on the periconceptional time period, which was defined as 2 months before through 2 months after conception. For example, queries specific to the periconceptional period included use of folic-acid containing vitamin supplements, use of alcohol and cigarettes, diabetes (gestational, Type I, and Type II), and seizure medication use. Body mass index (BMI) was estimated for each woman based on reported prepregnant weight and height (kg/m^2).

The interview also included a modified version of the National Cancer Institute's Health Habits and History Questionnaire, a well-known, semi-quantitative food frequency questionnaire with demonstrated reliability and validity (18,19). The food frequency questionnaire was modified to include ethnic foods appropriate to a diverse study population. This questionnaire provided information on numerous dietary nutrients examined below.

In total, 76% of eligible case mothers (176 TOF, 142 dTGA) 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 non-participants declined interview. Median time between estimated date of delivery and interview completion was 11 months for cases and 8 months for controls. Cases and controls with mothers who had type I or II diabetes were excluded from

analyses, given that those subjects may be different etiologically. After exclusions, available for analyses were 698 controls, 163 cases with TOF, and 140 cases with dTGA.

Analyses were performed for dTGA and TOF separately. We estimated risks using odds ratios (ORs) and 95% confidence intervals (SAS 9.1). We estimated dTGA and TOF risks associated with maternal periconceptional vitamin use alone as well as adjusted for potential confounding effects associated with maternal race/ethnicity, age, and education using logistic regression models.

Models were constructed to assess effects associated with categories of dietary nutrients. Specifically, we categorized nutrients as <25th percentile, 25th-74th percentile, and ≥ 75 th percentile based on the distribution of each nutrient among controls. The 25th-74th category served as the reference for risk estimation. For analyses involving maternal intakes of total fat (g), linoleic acid (g), oleic acid (g), total carbohydrates (g), fructose (g), glucose (g), galactose (g), sucrose (g), glycemic index, total protein (g), methionine (mg), choline (mg), and betaine (mg), we estimated risks based on these categories. For analyses involving maternal intakes of folate (mcg, dietary folate equivalents), niacin (mg), riboflavin (mg), thiamin (mg), vitamin B₆ (mg), vitamin B₁₂ (mcg), vitamin C (mg), vitamin E (mg), vitamin A (retinol equivalents), lutein (mcg), lycopene (mcg), zinc (mg), iron (mg), magnesium (mg), and calcium (mg), we restricted analyses to women who did not use vitamin supplements in the periconceptional period under the assumption that women who did not use supplements would have a different risk of offspring with dTGA or TOF than would women who used supplements and because these nutrients are likely contained in vitamin supplements. All nutrient analyses were adjusted for energy (kcal) intake, and further adjusted for maternal race/ethnicity (Latina, foreign-born; Latina, US-born; white, nonLatina; other), education (<high school; high school graduate; some college; college graduate or more), age (<25; 25-29; 30-34; and >34 years), gravidity (0,1,2, and >2), cigarette smoking (yes or no), alcohol use (yes or no), and body mass index (kg/m²). We also compared results including and excluding infants with a history of a heart defect in a first degree relative of the proband.

Results

As shown in Table 1, compared with control mothers, mothers of infants with dTGA and TOF were more likely to be nonHispanic white, and mothers of infants with dTGA were more likely to have college degrees or more. Infants with dTGA were more likely to be male than control infants.

Also in Table 1 is the frequency of periconceptional use of supplemental vitamins that contained folic acid. The odds ratio (OR) for dTGA associated with supplemental vitamin use was 1.0 (95% confidence interval, 0.7-1.5) and for TOF was 0.9 (0.6-1.3). Adjusting for maternal race/ethnicity, age, and education revealed an OR of 0.9 (0.6-1.3) for dTGA and of 0.9 (0.6-1.4) for TOF. We also investigated risks associated with vitamin supplement use across quartile categories of dietary folate postulating that maternal periconceptional use of supplements would reveal the strongest effect among those whose dietary folate intake was the lowest. We observed some evidence for this for dTGA. That is, among those with the lowest quartile, the 25th-74th quartiles, and the highest quartile of dietary folate intakes we observed the following ORs for supplement use for dTGA 0.6 (0.3-1.2), 1.1 (0.7-1.9), and 2.0 (0.8-5.4), respectively. ORs for supplement use for TOF were 0.8 (0.4-1.5), 1.1 (0.6-1.7), and 0.6 (0.3-1.4), respectively.

Displayed in Table 2 are ORs, relative to the 25th-75th percentile, for dTGA and TOF, for maternal intakes of fat, linoleic acid, oleic acid, total carbohydrates, fructose, glucose, galactose, sucrose, glycemic index, total protein, methionine, choline, and betaine. We

observed increased risks of dTGA ($\geq 50\%$) associated with 1) lowest quartile intakes of linoleic acid, total carbohydrate, and fructose, and 2) highest quartile intakes of galactose. For TOF, decreased risks ($\geq 50\%$) were observed for lowest quartile intakes of total protein and methionine associated with lowest quartile intakes. Observed risk estimates were not substantially altered after adjustment for maternal race/ethnicity, age, education, energy intake, body mass index, smoking, alcohol use, periconceptional vitamin supplement use, and gravidity (not shown).

Results of analyses involving maternal intakes of the micronutrients folate, niacin, riboflavin, thiamin, vitamin B₆, vitamin B₁₂, vitamin C, vitamin E, vitamin A, lutein, lycopene, zinc, iron, magnesium, and calcium are displayed in Table 3 for dTGA and Table 4 for TOF. These analyses were restricted to the subset of women who did not use vitamin supplements in the periconceptional period. These nutrient quartile analyses were adjusted for energy (kcal) intake. For dTGA, ORs were elevated for the lowest quartiles of intake of each nutrient, except for lutein and lycopene (Table 3). Also shown in Table 3 is that observed risks became larger after adjustment for energy intake, race/ethnicity, age, education, body mass index, smoking, alcohol use, gravidity, and child sex. Simultaneous adjustment of all nutrients (including energy intake) appeared to attenuate risks somewhat, but substantially elevated risks ($>50\%$) remained for lowest quartile intakes of folate, niacin, riboflavin, vitamin B₁₂, vitamin E, and vitamin A (not shown).

For TOF (Table 4), the same general risk pattern seen for dTGA was not observed. In terms of low quartile intakes and increased risk, only intakes of vitamin C and calcium were associated with increased risks. Higher quartile intakes of niacin, thiamin, zinc, iron, and magnesium were associated with increased ($\geq 50\%$) risks. Many of these ORs were imprecise and therefore their interpretation is consistent with random variation. Further, adjustment for energy intake, race/ethnicity, age, education, body mass index, smoking, alcohol use, gravidity, and child sex did not provide substantially different results (Table 4). Elevated risks associated with low quartile intakes of vitamin C and calcium were also observed after simultaneous adjustment of all nutrients (not shown). Further, after simultaneous adjustment of all nutrients, elevated risks associated with high quartile intakes were only observed for iron and magnesium (not shown). The OR for magnesium was substantially altered, OR=5.2 (1.5-18.6).

Discussion

Our analyses investigated whether women's intake of selected nutrients in the periconceptional period, including folate, decreased or increased risks of two conotruncal heart defects, dTGA and TOF. These data did not find reduced risks for either phenotype associated with maternal intake of vitamin supplements containing folic acid. Some evidence was observed for increased risks associated with lower dietary intakes of linoleic acid, total carbohydrate, and fructose for dTGA, whereas decreased risks were observed for lower intakes of total protein and methionine for TOF. Lower dietary intake of several micronutrients, namely folate, niacin, riboflavin, and vitamins B₁₂, A, and E, even after simultaneous adjustment for other studied nutrients, were associated with increased risks of dTGA, but not for TOF. These associations were observed among women who did not use vitamin supplements periconceptionally - the implication being that these women would have the lowest overall intakes of these nutrients. Analytic consideration of several potential confounders did not reveal alternative interpretations of the results.

Our observations contribute to the limited body of evidence suggesting that components of a woman's periconceptional diet may influence risks of heart defects in her offspring. However, not observing a reduced risk of these conotruncal heart defects associated with periconceptional folate intake is inconsistent with some earlier studies (14-17), but not all (20-23). The reason

for the lack of an association in the current study is unknown. We speculated that the protection afforded by folic acid through supplements might no longer be operating owing to higher dietary levels of folic acid from fortification of the US food supply during the study time period. Thus, we estimated risks associated with maternal supplement use among women whose dietary folate intake was within the lowest quartile of intake of all control mothers. The use of vitamin supplements was associated with somewhat reduced risks among this subset of the study population, but the estimated risks were imprecise.

Although we did not observe an association with the use of vitamin supplements that contained folic acid, we did observe that low folate intake from diet among women who did not use supplements was associated with an increased risk of dTGA, suggesting low levels of intake are a risk factor. Of note, however, low levels of several other nutrients, including niacin, riboflavin, thiamin, and vitamins B₆, B₁₂, C, E, and A, were associated with increased risk of dTGA (Table 3). Despite the fact that these associations were also observed for each nutrient simultaneously adjusted for the others, the results cannot fully distinguish between potentially poorer composite dietary quality and lower intake of a single nutrient.

Although folic acid intake has been the focus for many of the inquiries about periconceptional nutrition and heart defects, there have been a few observations made about other nutrients. In particular, a Dutch study recently reported higher risks of a collection of heart defect phenotypes (approximately 25% of which were dTGA and TOF) among mothers with 1) higher intakes of vitamin E (24) and 2) lower intakes of riboflavin and nicotinamide (a niacin metabolite), particularly among nonsupplement users (25). The latter finding is supported by our finding (Table 3) that low dietary intakes of niacin and riboflavin were associated with increased risk of dTGA. The Dutch study did not observe associations with folic acid supplement use or dietary folate intake. We did not find evidence in the current study to support their observation that increased intake of vitamin E was a risk factor for selected heart defects. Indeed, data shown in Table 3 indicate that lower intake of vitamin E may be a risk factor for dTGA. In additional analyses (not shown), we did not observe elevated risks of dTGA or TOF among women who used vitamin supplements (usually a source of vitamin E) and had intakes of dietary vitamin E in the highest quartile.

Our observations involving B vitamins (folate, B₁₂, B₆) support previous findings from four small studies (26-31) that have indicated that compromised homocysteine remethylation and lack of methyl group nutrients may contribute to risks of heart defects. Methylation of DNA is influenced by dietary contributions of nutrients that contribute to the methyl donor pathway such as folate and vitamin B₁₂. A less than optimal methyl-donor supply has been suggested as an area of research focus for certain birth defects (32). A Netherlands study (26) observed that median fasting plasma homocysteine was higher and mean plasma B₁₂ levels were lower in mothers of children with heart defects. Similarly, an Arkansas study (27-29) observed plasma concentrations that were substantially higher in homocysteine, substantially lower in methionine, and lower in folate and B₁₂, in mothers who had delivered babies with heart defects compared to mothers who delivered babies without birth defects. These studies analyzed all heart defects as a single group, which included various phenotypes such as conotruncal and septal defects. A third study (30) reported an increased risk for heart defects among Dutch women who had compromised B₁₂ status and who had the methionine synthase reductase *MTRR* 66GG genotype. A fourth study (31) found an elevated risk of heart defects among Dutch mothers with lower B₁₂ levels and who had the transcobalamin II (rs1801198) genotype 776GG, which is related to B₁₂ transport.

The strengths of our study include its population-based ascertainment of cases and controls, its relatively short period for maternal recall between periconceptional event of interest and interview, its relatively high participation by study subjects, and its separate investigation of

the two most frequent conotruncal phenotypes. Nevertheless, our study had some potentially important limitations. Some of our analytic models included nutrients that were correlated; thus, precision of risk estimation was reduced in some circumstances. These data relied upon a food frequency questionnaire to assess nutrient intake. Limitations of this type of instrument have been described (33-35). Although the instrument we used was not internally validated, validation studies have revealed that it provides reasonable estimates of usual dietary intake for diets consumed by women even in the distant past. Indeed, many studies have demonstrated the utility of this type of instrument for estimating most nutrients with recent studies, for example, showing these instruments utility of estimating glycemic load and choline (36,37). This study estimated risks for intake levels of nutrients. Given individual variation in gut absorption and maternal-fetal exchange, it is unknown how well maternal intake approximates the level of a particular nutrient that reaches the developing fetus. Lastly, additional study of genetic variants coupled with nutrient measures would be informative owing to the known or suspected function of selected genes (38).

Evidence continues to accumulate to show that nutrients, particularly folate, influence risks of structural birth defects. Our results substantially extend observations that other nutrients may also be important in heart development.

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Table 1

Characteristics of cases and controls.

	d-Transposition of the Great Arteries, n=140 (%)^I	Tetralogy of Fallot, n=163 (%)^I	Controls, n=698 (%)^I
Maternal Race/Ethnicity			
US-born Hispanic	29 (21)	19 (12)	154 (22)
Foreign-born Hispanic	50 (36)	61 (37)	263 (38)
Non-Hispanic White	38 (27)	48 (29)	144 (21)
Other	21 (15)	32 (20)	127 (18)
Maternal Age			
<25	36 (26)	43 (26)	215 (31)
25-29	29 (21)	38 (23)	160 (23)
30-34	44 (31)	43 (26)	193 (28)
>34	30 (21)	39 (24)	127 (18)
Maternal Education			
<High School	34 (24)	41 (25)	200 (29)
High School	24 (17)	34 (21)	166 (24)
Some College	32 (23)	43 (26)	151 (22)
≥4-year College Degree	48 (34)	42 (26)	168 (24)
Periconceptional use of vitamins with folic acid			
Yes	86 (61)	96 (59)	426 (61)
No	53 (38)	67 (41)	270 (39)
Cigarette use			
No	135 (96)	148 (91)	636 (91)
Yes	4 (3)	13 (8)	54 (8)
Alcohol use			
No	107 (76)	129 (79)	566 (81)
Yes	32 (23)	32 (20)	122 (17)
Gravidity			
0	31 (22)	41 (25)	207 (30)
1	41 (29)	39 (24)	189 (27)
2	28 (20)	36 (22)	136 (19)
>2	40 (29)	47 (29)	165 (24)
History of Heart Defect in First Degree Relative of Proband			
Yes	2 (1)	3 (2)	0 (0)
No	138 (99)	160 (98)	698 (100)
Child Sex			
Male	96 (69)	80 (49)	364 (52)
Female	44 (31)	83 (51)	334 (48)
Daily Energy Intake	2605 (1056)	2565 (893)	2692 (964)

	d-Transposition of the Great Arteries, n=140 (%)^I	Tetralogy of Fallot, n=163 (%)^I	Controls, n=698 (%)^I
(Kcal), mean (SD)			
Body Mass Index (Kg/M²), mean (SD)	24.8 (5.5)	23.9 (4.7)	24.7 (5.4)

^I Percentages may not equal 100 owing to missing data or rounding.

Table 2

Risks of d-transposition of the great arteries (dTGA) and Tetralogy of Fallot (TOF) associated with periconceptional dietary nutrient intakes, California 1999-2004.

Nutrient Quartiles ¹	dTGA Cases ²	dTGA Odds Ratio ³	95% CI	TOF Cases ²	TOF Odds Ratio ³	95% CI
Total fat (g)						
< 84.9	41	1.2	0.7-2.0	43	0.9	0.5-1.5
84.9 – 143.0	63	Ref		80	Ref	
≥ 143.1	33	1.2	0.6-2.3	34	1.1	0.6-2.1
Linoleic acid (g)						
< 14.0	47	1.6	1.0-2.6	40	0.8	0.5-1.3
14.0 – 29.0	61	Ref		87	Ref	
≥ 29.1	29	0.9	0.5-1.5	30	0.8	0.5-1.2
Oleic acid (g)						
< 31.2	37	1.0	0.6-1.6	37	0.7	0.4-1.1
31.2 – 55.2	68	Ref		85	Ref	
≥ 55.3	32	1.1	0.6-2.0	35	1.2	0.7-2.0
Total carbohydrate(g)						
< 226.0	47	1.7	1.0-3.0	50	1.4	0.9-2.4
226.0 – 381.9	57	Ref		79	Ref	
≥ 382.0	33	1.1	0.5-2.1	28	0.6	0.3-1.1
Fructose (g)						
< 22.8	50	1.8	1.2-2.9	50	1.2	0.8-1.9
22.8 – 48.8	55	Ref		79	Ref	
≥ 48.9	32	1.2	0.7-1.9	28	0.7	0.4-1.2
Glucose (g)						
< 19.5	39	1.1	0.7-1.8	53	1.4	0.9-2.2
19.5 – 40.7	65	Ref		73	Ref	
≥ 40.8	33	1.1	0.7-1.8	31	0.9	0.5-1.4
Galactose (g)						

Nutrient Quartiles ¹	dTGA Cases ²	dTGA Odds Ratio ³	95% CI	TOF Cases ²	TOF Odds Ratio ³	95% CI
<0.3	30	1.0	0.6-1.6	39	1.0	0.6-1.5
0.3 – 0.9	59	Ref		77	Ref	
≥ 1.0	48	1.8	1.2-2.9	41	1.2	0.8-1.8
Sucrose (g)						
< 26.9	41	1.3	0.8-2.0	53	1.4	0.9-2.2
26.9 – 51.9	59	Ref		74	Ref	
≥ 52.0	37	1.4	0.8-2.4	30	0.8	0.5-1.4
Glycemic Index						
< 49.4	37	1.0	0.7-1.6	35	0.8	0.5-1.2
49.4 – 53.1	72	Ref		86	Ref	
≥ 53.2	28	0.8	0.5-1.2	36	0.8	0.5-1.3
Total protein (g)						
< 75.0	42	1.2	0.7-2.2	33	0.5	0.3-0.9
75.0 – 131.8	61	Ref		91	Ref	
≥ 131.9	34	1.3	0.7-2.4	33	1.2	0.7-2.2
Methionine (mg)						
< 1526.4	40	1.1	0.6-1.9	30	0.4	0.3-0.7
1526.4 – 2695.7	62	Ref		94	Ref	
≥ 2695.8	35	1.4	0.8-2.6	33	1.2	0.7-2.1
Choline (mg)						
< 291.0	39	1.1	0.6-1.8	41	0.8	0.5-1.4
291.0 – 509.9	66	Ref		86	Ref	
≥ 510.0	32	1.1	0.6-2.0	30	0.8	0.5-1.5
Betaine (mg)						
< 88.4	40	1.2	0.7-1.9	36	0.7	0.4-1.1
88.4 – 193.3	63	Ref		93	Ref	
≥ 193.4	34	1.2	0.7-2.0	28	0.7	0.4-1.2

¹ Quartiles, denoted as Q1 – Q4, determined from intake levels among control mothers.

²The number of controls in each quartile was 162, 324, and 163 for Q1, Q2-3, and Q4, respectively.

³Odds ratio adjusted for maternal total energy intake.

Table 3

Risks of d-transposition of the great arteries (dTGA) associated with periconceptional dietary nutrient intakes for women who did not use vitamin supplements, California 1999-2004.

Nutrient Quartile/ Folate (µg)	Cases	Controls	Odds Ratio ²	95% CI	Odds Ratio ³	95% CI
< 293.8	20	61	2.2	1.0-4.9	3.1	1.2-7.8
293.8 – 546.3	26	124	Ref		Ref	
≥ 546.4	6	66	0.3	0.1-0.8	0.2	0.1-0.7
Niacin (mg)						
< 18.3	21	61	2.9	1.2-7.0	3.8	1.4-10.5
18.3 – 31.5	17	126	Ref		Ref	
≥ 31.6	14	64	1.4	0.5-3.7	2.2	0.7-6.8
Riboflavin (mg)						
< 1.8	21	60	3.1	1.3-7.4	3.7	1.4-9.8
1.8 – 3.2	20	123	Ref		Ref	
≥ 3.3	11	68	0.6	0.2-1.7	0.6	0.2-1.9
Thiamin (mg)						
< 1.4	20	67	2.1	0.9-5.1	2.8	1.0-7.7
1.4 – 2.3	20	124	Ref		Ref	
≥ 2.4	12	60	1.1	0.4-3.1	1.2	0.4-4.1
Vitamin B ₆ (mg)						
< 1.8	16	59	1.5	0.6-3.4	2.0	0.7-5.2
1.8 – 3.1	25	126	Ref		Ref	
≥ 3.2	11	66	0.8	0.3-1.9	0.7	0.2-2.0
Vitamin B ₁₂ (µg)						
< 3.6	20	54	3.1	1.3-7.3	4.0	1.6-10.4
3.6 – 7.0	19	130	Ref		Ref	
≥ 7.1	13	67	1.1	0.4-2.6	1.2	0.4-3.3
Vitamin C (mg)						

Nutrient Quartile ¹	Cases	Controls	Odds Ratio ²	95% CI	Odds Ratio ³	95% CI
< 138.8	18	58	1.6	0.8-3.3	2.2	1.0-4.9
138.8 – 289.8	24	121	Ref		Ref	
≥ 289.9	10	72	0.7	0.3-1.5	0.6	0.2-1.6
Vitamin E (mg)						
< 11.6	16	50	1.9	0.9-4.1	3.3	1.3-8.1
11.6 – 20.5	22	128	Ref		Ref	
≥ 20.6	14	73	1.1	0.5-2.5	1.2	0.5-3.2
Vitamin A (RE)						
< 1044.7	22	63	2.7	1.2-5.9	3.4	1.4-8.6
1044.7 – 2152.5	19	122	Ref		Ref	
≥ 2152.6	11	66	0.9	0.4-2.2	0.6	0.2-1.8
Lutein (µg)						
< 1238.8	17	73	0.9	0.5-1.8	1.0	0.5-2.3
1238.8 – 5188.9	30	119	Ref		Ref	
≥ 5189.0	5	59	0.3	0.1-0.9	0.3	0.1-0.8
Lycopene (µg)						
< 2457.0	16	71	1.1	0.5-2.3	1.7	0.7-4.1
2457.0 – 7085.7	22	116	Ref		Ref	
≥ 7085.8	14	64	1.3	0.6-2.9	1.4	0.6-3.3
Zinc (mg)						
< 10.2	18	57	2.0	0.9-4.9	3.1	1.1-8.5
10.2 – 18.4	18	131	Ref		Ref	
≥ 18.5	16	63	2.1	0.8-5.6	2.7	0.9-8.2
Iron (mg)						
< 12.9	18	66	1.6	0.6-4.0	2.3	0.8-6.6
12.9 – 22.7	23	129	Ref		Ref	
≥ 22.8	11	56	1.0	0.4-3.0	0.8	0.2-3.0
Magnesium(mg)						
< 271.0	17	61	1.6	0.7-3.8	2.0	0.7-5.4

Nutrient Quartile ¹	Cases	Controls	Odds Ratio ²	95% CI	Odds Ratio ³	95% CI
271.0 – 502.4	25	138	Ref		Ref	
≥ 502.5	10	52	1.0	0.4-2.8	1.0	0.3-3.1
Calcium (mg)						
< 818.5	16	54	1.8	0.8-4.1	1.8	0.7-4.8
818.5 – 1584.0	24	130	Ref		Ref	
≥ 1584.1	12	67	0.9	0.4-2.1	0.7	0.3-2.0

¹ Quartiles, denoted as Q1-Q4, determined from intake levels among control mothers.

² Odds ratio adjusted for total energy intake.

³ Odds ratio adjusted for energy intake as well as maternal race/ethnicity, age, education, body mass index, smoking, alcohol use, and gravidity.

Table 4

Risks of tetralogy of Fallot (TOF) associated with periconceptional nutrient intakes for women who did not use vitamin supplements, California 1999-2004.

Nutrient Quartile/ Folate (µg)	Cases	Controls	Odds Ratio ²	95% CI	Odds Ratio ³	95% CI
< 293.8	20	61	1.2	0.6-2.4	1.5	0.7-3.4
293.8 – 546.3	30	124	Ref		Ref	
≥ 546.4	16	66	1.2	0.6-2.7	1.1	0.4-3.0
Niacin (mg)						
< 18.3	15	61	0.6	0.3-1.3	0.7	0.3-1.7
18.3 – 31.5	35	126	Ref		Ref	
≥ 31.6	16	64	1.5	0.6-3.5	1.3	0.5-3.5
Riboflavin (mg)						
< 1.8	20	60	1.2	0.5-2.4	1.3	0.6-3.2
1.8 – 3.2	29	123	Ref		Ref	
≥ 3.3	17	68	1.4	0.6-3.3	1.2	0.4-3.4
Thiamin (mg)						
< 1.4	20	67	0.8	0.4-1.9	0.7	0.3-1.7
1.4 – 2.3	31	124	Ref		Ref	
≥ 2.4	15	60	1.6	0.6-4.0	1.7	0.6-5.0
Vitamin B ₆ (mg)						
< 1.8	19	59	1.1	0.5-2.3	1.5	0.6-3.5
1.8 – 3.1	30	126	Ref		Ref	
≥ 3.2	17	66	1.4	0.6-3.1	1.8	0.7-4.5
Vitamin B ₁₂ (µg)						
< 3.6	16	54	0.9	0.4-2.0	1.2	0.5-2.9
3.6 – 7.0	33	130	Ref		Ref	
≥ 7.1	17	67	1.3	0.6-3.0	1.1	0.5-2.9
Vitamin C (mg)						
< 138.8	24	58	2.0	1.0-3.9	2.2	1.0-4.8

Nutrient Quartile ¹	Cases	Controls	Odds Ratio ²	95% CI	Odds Ratio ³	95% CI
138.8 – 289.8	24	121	Ref		Ref	
≥ 289.9	18	72	1.3	0.7-2.7	1.4	0.6-3.3
Vitamin E (mg)						
< 11.6	17	50	1.3	0.6-2.6	1.2	0.5-2.7
11.6 – 20.5	30	128	Ref		Ref	
≥ 20.6	19	73	1.4	0.7-2.8	1.1	0.5-2.7
Vitamin A (RE)						
< 1044.7	20	63	1.1	0.6-2.3	1.5	0.6-3.4
1044.7 – 2152.5	29	122	Ref		Ref	
≥ 2152.6	17	66	1.3	0.6-2.9	1.8	0.7-4.6
Lutein (µg)						
< 1238.8	20	73	0.8	0.4-1.5	1.0	0.5-2.2
1238.8 – 5188.9	37	119	Ref		Ref	
≥ 5189.0	9	59	0.5	0.2-1.1	0.4	0.2-1.0
Lycopene (µg)						
< 2457.0	14	71	0.5	0.2-1.0	0.4	0.2-0.9
2457.0 – 7085.7	40	116	Ref		Ref	
≥ 7085.8	12	64	0.7	0.3-1.4	0.7	0.3-1.8
Zinc (mg)						
< 10.2	17	57	0.9	0.4-1.9	0.9	0.4-2.3
10.2 – 18.4	32	131	Ref		Ref	
≥ 18.5	17	63	1.7	0.7-4.0	1.6	0.6-4.2
Iron (mg)						
< 12.9	20	66	0.8	0.4-1.8	0.9	0.4-2.2
12.9 – 22.7	30	129	Ref		Ref	
≥ 22.8	16	56	2.2	0.9-5.6	2.4	0.8-7.3
Magnesium(mg)						
< 271.0	19	61	0.9	0.4-2.0	0.8	0.3-2.0
271.0 – 502.4	29	138	Ref		Ref	

Nutrient Quartile ¹	Cases	Controls	Odds Ratio ²	95% CI	Odds Ratio ³	95% CI
≥ 502.5	18	52	3.0	1.3-7.0	3.4	1.3-9.2
Calcium (mg)						
< 818.5	22	54	1.8	0.9-3.8	2.0	0.8-4.6
818.5 – 1584.0	32	130	Ref		Ref	
≥ 1584.1	12	67	0.7	0.3-1.5	0.4	0.1-1.2

¹ Quartiles, denoted as Q1-Q4, determined from intake levels among control mothers.

² Odds ratio adjusted for total energy intake.

³ Odds ratio adjusted for energy intake as well as maternal race/ethnicity, age, education, body mass index, smoking, alcohol use, and gravidity.