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Maternal intake of vitamin E and birth defects, National Birth Defects Prevention Study, 1997–2005

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Abstract

Background—In a recent study, high maternal periconceptional intake of vitamin E was found to be associated with risk of congenital heart defects (CHDs). To explore this association further, we investigated the association between total daily vitamin E intake and selected birth defects.

Methods—We analyzed data from 4,525 controls and 8,665 cases from the 1997–2005 National Birth Defects Prevention Study. We categorized estimated periconceptional energy-adjusted total daily vitamin E intake from diet and supplements into quartiles (referent, lowest quartile). Associations between quartiles of energy-adjusted vitamin E intake and selected birth defects were adjusted for demographic, lifestyle, and nutritional factors.

Results—We observed a statistically significant association with the third quartile of vitamin E intake (OR 1.17; 95% CI 1.01 – 1.35) and all CHDs combined. Among CHD sub-types, we observed associations with left ventricular outflow tract obstruction defects, and its sub-type, coarctation of the aorta and the third quartile of vitamin E intake. Among defects other than

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CHDs, we observed associations between anorectal atresia and the third quartile of vitamin E intake (OR 1.66; 95% CI 1.01 – 2.72) and hypospadias and the fourth quartile of vitamin E intake (OR 1.42; 95% CI 1.09 – 1.87).

Conclusions—Selected quartiles of energy-adjusted estimated total daily vitamin E intake were associated with selected birth defects. However, because these few associations did not exhibit exposure-response patterns consistent with increasing risk associated with increasing intake of vitamin E, further studies are warranted to corroborate our findings.

Keywords

birth defects; congenital heart defects; vitamin E

INTRODUCTION

Vitamin E (tocopherol) is an essential, lipid soluble antioxidant that exists in eight chemical forms; alpha-tocopherol is the only form that is recognized to meet human requirements. Dietary sources of vitamin E include nuts, seeds, fats/oils, meats, green leafy vegetables and fortified cereals. The recommended dietary allowance for vitamin E among women 14 years of age and older is 15 mg/day; the tolerable upper intake levels is 800 mg/day for women 14–18 years old and 1,000 mg/day for women 19 years of age or older (Institute of Medicine Food and Nutrition Board, 2000). Because of its antioxidant properties and roles in anti-inflammatory processes and immune enhancement (Institute of Medicine Food and Nutrition Board, 2000), vitamin E has been hypothesized to protect against adverse pregnancy outcomes such as preeclampsia and spontaneous preterm delivery (Bartfai and others, 2012; Hauth and others, 2010; Rumbold and Crowther, 2005; Rumbold and others, 2006; Villar and others, 2009), as well as against morbidity and mortality in very low birth weight or preterm infants (Brion and others, 2003). Concern about the safety of excessive vitamin E intake has focused on its potential for hemorrhagic effects (Institute of Medicine Food and Nutrition Board, 2000).

Animal data indicate that vitamin E is necessary for embryonic development (Miller and others, 2012) and might have a role in mediating the embryotoxic effects of alcohol and diabetes (Siman and Eriksson, 1997; Wentzel and others, 2006). There are four previously published epidemiologic studies exploring the association between maternal vitamin E intake and birth defects in the offspring (Boskovic and others, 2005; Smedts and others, 2009; The and others, 2007; Yang and others, 2008). In the first publication, using data from the Motherisk Program, Boskovic and colleagues compared pregnant women exposed to high doses (≥ 400 IU/day [363 mg/day]) of vitamin E during the first trimester of pregnancy with unexposed pregnant women and reported no association when looking at all major malformations combined (Boskovic and others, 2005). In the second publication, The and colleagues conducted an exploratory analysis of risk factors for biliary atresia in the National Birth Defects Prevention Study (NBDPS), and reported an increased risk of biliary atresia of borderline significance associated with low daily vitamin E intake (<3.9 mg per 1,000 calories) (adjusted odds ratio [OR] 2.02; 95% confidence interval [CI] 0.95 – 4.31) (The and others, 2007). The third publication was an exploratory analysis of nutritional risk factors for congenital diaphragmatic hernia in the NBDPS, and reported a borderline

protective effect of dietary intake of vitamin E among vitamin supplement users (OR 0.6; 95% CI 0.3 – 1.1) (Yang and others, 2008). In the fourth publication, an analysis of the Dutch HAVEN study (a Dutch acronym for Heart Defects Vascular Status, Genetic Factors and Nutrition) (Smedts and others, 2009), the authors reported an increased risk for CHDs (OR 1.6; 95% CI 1.03 – 2.6) associated with dietary vitamin E intake in the fourth quartile (14.9 – 33.8 mg/day) compared to the first quartile (4.0 – 10.6 mg/day). In a small subgroup of mothers who took supplements containing vitamin E (12.5% of the study population), strong, yet imprecise associations were reported between the third (12.6 – < 14.9 mg/day) and fourth highest quartiles of vitamin E intake from foods and CHDs (third quartile: OR 9.1; 95% CI 2.0 – 41.4; fourth quartile: OR 4.8; 95% CI 1.1 – 20.2). Among mothers who did not take any supplements or who took supplements containing folic acid, there was no association between CHDs and dietary vitamin E intake (Smedts and others, 2009).

Given this noteworthy and concerning result from the Dutch HAVEN study, and the inconsistency of this result with a prior-held belief that intake of antioxidants such as vitamin E would be beneficial, rather than harmful during pregnancy, we investigated the relation between total maternal vitamin E intake from diet and supplements and birth defects using data from the NBDPS.

METHODS

Study Population

The NBDPS is an ongoing, population-based case-control study comprising data collected by 10 birth defects surveillance systems in the United States (Cogswell and others, 2009; Yoon and others, 2001). Cases include live-born infants (all sites), stillbirths ≥20 weeks gestation (all sites except NJ, and NY before the year 2000), and elective terminations ≥20 weeks gestation (all sites except MA and NJ, and NY before the year 2000). Cases with major chromosomal abnormalities or single-gene disorders are excluded (Rasmussen and others, 2003). Live-born control infants without major birth defects are randomly selected either from birth certificates or birth hospital records (Cogswell and others, 2009). The NBDPS was approved by the institutional review boards of CDC and the participating study centers.

Clinical Review and Classification of Birth Defects

Information on case infants derived from each participating state's birth defects surveillance system was reviewed by clinical experts. According to NBDPS criteria, cases with a single or multiple birth defect affecting only one major organ system were classified as having an isolated defect (Botto and others, 2007; Rasmussen and others, 2003). For the current analysis only isolated cases were included; cases with birth defects in multiple organ systems were excluded to ensure greater homogeneity within outcome groups. Because of the previously published findings for biliary atresia (The and others, 2007) and diaphragmatic hernia (Yang and others, 2008) these two birth defects were excluded from the current analyses. For case infants with a 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) (Botto and

others, 2007; Rasmussen and others, 2003) For CHDs, analyses were restricted to simple, isolated CHDs. Results are shown for birth defects with at least 50 isolated cases to ensure the reporting of stable effect estimates.

Inclusion Criteria

Mothers of singleton, isolated case and control infants delivered on or after October 1, 1997 who had an estimated date of delivery on or before December 31, 2005 were eligible for this study (n=6,594 controls; n=12,958 cases). We excluded mothers with: self-reported pre-existing diabetes (type I or type II) or missing information on diabetes; improbably low or high average daily caloric intake of ≤ 500 kilocalories (kcal) or ≥ 5000 kcal; missing information for more than one food item in the 58-item modified Harvard Food Frequency Questionnaire (FFQ) (Willett and others, 1987; Willett WC and others, 1985); missing information on covariates used in the analysis; missing information on vitamin E supplement intake; or missing information on quantity of vitamin E from supplements (Figure 1).

Estimation of Vitamin E Intake through Diet and Supplements

Mothers were interviewed by telephone in English or Spanish using a computer-based questionnaire six weeks to 24 months after the estimated date of delivery. Interviewers obtained information on maternal demographic characteristics, exposures (e.g., nutritional, behavioral, occupational) and medication use before and during pregnancy. The participation rate for mothers of control infants was 66% and for mothers of cases was 69%.

Maternal dietary intake was based on completion of the FFQ on which participants reported how often they consumed food items in the year before they became pregnant. In addition, study participants were asked about their intake of cereal and beverages from the three months before they became pregnant to delivery – specifically the name, the month of consumption, and the frequency. Vitamin E (alpha-tocopherol equivalents and other tocopherols) content of foods was based on the U.S. Department of Agriculture's National Nutrient Database for Standard Reference 20 (US Department of Agriculture, 2007). Nutrient intakes were computed by multiplying the frequency with which each food item was consumed by its nutrient content for the portion size listed. For cereals, only consumption during the three months before pregnancy was included.

Mothers were also asked about use of a multivitamin, prenatal vitamin, or single component vitamin by month, from three months before pregnancy through the last month of pregnancy. For each product, mothers reported start and stop dates and frequency of intake. Trained pharmacists at the Slone Epidemiology Center at Boston University classified whether the specific supplement reported by each participant contained vitamin E or not, but not the dose. To quantify the dose in each supplement with vitamin E (n=694), we developed a dietary supplement database. Supplements with vitamin E were matched by name, to supplements with vitamin E reported by participants in the National Health and Nutrition Examination Survey (NHANES) Dietary Supplement Database (DSD) for the years 1999 – 2006 (US Department of Agriculture, 2009). Exact or near exact matches were found for 157 (22.7%) supplements; an additional 214 (30.8%) were probable matches

(supplement type and key words matched). When supplements reported in the NBDPS did not match with supplements from the DSD, other sources (i.e., company web sites, catalogs, and the Physician's Desk Reference [PDR]) were used to determine the amount of vitamin E contained in the supplement. This approach yielded an additional 143 exact, near exact or probable matches (20.7%). All but two of the remaining supplements that could not be assigned a vitamin E content based on the aforementioned approaches were assigned a default value of vitamin E content (n=178). We established four categories of default values for the assumed quantity of vitamin E in the supplement based on the most frequently reported supplements of that type in NHANES found in the DSD (Appendix 1). We examined use of vitamin E containing supplements from the three months before pregnancy through the first two months of pregnancy (B3-P2). We first classified each mother's use of supplements containing vitamin E as yes or no at any time (for any duration) during B3-P2. For each reported specific supplement (e.g., Brand X multivitamin), we then multiplied the amount of vitamin E contained in the specified supplement (as shown on the nutrition facts panel) by the reported number of tablets or pills consumed over the time period (B3-P2) and then divided by the number of tablets or pills corresponding to the specified supplement serving size (as shown on the nutrition facts panel). For each mother, the amount of vitamin E per day consumed from all specified supplements was calculated as the sum of vitamin E from all supplements divided by the number of days in B3-P2.

We calculated total daily vitamin E intake as the sum of vitamin E intake from supplements plus foods. We then adjusted total vitamin E intake for total calories using the nutrient residual method (Willett, 1998; Willett and others, 1997). Briefly, this approach is based on regressing individuals' total daily vitamin E intakes on their total daily energy (calorie) intakes. The residuals from this regression model represent the difference between actual vitamin E intake and expected vitamin E intake based on total energy intake, or vitamin E intake unexplained by energy intake. The nutrient residual was then used to calculate an "energy-adjusted" vitamin E intake. The distribution of energy-adjusted vitamin E intake among the controls was then used to determine energy-adjusted vitamin E intake quartiles, which were used for all further analyses. The lowest quartile of intake was the referent.

Covariates of Interest

Maternal covariates selected a priori included age at delivery, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education (less than high school, high school, more than high school), study center, and pre-pregnancy body mass index (BMI) in kilograms per square meter (kg/m^2) [$<18.5\ kg/m^2$, $18.5–<25.0\ kg/m^2$ (reference category), $25.0–<30.0\ kg/m^2$, and $\geq 30.0\ kg/m^2$]. Total daily intake of fat, calories, and dietary folate were also calculated based on the FFQ and considered potential confounders in the analysis. Total daily dietary folate was expressed as dietary folate equivalents (DFE) (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 1998). Smoking, alcohol use, and use of folic acid supplements, were all defined as any use or intake during the period of B3-P2.

Data Analysis

Among control mothers, we assessed the association of demographic and lifestyle factors, and intake of selected nutrients with quartiles of energy-adjusted total vitamin E intake. Then to estimate the risk of selected major birth defects associated with quartiles of energy-adjusted total maternal vitamin E intake, we computed the crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) using logistic regression. The multivariable model included study center, folate intake (as DFE), maternal race/ethnicity, age, education, pre-pregnancy body mass index, smoking, alcohol use, use of folic acid supplements, and total energy intake. In addition, in an attempt to replicate the results of the Dutch HAVEN study, we conducted an analysis of the association between any CHD and dietary intake of vitamin E, among vitamin E-containing supplement users.

We also conducted sensitivity analyses to explore the effect of missing data on vitamin E intake from supplements (Figure 1, lower left, n=2,421 cases and controls combined) under two extreme scenarios. In the first, we assumed that those with missing information on vitamin E from supplements were non-users (assigned them a value of 0 mg of vitamin E from supplements). In the second scenario, we assumed that these same individuals were users in the highest quartile, and assigned them the median for this quartile (18.49 mg/day of vitamin E from supplements). We also conducted a post-hoc sensitivity analysis to explore the impact of excluding mothers of cases and controls with a first degree family history of a birth defect.

All analyses use SAS version 9.2 statistical software (SAS Institute, Cary, NC).

RESULTS

After the stated exclusions, there were 4,525 controls and 8,665 isolated cases remaining (Figure 1). Selected characteristics of included control mothers are reported by quartile of energy-adjusted daily total vitamin E intake in Table 1. All differed significantly across quartiles of daily total vitamin E intake. For several characteristics, trends with increasing total vitamin E intake were suggested: increasing proportions of mothers with greater than a high school education, decreasing proportions of mothers who reported smoking during the period of B3-P2, and increasing proportions of mothers who reported using alcohol and vitamin supplements during the period of B3-P2. Overall 82.6% of controls reported taking a supplement containing vitamin E; this increased from 49.8% of individuals in the first quartile of energy-adjusted total intake to 98.7% of individuals in the fourth quartile intake (Table 1).

Total median energy-adjusted vitamin E intake was 7.79 mg, below the RDA of 15 mg/day. Of note, energy-adjusted intakes differed only slightly from the unadjusted intakes (energy-adjusted mean = 13.52 mg; unadjusted mean = 13.59 mg). The daily mean (and median) intake of dietary folate, vitamin E from foods, and vitamin E from supplements increased with increasing quartiles of energy-adjusted total vitamin E intake (Table 2). Total fat and energy intake, however, did not increase with increasing quartiles of total vitamin E intake. In addition, daily vitamin E intake from supplements was substantially higher among

mothers in the fourth quartile of total energy-adjusted vitamin E intake (27.12 mg) compared with the other three quartiles (0.59–4.99 mg).

The results of multivariable models are presented in Tables 3 and 4. Considering all simple, isolated CHDs as a single outcome group, we observed a significant association with the third quartile of energy-adjusted vitamin E intake (OR 1.17; 95% CI 1.01–1.35), and an association of borderline significance with the second quartile of vitamin E intake (OR 1.14; 95% CI 0.99–1.31). Among CHD sub-types, we observed additional associations with the grouping of left ventricular outflow tract obstruction defects (LVOTO), and its sub-type, coarctation of the aorta and the third quartile of vitamin E intake. There was also an association of borderline significance between septal defects and the second quartile of vitamin E intake. There was no evidence, however, of a vitamin E dose-response pattern of increased risk with increased quartiles of exposure for any of the CHDs under study (Table 3).

For the analysis attempting to replicate the findings from the Dutch HAVEN study, we found that among supplement users, there was no association between dietary vitamin E intake and all simple, isolated CHDs with the exception of a protective effect in the fourth quartile of exposure (quartile 2: OR 0.98; 95% CI 0.86–1.11; quartile 3: OR 0.89; 95% CI 0.78–1.02; quartile 4: OR 0.81; 95% CI 0.69–0.95).

Among isolated birth defects other than CHDs (Table 4), we observed a significant association between anorectal atresia and the third quartile of energy-adjusted total vitamin E intake (OR 1.66; 95% CI 1.01–2.72) and hypospadias and the fourth quartile of vitamin E intake (OR 1.42; 95% CI 1.09–1.87). Elevated, but not statistically significant associations were observed for esophageal atresia and small intestinal atresias and the fourth quartile of intake (Table 4).

The results of the two sensitivity analyses we conducted of missing data on vitamin E intake from supplements, indicated that the reported findings were robust to our assumptions regarding whether those with missing information were non-users (0 mg was used as the daily vitamin E intake value) or had high levels of vitamin E intake (18.49 mg was used as the daily vitamin E intake value) (data not shown). Our post-hoc analysis excluding study participants with a first degree family history of a birth defect resulted in qualitatively similar findings (data not shown).

DISCUSSION

Our results suggest that maternal vitamin E intake from foods and supplements is not a risk factor for CHDs. The few observed associations with CHDs do not exhibit an exposure-response pattern that is consistent with increased risk of CHD with increased maternal intake of vitamin E. The most suggestive findings for associations with vitamin E intake were among birth defects other than CHDs - anorectal atresia and hypospadias. These associations have not been previously reported in the literature and are in need of replication. These results must be interpreted in light of the large number of comparisons conducted and the possibility that these could be sporadic, chance findings.

The primary motivator to explore the association between vitamin E intake and selected birth defects in the NBDPS was the 2009 publication of data from the Dutch HAVEN study which reported a 60% increased odds of CHDs in the fourth quartile of dietary maternal exposure to vitamin E (Smedts and others, 2009). In the current analysis, we report a 19% increased odds of CHDs in the third quartile of exposure, and no increase in the fourth quartile (OR 1.03; 95% CI 0.88–1.20). The HAVEN study also reported, among the subgroup of vitamin E supplement users, a 9-fold and 5-fold increase in the odds of CHDs in the third and fourth quartiles of dietary vitamin E intake. We were unable to replicate these findings; among users of supplements containing vitamin E we found no association (and a protective effect in the fourth quartile of exposure) between dietary intake of vitamin E and CHDs.

The NBDPS analysis was able to improve upon two methodological limitations in the HAVEN study: a small case sample, which did not permit any analyses of individual CHD subtypes; and no quantification of the amount of vitamin E consumed in the prenatal, multivitamin, or single component supplements. The HAVEN study included a total of 276 CHD cases composed of a limited number of subtypes – tetralogy of Fallot, atrioventricular septal defect, perimembranous ventricular septal defect, aortic valve stenosis, pulmonary valve stenosis, coarctation of the aorta, transposition of the great arteries, hypoplastic left heart syndrome and a “miscellaneous” (Smedts and others, 2009; p.417) category. The population included a mixture of isolated and non-isolated CHD, including 40 cases with a recognized genetic syndrome. In contrast, the NBDPS excluded infants with suspected single gene or chromosomal disorders, an important strength in analyses of possible associations with non-genetic risk factors. Also in the NBDPS analysis, we had over 3,000 cases with isolated CHDs, and were able to consider possible heterogeneity of effects among 16 CHD subtypes in addition to the grouping of all CHDs combined.

The associations observed for birth defects other than CHDs –anorectal atresia and hypospadias, were unexpected, and warrant further analysis and replication in other study populations. A recent study of nutrient intake and hypospadias in the NBDPS found no association with dietary intake of vitamin C, an antioxidant vitamin, but vitamin E was not investigated (Carmichael and others, 2012).

Because over 80% of NBDPS study participants reported use of multivitamins or prenatal supplements containing vitamin E, it was critical to quantify the amount of vitamin E in these supplements, and to incorporate this intake into our analysis in order to determine the potential role of total vitamin E intake. However, the strongest associations reported in the HAVEN study (9-fold and 5-fold increases in odds) were with vitamin E consumed from foods in the small group of users of supplements containing vitamin E. We did attempt to replicate this analysis in our data, and did not find evidence of an increase in risk of CHDs.

Our study had several limitations. First, there was possible measurement error in our estimation of vitamin E intake from supplements. The accuracy of our calculation of the vitamin E intake from reported supplements relied on maternal report of various exposure/dose metrics, including the type and brand of supplement as well as the timing, frequency and duration of use. Any errors in these metrics could have led to misclassification of

exposure. In addition, vitamin E intake from supplements was largely (approximately 90%) derived from intake of multivitamins and prenatal vitamins, rather than from a single ingredient vitamin E supplement. This suggests that there may be other components in these multivitamins or prenatal vitamins that could be important to consider as potential confounders. To help account for this, we adjusted our analyses for use of supplements containing folic acid and for dietary folate.

Second, there was potential for measurement error in the estimation of vitamin E intake from foods. For cereals, we limited our use of the these data to the period from three months before pregnancy to conception in order to have this information more closely correspond with the FFQ data for other food items. The semi-quantitative FFQ used by the NBDPS asks about the intake of 58 specific food items during the year before pregnancy and there are limitations inherent in this mode of dietary data collection. The FFQ is limited in its ability to evaluate individual micronutrients and macronutrients (Willett WC and others, 1985). In addition, since it is shorter than the original Willett FFQ, it may be missing important foods which could result in lower estimates of overall calorie or specific nutrient intake (Willett WC and others, 1985). For vitamin E in particular, it has been observed that intake estimates might be low because the amounts and types of fat added during cooking are often unknown, or not accurately reported (Institute of Medicine Food and Nutrition Board, 2000). The FFQ is used with the assumption that women's general food consumption patterns before pregnancy are representative of their consumption patterns during early pregnancy and that it can help rank individuals according to intake relative. Qualitative longitudinal data suggests this is a valid assumption (Devine and others, 2000). Although the NBDPS FFQ has not been internally validated, the use of food frequency questionnaires for dietary recall has been validated against one-year diet records though errors in recall are possible (Willett and others, 1987). However, given that dietary vitamin E intake was captured through several questions on the FFQ, and vitamin E is not generally considered a risk factor for adverse pregnancy outcomes, those errors are likely to be non-differential with respect to case-control status with possible attenuation of effects but unlikely to have resulted in recall bias by case-control status.

The third limitation is the possibility of selection bias if vitamin E intake were associated with fetal death earlier than 20 weeks' gestation, or multiple co-occurring birth defects. Miscarriages and early fetal losses are not eligible for inclusion in the NBDPS and any association between an exposure and these outcomes would not be detected in the NBDPS; the exclusion from this analysis of cases with multiple co-occurring birth defects was made in order to maintain as much etiologic homogeneity as possible within outcomes.

It is noteworthy that the first three quartiles of energy-adjusted daily total vitamin E intake are below the RDA of 15 mg/day. Only mothers in the fourth quartile of intake are at or above the RDA for total daily vitamin E intake. These low values might be due to misreporting of either dietary intake or supplement intake as noted above. According to NHANES 1999–2000 and 2001–2002 data derived from participants' 24-hour dietary recalls, U.S. women aged 19 years or older (up to age ≥70) consumed, on average 6.2 mg/day of vitamin E from diet and 14.1 mg/day from supplements (Chun and others, 2010). The mean values for NBDPS participants were somewhat lower than these national

estimates, in part because individuals 50 years of age or older tend to consume at least twice as much vitamin E than younger Americans (Chun and others, 2010; Millen and others, 2004).

In summary, our results provided no substantial evidence of an association between total daily vitamin E from foods and supplements and CHDs. The observed associations of vitamin E intake with other birth defects might represent chance findings, and thus warrant corroboration in other population-based studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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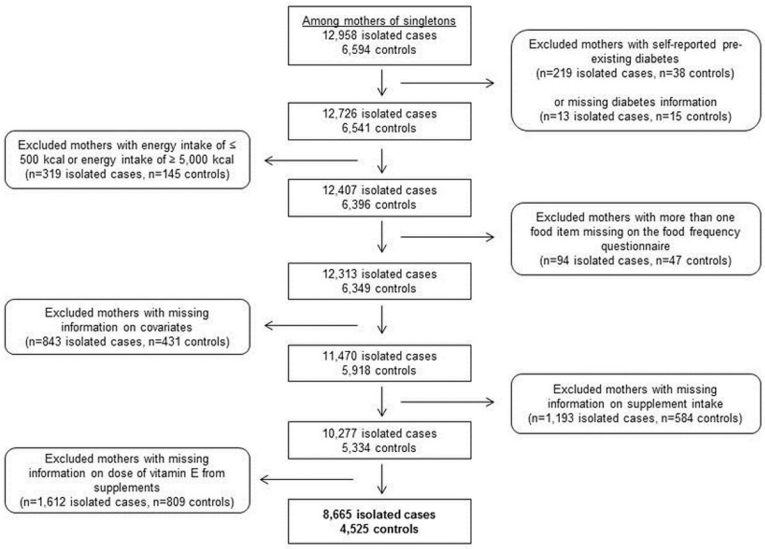

Figure 1.

Included participants

Study participation and exclusion criteria among case and control mothers, National Birth Defects Prevention Study, 1997–2005.

TABLE 1

Demographic and behavioral characteristics of control mothers, by quartile of energy-adjusted daily total vitamin E intake, National Birth Defects Prevention Study, 1997–2005

		Quartiles[a] of Energy-Adjusted Daily Total Vitamin E Intake				
	Total (N=4525)	**Q1 (0.67 – 5.12 mg) (N=1130)**	**Q2 (5.13 – 7.79 mg) (N=1133)**	**Q3 (7.80 – 14.19 mg) (N=1129)**	**Q4 (>14.19 mg) (N=1133)**	
Characteristic	**% (N)**	**% (N)**	**% (N)**	**% (N)**	**% (N)**	**P-value[b]**
Maternal age						
<20	13.28 (601)	22.65 (256)	16.06 (182)	10.19 (115)	4.24 (48)	<.0001
20–34	72.57 (3284)	68.50 (774)	73.35 (831)	75.38 (851)	73.08 (828)	
≥35	14.14 (640)	8.85 (100)	10.59 (120)	14.44 (163)	22.68 (257)	
Maternal race/ethnicity						
White, non-Hispanic	64.07 (2899)	57.17 (646)	58.08 (658)	62.27 (703)	78.73 (892)	<.0001
Black, non-Hispanic	12.15 (550)	18.94 (214)	13.33 (151)	9.21 (104)	7.15 (81)	
Hispanic	17.61 (797)	18.50 (209)	21.80 (247)	20.90 (236)	9.27 (105)	
Others[c]	6.17 (279)	5.40 (61)	6.80 (77)	7.62 (86)	4.85 (55)	
Study center						<.0001
Arkansas	15.51 (702)	18.50 (209)	16.42 (186)	13.91 (157)	13.24 (150)	
California	12.42 (562)	12.30 (139)	14.65 (166)	14.08 (159)	8.65 (98)	
Iowa	12.53 (567)	12.65 (143)	11.56 (131)	10.81 (122)	15.09 (171)	
Massachusetts	6.63 (300)	3.45 (39)	6.18 (70)	7.97 (90)	8.91 (101)	
New Jersey	7.18 (325)	5.22 (59)	7.50 (85)	7.88 (89)	8.12 (92)	
New York	10.74 (486)	12.83 (145)	10.24 (116)	9.21 (104)	10.68 (121)	
Texas	9.83 (445)	9.56 (108)	11.74 (133)	11.51 (130)	6.53 (74)	
CDC/Atlanta	12.04 (545)	12.48 (141)	11.74 (133)	11.34 (128)	12.62 (143)	
North Carolina	6.78 (307)	6.99 (79)	5.38 (61)	6.38 (72)	8.38 (95)	
Utah	6.32 (286)	6.02 (68)	4.59 (52)	6.91 (78)	7.77 (88)	
Pre-pregnancy body mass index (kg/m^2)[d]						
<18.5	5.55 (251)	6.55 (74)	6.27 (71)	4.61 (52)	4.77 (54)	0.0052
18.5–25.0	56.44 (2554)	53.89 (609)	53.49 (606)	58.10 (656)	60.28 (683)	
25.0–30.0	22.12 (1001)	22.65 (256)	22.95 (260)	20.73 (234)	22.15 (251)	

	Quartiles[a] of Energy-Adjusted Daily Total Vitamin E Intake					
	Total (N=4525)	**Q1 (0.67 – 5.12 mg) (N=1130)**	**Q2 (5.13 – 7.79 mg) (N=1133)**	**Q3 (7.80 – 14.19 mg) (N=1129)**	**Q4 (>14.19 mg) (N=1133)**	
Characteristic	**% (N)**	**% (N)**	**% (N)**	**% (N)**	**% (N)**	**P-value[b]**
>30.0	15.89 (719)	16.90 (191)	17.30 (196)	16.56 (187)	12.80 (145)	
Maternal education						
< High school	12.84 (581)	18.94 (214)	15.36 (174)	11.87 (134)	5.21 (59)	<.0001
High school or GED	24.15 (1093)	34.42 (389)	27.01 (306)	21.43 (242)	13.77 (156)	
> High school	63.01 (2851)	46.64 (527)	57.63 (653)	66.70 (753)	81.02 (918)	
Smoking during B3-P2[e]						
Yes	19.89 (900)	27.17 (307)	22.86 (259)	15.94 (180)	13.59 (154)	<.0001
No	80.11 (3625)	72.83 (823)	77.14 (874)	84.06 (949)	86.41 (979)	
Alcohol during B3-P2[e]						
Yes	44.07 (1994)	40.44 (457)	41.48 (470)	43.40 (490)	50.93 (577)	<.0001
No	55.93 (2531)	59.56 (673)	58.52 (663)	56.60 (639)	49.07 (556)	
Use of supplements with folic acid during B3-P2[e]						
Yes	84.09 (3805)	54.51 (616)	88.26 (1000)	95.48 (1078)	98.06 (1111)	<.0001
No	15.91 (720)	45.49 (514)	11.74 (133)	4.52 (51)	1.94 (22)	
Use of supplements with vitamin E during B3-P2[e]						
Yes	82.63 (3739)	49.82 (563)	86.76 (983)	95.13 (1074)	98.76 (1119)	<.0001
No	17.37 (786)	50.18 (567)	13.24 (150)	4.87 (55)	1.24 (14)	

Q: Quartile, GED: General Educational Development

[a] Quartiles determined from energy-adjusted intake of vitamin E from foods and supplements among control mothers.

[b] P-value for Chi-square test for differences in distribution of the characteristic by quartile of total vitamin E intake.

[c] Other includes Asian Pacific Islander, Native American or Alaskan Native, and others.

[d] Body mass index, weight in kilograms divided by height in meters-squared.

[e] Exposure any time from the three months before pregnancy through the first two months of pregnancy.

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Table 2

Daily mean and median intake of selected nutrients among control mothers, by quartile of energy-adjusted daily total vitamin E intake, National Birth Defects Prevention Study, 1997–2005

		Quartiles [a] of Energy-Adjusted Daily Total Vitamin E Intake			
	Total (N=4525)	**Q1 (0.67 – 5.12 mg) (N=1130)**	**Q2 (5.13 – 7.79 mg) (N=1133)**	**Q3 (7.80 – 14.19 mg) (N=1129)**	**Q4 (>14.19 mg) (N=1133)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Total energy intake (kcal)	1569.43 (649.80)	1474.19 (578.62)	1641.12 (702.78)	1676.82 (712.59)	1485.71 (566.51)
	1438.83 (755.83)	1374.27 (686.12)	1486.92 (852.34)	1525.09 (839.35)	1390.13 (668.95)
Total fat (g)	49.81 (23.10)	45.46 (19.24)	52.32 (24.95)	53.70 (25.48)	47.77 (21.20)
	45.24 (25.91)	42.42 (23.43)	47.11 (29.32)	48.54 (27.82)	43.95 (22.94)
Folate (DFE)	580.31 (394.74)	492.03 (341.47)	584.48 (387.61)	627.61 (404.36)	620.40 (432.45)
	487.63 (379.90)	404.79 (320.29)	493.84 (373.02)	537.40 (396.43)	519.47 (418.90)
Vitamin E from foods (mg)	4.89 (3.39)	3.12 (1.26)	4.52 (1.98)	5.73 (3.15)	6.17 (4.99)
	4.03 (3.14)	2.94 (1.77)	4.23 (2.88)	4.98 (4.19)	4.53 (3.89)
Vitamin E from supplements (mg)	8.71 (25.45)	0.59 (0.80)	2.10 (1.35)	4.99 (2.75)	27.12 (46.01)
	2.97 (7.54)	0 (1.07)	2.31 (1.94)	4.97 (3.33)	13.57 (1.88)
Total Vitamin E (from foods and supplements) (mg)	13.52 (26.3)	3.70 (0.97)	6.41 (0.76)	10.27 (1.82)	33.68 (46.86)
	7.79 (9.07)	3.84 (1.48)	6.38 (1.34)	9.85 (2.93)	18.86 (6.62)

Q: Quartile; DFE: Dietary Folate Equivalents; SD: Standard Deviation; IQR: Interquartile Range

[a] Quartiles determined from energy-adjusted intake of vitamin E from foods and supplements among control mothers.

Table 3

Adjusted[a] odds ratios (OR) and 95% confidence intervals (CI) for the association between energy-adjusted daily total maternal intake of vitamin E and simple, isolated congenital heart defects, National Birth Defects Prevention Study, 1997–2005

	Quartiles[b] of Energy-Adjusted Daily Total Vitamin E Intake						
	Q1 (0.67 – 5.12 mg)	Q2 (5.13 – 7.79 mg)		Q3 (7.80 – 14.19 mg)		Q4 (>14.19 mg)	
	N	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Controls	1130	1133		1129		1133	
Any included simple, isolated congenital heart defect	776	851	1.14 (0.99–1.31)	852	**1.17 (1.01–1.35)**	754	1.03 (0.89–1.21)
Conotruncal defects	157	179	1.19 (0.92–1.53)	180	1.21 (0.93–1.58)	161	1.06 (0.81–1.40)
Tetralogy of Fallot	79	79	1.02 (0.72–1.46)	96	1.23 (0.86–1.77)	81	0.98 (0.67–1.42)
D-transposition of the great arteries	54	67	1.35 (0.90–2.03)	55	1.18 (0.76–1.84)	61	1.34 (0.86–2.10)
Atrioventricular septal defect	13	24	1.82 (0.86–3.85)	13	0.99 (0.42–2.34)	16	1.08 (0.46–2.52)
Anomalous pulmonary venous return	23	28	1.24 (0.67–2.30)	26	1.21 (0.63–2.34)	29	1.58 (0.81–3.06)
Left ventricular outflow tract obstruction defects	115	126	1.05 (0.79–1.41)	179	**1.46 (1.10–1.94)**	135	1.02 (0.75–1.37)
Hypoplastic left heart syndrome	46	44	0.84 (0.54–1.31)	80	1.49 (0.98–2.26)	55	0.99 (0.63–1.56)
Coarctation of the aorta	37	44	1.20 (0.74–1.96)	66	**1.75 (1.09–2.82)**	47	1.18 (0.71–1.96)
Aortic stenosis	32	36	1.23 (0.72–2.10)	30	0.98 (0.55–1.75)	33	0.90 (0.50–1.60)
Right ventricular outflow tract obstruction defects	127	126	0.97 (0.73–1.30)	115	0.89 (0.66–1.20)	137	1.01 (0.75–1.36)
Pulmonary valve stenosis	95	90	0.98 (0.71–1.37)	90	1.00 (0.71–1.41)	108	1.13 (0.80–1.58)
Septal defects	340	369	1.19 (0.99–1.45)	339	1.15 (0.94–1.41)	276	1.01 (0.82–1.26)
Ventricular septal defect perimembranous	147	152	1.24 (0.95–1.62)	144	1.23 (0.93–1.65)	129	1.09 (0.81–1.47)
Ventricular septal defect muscular	28	24	0.90 (0.49–1.68)	26	0.95 (0.50–1.79)	18	0.52 (0.26–1.05)
Atrial septal defect secundum or NOS	157	182	1.19 (0.92–1.55)	165	1.15 (0.87–1.52)	126	1.08 (0.80–1.46)

Q: Quartile; NOS: Not otherwise specified

[a] Adjusted for study center and maternal total energy intake, folate intake (DFE), race/ethnicity, age, education, pre-pregnancy body mass index, smoking, alcohol use, and use of folic acid supplements

[b] Quartiles determined from energy adjusted intake of vitamin E from foods and supplements among control mothers.

Table 4

Adjusted[a] odds ratios (OR) and 95% confidence intervals (CI) for the association between energy-adjusted daily total maternal intake of vitamin E and isolated (non-congenital heart defect) birth defects, National Birth Defects Prevention Study, 1997–2005

	Quartiles [b] of Energy-Adjusted Daily Total Vitamin E Intake						
	Q1 (0.67 – 5.12 mg)	Q2 (5.13 – 7.79 mg)		Q3 (7.80 – 14.19 mg)		Q4 (>14.19 mg)	
	N	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Controls	1130	1133		1129		1133	
Neural tube defects	176	174	0.95 (0.74–1.21)	188	1.05 (0.81–1.35)	180	1.11 (0.85–1.43)
Anencephaly and craniorachischisis	45	53	1.13 (0.73–1.76)	59	1.28 (0.81–2.01)	45	1.09 (0.67–1.78)
Spina bifida	116	100	0.84 (0.62–1.14)	116	1.00 (0.73–1.36)	116	1.09 (0.80–1.50)
Encephalocele	15	21	1.29 (0.62–2.68)	13	0.81 (0.35–1.86)	19	1.29 (0.58–2.87)
Hydrocephaly	35	37	1.11 (0.66–1.85)	34	1.11 (0.64–1.91)	33	1.11 (0.63–1.95)
Cataracts	23	25	1.14 (0.61–2.12)	27	1.22 (0.64–2.32)	33	1.47 (0.78–2.78)
Anotia/microtia	51	51	1.02 (0.66–1.59)	34	0.69 (0.41–1.15)	33	0.91 (0.53–1.56)
Oral clefts	393	365	0.89 (0.74–1.07)	402	1.03 (0.85–1.24)	351	0.92 (0.76–1.12)
Cleft palate	116	118	0.97 (0.72–1.30)	142	1.17 (0.87–1.58)	108	0.85 (0.62–1.17)
Cleft lip with cleft palate	179	164	0.90 (0.70–1.16)	169	1.01 (0.78–1.31)	130	0.88 (0.66–1.16)
Cleft lip without cleft palate	98	83	0.80 (0.58–1.11)	91	0.89 (0.64–1.25)	113	1.07 (0.77–1.50)
Cleft lip with or without cleft palate	277	247	0.87 (0.70–1.07)	260	0.97 (0.78–1.20)	243	0.96 (0.77–1.20)
Esophageal atresia	22	28	1.47 (0.79–2.75)	24	1.20 (0.61–2.35)	39	1.75 (0.92–3.33)
Small intestinal atresia/stenosis	28	36	1.54 (0.88–2.68)	36	1.69 (0.94–3.05)	33	1.75 (0.95–3.24)
Anorectal atresia/stenosis	43	37	1.06 (0.65–1.74)	52	**1.66 (1.01–2.72)**	44	1.49 (0.88–2.51)
Hypospadias second/third degree	137	165	1.14 (0.87–1.50)	184	1.18 (0.89–1.56)	255	**1.42 (1.09–1.87)**
Limb deficiency	75	93	1.14 (0.81–1.61)	78	0.96 (0.66–1.38)	82	1.04 (0.72–1.51)
Longitudinal limb deficiency	25	29	1.14 (0.63–2.05)	18	0.71 (0.36–1.40)	21	0.84 (0.43–1.66)
Transverse limb deficiency	47	61	1.14 (0.75–1.74)	57	1.07 (0.69–1.66)	56	1.10 (0.70–1.73)
Craniosynostosis	104	111	1.06 (0.78–1.44)	137	1.21 (0.89–1.64)	132	0.98 (0.71–1.34)
Omphalocele	30	21	0.78 (0.42–1.44)	29	1.09 (0.60–2.01)	24	0.87 (0.45–1.66)
Gastroschisis	158	124	0.97 (0.72–1.30)	107	1.00 (0.72–1.37)	50	0.73 (0.49–1.08)

Q: Quartile

[a] Adjusted for study center and maternal total energy intake, folate intake (DFE), race/ethnicity, age, education, pre-pregnancy body mass index, smoking, alcohol use, and use of folic acid supplements

[b] Quartiles determined from energy adjusted intake of vitamin E from foods and supplements among control mothers.