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Craniosynostosis and Nutrient Intake during Pregnancy

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Abstract

OBJECTIVE—To examine the association of craniosynostosis with maternal intake of folic acid-containing supplements and dietary nutrients.

METHODS—The study included deliveries from 1997 to 2005 from the National Birth Defects Prevention Study. Nonsyndromic infants with craniosynostosis ($n = 815$) were compared to nonmalformed, population-based liveborn control infants ($n = 6789$), by estimating adjusted odds ratios (AORs) and 95% confidence intervals (CIs) from logistic regression models that included mother's age, parity, race-ethnicity, education, body mass index, smoking, alcohol, fertility treatments, plurality, and study center. We compared quartiles of intake and specified nutrients as continuous.

RESULTS—Intake of folic acid-containing supplements was not associated with craniosynostosis (AORs were close to 1). Analyses of dietary nutrients were restricted to mothers who took supplements during the first trimester (i.e., most women). Based on continuous specifications of nutrients, sagittal synostosis risk was significantly lower among women with higher intake of riboflavin and vitamins B₆, E, and C; metopic synostosis risk was significantly higher among women with higher intakes of choline and vitamin B₁₂; and coronal synostosis risk was significantly lower among women with higher intake of methionine and vitamin C. As examples, AORs for sagittal synostosis among women with intakes of vitamin B₆ and riboflavin in the highest versus lowest quartiles were 0.4 (95% CI, 0.2–0.6) and 0.5 (95% CI, 0.3–0.7), respectively.

CONCLUSION—This analysis suggests that dietary intake of certain nutrients may be associated with craniosynostosis, and results may vary by suture type.

Keywords

craniosynostosis; nutrition; folic acid; diet

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INTRODUCTION

The prevalence of craniosynostosis (i.e., premature closure of cranial sutures) is estimated at 3–5 per 10,000 births (Cohen, 1993). The critical period for development of craniosynostosis is unknown but may range from early gestation to postnatally (Cohen, 1993; Wilkie, 1997; Morriss-Kay and Wilkie, 2005). The sagittal, coronal, and lambdoid sutures originate from an interface between neural crest cells and mesoderm, whereas the metopic suture is wholly derived from the neural crest (Morriss-Kay and Wilkie, 2005). Numerous syndromes involve craniosynostosis, but about 85% of infants with craniosynostosis are nonsyndromic. The majority of studies of craniosynostosis have focused on genetic etiologies of syndromic cases. Many etiologies of craniosynostosis have been proposed, including various hormonal, mechanical, and genetic factors, but our causal understanding of suture closure is quite limited (Cohen, 2000; Rasmussen et al., 2008).

Maternal nutritional status has been implicated in the etiology of a variety of structural malformations. In particular, folic acid prevents neural tube defects, possibly because of its role as a methyl group donor in one-carbon metabolism (Blom et al., 2006). An in-depth investigation of the association of craniosynostosis with maternal nutrient intake has not been conducted previously but is warranted based on the following potential connections. Neural crest cells, which are folate-responsive (Blom et al., 2006), contribute to the development of the skull. Studies have also suggested that use of valproic acid, a folate antagonist, is associated with metopic synostosis (Ardinger et al., 1988; Lajeunie et al., 1998). Two studies have found no association between multivitamin use during pregnancy and craniosynostosis (Zeiger et al., 2002; Kallen and Robert-Gnansia, 2005). Unexpectedly, one of these studies also reported a relative risk of 5.6 (95% CI, 2.0, 12.1) for folic acid supplements during the first trimester but no association later in pregnancy (Kallen and Robert-Gnansia, 2005). These findings suggest that folate, and perhaps other nutrients that contribute to one-carbon metabolism, merit further research. High body mass index and hypoxia-related exposures also might contribute to craniosynostosis (Olshan and Faustman, 1989; Kallen, 1999; Honein and Rasmussen, 2000; Kallen and Robert-Gnansia, 2005; Waller et al., 2007; Carmichael et al., 2008), suggesting that nutrients that contribute to glycemic control and oxidative stress merit consideration.

This study investigated the association of nonsyndromic craniosynostosis with maternal intake of nutrients involved in one-carbon metabolism, glycemic control, and oxidative stress, using recent data from a large, multistate, population-based case–control study of birth defects, the National Birth Defects Prevention Study (NBDPS).

METHODS

This study included data on deliveries that occurred from 1997 to 2005 and were part of the NBDPS, a case–control study of many different birth defects being conducted in 10 states of the United States. Detailed study methods have been published previously (Yoon et al., 2001; Cogswell et al., 2009). In brief, most states included liveborn infants, fetal deaths (at >20 weeks gestation), and electively terminated cases. Each state randomly selected a set of nonmalformed, liveborn control infants during each study year from birth certificates or from birth hospitals; liveborn infants with major malformations were ineligible as controls.

Information on case infants obtained from multiple hospital reports and medical records was entered into a standardized database. A clinical geneticist in each state followed standard guidelines to review the diagnostic information to determine eligibility (Rasmussen et al., 2003). Each case received a final review by one clinical geneticist (S.A.R.), to ensure that cases from each study center met standard eligibility criteria. For inclusion, craniosynostosis

was verified by radiographic imaging (e.g., skull radiograph or head CT) or surgery. The geneticist also classified each case as isolated if there was no other major anomaly or only minor anomalies (e.g., sacral/ pilonidal dimple) or as nonisolated if there was one or more major, unrelated accompanying anomalies (Rasmussen et al., 2003). Infants with recognized or strongly suspected single-gene disorders or chromosomal abnormalities were excluded. The specific suture(s) involved was also identified (i.e., sagittal, coronal, metopic, lambdoid, multiple, or unknown). Infants with more than one type of involved suture (e.g., sagittal and coronal sutures both prematurely closed) were counted only in the multiple suture category.

Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, between 6 weeks and 24 months after their due date. Interviews were conducted with 73% of eligible case mothers ($n = 815$) and 67% of eligible control mothers ($n = 6789$). Mean time to interview was 13.9 months for case mothers and 8.8 months for control mothers. To assess intake of folic acid-containing vitamin/mineral supplements, women answered detailed questions about their intake of vitamin/mineral supplements, including the start and stop dates and frequency of intake. Women were grouped based on whether they (1) took folic acid-containing supplements during the first trimester of pregnancy, (2) began taking them during the second or third trimester, or (3) did not take them during pregnancy. We did not further refine supplement intake based on frequency or type of supplement, because among mothers who took folic acid-containing supplements, 88% of case and 89% of control mothers took them on a daily basis, and 96% of case and 94% of control mothers took prenatal multivitamin/mineral formulations.

To assess dietary intake of nutrients, mothers responded to a version of the Willett food frequency questionnaire that assessed the frequency of intake of 58 food items during the year before pregnancy (Willett et al., 1987). Intake of breakfast cereals, tea, coffee, and sodas was assessed by separate, more detailed questions, which covered intake during the 3 months before pregnancy. The USDA version 19 nutrient database was the source of nutrient values (U.S. Department of Agriculture Agricultural Research Service, 2006). The database is relatively complete for all of the studied nutrients with the exception of choline. For choline, we used recently released databases from the USDA that are more complete; that is, we used the USDA choline database as our primary source of information, and we used the USDA version 20 as a secondary source (U.S. Department of Agriculture Agricultural Research Service, 2007; U.S. Department of Agriculture Agricultural Research Service, 2008). Dietary folate intake was expressed as dietary folate equivalents, a measurement that was derived by multiplying the amount of folic acid from fortified foods by 1.7 to account for its greater bioavailability and then adding that amount to natural folate from foods (Bailey, 2000). Glycemic load, which reflects both quantity and quality of carbohydrate intake, was calculated by summing the product of the glycemic index and carbohydrate content for each food item. Dietary data were considered missing for 13 case women and 115 control women with more than one missing food item and for an additional 12 case women and 90 control women whose average daily kilocalorie consumption was calculated to be <500 or >5000 .

Analyses included the following variables as potential confounders: maternal race-ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), education (<12 , $=12$, >12 years), age (<25 , $25-34$, ≥ 35 years), number of previous live births (0, 1, or ≥ 2), body mass index (kg/m^2 , categorized as underweight, normal weight, overweight, or obese) (Institute of Medicine, 1990), plurality (singleton or multiple), smoking, or alcohol intake during the month before or the first 3 months of pregnancy, maternal or paternal fertility treatments or procedures (any vs. none), and study site. These variables were selected a priori based on their associations with nutrient intake or craniosynostosis; that is, they were all included in

the adjusted models, and no model reduction techniques were applied. In addition, energy intake was considered a potential confounder in all analyses related to dietary intakes of nutrients. Only results adjusted for all covariates are presented here; results adjusted only for energy intake were very similar unless noted below (results are available upon request).

Maximum likelihood estimates of the odds ratios adjusted for the potential confounders (AORs) and their corresponding 95% confidence intervals (CI) were calculated from logistic regression models to estimate relative risks. Odds ratios for craniosynostosis overall and odds ratios for each specific suture type were examined. We first compared odds ratios across the three levels of supplement intake described above. We then examined the association of dietary intake of each nutrient of interest with craniosynostosis, by comparing intake in the lowest quartile (based on the distribution among the controls) with intake in the other three quartiles. These analyses were restricted to women who took any folic acid-containing supplements during the first trimester of pregnancy, given that most of the dietary nutrients being explored are typical components of these supplements and/or contribute to common pathways. We did not conduct separate analyses of women who started taking supplements later in pregnancy or not at all because these groups were too small to generate informative results.

We also examined models that specified the nutrients as continuous variables and models that included quadratic terms to assess evidence for linear and nonlinear associations, respectively. We also created nutrient indices for nutrients related to one-carbon metabolism (folate, choline, betaine, methionine, vitamins B₆ and B₁₂, and riboflavin) and nutrients related to oxidative stress (beta-carotene and vitamins C and E), to provide a more in-depth analysis of these pathways; the scores reflect the number of relevant nutrients for which intakes were not in the lowest quartile (i.e., higher scores reflect higher intakes of more nutrients). Although these particular indices were not previously validated, the general approach is not novel (Goodman et al., 2007). We reran final analyses after excluding subjects with nonisolated craniosynostosis and subjects with a family history of craniosynostosis in their parents or siblings.

RESULTS

Among the 815 cases, 438 (54%) involved the sagittal suture, 145 (18%) the metopic suture, 137 (17%) the coronal suture, 27 (3%) the lambdoid suture, and 66 (8%) multiple sutures. Mothers of cases tended to be more likely than controls to be non-Hispanic white, have higher education, and be older (Table 1).

Analyses of supplement intake included 757 cases and 5946 controls with data on this variable and the covariates. AORs for supplement intake and overall craniosynostosis tended to be relatively weak (i.e., >0.7 and <1.5), and the confidence intervals included 1 (Table 2). For example, the AOR for craniosynostosis overall was 0.9 (CI 95%, 0.6, 1.3) for supplement intake during the second or third trimester of pregnancy and 1.2 (0.8, 1.7) for no intake during pregnancy, compared to intake during the first trimester. AORs comparing women who started taking supplements in the month before or the month after conception (i.e., very early users) to women who started taking them in the second or third month after conception were close to 1 (data not shown). Unadjusted ORs were similar to the AORs presented in Table 2, with the exception of the ORs for intake in the second or third trimester for all cases (unadjusted OR, 0.6; 95% CI, 0.4, 0.8, vs. AOR of 0.9) and for sagittal cases (unadjusted OR, 0.5; 95% CI, 0.3, 0.8, vs. AOR of 0.8), demonstrating substantial confounding was present for these particular associations.

Analyses of dietary nutrients were restricted to mothers who took folic acid-containing supplements during the first trimester (few women did not take supplements and were therefore excluded) and who had complete dietary intake data, and to cases of sagittal, metopic, or coronal synostosis (given the small numbers of lambdoid and multiple suture synostosis), that is, mothers of 591 cases and 5152 controls. For sagittal synostosis, AORs comparing highest to lowest quartiles of intake were ≤ 0.7 for folate, choline, methionine, riboflavin, glycemic load, and vitamins B₆, B₁₂, E, and C; however, only confidence intervals for riboflavin and vitamins B₆ and E excluded 1 (Table 3). Specifically, the AORs were 0.5 (0.3, 0.7) for riboflavin, 0.4 (0.2, 0.6) for vitamin B₆, and 0.6 (0.4, 0.9) for vitamin E. AORs were closer to 1 for other nutrients (i.e., betaine and beta-carotene). In addition, results supported a linear association with riboflavin and vitamins B₆, E, and C; that is, the *p* values for the linear specification of these nutrients were < 0.05 .

For metopic synostosis, AORs comparing highest to lowest quartiles of intake were ≤ 0.7 for vitamin C and ≥ 1.4 for choline, methionine, beta-carotene, and vitamin E, but none of the confidence intervals excluded 1 (Table 3). The continuous specification of the nutrients suggested a significant positive association with choline ($p = 0.03$) and vitamin B₁₂ ($p < 0.01$).

For coronal synostosis, AORs comparing highest to lowest quartiles of intake were ≤ 0.7 for folate, choline, methionine, and vitamins B₆, B₁₂, C, and E and ≥ 1.4 for glycemic load; only the confidence interval for methionine excluded 1 (Table 3). The continuous specification of the nutrients suggested a significant negative association with methionine ($p = 0.01$) and vitamin C ($p = 0.02$).

For analyses of each suture type, models that included the nutrients specified as continuous, plus quadratic terms, provided no evidence of nonlinearity of the associations with nutrients; that is, *p* values for the quadratic terms were all > 0.10 (data not shown).

For results related to the nutrient scores, higher values of the one-carbon nutrient score, which reflects the number of relevant nutrients for which intake was greater than the lowest quartile, were associated with lower risk of sagittal synostosis (AOR, 0.92; 95% CI, 0.87, 0.98) (Table 4). That is, a one-unit change in the score corresponded to an 8% reduction in risk; a seven-unit change in the score (the maximum change possible, given that seven nutrients comprised the score) corresponded to a 44% reduction ($1.0 - [0.92]^7 = 0.44$).

After removing subjects with a family history of craniosynostosis (24 cases, 5 controls) and 79 nonisolated cases, the pattern of results was essentially unchanged (data not shown).

DISCUSSION

This study examined the association of craniosynostosis with intake of folic acid-containing supplements and dietary intake of specific nutrients. Craniosynostosis was not associated with maternal intake of folic acid-containing supplements during pregnancy, regardless of when women started taking them. In this study population, almost all of the women ($> 95\%$) took supplements during the first trimester of pregnancy and took preparations that contained multiple vitamins and minerals (Carmichael et al., 2006). Among women who took supplements, increased dietary intake of most of the studied nutrients was associated with reduced risk of sagittal synostosis. The confidence intervals excluded 1 for the association of craniosynostosis with two nutrients associated with one-carbon metabolism (riboflavin and vitamin B₆) and two antioxidant nutrients (vitamins E and C). The pattern of results was similar for coronal synostosis, but the confidence intervals included 1, perhaps because of the smaller number of cases (113 vs. 362 sagittal cases). The pattern of results was different for metopic synostosis, with several of the nutrients being associated with

increased risk, but most of the confidence intervals for associations with this phenotype included 1.

Two previous studies have reported that multivitamin use during pregnancy is not associated with craniosynostosis, including a study of 323 cases in Sweden (Kallen and Robert-Gnansia, 2005) and a small study of 42 sagittal cases that was based on data from maternal interviews (Zeiger et al., 2002). The Swedish study reported that the relative risk for use of “multivitamins” during the first trimester (which was based on antenatal interviews conducted by midwives) was 3.4 (95% CI, 0.5, 3.5), and the relative risk for use later in pregnancy (which was based on prescribed drugs) was 1.0 (95% CI, 0.8, 1.6). The respective relative risks for use of folic acid supplements were 5.6 (95% CI, 2.0, 12.1) and 1.4 (95% CI, 0.9, 1.9). A subsequent study conjectured that in light of this finding of elevated risk during early pregnancy (albeit imprecise), in conjunction with suggested increases in craniosynostosis over time in some regions that coincide with increased maternal folic acid intake (Selber et al., 2008), perhaps increased maternal folic acid intake actually causes craniosynostosis (Selber et al., 2008). Our study does not support an increased risk of craniosynostosis among women who take folic acid–containing supplements or who have higher dietary folate intake, in addition to the folic acid they consume from supplements.

The pattern of findings was different for synostosis of the metopic sutures than for other types of synostosis; that is, AORs for several nutrients actually suggested increased risk with increased intake. Normal closure of cranial sutures is completed in adulthood, with the exception of the metopic suture, which usually closes by 18 months. The coronal, sagittal, and lambdoid sutures originate from an interface between neural crest cells and mesoderm, whereas the metopic suture is wholly derived from the neural crest (Morris-Kay and Wilkie, 2005). These unique features of the metopic suture are noteworthy, but it is uncertain whether or how they may have contributed to the observed findings.

Strengths of the current study include the large and diverse study population, rigorous case ascertainment and review, large sample size, recency of the data, examination of specific suture types, and the ability to examine multiple nutrients from the diet and supplements that represent multiple potential mechanistic pathways. Sample size for certain phenotypes, however, was relatively limited. Our attempt to examine supplements and diet separately was limited by the fact that the vast majority of women took supplements during early pregnancy and by the lack of available data on exact dosages of individual nutrients in supplements. Another potential limitation is that some infants with single-gene conditions or chromosome abnormalities might have been inadvertently included in our study. Clinical geneticists at each site review abstracted data from medical records (including information from clinical evaluations, radiographic imaging, and genetic laboratory studies) on infants with craniosynostosis and exclude infants with recognized or strongly suspected single-gene conditions. However, some of these conditions may have a subtle phenotype, and thus these infants might not have been recognized as affected by the examining clinician or appropriate laboratory studies may not have been performed. Inclusion of these cases would have biased our analyses toward the null. Another potential limitation is that we restricted our analyses of dietary nutrient intakes to women who took folic acid–containing supplements, and we did not have adequate sample size to examine the associations among women who did not take supplements. This restriction may limit the generalizability of our results, given that characteristics of women who do and do not take supplements may differ (Carmichael et al., 2006), and given that dietary intake would be in addition to intake from supplements for some nutrients. In addition, dietary data reflected intake during the year before pregnancy; it is uncertain whether dietary changes that occurred during pregnancy (e.g., as a result of pregnancy-related nausea and vomiting) would have been important etiologically, especially given that the timing of craniosynostosis is uncertain. Previous studies examining nutrient

intakes during pregnancy have not observed marked changes in most nutrients (Rifas-Shiman et al., 2006; Rad et al., 2009). Another study observed increased intake of many nutrients during versus before pregnancy, but whether actual rankings of intake across individuals changed was not reported (Brown et al., 1996). A substantial percentage of mothers did not participate in the study, which may limit its generalizability or may bias results if participation were related to factors associated with diet. Reporting accuracy and recall bias are potential limitations of all retrospective studies. There is always concern that mothers of malformed infants will more thoroughly report exposures than controls (Swan et al., 1992; Khoury et al., 1994). Relatively few studies have studied recall bias related to having a baby with a congenital malformation, and none have addressed dietary intake. Probably the most relevant studies examining recall bias related to dietary intake data have pertained to breast cancer, and they have tended to observe minimal to no bias (Friedenreich et al., 1991; Holmberg et al., 1996; Mannisto et al., 1999). Recall bias must be relatively severe to cause weak to moderate associations when none exists (Khoury et al., 1994). Nevertheless, we were unable to assess it and are therefore unable to rule it out as an alternative explanation for our findings. Another factor that could contribute to differential errors in reporting between case and control mothers is that time to interview was longer among case than control mothers. The extent to which this difference in time affected recall and whether it was differential is unknown.

The findings suggest that dietary intake of nutrients related to one-carbon metabolism and antioxidant nutrients may be associated with reduced risk of craniosynostosis, especially synostosis of the sagittal and coronal sutures. Given that this study is the first in-depth investigation of nutrient intake and craniosynostosis, and given the potential limitations described above, replication of the results is important before any firm conclusions may be reached regarding this research question. Ideally, further studies would incorporate prospectively collected data on dietary intake or biomarkers of nutritional status.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the National Institute of Child Health and Human Development, the National Institutes of Health, or the California Department of Public Health.

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Table 1

Descriptive Characteristics of 815 Infants with Craniosynostosis (Cases) and 6789 Liveborn Infants with No Major Birth Defects (Controls), National Birth Defects Prevention Study, 1997–2005

	Percent of cases ^a (n = 815)	Percent of controls ^a (n = 6,789)	p value
Maternal race-ethnicity			
White, non-Hispanic	74 (601)	59 (4018)	<0.001
Black, non-Hispanic	4 (36)	11 (767)	
Hispanic	17 (138)	22 (1498)	
Other	5 (39)	7 (477)	
Unknown	<1 (1)	<1 (29)	
Maternal education			
<High school	11 (90)	17 (1126)	<0.001
High school	23 (187)	24 (1647)	
>High school	65 (526)	58 (3908)	
Unknown	1 (12)	2 (108)	
Maternal age			
<25 years	22 (177)	34 (2278)	<0.001
25–34 years	58 (469)	52 (3555)	
≥35 years	21 (169)	14 (956)	
Number of previous live births			
0	35 (289)	40 (2715)	0.07
1	37 (300)	33 (2268)	
2 or more	27 (222)	26 (1786)	
Unknown	<1 (4)	<1 (20)	
Smoking ^b			
Any	18 (146)	19 (1272)	0.58
None	81 (657)	80 (5429)	
Unknown	1 (12)	1 (88)	
Alcohol ^b			
Any	37 (299)	37 (2469)	0.86
None	62 (502)	62 (4202)	
Unknown	2 (14)	2 (118)	
Maternal pre-pregnancy BMI (kg/m ²)			
Underweight BMI (<19.8)	12 (101)	13 (883)	0.05
Normal weight (19.8–26.0)	50 (408)	52 (3541)	
Overweight (26.1–29.0)	14 (112)	12 (799)	
Obese (>29.0)	21 (173)	19 (1279)	
Unknown	3 (21)	4 (287)	
Fertility treatments or procedures			
None	89 (729)	91 (6171)	<0.001
Any	9 (73)	5 (310)	
Unknown	2 (13)	5 (308)	

	Percent of cases ^a (n = 815)	Percent of controls ^a (n = 6,789)	p value
Plurality			
Singleton	95 (772)	96 (6542)	<0.001
Multiple birth	5 (41)	2 (166)	
Unknown	<1 (2)	1 (81)	
Study center			
AR	14 (114)	12 (846)	0.43
CA	11 (89)	13 (857)	
IA	13 (108)	11 (758)	
MA	15 (125)	13 (855)	
NJ	6 (48)	8 (574)	
NY	6 (52)	9 (600)	
TX	7 (58)	12 (790)	
CDC/Atlanta	10 (80)	11 (734)	
NC	5 (40)	6 (408)	
UT	12 (101)	5 (367)	

^aNumbers may not add to 100% because of rounding.

^bDuring the month before or the first 3 months of pregnancy.

Table 2

Adjusted Odds Ratios for the Association of Intake of Folic Acid–Containing Supplements with Craniosynostosis^a

Timing of supplement intake	No. controls	All cases (n = 757)		Sagittal (n = 407)		Metopic (n = 132)		Coronal (n = 128)		Multiple (n = 61)	
		No. cases	AOR (95% CI)	No. cases	AOR (95% CI)	No. cases	AOR (95% CI)	No. cases	AOR (95% CI)	No. cases	AOR (95% CI)
First trimester	5238	684	Ref.	370	Ref.	117	Ref.	115	Ref.	57	Ref.
Second or third trimester	427	36	0.9 (0.6, 1.3)	16	0.8 (0.5, 1.4)	10	1.4 (0.7, 2.7)	6	0.7 (0.3, 1.8)	1	—
None	281	37	1.2 (0.8, 1.7)	21	1.4 (0.9, 2.2)	5	1.0 (0.4, 2.4)	7	1.1 (0.5, 2.5)	3	1.1 (0.3, 3.7)

^aOdds ratios were adjusted for mother's race-ethnicity, education, age, parity, smoking, alcohol intake, body mass index categories, fertility treatments, plurality, and study center.

Table 3

Adjusted Odds Ratios for the Association between Craniosynostosis and Maternal Dietary Intake of Selected Nutrients, among Women Who Took Folic Acid-Containing Supplements during the First Trimester of Pregnancy^a

Nutrient quartiles ^b	No. controls (n = 5152)	Sagittal (n = 362)		Metopic (n = 116)		Coronal (n = 113)	
		No. cases	AOR (95% CI)	No. cases	AOR (95% CI)	No. cases	AOR (95% CI)
Folate DFE							
<335.2 µg	1302	118	Ref.	28	Ref.	34	Ref.
335.2–492.6 µg	1315	88	0.7 (0.5, 1.0)	35	1.3 (0.7, 2.1)	31	0.8 (0.5, 1.4)
492.7–718.1 µg	1311	90	0.8 (0.6, 1.1)	29	1.1 (0.6, 1.9)	24	0.6 (0.3, 1.1)
≥718.2 µg	1224	66	0.7 (0.5, 1.0)	24	1.0 (0.5, 2.0)	24	0.6 (0.3, 1.2)
Continuous			p = 0.12		p = 0.98		p = 0.26
Choline							
<189.8 mg	1330	114	Ref.	23	Ref.	26	Ref.
189.8–253.5 mg	1349	91	0.7 (0.5, 1.0)	36	1.6 (0.9, 2.8)	31	1.0 (0.6, 1.8)
253.6–342.5 mg	1314	97	0.8 (0.6, 1.2)	31	1.6 (0.8, 2.9)	40	1.2 (0.7, 2.2)
≥342.4 mg	1159	60	0.7 (0.4, 1.1)	26	1.9 (0.8, 4.3)	16	0.5 (0.2, 1.2)
Continuous			p = 0.48		p = 0.03		p = 0.39
Betaine							
<46.8 mg	1239	105	Ref.	26	Ref.	29	Ref.
46.8–75.4 mg	1319	86	0.7 (0.5, 1.0)	26	0.9 (0.5, 1.6)	26	0.8 (0.5, 1.4)
75.5–123.7 mg	1311	93	0.8 (0.6, 1.1)	39	1.5 (0.9, 2.6)	33	1.0 (0.6, 1.7)
≥123.8 mg	1283	78	0.8 (0.6, 1.2)	25	1.0 (0.5, 1.9)	25	0.8 (0.4, 1.5)
Continuous			p = 0.41		p = 0.88		p = 0.71
Methionine							
<1.1 grams	1296	108	Ref.	22	Ref.	27	Ref.
1.1–1.3 grams	1296	82	0.7 (0.5, 0.9)	33	1.4 (0.8, 2.5)	44	1.3 (0.8, 2.2)
1.4–1.8 grams	1309	98	0.8 (0.6, 1.2)	33	1.5 (0.8, 2.7)	23	0.6 (0.3, 1.1)
≥1.9 grams	1251	74	0.7 (0.5, 1.1)	28	1.4 (0.7, 3.2)	19	0.3 (0.1, 0.8)
Continuous			p = 0.94		p = 0.19		p = 0.01
Vitamin B ₆							
<1.4 mg	1318	116	Ref.	28	Ref.	31	Ref.
1.4–1.8 mg	1337	96	0.7 (0.5, 1.0)	31	1.0 (0.6, 1.8)	34	0.9 (0.6, 1.6)

Nutrient quartiles ^b	No. controls (n = 5152)	Sagittal (n = 362)		Metopic (n = 116)		Coronal (n = 113)	
		No. cases	AOR (95% CI)	No. cases	AOR (95% CI)	No. cases	AOR (95% CI)
1.9–2.6 mg	1298	106	0.8 (0.6, 1.1)	32	1.2 (0.6, 2.1)	28	0.7 (0.4, 1.3)
≥2.7 mg	1199	44	0.4 (0.2, 0.6)	25	1.1 (0.5, 2.3)	20	0.5 (0.2, 1.0)
Continuous			p < 0.01		p = 0.28		p = 0.21
Vitamin B ₁₂							
<3.5 µg	1294	95	Ref.	28	Ref.	32	Ref.
3.5–5.0 µg	1323	116	1.1 (0.8, 1.5)	36	1.2 (0.7, 2.0)	26	0.7 (0.4, 1.3)
5.1–7.3 µg	1324	98	1.0 (0.7, 1.3)	23	0.8 (0.4, 1.4)	31	0.8 (0.5, 1.4)
≥7.4 µg	1211	53	0.6 (0.4, 1.0)	29	1.1 (0.6, 2.2)	24	0.7 (0.3, 1.3)
Continuous			p = 0.12		p < 0.01		p = 0.24
Riboflavin							
<1.4 mg	1294	112	Ref.	31	Ref.	27	Ref.
1.4–1.8 mg	1325	107	0.8 (0.6, 1.1)	32	1.0 (0.6, 1.6)	33	1.1 (0.7, 1.9)
1.9–2.5 mg	1320	84	0.6 (0.5, 0.9)	23	0.7 (0.4, 1.3)	24	0.8 (0.4, 1.4)
≥2.6 mg	1213	59	0.5 (0.3, 0.7)	30	1.1 (0.5, 2.1)	29	1.1 (0.5, 2.2)
Continuous			p < 0.01		p = 0.21		p = 0.76
Glycemic load							
<78.6	1377	125	Ref.	34	Ref.	29	Ref.
78.6–106.7	1342	106	0.9 (0.6, 1.2)	30	0.9 (0.5, 1.6)	26	1.0 (0.6, 1.7)
106.8–148.7	1284	73	0.6 (0.4, 0.9)	30	1.0 (0.5, 1.8)	35	1.6 (0.8, 2.9)
≥148.8	1149	58	0.6 (0.4, 1.1)	22	0.9 (0.4, 2.1)	23	1.5 (0.6, 3.7)
Continuous			p = 0.40		p = 0.57		p = 0.08
Beta-carotene							
<1060.9 µg	1274	99	Ref.	24	Ref.	29	Ref.
1060.9–2011.7 µg	1335	78	0.7 (0.5, 0.9)	26	1.0 (0.6, 1.8)	22	0.7 (0.4, 1.2)
2011.8–3571.7 µg	1286	105	0.9 (0.7, 1.3)	30	1.2 (0.7, 2.2)	32	1.0 (0.6, 1.6)
≥3571.8 µg	1257	80	0.8 (0.6, 1.1)	36	1.6 (0.9, 2.9)	30	0.9 (0.5, 1.6)
Continuous			p = 0.08		p = 0.29		p = 0.73
Vitamin E							
<2.8 mg	1330	106	Ref.	23	Ref.	32	Ref.
2.8–4.1 mg	1314	115	1.0 (0.7, 1.3)	36	1.6 (0.9, 2.7)	22	0.6 (0.4, 1.1)

Nutrient quartiles ^b	No. controls (n = 5152)	Sagittal (n = 362)		Metopic (n = 116)		Coronal (n = 113)	
		No. cases	AOR (95% CI)	No. cases	AOR (95% CI)	No. cases	AOR (95% CI)
4.2–6.0 mg	1295	84	0.7 (0.5, 1.0)	26	1.3 (0.7, 2.4)	36	1.1 (0.6, 1.8)
≥6.1 mg	1213	57	0.6 (0.4, 0.9)	31	1.8 (0.9, 3.5)	23	0.7 (0.4, 1.4)
Continuous			<i>p</i> < 0.01		<i>p</i> = 0.40		<i>p</i> = 0.54
Vitamin C							
<59.4 mg	1343	111	Ref.	31	Ref.	32	Ref.
59.4–101.3 mg	1317	109	1.0 (0.7, 1.3)	31	1.0 (0.6, 1.6)	30	0.9 (0.5, 1.5)
101.4–154.0 mg	1308	89	0.9 (0.7, 1.2)	37	1.2 (0.7, 2.0)	34	1.0 (0.6, 1.6)
≥154.1 mg	1184	53	0.7 (0.5, 1.1)	17	0.6 (0.3, 1.3)	17	0.5 (0.2, 1.0)
Continuous			<i>p</i> = 0.02		<i>p</i> = 0.42		<i>p</i> = 0.02

^aOdds ratios were adjusted for mother's race-ethnicity, education, age, parity, smoking, alcohol intake, body mass index categories, fertility treatments, plurality, study center, and energy intake.

^bNutrient intake quartiles were based on the distribution among the controls; "continuous" refers to models for which the nutrient was included as a continuous variable (i.e., not categorized). AOR, adjusted odds ratio; CI, confidence interval; DFE, dietary folate equivalents.

Table 4

Adjusted Odds Ratios for the Association between Craniosynostosis and Maternal Nutrient Scores, among Women Who Took Folic Acid–Containing Supplements during the First Trimester of Pregnancy^a

	AOR (95% CI) ^b		
	Sagittal (<i>n</i> = 362)	Metopic (<i>n</i> = 116)	Coronal (<i>n</i> = 113)
One-carbon nutrient score	0.92 (0.87, 0.98)	1.05 (0.94, 1.17)	0.96 (0.86, 1.07)
Oxidative stress nutrient score	0.91 (0.81, 1.03)	1.12 (0.90, 1.40)	0.89 (0.72, 1.10)

^a Nutrient scores represent the number of relevant nutrients for which intake was greater than the lowest quartile. The one-carbon nutrient score included folate, choline, betaine, methionine, vitamins B₆ and B₁₂, and riboflavin. The oxidative stress nutrient score included beta-carotene and vitamins C and E. The analyses included 5152 controls.

^b AORs represent the change in risk for a one-unit change in the nutrient score; ORs were adjusted for mother's race-ethnicity, education, age, parity, smoking, alcohol intake, body mass index, fertility treatments, plurality, study center, and energy intake.

AOR, adjusted odds ratio; CI, confidence interval.