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Periconceptional folic acid and risk for neural tube defects among higher risk pregnancies

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Abstract

Background—Women with a previous neural tube defect (NTD)-affected pregnancy are recommended to consume 4,000 μg daily folic acid (FA) for prevention (10 times the general-population recommendation). Protection from doses between 400 and 4,000 μg for this and other higher risk groups is unclear.

Methods—In the case–control Slone Birth Defects Study (1988–2015), we examined the associations between periconceptional FA doses and NTDs among four higher risk groups: NTD family history, periconceptional antiepileptic drug exposure (AED), pregestational diabetes, and prepregnancy obesity. Mothers completed standardized interviews about pregnancy events and exposures. FA categorizations were based on (a) supplements only and (b) supplements and diet ("total folate"). We estimated odds ratios (ORs) and 95% confidence intervals (CIs) (adjusted for age and study center) using logistic regression.

Results—Cases and controls included: 45 and 119 with family history, 25 and 108 with AED exposure, 12 and 63 with pregestational diabetes, 111 and 1,243 with obesity. Daily FA supplementation was associated with lower NTD risk compared to no supplementation (adjusted ORs were 0.33 [95% CI 0.13, 0.76] for family history, 0.31 [0.09, 0.95] for AED exposure, 0.25 [0.04, 1.05] for pregestational diabetes, 0.65 [0.40, 1.04] for obesity). Though estimates were imprecise, as total folate increased stronger point estimates were observed, notably among family history. No mothers with a prior NTD-affected pregnancy supplemented with 4,000 μg.

Conclusions—Our findings reinforce that all women of childbearing potential should consume at least 400 μg FA/day to protect against NTDs. Higher risk groups may benefit from higher doses.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions. The data that support the findings of this study are available from the corresponding author upon reasonable request.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Keywords

folic acid; neural tube defects; obesity; prevention; recurrence

1 | INTRODUCTION

Czeizel, Dudas, Paput, & Banhidy, 2011; MRC, 1991; Werler & Mitchell, 1993; Werler, Shapiro, & Mitchell, 1993; Williams Maternal folic acid (FA) intake protects against neural tube et al., 2015). Women with a previously affected pregnancy are defect (NTD) occurrence and recurrence (Berry et al., 1999; at greater risk for NTDs in future pregnancies than the general population (3–5% (Cowchock et al., 1980; Czeizel & Metneki, 1984; Jorde, Fineman, & Martin, 1983; Liu, Li, Greene, Li, & Ren, 2017; Papp et al., 1997; Seller, 1981; Toriello & Higgins, 1983) versus 0.1% (Parker et al., 2010). Based on limited clinical trial data (ACMG, 2011; CDC, 1991), these women are recommended to consume 4,000 μg of FA daily (10 times the recommendation for the general population of women of reproductive potential) (ACOG, 2005; Bibbins-Domingo et al., 2017; CDC, 1992; Gomes, Lopes, & Pinto, 2016; IOM, 1998). The degree to which doses between 400 and 4,000 μg protect against NTD recurrence is unclear. Women with a family history of NTDs are also at higher risk (0.2–0.5%) (Dupepe et al., 2017; Nightingale, Scribanu, McCullough, & Quinn, 1975; Toriello & Higgins, 1983). Some organizations recommend that women who themselves or their partners have a family history of NTDs also consume higher doses (ACMG, 2011; ACOG, 2005; Bibbins-Domingo et al., 2017; CDC, 1992; Gomes et al., 2016; Wilson et al., 2015), although there are no trials to support this recommendation.

In addition to NTD family history, women who take antiepileptic drugs (AEDs) or who have pregestational diabetes or obesity are at higher risk for NTDs (Kennedy & Koren, 2012; Kondo, Kamihira, & Ozawa, 2009; Talaulikar & Arulkumaran, 2011). Folate deficiency may play a role in the pathogenetic pathways leading to NTDs in these higher risk groups. For example, many AEDs reduce circulating folate levels (Morrell, 2002), leading to the hypothesis that FA supplementation may ameliorate NTD risk (Zahn, Morrell, Collins, Labiner, & Yerby, 1998). Separate recommendations for these groups have been discussed but are not well-established (Kennedy & Koren, 2012; Kondo et al., 2009; Talaulikar & Arulkumaran, 2011).

We utilized the Slone Epidemiology Center Birth Defects Study to examine whether the strength of the association between FA and NTD risk differs by source, frequency, and dose among four groups of women at higher risk for NTDs: those with a family history of NTDs, periconceptional AED use, pregestational diabetes, or prepregnancy obesity.

2 | METHODS

The Slone Birth Defects Study (1976–2015) employed a multi-center case–control design and included deliveries affected by major malformations. Pregnancies were identified from tertiary care centers and birth hospitals in Boston, Philadelphia, and Toronto (until 2005), San Diego (starting in 2001), and Nashville (starting in 2012), and via birth defect registries in Massachusetts (starting in 2003) and parts of New York State (starting in 2004). Eligible

pregnancies included those with a major malformation resulting in live birth, stillbirth, or elective termination >12 weeks' gestation; beginning in 1993, routine inclusion of nonmalformed pregnancies began. Consenting mothers completed a standardized interview about pregnancy events and exposures administered by a study nurse within 6 months after delivery. The present analysis used 1988–2015 interviews which included details on supplementation and diet. Institutional review boards at participating facilities approved the research.

Cases with NTDs were pregnancies affected by anencephaly, spina bifida, or encephalocele based on clinical geneticist review (Parker, Yazdy, Mitchell, Demmer, & Werler, 2014). Conjoined twins and infants with amniotic bands, body wall defects, chromosomal anomalies, a known syndrome, or unconfirmed diagnoses were excluded. Because ascertainment of nonmalformed controls did not begin until 1993, during 1988–1992, controls were pregnancies affected by minor malformations only or by one of several major malformations not known to be associated with FA (i.e., hydronephrosis, club foot, intestinal atresia, heterotaxy, craniosynostosis, arthrogryposis, and pyloric stenosis); starting in 1993, controls were liveborns without major structural malformations.

Vitamin supplementation, including product (if known), dates of use, frequency, and dose were collected. Label information was transcribed when available. When product name was unknown, women were asked if the supplement was a prenatal vitamin and if so, whether it was prescription or over-the-counter. Products were linked to active ingredients using the Slone Drug Dictionary (Kelley, Kelley, Kaufman, & Mitchell, 2003). Mothers who reported any product containing FA during the periconceptional period, which we defined as 28 days before to 28 days after the first day of the last menstrual period, were categorized as less than daily or daily supplement users. To be classified as daily, mothers had to report supplementation containing FA every day during this 57-day period. In the less than daily and daily categories, the average daily dose was calculated as the sum of daily doses divided by number of days exposed and categorized as <400, 400 to <1,000, or ≥1,000 μg. When product name was unknown, FA dose was assumed to be 1,000 μg for prescription prenatals, 800 μg for nonprescription prenatals, and 400 μg for other nonprescription supplements, including FA-only supplements (Saldanha et al., 2017). Mothers who did not report any supplements containing FA during this period were categorized as nonsupplementers (denoted as "None") and constituted the reference category.

As part of the study interview, the mothers completed a food frequency questionnaire that ascertained intake 6 months before pregnancy, which should represent periconceptional diet since lifestyle does not usually change until pregnancy recognition (Willett, 2013). Daily dietary nutrients were estimated from nutrition matrices (Harvard, 2018; Lindberg, Maddow-Zimet, Kost, & Lincoln, 2015) and adjusted for total caloric intake (Willett & Stampfer, 1986). We summed estimated daily FA from both supplements and fortified foods with naturally-occurring folate discounted by 30% due to its lower bioavailability compared to synthetic FA (IOM, 1998); this quantity, which we refer to as "total folate," was expressed in units equivalent to synthetic FA and categorized as <400 (reference), 400 to <1,000, or ≥1,000 μg.

2.1 | NTD higher risk groups

2.1.1 | Family history—Each mother was asked whether any of her previous pregnancies or she, the baby's biological father, or other relatives (e.g., parents, brothers, sisters, or cousins) had any problems of the brain, head, eye, ear, or spinal cord; specific anomalies and affected relatives (in relation to the baby) were coded. We defined pregnancies with a "family history" as those with a first- (parent or full-sibling), second- (half-sibling, aunt, uncle, or grandparent), or third- (first cousin) degree relative affected with an NTD.

2.1.2 | AED use—The interview asked mothers about medications for several indications, including epilepsy and convulsions. For each medication, the product name, timing, frequency, and duration were recorded; a research pharmacist coded them using the Slone Drug Dictionary. The AED group included mothers who reported any periconceptional use of the following medications in the anticonvulsants class, regardless of indication: carbamazepine, clonazepam, diazepam, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, pregabalin, primidone, topiramate, or valproic acid.

2.1.3 | Pregestational diabetes—Mothers were asked whether they had ever been diagnosed with diabetes and, if so, the date of diagnosis. The pregestational diabetes group included mothers who reported diagnosis of Type 1 or 2 diabetes mellitus before the end of the periconceptional period (to avoid misclassification, as gestational diabetes is not usually diagnosed until after week 24) ("Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus," 1997).

2.1.4 | Prepregnancy obesity—Mothers reported prepregnancy weight in lbs or kg and height in feet and inches or cm; we converted these, where necessary, to kg and m, respectively, and computed BMI as kg/m^2. We defined obesity as BMI ≥ 30 kg/m^2 (NHLBI, n.d.). Because height was not asked until 1993, we excluded 1998–1992 interviews from the obesity analyses. NTDs are less strongly associated with obesity than the other risk factors (Agopian et al., 2013), so we also excluded mothers with NTD history, AED use, or pregestational diabetes from the obesity analysis. Due to the rarity of the other factors, the other higher risk groups were not mutually-exclusive.

2.2 | Statistical analysis

To characterize each higher risk group, we evaluated the distribution of the following covariates by case–control status: maternal race/ethnicity (white non-Hispanic, Black non-Hispanic, Asian non-Hispanic, Hispanic, other), maternal age (<25, 25–34, ≥35 years), maternal education (<12, 12, >12 years), planned pregnancy (yes/no), study center, and year of last menstrual period (1988–1997, 1998–2015).

We used unconditional logistic regression with Firth's penalized likelihood to estimate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between FA intake and NTD risk within each higher risk group. Firth's penalized-likelihood is a standard penalization to reduce bias in maximum likelihood estimates of beta coefficients with small sample sizes (Firth, 1993). We did not report ORs for models that did

not converge or exposure groups with only 1 case. We adjusted for maternal age, because it was hypothesized to be the strongest confounder a priori, and study center (Massachusetts, Philadelphia, Toronto, other) because center participation changed over the study period. We evaluated dose separately for FA supplementation only and for total folate intake because some clinical recommendations are restricted to supplements whereas others do not specify a preferred source. We descriptively evaluated patterns of use and dose among less than daily supplementers but did not compute ORs due to small numbers. We interpreted ORs as relative risks since NTDs are rare.

In sensitivity analyses, we first repeated the analysis adjusted for planned pregnancy instead of maternal age. Second, for all FA-containing products where dose was unknown, we uniformly assigned a dose of 400 μg. Third, we restricted the supplement analyses for NTD family history, AED use, and pregestational diabetes to 1993–2015 data when only non-malformed controls were used. Fourth, to assess if the patterns were different in pre- versus post-fortification years, we generated boxplots of continuous estimated total folate intake by case–control status and time period for each higher risk group. Fifth, we restricted the analysis to isolated NTD cases. Sixth, we conducted the NTD history analysis restricted to pregnancies with first-degree history. Lastly, we conducted a multidimensional quantitative bias analysis (Lash, Fox, & Fink, 2009) to evaluate the robustness of primary supplementation findings for the family Supplemental Materials).

3 | RESULTS

During 1988–2015, mothers of 1,201 cases with NTDs and 11,137 controls were interviewed in the Slone Birth Defects Study. We identified 45 cases and 119 controls with a family history of NTDs (14 cases and 20 controls with first-degree); 25 cases and 108 controls with periconceptional AED exposure; 12 cases and 63 controls whose mothers reported pregestational diabetes; and 111 cases and 1,243 controls whose mothers had prepregnancy obesity. The majority of cases were affected by spina bifida and were isolated (not affected by another major birth defect) (refer to Table 1). Three cases were in both the family history and AED groups and three controls were in both the family history and pregestational diabetes groups.

Among those with family history or periconceptional AED exposure, case mothers were younger than control mothers (Table 1). Among those with family history, case mothers were less educated than control mothers. Among the pregestational diabetes group, case mothers were more likely to be Black and 25 years or older. In the prepregnancy obesity group, case mothers were more likely to be white and less educated. In all groups, cases occurred more often in unplanned pregnancies. Case–control distributions differed by year and center, due to changes in ascertainment procedures during the study period.

A higher proportion of case compared to control mothers reported no periconceptional FA supplementation in all higher risk groups (Table 2). Approximately half of controls in each higher risk group reported no supplementation, whereas the prevalence of no supplementation among cases ranged from 64% for the obesity and AED groups to 83% for the pregestational diabetes group. Among all the higher risk groups, less than daily

supplementation was infrequent (≤12%); most of these supplementers started daily use midway through the periconceptional period (Table S1). A similar proportion of case and control mothers reported daily supplementation in the highest dose category in all groups except NTD family history, where a lower proportion of case than control mothers reported average daily doses ≥1,000 μg (4 vs. 18%).

Across all higher risk groups, daily FA supplementation (regardless of dose) was associated with lower NTD risk compared to no supplementation. Specifically, the adjusted ORs were: 0.33 (95% CI 0.13, 0.76) for family history, 0.31 (0.09, 0.95) for AED use, 0.25 (0.04, 1.05) for pregestational diabetes, and 0.65 (0.40, 1.04) for prepregnancy obesity (Table 2). We did not observe a clear dose–response pattern for higher doses in any group, although numbers were small.

When dietary folate was also considered, case mothers had lower estimated total folate compared to control mothers across all higher risk groups, with the most pronounced difference in the family history group (Table 2). Though estimates were imprecise, we observed stronger protective OR point estimates as folate intake increased.

3.1 | Sensitivity analyses

Results were similar when models were adjusted for pregnancy planning instead of maternal age, though some associations were attenuated among the pregestational diabetes group (Table 2).

Among women reporting FA supplementation, exact dose was unknown for at least one product in 18.5% of participants; among products with unknown dose, 31% were prescription prenatals, 30% were over-the-counter prenatals, and 41% were other multivitamins (non-exclusive). Results were similar when 400 μg was universally reassigned for these reports (instead of 1,000, 800, and 400 μg, respectively), except for the pregestational diabetes group, for which there were insufficient numbers to assess doses ≥1,000 μg (Table S2).

When we restricted the data to 1993 or later (when all controls had no major structural malformations), similar OR point estimates were observed except for supplementation ≥1,000 μg among the AED users, which approximated the null (Table 3).

The boxplots demonstrated that on average during post-fortification years women consumed more total folate (among controls in each higher risk group, pre-fortification median 261.9–369.3 μg and post-fortification 386.3–587.6 μg). Except AED users during post-fortification, controls consistently had higher estimated total folate compared to cases in both pre- and post-fortification years across all higher risk groups (refer to Figures S1–S4). Due to small sample size, we could not make this comparison in the pregestational diabetes group for prefortification years.

When we restricted to isolated NTD cases (Table S3), results were similar to the main analysis. Due to small sample size, we could not estimate associations in the pregestational diabetes group.

The first-degree family history group demonstrated slightly stronger results for daily supplementation relative to the broader family history group, but a dose–response effect could not be evaluated due to small numbers (Table S4). No mothers with first-degree family history reported supplementation with the recommended dose of 4,000 μg; though the subgroups were small, mothers who planned the pregnancy tended to report daily supplementation ≥1,000 μg (5 out of 15 pregnancy planners versus 2 out of 19 unplanned pregnancies).

The quantitative bias analysis for potential recall bias suggested that daily folic acid supplementation would be more beneficial than observed if the control mothers consistently reported less accurately than the case mothers or if the case mothers consistently overreported supplementation. If instead the control mothers overreported supplementation, our observed results would be an overestimate of the true association; however, based on our simulated scenarios, ≥30% of the mothers who did not actually supplement would have needed to misreport as daily supplementers for the attenuation to be substantial (see Supplemental Materials for more detail).

4 | DISCUSSION

Based on our data, women with elevated NTD risk due to family history, AED use, pregestational diabetes, or prepregnancy obesity appear to benefit from increased folate intake during the periconceptional period, though the degree of benefit may vary by the risk factor. Of note, daily FA supplementation at any dose was associated with a 67% reduced NTD risk among pregnancies with family history, with even greater risk reduction suggested for doses ≥1,000 μg. A possible benefit for ≥1,000 μg/day was also observed for women who are periconceptional AED users or who have diabetes or obesity.

4.1 | Family history

Among our participants with an NTD family history, only 4% of cases and 18% of controls reported taking ≥1,000 μg of FA daily and none supplemented with ≥4,000 μg/day, demonstrating low adherence to recommendations. It is unclear if this was because they were uninformed or because did not follow clinical guidance. The Medical Research Council trial (1983–1991) is the only study to date with sufficient numbers to evaluate doses as high as 4,000 μg (MRC, 1991). Among the mothers of 1,005 cases with NTDs and 8,239 controls in the National Birth Defects Prevention Study (NBDPS) (1997–2009), only 27 had a previous NTD-affected pregnancy (Arth et al., 2015). Periconceptional FA supplementation was 35% (10/17) among women with NTD recurrence compared to 80% (8/10) among those without recurrence (Arth et al., 2015), equating to a crude OR of 0.14. Our findings, using a broader definition of family history, were consistent with these NBDPS results.

4.2 | AED use and diabetes

We evaluated how FA is associated with NTD risk within diabetes and AED user subgroups, whereas prior studies have evaluated FA as a modifier of the associations between these risk factors and NTDs. Based on data distributions from these prior studies, we calculated crude

ORs for FA and NTD risk to compare to our results. For AED users, among 196 women (1980–1996), any FA supplementation 5–12 weeks from last menstrual period was associated with an OR of 0.72 (Kjaer et al., 2008); among 19 valporic acid users specifically (1981–2007), periconceptional FA of 400 μg daily yielded a null association (Jentink, Bakker, Nijenhuis, Wilffert, & de Jong-van den Berg, 2010). Another study (1990–2013) observed 4 nervous system malformations among 1,259 pregnancies with first trimester AED exposure but none among the 66 women who supplemented with ≥5 mg of FA (Ban et al., 2015); information was not provided to compute ORs. Pregestational diabetes was reported among 43 NBDPS participants (1997–2004), any periconceptional FA supplementation was associated with an OR of 0.19 (Correa et al., 2012). Among 47 Slone Birth Defects Study participants with pregestational diabetes (1976–2011), periconceptional daily FA ≥400 μg was associated with an OR of 0.23 for spina bifida (Parker, Yazdy, Tinker, Mitchell, & Werler, 2013).

4.3 | Obesity

A previous Slone Birth Defects Study analysis (1993–2011) found that, among women with obesity, spina bifida risk was reduced by approximately 15% with total folate ≥400 μg compared to <400 μg (Parker et al., 2013). In the present analysis, with expanded years and case definition, we observed a 35% reduction in overall NTD risk from daily FA supplementation at any dose, and the degree of benefit was similar for total folate from both diet and supplements ≥1,000 μg.

A recently study commented on the increase in NTD-affected pregnancies in Canada over the past decade and how these additional cases may be due to increased prevalence of several risk factors including pregestational diabetes and certain conditions which are sometimes treated with AEDs such as epilepsy and mood disorders (Liu et al., 2019). In addition, despite the high prevalence of obesity and its established association with NTD risk, research is lacking on an appropriate FA dose that might help to reduce, though perhaps not eliminate, NTD risk for this group. Our findings stress the need for further investigation into specific FA doses that may be needed to protect against NTDs in these groups of women at higher risk than the general population. Even a small decrease in NTD risk associated with FA would have an important impact on the general population because obesity continues to increase among women of childbearing age (Deputy, Dub, & Sharma, 2018).

The Slone Birth Defects Study has the benefit of spanning both pre- and post-fortification eras and included data on supplementation and medication use, family history of birth defects, demographic factors, and illness history. Unlike many prior studies, we were able to consider FA from both supplements and diet, and we were able to account for naturally-occurring food folate as well as synthetic FA from fortified foods. Despite the large size of the Slone Birth Defects Study, many of our findings were based on small numbers. For example, the higher risk groups were not mutually exclusive, except for women with prepregnancy obesity. While random errors in the dietary data are plausible, a validation study of the Willett food frequency questionnaire detected valid folate intake compared to biomarkers and 24-hour recall assessment (Yuan et al., 2018). We believe differential recall

of the dietary data is unlikely because most U.S. consumers have poor health literacy and are not aware of micronutrient levels in food (Persoskie, Hennessy, & Nelson, 2017). In addition, this hypothesis was not known to the participants at the time of data collection. Based on our bias analysis, our primary findings for folic acid supplementation appear to be robust to certain scenarios of differential recall. We were unable to evaluate folic acid dose cutoffs higher than ≥1,000 μg; we did not collect information on reasons for not supplementing as recommended (e.g., unaware of recommendations, intolerance to vitamin supplements), although we do know that a portion of the pregnancies were unplanned. In the AED analysis, we were not able to evaluate associations with individual medications or account for indication or dose. The control definition changed in 1993 onward; patterns were generally similar in the sample restricted to 1993+. Residual confounding may be present since we could not adjust for all possible confounding factors; still, established risk factors for NTDs are only weak predictors in absolute terms (Agopian et al., 2013). The direction of the associations observed were largely in line with expectations and biologic plausibility, based on what is known regarding the association between FA and NTD risk among the general population (Wald, Law, Morris, & Wald, 2001). Misclassification of FA categories may have occurred due to recall issues; however, our sensitivity analysis with reassigned categories for those with unknown dose did not meaningfully change our conclusions.

In conclusion, our study supports the recommendation that all women of childbearing potential should consume at least 400 μg of FA daily, either through supplementation only or along with fortified foods, to protect against NTDs. The neural tube typically closes within the first 28 days after conception (Greene & Copp, 2014), often before pregnancy recognition (Branum & Ahrens, 2017), so supplementation should start before pregnancy to be effective. Given that many mothers in our study took less FA than current guidelines, this work highlights the need for clinical initiatives before pregnancy to improve FA intake. This work suggested that further benefit may be provided by higher doses for women at higher risk for NTDs, though the degree appears to vary by risk factor. Additional research is needed to inform clinical guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Characteristics of groups of pregnancies at higher risk for neural tube defects, Slone Birth Defects Study (1988–2015)

	NTD family history				Periconceptional AED use				Pregestational diabetes				Prepregnancy obesity[a]			
	Cases (*n* = 45)		Controls (*n* = 119)		Cases (*n* = 25)		Controls (*n* = 108)		Cases (*n* = 12)		Controls (*n* = 63)		Cases (*n* = 111)		Controls (*n* = 1,243)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Case type			n/a				n/a				n/a				n/a	
Anencephaly	16	36			3	12			2	17			17	15		
Encephalocele	1	2			2	8			4	33			6	5		
Spina bifida	29	64			20	80			7	58			88	79		
Isolated	36	80			19	76			8	67			79	71		
Race/ethnicity																
White non-Hispanic	38	84	105	88	19	76	86	80	5	42	39	62	75	68	752	60
Black non-Hispanic	1	2	1	1	1	4	6	6	4	33	12	19	16	14	179	14
Hispanic	5	11	11	9	4	16	15	14	2	17	9	14	16	14	254	20
Asian non-Hispanic	0	0	2	2	1	4	0	0	0	0	2	3	1	0	26	2
Other	1	2	0	0	0	0	1	1	0	0	1	2	3	3	29	2
Unknown									1	8					3	0
Age (yrs)																
<25	15	33	15	13	7	28	22	20	1	8	12	19	22	20	291	23
25 to <35	22	49	74	62	10	40	63	58	7	58	31	50	72	65	730	59
35+	8	18	30	25	8	32	23	21	4	33	19	31	17	15	220	18
Unknown											1				2	
Education (yrs)																
<12	8	18	7	6	3	12	11	10	2	17	8	13	20	18	125	10
12	11	24	16	13	7	28	25	23	3	25	16	25	32	29	336	27
>12	26	58	96	81	15	60	72	67	7	58	38	60	59	53	782	63
Unknown											1					
Planned pregnancy																
Yes	17	38	72	61	11	44	60	56	6	50	37	59	59	53	721	58
No	26	58	47	39	13	52	48	44	6	50	25	40	51	46	520	42
Unknown	2	4			1	4							1	1	2	0

	NTD family history				Periconceptional AED use				Pregestational diabetes				Prepregnancy obesity[a]			
	Cases (*n* = 45)		Controls (*n* = 119)		Cases (*n* = 25)		Controls (*n* = 108)		Cases (*n* = 12)		Controls (*n* = 63)		Cases (*n* = 111)		Controls (*n* = 1,243)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Center																
Massachusetts	26	58	57	48	10	40	62	57	2	17	26	41	25	23	568	46
Philadelphia	8	18	16	13	9	36	17	16	5	42	17	27	45	41	285	23
Toronto	7	16	23	19	4	16	9	8	2	17	3	5	19	17	66	5
San Diego	2	4	20	17	1	4	8	7	2	17	8	13	6	5	187	15
New York	2	4	2	2	1	4	11	10	0	0	9	14	13	12	125	10
Nashville	0	0	1	1	0	0	1	1	1	8	0	0	3	3	12	1
LMP year																
1988–1997	34	76	19	16	13	52	17	16	2	17	5	8	41	37	91	7
1998–2015	11	24	100	84	12	48	91	84	10	83	58	92	70	63	1,152	93
Birth outcome																
Livebirth	28	62	119	100	18	72	108	100	10	83	100	100	88	79	1,243	100
Fetal loss	17	38	0	0	7	28	0	0	2	17	0	0	23	21	0	0

Abbreviations: AED, antiepileptic drugs; LMP last menstrual period; NTD, neural tube defect; yrs, years.

[a]The prepregnancy obesity group includes 1993–2015 only, which is when data were available to estimate BMI. In the rare event that height was not reported, we classified a woman as having obesity if she weighed more than 102 kg, which would classify a women as having obesity if she was 6 ft tall or less. (Only 2 women in the obesity group were added due to this definition.)

TABLE 2

Distributions of and estimated odds ratios for periconceptional folic acid intake among groups at high risk for neural tube defects, Slone Birth Defects Study (1988–2015)

	NTD family history							Periconceptional AED use						
	Cases (*n* = 45)		Cont (*n* = 119)					Cases (*n* = 25)		Cont (*n* = 108)				
Supplements only[a]	***n***	**%**	***n***	**%**	**COR (95% CI)**	**AOR1 (95% CI)**	**AOR2 (95% CI)**[b]	***n***	**%**	***n***	**%**	**COR (95% CI)**	**AOR1 (95% CI)**	**AOR2 (95% CI)**[b]
None	33	73	56	47	Ref	Ref	Ref	16	64	52	48	Ref	Ref	Ref
<Daily	4	9	9	8	0.80 (0.22–2.55)	0.87 (0.23–2.87)	0.89 (0.24–2.93)	3	12	12	11	0.89 (0.21–3.06)	0.60 (0.12–2.38)	0.68 (0.16–3.02)
Daily	8	18	54	45	0.25 (0.11–0.59)	0.33 (0.13–0.76)	0.32 (0.12–0.77)	6	24	44	41	0.47 (0.16–1.21)	0.31 (0.09–0.95)	0.42 (0.13–1.39)
<400 µg	1	2	2	2	NC	NC	NC	0	0	4	4	NC	NC	NC
400 to <1,000 µg	5	11	30	25	0.30 (0.10–0.78)	0.37 (0.12–0.97)	0.38 (0.12–1.02)	3	12	27	25	0.41 (0.10–1.28)	0.28 (0.06–1.01)	0.32 (0.08–1.35)
≥1,000 µg	2	4	22	18	0.19 (0.04–0.63)	0.25 (0.05–0.86)	0.26 (0.05–0.95)	3	12	13	12	0.83 (0.19–2.80)	0.56 (0.12–2.12)	0.67 (0.14–3.28)
Total (diet and supplements)[c]	**Cases (*n* = 45)**		**Cont (*n* = 118)**		**COR (95% CI)**	**AOR1 (95% CI)**	**AOR2 (95% CI)**[b]	**Cases (*n* = 25)**		**Cont (*n* = 105)**		**COR (95% CI)**	**AOR1 (95% CI)**	**AOR2 (95% CI)**[b]
	n	**%**	***n***	**%**				***n***	**%**	***n***	**%**			
<400 µg	32	71	47	40	Ref	Ref	Ref	15	60	49	47	Ref	Ref	Ref
400 to <1,000 µg	9	20	32	27	0.43 (0.18–0.97)	0.43 (0.18–1.01)	0.48 (0.19–1.10)	7	28	37	35	0.64 (0.23–1.64)	0.79 (0.26–2.26)	0.79 (0.28–2.13)
≥1,000 µg	4	9	39	33	0.17 (0.05–0.45)	0.21 (0.06–0.59)	0.22 (0.06–0.64)	3	12	19	18	0.57 (0.14–1.88)	0.49 (0.11–1.75)	0.61 (0.13–2.29)
	Pregestational diabetes							**Prepregnancy obesity**[d]						
	Cases (*n* = 12)		**Controls (*n* = 63)**					**Cases (*n* = 111)**		**Controls (*n* = 1,243)**				
Supplements only[a]	***n***	**%**	***n***	**%**	**COR (95% CI)**	**AOR1 (95% CI)**[b]	**AOR2 (95% CI)**	***n***	**%**	***n***	**%**	**COR (95% CI)**	**AOR1 (95% CI)**[b]	**AOR2 (95% CI)**[b]
None	10	83	33	52	Ref	Ref	Ref	72	64	717	58	Ref	Ref	Ref
<Daily	0	0	4	7	NC	NC	NC	12	12	123	10	1.00 (0.51–1.82)	0.99 (0.50–1.81)	1.02 (0.51–1.87)
Daily	2	17	26	41	0.30 (0.05–1.16)	0.25 (0.04–1.05)	0.37 (0.06–1.65)	27	24	403	32	0.68 (0.42–1.05)	0.65 (0.40–1.04)	0.69 (0.42–1.10)
<400 µg	0	0	2	3	NC	NC	NC	4	4	31	2	1.41 (0.44–3.56)	1.29 (0.40–3.37)	1.37 (0.42–3.56)
400 to <1,000 |µg	0	0	12	19	NC	NC	NC	14	13	284	23	0.50 (0.27–0.88)	0.54 (0.29–0.95)	0.57 (0.30–1.02)

≥1,000 μg	2	17	12	19	0.64 (0.11–2.63)	0.46 (0.07–2.08)	0.73 (0.11–3.91)	9	8	88	7	1.06 (0.49–2.07)	0.84 (0.38–1.68)	0.89 (0.40–1.82)
	Cases (*n* = 12)		**Controls (*n* = 60)**					**Cases (*n* = 111)**		**Controls (*n* = 1,243)**				
Total (diet + supplements)[c]	***n***	**%**	***n***	**%**	**COR (95% CI)**	**AOR1 (95% CI)[b]**	**AOR2 (95% CI)**	***n***	**%**	***n***	**%**	**COR (95% CI)**	**AOR1 (95% CI)[b]**	**AOR2 (95% CI)[b]**
<400 μg	8	67	30	52	Ref	Ref	Ref	72	65	689	55	Ref	Ref	Ref
400 to <1,000 μg	2	17	10	16	0.85 (0.14–3.77)	0.90 (0.15–4.33)	1.04 (0.17–4.90)	24	22	341	27	0.68 (0.42–1.08)	0.76 (0.46–1.23)	0.80 (0.48–1.28)
≥1,000 μg	2	17	20	32	0.44 (0.08–1.79)	0.35 (0.06–1.55)	0.54 (0.09–2.73)	15	14	213	17	0.69 (0.38–1.19)	0.67 (0.36–1.17)	0.71 (0.37–1.26)

Notes: AOR1 adjusted for maternal age (<25, 25–34, 35+ years) and study center (Massachusetts, Philadelphia, Toronto, other). AOR2 adjusted for planned pregnancy (yes, no) and study center (Massachusetts, Philadelphia, Toronto, other).

Abbreviations: AED, antiepileptic drugs; AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; NC, not calculated; NOS, not otherwise specified; NTD, neural tube defect; Ref, reference.

[a] If the dose of folic acid contained was unknown/NOS, we assumed the dose was as follows: prenatal Rx 1,000 μg, prenatal NOS μg, folic acid only or multi-vitamin NOS 400 μg.

[b] Models exclude participants who were missing maternal age or pregnancy planning status, respectively (refer to Table 1).

[c] Total defined as diet + average daily from supplements during periconception. Diet discounted by 30% due to reduced bioavailability. Excludes women with no dietary intake data.

[d] The prepregnancy obesity group includes 1993–2015 only when data were available to estimate BMI. In the rare event that height was not reported, we classified a woman as having obesity if she weighed more than 102 kg, which would classify a women as having obesity if she was 6 ft tall or less. (Only 2 women in the obesity group were added due to this definition.)

TABLE 3

Distributions of and estimated odds ratios for periconceptional folate intake among groups at higher risk for neural tube defects (NTDs), restricted to years with only non-malformed controls, Slone Birth Defects Study (1993–2015)

	Family history						AED use						Pregestational diabetes					
Supplements only[a]	Cases (*n* = 19)		Controls (*n* = 115)		COR (95% CI)	AOR (95% CI)	Cases (*n* = 15)		Controls (*n* = 104)		COR (95% CI)	AOR (95% CI)	Cases (*n* = 10)		Controls (*n* = 60)		COR (95% CI)	AOR (95% CI)[b]
	n	%	*n*	%			*n*	%	*n*	%			*n*	%	*n*	%		
None	13	68	52	45	Ref	Ref	8	53	50	48	Ref	Ref	8	80	30	50	Ref	Ref
<Daily	1	5	9	8	Nc	Nc	2	13	12	12	1.19 (0.21–5.03)	0.65 (0.09–3.30)	0	0	4	7	NC	NC
Daily	5	26	54	47	0.39 (0.13–1.09)	0.49 (0.15–1.47)	5	33	42	40	0.77 (0.23–2.39)	0.46 (0.11–1.66)	2	20	26	43	0.34 (0.06–1.36)	0.22 (0.04–1.03)
<400 μg	1	5	2	2	NC	NC	0	0	4	4	NC	NC	0	0	2	3	NC	NC
400 to <1,000 μg	3	16	30	26	0.45 (0.11–1.44)	0.55 (0.13–1.88)	2	13	25	24	0.58 (0.10–2.31)	0.36 (0.05–1.67)	0	0	12	20	NC	NC
≥1,000 μg	1	5	22	19	NC	NC	3	20	13	13	1.54 (0.34–5.84)	0.92 (0.19–3.81)	2	20	12	20	0.72 (0.12–3.09)	0.41 (0.06–2.10)

Note: AOR adjusted for maternal age (<25, 25–34, 35+ years) and study center (Massachusetts, Philadelphia, Toronto, other).

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; NC, not calculated; NOS, not otherwise specified; Ref, reference; Rx, prescription.

[a] If the dose of folic acid contained was unknown/NOS, we assumed the dose was as follows: prenatal Rx 1,000 μg, prenatal NOS μg, folic acid only or multi-vitamin NOS 400 μg.

[b] Models exclude participants who were missing maternal age (refer to Table 1).