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Periconceptional maternal fever, folic acid intake, and the risk for neural tube defects

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Abstract

Purpose—Previous studies have shown an association between maternal fever in early pregnancy and neural tube defects (NTDs) such as spina bifida. Periconceptional folic acid intake has been shown to reduce the risk of these outcomes.

Methods—Using data from the Slone Epidemiology Center Birth Defects Study (1998–2015), we examined the impact of folic acid on the relationship between maternal fever in the periconceptional period (28 days before and after the last menstrual period) and NTDs. Logistic regression models were used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results—Mothers of 375 cases and 8247 nonmalformed controls were included. We observed an elevated risk for NTDs for fever in the periconceptional period (OR: 2.4; 95% CI: 1.5–4.0). This association was weaker for mothers who reported consuming the recommended amount of folic acid (≥ 400 μg per day; OR: 1.8; 95% CI: 0.8–4.0) than mothers with low folic acid intake (<400 μg per day; OR: 4.2; 95% CI: 2.2–8.2).

Conclusions—Our data support an association between maternal periconceptional fever and an increased risk for NTDs and also provide evidence that this association was attenuated for mothers who reported consuming folic acid at recommended levels in the periconceptional period.

Keywords

Fever; Folic acid; Neural tube defects; Spina bifida

Introduction

Neural tube defects (NTDs) are severe malformations of the central nervous system that can be incompatible with life or cause lifelong disability. NTDs are estimated to affect 7 of 10,000 pregnancies in the United States annually [1]. Based on epidemiologic evidence

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showing that daily intakes of at least 400 μg of folic acid reduced NTD risk [2], fortification of cereal grain supplies in the United States and Canada began in 1998, which aimed to deliver, on average, this amount of folic acid to 90% of the childbearing aged women [3,4]. Since 1998, the prevalence of NTDs has decreased substantially, but the target for folic acid intake has not been met, and NTD cases continue to occur [1,5]. Thus, continued research is warranted to identify other risk factors for NTDs and to determine whether folic acid intake modifies the effects of these factors.

Maternal hyperthermia in early pregnancy has been identified as a risk factor for NTDs in both animal and human studies [6–8], but it is not clear if folic acid intake modifies the risk. Heat-induced NTDs in mice were less prevalent among those with folic acid exposure compared to those unexposed [9]. Similarly, three studies of febrile illness in pregnant women reported lower NTD risks among those using folic acid supplements or multivitamins in early pregnancy compared to those not supplementing [10–12]. However, one of these studies relied on a relatively small sample size [10], and all took place outside the context of folic acid fortification [10–12]. In addition, many studies of maternal fever are limited by a broad exposure definition and lack detail on hyperthermia timing and the role of antipyretic treatment. These limitations were addressed in the present analysis of data collected by the Slone Epidemiology Center Birth Defects Study (BDS).

Materials and methods

Study population

The BDS is a case-control study that recruited mothers from 1976 to 2015, whose pregnancies were or were not affected with a malformation. The current analysis is limited to NTD cases and nonmalformed controls born between 1998 and 2015, when cereal grains were fortified with folic acid in the United States and Canada. The methods have been described in detail previously [13,14]. For this analysis, infants, fetuses, and stillbirths with any major structural malformations (cases) were ascertained at participating hospitals or birth defect registries for parts of Massachusetts, areas surrounding Philadelphia, PA; San Diego, CA (since 2001); Toronto, Canada (until 2005); Nashville, TN (since 2012); and parts of New York State (since 2004). Control subjects were live-born infants who were ascertained from study hospitals and birth certificates in the catchment areas from which cases were recruited.

Within 6 months of delivery, mothers were invited to participate in a computer-assisted telephone interview conducted by trained study nurses. Subjects were asked about demographic factors, reproductive history, behaviors such as alcohol and tobacco use during pregnancy, as well as dietary patterns in the 6 months before pregnancy. Data were recorded on illness history and medications used during the 2 months before the last menstrual period (LMP) to the end of pregnancy. Medication data included information on use of prescription drugs, vaccines, over-the-counter medications, dietary supplements, and vitamin products. Detailed information on timing of illness and medication use was collected to relate exposures to developmental time periods of interest during pregnancy. Participation rates for cases and controls were 64% and 60%, respectively. This study has been approved by the

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institutional review boards of Boston University Medical Center and relevant participating institutions.

Measurements

Outcomes—For this analysis, NTD outcomes were examined as a group and included spina bifida, anencephaly, and encephalocele. Cases were categorized as multiple or isolated, with isolated cases having no other major defect diagnoses except those considered secondary to the NTD (e.g., clubfoot, hydrocephaly, and hip dislocation). NTD cases were excluded if they had an additional diagnosis of a chromosomal abnormality, Mendelian inheritance disorder, known syndrome, amniotic bands, body wall defect, or conjoined twin.

Exposure definitions—Mothers were asked if they experienced any of the following illnesses: fever alone, chicken pox, urinary tract infection, stomach virus/stomach bug, cold, flu, cough, bronchitis, pneumonia, sinus infection, congestion, flu-like illness, ear infection, strep throat, tooth abscess, and asthma with cold; if so, start and stop dates and details on type and timing of medication use were recorded. They were also asked if a fever accompanied the illness, and if so, whether the temperature of the fever was greater than or equal to 101°F. Dates of fever were not asked separately from the dates of illness.

For fever and other exposures, we defined the periconceptional period as the 2 lunar months beginning 28 days before the LMP and ending 28 days after the LMP. Any report of a fever during this interval was considered an exposure. We excluded women who reported fever only outside the periconceptional time period (75 cases, 1927 controls) or with unclear timing (3 cases, 95 controls). The unexposed referent group is therefore women who did not report fever from 2 months before the LMP until the end of pregnancy. Subgroups of fever-exposed women included those defined by reported temperature level (≥ 101°F, <101°, or undocumented) and antipyretic treatment (acetaminophen, aspirin, other nonsteroidal antiinflammatory drugs) of the reported fever.

Folic acid intake—Total periconceptional folic acid intake was calculated by combining the average daily synthetic folic acid intake from fortified foods and from supplements. Naturally occurring food folate was included but discounted by 30% because of its lower bioavailability [15]. Diet information was ascertained using an adapted Willett food frequency questionnaire (FFQ) focused on the 6 months before pregnancy, to reflect diet in the earliest stages of gestation when pregnancy might not yet be recognized. After calculating an average daily exposure amount from the FFQ, we adjusted these values for total caloric intake using the residual method [16]. We then added this value to the reported intake from supplements. Women who reported extreme caloric intake (<500 or >4000 kcal per day) were excluded (n = 88, 1% of subjects). Our primary folic acid intake variable was created by dichotomizing average daily exposure at the recommended intake level of greater than or equal to 400 μg per day, with intake of at least 400 μg per day considered to be “adequate” for NTD prevention. Women with missing FFQ data were included and categorized as having adequate folic acid intake if they reported vitamin supplementation greater than or equal to 400 μg per day (n = 246, 3% of subjects), or categorized as having a folic acid intake of less than 400 μg per day if they reported no vitamin intake (n = 524, 6%

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of subjects), because it is unlikely these women would achieve greater than or equal to 400 μg per day from diet alone [5]. Women with missing FFQ data were excluded if reported folic acid intake from vitamin supplementation was less than 400 μg per day, because they may or may not have reached 400 μg per day depending on diet (n = 103, 1% of subjects). In addition, less than 1% of subjects completed the FFQ with less than 400 μg per day but were excluded due to incomplete or unknown supplement data (n = 30).

Statistical analyses

We used logistic regression models to calculate crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between reported periconceptional fever and fever subgroups with NTDs. The distribution of demographic and maternal health characteristics for cases and controls and by reported periconceptional fever among controls only was calculated. These characteristics were also evaluated as potential confounders and were maternal age (categorized <20, 20–24, 25–29, 30–34, 35–39, and 40 + years), maternal education (<high school, high school graduate or equivalent, and greater than high school), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), study center, category of body mass index (kg/m^2; <18.5, 18.5–24.9, 25–29.9, and ≥30) [17], LMP year, and folic acid intake (<400 μg per day, ≥400 μg per day). We also considered any reported antipyretic medication exposure, the majority of which did not accompany fever, and periconceptional illnesses without fever as potential confounders because each could be independently associated with NTD risk. Variables that changed ORs by 10% or more were included in adjusted models.

We analyzed the joint effect between folic acid intake and reported fever on NTD risk by categorizing subjects into four groups: (1) greater than or equal to 400 μg per day of folic acid without fever (referent), (2) less than 400 μg per day of folic acid without fever, (3) greater than or equal to 400 μg per day of folic acid and fever, and (4) less than 400 μg per day of folic acid and fever and calculating the relative excess risk due to interaction (RERI) [18]. The RERI is a measure that can be used to assess whether the joint effect of fever and folic acid intake less than 400 μg per day is greater than would be expected, given the individual additive effects.

In a sensitivity analysis, we excluded subjects with any of the following established risk factors for NTDs: periconceptional exposure to antiepileptic drugs, family history of NTDs, and pre-existing diabetes. We also conducted sensitivity analyses in which we limited the case group to those with isolated NTDs and to those with just spina bifida. Finally, we performed an analysis in which we included in the unexposed group women whose fever was reported to have occurred in lunar month 3 or later. (These women were excluded from the primary analysis.) All analyses were conducted in SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

A total of 453 NTD cases and 10,269 nonmalformed controls were available for analysis. We excluded 78 cases (17.2%) and 2022 controls (19.7%) who reported fever outside the periconceptional period or fever with unclear timing, resulting in a final study population of

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375 cases and 8247 controls. Compared to controls, mothers of cases were more likely to be younger (<30 years old), non-Hispanic black or Hispanic, overweight, or obese, to report periconceptional illness without fever and to have LMP during 2003–2008; mothers of cases were less likely to have education beyond high school or to meet the recommended folic acid intake; no notable differences in prevalence of antipyretic use in the periconceptional period were noted. Differences between cases and controls were also observed for study center (Table 1).

Among controls, mothers who reported periconceptional fever ($n = 154$) were more likely to have education beyond high school, be non-Hispanic white, have their LMP in the earlier years of the study (1997–2002), and have greater than or equal to 400 μg of folic acid intake per day, compared to mothers who did not report periconceptional fever ($n = 8093$) (Table 1). Antipyretic medication use, for any indication, was more common in control mothers with periconceptional fever than among those without fever (60.4% compared to 32.3%).

Mothers of NTD cases reported periconceptional fever more commonly (5.1%, $n = 19$) than mothers of control infants (1.9%, $n = 154$; Table 2). Of these 19 NTD cases, 16 were spina bifida cases and three were anencephaly or encephalocele. The adjusted OR for any periconceptional fever was 2.4 (95% CI: 1.5–4.0). Study center was the only covariate that met the criterion for confounding and was therefore included in adjusted models. Among those mothers reporting periconceptional fever, 31.6% of case mothers ($n = 6$) and 40.3% of control mothers ($n = 62$) had a reported temperature of at least 101°F; information on fever temperature was missing for 4 case mothers (21.1% of those reporting fever) and 30 control mothers (19.5% of those reporting fever). Compared to mothers without fever, the adjusted OR for fevers of greater than or equal to 101°F was 2.1 (95% CI: 0.9–5.1), and for fevers of less than 101°F, the OR was 3.3 (95% CI: 1.6–6.9). Overall, the adjusted ORs stratified by use of antipyretic treatment were similar: 2.2 (95% CI: 1.0–4.9) for women who reported the use of antipyretics and 2.6 (95% CI: 1.4–5.0) for women who did not report the use of antipyretics. When the analysis considered the joint effects of reported temperature and antipyretic treatment, adjusted ORs were not higher for mothers with high fevers but were higher among mothers who reported using no antipyretic treatment than among mothers who reported using these medications within both the lower and higher temperature groups. However, numbers of cases in the joint effects analysis were quite small and 95% confidence intervals overlap considerably.

Overall, the 2.4-fold increased risk for NTDs among mothers with periconceptional fever appeared to be modified by folic acid intake. Among mothers who did not consume folic acid in amounts considered “adequate” for NTD prevention, the adjusted OR for periconceptional fever was 3.4 (95% CI: 1.8–6.6), whereas the adjusted OR for mothers whose intake was “adequate” was 1.8 (95% CI: 0.8–4.0) (Table 3). Mothers reporting both periconceptional fever and less than 400 μg per day of folic acid intake had an adjusted OR of 4.2 (95% CI: 2.2–8.2) compared to the reference group of mothers without fever and with greater than or equal to 400 μg per day of folic acid intake (Table 3). This association is larger than that would be expected due to independent additive effects of inadequate folic acid intake and periconceptional fever (RERI = 2.2 [95% CI: −0.9 to 5.3]).

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Findings did not appreciably change in the four sensitivity analyses: (1) exclusion of the 28 cases and 203 controls with exposure to antiepileptic drugs, family history of NTDs or pre-existing diabetes, (2) exclusion of the 76 nonisolated cases, and (3) restriction to spina bifida cases only (Supplementary Table). We also performed a sensitivity analysis (4) including as unexposed those mothers whose only fever was later in pregnancy (lunar month 3 through end of pregnancy); the adjusted OR for fever increased slightly to 2.6 (1.5–4.2) (data not shown).

Discussion

The results of this analysis support previous findings of an increased risk for NTDs in offspring born to mothers who report maternal fever in early pregnancy. We observed a 2.4 times greater risk for having an NTD-affected pregnancy among mothers reporting a fever in the month before or the month after LMP compared to mothers who reported no fevers during pregnancy. This association was similar after the exclusion of women with known risk factors for NTDs, including family history of NTDs, lending further support for a true association.

A 2005 meta-analysis of maternal hyperthermia and NTDs reported an overall OR of 1.9 (95% CI: 1.6–2.3) [8], which was lower than our observed 2.4-fold OR (95% CI: 1.5–4.0) and perhaps due to differences in exposure windows. Many previous studies examined fever in the first trimester, but our exposure window was the narrower 56-day period surrounding the LMP because NTDs develop shortly after conception. Fevers later in the first trimester should not influence the risk of NTDs, and the resulting misclassification would likely attenuate a true association. In addition, we were able to consider the risk associated with the level of reported temperature. Risk estimates for women reporting higher temperatures (≥101°F) were not greater than those reporting lower temperatures providing no evidence of a dose response, although our sample was small and estimates were therefore unstable. Our findings are similar to those of 2 previous reports of an increased NTD risk for fever in the first trimester that was attenuated but not eliminated by antipyretic medication treatment [19,20]. Although our observed NTD risks did not appear to be related to the temperature of the reported fever, antipyretic treatment appeared to reduce the NTD risk, whether the fever was high or low.

Our data showed that average intake of at least 400 μg per day of folic acid was associated with an attenuated, although still elevated, odds of having an NTD-affected pregnancy among women who reported periconceptional fever. Three previous studies also showed higher ORs for women with fever who did not take vitamin supplements [10–12], although two of them were based on very small numbers [10,11]. Another study observed an 11-fold increased NTD risk for women with early pregnancy fever and a variant of the folate carrier gene SLC19A1 [21]; however, folic acid exposure was not examined.

The mechanism by which fever might affect development of the neural tube is not known, nor has the pathway between folate deficiency and NTDs been well delineated. Animal studies suggest that hyperthermia-induced NTDs are caused by apoptosis of neurons, and folic acid has been hypothesized to reduce abnormal cell death in the developing fetus

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[9,22]. It is also worth noting that many women are exposed to folic acid through multivitamins, which contain myriad other vitamins and minerals; high folic acid–diets similarly include other vitamins and minerals [23]. Thus, we cannot exclude the possibility that the reduction of fever-associated NTD risk associated with folic acid intake may be due to confounding by intake of other nutrients.

Strengths of this study include our ability to identify exposures with greater detail than many previous studies [10,12,24], including the availability of information on fever temperature, average daily folic acid intake, and medication use. By including information on both dietary and supplemental folic acid, we were able to better estimate total folic acid intake to observe biologically plausible interactions. Another strength of the study is the short interval between the time of birth and data collection (maximum of 6 months), which likely improves recall accuracy. Nevertheless, retrospective reporting of exposures may have led to misclassification. We assumed that the timing of fever and antipyretic treatment was the same as that reported for the accompanying illness, which may not be the case. For fevers reported in the absence of illness, this assumption was not necessary. Whether reporting errors would be more common in cases than controls is not clear, but it is important to consider possible under-reporting by controls compared to cases (i.e., recall bias). Although we have no direct way to assess whether such a bias exists, it is of note that the proportions of fevers with undocumented temperature were similar for cases and controls (21% and 19%, respectively). Another possible source of under-reporting of fever is the fact that the interview did not specifically ask about fever accompanying sexually transmitted or vaginal infections. However, the prevalence of these illnesses in the periconceptional period was higher in NTD cases (4.5%) than that in the controls (1.1%); thus, under-ascertainment of fever due to these illnesses would likely have biased our results toward the null. Other potential limitations include the limited number of NTD cases with fever (n = 19) and minimal variability by phenotype (all but three NTD cases with fever were spina bifida cases).

In summary, we observed an elevated risk for NTDs for mothers reporting periconceptional fever, but this association was lower among mothers who consumed at least 400 μg per day of folic acid. Antipyretic treatment of fever also appeared to mildly attenuate NTD risk. It is difficult to prevent fever in pregnancy; although symptoms may be relieved by antipyretics, daily intake of 400 μg of folic acid among women of childbearing ages appears to be particularly important for pregnant women experiencing fever. Thus, following the recommended intake of at least 400 μg per day of folic acid among women capable of becoming pregnant may not only help reduce the risk of NTDs overall but may also reduce the risk of NTDs associated with fever. Reaching this level of intake is difficult by diet alone; folic acid supplementation is a more efficient and easier means to achieve the recommended level [25].

Supplementary Material

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References

1. Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ, Ethen M, et al. Updated estimates of neural tube defects prevented by mandatory folic acid fortification-United States, 1995–2011. MMWR Morb Mortal Wkly Rep. 2015; 64:1–5. [PubMed: 25590678]
2. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Recomm Rep. 1992; 41:1–7.
3. Hubbard, WK. Food Drug Administration HaHS. , editor. Food Standards: Amendment of standards of identity for enriched grain products to require addition of folic acid. 21 Code of Federal Regulations Parts 136, 137 and 139. 1996. Available at: https://www.gpo.gov/fdsys/browse/collectionCfr.action?collectionCode=CFR
4. Crider KS, Bailey LB, Berry RJ. Folic acid food fortification-its history, effect, concerns, and future directions. Nutrients. 2011; 3:370–84. [PubMed: 22254102]
5. Tinker SC, Cogswell ME, Devine O, Berry RJ. Folic acid intake among u.s. women aged 15–44 years, national health and nutrition examination survey, 2003–2006. Am J Prev Med. 2010; 38:534–42. [PubMed: 20347553]
6. Graham JM Jr, Ferm VH. Heat- and alcohol-induced neural tube defects: interactions with folate in a golden hamster model. Pediatr Res. 1985; 19:247–51. [PubMed: 3982887]
7. Finnell RH, Moon SP, Abbott LC, Golden JA, Chernoff GF. Strain differences in heat-induced neural tube defects in mice. Teratology. 1986; 33:247–52. [PubMed: 3738820]
8. Moretti ME, Bar-Oz B, Fried S, Koren G. Maternal hyperthermia and the risk for neural tube defects in offspring: systematic review and meta-analysis. Epidemiology. 2005; 16:216–9. [PubMed: 15703536]
9. Shin JH, Shiota K. Folic acid supplementation of pregnant mice suppresses heat-induced neural tube defects in the offspring. J Nutr. 1999; 129:2070–3. [PubMed: 10539786]
10. Botto LD, Erickson JD, Mulinare J, Lynberg MC, Liu Y. Maternal fever, multivitamin use, and selected birth defects: evidence of interaction? Epidemiology. 2002; 13:485–8. [PubMed: 12094106]
11. Acs N, Banhidy F, Puho E, Czeizel AE. Maternal influenza during pregnancy and risk of congenital abnormalities in offspring. Birth Defects Res A Clin Mol Teratol. 2005; 73:989–96. [PubMed: 16323157]
12. Shaw GM, Nelson V, Carmichael SL, Lammer EJ, Finnell RH, Rosenquist TH. Maternal periconceptional vitamins: interactions with selected factors and congenital anomalies? Epidemiology. 2002; 13:625–30. [PubMed: 12410002]
13. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med. 2007; 356:2675–83. [PubMed: 17596601]
14. Louik C, Kerr S, Van Bennekom CM, Chambers C, Jones KL, Schatz M, et al. Safety of the 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: Preterm delivery and specific

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malformations, a study from the case-control arm of VAMPSS. Vaccine. 2016; 34:4450–9. [PubMed: 27452865]

15. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academies Press; 1998. Available at: http://www.nap.edu/books/0309065542/html/index.html. Accessed November 7, 2017
16. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol. 1986; 124:17–27. [PubMed: 3521261]
17. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adultsethe evidence report. National Institutes of Health Obes Res. 1998; 2(6 Suppl):51S–209S.
18. Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. Am J Epidemiol. 2009; 169:756–60. [PubMed: 19211620]
19. Suarez L, Felkner M, Hendricks K. The effect of fever, febrile illnesses, and heat exposures on the risk of neural tube defects in a Texas-Mexico border population. Birth Defects Res A Clin Mol Teratol. 2004; 70:815–9. [PubMed: 15468073]
20. Shaw GM, Todoroff K, Velie EM, Lammer EJ. Maternal illness, including fever and medication use as risk factors for neural tube defects. Teratology. 1998; 57:1–7. [PubMed: 9516745]
21. Pei L, Zhu H, Ye R, Wu J, Liu J, Ren A, et al. Interaction between the SLC19A1 gene and maternal first trimester fever on offspring neural tube defects. Birth Defects Res A Clin Mol Teratol. 2015; 103:3–11. [PubMed: 24917213]
22. Hinoue A, Fushiki S, Nishimura Y, Shiota K. In utero exposure to brief hyperthermia interferes with the production and migration of neocortical neurons and induces apoptotic neuronal death in the fetal mouse brain. Brain Res Dev Brain Res. 2001; 132:59–67. [PubMed: 11744107]
23. Branum AM, Bailey R, Singer BJ. Dietary supplement use and folate status during pregnancy in the United States. J Nutr. 2013; 143:486–92. [PubMed: 23365107]
24. Lynberg MC, Khoury MJ, Lu X, Cocian T. Maternal flu, fever, and the risk of neural tube defects: a population-based case-control study. Am J Epidemiol. 1994; 140:244–55. [PubMed: 8030627]
25. Folic Acid to prevent neural tube defects: Preventive medication. U.S. Preventive Services Task Force; 2015. Final Update Summary. Available at: http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/folic-acid-to-prevent-neural-tube-defects-preventive-medication. Accessed August 10, 2016

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Table 1

Characteristics of mothers of neural tube defect cases and controls, Birth Defects Study, 1998–2015

			Controls only	
	NTD cases (*n* = 375)	Controls (*n* = 8247)	Reported periconceptional fever (*n* = 154)	No reported fever during pregnancy (*n* = 8093)
Characteristic	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Maternal age (years)				
<20	33 (8.8)	591 (7.2)	7 (4.5)	584 (7.2)
20–24	66 (17.6)	1232 (14.9)	21 (13.6)	1211 (15.0)
25–29	113 (30.1)	2203 (26.7)	47 (30.5)	2156 (26.6)
30–34	103 (27.5)	2710 (32.9)	48 (31.2)	2662 (32.9)
35–39	54 (14.4)	1270 (15.4)	24 (15.6)	1246 (15.4)
40+	6 (1.6)	220 (2.7)	6 (3.9)	214 (2.6)
Unknown	0 (0.0)	21 (0.3)	1 (0.6)	20 (0.2)
Maternal education				
< High school	59 (15.7)	793 (9.6)	7 (4.5)	786 (9.7)
High school	89 (23.7)	1614 (19.6)	19 (12.3)	1595 (19.7)
> High school	226 (60.3)	5830 (70.7)	128 (83.1)	5702 (70.5)
Missing	1 (0.3)	10 (0.1)	0 (0.0)	10 (0.1)
Maternal race/ethnicity				
Non-Hispanic white	211 (56.3)	5326 (64.6)	115 (74.7)	5211 (64.4)
Non-Hispanic black	51 (13.6)	726 (8.8)	8 (5.2)	718 (8.9)
Hispanic	78 (20.8)	1428 (17.3)	12 (7.8)	1416 (17.5)
Other	35 (9.3)	751 (9.1)	18 (11.7)	733 (9.1)
Missing	0 (0.0)	16 (0.2)	1 (0.6)	15 (0.2)
Study center				
Massachusetts	59 (15.7)	3990 (48.4)	69 (44.8)	3921 (48.4)
Philadelphia	108 (28.8)	1516 (18.4)	32 (20.8)	1484 (18.3)
Toronto	83 (22.1)	483 (5.9)	17 (11.0)	466 (5.8)
San Diego	66 (17.6)	1338 (16.2)	21 (13.6)	1317 (16.3)
New York	50 (13.3)	828 (10.0)	14 (9.1)	814 (10.1)
Nashville	9 (2.4)	92 (1.1)	1 (0.6)	91 (1.1)
Body mass index (kg/m^2)				
Underweight (<18.5)	17 (4.5)	345 (4.2)	4 (2.6)	341 (4.2)
Normal weight (18.5–24.9)	178 (47.5)	4914 (59.6)	93 (60.4)	4821 (59.6)
Overweight (25.0–29.9)	93 (24.8)	1676 (20.3)	38 (24.7)	1638 (20.2)
Obese (30+)	68 (18.1)	1076 (13.0)	18 (11.7)	1058 (13.1)
Missing	19 (5.1)	236 (2.9)	1 (0.6)	235 (2.9)
Year of last menstrual period				
1997–2002	133 (35.5)	3296 (40.0)	77 (50.0)	3219 (39.8)
2003–2008	112 (29.9)	1878 (22.8)	40 (26.0)	1838 (22.7)
2009–2014	130 (34.7)	3073 (37.3)	37 (24.0)	3036 (37.5)

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Characteristic	NTD cases (*n* = 375)	Controls (*n* = 8247)	Controls only	
			Reported periconceptional fever (*n* = 154)	No reported fever during pregnancy (*n* = 8093)
	N (%)	*N* (%)	*N* (%)	*N* (%)
Periconceptional * folic acid †				
≥400 mcg	165 (44.0)	4247 (51.5)	89 (57.8)	4158 (51.4)
<400 mcg	195 (52.0)	3794 (46.0)	63 (40.9)	3731 (46.1)
Missing	15 (4.0)	206 (2.5)	2 (1.3)	204 (2.5)
Periconceptional * antipyretic use				
Yes	124 (33.1)	2703 (32.8)	93 (60.4)	2610 (32.3)
No	176 (46.9)	3889 (47.2)	34 (22.1)	3855 (47.6)
Uncertain	75 (20.0)	1655 (20.1)	27 (17.5)	1628 (20.1)
Periconceptional * illness, without reported fever				
Yes	30 (8.0)	475 (5.8)	12 (7.8)	463 (5.7)
No	345 (92.0)	7772 (94.2)	142 (92.2)	7630 (94.3)

* Defined as the 28 days before to the 28 days after the last menstrual period.

† Average daily folic acid intake from supplements and diet in the periconceptional period.

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Table 2

Reported maternal fever, fever severity, and the use of antipyretic medication during the periconceptional period* and risk for neural tube defects, Birth Defects Study, 1998–2015

Characteristic	NTD case (total = 375)	Control (total = 8247)	Crude OR (95% CI)	Adjusted OR† (95% CI)
	N (%)	*N* (%)		
Maternal periconceptional fever reported				
Yes	19 (5.1)	154 (1.9)	2.8 (1.7–4.6)	2.4 (1.5–4.0)
No	356 (94.9)	8093 (98.1)	1.0 (Reference)	1.0 (Reference)
Reported temperature of fever				
≥101°F	6 (1.6)	62 (0.8)	2.2 (0.9–5.1)	2.1 (0.9–5.1)
<101°F	9 (2.4)	62 (0.8)	3.3 (1.6–6.7)	3.3 (1.6–6.9)
Not reported	4 (1.1)	30 (0.4)	–	–
Antipyretic treatment of reported fever				
Yes	8 (2.1)	62 (0.8)	2.9 (1.4–6.2)	2.2 (1.0–4.9)
No	11 (2.9)	91 (1.1)	2.8 (1.5–5.2)	2.6(1.4–5.0)
Combination of reported temperature and use of antipyretic treatment for fever				
≥101°F				
Antipyretic treatment	2 (0.5)	27 (0.3)	1.7 (0.2–6.8)	1.4 (0.2–6.2)
No antipyretic treatment	4 (1.1)	34 (0.4)	2.7 (0.7–7.6)	2.9 (0.7–8.5)
< 101°F				
Antipyretic treatment	3 (0.8)	26 (0.3)	2.6 (0.5–8.6)	2.2 (0.4–7.8)
No antipyretic treatment	6 (1.6)	36 (0.4)	3.8 (1.6–9.1)	4.2 (1.7–10.4)

*Defined as the 28 days before to the 28 days after last menstrual period.

†Adjusted for Study Center.

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Table 3

Reported maternal periconceptional* fever, average daily folic acid intake, and risk for neural tube defects, Birth Defects Study, 1998–2015

Average folic acid intake	Maternal fever reported	NTD case (total = 360†) N (%)	Control (total = 8041) N (%)	Crude OR (95% CI)	Adjusted OR‡ (95% CI)
Stratified analysis					
<400 μg/day	Total	195	3794		
	Yes	12 (6.2)	63 (1.7)	3.9 (2.1–7.3)	3.4 (1.8–6.6)
	No	183 (93.8)	3731 (98.3)	1.0 (Reference)	1.0 (Reference)
≥400 μg/day	Total	165	4247		
	Yes	7 (4.2)	89 (2.1)	2.1 (0.9–4.5)	1.8 (0.8–4.0)
	No	158 (95.8)	4158 (97.9)	1.0 (Reference)	1.0 (Reference)
Joint effects analysis					
<400 μg/day	Yes	12 (3.3)	63 (0.8)	5.0 (2.7–9.5)	4.2 (2.2–8.2)
≥400 μg/day	Yes	7 (1.9)	89 (1.1)	2.1 (0.9–4.5)	1.8 (0.8–4.0)
<400 μg/day	No	183 (50.8)	3731 (46.4)	1.3 (1.0–1.6)	1.3 (1.0–1.6)
≥400 μg/day	No	158 (43.9)	4158 (51.7)	Reference	Reference
RERI = 2.2 (95% Cl: −0.9 to 5.3)					

*Defined as the 28 days before to the 28 days after last menstrual period.

†221 missing for folic acid variable (15 cases, 206 controls).

‡Adjusted for Study Center.