Published in final edited form as:

Birth Defects Res A Clin Mol Teratol. 2009 November ; 85(11): 879–889. doi:10.1002/bdra.20624.

Maternal Caffeine Consumption and Risk of Neural Tube Defects

Rebecca J. Schmidt^{1,*}, Paul A. Romitti², Trudy L. Burns², Marilyn L. Browne³, Charlotte M. Druschel³, Richard S. Olney⁴, and National Birth Defects Prevention Study

¹Department of Psychiatry, University of California, Davis, California

²Department of Epidemiology, University of Iowa, Iowa City, Iowa

³Congenital Malformations Registry, New York State Department of Health, Troy, New York

⁴National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract

BACKGROUND—Animal studies demonstrate teratogenic effects of caffeine, whereas human studies are inconclusive.

METHODS—Associations between maternal caffeine consumption and neural tube defects (NTDs) by type of NTD (anencephaly, spina bifida, or encephalocele) were examined using data from the National Birth Defects Prevention Study (NBDPS). Total average daily caffeine from coffee, tea, soda, and chocolate consumption during the year before pregnancy was estimated for 768 mothers of infants with NTDs and 4143 mothers of infants without birth defects who gave birth during 1997 through 2002. Periconceptional use of caffeine-containing medications was evaluated separately. Adjusted odds ratios (OR) and 95% confidence intervals (CI) associated with consumption of total caffeine and each caffeine source were estimated from logistic regression models.

RESULTS—Positive associations were observed between spina bifida and total caffeine consumption (OR 1.4; 95% CI: 1.1–1.9) and each caffeine source except caffeinated tea, which showed a negative association with spina bifida (OR 0.7; 95% CI: 0.6–0.9). Associations with modestly increased risk of NTDs and encephalocele were also observed. The association between caffeine consumption and anencephaly differed by maternal race/ethnicity. No dose effects were found.

CONCLUSIONS—Additional studies should confirm whether women who consume caffeine are at increased risk for pregnancies complicated by NTDs.

Keywords

anencephaly; caffeine; coffee; encephalocele; neural tube defect; spinal dysraphism; pregnancy; tea

*Correspondence to: Rebecca J. Schmidt, The M.I.N.D. Institute, Department of Psychiatry, University of California Davis Medical Center, University of California, Davis, California. rjschmidt@ucdavis.edu.

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. No conflict of interest is declared.

INTRODUCTION

Neural tube defects (NTDs) arise from a defect in the neurulation process during the third and fourth gestational weeks. Several studies have shown a declining prevalence of NTDs in the United States (Honein et al., 2001; Boulet et al., 2008) after clinical trials showed that folic acid supplementation reduced the risk of NTDs (Smithells et al., 1983; Medical Research Council Vitamin Study Research Group, 1991; Czeizel and Dudas, 1992) and manufacturers of cereal products were mandated to fortify cereal products with folic acid. However, NTDs continue to affect more than 3000 pregnancies per year in the United States (CDC, 2004) with the highest rates occurring among Hispanics (Feuchtbaum et al., 1999).

NTDs are complex disorders, and multiple genetic and environmental factors likely play a role in their etiology. Although genetic syndromes and certain exposures, such as antiepileptic medications (Lindhout and Schmidt, 1986), are associated with increased risk of NTDs, these infrequent exposures explain only a small portion of NTD cases (Frey and Hauser, 2003). Although more common exposures including maternal obesity (Kallen, 1998; Koren, 2001; Waller et al., 2007), diabetes (Hendricks et al., 2001), and infections and fever during pregnancy (Lynberg et al., 1994; Shaw et al., 1998; Botto et al., 2002) are associated with smaller risk estimates, they may explain a greater proportion of NTDs given their higher prevalence.

Caffeine is the most commonly used pharmacologic agent in the world (Ellenhorn and Barceloux, 1988). Most of the nearly 90% of women of reproductive age in the United States who report caffeine use continue to consume caffeinated beverages during pregnancy (Hill et al., 1977; Frary et al., 2005). Moreover, during the last two decades, the percentage of people who consume caffeine has risen across all age groups (Frary et al., 2005). Given the pervasiveness of caffeine exposure during pregnancy, even a small increase in risk for birth defects would have an important public health impact.

Caffeine can cross the placenta during pregnancy. Animal studies have shown that high levels of caffeine consumption during gestation produce teratogenic effects resulting in malformations, including NTDs (Lee et al., 1982; Wilkinson and Pollard, 1994; Marret et al., 1997). The teratogenic effects observed in animal studies were stronger when caffeine exposure was combined with other exposures, such as low folate levels (Heid et al., 1992) and alcohol consumption (Ross and Persaud, 1989).

To date, human studies of the association between maternal caffeine consumption and congenital defects have been inconclusive (Nelson and Forfar, 1971; Fedrick, 1974; Heinonen et al., 1977; Borlee et al., 1978; Lechat et al., 1980; Jacobson et al., 1981; Linn et al., 1982; Rosenberg et al., 1982; Kurppa et al., 1983; Furuhashi et al., 1985; Kline et al., 1991; Olsen et al., 1991; McDonald et al., 1992). Few of these studies examined NTDs separately from other congenital defects (Fedrick, 1974; Heinonen et al., 1977; Linn et al., 1982; Rosenberg et al., 1982; Kurppa et al., 1983; McDonald et al., 1992), and even fewer examined NTDs by case type (Fedrick, 1974; Furuhashi et al., 1985); grouping etiologically heterogeneous malformations together could have obscured potential associations with caffeine consumption. Folic acid was not considered in previous studies on maternal caffeine

consumption because its relation to NTDs was unknown at the time the studies were conducted. The small sample size of many of these studies also limited their power to detect small effects and to stratify analyses. We overcame these limitations by using data from a large collaborative study, the National Birth Defects Prevention Study (NBDPS), to examine whether maternal caffeine consumption was associated with an increased risk of NTDs and whether associations differed by the caffeine source or by type of NTD.

METHODS

Subject Selection

The NBDPS is an ongoing, multicenter, population-based, case-control study of environmental and genetic risk factors for over 30 major structural birth defects (Yoon et al., 2001). Each center participating in the NBDPS obtained institutional review board approval. For our analyses, we included infants with anencephaly, spina bifida, or encephalocele diagnoses and an estimated date of delivery from October 1, 1997, through December 31, 2002, identified by population-based birth defects surveillance systems in eight states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas). Eligible case-infants were live births (all centers), stillbirths, or elective terminations (Arkansas, California, Georgia, Iowa, Massachusetts [stillbirths only], New York [starting in 2000], and Texas). Systematic clinical criteria were used to define NTD diagnoses and to classify cases as isolated (NTD and no other unrelated, major, structural birth defect) or as multiple (NTD and one or more additional unrelated, major, structural birth defects) (Rasmussen et al., 2003). Clinical geneticists at each site reviewed abstracted medical records before including them in the NBDPS, and each case was independently selected and classified for these analyses by one of two clinical geneticists. Eligible control-infants were a random sample of unaffected, live-born infants identified from birth certificates or birth hospital records within the same geographical region. Infants with known or strongly suspected chromosomal or single gene disorders were excluded (Rasmussen et al., 2003).

Maternal Caffeine Consumption

Biologic mothers of case-infants and control-infants were asked to complete a computer-assisted telephone interview that collected data on demographic characteristics; reproductive and pregnancy history; health conditions; and occupational, dietary, and environmental exposures. All interviews were completed within 24 months of the child's birth (or the estimated date of delivery for pregnancies not resulting in a live birth), with mean (SD) time to interview of 9.7 (6.0) months for mothers of NTD cases and 8.0 (5.0) months for mothers of controls. An estimate of total maternal caffeine consumption was determined from the sum of the reported average caffeine consumed per day from coffee, tea, soda, and chocolate for the year before pregnancy. Interview questions used to assess caffeine consumption are provided elsewhere (Browne et al., 2007). Exposure to caffeine in medications during the periconceptional period, one month before pregnancy through the third month of pregnancy, was examined but not combined into the measure of total caffeine consumption during the year before pregnancy because of the different time periods assessed. The Slone Epidemiology Center Drug Dictionary (Slone Epidemiology Center at Boston University, Boston, MA) was used to identify medications that contained caffeine from those reported

during the maternal interview. A standard amount of caffeine for each food or beverage was assigned on the basis of previous literature and was multiplied by the reported average number of servings per day. The caffeine content of coffee was based on the average caffeine amount found in a 10-ounce serving and estimated as 100 mg of caffeine per cup (Barone and Roberts, 1996; Bracken et al., 2002). We assigned each cup of tea 37 mg of caffeine as an average amount derived from different brew times (Bracken et al., 2002). For soda, the caffeine content was based on a 12-ounce serving of each reported brand consumed. We assigned an average value of 37 mg to brands that contained caffeine as an ingredient but in which the amount of caffeine was unknown. Each ounce of chocolate was assigned a value of 10 mg of caffeine as a weighted average of the amount of caffeine found in milk chocolate and dark chocolate (Mills et al., 1993) and on the basis of estimated preferences for each type of chocolate (National Confectioners Association, 2004). Categories of total caffeine exposure from all sources used were as follows: none (0–9 mg per day), very low (10–99 mg per day), low (100–199 mg per day), moderate (200–299 mg per day), and high to very high (300 or more mg per day). These categories were based on a combination of categories previously used in the literature (Rosenberg et al., 1982; Mills et al., 1993) and their correspondence to about 100 mg caffeine per cup of coffee. We collapsed categories to *none* or *any* for stratified analyses because differences in the strength of the associations across categories of total caffeine were minimal. We examined associations for each caffeine source (coffee, tea, soda, medication) individually to identify potential source-specific risks.

Statistical Analysis

Logistic regression models were constructed (SAS version 9.1 software; SAS Institute Inc., Cary, North Carolina) to estimate odds ratios (OR) and 95% confidence intervals (CI) for total caffeine consumption and consumption of each caffeine source. A number of risk factors for NTDs were assessed as covariates: maternal age at conception; race/ethnicity; education level; pre-pregnancy body mass index (BMI); Type 1 and Type 2 diabetes; gravidity; parity; history of miscarriage; nausea or vomiting during the first month of pregnancy (yes or no); timing of pregnancy confirmation; timing of first prenatal care visit; periconceptional alcohol consumption (yes or no, maximum consumption, average frequency of consumption); cigarette smoking (ever smoked, smoked during periconceptional period, yes or no); oral contraceptive use; diet soda consumption; and average folic acid, vitamin B6, vitamin B12, dietary fat, calcium, sugar, and total caloric intake for the year before pregnancy. Use of any vasoconstrictive drugs including antihypertensives, decongestants, bronchodilators, antiseizure medications (including valproic acid), antimigraine medications, and cocaine and use of any vasoactive medications including salicylates, and nonsteroidal anti-inflammatory drugs during the period one month before pregnancy through the first three months of pregnancy were examined as potential confounders and effect modifiers. Study center, household income, family history of NTDs, infant live status, and sex of infant were also evaluated. Our analyses started with a full model containing potential confounders identified in the bivariate analyses associated with both NTDs and any caffeine intake ($p < 0.20$), and variables were excluded using backward selection, retaining in the model variables that caused a 10% or more change in the exposure parameter estimate. All covariates were examined for multiplicative interaction with the addition of an interaction term, and those that showed minimally significant interaction

terms ($p < 0.2$) and made biologic sense as effect modifiers were followed up further. For covariates identified a priori as potential effect modifiers, including child sex, race/ethnicity, maternal age, smoking, alcohol consumption, and folic acid vitamin intake, interaction was evaluated with stratified analyses.

RESULTS

During the study period, 768 (67.3%) eligible case-mothers (218 anencephaly, 459 spina bifida, 91 encephalocele) and 4143 (67.9%) eligible control-mothers completed the telephone interview and were included in the analyses. Case-mothers were more likely to be of lower socioeconomic status, to be Hispanic, to have a pre-pregnancy BMI >30 , and were less likely to have consumed alcohol during the periconceptional period (Table 1). Mothers of NTD-affected pregnancies also were more likely to report a history of type 1 diabetes (1.3%) and periconceptional use of antiseizure medications (1.6%) than were control mothers (0.2% and 0.9%, respectively).

Of the eligible mothers who completed interviews, 761 (99%) case-mothers and 4108 (99%) control-mothers reported data on total caffeine consumption. Approximately 85% of control-mothers reported caffeine consumption for the year before pregnancy (Table 2). Coffee accounted for about one-half of the total average caffeine for case-mothers (49%) and control-mothers (52%). Caffeinated soda, the caffeine source most frequently consumed, accounted for 33% of total caffeine consumption for control-mothers and 37% for case-mothers. Caffeinated tea accounted for most of the remaining caffeine consumption (12%) for both groups. Among control-mothers, a greater percentage (87%) of non-Hispanic white mothers consumed caffeine compared to other mothers (80%) because a greater percentage of these control-mothers consumed caffeinated coffee (49% and 41%, respectively). Control-mothers aged 30 years or older were more likely than younger control-mothers to consume caffeinated coffee (57% and 39%, respectively) and were less likely to consume caffeinated soda (59% and 73%, respectively).

Odds ratios were increased for total caffeine consumption at or above 10 mg per day for NTDs combined, spina bifida, and encephalocele, but not for anencephaly (Table 3). Caffeinated coffee was associated with increased risk of spina bifida and encephalocele. Tea consumption was associated with decreased risk of spina bifida (Table 3), but an increased risk of encephalocele. Adjusted ORs for caffeinated soda were slightly increased for NTDs combined and spina bifida. Associations were not observed between spina bifida and consumption of caffeine-free soda (OR 0.9; 95% CI: 0.6–1.3) or diet soda (OR 0.9; 95% CI: 0.6–1.3). A nonsignificant increased risk was observed for caffeine-containing medications and spina bifida; this association was similar when mothers who reported use “as needed” were included in addition to those reporting specific timing of use. Associations were attenuated slightly when analyses were restricted to isolated NTDs (data not shown). Associations for isolated spina bifida cases ($n = 411$) were similar to those observed for the combined spina bifida group, but for the smaller group of multiple spina bifida cases ($n = 48$), the OR for caffeinated soda was larger (OR 2.7; 95% CI: 1.1–6.4). Little indication of a dose effect existed for any caffeine source or case group. Consumption of folic acid-containing supplements was neither a confounder nor an effect modifier of these

associations. Results were unchanged when children with a family history of NTDs, maternal history of diabetes, or maternal periconceptional use of antiseizure medications were excluded from analyses (data not shown).

For case groups other than anencephaly, associations between total caffeine consumption and increased risk were observed primarily or were stronger in racial/ethnic groups other than non-Hispanic white (Table 4). Caffeine was associated with increased risk of anencephaly among non-Hispanic white mothers and a decreased risk among mothers of other races/ethnicities. Further, the association between caffeine consumption and spina bifida was stronger among women who did not smoke cigarettes, who did not consume alcohol, and who conceived at <30 years of age (Table 5). A slightly stronger association between total caffeine consumption and spina bifida was observed for women interviewed within 1 year of their child's birth date (or estimated delivery date) (OR 1.5; 95% CI: 1.0–2.1) than women interviewed after 1 year (OR 1.3; 95% CI: 0.7–2.2). Finally, the associations were not confounded by different levels of case ascertainment across states (data not shown).

DISCUSSION

The findings from this population-based case-control study indicate that women who report drinking caffeinated beverages in the year before pregnancy may be at modestly increased risk for a pregnancy affected by an NTD. Reported consumption of caffeinated beverages for this period is likely to be similar to women's consumption during early pregnancy before their pregnancies were confirmed, which corresponds to the time of neural tube development.

Examination by case type revealed associations between total caffeine intake, coffee, and soda and increased risk of spina bifida and encephalocele, but ORs for anencephaly were near unity. Only two previous studies examined NTDs by type (Fedrick, 1974; Furuhashi et al., 1985). Based on very small numbers (4 meningocele cases, 12 anencephaly cases), Furuhashi and colleagues (1985) found a greater prevalence of infants with spina bifida and infants with anencephaly among pregnant women who consumed caffeinated coffee or tea (combined) than among women who did not consume these beverages. A case-control study by Fedrick (1974) found evidence for increased tea consumption (three cups or more daily) for mothers of infants with anencephaly. Our findings agree with the positive association between spina bifida and total caffeine and coffee found by Furuhashi et al., but we observed an association with reduced risk of spina bifida for tea.

A protective effect of tea seems biologically plausible given the many health benefits attributed to tea's antioxidant properties (Kamath et al., 2003; Iso et al., 2006; Kuriyama et al., 2006; Steptoe et al., 2007; Yang et al., 2007), including those associated with certain flavanols, such as catechins and epicatechins, which are absent in coffee and soda (Arts et al., 2000). In addition, our interview asked about 'caffeinated tea,' and women may have reported consumption of teas with very little caffeine (e.g., green tea). However, because tea was not associated with reduced risk of anencephaly and was associated with increased risk

of encephalocele, our finding of an association in the protective direction may also be due to recall bias, or chance, as discussed below.

In contrast to previous findings, we observed no association between caffeine consumption and anencephaly overall, and decreased ORs among Hispanic and non-white mothers. Nevertheless, an increased risk for anencephaly was found for non-Hispanic white mothers, the racial/ethnic group most similar to women in the Fedrick (1974) study. Differences by race/ethnicity in this study and others may result from different nutritional or genetic backgrounds, and types of caffeinated beverages consumed and their preparation methods. Differences in participation, case ascertainment, and recall across races/ethnicities are other potential explanations.

The NBDPS is one of the largest studies to date to investigate associations between caffeine consumption and NTDs. The NBDPS represents geographically, racially, and ethnically diverse populations and uses population-based control selection and case ascertainment. Detailed diagnostic classification allowed detection of important differences in associations by specific types of NTDs. Finally, information on a number of covariates was collected and used to examine confounding and effect modification.

Although the lack of a dose effect is evidence against a causal association and could indicate bias, persons who regularly consume caffeine develop a tolerance to the effects of caffeine within certain levels of consumption (Robertson et al., 1981; Evans and Griffith, 1992; Shi et al., 1993), which could have minimized a dose effect. Because of this tolerance effect, women who do not consume caffeine regularly but who happen to ingest moderate to large amounts of caffeine during the critical period of neural tube development may be at greatest risk for the effects of caffeine. The questionnaire used in our study asked about 'average intake' and did not allow identification of these women. However, these women would be expected to be the women who reported consuming coffee or soda only occasionally, fewer cups on average, and low to moderate average total caffeine amounts, the women associated with the greatest risk in our study. This pattern was observed in other studies of caffeinated beverages and their association with NTDs (Rosenberg et al., 1982; Kurppa et al., 1983). Lack of viability (and ascertainment) of cases at the highest consumption levels is also possible. The number of women in this study who reported consuming very high levels of caffeine (400 mg or more daily) offered insufficient power to detect ORs similar to those found for the lower levels of consumption.

Errors in the measurement of caffeine consumption also could have obscured a dose effect. The interview did not include information on type, brew method, and strength of coffee and tea and included only implied serving sizes (i.e., 'a cup'). The amount of caffeine consumed varies greatly depending on these details (Gilbert et al., 1976; Lelo et al., 1986; Stavric et al., 1988; Barone and Roberts, 1996; Bracken et al., 2002; McCusker et al., 2003). The interview also did not permit evaluation of additional sources of caffeine, including chocolate- and coffee-flavored ice cream, milk, syrup, cakes, donuts, muffins, or pie. However these sources contribute <2% of total caffeine consumed (Watkinson and Fried, 1985; Frary et al., 2005).

Although the measurement of caffeine consumption may not have been ideal, it was likely representative of typical caffeine use for the participants. Both the percentage of mothers consuming caffeine and the mean daily caffeine consumption for control-mothers in the current study (162 mg) were similar to the average caffeine consumption reported previously for females of childbearing age (Barone and Roberts, 1996; Frary et al., 2005). The measured caffeine values were sensitive enough to distinguish differences in consumption across maternal race and age, which have been described previously (Fenster et al., 1991; Mills et al., 1993; Fenster et al., 1997). In addition, the validity and reliability of caffeine assessment reported for the Willett food frequency questionnaire, on which the food frequency for the current study was based, are high (Munger et al., 1992). Finally, the problem of measurement error is unlikely to have affected the *any* or *none* comparisons.

Except for the association between caffeinated soda and all NTDs combined, adjustment for most potential confounders, including folic acid, alcohol, and smoking, tended to either not change or to strengthen the observed associations. However, residual confounding was possible from measured exposures if the measurement was imprecise and failed to detect the exposures' confounding effects during covariate selection. Unknown confounding variables also could have influenced our parameter estimates.

Given the retrospective design, this study is subject to recall bias. To determine whether recall bias was a likely explanation for the results, several factors were considered. First, other risk factors, including smoking, alcohol use, daily caloric intake, and consumption of caffeine-free soda, were not associated with elevated risk for spina bifida as might be expected if the association was primarily due to recall bias. Another consideration was whether a longer time to interview strengthened the association because a longer time to interview might make differences in recall (and associated OR) more pronounced. Instead, the association between total caffeine consumption and spina bifida was stronger in those with a shorter time to interview. Finally, use of caffeinated beverages is widespread and considered acceptable, at least in the year before pregnancy, making differential recall unlikely.

The inconsistent effects across NTD types were consistent with differences in etiologies across types as suggested by varied epidemiologic risk factors and developmental processes (Khoury et al., 1982; Sever, 1995). However, it is also possible the differences observed could have resulted from differential bias among NTD types. Maternal recall would be unlikely to differ by NTD type unless recall was affected by the severity of the defect or differences in the time to interview. In a study of reporting accuracy, Werler, et al. (1989) did not observe differences between mothers of infants with severe and nonsevere malformations. Differences in the time to interview likely would not explain differences in results across type of NTD because, in the present study, the time to interview was similar relative to controls for each type of NTD. A more plausible explanation for the lack of an association between caffeine and anencephaly (primarily in mothers who were not non-Hispanic white) is case ascertainment bias as a result of differences in ascertainment of anencephaly cases according to maternal characteristics that might be related to caffeine intake. Case ascertainment and participation bias is particularly an issue for anencephaly compared to other types of NTDs because anencephaly is more likely to result in early

pregnancy loss, elective terminations, and fetal death, which increases the likelihood of cases being missed and of families being unwilling to participate. Indeed, the rate of participation for anencephaly families (61%) is lower than that of the other NTD types (76% for spina bifida and 68% for encephalocele) in the NBDPS (unpublished data from start of study until December 31, 2003).

Levels of homocysteine are elevated after consuming caffeine (Grubben et al., 2000; Urgert et al., 2000; Verhoef et al., 2002) and high homocysteine levels are associated with increased NTD risk (Steegers-Theunissen et al., 1994; Mills et al., 1995). This provides one potential explanation for the association between total caffeine and NTDs. Other previously proposed mechanisms, including synergistic effects with other teratogens, inhibitory effects on DNA repair, and release of catecholamines or corticosterone (Nehlig and Debry, 1994), also remain plausible. Another possible explanation could be nutritional factors associated with consumption of caffeinated beverages. However, no confounding was detected by increased energy, sugar intake, body weight, diabetes, and decreased intake of calcium, which are associated with soda consumption (Vartanian et al., 2007), and no associations were observed for caffeine-free or diet soda. This, in combination with the modest, yet consistent association found between caffeine-containing medications and spina bifida, lends support for caffeine as a risk factor rather than other components; nevertheless, confounding by differences in unmeasured factors cannot be excluded. Finally, it should be recognized that multiple statistical comparisons were made in this study and some of our findings may be due to chance.

Our results suggest that the risk associated with caffeine consumption is greater for women unexposed to other potential risk factors for NTDs, including alcohol (Grewal et al., 2008), smoking (Suarez et al., 2008), and advanced maternal age (Vieira and Castillo Taucher, 2005). Cigarette smoke's activation of enzymes involved in caffeine metabolism for more rapid clearance and lower plasma concentrations of caffeine (Tantcheva-Poor et al., 1999; de Leon et al., 2003) could explain the lack of an association in women who smoked. Differences in the types of beverages consumed across groups, as observed between older and younger mothers, and bias from unmeasured confounding also could have produced differences in effects.

If others confirm the increased risk for spina bifida and encephalocele estimated for maternal caffeine consumption in our study, the effect appears large enough to warrant public health concern, especially given the high prevalence of caffeine exposure that continues to rise with increased consumption of soft drinks (French et al., 2003; Nielsen and Popkin, 2004) and growing popularity of specialty coffees (Watkinson and Fried, 1985) and energy drinks (Merrett, 2007). If the found association is causal, an estimated 21% of spina bifida and encephalocele cases in the United States could be prevented by eliminating maternal caffeine intake (adjusted population attributable risk = 0.21). Given this possibility and with consideration of studies that show increased risk for miscarriage associated with caffeine consumption during pregnancy (Giannelli et al., 2003; Weng et al., 2008), the findings presented here should be replicated by sizable studies that include more detailed caffeine information to confirm the results and to better understand mechanisms that could help identify markers of susceptibility to caffeine.

Acknowledgments

This work was supported by a grant from the Centers for Disease Control and Prevention (U50/CCU 713238). The authors acknowledge the investigators and staff of the National Birth Defects Prevention Study (NBDPS) for their valuable contributions.

We thank the participating centers and families of the National Birth Defects Prevention Study for their valuable contributions. Coding of drug information in the NBDPS used the Slone Drug Dictionary, under license from the Slone Epidemiology Center at Boston University, Boston, MA.

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Characteristics of Mothers of Infants With Neural Tube Defects and of Infants without Birth Defects in the National Birth Defects Prevention Study, United States, 1997–2002

	Controls (N = 4143)			NTD (N = 768)			Spina bifida (N = 459)			Anencephaly (N = 218)			Encephalocele (N = 91)		
	N	(%) ^a		N	(%) ^a	P ^b	N	(%) ^a	P ^b	N	(%) ^a	P ^b	N	(%) ^a	P ^b
Age at conception (years)						0.01			0.02			0.61			0.46
12–19	604	(14.6)		122	(15.9)		69	(15.0)		38	(17.4)		15	(16.5)	
20–29	2030	(49.0)		404	(52.6)		249	(54.2)		107	(49.1)		48	(52.7)	
30–34	1031	(24.9)		149	(19.4)		85	(18.5)		48	(22.0)		16	(17.6)	
35 or older	478	(11.5)		93	(12.1)		56	(12.2)		25	(11.5)		12	(13.2)	
Race/Ethnicity						<0.01			<0.01			<0.01			0.01
Non-Hispanic white	2477	(59.9)		399	(52.0)		252	(55.0)		107	(49.1)		40	(44.0)	
Non-Hispanic black	498	(12.1)		79	(10.3)		44	(9.6)		22	(10.1)		13	(14.3)	
Hispanic	940	(22.7)		251	(32.7)		142	(31.0)		76	(34.9)		33	(36.3)	
Other	217	(5.3)		38	(5.0)		20	(4.4)		13	(6.0)		5	(5.5)	
Birthplace						0.02			0.05			0.41			0.67
United States	3346	(81.5)		591	(77.5)		352	(77.0)		168	(78.1)		71	(78.0)	
Other	758	(18.5)		172	(22.6)		105	(23.0)		47	(21.9)		20	(22.0)	
Education						<0.01			<0.01			<0.01			0.01
<High school graduate	679	(16.6)		167	(22.1)		92	(20.1)		54	(25.1)		21	(23.1)	
High school graduate	1032	(25.2)		230	(30.0)		136	(29.8)		63	(29.3)		31	(34.1)	
College	2390	(58.3)		366	(47.9)		229	(50.1)		98	(45.6)		39	(42.9)	
Household income						<0.01			<0.01			0.09			0.07
\$50,000	2334	(64.5)		513	(74.7)		315	(76.8)		138	(70.4)		60	(74.1)	
>\$50,000	1284	(35.5)		174	(25.3)		95	(23.2)		58	(29.6)		21	(25.9)	
Pregnancy obesity						<0.01			<0.01			0.52			0.06
BMI <30 kg/m ²	3386	(85.2)		553	(76.1)		313	(72.1)		173	(83.6)		67	(77.9)	
BMI ≥30 kg/m ²	587	(14.8)		174	(23.9)		121	(27.9)		34	(16.4)		19	(22.1)	
Cigarette smoking ^c						0.29			0.80			0.09			0.22
No	3315	(80.5)		627	(82.2)		365	(80.0)		184	(85.2)		78	(85.7)	

	Controls (N = 4143)			NTD (N = 768)			Spina bifida (N = 459)			Anencephaly (N = 218)			Encephalocele (N = 91)		
	N	(%) ^a		N	(%) ^a	<i>p</i> ^b	N	(%) ^a		N	(%) ^a	<i>p</i> ^b	N	(%) ^a	<i>p</i> ^b
Yes	801	(19.5)		136	(17.8)		91	(20.0)		32	(14.8)		13	(14.3)	
Alcohol consumption ^c						<0.01						0.03			0.03
No	2497	(60.9)		511	(67.1)		298	(65.5)		148	(68.5)		65	(72.2)	
Yes	1602	(39.1)		250	(32.9)		157	(34.5)		68	(31.5)		25	(27.8)	
Intake of folic acid-containing supplement ^d						0.75						0.74			0.59
No	1934	(47.8)		360	(48.5)		220	(49.9)		98	(46.7)		40	(44.9)	
Yes	2110	(52.2)		383	(51.5)		221	(50.1)		112	(53.3)		49	(55.1)	
Parity						0.01						0.07			0.45
0	1655	(40.0)		271	(35.3)		157	(34.3)		74	(33.9)		40	(44.0)	
1	2479	(60.0)		496	(64.7)		301	(65.7)		144	(66.1)		51	(56.0)	

^aNumbers of cases and controls may vary due to missing or incomplete data. Percentages may not sum to 100 due to rounding.

^b*P*values derived from chi-squared tests.

^cAny, one month before through the third month of pregnancy.

^dAny, three months before through the first month of pregnancy.

BMI, body mass index; NTD, neural tube defects.

Average Maternal Caffeine Consumption Reported for the Year prior to Pregnancy for Case-Infants and Control-Infants in the National Birth Defects Prevention Study, United States, 1997–2002

Table 2

	Controls (N = 4143)		NTD (N = 768)		Spina bifida (N = 459)		Anencephaly (N = 218)		Encephalocele (N = 91)	
	N	(%) ^a	N	(%) ^a	N	(%) ^a	N	(%) ^a	N	(%) ^a
Total caffeine (mg/day)										
None (0–9)	635	(15.5)	97	(12.8)	55	(12.0)	31	(14.5)	11	(12.2)
Very low (10–99)	1438	(35.0)	285	(37.5)	169	(37.0)	80	(37.4)	36	(40.0)
Low (100–199)	958	(23.3)	190	(25.0)	117	(25.6)	52	(24.3)	21	(23.3)
Moderate (200–299)	557	(13.6)	99	(13.0)	58	(12.7)	30	(14.0)	11	(12.2)
High (≥ 300)	520	(12.7)	90	(11.8)	58	(12.7)	21	(9.8)	11	(12.2)
Caffeinated coffee										
Never or 1 cup/month	2232	(54.3)	415	(54.3)	245	(53.6)	125	(57.9)	45	(50.0)
1 cup/month–6 cups/week	536	(13.0)	116	(15.2)	69	(15.1)	35	(16.2)	12	(13.3)
1 cup/day	581	(14.1)	115	(15.1)	71	(15.5)	25	(11.6)	19	(21.1)
2 cups/day	410	(10.0)	59	(7.7)	35	(7.7)	18	(8.3)	6	(6.7)
3 cups/day	355	(8.6)	58	(7.6)	37	(8.1)	13	(6.0)	8	(8.9)
Caffeinated tea										
Never or <1 cup/month	2140	(52.0)	415	(54.3)	267	(58.4)	111	(51.4)	37	(41.1)
1 cup/month–6 cups/week	1155	(28.1)	204	(26.7)	111	(24.3)	64	(29.6)	29	(32.2)
1 cup/day	437	(10.6)	82	(10.7)	40	(8.8)	24	(11.1)	18	(20.0)
2 cups/day	206	(5.0)	28	(3.7)	17	(3.7)	9	(4.2)	2	(2.2)
3 cups/day	175	(4.3)	34	(4.5)	22	(4.8)	8	(3.7)	4	(4.4)
Caffeinated soda (mg/day)										
None (0)	1322	(32.2)	204	(26.8)	113	(24.7)	63	(29.4)	28	(30.8)
>0–<½ (1–16)	746	(18.2)	136	(17.9)	82	(17.9)	35	(16.4)	19	(20.9)
½–<1 (17–33)	673	(16.4)	122	(16.0)	72	(15.9)	31	(14.5)	19	(20.9)
1–<2 (34–67)	277	(6.7)	68	(8.9)	41	(9.0)	21	(9.8)	6	(6.6)
2–<3 (68–101)	454	(11.0)	99	(13.0)	64	(14.0)	26	(12.2)	9	(9.9)
3 (102)	639	(15.5)	133	(17.5)	85	(18.6)	38	(17.8)	10	(11.0)
Chocolate										

	Controls (N = 4143)		NTD (N = 768)		Spina bifida (N = 459)		Anencephaly (N = 218)		Encephalocele (N = 91)	
	N	(%) ^a	N	(%) ^a	N	(%) ^a	N	(%) ^a	N	(%) ^a
Never or <1 oz./month	807	(19.6)	169	(22.1)	105	(22.3)	42	(19.5)	22	(24.2)
1 oz./month	3311	(80.4)	594	(77.9)	352	(77.7)	173	(80.5)	69	(75.8)
Caffeine-containing medications ^b										
None	4066	(99.0)	753	(99.2)	448	(98.7)	216	(100.0)	89	(100.0)
Any	42	(1.0)	6	(0.8)	6	(1.3)	0	(0.0)	0	(0.0)

^aNumbers of cases and controls may vary because of missing or incomplete data. Percentages may not sum to 100 due to rounding.

^bMedications reported for one month before through the third month of pregnancy. Caffeine from medications not included in estimate of total caffeine.
NTD, neural tube defect.

Adjusted Odds Ratios for Associations Between Maternal Caffeine Consumption and Neural Tube Defects in the National Birth Defects Prevention Study, United States, 1997–2002

	NTD		Spina bifida		Anencephaly		Encephalocele	
	OR ^a	(95% CI)	OR ^b	(95% CI)	OR ^c	(95% CI)	OR ^d	(95% CI)
Total caffeine (mg/day)								
None (0–9)	1.0		1.0		1.0		1.0	
Any (10)	1.3	(1.0, 1.6)	1.4	(1.1, 1.9)	1.1	(0.7, 1.6)	1.4	(0.7, 2.7)
Very low (10–99)	1.3	(1.0, 1.7)	1.4	(1.0, 1.9)	1.1	(0.7, 1.7)	1.5	(0.7, 2.9)
Low (100–199)	1.3	(1.0, 1.7)	1.5	(1.1, 2.1)	1.1	(0.7, 1.8)	1.4	(0.7, 2.9)
Moderate (200–299)	1.2	(0.9, 1.7)	1.3	(0.9, 1.9)	1.1	(0.7, 1.8)	1.3	(0.6, 3.0)
High (300)	1.2	(0.8, 1.6)	1.4	(0.9, 2.1)	0.8	(0.5, 1.5)	1.4	(0.6, 3.3)
Caffeinated coffee								
Never or <1 cup/month	1.0		1.0		1.0		1.0	
Any (1 cup/month)	1.0	(0.9, 1.2)	1.3	(1.0, 1.6)	1.0	(0.7, 1.3)	1.3	(0.9, 2.0)
1 cup/month– 6 cups/week	1.2	(0.9, 1.5)	1.3	(1.0, 1.8)	1.1	(0.8, 1.7)	1.2	(0.6, 2.3)
1 cup/day	1.1	(0.8, 1.3)	1.4	(1.1, 1.9)	0.9	(0.6, 1.4)	1.8	(1.0, 3.0)
2 cups/day	0.8	(0.6, 1.0)	1.1	(0.7, 1.6)	1.0	(0.6, 1.6)	0.8	(0.4, 2.0)
3 cups/day	0.9	(0.7, 1.2)	1.1	(0.9, 1.2)	0.9	(0.5, 1.6)	1.3	(0.6, 2.9)
Caffeinated tea								
Never or <1 cup/month	1.0		1.0		1.0		1.0	
Any (1 cup/month)	0.9	(0.8, 1.1)	0.7	(0.6, 0.9)	1.0	(0.8, 1.3)	1.4	(0.9, 2.2)
1 cup/month– 6 cups/week	0.9	(0.8, 1.1)	0.7	(0.6, 0.9)	1.1	(0.8, 1.5)	1.4	(0.8, 2.3)
1 cup/day	1.0	(0.7, 1.3)	0.7	(0.5, 1.1)	1.1	(0.7, 1.7)	2.4	(1.3, 4.3)
2 cups/day	0.7	(0.5, 1.1)	0.6	(0.4, 1.1)	0.8	(0.4, 1.7)	0.9	(0.4, 2.1)
3 cups/day ^e	1.0	(0.7, 1.5)	0.9	(0.6, 1.5)	0.9	(0.4, 1.8)		
Caffeinated soda (mg)/day								
None (0)	1.0		1.0		1.0		1.0	
Any	1.2	(1.0, 1.4)	1.2	(1.0, 1.6)	0.9	(0.7, 1.2)	1.1	(0.7, 1.7)
>0–<½ (1–16)	1.2	(0.9, 1.5)	1.2	(0.9, 1.6)	0.8	(0.5, 1.3)	1.3	(0.7, 2.3)
½–<1 (17–33)	1.5	(1.1, 2.1)	1.5	(1.0, 2.2)	1.3	(0.7, 2.1)	1.1	(0.5, 2.7)

	NTD		Spina bifida		Anencephaly		Encephalocele	
	OR ^a	(95% CI)	OR ^b	(95% CI)	OR ^c	(95% CI)	OR ^d	(95% CI)
1–<2 (34–67)	1.1	(0.9, 1.4)	1.1	(0.8, 1.5)	0.8	(0.5, 1.2)	1.4	(0.8, 2.5)
2–<3 (68–101)	1.2	(0.9, 1.6)	1.3	(0.9, 1.8)	0.9	(0.6, 1.5)	0.9	(0.4, 2.0)
3 (102)	1.1	(0.9, 1.5)	1.3	(0.9, 1.8)	1.0	(0.6, 1.5)	0.7	(0.3, 1.5)
Caffeine-containing medications ^f								
None	1.0		1.0					
Any	0.8	(0.3, 1.8)	1.3	(0.6, 3.1)				

^aORs for total caffeine adjusted for any maternal alcohol consumption one month before through the third month of pregnancy and maternal education (<16, 16+ yrs). ORs for caffeinated soda adjusted for maternal education and maternal prepregnancy obesity (body mass index >30 kg/cm²).

^bORs for total caffeine adjusted for any maternal alcohol consumption one month before through the third month of pregnancy. ORs for caffeinated coffee adjusted for study center and household income (<\$50,000, \$50,000+). ORs for caffeinated tea adjusted for study center. ORs for caffeinated soda adjusted for study center and maternal prepregnancy obesity.

^cORs for caffeinated coffee and soda adjusted for study center.

^dORs for total caffeine, caffeinated coffee, and caffeinated tea adjusted for any maternal alcohol consumption one month before through the third month of pregnancy. ORs for caffeinated tea also adjusted for study center. ORs for caffeinated soda adjusted for maternal education and any diet soda consumption in year prior to pregnancy.

^eCombined with “2 cups/day” category for encephalocele due to the small frequency of cases.

^fToo few mothers reported exposure to caffeinated medications in this group to calculate an OR and CI.

CI, confidence interval; NTD, neural tube defect; OR, odds ratio.

Association between Maternal Caffeine Consumption and Each Neural Tube Defect Type Stratified by Maternal Race/Ethnicity in the National Birth Defects Prevention Study, United States, 1997–2002

Table 4

	Maternal caffeine (mg/day)	NTD				Spina bifida				Anencephaly				Encephalocele			
		Cases (N)	Controls (N)	OR ^a	(95% CI)	Cases (N)	Controls (N)	OR ^b	(95% CI)	Cases (N)	Controls (N)	OR	(95% CI)	Cases (N)	Controls (N)	OR ^b	(95% CI)
Race/ethnicity	Non-Hispanic	51	309	1.0		25	309	1.0		20	309	1.0		6	309	1.0	
	white	345	2138	1.0	(0.7, 1.3)	226	2142	1.3	(0.9, 2.1)	86	2153	1.6	(1.0, 2.7)	33	2142	0.8	(0.3, 2.0)
	Hispanic ^c	28	151	1.0		18	152	1.0									
		218	778	1.5	(1.0, 2.4)	123	780	1.4	(0.8, 2.3)								
Other ^d	None (0–9)	16	168	1.0		10	170	1.0		11	322	1.0		5	322	1.0	
	Any (10)	98	524	2.0	(1.1, 3.5)	52	527	1.7	(0.9, 3.4)	97	1313	0.5	(0.2, 0.9)	45	1307	2.3	(0.9, 5.9)

^a Adjusted for maternal education (<16, 16+ years), alcohol consumption (any, one month before through the third month of pregnancy).

^b Adjusted for maternal alcohol consumption (any, one month before through the third month of pregnancy).

^c Hispanic mothers combined with mothers of “Other” races for anencephaly and encephalocele because of small numbers in strata; ORs for the two groups were similar.

^d Includes non-Hispanic black, Asian or Pacific Islander, Native American or Alaskan Native, or other race. Also includes Hispanic for anencephaly and encephalocele.

CI, confidence interval; NTD, neural tube defect; OR, odds ratio.

Table 5

Association between Maternal Caffeine Consumption and Spina Bifida Stratified by Maternal Cigarette Smoking, Alcohol Consumption, and Maternal Age at Conception for Index Pregnancy in the National Birth Defects Prevention Study, United States, 1997–2002

	Maternal caffeine (mg/day)	Spina bifida (N)	Controls (N)	OR ^b	(95% CI)
Cigarette smoking ^a					
No	None (0–9)	48	597	1.0	
	Any (10)	315	2704	1.5	(1.1, 2.0)
Yes	None (0–9)	6	38	1.0	
	Any (10)	85	752	0.7	(0.3, 1.7)
Alcohol consumption ^a					
No	None (0–9)	36	471	1.0	
	Any (10)	262	2020	1.7	(1.2, 2.4)
Yes	None (0–9)	18	164	1.0	
	Any (10)	139	1436	0.9	(0.5, 1.5)
Maternal age at conception					
<30 years	None (0–9)	34	391	1.0	
	Any (10)	282	2208	1.5	(1.0, 2.2)
30 years	None (0–9)	20	244	1.0	
	Any (10)	119	1248	1.2	(0.7, 1.9)

^aAny, one month before through the third month of pregnancy.

^bORs stratified by cigarette smoking and age at conception adjusted for alcohol consumption. Additional adjustment for maternal pre-pregnancy obesity produced similar results.

CI, confidence interval; OR, odds ratio.