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Maternal Caffeine Intake and Risk of Selected Birth Defects in the National Birth Defects Prevention Study

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Abstract

BACKGROUND—Caffeine intake is common during pregnancy, yet few epidemiologic studies have examined the association between maternal caffeine consumption and birth defects. Using data from the National Birth Defects Prevention Study (NBDPS), we examined the association between maternal caffeine consumption and anotia/microtia, esophageal atresia, small intestinal atresia, craniosynostosis, diaphragmatic hernia, omphalocele, and gastroschisis.

METHODS—The NBDPS is a multi-site population-based case-control study. The present analysis included 3,346 case infants and 6,642 control infants born from October 1997 through December 2005. Maternal telephone interview reports of demographic characteristics and conditions and exposures before and during pregnancy were collected. Odds ratios and 95% confidence intervals, adjusted for relevant covariates, were calculated to estimate the associations between maternal dietary caffeine intake (coffee, tea, soda, and chocolate) and maternal use of caffeine-containing medications and each defect.

RESULTS—We observed small, statistically significant elevations in adjusted odds ratios ranging from 1.3 to 1.8 for total maternal dietary caffeine intake or specific types of caffeinated beverages and anotia/microtia, esophageal atresia, small intestinal atresia, and craniosynostosis; however, dose-response patterns were absent. Periconceptional use of caffeine-containing medications was infrequent and estimates were imprecise.

CONCLUSIONS—We did not find convincing evidence of an association between maternal caffeine intake and the birth defects included in this study. The increasing popularity of caffeine-

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containing energy drinks and other caffeinated products may result in higher caffeine intake among women of childbearing age. Future studies should consider more detailed evaluation of such products.

Keywords

caffeine; coffee; tea; soft drinks; congenital abnormalities; birth defects

INTRODUCTION

A 1994 to 1996 United States survey found that 68% of pregnant women consumed caffeine, with an average intake of 125 mg (approximately equivalent to 1.25 cups of coffee) per day (Frary et al., 2005). The increasing popularity of caffeine-containing energy drinks (Mintel International, 2008), along with a variety of newly marketed caffeinated products, may be resulting in higher caffeine intake among women of childbearing age. The potential for an increase in caffeine consumption strengthens the importance of understanding whether there are associated risks with such exposure during pregnancy.

Caffeine easily crosses the placenta (Mose et al., 2008) and is known to decrease placental blood flow and fetal heart rate (Kirkinen et al., 1983; Salvador and Koos, 1989). Results of epidemiologic studies investigating caffeine teratogenicity have been mixed; however, relatively few have examined exposure from all major sources of caffeine in association with specific types of birth defects. Among those studies that have assessed maternal caffeine consumption and the risk of specific birth defects are several previous studies using data from the National Birth Defects Prevention Study (NBDPS). No statistically significant associations with maternal dietary caffeine intake overall were observed for congenital heart defects (Browne et al., 2007), orofacial clefts (Collier et al., 2009), or bilateral renal agenesis or hypoplasia (Slickers et al., 2008); a borderline statistically significant odds ratio (OR, 1.5; 95% confidence interval (CI), 1.0–2.2) was noted for anorectal atresia (Miller et al., 2009); and a statistically significant OR (1.4; 95% CI, 1.1–1.9) was detected for spina bifida (Schmidt et al., 2009).

Caffeine has the potential to interact with many other exposures. For example, smoking is known to increase the rate of caffeine metabolism in humans (Landi et al., 1999). In rodents and chicken embryos, caffeine enhanced the teratogenicity of substances such as nicotine, alcohol, bronchodilators, and anti-seizure medications (Nehlig and Debry, 1994).

As the NBDPS continues to accrue case and control infants, there are sufficient numbers to examine maternal caffeine exposure and the risks of additional types of birth defects. In this study, we analyzed a number of birth defect types for which there were 200 or more case infants in the NBDPS (excluding those birth defect types already analyzed and published as noted above): anotia/ microtia, esophageal atresia, small intestinal atresia, craniosynostosis, diaphragmatic hernia, omphalocele, and gastroschisis. Few previous studies have examined the influence of maternal caffeine consumption on the risk of any of these specific birth defects; none has evaluated additive interaction with potential effect modifiers. We hypothesized that any causal associations between caffeine exposure and risk of birth defects would exist for certain types of birth defects, given the etiologic and pathogenetic

heterogeneity of birth defects, and possibly only for exposure to caffeine in combination with other exposures. We evaluated additive interaction with maternal smoking; use of folic acid-containing vitamin supplements, alcohol, and vasoconstrictive medications; and infant sex. We considered folic acid supplementation because it is known to reduce the risk of neural tube defects (MRC Vitamin Study Research Group, 1991) and may reduce the risk of other birth defects (Goh et al., 2006) and modify the effects of environmental teratogens (Acs et al., 2005). Because the effects of other risk factors for gastroschisis have varied by maternal age (Werler et al., 2009), we also evaluated effect modification by maternal age for caffeine exposure and gastroschisis.

METHODS

The NBDPS is an ongoing multisite population-based case-control study that began in 1997 (Yoon et al., 2001). Infants with one or more of over 30 different categories of major structural defects (cases), excluding those attributed to a known chromosomal abnormality or single-gene condition, have been ascertained through birth defects surveillance systems in 10 states. Each study site obtained institutional review board approval for the NBDPS. Control infants were liveborn infants without birth defects randomly selected from hospital records or birth certificates in the same time period and geographic areas as the cases.

Included in the present study, were births with an estimated date of delivery (EDD) from October 1997 through December 2005. Control infants and infants with the following types of birth defects were included: anotia/ microtia, esophageal atresia, small intestinal atresia, craniosynostosis, diaphragmatic hernia, omphalocele, and gastroschisis. We excluded infants with a maternal history of type 1 or type 2 diabetes diagnosed before pregnancy since pre-existing diabetes is associated with an increased risk of a variety of birth defects (Nielsen et al., 2005; Correa et al., 2008). Participation rates were 72% and 67% for eligible case and control mothers, respectively.

Case inclusion criteria have been described by Yoon et al. (2001). Clinical geneticists reviewed and classified each case infant as isolated or multiple birth defects (two or more major unrelated defects; Rasmussen et al., 2003). Microtia included dysplastic ear pinna and stenosis or atresia of the external auditory canal. Infants with intestinal atresia limited to the duodenum were not counted as small intestinal atresias for this analysis; only ileal, jejunal, and multiple intestinal atresias or stenoses were included. Infants with esophageal or small intestinal atresia that occurred as a component of VATER or VAC-TERL association of defects were included in the study and were classified as having multiple defects. To reduce etiologic heterogeneity within case groups, we excluded infants classified as having a complex sequence (a group of defects that are believed to be pathogenetically related, but for which the primary defect is not apparent), for example, infants with a diaphragmatic hernia identified as part of Pentalogy of Cantrell or with a limb-body wall defect.

A computer-assisted telephone interview was used to collect information from case and control mothers, requesting information about demographic characteristics, pregnancy history, and various maternal conditions and exposures before and during pregnancy. The

interviews were conducted by trained interviewers between 6 weeks and 24 months after the EDD.

The interview questions and method of calculating caffeine intake have been described previously (Browne et al., 2007). Briefly, mothers were asked about their usual intake of coffee, tea, soda, and chocolate during the year before they became pregnant. Frequency categories ranged from none or less than once per month to six or more times per day. Caffeine exposure was estimated at 100 mg for a cup of coffee, 37 mg for a cup of tea (Bracken et al., 2002), 10 mg per ounce of chocolate, and according to the manufacturer or published caffeine contents for soda and other soft drinks by brand and variety. Dietary caffeine intake was analyzed as five categories: <10 mg/day, 10 to <100 mg/day, 100 to <200 mg/day, 200 to <300 mg/day, and 300 or more mg/day; representing approximately the daily caffeine equivalent of less than one cup per day, one cup, two cups, and three or more cups of coffee, respectively.

Exposure to caffeine in medications was evaluated separately from caffeine in beverages and chocolate. A medication dictionary developed by the Slone Epidemiology Center at Boston University was used to identify medications with caffeine as a pharmacologic component. Medication data were collected for the period three months before pregnancy through delivery. Use of caffeine-containing medications during the periconceptional period (one month before pregnancy through the third month of pregnancy) was examined. The amount of caffeine per dose based on the usual dose for each medication was determined from online product information and was categorized as <100 mg or ≥100 mg. The dose estimates do not account for the actual number of doses taken per day, for which detailed information was not available. Case and control mothers for whom information on timing of medication use was missing were excluded from analysis of caffeine-containing medications.

Covariates included the following maternal characteristics: age at delivery (<20, 20–24, 25–29, 30–34, or 35+), parity (primiparous, multiparous), race/ethnicity (white non-Hispanic, black non-Hispanic, Hispanic, other), education (less than high school, high school, college), pre-pregnancy body mass index (weight in kg/height in m^2; <18.5, 18.5–<25, 25–<30, or 30+), the mother's state of residence at the time of the infant's birth, and dichotomous variables for: gestational diabetes, use of fertility medications or procedures, fever during the first trimester, and nausea or vomiting during month one of the index pregnancy. We also considered folic acid-containing vitamin supplement use (any use during one month before pregnancy through month one, any during month two or three, later in pregnancy, or none) and periconceptional exposure to the following: cigarette smoking (yes, no), maximum number of alcoholic drinks on one occasion (none, 1–3, or 4+), and use of vasoconstrictive medications (yes, no; including decongestants, ergot anti-migraine medications, amphetamines, and cocaine). The influence of family history of a defect of the same organ system and multiple gestation pregnancies were assessed by conducting additional analyses that excluded case and control infants with these characteristics.

Bivariate and stratified analyses were conducted to assess potential confounding and effect modification. Factors evaluated as effect modifiers based on a priori expectations were maternal smoking; use of alcohol, vasoconstrictive medications, folic acid-containing

vitamin supplements; and infant sex. The regression coefficients (Wald test; $p < 0.05$) of caffeine-effect modifier cross-product terms were examined to determine whether confounder selection should be conducted in models stratified by effect modifiers. Additive interaction between maternal dietary caffeine as a continuous variable and selected effect modifiers was assessed by calculation of the relative excess risk due to interaction (RERI), also known as the interaction contrast ratio (ICR), described by Rothman (1986) and adapted for use with a continuous variable by Knol et al. (2007). Total caffeine values were divided by 300 to evaluate the effect of caffeine per 300 mg increase; 95% CIs were calculated. Relative excess risk due to interaction values greater than zero suggest that combined exposure results in a greater than additive effect, whereas values less than zero suggest a less than additive effect. To assess effect modification of the association between maternal dietary caffeine intake and gas-troschisis, we compared results for multiple levels of maternal age in a stratified analysis.

Multiple logistic regression models were constructed to estimate adjusted odds ratios (aORs) and 95% CIs for the association between maternal exposure to caffeine and each type of birth defect, while controlling for confounding variables. To distinguish caffeine associations from associations that may be due to other components in caffeinated beverages, in addition to total dietary caffeine, we examined each caffeinated beverage (coffee, tea, and soda) separately (chocolate accounted for only a small proportion of dietary caffeine intake). Separate logistic regression models were fitted for each of the caffeine exposure variables (total caffeine, coffee, tea, soda, and caffeine-containing medications) paired with each type of birth defect. Starting with a full model including potential confounders identified in the bivariate analysis, variables were dropped using the change-in-estimate selection method with those causing a 10% or more change in an exposure estimate retained in the model. To streamline the analysis and presentation of results, three covariates remaining in the final models of many birth defect groups were included for all analyses: maternal age, race/ethnicity, and the mother's state of residence at the time of the infant's birth. Other covariates were included only in the analyses of birth defect groups for which they demonstrated confounding. Analyses using the same models were repeated separately for isolated birth defects and for multiple defects. Odds ratios are not presented for analyses with less than three exposed case infants. All analyses were performed using SAS software, version 9.1 (SAS Institute Inc., 2002).

RESULTS

Mothers of 3445 case infants with birth defect types evaluated in the present analysis (anotia/microtia, esophageal atresia, small intestinal atresia, craniosynostosis, diaphragmatic hernia, omphalocele, and gastroschisis) and 6,789 control infants with an EDD from 1997 through 2005 were interviewed for the NBDPS. After excluding infants missing maternal caffeinated beverage data (53 case infants, 98 control infants) and those with maternal history of type 1 or type 2 diabetes diagnosed prior to the index pregnancy (44 case infants, 39 control infants) or missing information on diabetes status (2 case infants, 10 control infants), 3,346 case infants and 6,642 control infants remained. The interval between the EDD and interview varied by outcome category, with average intervals ranging from 9.3 to

13.9 months (average = 11.0 months) among the birth defects included in the present analysis and 8.8 months for controls.

Table 1 displays the distribution of selected characteristics of study mothers. Differences were observed between case infants and control infants or among the various types of birth defects for a number of maternal characteristics. There was a higher proportion of older mothers among infants with esophageal atresia, craniosynostosis, and omphalocele and a smaller proportion of infants with older mothers among infants with gastroschisis. As expected, mothers of infants with gastroschisis differed from mothers of controls and mothers of infants with other birth defects on a number of characteristics.

Overall, approximately 50% of caffeine intake was from coffee, 35% from soda, 12% from tea, and 3% from chocolate, with nearly identical proportions observed for case and control mothers (data not shown). Among mothers of both case infants and control infants, 31% reported an average of one serving or more per day of coffee and 18% reported an average of one serving or more per day of tea. A small difference, 43 versus 41%, was observed in the proportion reporting at least one serving per day of caffeine-containing soft drinks among case and control mothers, respectively. Among mothers of infants with gastroschisis, the proportion reporting at least one serving of caffeine-containing soft drinks per day was 50%. Caffeine consumption both in total milligrams of caffeine and by source of caffeine differed by maternal age. Among control mothers, 62% of mothers under age 20 years and 38% of mothers aged 40 years or more reported <100 mg caffeine/day (data not shown). Coffee consumption was more frequently reported by older mothers whereas soda consumption was more common among younger mothers (data not shown).

Elevated aORs ranging from 1.3 to 1.8 were observed for associations between dietary caffeine consumption and anotia/microtia, small intestinal atresia, craniosynostosis, omphalocele, and gastroschisis (Table 2). Statistically significant associations were observed between both low (10–<100 mg/day) and moderate (200–<300 mg/day) total caffeine intake and small intestinal atresia and between high (300+ mg/day) dietary caffeine consumption and craniosynostosis. Consistent increases were generally not observed across increasing caffeine categories. Although the aOR for the association between high dietary caffeine intake and gastroschisis was 1.26 (95% CI, 0.90–1.78), in analyses stratified by maternal age, the aORs for high dietary caffeine intake increased as maternal age increased. The aORs increased from 0.99 (0.66–1.48) for age <25 years to 1.93 (95% CI, 0.77–4.87) and 2.90 (95% CI, 0.86–9.79) for 25 to <30 years and 30+ years, respectively (data not shown).

In beverage-specific analyses (Table 2), no dose-response relationship was evident for any birth defect type for any type of caffeinated beverage (i.e., coffee, tea, or soda). For coffee intake, statistically significant elevated aORs were observed for the associations between 3+ cups/day and anotia/microtia (aOR = 1.60; 95% CI, 1.07–2.41) and between 2 cups/day and small intestinal atresia (aOR = 1.62; 95% CI, 1.06–2.46). For soda consumption, a statistically significant aOR of 1.43 (95% CI, 1.04–1.98) was observed for the association between 3+ cups/day and esophageal atresia. Confounding by caffeine source was not present; models that contained exposure variables for all three caffeinated beverages in the same model produced results very similar to those presented in Table 2.

The analysis of caffeine-containing medications was based on relatively small numbers of exposed case infants. Elevated aORs ranging from 1.6 to 2.6 were observed for periconceptional use of medications with 100+ mg caffeine/dose and anotia/microtia, esophageal atresia, craniosynostosis, diaphragmatic hernia, omphalocele, and gastroschisis. The estimates for anotia/microtia and esophageal atresia were statistically significant (aOR, 2.60; 95% CI, 1.00–6.73 and aOR, 2.33; 95% CI, 1.03–5.28, respectively).

When total dietary caffeine consumption was cross-classified by potential effect modifiers, there was no strong evidence of additive interaction and none of the interaction contrast ratios were statistically significant (data not shown). Table 3 presents estimates cross-classified by periconceptional smoking status and folic acid use for birth defect types showing some evidence of an association in the main analysis. As mentioned, patterns suggesting additive interaction were not observed.

When separate analyses of total dietary caffeine were conducted for infants with isolated defects, risk estimates were similar to those for all case infants with only a few exceptions. Adjusted ORs were closer to the null for the association between dietary caffeine and isolated omphalocele and there was no longer a statistically significant aOR for soda and esophageal atresia. The risk estimates for isolated defects are provided in the supplementary material at: http://www.interscience.wiley.com/.../. Statistically significant estimates were observed for the corresponding associations among infants with multiple defects (data not shown). The aORs were 1.77 (95% CI, 1.18–2.65) for the association between the highest category of caffeinated soda and esophageal atresia and 2.70 (95% CI, 1.18–6.20) for the association between 200 to <300 mg caffeine/day and omphalocele. For some birth defect types, there were too few infants with multiple defects to permit calculation of estimates for all exposure categories.

Total dietary caffeine, coffee, tea, soda, and caffeine-containing medication analyses were repeated excluding multiple gestations and infants with family history of a first-degree relative with the same defect (among both case infants and control infants for each birth defect in the study; data not shown). Results were similar to those for the main analysis.

A total of 112 risk estimates were generated for the main analysis of dietary caffeine, coffee, tea, soda, and caffeine-containing medications. Approximately six statistically significant associations would be expected by chance alone based on a 5% type I error rate and we observed seven; all seven were increased aORs.

DISCUSSION

Overall, we did not find evidence of an association between maternal dietary caffeine consumption and the birth defects included in this study. No dose-response relation was apparent for any birth defect studied. Small statistically significant elevations in effect estimates were observed for total caffeine or specific types of caffeinated beverages and anotia/microtia, esophageal atresia, small intestinal atresia, and craniosynostosis. The small numbers and less precise estimates for some strata of high dietary caffeine intake could have contributed to the lack of dose-response we observed. Alternatively, some of the positive

findings may have been due to chance. Periconceptional use of caffeine-containing medications was infrequent and estimates were imprecise.

Our assessment of caffeine exposure allowed us to assess birth defect risk estimates across low to high levels of caffeine intake. Some caffeinated beverages contain other components that may have health effects, including sugar, flavonoids, and other antioxidants, complicating evaluation of risks due to caffeine. We were able to examine different caffeinated beverages and caffeine-containing medications to evaluate differences between sources of caffeine exposure. In addition, we were able to evaluate effect modification for maternal cigarette smoking, alcohol use, vasoconstrictive medications, folic acid-containing supplements, and infant sex.

Our findings should be considered in light of the limitations and strengths of this study. The results of our study may have been influenced by misclassification of caffeine exposure estimated through maternal self-reporting. Variations in portion size and in the caffeine content of caffeinated beverages, and changes in consumption patterns during pregnancy may have contributed to exposure misclassification. In the NBDPS, women are asked to report their usual consumption of caffeinated beverages and chocolate during the year prior to pregnancy to capture intake very early in pregnancy, before pregnancy recognition and pregnancy-related aversions or nausea. Study mothers were also asked whether they drank more, the same, less, or no caffeinated coffee, tea, and soda when they were pregnant. Among mothers reporting a pre-pregnancy average intake of one or more servings per day, 16%, 35%, and 25% reported the same or more caffeinated coffee, tea, and soda, respectively, during pregnancy. Thus, the majority of ‘‘regular’’ drinkers of caffeinated beverages reduced their intake during pregnancy. Data were not collected on the timing of any changes in intake; however, 51% of those reporting regular intake of at least one caffeinated beverage did not find out that they were pregnant until the second month of pregnancy or later. For some women, the change probably occurred after the beginning of organogenesis given that the onset of pregnancy symptoms including aversions and nausea is about six to seven weeks after the last menstrual period (Lacroix et al., 2000; Bayley et al., 2002). The higher proportion of mothers reporting less or no coffee consumption during pregnancy is consistent with reports that show that pregnancy-related taste aversion to coffee is common (Lawson et al., 2002). Establishing exposure using pre-pregnancy caffeine intake is most appropriate for birth defects for which the critical period of development begins within the first month postconception. However, the critical period for some of the birth defects in this study, such as craniosynostosis may be later. In addition, some women who planned their pregnancies or who experienced very early pregnancy-related symptoms may have changed their consumption before the start of organogenesis.

Caffeine-containing energy drinks started to gain popularity during the last several years of the study period. The NBDPS interview asks about ‘‘sodas or soft drinks’’ but does not ask about caffeine-containing energy drinks in particular. Intake of caffeine-containing energy drinks may not have been completely captured, contributing to misclassification of exposure.

Compared to our assessment of dietary caffeine intake, we had better information on timing of use for caffeine-containing medications and observed aORs of 1.6 to 2.6 between

periconceptional use of medications containing ≥100 mg per dose and most of the birth defects examined. However, associations between medication use and birth defects could reflect the indication for medication use or other medications taken concurrently, which we did not explore in this study.

Since extended time-to-interview could contribute to errors in reporting exposures, we conducted an analysis restricted to interviews within 12 months of the subject's EDD. Risk estimates were similar to those for the main analysis, suggesting that intervals of 13 to 24 months between the EDD and the interview did not tend to affect our findings.

Although our study included over 200 case infants for each type of birth defect, there were small numbers in some strata of high dietary caffeine intake, for analysis of caffeine-containing medications, and for analysis of additive interaction. Given the number of birth defects examined and the number of caffeine measures and levels of exposure analyzed, some of the positive associations observed may be chance findings.

The strengths of our study include the clinically well-characterized, homogenous case groups. The overall study design excluded case infants with known chromosomal or single-gene defects, which can increase homogeneity and improve the opportunity to identify risk factors. Clinical geneticists' classification of case infants using pathogenetically uniform case definitions (Rasmussen et al., 2003) is a strength of the NBDPS. The NBDPS provides access to large sample sizes for most types of birth defects and standardized interviews reduce bias. Case and control mothers are asked to remember their exposures in a similar way. Although recall bias is always a concern in case-control studies, given the mostly negative findings of this study, we do not believe it substantially affected our risk estimates for maternal exposure to dietary caffeine.

Only two previous epidemiologic studies have examined the relationship between maternal consumption of caffeine or caffeinated beverages and the risks of the types of birth defects included in this study. In agreement with Werler et al. (1992), we did not find an association between caffeinated coffee and risk of gastroschisis. We did not observe a protective effect for tea consumption and microtia as was reported in the abstract of a Chinese language report by Du et al. (2006), however, the type of tea consumed, study population risk factors, and study design considerations may account for the discrepancy in these results. A previous study found that the effects of some risk factors for gastroschisis varied by maternal age (Werler et al., 2009). In our study, the aORs for total caffeine intake of 300+ mg/day and gastroschisis increased as maternal age increased but did not achieve statistical significance. This increase in the aORs may simply represent ‘‘modification by baseline risk’’ (Rothman et al., 2008). Any effect of caffeine might be independent of maternal age but could be overshadowed by the high baseline risk (of unknown cause) among younger women. The findings of previous research led us to hypothesize that caffeine might act as a teratogen only in combination with other exposures (additive interaction). Our study does not provide evidence that caffeine potentiates a teratogenic effect of alcohol or vasoconstrictive medications. Nor did we observe a sex-specific effect or effect modification by maternal smoking or use of folic acid-containing supplements.

CONCLUSION

In summary, we observed relatively small elevations in effect estimates for total dietary caffeine or specific types of caffeinated beverages and anotia/microtia, esophageal atresia, small intestinal atresia, and craniosynostosis; however, dose-response patterns were absent. Periconceptional use of caffeine-containing medications was infrequent and estimates were imprecise. Thus, we did not find convincing evidence of an association between maternal caffeine consumption and the birth defects included in this study. The increasing popularity of caffeine-containing energy drinks and other caffeinated products may result in higher caffeine intake among women of childbearing age. Future studies should consider more detailed evaluation of such products.

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Table 1

Selected Characteristics of Mothers of Nonmalformed Control Infants and Mothers of Infants with Selected Birth Defects, National Birth Defects Prevention Study, 1997 to 2005 *

	Controls N = 6642		Anotia/microtia N = 403		Esophageal atresia N = 430		Small intestinal atresia N = 266		Craniosynostosis N = 797		Diaphragmatic hernia N = 497		Omphalocele N = 255		Gastroschisis N = 723	
	N†	%	N†	%	N†	%	N†	%	N†	%	N†	%	N†	%	N†	%
Age (years)																
12–19	703	10.6	46	11.4	38	8.8	36	13.5	38	4.8	47	9.5	24	9.4	285	39.4
20–24	1514	22.8	95	23.6	85	19.8	70	26.3	135	16.9	107	21.5	67	26.3	292	40.4
25–29	1760	26.5	109	27.1	104	24.2	61	22.9	215	27.0	139	28.0	56	22.0	95	13.1
30–34	1733	26.1	90	22.3	120	27.9	50	18.8	245	30.7	127	25.6	57	22.4	41	5.7
35+	932	14.0	63	15.6	83	19.3	49	18.4	164	20.6	77	15.5	51	20.0	10	1.4
Race/ethnicity																
White non-Hispanic	3969	60.0	151	37.8	299	69.5	127	47.7	595	74.8	306	61.9	150	58.8	388	53.7
Black non-Hispanic	752	11.4	11	2.8	16	3.7	38	14.3	35	4.4	41	8.3	39	15.3	54	7.5
Hispanic	1480	22.4	210	52.5	84	19.5	82	30.8	134	16.8	112	22.7	46	18.0	217	30.1
Other	412	6.2	28	7.0	31	7.2	19	7.1	32	4.0	35	7.1	20	7.8	63	8.7
Education (grade)																
<12	1110	16.8	120	29.9	64	14.9	64	24.2	90	11.3	78	15.8	35	13.8	220	30.7
12	1630	24.6	100	24.9	92	21.4	74	27.9	186	23.4	120	24.3	76	29.9	277	38.7
12+	3878	58.6	181	45.1	274	63.7	127	47.9	520	65.3	296	59.9	143	56.3	219	30.6
Parity																
0	2668	40.2	155	38.5	240	55.8	108	40.6	285	35.8	228	45.9	142	55.7	478	66.1
1 or more	3973	59.8	248	61.5	190	44.2	158	59.4	511	64.2	269	54.1	113	44.3	245	33.9
Prepregnancy BMI																
<18.5	355	5.6	20	5.5	20	4.9	19	7.5	38	4.9	22	4.6	12	4.9	62	8.8
18.5–<25	3568	55.9	202	56.0	239	58.3	130	51.2	407	52.2	271	56.8	120	49.0	502	70.9
25–<30	1436	22.5	74	20.5	82	20.0	55	21.7	197	25.3	94	19.7	58	23.7	111	15.7
30+	1021	16.0	65	18.0	69	16.8	50	19.7	138	17.7	90	18.9	55	22.5	33	4.7
Smoking‡																
No	5385	81.1	336	83.4	351	81.6	204	76.7	652	81.8	396	79.7	204	80.3	456	63.2

	Controls N = 6642		Anotia/microtia N = 403		Esophageal atresia N = 430		Small intestinal atresia N = 266		Craniosynostosis N = 797		Diaphragmatic hernia N = 497		Omphalocele N = 255		Gastroschisis N = 723	
	N[†]	%	N[†]	%	N[†]	%	N[†]	%	N[†]	%	N[†]	%	N[†]	%	N[†]	%
Yes	1253	18.9	67	16.6	79	18.4	62	23.3	145	18.2	101	20.3	50	19.7	266	36.8
Alcohol (max per occasion)[‡]																
0	4161	63.2	265	66.1	240	56.3	185	70.3	499	62.9	321	64.9	137	53.9	426	59.9
1–3	1615	24.5	92	22.9	138	32.4	47	17.9	197	24.8	114	23.0	74	29.1	134	18.9
4+	804	12.2	44	11.0	48	11.3	31	11.8	97	12.2	60	12.1	43	16.9	151	21.2
Folic acid-supplement use																
No	3074	46.9	237	59.3	175	41.1	138	52.3	307	39.1	229	46.8	119	46.7	434	61.2
Yes[§]	3477	53.1	163	40.8	251	58.9	126	47.7	478	60.9	260	53.2	136	53.3	275	38.8

BMI, body mass index (weight in kg/height in m^2).

[*] Women with pre-existing diabetes or missing information about dietary caffeine consumption were excluded from this analysis.

[†] Numbers vary due to missing values.

[‡] During the period from one month pre-pregnancy through the third month of pregnancy.

[§] Yes = any use one month pre-pregnancy through the first month of pregnancy.

Table 2

Adjusted Odds Ratios for Associations between Maternal Caffeine Consumption and Selected Birth Defects, National Birth Defects Prevention Study, 1997 to 2005

	Controls	Anotia/Microtia		Esophageal Atresia		Small Intestinal Atresia		Craniosynostosis		Diaphragmatic Hernia		Omphalocele		Gastroschisis	
Source of caffeine	**N***	**N**	**aOR† (CI)**	**N**	**aOR†,‡ (CI)**	**N**	**aOR†,§ (CI)**	**N**	**aOR† (CI)**	**N**	**aOR† (CI)**	**N**	**aOR†,‖ (CI)**	**N**	**aOR†,¶ (CI)**
Total caffeine (mg/day)															
<10	1146	66	1.0	67	1.0	32	1.0	133	1.0	80	1.0	34	1.0	104	1.0
10–<100	2391	133	0.94 (0.69–1.28)	145	1.12 (0.83–1.53)	100	1.54 (1.02–2.33)	264	1.10 (0.87–1.38)	176	1.07 (0.81–1.41)	82	1.15 (0.76–1.74)	260	1.01 (0.78–1.31)
100–<200	1521	99	1.09 (0.78–1.51)	111	1.22 (0.88–1.68)	63	1.55 (0.99–2.41)	204	1.26 (0.99–1.61)	123	1.16 (0.86–1.56)	58	1.30 (0.83–2.02)	175	1.24 (0.93–1.64)
200–<300	834	56	1.24 (0.85–1.81)	62	1.18 (0.82–1.71)	39	1.79 (1.09–2.93)	85	0.90 (0.67–1.21)	65	1.10 (0.78–1.56)	40	1.51 (0.93–2.44)	77	0.98 (0.69–1.38)
300+	721	46	1.36 (0.91–2.04)	45	1.01 (0.68–1.51)	29	1.53 (0.89–2.64)	110	1.34 (1.01–1.77)	50	1.00 (0.69–1.45)	30	1.28 (0.76–2.16)	90	1.26 (0.90–1.78)
Coffee															
0–<1/month	3662	181	1.0	224	1.0	130	1.0	443	1.0	269	1.0	127	1.0	429	1.0
1/month – 6/weeks	927	71	1.31 (0.97–1.75)	67	1.16 (0.87–1.55)	43	1.26 (0.88–1.80)	97	0.92 (0.73–1.17)	76	1.09 (0.83–1.42)	29	0.91 (0.60–1.38)	109	1.01 (0.79–1.29)
1/day	958	77	1.34 (1.00–1.78)	65	0.95 (0.71–1.28)	39	1.11 (0.76–1.62)	115	0.95 (0.76–1.20)	80	1.09 (0.83–1.42)	41	1.29 (0.89–1.88)	74	0.95 (0.72–1.27)
2/day	597	39	1.33 (0.92–1.93)	42	0.93 (0.65–1.33)	32	1.62 (1.06–2.46)	67	0.80 (0.60–1.06)	40	0.86 (0.60–1.22)	29	1.35 (0.87–2.08)	49	1.05 (0.74–1.48)
3+/day	469	32	1.60 (1.07–2.41)	32	0.91 (0.61–1.35)	19	1.16 (0.68–1.95)	74	1.14 (0.87–1.50)	29	0.81 (0.54–1.21)	18	1.01 (0.60–1.71)	45	1.21 (0.84–1.75)
Tea															
0–<1/month	3564	233	1.0	247	1.0	135	1.0	460	1.0	251	1.0	120	1.0	387	1.0
1/mo. – 6/weeks	1836	102	0.90 (0.70–1.15)	111	0.94 (0.74–1.19)	76	1.12 (0.83–1.50)	186	0.94 (0.78–1.13)	143	1.15 (0.92–1.43)	73	1.07 (0.79–1.46)	201	0.98 (0.80–1.20)
1–2/day	937	49	0.86 (0.62–1.19)	54	0.81 (0.59–1.11)	37	1.07 (0.73–1.56)	106	1.01 (0.80–1.28)	74	1.14 (0.87–1.51)	35	1.01 (0.68–1.50)	77	0.76 (0.58–1.01)
3+/day	276	16	1.15 (0.67–1.99)	18	0.95 (0.57–1.59)	15	1.55 (0.87–2.75)	44	1.37 (0.96–1.94)	26	1.39 (0.90–2.14)	16	1.52 (0.87–2.66)	41	1.00 (0.68–1.48)
Soda **															
0	2189	127	1.0	134	1.0	78	1.0	282	1.0	166	1.0	83	1.0	167	1.0
<1/day	1733	100	0.88 (0.66–1.16)	115	1.21 (0.93–1.58)	70	1.17 (0.84–1.64)	207	0.97 (0.80–1.19)	117	0.89 (0.69–1.14)	64	0.98 (0.70–1.38)	185	1.14 (0.90–1.45)
1–2/day	1736	116	1.08 (0.82–1.41)	112	1.20 (0.91–1.57)	74	1.22 (0.87–1.71)	179	0.85 (0.70–1.05)	134	1.03 (0.80–1.31)	59	0.88 (0.62–1.26)	195	1.09 (0.86–1.39)
3+/day	955	57	1.14 (0.81–1.61)	69	1.43 (1.04–1.98)	41	1.24 (0.82–1.87)	128	1.15 (0.91–1.46)	77	1.11 (0.83–1.50)	38	1.01 (0.67–1.53)	159	1.21 (0.93–1.58)
Medication ††															
None	6514	392	1.0	421	1.0	261	1.0	781	1.0	485	1.0	236	1.0	692	1.0
<100 mg	23	1	0.82 (0.11–6.28)	2	1.46 (0.34–6.32)	1	1.44 (0.19–10.86)	1	0.26 (0.03–1.95)	1	0.62 (0.08–4.63)	2	2.34 (0.54–10.2)	3	1.60 (0.40–6.35)
≤100 mg	43	5	2.60 (1.00–6.73)	7	2.33 (1.03–5.28)	1	0.63 (0.09–4.65)	9	1.67 (0.80–3.49)	6	1.81 (0.76–4.30)	4	2.45 (0.86–7.01)	7	1.61 (0.66–3.91)

[*] N's for analyses adjusted for maternal age, race, and state of residence at time of infant's birth; N's for analyses with additional covariates may be slightly lower due to missing values for those variables.

[†] All odds ratios are adjusted for maternal age, race, and state of residence at time of infant's birth; medication estimates are also adjusted for intake of coffee, tea, and soda.

[‡] Adjusted for maternal fertility treatment.

[§] Adjusted for maternal alcohol consumption and smoking status.

[‖] Adjusted for maternal alcohol consumption and body mass index.

[¶] Adjusted for maternal smoking status and body mass index.

[**] Milligrams of caffeine per day from soft drinks were converted into frequencies based on the following amounts per serving: <34 mg = <1 serving, 34– <102 mg = 1–2 servings, 102+ mg = 3+ servings.

[††] Caffeine per dose based on usual dose for each medication (does not account for actual number of doses taken per day). aOR, adjusted odds ratio; CI, confidence interval.

Table 3

Maternal Caffeine Consumption and Risk of Selected Birth Defects, Overall and Cross-Classified by Potential Effect Modifiers, National Birth Defects Prevention Study, 1997 to 2005

	Controls	Anotia/microtia		Small intestinal atresia		Craniosynostosis		Omphalocele		Gastroschisis	
Caffeine intake category	**N***	**N**	**aOR† (CI)**	**N**	**aOR†,‡ (CI)**	**N**	**aOR†,§ (CI)**	**N**	**aOR† (CI)**	**N**	**aOR†,‖ (CI)**
Nonsmokers											
<10 mg/day	1079	60	1.0	31	1.0	122	1.0	33	1.0	86	1.0
10–<100 mg/day	2079	122	1.00 (0.72–1.39)	84	1.46 (0.96–2.24)	243	1.19 (0.94–1.51)	70	1.10 (0.71–1.68)	179	1.00 (0.75–1.33)
100–<200 mg/day	1226	83	1.12 (0.79–1.59)	42	1.26 (0.78–2.04)	163	1.28 (0.99–1.66)	43	1.15 (0.72–1.85)	107	1.30 (0.94–1.79)
200–<300 mg/day	600	42	1.27 (0.83–1.94)	31	2.01 (1.19–3.39)	58	0.85 (0.61–1.20)	31	1.56 (0.93–2.62)	37	1.04 (0.68–1.59)
300+ mg/day	376	27	1.38 (0.85–2.25)	15	1.64 (0.86–3.12)	66	1.57 (1.12–2.18)	18	1.39 (0.76–2.54)	32	1.59 (1.00–2.52)
Smokers											
<10 mg/day	67	6	1.99 (0.81–4.92)	1	0.57 (0.08–4.27)	11	1.81 (0.91–3.57)	1	0.36 (0.05–2.72)	18	2.23 (1.20–4.14)
10–<100 mg/day	311	11	0.87 (0.45–1.71)	16	2.20 (1.16–4.19)	21	0.79 (0.48–1.29)	12	1.03 (0.51–2.08)	81	2.14 (1.49–3.07)
100–<200 mg/day	293	16	1.28 (0.71–2.30)	21	3.27 (1.80–5.94)	41	1.47 (1.00–2.18)	15	1.49 (0.78–2.88)	68	2.26 (1.54–3.31)
200–<300 mg/day	234	14	1.40 (0.75–2.59)	8	1.55 (0.69–3.47)	27	1.17 (0.74–1.84)	9	1.09 (0.50–2.37)	40	1.80 (1.16–2.80)
300+ mg/day	344	19	1.52 (0.87–2.64)	14	1.89 (0.97–3.69)	44	1.19 (0.81–1.73)	12	1.01 (0.50–2.04)	58	2.15 (1.45–3.20)
Folic Acid											
<10 mg/day	647	30	1.0	21	1.0	87	1.0	20	1.0	31	1.0
10–<100 mg/day	1189	54	1.04 (0.65–1.67)	45	1.23 (0.72–2.09)	154	1.10 (0.82–1.46)	44	1.20 (0.70–2.07)	103	1.57 (1.01–2.44)
100–<200 mg/day	789	32	0.91 (0.54–1.53)	25	1.01 (0.56–1.85)	125	1.35 (0.99–1.83)	30	1.26 (0.70–2.27)	60	1.62 (1.00–2.63)
200–<300 mg/day	448	22	1.16 (0.65–2.07)	19	1.41 (0.73–2.69)	51	0.90 (0.62–1.31)	23	1.56 (0.83–2.93)	31	1.57 (0.90–2.75)
300+ mg/day	388	23	1.52 (0.85–2.70)	15	1.17 (0.58–2.35)	61	1.27 (0.88–1.82)	17	1.31 (0.67–2.59)	46	2.24 (1.33–3.79)
No Folic Acid											
<10 mg/day	477	36	1.34 (0.80–2.24)	11	0.57 (0.27–1.20)	42	0.96 (0.65–1.43)	14	0.98 (0.48–1.99)	72	1.96 (1.22–3.16)
10–<100 mg/day	1187	78	1.10 (0.70–1.73)	55	1.18 (0.69–2.01)	106	1.08 (0.78–1.48)	38	1.05 (0.59–1.85)	155	1.51 (0.98–2.33)
100–<200 mg/day	713	67	1.53 (0.96–2.44)	37	1.36 (0.77–2.40)	75	1.13 (0.80–1.59)	28	1.30 (0.71–2.37)	109	1.96 (1.25–3.09)
200–<300 mg/day	371	32	1.58 (0.92–2.69)	20	1.41 (0.74–2.70)	34	0.94 (0.61–1.45)	17	1.41 (0.72–2.77)	43	1.40 (0.83–2.36)
300+ mg/day	315	23	1.60 (0.90–2.86)	13	1.17 (0.56–2.45)	49	1.52 (1.03–2.24)	13	1.25 (0.60–2.60)	44	1.83 (1.07–3.11)

*N's for analyses adjusted for maternal age, race, and state of residence at time of infant's birth; N's for analyses with additional covariates may be slightly lower due to missing values for those variables.

† All odds ratios are adjusted for maternal age, race, and state of residence at time of infant's birth; medication estimates are also adjusted for intake of coffee, tea, and soda.

‡ Adjusted for maternal alcohol consumption and smoking status.

§ Adjusted for maternal alcohol consumption and body mass index.

‖ Adjusted for maternal smoking status and body mass index.

Nonsmokers reporting little or no caffeine intake and those reporting use of folic acid-containing supplements during the month before pregnancy or the first pregnancy month and little or no caffeine intake comprise the referent group for all other strata cross-classified by exposure to caffeine and smoking/folic acid-containing supplement use, respectively.

aOR, adjusted odds ratio, CI, 95% confidence interval.