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Maternal Caffeine Consumption and Risk of Congenital Limb Deficiencies

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Abstract

BACKGROUND—Animal studies have shown that high doses of caffeine might cause congenital limb deficiencies (LDs); however, no epidemiologic studies have explored this relation.

METHODS—This case-control study assessed associations between maternal dietary caffeine and congenital LDs using data from the National Birth Defects Prevention Study (NBDPS), with 844 LD cases and 8069 controls from 1997 to 2007. Caffeine intakes from beverages (coffee, tea, and soda) and chocolate combined and by beverage type were examined. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated for subtypes of isolated LDs (no additional major anomalies) and LDs with other major anomalies separately, comparing the odds of 10 to <100, 100 to <200, 200 to <300, and 300+ mg/day total caffeine intake to 0 to <10 mg/day.

RESULTS—All total dietary caffeine intake categories of 10 mg/day and above were marginally associated with odds of all isolated LDs combined (aOR, 1.4–1.7), isolated longitudinal LDs (aOR, 1.2–1.6), and isolated transverse LDs (aOR, 1.3–1.8) compared to the lowest intake category. A dose-response pattern for total dietary caffeine intake was not observed.

CONCLUSIONS—A weak increased risk of congenital LDs associated with maternal dietary caffeine consumption was observed in this study; however, risk did not vary by amount of caffeine consumed.

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Keywords

caffeine; coffee; tea; soda; congenital limb deficiencies

INTRODUCTION

Pregnant women in the United States are widely exposed to caffeine from consumption of coffee, soda, tea, and chocolate (Knight et al., 2004; Frary et al., 2005). Dietary caffeine is absorbed by the gastrointestinal tract and reaches almost all tissues of the body within 45 minutes (Marks and Kelly, 1973). In healthy adult women, the half-life of caffeine is about 2 to 6 hours (Patwardhan et al., 1980; Charles et al., 2008), which may be increased to 11 hours among those taking oral contraceptives (Patwardhan et al., 1980) or who are pregnant (Knutti et al., 1982). Also, caffeine crosses the placenta but the enzymes necessary to metabolize caffeine are absent in the fetus until several days after birth (Weathersbee and Lodge, 1977).

In addition, animal models have shown a teratogenic effect of maternal caffeine intake at high doses (Fujii et al., 1969; Nishimura and Nakai, 1960; Scott, 1983). Limb deficiencies (LDs), along with cleft palate, and neural tube defects (NTDs) are among the most frequent congenital malformations induced in animals by caffeine doses of 100 to 200 mg/kg (Fujii et al., 1969; Scott, 1983; Moriguchi and Scott, 1986). Synergistic teratogenic effects of subteratogenic doses of caffeine with certain agents, such as acetazolamide, treatment for glaucoma, and seizures (Ritter et al., 1982; Beck and Urbano, 1991), or mitomycin C, a hemotherapeutic agent (Fujii and Nakatsuka, 1983), have been observed in rodents.

In adult humans, caffeine intake has been associated with increased plasma cholesterol and homocysteine levels. Increased maternal plasma cholesterol level may be related to development of congenital vascular disease (Manderson et al., 2002), and increased maternal homocysteine level has been associated with congenital heart defects (Wenstrom et al., 2001) and NTDs (Mills et al., 1995). Although the literature has generally indicated that dietary caffeine is likely to be a weak teratogen at most for humans (Nelson and Forfar, 1971; Fedrick, 1974; Aro et al., 1982; Linn et al., 1982; Rosenberg et al., 1982; Kurppa et al., 1983; Furuhashi et al., 1985; Adams et al., 1989; Tikkanen and Heinonen, 1990; Olsen et al., 1991; Tikkanen and Heinonen, 1991; McDonald et al., 1992; Tikkanen and Heinonen, 1992a; Tikkanen and Heinonen, 1992b; Werler et al., 1992; Ferencz et al., 1993; Tikkanen and Heinonen, 1994; Fixler and Threlkeld, 1998; Samrén et al., 1999; Torfs and Christianson, 1999; Torfs and Christianson, 2000; Browne, 2006; Browne et al., 2007; Miller, 2008; Mongraw–Chaffin et al., 2008; Collier et al., 2009; Schmidt et al., 2009), considering the common use of caffeine by pregnant women, a slight risk elevation could have a significant impact at the population level. Given that LDs are the most frequent malformations induced by caffeine exposure in some animal studies (Fujii et al., 1969; Scott, 1983; Moriguchi and Scott, 1986) and that this relationship between LDs and maternal caffeine consumption has not been examined in humans, the current study explored the association between maternal caffeine consumption and LDs.

Lumping etiologically different groups of malformations together (Nelson and Forfar, 1971; Linn et al., 1982; Olsen et al., 1991) or into broad categories (Rosenberg et al., 1982; Kurppa et al., 1983; Furuhashi et al., 1985; McDonald et al., 1992; Samrén et al., 1999; Torfs and Christianson, 1999; Natsume et al., 2000) may have obscured identification of positive associations for a specific defect group. In addition, many studies assessed the dietary caffeine intake only from coffee and tea consumption.

This study attempts to address these limitations by measuring maternal caffeine intake from caffeinated coffee, tea, soda, and chocolate and by exploring the effect of caffeine exposure on the etiologically different subtypes of LDs using the National Birth Defects Prevention Study (NBDPS) data. Analyses previously conducted using NBPDS data examined associations between maternal dietary caffeine consumption and congenital heart defects (Browne et al., 2007), orofacial defects (Collier et al., 2009), NTDs (Schmidt et al., 2009), anorectal atresia (Miller et al., 2009), and bilateral renal agenesis or hypoplasia (Slickers et al., 2008), as well as other birth defect groups (Browne et al., 2011). The accumulated number of cases from NBDPS is now sufficient to examine subtypes of LDs. Potential effect modification by maternal smoking, alcohol consumption, and use of vasoconstrictive medication was also evaluated.

MATERIALS AND METHODS

Study Population

The study population included participants in the NBDPS with estimated date of delivery (EDD) from October 1997 through December 2007. The NBDPS is an ongoing multisite, population-based case-control study of infants with one or more of 37 different types of major structural defects, excluding infants with defects attributed to a known chromosomal or single-gene abnormality (Yoon et al., 2001). Cases are identified by the existing birth defect surveillance system of each participating site (Arkansas, California, Georgia [CDC], Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) and must have been diagnosed with at least one major, eligible birth defect within the first year of life, as described elsewhere (Rasmussen et al., 2003). Live births were included in all study sites throughout the study period. Fetal deaths and elective terminations were recorded by some sites during the whole or part of the study period. Details are described elsewhere (State birth defects surveillance program directly, 2000; State birth defects surveillance program directory, 2007). Controls were live born infants without birth defects randomly selected from birth certificates (Iowa, Massachusetts, New Jersey, North Carolina, and Utah) or hospitals (California, New York, and Texas) (Cogswell et al., 2009) from the same time period and geographic region as case infants. Participation rates for limb deficiency cases and control infants were 69% and 65%, respectively.

The current analysis included case infants (live births from 10 study sites, stillbirths from 9 study sites, and elected terminations from 6 study sites) with a diagnosis of an LD. Eligible LDs were (1) absent or partially absent bony elements of the extremities, diagnosed by radiography or reliable physical examination or (2) diagnoses of split hand/split foot if there was a ‘‘deep cleft’’ in the hand or foot. Ineligible LD diagnoses were: (1) generalized limb shortening without confirmation or absent bones; (2) brachydactyly types A–E; (3) known

or strongly suspected single gene conditions or chromosome abnormalities; (4) unconfirmed LD diagnoses; (5) deficiencies related to twinning such as acephalus-acardia; (6) sirenomelia; and (7) limb-body wall and amniotic band phenotypes.

Because LDs are often associated with other birth defects (Sadler, 2009) and the presence of additional defects might reflect the underlying mechanism(s) of a teratogen (Holmes, 2002), the study included LD cases with and without an additional major nonlimb anomaly. Case deliveries were classified as an isolated LD if they had no major nonlimb anomaly (Rasmussen et al., 2003), although an isolated LD case could have a defect in more than one limb. Cases with one or more major unrelated nonlimb anomalies were classified as a multiple congenital anomaly (MCA) cases with LDs. The multivariable analysis was conducted separately for isolated LD cases and MCA LD cases. The subtypes of the eligible LDs were longitudinal LDs, transverse LDs, intercalary LDs, and not otherwise specified LDs. Longitudinal LDs include two major subtypes, preaxial longitudinal LDs and postaxial longitudinal LDs. Preaxial LDs have a higher prevalence than postaxial LDs, and the two subtypes might have different etiologies (Holmes, 2011). With adequate number of cases, our analysis was able to include preaxial LD subtype as a separate case group. The analysis only included subtypes with 100 or more cases.

Exclusion Criteria

Information on maternal caffeine exposure from dietary sources and medication, as well as maternal demographic characteristics and health history was collected using a maternal telephone interview administered in English or Spanish language. Case and control mothers who did not speak English or Spanish were excluded. Interviews were completed between 6 weeks and 24 months after EDD of the LD case or control infant.

Maternal type 1 or type 2 diabetes is a known risk factor for many birth defects, including LDs (Aberg et al., 2001). Because very small percentages of mothers (3.0% of case mothers and 0.6% of control mothers) were diagnosed with type 1 or type 2 diabetes before pregnancy, births with maternal history of type 1 or type 2 diabetes diagnosed before conception were excluded from the analysis. Infants whose mother had chorionic villus sampling during pregnancy were also excluded because this procedure has been associated with an increased risk for LDs (Holmes, 2002) (3.8% of case mothers and 2.8% of control mothers).

Exposure Assignment

Total dietary caffeine intake was defined as the sum of the estimated average daily intake of caffeine from caffeinated coffee, non-herbal tea, soda, and chocolate during the year before the index pregnancy. For coffee and tea, mothers were asked ‘How many cups of caffeinated or regular (coffee/tea) did you usually drink?’ Information was not collected on consumption of decaffeinated coffee or tea. For soda consumption, mothers were asked about the brands they usually drank, the frequency (per month) of consumption, and whether the soda consumed were diet or caffeine free. Mothers were also asked if the consumption of coffee, tea, or soda increased, decreased, or maintained the same during pregnancy

compared to their reported consumption during the year before pregnancy. Caffeine intake was examined from all sources combined and for each beverage type separately.

The caffeine contents assignment was based on previous literature (Bracken et al., 2002; Browne et al., 2007; Schmidt et al., 2009). The study used the estimate from Bracken (Bracken et al., 2002) of 100 mg caffeine for a cup of coffee and 37 mg caffeine for each cup of tea. Brand-specific caffeine contents for soda were based on the caffeine content per 12 ounce serving obtained from soda manufacturers (Schmidt, 2007; Schmidt et al., 2009). An average value of 37 mg was assigned to caffeinated soda for which caffeine was an ingredient but the amount could not be determined, based on a review of manufacturers provided information (Schmidt, 2007). A weighted average of 10 mg per ounce was used for chocolate (National Confectioners Association, 2009).

Consistent with previous literature (Browne et al., 2011; Collier et al., 2009; Schmidt et al., 2009), total caffeine consumption was classified as <10 mg/day, 10 to <100 mg/day, 100 to <200 mg/day, 200 to <300 mg/ day, and ≥300 mg/day. Coffee consumption was classified as <1 cup/month, 1 cup/month to 6 cups/week, 1 cup/day, 2 cups/day, and ≥3 cups/day for coffee consumption. Tea consumption was classified as <1 cup/ month, 1 cup/month to 6 cups/week, 1 to 2 cups/day, and ≥3 cups/day. Given that soda consumption was estimated combining reported consumption frequencies and brand-specific caffeine content, the soda consumption for the analysis was classified as 0, <34 mg/day, 34 to <102 mg/day, and ≥102 mg/day (caffeinated sodas generally contain 34+ mg of caffeine, we used 34 as the cut-point to approximate <1 servings, 1–2 servings, and 3 or more servings per day).

The lowest caffeine intake categories (0–10 mg/day for total caffeine intake, 0–<1 cup/ month for coffee consumption, 0–<1 cup/month for tea consumption, and 0–<1 12 ounce serving/month for soda consumption) were used as the reference group when evaluating the crude and adjusted associations between maternal caffeine exposure and LD.

The Slone Epidemiology Center Drug Dictionary (Slone Epidemiology Center at Boston University, Boston, MA) was used to identify caffeine-containing medications reported during the maternal interview. This source of exposure was not further analyzed as a major source of caffeine because only 1% of the study participants had maternal exposure to medications with caffeine.

Potential Confounders and Effect Modifiers

Maternal and pregnancy characteristics were examined as potential confounders and effect modifiers. Maternal characteristics examined were: age at conception (<20 years, 20–34 years, or ≥35 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), education (≤12 years or >12 years), body mass index (<18.5, 18.5–<25, or ≥25), parity (0 or ≥1 live births), initiation of prenatal care (first trimester, second trimester, or third trimester), gestational diabetes (yes or no), nausea or vomiting during the first month of pregnancy (yes or no), fever in the first trimester (yes or no), and study site. Periconceptional exposures examined for the period 1 month before pregnancy through the first trimester included: cigarette smoking (none, environmental smoking exposure only, or active smoking with or without environmental smoking exposure), smoking frequency

(none, <1 pack/day, or ≥1 pack/day), alcohol consumption (yes or no), alcohol consumption frequency (none, <1 drink/day, or ≥1 drink/day), binge drinking (no drinking, drink but not binge drinking, or ≥4 drinks/occasion), oral contraception use (yes or no), use of vasoconstrictive medicine including decongestants, ergot anti-migraine medications, amphetamines, and cocaine (yes or no), and use of folic acid-containing supplements during 1 month before pregnancy through the first month of gestation was also considered (yes or no). Illicit drug use was not analyzed separately because <1% of study participants reported any maternal use during 1 month before pregnancy through the first trimester.

Data Analysis

The study examined the association between total dietary caffeine intake and LDs, and the independent associations between coffee, tea, and soda consumption and LDs. Bivariable and stratified analyses were conducted to identify potential confounders and effect modifiers. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the associations between caffeine intake and LDs, and between maternal characteristics and LDs.

Crude caffeine-LD ORs were further stratified by selected maternal exposures, specifically smoking, alcohol, and vasoconstrictive medicines. The rationales were that smoking might modify caffeine metabolism (Parsons and Neims, 1978; Vistisen et al., 1992; Wilson, 2004), and caffeine exposure might enhance teratogenicity of substances such as nicotine, alcohol, bronchodilators, and antiseizure medication in some animal studies (Nehlig and Debry, 1994), and that limb development might be influenced through vascular disruption (Van Allen, 1981). Additive interactions (risk-difference modification) were assessed using relative excess risk due to interaction (RERI) described by Rothman et al. (2008). The statistical test of RERI used the bootstrapping method developed by Knol et al. (2011).

Logistic regression models were computed to estimate ORs and 95% CIs for the association between LDs and maternal caffeine intake. Separate logistic regression models were estimated for each LD subtype with total maternal dietary caffeine intake, and for each combination of LD subtype and intake of coffee, tea, or soda. Model building started from a full model containing all the potential confounders identified from the bivariable analysis. If removing a variable resulted in a <10% change in caffeine exposure effect, and if the removal did not change the model fit significantly by the log-likelihood ratio test (Akaike, 1974), the variable was removed from the model. The Hosmer and Lemeshow test was used to assess the goodness-of-fit (Hosmer and Lemeshow, 2000). The above model construction was conducted for isolated cases and MCA cases separately.

Sensitivity analyses were conducted to assess the impact of exposure misclassification using the method described by Greenland and Rothman (2008). A subanalysis was conducted restricted to those mothers who completed the interview within 12 months after the EDD of the infant to limit potential recall bias. Another subanalysis excluded the mothers taking any caffeine-contained medication to avoid the potential confounding effect of caffeine in medication. Because a substantial proportion of women decreased their consumption of coffee, tea, or soda during pregnancy, which might be related to birth planning or early recognition of pregnancy, the analysis also compared the results among mothers who had

early recognition of pregnancy, planned pregnancy, or nausea or vomiting during early pregnancy to those who did not meet these conditions. All analyses were conducted using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

During the study period, 23,306 case and 8488 control infants were enrolled in the NBDPS. Among all case infants, 920 were identified with LDs, which included 871 live births, 19 stillbirths, and 30 induced abortions. After excluding infants with amniotic band syndrome (3 cases), LD case and control infants missing maternal caffeine exposure information (11 cases and 141 controls), mothers reported to have had chorionic villus sampling procedures during the index pregnancy (35 cases and 234 controls), and mothers diagnosed with type 1 or type 2 diabetes before pregnancy (28 cases and 51 controls), 844 LD cases and 8069 control infants remained.

As shown in Table 1, the LD subtypes with the largest numbers were transverse, longitudinal, and preaxial, of which 85%, 55%, and 38% were isolated LD cases, respectively.

Table 2 presents the distribution of maternal and pregnancy characteristics of the study participants. A larger proportion of case infants were boys compared to control infants. Compared to the control mothers, a higher proportion of case mothers tended to be younger in age and not to have children before the index pregnancy, to be of Hispanic ethnicity, to have 12 years of education or less, and to be overweight or obese. Case mothers were less likely to report nausea or vomiting during the first month compared to control mothers. Fever during pregnancy, active periconceptional smoking, and vasoconstrictive medication use were more common among case mothers compared to control mothers. Alcohol drinking, including binge drinking, was less often reported among case mothers compared to control mothers. Folic acid supplement use was slightly more common among mothers of all LD subtypes, except transverse LD subtype, compared to control mothers.

Among all eligible control mothers, 97% (n = 7806) reported caffeine consumption, with a mean intake of 129.4 mg/day. Of those control mothers who reported caffeine consumption, 47% reported coffee consumption, 48% reported tea consumption, and 68% reported soda consumption, with mean caffeine intakes of 139.5 mg/day, 34.0 mg/day, and 64.7 mg/day, respectively. Among mothers of infants with LDs, 96% consumed dietary caffeine (data not shown).

The associations between maternal caffeine consumption and odds of each LD subtype were adjusted for 0, 1, or 2 confounders, depending on the subtype. Including all three beverage types together produced very similar results to the models with individual beverages, indicating that exposure sources did not act as confounders to each other. Therefore, the final models presented only included the individual beverage type of interest. No covariables were adjusted for in the final model of isolated longitudinal LDs, for which crude ORs were reported. ORs are presented in Table 3 by LD subtype for isolated cases and in Table 4 for MCA LD cases for total dietary caffeine, coffee, tea, and soda consumption.

Increased odds for all isolated LDs combined and for isolated transverse LDs were observed for all total dietary caffeine intake categories compared to the referent category (Table 3). ORs were weakly to moderately elevated for all total daily dietary caffeine categories and isolated longitudinal LDs. Odds of isolated preaxial LDs were not associated with any caffeine consumption category compared to the no to low consumption category. No pattern of dose response was observed for any isolated LD subtype.

Coffee and tea consumptions were not associated with increased odds of any isolated LD subtype (Table 3). Tea consumption at 1 cup/month to 6 cups/week and 1 to 2 cups/day were inversely related to the odds of isolated longitudinal LDs (adjusted odds ratios [ORs], 0.6). Soda consumption was moderately associated with all isolated LDs (aORs, 1.2–1.4). The OR was marginally statistically significantly elevated for the association between isolated longitudinal LDs (aOR, 1.6; 95% CI, 1.0–2.5) and three or more servings of soda per day.

None of the MCA LD subtypes were associated with total caffeine, coffee, or tea consumption, except that consumption of 1 or 2 cups of coffee per day was marginally associated with decreased odds of MCA with longitudinal LDs and 1 cup per day was marginally associated with MCA with preaxial LDs compared to the referent (Table 4).

Odds of MCA with longitudinal LDs and MCA with preaxial LDs were elevated with soda consumption of 1 serving/month to <1 serving/day and 1 to 2 servings/day, with similar magnitudes between the two exposure categories (Table 4). However, the ORs decreased for the three or more servings/day category. Similarly, odds of MCA with transverse LDs were elevated among the 1 serving/month to < 1 serving/day (OR, 1.5; 95% CI, 0.8–2.6) soda consumption category, and then decreased in the higher exposure categories (Table 4).

To assess additive interaction for active maternal smoking, LD cases and control infants whose mothers were nonsmokers and had no to little dietary caffeine intake (0–<10 mg/day) served as the reference group. Compared to the reference group, the ORs across caffeine levels were similar among smoking and nonsmoking mothers. A pattern of less than additive interaction for caffeine consumption and active maternal smoking was observed for all isolated LDs combined, isolated transverse LDs, and all MCA LDs combined (Table 5). The ORs for smoking only (mothers who smoked and consumed little or no caffeine) were higher than the ORs for smoking and caffeine consumption for all intake categories. However, the RERI were not statistically significant. We did not observe additive interaction for environmental smoking exposure; neither did we observe effect modification for maternal alcohol consumption or vasoconstrictive medication after investigation.

Patterns of associations were not different from the main analyses when the analyses were restricted to mothers who completed the interview within 12 months of EDD (25 cases and 663 controls), or mothers reported no caffeine contained medication use (833 cases and 7966 controls). The results were also not different between those who had early recognition of pregnancy, planned pregnancy, or nausea/vomiting during early pregnancy (818 cases and 7890 controls) and those who did not meet those criteria (26 cases and 179 controls) (data not shown).

DISCUSSION

Results of the current study showed that maternal consumption of dietary caffeine was associated with a weak to moderate increased risk for all isolated LDs combined, isolated longitudinal LDs, and isolated transverse LDs. An elevated OR was observed for high soda consumption and isolated longitudinal LDs. The associations for isolated preaxial LD subtype were closer to the null compared to isolated longitudinal LDs. Coffee and tea consumption were not associated with any LD subtype. We did not observe a pattern of dose response for total dietary caffeine intake or for soda consumption. The observed results had no comparison to previous literature because no previous human epidemiology studies have examined caffeine and limb defects.

We suspected that maternal smoking might modify the effect of caffeine because smoking significantly increases the rate of caffeine metabolism by inducing CYP1A2 (Parsons and Neims, 1978; Vistisen et al., 1992). In our study, smoking and consuming caffeine together resulted in a lower risk than the sum of the risk for caffeine consumption alone and smoking alone. However, the ORs were similar across all levels of caffeine among both smokers and nonsmokers, and a higher OR was observed only for smokers who consumed little to no caffeine. Given that smoking status is often correlated with caffeine consumption, relatively few mothers smoked but consumed little to no caffeine and may differ with regard to potential confounding characteristics. Therefore, unmeasured or residual confounding and chance may have influenced the observed associations.

About 18% of women have total average caffeine intake of <10 mg per day (the referent group), meaning that on most days they drink no caffeinated coffee, caffeinated tea, or caffeinated sodas. It is possible that these women who avoid caffeine have healthier diets in terms of fruits and vegetables. That might explain the elevated ORs for those who have more usual intake of caffeine.

Besides estimating the dietary caffeine in mg/day, we categorized the frequency of consumption of coffee, tea, and soda and conducted the beverage-specific analyses to evaluate whether it was caffeine or other components in those beverages that might be playing a role in any observed associations. The association with soda and LDs is worth noting given the lack of association for coffee or tea. It might be explained by other constituents in these beverages, such as antioxidants present in coffee and tea that may be protective and that the sugar present in sodas may increase risk.

An important concern in this study is potential nondifferential error in the classification of caffeine consumption. The NBDPS measured caffeine intake in the year before pregnancy to better represent the actual exposure during the critical period of organogenesis (third–eighth weeks). According to previous studies, a large proportion of women change their caffeine consumption after pregnancy recognition or as the result of nausea or vomiting (Lawson et al., 2002), either of which can happen after limb development starts (Bayley et al., 2002). Retrospective assessment of women’s consumption in the first trimester may reflect that changed pattern of consumption. Caffeine intake in the year before pregnancy was considered to represent intake during the critical period which is the fourth to fifth

gestational week (Sadler, 2009); however, women might start to change or stop their caffeine intake sometime before conception due to pregnancy planning or for other reasons. In such cases, the caffeine intake in the year before pregnancy might not reflect the actual consumption during the target period. We assessed this source of potential misclassification by comparing results for mothers who recognized pregnancy early, had an intended pregnancy, or reported nausea or vomiting in the first gestational month to those for mothers who did not meet these conditions. The results of the stratified analysis were not significantly different from the primary analysis.

Another source of potential misclassification is the estimation of caffeine dose. The actual caffeine content was not measured directly in our analysis. Instead, standardized caffeine content was assigned to each unit size of coffee, tea, soda, and chocolate based on previously published guidelines. However, each serving of the beverage might differ widely in caffeine level or dose of intake. For example, caffeine levels in each cup of coffee may vary by brand, type of coffee bean, brewing time and method, serving size, seasonal variation of intake, or patterns of intake.

A complication with the soda classification concerns the reporting of energy drink consumption, which has increased in recent years (Reissig et al., 2009). These drinks were recorded in response to a question about consumption of sodas or soft drinks in the maternal interview for the years of this analysis. Women were not prompted to include energy drinks when they were asked to provide frequency of soda consumption, therefore, if women did not think to report energy drinks as sodas or soft drinks, misclassification of total caffeine intake occurred. With the growing energy drink market (Reissig et al., 2009), it will be of interest to ask specifically about energy drink consumption to ensure adequate recording of caffeine from this source.

The study did not observe a dose-response either for total caffeine intake or for the individual caffeinated beverages. Due to the potential misclassification of caffeine levels, the lack of a dose-response relation for elevated LD risk with increasing total caffeine intake should be interpreted with caution. Theoretically, a ‘dose-response fallacy’ (Selevan and Lemasters, 1987) may exist if a very high dose of caffeine exposure caused infertility or early fetal loss, resulting in that the lower dose of exposure was observed among the fetuses that survived to delivery. Without complete data on early loss and termination from all centers, it is possible that, if congenital anomalies within these outcome categories are related to high doses of caffeine, we may have missed associations for high caffeine consumption and LDs. However, results of animal studies did not show increased risk of embryonic death associated with oral administration of caffeine (Brent et al., 2011). We were not able to conduct separate analysis of postaxial or split hand/foot due to small numbers.

Recall bias might occur if case parents underreported or overreported exposures due to guilt or concern. Given that March of Dimes recommendations are to not consume more than 200 mg/day of coffee (or caffeinated beverages) during pregnancy (March of Dimes, 2011), case mothers might be less likely to report consuming over 2 cups/day, which could be another explanation for no observed dose-response.

The NBDPS reported a slightly higher response rate among cases versus controls (Cogswell et al., 2009). Case and control parents may have different motives for participating in the study; however, the possibility that participation was associated with caffeine intake seems small given that our control mothers had similar distributions for demographic characteristics compared to the base population (Cogswell et al., 2009).

In conclusion, the current study explored the effect of maternal dietary caffeine on the risk of congenital limb deficiencies overall, as well as in subtypes including longitudinal, preaxial longitudinal, and transverse limb deficiencies. We observed a moderate increase in the risk for limb deficiencies overall and for transverse LDs with maternal dietary caffeine consumption. Maternal soda consumption of one to two servings per day was associated with an elevated risk of MCA preaxial longitudinal LDs, and soda consumption of three or more servings per day was associated with elevated risk of isolated longitudinal LDs. No dose-response pattern was observed and no risk increase was observed for maternal coffee or tea consumption. Risk of isolated LDs overall, isolated transverse LD subtype, and MCA LDs overall associated with caffeine consumption above the lowest intake level among active tobacco smokers did not differ from that among nonsmokers. Future studies might improve exposure assessment by collecting more detailed information on change in consumption in early pregnancy, more accurately measuring caffeine contents in beverages, and measuring energy drink intake in addition to intake of soda and other soft drinks. Genetic epidemiologic studies including gene-caffeine and gene-gene interaction in the *CYP1A2* and *NAT2* genes would be of interest to further explore any relationship between caffeine and LDs.

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Table 1

LD Case Groups Included in Current Analysis, the NBDPS 1997 to 2007

	All		Isolated	
LD case groups	**No.**	**%**	**No.**	**%**
All LDs	844	100	619	100
Longitudinal	324	38.4	178	28.8
Longitudinal preaxial	194	23.0	73	11.8
Transverse	488	57.8	413	66.7
Intercalary	39	4.6	33	5.3
Other	19	2.3	13	2.1

LD, limb deficiency; NBDPS, National Birth Defects Prevention Study.

Table 2

Characteristics of Controls and Cases of LD Case Groups, the NBDPS 1997 to 2007

	Controls		All limb deficiencies		Longitudinal		Longitudinal preaxial		Transverse	
Maternal and pregnancy characteristics	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Sex										
Male	4104	(50.9)	477	(56.5)	185	(57.1)	108	(55.7)	275	(56.4)
Female	3957	(49.0)	360	(42.7)	134	(41.4)	82	(42.3)	211	(43.2)
Maternal age at conception										
12–19	1066	(13.2)	128	(15.2)	52	(16.0)	34	(17.5)	69	(14.1)
20–34	6106	(75.7)	638	(75.6)	244	(75.3)	142	(73.2)	372	(76.2)
35+	897	(11.1)	78	(9.2)	28	(8.6)	18	(9.3)	47	(9.6)
Maternal race/ethnicity										
Non-Hispanic White	4852	(60.1)	478	(56.6)	181	(55.9)	102	(52.6)	278	(57.0)
Non-Hispanic Black	898	(11.1)	82	(9.7)	43	(13.3)	31	(16.0)	36	(7.4)
Hispanic	1803	(22.3)	237	(28.1)	82	(25.3)	49	(25.3)	148	(30.3)
Other	513	(6.4)	47	(5.6)	18	(5.6)	12	(6.2)	26	(5.3)
Maternal education										
0–12 years	3283	(40.7)	374	(44.3)	144	(44.4)	99	(51.0)	214	(43.9)
>12 years	4755	(58.9)	465	(55.1)	179	(55.2)	95	(49.0)	271	(55.5)
Parity										
0	3230	(40.0)	391	(46.3)	163	(50.3)	106	(54.6)	217	(44.5)
≥1	4838	(60.0)	453	(53.7)	161	(49.7)	88	(45.4)	271	(55.5)
BMI										
Underweight (BMI <18.5)	420	(5.2)	49	(5.8)	20	(6.2)	12	(6.2)	26	(5.3)
Normal weight (18.5 ≤ BMI <25)	4279	(53.0)	421	(49.9)	159	(49.1)	98	(50.5)	242	(49.6)
Overweight or obese (BMI ≥25)	3047	(37.8)	329	(39.0)	130	(40.1)	77	(39.7)	193	(39.5)
Fever during pregnancy										
No	7254	(89.9)	728	(86.3)	283	(87.3)	167	(86.1)	418	(85.7)
Yes	815	(10.1)	116	(13.7)	41	(12.7)	27	(13.9)	70	(14.3)
Nausea or vomiting in the first month of pregnancy										

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Maternal and pregnancy characteristics	Controls		All limb deficiencies		Longitudinal		Longitudinal preaxial		Transverse	
	No.	%	No.	%	No.	%	No.	%	No.	%
No	4588	(56.9)	522	(61.8)	208	(64.2)	124	(63.9)	289	(59.2)
Yes	3469	(43.0)	319	(37.8)	115	(35.5)	69	(35.6)	198	(40.6)
Active and ETS[a]										
No smoking or ETS	5480	(67.9)	553	(65.5)	205	(63.3)	116	(59.8)	323	(66.2)
ETS only	1085	(13.4)	116	(13.7)	48	(14.8)	30	(15.5)	65	(13.3)
Active smoking w/o ETS	1486	(18.4)	172	(20.4)	70	(21.6)	47	(24.2)	98	(20.1)
Alcohol drinking[a]										
No	5038	(62.4)	565	(66.9)	221	(68.2)	138	(71.1)	319	(65.4)
Yes	2994	(37.1)	276	(32.7)	102	(31.5)	55	(28.4)	167	(34.2)
Binge drinking[a]										
No drinking	5038	(62.4)	565	(66.9)	221	(68.2)	138	(71.1)	319	(65.4)
Drinking, not binge drinking	1975	(24.5)	171	(20.3)	67	(20.7)	32	(16.5)	101	(20.7)
Binge drinking (≥4 drinks/occasion)	986	(12.2)	100	(11.8)	34	(10.5)	23	(11.9)	62	(12.7)
Vasoconstrictive medicine use[a]										
No	7304	(90.5)	752	(89.1)	292	(90.1)	172	(88.7)	431	(88.3)
Yes	682	(8.5)	86	(10.2)	31	(9.6)	21	(10.8)	53	(10.9)
Folic acid supplement[b]										
No	3917	(48.5)	401	(47.5)	142	(43.8)	89	(45.9)	244	(50.0)
Yes	4152	(51.5)	443	(52.5)	182	(56.2)	105	(54.1)	244	(50.0)
Site										
Arkansas	1036	(12.8)	89	(10.5)	47	(14.5)	27	(13.9)	34	(7.0)
California	964	(11.9)	128	(15.2)	51	(15.7)	29	(14.9)	70	(14.3)
Georgia (CDC)	829	(10.3)	82	(9.7)	31	(9.6)	20	(10.3)	46	(9.4)
Iowa	910	(11.3)	86	(10.2)	30	(9.3)	20	(10.3)	55	(11.3)
Massachusetts	1018	(12.6)	104	(12.3)	41	(12.7)	20	(10.3)	63	(12.9)
New Jersey	561	(7.0)	76	(9.0)	23	(7.1)	14	(7.2)	51	(10.5)
New York	707	(8.8)	61	(7.2)	24	(7.4)	13	(6.7)	38	(7.8)
North Carolina	539	(6.7)	32	(3.8)	8	(2.5)	2	(1.0)	22	(4.5)

Maternal and pregnancy characteristics	Controls		All limb deficiencies		Longitudinal		Longitudinal preaxial		Transverse	
	No.	%	No.	%	No.	%	No.	%	No.	%
Texas	905	(11.2)	104	(12.3)	37	(11.4)	28	(14.4)	63	(12.9)
Utah	600	(7.4)	82	(9.7)	32	(9.9)	21	(10.8)	46	(9.4)

[a] During 1 month before pregnancy through the first trimester.

[b] During 1 month before pregnancy through the first month of gestation.

LD, limb deficiency; NBDPS, National Birth Defects Prevention Study; BMI, body mass index; ETS, environmental tobacco smoking; CDC, Centers for Disease Control.

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Table 3

Maternal Caffeine Consumption and Risk of Isolated LDs, the NBDPS 1997 to 2007

	All LDs				Longitudinal				Longitudinal preaxial				Transverse			
	Cases	Controls	aOR[a,b]	95% CI	Cases	Controls	aOR[c]	95% CI	Cases	Controls	aOR[d]	95% CI	Cases	Controls	aOR[b]	95% CI
Total caffeine (mg/day)																
0–<10	79	1440		1.0	24	1440		1.0	10	1437		1.0	53	1440		1.0
10–<100	228	2877	1.5	(1.2–2.0)	57	2877	1.2	(0.7–1.9)	25	2872	1.1	(0.5–2.4)	155	2877	1.5	(1.1–2.1)
100–<200	167	1850	1.7	(1.3–2.3)	47	1850	1.5	(0.9–2.5)	17	1843	1.2	(0.5–2.5)	113	1850	1.8	(1.3–2.5)
200–<300	81	1023	1.5	(1.1–2.1)	26	1023	1.5	(0.9–2.7)	12	1022	1.4	(0.6–3.2)	53	1023	1.5	(1.0–2.2)
300+	64	879	1.4	(1.0–2.0)	24	879	1.6	(0.9–2.9)	9	877	1.0	(0.4–2.7)	39	879	1.3	(0.9–2.0)
Coffee (cups)																
0–<1/month	332	4420		1.0	98	4420		1.0	44	4409		1.0	221	4420		1.0
1/month–6 weeks	80	1182	0.9	(0.7–1.2)	18	1182	0.7	(0.4–1.1)	7	1180	0.6	(0.3–1.3)	53	1182	0.9	(0.7–1.2)
1/day	107	1183	1.2	(0.9–1.5)	27	1183	1.0	(0.7–1.6)	9	1180	0.8	(0.4–1.6)	76	1183	1.2	(0.9–1.6)
2/day	56	723	1.0	(0.8–1.4)	19	723	1.2	(0.7–1.9)	7	721	0.9	(0.4–2.0)	35	723	0.9	(0.7–1.4)
3+/day	44	561	1.0	(0.7–1.4)	16	561	1.3	(0.8–2.2)	6	561	0.8	(0.3–2.0)	28	561	1.0	(0.6–1.5)
Tea (cups)																
0–<1/month	359	4361		1.0	112	4361		1.0	43	4349		1.0	237	4361		1.0
1/month–6 weeks	148	2230	0.8	(0.7–1.0)	37	2230	0.6	(0.4–0.9)	17	2227	0.8	(0.4–1.3)	99	2230	0.8	(0.7–1.1)
1–2/day	85	1126	0.9	(0.7–1.2)	18	1126	0.6	(0.4–1.0)	8	1124	0.7	(0.3–1.5)	62	1126	1.0	(0.8–1.4)
3+/day	27	352	1.0	(0.7–1.6)	11	352	1.2	(0.6–2.3)	5	351	1.2	(0.5–3.0)	15	352	1.0	(0.6–1.6)
Soda (12 ounce serving)[e]																
0 mg/day	187	2776		1.0	51	2776		1.0	21	2772		1.0	129	2776		1.0
1/month–<1/day	164	2085	1.2	(1.0–1.5)	44	2085	1.1	(0.8–1.7)	17	2081	1.1	(0.6–2.0)	112	2085	1.2	(0.9–1.5)
1–2/day	169	2036	1.3	(1.0–1.6)	49	2036	1.3	(0.9–1.9)	19	2032	1.1	(0.6–2.1)	110	2036	1.2	(0.9–1.6)
3+/day	99	1172	1.4	(1.1–1.8)	34	1172	1.6	(1.0–2.5)	16	1166	1.4	(0.7–2.8)	62	1172	1.3	(0.9–1.8)

[a] aOR and associated 95% CIs.

[b] ORs adjusted for study site.

[c] Not adjusted for any covariates. Crude ORs are reported.

[d] OR adjusted for maternal exposure to environmental smoking and active smoking during 1 month before pregnancy through the first trimester.

[e] 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 = 1–2 servings; and 102 + mg = 3 + servings.

LD, limb deficiency; NBDPS, National Birth Defects Prevention Study; aOR, adjusted odds ratio; CI, confidence interval.

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Table 4

Maternal Caffeine Consumption and Risk of Multiple Congenital Anomaly with LDs, the NBDPS 1997 to 2007

	All LDs				Longitudinal				Longitudinal preaxial				Transverse			
	Cases	Controls	aOR[a,b]	95% CI	Cases	Controls	aOR[c]	95% CI	Cases	Controls	aOR[d]	95% CI	Cases	Controls	aOR[c]	95% CI
Total caffeine (mg/day)																
0–<10	40	1429		1.0	25	1437		1.0	19	1434		1.0	11	1437		1.0
10–<100	93	2857	1.2	(0.8–1.7)	69	2866	1.5	(0.9–2.3)	58	2862	1.5	(0.9–2.6)	25	2866	1.2	(0.6–2.5)
100–<200	44	1832	0.9	(0.6–1.4)	26	1837	0.9	(0.5–1.6)	22	1832	0.9	(0.5–1.7)	16	1837	1.3	(0.6–2.7)
200–<300	26	1015	1.0	(0.6–1.7)	15	1017	1.0	(0.5–1.9)	13	1016	1.0	(0.5–2.1)	11	1017	1.7	(0.7–3.9)
300+	20	873	0.9	(0.5–1.6)	10	875	0.8	(0.4–1.6)	7	874	0.6	(0.2–1.4)	11	875	2.0	(0.8–4.6)
Coffee (cups)																
0–<1/month	139	4384		1.0	98	4403		1.0	81	4395		1.0	38	4403		1.0
1/month–6 weeks	31	1174	0.9	(0.6–1.3)	20	1175	0.8	(0.5–1.3)	18	1173	0.9	(0.5–1.5)	10	1175	1.0	(0.5–2.1)
1/day	24	1174	0.7	(0.4–1.1)	14	1177	0.6	(0.3–1.0)	10	1174	0.5	(0.3–1.0)	10	1177	1.1	(0.5–2.1)
2/day	15	716	0.8	(0.5–1.3)	6	718	0.4	(0.2–1.0)	5	717	0.4	(0.2–1.1)	9	718	1.7	(0.8–3.6)
3+/day	14	558	0.9	(0.5–1.6)	7	559	0.7	(0.3–1.4)	5	559	0.5	(0.2–1.3)	7	559	1.8	(0.8–4.0)
Tea (cups)																
0–<1/month	121	4326		1.0	82	4340		1.0	67	4331		1.0	37	4340		1.0
1/month–6 weeks	58	2216	1.0	(0.7–1.4)	37	2220	0.9	(0.6–1.4)	29	2217	0.9	(0.6–1.4)	22	2220	1.2	(0.7–2.1)
1–2/day	35	1113	1.2	(0.8–1.7)	22	1121	1.1	(0.7–1.8)	20	1119	1.2	(0.7–2.0)	11	1121	1.2	(0.6–2.4)
3+/day	9	351	0.9	(0.4–1.8)	4	351	0.6	(0.2–1.7)	3	351	0.5	(0.2–1.6)	4	351	1.3	(0.5–3.8)
Soda (12 ounce serving)[e]																
0 mg/day	66	2748		1.0	40	2763		1.0	30	2760		1.0	24	2763		1.0
1/month–<1/day	71	2075	1.4	(1.0–2.0)	44	2077	1.5	(1.0–2.3)	35	2074	1.6	(1.0–2.6)	26	2077	1.5	(0.8–2.6)
1–2/day	61	2021	1.2	(0.9–1.8)	44	2028	1.5	(1.0–2.4)	38	2024	1.7	(1.1–2.8)	15	2028	0.9	(0.5–1.7)
3+/day	25	1162	0.9	(0.5–1.4)	17	1164	1.0	(0.6–1.9)	16	1160	1.2	(0.6–2.2)	9	1164	0.9	(0.4–2.0)

[a] aOR and associated 95% CIs.

[b] ORs adjusted for education and any alcohol drinking during 1 month before pregnancy through the first trimester.

[c] ORs adjusted for any alcohol drinking during 1 month before pregnancy through the first trimester.

[d] ORs adjusted for maternal exposure to environmental smoking and active smoking during 1 month before pregnancy through the first trimester and any alcohol drinking during 1 month before pregnancy through the first trimester.

[e] 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 = 1–2 servings; 102+ mg = 3 + servings.

LD, limb deficiency; NBDPS, National Birth Defects Prevention Study; aOR, adjusted odds ratio; CI, confidence interval.

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Table 5

Maternal Caffeine Consumption and Risk of Selected LDs Overall and Cross-Classified by Smoking Status, the NBDPS 1997 to 2007

	Isolated LDs				Isolated transverse				MCA LDs			
Total caffeine (mg/day)	**Cases**	**Controls**	**aOR[a,b]**	**95% CI**	**Cases**	**Controls**	**aOR[b]**	**95% CI**	**Cases**	**Controls**	**aOR[c]**	**95% CI**
All subjects												
0–<10	79	1440		1.0	53	1440		1.0	40	1429		1.0
10–<100	228	2877	1.5	(1.2–2.0)	155	2877	1.5	(1.1–2.1)	93	2857	1.2	(0.8–1.7)
100–<200	167	1850	1.7	(1.3–2.3)	113	1850	1.8	(1.3–2.5)	44	1832	0.9	(0.6–1.4)
200–<300	81	1023	1.5	(1.1–2.1)	53	1023	1.5	(1.0–2.2)	26	1015	1.0	(0.6–1.7)
300+	64	879	1.4	(1.0–2.0)	39	879	1.3	(0.9–2.0)	20	873	0.9	(0.5–1.6)
Nonsmokers												
0–<10	71	1363		1.0	47	1363		1.0	35	1353		1.0
10–<100	194	2501	1.6	(1.2–2.1)	133	2501	1.6	(1.1–2.3)	81	2486	1.3	(0.9–1.9)
100–<200	135	1502	1.8	(1.4–2.5)	90	1502	1.9	(1.3–2.7)	39	1487	1.1	(0.7–1.7)
200–<300	56	742	1.5	(1.1–2.2)	39	742	1.6	(1.0–2.5)	16	738	0.9	(0.5–1.7)
300+	34	470	1.5	(1.0–2.3)	20	470	1.3	(0.8–2.3)	9	467	0.9	(0.4–1.8)
Smokers												
0–<10	8	77	2.1	(1.0–4.6)	6	77	2.5	(1.0–6.0)	5	76	2.9	(1.1–7.6)
10–<100	34	375	1.9	(1.2–2.9)	22	375	1.9	(1.1–3.2)	12	371	1.4	(0.7–2.8)
100–<200	32	346	2.0	(1.3–3.0)	23	346	2.2	(1.3–3.6)	5	345	0.6	(0.2–1.7)
200–<300	25	281	1.9	(1.2–3.0)	14	281	1.6	(0.9–3.0)	10	277	1.6	(0.8–3.4)
300+	30	407	1.6	(1.0–2.5)	19	407	1.6	(0.9–2.7)	11	405	1.2	(0.6–2.4)

[a] aOR and associated 95% CIs.

[b] ORs adjusted for study site.

[c] ORs adjusted for education and any alcohol drinking during 1 month before pregnancy through the first trimester.

LD, limb deficiency; NBDPS, National Birth Defects Prevention Study; MCA, multiple congenital anomalies; aOR, adjusted odds ratio; CI, confidence interval.