Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Matern Child Health J. Author manuscript; available in PMC 2018 April 12.

Published in final edited form as:

Matern Child Health J. 2014 August ; 18(6): 1540–1551. doi:10.1007/s10995-013-1397-4.

Maternal Caffeine Consumption and Small for Gestational Age Births: Results from a Population-Based Case–Control Study

Adrienne T. Hoyt,

Birth Defects Epidemiology and Surveillance Branch, Texas Center for Birth Defects Research and Prevention, Texas Department of State Health Services, PO Box 149347, MC 1964, Austin, TX 78714-9347, USA

Marilyn Browne,

Congenital Malformations Registry, New York State Department of Health, Albany, NY, USA, University at Albany School of Public Health, Rensselaer, NY, USA

Sandra Richardson,

Office of Quality and Patient Safety, New York State Department of Health, Albany, NY, USA

Paul Romitti, and

Department of Epidemiology, The University of Iowa, Iowa City, IA, USA

Charlotte Druschel

Congenital Malformations Registry, New York State Department of Health, Albany, NY, USA, University at Albany School of Public Health, Rensselaer, NY, USA

The National Birth Defects Prevention Study

Abstract

Caffeine is consumed in various forms during pregnancy, has increased half-life during pregnancy and crosses the placental barrier. Small for gestational age (SGA) is an important perinatal outcome and has been associated with long term complications. We examined the association between maternal caffeine intake and SGA using National Birth Defects Prevention Study data. Non-malformed live born infants with an estimated date of delivery from 1997–2007 (n = 7,943) were included in this analysis. Maternal caffeine exposure was examined as total caffeine intake and individual caffeinated beverage type (coffee, tea, and soda); sex-, race/ethnic-, and parity-specific growth curves were constructed to estimate SGA births. Crude and adjusted odds ratios (aORs) and 95 % confidence intervals were estimated using unconditional logistic regression. Interaction with caffeine exposures was assessed for maternal smoking, vasoconstrictor medication use, and folic acid. Six hundred forty-eight infants (8.2 %) were found to be SGA in this analysis. Increasing aORs were observed for increasing intakes of total caffeine and for each caffeinated beverage with aORs (adjusting for maternal education, high blood pressure, and smoking) ranging from 1.3 to 2.1 for the highest intake categories (300+ mg/day total caffeine and 3+ servings/day for each beverage type). Little indication of additive interaction by maternal smoking, vasoconstrictor medication use, or folic acid intake was observed. We observed an

Correspondence to: Adrienne T. Hoyt.

Conflict of interest The authors declare that they have no competing interests, financial or otherwise.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

increase in SGA births for mothers with higher caffeine intake, particularly for those consuming 300+ mg of caffeine per day. Increased aORs were also observed for tea intake but were more attenuated for coffee and soda intake.

Keywords

Caffeine; Tea; Small for gestational age births; SGA; Growth curves

Introduction

Worldwide, caffeine is ingested in a variety of forms, the most common being coffee, tea, soda, chocolate, and certain nonprescription drugs [1]. In the United States, average caffeine intake is estimated at 91–109 mg/day (229–247 mg/day at the 90th percentile) among women of reproductive age, and 58 mg/day (157 mg/day at the 90th percentile) among pregnant women [2]. During pregnancy the half-life of caffeine is increased [3], and can be as long as 15 h in the third trimester [4]. Caffeine also crosses the placental barrier [5]; however, the main metabolic enzyme involved in caffeine metabolism, cytochrome P450 1A2, is not expressed in the fetus. As caffeine is the most common xenobiotic compound consumed during pregnancy [6], it is important to understand its impact on the developing fetus.

Small for gestational age (SGA) has been associated with increased neonatal mortality and morbidity from polycythemia (increased red blood cells), hypoglycemia (low blood sugar), hypothermia (low body temperature), and other adverse health outcomes later in life—such as metabolic and cardiovascular disease in adulthood [7, 8]. SGA is generally characterized as a fetal or newborn birth weight below the 10th percentile [7] and is often used in clinical settings as a proxy for intrauterine growth restriction (IUGR) [8]. Although some studies have not found an association between maternal consumption of high levels of caffeine and delivering a small for gestational age and/or low birth weight infant [9–20], other studies have noted an association [21–32], and when further risk factors are taken into account such as maternal tobacco smoking and alcohol consumption, the association remains [23, 27, 28]. While a 2010 review released by the *American College of Obstetricians and Gynecologists* noted that the relationship between maternal caffeine consumption and fetal growth restriction is still undetermined [33], recent findings from two large European cohort studies point to compelling evidence for an increase in fetal growth restriction associated with increasing levels of caffeine intake, particularly for mothers consuming 200+ mg of caffeine per day during pregnancy [27, 28]. While current recommendations suggest limiting caffeine intake to 200 mg/day (approximately one and a half to two cups of fresh coffee) during pregnancy [34], the threshold of caffeine exposure has still not been well established, and a better understanding of the association between caffeine and fetal growth, especially in varying amounts and in the presence of a range of other maternal exposures, remains an important area of maternal and child health research.

This analysis examined the association between maternal caffeine consumption and SGA among live born infants using National Birth Defects Prevention Study (NBDPS) data. It

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

also examined potential effect modification by smoking, folic acid use, and vasoconstrictor medication use during pregnancy.

Methods

Ten sites participate in the NBDPS, which has been approved by the institutional review boards of each site. The NBDPS includes case infants that have at least one of over 30 different birth defect types and non-malformed live born control infants randomly selected and unmatched from hospital records or birth certificates during the same time and geographic area as case subjects (see Yoon et al. [35] for more detail on study criteria, selection, and clinical categorizations). The NBDPS uses computer-assisted telephone interviews to collect information from mothers of case and control infants. For this analysis, only data collected from mothers of control infants with an estimated date of delivery from October 1, 1997 through December 31, 2007 were used. Subjects missing gestational age, birth weight, or any caffeine-related information were excluded. The NBDPS interview is conducted from 6 weeks to 2 years after estimated delivery. Along with questions on demographic, occupational, and medical history, participants are also asked how often they consumed a particular food or beverage during the year before becoming pregnant. Questions on caffeine intake include: how many cups of caffeinated or regular coffee, tea, and/or soda they drank; what type of soda they usually drank (subjects are given a list of common soda brands); and during pregnancy, whether they drank more, the same, or less of the beverages above (see Appendix 1 for a more detailed overview). Some caffeine-containing energy drinks, while not specifically asked about in the interview, were collected in the ‘soda/soft drink’ section of the questionnaire, as participants were given the opportunity to indicate, ‘Other/specify’ in the soda brand listing. Caffeinated beverage use during the first trimester was added to the interview for estimated dates of delivery beginning January 1, 2006, but was not included in this analysis because sufficient data have not yet accumulated on these measures.

SGA status was estimated with sex-, race/ethnic-, and parity-specific growth curves based on the methods of Zhang and Bowes [36], and Overpeck et al. [37]. A total of 8,492 control infants without birth defects were identified for this analysis. We additionally excluded mothers reporting history of type 1 or 2 diabetes (n = 63), missing gestational age (n = 1) or birth weight information (n = 27), missing caffeine exposure information (n = 141), plural births (n = 249), missing infant sex (n = 8), race (n = 2), or parity (n = 1), or falling outside of range for calculated growth curves (n = 57).

For this analysis, we focused on three commonly consumed caffeinated beverages (coffee, tea, and soda) as well as chocolate consumed during the year before the participant became pregnant. As outlined by Bracken et al. [38], one cup of coffee was estimated to contain 100 mg of caffeine, a cup of tea 37 mg, published amounts of caffeine contained in specific soft drinks were used to estimate caffeine contents, and one ounce of chocolate was estimated to contain approximately 10 mg of caffeine. Additional information for NBDPS interview items on caffeine exposure and calculating caffeine intake can be found in a recent analysis [39]. Total caffeine intake was categorized into five groupings: <10 mg/day, 10 to <100 mg/day, 100 to <200 mg/day, 200 to <300 mg/day, and 300 mg/day or more, which

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

approximately correspond with the daily caffeine equivalent of less than one cup per day and, one cup, two cups, or three or more cups of coffee per day, respectively. Chocolate, which contains approximately 10 mg per 1 oz. serving, was accounted for in total caffeine intake measurements. Beverage intakes were categorized as: coffee (0 to less than one cup/month; one cup/month to 6 cups/week, one cup/day, two cups/day, and three or more cups/day); tea (0 to less than one cup/month; one cup/month to 6 times/week; one to two cups/day; and three or more cups/day); and soda intake (milligrams of caffeine per day from all soft drinks were converted into the same frequency categories as tea based on the following amounts per serving: <34 mg = <1 serving per day, 34 to <102 mg = 1–2 servings per day, 102+ mg = 3+ servings per day).

Caffeine containing medication use was also evaluated (yes/no use during pregnancy) based on a medication dictionary developed by the Slone Epidemiology Center at Boston University to identify medications with caffeine as a pharmacologic component and evaluated separately from caffeine in beverages and chocolate. Caffeine-containing medications were not included in the total caffeine intake measurements as this particular exposure was collected differently than other sources of caffeine in this analysis, specifically, 3 months prior to conception through the end of the pregnancy. As caffeine containing medication use was uncommon (only four mothers of SGA infants reported use of caffeine-containing medications), this exposure was not examined further.

After construction and examination of a directed acyclic graph (DAG) representing an array of potential covariates to be considered in this analysis, the following variables were chosen which seemed to have the greatest potential for influencing the association of interest. Covariates examined in the analysis include the following maternal factors: age at delivery (12–19, 20–24, 25–29, 30–34, and 35+); parity (0, 1, 2+); race/ethnicity (non-Hispanic white; non-Hispanic black; Hispanic; other); education (<12, 12, 12+ years); pre-pregnancy body mass index defined as weight in kg/height in m^2 (<18.5, 18.5 to <25, 25 to <30, and 30+); total caloric intake; high blood pressure during the index pregnancy; folic acid-containing supplement use (yes/no use 1 month prepregnancy through the first month of pregnancy); smoking (yes/no 1 month prepregnancy through the first trimester); and alcohol use (yes/no 1 month prepregnancy through the first trimester); as well as infant sex and mother's state of residence at the time of the infant's birth (study site). Maternal exposure to folic acid, alcohol consumption, and tobacco smoking in the second and third trimesters (yes/no use second trimester through the third trimester) were also evaluated. To check for confounding by beverage source, we also used a model containing all three beverage types to check for confounding of one beverage type (e.g. coffee) by other beverage types (e.g. tea and soda).

Odds ratios and 95 % confidence intervals (CI) to assess the association between caffeine exposure and SGA were estimated using multivariable logistic regression. Backwards selection was used to assess variables in the models impacting a 10 % change or greater in the odds ratio estimates. Confounders found to produce a 10 % or greater change in the overall estimates of any of the models assessed were controlled for across all models for ease of presentation. Based on the evidence in prior literature, maternal cigarette smoking, vasoconstrictor medication use, and folic acid intake were examined as potential effect

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

modifiers and examined for additive interaction. Smoking has been found to influence the rate of caffeine metabolism [40], some vasoconstrictor medications have been associated with SGA births due to a proposed mechanism of diminished placental blood flow due to selective vasoconstriction of placental vessels [41, 42], and preconceptional maternal folic acid use has been found to be associated with increased birth and placental weight [43]. Statistical interaction (multiplicative interaction) was assessed by examining a change in the *−2 log maximum likelihood ratio*. Effect modification in the form of additive interaction was assessed using methods outlined by Rothman [44]. Caffeine intake was examined as a continuous variable and the selected effect modifiers were assessed by calculation of a relative excess risk due to interaction (RERI), also called the interaction contrast ratio (ICR), described by Rothman and adapted for use with a continuous variable by Knol et al. [45].

RERI 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. Total caffeine values were divided by 300 to evaluate the effect of caffeine per 300 mg increase and a variable representing the number of cigarettes smoked from 1 month prior to conception through the first trimester was added to all parsimonious models to check for residual confounding. A Cochran–Armitage test for trend was conducted on final adjusted models for both total caffeine and individual beverages to test for dose–response relationships across increasing levels of intake. To assess the impact of later cigarette smoking exposure and folic acid intake during pregnancy, we also examined whether the number of cigarettes smoked per day in the second and third trimesters had an impact on our overall associations.

To evaluate the potential for differential length of recall bias, we conducted a Breslow-Day test for homogeneity comparing SGA and non-SGA mothers participating in the interview within 12 months from their estimated delivery date and those participating after 12 months across individual beverage types and total caffeine reported. Exposure changes were also examined for mothers reporting pre-pregnancy average beverage (coffee, tea, soda) intakes and whether they reported consuming less, the same, or more of these beverages during pregnancy. These exposure patterns were examined by SGA status and a Breslow-Day test for homogeneity was additionally conducted. All analyses were performed using SAS software, version 9.3 (SAS Institute Inc., 2011).

Results

Of the 7,943 eligible control infants whose mothers completed the NBDPS interview, 648 (8.2 %) were determined to be SGA. Table 1 presents the results of cross-tabulation frequencies of selected variables by SGA status for the total sample. An increased frequency of SGA infants was observed among mothers who reported smoking 1 month prior to conception through the first trimester or reported high blood pressure during pregnancy, and slightly decreased proportions of SGA births were observed among mothers reporting folic acid intake 1 month prior to conception through the first month of pregnancy compared to those not reporting such intake during this period.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Crude and adjusted odds ratios (aORs) for the association between caffeine intake and SGA were very similar (see Table 2 and Appendix 2). Increasing aORs were observed for increasing intakes of total caffeine and each caffeinated beverage with statistically significant aORs ranging from 1.3 to 2.1. Results were slightly attenuated after adding the variable for the number of cigarettes smoked per day to our models as shown in Table 2 and Appendix 2. Significant increases in our estimates were noted for total caffeine and tea intake in the highest intake categories (300+ mg/day and 3+ servings/day); aORs, 95 % CIs = [(1.57 (1.16–2.13)) and (2.05 (1.50–2.80))], respectively, for the most parsimonious models adjusting for maternal education, high blood pressure during the index pregnancy, and maternal smoking (one month prepregnancy through the first trimester). After additionally adjusting for number of cigarettes smoked per day, estimates remained significant, aORs, 95 % CIs = [(1.52 (1.12–2.08)) and (2.00 (1.46–2.74))]. Results for soda intake were more attenuated, aOR, 95 % CI = 1.20 (0.93-1.54) for the highest intake category (3+ serving/day), and overall did not reach statistical significance for any of the categories assessed. However, a dose–response trend was noted (p-trend ≤ 0.05 for the most parsimonious models and those additionally adjusted for number of cigarettes smoked per day). Mothers reporting usual coffee intake of once/day had an increase in SGA births in both our most parsimonious models and those also adjusting for cigarettes per day: aORs, 95 % CIs = [(1.28 (1.02–1.61)) and (1.31 (1.04–1.64))], respectively, although estimates were attenuated and lost significance in the two highest categories of intake. We did not observe confounding by beverage source and therefore did not include all beverages in the same model. Additionally, we did not observe a significant change in either our caffeine or beverage specific odds ratios when adjusting for maternal folic acid, alcohol consumption, or tobacco exposures later in pregnancy (data not shown). Little indication of multiplicative interactions (data not shown) or additive interaction by smoking status (Appendices 3–6), vasoconstrictor medication use, or folic acid intake was observed for associations between caffeine or individual beverage types and SGA, particularly when number of cigarettes per day was included in statistical models.

When we assessed for length of recall bias comparing mothers reporting their interview conducted within 12 months from the child’s estimated delivery date to those completing the interview after this period, we did not observe significant differences across our SGA associations by individual beverage type or total calculated caffeine intake (data not shown). Additionally, we did not observe significant differences across SGA status for changes in the mother’s reported caffeinated beverage intake during pregnancy. Among all mothers in our sample, the majority of those reporting ‘regular’ (one or more servings per day) of a caffeinated beverage, reduced their intake during pregnancy of coffee, tea, or soda, with 17.3, 35.0, and 24.8 % reporting the same or more of these beverages during the course of their pregnancy.

Discussion

Overall, modest dose–response associations between caffeine intake and SGA were found. A two-fold increase in the odds was observed for high tea intake, but ORs were closer to the null for coffee and soda intake. These findings generally support previous studies that have suggested that high caffeine intake is associated with a small increase in risk of SGA.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Recently, a large prospective cohort study conducted in Scandinavia found that maternal caffeine intake during pregnancy (200–300 mg/day and >300 mg per day compared to a low intake group consuming 0–50 mg/day) was consistently associated with decreased birth weight and increased odds of SGA [27]. Additionally, at least one author has found that high levels of tea slightly increased risk of low birth weight in a large population-based prospective cohort in Denmark (aOR = 1.3 (1.0–1.7) for women consuming 4–7 cups per day) [46], although other investigators have not found significant associations between tea and SGA [16, 47, 48]. While the stronger association between high tea intake and SGA in this analysis may have been spurious or due to uncontrolled confounding, the support for a biologically plausible association between tea and SGA has generally been based on catechin content, an antioxidant found in tea. Catechin, present in tea but not coffee [49], has been associated with reduced folic acid levels [50, 51]. In addition, a recent analysis using data from the Slone Epidemiology Center Birth Defects Study [52] points to a possible interaction effect between high folic acid consumption and tea consumption. While adequate folic acid intake is thought to support optimal fetal growth, increased levels of maternal catechin from sources such as tea may reduce folic acid levels and thereby contribute to adverse pregnancy outcomes.

A few recent studies examining maternal caffeine consumption and fetal growth have examined the influence of caffeine during pregnancy on the fetal skeletal system. One recent European study conducted by Bakker et al. 2010 found an association between high maternal caffeine intake (>540 mg/day during pregnancy) and diminished first-trimester crown rump length, and smaller femur in the second and third-trimester and birth length [21]. This is in line with a recent Chinese study [31] that found an association between maternal prenatal caffeine exposure in rats and decreased fetal femur lengths and inhibited synthesis of extracellular matrices in the fetal growth plates. The authors note that caffeine exposure was found to significantly increase levels of fetal blood corticosterone and decrease levels of IGF-1mRNA expression in the fetal liver and growth plate, pointing to a possible mechanism of action for which caffeine negatively affects fetal growth.

Additionally, maternal caffeine exposure appears to play a role in the activity of an important placental enzyme, 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2)—which is involved in the regulation of fetal growth [53–55]. A recent animal study conducted by researchers in China found that when pregnant Wistar rats were given caffeine intragastrically, prenatal caffeine significantly increased the expression of maternal and fetal blood corticosterone and decreased the expression of placental 11β-hydroxy-steroid dehydrogenase-2 (11β-HSD-2) [56]—a barrier enzyme found in the placenta that protects the fetus from high concentrations of endogenous maternal glucocorticoids [57]. A decrease in placental 11β-HSD-2 activity has been associated with reduced human fetal growth [54], although others have found no correlation between placental 11β-HSD-2 activity and birth weight in healthy term pregnancies or in pregnancies complicated by IUGR [58]. Future studies are needed to better understand these underlying biological mechanisms.

Strengths of this analysis included the ability to control for a number of maternal characteristics and a large study population which increased the ability to detect meaningful differences across strata. Also, the ability to control for the number of cigarettes per day was

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

useful in reducing residual confounding. Estimates were closer to the null when a continuous variable for number of cigarettes per day was used compared to a dichotomous variable for smoking.

It is possible additional residual confounding could remain due to under-reporting of smoking by mothers in the study. Cotinine biomarkers collected over the course of the pregnancy would have provided a more complete picture of smoking status in our sample; however these are not collected by the NBDPS. Given the strong association between cigarette smoking and caffeine intake in both the current study and others, it is possible that conflicting evidence from earlier studies at least partially reflects residual confounding by smoking.

One of the primary limitations of this analysis involves recall of past caffeine exposure. Computer-assisted interviews used by the NBDPS are conducted between 6 and 24 months after the expected date of delivery. Recalling caffeine intake during the year prior to pregnancy may have been difficult for some mothers, resulting in misclassification of exposure. Assuming mothers with and without SGA infants had similar issues in recalling past caffeine exposure, our misclassification would most likely be non-differential, biasing our estimates towards the null [44]. While recall bias is a limitation of retrospective interview data, the NBDPS attempts to minimize this type of bias by administering the same standard questionnaire to all study participants through trained computer-assisted telephone interviewers. Additionally, all mothers used in this analysis were control mothers from the NBDPS and were thus not selected or informed they were selected as case mothers, also reducing the possibility for recall bias. We also found little evidence for differential length of recall bias in our data as we did not observe significant differences in our total caffeine and beverage specific SGA associations between mothers completing their interview within 12 months versus those completing the interview after this period. In our overall sample, the median time from the date of delivery to interview was 240 days, and for SGA and non-SGA mothers, 261 and 238 days respectively.

Additionally, other sources of caffeine such as energy drinks were not specifically queried in the NBDPS interview, which may lead to underestimates of caffeine exposure in the population, especially for younger mothers who have had more exposure to these newly marketed types of caffeinated beverages. We were also unable to assess for various types of coffee (i.e. lattes, mochas, cappuccinos), how they were prepared, or specific cup sizes. Thus, our exposure assessment did not produce a continuous variable representing a direct measure of caffeine intake or internal dose and variations in portion size may have contributed to exposure misclassification. While potential inaccuracies in our caffeine intake estimates may have been present, applying a standard conversion factor to each serving and assigning study participants into categories of low/no, moderate, and high intake can still provide important clues into usual caffeine habits.

Another limitation of the study was our inability to evaluate the influence of possible differential taste aversions between mothers with SGA and non-SGA infants. If mothers delivering healthy infants were more likely to avoid caffeine due to heightened taste aversions, a stronger relationship between SGA and caffeine consumption would be

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

expected. Since we found only modest associations and small dose response associations, it is unlikely that differential taste aversion had a major influence on our results.

Timing of maternal exposure to caffeinated beverages may have also been problematic. The NBDPS interview questions ask about usual consumption of caffeinated beverages for the year prior to pregnancy in order to measure intake during early pregnancy, prior to any changes associated with pregnancy-related aversions or nausea. This is in line with some studies that point to the importance of early exposures to explain later impacts on fetal growth [59–61]. However, exposures in the second and third trimesters may also be relevant [17, 30, 62–65]. While the NBDPS does not specifically collect data on the timing of changes in intake of the caffeinated beverages examined in this analysis, we found that the majority of ‘regular’ drinkers, consuming at least one serving per day of coffee, tea, or soda pre-pregnancy, reduced their intake of these beverages during pregnancy. Additionally, 49 % of those reporting ‘regular’ intake of at least one caffeinated beverage per day did not find out that they were pregnant until after the first month of pregnancy.

A more accurate characterization of caffeine exposure in our sample, namely, by repeatedly collecting biomarkers and administering questionnaires on caffeine intake and other confounders over the course of pregnancy, would have reduced the potential for random error in our estimates. Given the limited accuracy of the retrospective measurement of caffeine intake obtained on a single occasion in our study, we were unable to develop precise measurements of usual caffeine intake. As these forms of error in our exposure assessment would be present in both our SGA and non-SGA mothers to an equal degree, we would expect a systematic underestimation of the strength of the relationship between caffeine intake and SGA in our sample. To address the potential for regression dilution biases, due to the diluting effects of random changes in a measured exposure over a period of time and leading to underestimations of the true associations of interest [66, 67], future studies examining caffeine and SGA would benefit from incorporating repeated measurements of caffeine intake both prior to and over the entire course of the pregnancy.

In conclusion, a modest increase in SGA births was observed for mothers with higher caffeine intake and, given the limitations of our caffeine assessment, this relationship was likely underestimated. For individual caffeinated beverages, an association was observed for tea intake, although the association was much weaker for increasing amounts of coffee and soda. Overall, this analysis adds strength to the body of evidence that caffeine intake, particularly for women consuming 300+ mg/day, is detrimental for fetal growth.

Acknowledgments

This publication was supported through cooperative agreements (U01-DD00048702 and U01-DD000494)) with the Centers for Disease Control and Prevention. We thank the participants, staff, and scientists of the National Birth Defects Prevention Study. We would additionally like to thank Dr. Tania Desrosiers from the University of North Carolina Gillings School of Global Public Health and Mrs. Katie Tengelsen from the Texas Department of State Health Services for their assistance with classification of SGA. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, the New York State Health Department, nor the Texas Department of State Health Services.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Appendix 1: National Birth Defects Prevention Study interview questions used to assess caffeine exposure

Caffeinated beverages

The next questions are about caffeine. We will be asking you about your average use of coffee, tea, and soda during the year before you became pregnant.

How many cups of caffeinated or regular coffee did you usually drink?[1]

How many cups of caffeinated or regular tea did you usually drink? (see footnote [1])

Did you drink sodas or soft drinks?

What brand(s) or types did you usually drink?

Is (brand) diet?

Is (brand) caffeine free?

How many cans/glasses/bottles of (brand) did you usually drink? (see footnote [1])

When you were pregnant with … did you drink more, the same, less, or no caffeinated coffee?

When you were pregnant with … did you drink more, the same, less, or no caffeinated tea?

When you were pregnant with … did you drink more, the same, less, or no caffeinated sodas?

Chocolate

As part of the dietary assessment based on a modified Willett food frequency questionnaire [68], subjects were asked the average frequency of use of food items, including chocolate (1 oz) during the year prior to pregnancy (see footnote [1]).

Medications

Subjects were asked about medication use in general and in relation to specific medical conditions: diabetes, high blood pressure, epilepsy, respiratory illnesses, bladder infections, fevers, and other diseases. For each medication reported, subjects were asked about timing and frequency of use.

Appendix 2: Counts and crude odds ratios (cORs) for maternal total caffeine and caffeinated beverage intake and small for gestational age

[1]Sixteen frequency categories were provided: never or less than 1 per month, 1 per month, 2 per month, 3 per month, 1 per week, 2 per week, 3 per week, 4 per week, 5 per week, 6 per week, 1 per day, 2 per day, 3 per day, 4 per day, 5 per day, 6 + per day.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(SGA) status among control infants, National Birth Defects Prevention Study, 1997–2007

	Crude models					
	SGA		Non-SGA		cOR	95 % CI[a]
	N	%	N	%		
Total	648	8.2	7,295	91.8		
Total caffeine intake (mg/day) *						
< 10	100	15.4	1,314	18.0	1.00	Referent
10 to <100	202	31.2	2,640	36.2	1.01	0.78–1.29
100 to <200	156	24.1	1,676	23.0	1.22	0.94–1.59
200 to <300	90	13.9	899	12.3	1.32	0.98–1.77
300+	100	15.4	766	10.5	**1.72**	**1.28–2.30**
Tea intake (servings) *						
0 to <1/month	332	51.2	3,954	54.2	1.00	Referent
1/mo–6/wk	161	24.8	2,045	28.0	0.94	0.77–1.14
1–2/day	99	15.3	1,002	13.8	1.18	0.93–1.49
3+/day	56	8.6	294	4.0	**2.27**	**1.67–3.08**
Soda intake (servings) *						
0 to <1/month	200	30.9	2,505	34.3	1.00	Referent
1/mo–6/wk	157	24.2	1,902	26.1	1.03	0.83–1.28
1–2/day	174	26.8	1,850	25.4	1.18	0.95–1.46
3+/day	117	18.1	1,038	14.2	**1.41**	**1.11–1.79**
Coffee intake (servings) *						
0 to < 1/month	327	50.5	4,010	55.0	1.00	Referent
1/mo–6/wk	94	14.5	1,084	14.9	1.06	0.84–1.35
1/day	111	17.1	1,070	14.7	**1.27**	**1.02–1.59**
2/day	63	9.7	639	8.8	1.21	0.91–1.60
3+/day	53	8.2	492	6.7	1.32	0.97–1.79

Note Significant cORs and corresponding CIs bolded at the $p < 0.05$ level

Excluded subjects missing data for specific beverage types, gestational age, birth weight, multiple birth, diagnosed with preconceptional type I/II diabetes, or categorized as too big or small according to growth curve criteria [36, 37]

* Test for trend significant ($p \leq 0.05$)

[a] *CI* confidence interval

Appendix 3: Counts and adjusted odds ratios (aOR) for maternal total caffeine intake and small for gestational age (SGA) status among control

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

infants, cross-classified by maternal smoking status, National Birth Defects Prevention Study, 1997–2007

Total caffeine intake (mg/day)	SGA		Non-SGA		aOR[a]	95 % CI[b]	ICR[c]	95 % CI[b]
	N	%	N	%				
No smoking[d]								
<10	95	14.8	1,236	17.1	1.00	Referent	0.07	−0.03 to 0.16
10 to <100	171	26.5	2,290	31.6	0.94	0.73–1.23		
100 to <200	130	20.2	1,352	18.7	1.21	0.92–1.60		
200 to <300	60	9.3	660	9.1	1.18	0.84–1.66		
300+	40	6.2	421	5.8	1.24	0.84–1.82		
Smoking[d]								
<10	4	0.6	68	0.9	0.50	0.17–1.47		
10 to <100	30	4.7	336	4.6	0.77	0.44–1.34		
100 to <200	26	4.0	310	4.3	0.72	0.40–1.29		
200 to <300	28	4.4	236	3.3	1.01	0.56–1.82		
300+	60	9.3	339	4.7	1.40	0.79–2.48		

Excluded subjects missing data for specific beverage types, gestational age, birth weight, multiple birth, diagnosed with preconceptional type I/II diabetes, or categorized as too big or small according to growth curve criteria [36, 37]

[a] Adjusted for maternal education, high blood pressure during the index pregnancy, and cigarettes smoked per day

[b] *CI* confidence interval

[c] *ICR* interaction contrast ratio

[d] Maternal smoking during the period from 1 month prepregnancy through the third month of pregnancy

Appendix 4: Counts and adjusted odds ratios (aOR) for maternal tea intake and small for gestational age (SGA) status among control infants, cross-classified by maternal smoking status, National Birth Defects Prevention Study, 1997–2007

Tea intake (servings)	SGA		Non-SGA		aOR[a]	95 % CI[b]	ICR[c]	95 % CI[b]
	N	%	N	%				
No smoking[d]								
0 to < 1/month	274	42.6	3,301	45.5	1.00	Referent	0.11	−0.02 to 0.23
1/mo–6/wk	126	19.6	1,674	23.1	0.92	0.74–1.15		
1–2/day	66	10.3	797	11.0	1.00	0.75–1.32		
3+/day	30	4.7	187	2.6	**1.86**	**1.24–2.79**		
Smoking[d]								
0 to < 1/month	55	8.5	631	8.7	0.63	0.38–1.03		
1/mo–6/wk	35	5.4	363	5.0	0.73	0.43–1.23		
1–2/day	33	5.1	191	2.6	1.22	0.70–2.13		
3+/day	25	3.9	104	1.4	1.54	0.82–2.90		

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Note Significant aORs and corresponding CIs bolded at the $p < 0.05$ level

Excluded subjects missing data for specific beverage types, gestational age, birth weight, multiple birth, diagnosed with preconceptional type I/II diabetes, or categorized as too big or small according to growth curve criteria [36, 37]

[a] Adjusted for maternal education, high blood pressure during the index pregnancy, and cigarettes smoked per day

[b] *CI* confidence interval

[c] *ICR* interaction contrast ratio

[d] Maternal smoking during the period from 1 month prepregnancy through the third month of pregnancy

Appendix 5: Counts and adjusted odds ratios (aOR) for maternal soda intake and small for gestational age (SGA) status among control infants, cross-classified by maternal smoking status, National Birth Defects Prevention Study, 1997–2007

Soda intake (servings)	SGA		Non-SGA		aOR[a]	95 % CI[b]	ICR[c]	95 % CI[b]
	N	%	N	%				
No smoking[d]								
0 to < 1/month	166	25.8	2,221	30.6	1.00	Referent	−0.01	−0.20 to 0.11
1/mo–6/wk	139	21.6	1,654	22.8	1.11	0.88–1.40		
1–2/day	135	21.0	1,456	20.1	1.17	0.92–1.49		
3+/day	56	8.7	628	8.7	1.09	0.79–1.50		
Smoking[d]								
0 to < 1/month	33	5.1	265	3.7	1.01	0.58–1.73		
1/mo–6/wk	18	2.8	241	3.3	0.62	0.33–1.16		
1–2/day	37	5.8	383	5.3	0.76	0.45–1.30		
3+/day	60	9.3	400	5.5	1.06	0.62–1.81		

Excluded subjects missing data for specific beverage types, gestational age, birth weight, multiple birth, diagnosed with preconceptional type I/II diabetes, or categorized as too big or small according to growth curve criteria [36, 37]

[a] Adjusted for maternal education, high blood pressure during the index pregnancy, and cigarettes smoked per day

[b] *CI* confidence interval

[c] *ICR* interaction contrast ratio

[d] Maternal smoking during the period from 1 month prepregnancy through the third month of pregnancy

Appendix 6: Counts and adjusted odds ratios (aOR) for maternal coffee intake and small for gestational age (SGA) status among control infants, cross-classified by maternal smoking status, National Birth Defects Prevention Study, 1997–2007

Coffee intake (servings)	SGA		Non-SGA		aOR[a]	95 % CI[b]	ICR[c]	95 % CI[b]
	N	%	N	%				
No smoking[d]								
0 to < 1/month	263	40.8	3,407	47.0	1.00	Referent	0.02	−0.09 to 0.10

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Coffee intake (servings)	SGA		Non-SGA		aOR[a]	95 % CI[b]	ICR[c]	95 % CI[b]
	N	%	N	%				
1/mo–6/wk	81	12.6	908	12.5	1.13	0.87–1.47		
1/day	90	14.0	884	12.2	1.32	1.03–1.70		
2/day	41	6.4	482	6.7	1.19	0.84–1.68		
3+/day	21	3.3	278	3.8	1.05	0.66–1.66		
Smoking[d]								
0 to < 1/month	60	9.3	570	7.9	0.78	0.48–1.28		
1/mo–6/wk	13	2.0	174	2.4	0.59	0.30–1.17		
1/day	21	3.3	179	2.5	0.97	0.54–1.73		
2/day	22	3.4	154	2.1	1.13	0.61–2.11		
3+/day	32	5.0	212	2.9	0.93	0.47–1.83		

Excluded subjects missing data for specific beverage types, gestational age, birth weight, multiple birth, diagnosed with preconceptional type I/II diabetes, or categorized as too big or small according to growth curve criteria [36, 37]

[a] Adjusted for maternal education, high blood pressure during the index pregnancy, and cigarettes smoked per day

[b] *CI* confidence interval

[c] *ICR* interaction contrast ratio

[d] Maternal smoking during the period from 1 month prepregnancy through the third month of pregnancy

References

1. Morris MB, Weinstein L. Caffeine and the fetus: Is trouble brewing? American Journal of Obstetrics and Gynecology. 1981; 140(6):607–608. [PubMed: 7258232]
2. Knight CA, Knight I, Mitchel DC, et al. Beverage caffeine intake in the US consumers and subpopulations of interest: Estimates from the Share of Intake Panel survey. Food and Chemical Toxicology. 2004; 42(12):1923–1930. [PubMed: 15500929]
3. Brazier JL, Ritter J, Berland M, et al. Pharmacokinetics of caffeine during and after pregnancy. Developmental Pharmacology and Therapeutics. 1983; 6(5):315–322. [PubMed: 6628163]
4. Fredholm BB, Bättig K, Holmén J, et al. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacological Reviews. 1999; 51(1):83–133. [PubMed: 10049999]
5. Burg AW. Physiological disposition of caffeine. Drug Metabolism Reviews. 1975; 4(2):199–228. [PubMed: 816628]
6. Da Silva, RS. Caffeine. In: Gupta, RC., editor. Reproductive and developmental toxicology. London, UK: Academic Press/Elsevier; 2011. chap 27
7. Carlo, WA. Prematurity and intrauterine growth restriction. In: Kliegman, RM.Behrman, RE.Jenson, HB., Stanton, BF., editors. Nelson textbook of pediatrics. 19th. Philadelphia, PA: Saunders Elsevier; 2011. chap 91.2
8. Kramer MS. The epidemiology of adverse pregnancy outcomes: An overview. Journal of Nutrition. 2003; 133(5 Suppl 2):1592S–1596S. [PubMed: 12730473]
9. Brooke OG, Anderson HR, Bland JM, et al. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. BMJ. 1989; 298(6676):795–801. [PubMed: 2496859]
10. Caan BJ, Goldhaber MK. Caffeinated beverages and low birthweight: A case–control study. AJPH. 1989; 79(9):1299–1300.
11. Conde A, Teves C, Figueiredo B. Maternal coffee intake and associated risk factors: Effects on fetal growth and activity. Acta Medica Portuguesa. 2011; 24(2):241–248.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

12. Clausson B, Granath F, Ekborn A, et al. Effect of caffeine exposure during pregnancy on birth weight and gestational age. American Journal of Epidemiology. 2002; 155(5):429–436. [PubMed: 11867354]
13. Grosso LM, Rosenberg KD, Belanger K, et al. Maternal caffeine intake and intrauterine growth retardation. Epidemiology. 2001; 12(4):447–455. [PubMed: 11428387]
14. Infante-Rivard C. Caffeine intake and small-for-gestational-age birth: Modifying effects of xenobiotic-metabolising genes and smoking. Paediatric and Perinatal Epidemiology. 2007; 21(4): 300–309. [PubMed: 17564586]
15. Larroque B, Kaminski M, Lelong N, et al. Effects on birth weight of alcohol and caffeine consumption during pregnancy. American Journal of Epidemiology. 1993; 137(9):941–950. [PubMed: 8317451]
16. Linn S, Schoenbaum SC, Monson RR, et al. No association between coffee consumption and adverse outcomes of pregnancy. New England Journal of Medicine. 1982; 306(3):141–145. [PubMed: 7054656]
17. Mills JL, Holmes LB, Aarons JH, et al. Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. JAMA. 1993; 269(5):593–597. [PubMed: 8421363]
18. Parazzini F, Chiaffarino F, Chatenoud L, et al. Maternal coffee drinking in pregnancy and risk of small for gestational age birth. European Journal of Clinical Nutrition. 2005; 59(2):299–301. [PubMed: 15454971]
19. Santos IA, Victora CG, Huttly S, et al. Caffeine intake and low birth weight: A population-based case–control study. American Journal of Epidemiology. 1998; 147(7):620–627. [PubMed: 9554600]
20. Shu XO, Hatch MC, Mills J, et al. Maternal smoking, alcohol drinking, caffeine consumption, and fetal growth: Results from a prospective study. Epidemiology. 1995; 6(2):115–120. [PubMed: 7742395]
21. Bakker R, Steegers EAP, Obradov A, et al. Maternal caffeine intake from coffee and tea, fetal growth, and the risks of adverse birth outcomes: The Generation R Study. American Journal of Clinical Nutrition. 2010; 91(6):1691–1698. [PubMed: 20427730]
22. Fenster L, Eskenazi B, Windham GC, et al. Caffeine consumption during pregnancy and fetal growth. American Journal of Public Health. 1991; 81(4):458–461. [PubMed: 2003624]
23. Peacock JL, Bland JM, Anderson HR. Effects on birth weight of alcohol and caffeine consumption in smoking women. Journal of Epidemiology and Community Health. 1991; 45(2):159–163. [PubMed: 2072076]
24. Vik T, Bakketeig LS, Trygg KU, et al. High caffeine consumption in the third trimester of pregnancy: Gender-specific effects on fetal growth. Paediatric and Perinatal Epidemiology. 2003; 17(4):324–331. [PubMed: 14629313]
25. Watkinson B, Fried PA. Maternal caffeine use before, during and after pregnancy and effects upon offspring. Neurobehavioral Toxicology & Teratology. 1985; 7(1):9–17. [PubMed: 4000371]
26. Beaulac-Baillargeon L, Desrosiers C. Caffeine-cigarette interaction on fetal growth. American Journal of Obstetrics and Gynecology. 1987; 157(5):1236–1240. [PubMed: 3688080]
27. Sengpiel V, Elind E, Bacelis J, et al. Maternal caffeine intake during pregnancy is associated with birth weight but not with gestational length: Results from a large prospective observational cohort study. BMC Medicine. 2013; 11(1):42. [PubMed: 23421532]
28. CARE Study Group. Maternal caffeine intake during pregnancy and risk of fetal growth restriction: A large prospective observational study. BMJ. 2008; 337:a2332. [PubMed: 18981029]
29. Fortier I, Marcoux S, Beaulac-Baillargeon L. Relation of caffeine intake during pregnancy to intrauterine growth retardation and preterm birth. American Journal of Epidemiology. 1993; 137(9):931–940. [PubMed: 8317450]
30. Klebanoff MA, Levine RJ, Clemens JD, et al. Maternal serum caffeine metabolites and small-for-gestational age birth. American Journal of Epidemiology. 2002; 155(1):32–37. [PubMed: 11772782]
31. Tan Y, Liu J, Deng Y, et al. Caffeine-induced fetal rat over-exposure to maternal glucocorticoid and histone methylation of liver IGF-1 might cause skeletal growth retardation. Toxicology Letters. 2012; 214(3):279–287. [PubMed: 22995397]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

32. Sharmin S, Guan H, Williams AS, et al. Caffeine reduces 11β-hydroxysteroid dehydrogenase type 2 expression in human trophoblast cells through the adenosine A2B receptor. PLoS One. 2012; 7(6):e38082. [PubMed: 22701600]
33. Committee on Obstetric Practice. Moderate caffeine consumption during pregnancy. Obstetrics and Gynecology. 2010; 116(2):467–468. [PubMed: 20664420]
34. http://www.marchofdimes.com/printableArticles/nutrition_caffeine.html
35. Yoon PW, Rasmussen SA, Lynburg MC, et al. The National Birth Defects Prevention Study. Public Health Reports. 2001; 116(Suppl 1):32–40.
36. Zhang J, Bowes W Jr. Birth weight-for-gestational-age patterns by race, sex, and parity in the United States population. Obstetrics and Gynecology. 1995; 86(2):200–208. [PubMed: 7617350]
37. Overpeck MD, Hediger ML, Zhang J, et al. Birth weight for gestational age 16 of Mexican American infants born in the United States. Obstetrics and Gynecology. 1999; 93(6):943–947. [PubMed: 10362159]
38. Bracken MB, Triche E, Grosso L, et al. Heterogeneity in assessing self-reports of caffeine exposure: Implications for studies of health effects. Epidemiology. 2002; 13(2):165–171. [PubMed: 11880757]
39. Browne ML, Bell EM, Druschel CM, et al. Maternal caffeine consumption and risk of cardiovascular malformations. Birth Defects Research Part A: Clinical and Molecular Teratology. 2007; 79(7):533–543. [PubMed: 17405163]
40. Arnaud MJ. Pharmacokinetics and metabolism of natural methylxanthines in animal and man. Handbook of Experimental Pharmacology. 2011; 200:33–91.
41. Petersen PM, Jimenez-Solem E, Anderson JT, et al. β-Blocker treatment during pregnancy and adverse pregnancy outcomes: A nationwide population-based cohort study. BMJ. 2012; 2:e001185.
42. Lennestal R, Otterblad OP, Kallen B. Maternal use of antihypertensive drugs in early pregnancy and delivery outcome, notably the presence of congenital heart defects in the infants. European Journal of Clinical Pharmacology. 2009; 65(6):615–625. [PubMed: 19198819]
43. Timmermans S, Jaddoe VW, Hofman A, et al. Periconception folic acid supplementation, fetal growth and the risks of low birth weight and preterm birth: The Generation R Study. British J of Nutrition. 2009; 102(5):777–785.
44. Rothman, KJ. Modern epidemiology. Boston/Toronto: Little, Brown and Company; 1986.
45. Knol MJ, van der Tweel I, Grobbee DE, et al. Estimating Interaction on an additive scale between continuous determinants in a logistic regression model. International Journal of Epidemiology. 2007; 36(5):1111–1118. [PubMed: 17726040]
46. Olsen J, Overvad K, Fische G. Coffee consumption, birth weight and reproductive failures. Epidemiology. 1991; 2(5):370–374. [PubMed: 1742388]
47. Furuhashi N, Sato S, Suzuki M, et al. Effects of caffeine ingestion during pregnancy. Gynecologic and Obstetric Investigation. 1985; 19(4):187–191. [PubMed: 4040880]
48. Eskenazi B, Stapleton AL, Kharrazi M, et al. Associations between maternal decaffeinated and caffeinated coffee consumption and fetal growth and gestational duration. Epidemiology. 1999; 10(3):242–249. [PubMed: 10230832]
49. Arts I, van De Putte B, Hollman P. Catechin contents of foods commonly consumed in the Netherlands. Journal of Agriculture and Food Chemistry. 2000; 48(5):1752–1757.
50. Alemdaroglu N, Dietz U, Wolffram S, et al. Influence of green and black tea on folic acid pharmacokinetics in healthy volunteers: Potential risk of diminished folic acid bioavailability. Biopharmaceutics & Drug Disposition. 2008; 29(6):335–348. [PubMed: 18551467]
51. Shiraishi M, Haruna M, Matsuzaki M, et al. Association between the serum folate levels and tea consumption during pregnancy. Bioscience Trends. 2010; 4(5):225–230. [PubMed: 21068474]
52. Yazdy M, Tinker S, Mitchell A, et al. Maternal tea consumption during early pregnancy and the risk of spina bifida. Birth Defects Research Part A, Clinical and Molecular Teratology. 2012; 94(10):756–761. [PubMed: 22641606]
53. Murphy VE, Zakar T, Smith R, et al. Reduced 11β-hydroxysteroid dehydrogenase type 2 activity is associated with decreased birth weight centile in pregnancies complicated by asthma. Journal of Clinical Endocrinology and Metabolism. 2002; 87:1660–1668. [PubMed: 11932298]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

54. Shams M, Kilby MD, Somerset DE, et al. 11β-Hydroxysteroid dehydrogenase type 2 in human pregnancy and reduced expression in intrauterine growth restriction. Human Reproduction. 1998; 13:799–804. [PubMed: 9619527]
55. Kajantie E, Dunkel L, Turpeinen U, et al. Placental 11β-hydroxysteroid dehydrogenase type 2 and fetal cortisol/cortisone shuttle in small preterm infants. Journal of Clinical Endocrinology and Metabolism. 2003; 88:493–500. [PubMed: 12519895]
56. Xu D, Zhang B, Liang G, et al. Caffeine-induced activated glucocorticoid metabolism in the hippocampus causes hypothalamic-pituitary-adrenal axis inhibition in fetal rats. PLoS ONE. 2012; 7(9):e44497. [PubMed: 22970234]
57. Benediktsson R, Calder AA, Edwards CR, et al. Placental 11β-hydroxysteroid dehydrogenase: A key regulator of fetal glucocorticoid exposure. Clinical Endocrinology. 1997; 46:161–166. [PubMed: 9135697]
58. Hoffman M, Pollow K, Bahlmann F, et al. 11β-hydroxysteroid dehydrogenase (11β-HSD-II) activity in human placenta: Its relationship to placental weight and birth weight and its possible role in hypertension. Journal of Perinatal Medicine. 2001; 29:23–30. [PubMed: 11234613]
59. Bergen NE, Jaddoe VW, Timmermans S, et al. Homocysteine and folate concentrations in early pregnancy and the risk of adverse pregnancy outcomes: The Generation R Study. BJOG. 2012; 119(6):739–751. [PubMed: 22489763]
60. Han M, Neves AL, Serrano M, et al. Effects of alcohol, lithium, and homocysteine on nonmuscle myosin-II in the mouse placenta and human trophoblasts. American Journal of Obstetrics and Gynecology. 2012; 207(2):e7–e19.
61. Nelissen EC, van Montfoort AP, Dumoulin JC, et al. Epigenetics and the placenta. Human Reproduction. 2011; 17(3):397–417.
62. Bracken MB, Triche EW, Belanger K, et al. Association of maternal caffeine consumption with decrements in fetal growth. American Journal of Epidemiology. 2003; 157(5):456–466. [PubMed: 12615610]
63. Prabhu N, Smith N, Campbell D, et al. First trimester maternal tobacco smoking habits and fetal growth. Thorax. 2010; 65(3):235–240. [PubMed: 20335293]
64. Zeitlin JA, Ancel P, Saurel-Cubizolles MJ, et al. Are risk factors the same for small for gestational age versus other preterm births? American Journal of Obstetrics and Gynecology. 2001; 185(1): 208–215. [PubMed: 11483930]
65. Whitehead N, Lipscomb L. Patterns of alcohol use before and during pregnancy and the risk of small-for-gestational-age birth. American Journal of Epidemiology. 2003; 158(7):654–662. [PubMed: 14507601]
66. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. Lancet. 1990; 335:765–774. [PubMed: 1969518]
67. Grandjean P, Budtz-Jorgensen E. Total imprecision of exposure biomarkers: Implications for calculating exposure limits. American Journal of Industrial Medicine. 2007; 50:712–719. [PubMed: 17492658]
68. Willett, WC. Food-frequency methods. In: Willett, WC., editor. Nutritional epidemiology. New York: Oxford University Press; 1998. p. 74-100.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Selected maternal and infant characteristics for control infants by small for gestational age (SGA) status, National Birth Defects Prevention Study, 1997–2007

	SGA		Non-SGA		*p* value
	N	%	N	%	
Total	648	8.2	7,295	91.8	
Maternal age (years)					
12–19	79	12.2	745	10.2	0.01
20–24	178	27.5	1,671	22.9	
25–29	173	26.7	2,023	27.7	
30–34	119	18.4	1,878	25.7	
35+	99	15.3	978	13.4	
Race/ethnicity					
White non-Hispanic	356	54.9	4,344	59.5	<0.01
Black non-Hispanic	59	9.1	822	11.3	
Hispanic	173	26.7	1,671	22.9	
Other	60	9.3	458	6.3	
Education (years)					
<12	145	22.4	1,200	16.5	<0.01
12	177	27.4	1,747	24.1	
13–15	173	26.7	1,979	27.2	
16+	152	23.5	2,340	32.2	
Smoking[a]					
No	497	76.7	5,988	82.1	<0.01
Yes	151	23.3	1,302	17.8	
Prepregnancy BMI					
Under weight (<18.5)	63	9.7	352	4.9	<0.01
Normal weight (18.5–25)	368	59.8	3,849	52.8	
Overweight (25–30)	113	17.4	1,625	22.3	
Obese (30+)	73	11.3	1,182	16.2	
Infant sex					

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

	SGA		Non-SGA		*p* value
	N	%	N	%	
Female	290	44.8	3,606	49.4	0.02
Male	358	55.2	3,689	50.6	
Parity					
0	260	40.1	2,919	40.0	0.27
1	237	36.6	2,416	33.1	
2+	151	23.3	1,960	26.9	
Folic acid use[b]					
No	357	55.1	3,546	48.6	<0.01
Yes	291	44.9	3,749	51.4	
High blood pressure during index pregnancy					
No	576	88.9	6,657	91.3	0.04
Yes	72	11.1	638	8.7	
Alcohol[a]					
No	413	64.7	4,559	62.5	0.45
Yes	230	35.5	2,707	37.1	

Note Totals for individual characteristics may vary due to missings Excluded subjects missing data for specific beverage types, gestational age, birth weight, multiple birth, diagnosed with preconceptional type I/II diabetes, or categorized as too big or small according to growth curve criteria [36, 37]

[a]During the period from 1 month prepregnancy through the third month of pregnancy

[b]During the period from 1 month prepregnancy through the first month of pregnancy

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Counts and adjusted odds ratios (aOR) for maternal total caffeine and caffeinated beverage intake and small for gestational age (SGA) status among control infants, National Birth Defects Prevention Study, 1997–2007

	Basic adjusted models[a]						Also adjusting for cigarettes per day					
	SGA		Non-SGA		aOR	95 % CI[c]	SGA		Non-SGA		aOR[d]	95 % CI[c]
	N[b]	%	N[b]	%			N[b]	%	N[b]	%		
Total	648	8.2	7,295	91.8								
Total caffeine intake (mg/day) *												
<10	99	15.3	1,305	18.0	1.00	Referent	99	15.4	1,304	18.0	1.00	Referent
10 to <100	202	31.2	2,629	36.2	0.96	0.75–1.24	201	31.2	2,626	36.2	0.96	0.75–1.24
100 to <200	156	24.1	1,666	23.0	1.17	0.90–1.53	156	24.2	1,662	22.9	1.18	0.90–1.53
200 to <300	90	13.9	898	12.4	1.26	0.93–1.70	88	13.7	896	12.4	1.24	0.91–1.68
300+	100	15.5	762	10.5	**1.57**	**1.16–2.13**	100	15.5	760	10.5	**1.52**	**1.12–2.08**
Tea intake (servings) *												
0 to <1/month	331	51.2	3,936	54.2	1.00	Referent	329	51.1	3,932	54.3	1.00	Referent
1/mo–6/wk	161	24.9	2,040	28.1	0.95	0.78–1.16	161	25.0	2,037	28.1	0.96	0.79–1.17
1–2/day	99	15.3	991	13.7	1.17	0.92–1.48	99	15.4	988	13.6	1.18	0.93–1.50
3+/day	56	8.7	293	4.0	**2.05**	**1.50–2.80**	55	8.5	291	4.0	**2.00**	**1.46–2.74**
Soda intake (servings) *												
0 to < 1/month	199	30.8	2,488	34.3	1.00	Referent	199	30.9	2,486	34.3	1.00	Referent
1/mo–6/wk	157	24.3	1,898	26.1	1.02	0.82–1.27	157	24.4	1,895	26.2	1.02	0.82–1.27
1–2/day	174	26.9	1,841	25.4	1.09	0.88–1.35	172	26.7	1,839	25.4	1.08	0.87–1.34
3+/day	117	18.1	1,033	14.2	1.20	0.93–1.54	116	18.0	1,028	14.2	1.16	0.90–1.50
Coffee intake (servings)												
0 to < 1/month	326	50.4	3,985	54.9	1.00	Referent	323	50.2	3,977	54.9	1.00	Referent
1/mo–6/wk	94	14.5	1,082	14.9	1.05	0.82–1.33	94	14.6	1,082	14.9	1.06	0.84–1.35
1/day	111	17.2	1,066	14.7	**1.28**	**1.02–1.61**	111	17.2	1,063	14.7	**1.31**	**1.04–1.64**
2/day	63	9.7	636	8.8	1.27	0.95–1.69	63	9.8	636	8.8	1.27	0.95–1.69
3+/day	53	8.2	491	6.8	1.28	0.93–1.75	53	8.2	490	6.8	1.24	0.90–1.70

Note Significant aORs and corresponding CIs bolded at the $p < 0.05$ level

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Excluded subjects missing data for specific beverage types, gestational age, birth weight, multiple birth, diagnosed with preconceptional type I/II diabetes, or categorized as too big or small according to growth curve criteria [36, 37]

[*] Test for trend significant ($p \leq 0.05$)

[a] Adjusted for maternal education, high blood pressure during the index pregnancy, and maternal smoking during the period from 1 month pre-pregnancy through the third month of pregnancy

[b] Sums may not add to total due to exclusion of records with missing values used in adjusted models

[c] *CI* confidence interval

[d] Models additionally adjusted for number of cigarettes smoked per day during the period from 1 month prepregnancy through the third month of pregnancy