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ORIGINAL ARTICLE

Maternal caffeine intake during pregnancy and risk of obesity in offspring: a prospective cohort study

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BACKGROUND/OBJECTIVES: *In-utero* exposures through adverse fetal programming are emerging as an important contributing factor to the epidemic of childhood obesity. This study examines the impact of *in-utero* exposure to caffeine on the risk of childhood obesity in offspring.

SUBJECTS/METHODS: A prospective study of pregnant women with 15 years follow-up of their offspring was conducted to examine the impact of *in-utero* exposure to caffeine on the risk of childhood obesity. Maternal caffeine intake was prospectively ascertained during pregnancy and outcome measures (body mass index (BMI)) were ascertained from medical charts, with 17 BMI measurements per child, on average, during the follow-up period. Potential confounders including known perinatal risk factors for childhood obesity were adjusted for using the generalized estimating equations model with repeated measurements.

RESULTS: After controlling for potential confounders, compared with those without caffeine exposure, *in-utero* exposure to caffeine overall is associated with 87% increased risk of childhood obesity: odds ratio (OR) = 1.87, 95% confidence interval (CI): 1.12–3.12. This association demonstrated a dose–response relationship: OR = 1.77 (1.05–3.00) for maternal daily caffeine intake < 150 mg per day, OR = 2.37 (1.24–4.52) for caffeine intake ⩾ 150 mg per day during pregnancy, respectively. We also observed a linear relationship: every one unit increase *(log₁₀ scale)* in the amount of maternal caffeine intake was associated with 23% increased risk of obesity in offspring. The dose–response relationship appears stronger for persistent obesity than for transitory obesity (occasional high BMI), and for girls than for boys.

CONCLUSIONS: We observed an association of *in-utero* exposure to caffeine with increased risk of childhood obesity. If this observation is further replicated in other studies, the finding will contribute to the understanding of fetal programming of childhood diseases and development of intervention strategy to prevent childhood obesity.

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INTRODUCTION

The prevalence of childhood obesity has been increasing at an alarming pace worldwide and has contributed significantly to the increase in an array of adverse chronic health outcomes, including type 2 diabetes and metabolic disorders.[1–3] The World Health Organization (WHO) considers the worldwide rapid increase in obesity as a top public health challenge of the twenty-first century.[4]

Conventional wisdom regarding the possible causes of obesity has been based on the theory of energy imbalance. However, efforts solely focusing on diet and physical activity to reduce obesity during the last three decades, while important, have not stemmed the rise of obesity worldwide. Environmental factors including diet that impact internal hormonal balance and normal brain functions leading to excessive energy intake have been recognized as important contributing causes of the worldwide obesity epidemic.[4–9] Emerging evidence has revealed that the most critical exposure window for the impact of exogenous factors (dietary or environmental) is *in utero,* which exerts amplifying and long-lasting effects on health outcomes in childhood and adulthood through adverse fetal programming.[4,10–15] One such chemical, which developing fetuses are widely exposed to, is caffeine through maternal consumption during pregnancy.

A pharmacologically active agent, caffeine, 1,3,7-trimethyl-xanthine, is among the most widely consumed substances in the world.[16] In the United States, > 75% of pregnant women reported intake of caffeine-containing products.[17] Caffeine can penetrate the placental barrier and enter into fetal circulation.[18] Its clearance is prolonged in pregnant women, and its rate of metabolism is low in the fetus because of low levels of metabolic enzymes.[19,20] Both factors can lead to a prolonged higher *in-utero* caffeine exposure to the fetus than a comparable exposure in adults. Caffeine may also influence cell development through increasing cellular cyclic adenosine monophosphate concentrations,[21] and decrease intervillous placental blood flow via increasing circulating catecholamines.[22] Therefore, caffeine could have an adverse effect on fetal development through multiple mechanisms. Indeed, caffeine intake during pregnancy has been reported to increase the risk of miscarriage, fetal death and impaired neurological development in offspring.[17,23–28]

Emerging results from animal studies have revealed that brain functioning is critically important in maintaining homeostasis including regulating appetite and other metabolic processes.[29–33] Caffeine is a neural stimulant and several potential mechanisms have emerged linking *in-utero* caffeine exposure to developmental growth. These include: (a) mal-development of the fetal hippocampus and the hypothalamic–pituitary–adrenal axis, (b) fetal

hypothalamic–pituitary–adrenal axis-associated neuroendocrine alteration and (c) interaction with genetic polymorphism.[34–37] In addition, caffeine has been shown to increase insulin resistance and interfere with glucose metabolism.[38–41]

In human studies, *in-utero* caffeine exposure has been associated with increased risk of abnormal fetal growth including small-for-gestational-age.[42–47] Small-for-gestational-age has been associated with higher risk of obesity and metabolic syndrome after birth, and is considered to be an early indicator of adverse fetal programming for childhood and adult metabolic diseases.[12,15,48,49] Thus, emerging evidence from both human and experimental studies provides support to examine an association between *in-utero* caffeine exposure and the risk of childhood obesity.

Taking advantage of our prospective cohort study with information on *in-utero* caffeine exposure and measurements of weight and height in offspring with up to 15 years of longitudinal follow-up,[17,50] this study examined the relationship between maternal caffeine intake during pregnancy and the risk of childhood obesity in offspring.

MATERIALS AND METHODS

From 1996 to 1998, we conducted a study examining risk factors for miscarriage among pregnant members of Kaiser Permanente Northern California (KPNC), an integrated health-care delivery system. The study was approved by the KPNC Institutional Review Board.

Study population

The study was conducted in the San Francisco area. During the study period, all KPNC women who resided in the study area and had a positive pregnancy test were eligible to participate. We recruited 1063 women in early pregnancy. Of them, 829 delivered a live-born infant, thus were eligible for this study of childhood obesity. We excluded 28 children who did not receive pediatric care in the KPNC system after birth.

Exposure assessment

Maternal caffeine consumption during pregnancy was ascertained during an in-person interview conducted during the first or early second trimesters. Women were asked to report their intake of beverages since their last menstrual period, including caffeine-containing beverages. They were asked about the types of drinks, timing of initial drink, the frequency and amount of intake. They were also asked whether they changed consumption patterns since becoming pregnant, and, if so, the time, frequency and amount of consumption after the change. Women reported their caffeine intake on a daily or weekly basis, and average daily intake was then calculated. Sources of caffeine included coffee (caffeinated or decaffeinated), tea (caffeinated or decaffeinated), caffeinated soda including 17 brands of soda (reported energy drinks were very rare during the study period) and hot chocolate. We used the following conversion factors, based on the literature, to estimate the amount of caffeine intake: for every 150 ml (about 5 oz) of a beverage: 100 mg for caffeinated coffee, 2 mg for decaffeinated coffee, 39 mg for caffeinated tea, 15 mg for caffeinated soda and 2 mg for hot chocolate.[24] Caffeine from all sources was totaled to calculate the amount of daily caffeine intake. As caffeine content for decaffeinated teas is uncertain, varying from 0 to 12 mg per 8-oz cup, and as we did not have information on the types of decaffeinated teas women drank, we excluded those who reported drinking decaffeinated teas only (N = 46).

We did not ascertain information on paternal caffeine intake.

Outcome: anthropometric measurements in offspring after birth

Through medical charts and electronic medical records, information on weight and height were ascertained longitudinally from birth until either (a) the participants left the KPNC system or (b) the end of the study period (31 May 2013), with >15 years of follow-up of growth for those who remained in the KPNC system at the end of the study. Body mass index (BMI) was calculated if both weight and height were measured on the same day. More than 99.7% of the mother–infant pairs included had multiple measurements for BMI, thus providing rich information on a

child's growth pattern. The average number of measurements for BMI was 17 per child.

We used BMI as the primary measure of obesity as recommended by WHO and American Academy of Pediatrics.[1,51] Age- and gender-specific percentile of BMI was determined by using the 2000 Centers for Disease Control and Prevention growth charts.[52] Given that the Centers for Disease Control and Prevention standard for BMI starts at age 2, measurements before 2 years of age were not used. Thus, only those with BMI measures at age 2 or above were included in the final analysis (N = 661). We used the standard 95th percentile or higher as the cutoff for obesity.

To separate children with more severe persistent obesity throughout their childhood from those with temporary/transitory obesity, we considered children to have persistent obesity if (a) at least 50% of their BMI measurements throughout the follow-up period were above the 95th percentile cutoff for obesity, and (b) their last measurement also met the cutoff for obesity among those followed to at least 11 years old, indicating that they remained obese as they entered adolescence.

Potential confounders

Although there is no literature on potential confounders for the association examined, we included known perinatal risk factors for childhood obesity including maternal prepregnancy BMI, race/ethnicity, preexisting and gestational diabetes, maternal smoking during pregnancy, and absence of breastfeeding. We also included common demographic characteristics (maternal age, education, household income, marital status, child gender), and reproductive history including parity and preterm delivery. Information on some potential risk factors for childhood obesity after birth including eating habits, time spent watching TV and amount of exercise was only available for a subset of children (47–63%) from the KPNC electronic medical records. Thus, the evaluation of potential confounders for childhood factors was conducted among the subset of participants. Information on prepregnancy BMI was missing for 23 mothers for whom we imputed BMI based on the distribution of race/ethnicity-specific BMI of our study population. This was to preserve those 23 dyads from being deleted because of missing information on the adjusted variable (that is, maternal BMI). We compared results with and without including these 23 dyads in the final analysis.

Statistical analysis

Logistic regression for repeated measurements was used to obtain point and interval estimates of association (odds ratios (ORs)) after controlling for confounders. Regression coefficients and associated standard error estimates were estimated via generalized estimating equations, accounting for the non-independence of the multiple longitudinal measurements per child.[53] We assumed an autoregressive working correlation structure, given that nearby weight measurements are more correlated than measurements farther apart in time. Alternative working correlation structures (that is, exchangeable and unstructured) were examined in sensitivity analyses, and results were consistent.

When the association was examined by using persistent and transitory obesity (dichotomized outcomes), regular logistic regression without repeated measurements was used.

Children's age at each BMI measurement was included in all models. Although most variables evaluated were not confounders, we included in the final model common sociodemographic variables such as maternal age, education and race/ethnicity, and the main risk factors for childhood obesity.

Average daily caffeine intake during pregnancy was categorized as 0, <150 mg per day, ⩾150 mg per day in the overall analysis. In addition, the level of daily caffeine intake amount was used as a continuous variable to evaluate a dose–response relationship. As a result of the skewed distribution of maternal caffeine daily intake, data were $\log_{10}$ transformed to normalize the distribution. In order to keep those without caffeine intake (0 mg per day) during pregnancy in the analysis, we added 1 to all caffeine measurements before log transformation, according to standard practice, resulting in no caffeine intake as '0' on the $\log_{10}$ scale after transformation. All statistical analyses were performed using SAS 9.3 (Cary, NC, USA).

RESULTS

The characteristics of the study population cohorts based on maternal caffeine exposure during the index pregnancy are presented in Table 1. Compared with those without caffeine intake, those with high caffeine intake (⩾150 mg per day) tended

Table 1. Characteristics of the study population by maternal caffeine intake

Characteristics	Category	Caffeine intake (mg per day)			
		No caffeine N = 124 (%)	*< 150* N = 373 (%)	*⩾ 150* N = 118 (%)	*Chi-square P-value*
Maternal factors					
Age at delivery	< 25	19 (15.3)	59 (15.8)	10 (8.5)	
	25–30	44 (35.5)	108 (29.0)	26 (22.0)	
	30–35	40 (32.3)	129 (34.6)	46 (39.0)	
	35+	21 (16.9)	77 (20.6)	36 (30.5)	0.03
Education	< College	76 (61.8)	210 (56.3)	63 (53.4)	
	College degree	32 (26.0)	108 (29.0)	36 (30.5)	
	Graduate school	15 (12.2)	55 (14.8)	19 (16.1)	0.75
Race	White	28 (22.6)	129 (34.6)	55 (46.6)	
	Black	10 (8.1)	24 (6.4)	4 (3.4)	
	Hispanic	35 (28.2)	94 (25.2)	16 (13.6)	
	Asian/Pacific Islander	47 (37.9)	108 (29.0)	35 (29.7)	
	Other/unknown	4 (3.2)	18 (4.8)	8 (6.8)	0.003
Income	< $30 000	27 (22.9)	68 (19.1)	18 (16.2)	
	$30 000–60 000	45 (38.1)	152 (42.7)	46 (41.4)	
	⩾ $60 000	46 (39.0)	136 (38.2)	47 (42.3)	0.71
Marital status	Single	7 (5.7)	21 (5.6)	4 (3.4)	
	Married	106 (86.2)	302 (81.0)	96 (81.4)	
	Live with partner	9 (7.3)	42 (11.3)	13 (11.0)	
	Other	1 (0.8)	8 (2.1)	5 (4.2)	0.44
Prepregnancy BMI	< 25	90 (72.6)	245 (65.7)	83 (70.3)	
	⩾ 25	34 (27.4)	128 (34.3)	35 (29.7)	0.30
Preexisting or gestational diabetes	No	113 (95.0)	332 (93.0)	100 (88.5)	
	Yes	6 (5.0)	25 (7.0)	13 (11.5)	0.15
Number of previous live births	0	59 (47.6)	157 (42.1)	48 (40.7)	
	1	46 (37.1)	145 (38.9)	45 (38.1)	
	2+	19 (15.3)	71 (19.0)	25 (21.2)	0.72
Index pregnancy factors					
Maternal smoking during pregnancy	No	123 (99.2)	339 (90.9)	92 (78.0)	
	Yes	1 (0.8)	34 (9.1)	26 (22.0)	< 0.001
Preterm delivery	No	113 (91.9)	346 (93.5)	111 (94.9)	
	Yes	10 (8.1)	24 (6.5)	6 (5.1)	0.64
Small-for-gestational-age	No	108 (88.5)	338 (91.6)	107 (92.2)	
	Yes	14 (11.5)	31 (8.4)	9 (7.8)	0.52
Child sex	Male	61 (49.2)	188 (50.4)	61 (51.7)	
	Female	63 (50.8)	185 (49.6)	57 (48.3)	0.93
Childhood characteristics					
Breastfed	No	9 (7.3)	21 (5.7)	16 (13.6)	
	Yes	114 (92.7)	351 (94.4)	102 (86.4)	0.02
Eat at least 5 servings of fruits and vegetables per day[a]	No	24 (24.0)	85 (30.4)	22 (25.0)	
	Yes	76 (76.0)	195 (69.6)	66 (75.0)	0.38
TV, computer, video game time limited to 1h per day[a]	No	15 (16.9)	56 (21.1)	21 (25.9)	
	Yes	74 (83.2)	210 (79.0)	60 (74.1)	0.35
Exercise at least 30 min per day[a]	No	8 (9.1)	25 (9.4)	9 (11.1)	
	Yes	80 (90.9)	242 (90.6)	72 (88.9)	0.88
Play any sports[a]	No	10 (13.3)	40 (19.4)	11 (17.2)	
	Yes	65 (86.7)	166 (80.6)	53 (82.8)	0.49
Outcome measurements					
Number of BMI measurements[b] included in repeated-measures analysis (mean ± s.d.)		9.4 ± 6.8	9.6 ± 12.1	8.5 ± 6.0	0.60[c]
Age at most recent BMI measurement (mean ± s.d.)		12.7 ± 3.6	11.9 ± 4.1	11.8 ± 4.2	0.11[c]

Abbreviations: ANOVA, analysis of variance; BMI, body mass index. [a]Childhood characteristics from a subsample of children whose data was collected during clinical visits including well-child visits. [b]Measurements above age 2 only. [c]*P*-value from ANOVA *F*-test.

to be older, White, and to have smoked during pregnancy. They were less likely to be nulliparous or to have breastfed their children, although not all differences were statistically significant. There was no appreciable difference in other sociodemographic characteristic, maternal risk factors for childhood obesity (for example, maternal prepregnancy BMI, preexisting or gestational diabetes), childhood risk factors for obesity, number of BMI measurements and age at the last BMI measurement (Table 1).

After controlling for children's age at each weight measurement, gender, maternal age at delivery, maternal smoking during pregnancy, prepregnancy BMI and race/ethnicity, compared with no caffeine intake, maternal caffeine intake overall was associated with 87% increased risk of obesity in their offspring: OR = 1.87, 95% confidence interval (CI): 1.12–3.12 (Table 2). There was a dose–response relationship for the observed association. Maternal caffeine intake ⩾ 150 mg per day during pregnancy (high-dose

Table 2. *In-utero* exposure to caffeine and the risk of obesity[a] in offspring

Caffeine intake	N Children	aOR[b]	95% CI
No	124	Reference	
Yes	491	1.87	1.12–3.12
Dose-response			
Categorical			
< 150 mg per day	373	1.77	1.05–3.00
⩾ 150 mg per day	118	2.37	1.24–4.52
		P-value for trend < 0.01	
Linear			
Caffeine mg per day[c]	615	1.23	0.99–1.53

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; GEE, generalized estimating equation. [a]Obesity defined as ⩾ 95 percentile of age- and gender-specific BMI based on the Centers for Disease Control and Prevention criteria.[52] [b]OR from GEE model with repeated measurements, adjusted for child's exact age at each measurement, child gender, maternal age at delivery, smoking during pregnancy, prepregnancy BMI and race. Further adjustment for following factors did not change the results: maternal education level, marital status, parity, preexisting or gestational diabetes, income, preterm delivery, small-for-gestational-age or birthweight, breastfeeding, and childhood characteristics such as fruit and vegetable intake, TV watching and exercise. [c]Caffeine intake (mg per day) was $\log_{10}$ transformed because of skewed distribution.

Table 3. Relationship between *in-utero* exposure to caffeine and obesity[a] in offspring, by source of caffeine

Caffeine source	N Children	aOR[b]	95% CI
None	124	Reference	
Coffee only	85	2.26	1.12–4.58
Tea only	34	1.43	0.61–3.36
Soda only	107	1.93	1.02–3.65
Other/multiple sources	265	1.79	1.03–3.12

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; GEE, generalized estimating equation. [a]Obesity defined as ⩾ 95 percentile of age- and gender-specific BMI based on the Centers for Disease Control and Prevention criteria.[52] [b]OR from GEE model with repeated measurements, adjusted for child's exact age at each measurement, child gender, maternal age at delivery, smoking during pregnancy, prepregnancy BMI and race. Further adjustment for following factors did not change the results: maternal education level, marital status, parity, preexisting or gestational diabetes, income, preterm delivery, small-for-gestational-age or birthweight, breastfeeding, and childhood characteristics such as fruit and vegetable intake, TV watching and exercise.

Table 4. *In-utero* exposure to caffeine and the risk of obesity[a] in offspring among children with at least 11 years of follow-up

Caffeine intake (mg per day)	No n (%)	Yes n (%)	aOR[b]	95% CI
Persistent obesity[c]				
No caffeine	79 (88.8)	10 (11.2)	Reference	
< 150	181 (83.0)	37 (17.0)	1.44	0.65–3.18
⩾ 150	53 (72.6)	20 (27.4)	3.21	1.27–8.07
			P-value for trend = 0.01	
Temporary obesity[d]				
No caffeine	79 (85.9)	13 (14.1)	Reference	
< 150	181 (75.4)	59 (24.6)	1.93	0.98–3.79
⩾ 150	53 (77.9)	15 (22.1)	1.97	0.83–4.67
			P-value for trend = 0.10	

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval. [a]Obesity defined as ⩾ 95th percentile of age- and gender-specific BMI based on the Centers for Disease Control and Prevention criteria.[52] [b]From logistic regression model, adjusted for child gender, maternal age at delivery, prepregnancy BMI, smoking during pregnancy and race. Further adjustment for following factors did not change the results: maternal education level, marital status, parity, preexisting or gestational diabetes, income, preterm delivery, small-for-gestational-age or birthweight, breastfeeding, and childhood characteristics such as fruit and vegetable intake, TV watching and exercise. [c] ⩾ 50% of measurements met the definition of obesity and the child remained obese at the end of follow-up (vs never obese). [d] < 50% of measurements met the definition of obesity or the child was no longer obese at the end of follow-up (vs never obese).

group) was associated with a more than twice the risk of childhood obesity: OR = 2.37, 95% CI: 1.24–4.52, while daily caffeine intake < 150 mg per day (low-dose group) was associated with 77% increased risk of childhood obesity. The dose–response relationship was statistically significant (*P* < 0.01) (Table 2). In addition, using continuous measure of caffeine intake, there was a linear dose–response relationship between amount of daily maternal caffeine intake during pregnancy and the risk of obesity in offspring. Every one unit increase ($\log_{10}$ scale) in the amount of maternal caffeine intake was associated with 23% increased risk of obesity in offspring (Table 2). Additional categorization of caffeine intake below 150 mg per day showed similar results (OR = 1.94 for < 50 mg per day, and OR = 1.52 for 50–149 mg per day). Further adjustment for additional factors including maternal parity, marital status, education level, breastfeeding, preexisting or gestational diabetes, income, preterm delivery, small-for-gestational-age or birthweight, and childhood characteristics such as fruit and vegetable intake, TV watching and exercise did not change the results. Also, excluding 23 mothers with imputed prepregnancy BMI as an adjusted variable produced essentially the same results.

The observed association between maternal caffeine intake and obesity risk in offspring did not appear to be source specific: caffeine from coffee, soda, tea and other sources were all associated with an increased risk of childhood obesity as long as they contain caffeine (Table 3). The consistent results, regardless of caffeine source, reduce the likelihood that substances other than caffeine may explain the observed association.

To examine whether the observed association between *in-utero* exposure to high caffeine intake and obesity risk in offspring differed for those with more severe persistent obesity from those with only temporary obesity, we conducted separate analyses for children who were persistently obese, and those who had only transitory obesity. Children with persistent obesity throughout childhood were more likely to have obesity in adulthood, whereas those with occasional measurements reaching obesity level (transitory obesity) were less likely to do so. Results in Table 4 show that the observed dose–response relationship largely existed for persistent obesity only (*P* = 0.01 for trend test); there

was no such a dose–response relationship with transitory obesity (*P* = 0.10 for trend test).

Similarly, the observed dose–response relationship appeared to differ between girls and boys: the dose–response relationship only existed among girls (*P* = 0.007 for trend test), but not among boys (*P* = 0.50 for trend test) (Table 5).

DISCUSSION

In this prospective cohort study of the effect of *in-utero* caffeine exposure on childhood obesity with up to 15 years of follow-up, we observed an overall increased risk of childhood obesity associated with high maternal caffeine intake during pregnancy. This association was further supported by (1) a dose–response

Table 5. *In-utero* exposure to caffeine and the risk of obesity[a] in offspring, by gender

Caffeine intake (mg per day)	N Children	aOR[b]	95% CI
Girls			
No caffeine	63	Reference	
< 150	185	1.24	(0.61–2.50)
⩾ 150	57	3.32	(1.49–7.41)
		P-value for trend = 0.007	
Boys			
No caffeine	61	Reference	
< 150	188	2.48	(1.19–5.17)
⩾ 150	61	1.53	(0.60–3.92)
		P-value for trend = 0.50	

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; GEE, generalized estimating equation. [a]Obesity defined as ⩾95 percentile of age- and gender-specific BMI based on the Centers for Disease Control and Prevention criteria.[52] [b]OR from GEE model with repeated measurements, adjusted for child's exact age at each measurement, maternal age at delivery, prepregnancy BMI, smoking during pregnancy and race. Further adjustment for following factors did not change the results: maternal education level, marital status, parity, preexisting or gestational diabetes, income, preterm delivery, small-for-gestational-age or birthweight, breastfeeding, and childhood characteristics such as fruit and vegetable intake, TV watching and exercise.

relationship between amount of maternal caffeine intake during pregnancy and further increased obesity risk in offspring (Table 2), and (2) consistent findings regardless of the sources of caffeine, reducing the likelihood of other substances in beverages as the explanation. In addition, the observed dose–response relationship appears to be stronger among those with persistent obesity than those with transitory obesity (Table 4), and among girls than boys (Table 5). These results from a long-term prospectively conducted study provide the first piece of evidence that caffeine intake during pregnancy may impact childhood obesity risk in offspring.

Given the prospective design (that is, maternal caffeine intake in pregnancy as the exposure and obesity in offspring as the outcome), the potential for some common biases (for example, selection and recall biases) is likely reduced. In addition, we controlled for important known perinatal risk factors for childhood obesity (for example, maternal prepregnancy BMI, race/ethnicity, education, prenatal smoking, diabetes, small-for-gestational-age or birthweight, and breastfeeding). Maternal caffeine intake during pregnancy was not related to other risk factors for childhood obesity (for example, a lack of physical activity and unbalanced diet) in this study population (Table 1). Nevertheless, no single study can completely rule out all potential confounders. For example, sugar sometimes added to coffee may be argued as a possible alternative explanation. Although we do not have information on added sugar for this study, in another study of the same KPNC study population, only about one-third of pregnant women reported adding sugar to their coffee or tea drinks. In addition, it has been reported that about 5% of total daily calories come from added sugar in beverages among women aged 20–39 years.[54] Finally, we controlled for the factors related to maternal obesity and metabolic disorders including maternal prepregnancy BMI, preexisting diabetes and gestational diabetes in the analysis and they did not change the results. Thus, although it cannot be completely ruled out, added sugar in caffeinated beverages is unlikely to explain the observed association.

In-utero caffeine exposure in this study was ascertained prospectively during pregnancy; thus, it was not subject to recall bias because of the presence of outcomes (that is, childhood obesity). Daily maternal caffeine intake was ascertained during the first and second trimesters. To the extent that pregnant women changed their caffeine intake in late pregnancy, the estimated maternal caffeine intake may not be totally accurate. However, although pregnant women were found to have reduced their caffeine intake in early pregnancy (from before pregnancy to 11 weeks of gestation), there was little change after that (from 11 to 34 weeks).[55] In addition, given that maternal caffeine intake was grouped into large categories (< 150 vs ⩾ 150 mg per day), any small change in the amount of caffeine intake would not likely have led to a change in the category of caffeine intake, thus it would not have impacted the results. Furthermore, given its prospective design, any misclassification of caffeine intake categories because of inaccurate measure of caffeine intake, if it existed, would have been non-differential (that is, unrelated to childhood obesity), resulting in attenuation of the observed association. Without such attenuation, the observed association would likely have been even stronger.

The study has the following strengths. First, it was a prospective study with 15 years of follow-up of offspring. The longitudinal follow-up allowed collection of multiple growth measurements for each child, providing rich information on growth and obesity patterns throughout childhood. Second, information on weight and height was ascertained prospectively and recorded objectively by medical professionals rather than self-report, avoiding recall bias and improving accuracy of the outcome measures. Third, the relatively large study population reduced the likelihood of unstable estimates because of small sample size. These strengths improve the validity of the observed association.

Brain functions have increasingly been shown to have an important role in regulating appetite and other metabolic processes. Caffeine, a neural stimulant, can alter fetal brain development impacting normal neural transmission vital to normal brain function, thus metabolic processes. *In-utero* caffeine exposure has been linked to abnormal fetal growth through several potential mechanisms: impacting normal development of the fetal hippocampus and the hypothalamic–pituitary–adrenal axis, abnormal neuroendocrine changes associated with hypothalamic–pituitary–adrenal axis functions, and possible interaction with genetic polymorphism including epigenetic effects.[34–37] In addition, animal studies have shown that caffeine increases insulin resistance and disturbs glucose metabolism.[38–41] *In-utero* caffeine exposure has been reported to have a multi-generational effect, probably through epigenetic mechanisms.[56] Clearly, the effect of *in-utero* caffeine exposure on fetal programming and health of offspring has multiple plausible mechanisms and is an emerging research area. This report provides supporting evidence of such an association from a human study. Additional human studies are needed to further examine this potentially important association.

Although *in-utero* caffeine intake was associated with childhood obesity in both male and female offspring, we observed tentative evidence of a difference in the dose–response relationship between boys and girls. Several studies, both from experimental and human studies, have reported sex dimorphism in the adverse effect of *in-utero* exposures on offspring.[57–61] Future studies of *in-utero* exposure may need to further explore gender differences in the fetal programming effect.

The observed association between *in-utero* caffeine exposure and the risk of childhood obesity, if further confirmed by other studies, should have important clinical and public health significance because caffeine, one of the most widely used pharmacologically active agents, is consumed by > 75% of pregnant women.

CONCLUSION

In this prospectively conducted cohort study, maternal caffeine intake during pregnancy was associated with an 87% increased risk of childhood obesity in offspring compared with no maternal caffeine intake during pregnancy. This association was supported by a dose–response relationship.

REFERENCES

1 Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007; **120** (Suppl 4): S164–S192.

2 Kosti RI, Panagiotakos DB. The epidemic of obesity in children and adolescents in the world. *Cent Eur J Public Health* 2006; **14**: 151–159.

3 Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes* 2006; **1**: 11–25.

4 Newbold RR, Padilla-Banks E, Jefferson WN, Heindel JJ. Effects of endocrine disruptors on obesity. *Int J Androl* 2008; **31**: 201–208.

5 Wells JC, Siervo M. Obesity and energy balance: is the tail wagging the dog? *Eur J Clin Nutr* 2011; **65**: 1173–1189.

6 Taubes G. The science of obesity: what do we really know about what makes us fat? An essay by Gary Taubes. *BMJ* 2013; **346**: f1050.

7 Taubes G. Treat obesity as physiology, not physics. *Nature* 2012; **492**: 155.

8 Thayer KA, Heindel JJ, Bucher JR, Gallo MA. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program Workshop Report. *Environ Health Perspect* 2012; **120**: 779–789.

9 Heindel JJ. Endocrine disruptors and the obesity epidemic. *Toxicol Sci* 2003; **76**: 247–249.

10 Whyatt RM, Liu X, Rauh VA, Calafat AM, Just AC, Hoepner L *et al*. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. *Environ Health Perspect* 2012; **120**: 290–295.

11 Kim Y, Ha EH, Kim EJ, Park H, Ha M, Kim JH *et al*. Prenatal exposure to phthalates and infant development at 6 months: prospective Mothers and Children's Environmental Health (MOCEH) study. *Environ Health Perspect* 2011; **119**: 1495–1500.

12 Luo ZC, Xiao L, Nuyt AM. Mechanisms of developmental programming of the metabolic syndrome and related disorders. *World J Diabetes* 2010; **1**: 89–98.

13 Sullivan EL, Grove KL. Metabolic imprinting in obesity. *Forum Nutr* 2010; **63**: 186–194.

14 Heerwagen MJ, Miller MR, Barbour LA, Friedman JE. Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. *Am J Physiol Regul Integr Comp Physiol* 2010; **299**: R711–R722.

15 Leduc L, Levy E, Bouity-Voubou M, Delvin E. Fetal programming of atherosclerosis: possible role of the mitochondria. *Eur J Obstet Gynecol Reprod Biol* 2010; **149**: 127–130.

16 Matijasevich A, Santos IS, Barros FC. Does caffeine consumption during pregnancy increase the risk of fetal mortality? A literature review. *Cad Saude Publica* 2005; **21**: 1676–1684.

17 Weng X, Odouli R, Li DK. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. *Am J Obstet Gynecol* 2008; **198**: 279–8.

18 Goldstein A, Warren R. Passage of caffeine into human gonadal and fetal tissue. *Biochem Pharmacol* 1962; **11**: 166–168.

19 Aldridge A, Bailey J, Neims AH. The disposition of caffeine during and after pregnancy. *Semin Perinatol* 1981; **5**: 310–314.

20 Aldridge A, Aranda JV, Neims AH. Caffeine metabolism in the newborn. *Clin Pharmacol Ther* 1979; **25**: 447–453.

21 Weathersbee PS, Lodge JR. Caffeine: its direct and indirect influence on reproduction. *J Reprod Med* 1977; **19**: 55–63.

22 Kirkinen P, Jouppila P, Koivula A, Vuori J, Puukka M. The effect of caffeine on placental and fetal blood flow in human pregnancy. *Am J Obstet Gynecol* 1983; **147**: 939–942.

23 Bech BH, Nohr EA, Vaeth M, Henriksen TB, Olsen J. Coffee and fetal death: a cohort study with prospective data. *Am J Epidemiol* 2005; **162**: 983–990.

24 Cnattingius S, Signorello LB, Anneren G, Clausson B, Ekbom A, Ljunger E *et al*. Caffeine intake and the risk of first-trimester spontaneous abortion. *N Engl J Med* 2000; **343**: 1839–1845.

25 Parazzini F, Chatenoud L, Di Cintio E, Mezzopane R, Surace M, Zanconato G *et al*. Coffee consumption and risk of hospitalized miscarriage before 12 weeks of gestation. *Hum Reprod* 1998; **13**: 2286–2291.

26 Signorello LB, McLaughlin JK. Maternal caffeine consumption and spontaneous abortion: a review of the epidemiologic evidence. *Epidemiology* 2004; **15**: 229–239.

27 Matijasevich A, Barros FC, Santos IS, Yemini A. Maternal caffeine consumption and fetal death: a case-control study in Uruguay. *Paediatr Perinat Epidemiol* 2006; **20**: 100–109.

28 Yoshino S, Narayanan CH, Joseph F Jr, Saito T, Nakamoto T. Combined effects of caffeine and malnutrition during pregnancy on suckling behavior in newborn rats. *Physiol Behav* 1994; **56**: 31–37.

29 Carnell S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: current knowledge and future directions. *Obes Rev* 2012; **13**: 43–56.

30 Pannacciulli N, Del PA, Chen K, Le DS, Reiman EM, Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. *Neuroimage* 2006; **31**: 1419–1425.

31 Moreno-Lopez L, Soriano-Mas C, Delgado-Rico E, Rio-Valle JS, Verdejo-Garcia A. Brain structural correlates of reward sensitivity and impulsivity in adolescents with normal and excess weight. *PLoS One* 2012; **7**: e49185.

32 Picard A, Rouch C, Kassis N, Moulle VS, Croizier S, Denis RG *et al*. Hippocampal lipoprotein lipase regulates energy balance in rodents. *Mol Metab* 2014; **3**: 167–176.

33 Kennedy J, Dimitropoulos A. Influence of feeding state on neurofunctional differences between individuals who are obese and normal weight: a meta-analysis of neuroimaging studies. *Appetite* 2014; **75**: 103–109.

34 Xu D, Zhang B, Liang G, Ping J, Kou H, Li X *et al*. Caffeine-induced activated glucocorticoid metabolism in the hippocampus causes hypothalamic-pituitary-adrenal axis inhibition in fetal rats. *PLoS One* 2012; **7**: e44497.

35 Xu D, Wu Y, Liu F, Liu YS, Shen L, Lei YY *et al*. A hypothalamic-pituitary-adrenal axis-associated neuroendocrine metabolic programmed alteration in offspring rats of IUGR induced by prenatal caffeine ingestion. *Toxicol Appl Pharmacol* 2012; **264**: 395–403.

36 Signorello LB, Nordmark A, Granath F, Blot WJ, McLaughlin JK, Anneren G *et al*. Caffeine metabolism and the risk of spontaneous abortion of normal karyotype fetuses. *Obstet Gynecol* 2001; **98**: 1059–1066.

37 Bech BH, Autrup H, Nohr EA, Henriksen TB, Olsen J. Stillbirth and slow metabolizers of caffeine: comparison by genotypes. *Int J Epidemiol* 2006; **35**: 948–953.

38 Liu Y, Xu D, Feng J, Kou H, Liang G, Yu H *et al*. Fetal rat metabonome alteration by prenatal caffeine ingestion probably due to the increased circulatory glucocorticoid level and altered peripheral glucose and lipid metabolic pathways. *Toxicol Appl Pharmacol* 2012; **262**: 205–216.

39 Egawa T, Tsuda S, Ma X, Hamada T, Hayashi T. Caffeine modulates phosphorylation of insulin receptor substrate-1 and impairs insulin signal transduction in rat skeletal muscle. *J Appl Physiol* 2011; **111**: 1629–1636.

40 Kolnes AJ, Ingvaldsen A, Bolling A, Stuenaes JT, Kreft M, Zorec R *et al*. Caffeine and theophylline block insulin-stimulated glucose uptake and PKB phosphorylation in rat skeletal muscles. *Acta Physiol (Oxf)* 2010; **200**: 65–74.

41 Tan Y, Liu J, Deng Y, Cao H, Xu D, Cu F *et al*. Caffeine-induced fetal rat overexposure to maternal glucocorticoid and histone methylation of liver IGF-1 might cause skeletal growth retardation. *Toxicol Lett* 2012; **214**: 279–287.

42 Klebanoff MA, Levine RJ, Clemens JD, Wilkins DG. Maternal serum caffeine metabolites and small-for-gestational age birth. *Am J Epidemiol* 2002; **155**: 32–37.

43 Infante-Rivard C. Caffeine intake and small-for-gestational-age birth: modifying effects of xenobiotic-metabolising genes and smoking. *Paediatr Perinat Epidemiol* 2007; **21**: 300–309.

44 Sengpiel V, Elind E, Bacelis J, Nilsson S, Grove J, Myhre R *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 Med* 2013; **11**: 42.

45 Bakker R, Steegers EA, Obradov A, Raat H, Hofman A, Jaddoe VW. Maternal caffeine intake from coffee and tea, fetal growth, and the risks of adverse birth outcomes: the Generation R Study. *Am J Clin Nutr* 2010; **91**: 1691–1698.

46 Vik T, Bakketeig LS, Trygg KU, Lund-Larsen K, Jacobsen G. High caffeine consumption in the third trimester of pregnancy: gender-specific effects on fetal growth. *Paediatr Perinat Epidemiol* 2003; **17**: 324–331.

47 Fortier I, Marcoux S, Beaulac-Baillargeon L. Relation of caffeine intake during pregnancy to intrauterine growth retardation and preterm birth. *Am J Epidemiol* 1993; **137**: 931–940.

48 Ibanez L, Lopez-Bermejo A, Diaz M, Suarez L, de Zegher F. Low-birth weight children develop lower sex hormone binding globulin and higher dehydroepiandrosterone sulfate levels and aggravate their visceral adiposity and hypoadiponectinemia between six and eight years of age. *J Clin Endocrinol Metab* 2009; **94**: 3696–3699.

49 Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull* 2001; **60**: 5–20.

50 Li DK, Odouli R, Wi S, Janevic T, Golditch I, Bracken TD *et al*. A population-based prospective cohort study of personal exposure to magnetic fields during pregnancy and the risk of miscarriage. *Epidemiology* 2002; **13**: 9–20.

51 Grummer-Strawn LM, Reinold C, Krebs NF. Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States. *MMWR Recomm Rep* 2010; **59**: 1–15.

52 Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R *et al.* 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat* 2002; **11**.

53 Hosmer DW, Lemeshow S. *Logistic Regression* 2nd edn John Wiley and Sons, Inc.: New York, 2000.

54 Ervin RB, Ogden CL. Consumption of added sugars among U.S. adults, 2005-2010. 122, 1-8. 2013. Hyattsville, MD, National Center for Health Statistics. NCHS Data Brief.

55 Crozier SR, Robinson SM, Borland SE, Godfrey KM, Cooper C, Inskip HM. Do women change their health behaviours in pregnancy? Findings from the Southampton Women's Survey. *Paediatr Perinat Epidemiol* 2009; **23**: 446–453.

56 Luo H, Deng Z, Liu L, Shen L, Kou H, He Z *et al.* Prenatal caffeine ingestion induces transgenerational neuroendocrine metabolic programming alteration in second generation rats. *Toxicol Appl Pharmacol* 2013; **274**: 383–392.

57 Braun JM, Kalkbrenner AE, Calafat AM, Yolton K, Ye X, Dietrich KN *et al.* Impact of early-life bisphenol A exposure on behavior and executive function in children. *Pediatrics* 2011; **128**: 873–882.

58 Li DK, Miao M, Zhou Z, Wu C, Shi H, Liu X *et al.* Urine bisphenol-A level in relation to obesity and overweight in school-age children. *PLoS One* 2013; **8**: e65399.

59 Wen X, Kleinman K, Gillman MW, Rifas-Shiman SL, Taveras EM. Childhood body mass index trajectories: modeling, characterizing, pairwise correlations and socio-demographic predictors of trajectory characteristics. *BMC Med Res Methodol* 2012; **12**: 38–12.

60 Dubois L, Ohm KK, Girard M, Tatone-Tokuda F, Perusse D, Hjelmborg J *et al.* Genetic and environmental contributions to weight, height, and BMI from birth to 19 years of age: an international study of over 12,000 twin pairs. *PLoS One* 2012; **7**: e30153.

61 Svensson V, Jacobsson JA, Fredriksson R, Danielsson P, Sobko T, Schioth HB *et al.* Associations between severity of obesity in childhood and adolescence, obesity onset and parental BMI: a longitudinal cohort study. *Int J Obes (Lond)* 2011; **35**: 46–52.