

## Effect of Caffeine Exposure during Pregnancy on Birth Weight and Gestational Age

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Epidemiologic studies have been unable to conclusively evaluate whether caffeine intake during pregnancy is associated with reduced birth weight and/or fetal growth restriction. The authors conducted a prospective, population-based cohort study to investigate the effect of caffeine on birth weight, gestational age, and birth weight standardized for gestational age (birth weight ratio). Of 953 women recruited in early pregnancy in Uppsala County, Sweden, from 1996 to 1998, 873 women delivering liveborn singleton infants were included in the analysis. Caffeine exposures were ascertained from in-person interviews at 6–12 and 32–34 completed gestational weeks, and maternal plasma was analyzed for cotinine levels as an indicator of smoking. Analysis of variance was used to estimate the effect of caffeine on birth weight, gestational age at delivery, and birth weight ratio after accounting for the effects of other covariates, such as maternal sociodemographic characteristics, plasma cotinine, and pregnancy symptoms. There were no associations between caffeine consumption and birth weight, gestational age, and birth weight ratio, neither when caffeine exposure was averaged from conception to the 32nd to 34th gestational weeks, nor when caffeine exposure was stratified by trimesters of pregnancy. These results do not support an association between moderate caffeine consumption and reduced birth weight, gestational age, or fetal growth. *Am J Epidemiol* 2002;155:429–36.

birth weight; caffeine; coffee; fetal growth retardation; pregnancy

Since 1974, various studies have suggested that maternal caffeine intake may be associated with fetal growth retardation in humans (1). This is biologically plausible, as caffeine crosses the placental barrier, increases levels of adenosine 3',5'-cyclic monophosphate and maternal epinephrine (2), decreases intervillous placental blood flow (3), and is metabolized more slowly by the mother during pregnancy (4). Because intrauterine growth retardation is an important determinant of stillbirth and is also associated with impaired development later in life (5), and given the relatively high prevalence of caffeine exposure during pregnancy (6–11), the potential influence of caffeine on fetal growth is an important public health issue.

Several epidemiologic studies have found associations between caffeine intake during pregnancy and increased

risks of low birth weight and/or small for gestational age births (7, 8, 11–15). These studies, however, relied on retrospectively collected information from questionnaires or interviews, which may result in imprecise and inadequate assessment of exposure. Among prospective studies, results are inconsistent, with some (16–20), but not all (9, 10, 21–23), authors reporting an association. It has also been suggested that a possible association between caffeine and fetal growth may be confounded by smoking (24); smoking is causally related to fetal growth (25), and smoking is also more common among caffeine consumers (17, 18, 22).

In Sweden, the consumption of caffeine (coffee) intake is high (26). We conducted a population-based, prospective study of the effect of caffeine on birth weight, gestational age, and birth weight standardized for gestational age (birth weight ratio), in which caffeine consumption was self-reported during in-person interviews twice during pregnancy. We also collected detailed information on potentially confounding factors, including smoking (as measured by plasma cotinine levels) and pregnancy symptoms.

### MATERIALS AND METHODS

#### Study participants

This prospective study was planned to study the associations between caffeine consumption and birth outcomes. These study participants were also recruited as controls in a case-control study of first trimester miscarriage (6). From

Received for publication May 29, 2001, and accepted for publication September 21, 2001.

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January 1996 through September 1998, 1,037 women in Uppsala County, Sweden, were asked to participate. Criteria for inclusion were that the women were living and seeking prenatal care in Uppsala County, Swedish-speaking, and, upon entering the study, between 42 and 90 days pregnant (i.e., 6–12 completed gestational weeks), according to the last menstrual period. The participation rate was 92 percent ( $n = 953$ ). For verification of the existence of a viable intrauterine pregnancy, a vaginal ultrasound examination was performed by an obstetrician/gynecologist at the time of the first interview. Criteria for a viable pregnancy were either a live fetus or, in very early pregnancy, a gestational sac with a diameter corresponding to the time elapsed since the last menstrual period. Further details about the study methods have been published previously (6).

In-person interviews were conducted at 6–12 and 32–34 completed gestational weeks. Of the 953 women who completed the first interview, six pregnancies were later terminated via induced abortions and 22 via miscarriage. Twelve women opted to withdraw from the study, six moved outside Uppsala County, and six were lost to follow-up. We also excluded mothers with multiple pregnancies ( $n = 14$ ), stillbirths ( $n = 4$ ), and livebirths with chromosomal abnormalities ( $n = 2$ ). Eight women delivered liveborn singleton infants before the second interview. Thus, the study included 873 singleton pregnancies with liveborn infants with questionnaire data from both the first and third trimesters.

All cohort members agreed to participate in the study, which was approved by the Ethics Committee of the Medical Faculty at Uppsala University.

### Data collection

In-person interviews using a structured questionnaire were conducted by three midwives. The first interview occurred between the sixth and the 12th completed weeks of gestation. Participants reported caffeine intake and pregnancy symptoms (nausea, vomiting, and fatigue) on a week-by-week basis from 4 weeks before the last menstrual period up to the most recently completed week of gestation. Blood samples for the analysis of cotinine levels were also drawn at the time of the baseline interview. In addition, data on maternal characteristics were ascertained, including age, height, prepregnancy body mass index, parity, a previous low birth weight infant (less than 2,500 g), years of education, mother's country of birth, work hours per week, changes in eating habits during pregnancy, and alcohol intake. The body mass index was defined as weight (kg)/height (m)<sup>2</sup> and stratified into four categories (<20, 20–24.9, 25–29.9, and  $\geq 30$ ) (27). At 15–18 completed gestational weeks, study participants had a second routine ultrasound examination. The results of this examination, in which the biparietal diameter and femur length were measured, were used for assessing the gestational length of the pregnancy (28). The second interview took place at 32–34 gestational weeks. Assessment of caffeine intake and pregnancy symptoms was performed as in the first interview, but on a biweekly basis from the seventh gestational week up to the most recently completed week of gestation. At this inter-

view, blood samples were again collected for the analysis of cotinine levels. After delivery and hospital discharge, data on outcomes such as birth weight, gestational age at delivery, sex, and maternal and fetal diagnoses were retrieved from the prenatal and delivery records.

In addition, information about chronic diseases, such as pregestational diabetes and essential hypertension, was collected during the first interview. Information about pregnancy complications was collected after delivery through scrutinization of prenatal and delivery records. Anemia was defined as a hemoglobin concentration under 110 g/liter at any time during pregnancy (29). For the diagnosis of gestational diabetes, all prenatal and delivery records with the diagnostic codes E10–14 and O24 (*International Classification of Diseases*, 10th Revision) and all prenatal records with one or more instances of glucose in the urine were reviewed by an obstetrician (B. C.). Gestational diabetes was defined as a glucose tolerance test with a blood sugar level higher than 8 mmol/liter after 2 hours (30). For the diagnosis of pregnancy-induced hypertensive diseases (gestational hypertension and preeclampsia), a similar procedure was used. An obstetrician (B. C.) scrutinized all prenatal records with a recording of blood pressure at or above 140/90 mmHg, or an elevation of blood pressure of more than 15 units of diastolic pressure, and also checked all prenatal and delivery records with *International Classification of Diseases*, 10th Revision, diagnoses O10 and O13–15. Gestational hypertension was defined as blood pressure at or above 140/90 mmHg (in at least two readings 6 or more hours apart) and no recording of proteinuria. Preeclampsia was defined as the existence of this blood pressure level accompanied with proteinuria (two urinary protein dip sticks of at least 1+ or 300 mg of protein in a 24-hour urine collection) (31).

### Assessment of caffeine

Caffeine sources included coffee (brewed, boiled, instant, and decaffeinated), tea (loose, tea bags, and herbal), cocoa, chocolate, soft drinks, and caffeine-containing medications. Respondents were offered four cup sizes (1 dl, 1.5 dl, 2 dl, 3 dl) from which to choose. Weekly soft drink intake in centiliters was estimated by the participants. Caffeine intake was estimated using the following conversion factors: 150 ml of coffee: brewed = 115 mg, boiled = 90 mg, and instant coffee = 60 mg; 150 ml of loose tea or tea bags = 39 mg (herbal tea = 0 mg); 150 ml of soft cola drinks = 15 mg; 150 ml of cocoa = 4 mg; 1 g of a chocolate bar = 0.3 mg; and a few drugs contained 50–100 mg of caffeine per tablet (32). Eighty-eight percent of the coffee drinkers used predominantly brewed coffee, 6 percent used boiled coffee, 6 percent used instant coffee, and none used predominantly decaffeinated coffee during pregnancy. To determine the total caffeine intake during pregnancy, intake was summed for each subject from the time of estimated conception (i.e., 2 weeks after the last menstrual period) until the second in-person interview. The mean daily caffeine intake during this period was then computed as the total intake divided by the (number of completed gestational weeks  $\times$  7). We used infor-

mation from the first interview to reflect exposure through the first 6 completed gestational weeks and information from the second interview to reflect exposure thereafter. Of all the caffeine ingested, coffee accounted for 70 percent, tea for 26 percent, and other sources for 4 percent.

#### Assessment of smoking and pregnancy symptoms

Plasma samples for cotinine measurements were analyzed by gas chromatography using *N*-ethylnorcotinine

as an internal standard (33). Smokers in the first and the third trimesters were defined as subjects who had a cotinine level above 15 ng/ml at the time of the first or second interview, respectively. Passive smokers in the first and the third trimesters were defined as subjects who had a cotinine level between 1 and 15 ng/ml at the time of the first or second interview, respectively (34). Pregnancy symptom scores were determined for each week of pregnancy by assigning a score for nausea (0 = never; 1 = sometimes; 2 = daily but not all day; 3 = daily, all day),

**TABLE 1. Univariate analysis of caffeine consumption and smoking during pregnancy in relation to birth weight, gestational age, and birth weight ratio of liveborn, singleton, nonanomalous infants, Uppsala County, Sweden, 1996–1999**

	No.	Birth weight (g)		Gestational age (days)		Birth weight ratio	
		Mean	SE*	Mean	SE	Mean	SE
Mean caffeine intake (mg/day)							
During pregnancy							
0–99	353	3,660	28	278.0	0.6	0.030	0.006
100–299	405	3,661	25	277.9	0.5	0.035	0.006
300–499	77	3,597	58	278.0	1.1	0.013	0.013
≥500	38	3,694	82	277.0	1.5	0.047	0.021
<i>p</i> value		0.73		0.95		0.43	
During first trimester							
0–99	386	3,680	27	278.0	0.6	0.036	0.006
100–299	394	3,635	25	277.8	0.5	0.028	0.006
300–499	72	3,630	63	277.1	1.1	0.026	0.016
≥500	21	3,735	107	279.3	2.3	0.041	0.025
<i>p</i> value		0.54		0.84		0.77	
During second trimester							
0–99	395	3,649	26	277.7	0.6	0.030	0.006
100–299	346	3,673	28	278.3	0.5	0.034	0.007
300–499	80	3,601	57	277.6	1.1	0.020	0.013
≥500	52	3,696	67	277.6	1.3	0.042	0.017
<i>p</i> value		0.64		0.85		0.72	
During third trimester							
0–99	383	3,653	27	277.7	0.6	0.031	0.006
100–299	349	3,665	28	278.1	0.5	0.033	0.006
300–499	94	3,643	54	278.0	1.1	0.026	0.012
≥500	47	3,655	70	277.3	1.2	0.033	0.017
<i>p</i> value		0.98		0.91		0.97	
Cotinine (ng/ml)							
First trimester							
<1	589	3,673	22	278.0	0.4	0.035	0.005
1–15	168	3,659	37	277.9	0.8	0.035	0.008
>15	95	3,542	52	277.1	0.9	0.004	0.014
Missing	21	3,697	111	279.4	2.2	0.039	0.025
<i>p</i> value		0.07		0.77		0.06	
Third trimester							
<1	686	3,666	20	278.1	0.4	0.033	0.005
1–15	65	3,765	59	278.8	1.1	0.054	0.012
>15	87	3,531	54	276.5	1.0	0.004	0.015
Missing	35	3,597	102	275.6	2.2	0.028	0.019
<i>p</i> value		0.02		0.34		0.03	
Total	873	3,657	17	277.9	0.4	0.031	0.004

\* SE, standard error.

**TABLE 2. Univariate analysis of maternal characteristics, pregnancy symptoms, and complications in relation to birth weight, gestational age at delivery, and birth weight ratio, Uppsala County, Sweden, 1996–1999**

	No.	Birth weight (g)		Gestational age (days)		Birth weight ratio	
		Mean	SE*	Mean	SE	Mean	SE
<b>Age (years)</b>							
≤24	161	3,632	38	277.5	0.9	0.029	0.009
25–29	343	3,640	27	277.6	0.5	0.030	0.006
30–34	290	3,671	32	278.1	0.6	0.031	0.008
≥35	79	3,729	63	278.8	1.3	0.044	0.013
<i>p</i> value		0.48		0.77		0.80	
<b>Height (cm)</b>							
<155	15	3,312	107	274.7	2.9	−0.039	0.037
155–164	283	3,520	29	276.3	0.7	0.006	0.007
165–170	267	3,704	32	278.4	0.6	0.040	0.007
>170	295	3,756	30	278.8	0.6	0.052	0.007
Missing	13						
<i>p</i> value		<0.001		0.01		<0.001	
<b>Body mass index</b>							
<20	136	3,491	40	276.2	0.9	0.000	0.009
20–24.9	528	3,668	23	278.4	0.4	0.029	0.005
25–29.9	133	3,758	46	278.5	1.0	0.054	0.010
≥30	65	3,690	64	275.0	1.5	0.066	0.013
Missing	11						
<i>p</i> value		<0.001		0.02		<0.001	
<b>Country of birth</b>							
Nordic	832	3,667	18	278.0	0.4	0.034	0.004
Non-Nordic	41	3,445	72	275.9	1.7	−0.011	0.014
<i>p</i> value		0.007		0.21		0.021	
<b>Parity</b>							
0	390	3,592	26	278.8	0.5	0.007	0.006
1–2	446	3,700	24	277.1	0.5	0.049	0.006
≥3	37	3,816	104	277.7	1.6	0.073	0.022
<i>p</i> value		0.002		0.07		<0.001	
<b>Previous LBW* infant†</b>							
No	457	3,730	24	277.5	0.5	0.053	0.005
Yes	26	3,348	96	271.3	3.2	0.008	0.029
<i>p</i> value		<0.001		0.03		0.06	
<b>Education (years)</b>							
<12	304	3,642	30	277.0	0.6	0.034	0.007
12–13	174	3,717	40	278.5	0.7	0.040	0.009
14–15	186	3,671	39	277.9	0.8	0.037	0.009
>15	209	3,615	33	278.7	0.7	0.015	0.008
<i>p</i> value		0.24		0.24		0.15	

Table continues

vomiting (0 = never; 1 = sometimes but not daily; 2 = daily), and fatigue (0 = no; 1 = yes but unchanged sleeping habits; 2 = yes and slightly changed sleeping habits; 3 = yes and pronounced change in sleeping habits). The weekly score for each symptom was summed from the estimated time of conception to the most recently completed week of gestation and then divided by the number of weeks to arrive at an average score for each symptom.

### Outcome variables

Outcomes were birth weight (in grams), gestational age (in completed days of gestation according to the second trimester ultrasound scan), and birth weight ratio (defined as a deviation from the expected gestation and sex-standardized birth weight, according to Swedish fetal growth standards) (35). The birth weight ratio was calculated by standardizing the birth weight by subtracting the gestational age- and sex-

TABLE 2. Continued

	No.	Birth weight (g)		Gestational age (days)		Birth weight ratio	
		Mean	SE	Mean	SE	Mean	SE
Work (hours/week)							
≤35	267	3,665	32	276.6	0.6	0.044	0.007
>35	450	3,626	24	278.7	0.5	0.016	0.006
Not employed	156	3,730	41	277.7	0.9	0.054	0.009
<i>p</i> value		0.09		0.03		<0.001	
Nausea‡							
<1	783	3,644	18	277.8	0.4	0.028	0.004
≥1	89	3,768	58	278.5	1.2	0.057	0.012
<i>p</i> value		0.03		0.55		0.03	
Vomiting‡							
<1	844	3,657	17	277.9	0.4	0.031	0.004
≥1	29	3,652	136	277.6	2.4	0.030	0.025
<i>p</i> value		0.96		0.89		0.94	
Fatigue‡							
0<1	385	3,608	28	277.9	0.6	0.017	0.006
1<2	370	3,686	25	277.6	0.5	0.043	0.006
≥2	117	3,721	49	278.7	1.0	0.042	0.011
Missing	1						
<i>p</i> value		0.04		0.59		0.006	
Diabetes							
No	857	3,653	18	278.0	0.4	0.029	0.004
Gestational	11	3,807	115	269.1	4.0	0.153	0.040
Pregestational	5	3,942	184	272.0	5.8	0.157	0.056
<i>p</i> value		0.29		0.009		<0.001	
Hypertensive disorders							
No	831	3,662	18	278.0	0.4	0.032	0.004
Gestational hypertension	12	3,769	93	280.0	2.5	0.046	0.021
Essential hypertension	3	3,167	147	268.0	5.2	-0.013	0.003
Preeclampsia	27	3,486	143	272.4	2.8	-0.013	0.029
<i>p</i> value		0.10		0.01		0.74	

\* SE, standard error; LBW, low birth weight (<2,500 g).

† Previous low birth weight infant was calculated for parous women only.

‡ Based on mean severity score during pregnancy.

specific expected weight and dividing by the standard deviation and, thereafter, applying a logarithmic transformation. Because the birth weight ratio is close to zero, it can be interpreted as the number of standard deviations above or below the expected gestational age- and sex-specific birth weight.

### Statistical analysis

Univariate associations between birth weight, gestational age, and the birth weight ratio and the potential risk factors were studied by one-way analysis of variance and are presented as the means and standard errors (tables 1 and 2). In multivariate analyses, the models included the average caffeine intake during pregnancy, the cotinine levels in the third trimester, and all the variables presented in table 2. Because the data are unbalanced with respect to the covariates and the applied models are additive, the absolute level after adjustment is arbitrary. The adjusted means for the caffeine intake

categories were therefore normalized to have the same mean in the lowest intake category in both the univariate and the multivariate analyses, facilitating the assessment of potential confounding. Furthermore, the lower two-sided 95 percent confidence limits of the pairwise differences between the lowest intake category (0–99 mg of caffeine per day) and the remaining categories (100–299 mg, 300–499 mg, and ≥500 mg of caffeine per day) are presented, indicating the largest detrimental effect of mean caffeine intake that cannot be excluded in our data set. Interaction terms between caffeine intake and both smoking and pregnancy symptoms were introduced into the multivariate models to assess the potential effect modification. In these interaction analyses, caffeine intake was used as both a categorical and a continuous variable, the latter in order to improve the statistical power. The *p* value for testing the homogeneity of the means for all categorized variables is provided for both crude and multivariate models and was assessed by *F* tests in the analysis of variance

models. Statistical analyses were performed using PROC GLM SAS software (SAS Institute, Inc., Cary, North Carolina). A post hoc power analysis showed that the study had 80 percent statistical power (at a 5 percent two-sided significance level) to detect the following differences between intake groups 0–99 mg per day and >300 mg per day: 169 g in birth weight, 3.6 days in gestational age, and 3.6 percent difference in birth weight ratio.

## RESULTS

Table 1 presents a univariate analysis of caffeine consumption during pregnancy and of cotinine levels in early (6–12 weeks) and late (32–34 weeks) pregnancy in relation to birth weight, gestational age at delivery, and the birth weight ratio. Caffeine exposure expressed as categories of mean daily consumption during the entire pregnancy or by trimester was not associated with any of the outcome variables (table 1). We also analyzed the mean caffeine consumption during pregnancy as a continuous variable, with similar negative results (data not shown). Smoking in late, but not in early, pregnancy was significantly associated with a reduction in birth weight and birth weight ratio. Smoking did not affect the gestational age at delivery.

In univariate analyses, maternal height, prepregnancy body mass index, mother's country of birth, parity, and a previous low birth weight infant all significantly affected birth weight and the birth weight ratio and generally also gestational age (table 2). Neither the maternal age nor the educational level influenced birth weight, gestational age, or the birth weight ratio. Compared with women who worked 35 hours or more per week, women who worked less than 35 hours per week had infants with a lower mean gestational age but a higher mean birth weight ratio. Both nausea and fatigue during pregnancy were associated with birth weight and the birth weight ratio. Pregestational and gestational diabetes both appeared to be positively associated with the birth weight ratio and negatively associated with gestational

age. Women with essential hypertension and preeclampsia had shorter gestations than did women without these disorders. No significant effects on birth weight or gestational age were seen for changes in dietary preferences or for the presence of anemia in pregnancy (data not shown).

Table 3 shows the relations between caffeine intake and the birth outcomes in multivariate analyses. Because we observed no differences in birth outcomes in relation to the mean daily caffeine consumption in separate trimesters, we used the mean daily caffeine consumption during pregnancy (i.e., from conception to 32–34 weeks of gestation) as the exposure variable in the multivariate models. Caffeine exposure was not associated with any of the outcome variables (table 3). Compared with the results from the univariate analyses, there were no substantial changes of the caffeine-related estimates, suggesting that none of the adjustment variables acted as strong confounders. To illustrate potential detrimental effects due to caffeine intake that cannot be excluded because of lack of statistical power, lower 95 percent confidence limits for the differences in the means of the outcome variables between the lowest intake category and the higher categories are presented. For instance, we cannot exclude the possibility that consuming 100–299 mg of caffeine per day will, compared with maternal intake of 0–99 mg of caffeine per day, reduce birth weight up to 70 g. The estimated mean values of birth weight, gestational age, and the birth weight ratio for the categories of the other variables included in the analyses were essentially the same in the multivariate as in the univariate analyses and are therefore not presented.

Smoking substantially influenced caffeine intake. In the third trimester, the mean caffeine consumption per day was significantly higher among smokers (326 mg/day) than among nonsmokers (155 mg/day) or passive smokers (164 mg/day) ( $p < 0.001$  for each comparison). Potential effect modification by smoking on associations between caffeine and each pregnancy outcome was investigated separately. These interactions were not statistically significant with regard to birth weight ( $p = 0.74$ ), gestational age ( $p = 0.26$ ), and the birth weight ratio ( $p = 0.29$ ) when caffeine was used

**TABLE 3. Adjusted\* means of birth weight, gestational age, and birth weight ratio according to caffeine intake, and two-sided lower 95% confidence limits for the differences in the adjusted means by caffeine intake category, Uppsala County, Sweden, 1996–1999**

Mean caffeine intake during pregnancy (mg/day)	Birth weight (g)		Gestational age (days)		Birth weight ratio	
	Mean	Lower† 95% confidence limit	Mean	Lower 95% confidence limit	Mean	Lower 95% confidence limit
0–99	3,660	Referent	278.0	Referent	0.030	Referent
100–299	3,664	–70	278.0	–1.6	0.035	–0.013
300–499	3,611	–181	278.0	–2.8	0.018	–0.041
≥500	3,647	–197	277.2	–4.7	0.032	–0.039
<i>p</i> value	0.98		0.88		0.70	

\* Adjustments were made for all variables included in table 2 (age, height, body mass index, country of birth, parity, previous low birth weight infant (<2,500 g), education, work, nausea, vomiting, fatigue, diabetes, hypertensive disorders).

† Two-sided 95% lower confidence limits for the difference in the mean value of the outcome variables versus 0–99 mg per day.

as a continuous variable. Similarly, although caffeine consumption also varied with pregnancy symptoms, there was no effect modification of the caffeine association with regard to pregnancy symptoms (data not shown).

## DISCUSSION

Our study finds no support for an association between moderate caffeine consumption during pregnancy and restricted fetal growth. This is in agreement with some (9, 10, 21–23), but not all (16–20), previously published prospective studies. Our results are also in contrast to a number of studies using retrospectively collected data, which have reported such associations (7, 8, 11–15, 36).

Even in prospective studies that have shown an effect of caffeine on birth weight, the evidence is inconsistent with respect to dose and whether the association is modified or confounded by smoking. Martin and Bracken (16) found daily caffeine consumption over 150 mg to be associated with low birth weight at term. Peacock et al. (17) found a reduced birth weight for consumers of 2,800 mg of caffeine per week among smokers, and Olsen et al. (18) found an increased odds ratio for low birth weight among nonsmoking nulliparas who consumed more than 8 cups (1.89 liters) of coffee per day. Cook et al. (19) found that, although blood caffeine concentrations during pregnancy were not related to fetal growth, self-reported caffeine intake was, in smoking mothers, inversely associated with birth weight. The latter finding is consistent with the hypothesis that the observed associations between caffeine and birth weight may be due to residual confounding by smoking. Morrison (24) suggested that, although smoking is perceived to be socially undesirable, caffeine consumption is not, and the true quantity smoked may be better reflected by the admitted level of caffeine consumption. Previously reported associations between caffeine intake and fetal growth may also have been confounded by unmeasured factors, such as pregnancy-related symptoms (37).

In the present investigation, measurements of plasma cotinine were used to indicate maternal smoking exposure, and the influence of a number of other possible confounders has been taken into account. Although we tried to optimize data collection on caffeine exposure by obtaining two interviews, the quality of measuring caffeine exposure may be a concern. First, inexact measurements may have resulted from obtaining the data retrospectively. However, measurement of exposure was collected before delivery, and the misclassification should thus be nondifferential with regard to birth weight and gestational age. Second, we lack information about caffeine exposure after 32–34 weeks of gestation. Growth of the normal fetus increases with gestational age (35), and the influence of growth-constraining factors may be more easily detected in late pregnancy. As caffeine exposure was essentially unchanged in the second trimester compared with the first part of the third trimester, we find it unlikely that caffeine exposure was substantially changed during the last weeks of pregnancy.

Birth weights of infants in this study were higher than birth weights in general in Sweden. The study cohort was

restricted to a county dominated by a university city, and for practical purposes we recruited only women fluent in Swedish. Smoking during pregnancy is also less common in Uppsala County compared with Sweden in general (38). Thus, the women included in this study represent a relatively homogeneous population, with a somewhat better health status than that of the general population. In this population, the possibility of detecting effects of environmental factors on birth weight is optimal, as a large proportion of births can be assumed to attain their full birth weight potential.

Although our study is limited in size, it has sufficient statistical power to detect relatively small differences in birth weight between infants of moderate versus none or low caffeine consumers, i.e., the vast majority of women. Furthermore, the validity of our data is supported by the significant associations with other well-established risk factors for low birth weight and small for gestational age births. We therefore conclude that caffeine intake during pregnancy does not impose a major public health issue with regard to fetal growth.

## ACKNOWLEDGMENTS

Financial support was provided by the International Epidemiology Institute through a grant from the National Soft Drink Association.

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