



## Association of Maternal Caffeine Consumption with Decrements in Fetal Growth

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Whether caffeine consumption during pregnancy represents a fetal hazard remains uncertain. The authors report on a large prospective study designed to examine this question. In 1996–2000, 2,291 mothers with singleton livebirths in Connecticut and Massachusetts were evaluated after their first prenatal visit and were questioned about caffeine consumption and important confounding factors. Urine samples were provided to analyze urinary caffeine, cotinine, and creatinine levels. Mothers were followed throughout pregnancy to monitor changes in consumption. Pregnancy outcomes were obtained from medical records. Self-reports of caffeine consumption in the first and third trimesters were not associated with intrauterine growth retardation, low birth weight, or preterm delivery. For every 1 mg/g creatinine increase in urinary caffeine, risk of intrauterine growth retardation was essentially unchanged (odds ratio (OR) = 0.96, 95% confidence interval (CI): 0.85, 1.08). In contrast, a 0.005 mg/g creatinine increase in urinary cotinine significantly increased risk (OR = 1.003, 95% CI: 1.001, 1.005). Mean birth weight was reduced by reported caffeine consumption (–28 g per 100 mg of caffeine consumed daily, 95% CI: –0.10, –0.46,  $p = 0.001$ ) but not mean gestational age. Decaffeinated coffee did not increase risk for any perinatal outcome. This small decrease in birth weight, observed for maternal caffeine consumption, is unlikely to be clinically important except for women consuming  $\geq 600$  mg of caffeine daily (approximately six 10-ounce (1 ounce = 28.3 g) cups of coffee).

birth weight; caffeine; coffee; fetal growth retardation; gestational age; pregnancy; reproduction

Abbreviations: CI, confidence interval; IUGR, intrauterine growth retardation; OR, odds ratio.

Risks associated with maternal caffeine consumption during pregnancy and perinatal outcomes have proved difficult to estimate. Caffeine is consumed by some 75 percent of pregnant women (1), and small risks influence large numbers of pregnancies. A principal difficulty is heterogeneity in exposure to caffeine, which is consumed from several sources, in many serving sizes, and in different concentrations per serving (2). Other concerns are whether caffeine or a metabolite should be studied and difficulty in controlling confounding variables, particularly maternal cigarette smoking (3). Moreover, maternal caffeine consumption appears to be changing, and earlier studies may not be relevant for current estimation.

In 1980, the US Food and Drug Administration recommended that pregnant women avoid caffeine (4). Subsequent

epidemiologic studies have linked relatively high caffeine consumption (typically  $>300$  mg per day) to subfecundity (5–8), low birth weight (5, 9–15), spontaneous abortion (16–21), and fetal growth retardation (10, 22, 23). Other studies suggest that caffeine is not a reproductive hazard (24–26) and does not affect fetal growth, especially when cigarette smoking is controlled (27–32). The current study was designed to test the hypothesis that caffeine consumption reduces fetal growth.

### MATERIALS AND METHODS

Pregnant women were recruited from 56 obstetric practices and 15 clinics associated with six hospitals in Connect-

icut and Massachusetts between September 1996 and January 2000. Exclusion criteria included the gestational age of the fetus being >24 weeks at maternal interview and the mother having insulin-dependent diabetes mellitus, not speaking English or Spanish, and intending to terminate the pregnancy.

Some 11,267 women were screened, and 9,576 (85.0 percent) were eligible. On the basis of a simple preliminary screening question, all women drinking  $\geq 150$  mg of caffeine daily during the past week ( $n = 718$ ), along with a random sample of those drinking <150 mg per day ( $n = 2,915$ ), were invited to participate. In all, 3,633 women were invited to participate; 2,478 (68.2 percent) enrolled, 639 (17.6 percent, same percentage by caffeine exposure) refused, 20 (0.6 percent) were not eligible at the time of the home interview, 72 (2.0 percent) miscarried before the interview, and 424 (11.7 percent) were lost to follow-up or could not be contacted for interview before the 24th-gestational-week eligibility limit expired.

All study participants agreed to be in the study, which was approved by the Human Investigation Committee at Yale University (New Haven, Connecticut) and all participating institutions.

### Assessment of caffeine exposure

To obtain first-trimester exposures, we interviewed the respondent (usually at home) before the 25th week of gestation. The average length of gestation at interview was 14.4 weeks. Detailed questions were asked about consumption of caffeinated and decaffeinated beverages before and each month during pregnancy. Coffee type (regular or instant), preparation method, and brand were ascertained. We asked about tea (hot or iced), tea preparation (steeping time), and tea brands, including herbal. We collected information on frequency and quantity of coffee, tea, and soda consumption. To improve recall, respondents were shown model cup sizes from which to choose their usual size. We computed daily caffeine intake (mg/day) for all study women based on detailed analysis of an intensively monitored group's consumption of caffeinated beverages, serving size, and methods of preparation. These calculations determined that a 10-ounce (1 ounce = 28.3 g) cup of drip-prepared coffee contained 100 mg of caffeine. Tea brewed for 3 minutes contained 42 mg of caffeine (2). Average caffeine consumption, estimated from each of the first 3 months of pregnancy, provided first-trimester exposure. We also collected information on demographics, pregnancy history, and other potential perinatal risk factors.

Women were contacted throughout pregnancy to evaluate changes in health indicators and to validate exposures of interest. On the basis of gestational age at interview, caffeine consumption, and random selection, we placed respondents into one of three subgroups: a telephone, an intensively monitored, or a biochemically monitored group. The telephone group ( $n = 1,882$ ) was interviewed once during pregnancy, randomly assigned for 20, 28, or 36 weeks of gestation. The intensively monitored ( $n = 164$ ) and the biochemically monitored ( $n = 245$ ) groups were contacted at all three times. Beverage samples were collected from inten-

sively monitored women during two randomly selected visits. Samples included caffeinated and decaffeinated coffee and tea, purchased or prepared by the woman's usual method (2). For third-trimester exposures, each respondent was reinterviewed postnatally, usually during her hospital stay, to assess exposure to caffeine and to obtain smoking and other risk factor information for the last 3 months of pregnancy. Caffeine exposures used in the analysis were assessed in an identical way among women in all study groups.

### Sample collection and analysis

All 2,291 respondents received urine containers shortly before the face-to-face interview. A research assistant called each respondent the night before her interview to remind her to collect urine between dinner and bedtime and to refrigerate the container in a sealed bag. Samples were analyzed for urinary caffeine by Labstat, Inc. (Kitchener, Ontario, Canada) using gas chromatography (Varian 3600; Varian, Inc., Palo Alto, California) that incorporated capillary column methodology and nitrogen-selective detection. No other caffeine metabolites were assessed, and urinary samples were corrected for creatinine to standardize for the concentration of urine collected. Analysis of nicotine, cotinine, and creatinine followed similar procedures.

### Pregnancy outcomes

Obstetric records were abstracted to identify pregnancy outcomes. A total of 187 women did not deliver a singleton at term: 70 miscarried, 53 delivered multiple infants, nine terminated their pregnancies, six experienced stillbirths, five withdrew from the study, and 44 could not be traced. Thus, we analyzed 2,291 singleton births. Fetal growth retardation was defined as <10th percentile of birth weight for gestational age by using an external standard of birth weight for gestational age, adjusted for gender and ethnicity, that we developed from all 1999 singleton births in the United States (33). Birth weights were obtained within 24 hours of delivery, and low birth weight was defined as <2,500 g. Gestational age was calculated as completed days from the first day of the last menstrual period or the physician's estimated date of delivery if the last menstrual period was uncertain. We gave preference to sonography estimates, which confirmed gestational age for 61.2 percent of the women. Preterm delivery was defined as <37th week of gestation.

### Analytic methods

For our analyses, we used PC-SAS version 8.02 software (34). Odds ratios between caffeine consumption during the first and third trimesters and intrauterine growth retardation (IUGR), preterm delivery, and low birth weight were calculated from multiple logistic regression. Urinary caffeine and cotinine were initially evaluated in quartiles (caffeine: <0.08, 0.08–0.24, 0.25–0.79,  $\geq 0.80$ ; cotinine: 0,  $\leq 0.0024$ , 0.0024–0.007, >0.007 mg/g creatinine). Final models were built by using backward elimination from models including potential confounders and exposures of interest. Nonsignifi-

**TABLE 1. Association of selected characteristics of the study population with first-trimester caffeine consumption categories, Connecticut and southern Massachusetts, 1996–2001**

Characteristic	No.	Caffeine consumption (mg/day; first-trimester average)			
		None	1–149	150–299	≥300
Study population	2,291	42.9	45.3	7.5	4.4
Respondent's age (years)					
≤24	490	30.2	48.8	12.0	9.0
25–29	578	45.3	45.0	6.4	3.3
30–34	790	48.2	44.3	4.6	2.9
≥35	433	44.3	43.4	9.0	3.2
Parity					
0	996	48.2	44.1	5.2	2.5
1	815	43.3	44.7	7.7	4.3
≥2	477	31.0	48.8	11.7	8.4
Previous no. of abortions					
0	1,788	44.7	45.0	6.5	3.9
1	357	37.2	47.3	9.8	5.6
≥2	143	34.3	44.1	14.0	7.7
Previous no. of pregnancies					
0	662	48.2	44.3	5.1	2.4
1	689	47.5	44.0	5.5	3.0
2	475	38.9	48.0	8.6	4.4
≥3	462	32.5	45.9	12.5	9.1
Marital status					
Currently married	1,625	49.3	43.4	5.1	2.1
Never married	557	27.8	49.9	13.5	8.8
Previously married	109	24.8	48.6	11.9	14.7
Race					
White	1,599	46.7	44.5	5.9	2.9
Black	191	46.6	43.5	7.3	2.6
Hispanic	439	26.9	48.5	13.4	11.2
Asian/other	58	50.0	44.8	5.2	0.0
Education					
<High school	304	21.7	49.0	15.8	13.5
High school graduate	410	35.4	47.6	11.5	5.6
Some college	519	37.2	50.7	7.1	5.0
College graduate	583	52.7	42.4	3.9	1.0
>College	474	57.2	38.6	3.4	0.8

Table continues

cant confounders remained in the models if their removal resulted in ≥10 percent change in the parameter estimate. Models were built for birth weight by using linear regression analysis (34).

## RESULTS

Higher caffeine consumption was associated with maternal age of 24 years or younger, increased parity and gravidity, being previously married, being Hispanic, not graduating from high school, smoking ≥10 cigarettes per day

during the first and third trimesters, and drinking >1 ounce of alcohol a day during the first trimester (table 1).

The overall rate of IUGR was 8.4 percent, and women at high risk had no prior pregnancies or deliveries, were married previously, were not high school graduates, and had a prepregnancy weight of <120 pounds (1 pound = 0.45 kg) and height of <63 inches (1 inch = 2.54 cm) (table 2). Smoking during the first and third trimesters strongly increased risk. Race and gender were adjusted in the estimation of growth retardation.

TABLE 1. Continued

Characteristic	No.	Caffeine consumption (mg/day; first-trimester average)			
		None	1–149	150–299	≥300
Pregpregnancy weight (pounds)*					
<120	439	44.0	44.6	6.8	4.6
120–139	744	46.4	42.6	7.3	3.8
140–159	516	43.6	45.7	6.2	4.5
≥160	539	37.7	48.6	9.1	4.6
Height (inches)†					
<63	605	39.8	45.9	8.4	5.8
63–64	621	41.1	46.2	7.7	5.0
65–66	539	45.4	44.5	7.6	2.4
≥67	512	46.9	43.9	5.5	3.7
Smoking, first trimester (average no. of cigarettes/day)					
0	1,943	47.7	44.8	5.4	2.1
≤9	233	19.3	52.8	18.4	9.4
>9	113	8.8	38.0	20.3	32.7
Smoking, third trimester (average no. of cigarettes/day)					
0	2,078	45.9	45.8	5.9	2.4
≤9	92	12.0	52.2	19.6	16.3
>9	63	9.5	28.6	31.7	30.2
Alcohol, first trimester (average absolute alcohol ounces‡/day)					
≤0.1	2,029	45.5	43.5	6.9	4.1
>0.1–≤0.25	108	32.4	52.8	11.1	3.7
>0.25–≤1	111	15.3	69.4	8.1	7.2
>1	42	19.0	45.2	23.8	11.9
Alcohol, third trimester (average absolute alcohol ounces/day)					
≤0.1	1,933	44.4	44.7	6.9	4.0
>0.1–≤0.25	46	32.6	54.3	10.9	2.2
>0.25–≤1	28	14.3	67.9	17.9	0.0
>1	5	40.0	60.0	0.0	0.0

\* One pound = 0.45 kg.

† One inch = 2.54 cm.

‡ One ounce = 28.3 g.

In this study, overall rates of low birth weight and preterm delivery were 4.7 percent and 7.0 percent, respectively. Associations with potential confounding factors were similar to those found for IUGR (data not shown). Primary risk factors, identified in logistic models, are presented below.

Unadjusted associations of caffeine consumption during the first and third trimesters with IUGR, low birth weight, and preterm delivery are shown in table 3. First-trimester caffeine consumption was associated with increased risk of IUGR (linear-trend  $p = 0.009$ ), with daily first-trimester caffeine consumption of  $\geq 300$  mg/day seeming to particularly increase the risk (odds ratio (OR) = 2.74, 95 percent confidence interval (CI): 1.52, 4.95). Similar increases in risk were shown for low birth weight ( $p$  for trend = 0.045), with caffeine consumption of  $\geq 300$  mg/day increasing the risk (OR = 2.55, 95 percent CI: 1.14, 5.70), and for preterm

delivery ( $p$  for trend = 0.009), with increased risk in the highest caffeine consumption group (OR = 2.03, 95 percent CI: 1.03, 4.01). For third-trimester caffeine intake, these trends were less evident, and only low birth weight was statistically significant ( $p$  for trend = 0.037).

We modeled the first-trimester caffeine's association with reproductive outcomes, adjusting for eight principal confounding factors (table 4). For each outcome, the caffeine effect was reduced and did not differ significantly from unity. Risk factors for IUGR remaining in the model were smoking 1–9 cigarettes per day (OR = 5.66, 95 percent CI: 3.26, 9.81) or  $\geq 10$  cigarettes (OR = 3.45, 95 percent CI: 1.61, 7.41) during the third trimester, being in any prepregnant maternal weight category  $>120$  pounds (with an approximately doubled risk for the lighter women), and experiencing a second delivery (vs. the first, OR = 0.45, 95 percent

**TABLE 2. Association of selected characteristics of the study population with intrauterine growth retardation, Connecticut and southern Massachusetts, 1996–2001\***

Characteristic	No.	% with IUGR†	OR†	95% CI†
Respondent's age (years)				
≤24	487	9.03	Referent	
25–29	573	9.95	1.11	0.73, 1.68
30–34	788	7.49	0.81	0.54, 1.22
≥35	430	7.21	0.78	0.48, 1.26
Parity				
0	991	11.10	Referent	
1	810	4.94	0.42	0.29, 0.61
≥2	474	8.65	0.76	0.52, 1.10
Previous no. of abortions				
0	1,779	8.77	Referent	
1	354	5.93	0.66	0.41, 1.05
≥2	142	9.86	1.14	0.64, 2.02
Previous no. of pregnancies				
0	660	11.67	Referent	
1	685	6.86	0.56	0.38, 0.82
2	472	7.42	0.61	0.40, 0.92
≥3	458	6.99	0.57	0.37, 0.87
Marital status				
Currently married	1,619	7.60	Referent	
Never married	551	9.80	1.32	0.94, 1.85
Previously married	108	12.96	1.81	1.00, 3.27
Race				
White	1,594	8.28	Referent	
Black	189	7.41	0.88	0.50, 1.57
Hispanic	437	9.15	1.11	0.77, 1.62
Asian/other	58	8.62	1.04	0.41, 2.66
Education				
<High school	302	14.24	2.01	1.25, 3.21
High school graduate	407	7.13	0.93	0.56, 1.54
Some college	516	7.17	0.93	0.58, 1.50
College graduate	581	7.92	1.04	0.66, 1.64
>College	471	7.64	Referent	

Table continues

CI: 0.27, 0.75). Almost-identical risk factors remained in the model of third-trimester caffeine exposure with essentially the same estimates of risk.

In the logistic model for first-trimester caffeine consumption and low birth weight, Black (OR = 3.84, 95 percent CI: 1.92, 7.65) or Hispanic (OR = 2.26, 95 percent CI: 1.16, 4.42) ethnicity, one (OR = 0.51, 95 percent CI: 0.30, 0.85) or more (OR = 0.50, 95 percent CI: 0.26, 0.94) prior livebirths, prepregnancy weight of 140–160 (OR = 0.48, 95 percent CI: 0.24, 0.93) or ≥160 (OR = 0.50, 95 percent CI: 0.26, 0.94) pounds, and third-trimester smoking of 1–9 cigarettes daily (OR = 4.32, 95 percent CI: 2.15, 8.67) remained in the model. For third-trimester caffeine exposure, the risk factors retained in the model were essentially unchanged except for

cigarette smoking, which further increased risk (OR = 4.87, 95 percent CI: 2.37, 10.00).

The only significant risk factor for preterm delivery retained in the final model for first-trimester caffeine consumption was delivering a second or higher-order child (OR = 0.56, 95 percent CI: 0.34, 0.92). Risk factors in the third-trimester caffeine models included only a second or higher-order child (OR = 0.36, 95 percent CI: 0.17, 0.77).

We stratified analyses of caffeine exposure and the three major reproductive outcomes by cigarette smoking (ever vs. none during pregnancy) to examine potential interactions between these exposures. For IUGR, the only increased risk was for women who smoked and for whom daily first-trimester caffeine exposure of ≥300 mg doubled IUGR (24.6 percent) over the rate for women consuming no caffeine or

TABLE 2. Continued

Characteristic	No.	% with IUGR†	OR†	95% CI†
Pregnancy weight (pounds‡)				
<120	437	14.19	Referent	
120–139	737	7.73	0.51	0.35, 0.74
140–159	514	7.39	0.48	0.32, 0.74
≥160	537	5.96	0.38	0.24, 0.60
Height (inches§)				
<63	599	11.52	Referent	
63–64	617	7.94	0.66	0.45, 0.97
65–66	538	7.06	0.58	0.38, 0.88
≥67	510	6.47	0.53	0.34, 0.82
Smoking, first trimester (average no. of cigarettes/day)				
0	1,931	7.04	Referent	
≤9	233	15.02	2.33	1.56, 3.48
>9	111	17.12	2.72	1.61, 4.60
Smoking, third trimester (average no. of cigarettes/day)				
0	2,067	7.21	Referent	
≤9	92	28.26	5.07	3.12, 8.22
>9	63	17.46	2.72	1.39, 5.33
Alcohol, first trimester (average absolute alcohol ounces¶/day)				
≤0.1	2,018	8.37	Referent	
>0.1–≤0.25	108	11.11	1.37	0.74, 2.54
>0.25–≤1	110	6.36	0.78	0.40, 1.50
>1	41	7.32		
Alcohol, third trimester (average absolute alcohol ounces/day)				
≤0.1	1,931	8.70	Referent	
>0.1–≤0.25	46	8.70	1.00	0.35, 2.82
>0.25–≤1	28	3.57	0.33	0.04, 2.41
>1	5	0.00		
Gender				
Male	1,153	7.8	Referent	
Female	1,113	9.2	1.21	0.90, 1.62

\* Total numbers may differ because of missing data.

† IUGR, intrauterine growth retardation; OR, odds ratio; CI, confidence interval.

‡ One pound = 0.45 kg.

§ One inch = 2.54 cm.

¶ One ounce = 28.3 g.

lesser quantities (approximately 11–15 percent in other categories). This estimate was based on only 15 exposed women who experienced IUGR, and the overall precision was low ( $p = 0.11$ ). Among smokers who consumed large quantities of caffeine during the first trimester, doubled risks were also observed for low birth weight and preterm delivery, but the precision was also low ( $p = 0.44$  and  $p = 0.31$ , respectively).

Urinary caffeine was first evaluated in quartiles, the lowest value being the referent group. No significant associations were found for urinary caffeine or cotinine. For example, the highest odds ratios for urinary caffeine quartiles were 0.72

(95 percent CI: 0.44, 1.17) for IUGR, 0.54 (95 percent CI: 0.26, 1.10) for low birth weight, and 0.65 (95 percent CI: 0.37, 1.13) for preterm delivery. For urinary cotinine, the respective odds ratios were 1.45 (95 percent CI: 0.90, 2.33), 1.85 (95 percent CI: 0.94, 3.66), and 1.30 (95 percent CI: 0.74, 2.28).

From logistic regression analysis of urinary caffeine and cotinine (table 5), no increased risk of IUGR or preterm delivery was observed for every 1 mg increase in urinary caffeine per gram of creatinine. However, there was evidence of a protective effect of urinary caffeine on low

**TABLE 3. Crude associations between caffeine consumption and birth outcomes (intrauterine growth retardation, low birth weight, and preterm delivery), Connecticut and southern Massachusetts, 1996–2001**

Exposure	No.	IUGR*			Low birth weight			Preterm delivery		
		No.	OR*	95% CI*	No.	OR	95% CI	No.	OR	95% CI
Caffeine consumption, first trimester (average mg/day)										
0	983	65	Referent		33	Referent		57	Referent	
1–149	1,040	95	1.42	1.02, 1.97	54	1.58	1.01, 2.45	74	1.24	0.87, 1.78
150–299	170	15	1.36	0.76, 2.44	13	2.38	1.22, 4.62	18	1.92	1.10, 3.36
≥300	99	16	2.74	1.52, 4.95	8	2.55	1.14, 5.70	11	2.03	1.03, 4.01
Caffeine consumption, third trimester (average mg/day)										
0	1,100	86	Referent		40	Referent		70	Referent	
1–149	906	76	1.08	0.78, 1.49	37	1.13	0.71, 1.78	50	0.86	0.59, 1.25
150–299	117	15	1.73	0.96, 3.10	8	1.94	0.89, 4.25	10	1.38	0.69, 2.75
≥300	34	2	0.74	0.17, 3.12	2	1.65	0.38, 7.14	4	1.96	0.67, 5.73

\* IUGR, intrauterine growth retardation; OR, odds ratio; CI, confidence interval.

birth weight (OR = 0.74, 95 percent CI: 0.54, 1.00). For each 0.005 mg increase in urinary cotinine per gram of creatinine, the odds of IUGR increased significantly (OR = 1.003, 95 percent CI: 1.001, 1.005), with smaller increased risks for low birth weight and preterm delivery. Similar results were observed when creatinine-adjusted urinary nicotine replaced the cotinine measure in the models (data not shown).

When gestational age was analyzed as a continuous variable, no association was found with self-reported first-trimester caffeine consumption (mg/day) ( $p = 0.60$ ) after adjustment for cigarette smoking and other risk factors. When mean birth weight was analyzed by first-trimester

caffeine consumption, adjusting for gestational age, smoking, and other risk factors, we found a highly significant association ( $p = 0.002$ ) (table 6). For each 100 mg of caffeine consumed per day, there was a decrement of 28 g in birth weight (95 percent CI: 10 g, 46 g). In comparison, smoking 10 cigarettes and 20 cigarettes during pregnancy lowered birth weight by 178 g and 356 g, respectively. The risk of delivering a clinically low-birth-weight infant was unaffected by every 100 mg of caffeine consumed during the first trimester (OR = 1.00, 95 percent CI: 0.98, 1.00).

To examine any effect from consuming decaffeinated coffee during pregnancy, we compared women who drank

**TABLE 4. Adjusted\* associations of caffeine consumption with birth outcomes (intrauterine growth retardation, low birth weight, and preterm delivery), Connecticut and southern Massachusetts, 1996–2001**

Exposure	IUGR†		Low birth weight		Preterm delivery	
	OR†	95% CI†	OR	95% CI	OR	95% CI
Caffeine consumption, first trimester (average mg/day)						
0	Referent‡		Referent§		Referent¶	
1–149	1.35	0.95, 1.92	1.45	0.89, 2.35	1.20	0.82, 1.76
150–299	1.05	0.53, 2.09	1.59	0.70, 3.60	1.74	0.93, 3.27
≥300	1.75	0.81, 3.76	1.32	0.46, 3.78	1.67	0.74, 3.81
Caffeine consumption, third trimester (average mg/day)						
0	Referent#		Referent**		Referent††	
1–149	1.03	0.73, 1.46	1.00	0.61, 1.65	0.84	0.56, 1.24
150–299	1.42	0.72, 2.82	1.12	0.43, 2.91	1.19	0.56, 2.53
≥300	0.32	0.06, 1.54	0.77	0.14, 4.25	1.79	0.54, 6.00

\* Controlling for age, parity, no. of prior pregnancies, marital status, race, education, height, smoking during the third trimester, and weight.

† IUGR, intrauterine growth retardation; OR, odds ratio; CI, confidence interval.

‡  $n = 2,159$ .

§  $n = 2,163$ .

¶  $n = 2,167$ .

#  $n = 2,070$ .

\*\*  $n = 2,070$ .

††  $n = 2,072$ .

**TABLE 5. Association of urinary caffeine and cotinine with intrauterine growth retardation, low birth weight, and preterm delivery, Connecticut and southern Massachusetts, 1996–2001**

Exposure*	No.	OR†	95% CI‡
IUGR‡	1,848		
Urine caffeine		0.96	0.85, 1.08
Urine cotinine		1.003	1.001, 1.005
Low birth weight	1,853		
Urine caffeine		0.74	0.54, 1.00
Urine cotinine		1.002	0.999, 1.005
Preterm delivery	1,854		
Urine caffeine		0.92	0.79, 1.07
Urine cotinine		1.001	0.999, 1.004

\* For each outcome, the model was adjusted for caffeine or cotinine and also for maternal age, parity, gravidity, marital status, race, education, and height.

† Change in the odds ratio (OR) per 1 mg increase in urinary caffeine and per 0.005 mg increase in urinary cotinine per gram of creatinine.

‡ CI, confidence interval; IUGR, intrauterine growth retardation.

only decaffeinated coffee ( $n = 162$ ) with women who drank both caffeinated and decaffeinated coffee, caffeinated coffee alone, or no coffee at all ( $n = 2,132$ ). Analyses controlling for potential confounders found no meaningful difference in any perinatal outcome: IUGR, OR = 1.11 (95 percent CI: 0.59, 2.09); low birth weight, OR = 0.70 (95 percent CI: 0.24, 2.00); and preterm delivery, OR = 0.46 (95 percent CI: 0.18, 1.16).

## DISCUSSION

There is considerable evidence for the plausibility of caffeine affecting fetal growth. Caffeine passes through

body tissues and crosses blood-brain and placental barriers (35, 36). During human pregnancy, caffeine half-life increases to 10 hours at 17 weeks' gestation and 18 hours in the third trimester (37), during which the fetus is exposed to caffeine for long periods because neither the fetus nor the placenta can metabolize caffeine. Hypothesized mechanisms of effect include impairment of uteroplacental, fetoplacental, or villous blood flow (38, 39). Intervillous placental blood flow decreases after maternal ingestion of only 200 mg of caffeine (40).

Among pregnant women typically exposed to current levels of caffeine, we found an association with small decrements in birth weight of some 28 g per cup of coffee. Although statistically significant, these decrements are unlikely to be clinically important except for women drinking  $\geq 600$  mg of caffeine daily (equivalent to six 10-ounce cups of coffee (2)), which produced birth-weight decrements equivalent to smoking 1–10 cigarettes daily or a decrement of some 170 g. No caffeine effect was observed on preterm delivery, gestational age at delivery, IUGR, or low birth weight, suggesting that moderate caffeine consumption reduces birth weight without affecting the number of clinically small babies. The absence of effect on gestational age indicates that caffeine influences fetal growth, not gestational age at delivery.

The small effect on birth weight may explain why some studies find significant effects of caffeine on pregnancy outcomes while others do not. For preterm delivery, our study agrees with many reports not finding an association with caffeine exposure (10, 15, 22, 23, 28, 30, 32, 41–43). Eskenazi et al. reported increased preterm birth among women who drank caffeinated and decaffeinated coffee, suggesting increased risk due to agents other than caffeine (15). To our knowledge, that study has not been replicated, and our analysis did not support it. Gestational age is difficult to assess accurately (44), and misclassification may account for some null results with it and its derivative, IUGR.

**TABLE 6. Changes in mean birth weight due to caffeine consumption and selected risk factors, Connecticut and southern Massachusetts, 1996–2001**

Risk factor*	Change in birth weight (g)	95% CI†	<i>p</i> value
Caffeine (per 100 mg)‡	–28	–46, –10	0.002
Cigarettes (per 10)§	–178	–246, –110	<0.000
Gestation (per week)	174	165, 183	<0.000
Black (vs. White) race	–219	–290, –148	<0.000
Hispanic (vs. White) race	–33	–93, 27	0.28
Height (per inch¶)	22	16, 28	<0.000
Weight (per 10 pounds)#	26	20, 32	<0.000
Gravidity (each pregnancy)	33	20, 46	<0.000

\* Also in the model, but having no statistically significant effect on birth weight, were education (each completed year) and respondent's age ( $\leq 24$ , 25–29, 30–34,  $\geq 35$  years).

† CI, confidence interval.

‡ Caffeine consumption during the first trimester; 100 mg is approximately equivalent to the caffeine content of one 10-ounce cup of coffee (1 ounce = 28.3 g).

§ Cigarettes smoked during the third trimester.

¶ One inch = 2.54 cm.

# Prepregnancy weight; one pound = 0.45 kg.

Fetal growth retardation is typically assessed as IUGR, small for gestational age, or birth weight in term infants, and results are inconsistent. Associations with caffeine were reported in several studies (10, 12, 22, 45, 46), but others found no association with IUGR (15, 27, 29, 47) or only from caffeine derived solely from coffee (23).

Low birth weight was associated with caffeine in some studies (9, 10, 12, 14, 48, 49) but not others (13, 15, 22, 23, 26, 28, 30–32, 41). Mean birth weight decrements are infrequently examined: estimates similar to ours,  $-105$  g for  $\geq 301$  g of caffeine (10) and  $-93$  g for 200–400 mg (49), were found in two studies and  $-102$  g for 71–140 mg of caffeine in another (14). Other investigators reported smaller birth-weight decrements per cup of coffee (13, 15). Clausson et al. recently reported finding no association with mean birth weight, gestational age, or birth weight ratio and were able to exclude with 95 percent confidence a birth-weight decrement of  $>181$  g for women consuming 300–499 mg of caffeine daily (50), which is in accordance with the findings in the current study that predicts decrements of 84–140 g for this level of caffeine consumption.

Most studies report effects (16–18, 20, 51, 52) of caffeine on spontaneous abortion, but not all (22, 25, 29). In one study, the association appeared stronger for coffee than caffeine in general and was primarily found in later-trimester abortions, presumably largely of normal karyotype (20). In another study, the effects seemed particularly strong among smokers and only in normal karyotyped abortions (53). Only one study used serum paraxanthine, a caffeine biomarker, to assess risk, and the highest levels were associated (54). Our study included too few spontaneous abortions to provide reliable estimates of a caffeine effect. Nausea or vomiting in early pregnancy has been considered a possible confounder in studies of caffeine and spontaneous abortion, but, in this study, they were unrelated to any of the outcomes studied and occurred in 81.5 percent of respondents.

For decaffeinated coffee, our study replicates those by Fortier et al. (23) and Eskenazi et al. (15), who found no association with IUGR. Eskenazi et al. (15) reported additive risks of drinking caffeinated and decaffeinated coffee on IUGR, but this finding seems biologically plausible only if some component in coffee other than caffeine is implicated.

Caffeine consumption is difficult to measure (3), and substantial misclassification occurs when consumption fails to account for actual cup size used or when caffeine content is estimated by using traditional laboratory standards (2). Unlike most prior studies, ours was specifically designed to test the caffeine–perinatal outcome hypothesis. Caffeine content and serving sizes actually consumed by respondents were measured in a large sample to estimate exposure (2). Urinary caffeine was not associated with increased risk, raising doubt about the utility of this biomarker. Only 0.5–2.0 percent of caffeine is excreted as such in the urine because of 98 percent tubular reabsorption (35), providing considerable opportunity for error in estimating caffeine from such a small residual amount in urine. Additional imprecision will occur when urine is a single measurement and when caffeine sources from nonbeverages are excluded, which occurred here.

The one prior study that used serum caffeine as a biomarker of exposure reported that it was not associated with fetal growth, although self-reported caffeine intake was (31). Klebanoff et al. recently reported a modest association of small-for-gestational-age births with serum paraxanthine in the Collaborative Perinatal Project; however, serum caffeine was not associated with reduced fetal growth (55). The study by Klebanoff et al. is the only one known to use paraxanthine as a biomarker of caffeine exposure, but no self-report measures were available. Paraxanthine is the major metabolite from caffeine and so may represent a more stable and valid measure of exposure than caffeine itself (56).

We observed a significantly *reduced* risk of low birth weight associated with urinary caffeine. Similar reductions in IUGR risk have been reported in the two highest urinary caffeine quartiles (adjusted OR = 0.22, 95 percent CI: 0.04, 1.09 and adjusted OR = 0.25, 95 percent CI: 0.06, 1.06) in an earlier cohort we studied (57). These seemingly paradoxical results may be explicable if caffeine metabolites, rather than caffeine, influence fetal growth. More rapid elimination of caffeine may lead to lower levels of metabolites. More detailed study of caffeine metabolites is needed to further explain the possible health effects of caffeine during pregnancy and the equivocal results observed in the extant epidemiologic literature.

Timing teratogenic exposure during pregnancy is important. Some exposures influence outcome if they occur during only a specific period (58). For example, women who quit smoking before the third trimester may reduce the effect on fetal development (59). In our study, first-trimester caffeine exposure seemed more predictive of risk for reasons that are unclear. First-trimester data were collected prospectively and may have been less biased than the retrospectively collected third-trimester exposure. However, when we compared prospective data collected at 28 and 36 weeks of pregnancy with the respective data ascertained retrospectively, in the subsamples of women in which this comparison was possible, quite good agreement was observed (weighted kappa values of 0.62 and 0.58, respectively).

This study confirms the importance of cigarette smoking during pregnancy as a risk factor for IUGR and low birth weight (60). It also suggests that the strong association of cigarette smoking with caffeine consumption, if not fully controlled, may confound associations of caffeine with perinatal outcomes. In a Nordic study, an association of maternal caffeine intake with sudden infant death syndrome disappeared after adjustment for maternal smoking (61). Klebanoff et al. found a modest association of increased risk of small-for-gestational-age birth with increasing serum paraxanthine but only for those women who also smoked. Because of the high correlation of paraxanthine level and smoking, reflecting increased smoking with increasing caffeine consumption, and the difficulty of statistically adjusting for all the effects of smoking even when daily cigarette smoking was used, it is possible that this finding represents residual confounding from smoking. In Klebanoff et al.'s analysis, no association was found between paraxanthine and small-for-gestational-age births among nonsmokers (55).

The interaction between caffeine and smoking is particularly important. It is possible that smoking and caffeine interact with each other to reduce fetal growth, but the mechanisms by which caffeine may reduce fetal growth are unclear and may differ from those by which smoking induces its effects. Women who drink caffeine also tend to smoke, and women who smoke metabolize caffeine more quickly, which may protect the fetus from developmental effects. There was no evidence of any interaction between smoking and caffeine exposure in our study, and the evidence for this interaction from prior research is mixed; some studies reported effects (9, 23, 31), but others found none (12, 22, 32).

This study provides reassurance that moderate caffeine consumption during pregnancy does not meaningfully influence fetal growth. Large quantities of caffeine should be avoided, but we found no evidence of risk from consumption of decaffeinated coffee.

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