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Caffeine Intake and Low Birth Weight: A Population-based Case-Control Study

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The authors conducted a matched case-control study to investigate the effects of caffeine intake during pregnancy on birth weight. From January to November 1992, in the first 24 hours after delivery, 1,205 mothers (401 cases and 804 controls) were interviewed and their newborns were examined to assess birth weight and gestational age by means of the method of Capurro et al. (*J Pediatr* 1978;93:120–2). The cases were children with birth weight <2,500 g and gestational age ≥28 weeks. Cases and controls were matched for time of birth and hospital of delivery and were recruited from the four maternity hospitals in Pelotas, southern Brazil. Daily maternal caffeine intake during pregnancy for each trimester was estimated. To assess caffeine intake, 10% of the mothers were reinterviewed at their households and samples of reported information on drip coffee and maté (a caffeine-containing drink widely used in South America) were collected and sent to the laboratory for caffeine determination through liquid chromatography. When instant coffee was reported, the weight of powder was measured using a portable scale, and caffeine intake was estimated from a reference table. Caffeine intake from tea, chocolate, soft drinks, and medicines was estimated from a reference table. Analyses were performed by conditional logistic regression. Crude analyses showed no effect of caffeine on low birth weight, preterm births or intrauterine growth retardation. The results did not change after allowing for confounders. *Am J Epidemiol* 1998;147:620–7.

caffeine; fetal growth retardation; infant, low birth weight; infant, premature

Birth weight is a major risk factor for morbidity and mortality in the first year of life (1–4). Low birth weight may result from intrauterine growth retardation (IUGR) or from preterm delivery. Most low birth weight children are born in developing countries (5), where IUGR is its predominant cause (6). There are many well-established risk factors for low birth weight, including socioeconomic factors, maternal nutritional status, birth interval, and smoking (6, 7).

Caffeine intake during pregnancy has also been suggested as a risk factor (6). Caffeine (1,3,7-trimethylxanthine) is a plant alkaloid (8), structurally related to DNA purine bases. Major sources of caffeine are coffee, tea, chocolate/cocoa, and cola soft drinks. It is estimated that almost 200 nonprescribed drugs contain caffeine and this may be an important source for a minority of people (8). In pregnant women, clearance of caffeine from the body is delayed, mainly in the second and third trimesters, when it decreases to one-half and to one-third of the normal rate, respectively (9). Caffeine crosses the placental barrier so that maternal blood levels are virtually equal to fetal blood levels (10). The enzymes needed for caffeine metabolism, however, are absent in the fetus and up to the eighth month after delivery (11). Concern about the possible harmful effects of caffeine in pregnancy has evolved mainly from studies in animals (12, 13), which have indicated a decrease in intrauterine fetal growth, a lower birth weight, and skeletal abnormalities. Nevertheless, the implications of these findings for human beings are unclear because of differences in the mode of exposure to caffeine, the amounts consumed, and the metabolism of the drug.

A review of the literature on MEDLINE (1966 to 1995) revealed that, of 22 studies on caffeine and birth weight (14–35), 12 showed that higher intakes of caffeine or coffee were associated with lower birth weight (14–17, 19–21, 23, 25, 31–33). Dose-response effects were demonstrated in eight studies (14, 16, 23, 26, 27, 29, 30, 33). These studies also showed that coffee drinking was related to smoking (14, 18, 21–25,

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Abbreviations: IUGR, intrauterine growth retardation; LRS, likelihood ratio statistic; OR, odds ratio.

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27–29, 30, 33) and to alcoholic beverage intake (15, 23, 28, 29, 32). After allowing for smoking, caffeine intake remained as a risk factor for low birth weight in 12 studies (14, 18, 21–25, 27–30, 33) out of 17 studies. The effect of caffeine intake on preterm deliveries was less clear, with only three out of 11 studies (16, 19, 21, 23, 28, 30, 33, 36–39) showing a significant association (16, 36, 38).

Most of the studies published to date, however, have had methodological flaws in their design. These flaws include 1) inadequate measurement of intake (almost all studies have relied on reported intakes, some were limited to coffee consumption and ignored other sources of caffeine, and most ignored distinctions between different types of preparation and different strengths of coffee); 2) inadequate control for the possible confounding effects of variables such as smoking, alcohol, and maternal age; and 3) insufficient statistical power in some studies. Therefore, the association between caffeine consumption and low birth weight or duration of pregnancy remains controversial.

In Pelotas, southern Brazil, 9 percent of children born in 1982 had a low birth weight, 14.9 percent had IUGR, and 6.3 percent were preterm (7). In the same city in 1993, the corresponding prevalences were 9.7, 16.7, and 11.5 percent (40). Over 99 percent of births take place in hospital in this region of Brazil (3, 7). Besides coffee, caffeine consumption is common through a local drink, maté. To prepare maté, ground leaves of *Ilex paraguayensis* are poured into a gourd and small volumes of hot water are added. Then the consumer sips through a metal straw with a filtering head which is introduced to the bottom of the gourd. A previous study in Pelotas (41) showed that 29 percent of the adult female population were daily consumers of maté. These patterns make Pelotas a suitable place to test the hypothesis that increased caffeine intake is linked with low birth weight.

MATERIALS AND METHODS

A population-based matched case-control study was conducted. An inclusive design was adopted (42) whereby controls were selected from all individuals of the target population, independent of whether or not they had the outcome of interest (low birth weight). The odds ratio obtained from inclusive case-control studies estimates the risk ratio that could be obtained from the corresponding cohort study, without the overestimation that would be obtained from the classic case-control design when the outcome is relatively common (42). The study was planned to have a power of 90 percent to detect a relative risk of 1.5 or more as significant at the 5 percent level, for an exposure affecting 30 percent of the controls. With two controls per case and allowing 30 percent for confounding, losses, or refusals (43), a sample size of 400 cases and 800 controls was deemed adequate. Assuming that 40 percent of the cases ($n = 160$) would be preterm, the study would have 80 percent power of detecting a relative risk of 2.0 for analyses in this subgroup.

From January to November 1992, all low birth weight singleton infants born in hospitals in Pelotas were included in the study as cases. Stillbirth cases were included if they had at least 28 weeks of gestational age or, if their gestational age was not known, they weighed at least 1,000 g. The next two singleton infants born in the same hospital as the case were selected as controls, independent of their birth weight. With such a design, a child could be selected both as a case and as a control. For example, if two low birth weight children were born consecutively, then they were both included as cases and the latter was also a control for the former. The same exclusion criteria were used for cases and controls.

Cases and controls were weighed and measured and their gestational age was assessed according to the method of Capurro et al. (44) in the first 24 hours after birth. Structured interviews were conducted with mothers of cases and controls during their stay in hospital. The questionnaire ascertained information on caffeine intake and on potential confounders such as age, education level, marital status, place of residence, family income, anthropometric measures, skin color, alcoholic intake, prenatal attendance, morbidity, and passive and active smoking during pregnancy.

Outcome definitions

The outcomes studied were as follows: low birth weight (birth weight <2,500 g); preterm birth (birth that occurred prior to 37 completed weeks of pregnancy); and intrauterine growth retardation (IUGR) (birth weight <2,500 g and gestational age ≥37 weeks of pregnancy).

Exposure assessment

Caffeine intake was assessed through a series of questions on the consumption of caffeinated and decaffeinated coffee, tea, maté, cola soft drinks, drinking chocolate, chocolate, and medicines. For each of these caffeine sources, the frequency of consumption per day was obtained separately for each trimester of pregnancy. Mothers were considered as "consumers" of each of these sources if they reported at least a weekly intake.

For coffee, information was collected on the usual method of preparation (filter or instant), the reported

strength (strong, medium, or weak), and the size of the serving (cup, 180 ml; small cup, 50 ml; glass, 200 ml; mug, 190 ml), with serving sizes calculated from local measures (45). The caffeine content in different coffee preparations and in maté drink was obtained from samples collected in the households of about 10 percent (n = 114) of the women. During household visits, mothers were reinterviewed about coffee and maté drinking habits in the third trimester of pregnancy. Samples of filtered coffee (without adding sugar or milk) and the used leaves of maté drink were assessed for caffeine content by liquid chromatography (46). The caffeine content of maté drink was estimated by measuring the difference in caffeine concentration between the used leaves and the same amount of fresh maté of the same trademark. From these analyses, for women who drank strong coffee, it was possible to infer the following average mg of caffeine per ml: strong coffee, 0.25 mg/ml (45 mg per cup); medium strength coffee, 0.20 mg/ml (36 mg per cup); and weak coffee, 0.11 mg/ml (19.8 mg per cup). For maté drink, the analyses showed an average concentration of 17 mg of caffeine per 100 ml of liquid (about 10 mg per gourd). These results were used to estimate caffeine intake of the whole sample. For instant coffee, mothers were asked about the size of the spoon used to serve (full coffee spoon, 2.6 g; level coffee spoon, 2.3 g; full small coffee spoon, 2.5 g; level small coffee spoon, 1.5 g; full dessert spoon, 7.5 g; and level dessert spoon, 7.0 g) and the number of spoons per serving. Spoon sizes were obtained from household measurements. Photographs of spoons and of chocolate bars (large, 200 g; medium, 80 g; and small, 30 g) were used during the interview to avoid misclassification of information on instant coffee, drinking chocolate, and chocolate bars. For instant coffee, the manufacturer's information of an average 3 mg of caffeine per g of powder was used. For tea, soft drinks, and chocolate, the amount of caffeine consumed was estimated from international references (47), i.e., 54 mg/180 ml for strong tea; 43 mg/180 ml for medium tea; 34 mg/180 ml for weak tea; 20 mg/200 ml glass for soft drinks; 4 mg/200 ml for drinking chocolate; and 20 mg/30 g for chocolate bars. Mothers were also asked about the use of symptomatic medicines to relieve pain or cold, including the trade name of the medicine, dose, frequency of intake per day, and the number of days used per trimester.

For each mother, these estimates were transferred to a spreadsheet, and daily maternal caffeine intakes, by source, by trimester, and throughout the entire pregnancy, were calculated.

Data analysis

Odds ratios and their 95 percent confidence intervals were calculated using conditional logistic regression. Statistical significance was assessed through the likelihood ratio test (43). We also examined the linear effects of increasing levels of ordinal variables, such as caffeine intake, on the risk of low birth weight.

Multivariate analyses were conducted taking into account the hierarchical relations between the risk factors (48) according to the conceptual framework shown in figure 1. At the first step of the multivariate analyses, all socioeconomic variables were entered, and those which had a significant effect at the 0.1 level were retained in the model. Next, the biologic variables were added with the same retention criteria, and a similar procedure was repeated for subsequent levels. The adjusted odds ratios for caffeine intake take into account the factors at or above the maternal behavior level.

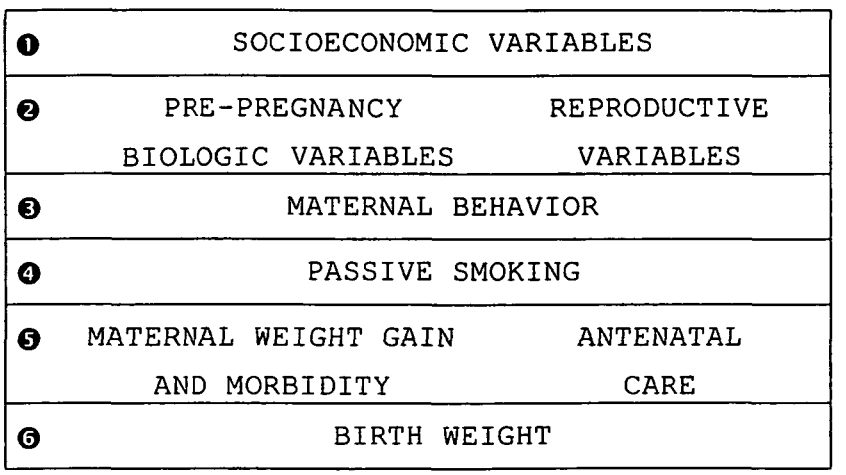

FIGURE 1. Conceptual framework of risk factors for low birth weight: Pelotas, Brazil, 1992.

Analyses were conducted initially with all low birth weight infants and then separately for term cases and for preterm cases with their respective controls. Because the measured levels of caffeine in filtered coffee were substantially lower than the international reference levels (45) of 80 mg of caffeine per 150 ml of filtered coffee, analyses were repeated using the latter.

The potential modifying effects of smoking and of maternal pre-pregnancy weight on the caffeine-birth weight association were assessed by tests for heterogeneity of odds ratios (43).

RESULTS

A total of 401 cases and 804 controls were recruited into the study. Only 19 mothers (1.6 percent) were missed: seven cases and 12 controls, including only one refusal. Among the cases, 169 (42.1 percent) were full-term newborns, 176 (43.9 percent) were preterm, and 56 (14.0 percent) did not have their gestational age assessed. Eighty-nine cases (22 percent) were also included as controls. Seven of these cases entered the study three times: once as a case, once as a first control, and once as a second control. A total of 13 controls (1.6 percent), including the above seven cases, were included twice as controls.

Table 1 shows the patterns of caffeine intake among cases and controls. The mean caffeine intake from each source and from all sources together was highly correlated in the three trimesters of pregnancy ($p < 0.001$). Thus, the results are based on the average daily caffeine intake throughout the entire pregnancy. Although coffee was the most commonly used source, maté drink was the main source of caffeine among users, accounting for nearly 50 percent of the intake in both groups. Seventy percent of mothers of the cases and 60 percent of mothers of the controls were daily consumers of coffee during the entire pregnancy. About 40 percent of all mothers were daily consumers of maté drink. For all sources, mean daily caffeine intake was very similar among cases and controls.

Heavy caffeine consumers (≥300 mg per day throughout pregnancy) were more likely to live in urban areas, to be white, thinner, and taller, and to have smaller body mass indices. They were also more likely to be smokers, to consume alcoholic drinks, to have less sexual intercourse in the last month of pregnancy, and to attend antenatal care less frequently (data not shown).

Crude and adjusted odds ratios, using the strategy described in Materials and Methods, are presented in table 2 for each source of caffeine. The crude odds ratios show that the effect of caffeine on low birth weight was not consistent nor statistically significant. After allowing for confounders, for almost all sources, higher caffeine consumption was associated with lower risks of low birth weight, although not significantly so. An exception occurred with the consumption of chocolate bars or sweets, where the reverse was found and a borderline significant trend was seen. Similar results were observed when the frequency of consumption for each source was considered (data not shown). Because caffeine intake was positively associated with other risk factors for low birth weight (e.g., smoking and low maternal anthropometry), its "protective" effect was underestimated in the crude analyses.

When all sources were combined and the impact on birth weight estimated, crude analyses showed no association with total daily caffeine intake (table 3). After allowing for confounding factors, a similar increase in risk of low birth weight was found for intermediate caffeine consumption compared with low consumption (odds ratio (OR) = 1.07) and a lower risk for heavy consumption (OR = 0.73). The use of

TABLE 1. Number of consumers, mean daily caffeine intake throughout pregnancy, and proportion of caffeine consumed by source among cases and controls*: Pelotas, Brazil, 1992

Source	Cases				Controls			
	Consumers		Caffeine (mg/day)	% of total caffeine intake†	Consumers		Caffeine (mg/day)	% of total caffeine intake†
	No.	%			No.	%		
Coffee	366/395	93	44.5	40.3	726/791	92	47.3	42.7
Maté drink	284/390	73	100.5	50.1	548/760	72	94.5	48.5
Chocolate bars/sweets	106/390	27	42.5	26.5	192/772	25	41.2	26.2
Soft drinks	192/382	50	33.4	26.8	371/768	48	34.0	29.1
Black tea	23/392	6	33.2	24.3	65/788	8	45.0	23.2
Chocolate drink	124/390	32	5.1	7.0	267/778	34	5.8	7.4
Medicines	3/401	1	40.3	5.7	6/804	1	21.0	4.3
Total			147.76				145.90	

* Among the cases, 93% of the mothers consumed coffee at least once a week during at least one trimester of pregnancy. Among mothers who consumed coffee, the mean daily intake was 44.5 mg/day and was the source of 40.3% of their caffeine intake during pregnancy.
† Nonconsumers excluded.

TABLE 2. Distribution among cases and controls and crude and adjusted* odds ratios for the effects on low birth weight of caffeine intake throughout pregnancy: Pelotas, Brazil, 1992

Source of caffeine by daily intake (mg)	Cases		Controls		Crude odds ratio	95% CI†	Adjusted odds ratios	95% CI	LRS†	df†	*p* value
	No.	%	No.	%							
Filtered coffee	(*n* = 393)		(*n* = 784)								
(Local parameters)											
0	155	39	322	42	1.00		1.00		1.77	3	0.62
1–39	120	31	246	31	1.00	0.74–1.34	1.11	0.79–1.56			
40–99	91	23	161	20	1.17	0.85–1.62	1.24	0.84–1.83			
≥100	27	7	55	7	1.05	0.64–1.72	0.88	0.50–1.55			
(International parameters)											
0	155	39	322	41	1.00		1.00		3.21	2	0.20
1–99	72	18	122	16	1.22	0.85–1.75	1.43	0.95–2.17			
≥100	166	42	340	43	1.01	0.78–1.32	1.02	0.74–1.39			
Instant coffee	(*n* = 393)		(*n* = 782)								
0	251	64	494	63	1.00		1.00		2.28	2	0.32
1–99	59	15	105	13	1.11	0.77–1.60	1.16	0.76–1.75			
≥100	83	21	183	23	0.88	0.65–1.19	0.82	0.57–1.17			
Maté drinking	(*n* = 390)		(*n* = 760)								
0	212	28	106	27	1.00		1.00		1.16	3	0.76
1–39	223	29	99	25	0.87	0.62–1.21	0.81	0.56–1.19			
40–99	183	24	92	24	1.02	0.72–1.45	0.86	0.58–1.29			
≥100	142	19	93	24	1.28	0.90–1.81	0.88	0.57–1.17			
Black tea	(*n* = 392)		(*n* = 788)								
0	369	94	723	92	1.00		1.00		2.81	2	0.24
1–39	20	5	51	6	0.77	0.45–1.33	0.85	0.46–1.57			
≥40	3	1	14	2	0.45	0.13–1.60	0.36	0.10–1.38			
Chocolate bars/sweets	(*n* = 390)		(*n* = 772)								
0	284	73	580	75	1.00		1.00		3.46	2	0.18
1–39	86	22	168	22	1.04	0.77–1.40	1.23	0.88–1.73			
≥40	20	5	24	3	1.80	0.95–3.43	1.77	0.85–3.67			
Chocolate drink	(*n* = 390)		(*n* = 778)								
0	266	68	511	66	1.00		1.00		0.00	1	0.95
1–50	124	32	267	34	0.91	0.70–1.19	1.05	0.75–1.36			
Cola soft drinks	(*n* = 382)		(*n* = 768)								
0	190	50	397	52	1.00		1.00		0.73	2	0.69
1–39	174	45	329	43	1.08	0.84–1.41	1.14	0.84–1.54			
≥40	18	5	43	6	1.75	0.41–1.38	1.07	0.55–2.10			

* Adjusted by conditional logistic regression for cigarette smoking (yes or no), pregestational weight in kg (<45, 45–49, 50–54, 55–59, ≥60), skin color (white, black, mixed), living with partner (yes or no), place of residence (urban or rural), maternal education in years (none, 1–4, 5–8, ≥9), and weekly frequency of sexual intercourse in the last month of pregnancy (<1, 1, ≥2).

† CI, confidence interval; LRS, likelihood ratio statistic; df, degrees of freedom.

TABLE 3. Crude and adjusted odds ratios for low birth weight, by level of caffeine intake throughout pregnancy, according to local parameters for filtered coffee: Pelotas, Brazil, 1992

Caffeine intake (mg/day)	% of cases	% of controls	Crude odds ratio	95% CI*	Adjusted odds ratio	95% CI	LRS*	df*	p value
All births	(*n* = 394)	(*n* = 787)							
<100	27	30	1.00		1.00		4.28	2	0.12
100–299	53	50	1.18	0.89–1.58	1.07†	0.77–1.50			
≥300	20	20	1.07	0.75–1.52	0.73†	0.48–1.12			
Preterm cases only	(*n* = 166)	(*n* = 314)							
<100	36	38	1.00		1.00		2.55	2	0.28
100–299	50	44	1.09	0.69–1.70	1.08‡	0.65–1.77			
≥300	14	18	0.82	0.45–1.47	0.65‡	0.33–1.29			
Term cases only	(*n* = 166)	(*n* = 329)							
<100	34	39	1.00		1.00		5.35	2	0.07
100–299	50	43	1.29	0.85–1.96	0.98§	0.59–1.64			
≥300	16	18	1.01	1.58–1.78	0.47§	0.23–0.97			

* CI, confidence interval; LRS, likelihood ratio statistic; df, degrees of freedom.
† Adjusted by conditional logistic regression for cigarette smoking, pregestational weight, skin color, living with partner, place of residence, maternal education in years, and frequency of sexual intercourse in the last month of pregnancy.
‡ Adjusted by conditional logistic regression for cigarette smoking, pregestational weight, and living with partner.
§ Adjusted by conditional logistic regression for cigarette smoking, pregestational weight, skin color, and place of residence.

international parameters to calculate caffeine intake from filtered coffee produced similar results (ORs = 0.95 and 0.73, respectively).

Table 3 also shows the effects of caffeine separately for preterm and IUGR cases. After allowing for confounding variables, a protective effect of high caffeine consumption was seen in both subgroups but especially for IUGR cases. When the international parameters for filtered coffee were used, the odds ratios (95 percent confidence intervals) for preterm birth and IUGR associated with high consumption were 0.48 (0.25–0.92) and 0.84 (0.4–1.79), respectively.

No significant effect modification by smoking or maternal pre-pregnancy weight was detected in the whole group nor in the subgroups of cases.

DISCUSSION

The results presented here show that in this population caffeine consumption during pregnancy is not associated with increased risks of low birth weight, intrauterine growth retardation, or preterm deliveries. Previous studies have produced inconsistent results. Incomplete information on caffeine consumption, recall bias, and inadequate control of confounding may account for some of the inconsistency in findings. Obtaining reliable measures of caffeine use during pregnancy is particularly difficult. Although we had to rely on reported consumption, we attempted to reduce error in assessing intake by other means. Information on all known sources of caffeine, including decaffeinated coffee and medicines, was collected. Special attention was paid to variations in caffeine content, the size of the cup or drink, and the method of preparation of food containing caffeine.

The results concerning the caffeine content of filtered coffee were surprising, but there is little reason to suspect that this was due to laboratory errors, because the caffeine concentration of maté drink was very close to findings in the international literature. There is evidence that the caffeine content of instant coffee manufactured in Brazil is also somewhat lower (47). In addition, most mothers belong to low socioeconomic groups who prefer inexpensive coffee brands for economic reasons. The brands are often found to be adulterated by mixtures of maize and barley (47). The method of preparation of coffee is also related to its caffeine content, and this was taken into consideration. The lower caffeine levels according to the actual measurements, compared with the international standards, explain why there were differences in the two sets of odds ratios.

Realistically, the precise estimation of caffeine intake has also to rely on mothers' information rather than direct measurement. In retrospective studies, recall bias may contribute to exposure misclassification. The usual direction of recall bias is overreporting of potential risk factors by people with poor outcomes, leading to an increased probability of a positive association. This was not the case in this study, where no association was found. Alternatively, mothers with unfavorable outcomes might underreport their consumption if they were embarrassed to admit to high intakes. This is unlikely to be the case in Brazil where there have been no warnings regarding caffeine intake

during pregnancy. Nondifferential misclassification of exposure, leading to underestimation of the effect of caffeine, is a possibility due to the difficulty in remembering exposure over a long period such as 9 months. Self-reported volumes and beverage strength of coffee and tea have, however, been found to be valid predictors of true consumption habits (49, 50).

Changes in the habits of consumption in different periods of pregnancy could also lead to nondifferential misclassification of the exposure. Even though some women may reduce coffee intake (9), there is evidence that the average intake remains constant throughout pregnancy (21, 37). In this study, mean daily caffeine intakes were highly correlated ($p < 0.01$) between the three trimesters.

Caffeine sources other than coffee and maté drink may be more affected by reporting bias due to their lower frequency of consumption. The amount of caffeine in these sources, however, is much lower than that present in coffee or in maté drink and is thus unlikely to affect greatly the total estimate of intake.

For logistical reasons, whereby cases had to be selected immediately because hospital discharges often occur within 24 hours of delivery, it was not possible to select cases on the basis of weight for gestational age, and a fixed cutoff had to be used (6). However, the analyses were repeated using the 10th percentile of weight for gestational age (51) as the cutoff, and the results were very similar (data not shown).

The validity of the estimates of caffeine intake is supported by the confirmation of known associations of other factors with caffeine consumption, particularly smoking and alcohol consumption. Comprehensive control of all potential confounders was also made in the analyses, thus reducing the likelihood that the lack of effect of caffeine was due to confounding.

The use of an inclusive case-control design is not common in the literature, but we believe this design is the best choice for the particular problem of concern here. Because the frequency of low birth weight is a measure of prevalence, the denominator must contain all individuals under study, regardless of whether or not they already have the outcome. Using this method, the odds ratio corresponds to the prevalence ratio in a cross-sectional study. In this kind of case-control design, the role of the control group is to estimate the proportion of population under exposure. If the exposure increases the risk of disease, for example, excluding cases from the control group would result in overestimation of the prevalence and of the odds ratio. For comparison, however, analyses were also conducted which excluded cases from the control group, as in a classic case-control study. Similar results were obtained to those presented here (data not shown).

There are few studies in the literature which show no effect of caffeine on birth weight and duration of pregnancy, and a publication bias in favor of positive studies may be suspected. It is possible that the differences between studies are due to genetic or cultural factors in the study populations, although unknown study bias may also be involved. Thus, a complete prohibition of caffeine use during pregnancy seems not to be recommended. However, because caffeine consumption is very prevalent in pregnancy, further studies of its effect on reproduction are needed.

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