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Original Contribution

Maternal Smoking During Pregnancy and Fetal Biometry

The INMA Mother and Child Cohort Study

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In utero tobacco exposure has been associated with fetal growth restriction, but uncertainty remains about critical windows of exposure and specific effects on body segments. In the present study, we aimed to examine the association of maternal smoking with fetal biometry in different stages of pregnancy. The study population comprised 2,478 fetuses from a Spanish birth cohort study that was established between 2003 and 2008. Biparietal diameter, femur length, abdominal circumference, and estimated fetal weight were evaluated at 12, 20, and 34 weeks of gestation. Fetal size and growth were assessed by standard deviation scores adjusted by maternal and fetal characteristics. Maternal smoking was assessed using questionnaire and a sample of urinary cotinine at week 32 of gestation. Associations were estimated using multiple regression analysis. Smokers at week 12 of gestation showed decreased fetal growth as reflected by all growth parameters at 20–34 weeks, leading to a reduced fetal size at week 34. The reduction was greatest in femur length, at −9.4% (95% confidence interval −13.4, −5.4) and least in abdominal circumference, at −4.4% (95% CI: −8.7, −0.1). Fetuses of smokers who quit smoking before week 12 showed reduced growth only in femur length (−5.5; 95% CI: −10.1, −0.9). Dose–response curves for smoking versus fetal growth parameters (abscissa: $\log_2$ cotinine) were linear for biparietal diameter and femur length.

cohort studies; fetal development; pregnancy; prenatal exposure; tobacco smoke

Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; CI, confidence interval; EFW, estimated fetal weight; FL, femur length; INMA, Infancia y Medio Ambiente.

Maternal smoking during pregnancy is a major modifiable cause of intrauterine growth restriction (1). Fetal growth is a good marker of perinatal survival and postnatal development (2–4). The study of the effects of maternal smoking on fetal growth is therefore important because it may be the first step in delineating the causal pathway in the well-documented association between prenatal exposure to tobacco smoke and health problems later in life, such as respiratory tract infections, impaired neurodevelopment, and childhood obesity (5–7).

Despite the number of studies over a period of several decades that have shown adverse associations between smoking and prenatal growth (8), some clinically relevant issues remain unclear. Among these areas of uncertainty are the following (9–11): 1) the specific critical periods for the effects of maternal smoking during pregnancy, and especially the age at which fetal growth failure begins (10, 12–16). This may be relevant because it may improve understanding of the pathological processes through which smoking affects fetal growth (12). To our knowledge, only 3 studies (10, 17, 18) based on prenatal measurements have used data covering all 3 trimesters of pregnancy, thereby prompting the present investigation. 2) Whether reducing or stopping smoking might attenuate fetal growth retardation or, otherwise, the effects are persistent. Reports on this key issue are inconsistent (9, 19, 20), and the

use of repeated measurements may be crucial to investigating it. In this regard, a longitudinal study design has the advantage of minimizing the influence of confounding factors (10, 15). 3) The specific body segments affected by maternal prenatal smoking. Although some studies have suggested that smoking during pregnancy may lead to symmetric growth retardation (16, 21), others hypothesize that it may selectively affect individual body segments depending on the time, duration, and intensity of exposure (11). Recent studies have suggested that developmental delays in specific parameters may have specific consequences for future health (22–23).

The Infancia y Medio Ambiente (INMA)–Environment and Childhood Study is a network of 7 population-based birth cohorts in various areas of Spain that was established to evaluate the role of the environment on fetal and childhood health (24). In a previously published study, Iñiguez et al. (18) assessed the association between maternal smoking during pregnancy and fetal growth in 1 of these 7 cohorts, the cohort of Valencia. That study found no difference in fetal anthropometry in early pregnancy between mothers who smoked and those who did not, a finding that may reflect the sample size required to detect an association at that stage of gestation. To increase the statistical power for detecting differences according to the period of pregnancy, a joint analysis is convenient. We conducted such a study with the main goal of evaluating the association of prenatal exposure to maternal smoking with fetal biometry in different stages of pregnancy.

MATERIALS AND METHODS

Population and study design

The present study was based on the 4 de novo INMA cohorts located in Asturias, Gipuzkoa (Basque Country), Sabadell (Catalonia), and Valencia, Spain. Recruitment took place between 2003 and 2008. Inclusion criteria were a maternal age of 16 years or older, singleton pregnancy, enrollment at 10–13 weeks of gestation, unassisted conception, delivery scheduled at the reference hospital, and no handicap in communication. A total of 2,644 subjects, ranging from 45% (in Asturias) to 68% (in Sabadell) of the eligible pregnant women in the 4 cohort areas, agreed to participate and signed informed consent agreements. After the exclusion of women who withdrew ($n = 61$), were lost to follow-up ($n = 5$), experienced induced or spontaneous abortions ($n = 62$) or fetal death ($n = 10$), or lacked the results of at least 2 valid ultrasound examinations ($n = 28$), 2,478 pregnant women constituted the study population. The study was approved by the hospital ethics committees in the participating regions (25).

Fetal ultrasonography

Ultrasound examinations of all of the women enrolled in the study were scheduled for weeks 12, 20, and 34 of gestation and performed by specialized obstetricians. The characteristics examined in this aspect of the study were biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC). We had access to participants' hospital records, thus allowing us to obtain the findings in from 2–7 valid ultrasound examinations per subject conducted between 7 and 42 weeks of gestation. An early crown–rump length measurement was used to determine the approximate date of conception. Gestational age was established by using crown–rump length when the calculated date of conception differed from the fetal age based on the subject's self-reported last menstrual period by 7 days or more. Women for whom this difference exceeded 3 weeks were removed from the study to avoid possible bias. Pregnancies for which data on gestational age fell outside of the range of the mean plus or minus 4 standard deviations were also eliminated to avoid the influence of extreme values.

Linear mixed models (26) were used separately in each cohort to obtain longitudinal growth curves for BPD, AC, and FL, as well as to determine estimated fetal weight (EFW) (27). Box-Cox transformations were applied to these outcomes to normalize them. Each transformed outcome was modeled as a polynomial of gestational age in days until degree 3. Models were adjusted for the following constitutional factors known to affect fetal growth: maternal age, height, parity, prepregnancy weight, and country of origin; father's height; and fetal sex. These constitutional factors and their interactions with days of gestation were tested with the likelihood ratio test ($P < 0.05$) through a forward-selection procedure. Models were adjusted for constitutional factors to obtain an individualized rather than a population-based growth standard (28, 29). The length of time between ultrasound examinations was used to model the correlation structure for intrasubject errors. Gestational age, sex, parity, ethnicity, and dummy variables identifying mothers who had ultrasound examinations spaced too closely in time to show changes in fetal growth parameters were used to estimate variance (heteroscedasticity). Random effects of the curves of constitutional factors versus growth on intercept, slope (days of gestation), or both were considered and tested with the likelihood ratio test ($P < 0.05$). Goodness of fit was assessed by consideration of the normality and independence of the residuals.

Fetal growth curves provided mean values, standard deviations, and predictions for weeks 12, 20, and 34 of gestation conditioned on the nearest measurements that were used to calculate unconditional standard deviation scores at 12, 20, and 34 weeks of gestation and conditional standard deviation scores for 12–20 and 20–34 weeks of gestation. An unconditional standard deviation score at a certain time point describes the size of a fetus at this time, whereas a conditional standard deviation score describes the growth of a fetus during the respective time interval, that is, evaluates the size at the final time point using conditional mean and standard deviation values based on the size at the initial time point (30, 31).

Maternal smoking

Active maternal smoking was assessed through a questionnaire administered by trained interviewers in week 32 of pregnancy. The main exposure variable was the classification of smoking status: "non-smokers during pregnancy," "smokers who gave up smoking before week 12," and "smokers continuing to smoke at week 12." Occasional smokers, consisting of those consuming less than 1 cigarette per day, were considered to be nonsmokers. For validation of the questionnaire information according to the results of analyses of urine specimens for

cotinine the 2 additional variables of smoking at conception (no vs. yes) and smoking at week 32 (no vs. yes) were added.

Cotinine samples

Urine samples from 2,244 mothers were collected in the interview sessions in which the questionnaire was administered during the third trimester of pregnancy. The analysis of urine cotinine concentration was done with a competitive enzyme immunoassay at the Public Health Laboratory of Bilbao (Bilbao, Spain). Sensitivity (0.96) and specificity (0.95) for the cutoff point of 50 ng/mL showed good agreement between self-reported smoking and urine cotinine concentration (32).

Covariates

Detailed information about covariates was obtained from questionnaires administered at weeks 12 and 32 of pregnancy. This information consisted of gestational weight gain, socio-occupational status, educational level, employment, zone of residence (rural vs. urban), country of origin, marital status, season of conception, alcohol and caffeine consumption, vegetable and fruit consumption, energy intake, and exposure to outdoor air pollution, measured as nitrogen dioxide (33). Gestational weight gain was classified according to guidelines of the Institute of Medicine (34). Social class was defined according to 1 of 3 occupational categories based on current or most recent occupation (35). Eating and drinking habits were determined in week 12 of pregnancy.

Statistical analysis

Multivariate linear regression models were constructed to assess the relation between maternal smoking during pregnancy and fetal growth. First, a core model was built for each standard deviation score, using as possible predictors all of the covariates found to be significant at a level of $P < 0.2$ (likelihood ratio test) in crude analyses (adjusted only by cohort). Following a backward procedure, all covariates not associated with outcomes at a level of $P > 0.1$ were excluded from the model. Each exposure variable was then incorporated into the model, and those covariates that changed the magnitude of the main associations by more than 10% were also included. Models were examined for collinearity, normality of residuals, and influential data. The model obtained for each standard deviation score and smoking variable was separately applied to each cohort, and β coefficients and 95% confidence intervals were obtained.

Lastly, combined estimates were obtained by means of meta-analysis. Heterogeneity was quantified with the I^2 statistic (36) and, if detected ($I^2 > 50\%$), the random-effects model was used.

Two sensitivity analyses were performed, the first by excluding preterm infants from the study and the second by classifying mothers who smoked fewer than 1 cigarette per day as smokers. Fetal sex and maternal alcohol consumption were considered as potential effect modifiers based on findings reported in the literature (12, 37). Effect modification was assessed through stratified analyses.

The associations of fetal outcomes with maternal smoking at week 12 and maternal smoking at week 32 obtained from questionnaires administered at these points were compared with the association of maternal smoking determined by the results of urine cotinine assays, using a cotinine concentration of 50 ng/mL as a cutoff value for identifying active smoking. Generalized additive models were used to explore the shape of the curve of the relation between fetal growth and total cotinine and were transformed to $\log_2$ values because of the bias to the right in the distribution of this relation. In these models, natural splines with 1 or 2 interior knots were used as smoother functions of exposure to maternal smoking. Different nonlinear models were compared to the linear model using the Akaike information criterion.

All measures of the association between maternal smoking and fetal development are expressed as percent changes in standard deviation scores to enable comparisons of outcomes. All results are presented with their 95% confidence intervals. Statistical analyses were done using R software, version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Subject and exposure characteristics

A total of 2,478 mothers provided ultrasound data. Most of them (93.4%) underwent at least 3 examinations, providing a total of 7,602 ultrasound examinations. Gestational ages at ultrasound examination were very close to those of the planned schedule (12, 20, and 34 weeks of gestation). Of the 2,407 mothers for whom information about tobacco use was available, 762 (32%) smoked during pregnancy. Detailed descriptions of fetal tobacco exposure and outcomes by cohort may be found in Table 1.

Cohort-adjusted analyses showed that mothers who still smoked at week 12 of gestation were younger, less educated, more often Spanish, and more frequently unemployed than were nonsmokers at the corresponding point in gestation. Smokers also reported higher frequencies of alcohol and caffeine consumption than did nonsmokers. Characteristics of mothers by smoking category are presented in Web Table 1 (available at http://aje.oxfordjournals.org/).

Fetal growth and maternal smoking

Maternal smoking was not associated with the magnitude of any fetal growth parameter at either week 12 or week 20 of gestation (results not shown). However, continued smoking at week 12 was associated with impaired growth, as reflected in all measured parameters at 20–34 weeks of gestation, leading to decreased fetal size at week 34. Fetal size at week 34 was greatly influenced by growth from 20–34 weeks (Table 2). The fetuses of the group of mothers who gave up smoking before week 12 exhibited the same adverse outcomes on FL (and marginally on EFW) as did those of mothers who continued to smoke, with the latter perhaps mediated by the reduction in FL. Except for BPD, adverse associations were of a lesser magnitude in the fetuses of mothers who were exsmokers than in those of mothers who continued to smoke. Only BPD showed a marginal deficit in growth in 12–20 weeks

Table 1. Maternal Smoking and Ultrasound Information by Cohort in the Infancia y Medio Ambiente–Environment and Childhood Study, Spain, 2003–2008

Study Variable	Cohort																			
	Asturias ($n = 478$)				Gipuzkoa ($n = 603$)				Sabadell ($n = 611$)				Valencia ($n = 786$)				Overall ($n = 2,478$)			
	No.	%	Median	5th Percentile, 95th Percentile	No.	%	Median	5th Percentile, 95th Percentile	No.	%	Median	5th Percentile, 95th Percentile	No.	%	Median	5th Percentile, 95th Percentile	No.	%	Median	5th Percentile, 95th Percentile
Maternal smoking																				
Missing values		6.3				3.3				2.3				0.9				2.9		
Smokers at start of gestation		28.5				23.5				30.2				40.9				31.7		
Nonsmokers		71.7				76.7				69.8				59.1				68.3		
Smokers who quit before week 12		10.0				11.0				14.7				16.2				13.4		
Smokers who quit at 12–32 weeks		0.9				1.0				1.0				1.9				1.3		
Smokers at week 32		17.4				11.3				14.4				22.8				17.0		
Cotinine samples																				
Missing values		11.9				10.6				4.9				10.6				9.4		
Log_2 cotinine			2.5	1.5, 11.4			2.4	1.5, 11.2			2.8	1.5, 11.5			3.5	1.5, 11.6			2.9	1.5, 11.5
Cotinine >50 ng/mL		21.6				13.4				20.1				29.0				21.6		
Availability of early CRL data		98.7				99.5				100				98.9				99.3		
CRL-based GA, weeks		11.3				10.3				12.9				12.3				11.8		
No. of ultrasound examinations[a]																				
First trimester	461				600				602				775				2,438			
Second trimester	494				592				609				811				2,506			
Third trimester	606				586				622				844				2,658			
Total	1,561				1,778				1,883				2,430				7,602			
Women with at least 1 ultrasound examination																				
First trimester		83.3				94.4				88.7				93.5				90.6		
Second trimester		99.8				98.0				99.5				99.2				99.1		
Third trimester		99.2				95.7				98.7				95.0				96.9		
GA at ultrasound examination, weeks																				
First trimester			12.6	11.3, 15.7			12.4	11.4, 13.6			12.1	10.9, 14.0			12.4	11.4, 13.4			12.4	11.3, 13.7
Second trimester			20.7	19.7, 21.9			21.1	19.8, 22.1			21.1	20.0, 22.4			20.3	19.1, 21.9			20.7	19.6, 22.1
Third trimester			33.9	31.0, 37.0			34.1	31.6, 35.3			34.0	32.3, 35.7			32.3	30.7, 38.1			33.7	31.0, 36.6

Abbreviations: CRL, crown–rump length; GA, gestational age.

[a] Except at week 12 in Asturias, ultrasound examinations were generally complete regarding biparietal diameter (Asturias, $n = 458$), abdominal circumference (Asturias, $n = 39$), and femur length (Asturias, $n = 69$).

Table 2. Association Between Maternal Smoking Information and Fetal Growth, Infancia y Medio Ambiente–Environment and Childhood Study, Spain, 2003–2008

Outcome	No.[a]	Exsmokers Before Week 12				Smokers at Week 12			
		% Change[b]	95% CI	*P* Value[c]	I^2, %[d]	% Change[b]	95% CI	*P* Value[c]	I^2, %[d]
Estimated fetal weight[e]									
Growth in weeks 12–20	2,366	−1.4	−6.1, 3.2	0.54	0	−1.9	−6.1, 2.3	0.37	26.3
Growth in weeks 20–34	2,316	−4.0	−8.6, 0.8	0.10	0	−8.7**	−12.9, −4.5	0.00	28.2
Size at week 34	2,313	−4.7*	−9.4, 0.0	0.05	0	−7.7**	−11.8, −3.5	0.00	42
Femur length[f]									
Growth in weeks 12–20	2,327	−1.0	−5.7, 3.7	0.67	11.6	−0.7	−4.8, 3.5	0.76	41
Growth in weeks 20–34	2,320	−6.0*	−10.7, −1.3	0.01	0	−10.0**	−14.0, −5.9	0.00	0
Size at week 34	2,393	−5.5*	−10.1, −0.9	0.02	0	−9.4**	−13.4, −5.4	0.00	27
Biparietal diameter[g]									
Growth in weeks 12–20	2,297	−4.8	−9.6, 0.0	0.05	37.2	−2.8	−7.2, 1.7	0.22	16.4
Growth in weeks 20–34	2,257	−3.3	−8.1, 1.6	0.19	0	−8.0**	−12.3, −3.6	0.00	0
Size at week 34	2,261	−3.5	−8.4, 1.4	0.16	0	−7.8**	−12.0, −3.5	0.00	43.1
Abdominal circumference[h]									
Growth in weeks 12–20	2,300	−2.1	−6.8, 2.7	0.39	0	−2.4	−6.6, 1.9	0.27	0
Growth in weeks 20–34	2,319	−2.4	−7.2, 2.4	0.33	0	−4.8*	−9.1, −0.4	0.03	34.4
Size at week 34	2,316	−2.7	−7.4, 2.1	0.26	0	−4.4*	−8.7, −0.1	0.05	41

Abbreviation: CI, confidence interval.

* $P < 0.05$; ** $P < 0.01$.

[a] No. of individuals included in the adjusted models; that is, no. without missing values for any variable included in each model.

[b] Percent of change in the standard deviation score; obtained from fetal growth curves.

[c] *P* value of estimated coefficients from meta-analysis.

[d] I^2 statistic of heterogeneity. If $I^2 > 50\%$, the random-effects model was used.

[e] Models were adjusted for maternal alcohol consumption, employment, level of education, height, and weight gain.

[f] Models were adjusted for maternal exposure to nitrogen dioxide during pregnancy, marital status, and weight gain.

[g] Models were adjusted for maternal alcohol consumption, employment, exposure to nitrogen dioxide during pregnancy, level of education, mean energy intake, mean fruit intake, parity, rural versus urban environment, and weight gain.

[h] Models were adjusted for maternal alcohol consumption, employment, social class, parity, height, level of education, and weight gain and season of conception.

of gestation in fetuses of mothers who continued to smoke, although this had no relevance to the final size measured by BPD reached at week 20 (data not shown). The most affected parameter at week 34 was FL; it was 9.4% (95% confidence interval (CI): −13.4, −5.4) shorter in the fetuses of smokers than in those of nonsmokers and 5.5% (95% CI: −10.1, −0.9) shorter in the fetuses of women who quit smoking relative to those of nonsmokers. In contrast, the least affected parameter was AC, with values of 4.4% (95% CI: −8.7, −0.1) and 2.7% (95% CI: −7.4, 2.1) lower than those of the fetuses of nonsmokers and mothers who quit smoking, respectively.

Using smoking or not smoking at conception as a variable (Web Table 2), the pattern of results was the same for FL and EFW. We found no association of maternal smoking with AC and a clearly significant adverse association of maternal smoking with increase in BPD at 12–20 weeks (percent change: −3.7, 95% CI: −7.2, −0.2; $P = 0.04$, likelihood ratio test). With smoking or not smoking at week 32 used as a variable (data not shown), the results for FL, EFW, AC, and BPD were almost identical to those presented in Table 2 for the category of smokers at week 12.

Results remained very stable after the exclusion of preterm fetuses and also after the inclusion of occasional smokers in the category of smokers. In this last case, adverse associations between maternal smoking and EFW were slightly greater and more significant after the inclusion of occasional smokers.

Without reaching statistical significance, estimated adverse associations of maternal smoking with BPD and FL were of high magnitude in male fetuses, whereas those for AC and EFW were of greater magnitude in female fetuses. Interactions of smoking and alcohol consumption were widely nonsignificant, probably because of the small proportion of mothers who drank during pregnancy (Web Table 3).

A comparison of associations based on the source of information about maternal smoking (questionnaire vs. biomarker) and the timing of fetal exposure (week 12 vs. week 32) is presented in Figure 1. The comparison shows great concordance between the association of fetal characteristics and maternal smoking when smoking at week 32 as based on the questionnaire and the association when smoking status was determined by the cotinine concentrations in urine samples taken at week 32. The adverse association between fetal characteristics (mainly BPD) and maternal smoking at week 12 was slightly greater than that of fetal characteristics and maternal smoking at week 32 in both the questionnaire or biomarker results.

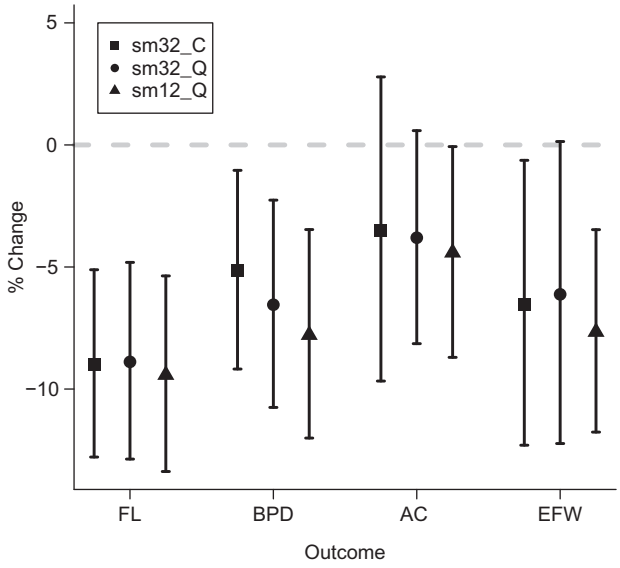

Figure 1. Percent change in femur length (FL), biparietal diameter (BPD), abdominal circumference (AC), and estimated fetal weight (EFW) at week 34 of gestation associated with maternal smoking, Infancia y Medio Ambiente–Environment and Childhood Study, 2003–2008. sm32_C, maternal smoking defined from cotinine concentrations in urine samples taken at week 32 (total cotinine >50 ng/mL); sm32_Q, maternal smoking at week 32 determined using a questionnaire; sm12_Q, maternal smoking at week 12 determined using a questionnaire.

Regarding the shape of the relationship between $\log_2$ cotinine levels and fetal size at week 34, linearity was accepted for BPD and FL, whereas for AC and EFW the best model was nonlinear, with a single breakpoint (at a cotinine concentration of approximately 50 ng/mL) that clearly marked a trigger value for adverse associations (Figure 2).

DISCUSSION

The present study showed an association between continued maternal smoking after week 12 of gestation and impaired fetal growth in all parameters examined and as early as midpregnancy. Statistically significant reductions in fetal size were first noticed in the third trimester, in accord with the results of other studies (9, 10, 16, 21), as well as with those of our own previous work (18). Fetal length and, to lesser extent, BPD were also vulnerable to maternal exposure to tobacco smoke, even in exsmokers at week 12 of gestation. This relationship was weak but immediate in the case of BPD.

The observable effect of maternal smoking later in pregnancy, when nutritional fetal needs are greater, is linked to vascular damage to the placenta from smoking, which causes placental insufficiency and nutritional deprivation (15). The relevance of early fetal exposure to maternal smoking in terms of reductions in FL and BPD coheres with the stated premise that the head and bones of a fetus develop more rapidly in early pregnancy than in mid and late pregnancy. Nevertheless, a direct effect of nicotine acting in a toxic rather than in a nutrient-restrictive way has been also proposed to explain the adverse effect of maternal smoking on the developing brain (12, 16, 17, 38), which usually occurs in midpregnancy.

With regard to the magnitude of the associations between maternal smoking and fetal development, we found the greatest association with FL. This differential effect of exposure to tobacco smoke on fetal anthropometric measures has been previously reported (10, 14, 39) and has also been found in animal experiments (40), suggesting that fetal exposure to toxins may have a greater effect on bone development or peripheral tissues than on fetal body volume or central organs.

Results of urine cotinine assay matched those of self-reported smoking status at week 32, thus supporting the use of questionnaire information in studies of fetal development. This analysis also showed a smaller association between BPD and smoking at week 32 than between BPD and continued smoking at week 12, again indicating a possible vulnerability of BPD in midpregnancy.

Dose–response curves for maternal urinary cotinine concentration versus change in the fetal parameters measured in the study were linear for FL and BPD across the entire range of $\log_2$-transformed cotinine levels and almost linear for AC and EFW beginning at about the concentration of cotinine associated with active smoking. This indicates an adverse association of BPD and FL with maternal smoking of any degree, including that within the usual range for exclusively passive smoking. After the triggering point for a noticeable association, negative slopes of the dose–response curves for urinary cotinine versus changes in the measured fetal parameters were more pronounced for AC and EFW, probably indicating a greater susceptibility of these parameters to tobacco exposure independent of its intensity or source.

Relating to the specificity of the relationship between maternal smoking and BPD, our results suggested a greater negative association in male fetuses. This sex-related association BPD was found in previous studies (12, 15), in which it was suggested as a possible explanation for a greater intrauterine growth velocity in male fetuses than in female fetuses because of a greater demand in male fetuses for blood circulation, oxygen, or nutrients (12).

Regarding the possible long-term consequences of this association, Vik et al. (22) stated that during the first 5 years of life, children of smokers had completely caught up in weight and partially caught up in height but their reduced head dimensions were irreversible. In general, it has been stated that restricted growth in weight, length, and head size from mid to late pregnancy predicts a higher risk of delayed infant development independently of postnatal growth (41). In particular, poor prenatal head growth may represent a risk for adverse behavioral and cognitive development (22, 23).

Some methodological considerations should be noted with regard to our study. First, maternal smoking status was recorded at week 32, which could have led to some misclassification of exposure early in pregnancy, with possible dilution of the data for associations with smoking. Second, we confirmed or corrected gestational age on the basis of last menstrual period by using an early crown–rump length measurement. This procedure could lead to underestimation of the effect of maternal smoking if adverse effects occurred before this first ultrasound-based measurement (42). We preferred this conservative procedure because the use of self-reported dates of last

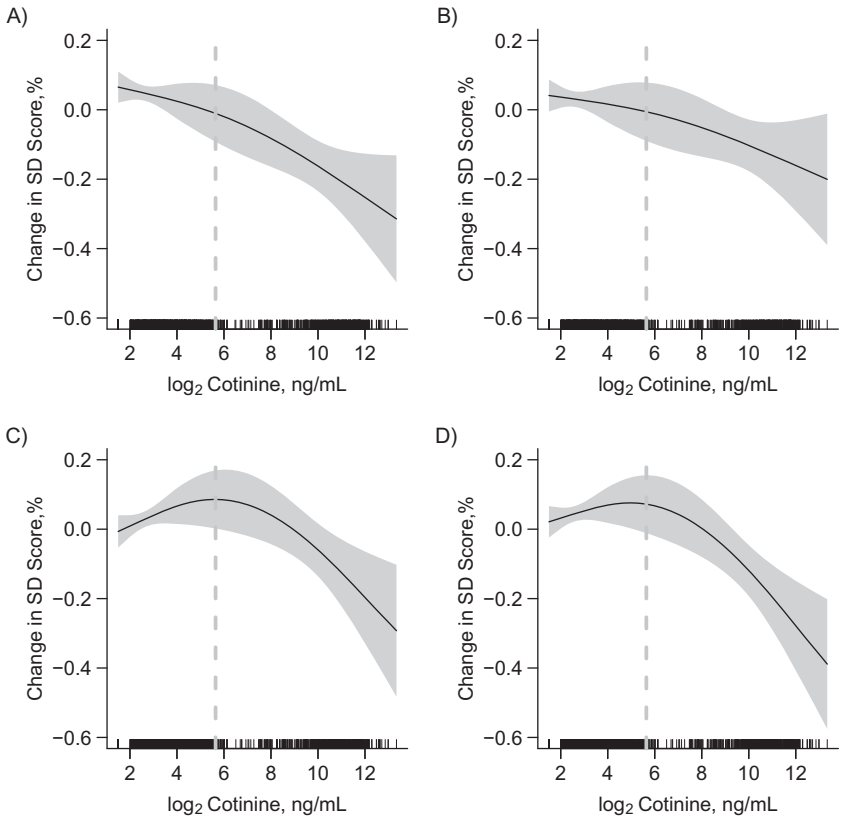

Figure 2. Shape of the relationship between $\log_2$ cotinine at week 32 and magnitudes of fetal parameters at week 34, Infancia y Medio Ambiente–Environment and Childhood Study, 2003–2008. A) Femur length; B) biparietal diameter; C) abdominal circumference; and D) estimated fetal weight. According to the Akaike information criterion, linearity was accepted for femur length and biparietal diameter and nonlinearity ($k = 3$) was stated as the best model for abdominal circumference and estimated fetal weight. The vertical line at a cotinine concentration of 50 ng/mL represents the cutoff value for the identification of active maternal smoking. Marks on the *x* axis represent the frequency distribution of $\log_2$ cotinine levels. SD, standard deviation.

menstrual period for gestational dating is prone to large random-measurement error, with more severe effects on estimates than would occur with a smaller systematic error (43, 44). Strengths of our study are the use of repeated measurements of fetal biometry, which allowed the detection of specific associations between maternal smoking on different parameters and the identification of transient periods of restricted fetal growth; the careful assessment of fetal growth, taking into account the individual growth potential of each fetus (28, 29); and the availability and quality of individual information on potential confounders.

In conclusion, our results on the associations of active smoking during pregnancy with fetal characteristics indicated that smoking cessation early in pregnancy (before week 12) may lead to noticeably better fetal growth than would be seen with continued smoking throughout pregnancy, reinforcing the need to encourage women to avoid smoking during pregnancy.

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