



Original Contribution

Maternal Smoking and Fetal Growth Characteristics in Different Periods of Pregnancy

The Generation R Study

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The authors examined the associations of maternal smoking in pregnancy with various fetal growth characteristics among 7,098 pregnant women participating in the Generation R Study (2002–2006), a population-based prospective cohort study of pregnant women and their children in Rotterdam, the Netherlands. Maternal smoking was assessed by questionnaires administered in early, mid-, and late pregnancy. Fetal growth characteristics evaluated included head circumference, abdominal circumference, and femur length measured repeatedly in mid- and late pregnancy. Maternal smoking during pregnancy was associated with reduced growth in head circumference (–0.56 mm/week; 95% confidence interval (CI): –0.73, –0.40), abdominal circumference (–0.58 mm/week; 95% CI: –0.81, –0.34), and femur length (–0.19 mm/week; 95% CI: –0.23, –0.14). This reduced growth resulted in a smaller femur length from midpregnancy (gestational age 18–24 weeks) onwards and smaller head and abdominal circumferences from late pregnancy (gestational age ≥ 25 weeks) onwards. Analyses using standard deviation scores for the growth characteristics demonstrated the largest effect estimates for femur length. The authors concluded that maternal smoking during pregnancy is associated with reduced growth in fetal head circumference, abdominal circumference, and femur length. The larger effect on femur length suggests that smoking during pregnancy affects primarily peripheral tissues.

cohort studies; fetal development; pregnancy; smoking

Abbreviations: CI, confidence interval; SD, standard deviation.

Maternal smoking during pregnancy is the most important modifiable risk factor for low birth weight in Western countries (1, 2). Smoking in pregnancy leads to low birth weight through decreased fetal supplies of nutrients and oxygen. Birth weight is 150–250 g lower among offspring of mothers who smoke during pregnancy (1, 2). However, low birth weight is an inappropriate measure for assessing

the adverse effects of smoking in pregnancy on fetal growth and development. Various fetal growth patterns and their exposures may result in the same birth weight. Thus, similar births in different subjects may represent both normal and abnormal fetal growth and development.

A limited number of studies have examined the effect of maternal smoking in pregnancy on fetal growth (3–8). The

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results of these studies suggested that smoking during pregnancy is associated with impaired fetal growth from a gestational age of 20 weeks onwards. However, these studies were conducted in small groups or in hospital-based populations, and the investigators were not able to adjust for potential confounders and did not examine the effects of smoking on various fetal growth characteristics during different periods of pregnancy (3–8). This may be relevant for identifying specific critical periods for the effect of maternal smoking on fetal growth.

In a population-based prospective cohort study of pregnant women, we examined the associations of maternal smoking during pregnancy with longitudinally measured fetal growth characteristics.

MATERIALS AND METHODS

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study of pregnant women and their children from fetal life to young adulthood. This study was designed to identify early environmental and genetic determinants of growth, development, and health in fetal life, childhood, and adulthood and has been described previously in detail (9, 10). Briefly, the cohort includes 9,778 mothers of different ethnicities living in Rotterdam, the Netherlands, and their children. Enrollment in the study was aimed at early pregnancy (gestational age <18 weeks) but was possible until the birth of the child. Mothers were informed about the study by health-care workers routinely encountered during pregnancy (midwives, obstetricians) and were enrolled in the study at a routine fetal ultrasound examination. Mothers who were missed during pregnancy were approached and enrolled in the study during the first month after the birth of their child during routine visits at child health centers.

Assessments made during pregnancy, including physical examinations, fetal ultrasound examinations, and administration of questionnaires, were planned for early pregnancy (gestational age <18 weeks), midpregnancy (gestational age 18–24 weeks), and late pregnancy (gestational age \geq 25 weeks). Mothers enrolled in early pregnancy (69 percent) had three assessments planned (early, mid-, and late pregnancy), whereas those enrolled in midpregnancy (19 percent) had two assessments planned (mid- and late pregnancy) and those enrolled in late pregnancy (3 percent) had one assessment planned (late pregnancy). The individual time schemes of these assessments depended on the specific gestational age at enrollment (10). All children were born between April 2002 and January 2006. Of all eligible children in the study area, 61 percent were participating in the study at birth (10).

The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all participants.

Maternal smoking

Information about maternal smoking was obtained by postal questionnaires sent in early, mid-, and late pregnancy.

Response rates for these questionnaires were 91 percent, 80 percent, and 77 percent, respectively (10). Maternal smoking at enrollment was assessed in the first questionnaire by asking the mother whether she smoked during the pregnancy (no, smoked until the pregnancy was known, or continued smoking after the pregnancy was known). This questionnaire was sent to all mothers, independently of gestational age at enrollment. In the second and third questionnaires, the mothers were asked whether they had smoked in the past 2 months (no, yes) during mid- and late pregnancy, respectively.

Mothers who reported on the first questionnaire that they had smoked until their pregnancy was known ($n = 861$) but still reported smoking on the second or third questionnaire ($n = 270$) were reclassified into the “continued smoking after pregnancy was known” category. The same strategy was used for mothers who reported not smoking on the first questionnaire ($n = 5,372$) but reported smoking on the second or third questionnaire ($n = 83$).

Among the mothers who smoked, the number of cigarettes smoked daily was assessed in six categories: <1, 1–2, 3–4, 5–9, 10–19, and \geq 20. To increase the number of subjects, we combined these categories and reclassified the participants into four categories: nonsmoking, <5 cigarettes/day, 5–9 cigarettes/day, and \geq 10 cigarettes/day.

Fetal ultrasonography

Fetal ultrasound examinations were carried out at the research centers in early, mid-, and late pregnancy. These fetal ultrasound examinations were used for both establishing gestational age and assessing fetal growth characteristics.

Gestational age was established by fetal ultrasound examination because using the last menstrual period has several limitations, including the large number of women who do not know the exact date of their last menstrual period or have irregular menstrual cycles (11–13). Pregnancy dating curves were constructed for subjects with complete data on gestational age measured by ultrasonography and the last menstrual period. Crown-rump length was used for pregnancy dating up to a gestational age of 12 weeks and 5 days (crown-rump length <65 mm), and biparietal diameter was used for pregnancy dating thereafter (gestational age from 12 weeks and 5 days onwards, biparietal diameter >23 mm).

Fetal growth measurements used in the present study included head circumference, abdominal circumference, and femur length measured in mid- and late pregnancy. Growth characteristics were measured to the nearest millimeter using standardized ultrasound procedures (14). Longitudinal growth curves and gestational-age-adjusted standard deviation (SD) score curves were constructed for all fetal growth measurements. Median gestational ages for the fetal ultrasound examinations conducted in early, mid-, and late pregnancy were 13.1 weeks (95 percent range: 9.3–17.5), 20.5 weeks (95 percent range: 18.4–23.3), and 30.4 weeks (95 percent range: 27.9–33.0), respectively.

Covariates

Information about educational level, ethnicity, and parity was obtained from the first questionnaire at enrollment in

the study. At the first ultrasound examination, maternal anthropometric factors, including height (m) and weight (kg), were measured while the participant stood without shoes and heavy clothing. Body mass index was calculated as weight (kg)/height (m)². Information about prepregnancy weight was collected by questionnaire. Because of the large number of missing values and the suboptimal quality of the questionnaire data, we used measured body mass index at enrollment in the analyses.

Population for analysis

Of the total of 9,778 mothers, 91 percent ($n = 8,880$) were enrolled during pregnancy (10). Mothers who did not provide information about smoking during pregnancy on the first questionnaire were excluded from the present study (14 percent; $n = 1,249$). Of the remaining 7,631 mothers, those with twin pregnancies ($n = 81$), fetal deaths ($n = 100$), or missing birth outcomes ($n = 352$) were excluded, since our main interest was in low-risk singleton pregnancies. Categories of active smoking were similarly distributed at baseline among women with singleton live-births as their pregnancy outcome and those lost to follow-up. The associations of maternal smoking during pregnancy with longitudinally measured fetal growth characteristics were analyzed in the remaining 7,098 mothers. Of these mothers, the pregnancies of 4.1 percent were their second ($n = 284$) or third ($n = 6$) pregnancies in the study. Since there were no differences in results after exclusion of these subjects, they were included in the analyses. Analyses that were focused on the effects of smoking on fetal growth in mid- and late pregnancy were restricted to mothers who were enrolled in the study during early pregnancy ($n = 5,502$), to minimize misclassification of smoking by pregnancy period. Of these mothers, information about smoking and fetal growth was available for 85 percent ($n = 4,655$) in midpregnancy and for 83 percent ($n = 4,542$) in late pregnancy.

Data analysis

The associations between maternal smoking during pregnancy and repeatedly measured growth characteristics (head circumference, abdominal circumference, femur length) were analyzed with unbalanced repeated-measurements regression analysis using the Statistical Analysis System (SAS) for Windows, version 8.2, including the PROC MIXED module (15). The best-fitting models were constructed using fractional polynomials of gestational age (16). Maternal smoking during pregnancy (in three categories: none, smoking until the pregnancy was known, or continued smoking after the pregnancy was known) was included in these models as an interaction term with gestational age ($p < 0.1$). These models can be written as:

Head circumference

$$\begin{aligned} &= \beta_0 + \beta_1 \times \text{smoking} + \beta_2 \times \text{gestational age}^2 + \beta_3 \\ &\quad \times \text{gestational age}^2 \times \ln(\text{gestational age}) + \beta_4 \\ &\quad \times \text{smoking} \times \text{gestational age}. \end{aligned}$$

Femur length

$$\begin{aligned} &= \beta_0 + \beta_1 \times \text{smoking} + \beta_2 \times \text{gestational age} + \beta_3 \\ &\quad \times \text{gestational age}^3 + \beta_4 \times \text{smoking} \times \text{gestational age}. \end{aligned}$$

The model structure for abdominal circumference was similar to that of the model for head circumference. In these models, “ $\beta_0 + \beta_1 \times \text{smoking}$ ” reflects the intercept and “ $\beta_2 \times \text{gestational age}^2 + \beta_3 \times \text{gestational age}^2 \times \ln(\text{gestational age})$ ” (for head circumference and abdominal circumference) and “ $\beta_2 \times \text{gestational age} + \beta_3 \times \text{gestational age}^3$ ” (for femur length) reflect the slope of growth per week. The terms including β_4 reflect the differences in growth of each fetal characteristic between the maternal smoking categories. All models were additionally adjusted for lifestyle-related and socioeconomic-status-related confounders (maternal body mass index at enrollment, educational level) and other known determinants of fetal growth (maternal age, height, ethnicity, and parity and fetal gender) (1). The patterns of increase with gestation and the distribution of these curves were similar to curves presented in other studies (17–19).

Using the same strategy, additional models were constructed for the SD scores of these growth characteristics. The best-fitting model for these growth characteristics included the following terms:

SD score

$$\begin{aligned} &= \beta_0 + \beta_1 \times \text{smoking} + \beta_2 \times \text{gestational age} + \beta_3 \\ &\quad \times \text{gestational age}^{-2} + \beta_4 \times \text{smoking} \times \text{gestational age}. \end{aligned}$$

This model was used for head circumference, abdominal circumference, and femur length. The associations between categories of the number of cigarettes smoked per day and these SD scores in mid- and late pregnancy were assessed using multiple regression models. These models were adjusted for maternal body mass index at enrollment, educational level, age, height, ethnicity, and parity and fetal gender. All measures of association are presented with 95 percent confidence intervals.

RESULTS

Subject characteristics

Characteristics of the mothers by smoking category are presented in table 1. Of all mothers, 25.5 percent ($n = 1,809$) reported actively smoking in early pregnancy, and 17.2 percent ($n = 1,218$) continued smoking after their pregnancy was known. The ages of women in the cohort ranged from 15.3 years to 46.3 years, with a mean of 29.8 years, and age was lowest in mothers who continued smoking after their pregnancy was known. The percentage of mothers with a higher educational level was also lowest in this group. The largest ethnic groups in the cohort were Dutch and other European women (58.0 percent), Surinamese women (9.1 percent), Turkish women (9.1 percent), and Moroccan women (6.5 percent). Table 1 demonstrates that the percentages of Turkish mothers and Moroccan mothers

TABLE 1. Characteristics of mothers according to category of smoking during pregnancy, Generation R Study cohort, Rotterdam, the Netherlands, 2002–2006†

	Smoking during pregnancy (<i>n</i> = 7,098)‡		
	No smoking (<i>n</i> = 5,289)	Smoked until pregnancy was known§ (<i>n</i> = 591)	Continued smoking after pregnancy was known§ (<i>n</i> = 1,218)
Age (years)	30.1 (5.1)¶	29.4 (5.2)**	28.3 (5.8)**
Height (cm)	167.4 (7.5)	168.3 (7.0)**	167.1 (7.0)
Weight (kg)	69.3 (13.2)	69.4 (12.8)	70.2 (14.0)**
Body mass index#	24.7 (4.5)	24.5 (4.5)	25.2 (4.8)**
Parity ≥1 (%)	45.2	31.7**	45.7
Education (%)			
Primary school	10.6	12.2	21.0**
Secondary school	41.6	44.9	60.5**
Higher education	47.8	42.9*	18.6**
Ethnicity (%)			
Dutch or other European	57.6	62.9*	57.1
Surinamese	8.4	12.4**	10.4*
Turkish	7.7	7.5	16.2**
Moroccan	8.1	1.2**	1.9**
Cape Verdian	3.7	4.6	4.8
Antillean	3.4	2.9	3.8
Other	11.0	8.5	5.8**
First child of the mother in the study†† (%)	95.8	95.2	96.2
Enrollment in study in early pregnancy (%)	76.4	85.8**	78.2
Ultrasonography for fetal growth (%)			
Midpregnancy	93.8	96.6	94.0
Late pregnancy	93.9	97.0	93.7
Birth outcome			
Birth weight (g)	3,454 (552)	3,441 (559)	3,251 (545)**
Gestational age (weeks)‡‡	40.0 (37.0–42.0)	40.0 (36.9–42.0)	39.9 (36.1–42.0)**

* $p < 0.05$; ** $p < 0.01$.

† Values presented are means (with standard deviations) or percentages unless otherwise noted.

‡ Some data were missing on height ($n = 11$), weight ($n = 27$), body mass index ($n = 38$), parity ($n = 409$), educational level ($n = 218$), and ethnicity ($n = 60$).

§ Differences in maternal characteristics (compared with the nonsmoking category) were evaluated using independent-sample t tests for continuous variables and chi-squared tests for proportions. Gestational age was log-transformed for the t test.

¶ Numbers in parentheses, standard deviation.

Weight (kg)/height (m)².

†† Some mothers had more than one child enrolled in the study.

‡‡ Median (90% range).

were highest (16.2 percent) and lowest (1.9 percent), respectively, among those who continued smoking after their pregnancy was known. Mean offspring birth weight was 3,454 g (SD, 552) for mothers who did not smoke during pregnancy and 3,251 g (SD, 545) for mothers who continued smoking after their pregnancy was known.

Maternal smoking during pregnancy

The associations between maternal smoking during pregnancy and longitudinally measured fetal growth characteristics are presented in table 2. Compared with nonsmoking, smoking until the pregnancy was known was not associated

TABLE 2. Associations between maternal smoking during pregnancy and fetal growth characteristics, Generation R Study cohort, Rotterdam, the Netherlands, 2002–2006

Growth characteristic and smoking category	Unadjusted difference	95% CI†	Adjusted difference‡	95% CI
Head circumference growth (mm/week)				
No smoking during pregnancy	Reference		Reference	
Smoked until pregnancy was known	0.05	−0.16, 0.26	0.10	−0.11, 0.31
Continued smoking after pregnancy was known	−0.62	−0.77, −0.46**	−0.56	−0.73, −0.40**
Abdominal circumference growth (mm/week)				
No smoking during pregnancy	Reference		Reference	
Smoked until pregnancy was known	0.23	−0.07, 0.52	0.35	0.05, 0.65*
Continued smoking after pregnancy was known	−0.68	−0.90, −0.46**	−0.58	−0.81, −0.34**
Femur length growth (mm/week)				
No smoking during pregnancy	Reference		Reference	
Smoked until pregnancy was known	0	−0.06, 0.06	0	−0.05, 0.06
Continued smoking after pregnancy was known	−0.18	−0.22, −0.14**	−0.19	−0.23, −0.14**

* $p < 0.05$; ** $p < 0.01$.

† CI, confidence interval.

‡ Adjusted for maternal age, body mass index at enrollment, height, educational level, ethnicity, and parity and fetal gender.

with growth differences in head circumference or femur length. Growth in fetal abdominal circumference was higher among mothers who stopped smoking after their pregnancy was known, as compared with nonsmokers (0.35 mm/week; 95 percent confidence interval (CI): 0.05, 0.65). In the fully adjusted models, continued smoking after the pregnancy was known was inversely associated with fetal growth in head circumference (−0.56 mm/week; 95 percent CI: −0.73, −0.40), abdominal circumference (−0.58 mm/week; 95 percent CI: −0.81, −0.34), and femur length (−0.19 mm/week; 95 percent CI: −0.23, −0.14).

Figure 1 presents the estimated differences in SD score for fetal head circumference, abdominal circumference, and femur length between mothers who did not smoke during pregnancy and mothers who continued to smoke after their pregnancy was known. Differences between the categories of nonsmoking and continuing to smoke after the pregnancy was known increased with increasing gestational age for all three fetal growth characteristics. The largest effect was seen for femur length. No differences in fetal growth characteristics, expressed as SD scores, were found between nonsmoking mothers and mothers who smoked until their pregnancy was known (not presented in figure 1).

Mid- and late-pregnancy smoking categories

Maternal smoking in midpregnancy was not associated with head circumference or abdominal circumference (table 3). Smoking fewer than five cigarettes per day was associated with a smaller femur length (SD score = −0.12, 95 percent CI: −0.23, −0.01). We did not find an association between smoking 5–9 cigarettes per day and femur length. A strong inverse association with femur length was found for smoking more than nine cigarettes per day (SD score = −0.37, 95 percent CI: −0.55, −0.18).

The associations of maternal smoking in late pregnancy with fetal growth characteristics are given in table 4. In the adjusted models, all categories of maternal smoking were inversely associated with head circumference, abdominal circumference, and femur length. For all three growth characteristics, the largest effect estimates were found for the highest smoking category, which included mothers who smoked more than nine cigarettes per day (SD scores: −0.26 (95 percent CI: −0.45, −0.08) for head circumference, −0.25 (95 percent CI: −0.43, −0.06) for abdominal circumference, and −0.40 (95 percent CI: −0.57, −0.22) for femur length).

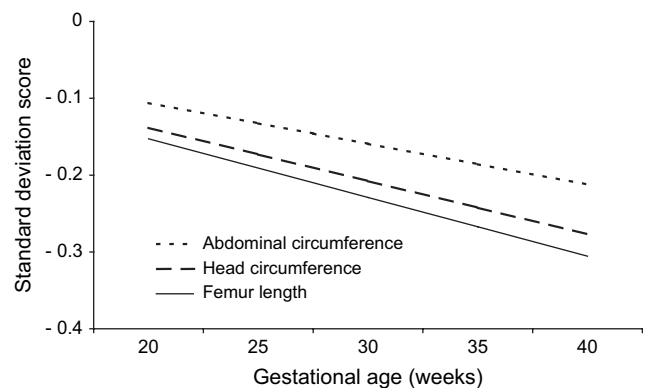


FIGURE 1. Standard deviation scores for fetal head circumference, abdominal circumference, and femur length among offspring of mothers who continued to smoke after discovering that they were pregnant as compared with offspring of mothers who did not smoke during pregnancy, Generation R Study cohort, Rotterdam, the Netherlands, 2002–2006. Values are estimates based on repeated-measurements regression models.

TABLE 3. Associations between maternal smoking during pregnancy and fetal growth characteristics in midpregnancy (18–24 weeks), Generation R Study cohort, Rotterdam, the Netherlands 2002–2006

Growth characteristic and category of smoking in midpregnancy (<i>n</i> = 4,655†)	Unadjusted difference	95% CI‡	Adjusted difference§	95% CI
Head circumference (SD‡ score)				
No smoking	Reference		Reference	
<5 cigarettes/day	−0.14	−0.25, −0.03*	−0.09	−0.21, 0.02
5–9 cigarettes/day	−0.10	−0.24, 0.04	−0.04	−0.19, 0.10
>9 cigarettes/day	−0.11	−0.29, 0.07	−0.03	−0.23, 0.16
Abdominal circumference (SD score)				
No smoking	Reference		Reference	
<5 cigarettes/day	−0.10	−0.21, 0	−0.06	−0.17, 0.05
5–9 cigarettes/day	−0.03	−0.16, 0.11	−0.01	−0.15, 0.13
>9 cigarettes/day	0	−0.17, 0.17	0.07	−0.11, 0.25
Femur length (SD score)				
No smoking	Reference		Reference	
<5 cigarettes/day	−0.12	−0.23, −0.02*	−0.12	−0.23, −0.01*
5–9 cigarettes/day	0	−0.13, 0.14	−0.02	−0.16, 0.12
>9 cigarettes/day	−0.31	−0.49, −0.14**	−0.37	−0.55, −0.18**

* $p < 0.05$; ** $p < 0.01$.

† No smoking: $n = 3,940$; <5 cigarettes/day: $n = 376$; 5–9 cigarettes/day: $n = 212$; >9 cigarettes/day: $n = 127$.

‡ CI, confidence interval; SD, standard deviation.

§ Adjusted for maternal age, body mass index at enrollment, height, educational level, ethnicity, and parity and fetal gender.

DISCUSSION

This population-based prospective cohort study showed associations between maternal smoking during pregnancy and impaired growth in fetal head circumference, abdominal circumference, and femur length. Differences between non-smoking mothers and mothers who continued to smoke after their pregnancy was known increased with increasing gestational age, resulting in smaller femur length from mid-pregnancy onwards and smaller head circumference and abdominal circumference from late pregnancy onwards.

Methodological considerations

One strength of this study was the population-based cohort, with a large number of subjects being studied from early pregnancy onwards and information about a large number of potential confounders being available. To our knowledge, this is the largest cohort study that has examined the associations of maternal smoking in pregnancy with fetal growth characteristics. Of all eligible children, 61 percent were participating in the study at birth. Information about smoking in pregnancy was missing at enrollment for 14 percent of all participating mothers. Birth weight was 41 g (95 percent CI: 6, 76) lower in the offspring of these mothers. Nonresponse would lead to biased effect estimates

if the association of maternal smoking in pregnancy with fetal growth differed between those with complete data and those without complete data. This seems unlikely. Biased estimates in large cohort studies primarily arise from loss to follow-up rather than from nonresponse at baseline (20). Since follow-up information at birth was available for 95 percent of all study pregnancies, we do not think the results were biased due to loss to follow-up. The percentage of mothers who smoked may have been higher among those not included in the present analysis than among those who were included. This might have led to loss of statistical power and some underestimation of the estimated effects of smoking on fetal growth characteristics.

Information about maternal smoking in pregnancy was collected by questionnaire, without reference to fetal growth characteristics. Although assessing smoking during pregnancy by questionnaire seems to be a valid method, misclassification may occur (21). Underreporting of maternal smoking across the various smoking categories may be present and would lead to misclassification. The estimated difference in fetal growth between the offspring of nonsmoking mothers and the offspring of low-to-moderately smoking mothers would be overestimated if this underreporting were selectively present among heavily smoking mothers who reported low-to-moderate smoking. To overcome these limitations, other investigators have used biomarkers of tobacco

TABLE 4. Associations between maternal smoking during pregnancy and fetal growth characteristics in late pregnancy (≥ 25 weeks), Generation R Study cohort, Rotterdam, the Netherlands, 2002–2006

Growth characteristic and category of smoking in late pregnancy ($n = 4,542$ †)	Unadjusted difference	95% CI‡	Adjusted difference§	95% CI
Head circumference (SD‡ score)				
No smoking	Reference		Reference	
<5 cigarettes/day	-0.24	-0.35, -0.12**	-0.17	-0.29, -0.05**
5–9 cigarettes/day	-0.15	-0.29, -0.02*	-0.08	-0.23, 0.06
>9 cigarettes/day	-0.29	-0.47, -0.11**	-0.26	-0.45, -0.08**
Abdominal circumference (SD score)				
No smoking	Reference		Reference	
<5 cigarettes/day	-0.21	-0.32, -0.10**	-0.15	-0.27, -0.03*
5–9 cigarettes/day	-0.22	-0.35, -0.08**	-0.19	-0.32, -0.05**
>9 cigarettes/day	-0.22	-0.40, -0.05*	-0.25	-0.43, -0.06**
Femur length (SD score)				
No smoking	Reference		Reference	
<5 cigarettes/day	-0.16	-0.26, -0.05**	-0.17	-0.29, -0.06**
5–9 cigarettes/day	-0.28	-0.41, -0.15**	-0.29	-0.42, -0.16**
>9 cigarettes/day	-0.41	-0.58, -0.24**	-0.40	-0.57, -0.22**

* $p < 0.05$; ** $p < 0.01$.

† No smoking: $n = 3,864$; <5 cigarettes/day: $n = 322$; 5–9 cigarettes/day: $n = 225$; >9 cigarettes/day: $n = 131$.

‡ CI, confidence interval; SD, standard deviation.

§ Adjusted for maternal age, body mass index at enrollment, height, educational level, ethnicity, and parity and fetal gender.

exposure, including cotinine, in maternal urine samples (22, 23). However, low correlations between cotinine levels and self-reported smoking habits have been demonstrated (24). Possible explanations for these low correlations include inaccurate maternal reporting of smoking during pregnancy, use of categorical rather than continuous variables for assessing the number of cigarettes smoked per day, and individual differences in inhalation, absorption, and metabolism. In a previous study, Haddow et al. (25) demonstrated that use of cotinine levels is not superior to the use of self-reports in studying the effect of maternal smoking in pregnancy on birth weight.

Gestational age was established by fetal ultrasound examination. This method seems to be superior to use of the last menstrual period because of the large number of women who do not know the exact date of their last menstrual period or have irregular menstrual cycles (11). The major disadvantage of establishing gestational age by ultrasonography is that the growth variation of the fetal characteristics used for pregnancy dating is assumed to be zero. Therefore, in our study, crown-rump length and biparietal diameter were used for pregnancy dating but not for assessing fetal growth (12, 13). Since pregnancy dating characteristics and growth characteristics are correlated throughout pregnancy, growth variation in head circumference, abdominal circumference, and

femur length may be reduced by dating the pregnancy on the other fetal characteristics. This may have led to underestimation of our effect estimates. However, we would expect this effect to have been small in our results. First, the longitudinal analyses (table 2 and figure 1) were focused on fetal growth or change in size during pregnancy within individuals. This change in size is unlikely to have been materially affected by our pregnancy dating method. Second, the analyses assessing the associations of maternal smoking with fetal growth characteristics in mid- and late pregnancy (tables 3 and 4) were restricted to mothers who were enrolled and had their pregnancies dated in early pregnancy (78 percent of the population for analysis). Since gestational age and fetal growth were not established concurrently, we believe that we minimized the effect of pregnancy dating on growth variation.

Smoking in pregnancy and fetal growth patterns

The associations of continued maternal smoking after pregnancy was known with lower growth in fetal head circumference, abdominal circumference, and femur length were independent of potential confounders. No adverse effects on fetal growth were found in mothers who stopped smoking after they discovered they were pregnant. Unexpectedly,

a higher rate of fetal abdominal circumference growth was found in mothers who stopped smoking after their pregnancy was known, as compared with nonsmokers. This finding is in line with previous studies demonstrating that quitting smoking in early pregnancy is associated with a normal or even slightly increased birth weight (2, 26). This association seems not to be explained by an increase in body mass index (26).

The number of studies examining the effects of maternal smoking during pregnancy on fetal growth is limited (3–8). Results from these studies are not conclusive and cannot easily be compared with our results because of the differences in study populations and growth measurements. More importantly, investigators in these studies were not able to appropriately adjust their results for possible confounders. After full adjustment for lifestyle- and socioeconomic-status-related variables, including maternal body mass index and educational level, and for known determinants of birth weight, including maternal age, height, ethnicity, and parity and fetal gender, our study demonstrated strong associations of maternal smoking with femur length from midpregnancy onwards and of maternal smoking with head circumference and abdominal circumference from late pregnancy onwards.

In midpregnancy, both smoking fewer than five cigarettes per day and smoking more than nine cigarettes per day were associated with smaller femur length. We did not find an effect of smoking 5–9 cigarettes per day on femur length in midpregnancy. This may be a chance finding, since we cannot explain this inconsistency and the effects were not caused by outliers in the data. Further studies are needed to assess these dose-response trends. Our findings are in line with those of studies demonstrating that maternal smoking in the third trimester has the largest effect on birth weight in the offspring (27). Both the timing and the size of the effects suggest that maternal smoking in pregnancy affects first peripheral tissues and then central tissues. Continued maternal smoking in late pregnancy seems to affect all fetal growth characteristics and tissues.

Perspectives for future studies

Our findings are in line with those of previous studies that showed prenatal and postnatal effects of fetal exposure to nicotine. Maternal smoking during pregnancy seems to be associated with an increased risk of sudden infant death syndrome and impaired cognitive development (28, 29). More recently, it has been suggested that maternal smoking during pregnancy is also associated with a higher blood pressure postnatally in the offspring (30). The underlying causal pathways for these associations are not known. The effects of maternal smoking on fetal growth characteristics shown in our study may reflect adaptations in fetal organ growth and development that may have consequences in childhood and adulthood. Further follow-up studies are needed to examine the gestational-age-specific effects of maternal smoking during pregnancy on organ growth and function and to examine whether these effects explain the previously demonstrated associations between maternal smoking during pregnancy and various postnatal health outcomes.

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