Parental smoking during pregnancy, early growth, and risk of obesity in preschool children: the Generation R Study

Buşra Durmuş, Claudia J Kruijthof, Matthew H Gillman, Sten P Willemsen, Albert Hofman, Hein Raat, Paul HC Eilers, Eric AP Steegers, and Vincent WV Jaddoe

ABSTRACT
Background: Maternal smoking during pregnancy seems to be associated with obesity in offspring. Not much is known about the specific critical exposure periods or underlying mechanisms for this association.

Objective: We assessed the associations of active maternal and paternal smoking during pregnancy with early growth characteristics and risks of overweight and obesity in preschool children.

Design: This study was a population-based, prospective cohort study from early fetal life until the age of 4 y in 5342 mothers and fathers and their children. Growth characteristics [head circumference, length, weight, and body mass index (BMI; in kg/m^2)] and overweight and obesity were repeatedly measured at the ages of 1, 2, 3, and 4 y.

Results: In comparison with children from nonsmoking mothers, children from mothers who continued smoking during pregnancy had persistently smaller head circumferences and heights until the age of 4 y, whereas their weights were lower only until the age of 3 mo. This smaller length and normal to higher weight led to an increased BMI [SD score difference: 0.11; 95% CI: 0.02, 0.20; P = 0.05] and an increased risk of obesity (odds ratio: 1.61; 95% CI: 1.03, 2.53; P < 0.05) at the age of 4 y. In nonsmoking mothers, paternal smoking was not associated with postnatal growth characteristics or risk of obesity in offspring. Maternal smoking during pregnancy was associated with a higher BMI at the age of 4 y in children with a normal birth weight and in those who were small for gestational age at birth.

Conclusion: Our findings suggest that direct intrauterine exposure to smoke until late pregnancy leads to different height and weight growth adaptations and increased risks of overweight and obesity in preschool children. 

INTRODUCTION
The hypothesis of developmental origins proposes that fetal adaptations in organ function and metabolism in response to adverse intrauterine conditions lead to fetal growth retardation and predispose the individual to increased risks of obesity and type 2 diabetes in adult life (1, 2). Not much is known about the influence of specific adverse exposures. In Western countries, active maternal smoking during pregnancy is a common and preventable specific adverse environmental exposure (3, 4). Maternal smoking during pregnancy is associated with fetal growth retardation and increased risks of preterm birth and low birth weight (5–7). It has been suggested that maternal smoking during pregnancy also increases risk of obesity in offspring (8, 9). A recent systematic review suggested that prenatal smoke exposure led to a 50% increased risk of overweight in childhood (10). Most previous studies were not able to assess the effect of maternal smoking exposure in different periods of pregnancy. This information is important because it might identify specific critical time windows. It is also not known whether the associations between maternal smoking during pregnancy and risk of childhood obesity are explained by intrauterine effects or just reflect various unmeasured environmental confounders. Stronger effect estimates for maternal smoking than for paternal smoking with childhood obesity may suggest direct intrauterine effects, whereas similar effect estimates may suggest that the associations are explained by unmeasured environmental exposures (11, 12).

Therefore, in a population-based prospective cohort study in 5342 mothers and fathers and their children, who were followed from early fetal life onwards, we examined associations of exposure to maternal and paternal smoking during pregnancy with early growth characteristics and risks of overweight and obesity until the age of 4 y.

SUBJECTS AND METHODS
Design and setting
This study was embedded in the Generation R Study, which is a population-based prospective cohort study of pregnant women and their children from fetal life onwards in Rotterdam, Netherlands (13, 14). Enrollment in the study was aimed at early pregnancy (gestational age <18 wk) but was possible until the...
birth of the child. Assessments during pregnancy, including physical examinations, fetal ultrasound examinations, and questionnaires, were planned in each trimester (14). All children were born between April 2002 and January 2006 and form a prenatally enrolled birth cohort that is currently followed until young adulthood. Postnatal growth data for the current study were available until the age of 4 y. Of all eligible children in the study area, 61% of children were participating in the study at birth (14). The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre (Rotterdam, Netherlands). Written informed consent was obtained from all participants or their parents.

Data collection and measurements

Maternal and paternal smoking during pregnancy

Information about maternal smoking was obtained by postal questionnaires sent in the first, second, and third trimesters of pregnancy. Response rates for these questionnaires were 91%, 80%, 77%, respectively (14). Active maternal smoking at enrollment was assessed in the first questionnaire by asking whether the mother smoked during her pregnancy. We grouped mothers into 3 categories as follows: 1) never smoked during pregnancy, 2) only smoked until their pregnancy was acknowledged (first trimester only), and 3) continued to smoke during pregnancy. This questionnaire was sent to all mothers independent of the gestational age at enrollment. In the second and third questionnaires, mothers were asked whether they had smoked during the past 2 mo (yes or no). Mothers who reported in the first questionnaire not to have smoked or to have smoked until their pregnancy was acknowledged but reported to have smoked in the second or third questionnaire were reclassified as continued smoking. Active paternal smoking was assessed in the first questionnaire by asking the mother whether the father smoked during pregnancy (yes, no, or do not know). Similar information completed by the father was available in a subset of participants \(n = 3558\). Agreement between these assessments was good (sensitivity: 91%; specificity: 95%). We used data collected from the mother’s questionnaire because this information was available for all children. No difference in effect estimates were observed when we used information completed by the father himself. In smokers, the numbers of cigarettes smoked daily was available in the following categories: no smoking, \(5\) cigarettes/d, and \(\geq 5\) cigarettes/d. All mothers included in these analyses were selected on the basis of complete information about the duration of smoking during pregnancy. Because we used 2 different questions (ie, Did you smoke? and What is the number of smoked cigarettes?\?), the number of cigarettes smoked per day was not known for all mothers.

Fetal growth characteristics

Fetal ultrasound examinations were carried out at the research centers in the first trimester (median: \(13.5\) wk; 95% range: \(11.0, 17.0\) wk), second trimester (median: \(20.7\) wk; 95% range: \(18.9, 22.8\) wk), and third trimester (median: \(30.5\) wk; 95% range: \(28.9, 32.4\) wk). The first ultrasound was used for establishing gestational age because these methods were superior than the use of the last menstrual period because of its limitations, including the large number of women who did not know the exact date of their last menstrual period or had irregular menstrual cycles (15–17). Second and third trimester ultrasounds were used to assess fetal growth. We measured fetal head circumference (HC), abdominal circumference (AC), and femur length (FL) to the nearest millimeter by using standardized ultrasound procedures (18), and the estimated fetal weight (EFW) was calculated by using the following formula of Hadlock et al (19):

\[
\text{Log}_{10}\text{EFW} = 1.5662 - 0.0108(\text{HC}) + 0.0468(\text{AC}) + 0.171(\text{FL}) + 0.00034((\text{AC})^2 - 0.003685(\text{AC} \times \text{FL})
\]

SD scores (SDS) for all fetal growth characteristics were constructed by using data from the study group. Ultrasound examinations were performed with an Aloka model SSD-1700 (Aloka Co Ltd, Tokyo, Japan) or ATL-Philips model HDI 5000 (Philips, Seattle, WA).

Postnatal growth characteristics

Information on weight at birth was obtained from community midwife and hospital registries. Because head circumferences and lengths were not routinely measured at birth, these measurements were only available in a subset. Postnatal growth was measured by well-trained staff at Community Health Centers according to a standard schedule and procedures at the ages of 3 mo (median: \(3.1\) mo; 95% range: \(1.3, 4.2\) mo), 6 mo (median: \(6.7\) mo; 95% range: \(5.5, 10.3\) mo), 12 mo (median: \(13.0\) mo; 95% range: \(11.1, 15.3\) mo), 24 mo (median: \(24.4\) mo; 95% range: \(18.6, 27.5\) mo), 36 mo (median: \(36.4\) mo; 95% range: \(31.1, 39.2\) mo), and 48 mo (median: \(45.3\) mo; 95% range: \(25.7, 47.8\) mo). Head circumferences were measured to the nearest millimeter with a standardized tape (SECA, Hamburg, Germany) until the age of 12 mo. Lengths were measured in a supine position to the nearest millimeter until the age of 12 mo with a neonatometer. From the age of 24 mo, heights were measured in a standing position with a Harpenden stadiometer (Holtain Ltd, Dyfed, United Kingdom). All measures were measured with a mechanical personal scale (SECA). Body mass index (BMI; in kg/m\(^2\)) was calculated. SDS for postnatal growth characteristics were obtained with Dutch reference growth charts (Growth Analyzer 3.0; Dutch Growth Research Foundation, Rotterdam, Netherlands). Definitions of overweight (BMI >1.1–2.3 SDS) and obesity (BMI >2.3 SDS) were based on the age- and sex-adjusted BMI distributions on the basis of the definition of Cole et al (20). Frederiks et al (21) transformed the international criteria for overweight and obesity to SDSs to identify the pediatric centiles at younger ages and showed that an adult BMI of 25 (overweight) corresponded to a +1.1 SD and that an adult BMI of 30 (obesity) corresponded to a +2.3 SD in the reference growth diagrams on the basis of the 1997 Dutch Growth Study. Therefore, the +1.1- and +2.3-SD lines in the 1997 BMI charts correspond to the recommended limits for overweight and obesity, respectively, that Cole et al (20) also used.

Covariates

Gestational age at birth and sex were obtained from midwife and hospital registries at birth. Information about parental
educational level and ethnicity were obtained from the first questionnaire at enrollment in the study. Ethnicity and educational level of parents were defined according to the classification of Statistics Netherlands (22, 23). Parental anthropometric measurements were assessed at enrollment. Height and weight were measured while the parent stood without shoes and heavy clothing, and BMI was calculated. Information on breastfeeding was obtained by postnatal questionnaires at the ages of 2, 6, and 12 mo.

Population for analysis

In total, 6969 children and their mothers had been included prenatally and fully participated in the postnatal phase of the study (see supplemental Figure 1 under “Supplemental data” in the online issue). Subjects without information about smoking during pregnancy in the 3 questionnaires were excluded from the current analyses (13%; n = 936). Of the remaining mothers, those with twin pregnancies (n = 125) and those with second or third participating infants of the same mother in the study (n = 382) were excluded from the current analyses to prevent a bias because of correlation. Of the remaining 5526 singleton live births with complete data on maternal smoking during pregnancy, information about at least one postnatal growth characteristic measure was available in 5342 children. There were no differences in categories of active smoking between participants compared with those of lost to follow-up subjects (P = 0.14).

Statistical analysis

Differences in baseline characteristics between maternal smoking categories were compared by using the t test and analysis of variance with Bonferroni correction in Table 1. Associations of the period of maternal smoking during pregnancy (no, first trimester only, or continued) with growth characteristics (SDS of head circumference, height, weight, and BMI) were assessed by using linear mixed models. These models take the correlation between repeated measurements of the same participant into account and allow for incomplete outcome data (24). To account for the within-child correlation, we included a random intercept in the model. The models were adjusted for potential confounders including the visit (second trimester, third trimester, birth, and 3, 6, 12, 24, 36, or 48 mo), because the intercept might not have been the same at every visit, child’s age at the visit relative to the mean per visit, sex, maternal ethnicity and education, maternal height and weight at enrollment, and breastfeeding (yes or no). All interactions between the visit and the other confounders where also included in the model because of the possible variability of confounder effects. Confounders were included in the models on the basis of their associations with postnatal BMI in previous studies or a change in effect estimates of interest >10% because this criterion took into account the covariate-outcome association and the change in the estimate upon removal of the covariate (25).

Similar linear mixed models were used for the assessment of associations of reported numbers of cigarettes smoked by the mother during pregnancy, smoking of the father, and the number of cigarettes smoked by the father with growth characteristics in offspring. Postnatal smoking, parity, and maternal alcohol consumption were not included in models because they did not materially change effect estimates. Multiple logistic regression models were used for the analysis of associations of the period of maternal and paternal smoking during pregnancy with risks of overweight and obesity at the age of 4 y. Analyses that focused on associations of maternal and paternal smoking with anthropometrics in offspring were not adjusted for multiple testing because these were closely correlated outcomes. Finally, to assess whether associations of maternal smoking during pregnancy with postnatal BMI and risks of overweight and obesity were modified by gestational age-adjusted birth weight, we repeated these analyses with overweight and obesity as outcomes in strata of small size for gestational age defined as the lowest 10% of gestational age-adjusted birth weight in the cohort. Tests for trends were performed by treating each categorized variable as a continuous term and entering the variable into the fully adjusted regression model. To handle missing values in covariates (<23% missing values), we performed multiple imputations for linear mixed models in Table 2 and supplemental Table 2 (under “Supplemental data” in the online issue) by using the chained equations approach in the R program (version 2.12.1; The R Foundation for Statistical Computing, Vienna, Austria) (26) and for Table 3 by generating 5 independent data sets using the Markov chain Monte Carlo method in the Statistical Package of Social Sciences program (version 17.0 for Windows; SPSS Inc, Chicago, IL). According to both methods, SEs from each of the 5 imputation sets were combined to an overall SE on the basis of the within-imputation variance and the between-imputation variance. All measures of associations are presented with their 95% CIs. Statistical analyses were performed with the Statistical Package of Social Sciences (version 17.0) for Windows; SPSS Inc) and R (version 2.12.1; The R Foundation for Statistical Computing) programs.

RESULTS

Subject characteristics

Of all mothers included in the analyses, 9.0% (n = 481) of them reported only smoking in the first trimester, and 15.6% (n = 833) of them continued smoking during pregnancy (Table). Mothers who continued smoking were younger and less educated than mothers who never smoked during pregnancy. The largest ethnic group was Dutch or other European (60.4%). Mean (±SD) birth weights of children from mothers who never smoked during pregnancy and who continued smoking were 3463 ± 540 and 3265 ± 540 g, respectively (see supplemental Table 1 under “Supplemental data” in the online issue for unadjusted growth characteristics per maternal smoking category).

Parental smoking during pregnancy, growth, and obesity in offspring

Compared with no maternal smoking, maternal smoking in the first trimester only was not associated with growth differences in head circumferences, lengths, weights, and BMI of offspring (Table 2). Children from mothers who continued smoking had smaller head circumferences until the age of 12 mo and smaller heights until the age of 4 y, whereas their weights were only lower until the age of 3 mo (P for trend < 0.01). The persistently smaller heights and normal to higher weights led to a higher BMI at the age of 4 y (difference: 0.11 SDS 95% CI: 0.02, 0.20 SDS; P < 0.05). In mothers who continued smoking, we observed the largest effect estimates for mothers who smoked ≥5 cigarettes/d at 4 y: height
Breastfeeding

Maternal characteristics

Age (y) 30.4 (21.4, 38.2) 29.7 (20.4, 37.5)* 29.0 (19.9, 37.8)** < 0.01
Height (cm) 167.6 (7.5) 168.7 (7.1)** 167.1 (7.2) < 0.01
Weight (kg) 69.0 (12.9) 69.2 (12.5) 70.1 (14.0) 0.10
BMI (kg/m²) 24.6 (4.4) 24.3 (4.3) 25.1 (4.7)** < 0.01
Education (%)
  Primary 9.0 7.9 16.6**
  Secondary 40.4 45.1 62.2**
  Higher 50.6 47.0 21.2**
Ethnicity (%)
  Dutch or European 60.4 65.1 58.0** 0.04
  Non-European 39.6 34.9 42.0**

Paternal characteristics

Age (y) 33.4 (24.5, 43.5) 32.2 (22.5, 41.9)** 31.7 (21.4, 42.3)** < 0.01
Weight (kg) 83.5 (12.7) 83.7 (12.7) 82.2 (13.3) 0.25
Height (cm) 181.4 (7.7) 182.5 (7.8) 179.9 (8.0)** < 0.01
BMI (kg/m²) 25.4 (3.4) 25.1 (3.3) 25.4 (3.6) 0.33
Smoking, yes (%) 34.7 65.1** 74.1** < 0.01

Birth

Male sex (%) 50 48 52 0.30
Gestational age (wk) 40.0 (37.1, 42.1) 39.9 (37.1, 42.0) 39.8 (36.4, 42.1)** < 0.01
Weight (g) 3463 (540) 3462 (532) 3265 (540)** < 0.01
Small for gestational age, <10% (%) 9.0 8.1 15.5** < 0.01
Low birth weight, <2500 g (%) 3.8 3.3 6.6** < 0.01
Preterm birth (%) 4.0 4.0 6.1* 0.02

Breastfeeding

Ever (%) 93.7 92.7 84.3** < 0.01
Duration (mo) 5.1 (0.5, 12.0) 4.0 (0.5, 12.0)** 3.4 (0.5, 12.0)** < 0.01

1 Differences in maternal and child characteristics (compared with the maternal nonsmoking category) were evaluated by using the t test and ANOVA with Bonferroni correction. Values were missing for maternal height (n = 6), maternal weight (n = 16), paternal education (n = 93), maternal ethnicity (n = 20), paternal age (n = 482), paternal height (n = 1227), paternal weight (n = 1232), paternal smoking (n = 83), birth weight (n = 2), ever breastfeeding (n = 553), and duration of breastfeeding (n = 1932). *P < 0.05. **P < 0.01.
2 Median; 90% range in parentheses (all such values; for variables with skewed distribution).
3 Mean; SD in parentheses (all such values).

Smoking during pregnancy, small size for gestational age, and obesity

The additional adjustment of the logistic regression models focused on associations between maternal smoking during pregnancy and risks of overweight and obesity for gestational age-adjusted birth weight resulted in stronger effect estimates in terms of the odds ratio [odds ratios at the age of 4 y: 1.10 (95% CI: 0.86, 1.41); P = 0.45] for overweight, 1.73 (95% CI: 1.09, 2.74; P = 0.02) for obesity, and 1.23 (95% CI: 0.98, 1.56; P = 0.08) for overweight or obesity. Maternal smoking during pregnancy was associated with a higher BMI at the age of 4 y in children with normal birth weight and in those who were small for gestational age at birth (interaction between smoking and SDS birth weight was P < 0.001). Compared with children from nonsmoking mothers who were normal size for gestational age, children from mothers who did not smoke during pregnancy and who were...
### TABLE 2
Associations of maternal smoking during pregnancy with repeatedly measured postnatal growth characteristics

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<tr>
<th></th>
<th>Birth</th>
<th>3 mo</th>
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<tr>
<td>First trimester only (n = 481)</td>
<td>-0.07 (−0.18, 0.05)</td>
<td>0.03 (−0.06, 0.12)</td>
<td>0.01 (−0.08, 0.10)</td>
<td>-0.03 (−0.13, 0.07)</td>
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<tr>
<td>Continued (n = 833)</td>
<td>-0.26 (−0.35, -0.17)**</td>
<td>-0.19 (−0.27, −0.11)**</td>
<td>-0.11 (−0.18, −0.03)**</td>
<td>-0.10 (−0.18, −0.01)*</td>
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<tr>
<td>0–4 cigarettes/d (n = 313)</td>
<td>-0.22 (−0.35, -0.08)**</td>
<td>-0.08 (−0.19, 0.02)</td>
<td>-0.04 (−0.14, 0.07)</td>
<td>-0.08 (−0.20, 0.03)</td>
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<tr>
<td>≥5 cigarettes/d (n = 296)</td>
<td>-0.31 (−0.45, -0.17)**</td>
<td>-0.31 (−0.43, −0.20)**</td>
<td>-0.20 (−0.31, −0.06)**</td>
<td>-0.13 (−0.25, −0.01)*</td>
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<td>P for trend</td>
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<td>-0.05 (−0.16, 0.05)</td>
<td>0 (−0.09, 0.10)</td>
<td>0 (−0.10, 0.09)</td>
<td>-0.02 (−0.12, 0.07)</td>
<td>0.04 (−0.06, 0.13)</td>
<td>0.01 (−0.10, 0.11)</td>
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<tr>
<td>Continued (n = 833)</td>
<td>-0.40 (−0.49, -0.31)**</td>
<td>-0.30 (−0.38, -0.23)**</td>
<td>-0.14 (−0.21, −0.06)**</td>
<td>-0.14 (−0.21, −0.06)**</td>
<td>-0.13 (−0.21, −0.05)**</td>
<td>-0.11 (−0.20, −0.03)**</td>
<td>-0.10 (−0.19, −0.01)*</td>
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<tr>
<td>0–4 cigarettes/d (n = 313)</td>
<td>-0.36 (−0.49, -0.23)**</td>
<td>-0.15 (−0.26, -0.04)**</td>
<td>-0.04 (−0.15, 0.07)</td>
<td>-0.04 (−0.14, 0.07)</td>
<td>-0.03 (−0.14, 0.07)</td>
<td>-0.04 (−0.15, 0.07)</td>
<td>0 (−0.12, 0.12)</td>
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<tr>
<td>≥5 cigarettes/d (n = 296)</td>
<td>-0.45 (−0.59, -0.31)**</td>
<td>-0.48 (−0.59, −0.37)**</td>
<td>-0.26 (−0.38, −0.14)**</td>
<td>-0.25 (−0.36, −0.14)**</td>
<td>-0.25 (−0.36, −0.13)**</td>
<td>-0.20 (−0.32, −0.08)**</td>
<td>-0.23 (−0.35, −0.10)**</td>
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<tr>
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<td>0 (−0.09, 0.09)</td>
<td>-0.03 (−0.12, 0.07)</td>
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<td>-0.17 (−0.24, −0.09)**</td>
<td>-0.05 (−0.13, 0.03)</td>
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<td>-0.08 (−0.19, 0.03)</td>
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<td>0.01 (−0.10, 0.12)</td>
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<td>-0.39 (−0.50, -0.28)**</td>
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<td>-0.13 (−0.25, −0.01)*</td>
<td>-0.10 (−0.21, 0.02)</td>
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<td>-0.07 (−0.18, 0.03)</td>
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<td>0.04 (−0.04, 0.12)</td>
<td>0.05 (−0.03, 0.13)</td>
<td>0.06 (−0.02, 0.14)</td>
<td>0.03 (−0.05, 0.11)</td>
<td>0.10 (0.02, 0.19)*</td>
<td>0.11 (0.02, 0.20)*</td>
</tr>
<tr>
<td>0–4 cigarettes/d (n = 313)</td>
<td>—</td>
<td>0.02 (−0.09, 0.13)</td>
<td>0.05 (−0.05, 0.16)</td>
<td>0.04 (−0.07, 0.14)</td>
<td>0.01 (−0.10, 0.12)</td>
<td>0.05 (−0.06, 0.16)</td>
<td>0.07 (−0.06, 0.19)</td>
</tr>
<tr>
<td>P for trend</td>
<td>—</td>
<td>0.02</td>
<td>0.27</td>
<td>0.24</td>
<td>0.24</td>
<td>0.02</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*All values are standardized regression coefficients (95% CIs) assessed by using linear mixed models. Trend tests for the number of cigarettes smoked per day were performed by using fully adjusted linear regression models and by treating categorized dose variables as continuous variables in these models. Models were adjusted for child age at visit, sex, maternal ethnicity and education, maternal height and weight, and breastfeeding (yes or no). *P < 0.05, **P < 0.01.
DISCUSSION

Main findings

This population-based prospective cohort study showed that continued maternal smoking during pregnancy, and not maternal smoking in the first trimester only, was associated with persistent smaller head and length growths and increased weights and BMI in offspring at the age of 4 y. Children of mothers who continued smoking during pregnancy also showed an increased risk of obesity at the age of 4 y. No association between paternal smoking during pregnancy and postnatal growth characteristics were observed.

Strengths and weaknesses

An important strength of this study was the population-based cohort with a large number of subjects who were studied from early pregnancy onwards, and information about a large number of potential confounders was available. To our knowledge, this was the largest population-based prospective cohort study that has examined the associations of maternal and paternal smoking habits during specific periods in pregnancy with postnatal growth characteristics. Some methodologies need to be considered. Information about smoking during pregnancy at enrollment was missing for 13% of all mothers. This nonresponse would lead to biased effect estimates if associations of maternal smoking in pregnancy with postnatal growth characteristics would be different between those mothers included and not included in the analyses. However, this bias seemed unlikely because biased estimates in large cohort studies mainly arise from a loss to follow-up rather than from a nonresponse at baseline (27). The percentage of mothers who smoked during pregnancy may have been higher in those who were not included in the current analyses than in those who were included. This might have led to loss of statistical power and some underestimation of estimated effects. In the current analysis, the loss to follow-up was limited (<5%). Because active-smoking categories were similarly distributed at baseline in women who participated and in women who did not participate, we did not expect that the results were biased because of the loss to follow-up. Information about maternal and paternal smoking during pregnancy was collected by questionnaires without reference to postnatal growth characteristics. Although the assessment of smoking during pregnancy by questionnaire seems to be a valid method, misclassifications may occur (28). Underreporting of maternal smoking across the various smoking categories may have been present and led to misclassification. In general, underreporting would lead to an underestimation of differences between children from smoking and nonsmoking mothers. To overcome these limitations, some smaller previous studies used biomarkers such as cotinine in maternal urine samples (29, 30). However, this method does not seem to be superior to the use of self-report data of smoke exposure because of the low correlations between cotinine amounts and self-reported smoking habits (31, 32).

Comparison of main findings with other studies

The associations of maternal smoking during pregnancy associated with fetal growth retardation and increased risks of preterm birth and low birth weight are well established (3, 4, 33–35). Various studies have suggested that exposure to smoke during fetal life led to overweight and obesity in childhood (9, 36, 37). A systematic review by Oken et al (10) suggested that prenatal smoke exposure led to a 50% increased risk of overweight in the offspring aged 3–33 y. Also, a recent meta-analysis that used 17 studies showed that maternal smoking was consistently associated with obesity in children with a mean age of 9 y (9). Our results are in line with this recent review (9) by showing that children of mothers who continued smoking during pregnancy had an increased risk of obesity (odds ratio: 1.61) at the age of 4 y. It is likely that this high risk of obesity at this young age is part of

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TABLE 3
Associations between maternal and paternal smoking with overweight and obesity at the age of 4 y compared with nonsmokers

<table>
<thead>
<tr>
<th>Maternal smoking category</th>
<th>Risk of overweight</th>
<th>Risk of obesity</th>
<th>Risk of overweight or obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>n²</td>
<td>4540 (590)</td>
<td>4540 (106)</td>
<td>4540 (696)</td>
</tr>
<tr>
<td>No (n = 4028)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>First trimester only (n = 481)</td>
<td>1.39 (1.04, 1.85)</td>
<td>0.76 (0.32, 1.79)</td>
<td>1.32 (0.99, 1.73)</td>
</tr>
<tr>
<td>Continued (n = 833)</td>
<td>1.00 (0.78, 1.28)</td>
<td>1.61 (1.03, 2.53)*</td>
<td>1.11 (0.89, 1.39)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.57</td>
<td>0.07</td>
<td>0.19</td>
</tr>
<tr>
<td>Paternal smoking category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n²</td>
<td>3394 (420)</td>
<td>3394 (69)</td>
<td>3394 (489)</td>
</tr>
<tr>
<td>No (n = 2527)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes (n = 1397)</td>
<td>1.17 (0.95, 1.45)</td>
<td>1.09 (0.66, 1.76)</td>
<td>1.16 (0.95, 1.42)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.15</td>
<td>0.75</td>
<td>0.16</td>
</tr>
</tbody>
</table>

¹ Models were adjusted for child age at visit, sex, parental ethnicity and education, parental height and weight, and breastfeeding (yes or no). Overweight was defined as age-and sex-adjusted BMI >1.1–2.3 SD score (SDS), obesity was defined as age-and sex-adjusted BMI >2.3 SDS, and overweight or obesity was defined as age-and sex-adjusted BMI >1.1 SDS. *P < 0.05.

² Odds ratios (95% CI) assessed by using multivariate logistic regression models (all such values).

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born small for gestational age had a lower BMI at the age of 4 y (difference: −0.56; 95% CI: −0.72, −0.41; P < 0.01), whereas no difference in BMI at the age of 4 y was observed in children from mothers who smoked during pregnancy and who were born small for gestational age (data not shown).
a trajectory, and risk of obesity tracks into late childhood and adolescence. Our results also showed that there was a dose-response relation between the number of cigarettes and postnatal growth characteristics and risk of obesity. Only a few studies assessed associations of exposure to maternal smoke in different periods of pregnancy with postnatal growth characteristics (10, 38, 39). However, this assessment might identify critical time periods that are important from a developmental and preventive perspective. In addition to Adams et al (38) and Mendez et al (39), we observed that smoking in only the first trimester was not associated with postnatal growth and childhood obesity, whereas continued smoking until the third trimester of pregnancy was associated with these outcomes. Similarly, it has been shown that smoking in only the first trimester did not adversely affect risks of spontaneous preterm birth and small size for gestational age compared with risks for nonsmoking mothers (40). Therefore, advising pregnant women and offering them help to quit smoking during pregnancy, by using proven methods is important (41). Encouraging reproductive-age women to quit smoking before pregnancy is also important. Previous studies suggested that the observed associations between maternal smoking during pregnancy and childhood obesity were not affected by the adjustment for potential confounders such as sociodemographic factors (10). However, residual confounding might still be an issue because of unmeasured social- and lifestyle-related factors. To overcome this limitation, we also examined whether paternal smoking during pregnancy in nonsmoking mothers is associated with postnatal growth and risks of childhood overweight and obesity. This approach was previously used for other outcomes (11, 12). We did not observe any associations between paternal smoking during pregnancy and these outcomes. This result was in line with results from a cross-sectional study in 5899 children in Bavaria that showed that paternal smoking could only partially explain the association of maternal smoking before or in pregnancy with childhood obesity (42). Our findings suggested that underlying mechanisms might include direct intrauterine processes. Smoking during pregnancy might permanently lead to impaired skeletal growth, a shorter stature, and a normal or higher weight. Maternal smoking may also lead to impaired embryonic growth and fetal growth retardation, which was associated with a more rapid postnatal weight gain (43, 44). We showed that maternal smoking during pregnancy is associated with a higher BMI in children with and without small size for gestational age at birth. Thus, the small size for gestational age did not explain the associations shown. The mechanisms by which maternal smoking during pregnancy may program postnatal child height and weight growths need to be studied further. We observed that continued maternal smoking, but not first trimester smoking, led to a persistent smaller length and higher BMI. Our results suggested that exposure to active maternal smoking during fetal life led to impaired skeletal growth and persistently a shorter height in postnatal life. The mechanisms of nicotine on skeletal growth might include programming effects on growth and adiposity hormones such as growth hormone, leptin, and ghrelin responsive pathways and a direct stimulation of the fetal hypothalamic-pituitary axis leading to increased adrenocorticotropic hormone (ACTH) and chronic changes in the proportion of body fat (45). It has also been shown that maternal smoking during pregnancy is related to changes in DNA methylation (46). However, whether these changes in methylation underlie the associations between fetal smoke exposure and postnatal obesity remains to be studied.

**Implications and future research**

Our results underlined the importance of health care interventions to reduce the smoking of mothers during pregnancy for the prevention of short-term outcomes during pregnancy and long-term outcomes in their children. Additional follow-up studies are needed in children at older ages and to identify associations of maternal smoking during pregnancy with more refined metabolic syndrome measures such as concentrations of glucose, triglycerides, and total cholesterol and detailed measures of body composition.

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of...
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the Erasmus University Rotterdam (Rotterdam, Netherlands), the Municipal Health Service Rotterdam area (Rotterdam, Netherlands), the Rotterdam Homecare Foundation (Rotterdam, Netherlands), and the Stichting Trombosedienst and Arsentenlaboratorium Rijnmond (Rotterdam, Netherlands). We gratefully acknowledge the contributions of participating mothers, general practitioners, hospitals, midwives, and pharmacies in Rotterdam, Netherlands.

The authors’ responsibilities were as follows—BD, SPW, and VWV: designed and conducted research, analyzed data, and wrote the manuscript; CJK: provided essential materials and analyzed data; MHG, AH, HR, PHCE, and EAPS: provided comments and consultation regarding analyses and the manuscript; VWV: had primary responsibility for the final content of the manuscript; and all authors: gave final approval of the version of the manuscript to be published. None of the authors declared a conflict of interest.

REFERENCES