Parental Smoking and Vascular Damage in Young Adult Offspring: Is Early Life Exposure Critical? The Atherosclerosis Risk in Young Adults Study

Caroline C. Geerts, Michiel L. Bots, Diederick E. Grobbee, Cuno S.P.M. Uiterwaal

Objective—Our purpose was to study the association between familial and particularly fetal tobacco smoke exposure and vascular damage in young adulthood.

Methods and Results—From a cohort of 732 young adults, birth data were collected and in young adulthood ultrasound measurement of common carotid artery intima-media thickness (CIMT) was performed. Data on parental smoking were obtained by standardized questionnaires. Twenty-nine percent of the mothers smoked during pregnancy. Offspring of mothers who smoked had 13.4 μm thicker CIMT (95% CI: 5.5, 21.3; P=0.001) than offspring of mothers who did not smoke in pregnancy. Adjustment for known CIMT risk factors (participant’s age, gender, BMI, pulse pressure, and LDL-cholesterol) yielded no change (9.4 μm, 95% CI: 1.9, 16.3, P=0.01) nor did adjustment for current smoking of parents (10.6 μm, 95% CI: 0.4 to 20.8, P=0.04), for participants’ current smoking and pack-years (11.5 μm, 95% CI: 3.5 to 19.4, P=0.004) or for parental socioeconomic status (SES; 13.0 μm, 95% CI: 5.0, 21.1, P=0.002). Thicker CIMT was associated with exclusive paternal smoking in pregnancy, somewhat stronger with exclusive maternal smoking and strongest with both parents smoking (P linear trend=0.001). Offspring of particularly mothers who smoked an above median number of cigarettes in pregnancy had thicker CIMT than those smoking less than median or no cigarettes (P linear trend <0.0001).

Conclusion—Permanent vascular damage is partly attributable to familial tobacco smoke exposure, an association that might be initiated in gestation. (Arterioscler Thromb Vasc Biol. 2008;28:2296-2302.)

Key Words: carotid intima-media thickness ■ prenatal exposure delayed effects ■ pregnancy ■ smoking ■ young adulthood

Cigarette smoking is a risk factor for cardiovascular disease.1 Active smoking in adulthood is associated with carotid artery intima-media thickness (CIMT),2 a measure of cardiovascular disease risk.3 Cardiovascular damage as a consequence of tobacco smoke exposure can already be shown at a young age. Active smoking in adolescence is associated with increased CIMT and decreased carotid artery elasticity in young adulthood.4–6 However, not only active smoking but also passive smoking of young adults, and recently this was shown in children as well,7 was associated with dose-related impairment of endothelium dependent dilation,8,9 and with thicker CIMT.10 Thus, exposure to tobacco smoke results in vascular damage already at a young age. However, it is unknown whether it is just a cumulative effect of smoke exposure in terms of dosage and duration that causes early vascular damage, or whether there are specific periods, particularly gestation, in which children are especially vulnerable to smoke exposure. Presently, some 10% of women in Western societies are reported to smoke during pregnancy.11 Maternal smoking in pregnancy hampers fetal growth resulting in substantially lower birth weight,12 and it induces acute fetal circulatory changes.13 There are indications that smoking in pregnancy affects cardiovascular risk factor levels in the young offspring. Several13–21 although not all22,23 studies have shown a relation between maternal tobacco smoke exposure during pregnancy and higher blood pressure in their offspring, to overweight and obesity in offspring,18,24–28 and to smaller offspring stature.29 Recently, it was indicated that maternal smoking in pregnancy is associated with an increased rise in total cholesterol levels and trends toward adverse lipoprotein profiles in the young offspring.30 There may also be direct effects of tobacco smoke on the fetal cardiovascular system. Intrauterine growth retardation, of which maternal smoking is one cause, is related to thicker aortic walls in newborns.31 Autopsy studies suggest that tobacco smoke exposure in pregnancy leads to structural changes in infant offspring airway wall thickness,32 but also to atherogenic changes in coronary arteries.33

We have used a birth cohort with documented smoking behavior of parents and 30 years of follow-up to investigate
whether tobacco smoke exposure, particularly in pregnancy, could lead to permanent vascular damage in offspring.

Methods

The Atherosclerosis Risk in Young Adults (ARYA) study is a birth cohort of children born in the 1970s who underwent general health examinations by school doctors in early adolescence and who underwent extensive cardiovascular risk profiling in young adulthood at around 30 years of age. The rationale and design of ARYA have been described elsewhere. The methods here described are confined to components that are relevant to the present research question.

Study Design and Population

The present study pertains to a cohort of 750 young adults born between 1970 to 1973, who attended secondary school in the city of Utrecht in the Netherlands and of whom original medical records were available from the Municipal Health Service. In 1999 all available Municipal Health Service charts of 1970 to 1973 (n=15,592) were checked for the presence of adequately registered birth weight and at least one blood pressure measurement during adolescence. All young adults with a complete chart (n=4208; 26.9%) were invited by mail, according to the last-known parental address, to participate in the study. 2191/4208 (52.1%) individuals did not respond despite regular mailings, 726/4208 (17.3%) letters were returned because of an inadequate address, 470/4208 (11.2%) subjects declined to take part, and 821/4208 (19.5%) were willing to participate. Of the eligible 821 young adults, 14 were excluded because of pregnancy and 55 declined to participate after they had given informed consent. Two candidates did not appear at our clinic. Ultimately, 750 young adults completed participation. Of these 18 did not provide data about smoking habits of parents during pregnancy, leaving 732 young adults for analysis. In the further text we will refer to these young adults as participants. From October 1999 to December 2000, the participants visited our ambulatory research clinic twice within a 3-week period. The ARYA-study was approved by the Medical Ethical Committee of the University Medical Center Utrecht. All participants gave written informed consent.

Measurements at Adolescence

In the Netherlands, routine physical examinations of all school children are performed by the Municipal Health Services during primary and secondary school period. Information about adolescent blood pressure (a single measurement using a manual sphygmomanometer), adolescent anthropometry, adolescent smoking habits, -alcohol intake and -oral contraceptive use as well as pubertal stage was available from the original school health records between the age of 12 to 16 years. The present study deals with data from the first visit to the school doctor in this age period, which was complete for all participants.

Measurements at Young Adulthood

At young adulthood (mean age: 28.4 years) cardiovascular risk factors of participants were measured. Blood pressure was measured 4 times, on 2 different occasions, with an automated device (Di-namap). Mean systolic and diastolic blood pressure were calculated as the average of the 4 measurements. Height and weight were measured with indoor clothes without shoes. Information about remaining cardiovascular risk factors, such as smoking habits, alcohol intake, family history, was obtained by a standardized written questionnaire. Participants were asked to hand over a questionnaire to (one of) their parents, containing questions about the smoking habits of either parent during pregnancy and about their current smoking habits. With these questionnaires also, information about specifics of the participants’ gestation and delivery was obtained, as well as information about the highest educational level of both parents.

Measurement of Common Carotid Intima-Media Thickness (CIMT) in Young Adulthood

Ultrasonography of both the left and right carotid artery was performed in all participants using a 7.5 MHz linear array transducer (Acuson Aspen). On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far walls of the carotid artery are displayed as two bright white lines separated by a hypoechoic space. The distance of the leading edge of the first bright line of the far wall and the leading edge of the second bright line indicated the intima-media thickness. When an optimal longitudinal image was obtained, it was frozen on the R-wave of the ECG and stored on video tape. This procedure was repeated at 4 predefined angles per side (180°, 150°, 120°, 90° for the right carotid artery and 180°, 210°, 240°, 270° for the left carotid artery) using the Meijer arc. The actual measurements were performed off-line. The frozen images on the video tape were digitized and displayed on a screen using additional dedicated software as described in detail by Wendelhag et al. In short, the interfaces of the distal common carotid artery were marked over a length of 10 mm using an automated edge detection approach. The beginning of the dilatation of the distal carotid artery served as a reference point for the start of the measurement. The average of the CIMT of the 8 predefined angles was used for each subject as a measure for current wall thickness of the common carotid artery. Both sonographer and reader were unaware of participants’ cardiovascular risk profile. Reproducibility of the CIMT-measurement was assessed by scanning 21 subjects on a second occasion by another sonographer. Absolute mean difference (+SE) of the repeated measurements between visits was 0.012 mm (0.004) for mean intima-media thickness of both carotid arteries. The intraclass correlation coefficient was 0.84.

Data-Analysis

Means and variance measures of baseline characteristics of parents and of participants were first calculated by maternal smoking in pregnancy. The same characteristics were also tested for differences between the group of fathers that did and did not smoke during pregnancy. Differences were tested using t tests or Mann–Whitney tests for continuous variables and using Chi-squared tests for proportional data.

We aimed at estimating the association between maternal exposure to tobacco smoke in pregnancy and offspring CIMT, independent of other risk factors for thicker CIMT in the ARYA study that were previously reported. Moreover, as smoking is a characteristic that clusters within families, we assessed whether the association was independent of current parental and participant smoking habits. We used linear regression models with offspring CIMT as dependent variable and an indicator of mother’s smoking during pregnancy as independent variable. We used this model to adjust for other possibly explanatory variables, CIMT risk factors (participants’ age, gender, BMI, pulse pressure, and LDL-cholesterol), parental current smoking habits, or participants’ current smoking habits and SES, defined as the highest educational level of the father (1, no education or primary school; 2, secondary school; 3, tertiary school). To assess whether pregnancy is a critical period we used linear regression with offspring CIMT as dependent variable and as independent variables dummies for combinations of maternal smoking in pregnancy (yes/no) and current maternal smoking (yes/no), with nonsmokers in pregnancy and currently as the reference group.

Finally, we assessed whether there was a dose–response relationship between tobacco smoke exposure in pregnancy and offspring CIMT. General linear models were used with offspring CIMT as dependent variable and dummy indicators for parental smoking habits as factors. First, we assessed whether there was an association between maternal or paternal or combined smoking in pregnancy and offspring CIMT. Second, we looked at whether there was an association between numbers of cigarettes smoked by fathers (none, below father specific median of 20, or above father specific median) or the number of cigarettes smoked by mother in pregnancy (none, below father specific median of 10, or above father specific median).
To further explore whether passive smoking of mother during pregnancy could be associated with offspring CIMT, linear regression was done in a subgroup of mothers not smoking in pregnancy with offspring CIMT as dependent variable and smoking of father (yes/no) as independent variable, adjustment was made for socioeconomic status.

Finally, to assess whether the effect on CIMT of tobacco exposure in utero was different for offspring that started smoking themselves later in life, we checked for interaction between maternal smoking during pregnancy and current smoking behavior in the offspring in linear regression analysis.

All analyses were performed with SPSS version 14.0 for Windows. Statistical significance was considered reached at \( P<0.05 \).

**Results**

Table 1 shows that mothers who smoked during pregnancy were younger and almost all reported to still smoke at the time of examination in 1999 to 2000. Smoking of mothers during pregnancy was strongly associated with smoking of fathers during pregnancy. Offspring of mothers who smoked during pregnancy were lighter and shorter at birth, heavier in both adolescence and young adulthood, but also shorter in adulthood than offspring of mothers who did not smoke in pregnancy. They also had higher systolic blood pressure levels in adolescence and they were more likely smokers in young adulthood. Offspring from smoking mothers had 13.4 \( \mu \)m thicker CIMT than offspring from mothers who did not smoke during pregnancy. Table 2 shows that offspring of smoking fathers during pregnancy had 12.4 \( \mu \)m thicker CIMT. Of the fathers who smoked, almost all reported to still smoke currently as well and they had a lower socioeconomic status. Offspring characteristics at adolescence and young adulthood pointed in the same direction as they did according to smoking category of mothers (Table 1). Birth weight and length did not differ between the offspring of smoking and nonsmoking fathers.

Current or ex-smoking participants had 9.3 \( \mu \)m higher CIMT than never smokers (95% CI: 2.0 to 16.5, \( P=0.012 \)). Also, parental current smoking habits were associated with probands’ CIMT levels. The difference in offspring CIMT for maternal current smokers versus maternal nonsmokers was 10.2 \( \mu \)m (95% CI: 3.0, 17.4, \( P=0.006 \)), the difference in offspring CIMT for paternal smokers versus paternal nonsmokers was 10.5 \( \mu \)m (95% CI: 2.7 to 18.4, \( P=0.008 \)).

Figure 1 shows that adult offspring of mothers who smoked in pregnancy had a 13.4 \( \mu \)m (95% CI: 5.5 to 21.3, \( P=0.001 \)) thicker CIMT than offspring of mothers who did not smoke in pregnancy. Adjusting for known CIMT risk factors (participants’ age, gender, BMI, pulse pressure, and LDL-cholesterol) only slightly attenuated the association (9.4 \( \mu \)m, 95% CI: 1.9 to 16.3, \( P=0.01 \)). Adjustment for current smoking of mothers (yes/no) and fathers (yes/no) did not materially change the association (10.6 \( \mu \)m, 95% CI: 0.4 to 20.8, \( P=0.04 \)) nor did adjustment for participants’ current smoking (yes/no) and pack-years (11.5 \( \mu \)m, 95% CI: 3.5 to 19.4, \( P=0.004 \)), and for parental SES (13.0 \( \mu \)m, 95% CI: 5.0, 21.1, \( P=0.002 \)). Furthermore, adjustment for participant’s highest level of education or income (below modal, modal, above modal) did not change the association (data not shown). Further, Figure 1 shows, with offspring of 369 persistently nonsmoking mothers as a reference, that offspring of smoking mothers during pregnancy had a 13.4 \( \mu \)m thicker CIMT than never smokers (95% CI: 2.0 to 16.5, \( P=0.004 \)).

**Table 1. Baseline Characteristics of Parents and Offspring: Smoking of Mothers During Pregnancy**

<table>
<thead>
<tr>
<th>Smoking of Mothers During Pregnancy</th>
<th>No (n=517)</th>
<th>Yes (n=215)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at pregnancy, years</td>
<td>27.7 0.2</td>
<td>25.7 0.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>28.6 0.1</td>
<td>96.7 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current body wt, kg</td>
<td>61.0 0.4</td>
<td>61.2 0.7</td>
<td>0.77</td>
</tr>
<tr>
<td>Current body height, cm</td>
<td>166.3 0.3</td>
<td>167.1 0.4</td>
<td>0.11</td>
</tr>
<tr>
<td>Fathers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>63.5 0.3</td>
<td>80.0 0.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking during pregnancy, %</td>
<td>61.1 0.2</td>
<td>83.7 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current body wt, kg</td>
<td>75.9 0.4</td>
<td>75.9 0.6</td>
<td>0.95</td>
</tr>
<tr>
<td>Current body height, cm</td>
<td>178.6 0.3</td>
<td>178.1 0.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Socioeconomic status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: no education or primary school</td>
<td>14.6 0.3</td>
<td>16.3 0.5</td>
<td></td>
</tr>
<tr>
<td>2: secondary school</td>
<td>39.3 0.4</td>
<td>41.8 0.5</td>
<td>0.57</td>
</tr>
<tr>
<td>3: tertiary school</td>
<td>46.1 0.4</td>
<td>41.8 0.5</td>
<td></td>
</tr>
<tr>
<td>Offspring at birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3472.1 22.8</td>
<td>3290.2 40.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birth length, cm</td>
<td>51.0 0.1</td>
<td>50.2 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Complications at delivery, %</td>
<td>18.5 0.3</td>
<td>16.3 0.4</td>
<td>0.47</td>
</tr>
<tr>
<td>Breast feeding, %</td>
<td>50.7 0.4</td>
<td>48.6 0.5</td>
<td>0.61</td>
</tr>
<tr>
<td>Offspring at adolescence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>13.4 0.05</td>
<td>13.6 0.08</td>
<td>0.07</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>48.8 0.4</td>
<td>51.0 0.7</td>
<td>0.009</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>162.3 0.4</td>
<td>162.5 0.6</td>
<td>0.88</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>18.4 0.1</td>
<td>19.2 0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>109.5 0.5</td>
<td>111.8 0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>66.2 0.4</td>
<td>67.6 0.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Offspring at young adulthood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>28.3 0.04</td>
<td>28.5 0.06</td>
<td>0.04</td>
</tr>
<tr>
<td>% males</td>
<td>47.6 0.4</td>
<td>43.3 0.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>76.4 0.7</td>
<td>78.2 1.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Body height, cm</td>
<td>177.1 0.4</td>
<td>175.3 0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.3 0.2</td>
<td>25.4 0.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125.3 0.6</td>
<td>125.0 0.9</td>
<td>0.75</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72.0 0.4</td>
<td>71.6 0.6</td>
<td>0.60</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>53.4 0.4</td>
<td>53.4 0.7</td>
<td>0.98</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>27.9 0.4</td>
<td>38.1 0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>CIMT, ( \mu )m</td>
<td>482.8 2.1</td>
<td>496.2 3.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are means, unless otherwise indicated. SEM indicates standard error of the mean.
spring of 148 women who did not smoke in pregnancy but did currently had no different CIMT (2.1 μm, 95% CI: 1.7, 2.7, P = 0.44). In contrast, offspring of 208 mothers who had smoked both in pregnancy and smoked currently did have thicker CIMT (13.9 μm, 95% CI: 5.5, 22.3, P = 0.001). The group of mothers who did smoke in pregnancy but not currently was too small for meaningful analysis.

Figure 2 shows that there was a positive association between parental smoking in pregnancy and mean offspring CIMT as compared to both nonsmoking parents (n = 197, 28%). There was an association with only paternal smoking (n = 310, 43%), a slightly stronger association with only maternal smoking (n = 34, 5%), and a strongest association with both parents (n = 174, 24%) smoking in pregnancy (p-trend over these categories in this order = 0.001). Of note, in 72% of families at least one of the parents smoked in pregnancy, more than 50% of parents showed concordant smoking behavior in pregnancy, and in 5% only the mother smoked. Offspring of mothers not smoking during pregnancy had thicker CIMT if their father did smoke during pregnancy (9.8 μm, 95% CI: 1.1, 18.4, P = 0.03) compared to offspring not exposed to tobacco smoke by their parents during pregnancy.
pregnancy. This effect was still seen after correcting for SES (9.4 μm, 95% CI: 0.7, 18.1, P=0.04). There were also positive associations between mean CIMT of offspring and number of cigarettes smoked by mothers in pregnancy and by fathers in pregnancy, although the latter was less strong.

There was significant interaction between participant’s current smoking behavior and maternal smoking during pregnancy (P=0.036). The difference in CIMT of nonsmoking participants who were exposed to tobacco intrauterine was 6.6 um (95% CI 3.1, 16.2, P=0.06), compared to nonsmoking nonexposed offspring. Offspring who smoke themselves had 24.3 um thicker CIMT if exposed to tobacco intrauterine, than smokers who were not exposed to smoke during pregnancy.

**Discussion**

To our knowledge this is the first report to demonstrate that offspring exposure to parental tobacco smoking may lead to permanent vascular damage in their offspring and that this might be initiated in early life.

Our cohort was an open population sample with substantial nonresponse because of its design. Selection could have biased our findings if eligible subjects refused participation based on specific associations between their CIMT and their parents’ smoking behavior during their gestation period, a scenario that we consider highly unlikely. Parental smoking data were collected by recall, and parents clearly rounded the recollected numbers of daily cigarette consumption in pregnancy. However, we concentrated on whether parents smoked or not during pregnancy, and pooled cigarette consumption to groups with above or below median consumption to reduce misclassification. We cannot be certain that all smoking data were indeed provided by the parents and not by the participant in their parents’ behalf. Possibly some misclassification did occur in assessing the exposure category. However, this must be nondifferential, as it seems highly unlikely that the reporting of smoking (yes/no) is in any way related to the outcome CIMT. Nondifferential misclassification would only lead to an underestimation of the results. Our classification of smoking in pregnancy was strongly related to birth weight, which supports the quality of the smoking data. Finally, our smoking data concern a period in the early seventies of last century, which is substantiated by the fact that almost 30% of women reported to smoke even in pregnancy like there is at present. This is compatible with recent findings concerning childhood growth trajectories of adult patients with cardiovascular disease. Our findings suggest that both smoking by mothers themselves in pregnancy and exposure to passive smoking could be important, and that more exposure leads to more vascular damage in the offspring. Trends between numbers of cigarettes smoked in pregnancy and CIMT in offspring were not as clear in fathers as in mothers, which might be understood realizing that not all reported smoking of fathers during pregnancy will have been in the vicinity of the pregnant mother. However, it is a challenge to really prove that passive smoking exposure will have the same biological effect as active maternal smoking, as it is difficult to rule out the effect of common confounding, with both maternal and paternal smoking being related to social trajectories that are themselves related to the CIMT measures. It is advocated that equal findings in offspring of smoking mothers and fathers in pregnancy are in fact supporting of common confounding. Alternatively, finding equal associations in mothers and fathers may also be attributable to the fact that to a large extent smoking behavior in parents is concordant (>50% in our study), with father’s smoking largely just being a marker of mother’s smoking behavior. We found exclusive paternal smoking in pregnancy to be associated with offspring CIMT as compared to both nonsmoking parents, slightly less strong than with maternal smoking in pregnancy, whereas smoking of both parents was more strongly associated than with either single smoking parent. Further, we found a dose-response relationship with smoking in pregnancy but less strong in fathers than in mothers. Therefore, although we recognize that residual confounding is a possible explanation, we feel that our findings may also be compatible with an in utero initiation of the damaging effects of familial exposure to tobacco smoke.

In our study, only a small proportion of women who smoked during pregnancy had given up smoking over the 30-year period. This may be explained by the fact that they were a selection of women who do continue smoking, despite their pregnancy, suggesting that they were heavier smokers and were thus less likely to quit. Secondly, there is a high relapse rate for nicotine addiction. In the Netherlands only some 7% of quitting attempts are successful in the long run. From both an etiologic and a prevention point of view an important question is whether the association between tobacco smoke exposure in pregnancy, if true, is based on direct effects of components in smoke on the vascular system of the fetus or through elevation of "classical" risk factors for cardiovascular disease in the offspring in childhood. Recently, we have shown persistent effects of maternal smoking in pregnancy through an excess rise in total cholesterol levels in the offspring throughout adolescence. Also, there are...
reported associations between maternal smoking in pregnancy and elevated blood pressure in offspring of various ages,14–21 although not in all studies.22,23 One reason for an association with higher blood pressure may be that smoking of the mother in pregnancy is associated with overweight or obesity in the offspring,18,23–25 including our present study, whereas relative weight is a strong determinant of blood pressure, also in childhood.44 Alternatively, there may be direct effects of smoking on the fetal vasculature. Smoking in pregnancy but, importantly, also passive smoking in pregnancy, is known to damage the placenta.45 Retarded fetal growth, a consequence of smoking in pregnancy, may be attributed to reduced dilatatory capacity of fetal vessels, as umbilical vein endothelium of newborns of smoking mothers produces less nitric oxide synthase.46 Experimental animal studies confirm that tobacco smoke exposure in pregnancy adversely affects vascular smooth muscle function,47 but also vascular connective tissue metabolism.48 There is evidence to suggest that the adverse effects of smoking on the fetal cardiovascular system is already set in utero. In our previous study it was shown that, already in early infancy, babies born from mothers who smoked had 5.4 mm Hg higher systolic blood pressure than babies who were not exposed to tobacco smoke in utero,20 an effect independent of birth weight.

Low birth weight, as a consequence of impaired intraterine growth caused by smoking, might serve as an intermediate in the association between smoking during pregnancy and offspring CIMT and thus explain our results. However, in the ARYA cohort, birth weight was not associated with offspring CIMT,49 supporting the mechanistic idea of a direct effect of tobacco smoke (nicotine) on the fetal vasculature.

Our findings were largely independent of other cardiovascular disease risk factors, including participant smoking habits, which suggests that such direct vascular influences may be plausible. We did find a borderline statistically significant interaction between maternal smoking in pregnancy and participants’ smoking habits, indicating that part of the effect of participants’ smoking on CIMT was mediated by the familial clustering of smoking. We postulate therefore that tobacco smoke exposure in pregnancy may have both direct and indirect adverse consequences for cardiovascular end organs.

CIMT is considered an indicator of vascular damage.50 In our study, smoking in pregnancy explained 0.27 SD of CIMT which would be associated with substantive differences in cardiovascular disease risks.50 Our study indicates that tobacco smoke exposure in pregnancy is associated with increased vascular damage in young adulthood, independent of later life risk factors. If true, this could have implications for the understanding of the early life origins of cardiovascular disease and for prevention.

In summary, our data show that permanent vascular damage appears partly attributable to familial tobacco smoke exposure, a process which might be initiated in gestation.

Sources of Funding
The Atherosclerosis Risk in Young Adults (ARYA) study was funded by The Netherlands Organization of Health Research and Development Council (ZonMW grants #2100.0008 and #2100.0042). The funding source had no role in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Disclosures
None.

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Arterioscler Thromb Vasc Biol. 2008;28:2296-2302
doi: 10.1161/ATVBAHA.108.173229

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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