Maternal cigarette smoking is associated with reduced high-density lipoprotein cholesterol in healthy 8-year-old children

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Received 10 January 2011; revised 9 April 2011; accepted 9 May 2011; online publish-ahead-of-print 21 June 2011

Aims

Smoking in pregnancy is common. Its effects on lipoprotein levels and arterial structure in childhood are not well characterized. We aimed to determine the effects of maternal smoking in pregnancy on lipoprotein levels and arterial wall thickness in healthy pre-pubertal children.

Methods and results

A community-based longitudinal study with prospective ascertainment of exposure to smoking in pregnancy and environmental tobacco smoke (ETS) since birth and then lipoprotein and arterial measurements at age 8 years. In 616 newborn infants (gestation > 36 weeks and birth weight > 2.5 kg) data were collected prospectively by questionnaire on smoking in pregnancy and ETS exposure in childhood. At age 8-years, 405 of the children had measurements of lipoproteins, blood pressure (BP) and carotid intima-media thickness. Children born to mothers who smoked in pregnancy had lower HDL cholesterol [1.32 vs. 1.50 mmol/L, 95% confidence interval (CI) for difference −0.28 to −0.08, P = 0.0005], higher triglycerides (1.36 vs. 1.20 mmol/L, 95% CI for ratio 1.01–1.30, P = 0.04) and higher systolic BP (102.1 vs. 99.9 mmHg, 95% CI for difference 0.6–3.8, P = 0.006). After adjustment for maternal passive smoking, post-natal ETS exposure, gender, breast feeding duration, physical inactivity, and adiposity, smoking in pregnancy remained significantly associated with lower HDL cholesterol (difference = −0.22 mmol/L, 95% CI −0.36 to −0.08, P = 0.003) but not with higher systolic BP. Neither smoking in pregnancy nor post-natal ETS exposure was associated with alterations of carotid artery wall thickness.

Conclusion

Smoking in pregnancy is independently associated with significantly lower HDL cholesterol in healthy 8-year-old children.

Keywords

Passive smoking • Pregnancy • Cholesterol • HDL • Paediatrics • Cardiovascular diseases

Introduction

The prevalence of maternal smoking during pregnancy remains high, ~15% in many Western countries.1–3 The documented associations between smoking in pregnancy and childhood behavioural problems, neurocognitive deficits and sudden infant death syndrome highlight the potential for smoking to result in adverse foetal programming. The independent effect of prenatal exposure to cigarette smoke on the risk of future cardiovascular disease (CVD), however, remains uncertain.

The plausibility for such a link is supported by the large number of epidemiologic studies showing a strong association between environmental tobacco smoke (ETS) exposure in adults and CVD.4 Furthermore, ETS exposure in adults is associated with impaired arterial endothelial function,5 increased arterial wall thickness6 and lipid alterations that favour atherosclerosis.7 As ETS exposure in childhood has also been shown to have a detrimental effect on measures of arterial structure and function in several8,9 but not all studies,10 childhood ETS exposure may potentially...
confound any association between maternal smoking in pregnancy and future CVD.

Therefore, we aimed to examine the effect of maternal smoking in pregnancy on the arterial wall thickness and lipoprotein levels of healthy 8-year-old children. We prospectively collected data on both smoking during pregnancy and long-term post-natal ETS exposure from a large sample of healthy boys and girls. We hypothesized that maternal smoking in pregnancy would have a significant independent effect on lipoprotein levels and arterial structure, in the first decade of life.

**Methods**

**Setting and participants**

The subjects were healthy 8-year-old children from Sydney, Australia. They had been enrolled prior to birth into the Childhood Asthma Prevention Study (CAPS), a randomized controlled trial of house-dust mite avoidance and dietary fatty acid modification from birth to 5 years in children at risk for asthma and allergic disease. The details of this trial have been published elsewhere and are available in the online-only Supplementary material online, Methods 1. Between September 1997 and December 1999 a total of 616 subjects (gestational age >36 weeks and birth weight >2.5 kg) were enrolled into the trial from birth. At the age of 8 years, families were invited to participate in a cardiovascular sub-study examining the effect of the dietary intervention on traditional vascular risk factors and non-invasive measures of arterial function. Results of this study have recently been published.

Four hundred and five of the original 616 children (66%) consented to participate in the cardiovascular study. Although maternal age and education were higher, the children who returned for vascular assessments were otherwise representative of the initial study population, for baseline characteristics. The analysis of lipoprotein levels was restricted to the 328 children who gave consent for blood collection; these children were also representative of the whole cohort with respect to baseline characteristics. This study complies with the Declaration of Helsinki and was approved by the Human Research Ethics Committees of the University of Sydney, the Children’s Hospital at Westmead and Western and South Western Sydney Area Health Services. The parent or legal guardian gave written informed consent.

**Assessment of tobacco smoke exposure in pregnancy**

Information on smoking during pregnancy was collected using a questionnaire that was completed by a face-to-face interview soon after birth. Mothers who had smoked during pregnancy were asked to quantify their smoking during the first, second, and third trimesters as ‘1–10/day’, ‘11–20/day’, ‘21–40/day’, or ‘≥41/day’. From these data, average smoking during pregnancy was calculated using mid-point values for each range (5, 15, 30, and 50, respectively). Those who denied smoking during pregnancy were classified as zero in all three trimesters. As the distribution of average smoking during pregnancy was highly positively skewed, this was analysed as a dichotomous variable (‘yes’ for any smoking during pregnancy or ‘no’ for no smoking during pregnancy).

Information on maternal exposure to passive smoking (‘Household Cigarette Exposure’) during pregnancy was also collected at the face-to-face interview soon after birth. Mothers were asked ‘Did others living in your home smoke inside the house during pregnancy?’. If the answer was ‘yes’, mothers were asked to quantify the number of cigarettes smoked by others in the home as ‘1–10/day’, ‘11–20/day’, ‘21–40/day’ or ‘41+/day’.

**Assessment of postnatal tobacco smoke exposure**

Information on ETS exposure during post-natal life was collected by study nurses during visits to the home or by telephone calls at the age of 4 weeks, then at three monthly intervals from the age of 3 months to age 5 years, and then at six monthly intervals to the age of 7.5 years. Mothers were asked ‘Do you smoke?’ and ‘Do other people living in your home smoke inside the house?’ Those who answered ‘yes’ to either of these questions were then asked to quantify, separately, the amount smoked by the mother, father, and other persons as ‘1–10/day’, ‘11–20/day’, ‘21–40/day’, or ‘≥41/day’. The total number of cigarettes smoked in the house at each time point was quantified as the sum of smoking by the mother, father, and others. Calculations were made by taking mid-point values for each range (5, 15, 30, and 50, respectively). Where the responses to ‘Do you smoke?’ and ‘Do other people living in your home smoke inside the house?’ were both ‘No’, and where there was no positive response to any of the quantitative questions about smoking, ETS exposure in the home was assumed to be zero. The number of months of any exposure to tobacco smoke in the first year of life (ETS-1st year, to assess the influence of ETS during the critical period of infancy) and first 7.5 years (ETS-7.5 years, to assess the influence of cumulative ETS exposure) was determined. As their distributions were highly positively skewed, ETS-1 year was categorized into two groups (‘yes’ for any exposure and ‘no’ for no exposure) and ETS-7.5 years into three ordered groups (‘None’, ‘Low’: >0 but <90th percentile (84 months) and ‘High’: ≥90th percentile (84 months) for exposure duration).

Current ETS exposure (ETS-8 years) was assessed at the 8-year clinic visit by questionnaire. Parents were asked, ‘Do any people living in the home where your child spends most of their time smoke inside the house?’ Those who answered ‘yes’ to this question were then asked to quantify ‘cigarettes smoked inside the house’ for up to four people using the same classification as above. As a result of its positive skew, ETS-8 years was analysed in two groups (‘yes’ for any current ETS exposure and ‘no’ for no exposure).

**Measurements at 8 years**

**Anthropometry**

Height, weight, and waist circumference were measured in a standardized fashion from a standing position. BMI, BMI z-score and waist-to-height ratio were calculated (refer to the Supplementary material online for further details).

**Blood pressure**

Brachial blood pressure (BP) was measured in a standardized fashion using an automated oscillometric device (Welch Allyn Vital Signs Monitor, Skaneateles Falls, NY, USA). Further details are available in the Supplementary material online.

**Carotid intima-media thickness**

Mean carotid intima-media thickness (CIMT) was measured by B-mode ultrasound using a portable ultrasound system (Terson 3000, Teratek, Burlington, MA, USA), a 5–12 MHz linear array transducer and electrocardiogram gating. The full details of CIMT measurement in this study have recently been reported and are available in the Supplementary material online. B-mode ultrasound examination of the arterial wall, performed during life, produces a characteristic image that correlates with the histological intima-media complex. In adults, CIMT is correlated with coronary and carotid atherosclerosis.
and is a significant predictor of future cardiovascular events. For these reasons, CIMT has been used in numerous cross-sectional and intervention studies as a surrogate endpoint for atherosclerosis.

**Blood analyses**

At the age of 8-years 328 (81%) subjects gave consent for the collection of a non-fasting venous blood sample. The subjects who had blood collected were representative of the whole cohort with respect to baseline characteristics. Samples underwent centrifugation at 1900 g for 5 min and the collected serum was stored at −20°C for less than 2 weeks before total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (using standard enzymatic procedures) and high-sensitivity C-reactive protein (hs-CRP, using an immunoturbidimetric method) were assayed on a modular autoanalyser (Roche, Basel, Switzerland). Non-HDL cholesterol (total cholesterol minus HDL cholesterol) was calculated for each subject. Apolipoprotein B (apo B, the major protein component of atherogenic lipoproteins) and apolipoprotein A1 (apo A1, the major protein component of HDL) were measured by immunoturbidimetry.

**Assessment of other potential confounders**

Information about breastfeeding was collected from participating families at 1, 3, 6, 9, and 12 months of age, using standardized questionnaires. The duration of breastfeeding was classified as ≤6 months or >6 months.

The level of physical inactivity at the age of 8 years was assessed from a standardized parental questionnaire. Parents were asked about the average number of hours per day their children watched television and physical inactivity was thus assessed in three ordered categories: low (0−1 h per day, n = 123), intermediate (2−3 h per day, n = 238), and high (>3 h per day, n = 42).

**Statistics**

Data are presented as mean [95% confidence interval (CI)], geometric mean (95% CI), median (interquartile range) or percentages, as appropriate. Comparison between groups was performed using Fisher’s exact and the χ² tests for proportions or analysis of variance. The association between ETS or smoking in pregnancy and systolic BP or HDL cholesterol was examined by multiple linear regression analysis.

A high co-linearity was found between maternal smoking in each trimester, which meant that the independent effects of smoking in each trimester could not be tested in the same model. However, the effect of maternal smoking in each trimester on HDL cholesterol was tested in separate models, adjusted for other potential confounders.

As hs-CRP had a skewed distribution and a lower limit of detection of 0.21 mg/L, this variable was assessed in four ordered categories: below detection limit (<0.21 mg/L, n = 128), low [0.21−0.305 mg/L (50th centile), n = 35], intermediate [0.306−1.11 mg/L (75th centile), n = 82], and high [>1.11 mg/L (75th centile), n = 81].

As we were testing specific hypotheses regarding the influence of maternal smoking on lipoprotein levels and arterial wall thickness, adjustments for multiple comparisons were not made, in accordance with recent recommendations. Statistical significance was inferred at a two-sided P-value of <0.05, and analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC, USA).

**Results**

Children whose mothers smoked during pregnancy had parents with lower levels of education and had shorter breastfeeding duration (Table 1). Pregnancy-induced hypertension and preeclampsia were higher in smoking than in non-smoking mothers (5.4 vs. 1.0%, P = 0.007). Children with and without maternal smoking exposure had similar gestational age, birth weight and head circumference, and height at 8 years. However, children with maternal smoking exposure were heavier at age 8 years than those without such exposure (Table 1).

In the univariate analysis, smoking in pregnancy was associated with lower HDL cholesterol (1.32 vs. 1.50 mmol/L, difference −0.18 mmol/L, 95% CI for difference is −0.28 to −0.08, P = 0.0005) and higher triglycerides (1.36 vs. 1.20 mmol/L, ratio of geometric means is 1.14, 95% CI for ratio 1.01−1.30, P = 0.04; Table 2). The direction of the difference in apo A1 was similar to that for HDL (1.42 vs. 1.48 mmol/L, difference −0.06, 95% CI −0.12 to 0.005, P = 0.07). Exposure to smoking during pregnancy was not associated with a significant alteration in the concentrations of apo B containing lipoproteins (Table 2).

Although smoking in pregnancy was associated with a higher systolic BP and hs-CRP in children at 8 years, CIMT was not significantly different from those with no such exposure (Table 3).

ETS exposure during all periods of childhood was also associated with lower parental education, shorter breastfeeding duration and younger maternal age (Supplementary material online, Table S1). However, ETS exposure in childhood was not associated with a significant difference in lipoprotein concentrations (Supplementary material online, Table S2). Similarly ETS exposure in the first year of life (data not shown) and higher cumulative ETS exposure over 7.5 years (Supplementary material online, Table S3) were not associated with a significant change in arterial wall thickness. Current ETS exposure (ETS-8 years) was associated only with a small increase in diastolic BP (Supplementary material online, Table S3).

In multivariate models adjusting for the effects of Household Cigarette Exposure during pregnancy, gender, breastfeeding duration, levels of physical inactivity and measures of body fat (Table 4), smoking in pregnancy remained significantly associated with lower HDL cholesterol (difference = −0.14 mmol/L, 95% CI for difference −0.25 to −0.03, P = 0.01). The addition of birth weight to these models did not alter this association. In models that also incorporated the cumulative ETS exposure over the first 7.5 years of life, smoking in pregnancy remained significantly related to lower HDL cholesterol at the age of 8 years (Table 4).

Testing of the association between maternal smoking in each individual trimester and HDL cholesterol, with adjustment for the same covariates, revealed a similar effect size for each trimester; this association was significant at P < 0.05 for the third trimester alone (first trimester b = −0.09, P = 0.1; second trimester b = −0.06, P = 0.08; third trimester b = −0.07, P = 0.035).

After adjustment for the effects of Household Cigarette Exposure during pregnancy, cumulative postnatal ETS exposure, adipose tissue, gender, breastfeeding duration, and physical inactivity the association between smoking in pregnancy and systolic BP was of borderline significance (Table 5).

**Discussion**

In this study, we have demonstrated a significant and independent association between maternal smoking in pregnancy and lower
levels of the atheroprotective lipoprotein HDL cholesterol. The strengths of this study include the large number of subjects, the assessment of children at an age (8-years) and (pre-pubertal) stage when the influence of other cardiovascular risk factors on lipoproteins are minimized, the prospective collection of data on pre- and post-natal exposure to tobacco smoke, and the systematic adjustment for a number of important potential confounders.

HDL cholesterol has a number of functions that are potentially protective against atherosclerosis, including promoting cholesterol efflux from macrophages and nitric oxide production from the endothelium, inhibiting lipid oxidation, and platelet activation, improving leucocyte adhesion and monocyte activation and preventing endothelial cell death and damage. 

Table 1  Baseline characteristics of 405 children studied, by smoking status in pregnancy

<table>
<thead>
<tr>
<th>smoking status in pregnancy</th>
<th>All Subjects</th>
<th>Smoking in pregnancy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Number, n (%)</td>
<td>405</td>
<td>312 (77%)</td>
<td></td>
</tr>
<tr>
<td>Diet intervention, n (%)</td>
<td>205 (50.6)</td>
<td>50.0%</td>
<td>0.60</td>
</tr>
<tr>
<td>HDM* intervention, n (%)</td>
<td>199 (49.14)</td>
<td>49.7%</td>
<td>0.70</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>204 (50.4)</td>
<td>51.3%</td>
<td>0.50</td>
</tr>
<tr>
<td>Prevalence of asthma (%)</td>
<td>29%</td>
<td>30%</td>
<td>0.40</td>
</tr>
<tr>
<td>Asthma medication use (%)</td>
<td>36%</td>
<td>37%</td>
<td>0.30</td>
</tr>
<tr>
<td>Maternal education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>11 (2.7)</td>
<td>1.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year 10</td>
<td>114 (28.2)</td>
<td>23.1%</td>
<td>45.2%</td>
</tr>
<tr>
<td>Year 12</td>
<td>73 (18.0)</td>
<td>16.7%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Tertiary</td>
<td>208 (51.1)</td>
<td>58.3%</td>
<td>26.9%</td>
</tr>
<tr>
<td>Paternal education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>14 (3.5)</td>
<td>2.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Year 10</td>
<td>129 (29.6)</td>
<td>24.4%</td>
<td>49.4%</td>
</tr>
<tr>
<td>Year 12</td>
<td>71 (17.5)</td>
<td>18.7%</td>
<td>14.6%</td>
</tr>
<tr>
<td>Tertiary</td>
<td>195 (48.2)</td>
<td>54.7%</td>
<td>28.1%</td>
</tr>
<tr>
<td>BF duration ≥6 months, n (%)</td>
<td>169 (41.7)</td>
<td>47.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pregnancy-induced hypertension or preeclampsia, n (%)</td>
<td>8 (2.0)</td>
<td>1.0%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Maternal age at pregnancy, years</td>
<td>29.5 (29.0–30.0)</td>
<td>29.8 (29.3–30.3)</td>
<td>28.5 (27.4–29.6)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>39.6 (39.4–39.7)</td>
<td>39.5 (39.4–39.7)</td>
<td>39.7 (39.4–39.9)</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.50 (3.45–3.54)</td>
<td>3.50 (3.45–3.55)</td>
<td>3.49 (3.38–3.60)</td>
</tr>
<tr>
<td>Head circumference at birth, cm</td>
<td>34.7 (34.6–34.8)</td>
<td>34.7 (34.5–34.9)</td>
<td>34.7 (34.3–35.0)</td>
</tr>
<tr>
<td>Height at 8 years, cm</td>
<td>128.4 (127.9–129.0)</td>
<td>128.4 (127.8–129.1)</td>
<td>128.5 (127.3–129.7)</td>
</tr>
<tr>
<td>Weight at 8 years, kg</td>
<td>29.10 (28.45–29.75)</td>
<td>28.58 (27.91–29.20)</td>
<td>30.92 (29.11–32.74)</td>
</tr>
<tr>
<td>BMI z-score at 8 years</td>
<td>0.52 (0.42–0.62)</td>
<td>0.64 (0.33–0.56)</td>
<td>0.80 (0.60–1.00)</td>
</tr>
<tr>
<td>Waist circumference at 8 years, cm, Median (IQR)</td>
<td>59.5 (58.7–60.2)</td>
<td>58.76 (58.0–59.5)</td>
<td>61.9 (59.9–63.9)</td>
</tr>
</tbody>
</table>

Table 2  Lipoproteins of the 328 children in whom blood was collected at the age of 8 years, by smoking status in pregnancy

<table>
<thead>
<tr>
<th>Smoking status in pregnancy</th>
<th>Differenceb</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL, mmol/L</td>
<td>2.92</td>
<td>3.08</td>
</tr>
<tr>
<td>Trigs*, mmol/L</td>
<td>1.20</td>
<td>1.36</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.50</td>
<td>1.32</td>
</tr>
<tr>
<td>apo A1, mmol/L</td>
<td>1.48</td>
<td>1.42</td>
</tr>
<tr>
<td>apo B, mmol/L</td>
<td>0.63</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Data are mean (95% CI) except for triglycerides (trigs), which is geometric mean (95% CI).

Data are mean (95% CI) unless otherwise specified.

a House-dust mite.

b Breast feeding.

levels of the atheroprotective lipoprotein HDL cholesterol. The strengths of this study include the large number of subjects, the assessment of children at an age (8-years) and (pre-pubertal) stage when the influence of other cardiovascular risk factors on lipoproteins are minimized, the prospective collection of data on pre- and post-natal exposure to tobacco smoke, and the systematic adjustment for a number of important potential confounders.

HDL cholesterol has a number of functions that are potentially protective against atherosclerosis, including promoting cholesterol efflux from macrophages and nitric oxide production from the endothelium, inhibiting lipid oxidation, and platelet activation, improving leucocyte adhesion and monocyte activation and preventing endothelial cell death and damage. Autopsy data from the Pathobiological Determinants of Atherosclerosis Study and the Bogalusa Heart Study indicate that atherosclerosis occurs in adolescents and young adults and that lower levels of HDL cholesterol are associated with greater histological progression of lesions. In the model adjusted for potential confounders, maternal smoking during pregnancy was associated with
0.14 mmol/L lower HDL cholesterol compared with the absence of maternal smoking during pregnancy. Although the effect of this degree of HDL cholesterol lowering in young children on the extent of atherosclerosis is uncertain, population studies in adults suggest that smaller changes in HDL cholesterol result in significant differences in the prevalence of coronary heart disease, after adjustment for the presence of other risk factors. For example, a HDL increment of merely 0.026 mmol/L (1 mg/dL) results in a 2–3% reduction in the risk for coronary heart disease. To our knowledge, only two studies have previously reported the associations between maternal smoking and lipoprotein levels in offspring. In data from the MCV Twin Study of 216 twin pairs (age: 11.8 ± 1.2 years, 105 twin pairs with and 111 without...
Maternal cigarette smoking is associated with reduced HDL cholesterol

Currently smoking parents), Muskowitz et al. found lower HDL cholesterol levels in the 8 twin pairs who had exposure to cigarette smoke only in pregnancy compared with the 33 twin pairs that had no exposure either in or ex utero (44.6 ± 2.2 vs. 50.2 ± 1.1 mg/dl, P < 0.05 after adjustment for age, height, weight, and sex).24 Definitive conclusions from this study on the effect of maternal smoking are limited, however, by the small sample size. Jaddoe et al. have also reported on the effect of smoking in pregnancy on age-related changes in lipoprotein levels amongst 350 subjects in whom measurements were performed annually between 1975 and 1993 and again in 2002.25 At baseline (age ~13 years), children born to mothers who smoked in pregnancy (n = 71) had significantly lower total cholesterol but non-significant differences in LDL and HDL cholesterol after adjustment for age and sex. In adolescence and young adulthood, total cholesterol levels showed a higher annual rate of rise in offspring born to mothers who smoked in pregnancy compared with that in the offspring of non-smoking mothers. However, important limitations of this study include the retrospective ascertainment of smoking in pregnancy (obtained by a questionnaire sent to parents when subjects were all aged over 18 years) and potential residual confounding by breastfeeding, pubertal status, and childhood ETS exposure. 

Our data therefore extend the findings of these studies by showing an association between smoking in pregnancy and lower HDL cholesterol in a large group of pre-pubertal children, utilizing contemporaneously collected data for smoking variables and fully adjusted models that include a number of important confounding/explanatory variables. Importantly, lower birth weight does not appear to influence the association between smoking in pregnancy and lower HDL levels.

Our finding of no difference in CIMT in offspring of smoking and non-smoking mothers is different to that of Geerts et al.26 In their study of 732 young adults (mean age 28.4 years), CIMT was thicker in those offspring whose parents smoked during pregnancy, after adjustment for several risk factors for thicker adult CIMT (current age, gender, BMI, pulse pressure and LDL cholesterol) and current parental and participant smoking status. CIMT was thickest if both parents smoked in pregnancy and was progressively thinner with maternal smoking only, paternal smoking only and no parental smoking. Importantly, however, the modifying effects of cumulative ETS exposure, either in childhood or adulthood, were not reported in this study. An interaction did exist between exposure to maternal smoking in pregnancy and the participant’s current smoking status; compared with non-exposed/currently non-smoking subjects, the CIMT in exposed/currently non-smoking and exposed/currently smoking participants was thicker by 6.6 and 24.3 μm, respectively. In combination with these data, our findings suggest that although arterial wall thickening from maternal smoking may not manifest in offspring during early childhood, the potential for accelerated vascular damage exists in the presence of exposure to tobacco smoke later in life.

Support for the biological plausibility of an association between maternal smoking and postnatal BP comes from studies that show an association between childhood BP and postnatal ETS exposure.27 Maternal smoking in pregnancy has been associated with significantly higher childhood systolic BP in some but

<table>
<thead>
<tr>
<th>Covariate</th>
<th>No adjustment for post-natal ETS exposure</th>
<th>Adjustment for ETS-7.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β  (95%CI)</td>
<td>Partial R²</td>
</tr>
<tr>
<td>Smoking in pregnancy</td>
<td>0.08</td>
<td>1.25 (−0.37 to 2.87)</td>
</tr>
<tr>
<td>ETS-7.5 years</td>
<td>Low</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>−0.03</td>
</tr>
<tr>
<td>Household cigarette exposure</td>
<td>−0.06</td>
<td>−0.83 (−2.04 to 0.39)</td>
</tr>
<tr>
<td>Gender</td>
<td>−0.02</td>
<td>−0.31 (−1.58 to 0.95)</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>0.41</td>
<td>2.74 (2.13 to 3.34)</td>
</tr>
<tr>
<td>TV viewing</td>
<td>Low</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>−0.02</td>
</tr>
<tr>
<td>HDM intervention group</td>
<td>0.06</td>
<td>0.76 (−0.46 to 1.97)</td>
</tr>
<tr>
<td>Diet intervention group</td>
<td>0.004</td>
<td>0.05 (−1.17 to 1.26)</td>
</tr>
</tbody>
</table>

β is the standardized estimate (in standard deviation units); b is the unstandardized coefficient (in the original units of measurement); the entered variables were Household Cigarette Exposure during pregnancy, gender (male compared with female), duration of breastfeeding, number of hours watching TV per day (compared with low [0–1 h]), 8 year BMI z-score, house-dust mite (HDM) intervention group and dietary intervention group. Adjustment for the cumulative ETS exposure (ETS-7.5 years) compared low or high exposure with no exposure. Neither addition of birth weight nor replacement of BMI z-score with waist circumference or waist/height ratio had any effect on the model estimates. *P-value is provided for the group variable. n/a is not applicable.
not all reports. The largest of these studies, by Brion et al., highlights that this inconsistency may relate, at least in part, to differing levels of adjustment for potential confounders. In their study, of 6509 children aged 7 years, a moderate association was found between maternal smoking in pregnancy and systolic BP after adjustment for the child’s age and sex only [β = 0.64 (0.09–1.20), P = 0.02]. However, this association was not significant in models that additionally adjusted for social factors (maternal education and social class) or breastfeeding or both. In our fully adjusted models, which included cumulative postnatal ETS exposure, household cigarette exposure during pregnancy and measures of adiposity and breastfeeding, the association between maternal smoking and systolic BP was of borderline significance (P = 0.07).

In contrast to most other reports, we found a higher prevalence of pregnancy-induced hypertension (PIH) and preeclampsia (PE) in smoking mothers. The significance of our finding is uncertain given that PIH and PE were self-reported and their prevalence (total of 2%) was lower than has been published elsewhere. Furthermore, the ‘protective’ effect of maternal smoking on PIH/PE appears to be greatest for pregnant women with low birthweight babies and non-existent for light smoking mothers with heavier babies. Therefore our findings may have been different had the original study not specified the exclusion of babies born <2.5 kg.

Our current study has several potential limitations. Firstly, rather than measurement of cotinine levels, we assessed childhood ETS exposure from questionnaires administered frequently to mothers, where information on smoking in the home was sought. Reassuringly, however, a significant proportion of the variance in early childhood cotinine levels has been shown to be due to maternal smoking, living in a home with other smokers and the number of cigarettes smoked in the home per day, which were directly assessed in our questionnaire. Furthermore, short parental questionnaires have previously been shown to accurately determine childhood ETS exposure.

Secondly non-fasting venous blood samples were collected. However, we assessed non-HDL cholesterol, HDL cholesterol, apoB, and apoA1, whose levels differ little between the fasting and non-fasted state. Thirdly, in our multivariable models, smoking in pregnancy explained only a small proportion in the variance of HDL cholesterol (partial R² = 0.03), highlighting the importance of other factors in determining levels of this lipoprotein. Fourthly, information on diet and the levels of exercise-based physical activity at the age of 8-years were not available, allowing the potential for residual confounding. Fifthly, original inclusion criteria for recruitment into the study included a gestational age >36 weeks and birth weight >2.5 kg. Therefore, our results may not be applicable to the low-birth weight group. Furthermore, these inclusion criteria may have been a factor in our inability to detect a difference in birth weight between children born to smoking and non-smoking mothers. Lastly, the design of our study does not allow confirmation of the mechanisms underlying the association between maternal smoking in pregnancy and lower HDL cholesterol.

In conclusion, we have demonstrated that maternal smoking in pregnancy is associated with lower HDL cholesterol (by ~0.14 mmol/L) in healthy 8-year-old children. This is independent of any subsequent effects of ETS exposure in the child. Such data may be important for informing population-based prevention of atherosclerosis, as smoking in pregnancy remains common and HDL cholesterol has important atheroprotective functionality.

Supplementary material

Supplementary material is available at European Heart Journal online.

Funding

This work is supported by an Australian Government National Health and Medical Research Council Project Grant (Number 222722 to D.C.). Funding for certain of the blood tests performed was obtained from a Pfizer CVL Grant. Funding for the original randomized control trial was obtained from the National Health and Medical Research Council of Australia, Cooperative Research Centre for Asthma, New South Wales, Department of Health and Children’s Hospital Westmead.

Conflict of interest: none declared.

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