Childhood Passive Smoking, Race, and Coronary Artery Disease Risk

The MCV Twin Study

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Background: Children with long-term exposure to passive cigarette smoke may be at elevated risk for the development of premature coronary artery disease (CAD).

Objective: To examine how CAD risk factors, exposure to passive smoking, sex, and race are related in pubertal children and to determine if there is an identifiable childhood risk profile (ie, does passive smoking interact with other coronary risk factors to increase the risk of developing premature CAD).

Design: Cohort analytic study.

Setting: The Medical College of Virginia (MCV) Twin Study, Richmond, Va.

Subjects: Randomly selected twins from 408 11-year-old twin pairs recruited from nearby schools.

Methods: Data collection occurred at 18-month intervals on family and health histories, smoking and alcohol consumption, blood pressure, anthropometrics, and biochemical assays. Data from cohorts of 11-year-olds studied through age 15 years were analyzed by repeated-measures analyses of variance using a mixed modeling approach. Models for high-density lipoprotein cholesterol (HDL-C) included race, sex, passive smoking status, weight, systolic and diastolic blood pressures, and all interactions.

Results: Passive smoke exposure was greater in white families than in black families. Levels of HDL-C and HDL2-C (HDL subfraction 2 cholesterol) were lower in white children than in black children (visit 1: HDL-C, mean ± SD, 1.21 ± 0.26 vs 1.31 ± 0.26 mmol/L [47.0 ± 10.1 vs 50.6 ± 10.1 mg/dL], P ≤ .01; HDL2-C, mean ± SD, 0.31 ± 0.18 vs 0.41 ± 0.19 mmol/L [12.3 ± 7.0 vs 15.9 ± 7.4 mg/dL], P ≤ .001). Children with a family history of cardiovascular disease had differences in HDL-C levels related to race that were worsened by exposure to cigarette smoke. In these children, HDL-C level was lower in those exposed to passive smoking (visit 1: 1.18 ± 0.23 vs 1.25 ± 0.23 mmol/L [45.6 ± 9 vs 48.2 ± 9 mg/dL] and visit 4: 0.98 ± 0.10 vs 1.19 ± 0.18 mmol/L [37.8 ± 4 vs 46.0 ± 7 mg/dL]; P < .001), with white children having lower HDL-C levels than black children (visit 1: 1.12 ± 0.21 vs 1.36 ± 0.23 mmol/L [43.2 ± 8 vs 52.7 ± 9 mg/dL] and visit 4: 0.97 ± 0.31 vs 1.01 ± 0.31 mmol/L [37.6 ± 12 vs 39.0 ± 12 mg/dL]; P = .004). In white families, as weight increased, boys exposed to passive smoking showed the greatest decrease in HDL-C level (P < .01 for weight by sex and passive smoking interaction). Risk factors for CAD, such as blood pressure, interacted with HDL-C and these relationships varied by race and sex.

Conclusions: Pubertal children with long-term passive cigarette smoke exposure have lower HDL-C levels. Racial differences in HDL-C levels are related to passive smoke exposure. In children with a family history of cardiovascular disease, interactions exist between passive smoking, HDL-C level, and blood pressure that differ by sex and race. White males exposed to passive smoking who have a family history of cardiovascular disease and higher weights and diastolic blood pressures may be at special risk for premature CAD.


The results of this intriguing study should be discussed with all parents who smoke. If they’re going to light up near their children, they might as well feel guilty.

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Atherosclerotic changes found in middle age begin in childhood. The mechanisms may relate to abnormal levels of risk factors. Certain risk factors, such as serum lipid and lipoprotein levels, hypertension, and smoking, are thought to be related to the earliest stages of atherosclerotic coronary artery disease (CAD). We know that, in adults, high levels of low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) and its major subfractions are associated with myocardial infarction. Families with special risk of CAD can be identified by the aggregation of lipoprotein levels and low levels of HDL-C and its subfractions in the children. Because serum lipid and lipoprotein levels and other risk factors in early pubertal children are under strong genetic influence, they may be responsible...
SUBJECTS AND METHODS

POPULATION

As part of an ongoing genetic longitudinal study of developmental changes in cardiovascular risk factors during adolescence, we recruited families with twins from nearby school systems. Using school rosters, we identified twin pairs living in the Commonwealth of Virginia. Descriptions of our study were sent by the school; affirmatively replying families were invited to participate. A total of 408 twin pairs (89% of affirmatively replying families) participated in the study. All twins were examined as close as possible to their 11th birthday. None of the twins were active cigarette smokers at entrance to the study and none initiated active cigarette smoking during the study period.

Families participated in a protocol that included the collection of data on family and health histories, smoking and alcohol consumption (questionnaire and personal interview), self-reported weekly exercise level, blood pressure, and collection of blood samples for biochemical assays. The protocol was repeated at 18-month intervals. Parents were asked about the family history, including the incidence of heart disease. A family history of cardiovascular disease was defined as hypertension or early cardiovascular death (before age 55 years) in a parent or in a first-degree relative of the parent or heart disease in either parent. The number of cigarettes smoked each day by the parents was recorded. Serum cotinine level was used both as the measure of smoke exposure and to verify nonsmoking status. No attempt was made to prescreen enrollees for the presence or absence of cardiovascular risk factors. Informed written consent, which had been approved by the Committee on the Conduct of Human Research, was obtained from each family before it entered the study.

PROCEDURES

Anthropometrics

Height and weight of each subject in stocking feet were measured with a calibrated stadiometer and digital scale, respectively. Anthropometric data were obtained in duplicate and averaged. Sexual staging was performed using a 5-scale score based on Tanner criteria.

Blood Pressure

Casual blood pressure was measured using a mercury sphygmomanometer with the appropriate compression cuff with the subject in the sitting position. Chosen cuff size was big enough to encircle at least half the upper arm without overlapping. The rubber bladder rested over the artery being compressed and had sufficient width to cover at least two thirds of the upper arm. Pressure within the compression cuff indicated by the level of the mercury column at the murmur of the first- and fourth-phase Korotkoff sound was recorded. Blood pressure was recorded 3 times and averaged. The interobserver intraclass correlation coefficients for blood pressure were 0.89 and 0.84 for systolic and diastolic blood pressures, respectively.

Blood Samples

A venipuncture sample of whole blood was obtained, stored on ice, and processed within 1 hour for quantitative lipoprotein cholesterol measurements using the vertical spin ultracentrifugation technique. The time elapsed from the last meal to the time of blood drawing was recorded and was found not to correlate with any of the lipoprotein levels. Serum cotinine concentration was quantitated by radioimmunoassay methods.

STATISTICAL ANALYSIS

Because twins share genes and environments and represent nonindependent observations, data from a single twin randomly ascertained from each family was used to determine group means for statistical testing. A random number table was generated and sequential twin pairs were assigned numbers. If an odd number was assigned to a pair, twin 1 was chosen from that pair. Changes in passive smoking status from one visit to the next are associated with alterations in lipoprotein levels. Therefore, data from families that changed smoking status (from smoking to nonsmoking or vice versa) anytime after the first visit were dropped from further analyses. Statistical differences between group means were assessed by 2-sided t tests, taking into account whether group variances were equal. Pooled t tests were used to test for differences in variables between boys and girls. Spearman nonparametric correlation coefficients were used when it was apparent that a given variable was not normally distributed, such as cigarettes smoked each day and HDL-C levels. Regression analysis was used to test for effects of confounding variables. Data are presented as mean ± SD.

Repeated-measures analyses of variance using a mixed modeling approach was performed for HDL-C levels. All analyses were performed in the SAS system using PROC MIXED. The mixed modeling approach allows for missing information over visits and allows for modeling of the variance and the mean. The missing data in our data set were missing completely at random and not covariate dependent missing at random. PROC MIXED will delete any observations with missing values for any variable in the model statement, ie, fixed effects. The analysis and results are valid with respect to the missing data provided that the cause of the missing data are independent of the outcome variable. For example, if twin pairs are treated as a repeated measure, unpaired twins will contribute to the regression, but not to the estimate of the covariance. Models for HDL-C included race, sex, passive smoking status, weight, systolic blood pressure, diastolic blood pressure, and all interactions among those variables.

for family clustering. Nonetheless, environmental effects account for a significant portion of the variance of coronary risk factors in pubertal children.

Cigarette smoking is an important environmental determinant of the early stages of atherosclerosis in adolescents and young adults. The pathogenesis may relate to the inverse dose-dependent relationship between cigarette smoking and HDL-C levels. In addition to active cigarette smoking, environmental tobacco smoke or passive smoking affects both plasma lipids and endothelium-dependent vasodilation. Adolescents exposed to their parents’ smoke have depressed levels of HDL-C and its
subfractions.\textsuperscript{9} Passive smoke exposure also causes, in a dose-dependent manner, endothelial dysfunction.\textsuperscript{30} Childhood passive cigarette smoking may therefore accelerate atherosclerotic changes and elevate the risk of developing CAD.

Despite a high prevalence of hypertension in black males, early reports suggest that the incidence of premature CAD is lower in black males than in white males.\textsuperscript{11} The lower CAD prevalence in black males despite the higher prevalence of hypertension may be engendered by higher levels of HDL-C in blacks.\textsuperscript{12} In a 1986 study, HDL-C distribution did not appear to fully account for the racial difference.\textsuperscript{13} While the risk of CAD may vary between blacks and whites, the standard major risk factors for CAD appear predictive for both blacks and whites.\textsuperscript{14} Racial differences in CAD risk factors observed in middle-age are incompletely documented in childhood and adolescence in part because of the confounding of pubertal changes. Because of the known differences in HDL-C levels in black compared with white adults, we pursued a study in adolescence to try to detect different effects of passive smoking on changes in HDL-C levels in a biracial adolescent population. The present study examines the following specific questions: (1) How are CAD risk factors, passive smoking, sex, and race related in pubertal children? (2) Are the effects of passive smoking different by race in families with a history of cardiovascular disease? (3) Is there an identifiable childhood risk profile, ie, does passive smoke exposure interact with other coronary risk factors to increase the risk of developing premature CAD?

## STUDY POPULATION AND SMOKE EXPOSURE

Population sample size and distribution for the entire study are shown in Table 1. A significant proportion of the subjects were lost to follow-up. These losses were due to deletion of families that changed their smoking status, and losses from families moving away or dropping out of the study. Selection bias was not operative as the sample population subjects completing the study were similar to those subsequently not included by sex (males, 43% vs 44%), race (black, 22% vs 25%), and all anthropometrics measures. The percentage of both black families and families with a history of cardiovascular disease was stable across visits at approximately 21%. The prevalence of smoking families decreased during the study from 35% to 27%. In smoking families, fathers began smoking at 18.2 ± 6.2 years of age and presently smoked 14.3 ± 14.7 cigarettes per day. Mothers began smoking at 18.4 ± 4.3 years of age and presently smoked 8.2 ± 10.4 cigarettes per day. The total daily number of cigarettes smoked by the parents at visit 1 ranged from 1 to 10 in 17%, 11 to 20 in 32%, and was more than 20 in 51%. The total daily number of cigarettes smoked by the parents did not vary significantly from visit to visit. However, within each visit, a greater daily number of cigarettes were smoked by white parents than by black parents (Figure 1). Cotinine was not detected in children who were not exposed to cigarette smoke but was present in children exposed to passive smoke (8.52 ± 17.6 nmol/L).

### ANTHROPOMETRIC AND BLOOD PRESSURE DATA

Anthropometric and blood pressure data are shown in Table 2. No significant differences were seen between the sexes for weight and height at earlier ages, although boys were significantly heavier and taller than girls at later visits. Black children were significantly heavier and taller than white children at the earlier visits. Significant differences existed for systolic blood pressure between older boys and girls. In younger children, systolic blood pressure was higher in black children than in white children. Diastolic blood pressure was similar in black and white children. Girls and black children overall were more sexually mature by Tanner staging at each of the first 3 visits. Passive smoking and nonpassive smoking groups by sex were similar in all anthropometric measurements. No difference was noted in weekly self-reported physical activity (the number of times each week vigorous exercise was performed) in any age, race, or sex group. Alcohol consumption was absent by self-report during the first 3 visits and only 1 twin at visit 4 reported any alcohol consumption.
The group means for lipoprotein levels by visit, sex, race, and passive smoking status are shown in Table 3. In the oldest children, LDL-C level was higher in blacks than in whites. The difference in LDL-C level between the non-smoking and passive smoking group of children was greater for whites than for blacks (P<.02). No other group differences were seen for LDL-C. White children had lower HDL-C and HDL subfraction 2 cholesterol (HDL2-C) levels than black children at all visits. Levels of HDL cholesterol were similar in white and black children in non-smoking families at visit 1 (1.24 ± 0.27 vs 1.27 ± 0.20 mmol/L [47.9 ± 10.3 vs 49.1 ± 7.9 mg/dL]). However, white children exposed to passive smoke had lower HDL

Table 2. Anthropometric and Blood Pressure Data by Visit, Race, and Sex*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Sex and Race</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>Girls</td>
<td>38.8 ± 9.5</td>
<td>45.7 ± 9.4</td>
<td>52.8 ± 9.1</td>
<td>55.6 ± 9.6†</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>37.8 ± 8.5</td>
<td>45.3 ± 11.4</td>
<td>53.4 ± 11.6</td>
<td>63.3 ± 15.2</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>42.8 ± 11.8†</td>
<td>49.5 ± 12.1†</td>
<td>55.7 ± 12.6</td>
<td>65.3 ± 20.6</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>37.2 ± 7.8</td>
<td>44.5 ± 9.7</td>
<td>52.5 ± 9.6</td>
<td>57.2 ± 9.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>Girls</td>
<td>146.4 ± 6.8</td>
<td>154.8 ± 6.4</td>
<td>160.1 ± 5.74†</td>
<td>161.7 ± 5.6‡</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>145.6 ± 6.8</td>
<td>153.9 ± 7.5</td>
<td>164.5 ± 7.9</td>
<td>171.9 ± 6.6</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>147.7 ± 7.1‡</td>
<td>155.9 ± 6.7§</td>
<td>161.9 ± 8.4</td>
<td>166.5 ± 9.1</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>145.5 ± 6.7</td>
<td>153.9 ± 6.9</td>
<td>162.1 ± 6.8</td>
<td>168.0 ± 7.6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>Girls</td>
<td>106.9 ± 9.9</td>
<td>108.6 ± 10.0</td>
<td>108.7 ± 9.5‡</td>
<td>108.5 ± 10.4</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>106.5 ± 9.4</td>
<td>108.7 ± 10.2</td>
<td>112.7 ± 9.5‡</td>
<td>114.9 ± 11.1</td>
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<tr>
<td></td>
<td>Black</td>
<td>109.9 ± 11.3§</td>
<td>111.5 ± 10.6§</td>
<td>112.4 ± 10.1</td>
<td>113.5 ± 14.5</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>105.9 ± 8.9</td>
<td>107.9 ± 9.9</td>
<td>110.2 ± 10.3</td>
<td>110.7 ± 9.9</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>Girls</td>
<td>62.7 ± 10.7</td>
<td>63.3 ± 10.3§</td>
<td>65.7 ± 9.6§</td>
<td>67.5 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>60.9 ± 11.5</td>
<td>60.8 ± 11.3</td>
<td>62.2 ± 11.8</td>
<td>66.1 ± 10.6</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>62.6 ± 12.2</td>
<td>60.9 ± 10.5</td>
<td>64.2 ± 12.2</td>
<td>67.4 ± 10.5</td>
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<tr>
<td></td>
<td>White</td>
<td>61.7 ± 10.8</td>
<td>62.4 ± 10.9</td>
<td>64.0 ± 10.5</td>
<td>66.7 ± 9.5</td>
</tr>
<tr>
<td>Tanner stage</td>
<td>Girls</td>
<td>2.4 ± 1.1†</td>
<td>3.9 ± 0.8†</td>
<td>4.5 ± 0.6†</td>
<td>4.8 ± 0.4</td>
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<tr>
<td></td>
<td>Boys</td>
<td>1.8 ± 0.8</td>
<td>2.9 ± 0.9</td>
<td>4.1 ± 0.7</td>
<td>4.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>2.7 ± 1.1†</td>
<td>3.9 ± 0.9†</td>
<td>4.7 ± 0.5†</td>
<td>4.7 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>1.9 ± 0.9</td>
<td>3.3 ± 1.0</td>
<td>4.2 ± 0.7</td>
<td>4.7 ± 0.5</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
†P<.001.
‡P<.01.
§P<.05.

Table 3. Lipoprotein Levels at Each Visit by Sex, Race, and Passive Smoking Status*

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Sex, Race, and Status</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C, mmol/L</td>
<td>Girls</td>
<td>2.14 ± 0.50</td>
<td>2.07 ± 0.53§</td>
<td>2.09 ± 0.53</td>
<td>2.14 ± 0.52</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>2.12 ± 0.47</td>
<td>2.19 ± 0.50</td>
<td>2.07 ± 0.52</td>
<td>2.07 ± 0.57</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>2.16 ± 0.50</td>
<td>2.19 ± 0.49</td>
<td>2.15 ± 0.52</td>
<td>2.34 ± 0.46§</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>2.12 ± 0.48</td>
<td>2.11 ± 0.52</td>
<td>2.07 ± 0.53</td>
<td>2.05 ± 0.55</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>2.14 ± 0.49</td>
<td>2.16 ± 0.50</td>
<td>2.08 ± 0.53</td>
<td>2.08 ± 0.51</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>2.11 ± 0.48</td>
<td>2.05 ± 0.55</td>
<td>2.10 ± 0.51</td>
<td>2.16 ± 0.61</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>Girls</td>
<td>1.22 ± 0.27</td>
<td>1.19 ± 0.23</td>
<td>1.15 ± 0.27</td>
<td>1.19 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>1.24 ± 0.27</td>
<td>1.20 ± 0.29</td>
<td>1.10 ± 0.24</td>
<td>1.06 ± 0.25</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>1.30 ± 0.26†</td>
<td>1.28 ± 0.32§</td>
<td>1.26 ± 0.23§</td>
<td>1.27 ± 0.31§</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>1.22 ± 0.26</td>
<td>1.17 ± 0.24</td>
<td>1.09 ± 0.24</td>
<td>1.10 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>1.26 ± 0.28†</td>
<td>1.21 ± 0.28</td>
<td>1.16 ± 0.25†</td>
<td>1.15 ± 0.26</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>1.19 ± 0.22</td>
<td>1.17 ± 0.22</td>
<td>1.05 ± 0.25</td>
<td>1.08 ± 0.21</td>
</tr>
<tr>
<td>HDL2-C, mmol/L</td>
<td>Girls</td>
<td>0.35 ± 0.19</td>
<td>0.35 ± 0.18</td>
<td>0.32 ± 0.17</td>
<td>0.32 ± 0.15†</td>
</tr>
<tr>
<td></td>
<td>Boys</td>
<td>0.33 ± 0.18</td>
<td>0.32 ± 0.21</td>
<td>0.29 ± 0.17</td>
<td>0.23 ± 0.15</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>0.41 ± 0.19†</td>
<td>0.45 ± 0.24†</td>
<td>0.41 ± 0.18</td>
<td>0.40 ± 0.21†</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>0.32 ± 0.18</td>
<td>0.31 ± 0.17</td>
<td>0.28 ± 0.16</td>
<td>0.25 ± 0.12</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>0.35 ± 0.20†</td>
<td>0.35 ± 0.20</td>
<td>0.32 ± 0.17§</td>
<td>0.29 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>PS</td>
<td>0.30 ± 0.16</td>
<td>0.31 ± 0.17</td>
<td>0.26 ± 0.17</td>
<td>0.25 ± 0.14</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD. HDL-C indicates high-density lipoprotein cholesterol; HDL2-C, HDL subfraction 2 cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, nonsmoking; and PS, passive smoking. To convert cholesterol from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.02586.
†P<.01.
‡P<.001.
§P<.05.

LIPOPROTEIN, SEX, RACE, AND PASSIVE SMOKING DIFFERENCES

The group means for lipoprotein levels by visit, sex, race, and passive smoking status are shown in Table 3. In the oldest children, LDL-C level was higher in blacks than in whites. The difference in LDL-C level between the non-smoking and passive smoking group of children was greater for whites than for blacks (P<.02). No other group differences were seen for LDL-C. White children had lower HDL-C and HDL subfraction 2 cholesterol (HDL2-C) levels than black children at all visits. Levels of HDL cholesterol were similar in white and black children in non-smoking families at visit 1 (1.24 ± 0.27 vs 1.27 ± 0.20 mmol/L [47.9 ± 10.3 vs 49.1 ± 7.9 mg/dL]). However, white children exposed to passive smoke had lower HDL

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levels than black children exposed to passive smoke at visit 1 (1.12 ± 0.21 vs 1.36 ± 0.22 mmol/L [43.2 ± 8.0 vs 52.7 ± 8.4 mg/dL]; P < .02). While HDL-C and HDL2-C levels changed little across visits in the girls, these levels decreased in boys and were significantly lower than the girls' at the last visit. Children exposed to passive smoke had lower HDL-C and HDL2-C levels than children not exposed to cigarette smoke at visits 1 and 3.

**HDL-C, RACE, ANTHROPOMETRICS, AND PASSIVE SMOKING INTERACTIONS**

We found racial differences in the HDL-C levels of children with a family history of cardiovascular disease. These differences were exaggerated by exposure to cigarette smoke. Children from passive smoking families had lower HDL-C levels than those in the nonpassive smoking group (P < .001, **Figure 2**). Of those children from passive smoking families, white children had lower HDL-C levels than black children (P = .004).

Using a mixed modeling approach with repeated-measures analysis of variance, we explored models for HDL-C that included race, sex, passive smoking status, weight, systolic blood pressure, diastolic blood pressure, and HDL-C level in children with a family history of cardiovascular disease showed significant differences exist by sex and passive smoking status (P = .01). Girls not exposed to cigarette smoke showed increasing levels of HDL-C with increasing diastolic blood pressure. In contrast, girls who were exposed to cigarette smoke had lower HDL-C levels that remained low with increasing diastolic blood pressure. The HDL-C level did not interact with diastolic blood pressure in boys from nonsmoking families but was lower in boys exposed to passive smoking with higher diastolic blood pressure.

**DIASTOLIC BLOOD PRESSURE, HDL-C, RACE, AND PASSIVE SMOKING INTERACTIONS**

Among the passive smoking group, HDL-C levels interacted to a greater extent with other risk factors in blacks than in whites. The interaction of HDL-C level and diastolic blood pressure in boys from families with a history of cardiovascular disease differed by both race and passive smoking status (**Figure 4**). Both black and white boys exposed to cigarette smoke and with family history of cardiovascular disease showed significant decreases in HDL-C level with increasing diastolic blood pressure (P < .01). However, in boys not exposed to cigarette smoke, as diastolic blood pressure increased, HDL-C level decreased more in blacks compared with whites. This interactive effect of HDL-C level and diastolic blood pressure in boys exposed to passive smoke was greater in those with a family history of cardiovascular disease.

**SYSTOLIC BLOOD PRESSURE, HDL-C, SEX, AND PASSIVE SMOKING INTERACTIONS**

We examined the interactions of systolic blood pressure and HDL-C level in children with a family history of cardiovascular disease (**Figure 5**). At lower levels of systolic blood pressure, HDL-C level was lower in boys exposed to cigarette smoke than in boys not exposed. As systolic blood pressure increased, the differences attributable to sex and passive smoking diminished.

**COMMENT**

We investigated the relationship of coronary risk factors to changes in HDL-C levels in adolescents by using
posed to cigarette smoke had lower levels of HDL2-C than
children, our group showed that preadolescent boys ex-
posed to the highest number of cigarettes smoked daily by the parents of the boys.9 The levels were related to the num-
ber of cigarettes smoked daily by the parents of the boys.9 The lowest HDL2-C levels were found in boys exposed
to cigarette smoke (top) with boys exposed to passive smoking (bottom). P < .01 for model using repeated-measures analysis of variance.

Figure 4. Plot of the diastolic blood pressure (DBP) by race interaction on high-density lipoprotein cholesterol (HDL-C) levels in boys with positive family history of cardiovascular disease. Comparison of boys not exposed to cigarette smoke (top) with boys exposed to passive smoking (bottom). P < .01 for model using repeated-measures analysis of variance.

Repeated-measures analyses of variance.18,21 Our data show that in children with a family history of cardiovascular disease, significant relations exist between HDL-C level and blood pressure that differ by sex and race, and interact with passive cigarette smoking. The mixed modeling approach used allowed for missing information over visits and allowed modeling of the mean and the variance. Because of the significant interactions in the model, the differences in lipoprotein levels between the races, sexes, and family smoking statuses change. The use of the mixed modeling approach may provide important insights into the mechanisms and interactions of genetic and environmental effects that underlie the childhood antecedents of atherosclerotic heart disease.

The present study confirms our earlier observations and those of others and shows that lower HDL-C levels are found in children exposed to passive smoking. We chose to study HDL-C cholesterol in addition to HDL-C for several reasons. Although the HDL subfractions are metabolically interrelated, most of the variability in HDL-C is due to the HDL2-C subfraction.22 Furthermore, Bodurtha et al13 have shown that CAD deaths occur more frequently in families with low levels of HDL-C. In a previous cross-sectional study of 11-year-old children, our group showed that preadolescent boys exposed to cigarette smoke had lower levels of HDL-C than boys not exposed. The levels were related to the number of cigarettes smoked daily by the parents of the boys.9 The lowest HDL-C levels were found in boys exposed to the highest number of cigarettes smoked by their mothers. The HDL-C subfraction was similarly lower in the passive smoking group of children, with greater differences seen in the girls. During puberty and early adolescence, levels of HDL-C and LDL-C decrease in children and the decrease in HDL-C is more pronounced in boys than in girls.24 The influence of sex hormones and their changes during puberty are obviously important, with HDL-C levels falling in boys in association with increases in testosterone levels.25 Passive cigarette smoking may further diminish HDL-C and its subfractions that may be associated with premature atherosclerotic changes. In a recent study, mean HDL-C levels were lower in dyslipidemic children from households with smokers than in those without household smoke exposure.26 Passive smoking may worsen the risk profile for early atherosclerosis among such high-risk children.

In this study we found racial differences in LDL-C and HDL-C in pubertal children that were related to passive smoke exposure. Levels of LDL-C were higher in the oldest black children than white children. At all visits, black children displayed higher LDL-C and HDL-C levels than white children. Previous studies have shown that as children reach preschool age, black children begin to have slightly higher levels of HDL-C than white children and this race-related trend becomes established at about 9 years of age.27,28 The black-white difference in HDL-C has been attributed to differences in lipoprotein particle number, with blacks having an inherently more efficient lipid-clearing mechanism. While these studies adjusted for active cigarette smoking in older children, the effects of passive smoke exposure and physical activity were not considered.22,23

We believe that racial differences in lipoprotein levels are related, at least in part, to long-term passive cigarette smoke exposure. At age 11 years, black and white children not exposed to cigarette smoke showed similar HDL-C levels whereas white children had lower HDL-C levels than black children among the passive smoking group. Among the passive smoking group, our sample size of black children was insufficient to test for differences from white children at subsequent visits. However, passive smoke exposure was greater at all visits in white than in black families. That fathers smoked more than mothers is consistent with current information ob-
tained from a recent population-based study. Therefore, long-term passive cigarette smoke exposure must be considered when examining lipoprotein levels in pediatric populations.

We found an inverse relation between HDL-C and weight in white pubertal boys and girls. Despite smoking status, boys showed a greater reduction in HDL-C with increasing weight than girls. More important, the greatest reduction in HDL-C with increasing weight was in children exposed to passive cigarette smoke long-term. Other authors have found an inverse relationship between HDL-C and weight in teenage boys and girls. Glueck et al found a significant inverse relationship between HDL-C level and Quetelet index in children ranging in age from 12 to 16 years. None of these studies examined the effects of cigarette smoke exposure. The consistent inverse associations between passive smoking, weight, and HDL-C level show that the effects of these variables on HDL-C levels and on CAD risk in adults are already present in early adolescence.

We have previously shown that the variance of HDL-C and HDL₃-C levels are influenced both by genetic and environmental influences. When we compared the self-reported weekly exercise level in our twins, the number of exercise episodes each week were similar for boys exposed to passive smoking and those who were not (4.7 ± 2.0 vs 4.2 ± 2.3 times per week) and for girls exposed to passive smoking and those not (4.3 ± 2.3 vs 4.7 ± 2.1 times per week). Analysis using χ² tests showed no association between smoking status and exercise in either the boys (χ² = 1.7, P < .2) or the girls (χ² = 0.5, P < .5). Exercise therefore was not examined as a variable in this study but was our focus in a recent study. Dietary changes, exercise, and weight reduction have resulted in sustained increases in HDL-C levels in obese children. Eliminating cigarette smoke exposure from a child’s home environment may be part of an effective interventional strategy to increase HDL-C levels.

Offspring with a family history of cardiovascular disease often show adverse risk factor clusters by puberty. The data from our study show that in children with a family history of cardiovascular disease significant associations exist between HDL-C level and blood pressure that differ by sex and race. These variables may interact proatherogenically with passive cigarette smoking. Racial and sex differences in lipoprotein levels and other CAD risk factors in adults with cardiovascular family history have been previously reported. Data from the CARDIA Study showed that blacks had higher systolic blood pressure and diastolic blood pressure than whites with racial differences being greater in women than in men. The present longitudinal study demonstrates the complicated relations of passive smoking and CAD risk factors within a biracial population of sexually maturing adolescents. Other lines of investigation, such as gene by environment interaction (ie, genetic background influence on the response to a given environmental stimulus), may have the potential to explain the genetic (racial, sex, developmental, and family history) and environmental (passive smoking) interrelationships of CAD risk variables.

We agree with the importance of establishing, early in life, a healthy lifestyle that includes regular exercise, avoidance of weight gain, and abstinence from tobacco use. Given the evidence that irreversible atherosclerotic changes may be caused by passive smoke exposure and that passive smoke exposure may act synergistically with other risk factors such as hypertension, avoidance of long-term passive smoke exposure during childhood is important, especially for children with known premature cardiovascular disease in their family. Our results suggest that white males exposed to passive cigarette smoke who have a family history of cardiovascular disease, weigh more than average, and have higher than average diastolic blood pressure may be individuals at special risk for developing premature atherosclerotic heart disease. These risk profiles may be helpful in developing preventive cardiovascular strategies for children.

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