Carotid Intimal-Medial Thickness Is Related to Cardiovascular Risk Factors Measured From Childhood Through Middle Age
The Muscatine Study

Patricia H. Davis, MD; Jeffrey D. Dawson, ScD; Ward A. Riley, PhD; Ronald M. Lauer, MD

Background—Higher carotid intimal-medial thickness (IMT) is associated with cardiovascular risk factors and is predictive of coronary artery disease and stroke in older adults. Carotid IMT was measured in young and middle-aged adults to determine its relationship with risk factors measured (1) in childhood, (2) currently, and (3) as a “load” from childhood to adulthood.

Methods and Results—Carotid ultrasound studies were performed in 346 men and 379 women aged 33 to 42 years who were representative of a cohort followed since childhood and who live in Muscatine, Iowa. The mean of the measurements of maximal carotid IMT at 12 locations was determined for each subject. A medical questionnaire was completed, and measurements of anthropometric characteristics and risk factors were obtained. The mean maximum carotid IMT was 0.79±0.12 mm for men and 0.72±0.10 mm for women. On the basis of multivariable analysis, the significant current predictors of IMT were age and LDL cholesterol in both sexes and diastolic blood pressure in women. Total cholesterol was a significant childhood predictor in both sexes, while childhood body mass index was significant only in women. For men, LDL cholesterol, HDL cholesterol, and diastolic blood pressure were predictive of carotid IMT in a risk factor load model, whereas in women, LDL cholesterol, body mass index, and triglycerides were predictive.

Conclusions—Higher carotid IMT in young and middle-aged adults is associated with childhood and current cardiovascular risk factors, as well as risk factor load. (Circulation. 2001;104:2815-2819.)

Key Words: atherosclerosis ■ epidemiology ■ carotid arteries

In children, adolescents, and young adults, information about risk factors for the development of the early atherosclerotic process is derived mainly from autopsy studies. In older adults, higher carotid intimal-medial thickness (IMT) is linked to the atherosclerotic process by the association of carotid IMT with known cardiovascular risk factors and prevalent and incident coronary artery disease and stroke. However, identification of young and middle-aged adults with premature atherosclerosis using noninvasive methods, such as measurement of carotid IMT, long before they develop clinical events would identify those at highest risk. In younger adults, the predictiveness of cardiovascular risk factors for clinical events in later life has not yet been established, but the association of these risk factors with carotid IMT would lend support to measuring risk factors at a young age.

A cohort of children in Muscatine, Iowa, has been followed since 1971. Their risk factors were measured in childhood (aged 8 to 18 years) and young adulthood (aged 20 to 33 years, and again at 29 to 37 years). This cohort has now reached the age of 33 to 42 years. Using B-mode ultrasound to noninvasively measure carotid artery atherosclerosis in a sample of this cohort, we previously demonstrated an association between higher carotid IMT and the presence of coronary artery calcification (CAC), another measure of subclinical atherosclerosis. In the present study, our objective was to determine the relationship of carotid IMT with childhood and current cardiovascular risk factors and a risk factor “load” from childhood to adulthood in this cohort.

Methods

Population
Between 1971 and 1981, school children aged 8 to 18 years in Muscatine, Iowa, underwent biennial examinations. A total of 14,066 children underwent 32,636 examinations. Between 1981 and 1991, 2,446 participants (67% of those eligible) who were then aged 20 to
34 years were examined again. From 1992 to 1996, a subset of this cohort (769 individuals) had a repeat examination with electron-beam computed tomography to measure CAC.10 Between 1996 and 1999, we re-examined these individuals, who had then reached the age of 33 to 42 years. Subjects were eligible to be included if they had previously participated in at least one childhood survey, one young adult survey, and the CAC study. There were 346 men and 379 women, which included 94% of those targeted for the study. Childhood risk factor levels (adjusted for age, sex, and calendar year) of these 725 participants did not differ significantly from the entire childhood cohort with respect to height, weight, blood pressure, triceps skin fold, total cholesterol, or triglycerides for either sex, or for body mass index (weight divided by height squared; BMI) for women. For men, the childhood BMI was 0.09 SDs higher in the participants compared with the rest of the original cohort (P<0.05). The protocol was approved by the University of Iowa Institutional Review Board, and informed consent was obtained from all subjects. Subjects were compensated for participating.

Risk Factor Assessment
After a 12-hour fast, we measured, in each subject, total cholesterol, HDL cholesterol, triglycerides, lipoprotein(a), homocysteine, glucose, and insulin, and we calculated LDL cholesterol. If triglycerides were ≥400 mg/dL, the LDL cholesterol could not be calculated, and these were treated as missing values. Height, weight, triceps skin fold, hip circumference, and waist circumference were recorded. Three random-zero blood pressure measurements were obtained after a 5-minute seated rest. Participants completed a medical and personal history questionnaire.

Carotid Ultrasound Studies
Carotid ultrasound studies were performed by a single technician. The protocol for measuring carotid IMT was the same as that used in the Asymptomatic Carotid Artery Plaque Study (ACAPS).11 For each subject, the maximum carotid IMT was imaged for the near and far wall of each common carotid artery (CCA), carotid bifurcation, and internal carotid artery. Scans were read at a central reading center (AUTREC, Inc), which had demonstrated high inter-reader reliability during the ACAPS trial.11 A 4.4% random sample underwent repeat carotid ultrasound studies during a second visit to assess intraoperator reliability.

Statistical Analyses
The mean of the maximum carotid IMT measured at the 12 locations (3 sites×2 sides×2 walls) was the primary outcome of interest. For subjects who had missing data, the mean of their non-missing walls was used. Because the walls of the internal carotid artery are more often missing and tend to be thinner, this method may lead to overestimating the IMT. To address this, we compared our estimates with those from a random effects model, using terms for subject and wall location.12 Childhood risk factors included BMI, triceps skin fold, systolic blood pressure, diastolic blood pressure (DBP), cholesterol, and triglycerides determined at the last childhood examination. These results were standardized by age, sex, and year of the childhood survey to produce a Z-score. A similar method was used to standardize the young adult measurements, which included waist-hip ratio, LDL cholesterol, and HDL cholesterol, in addition to those measured in childhood and the results from current risk factors. For current risk factors, we repeated the analysis after excluding participants taking lipid-lowering medication from the lipid analyses, those taking antihypertensives from the blood pressure analyses, and those taking hypoglycemic medications from the insulin and glucose determinations, with the same results.

To integrate the longitudinal risk factor data collected since childhood for each individual, we conducted an analysis based on a risk factor load, which was a time-weighted average for each risk factor. For men, the mean number of observations used to calculate risk factor load was 5.8; for women, the mean number was 5.7. Information about pack-years of smoking was included as a measure of risk load.

For each sex, the association between carotid IMT and risk factors at various ages and the risk factor load was tested using Spearman rank correlation coefficients. For multivariable associations, we dichotomized IMT into values above or below the upper quartile and used stepwise logistic regression after adjusting for age. This was done to define those with the highest levels of carotid atherosclerosis. To quantify the predictiveness of the logistic regression models, the area under the receiver operator characteristic curve was calculated.

To further investigate the relationship of childhood risk factors to young adult carotid IMT, instead of using the last childhood measurement of risk factors performed at a mean age of 15.2 years in boys and 15.5 years in girls, we repeated the analysis using only measurements performed at age 8 to 11 years.

Results
The means of the 12 maximum carotid IMT measurements were 0.79±0.12 mm for men and 0.72±0.10 mm for women (P<0.001). Most subjects (85.1%) had ≥10 wall measured, and nearly all (98.5%) had ≥6 walls measured. The completeness of the data measured according to site was as follows: near wall of internal carotid artery, 74.0%; far wall of internal carotid artery, 88.0%; near wall of carotid bifurcation, 92.7%; far wall of carotid bifurcation, 92.8%; near wall of CCA, 98.9%; and far wall of CCA, 99.7%. Our method of using the available IMT measurements to calculate the mean IMT gave estimates similar to those using the random effects model: they were only 0.6% higher on average. For the 4.4% sample of subjects with a second ultrasound done a mean of 107 days later, the within-subject reliability was 76%, with a mean absolute value of the within-subject deviation of 0.058 mm.

In Tables 1 and 2, the results of the univariate analysis of risk factors for men and women, respectively, are shown according to the time of measurement. In men, the only childhood risk factor associated with current IMT was cholesterol. In women, childhood risk factors associated with current IMT were BMI, triceps skin fold, cholesterol, systolic blood pressure, DBP, and triglycerides. Diabetes mellitus was not a significant current risk factor, but the prevalence in this cohort was low (1.2% in men and 6.4% in women). Smoking was also not a significant risk factor, with a prevalence of current smoking of 28.2% in women and 35.4% in men, with a mean number of pack-years of 5.7±9.3 in women and 9.8±12.1 in men. Although some risk factors were significant for only one sex, further analysis showed that the DBP load correlation was the only one that was significantly different for men and women.

In Tables 3 and 4, the multivariable models using childhood risk factors, currently measured risk factors, and risk factor loads are shown for men and women, respectively. For both sexes, LDL cholesterol was a significant current risk factor, and for women, DBP was also significant. For both sexes, cholesterol was a significant childhood risk factor, and childhood BMI was also significant for women. For men, the load model included LDL cholesterol, HDL cholesterol, and DBP. For women, the load model included LDL cholesterol, BMI, and triglycerides. In men, the area under the receiver operator characteristic curve was 0.629 for the childhood risk factors, 0.653 for young adulthood, 0.687 for current, and
TABLE 1. Univariate Spearman Rank Correlation Coefficients for IMT With Risk Factors in Men

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Childhood</th>
<th>Young Adult</th>
<th>Current</th>
<th>Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.11*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.09</td>
<td>0.09</td>
<td>0.16†</td>
<td>0.12†</td>
</tr>
<tr>
<td>Weight</td>
<td>0.06</td>
<td>0.07</td>
<td>0.14†</td>
<td>0.09</td>
</tr>
<tr>
<td>Triceps skin fold</td>
<td>0.04</td>
<td>0.05</td>
<td>0.09</td>
<td>0.08</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>—</td>
<td>−0.04</td>
<td>0.14†</td>
<td>0.13*</td>
</tr>
<tr>
<td>Total LDL cholesterol</td>
<td>0.17†</td>
<td>0.14*</td>
<td>0.24‡</td>
<td>0.21‡</td>
</tr>
<tr>
<td>Total HDL cholesterol</td>
<td>—</td>
<td>0.21‡</td>
<td>0.31‡</td>
<td>0.29‡</td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>—</td>
<td>0.23‡</td>
<td>0.25‡</td>
<td>0.21‡</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>—</td>
<td>—</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>Apolipoprotein A</td>
<td>—</td>
<td>—</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.10</td>
<td>0.13*</td>
<td>0.14*</td>
<td>0.16†</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.10</td>
<td>0.17†</td>
<td>0.19‡</td>
<td>0.21‡</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.06</td>
<td>0.12*</td>
<td>0.23‡</td>
<td>0.23‡</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>—</td>
<td>—</td>
<td>0.05</td>
<td>—</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>—</td>
<td>—</td>
<td>0.16†</td>
<td>—</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>—</td>
<td>—</td>
<td>0.05</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes</td>
<td>—</td>
<td>—</td>
<td>0.03</td>
<td>—</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td></td>
<td></td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

BP indicates blood pressure; —, not measured.
*P<0.05, †P<0.01, ‡P<0.001.

0.713 for load; in women, the respective areas were 0.650, 0.653, 0.669, and 0.689. There was no significant difference in the area under the receiver operator characteristic curve among the 4 models within either sex.

In the multivariable analysis using only measurements performed at age 8 to 11 years, total cholesterol was a significant risk factor in men, with an odds ratio of 1.47 (95% confidence interval: 1.16, 1.83) and in women, with an odds ratio of 1.71 (95% confidence interval: 1.02, 2.13), and in women, with an odds ratio of 1.47 (95% confidence interval: 1.16, 1.83) and in men, with an odds ratio of 1.71 (95% confidence interval: 1.02, 2.13). The Figure shows the median of the mean carotid IMTs according to tertile of the last childhood measurement of cholesterol and sex, thus demonstrating the significant association.

Discussion

Measurement of Carotid IMT and Atherosclerosis

In older adults, measuring carotid IMT has gained acceptance as a noninvasive, inexpensive method to assess the extent of atherosclerosis. Several pieces of evidence support the validity of this. Measuring carotid IMT with ultrasonography correlates well with pathological measurements and is reproducible. Increased carotid IMT is significantly related to known cardiovascular risk factors and to carotid plaque, a more advanced atherosclerotic lesion. Finally, carotid IMT is linked to prevalent stroke, coronary artery disease, and peripheral vascular disease, as well as incident myocardial infarction and stroke, and this association persists after adjustment for known cardiovascular risk factors. However, there are limited data concerning carotid IMT in young and middle-aged adults.

Current Risk Factors

In this study of young and middle-aged adults, LDL cholesterol was the strongest current predictor of higher carotid IMT in men, and no other risk factors remained significant after adjusting for LDL cholesterol and age. In women, both current LDL cholesterol and DBP remained significant after adjusting for age and each other. In prior smaller studies of subjects in this age group, significant risk factors for higher carotid IMT included age, systolic blood pressure, DBP, and pack-years of smoking, whereas HDL cholesterol and grams of alcohol consumed were significant protective factors. Case-control studies of children and young adults demonstrate that familial hypercholesterolemia and borderline hypertension are associated with greater IMT. Young adults with diabetes have also shown higher carotid IMT than controls. In the Muscatine cohort, the lack of association of IMT with diabetes and smoking pack-years may be due to a lack of a sufficient number of years of exposure. These risk factors may become of increasing importance as the cohort ages.

Several risk factors were not associated with carotid IMT in the present study, although studies in older adults have shown an association. Elevated plasma homocysteine has been shown to be a significant risk factor for higher carotid IMT. In the present study, plasma homocysteine was not a significant risk factor and, in the same cohort, Mahoney et al did not find an association between plasma homocysteine and CAC. These observations suggest that elevated homocysteine levels may not affect carotid IMT at a younger age. In the present study, fasting glucose was not associated with carotid IMT, although fasting insulin was significantly associated with carotid IMT in men by
TABLE 3. Multivariable Odds Ratios,* 95% CIs and SDs of Risk Factors Measured at Different Ages for Carotid IMT in the Upper Quartile Versus Lower Three Quartiles in Men

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Childhood (8–18 years)</th>
<th>Young Adult (20–34 years)</th>
<th>Current (33–42 years)</th>
<th>Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>1.53</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.19, 1.96</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SD</td>
<td>26.5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>NA</td>
<td>1.39</td>
<td>2.00</td>
<td>1.80</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.09, 1.76</td>
<td>1.50, 2.67</td>
<td>1.30</td>
<td>2.48</td>
</tr>
<tr>
<td>SD</td>
<td>30.2</td>
<td>30.7</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>NA</td>
<td>0.70</td>
<td>—</td>
<td>0.66</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.52, 0.93</td>
<td>—</td>
<td>0.46, 0.94</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>11.0</td>
<td>—</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>—</td>
<td>—</td>
<td>1.58</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>—</td>
<td>—</td>
<td>1.05, 2.37</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>—</td>
<td>—</td>
<td>0.66</td>
<td></td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; BP, blood pressure; NA, not available; and —, not significant.

*ORs are also age-adjusted and correspond to a 1SD increase in the risk factor.

univariate analysis. In an older cohort, an association between carotid IMT and fasting insulin and glucose was seen. Lipoprotein(a) has also been associated with increased carotid IMT. Comparing our results (Tables 1 and 2) with those obtained from the CCA method, we found more correlations >0.20 (9 versus 0), more correlations significant at P<0.05 (26 versus 19), and more correlations significant at P<0.001 (14 versus 1). In the Cardiovascular Health Study, risk factors accounted for 25% of the variability for a composite of CCA and internal carotid artery IMT but only 17% of the variability in the CCA IMT.

Method of Measuring IMT
Carotid IMT has been measured in both far walls of the CCA alone or at multiple sites. We used the average of 12 measurements of maximal IMT in the present study because we predicted more stable results than when using only 2 measurements, and we obtained stronger relationships with risk factors. We recalculated the 38 Spearman coefficients between current risk factors and the average of the far walls of the CCA (CCA method). Comparing our results (Tables 1 and 2) with those obtained from the CCA method, we found more correlations >0.20 (9 versus 0), more correlations significant at P<0.05 (26 versus 19), and more correlations significant at P<0.001 (14 versus 1). In the Cardiovascular Health Study, risk factors accounted for 25% of the variability for a composite of CCA and internal carotid artery IMT but only 17% of the variability in the CCA IMT.

Childhood Risk Factors and Risk Factor Load
We demonstrated that childhood total cholesterol, measured as early as aged 8 to 11 years, is a significant risk factor for carotid IMT measured in young adulthood. These findings support the recommendations of the National Cholesterol Education Program to screen children with a family history of elevated cholesterol or premature heart disease and to intervene in childhood. In a prior study of this cohort, Mahoney et al demonstrated that childhood BMI also significantly correlated with the presence of CAC. These observations support the assumption that higher carotid IMT also reflects the atherosclerotic process in young and middle-aged adults.
Carotid IMT and tertile of last childhood cholesterol measurement. The median of the mean carotid IMT measured in young and middle-aged adults is shown for each tertile of total cholesterol measured during the last childhood examination for each sex. IMT is significantly associated with childhood total cholesterol.

Factors were more associated with carotid stenosis than contemporaneously measured risk factors.31

Summary
In the Muscatine cohort, who were examined over the age range of 8 to 42 years, childhood risk factors, including total cholesterol for both sexes and BMI only for women, predicted carotid IMT. Both childhood obesity and cholesterol levels have been shown to track into young adulthood.29,32 Contemporaneous LDL cholesterol in both sexes and DBP in women are independent predictors of carotid IMT. A risk factor “load” model included LDL cholesterol in both sexes, HDL cholesterol and DBP in men, and triglycerides and BMI in women. Risk factors measured as early as ages 8 to 11 years are predictive of adult carotid IMT. In trials testing interventions to retard the atherosclerotic process in late adolescence and young adulthood, measures of carotid IMT may be considered surrogate markers of the degree of atherosclerotic process.

Acknowledgment
Funding for this project came from NIH-NHLBI grant HL54730 and grant RR00059 from the General Clinical Research Centers Program, National Center for Research Resources, NIH.

References
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Circulation. 2001;104:2815-2819
doi: 10.1161/hc4601.099486

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