Cardiovascular Risk Factors in Childhood and Carotid Artery Intima-Media Thickness in Adulthood
The Cardiovascular Risk in Young Finns Study

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THEROSCLEROSIS IS THOUGHT to begin in childhood and to develop silently for decades before clinical events such as myocardial infarction or stroke occur. Autopsy studies in children and adolescents have confirmed the presence of preclinical atherosclerotic lesions and shown their associations with antemortem vascular risk factors.1-3 Studies using ultrasound imaging have demonstrated atherosclerotic wall thickening in the arteries of children with risk factors.4-6 Longitudinal studies have shown that risk factor levels measured in childhood are predictive of risk factor levels in adulthood.7,9 Moreover, levels of serum cholesterol measured in young adult men have been associated with cardiovascular disease in midlife.10,11 All-cause mortality is associated with risk factors measured in adolescence.12-14

See also pp 2271 and 2320.

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though these observations suggest that risk factors identified in childhood are predictive of adult atherosclerosis, there is only limited direct evidence of this relationship.12,13

The common carotid artery intima-media thickness (IMT) measured by ultrasound imaging represents a marker of preclinical atherosclerosis because it correlates with vascular risk factors,14,15 relates to the severity and extent of coronary artery disease,16 and predicts the likelihood of cardiovascular events in population groups.17-21 To investigate the hypothesis that childhood and adolescent risk factors are associated with atherosclerosis in adulthood, we have measured common carotid artery IMT in a large cohort of adult men and women. These individuals were participants in the Cardiovascular Risk in Young Finns Study, and risk factor data dating to their childhood are available.

METHODS

Participants
The Cardiovascular Risk in Young Finns Study is an ongoing 5-center follow-up study of atherosclerosis risk factors in Finnish children and adolescents. The first cross-sectional survey was conducted in 1980. The original sample size was 4320 children and adolescents aged 3, 6, 9, 12, 15, and 18 years. The individuals were randomly chosen from the national register. There were 3596 participants (83.2% of those invited) who participated in 1980.22 Follow-up studies were conducted 3 years apart, in 1983 and 1986. In 2001, we reexamined these participants, who had then reached the age of 24 to 39 years. The loss of participants to follow-up was approximately 20%, 30%, and 34% after 3, 6, and 21 years, respectively. Based on our earlier observations, lack of time (33%), absence from the place of residence at the time of examination (13%), and unwillingness to participate (13%) have been the main reasons for nonparticipation. Twenty participants in the original cohort were not alive at the latest follow-up. For these individuals the causes of death were suicide (14 cases), motor vehicle crashes (3 cases), alcohol poisoning (1 case), subarachnoid hemorrhage (1 case), and pancreatitis (1 case).

In the study herein, we have analyzed the relationship of common carotid artery IMT measured in 2229 adults to current risk factors and risk factors measured in childhood. Participants gave written informed consent, and the study was approved by local ethics committees.

Risk Factors
All measurements of lipid levels were performed in duplicate in the same laboratory. Standard enzymatic methods were used for measuring levels of serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) concentration was calculated by the Friedewald formula.23 Details of these methods have been described previously.24-25 Blood pressure was measured with a standard mercury sphygmomanometer in 1980 and 1983 and with a random-zero sphygmomanometer in 1986 and 2001. The average of 3 measurements was used in statistical analysis. Body mass index (BMI) was calculated as participants’ weight in kilograms divided by the square of their height in meters. Smoking habits were determined using a questionnaire in participants aged 21 years or older. In 12- to 18-year-olds, the information on smoking habits was collected in connection with the medical examination in an isolated room where the participants could respond confidentially and undisturbed. In children, regular cigarette smoking on a weekly basis or more often was defined as a risk factor for smoking. In adults, smoking on a weekly basis or regular smoking in the past was defined as a risk factor for smoking. For the determination of serum lipid levels, venous blood samples were drawn after an overnight fast.

Carotid Artery Studies
Ultrasound studies were performed using ultrasound mainframes (Sequoia 512, Acuson, Mountain View, Calif) with 13.0-MHz linear array transducers. The studies were performed between September 2001 and January 2002.

The left common carotid artery was scanned by ultrasound technicians following a standardized protocol. The image was focused on the posterior (far) wall, and gain settings were used to optimize image quality. A resolution box function (zoom) was used to record an image 25 mm wide and 15 mm high. A magnified image was recorded from an angle that showed the greatest distance between the lumen-intima interface and the media-adventitia interface. A moving scan with a duration of 5 seconds, which included the beginning of the carotid bifurcation and the common carotid artery, was recorded and stored in digital format on optical disks for subsequent off-line analysis.

Digitally stored scans were manually analyzed by a single reader blinded to participants’ details, with analyses performed using ultrasonic calipers. From the 5-second clip image, the best-quality end-diastolic frame was selected (incident with the R wave on a continuously recorded electrocardiogram). From this image, at least 4 measurements of the common carotid far wall were taken approximately 10 mm proximal to the bifurcation to derive maximal carotid IMT. To assess reproducibility of IMT measurements, we reexamined 60 participants (2.5% random sample) 3 months after the initial visit. The between-visit coefficient of variation of IMT measurements was 6.4%. To assess reproducibility of IMT image analysis, 113 scans were reanalyzed by a second observer. The between-observer coefficient of variation was 5.2%.

Statistical Methods
Group comparisons were performed using t tests or χ2 tests as appropriate. The relationships between risk variables and common carotid artery IMT were examined using linear regression analysis. To examine whether age modifies the associations between risk variables and IMT, we included age × risk factor interaction terms in regression
models. The associations between current risk factors and IMT were of similar magnitude in all age groups. Therefore, the results concerning the associations between current risk variables and IMT are shown for all age groups combined. For current risk factors, we repeated the analysis after excluding participants with diabetes (1.0%) and those taking lipid-lowering (0.3%) or antihypertensive medications (3.1%), with similar results.

Risk variables measured at or before age 9 years were generally not related to adult IMT, whereas risk variables measured at or after age 12 years usually correlated with carotid IMT. Therefore, the associations between childhood risk variables and carotid IMT are shown stratified by 2 groups according to the age when the risk variables measurement was performed (in 3- to 9-year-olds or 12- to 18-year-olds). This age stratification paralleled pubertal staging, since 85% of the 12- to 18-year-olds at baseline were classified as having ongoing or completed puberty (Tanner staging). The results of the regression analysis were essentially similar using either pubertal stage or age group stratification. In both men and women, IMT correlated with age, with an approximately 0.006-mm increase per year. Therefore, the results of regression analysis are shown as age-adjusted regression coefficients.

To study the cumulative effects of longitudinally measured risk variables on adult IMT, we calculated the average of 3 risk variable measurements taken in 1980, 1983, and 1986 (risk load). We used an age- and sex-specific z score to calculate standardized values as the load variable. Only participants with complete data on each risk variable were included.

To examine the effects of multiple risk factors on IMT, we calculated a simple score according to the number of current and childhood risk factors. Risk factors were defined as values at or above the age- and sex-specific 80th percentile for LDL-C concentration, systolic blood pressure, and BMI, and for the presence or absence of cigarette smoking. All tests were performed with SAS version 8.01 (SAS Institute Inc, Cary, NC), and statistical significance was inferred at a 2-tailed P<.05.

RESULTS
Characteristics of study participants are shown in Table 1. A comparison of the baseline (1980) values of those participants who had dropped out (n=1367) with those who had complete risk factor and ultrasound data in 2001 showed that dropouts were more often male (43% vs 33%, P<.001), but there were no significant differences in serum lipoprotein levels, blood pressure, BMI, or the prevalence of smoking (data not shown).

Associations Between Current Risk Variables and Carotid IMT
In men, current risk variables that were associated with common carotid artery IMT included LDL-C level, total cholesterol level, LDL-C/HDL-C ratio, systolic blood pressure, diastolic blood pressure, and BMI (Table 2). Smoking also was associated with IMT; the age-adjusted carotid IMT value was 0.013 mm greater in smoking compared with nonsmoking men (P=.04). In women, current risk variables that were related to carotid IMT included LDL-C/HDL-C ratio, triglycerides level, systolic blood pressure, diastolic blood pressure, and BMI (Table 2). Smoking also was a significant correlate; the age-adjusted IMT value was 0.011 mm greater in smoking compared with nonsmoking women (P=.02). In multivariate analysis for current risk variables, systolic blood pressure, BMI, and smoking were all significantly associated with IMT in the model adjusted for age and sex (Table 3). The effect of LDL-C was not significant.

Associations Between Single Childhood Risk Variables and Cumulative Risk Load on Adult IMT
In men, childhood risk variables measured at ages 12 to 18 years that were associated with adult common carotid artery IMT included LDL-C level, total cholesterol level, LDL-C/HDL-C ratio, triglycerides level, systolic blood pressure, diastolic blood pressure, and BMI (Table 2). In women, childhood risk variables that were associated with adult IMT included systolic blood pressure and BMI. In both men and women, the regression coefficients remained similar or increased slightly when the
average of 3 measurements (1980-1986, load variable) was used in the regression analysis. In women, LDL-C/HDL-C ratio became a significant correlate for IMT when entered as a load variable (Table 2).

In multivariable analysis, childhood LDL-C level, systolic blood pressure, BMI, and smoking were all significantly associated with adult IMT in a model adjusted for age and sex (Table 4).

To study how the strength of the association between a childhood risk
variable and adult IMT changes after adjustment for the current risk variable, we entered the current risk variables shown in Table 4 into the multivariable model one by one. The effects of childhood LDL-C level and systolic blood pressure remained independently associated with carotid IMT when adjusted for the current risk variable values (P = .02 and P = .006, respectively). The effect of childhood smoking status on adult IMT was not significant (P = .06) after adjustment for adult smoking status. When current BMI was entered into the model, the effect of childhood BMI became nonsignificant.

**Relationship Between Multiple Risk Factors and Adult IMT**

The relationships between the number of childhood risk factors and adult common carotid artery IMT are shown in Figure 1. In both men and women, carotid IMT was significantly (P < .001 for both) related to multiple risk factors measured at ages 12 to 18 years. The number of risk factors measured at ages 3 to 9 years showed a weak association with carotid IMT in men (P = .02) but not in women (P = .63) (Figure 1).

To examine whether multiple childhood risk factors are associated with adult IMT independently of current risk factors, we stratified all men and women into groups according to the number of current and childhood risk factors (measured at the mean age of 14.9 [SD, 2.4] years). In every category of adults with 0, 1, or 2 or more current risk factors, there was a significant increasing trend in IMT values according to the number of childhood risk factors (Figure 2). In a multivariable regression model adjusted for age and sex, both current and childhood risk factor scores were significantly related to adult IMT (P < .001 for both).

**COMMENT**

Early life influences of risk factors may contribute to the development of future atherosclerosis. At present, however, there are no direct data linking childhood risk factors to adult cardiovascular disease. As an alternative to the use of cardiovascular events as disease end points, the ultrasound measurement of carotid artery IMT has been used as a surrogate marker of cardiovascular health.26 We found that risk factors measured in adolescence were significantly associated with common carotid artery IMT measured in adulthood. In addition, we found that this association remained strong and significant even after current adulthood risk factors were taken into account. Systolic blood pressure, LDL-C level, cigarette smoking, and BMI measured at ages 12 to 18 years were independently associated with adult IMT. In general, the cumulative risk load that integrated information from 3 risk variable measurements in childhood and young adulthood was only a marginally stronger correlate for IMT than a single measurement in childhood. Thus, measurements of single risk variables seem to be as informative as the risk load in identifying groups of children who are at increased risk for atherosclerosis as adults. This may partly be explained by the fact that risk variables measured in children have a tendency to maintain their rank order.7-9

The presence of multiple risk factors could lead to acceleration of atherosclerosis in young people.3 We examined the effects of multiple childhood risk factors on adult IMT by calculating a risk factor score that included high levels of LDL-C, systolic blood pressure, obesity, and cigarette smoking. Multiple

| Table 4. Multivariable Model of the Relationships Between Risk Variables Measured at Ages 12-18 Years and Common Carotid Artery Intima-Media Thickness Measured 21 Years Later (n = 1170)* |
|---------------------------------|-----------------|-------|-------|
| Risk Variable                  | Regression Coefficient† | SE    | P Value |
| Male sex                       | 0.023            | 0.006 | <.001 |
| Age                            | 0.002            | 0.001 | .24   |
| LDL-C                          | 0.010            | 0.003 | .001  |
| Body mass index                | 0.009            | 0.003 | .007  |
| Systolic blood pressure        | 0.013            | 0.003 | <.001 |
| Smoking (no/yes)               | 0.016            | 0.007 | .02   |

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
*Mean age at time of first measurement, 14.9 (SD, 2.4) years.
†Expressed in millimeters for a 1-unit change in age (year) and a 1-SD change in other continuous variables and for the presence or absence of smoking.

**Figure 1. Relationships Between Numbers of Childhood Risk Factors and Common Carotid Artery Intima-Media Thickness (IMT) in Adulthood**

Risk factors were measured at ages 12 to 18 years (A) and 3 to 9 years (B) and common carotid artery IMT was measured 21 years later in adulthood. P values are from regression analysis testing for increasing linear trend in IMT values across the categories. Risk factors include cigarette smoking (assessed in participants aged 12 years and older) as well as levels in the 80th percentile of low-density lipoprotein cholesterol, systolic blood pressure, and body mass index. Error bars indicate SDs.
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More recently, in the same cohort, Davis et al measured carotid IMT in 725 young adults and showed a link between childhood risk variables and adult carotid IMT. Our findings are consistent with these observations. In addition, our data indicate that the association between childhood risk variables and adult IMT is independent of current risk variables. For example, the relationship between LDL-C levels measured in adolescence and IMT measured in adults remained highly significant when adjusted for the current LDL-C level. The independent effect of childhood risk factor exposure on adult IMT was also demonstrated when the study participants were stratified into groups according to their childhood and current multiple risk factor scores. In every category of participants with 0, 1, or 2 or more current risk factors, there was an increasing trend in IMT values according to the number of childhood risk factors (Figure 2).

The measurement of carotid artery IMT has gained acceptance as a noninvasive method to assess the extent of atherosclerosis. Carotid IMT is significantly related to cardiovascular risk factors and to the extent of atherosclerosis elsewhere in the arterial system. Importantly, increased carotid IMT is an independent predictor of future myocardial infarction and stroke in asymptomatic adults. In the study herein, male participants who presented with several risk factors at ages 12 to 18 years had an approximately 0.1-mm higher IMT as adults compared with those who did not have risk factors in adolescence (Figure 1). Prospective studies in older adults have suggested that every 0.1-mm increase in common carotid IMT may increase the subsequent risk of coronary events by approximately 30%. The Atherosclerosis Risk in Communities (ARIC) study suggested that the risk of subsequent coronary heart disease may increase faster at the low levels of mean IMT (<1 mm). For example, ARIC investigators found that a 0.1-mm increase in IMT from 0.6 to 0.7 mm (corresponding to the difference between high-risk vs low-risk groups in our study) was associated with an approximately 50% increase in risk for subsequent coronary heart disease throughout 4 to 7 years among asymptomatic middle-aged adults. Although these values do not allow precise estimates of future risk, they nevertheless suggest a major impact of childhood risk factors on subsequent risk of coronary heart disease in the present study population.

We measured IMT in the far wall of the common carotid artery. In general, measurements of the common carotid artery IMT are more reliable and less difficult to obtain compared with measurements in other commonly used segments, such as the carotid bifurcation or the internal carotid artery. However, the prognostic value of IMT measurements to predict future cardiovascular events slightly increases when data from all 3 segments are combined compared with using data from only 1 site. Therefore, the present study may underestimate the relationships between childhood risk factors and carotid IMT.

It has been recommended that the long-term prevention of atherosclerosis should start early in life and focus on multiple cardiovascular risk factors. Our findings indicate that children and adolescents with several risk factors are at increased risk of developing atherosclerosis in adulthood. Risk factors such as obesity, dyslipidemia, and elevated blood pressure are metabolically linked, and reductions in these factors could be potentially achieved in children with lifestyle modifications such as inducing changes in the diet, increasing levels of physical activity, and controlling obesity. Ongoing research will determine whether young individuals benefit from efforts to change these risk factors through lifestyle modifications.

In conclusion, exposure to risk factors in childhood may contribute to the development of future atherosclerosis. These findings suggest that the prevention of atherosclerosis and its sequelae could be most effective when initiated in childhood or adolescence.
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