Cardiovascular Risk Factors and Increased Carotid Intima-Media Thickness in Healthy Young Adults

The Atherosclerosis Risk in Young Adults (ARYA) Study

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Background: The relation between cardiovascular risk factors and extent of atherosclerosis in middle-aged and elderly populations is well established. Autopsy studies have suggested that similar associations may be present at a young age. We evaluated the relationship between conventional risk factors and increased carotid intima-media thickness (CIMT) in 750 healthy young adults, aged 27 to 30 years.

Methods: All participants completed a questionnaire on cardiovascular risk factors, had a fasting blood sample drawn, and underwent an ultrasonographic examination of both common carotid arteries to assess common CIMT (CCIMT).

Results: Age (11.2 µm/SD), body mass index (10.3 µm/SD), pulse pressure (5.0 µm/SD), sex (4.8 µm/SD), and low-density lipoprotein cholesterol level (4.3 µm/SD) were independent determinants of increased CCIMT in young adults ($R^2=0.36$). Total pack-years of smoking, adjusted for age and sex, showed a linear trend with increased CCIMT ($P=.02$), which attenuated after further adjustment for body mass index. Common CIMT increased gradually and significantly with the number of cardiovascular risk factors present. The estimated absolute risk, based on the Framingham risk function, for development of coronary heart disease within 20 years was 2.5 times higher in individuals with mean CCIMT in the highest quartile compared with those in the lowest quartile of the distribution.

Conclusions: An unfavorable cardiovascular risk profile is associated with a marked increase in CCIMT in young adulthood. Efforts to change modifiable risk factors early in life may retard atherosclerosis development and hence delay the onset of clinical cardiovascular disease later in life.

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Although the pathogenesis of cardiovascular disease (CVD) is complex, atherosclerosis is thought to play an important role. Atherosclerosis is a slowly progressive process possibly starting at a young age. Preventive measures taken early in life might more effectively overcome the CVD epidemic by postponing atherosclerosis development and hence decreasing or retarding the occurrence of clinical CVD.

High-resolution B-mode ultrasonography provides a noninvasive method to quantify arterial wall thickening and atherosclerosis progression. In middle-aged subjects, an increased carotid intima-media thickness (CIMT) has been shown to be a strong predictor of cardiovascular morbidity and mortality in the future. Furthermore, increased common CIMT (CCIMT) may be regarded as a valid marker of generalized atherosclerosis because it is strongly associated with atherosclerosis in other parts of the arterial system. Studies in middle-aged and elderly individuals have shown that an unfavorable cardiovascular risk profile is associated with the extent of atherosclerosis. The independent determinants of (subclinical) atherosclerosis, assessed by noninvasive measurement of the intima-media thickness, have been studied extensively and are well documented in those age groups.

Anatomical evidence (from autopsy studies) suggests a relationship between arterial wall changes, such as the progression from fatty streaks through transitional lesions to atheromatous lesions, and cardiovascular risk factors already present in relatively young subjects. Nonetheless, evidence regarding the association between ultrasonographically assessed carotid atherosclerosis and cardiovascular risk profile in healthy young adults is limited. Knowledge about determinants of increased CIMT, eg, initiation and progression of atherosclerosis, in the young is essential to find modifiable risk factors and to estimate the benefit of primary prevention programs for CVD especially developed for this age group.
The aim of the present study was to explore the most important determinants of increased CCIMT, assessed by means of B-mode ultrasonography, in a population-based sample of 750 healthy men and women, aged 27 to 30 years.

STUDY DESIGN AND POPULATION

The Atherosclerosis Risk in Young Adults (ARYA) Study consists of 2 cohorts of young adults. The Utrecht cohort includes 750 young adults born between January 1, 1970, and December 31, 1973, who attended secondary school in the city of Utrecht in the Netherlands and for whom original medical records were available from the Municipal Health Service. Because vascular measurements were not performed in the cohort from The Hague, this report is restricted to the Utrecht participants of the ARYA Study.

To enroll the ARYA participants in Utrecht, a stepwise procedure was used. All available Municipal Health Service medical charts (n=15,992) were checked for the presence of adequately registered birth weight (birth weight notations with a sign were excluded) and at least 1 blood pressure measurement during adolescence. All young adults with a complete chart (n=4208; 27.0%) were invited by mail (at the last known residential address; 470 subjects (11.2%) declined to take part; and 821 (19.5%) were willing to participate. Of the eligible 821 young adults, 14 were excluded because of pregnancy and 57 declined to participate after they had given informed consent. Ultimately, 750 young adults completed participation in the Utrecht part of the ARYA Study. From October 1, 1999, through December 31, 2000, the participants visited our outdoor clinic twice within a 3-week period. The ARYA Study was approved by the Medical Ethical Committee of the University Medical Center Utrecht. All participants gave written informed consent.

CURRENT CARDIOVASCULAR RISK FACTORS

At each visit, blood pressure was measured twice, after 5 minutes of rest and at an interval of 5 to 15 minutes, on the left arm in sitting position, with an automated device (Dynamap; Portanje, Schiedam, the Netherlands) without replacing the cuff between the measurements. Mean systolic and diastolic blood pressure (SBP and DBP, respectively) were calculated as the average of 4 measurements. Pulse pressure (PP) was calculated by subtracting DBP from SBP. Mean arterial pressure was calculated using the formula DBP + (1/3 × PP). During the first visit, anthropometric measurements were performed. Height, weight, and waist-hip circumference were measured with indoor clothes and without shoes. Information about current and past smoking habits was obtained by a written standardized questionnaire. Family history of CVD was defined as positive if the participant reported 1 or more first-degree adult family members with CVD (myocardial infarction, stroke, peripheral artery disease, or coronary sclerosis) or unexplained sudden death at a young age (men, <55 years; women, <65 years). During the second visit, fasting venous blood samples were drawn. The samples were stored at −20°C until all participants were enrolled into the study. We determined levels of total (TC) and high-density lipoprotein (HDL) cholesterol, triglycerides (TG), and glucose using a dry-chemistry analyzer (Vitros950; Johnson & Johnson, Rochester, NY). We calculated low-density lipo-protein (LDL) cholesterol level using the following formula by Friedewald et al.\(^4\): TC−HDL−(0.45×TG) when TG level was no greater than 708 mg/dL (≥8.0 mmol/L).

COMMON CIMT

Ultrasonography of the left and right carotid arteries was performed in all participants, using a 7.5-MHz linear array transducer (Acuson Aspen; Siemens AG, Munich, Germany). On a longitudinal 2-dimensional ultrasonographic image of the carotid artery, the near and far wall of the carotid artery are displayed as 2 bright white lines separated by a hypoechoic space. The distance of the leading edge of the first bright line (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) indicated the intima-media thickness of the far wall, whereas the trailing edges on the near-wall boundaries were traced to estimate the near-wall-intima-media thickness. When an optimal longitudinal image was obtained, it was frozen on the R wave of the electrocardiogram and stored on videotape.\(^6\) This procedure was repeated at 4 predefined interrogation angles per side (180°, 150°, 120°, and 90° for the right carotid artery and 180°, 210°, 240°, and 270° for the left carotid artery) using the Meijer arc. The far and near walls were scanned at each angle, resulting in a maximum of 8 images with 16 (2×8) measurements per subject. The actual measurements were performed off-line. The frozen images on the videotape were digitized and displayed on a screen using additional dedicated software as described in detail by Wendelhag et al.\(^20\) In short, the interfaces of the distal common carotid artery were marked over a length of 10 mm using an automated edge-detection approach. The beginning of the dilatation of the distal carotid artery served as a reference point for the start of the measurement. Each angle image (8 images) gives rise to 1 mean near-wall CIMT and 1 mean far-wall CIMT. For each subject, these mean CIMTs were averaged to provide 1 measure of current wall thickness of the common carotid artery. The ultrasonographer and reader were unaware of the participants’ cardiovascular risk profile. The reproducibility of the CCIMT measurement was assessed by repeating the scans of 21 subjects on a second occasion by another ultrasonographer but with the same reader. Absolute mean difference (±SE) of the repeated measurements between visits was 0.012 mm (±0.004 mm) for mean intima-media thickness of both carotid arteries. The intraclass correlation coefficient was 0.84.

DATA ANALYSIS

The clinical and biochemical features of the population were presented as mean (SD). We tested the mean difference in CCIMT and conventional risk factors between men and women with unpaired t and χ² tests.

The relations between CCIMT and cardiovascular risk factors were evaluated using linear regression models. The CCIMT and cardiovascular risk factors were used as continuous variables, and all analyses were adjusted for the reader because CCIMT differed significantly between the 2 readers. To evaluate whether sex modifies the relation between the risk factors of interest and CCIMT, the reader-adjusted linear regression models were extended with interaction terms. Since all interaction terms were nonsignificant, all analyses were performed in the entire population only. Additional adjustments for sex and age were performed to evaluate the impact of other cardiovascular risk factors independent of these major confounders. The risk factors that remained significantly related to mean CCIMT after adjustment for reader, sex, and age were further adjusted for body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters). To determine independent determinants of subclinical atherosclerosis, a multivariate linear regression model was used that included mean...
As the dependent variable and all significant sex-, age-, BMI-, and reader-adjusted risk factors as independent variables.

To evaluate the combined effect of multiple risk factors on mean CCIMT, we applied the classification used by the Bogalusa Heart Study, in which values of BMI, SBP, TG, and LDL cholesterol levels above the sex-specific 75th percentile for the study group were considered risk factors for CVD.1

Finally, we calculated for each individual the absolute risk for development of coronary heart disease (CHD) within 20 years using the Framingham Risk Score21 and compared these risk estimates across quartiles of CCIMT using linear regression analyses with 3 dummy variables. The linear regression coefficients resulting from these analyses reflect the difference in absolute risk for the second, third, and fourth quartiles relative to the first quartile of the CCIMT distribution (reference group).

All associations were expressed as linear regression coefficients with corresponding 95% confidence intervals (CIs). Differences were considered statistically significant if 2-sided P values were less than .05. We performed statistical analysis with the statistical package SPSS version 9.0 for Windows (SPSS Inc, Chicago, III).

RESULTS

Among the 750 participants (352 men and 398 women), mean CCIMT was 0.49 mm (0.05 mm). Men had significantly higher CCIMT, SBP, DBP, and LDL cholesterol, fasting glucose, and TG levels as well as larger lumen diameter of the common carotid artery than women. The HDL cholesterol level was significantly lower in men compared with women, and significantly more men were current smokers. No sex difference was seen for age, BMI, and TC level (Table 1).

Male sex, age, blood pressure, BMI, waist-hip ratio, levels of TC, LDL cholesterol, and TG, number of pack-years of smoking, and lumen diameter of the common carotid artery were positively associated with a significant increase in CCIMT, whereas HDL cholesterol level was inversely associated with CCIMT in the univariate models. Additional adjustment for sex, age, and BMI attenuated the association between several variables and the CCIMT (Table 2). Age, pulse pressure, BMI, LDL cholesterol level, and male sex were independent predictors of mean CCIMT in our young population, after adjustment for reader, and explained 36% of the variation in CCIMT. In addition, the following tabulation shows that age and BMI had the largest individual contribution to the outcome variable:

<table>
<thead>
<tr>
<th>Independent Determinants</th>
<th>Linear Regression Coefficients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>11.2 (8.3-14.2)</td>
</tr>
<tr>
<td>Sex</td>
<td>4.8 (1.5-8.1)</td>
</tr>
<tr>
<td>BMI</td>
<td>10.3 (7.2-13.5)</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>5.0 (1.6-8.3)</td>
</tr>
<tr>
<td>LDL cholesterol level, mg/dL</td>
<td>4.3 (1.2-7.3)</td>
</tr>
</tbody>
</table>

*Expressed as change in mean CCIMT (in micrometers) per 1 SD of change in risk factor (95% CI), adjusted for the reader (R²=0.36).

The effect of smoking (smoking status, amount, and duration) on mean CCIMT is illustrated in Figure 1. Mean CCIMT did not differ significantly between current and never smokers after adjustment for reader and age (difference in CCIMT, 3 µm for women and 2 µm for men). In contrast, the increased number of cigarettes smoked daily and the total pack-years of smoking showed a linear trend with increased CCIMT (P = .10 and P = .02, respectively, for linear trend).

Figure 2 shows the sex-specific combined effect of the 4 risk factors (BMI, SBP, and TG and LDL cholesterol levels) used in the classification of the Bogalusa Heart Study1 on mean CCIMT adjusted for reader and age. Young adults without any risk factors (155/398 women and 148/352 men) had the lowest adjusted mean CCIMT (0.470 mm [95% CI, 0.464-0.476]) for women and 0.487 mm [95% CI, 0.479-0.495] for men), whereas those with 3 or 4 risk factors (36/398 women and 42/352 men) had the highest mean CCIMT (0.487 mm [95% CI, 0.482-0.510] and 0.518 mm [95% CI, 0.504-0.532] for women and men, respectively).

Figure 3 shows the 20-year absolute risk for CHD with increasing CCIMT. The 20-year risk for CHD (at a mean age of 28 years) increased from 1.1% (95% CI, 0.7%-1.5%) and 0.7% (95% CI, 0.4%-1.0%) for subjects in the lowest quartile to 2.8% (95% CI, 2.4%-3.2%) and 1.7% (95% CI, 1.4%-2.0%) for subjects in the highest quartile of CCIMT distribution when SBP and DBP, respectively, were used in the Framingham Risk Score.21

COMMENT

This report from the ARYA Study shows that age, BMI, pulse pressure, LDL cholesterol level, and male sex are all independent determinants of mean CCIMT in young adults. Moreover, although the absolute risk for development of
CHD within 20 years is small in our study population, it rises gradually with increasing CCIMT, as shown earlier in middle-aged individuals. Because there is no clear cut-off point above which the risk increased more rapidly, the CCIMT measurement may be of use as a marker of total burden of atherosclerosis present in an individual and may serve as a graded marker for cardiovascular risk.

Several aspects of the present study need to be addressed. First, CCIMT measured by B-mode ultrasonography cannot be unequivocally attributed to local atherosclerosis, because this technique cannot distinguish between the incipient atherosclerotic transformation of the arterial wall and other forms of medial thickening such as hyperplasia or hypertrophy. Mainly at lower degrees of CCIMT (0.6-0.9 mm), the thickening may reflect an adaptive response to changes in shear stress, lumen diameter, tensile stress, and pressure rather than atherosclerotic thickening. However, an increased CCIMT has been shown to relate to atherosclerosis elsewhere in the arterial system, suggesting that an increased CCIMT reflects generalized atherosclerosis.

Second, since carotid lumen diameter can be considered an intermediate variable in the relationship between cardiovascular risk factors and increased CCIMT, our analyses were not adjusted for the lumen diameter. Third, as the relation between subclinical atherosclerosis and cardiovascular risk factors was studied cross-sectionally, it does not allow determinations of temporal relations such as changes in cardiovascular risk profile and CCIMT. Our findings should therefore be confirmed in longitudinal studies to be able to draw conclusions on the relationship between cardiovascular risk and increase in CCIMT in young adulthood on the one hand and cardiovascular morbidity and mortal-risk on the other.

### Table 2. Determinants of Mean CCIMT

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Crude†</th>
<th>Sex Adjusted</th>
<th>Sex and Age Adjusted</th>
<th>Sex, Age, and BMI Adjusted‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (1=male; 0=female)</td>
<td>7.3 (4.1 to 10.4)</td>
<td>7.2 (4.2 to 10.3)</td>
<td>7.2 (4.3 to 10.1)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>12.7 (9.6 to 15.8)</td>
<td>12.7 (9.6 to 15.7)</td>
<td>12.2 (9.3 to 15.1)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, mm Hg Systolic</td>
<td>10.7 (7.6 to 13.8)</td>
<td>9.3 (5.9 to 12.7)</td>
<td>7.9 (4.7 to 11.2)</td>
<td>4.4 (1.0 to 7.7)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>5.1 (1.9 to 8.2)</td>
<td>4.2 (1.0 to 7.3)</td>
<td>3.1 (0.02 to 6.2)</td>
<td>0.9 (−2.1 to 3.9)</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>8.2 (5.0 to 11.3)</td>
<td>6.7 (3.4 to 10.0)</td>
<td>5.5 (2.3 to 8.6)</td>
<td>2.5 (−0.7 to 5.6)</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>10.6 (7.5 to 13.7)</td>
<td>9.2 (5.8 to 12.7)</td>
<td>8.3 (4.9 to 11.6)</td>
<td>5.1 (1.8 to 8.5)</td>
</tr>
<tr>
<td>BMI</td>
<td>12.6 (9.6 to 15.7)</td>
<td>12.6 (10.0 to 15.6)</td>
<td>12.1 (9.2 to 15.0)</td>
<td></td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>8.3 (5.2 to 11.5)</td>
<td>6.3 (2.7 to 10.0)</td>
<td>5.4 (1.9 to 8.9)</td>
<td>−0.3 (−4.0 to 3.4)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL Total</td>
<td>7.9 (4.7 to 11.1)</td>
<td>7.9 (4.7 to 11.0)</td>
<td>6.8 (3.7 to 9.9)</td>
<td>4.3 (1.3 to 7.3)</td>
</tr>
<tr>
<td>LDL</td>
<td>9.0 (5.7 to 12.2)</td>
<td>8.1 (5.9 to 11.3)</td>
<td>6.9 (3.9 to 10.1)</td>
<td>4.4 (1.3 to 7.5)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>4.3 (1.0 to 7.5)</td>
<td>3.6 (0.4 to 6.8)</td>
<td>3.7 (0.6 to 6.8)</td>
<td>0.3 (−2.8 to 3.5)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>−2.4 (−5.7 to 0.8)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pack-years of smoking</td>
<td>0.52</td>
<td>0.48</td>
<td>0.50</td>
<td>0.46</td>
</tr>
<tr>
<td>Lumen diameter, mm</td>
<td>11.5 (8.6 to 14.4)</td>
<td>10.8 (8.5 to 13.1)</td>
<td>9.3 (6.7 to 11.6)</td>
<td>8.4 (5.5 to 11.3)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CCIMT, common carotid intima-media thickness; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; glucose to millimoles per liter, multiply by 0.0555.

†Values are expressed as linear regression coefficients (95% confidence intervals) of change in mean CCIMT (in micrometers) per 1 SD of change.
‡A linear regression coefficient for a BMI of 22.6 means that an increase in BMI of 1 SD (5.0 for women and 3.7 for mean) relates to an increase in CCIMT of 12.6 µm.
ity in later decades on the other. Finally, because of within-subject biological variation in the risk factor variables, the single measurement available for each subject in this study will reflect long-term averages less precisely than multiple measurements. As a consequence, the associations between risk factors and CCIMT reported herein are likely to underestimate the true associations.

Similar to findings in middle-aged individuals, graded associations between CCIMT and cardiovascular risk factors were found in this young population. Men persistently had a thicker mean CCIMT than women in each tertile of conventional risk factors after adjustment for reader and age (data not shown). This sex difference was partly attributable to differences in carotid lumen diameter and may therefore reflect differences in physiology rather than differences in vascular damage. The extent of subclinical atherosclerosis in the common carotid arteries increased markedly in young people with multiple risk factors. The mean CCIMT in men and women with 3 or more risk factors was 6.4% and 3.6%, respectively, thicker than in their counterparts with no risk factors. This finding supports the view that multiple risk factors have a synergistic effect on the risk for CVD, as has been demonstrated by others.

Autopsy studies in young adults, as the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth study, have shown strong relationships between coronary atherosclerosis and cardiovascular risk factors, such as age, blood pressure, BMI, levels of TC and LDL cholesterol, and cigarette smoking. Our observations that age, BMI, blood pressure, hyperlipidemia, and lumen diameter are significantly related to an increased CCIMT expand the findings of these studies. In contrast, our observation that mean CCIMT did not differ between the smoking categories disagrees with the findings from anatomical studies in young adults. Although smoking was associated with a higher microscopic grade of coronary artery fatty streaks in the young Pathobiological Determinants of Atherosclerosis in Youth population, a stronger effect on raised lesions may become evident only after 35 years of age. Since the mean age of the ARYA participants is 28 years, it is probable that raised lesions had not occurred yet, and fatty streaks cannot be detected by ultrasonography while they are already visible in microscopic examination of the arterial wall. Alternatively, the mean exposure time to nicotine within the ARYA population (±10 years) might have been too short to induce subclinical atherosclerosis, as it has been suggested that duration of smoking is the most important risk factor for development of atherosclerosis. The linear trend observed in our population between total number of pack-years of smoking and increased CCIMT supports this view.

The number of epidemiological studies that have evaluated the determinants of subclinical atherosclerosis in healthy young adults is limited. Because these studies are not directly comparable with respect to outcome variables and age groups, unambiguous conclusions cannot be drawn. In contrast, several studies investigated the effects of cardiovascular risk factors on mean CCIMT in a middle-aged population. It is sometimes difficult to compare results regarding carotid atherosclerosis among studies because of differences in the measurement methods used to assess CIMT, the definition of atherosclerosis, and the demographics (age and ethnicity) of the study population. Nevertheless, most of these studies report age, blood pressure, dyslipidemia, and current smoking or number of pack-years of smoking to be independent determinants for atherosclerosis. Only 1 study showed an independent effect of BMI in the prediction of atherosclerosis, but its impact was far less important compared with the impact of blood pressure in this adult study population. The most obvious difference between the independent predictors of atherosclerosis observed in the elderly compared with results from our study is the importance of BMI in young adulthood. It has been suggested that different risk factors dominate in different stages of atherogenesis. Risk factors found to have a stable effect across age could be important in initiating atherosclerosis, whereas risk factors with increasing effect with age, such as hypertension and hyperlipidemia, may be more associated with the progression of atherosclerosis. Moreover, raised blood pressure and dyslipidemia seen in middle-aged individuals might be a consequence of exposure to long-existing overweight in previous years.

Obesity has become one of the major problems of Western society by inducing multiple metabolic abnor-
malities that contribute to the pathogenesis of CVD. The prevalence of overweight and obesity has dramatically increased worldwide in children and adults in previous decades.33–38 Because ample evidence exists for the importance of tracking of body size from childhood to adulthood,39 the social and health risks of childhood and adolescent obesity are substantial. Increasing evidence suggests that a reduction in initial weight of as little as 10% is sufficient to ameliorate common complications of obesity by reducing CVD risk factors and risk for (coronary) atherosclerosis.40 Moreover, existing data suggest that children may be more responsive to weight prevention than adults and that risk factors identified in children may be less difficult to change.41 Hence, the results from the ARYA Study support modification of the cardiovascular risk profile early in life to postpone the development and progression of subclinical atherosclerosis, which, in turn, would delay the onset of clinical manifestation of CVD later in life.

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