Conventional Cardiovascular Risk Factors and Metabolic Syndrome in Predicting Carotid Intima-Media Thickness Progression in Young Adults

The Cardiovascular Risk in Young Finns Study

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Background—Conventional risk factors and metabolic syndrome (MetS) are cross-sectionally associated with subclinical atherosclerosis in young adults. We evaluated the relations of conventional risk factors and MetS to the 6-year progression of carotid intima-media thickness (IMT) in a population of young adults.

Results and Methods—The study included 1809 subjects (aged 32±5 years) who had IMT measured in 2001 and 2007. Risk factor measurements included low-density lipoprotein cholesterol, body mass index, C-reactive protein, smoking, and family history of coronary disease in addition to MetS components. We used European Group for the Study of Insulin Resistance, revised National Cholesterol Education Program, and International Diabetes Federation definitions to diagnose MetS in 2001. Waist circumference (P<0.0001), low-density lipoprotein cholesterol (P=0.01), and insulin (P=0.003) were directly associated with IMT progression in a multivariable model adjusted for age, sex, and baseline IMT (model \( R^2 = 24\% \)). When the MetS/European Group for the Study of Insulin Resistance definition was included in the model, it was directly associated with IMT progression (P=0.03), but its inclusion did not improve the model’s predictive value. IMT increased 79±7 μm (mean±SEM) in subjects with MetS according to the MetS/European Group for the Study of Insulin Resistance definition and 42±2 μm in subjects without MetS (P<0.0001). In addition, the number of MetS components was linearly associated with IMT progression (P<0.0001). Similar results were seen with MetS/revised National Cholesterol Education Program and MetS/International Diabetes Federation definitions.

Conclusions—Obesity, high low-density lipoprotein cholesterol, and high insulin level predicted IMT progression in young adults. All MetS definitions identified young adults with accelerated IMT progression, but we found no evidence that MetS would predict IMT progression more than expected from the sum of its risk components. (Circulation. 2009; 120:229-236.)

Key Words: cardiovascular diseases ■ carotid arteries ■ cholesterol ■ insulin ■ obesity

Atherosclerotic diseases are the leading cause of death in developed countries. Although clinical manifestations of atherosclerosis do not occur until middle age, the development of vascular changes begins early in life.1 Increased carotid intima-media thickness (IMT), as assessed noninvasively by ultrasound, is a marker of structural atherosclerosis.2,3 Accelerated progression in IMT is a marker of atherosclerosis development that increases the risk of cardiovascular events.4

Clinical Perspective on p 236

Exposure to atherogenic risk factors in early life may induce changes in arteries that contribute to the development of atherosclerosis. In cross-sectional settings, conventional...
risk factors in adulthood have been related to IMT.\textsuperscript{1,5–7} We\textsuperscript{1} and others\textsuperscript{5–7} have also shown that elevated risk factor levels in childhood predict increased adulthood IMT. However, limited longitudinal data are available on the association between risk factors and IMT progression in young adults.\textsuperscript{8}

Metabolic syndrome (MetS) is a combination of several cardiometabolic risk factors including obesity, impaired glucose tolerance, hypertension, and dyslipidemia.\textsuperscript{9} Although controversy has surrounded both the pathophysiological basis and the clinical utility of the MetS,\textsuperscript{10,11} it has been associated with an increased risk of cardiovascular disease.\textsuperscript{12} Previous cross-sectional studies have demonstrated that young adults with MetS have increased IMT.\textsuperscript{1,3,14} Prospective data in this age group are lacking, and it is not known whether MetS predicts the progression of atherosclerosis in young adults. The objective of the present analysis was to explore whether the baseline levels (at ages 24 to 39 years) of conventional risk factors and MetS are related to the 6-year progression of IMT in the Cardiovascular Risk in Young Finns Study.

Methods

Subjects and Study Design

The Cardiovascular Risk in Young Finns Study was launched in 1980 to assess risk factors underlying cardiovascular disease in children and young adults. The first cross-sectional study was conducted in 1980 and included 3596 children and adolescents aged 3 to 18 years. Five university hospitals in Finland (Turku, Tampere, Helsinki, Kuopio, and Oulu) are taking part of the study, and the participants were randomly selected from these areas. Subjects were 24 to 39 years of age in 2001. IMT was measured in the follow-up studies in 2001 (n=2265) and 2007 (n=2197). Subjects who had missing IMT data from the year 2001 or 2007 were excluded from the present analysis. Conventional risk factor data were available for 1809 subjects. Complete MetS risk factor data were available for 1715 nonpregnant subjects. One subject had established cardiovascular disease, 43 subjects were on antihypertensive medication, and 7 subjects were on lipid-lowering medication. No significant difference in results was observed when these subjects were excluded from the cohort. All subjects gave written informed consent, and the study was approved by the local ethics committee.

Biochemical Assays

Venous blood samples were taken after the subject had fasted for 12 hours. Lipid determinations were done with the use of standard methods. Details of analytical procedures have been reported previously.\textsuperscript{15} Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula for subjects with <4 mmol/L triglycerides.\textsuperscript{16} Therefore, LDL cholesterol data were available for 1785 subjects. Coefficient of variation (CV) was 2.2% for total cholesterol, 2.3% for high-density lipoprotein (HDL) cholesterol, and 3.8% for serum triglycerides. Glucose concentrations were analyzed enzymatically with a clinical chemistry analyzer (Olympus, AU400; CV 2.0%), and serum insulin concentrations were measured by microparticle enzyme immunoassay kit (CV 2.1%) (Abbott Laboratories, Diagnostic Division, Dainabot). Serum C-reactive protein (CRP) was analyzed by an automated analyzer (Olympus AU400) with a latex turbidimetric immunoassay kit (CRP-UL assay, Wako Chemicals, Neuss, Germany). The detection limit reported by the manufacturer for the assay was 0.06 mg/L. The interassay CV was 3.3%.

Other Measurements and Questionnaires

Body height, weight, and waist circumference were measured. Body mass index was calculated with the following formula: weight (kg)/(height [m]\(^2\)). Blood pressure was measured with the use of a random zero sphygmomanometer. The average of 3 measurements was used in the analyses. Subjects were also asked to complete questionnaires that included questions about smoking habits and family history of coronary disease.\textsuperscript{17}

MetS Definitions

We used 3 definitions for MetS: the European Group of Insulin Resistance classification (MetS/EGIR);\textsuperscript{18} the modification of the original National Cholesterol Education Program definition by a joint expert group of the National Heart, Lung, and Blood Institute and the American Heart Association (MetS/revNCEP);\textsuperscript{19} and the International Diabetes Federation classification (MetS/IDF).\textsuperscript{20} The results for MetS/EGIR are shown in this report, and those for MetS/revNCEP and MetS/IDF are shown in the online-only Data Supplement. MetS/EGIR was defined as the presence of hyperinsulinemia (defined as nondiabetic subjects having fasting insulin level in the highest quartile; the cutoff point in our study was 9 mU/L) and at least 2 of the following abnormalities: fasting blood glucose ≥6.1 mmol/L, blood pressure ≥140/≥90 mm Hg or current use of antihypertensive medication, serum triglycerides ≥2.0 mmol/L or HDL cholesterol level ≤1.0 mmol/L, and waist circumference at least 94 cm in men and 80 cm in women.\textsuperscript{18} Definitions of the MetS/revNCEP and MetS/IDF are shown in the online-only Data Supplement.

Ultrasound Imaging

Ultrasound studies were performed by trained sonographers following standardized protocol in 5 centers. The image was focused on the posterior (far) wall to derive the mean IMT. A moving scan with duration of 5 seconds was recorded including the beginning of the carotid bifurcation and the common carotid artery. Measurements were made afterward during the following spring (2002 and 2008) from stored digital images by 1 experienced reader blinded to the subjects’ clinical characteristics. IMT was measured at a minimum of 4 times from the left common carotid artery ~10 mm proximal to the carotid bifurcation. We used an ultrasound imaging device with a high-resolution system (Sequoia 512, Acuson). Details of the methods have been described previously.\textsuperscript{1} A total of 57 subjects (2.5%) were randomly selected to be reexamined 3 months after the first visit to assess intra-individual reproducibility in 2001. CV between visits was 6.4%, the correlation coefficient between these exams was r=0.68, and the estimate of variance of the measurement error was 0.0021 mm\(^2\).

Statistical Methods

Values for plasma triglycerides, CRP, insulin, and glucose were log transformed to correct for skewness. The representativeness of the present study subjects was tested by comparing the baseline (1980) characteristics with the nonparticipants with a regression model adjusted for age. The baseline (2001) characteristics of the study subjects were compared with the t test for continuous variables and \(\chi^2\) test for categorical variables. Pearson correlation coefficients were calculated to assess associations between risk factors and ultrasound variables (IMT and IMT progression). To assess the independent relations between risk factors and ultrasound variables, we performed stepwise multivariable regression modeling using backward selection. In initial models, all variables with \(P<0.05\) in univariable models were included. Next, variables were removed from the model 1 by 1 until all the variables remaining in the model were statistically significant (\(P<0.05\)). At each step, the variable showing the smallest contribution to the model was removed.

In agreement with prior reports,\textsuperscript{8,21,22} we found an inverse correlation between baseline IMT and IMT progression (\(r=-0.39\); see also Figure IV in the online-only Data Supplement). Therefore, all analyses were adjusted for baseline IMT and also were repeated after the use of correction techniques for possible measurement error in IMT. If regression analysis is made with explanatory variables that include measurement error, the parameter estimates are biased.\textsuperscript{23} The situation in which the change in outcome variable is the dependent variable and baseline measurement of the outcome variable is included as an explanatory variable creates such a problem. We used a technique described by Yanez et al\textsuperscript{24} to perform corrections to the
Table 1. Comparison of Baseline Characteristics (in 1980) Between Study Participants and Nonparticipants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male Subjects</th>
<th>Female Subjects</th>
<th>Male Subjects</th>
<th>Female Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>794</td>
<td>970</td>
<td>1015</td>
<td>817</td>
</tr>
<tr>
<td>Age in 1980, y</td>
<td>10.9</td>
<td>9.9§</td>
<td>10.9</td>
<td>10.1§</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>17.5</td>
<td>17.6</td>
<td>17.5</td>
<td>17.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>113</td>
<td>113</td>
<td>112</td>
<td>112</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73</td>
<td>74</td>
<td>73</td>
<td>74</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.21</td>
<td>5.23</td>
<td>5.38</td>
<td>5.34</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.37</td>
<td>3.38</td>
<td>3.50</td>
<td>3.47</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.56</td>
<td>1.56</td>
<td>1.57</td>
<td>1.55</td>
</tr>
<tr>
<td>Triglycerides, mmol/L†</td>
<td>0.57</td>
<td>0.58</td>
<td>0.63</td>
<td>0.64</td>
</tr>
<tr>
<td>Insulin, IU/L†</td>
<td>5.8</td>
<td>5.5</td>
<td>6.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Smoking prevalence, %‡</td>
<td>13.7</td>
<td>17.1</td>
<td>9.9</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*Nonparticipants (n=1787), including subjects lost in follow-up or missing IMT data in 2001 (n=1326) or in 2007 (n=461).
†Results are geometric mean values.
‡Among subjects aged 12 to 18 years.
§P<0.0005; differences in age between participants and nonparticipants were examined with t test.
¶P=0.005 in age-adjusted regression model.

Results

Characteristics of Study Subjects

The representativeness of the present study cohort is shown in Table 1. The characteristics at the original baseline study (1980) were compared between the participants of the present study and nonparticipants with age-adjusted analysis. Nonparticipants were younger in both sexes than participants. Body mass index was higher in female nonparticipants than in participants. No statistically significant differences were seen in other risk factors.

The characteristics of 1809 study subjects at study baseline (in 2001) are shown in Table 2. Overall, men had worse risk factor profiles compared with women. In addition, men had higher IMT values in both 2001 and 2007, as well as higher IMT progression rate. At baseline, the prevalence of MetS was 12.5% in men and 6.5% in women. Details about changes in waist circumference, insulin levels, and manifestation of MetS during the 6-year study period are available in the online-only Data Supplement.

Risk Factors and IMT

Correlation coefficients between baseline risk factors and IMT measured in 2001, between risk factors and IMT measured in 2007, and between baseline (2001) risk factors and IMT progression (2001–2007) are shown in Table 3.

The results of stepwise multivariable regression analyses including individual risk factors in predicting IMT in 2001

Table 2. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male Subjects</th>
<th>Female Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>794</td>
<td>1015</td>
</tr>
<tr>
<td>Age, y</td>
<td>31.9±5.0</td>
<td>31.9±4.9</td>
</tr>
</tbody>
</table>

Risk factors

Waist circumference, cm 90±11 79±11
Body mass index, kg/m² 25.7±4.0 24.4±4.5
Systolic blood pressure, mm Hg 121±12 112±12
Diastolic blood pressure, mm Hg 73±11 69±10
Total cholesterol, mmol/L 5.24±1.03 5.08±0.93
LDL cholesterol, mmol/L 3.43±0.92 3.16±0.76
HDL cholesterol, mmol/L 1.15±0.27 1.41±0.31
Triglycerides, mmol/L 1.29 (0.90–1.80) 1.05 (0.80–1.35)
Glucose, mmol/L 5.2 (4.9–5.4) 4.9 (4.6–5.1)
Insulin, mU/L 6.4 (5.0–9.0) 6.6 (5.0–9.0)
CRP, mg/L 0.7 (0.3–1.4) 0.7 (0.4–2.4)
Daily smoking, % 27 18

IMT data:

| IMT 2001, mm | 0.59±0.10 | 0.57±0.09 |
| IMT 2007, mm | 0.64±0.11 | 0.61±0.09 |
| IMT progression, µm | 54±89 | 40±79 |

Values are mean±SD or geometric mean (25th to 75th percentile) or percentage of subjects. All comparisons (t tests) between men and women P<0.001, except for age and insulin (P>0.4).
and 2007 and IMT progression are shown in Table 4. Waist circumference and systolic blood pressure were independently and directly associated with cross-sectionally measured IMT in both study years. In a model adjusted for age, sex, and baseline IMT, the multivariable correlates of IMT progression included waist circumference, LDL cholesterol, and insulin. In an analysis adjusting for measurement error bias (see Methods), the parameter estimates remained nearly identical: waist circumference ($\beta \pm SE = 10.1 \pm 3.7; P = 0.005$), LDL cholesterol ($\beta \pm SE = 4.6 \pm 2.8; P = 0.09$), and insulin ($\beta \pm SE = 6.4 \pm 3.1; P = 0.045$).

### MetS and IMT Progression

To examine the association between MetS/EGIR and IMT, we compared IMT progression rates in subjects with and without MetS/EGIR in 2001. The rate of IMT progression was increased in the MetS/EGIR group compared with subjects without MetS/EGIR. Figure 1A shows unadjusted mean values for the 6-year IMT progression according to MetS/EGIR status, and Figure 1B shows mean values in MetS groups adjusted for age, sex, and baseline IMT. In Figure 1C, mean values are additionally adjusted for risk variables not included in the MetS definition (smoking, CRP, etc.).

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### Table 3. Pearson Correlation Coefficients Between Risk Factors and IMT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>IMT 01*</th>
<th>P</th>
<th>IMT 07†</th>
<th>P</th>
<th>IMT Progression 01–07‡</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$</td>
<td>$P$</td>
<td>$r$</td>
<td>$P$</td>
<td>$r$</td>
<td>$P$</td>
</tr>
<tr>
<td>Age</td>
<td>0.31</td>
<td>0.0001</td>
<td>0.34</td>
<td>0.0001</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>Sex</td>
<td>0.10</td>
<td>0.0001</td>
<td>0.17</td>
<td>0.0001</td>
<td>0.08</td>
<td>0.0009</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>0.23</td>
<td>0.0001</td>
<td>0.30</td>
<td>0.0001</td>
<td>0.13</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.19</td>
<td>0.0001</td>
<td>0.28</td>
<td>0.0001</td>
<td>0.11</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.18</td>
<td>0.0001</td>
<td>0.25</td>
<td>0.0001</td>
<td>0.06</td>
<td>0.018</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>0.21</td>
<td>0.0001</td>
<td>0.21</td>
<td>0.0001</td>
<td>0.06</td>
<td>0.0002</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.10</td>
<td>0.0001</td>
<td>0.15</td>
<td>0.0001</td>
<td>0.09</td>
<td>0.0002</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.12</td>
<td>0.0001</td>
<td>0.17</td>
<td>0.0001</td>
<td>0.09</td>
<td>0.0002</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.05</td>
<td>0.03</td>
<td>−0.17</td>
<td>0.0001</td>
<td>−0.09</td>
<td>0.0002</td>
</tr>
<tr>
<td>Log triglycerides</td>
<td>0.05</td>
<td>0.03</td>
<td>0.18</td>
<td>0.0001</td>
<td>0.11</td>
<td>0.0002</td>
</tr>
<tr>
<td>Log insulin</td>
<td>0.02</td>
<td>0.47</td>
<td>0.04</td>
<td>0.013</td>
<td>0.13</td>
<td>0.0001</td>
</tr>
<tr>
<td>Log glucose</td>
<td>0.12</td>
<td>0.0001</td>
<td>0.16</td>
<td>0.0001</td>
<td>0.04</td>
<td>0.09</td>
</tr>
<tr>
<td>Log CRP</td>
<td>0.02</td>
<td>0.32</td>
<td>0.07</td>
<td>0.002</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.02</td>
<td>0.52</td>
<td>0.02</td>
<td>0.35</td>
<td>0.01</td>
<td>0.64</td>
</tr>
<tr>
<td>Family risk of coronary disease</td>
<td>0.07</td>
<td>0.004</td>
<td>0.09</td>
<td>0.0002</td>
<td>−0.04</td>
<td>0.86</td>
</tr>
</tbody>
</table>


### Table 4. Stepwise Multivariable Model of Relationships Between Risk Factors and Ultrasound Variables

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>IMT 01* $\beta \pm SE$</th>
<th>P</th>
<th>IMT 07† $\beta \pm SE$</th>
<th>P</th>
<th>IMT Progression 01–07‡ $\beta \pm SE$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>25.7 ±2.1</td>
<td>0.0001</td>
<td>29.7 ±2.1</td>
<td>0.0001</td>
<td>14.5 ±1.90</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>1.7 ±0.7</td>
<td>0.07</td>
<td>3.37 ±4.8</td>
<td>0.49</td>
<td>11.2 ±4.12</td>
<td>0.007</td>
</tr>
<tr>
<td>Waist</td>
<td>12.5 ±2.5</td>
<td>0.0001</td>
<td>17.2 ±2.5</td>
<td>0.0001</td>
<td>10.5 ±2.43</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>6.9 ±1.8</td>
<td>0.0001</td>
<td>13.5 ±2.3</td>
<td>0.0001</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>4.71 ±1.86</td>
<td>0.010</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>...</td>
<td>...</td>
<td>−8.4 ±2.4</td>
<td>0.0004</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Log insulin</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>6.17 ±2.09</td>
<td>0.003</td>
</tr>
<tr>
<td>Family risk of coronary disease</td>
<td>16.8 ±6.2</td>
<td>0.007</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

$R^2=14\ %$ $R^2=21\ %$ $R^2=24\ %$

Values are regression coefficients (expressed in micrometers) for absence/presence of family risk of coronary disease and for a 1-SD change in continuous variables.

LDL cholesterol, and family history of coronary disease). When we adjusted for measurement error bias, the results were essentially similar. Results were similar for MetS/revNCEP and MetS/IDF (Figure I in the online-only Data Supplement).

Does MetS Provide Information Over and Above Individual Risk Factors?
To analyze whether MetS provides information beyond individual risk factors, we first examined whether the 2-level MetS variable was associated with IMT progression in the multivariable model shown in Table 4. MetS/EGIR was significantly associated with IMT progression in the multivariable model ($\beta=16.2; P=0.03$), but the model’s $R^2$ value did not improve (24% versus 24%) after its inclusion. When the dichotomous MetS/EGIR definition was replaced by the number of metabolic components, such risk score was not significantly associated with IMT progression in the multivariable model. In addition, the statistical significance of MetS/EGIR in the model was attenuated after correction for measurement error bias ($\beta=16.3; P=0.16$). Finally, we assessed whether the association between the number of MetS/EGIR components and IMT progression showed evidence of nonlinearity. To examine this, we plotted the IMT progression against the number of MetS/EGIR components (Figure 2). There was an increasing trend in IMT progression with increasing number of MetS/EGIR components. Second-order polynomial regression showed no quadratic association between the number of MetS components and IMT progression ($P=0.19$). Similar results were observed when IMT measured in 2001 or 2007 was used as the outcome variable.

Risk Factor Change and IMT Progression
To assess whether the 6-year changes in risk factors were associated with IMT progression, we calculated Pearson correlation coefficients. The changes in waist circumference ($r=0.05; P=0.03$), systolic blood pressure ($r=0.05; P=0.03$), and HDL cholesterol ($r=-0.065; P=0.006$) were associated with IMT progression. In a stepwise multivariable regression model adjusted for age, sex, and baseline IMT, the change in HDL cholesterol remained independently associated with IMT progression ($\beta=-6.2; P=0.001$).

Discussion
These data demonstrate that conventional risk factors contribute to the development of atherosclerosis progression in young adults. In this cohort, baseline waist circumference, insulin, and LDL cholesterol were directly associated with IMT progression, and the 6-year change in HDL cholesterol was inversely associated with IMT progression. We also
demonstrated that MetS was significantly associated with accelerated IMT progression.

Waist circumference had a strong association with IMT progression. This observation may suggest that increased waist circumference is a risk marker that reflects long-term deviations in several metabolic risk variables. Central obesity predisposes to MetS,19 hypertension,24 development of insulin resistance,25 and cardiovascular diseases.20 It is also possible that part of the risk associated with increased waist circumference is mediated by some unmeasured factors. Potential candidates may include increased oxidative stress26 and inflammatory cytokines secreted by adipose tissue.27

Insulin levels were also independently associated with IMT progression. Two prospective studies using insulin sensitivity index derived from euglycemic clamp studies have shown that insulin resistance is associated with increased cardiovascular disease risk.28,29 Moreover, evidence from 3 large-scale meta-analyses examining the longitudinal relationship between plasma insulin and cardiovascular disease suggests that hyperinsulinemia is moderately associated with increased cardiovascular morbidity, independently of other cardiovascular risk factors.30–32 Various mechanisms have been hypothesized by which hyperinsulinemia could promote atherosclerosis.33 Previous reports have suggested that the association of hyperinsulinemia with cardiovascular disease is at least partly mediated by the clustering of several risk factors caused by insulin resistance.34,35 Thus, hyperinsulinemia may be a surrogate marker of insulin resistance, which we were not able to measure.36 These population-based data do not allow us to determine whether insulin has a direct role in promoting atherosclerosis or whether high insulin level is a marker of underlying insulin resistance.

Exposure to an atherogenic lipid profile in early life may induce changes in arteries that contribute to the development of atherosclerosis. We1,37 and others5–7 have shown that low apolipoprotein A1 levels and elevated LDL cholesterol and apolipoprotein B levels in childhood predict increased carotid IMT in adulthood. The present results are in agreement with earlier reports suggesting that a high LDL cholesterol concentration predisposes to the progression of subclinical atherosclerosis. LDL particles, which may be enzymatically and oxidatively modified, have been suggested to predict increased risk of atherosclerotic diseases because of their toxicity to the endothelium and underlying smooth muscle, adhesion to glycosaminoglycans in the endothelial basement membrane, and high susceptibility to scavenger receptors on macrophages.38 The internalization by macrophages results in the formation of foam cells, which are known to predispose to fatty-streak formation in atherosclerosis.39

This is the first population-based study demonstrating that by diagnosing MetS in young adults, it is possible to identify groups of individuals who have accelerated progression of carotid IMT suggestive of increased atherosclerosis development. Our results in almost 2000 young adults are in agreement with previous studies in elderly or hypertensive subjects. Hassinen et al21 demonstrated in 102 women (baseline age, 60 to 70 years) that MetS/revNCEP predicted IMT progression during a 12-year follow-up. In the European Lacidipine Study on Atherosclerosis (ELSA), MetS was associated in a bivariate model with the 4-year change in IMT among 1734 hypertensive subjects aged 45 to 75 years at baseline.40 However, in the ELSA study the association between MetS and IMT progression became nonsignificant after adjustment for covariates. We observed that the association between MetS and IMT progression was independent of the main cardiovascular risk factors. However, inclusion of the dichotomous MetS variable in the multivariable model did not improve the overall predictive value. Moreover, the relation between the number of MetS components and IMT progression was linear (ie, we found no evidence to suggest that the MetS constellation would predict IMT progression more than would be expected from the sum of its risk components). These results are in agreement with recent observations suggesting that MetS does not increase cardiovascular morbidity and mortality41,42 over and above its individual components.

Our study had limitations. We measured IMT in the far wall of the common carotid artery. Measurements of IMT in the common carotid artery are more reliable and less difficult to obtain than IMT measurements in the carotid bifurcation or in the internal carotid artery but also less sensitive to local atherosclerotic changes.43 Therefore, it is possible that the IMT data from only 1 site may underestimate the relationships between MetS and IMT progression compared with using data from all 3 segments.2 Another potential limitation of our study was the loss of original participants during the long-term follow-up. However, baseline characteristics in 1980 were virtually similar between participants and nonparticipants, and the study cohort seems to be representative of the original study population. Because our study cohort was racially homogeneous, the generalizability of our results is limited to white European subjects. In addition, thus far it was not possible to study the associations between risk factors and cardiovascular events. Instead, we have used vascular ultrasound measurement as an indicator of an atherogenic process. The implications of IMT progression in population-based samples, however, are not entirely clear, and more studies are needed to confirm the role of IMT progression as an indicator of clinical atherosclerotic disease.4 There is controversy relative to the effect of measurement error bias in analyses evaluating IMT progression with baseline IMT used as a covariate.23,44 We found, however, that the results from analyses correcting for measurement error bias were quite similar to those obtained from the models adjusted for baseline IMT. Because of the number of potential confounding factors, the unadjusted results should be interpreted with caution. The strength of this study was the large randomly selected cohort of young men and women free of clinical cardiovascular disease.

In conclusion, we found that conventional risk factors and MetS are associated with accelerated IMT progression in young adults. These observations suggest a pathophysiological role for obesity, dyslipidemia, and hyperinsulinemia in predicting atherosclerosis development in young adults. Furthermore, the diagnosis of MetS may be helpful in identifying groups of individuals who have accelerated progression of carotid IMT indicative of atherosclerosis development. Adverse lifestyle developments in childhood and young adult-
hod, such as the increasing prevalence of obesity and a sedentary lifestyle, are known to have a strong influence on all the components of MetS. As shown in our study, this becomes translated into accelerated atherosclerosis early in adult life. Therefore, in addition to identification of individuals who are at particularly high risk, a major effort is needed for the reduction of overweight in the whole population of children, adolescents, and young adults to reduce the burden of cardiovascular disease late in their life.

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Disclosures

None.

References

Accelerated progression in carotid intima-media thickness (IMT) is a marker of atherosclerosis development that is associated with increased risk of cardiovascular events. Exposure to elevated cardiovascular risk factor levels and the metabolic syndrome has been shown to predict increased IMT. However, limited longitudinal data are available on the association of risk factors and metabolic syndrome with IMT progression in young adults. On the basis of a large, population-based study of young adults (n=1809; aged 24 to 39 years), our results suggest a pathophysiological role of obesity, dyslipidemia, and hyperinsulinemia in predicting atherosclerosis development. In addition, the diagnosis of metabolic syndrome may be helpful in identifying groups of individuals who have accelerated progression of carotid IMT. However, we found no evidence to suggest that metabolic syndrome would predict IMT progression more than would be expected from the sum of its risk components. As shown in our study, adverse developments of lifestyles leading to obesity are translated into accelerated atherosclerosis early in adult life. Therefore, in addition to identification of individuals who are at particularly high risk, a major effort is needed for the reduction of obesity in the entire population of children, adolescents, and young adults to reduce the burden of cardiovascular disease late in their life.
Conventional Cardiovascular Risk Factors and Metabolic Syndrome in Predicting Carotid Intima-Media Thickness Progression in Young Adults: The Cardiovascular Risk in Young Finns Study
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Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults

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Koskinen et al.

SUPPLEMENTAL METHODS

MetS definitions

Three different classifications of MetS were used in this study: MetS/EGIR was defined as the presence of hyperinsulinemia (defined as non-diabetic subjects having fasting insulin level in the highest quartile, the cutoff point in our study was 9 mU/l), and at least two of the following abnormalities: fasting blood glucose $\geq 6.1$ mmol/l, blood pressure $\geq 140/\geq 90$ mmHg or current use of antihypertensive medication, serum triglycerides $\geq 2.0$ mmol/l or HDL-cholesterol level $\leq 1.0$ mmol/l, and waist circumference at least 94 cm in men and 80 cm in women.\footnote{MetS/revNCEP is a modification of the original National Cholesterol Education Program definition by a joint expert group of the National Heart, Lung and Blood Institute and the American Heart Association.} MetS/revNCEP was identified when three or more of the following five criteria were present: waist circumference $\geq 102$ cm in men or $\geq 88$ cm in women, triglycerides $\geq 1.695$ mmol/l, HDL-cholesterol $<1.036$ mmol/l in men or $<1.295$ mmol/l in women, blood pressure $\geq 130/\geq 85$ mmHg or on antihypertensive medication, fasting glucose $\geq 5.6$ mmol/l.\footnote{MetS/IDF was diagnosed as: waist circumference $\geq 94$ cm for men and $\geq 80$ cm for women plus any two of the following four factors: raised triglycerides: $>1.695$ mmol/l, or specific treatment for this lipid abnormality, reduced HDL-cholesterol: $<1.036$ mmol/l in males and $<1.295$ mmol/l in females, or specific treatment for this lipid abnormality, raised blood pressure: blood pressure $\geq 130/85$ mm Hg, or treatment of previously}
diagnosed hypertension, raised fasting plasma glucose ≥5.6 mmol/L, or previously diagnosed type 2 diabetes.
SUPPLEMENTAL RESULTS

MetS definitions and 6-year progression of IMT

The rate of IMT progression was increased in subjects with MetS compared to subjects without MetS (Figure IA). Figure IB shows the mean values for the 6-year IMT progression after adjusting for age, sex, and baseline IMT. The differences in IMT progression remained significant for all three MetS groups (Figure IC) when further adjusting for risk factors not included in the MetS definition (smoking, CRP, LDL-cholesterol and family history of coronary disease).

Changes in MetS prevalence, waist circumference, and insulin levels by age.

Figure II shows the prevalence of MetS stratified according to the age groups of 24 to 45-year-olds in study years 2001 and 2007 according to the MetS/EGIR classification. In men, the prevalence of MetS increased linearly by age both in 2001 (P<0.0001) and 2007 (P=0.01). Whereas in women, no such age trend was observed (in 2001, P=0.88; in 2007 P=0.66).

Figure III shows trends of waist circumference and insulin levels among study subjects during 2001 and 2007. Waist circumference increased significantly by age in both study years and in both sexes (P always <0.0001). The age trend in serum insulin level was non-significant in analysis when sexes were pooled.

Associations between baseline and the 6-year change in study variables

As shown in Figure IV, there was an inverse association between baseline IMT (in 2001) and 6-year change in IMT (2001-2007). For continuous IMT variables, the correlation coefficient between baseline IMT and ΔIMT was r=-0.39 (P<0.0001). Similarly, we observed a significant inverse associations between baseline and 6-year Δ-values for CRP (r=-0.71, P<0.0001), LDL-cholesterol (r=-0.48, P<0.0001), HDL-cholesterol (r=-0.32, P<0.0001), systolic blood pressure (r=-0.29,
P<0.0001), glucose (r=-0.31, P<0.0001), BMI (r=-0.10, P<0.0001), and height (r=-0.08, P=0.0005).

These associations are consistent with the regression to the mean phenomenon\(^4\).
SUPPLEMENTAL FIGURE LEGENDS

Figure I
A) Mean±SEM values of IMT progression in subjects with and without MetS.
B) Comparison of IMT progression in subjects with and without MetS after adjusting for age, sex, and baseline IMT.
C) IMT progression values between subjects with and without MetS after further adjustment for smoking, LDL-cholesterol, CRP and family history of coronary disease.

Figure II
Details (percentages) about MetS/EGIR prevalence in men and women in 2001-2007

Figure III
Waist circumference and insulin levels (Mean±SEM) in 2001 and 2007 according to age.

Figure IV
The mean values of IMT progression according to baseline IMT quintiles.
SUPPLEMENTAL FIGURES

Figure I

A

B
C

Change in IMT (μm)

MetS/EGIR  MetS/revNCEP  MetS/IDF

MetS
No  Yes

P<0.0001  P=0.0005  P<0.0001
Figure II

A

B
Figure III

A

P-value 0.0002

B

P-value 0.77
Figure IV

![Bar chart showing IMT change (μm) with baseline IMT and P<0.0001 for trend](chart)

- Baseline IMT:
  - I: N=391
  - II: N=349
  - III: N=377
  - IV: N=339
  - V: N=353

P<0.0001 for trend
SUPPLEMENTAL REFERENCES


