Sex Differences in the Relationship of Risk Factors to Subclinical Carotid Atherosclerosis Measured 15 Years Later
The Tromsø Study

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Background and Purpose—Ultrasound measurement of carotid artery intima-media thickness (IMT) is regarded as a valid index of atherosclerosis. Determinants of IMT in cross-sectional studies have been established, but the long-term relationship between cardiovascular risk factors and subclinical atherosclerosis has not been investigated thoroughly.

Methods—We included in the study 3128 middle-aged men and women in Tromsø, Norway, who in 1980 attended the baseline examination with measurements of cardiovascular risk factors and who underwent carotid ultrasonography after 15 years of follow-up.

Results—Age, blood pressure, total cholesterol, HDL cholesterol, and body mass index were independent long-term predictors of IMT in both men and women. Triglyceride levels were associated with an increase in IMT in women only, while physical activity and smoking were predictors of IMT in men only. However, smoking was associated with increased risk of having atherosclerotic plaque in both men and women. There were no differences in the strength of risk factor effects on IMT in the common carotid artery and the carotid bifurcation.

Conclusions—The present study indicates that established cardiovascular risk factors are independent predictors of subclinical atherosclerosis measured after 15 years of follow-up. However, there may be significant sex differences in the relationship between triglycerides, smoking, and physical activity and the risk of atherosclerosis. (Stroke. 2000;31:574-581.)

Key Words: atherosclerosis ■ carotid arteries ■ follow-up studies ■ risk factors ■ ultrasonography

Clinical cardiovascular disease represents the interaction of different pathophysiological mechanisms, such as the development of atherosclerosis, the acute occlusion usually caused by thrombosis, and the susceptibility to myocardial ischemia, all of which may have different risk factors. High-resolution B-mode ultrasonography provides a noninvasive method of quantifying subclinical arterial wall thickening and atherosclerotic progression, and ultrasound therefore makes it possible to conduct population-based studies focusing specifically on the determinants of subclinical atherosclerosis. An increased carotid artery intima-media thickness (IMT) has in cross-sectional studies been associated with unfavorable cardiovascular risk factor levels,1-3 prevalent cardiovascular disease,4 and atherosclerosis in other parts of the arterial system,5 indicating that carotid artery IMT may be regarded as a valid index of generalized atherosclerosis. Furthermore, several studies have shown an association between carotid artery IMT and incidence of myocardial infarction and stroke.6 Because ultrasound measures the dependent variable on a continuous scale, the power to quantify the effect of risk factors, as well as interaction among risk factors, is increased in ultrasound studies compared with studies in which the end point is defined only by the presence or absence of clinical disease.

Atherosclerosis is a gradually developing disease, and single measurements of cardiovascular risk factors at the time of IMT measurements may not accurately reflect a person’s past exposure to those risk factors. Prospective data on risk factors for IMT in general populations are very limited. A 5-year follow-up study of predictors of IMT in elderly subjects has been published,7 and another study examined the association between previous smoking and IMT in middle-aged subjects.8 However, no population-based longitudinal study has examined the long-term effect of blood pressure, serum lipids, body mass index, and physical activity on IMT in middle-aged subjects.

We examined determinants of ultrasonographically measured IMT in a 15-year follow-up study of 3128 middle-aged men and women.

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Attending (n=1860)</th>
<th>Not Attending (n=378)</th>
<th>Attending (n=1385)</th>
<th>Not Attending (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46.6 (4.4)</td>
<td>46.7 (4.5)</td>
<td>44.3 (2.9)</td>
<td>44.1 (2.8)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>132.0 (14.8)</td>
<td>135.3 (17.7)‡</td>
<td>127.2 (16.3)</td>
<td>129.3 (17.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85.3 (10.2)</td>
<td>87.8 (10.7)‡</td>
<td>82.3 (9.5)</td>
<td>84.7 (11.0)†</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.59 (1.24)</td>
<td>6.66 (1.19)</td>
<td>6.36 (1.20)</td>
<td>6.45 (1.34)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.49 (0.49)</td>
<td>1.54 (0.55)</td>
<td>1.83 (0.43)</td>
<td>1.81 (0.43)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.72 (0.99)</td>
<td>1.64 (0.93)</td>
<td>1.15 (0.63)</td>
<td>1.22 (0.58)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.0 (2.8)</td>
<td>24.9 (3.0)</td>
<td>23.9 (3.5)</td>
<td>24.5 (4.3)*</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>47.2</td>
<td>62.4‡</td>
<td>38.3</td>
<td>47.7*</td>
</tr>
<tr>
<td>No. of cigarettes smoked daily</td>
<td>13</td>
<td>15*</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Physical activity in leisure time, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedentary</td>
<td>18.9</td>
<td>28.4‡</td>
<td>18.6</td>
<td>20.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>52.0</td>
<td>46.4</td>
<td>67.6</td>
<td>71.5</td>
</tr>
<tr>
<td>High</td>
<td>29.2</td>
<td>25.2</td>
<td>13.6</td>
<td>7.8*</td>
</tr>
<tr>
<td>History of CVD, %</td>
<td>2.3</td>
<td>4.2*</td>
<td>1.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Values are mean (SD) and percentages. CVD indicates cardiovascular disease. *P<0.05; †P<0.01; ‡P<0.001 compared with attenders.

Subjects and Methods

Study Design and Subjects

The Tromsø Study is a single-center prospective follow-up study of inhabitants in the municipality of Tromsø, Norway. The main focus is on cardiovascular diseases. The study design includes repeated population health surveys to which total birth cohorts and random samples are invited. The University of Tromsø conducted all surveys in cooperation with the National Health Screening Service.

The study subjects were men and women who participated in the 1979–1980 (baseline) and the 1994–1995 (follow-up) surveys of the Tromsø population. At baseline all men born in 1925–1959 and all women born in 1930–1959 were invited, and 16,621 subjects (78% of those who were invited) attended. In 1994–1995 all subjects born in 1925–1939 who attended the baseline survey and who were still living in the community (n=3816) were invited to a follow-up survey that included ultrasonic examination of the carotid arteries. A total of 3245 subjects (85% of the eligible population) attended the follow-up survey (Table 1). After exclusion of 117 subjects with missing ultrasound data, 1804 men and 1324 women were included in the analyses. The Regional Board of Research Ethics approved the study, and each subject gave informed consent.

Ultrasanographic Scanning

IMT measurements of the right carotid artery were obtained with the use of a high-resolution ultrasound Acuson 128 XP/10c ART-upgraded scanner equipped with a linear transducer with 7 MHz in B-mode. Three frozen images of IMT from 3 locations of the carotid artery—the near and far walls of the common carotid artery and the far walls of the bifurcation—were stored on high-resolution videotapes. The ultrasonic images were analyzed offline with a computerized technique for automated ultrasonic image analysis. Measurements of IMT were performed in 10-mm segments, and mean IMT from the 3 preselected images was calculated for each location. Plaques (defined as focal widening of the IMT relative to adjacent segments) located in the common carotid artery, the carotid bifurcation, or the internal carotid artery were registered, and the maximum thickness was measured. Plaques were included in measurements of IMT if located in areas predefined for IMT registrations. The scanning and reading procedures and the reproducibility of the ultrasound measurements have been published previously.

Cardiovascular Risk Factors

Cardiovascular risk factors were assessed at baseline. Height and weight were measured with the subjects in light clothing without shoes. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Personnel trained according to tape recordings produced by the London School of Hygiene and Tropical Medicine measured blood pressure using a mercury sphygmomanometer. After 4 minutes of rest, 2 readings were taken with a 1-minute interval. The lower value is used in this report. A nonfasting blood sample was taken and analyzed at the Department of Clinical Chemistry, University Hospital of Tromsø. Total cholesterol concentration was measured directly by the enzymatic oxidase method with a commercially available kit (Boehringer-Mannheim), and HDL cholesterol was assayed by the same procedure after the precipitation of lower-density lipoprotein with heparin and manganese chloride. Serum triglyceride concentration was enzymatically determined as glyceral (Boehringer 15725, Boehringer-Mannheim). The laboratory was standardized against the World Health Organization Lipid Reference Laboratory in Prague, Czech Republic. Participants were examined about time since last meal. Information about current cigarette smoking, a history of cardiovascular disease (stroke, myocardial infarction, and angina pectoris), and physical activity was obtained from a self-administered questionnaire. Physical activity in leisure time was graded from 1 to 4 according to which of the following categories would best describe the participant’s usual level of physical activity: 1, reading, watching TV, or activities that do not require physical exertion; 2, walking, cycling, or some other form of physical activity for at least 4 hours per week; 3, exercise to keep fit, heavy gardening, etc, for at least 4 hours per week; or 4, regular hard training or participation in competitive sports regularly and several times a week. Because only 40 men and 2 women reported regular hard training (level 4), levels 3 and 4 were merged in the analyses. The questionnaire was checked for logical inconsistencies at the examination. The validity of the responses to the question on smoking has been investigated in 140 randomly selected men. The mean±SD level of serum thiocyanate was 109.9±46.7 and 45.9±32.7 μmol/L in smokers and nonsmokers, respectively. The question on physical activity in this study has been widely used in Scandinavian studies and has been found to segregate groups according to an objective measure of physical fitness. In a random sample (n=609) from the Tromsø Study...
population, self-reported physical activity in leisure time was positively associated ($P<0.001$ in both sexes) with physical fitness as measured by bicycle ergometry.\textsuperscript{12}

### Statistical Analysis

Analyses were done separately for men and women. The average of the mean IMT in the 3 locations (ie, the near and far walls of the common carotid artery and the far wall of the bifurcation) was calculated and is used as the dependent variable in the analyses unless otherwise specified. All subjects included in the analyses ($n=3128$) had valid IMT measurements from the near and the far walls of the carotid bifurcation, and 2958 subjects (95\%) had valid IMT measurements from the near and the far walls of the common carotid artery.

Values of triglycerides were log transformed. Number of pack-years of smoking was assessed by dividing number of cigarettes smoked daily at baseline by 20 and multiplying by number of years of smoking. Number of pack-years of smoking was assessed by dividing number of cigarettes smoked daily at baseline by 20 and multiplying by number of years of smoking at baseline. Differences in mean values of baseline characteristics between attenders and nonattenders were tested for statistical significance by $t$ tests. Age-adjusted regression coefficients were calculated to estimate the effect of risk factors on IMT, and multiple linear regression analysis was used to assess independent relationships. To test for interaction with sex, a pooled multiple linear regression analysis was run including the following interaction terms: sex$\times$HDL cholesterol, sex$\times$triglycerides, sex$\times$smoking, and sex$\times$physical activity. Adjustment for time since last meal did not change coefficients notably. Residual analysis of univariate and multivariate regression models confirmed that model assumptions were met. The difference between the regression coefficients was tested for statistical significance by $Z$ tests. Age-adjusted mean values of IMT within strata were calculated with ANCOVA. Two-sided $P$ values $<0.05$ were considered statistically significant. SAS statistical software package version 6.12 was used.\textsuperscript{13}

### Results

Table 1 shows baseline characteristics among those who attended and those who did not attend the follow-up examination. Nonattenders had slightly higher blood pressure than attenders, and the percentage of current smokers was higher among nonattenders than attenders (Table 1). In general, men had a more unfavorable risk factor profile than women. The mean values of IMT in different locations of the carotid artery are given in Table 2. Men had higher IMT values than women in all locations (all $P<0.0001$).

Table 3 shows age-adjusted effects of risk factors on IMT. There were no significant differences in effect of risk factors on IMT among the segments of the carotid artery. Age was a strong determinant of IMT in both sexes. Systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, and body mass index were significantly associated with IMT in both men and women. HDL cholesterol and triglycerides had a greater effect on IMT in women than in men (Table 3) ($P=0.049$ and $P=0.068$ for sex difference in mean values of 3 locations, respectively). Figure 1 illustrates the independent effects of total cholesterol and systolic blood pressure on IMT. The slope for total cholesterol on IMT did not differ significantly across tertiles of systolic blood pressure (data not shown). Smoking was not associated with IMT in women, whereas a strong association was seen in men (Table 3) ($P=0.0007$ for sex difference in mean values of 3 locations). Furthermore, in men there was a linear increase in IMT across groups of never smokers, former smokers, and current smokers ($P<0.001$ for linear trend), and there was a linear dose-response relationship between the number of cigarettes smoked per day and IMT ($P<0.001$ for linear trend) (Figure 2). In contrast, in women there was no apparent adverse effect of smoking on IMT except in those women who smoked $\geq$20 cigarettes per day, suggesting a threshold effect of smoking on IMT in these middle-aged women (Figure 2). Furthermore, there was a linear dose-response relationship between increasing number of pack-years of smoking and IMT in men ($P<0.001$) but not in women ($P=0.20$) (data not shown). However, the age-adjusted odds ratio (95\% CI) for carotid plaque in smokers compared with nonsmokers was highly significant both in women (1.85 [1.47 to 2.32]) and in men (1.91 [1.58 to 2.32]). These odds ratios did not change notably after adjustment for systolic blood pressure.
pressure, total cholesterol, HDL cholesterol, body mass index, and physical activity. Physical activity during leisure time was associated with lower IMT in men but not in women (Table 3) (P = 0.012 for sex difference in mean values of 3 locations).

Table 4 shows determinants of IMT in a multiple linear regression model stratified by sex. There were no significant differences in independent effect of risk factors on IMT among the segments of the carotid artery. However, the R^2 of the full model was highest when mean IMT of 3 locations was used as the dependent variable, and R^2 was lower for the bifurcation than for the common carotid artery. Age, systolic blood pressure, total cholesterol, HDL cholesterol, and body mass index were strong independent predictors of IMT in both men and women. Triglycerides were independently associated with IMT when we controlled for HDL cholesterol level in women only (P = 0.08 for interaction with sex). The significant age-adjusted association between triglycerides and IMT in men (Table 3) was attenuated in multivariate analysis, mainly by the inclusion of HDL cholesterol and total cholesterol in the regression model (Table 4). However, even when we excluded total cholesterol and HDL cholesterol from the regression model, triglycerides remained a nonsignificant predictor for IMT in men, suggesting that the sex difference in effect of triglycerides on IMT is not a result of sex differences in metabolic interrelationships among serum lipids. Smoking and physical inactivity were significant predictors of IMT in men but not in women (P = 0.0003 and P = 0.029 for interaction with sex, respectively). When systolic blood pressure was exchanged with diastolic blood pressure in the model, diastolic blood pressure was independently associated with IMT in both men and women (data not shown). These results were not altered when we excluded from the analysis 338 men and 92 women with prevalent cardiovascular disease at follow-up.

There was an additive effect of risk factors on IMT (Figure 3). When current smoking was added to hypertension, the IMT increased significantly compared with subjects exposed to hypertension (P = 0.006) or current smoking (P < 0.0001) only. Similarly, subjects with the combination of hypercholesterolemia and current smoking had higher IMT values than subjects with hypercholesterolemia (P = 0.007) or current smoking (P = 0.001) only. Subjects exposed to all 3 risk factors had the highest IMT. Similar results were found in sex-specific analyses (data not shown).

**Discussion**

The present study shows significant sex differences in the effect of triglycerides, smoking, and physical activity on subclinical atherosclerosis in middle-aged men and women in a 15-year population-based follow-up study. Furthermore,
age, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and body mass index were independent long-term predictors of IMT in both sexes. Our findings are of importance in the view of the etiology of atherosclerosis and cover a field in cardiovascular research that has not been dealt with very often.

The association of exposure in 1980 with atherosclerosis in 1994–1995 suggests that exposure is likely to have preceded wall thickening, although the absence of wall thickness measurements at baseline makes it impossible to firmly establish a temporal relationship between cardiovascular risk factors and IMT. Atherosclerosis is a chronic disease that develops over a long time as a consequence of past and persistent atherogenic exposures. Associations with past exposures are more consistent with a biologically plausible process of atherogenesis than associations with current exposures. The use of noninvasively determined carotid IMT rather than clinically defined atherosclerotic disease as the outcome measure makes selection bias less likely.

Whether increased carotid IMT itself reflects atherosclerosis is still subject to debate. It has been suggested that IMT <1.0 mm merely reflects an adaptive response of the vessel wall to changes in shear and tensile stress. Still, several cross-sectional studies have shown that increased IMT may be a marker of atherosclerosis elsewhere in the arterial system, and findings from prospective studies indicate that increased IMT confers an increased risk of future cerebrovascular and cardiovascular diseases. There appears to be no clear cutoff point above which the risk increases more rapidly. Thus, even if low values of IMT may not represent local atherosclerosis, measurement of IMT may be used as a marker of the total burden of atherosclerosis present in the individual, and it may serve as a graded marker for future risk of clinical cardiovascular disease.

Several population-based studies have found cross-sectional associations between IMT and unfavorable levels of systolic blood pressure, total cholesterol, HDL cholesterol, body mass index, and smoking. Previous prospective stud-

### TABLE 4. Determinants of Mean IMT by Multiple Linear Regression in Men (n=1804) and Women (n=1324): The Tromsø Study

<table>
<thead>
<tr>
<th>Age</th>
<th>Systolic blood pressure</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
<th>Triglycerides</th>
<th>Current smoking (no/yes)</th>
<th>Body mass index</th>
<th>Physical activity (3 levels)</th>
<th>Adjusted R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of 3 Locations</td>
<td>Far Wall Common Carotid Artery</td>
<td>Far Wall Carotid Bifurcation</td>
<td>Far Wall Common Carotid Artery</td>
<td>Far Wall Carotid Bifurcation</td>
<td>Far Wall Common Carotid Artery</td>
<td>Far Wall Carotid Bifurcation</td>
<td>Far Wall Common Carotid Artery</td>
<td>Far Wall Carotid Bifurcation</td>
</tr>
<tr>
<td>Mean of 3 Locations</td>
<td>Far Wall Common Carotid Artery</td>
<td>Far Wall Carotid Bifurcation</td>
<td>Far Wall Common Carotid Artery</td>
<td>Far Wall Carotid Bifurcation</td>
<td>Far Wall Common Carotid Artery</td>
<td>Far Wall Carotid Bifurcation</td>
<td>Far Wall Common Carotid Artery</td>
<td>Far Wall Carotid Bifurcation</td>
</tr>
<tr>
<td>Age</td>
<td>0.040±0.004†</td>
<td>0.032±0.004†</td>
<td>0.045±0.007†</td>
<td>0.009±0.004*</td>
<td>0.022±0.008‡</td>
<td>0.013±0.004†</td>
<td>0.010±0.005*</td>
<td>0.014±0.007</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.020±0.004†</td>
<td>0.022±0.005‡</td>
<td>0.028±0.008‡</td>
<td>0.008±0.004*</td>
<td>0.002±0.009</td>
<td>0.012±0.004†</td>
<td>0.006±0.005*</td>
<td>0.006±0.009</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.013±0.004†</td>
<td>0.010±0.005*</td>
<td>0.022±0.008‡</td>
<td>0.016±0.008</td>
<td>0.002±0.009</td>
<td>0.012±0.004†</td>
<td>0.006±0.005*</td>
<td>0.006±0.009</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>−0.009±0.004*</td>
<td>−0.008±0.004</td>
<td>−0.016±0.008</td>
<td>−0.024±0.008†</td>
<td>−0.014±0.004*</td>
<td>−0.012±0.005†</td>
<td>−0.012±0.005*</td>
<td>−0.017±0.009</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.002±0.004</td>
<td>0.002±0.005</td>
<td>0.002±0.009</td>
<td>0.008±0.008</td>
<td>0.002±0.006</td>
<td>0.012±0.003‡</td>
<td>0.012±0.003‡</td>
<td>0.016±0.006*</td>
</tr>
<tr>
<td>Current smoking (no/yes)</td>
<td>0.049±0.008‡</td>
<td>0.046±0.009†</td>
<td>0.067±0.016‡</td>
<td>0.008±0.008</td>
<td>−0.002±0.008</td>
<td>0.012±0.003‡</td>
<td>0.012±0.003‡</td>
<td>0.008±0.015</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.020±0.005‡</td>
<td>0.025±0.005†</td>
<td>0.017±0.009</td>
<td>0.011±0.006</td>
<td>0.003±0.006</td>
<td>0.011±0.006</td>
<td>0.003±0.006</td>
<td>0.002±0.012</td>
</tr>
<tr>
<td>Physical activity (3 levels)</td>
<td>−0.012±0.006*</td>
<td>−0.013±0.007</td>
<td>−0.015±0.012</td>
<td>0.011±0.006</td>
<td>0.003±0.006</td>
<td>0.011±0.006</td>
<td>0.003±0.006</td>
<td>0.002±0.012</td>
</tr>
</tbody>
</table>

Values are regression coefficients±SE (expressed in millimeters) for a 1-SD change in continuous variables, for a 1-unit change in physical activity, and for presence/absence of smoking.

*P<0.05; †P<0.01; ‡P<0.001.
ies have revealed age, smoking, LDL cholesterol, and triglycerides to be predictors of IMT progression.\textsuperscript{16–18} However, these studies were performed on selected populations with short follow-up time (2 to 3 years). Information about the effect of risk factors on IMT in long-term population-based longitudinal studies is scarce.\textsuperscript{7,8,19} A 5-year follow-up study reported that age and pack-years of smoking were independent predictors of IMT in men, while age and systolic blood pressure were associated with IMT in women.\textsuperscript{7}

**Triglycerides and IMT**

An inconsistent association between triglycerides and IMT has been reported in cross-sectional studies,\textsuperscript{1,2,20} and progression of IMT has been found to correlate with changes in levels of triglyceride-rich lipoproteins.\textsuperscript{17} However, the role of serum triglycerides as a risk factor for coronary heart disease remains controversial, partly because multivariate analyses controlling for HDL cholesterol usually reduce the strength of triglycerides in predicting coronary heart disease. Findings from the present study suggest an association between subclinical atherosclerosis and triglycerides independent of HDL cholesterol levels in women but not in men. Supportive of our findings, a meta-analysis of prospective studies reported a stronger association between plasma triglyceride levels and risk of clinical cardiovascular disease in women than in men.\textsuperscript{21}

**Smoking and IMT**

Results from the present study indicate that the effect of current smoking on IMT was strong in men, while a threshold effect of smoking on IMT in women was found. In a study from the Atherosclerosis Risk in Communities (ARIC) cohort of 2073 subjects aged 31 to 52 years at baseline, active smoking was associated with increased IMT 12 to 14 years later.\textsuperscript{8} They found an effect of smoking in both sexes, but the difference in IMT between never smokers and subjects smoking at both baseline and follow-up appeared to be greater in men than in women (0.162 versus 0.072 mm, respectively). Furthermore, a 5- to 8-year longitudinal study of 200 women aged 42 to 50 years at baseline found a positive association between smoking and IMT.\textsuperscript{22} In contrast, a 5-year follow-up of 1106 subjects aged 55 to 74 years at baseline reported no association between smoking and IMT in women, while a strong association was found in men.\textsuperscript{7} Conflicting results regarding the effect of smoking on IMT in women have also been reported from cross-sectional studies.\textsuperscript{20,23} Differences in age distributions in the study samples, sample sizes, and different methods in assessment of smoking status and IMT measurements may be related to the inconsistent findings.

Sex-related differences in the effect of smoking could be related to different smoking frequencies or possible sex-specific smoking habits. A misclassification of smoking status due to sex differences in smoking cessation during follow-up could possibly explain the differences between men and women. We were able to explore this indirectly because smoking status was also registered at the follow-up examination. The number of cigarettes smoked daily was similar at baseline and follow-up in both sexes, and more men than women reported to have quit smoking since the baseline examination (17\% versus 9\%; $P<0.001$). Thus, misclassification of the exposure variable is unlikely to explain the sex differentials.

Interestingly, we observed in women that whereas smoking was not associated with IMT, smoking was strongly associated with risk of having atherosclerotic plaque. It has been suggested that IMT (diffuse thickening) and plaques (localized thickening) are 2 related but not identical components in the development of atherosclerosis and that some risk factors may have different effects on IMT and on plaque development.\textsuperscript{24} Hormone replacement therapy has been associated with increased thickness of the carotid artery media layer and hence the IMT.\textsuperscript{23} Furthermore, a recent article reported that pregnant women had a thicker media layer than nonpregnant fertile controls,\textsuperscript{26} suggesting that endogenous estrogens also have a media-thickening effect (because of changes in the content of connective tissue). Therefore, it may be hypothesized that in the middle-aged women in the present study, smoking could in fact decrease thickness of the intima-media complex because of the well-known antiestrogenic effect of smoking.\textsuperscript{27} In the present study female smokers actually had a slightly thinner IMT than female nonsmokers (0.753 mm [SE, 0.007] versus 0.765 mm [SE, 0.005]), respectively, when subjects with plaques were excluded from the analyses ($P=0.15$ for difference between groups). Our data therefore indicate that in women, smoking, in addition to promoting atherosclerosis in the vessel wall intima layer, may also weaken the media layer of the vessel wall, placing smoking women at particular risk for cardiovascular events associated with weakening or rupture of the vessel wall, such as cerebral hemorrhage and abdominal aortic aneurysms. In fact, unpublished data from our group (K. Singh, K.H. Botnaa, et al, unpublished data, 1999) show that current smoking carries significantly greater relative risk of abdominal aortic aneurysm in women than in men.

**Physical Activity and IMT**

In men, physical activity has been associated with a decreased risk of cardiovascular disease morbidity and mortality,\textsuperscript{28,29} while studies in women have produced mixed results.\textsuperscript{29,30} The effect of physical activity on IMT has previously not been examined in prospective studies. A cross-sectional analysis from the ARIC study\textsuperscript{31} showed that physical activity at work was a protective factor for IMT in both sexes but slightly stronger in men than in women. No effect on IMT was found for physical activity during leisure time and in sport. In the present longitudinal study we found an independent protective effect of leisure time physical activity on IMT in men but not in women (Tables 2 and 3). Paffenbarger et al\textsuperscript{32} suggested that the explanation for a lack of an association between increased activity and decreased coronary heart disease risk in some studies was the low activity level in the so-called active group. In our study men were more physically active than women, and it is possible that the activity level among women was too low to show a benefit. There is a possibility of a greater degree of misclassification among women compared with men in the sedentary groups, because women classified as sedentary probably still attend to activities like...
housework and gardening. Furthermore, a sex difference in change of level of physical activity during follow-up could be present. Another possible explanation for the lack of protection of physical activity on IMT in women could be that the benefit of exercise is mediated by improving levels of something women already have, such as high levels of HDL cholesterol. However, in women there was no significant association between physical activity and IMT within strata of HDL cholesterol (data not shown).

**Blood Pressure and IMT**

Progression of atherosclerosis reduces the compliance of the aorta and large arteries, which may lead to an increase in systolic blood pressure and a decrease in diastolic blood pressure. The time-dependent relation between atherosclerosis, reduced arterial compliance, and systolic hypertension cannot be determined in cross-sectional studies. In our study there was a strong association between baseline systolic blood pressure and subclinical atherosclerosis determined after 15 years follow-up, indicating that systolic blood pressure is a precursor of atherosclerosis. The effect of blood pressure was independent of cholesterol levels (Figure 1), suggesting that blood pressure may promote atherosclerosis through mechanisms other than by causing endothelial injury and thereby promoting more rapid influx of cholesterol into the arterial wall.

**Multiple Risk Factors**

The possible additive effect of risk factors on IMT has to our knowledge not been investigated previously. We found that mean IMT in the carotid arteries increased markedly in subjects with multiple risk factors. This finding is supported by a recent autopsy study in which the severity of atherosclerosis in young people increased with increasing number of cardiovascular risk factors and by results from the Framingham Study indicating that multiple risk factors have a synergistic effect on development of morbidity and mortality from coronary heart disease.

**Segment-Specific Analyses of IMT**

In the present study segment-specific analyses revealed no differences in the strength of associations between risk factors and IMT in the common carotid artery and the carotid bifurcation. This finding is supported by similar results from a recent report in which both near and far walls of the common carotid artery only were related to IMT. Smoking was associated with IMT in the bifurcation/internal carotid artery only.

Restricting measurements of IMT to the common carotid segment has been justified by the greater reproducibility of measurements from this site and the difficulty in obtaining measurements from the bifurcation or the internal carotid artery in some populations. In the present study virtually all subjects examined had valid IMT measurements from both the common carotid artery and the carotid bifurcation. Protocols that involve additional segments have several advantages. First, plaques are more often found in the bifurcation and the internal carotid artery. Thus, including these sites may provide the most sensitive and statistically powerful assessment of atherosclerosis. Second, aggregating data across segments may provide measures that are stable and less sensitive to measurement error.

In conclusion, findings from the present study indicate that established cardiovascular risk factors are independent predictors of subclinical atherosclerosis in a 15-year longitudinal population-based study. Furthermore, our data point to significant sex differences in the effect of triglycerides, physical activity, and smoking on IMT.

**Acknowledgment**

This study was supported by grants from the Norwegian Research Council.

**References**


Sex Differences in the Relationship of Risk Factors to Subclinical Carotid Atherosclerosis Measured 15 Years Later: The Tromsø Study
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Stroke. 2000;31:574-581
doi: 10.1161/01.STR.31.3.574

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/31/3/574

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