

## Cardiorespiratory Fitness and the Progression of Carotid Atherosclerosis in Middle-Aged Men

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**Background:** Good cardiorespiratory fitness has been associated with reduced risk for clinical events of atherosclerotic vascular diseases, but whether it is related to slower progression of early atherosclerosis is unclear.

**Objective:** To study the association between cardiorespiratory fitness and the progression of early carotid atherosclerosis.

**Design:** 4-year follow-up study.

**Setting:** Eastern Finland.

**Participants:** Population-based sample of 854 men 42 to 60 years of age.

**Measurements:** Maximal oxygen uptake ( $\text{Vo}_2\text{max}$  [mL/kg per minute]) was measured directly by using respiratory gas exchange in a cycle ergometer exercise test. Carotid atherosclerosis was assessed by using B-mode ultrasonography.

**Results:** After adjustments for age, technical covariates, and cigarette smoking,  $\text{Vo}_2\text{max}$  had strong, inverse, and graded associations with 4-year increases in maximal intima-media thickness (IMT) (standardized regression coefficient  $\beta = -0.120$ ;  $P =$

0.002), plaque height ( $\beta = -0.140$ ;  $P < 0.001$ ), surface roughness ( $\beta = -0.147$ ;  $P < 0.001$ ), and mean IMT ( $\beta = -0.080$ ;  $P = 0.035$ ). These associations weakened but remained statistically significant after additional adjustment for systolic blood pressure, serum levels of apolipoprotein B, diabetes, and plasma fibrinogen levels. The increases in maximal IMT, surface roughness, and mean IMT (23%, 31%, and 100%, respectively) were larger among men in the lowest quartile of  $\text{Vo}_2\text{max}$  (<26.1 mL/kg per minute) than among those in the highest quartile (>36.2 mL/kg per minute).

**Conclusions:** Good cardiorespiratory fitness is associated with slower progression of early atherosclerosis in middle-aged men. These findings are important because they emphasize that middle-aged men can be evaluated for cardiorespiratory fitness to estimate their future risk for atherosclerotic vascular diseases. Additional research is warranted to investigate a possible causal relationship between cardiorespiratory fitness and atherosclerosis.

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**A**ccumulating epidemiologic and clinical evidence indicates that physical inactivity and poor cardiorespiratory fitness are major risk factors for atherosclerotic vascular diseases. The increased risk is similar to that seen for conventional modifiable risk factors, including hypercholesterolemia, cigarette smoking, and hypertension (1). Physical inactivity, which causes an estimated 12% of all deaths in the United States, is currently considered one of the most important public health problems (1). In prospective population studies, regular physical activity (2-6) and good cardiorespiratory fitness (6-9), as well as increased physical activity (10) and improved cardiorespiratory fitness (11), have been associated with reduced risk for clinical events of atherosclerotic vascular diseases. Clinical trials have provided additional evidence for the antiatherogenic effect of regular physical activity and good cardiorespiratory fitness. Physical activity alone (12), physical activity combined with a low-fat diet (13, 14) or comprehensive lifestyle modification (15-17), together with concomitant im-

provement in cardiorespiratory fitness, slows the progression of angiographically quantified coronary atherosclerosis in patients with coronary heart disease.

Atherosclerosis in the human arteries develops from an asymptomatic phase to a manifest disease over decades. The occurrence of clinically significant atherosclerotic lesions and consequent symptomatic atherosclerotic vascular diseases increases progressively in middle age. Ultrasonography of the arteries allows noninvasive investigation of preclinical stages of atherosclerosis in unselected human populations (18, 19). When assessed by ultrasonography, carotid intima-media thickening—which is related to an atherogenic risk factor profile, increased prevalence of coronary and peripheral atherosclerosis, and increased incidence of coronary heart disease and stroke (18-21)—is regarded as a valid indicator of generalized atherosclerosis.

In some cross-sectional population-based studies, regular physical activity (22, 23) and good cardiorespiratory fitness (24) have been associated with reduced

prevalence of early atherosclerosis, as indicated by ultrasonographically assessed carotid intima-media thickening. However, no prospective evidence from population-based studies shows that physical activity or good cardiorespiratory fitness is related to slower progression of early atherosclerosis. We therefore investigated the associations of cardiorespiratory fitness and physical activity with the progression of carotid atherosclerosis in a population-based sample of middle-aged men. Cardiorespiratory fitness was evaluated by directly measuring maximal oxygen uptake ( $\text{VO}_2\text{max}$ ), and physical activity was assessed by using a detailed quantitative questionnaire. Atherosclerosis in the common carotid arteries was assessed over a 4-year period by using high-resolution B-mode ultrasonography to evaluate maximal intima-media thickness (IMT), plaque height, surface roughness, and mean IMT.

## METHODS

### Participants

We studied participants in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), an ongoing population study designed to investigate risk factors for atherosclerotic vascular diseases and related outcomes. The study involves men from eastern Finland (25), an area known for its high prevalence and incidence of atherosclerotic vascular diseases (26). The study group is a representative sample of men who lived in the town of Kuopio or neighboring rural communities and were 42, 48, 54, or 60 years of age at baseline examinations between March 1984 and December 1989. Of 3235 eligible men, 2682 (82.9%) participated. The KIHD was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland. Each participant gave written informed consent.

A total of 1229 men who had undergone ultrasonographic examination of the common carotid arteries in the KIHD baseline study between February 1987 and December 1989 were invited to participate in the KIHD 4-year follow-up study. Of the invited men, 1038 (84.5%) participated; 107 declined; 52 could not participate because of death, severe illness, or relocation; and 32 could not be contacted. Of the 1038 participants, 184 had missing baseline data on some of the study variables. Our study is based on the remaining 854 men who had complete data on all study variables.

Of these 854 men, 73 were in the pravastatin treatment group in the Kuopio Atherosclerosis Prevention Study (KAPS) between 1990 and 1993 (27).

### Assessment of Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed in the baseline study between August 1986 and December 1989 by use of a maximal but symptom-limited exercise test on an electrically braked 400 L-cycle ergometer (Medical Fitness, Mearns, the Netherlands), as explained in detail elsewhere (6). For safety reasons, and to obtain reliable information about exercise test variables, the tests were supervised by an experienced physician with the assistance of an experienced nurse. The exercise tests were performed between 8:00 a.m. and 10:00 a.m. by using a standardized testing protocol, which called for a linear increase in the workload by 20 W/min. Oxygen consumption was measured by using the breath-by-breath method of respiratory gas exchange (Medical Graphics, St. Paul, Minnesota). The  $\text{VO}_2\text{max}$  was defined as the highest value for or the plateau in oxygen uptake and was indexed by body weight (mL/kg per minute).

### Assessment of Physical Activity

Physical activity was assessed in the baseline study between August 1986 and December 1989 by using the KIHD 12-Month Leisure-Time Physical Activity History, as explained elsewhere (6, 28). This detailed quantitative questionnaire deals with the most common physical activities of middle-aged Finnish men and enables the assessment of all components of physical activity, including energy expenditure, duration, frequency, and mean intensity (28). Physical activity was categorized according to type: 1) conditioning physical activity (walking; jogging; cross-country skiing; bicycling; swimming; rowing; ball games; and gymnastics, dancing, or weightlifting), 2) nonconditioning physical activity (crafts, repairs, or building; yard work, gardening, farming, or shoveling snow; hunting, picking berries, or gathering mushrooms; fishing; and forest work) and 3) walking or bicycling to work.

### Assessment of Carotid Atherosclerosis

The extent and severity of carotid atherosclerosis were assessed in the baseline study between February 1987 and December 1989 and in the 4-year follow-up

study between March 1991 and December 1993. High-resolution B-mode ultrasonography was used to examine a 1.0- to 1.5-cm section at the distal end of the left and right common carotid artery proximal to the carotid bulb, as explained in detail elsewhere (18). Time from the baseline exercise test to baseline carotid ultrasonography was less than 1 month (range, 0 to 812 days) for 94% of the men. The ultrasonographers and the exercise testers were blinded with regard to each other's findings. Average time from baseline to follow-up carotid ultrasonography was 4.2 years (range, 3.8 to 5.2 years).

Four indicators of carotid atherosclerosis were used in our study: 1) the maximal IMT (the average of the maximal IMT values from the right and left common carotid arteries, an indicator of how deep the intima-media layer protruded into the lumen), 2) plaque height (the average of the differences between the maximal and minimal IMT of the right and left common carotid arteries, an indicator of how steeply atherosclerotic lesions protruded into the lumen), 3) surface roughness (the standard deviation of the approximately 100 IMT measurements from the right and left common carotid arteries, an indicator of variability in IMT [for example, roughness of the surface of the artery wall]), and 4) the mean IMT (the mean of the approximately 100 IMT values from the right and left common carotid arteries, an overall indicator of atherosclerosis).

The baseline IMT recordings were classified into four categories according to their severity: 1) no atherosclerotic lesion, 2) intima-media thickening (a distance of >1.0 mm between the lumen-intima and the media-adventitia interfaces), 3) a nonstenotic plaque (a distinct area of mineralization or focal protrusion into the lumen), and 4) a large stenotic plaque (obstruction of >20% of the lumen diameter). A participant was considered to have advanced atherosclerosis if he had a nonstenotic plaque (category 3) or a large stenotic plaque (category 4).

#### Assessment of Other Variables

The examination protocol (25) and the assessment of medical history, medications, cigarette smoking, dietary intake of nutrients (29), blood pressure, body mass index, waist-to-hip ratio (30), and adult socioeconomic status (29) have been described in detail elsewhere. Collection of blood specimens and the measurement of lev-

els of serum lipids and lipoproteins (29), blood glucose, serum insulin (30), and plasma fibrinogen (29) have been presented in detail elsewhere. All of these variables were assessed in the baseline and 4-year follow-up studies.

#### Statistical Analysis

The heterogeneity of the means of baseline variables between the quartiles of  $\text{VO}_2\text{max}$  was tested by using analysis of variance. Baseline risk factors for a 4-year increase in indicators of carotid atherosclerosis were selected by using multiple linear regression analyses. First, each potential risk factor was forced one at a time into a linear regression model with age and technical covariates (examination years, follow-up time, baseline zooming depth given separately for right and left side, baseline indicator of carotid atherosclerosis, baseline sonographer, and pravastatin treatment in KAPS). Second, all baseline risk factors that were statistically significantly associated with a 4-year increase in any of the indicators of carotid atherosclerosis (except those that were strongly correlated with one another, such as serum levels of low-density lipoprotein cholesterol and triglycerides, coronary heart disease, and cardiovascular or pulmonary reasons for stopping the exercise test) were entered simultaneously into the linear regression model by using a stepwise method. A *P* value less than 0.05 was used as a selection criterion, and age and the technical covariates were again forced into the model. From these analyses, we selected as covariates for the fixed analyses only variables that remained statistically significant predictors of a 4-year increase in any of the indicators of carotid atherosclerosis. The heterogeneity of the means of the 4-year increase in these indicators between the quartiles of  $\text{VO}_2\text{max}$  was tested by using covariance analyses, and the linear trend across these quartiles was tested by using multiple linear regression analyses. Statistical analyses were performed by using SPSS 9.0 for Windows (SPSS, Inc., Chicago, Illinois) (31).

#### RESULTS

##### Maximal Oxygen Uptake and Other Baseline Characteristics

The mean  $\pm$  SD of  $\text{VO}_2\text{max}$  was  $31.6 \pm 8.2$  mL/kg per minute (range, 6.4 to 58.0 mL/kg per minute). The means  $\pm$  SD of maximal IMT, plaque height, surface roughness, and mean IMT were  $0.947 \pm 0.231$  mm

Table 1. Baseline Characteristics according to Quartiles of Maximal Oxygen Uptake\*

Characteristic	Quartiles of Maximal Oxygen Uptake				P Value
	<26.1 mL/kg per minute	26.1–30.9 mL/kg per minute	31.0–36.2 mL/kg per minute	>36.2 mL/kg per minute	
Maximal intima-media thickness, mm	1.047 ± 0.300	0.956 ± 0.216	0.916 ± 0.184	0.868 ± 0.162	<0.001
Plaque height, mm	0.430 ± 0.221	0.385 ± 0.164	0.370 ± 0.137	0.356 ± 0.142	<0.001
Surface roughness, mm	0.100 ± 0.053	0.090 ± 0.045	0.085 ± 0.031	0.083 ± 0.032	<0.001
Mean intima-media thickness, mm	0.834 ± 0.207	0.766 ± 0.151	0.737 ± 0.143	0.697 ± 0.119	<0.001
Advanced atherosclerosis, %	48.4	29.0	18.7	10.3	<0.001
Age, y	56.1 ± 5.5	52.6 ± 6.3	50.0 ± 6.2	46.9 ± 5.0	<0.001
Score for adult socioeconomic status†	9.2 ± 3.7	7.6 ± 4.0	7.0 ± 3.4	6.0 ± 4.0	<0.001
Body mass index, kg/m <sup>2</sup>	28.1 ± 3.8	27.1 ± 3.3	26.5 ± 2.9	25.3 ± 2.4	<0.001
Waist-to-hip ratio	0.969 ± 0.056	0.946 ± 0.053	0.934 ± 0.049	0.907 ± 0.064	<0.001
Systolic blood pressure, mm Hg	132.9 ± 17.3	134.4 ± 15.9	131.6 ± 14.7	127.9 ± 12.7	<0.001
Diastolic blood pressure, mm Hg	87.9 ± 10.6	89.7 ± 9.9	88.0 ± 10.2	85.5 ± 9.2	<0.001
Cigarette smoker, %	38.5	34.6	32.4	22.7	<0.001
Cigarette smoking, pack-years	10.7 ± 18.7	8.5 ± 14.4	7.9 ± 14.2	3.6 ± 8.4	<0.001
Dietary intake of vitamin C, mg/d	75.2 ± 42.7	86.3 ± 58.5	85.6 ± 49.9	100.9 ± 49.7	<0.001
Energy expenditure of physical activity, kJ/d	1411 ± 1235	1596 ± 1210	1554 ± 1436	1827 ± 1466	0.012
Mean intensity of physical activity, MET	4.3 ± 0.9	4.5 ± 1.0	4.5 ± 1.0	5.4 ± 1.3	<0.001
Plasma fibrinogen level, g/L	3.20 ± 0.55	3.06 ± 0.56	2.87 ± 0.47	2.81 ± 0.53	<0.001
Serum low-density lipoprotein cholesterol level, mmol/L (mg/dL)	3.87 ± 0.90 (150 ± 35)	3.92 ± 0.84 (152 ± 32)	3.95 ± 0.97 (153 ± 38)	3.61 ± 0.85 (140 ± 33)	<0.001
Serum high-density lipoprotein cholesterol level, mmol/L (mg/dL)	1.22 ± 0.27 (47 ± 10)	1.29 ± 0.29 (50 ± 11)	1.29 ± 0.30 (50 ± 12)	1.41 ± 0.29 (55 ± 11)	<0.001
Serum triglyceride level, mmol/L (mg/dL)	1.68 ± 1.00 (149 ± 89)	1.38 ± 0.68 (122 ± 60)	1.44 ± 1.01 (128 ± 89)	1.10 ± 0.56 (97 ± 50)	<0.001
Serum apolipoprotein B level, g/L	1.047 ± 0.230	1.025 ± 0.203	1.027 ± 0.246	0.938 ± 0.216	<0.001
Fasting serum insulin level, pmol/L	89 ± 49	81 ± 45	72 ± 30	59 ± 22	<0.001
Diabetes, %	5.2	3.7	3.3	0.9	0.102
Coronary heart disease, %	44.1	21.0	13.6	4.7	<0.001
Heart failure, %	13.2	2.8	3.8	1.4	<0.001
Stroke history, %	3.8	3.3	0.9	0.0	0.013
Claudication, %	8.5	2.3	0.5	0.0	<0.001
Asthma, %	7.1	1.9	3.3	1.4	0.005
Chronic obstructive pulmonary disease, %	8.0	7.0	5.6	3.3	0.190
Pulmonary tuberculosis history, %	4.7	4.2	0.9	1.9	0.061
Cardiovascular or pulmonary reasons for stopping exercise test, %‡	26.8	10.3	3.3	4.7	<0.001
Medication for dyslipidemia, %	2.8	0.5	0.5	0.0	0.011

\* Values presented with a plus/minus sign are the mean ± SD and are derived from analyses of variance. MET = metabolic equivalent of oxygen consumption.

† A low value indicates high adult socioeconomic status.

‡ Dyspnea, chest pain, ischemic electrocardiographic changes, arrhythmia, a marked change in blood pressure, dizziness, or unconsciousness.

(range, 0.552 to 2.705 mm),  $0.385 \pm 0.171$  mm (range, 0.086 to 2.044 mm),  $0.090 \pm 0.042$  mm (range, 0.022 to 0.445 mm), and  $0.759 \pm 0.166$  mm (range, 0.422 to 2.116 mm), respectively. Baseline characteristics of participants in each quartile of  $\text{VO}_2\text{max}$  are shown in

Table 1. Unadjusted inverse associations were seen between  $\text{VO}_2\text{max}$  and all baseline indicators of carotid atherosclerosis (maximal IMT, plaque height, surface roughness, mean IMT, advanced atherosclerosis), age, body mass index, waist-to-hip ratio, systolic and dia-

Table 2. Baseline Risk Factors for the Progression of Carotid Atherosclerosis\*

Risk Factor	4-Year Increase in Maximal Intima-Media Thickness		4-Year Increase in Plaque Height		4-Year Increase in Surface Roughness		4-Year Increase in Mean Intima-Media Thickness	
	$\beta$ Coefficient	P Value	$\beta$ Coefficient	P Value	$\beta$ Coefficient	P Value	$\beta$ Coefficient	P Value
Maximal oxygen uptake	-0.132	0.001	-0.146	<0.001	-0.162	<0.001	-0.094	0.014
Cigarette smoking	0.101	0.004	0.060	0.071	0.118	<0.001	0.108	0.002
Systolic blood pressure	0.098	0.003	0.070	0.024	0.062	0.037	0.094	0.004
Plasma fibrinogen level	0.090	0.007	0.061	0.053	0.072	0.016	0.092	0.005
Cardiovascular or pulmonary reasons for stopping exercise test†	0.080	0.018	0.096	0.002	0.109	<0.001	0.074	0.028
Score for adult socioeconomic status‡	0.078	0.021	0.055	0.085	0.063	0.036	0.083	0.013
Waist-to-hip ratio	0.073	0.031	0.061	0.054	0.054	0.071	0.064	0.054
Serum triglyceride level	0.071	0.034	0.067	0.033	0.098	0.001	0.044	0.186
Coronary heart disease	0.067	0.051	0.084	0.008	0.103	0.001	0.036	>0.2
Heart failure	0.055	0.099	0.070	0.025	0.063	0.032	0.044	0.177
Serum apolipoprotein B level	0.055	0.107	0.079	0.013	0.100	0.001	0.061	0.068
Serum low-density lipoprotein cholesterol level	0.046	0.196	0.078	0.018	0.079	0.012	0.051	0.145
Dietary intake of vitamin C	-0.042	>0.2	-0.069	0.026	-0.076	0.009	-0.033	>0.2
Diabetes	0.034	>0.2	0.027	>0.2	0.089	0.002	0.022	>0.2
Claudication	0.030	>0.2	0.062	0.049	0.085	0.004	0.033	>0.2

\* Data are derived from multiple linear regression analyses in which each risk factor was forced one at a time into the model with age and the technical covariates (examination years, zooming depth at baseline for right and left side, baseline indicator of carotid atherosclerosis, sonographer, follow-up time, and pravastatin treatment in the Kuopio Atherosclerosis Prevention Study).

† Dyspnea, chest pain, ischemic electrocardiographic changes, arrhythmia, a marked change in blood pressure, dizziness, or unconsciousness.

‡ A low score indicates high socioeconomic status.

stolic blood pressure, cigarette smoking, plasma fibrinogen level, serum low-density lipoprotein cholesterol level, triglycerides and apolipoprotein B levels, fasting serum insulin level, diabetes, coronary heart disease, heart failure, stroke, claudication, asthma, cardiovascular or pulmonary reasons for stopping the exercise test, and medication for dyslipidemia. Unadjusted direct associations were seen between  $\text{VO}_2\text{max}$  and adult socioeconomic status, dietary intake of vitamin C, energy expenditure and mean intensity of physical activity, and serum high-density lipoprotein cholesterol level.

#### Baseline Risk Factors for the Progression of Carotid Atherosclerosis

Table 2 shows the baseline risk factors that were statistically significantly associated with a 4-year increase in any of the indicators of carotid atherosclerosis after adjustment for age and the technical covariates. We used a stepwise method to simultaneously enter all of these baseline risk factors, except those that were strongly correlated with one another, into a linear regression model. A *P* value less than 0.05 was used as a selection criterion, and age and the technical covariates were forced into the model. We found that the statistically significant predictors of a 4-year increase in maximal IMT were  $\text{VO}_2\text{max}$  (standardized regression coefficient  $\beta = -0.112$ ; *P* =

0.003), systolic blood pressure ( $\beta = 0.096$ ; *P* = 0.004), and cigarette smoking ( $\beta = 0.093$ ; *P* = 0.008). The statistically significant predictors of 4-year increases in plaque height, surface roughness, and mean IMT were  $\text{VO}_2\text{max}$  ( $\beta = -0.141$ ; *P* < 0.001) and systolic blood pressure ( $\beta = 0.061$ ; *P* = 0.048);  $\text{VO}_2\text{max}$  ( $\beta = -0.122$ ; *P* < 0.001), cigarette smoking ( $\beta = 0.098$ ; *P* = 0.001), diabetes ( $\beta = 0.071$ ; *P* = 0.013), and serum apolipoprotein B level ( $\beta = 0.070$ ; *P* = 0.020); and cigarette smoking ( $\beta = 0.097$ ; *P* = 0.006), systolic blood pressure ( $\beta = 0.097$ ; *P* = 0.003), and plasma fibrinogen level ( $\beta = 0.069$ ; *P* = 0.041), respectively.

#### Maximal Oxygen Uptake and the Progression of Carotid Atherosclerosis

After adjustments for age, the technical covariates, and cigarette smoking, we found strong inverse associations between  $\text{VO}_2\text{max}$  and 4-year increases in maximal IMT ( $\beta = -0.120$ ; *P* = 0.002), plaque height ( $\beta = -0.140$ ; *P* < 0.001), surface roughness ( $\beta = -0.147$ ; *P* < 0.001), and mean IMT ( $\beta = -0.080$ ; *P* = 0.035). Additional adjustment for systolic blood pressure, serum apolipoprotein B level, diabetes, and plasma fibrinogen level weakened the associations of  $\text{VO}_2\text{max}$  with the 4-year increase in maximal IMT ( $\beta = -0.094$ ; *P* = 0.019), plaque height ( $\beta = -0.117$ ; *P* = 0.002), and

surface roughness ( $\beta = -0.117$ ;  $P = 0.001$ ). The association between  $\text{VO}_2\text{max}$  and the 4-year increase in the mean IMT was no longer statistically significant after these adjustments ( $\beta = -0.050$ ;  $P = 0.206$ ). Adjustment for any other baseline variable or the 4-year change in any baseline variable had little if any effect on the associations of  $\text{VO}_2\text{max}$  with the 4-year increase in indicators of carotid atherosclerosis.

The quartiles of  $\text{VO}_2\text{max}$  were less than 26.1 mL/kg per minute, 26.1 to 30.9 mL/kg per minute, 31.0 to 36.2 mL/kg per minute, and greater than 36.2 mL/kg per minute. Over 4 years, after adjustment for age, technical covariates, and cigarette smoking, maximal IMT in these quartiles increased 0.297 mm (95% CI, 0.269 to 0.325 mm), 0.267 mm (CI, 0.241 to 0.293 mm), 0.243 mm (CI, 0.217 to 0.269 mm), and 0.242 mm (CI, 0.214 to 0.270 mm), respectively ( $P = 0.007$  for linear trend across quartiles;  $P = 0.036$  for difference between quartiles). The respective increases in plaque height over 4 years were 0.313 mm (CI, 0.287 to 0.339 mm), 0.264 mm (CI, 0.240 to 0.288 mm), 0.246 mm (CI, 0.222 to 0.270 mm), and 0.239 mm (CI, 0.213 to 0.265 mm) ( $P < 0.001$  for linear trend;  $P = 0.001$  for difference). The respective increases in surface roughness over 4 years were 0.032 mm (CI, 0.027 to 0.037 mm), 0.021 mm (CI, 0.016 to 0.025 mm), 0.017 mm (CI, 0.012 to 0.021 mm), and 0.016 mm (CI, 0.014 to 0.021 mm) ( $P < 0.001$  for linear trend;  $P < 0.001$  for difference). The respective increases in maximal IMT, surface roughness, and mean IMT were 23%, 31%, and 100% larger among men in the lowest quartile of  $\text{VO}_2\text{max}$  than among those in the highest quartile.

#### Physical Activity and the Progression of Carotid Atherosclerosis

After adjustment for age, technical covariates, and cigarette smoking, none of the components of total, conditioning, or nonconditioning physical activity or walking or bicycling to work (energy expenditure, duration, frequency, and mean intensity) was statistically significantly associated with the progression of carotid atherosclerosis. Of all measures of physical activity, the energy expenditure of conditioning physical activity had the strongest association with the 4-year increase in plaque height ( $\beta = -0.048$ ;  $P = 0.122$ ) and surface roughness ( $\beta = -0.048$ ;  $P = 0.098$ ). The frequency of

conditioning physical activity had the strongest association with the 4-year increase in maximal IMT ( $\beta = -0.033$ ;  $P > 0.2$ ) and mean IMT ( $\beta = -0.036$ ;  $P > 0.2$ ).

#### DISCUSSION

This 4-year follow-up study in a population-based sample of middle-aged men provides evidence that higher levels of  $\text{VO}_2\text{max}$  (as measured directly by respiratory gas exchange in a maximal symptom-limited cycle ergometer exercise test) are independently associated with slower increase in the indicators of carotid atherosclerosis (as assessed by high-resolution B-mode ultrasonography). Of interest, low  $\text{VO}_2\text{max}$  was the strongest risk factor for the progression of carotid atherosclerosis in multivariate analyses, even compared with conventional risk factors.

We previously found a strong association between higher levels of  $\text{VO}_2\text{max}$  and reduced risk for a first acute myocardial infarction in middle-aged men with no previous cardiovascular diseases or cancer who were from the same cohort as our present study sample (6). Good cardiorespiratory fitness, as assessed by work capacity, exercise test duration, or heart rate response to exercise in a cycle ergometer or treadmill exercise test, has been related to greatly reduced premature cardiovascular mortality rates in other prospective population-based studies (7–9, 11). Ultrasonographically assessed carotid intima-media thickening, in turn, has been associated with increased risk for coronary heart disease and stroke in prospective population-based studies (20, 21). Together with this epidemiologic evidence, our results suggest that good cardiorespiratory fitness is associated with slower progression of atherosclerosis and could therefore reduce the risk for clinical events of atherosclerotic vascular diseases. To our knowledge, however, there are no published reports concerning the association between cardiorespiratory fitness and the risk for stroke. Therefore, prospective population-based studies are needed to test whether good cardiorespiratory fitness reduces stroke risk.

Only one previous population-based study has examined the association between cardiorespiratory fitness and early atherosclerosis. In this cross-sectional study in middle-aged men (24),  $\text{VO}_2\text{max}$  was inversely associated with carotid bifurcation IMT. Similarly, we found an inverse relationship between  $\text{VO}_2\text{max}$  and the indicators

of carotid atherosclerosis in our cross-sectional analyses. On the basis of a cross-sectional study, however, it is impossible to draw a conclusion regarding the time order of the relationship—for example, whether poor cardiorespiratory fitness is a true risk factor for atherosclerosis or a result of preexisting disease associated with atherosclerosis. In our prospective analyses,  $\text{VO}_2\text{max}$  was inversely associated with the 4-year increase in the indicators of carotid atherosclerosis after careful adjustment for other atherosclerotic risk factors, including cardiovascular, pulmonary, and metabolic diseases and cardiovascular and pulmonary reasons for stopping the exercise test. It is therefore unlikely that our observed associations are due to confounding, but they may be partly due to self-selection bias.

Clinical trials have shown that aerobic exercise can increase  $\text{VO}_2\text{max}$  by up to 30% in sedentary persons (32). One explanation for the inverse association between  $\text{VO}_2\text{max}$  and the 4-year increase in the indicators of carotid atherosclerosis could be that physical activity slows the progression of atherosclerosis by improving cardiorespiratory fitness, as suggested by clinical trials in patients with coronary heart disease (12–17). However, physical activity was not related to the 4-year increase in the indicators of carotid atherosclerosis in our study. One reason for this could be large variability in the measurement of physical activity and true variability in physical activity over time. However,  $\text{VO}_2\text{max}$  measured in a cycle ergometer exercise test under standardized conditions is an accurate and highly reproducible measure of cardiorespiratory fitness (33), as indicated by low intraindividual variability over time and high test–retest correlation observed in previous studies (34). This supports the view that a single measurement of  $\text{VO}_2\text{max}$  is a clinically useful method for assessing a person's cardiorespiratory fitness.

Another reason that we did not observe an association between physical activity and a 4-year increase in the indicators of carotid atherosclerosis may be that the quantity and especially the intensity of exercise in most middle-aged men is too low to improve cardiorespiratory fitness and to slow the progression of atherosclerosis. Indeed, we previously found that  $\text{VO}_2\text{max}$  has a modest association with amount of physical activity but a much stronger relationship with mean intensity (28). Only greater amounts of exercise intensive enough to improve cardiorespiratory fitness had an antiatherogenic

effect in a clinical trial (12). However, additional exercise intervention trials are needed to provide information about the amount and degree of physical activity required to slow the progression of atherosclerosis.

The same training program may increase  $\text{VO}_2\text{max}$  by up to 1 L/min in some persons but cause almost no change in others (35). This suggests that genetic factors contribute greatly to interindividual variation in  $\text{VO}_2\text{max}$  and the sensitivity of  $\text{VO}_2\text{max}$  to exercise training (36). On the basis of twin studies, heritability of  $\text{VO}_2\text{max}$  is 25% to 50% (35). In our study of a representative sample of middle-aged men, other risk factors for atherosclerosis only partly explained the inverse associations of  $\text{VO}_2\text{max}$  with the 4-year increase in indicators of carotid atherosclerosis. One reason for this could be that the observed relationships are partly due to genetic factors, although no good evidence supports this view.

The results of some clinical trials suggest that health habits other than physical activity affect  $\text{VO}_2\text{max}$ . Both aerobic exercise and dietary energy restriction increased  $\text{VO}_2\text{max}$  indexed by body weight in obese men and women, and the effect of dietary change on  $\text{VO}_2\text{max}$  was largely due to weight loss (37). An important finding of this trial was that the combination of aerobic exercise and dietary energy restriction increased  $\text{VO}_2\text{max}$  more than either factor alone. Inconsistently, however, aerobic exercise but not weight loss increased  $\text{VO}_2\text{max}$  indexed by body weight in two other trials in obese men (38, 39). In addition, the results of some trials suggest that cigarette smoking acutely decreases  $\text{VO}_2\text{max}$  (40). However, most trials do not support this view (41). It is not known whether long-term cigarette smoking decreases  $\text{VO}_2\text{max}$ .

Physical activity and good cardiorespiratory fitness are known to have a favorable effect on risk factors for atherosclerosis, including hypertension, dyslipidemia, type 2 diabetes, insulin resistance, obesity, and hemostatic factors (42). In our study, systolic blood pressure, serum apolipoprotein B level, diabetes, and plasma fibrinogen level partly explained the inverse associations of  $\text{VO}_2\text{max}$  with the 4-year increase in indicators of carotid atherosclerosis. Physical activity and good cardiorespiratory fitness may also 1) enhance endothelial function by increasing the production of nitric oxide and prostacyclin (43, 44), 2) reduce low-density lipoprotein oxidation (45), 3) decrease the atherogenic activity of blood mononuclear cells by affecting the production of

cytokines (46), 4) decrease the number of atherosclerotic lesions by reducing heart rate and pulsatile stress (47), and 5) decrease the accumulation of collagen in the artery wall (48).

We found that good cardiorespiratory fitness, as indicated by higher levels of  $\text{VO}_2\text{max}$ , is associated with slower progression of early atherosclerosis in a population-based sample of middle-aged men. This finding is important because it emphasizes the possibility of evaluating cardiorespiratory fitness in middle-aged men to estimate their future risk for atherosclerotic vascular diseases. Additional research is warranted to determine whether a possible causal relationship exists between cardiorespiratory fitness and atherosclerosis.

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