Effects of Aerobic Physical Exercise on Inflammation and Atherosclerosis in Men: The DNASCO Study

A Six-Year Randomized, Controlled Trial

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Background: **Although regular physical activity is recommended for prevention of cardiovascular diseases, no data are available on its antiatherosclerotic effects in the general population.**

Objective: **To determine whether progressive aerobic exercise compared with usual activity slows progression of atherosclerosis in men.**

Design: **A 6-year randomized, controlled trial.**

Setting: **Eastern Finland.**

Participants: **140 middle-aged men randomly selected from the population registry.**

Intervention: **Low- to moderate-intensity aerobic exercise.**

Measurements: **Atherosclerosis was quantitated ultrasonographically as the mean intima–media thickness in the carotid artery at baseline and at years 2 through 6.**

Results: **On the basis of intention-to-treat analyses, a 19.5% net increase ($P < 0.001$) in ventilatory aerobic threshold was evident in the exercise group after 6 years. High-sensitivity C-reactive protein levels were statistically nonsignificantly lower in the exercise group than in the control group ($P > 0.2$). The progression of intima–media thickness in the carotid artery did not differ between the study groups ($P > 0.2$). A subgroup analysis that excluded men taking statins showed that the 6-year progression of intima–media thickness, adjusted for smoking and annual measures of low-density lipoprotein cholesterol level, systolic blood pressure, and waist circumference, was 40% less in the exercise group (0.12 mm [95% CI, −0.010 to 0.26 mm]) than in the control group (0.20 mm [CI, 0.05 to 0.35 mm]).**

Limitations: **Only middle-aged white men were included. The intervention included mainly aerobic exercises.**

Conclusions: **Aerobic physical exercise did not attenuate progression of atherosclerosis, except in a subgroup of men not taking statins.**

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Observational studies suggest that physical inactivity and low cardiorespiratory fitness predict atherosclerotic cardiovascular disease (CVD) (1–6) and that an increase in habitual physical activity (7) and cardiorespiratory fitness (8) are associated with decreased mortality. These findings are the basis for a general public health message recommending a minimum of 30 minutes of regular moderate exercise per day (9). While exercise training at a weekly energy expenditure of 1500 kcal or more attenuates the progression of angiographically established coronary atherosclerosis (10), there are no data from randomized, controlled trials on the antiatherosclerotic effects of regular physical exercise in a general population. Moreover, studies using CVD mortality as an end point would require enormous sample sizes, and ethical issues limit the use of intracoronary arteriography in asymptomatic persons.

Ultrasonographically assessed intima–media thickness of the carotid arteries allows noninvasive investigation of preclinical stages of atherosclerosis in unselected human populations (11). Intima–media thickness has been used as a surrogate end point for clinical coronary events (12) and in clinical trials (13). We previously reported an inverse association of cardiorespiratory fitness to carotid artery intima–media thickness (14) and its progression rate (15). Clinical trials have revealed several plausible antiatherogenic mechanisms of exercise, such as favorable changes in plasma lipid levels, blood pressure, body adiposity, plasma glucose levels, insulin levels, and hemostatic factors (9). However, these effects only partially explain the inverse association between physical activity and CVD. Inflammation plays a major role in the pathogenesis of atherosclerosis (16). High-sensitivity C-reactive protein (CRP) levels are a marker of inflammation, and even slightly elevated serum levels of CRP predict clinical manifestations of atherosclerotic CVD (17). Short-term uncontrolled studies suggest that physical activity has a beneficial impact on the inflammatory reaction (18). In the DNASCO (DNA Polymorphism and Carotid Atherosclerosis) Study, a 6-year randomized, controlled trial in a population-based sample of middle-aged men, we investigated the effect of regular long-term physical exercise on chronic low-grade inflammation and the progression of atherosclerosis, as assessed by noninvasive repeated measurements of carotid artery intima–media thickness.

METHODS

Study Design

The primary end point was progression of the mean intima–media thickness of the carotid artery in a 6-year randomized, controlled trial of an exercise intervention. The Research Ethics Committee of the Kuopio University Hospital approved the protocol. **Figure 1** shows the flow of patients through the study during recruitment, interven-

Context

Few data address whether exercise slows progression of atherosclerosis.

Contribution

In this 6-year trial, middle-aged Finnish men were randomly assigned to progressive aerobic exercise or usual activity. Progressive exercise targeted 45- to 60-minute sessions 5 times weekly of activities such as walking, jogging, or cycling. Exercisers improved their ventilatory aerobic threshold and decreased their resting heart rate. However, intima–media thickness of the carotid artery measured by ultrasonography did not differ between groups, except in a subgroup of men not taking statins.

Implications

Aerobic exercise did not slow progression of atherosclerosis in middle-aged men, except for those not taking statins.

–The Editors

tion allocation, and follow-up to data analysis. Participants were a random sample obtained from the population registry. Men were sent a letter inviting them to participate, and all participants provided signed informed consent. Forty-eight men did not respond to the invitation, and another 40 men did not present to the laboratory for the baseline examinations; no data are available on the characteristics of these 88 men.

In 1994 to 1995, 140 men were randomly assigned to the exercise group ($n = 70$) or the control group ($n = 70$) by selecting a sealed, opaque envelope that contained the group assignment. The envelopes appeared identical, and an equal number was reserved for both study groups. Exclusion criteria were diseases or physical conditions restricting participation in regular exercise and malignant diseases or mental states restricting cooperation. During the 6-year intervention, 20 men (9 in the exercise group and 11 in the control group) dropped out because of death (2 in the exercise group and 4 in the control group), severe diseases (4 in the control group), relocation (1 in the exercise group), or loss of motivation (6 in the exercise group and 3 in the control group).

For statistical analyses, multiple imputation methods were applied to replace missing end-point values. The first dropouts, all due to death, did not take place until the third year. **Table 1** shows the number of patients with common chronic diseases as well as the number of patients who received drug treatment during the intervention.

Primary End Point

Carotid artery atherosclerosis was measured ultrasonographically as the mean intima–media thickness. The same certified sonographer performed all biannual scannings during the 6 years, and we report results from 6 study visits (at baseline and at years 2 through 6). An ultrasound device with a high-resolution 10-MHz transducer was used, following a standardized and pretested protocol, and the scannings were recorded on super VHS videotape. The calibration of the ultrasound unit was routinely checked. Another certified sonographer measured intima–media thickness of the far wall of the right carotid artery. Both sonographers were blinded to the randomization status of the study participants. The measurement of intima–media thickness extended to the longest wall region where the lumen–intimal and media–adventitial boundaries could be clearly identified by an automated edge-detection program on the basis of active contour (19). The mean intima–media thickness of the traced region was used for the statistical analysis.

Cardiorespiratory Performance, Exercise Electrocardiography, and Blood Pressure

To allow assessment of changes in cardiorespiratory fitness and to monitor exercise habits more objectively, all participants annually performed a bicycle ergospirometry test. The patients' electrocardiograms were continuously monitored and recorded every minute during the test and up to 7 minutes after exercise. An exercise physiologist visually defined ventilatory aerobic threshold as the first nonlinear increase of ventilation in the ergospirometry test. A trained nurse measured blood pressure annually. After the men had been lying on an examination bed for 45 minutes, blood pressure was measured by a random-zero mercury sphygmomanometer, according to the MONICA (MONItoring CArdiovascular disease) protocol (20).

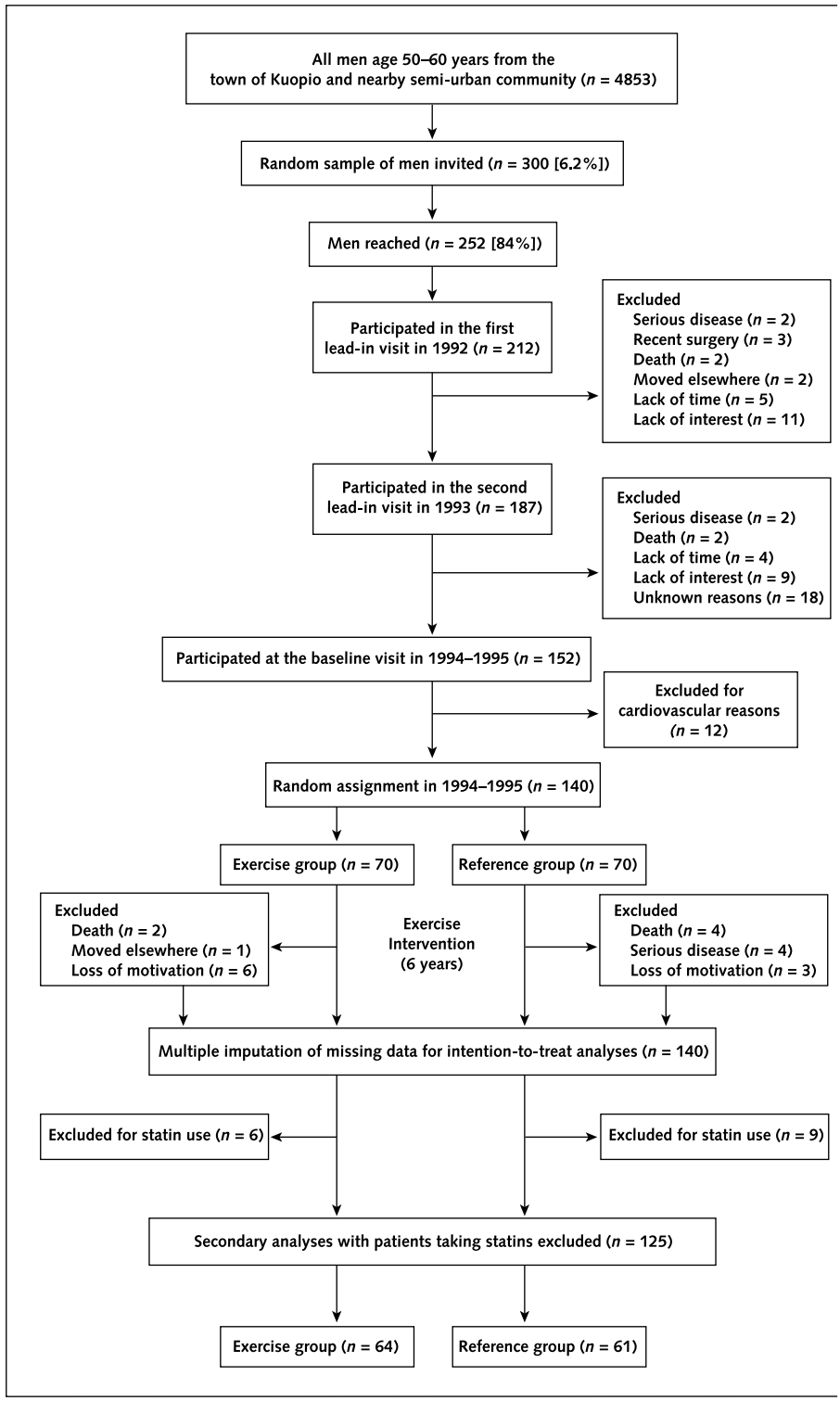
Exercise Intervention

The men in the exercise group were prescribed walking, jogging, cross-country skiing, swimming, and cycling as the main methods of aerobic exercise. The program was progressive: During the first 3 months, the men were advised to exercise 3 times per week for 30 to 45 minutes per session. Thereafter, they were asked to exercise 5 times per week for 45 to 60 minutes per session. Exercise intensity was determined individually, and modified when necessary, to correspond to ventilatory threshold level, that is, 40% to 60% of maximal oxygen uptake. The men in the exercise group were given heart rate monitors to help them adhere to the prescribed training heart rate. The participants performed the program on their own and were asked to report each exercise session in a diary, which was checked in a face-to-face meeting with an exercise physiologist at 6-month intervals. In accordance with the regulations of the Ethics Committee, men in the control group were allowed to choose whether to engage in physical exercise, but no efforts were made to change their habitual activity. Accordingly, the participants in the control group were not asked to report their exercise habits in a diary.

Biochemical Analyses

Blood sampling and serum assays for fasting cholesterol and its subfractions have been described elsewhere

Figure 1. **Flow of participants through the study.**



(21). Serum high-sensitivity CRP levels were measured by a commercial immunoassay (IMMULITE 2000 High-Sensitivity CRP, Diagnostic Products Corp., Los Angeles, California) using the IMMULITE 2000 Analyzer (Diagnostic Products Corp.).

Other Methods

Participants were asked about smoking habits and were classified as smokers or nonsmokers on the basis of current smoking status. Dietary energy and fat intake were assessed annually with 4-day food records (3 weekdays and

Table 1. **Patients with Chronic Diseases and Those Who Received Drug Treatment during the Intervention***

Variable	Exercise Group		Control Group	
	Baseline	End of the Trial	Baseline	End of the Trial
	← n →			
Chronic disease				
CAD	6	8	6	9
CVD	1	2	0	1
Diabetes	2	4	1	3
Hypertension	12	13	12	13
Medication				
ACE inhibitors	7	7	6	10
β-Blockers	10	16	16	18
Aspirin	11	15	7	15
Analgesics	16	6	9	6
Nitroglycerin	6	9	5	10

* ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CVD = cardiovascular disease.

Sunday). Portion sizes were estimated by using a picture booklet or household measurement units. Records were analyzed by using MicroNutrica software (The Social Insurance Institution, Turku, Finland), based on nutrient files from Finnish food analyses (22).

Statistical Analysis

An estimate of the sample size ($2n = 114$) was based on assumptions about the reduction (25%) in the rate of progression of intima–media thickness between the exercise and control groups, the duration of the trial (6 years), the number of equally spaced end-point measurements (7), variability due to participants and measurement error (0.4 mm), and dropout rate (25%). The significance level was 5%, with a power of 90% (23). Statistical analyses were based primarily on an intention-to-treat approach with 140 participants. For secondary analyses, patients treated with cholesterol synthesis inhibitors, which are known to have a powerful antiatherosclerotic effect (24), were excluded (6 in the exercise group and 9 in the control group) (**Figure 1**). Multiple imputation methods available in S-PLUS (version 6.1, Insightful Corp., Seattle, Washington) were applied for the primary end-point analyses (25). We imputed missing data by first obtaining maximum likelihood estimates using the expectation-maximization algorithm and then using data augmentation methods to iteratively impute missing data. Two hundred iterations were used, and 3 consecutive data sets were imputed. Estimates were consolidated by using a linear mixed-effects model as described by Rubin (26). Statistical analyses for high-sensitivity CRP level were performed after logarithmic transformation of the original values. In the repeated-measures analysis of variance (ANOVA) models, interaction terms for time by study group were used to compare patterns over time in the dependent variable between the study groups. Patterns over time were detected by Helmert contrasts, which compare the mean of the dependent variable at one time point with the mean of the successive values (27), thereby indicating the time point of the appearance of the intervention effect. Results are expressed as means and 95% CIs. For illustration, means in **Figures 2** through **4** are adjusted for respective baseline values.

Role of the Funding Sources

The funding sources included the Ministry of Education in Finland, the Academy of Finland, the City of Kuopio, the Finnish Heart Association, the Juho Vainio Foundation, Freiburg University Hospital, and Centre de Recherche et d'Information Nutritionnelles de Paris, France. The funding sources had no role in the design, conduct, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Characteristics of Participants

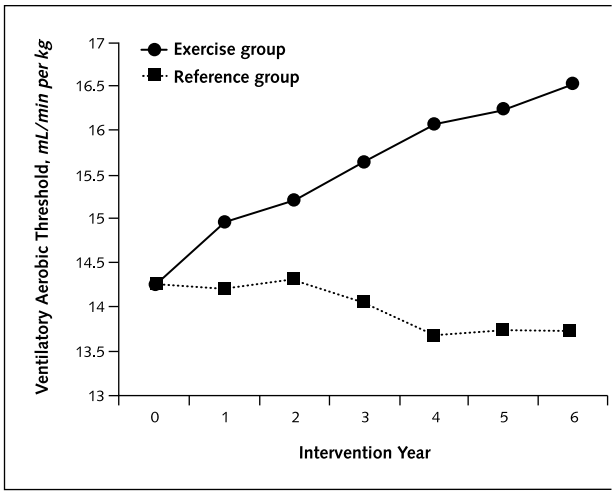
At randomization, the participants were similar in the exercise and control groups (**Table 2**). Men in the exercise group improved their ventilatory aerobic threshold, a proxy measure of submaximal aerobic performance capacity and health-related fitness, by 16%, compared with a decrease of 3.5% in the control group ($P < 0.001$ for interaction with

Table 2. **Characteristics of the Participants at Baseline***

Variable	Exercise Group ($n = 70$)	Reference Group ($n = 70$)
Age, *y*	57.1 (56.4–57.8)	57.2 (56.6–57.9)
Ventilatory aerobic threshold, *mL/min per kg of body weight*	14.4 (13.5–15.3)	14.1 (13.2–14.9)
Maximal oxygen uptake, *mL/min per kg*	31.1 (29.4–32.8)	30.8 (29.2–32.5)
Waist circumference, *cm*	95.4 (93.2–97.5)	95.6 (93.2–98.0)
BMI, kg/m^2	27.1 (26.3–27.8)	27.2 (26.2–28.1)
Heart rate at rest, *beats/min*	62.0 (58.4–65.4)	59.0 (56.4–60.9)
Systolic blood pressure, *mm Hg*	134.5 (130.2–138.9)	133.4 (129.5–137.2)
Diastolic blood pressure, *mm Hg*	87.2 (85.0–89.5)	86.9 (84.7–89.2)
LDL cholesterol level, *mmol/L [mg/dL]*	3.83 (3.59–4.03) [148 (139–156)]	3.93 (3.70–4.19) [152 (143–162)]
HDL cholesterol level, *mmol/L [mg/dL]*	1.24 (1.16–1.29) [48 (45–50)]	1.24 (1.16–1.29) [48 (45–50)]
Energy intake, *kcal/d*	2263 (2105–2420)	2257 (2137–2377)
Fat intake, *% of caloric intake*	34.9 (33.5–36.4)	34.8 (33.5–36.1)
Smokers, *n*	15	9

* Values in parentheses are 95% CIs. BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Figure 2. **Mean ventilatory aerobic threshold in the exercise and control groups during the intervention.**



$P < 0.001$ (repeated-measures analysis of variance based on intention-to-treat analysis for 140 patients with covariates).

repeated-measures ANOVA) (**Figure 2**), a 19.5% net increase ($P < 0.001$). An increase of at least 15% in ventilatory aerobic threshold was observed in 54% and 27% of the men in the exercise group and control group, respectively. During the intervention, resting heart rate decreased from 62 to 56 beats/min ($P = 0.003$) in the exercise group but remained unchanged (59 vs. 58 beats/min; $P > 0.2$) in the control group. Based on the exercise diaries of the men in the exercise group, the mean weekly energy expenditure was 1515 kcal during the entire intervention and increased by approximately 10% from the beginning to the end of the trial. Both at baseline and during the intervention, dietary fat contributed 35% of the total energy intake in both groups. Two men in both groups quit smoking, but smoking habits did not change in other participants.

High-Sensitivity CRP

At randomization, the mean CRP level was 16.1 nmol/L (95% CI, 10.2 to 23.7 nmol/L) in the exercise group and 15.2 nmol/L (CI, 10.2 to 20.3 nmol/L) in the control group. During the intervention, CRP level remained constantly lower in the exercise group than in the control group, although the difference was statistically nonsignificant ($P > 0.2$ for the interaction on repeated-measures ANOVA) (**Figure 3**).

Intima–Media Thickness

At randomization, the mean intima–media thickness of the carotid bifurcation was 1.12 mm (CI, 1.05 to 1.20 mm) in the exercise group and 1.05 mm (CI, 0.97 to 1.13 mm) in the control group, a statistically nonsignificant difference. The progression in mean intima–media thickness in the intention-to-treat population did not differ between the exercise and control groups ($P > 0.2$ for interaction on repeated-measures ANOVA, adjusted for smoking, annual levels of low-density lipoprotein cholesterol, systolic blood pressure, and waist circumference) (**Figure 4**, *top*). In this sample, progression assessed by a global measure of intima–media thickness (mean of distal carotid communis, carotid bifurcation, and proximal internal carotid) also was not statistically significantly different between groups ($P > 0.2$ for interaction by repeated-measures ANOVA with covariates).

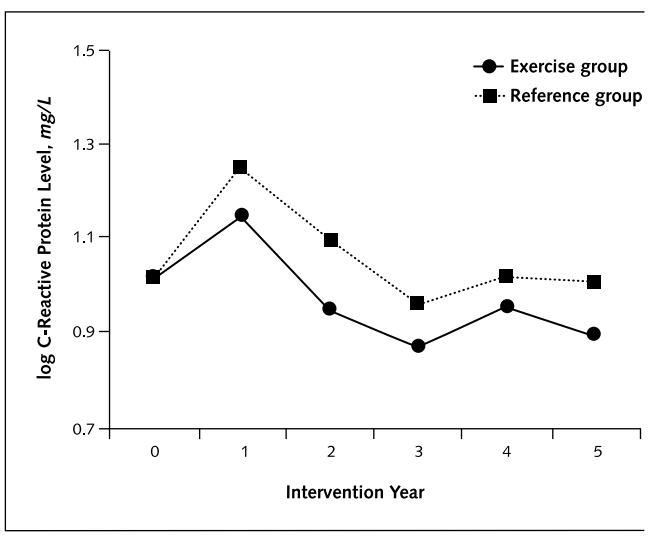
A subgroup analysis that excluded 15 patients taking statins (**Figure 4**, *bottom*) showed that the 6-year progression of intima–media thickness was 40% less in the exercise group (0.12 mm [CI, −0.01 to 0.26 mm]) than in the control group (0.20 mm [CI, 0.05 to 0.35 mm]). The progression leveled off in the exercise group after 3 years of intervention but continued in a linear fashion in the control group ($P = 0.02$ for interaction by repeated-measures ANOVA with covariates).

DISCUSSION

The main finding of this 6-year randomized, controlled trial is that regular physical exercise at low to moderate intensity did not slow the progression of carotid atherosclerosis, except in the subgroup of men who were not taking statins. These subgroup findings, if applicable to the coronary circulation, support the data from observational studies of an inverse relationship between physical activity and the risk for coronary heart disease (1, 3, 6, 7, 28, 29) and provide evidence for the antiatherosclerotic effects of an increase in regular physical exercise in some men.

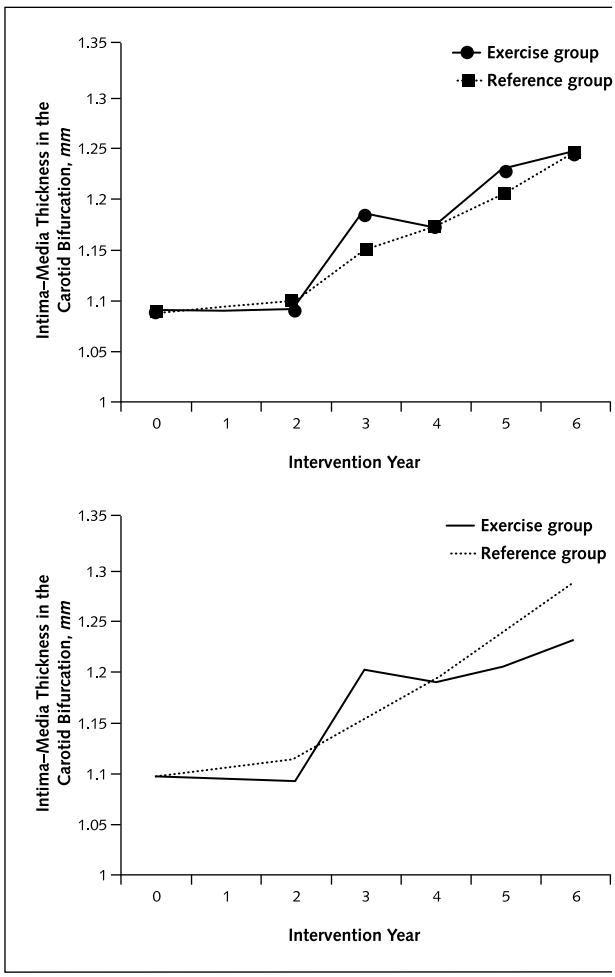
Traditional risk factors (smoking, annually measured systolic blood pressure, low-density lipoprotein cholesterol level, obesity) did not explain the subgroup findings. Other pathways may mediate the possible effects of regular phys-

Figure 3. **Mean high-sensitivity C-reactive protein level in the exercise and control groups during the intervention.**



$P > 0.2$ (repeated-measures analysis of variance based on intention-to-treat analysis for 140 patients with covariates). To convert mg/L to nmol/L, multiply by 8.45.

Figure 4. **Mean intima–media thickness during the intervention in all participants (*top*) and excluding men taking statins (*bottom*).**



In the top panel, $P > 0.2$; in the bottom panel, $P = 0.02$ (repeated-measures analysis of variance based on intention-to-treat analysis for 140 patients with covariates).

ical exercise on atherosclerosis. One plausible mechanism is exercise-induced improvement in endothelial function (30). The present data, in agreement with other studies (18), suggest that exercise may decrease the inflammatory response. Skeletal muscle is a source of interleukin-6, a potential inhibitor of a proinflammatory cytokine, tumor necrosis factor-α. A decrease in tumor necrosis factor-α induced by regular physical exercise could alleviate insulin resistance and possibly slow the progression of atherosclerosis (31). However, until more data are available, an enhancing effect of regular exercise on the inflammatory response as an antiatherosclerotic mechanism remains hypothetical.

The effect of exercise on intima–media thickness in the subgroup of men not taking statins was seen after 3 years of intervention in the carotid bifurcation, an area prone to atherosclerosis (32, 33). One explanation for the delayed effect might be that the participants were in their late 50s. Men in this age group may be prone to atherosclerosis and slow responders to therapy. In addition, the exercise behavior in both groups may have obscured between-group differences. While half of the men in the exercise group clearly improved their aerobic capacity, one fourth of the men showed a decrease in cardiorespiratory fitness during the 6 years. Despite this, the mean 20% net increase in the submaximal cardiorespiratory performance capacity and the mean weekly exercise energy expenditure (1515 kcal), which corresponds with the exercise prescription (5 times per week for an hour), are indicators of a reasonable adherence in the exercise group. Although men in the control group were neither asked nor forbidden to exercise, one fourth of them increased their fitness level. Dietary data, assessed annually in both groups throughout the 6-year period, showed that both groups consumed, on average, 35% of their calories from fat. The use of angiotensin-converting enzyme inhibitors, β-blocking agents, or analgesics also did not affect the exercise-induced effect on intima–media thickness (data not shown). Two men in both groups quit smoking during the 6-year intervention. Thus, it is unlikely that interventions other than exercise explained the effect on intima–media thickness in the men not taking statins. On the other hand, cholesterol synthesis inhibitors have powerful antiatherosclerotic effects, and intention-to-treat analyses that included men taking statins showed exercise had no statistically significant effects on progression of intima–media thickness. It may be that the powerful antiatherosclerotic effects of statins minimize or mask effects of exercise. In addition, by excluding men taking statins, we may have excluded patients with greater atherosclerosis progression compared with those who did not take cholesterol synthesis inhibitors.

The strengths of our study were the long duration of the exercise program, the use of low- to moderate-intensity exercise, randomization into an exercise group or a control group, and the repeated end point and other measurements. A unique feature of the study was the very low dropout rate: Only 14% of randomly assigned men were lost to follow-up. Of note, participants were a randomly selected population sample; they were not a group of volunteers, who typically are highly motivated to participate in physical exercise and other habitual health behaviors. One experienced certified sonographer performed all ultrasonography scans throughout the trial. Intima–media thickness was measured by using an automated software for edge detection (19), and the 2 readers were blinded to the participants' group assignments. The statistical analyses followed an intention-to-treat principle, and missing values were addressed by using multiple imputation methods. Multiple imputations use information from different sources: the complete observations, the complete-data model, and the prior distribution for the parameters (34).

Our study also had major limitations. It included only middle-aged white men, and the age range was relatively narrow. Another flaw is that in practical terms, the only

exercise method was aerobic exercise. Sample size estimates were based on expected changes in the primary end point, the intima–media thickness of the carotid artery bifurcation, and not on other end points. In fact, the study was small and underpowered to detect changes in high-sensitivity CRP level. In future larger studies, sex, age, dose response, and exercise methods should be addressed, as should the interactions of regular exercise and the use of statins.

In conclusion, our data demonstrated a statistically significant exercise-induced attenuation in the progression of intima–media thickness in middle-aged white men who were not taking statins. This finding shows that regular aerobic exercise probably helps prevent atherosclerotic CVD in some men. It also supports current public health recommendations for at least 30 minutes of low- to moderate-intensity physical activity on most days of the week.

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