

Cardiorespiratory Fitness and the Risk for Stroke in Men

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Background: Low cardiorespiratory fitness is considered to be a major public health problem. We examined the relationship of cardiorespiratory fitness, as indicated by maximum oxygen consumption ($\dot{V}O_2\text{max}$) with subsequent incidence of stroke. We also compared $\dot{V}O_2\text{max}$ with conventional risk factors as a predictor for future strokes.

Methods: Population-based cohort study with an average follow-up of 11 years from Kuopio and surrounding communities of eastern Finland. Of 2011 men with no stroke or pulmonary disease at baseline who participated in the study, 110 strokes occurred, of which 87 were ischemic. The $\dot{V}O_2\text{max}$ was measured directly during exercise testing at baseline.

Results: The relative risk for any stroke in unfit men ($\dot{V}O_2\text{max}$, <25.2 mL/kg per minute) was 3.2 (95% confidence interval [CI], 1.71-6.12; $P < .001$; $P < .001$ for the trend across the quartiles); and for ischemic stroke, 3.50 (95% CI, 1.66-7.41; $P = .001$; $P < .001$ for trend

across the quartiles), compared with fit men ($\dot{V}O_2\text{max}$, >35.3 mL/kg per minute), after adjusting for age and examination year. The associations remained statistically significant after further adjustment for smoking, alcohol consumption, socioeconomic status, energy expenditure of physical activity, prevalent coronary heart disease, diabetes, systolic blood pressure, and serum low-density lipoprotein cholesterol level for any strokes or ischemic strokes. Low cardiorespiratory fitness was comparable with systolic blood pressure, obesity, alcohol consumption, smoking, and serum low-density lipoprotein cholesterol level as a risk factor for stroke.

Conclusions: Our findings show that low cardiorespiratory fitness was associated with an increased risk for any stroke and ischemic stroke. The $\dot{V}O_2\text{max}$ was one of the strongest predictors of stroke, comparable with other modifiable risk factors.

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PREVIOUS STUDIES have shown that physical activity¹⁻⁶ and good cardiorespiratory⁷⁻¹⁰ fitness have protective effects on atherosclerotic cardiovascular disease, including coronary heart disease (CHD) and hypertension. In addition, physical activity may protect against future stroke,¹¹⁻¹⁶ although the relation between physical activity and the risk for stroke has been inconsistent. In one study, Herman et al¹⁷ reported a graded dose-response relation, whereas other studies¹⁸⁻²⁰ have reported a nonlinear association between physical activity and the risk for stroke. Our previous study showed that low maximum oxygen capacity ($\dot{V}O_2\text{max}$) is associated with accelerated progression of carotid atherosclerosis.¹⁰ However, there are no cohort studies concerning the association between cardiorespiratory fitness and the risk for stroke.

It is difficult to measure the total amount, duration, frequency, or intensity of habitual physical activity according to self-reported questionnaires. Some studies on physical activity and stroke risk have been based on crude physical activity measurements classified as low or high category during leisure time or at work.^{13,14} On the other hand, cardiorespiratory fitness measured directly by $\dot{V}O_2\text{max}$ during exercise testing provides a quantitative measure of physical activity, although it is generally assumed that cardiorespiratory fitness represents mainly physical activity, besides other contributing factors such as age and heredity. One of the most important advantages of directly measured $\dot{V}O_2\text{max}$ is that it is an objective and quantitative measure of cardiorespiratory fitness.

In this study, we investigated the association of $\dot{V}O_2\text{max}$ as a measure of cardiorespiratory fitness with the risk for any

stroke in a representative population-based sample of men from eastern Finland. In addition, we compared $\dot{V}O_2\text{max}$ with conventional risk factors as a predictor of future strokes.

METHODS

SUBJECTS

Subjects were participants in the Kuopio Ischaemic Heart Disease Risk Factor Study, designed to investigate risk factors for cardiovascular disease, carotid atherosclerosis, and related outcomes in a population-based, randomly selected sample of men in eastern Finland.²¹ Of the 3433 men aged 42, 48, 54, or 60 years who resided in the town of Kuopio or its surrounding rural communities, 198 were excluded because of death, serious disease, or migration away from area. At baseline, examinations were conducted on 2682 (82.9%) between March 20, 1984, and December 5, 1989, and 314 men had missing of $\dot{V}O_2\text{max}$ values. Men who had a history of stroke (n=69) or any pulmonary disease such as bronchial asthma (n=96), chronic obstructive pulmonary disease (n=197), and lung tuberculosis (n=104) were excluded. Some men (n=13) had 2 or more of these diseases at the same time. Thus, complete data were available for 2011 men.

ASSESSMENT OF CARDIORESPIRATORY FITNESS

Cardiorespiratory fitness was assessed with a maximal symptom-limited, exercise-tolerance test on an electrically braked bicycle ergometer. For the 614 men examined by May 8, 1986, the testing protocol consisted of a 3-minute warm-up at 50 W followed by a step-by-step increase in the workload by 20 W/min. The remaining 1698 men underwent testing with a linear increase in workload by 20 W/min.

We used $\dot{V}O_2\text{max}$ as the measure of cardiorespiratory fitness. A detailed description of the measurement of $\dot{V}O_2\text{max}$ has been given elsewhere.² In short, the respiratory gas exchange was measured for the first 614 men by the mixing-chamber method, and for the remaining 1698 men by a breath-by-breath method. The $\dot{V}O_2\text{max}$ was defined as the highest value for the plateau on oxygen uptake. The $\dot{V}O_2\text{max}$ was also expressed in metabolic units (metabolic equivalents of oxygen consumption). The metabolic unit is the ratio of the metabolic rate during exercise to the metabolic rate at rest. One metabolic unit corresponds to oxygen uptake of 3.5 mL/kg per minute. An electrocardiogram was registered continuously during the exercise stress test.

The common reasons for early stopping of the exercise test were leg fatigue (n=735), exhaustion (n=207), breathlessness (n=155), and pain in the legs, joints, or back (n=50). The test was discontinued because of cardiorespiratory symptoms or abnormalities in 110 men. These included arrhythmias (n=36), a marked change in systolic (SBP) (n=8) or diastolic blood pressure (n=24), dizziness (n=7), chest pain (n=7), or ischemic electrocardiographic changes (n=4).

ASSESSMENT OF COVARIATES

We assessed smoking, alcohol consumption, and blood pressure^{2,22,23} as described previously. Body mass index was computed as the ratio of weight in kilograms to the square of height in meters; waist-to-hip ratio, the ratio of the circumferences of the waist and the hip. Diabetes was defined as a fasting blood glucose level greater than 110 mg/dL (>6.1 mmol/L) or clinical diagnosis of diabetes with dietary, oral, or insulin treatment. We assessed socioeconomic status (SES) using a summary index that combined measures of income, education, occupation, occupational prestige, material standard of living, and housing conditions, all of which were assessed with the

self-administered questionnaire. A high value on the SES index indicated a low SES. Energy expenditure of physical activity was computed by multiplying the duration and intensity of each physical activity by body weight. The collection of blood specimens and the measurement of serum lipid levels has been described elsewhere.^{22,23}

ASCERTAINMENT OF FOLLOW-UP EVENTS

Incident strokes from March 20, 1984, through December 5, 1989, were ascertained through the FINMONICA stroke register.²⁴ (FINMONICA indicates the Finnish part of the MONICA [Monitoring of Trends and Determinants in Cardiovascular Disease] Stroke Study.) Information on stroke incidence from January 1, 1993, through December 31, 1998, was obtained by means of computerized linkage to the Finnish national hospital discharge registry and death certificate registers. Diagnostic information was collected from hospitals and classified by a neurologist (J.S.) with diagnostic criteria identical to the FINMONICA criteria. The sources of information on stroke were hospital documents, death certificates, autopsy reports, and medicolegal reports. The diagnosis of stroke was based on sudden onset of clinical signs or focal or global disturbance of cerebral function lasting more than 24 hours (except in the case of sudden death or if interrupted by surgical intervention) with no apparent cause other than a vascular origin. Each suspected stroke (*International Classification of Diseases, Ninth Revision [ICD-9] codes 430-431 and International Classification of Diseases, 10th Revision [ICD-10] codes 160-161, 163, and G45-G46*) was classified as (1) a definite stroke, (2) no stroke, or (3) an unclassifiable event. The FINMONICA stroke register data were annually rechecked with the data obtained from the computerized national hospital discharge and death registers. Definite strokes and unclassifiable events were included in the group of any stroke. Each definite stroke was classified as (1) an ischemic stroke (*ICD-9 codes 433-434 and ICD-10 code 163*) or (2) a hemorrhagic stroke (*ICD-9 codes 430-431 and ICD-10 codes 160-161*). If the subject had multiple nonfatal strokes during the follow-up, the first stroke was considered the end point. The average follow-up time was 11 years (range, 0.2-14.8 years). A total of 110 first strokes occurred, of which 87 were ischemic and 23 hemorrhagic strokes.

STATISTICAL ANALYSIS

We examined the associations of $\dot{V}O_2\text{max}$ with the risk factors for strokes by covariate analyses and with the risk for stroke by Cox proportional hazards modeling. The levels of $\dot{V}O_2\text{max}$ were entered as dummy variables into forced Cox models. In these analyses, $\dot{V}O_2\text{max}$ was divided according to quartiles. Covariates were entered uncategorized, when possible, into the Cox models. The following 2 different sets of covariates were used: (1) age and examination years, and (2) age, examination years, cigarette smoking, alcohol consumption, SES, energy expenditure of physical activity, prevalent CHD, diabetes, SBP, and serum low-density lipoprotein (LDL) cholesterol level. We analyzed the predictive power of fully adjusted Cox models by representing receiver operating characteristic curves of these models together with the risk factors. The association between other conventional risk factors and the risk for stroke was analyzed in the Cox model entering SBP, body mass index, alcohol consumption, and serum LDL cholesterol level as quartiles except for smoking (yes or no), with age and examination years adjusted into models. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariate models. All tests for statistical significance were 2-sided. The fit of the proportional hazards models was examined by plotting the hazard functions in different categories of risk factors over time. The results indicated that the application of the models was appropriate. All statistical

Table 1. Characteristics of Men With No Stroke at Baseline in the Quartiles of Maximal Oxygen Uptake*

	Baseline	Quartile†				P Value
		1	2	3	4	
Age, y	52.8 (5.1)	50.3 (5.38)	52.2 (4.94)	53.6 (4.64)	55.1 (3.97)	<.001
Cigarette smoking, pack-years‡	8.65 (17.09)	4.4 (11.1)	7.9 (15.3)	9.2 (16.7)	12.1 (20.4)	<.001
Serum LDL cholesterol, mg/dL	156 (39)	150 (37)	157 (39)	158 (38)	159 (42)	<.001
Systolic blood pressure, mm Hg	134.2 (17.1)	129.7 (13.9)	133.7 (15.8)	135.5 (16.8)	136.8 (19.3)	.001
Alcohol consumption, g/wk	74.4 (121.8)	60.6 (91.6)	69.4 (103.6)	84.5 (128.2)	82.8 (153.0)	.002
Prevalent coronary heart disease, %	22.0	0.07	14.5	21.5	44.9	.001

Abbreviations: LDL, low-density lipoprotein; $\dot{V}O_2\text{max}$, maximum oxygen consumption.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

*Unless otherwise indicated, data are expressed as mean (SD).

†Quartile 1 indicates $\dot{V}O_2\text{max}$ of >35.3 mL/kg per minute; quartile 2, 30.3-35.3 mL/kg per minute; quartile 3, 25.2-30.2 mL/kg per minute; and quartile 4, <25.2 mL/kg per minute.

‡Denotes the lifelong exposure to smoking that was estimated as a product of years smoked and the number of tobacco products smoked daily at the time of examination.

Table 2. Relative Risk for Stroke in the Quartiles of Maximal Oxygen Uptake in Men With No History of Stroke or Pulmonary Disease at Baseline*

$\dot{V}O_2\text{max}$ Quartile, mL/kg per Minute (No. of Cases)	Any Strokes (n = 110)					Ischemic Strokes (n = 87)				
	RR (95% CI)†‡	P Value	RR (95% CI)§	P Value	No. of Cases	RR (95% CI)†	P Value	RR (95% CI)§	P Value	No. of Cases
>35.3 (n = 503)	1.00		1.00		13	1.00		1.00		9
30.3-35.3 (n = 503)	1.65 (0.94-3.26)	.15	1.39 (0.70-2.77)	.34	24	1.54 (0.68-3.50)	.30	1.28 (0.56-2.94)	.55	16
25.2-30.2 (n = 504)	1.62 (0.82-3.22)	.16	1.32 (0.66-2.65)	.43	24	2.05 (0.93-4.50)	.07	1.64 (0.74-3.65)	.22	22
<25.2 (n = 502)	3.24 (1.71-6.12)	<.001	2.30 (1.18-4.06)	.01	49	3.50 (1.66-7.41)	.001	2.40 (1.09-5.25)	.03	40

Abbreviations: CI, confidence interval; RR, relative risk; $\dot{V}O_2\text{max}$, maximum oxygen consumption.

*Pulmonary disease includes chronic bronchitis, bronchial asthma, and pulmonary tuberculosis.

†Adjusted for age and examination years.

‡P<.001 for linear trend.

§Adjusted for age, examination years, cigarette smoking, alcohol consumption, socioeconomic status, energy expenditure of physical activity, diabetes mellitus, systolic blood pressure, and serum low-density lipoprotein cholesterol level.

||P = .01 for linear trend.

analyses were performed using the SPSS software, version 10.0 for Windows (SPSS Inc, Chicago, Ill).

RESULTS

BASELINE CHARACTERISTICS

In the beginning of the follow-up, the mean age of the subjects was 52.8 years (range, 42.0-61.3 years). The mean of $\dot{V}O_2\text{max}$ was 30.2 mL/kg per minute (range, 6.36-65.4 mL/kg per minute). In our study, men with a low $\dot{V}O_2\text{max}$ were older, consumed more alcohol, smoked, and had higher serum LDL cholesterol levels and SBP compared with those who had a high $\dot{V}O_2\text{max}$ (**Table 1**).

RISK FACTORS FOR STROKE

As continuous variables, the strongest and statistically significant risk factors for any stroke were $\dot{V}O_2\text{max}$ (P<.001), SBP (P<.001), SES (P<.001), and diabetes (P=.02) after adjustment for age and examination years. The respective risk factors as continuous variables for ischemic stroke were $\dot{V}O_2\text{max}$ (P<.001), SBP (P<.001), SES (P<.001), and diabetes (P=.003). An SD increase in $\dot{V}O_2\text{max}$ (3.5 mL/kg per minute) decreased the risk for

any strokes by 17% (95% confidence interval [CI], 14%-8%) and ischemic stroke by 17% (95% CI, 25%-8%).

For testing the discriminatory power of the adjusted Cox model, we included age, examination years, cigarette smoking, alcohol consumption, SES, energy expenditure of physical activity, prevalent CHD, diabetes, SBP, and serum LDL cholesterol level into the same model. The area under the curve was 0.72 (95% CI, 0.68-0.78) for ischemic stroke. After adding the $\dot{V}O_2\text{max}$ into the model, the receiver operating characteristic curve value was 0.74 (95% CI, 0.67-0.76), representing good discriminatory power of the model adjusted for the risk factors, although the area under the receiver operating characteristic curve did not markedly change.

CARDIORESPIRATORY FITNESS AND RISK FOR STROKE

Cardiorespiratory fitness was inversely related to the risk for stroke (**Table 2**). Low cardiorespiratory fitness was associated also with an increased risk for any stroke and ischemic stroke. Men with low cardiorespiratory fitness ($\dot{V}O_2\text{max}$, <25.2 mL/kg per minute [lowest quartile]) had a 3.24-fold risk for any stroke (95% CI, 1.71-6.12; P<.001; P<.001 for linear trend across the quartiles) and a 3.50-

Table 3. Relative Risks of Stroke According to Systolic Blood Pressure, Body Mass Index, Alcohol Consumption, Serum LDL Cholesterol Level, and Smoking

Risk Factor, Quartiles	Any Strokes		Ischemic Strokes	
	RR (95% CI)*	P Value	RR (95% CI)*	P Value
Systolic blood pressure, mm Hg				
<122	1.00		1.00	
122-132	1.68 (0.91-3.12)	.10	1.95 (0.97-3.92)	.06
133-143	2.01 (1.10-3.65)	.02	2.13 (1.08-4.23)	.03
>143	2.73 (1.54-4.81)	<.001	2.97 (1.55-5.69)	.001
BMI				
<24.5	1.00		1.00	
24.5-26.4	1.63 (0.94-2.85)	.08	1.70 (0.91-3.13)	.09
26.5-28.8	1.43 (0.81-2.52)	.22	1.10 (0.57-2.14)	.78
>28.8	2.04 (1.20-3.49)	.009	2.27 (1.26-4.10)	.006
Alcohol consumption, g/wk				
<6.1	1.00		1.00	
6.1-31.8	0.55 (0.32-0.95)	.03	0.54 (0.29-1.00)	.05
31.9-93.7	0.99 (0.62-1.60)	.99	1.02 (0.60-1.73)	.94
>93.8	1.08 (0.6801-1.73)	.73	1.25 (0.75-2.08)	.40
Serum LDL cholesterol level, mg/dL				
<129	1.00		1.00	
129-152	0.66 (0.38-1.15)	.14	0.76 (0.41-1.40)	.38
153-180	0.78 (0.46-1.32)	.35	0.77 (0.42-1.41)	.40
180	1.15 (0.72-1.83)	.57	1.33 (0.79-2.26)	.29
Smoking, %				
Nonsmokers (68%)	1.00		1.00	
Smokers (32%)†	1.23 (0.85-1.79)	.27	1.16 (0.76-1.76)	.49

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; LDL, low-density lipoprotein; RR, relative risk.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

*Adjusted for age and examination years.

†A smoker was one who had ever smoked cigarettes, cigars, or a pipe regularly.

fold risk for ischemic stroke (95% CI, 1.66-7.41; $P = .001$; $P < .001$ for linear trend across the quartiles), compared with men who had high cardiorespiratory fitness ($\dot{V}O_2\text{max}$, >35.3 mL/kg per minute [highest quartile]) after adjusting for age and examination years.

Low cardiorespiratory fitness was associated with a 2.30-fold risk for any stroke and a 2.40-fold risk for ischemic stroke, after additional adjustment for cigarette smoking, alcohol consumption, SES, energy expenditure of physical activity, prevalent CHD, diabetes, SBP, and serum LDL cholesterol level (Table 2). When we excluded men with prevalent CHD ($n = 677$), low cardiorespiratory fitness ($\dot{V}O_2\text{max}$, <25.2 mL/kg per minute) was related to a 1.93-fold risk for stroke (95% CI, 1.10-3.22; $P = .02$) after adjustment for age, examination year, cigarette smoking, alcohol consumption, SES, energy expenditure of physical activity, diabetes, SBP, and serum LDL cholesterol level.

OTHER RISK FACTORS FOR STROKE

The relative risks for stroke according to the quartiles of SBP, body mass index, alcohol consumption, serum LDL cholesterol level, and smoking status, adjusted for age and examination year, are presented in **Table 3**. Hypertensive men (SBP, >143 mm Hg) had a 2.73-fold risk for any stroke and a 2.97-fold risk for ischemic stroke compared with men with SBP of less than 122 mm Hg (Table 3). Furthermore, men with slightly increased SBP

(133-143 mm Hg) had a more than 2-fold risk for any stroke, as shown in Table 3.

Obesity (body mass index, >28.8) was associated with a greater than 2-fold risk for any stroke and ischemic stroke (Table 3). On the other hand, alcohol consumption had a protective effect because men who drank moderate amounts of alcohol had a reduced risk for stroke, indicating a U-shaped association between alcohol consumption and stroke. Men consuming alcohol at 6.1 to 31.8 g/wk had a relative risk of 0.55 for any stroke and 0.54 for ischemic stroke (Table 3). Serum LDL cholesterol level and smoking were not significantly associated with the risk for strokes in our study population.

COMMENT

Cardiorespiratory fitness, as measured by $\dot{V}O_2\text{max}$ during exercise, had a strong inverse relation to the risk for any stroke and ischemic stroke in middle-aged men from eastern Finland. Furthermore, cardiorespiratory fitness was at least as strong a risk factor as conventional risk predictors for stroke, including SBP, obesity, alcohol consumption, serum LDL cholesterol level, and smoking.

To our knowledge, this is the first population-based follow-up study showing an inverse association between cardiorespiratory fitness, as indicated by directly measured $\dot{V}O_2\text{max}$, and the risk for stroke. Our study shows that excessive risk for stroke was observed among men with the lowest level of $\dot{V}O_2\text{max}$ (<25.2 mL/kg per

minute). There seems to be a threshold between the 2 lowest quartiles of $\dot{V}O_2\text{max}$, indicating that men with a $\dot{V}O_2\text{max}$ below this level were at high risk for stroke. However, a change in $\dot{V}O_2\text{max}$ of 3.5 mL/kg per minute corresponds to a 17% decrease in the risk for stroke among these men. Previous studies have found an association between physical activity at work¹³ or during leisure time^{12,14,15,17} and subsequent risk for stroke. Leisure-time physical activity has been related to a decreased risk for ischemic stroke.¹⁶ Furthermore, low levels of occupational physical activity have been shown to increase the risk for stroke.¹⁴ However, some studies have provided an indication of a U-shaped relationship between physical activity and stroke.¹⁸⁻²⁰ Although these reports provide some indication that a very high level of intense physical activity could even increase the risk for stroke, there is no consistent evidence of this, and no significant results regarding this kind of U-shaped relationship,¹⁸⁻²⁰ since there are few people doing vigorous activity, and the absolute number of strokes is small in the average population who performed vigorous exercise. High-intensity exercise is more effective than low-intensity exercise for improving $\dot{V}O_2\text{max}$ in healthy persons, whereas lower-intensity physical activity may be sufficient to improve $\dot{V}O_2\text{max}$ in high-risk individuals, but the optimal intensity of exercise in different risk groups for the prevention of stroke remains unclear.

Low cardiorespiratory fitness has been associated with increased risk for cardiovascular disease in previous studies.⁷⁻⁹ On the other hand, a high cardiorespiratory fitness may delay the progression of atherosclerosis¹⁰ considered to be the general underlying pathologic basis of CHD and ischemic stroke. A few clinical trials have suggested that regular physical exercise may retard the progression of atherosclerosis.²⁵⁻²⁸ Good cardiorespiratory fitness and physical activity may reduce the risk for stroke by affecting modifiable risk factors, including hypertension,²⁹ obesity,³⁰ and dyslipidemia.³¹ Studies show that physical activity can lower blood pressure and serum LDL cholesterol levels,³²⁻³⁴ and some previous studies have shown that especially moderate to high levels of intense physical activity are inversely associated with LDL cholesterol level.^{33,35,36} Regular exercise improves the plasma lipoprotein profile that results from adaptation of a diet with low levels of saturated fat and cholesterol.³⁶ Furthermore, it was observed that diets containing low levels of fat combined with aerobic exercise decrease LDL cholesterol levels in hypercholesterolemic individuals.³¹ These findings highlight the importance of physical exercise in the protection against the atherogenic lipid profile.

On the basis of existing data, light to moderate exercise appears to be beneficial in blood pressure reduction, which may help in reducing atherogenesis and decreasing the risk for stroke due to ischemic and hemorrhagic pathophysiological reasons.³⁷ A high intraluminal pressure will lead to extensive change in endothelium and smooth muscle function in intracerebral arteries. In subjects with preclinical atherosclerotic changes and elevated SBP at rest or during exercise, the increased stress on the vessel wall can increase the risk for endothelial injury and permeability over the blood-

brain barrier and result in local or multifocal edema.³⁸ Endothelial damage and change in blood cell-endothelium interaction can lead to local thrombi formation and ischemic lesions. More specific mechanisms for the prevention of hemorrhagic stroke are the decrease in blood pressure and beneficial effects on endothelial function. However, in our study, adjustment for known risk factors did not markedly change the association between cardiorespiratory fitness and risk for stroke, and there was an independent relationship between cardiorespiratory fitness and risk for stroke.

Previous studies have suggested that low cardiorespiratory fitness is comparable with other conventional risk factors for cardiovascular disease.^{7,39} Furthermore, this study also shows that low cardiorespiratory fitness is comparable to other conventional risk factors for stroke such as high SBP, obesity, high serum LDL cholesterol level, and smoking. However, we demonstrated that serum LDL cholesterol level was not a significant independent predictor for stroke, and that it is a weaker predictor than $\dot{V}O_2\text{max}$. Existing data also suggest that the association between serum LDL cholesterol level and the risk for stroke is weak or nonsignificant. This may be partly due to the fact that a low level of serum LDL cholesterol is a risk factor for hemorrhagic strokes in some studies.⁴⁰ One factor contributing to this association is that an average LDL cholesterol level was relatively high at the beginning of the follow-up, and, on the other hand, current findings recommend more aggressive therapy to lower lipid levels. Thus, in our study population, more high-risk and hypercholesterolemic men may have been treated and thereby decreased their risk for ischemic stroke.⁴⁰ In general, any other new preventive measures started during the follow-up may weaken the observed associations in this study.

The major part of the predictive power of $\dot{V}O_2\text{max}$ may be contained in the other risk factors included in the models. Hence, the increase in predictive power of $\dot{V}O_2\text{max}$ alone was minimal, but this does not undermine the important predictive power of the $\dot{V}O_2\text{max}$ for stroke. As $\dot{V}O_2\text{max}$ was a predictive factor before and after adjustment for the known risk factors, the knowledge about the level of cardiorespiratory fitness provides new information for the risk for stroke. We observed that cardiorespiratory fitness has a strong and independent predictive value of stroke. Our findings suggest that it may be useful to assess the level of cardiorespiratory fitness in clinical practice, as low cardiorespiratory fitness is an independent predictor of future stroke. Given the high cost of treating stroke patients and the limited success of acute-phase treatments, prevention is one of the most effective ways to decrease the risk for stroke that is considered to be an enormous public health problem. As low cardiorespiratory fitness is a modifiable factor, any physical exercise programs that could improve the level of cardiorespiratory fitness in a population should be recommended. On the basis of previous studies, it seems that at least 6 months of regular training with moderate intensity can improve exercise capacity by 1 metabolic unit, corresponding to 3.5 mL/kg per minute of directly measured $\dot{V}O_2\text{max}$. However, training history and the duration and intensity of exercise may have a marked effect

on the improvement of $\dot{V}O_2\text{max}$, and accumulating evidence from exercise intervention trials show that it is possible to achieve a beneficial effect on risk factors without improvements of exercise capacity.

It is generally assumed that low cardiorespiratory fitness represents mainly physical inactivity. The $\dot{V}O_2\text{max}$, which is the product of cardiac output and the arteriovenous oxygen difference, is determined by age; sex; duration, frequency, intensity, and type of physical activity; genetic factors; and clinical and subclinical diseases. The genetic component of variation in cardiorespiratory fitness is thought to range from 25% to 40%.⁴¹ For most individuals, increases in physical exercise produce an increase in $\dot{V}O_2\text{max}$, although the amount of adaption in $\dot{V}O_2\text{max}$ to a standard exercise dosage varies widely and may be due to genetic factors. Therefore, the optimal level of physical activity required to improve cardiorespiratory fitness depends on the initial health and fitness status as well as familial factors. The $\dot{V}O_2\text{max}$ usually decreases by 5% to 15% per decade from the ages of 20 to 80 years, and the rate at which oxygen uptake declines is directly related to the maintenance of physical activity level, emphasizing the importance of physical activity.

The $\dot{V}O_2\text{max}$ is considered to be a gold standard for measuring cardiorespiratory fitness. Thus, we recommend it for measurement of cardiorespiratory fitness in this population. The self-reported format for physical activity assessment in population studies may result in inaccuracy, whereas the use of $\dot{V}O_2\text{max}$ helps to reduce such measurement errors. It is suggested that cardiorespiratory fitness is an objective marker that indicates the level of physical activity.³⁵ The strength of our study is that we have a representative population-based sample of middle-aged men with a high participation rate. There were no losses during follow-up, as each subject was identified on the basis of the national social security number. The diagnostic information was standardized, and the diagnosis of valid strokes was ascertained by the practices and criteria used in the FINMONICA stroke register. In the present study, we could study the stroke subtypes (ischemic strokes), whereas several previous studies defining the effects of fitness or physical activity were not able to differentiate between the subtypes of stroke due to different pathophysiological features. Furthermore, we have reliable data on baseline health status and risk factors that allowed the statistical adjustment of potential confounders.

The limitation of this study is that we measured the $\dot{V}O_2\text{max}$ only once, at the baseline examination. It would be more informative to measure the $\dot{V}O_2\text{max}$ over time to study whether changes in the $\dot{V}O_2\text{max}$ would predict the risk for stroke. However, no studies have presented information on behavioral changes in physical activity or cardiorespiratory fitness and how these changes may relate to the risk for stroke over time. According to previous studies, the real changes over time in fitness have an effect on mortality,^{42,43} because individuals who maintain or improve physical fitness have a decreased risk for mortality compared with those who were persistently unfit. In addition, our results are based on an ethnically and genetically homogeneous population, and in the same sex, which may limit the generalization of our results. It is

possible that the pathogenesis of stroke is different in middle-aged than in older patients. Therefore, more studies are needed in different study populations and especially in women.

This prospective population-based study provides the evidence that poor cardiorespiratory fitness is associated with an increased risk for first stroke event. The $\dot{V}O_2\text{max}$ may be used clinically in the evaluation of the risk for future stroke because it seems to be an independent predictor, as are other modifiable risk factors.

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