minute). There seems to be a threshold between the 2 lowest quartiles of $\dot{V}O_2$max, indicating that men with a $\dot{V}O_2$max below this level were at high risk for stroke. However, a change in $\dot{V}O_2$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 work[13] 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 $\dot{V}O_2$max in healthy persons, whereas lower-intensity physical activity may be sufficient to improve $\dot{V}O_2$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 progession of atherosclerosis[10] 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 adaption 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 $\dot{V}O_2$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 $\dot{V}O_2$max may be contained in the other risk factors included in the models. Hence, the increase in predictive power of $\dot{V}O_2$max alone was minimal, but this does not undermine the important predictive power of the $\dot{V}O_2$max for stroke. As $\dot{V}O_2$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, correponding to 3.5 mL/kg per minute of directly measured $\dot{V}O_2$max. However, training history and the duration and intensity of exercise may have a marked effect

on the improvement of $\dot{V}O_2$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 $\dot{V}O_2$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 $\dot{V}O_2$max, although the amount of adaption in $\dot{V}O_2$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 $\dot{V}O_2$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 maintainance of physical activity level, emphasizing the importance of physical activity.

The $\dot{V}O_2$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 $\dot{V}O_2$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 $\dot{V}O_2$max only once, at the baseline examination. It would be more informative to measure the $\dot{V}O_2$max over time to study whether changes in the $\dot{V}O_2$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 $\dot{V}O_2$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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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	42-60歳			( )		前向き研究
	対象数	1000～5000	空白		( )		( )

調査の方法	質問紙	( )					
アウトカム	予 防	脳血管障害予防	な し	な し	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表	
図表掲載箇所	
概 要 (800字まで)	最大酸素消費量(VO2)により評価した循環器系体力と脳卒中発症の関係を検討した。さらに、最大酸素摂取量を脳卒中発症の予測因子として他のリスクファクターと比較した。を示すことによって心臓・呼吸性フィットネスの相関を調べた。 本調査は,東フィンランドのクオピオと周辺住民を対象として平均11年間追跡したコホート研究である。 この研究に参加したベースラインで脳卒中、呼吸器系統疾患の既応のない2011人の男性のうち110人が脳卒中を発症し,その内87人が虚血性だった。VO2はベースラインで運動負荷試験により直接測定した。 年齢と調査年度で調整すると、体力の高い男性(VO2、>35.3mL/kg/min)と比べて、体力のない男性(VO2、<25.2mL/kg/min)での全脳卒中の相対危険度は3.2(95%CI, 1.71-6.12;P<.001;P<.001)), および虚血性脳卒中は3.50((95% CI、1.66-7.41; P=.001; (P<.001))であった。 その関係は喫煙, アルコール摂取, 社会経済状態, 身体的活動のエネルギー消費量, 虚血性心疾患の既応, 糖尿病, 収縮期血圧, 血清LDLコレステロール値でさらに調整した後と統計的に有意なままであった。循環器系体力が低いことは脳卒中のリスクファクターとして収縮期血圧, 肥満, アルコール摂取, 喫煙, 血清LDLコレステロール値に匹敵していた。
結 論 (200字まで)	循環器系体力が低いことは全脳卒中、虚血性脳卒中のリスクを増加させる。VO2は他の危険要素に匹敵する脳卒中の強い予測因子の1つである。
エキスパートによるコメント (200字まで)	脳卒中発症に対する体力の影響を他のリスクファクターとの比較で示した、クオピオ虚血性心疾患リスクファクタースタディーのデータである。

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Cardiorespiratory Fitness Is Inversely Associated With the Incidence of Metabolic Syndrome

A Prospective Study of Men and Women

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Background—Few studies have reported the relationship between cardiorespiratory fitness and metabolic syndrome incidence, particularly in women.

Methods and Results—We prospectively studied 9007 men (mean±SD age, 44±9 years; body mass index, 25±3 kg/m^2) and 1491 women (age, 44±9 years; body mass index, 22±2 kg/m^2) who were free of metabolic syndrome and for whom measures of waist girth, resting blood pressure, fasting lipids, and glucose were taken during baseline and follow-up examinations. Baseline cardiorespiratory fitness was quantified as duration of a maximal treadmill test. Metabolic syndrome was defined with NCEP ATP-III criteria. During a mean follow-up of 5.7 years, 1346 men and 56 women developed metabolic syndrome. Age-adjusted incidence rates were significantly lower (linear trend, $P<0.001$) across incremental thirds of fitness in men and women. After further adjustment for potential confounders, multivariable hazard ratios for incident metabolic syndrome among men in the low, middle, and upper thirds of fitness, were 1.0 (referent), 0.74 (95% CI, 0.65 to 0.84), and 0.47 (95% CI, 0.40 to 0.54) (linear trend $P<0.001$); in women, they were 1.0 (referent), 0.80 (95% CI, 0.44 to 1.46), and 0.37 (95% CI, 0.18 to 0.80) (linear trend $P=0.01$), respectively. Similar patterns of significant inverse associations between fitness and metabolic syndrome incidence were seen when men were stratified on categories of body mass index, age, and number of baseline metabolic risk factors, but patterns were variable in women.

Conclusions—Low cardiorespiratory fitness is a strong and independent predictor of incident metabolic syndrome in women and men. Clinicians should consider the potential benefits of greater cardiorespiratory fitness in the primary prevention of metabolic syndrome, particularly among patients who have already begun to cluster metabolic syndrome components. (***Circulation.* 2005;112:505-512.**)

Key Words: atherosclerosis ■ exercise ■ glucose ■ metabolic syndrome X ■ prevention

Metabolic syndrome is a condition of high-risk phenotypes that include elevated blood pressure, dyslipidemia, impaired glycemic control, and abdominal obesity.[1] The etiology of metabolic syndrome is complex and characterizes defects in several homeostatic regulatory systems[2] that, when coexisting, increase the risk of cardiovascular events[3–5] and diabetes.[4,6,7] Recent data suggest that metabolic syndrome may be particularly associated with significant underlying atherosclerotic coronary disease in women.[8] Therefore, detecting metabolic syndrome in otherwise asymptomatic individuals has been recognized as a clinical tool for identifying high-risk individuals for intensive primary preventive therapy.[9]

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Several investigators have identified predictors of metabolic syndrome.[10–16] Few studies, however, have included measures of physical activity or cardiorespiratory fitness.[10,11,16] Experimental data have shown that increases in physical activity improve each metabolic syndrome risk factor.[17–21] Cross-sectional studies,[22,23] including our analyses in the Aerobics Center Longitudinal Study (ACLS),[24,25] have demonstrated an inverse association for physical activity and cardiorespiratory fitness with metabolic syndrome prevalence. Furthermore, a recent study showed that participation in 20 weeks of supervised aerobic exercise training resulted in a 31% reduction in metabolic syndrome prevalence among 105 adults.[21]

Prospective data on physical activity and cardiorespiratory fitness as predictors of metabolic syndrome incidence are sparse.[10,11,16] Studies using fitness exposures have consistently shown an inverse association with incident metabolic syndrome,[10,11] whereas studies using self-reported physical activity exposures have been equivocal.[11,16] Cardiorespiratory fitness, assessed with maximal exercise testing, is stronger than self-reported physical activity as a predictor of health

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outcomes because fitness assessment is less prone to misclassification[26] and because factors other than physical activity may influence fitness levels and health status through related biological pathways.[27] A weakness in existing prospective data relating activity or fitness with incident metabolic syndrome is a limited understanding of whether the association varies by sex, age, weight status, and the number of baseline metabolic syndrome components. We therefore examined these issues in a large prospective study of men and women.

Methods

Participants were men and women 20 to 80 years of age who had preventive medical examinations at the Cooper Clinic (Dallas, Tex) between 1979 and 2003 and who are enrolled in the ACLS.[28,29] Inclusion criteria required participants to have at least 2 clinic examinations with complete measurements for each metabolic syndrome variable and a baseline cardiorespiratory fitness measurement (n=13 628). Exclusions (n=3130) were prevalent metabolic syndrome (n=2067), an abnormal resting (n=327) or exercise (n=441) ECG, and a history of physician-diagnosed coronary heart disease (n=48), stroke (n=11), or cancer (n=236) at baseline. The remaining 9007 men and 1491 women met all criteria and were included in the analysis. Participants were mostly non-Hispanic whites (>95%) of middle to high socioeconomic status. The average number of clinic visits and years between first and last visits were 4.3±3.3 (range, 2 to 28) and 5.8±5.1 years (range, 0.01 to 23.9) in men and 3.1±1.9 (range, 2 to 16) and 5.5±5.1 years (range, 0.03 to 22.8) in women, respectively. The Cooper Institute Institutional Review Board approved the study protocol, and participants provided written informed consent.

The clinic examination followed a 12-hour fast as described elsewhere.[24,28,29] Body mass index (BMI; kg/m^2) was computed from measured height and weight. Waist girth was measured at the umbilicus. After a brief period of quiet sitting, resting systolic and diastolic blood pressures were recorded as the first and fifth Korotkoff sounds using standard auscultation methods.[30] Concentrations of triglycerides, HDL cholesterol, and glucose were measured in antecubital venous blood with automated bioassays according to Centers for Disease Control and Prevention standards.[28]

We quantified cardiorespiratory fitness as the duration of a maximal treadmill exercise test using a modified Balke protocol.[24,28] Patients began walking at 3.3 mph (88 m/min) with no elevation. The incline was increased to 2% after the first minute and was increased 1% each minute thereafter until the 25th minute. For participants who were still able to exercise beyond 25 minutes, the elevation was maintained at 25%, and the speed was increased by 0.2 mph (5.4 m/min) each minute until volitional exhaustion. Duration of this treadmill test is highly correlated with measured maximal oxygen uptake in men (r=0.92) and women (r=0.94).[31,32] Maximal MET levels of cardiorespiratory fitness (1 MET=3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) were estimated from the final treadmill speed and grade.[33] Sex-specific distributions of treadmill exercise duration were formed within the following age groups: 20 to 39, 40 to 49, 50 to 59, and ≥60 years. Each sex- and age-specific distribution was divided into thirds of low, middle, and high cardiorespiratory fitness (Table 1). Use of tertile cutpoints is not the standard method of categorizing fitness in the ACLS. Previous ACLS reports that showed that low fitness is an independent predictor of mortality have used the lowest fifth of age- and sex-standardized treadmill duration to define low fitness, and moderate fitness and high fitness have been defined by the middle 40% and upper 40% of the distribution, respectively.[28,29,34] In the present analysis, however, low-fit individuals by the previous definition were rarely free of metabolic syndrome at baseline. Therefore, fitness was defined according to tertile cutpoints.

The outcome variable was metabolic syndrome defined as ≥3 of the following criteria[1]: abdominal obesity (waist girth >102 cm [40 in] in men and >88 cm [35 in] in women), triglycerides ≥1.69 mmol/L (150 mg/dL), HDL <1.04 mmol/L (40 mg/dL) in men and <1.3 mmol/L (50 mg/dL) in women, blood pressure ≥130 mm Hg systolic or ≥85 mm Hg diastolic, and glucose ≥6.1 mmol/L (110 mg/dL). Histories of physician-diagnosed hypertension and diabetes were included in the definition of abnormal blood pressure and glucose, respectively, as done in other epidemiological studies of metabolic syndrome incidence.[3,10,16] Other variables included in the analysis were current smoking status, alcohol intake, and family history of hypertension, diabetes, and premature coronary disease obtained from a standardized medical history questionnaire. Alcohol intake was quantified as drinks per week, with a drink standardized to 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of liquor.

TABLE 1. Age- and Sex-Specific MET Values According to Tertile of Cardiorespiratory Fitness

	Men			Women		
Age Groups, y	Low	Middle	High	Low	Middle	High
20–39	<12.2	12.2–13.9	>13.9	<9.9	9.9–11.6	>11.6
40–49	<11.6	11.6–13.5	>13.5	<9.3	9.3–11.2	>11.2
50–59	<10.8	10.8–12.6	>12.6	<8.5	8.5–9.8	>9.8
≥60	<9.9	9.9–11.7	>11.7	<8.0	8.0–9.0	>9.0

1 MET=3.5 mL O_2 uptake·kg^{-1}·min^{-1}. METs were estimated from the final treadmill speed and grade of a modified Balke-Ware protocol as described in Methods.

Statistical Analysis

Cases were defined as meeting the metabolic syndrome definition at any clinic examination after baseline. Among noncases, follow-up time was computed as the difference between the date of the baseline and the last clinic examination. Because the exact date of metabolic syndrome development is unknown, we used the midpoint between the date of the case-finding clinic examination and the date of the previous examination when participants were known to be free of metabolic syndrome. Follow-up time among cases was then computed as the difference between this date and the date of the baseline examination. Person-years of exposure were computed as the sum of follow-up time among cases and noncases. Incident rates (per 1000 person-years) were computed as the number of cases divided by person-years of exposure for the total sample according to sex, cardiorespiratory fitness level, and other categories of risk predictors.

We used Cox regression to estimate sex-specific hazard ratios (HRs) and 95% CIs as an index of the strength of association between cardiorespiratory fitness and incident metabolic syndrome. Multivariable analyses were adjusted for year of baseline examination, age (years), current smoking (yes/no), alcohol intake (drinks/week), number of baseline metabolic syndrome risk factors (0, 1, or 2), and family history (yes/no) of hypertension, diabetes, and premature coronary disease. Henceforth, "covariables" refers to these factors unless otherwise specified. Additional Cox regression analyses were performed separately for men and women according to baseline BMI (<25 and ≥25 kg/m^2), age (20 to 39, 40 to 49, and ≥50 years), and metabolic syndrome components (0, 1, or 2).

We estimated population-attributable risk (PAR) of metabolic syndrome for the lowest third of cardiorespiratory fitness and each metabolic syndrome risk factor to quantify the influence that eliminating these risk factors might have on metabolic syndrome incidence in the source population of our cohort. PAR was computed as $P_c(1-1/HR_{adj})$, where P_c is the prevalence of a risk factor among metabolic syndrome cases and HR_{adj} is the multivariable adjusted HR for metabolic syndrome associated with the specified risk factor.[35] We computed 95% CIs around the point estimate PAR using standard methods.[35] There were no a priori hypotheses on sex differences in metabolic syndrome incidence or the association between fitness and metabolic syndrome. Probability values are 2 sided, and P<0.05 was regarded as statistically significant.

TABLE 2. Baseline Characteristics for Men and Women According to Metabolic Syndrome Status at Follow-Up

	Men		Women	
	Metabolic Syndrome	No Metabolic Syndrome	Metabolic Syndrome	No Metabolic Syndrome
n	1346	7661	56	1435
Age, y	44.4±8.4	43.5±9.2	48.0±9.6	44.1±9.1
BMI, kg/m^2	26.7±2.9	25.0±2.6	25.2±4.0	22.0±2.8
Waist, cm	95.3±8.1	89.8±8.0	78.6±9.0	70.4±7.9
Systolic BP, mm Hg	120.3±12.0	117.6±12.0	118.7±12.8	110.6±13.0
Diastolic BP, mm Hg	80.9±8.4	78.7±8.7	79.7±9.0	74.9±9.0
Triglycerides, mmol/L	1.67±1.02	1.17±0.67	1.48±0.59	0.92±0.51
HDL-C, mmol/L	1.08±0.24	1.27±0.29	1.37±0.25	1.61±0.34
Glucose, mmol/L	5.50±0.57	5.40±0.62	5.28±0.49	5.18±0.81
Maximal METs	11.8±1.9	12.7±2.3	9.0±1.9	10.1±2.0
Current smoker, %	16.5	14.1	10.7	8.0
≥5 Alcoholic drinks per week, %	43.2	43.1	19.6	24.1
Family history, %				
Hypertension	44.7	41.9	48.2	53.2
Diabetes	29.3	25.8	41.1	33.9
Premature coronary heart disease	17.9	15.5	23.2	16.8
Abdominal obesity, %	15.9	5.3	10.7	2.8
High blood pressure, %	38.0	29.9	39.2	19.1
High triglycerides, %	32.9	12.5	25.0	6.0
High glucose, %	8.6	7.2	8.9	3.9
Low HDL-C, %	41.0	20.3	35.7	14.0
No. of metabolic syndrome factors, %				
0	14.3	43.5	23.2	61.4
1	34.8	37.6	33.9	31.2
2	50.9	18.9	42.9	7.4

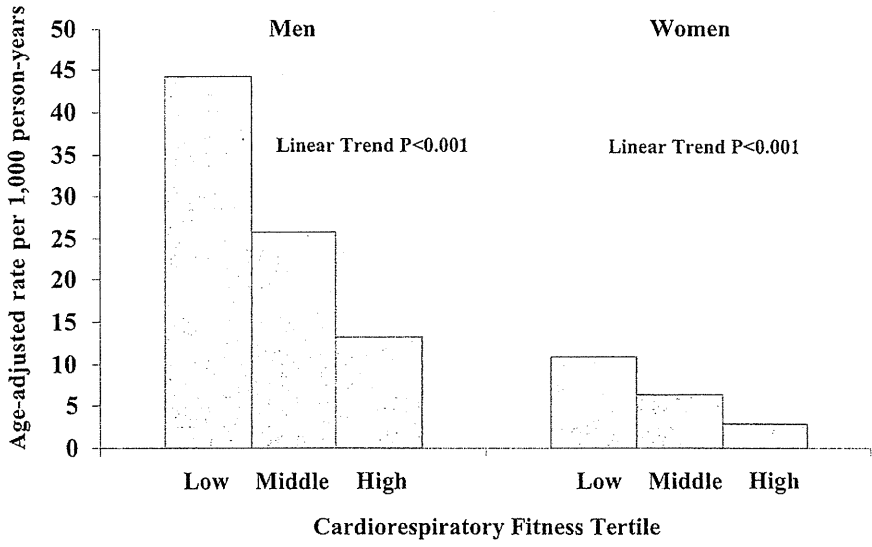
BP indicates blood pressure; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol. Data shown as mean±SD unless specified otherwise.

Results

A total of 1346 men and 56 women developed metabolic syndrome during 52 060 and 8275 person-years of exposure, respectively. The crude incidence rate of metabolic syndrome per 1000 person-years was 25.9 in men and 6.8 in women. Men and women who developed metabolic syndrome were broadly similar in age, average risk factor values, and average maximal MET levels of cardiorespiratory fitness as their same-sex peers who remained free of metabolic syndrome (Table 2). In men and women, cases had higher prevalence of each metabolic syndrome risk factor at baseline than noncases. The number of baseline metabolic risk factors was significantly associated with metabolic syndrome case status in men ($\chi^2_{df=1}=709.4$; P for trend <0.001) and in women ($\chi^2_{df=1}=68.9$; P for trend <0.001). These values were similar for cases and noncases in both sexes.

We observed a steep inverse gradient (linear trend, $P<0.001$) of age-adjusted metabolic syndrome incidence rates across incremental thirds of cardiorespiratory fitness in men and women (the Figure). Multivariable Cox regression was then used to quantify the strength of association between fitness and incidence of metabolic syndrome with adjustment for covariables (Table 3). The adjusted risk of metabolic syndrome was 26% (16% to 35%) and 53% (46% to 60%) lower for men in the middle and upper thirds of fitness (linear trend $P<0.001$), respectively, compared with men in the lower third. In women, the adjusted risk of metabolic syndrome was 20% (−46% to 56%) and 63% (20% to 82%) lower among those in the middle and upper thirds of fitness (linear trend $P=0.01$), respectively, compared with women in the lower third. On average, a 1-MET increment in maximal treadmill performance was associated with a 16% (12% to 17%, $P<0.001$) and 17% (4% to 29%, $P=0.02$) lower multivariable-adjusted risk of metabolic syndrome in men and women, respectively.

We examined whether the association between cardiorespiratory fitness and incident metabolic syndrome varied according to strata of BMI, age, and number of metabolic syndrome components at baseline (Table 3). An inverse dose-response relationship ($P<0.001$) between fitness and metabolic syndrome was observed in men who were normal weight (BMI <25 kg/m^2) and overweight/obese (BMI ≥25 kg/m^2). Men in the top two thirds of the fitness distribution in



Age-adjusted incidence rates (per 1000 person-years) of metabolic syndrome by thirds of cardiorespiratory fitness in men and women. Number at risk (and number of cases) in low, middle, and high tertile of fitness was 3011 (636), 2984 (437), and 3012 (273) in men and 494 (28), 500 (19), and 497 (9) in women, respectively.

the normal and overweight/obese categories, respectively, had an ≈21% and ≈42% lower risk of developing metabolic syndrome than men in the lowest third of fitness within the same weight category ($P<0.001$). A trend for lower metabolic syndrome risk across thirds of fitness was present but not significant for women in the normal weight category.

Strong inverse gradients in the risk of metabolic syndrome were seen across thirds of fitness in men who were 20 to 39, 40 to 49, and ≥50 years. The adjusted risks of metabolic syndrome were 22% to 32% and 52% to 54% lower for men in the middle and upper thirds of fitness, respectively, compared with men of the same age who were in the lowest third ($P<0.001$). A nonsignificant trend for lower metabolic syndrome risk with higher fitness was observed for women in each age group.

We examined the influence that the number of baseline metabolic syndrome risk factors had on the association between fitness and metabolic syndrome. The number of metabolic syndrome components was a significant predictor of developing metabolic syndrome in men and women. After adjustment for age and year of baseline examination, HRs for metabolic syndrome in individuals with 1 and 2 baseline risk factors were 2.9 (95% CI, 2.4 to 3.4; $P<0.001$) and 9.0 (95% CI, 7.6 to 10.6; $P<0.001$) in men and 2.9 (95% CI, 1.4 to 5.9; $P=0.004$) and 16.3 (95% CI, 8.1 to 32.8; $P<0.001$) in women, respectively, compared with their same-sex peers with no metabolic syndrome components at baseline. Significant ($P<0.001$) inverse associations between fitness and metabolic syndrome were seen in men with 0, 1, and 2 metabolic syndrome risk factors at baseline (Table 3). Adjusted HRs were 22% to 35% and 43% to 63% lower for men in the middle and upper thirds of fitness, respectively, compared with men in the lowest third ($P<0.001$). Similar patterns of association were seen in women, but a significant trend was seen only for those with no baseline metabolic syndrome components ($P=0.02$).

The relative importance of low cardiorespiratory fitness and metabolic risk factors as predictors of metabolic syndrome is shown in Table 4. After adjustment for age, smoking, year of baseline examination, and each risk factor in Table 4, low fitness was a significant predictor of metabolic syndrome in men but not women. We computed PAR estimates to place the risk of metabolic syndrome for each exposure in the context of population-disease burden. Accordingly, if all individuals from our population sample who were in the lowest third of fitness had been in the middle or highest third of fitness, the incidence of metabolic syndrome may have been 15% and 20% lower in men and women, respectively. Because the metabolic risk factor may be viewed as intermediate in the causal pathway from fitness to metabolic syndrome, we also computed HRs and PAR estimates for low fitness, adjusting only for age, smoking, and examination year. The HRs and PARs for metabolic syndrome associated with low fitness were 2.3 (95% CI, 2.1 to 2.6) and 26.7% (95% CI, 22.9 to 30.4) for men and 2.4 (95% CI, 1.4 to 4.0) and 28.9% (95% CI, 7.5 to 45.3) for women.

Discussion

Metabolic syndrome afflicts ≈25% of US adults and is associated with increased risk of cardiovascular disease and diabetes.[1] Current clinical guidelines indicate a role for physical activity in the etiology and management of metabolic syndrome.[9] Whether higher levels of activity and fitness may help prevent metabolic syndrome development is less understood, particularly in women.[10,11,16] The results reported here show that cardiorespiratory fitness, an objective marker of recent physical activity patterns, was inversely associated with metabolic syndrome incidence in asymptomatic adults. The overall findings are consistent in women and men and hold after adjustment for several potential confounders, including the number of metabolic syndrome components at baseline. Strengths of the study are the use of maximal treadmill exercise testing to quantify cardiorespiratory fitness; use of a comprehensive physical examination, health history, and resting and stress ECGs to rule out subclinical disease at baseline; use of a large sample of men and women to permit meaningful sex-specific analyses; and an extensive follow-up for incident cases.

Associations between physical activity and metabolic syndrome incidence have been inconsistent,[11,16] which may

TABLE 3. HRs and 95% CIs for Metabolic Syndrome According to Cardiorespiratory Fitness and Other Predictors

	N	Cases	Follow-Up, person-y	Age-Adjusted Rate per 1000 person-y	Cardiorespiratory Fitness Tertile			Linear Trend *P*
					Low	Middle	High	
Men								
Total	9007	1346	52 241	25.8*	1.0 (Referent)	0.74 (0.65–0.84)	0.47 (0.40–0.54)	<0.001
BMI, kg/m^2								
<25	4440	377	29 866	13.0	1.0 (Referent)	0.77 (0.59–0.99)	0.57 (0.44–0.74)	<0.001
≥25	4567	969	22 228	43.0	1.0 (Referent)	0.81 (0.70–0.93)	0.59 (0.48–0.71)	<0.001
Age, y								
20–39	3121	388	16 218	23.3*	1.0 (Referent)	0.78 (0.62–0.98)	0.48 (0.36–0.64)	<0.001
40–49	3587	600	18 311	32.9	1.0 (Referent)	0.75 (0.62–0.90)	0.46 (0.37–0.58)	<0.001
≥50	2299	358	11 255	32.5	1.0 (Referent)	0.68 (0.53–0.87)	0.47 (0.35–0.62)	<0.001
Metabolic syndrome risk factors at baseline								
0	3524	193	23 839	8.4	1.0 (Referent)	0.65 (0.46–0.92)	0.37 (0.26–0.53)	<0.001
1	3353	468	19 410	24.4	1.0 (Referent)	0.70 (0.57–0.86)	0.43 (0.34–0.54)	<0.001
2	2130	685	8841	76.1	1.0 (Referent)	0.78 (0.66–0.93)	0.57 (0.45–0.71)	<0.001
Women								
Total	1491	56	8350	6.7*	1.0 (Referent)	0.80 (0.44–1.46)	0.37 (0.18–0.80)	0.01
BMI, kg/m^2								
<25	1278	31	7523	4.2	1.0 (Referent)	0.96 (0.42–2.19)	0.48 (0.18–1.24)	0.13
≥25	213	25	749	32.8	1.0 (Referent)	1.04 (0.41–2.69)	1.33 (0.29–6.22)	0.75
Age, y								
20–39	459	12	2614	4.7*	1.0 (Referent)	0.99 (0.24–4.11)	0.46 (0.07–2.79)	0.43
40–49	614	20	3122	6.4	1.0 (Referent)	1.37 (0.51–3.65)	0.24 (0.05–1.15)	0.11
≥50	418	24	1875	12.7	1.0 (Referent)	0.47 (0.17–1.28)	0.36 (0.12–1.07)	0.05
Metabolic syndrome risk factors at baseline								
0	894	13	5320	2.7	1.0 (Referent)	0.35 (0.10–1.24)	0.15 (0.03– 1.24)	0.02
1	467	19	2441	7.8	1.0 (Referent)	1.17 (0.42–3.27)	0.58 (0.17–2.03)	0.43
2	130	24	510	44.3	1.0 (Referent)	0.64 (0.25–1.68)	0.34 (0.09–1.27)	0.09

The lowest third of fitness is the referent group. The HRs for the total sample of men and women and within stratum of BMI and age are adjusted for age, current smoking, alcohol intake, family history of disease, year of baseline examination, and number of baseline metabolic risk factors. The HRs within stratum of baseline metabolic syndrome risk factors are adjusted for each of these covariables except number of baseline metabolic syndrome risk factors.

*The incidence rates for the total sample of men and women and across stratum of age are crude rates.

largely reflect the inaccuracy of self-reported physical activity assessment, particularly in women.[36] Cardiorespiratory fitness, an objective measure of recent physical activity patterns,[26] is less prone to misclassification than self-reported physical activity habits. The 2 existing studies that used maximal cardiorespiratory fitness exposures have shown an inverse association with metabolic syndrome incidence.[10,11] Laaksonen et al[11] reported 47% and 75% lower odds of developing metabolic syndrome among men in the middle and highest thirds of measured maximal oxygen uptake, respectively, compared with men in the lowest third. The association, however, was no longer significant after adjustment for baseline metabolic risk factors. Carnethon et al[10] reported on men and women combined and showed that only participants in the highest 40% of maximal treadmill performance were protected against developing metabolic syndrome. In our analysis, compared with individuals in the lowest third of fitness, the risk of developing metabolic syndrome was 20% to 26% lower among participants in the middle third and 53% to 63% lower among those in the highest third. The protective effect of fitness was observed in women and men and remained significant even after adjustment for the number of baseline metabolic syndrome factors. Our findings extend existing data by demonstrating that moderate and high levels of fitness provide substantial protection against developing metabolic syndrome in women and in men. Controlled clinical trials are needed to confirm these epidemiological observations.

Metabolic syndrome occurs across the distribution of age and BMI, although the prevalence is higher in older age groups and in overweight and obese individuals.[37] In our study, the pattern and strength of the inverse association between fitness and metabolic syndrome were similar across a broad range of ages (20 to >50 years) in our cohort of men. The same overall pattern of association was observed in these age categories for women; however, the small number of cases limited the statistical power to detect significant differences. Our findings underscore the importance of adequate

TABLE 4. Relative Association of Low Fitness and Each Metabolic Syndrome Risk Factor With Incident Metabolic Syndrome and the Related PAR in Men and Women

	Prevalence, %*	HR†	95% CI	PAR, %‡	95% CI
Men					
Low fitness	33.4	1.45	1.30–1.63	14.7	10.0–19.1
Abdominal obesity	6.9	4.51	3.84–5.30	12.3	10.3–14.4
High blood pressure	31.2	2.17	1.92–2.45	20.5	17.0–23.9
High glucose	7.4	2.01	1.65–2.44	4.3	2.7–5.9
High triglycerides	15.6	3.21	2.84–3.64	22.6	19.7–25.5
Low HDL	14.8	2.87	2.54–3.23	26.7	23.3–30.0
Women					
Low fitness	33.1	1.64	0.95–2.81	19.5	−5.1–38.4
Abdominal obesity	3.2	5.26	2.06–13.4	8.7	0.0–16.6
High blood pressure	19.9	2.81	1.58–5.03	25.3	7.4–39.8
High glucose	4.1	3.80	1.45–9.99	6.6	−1.4–13.9
High triglycerides	6.8	4.78	2.48–9.21	19.7	6.6–31.3
Low HDL	14.8	4.53	2.55–8.07	27.8	12.2–40.7

*Prevalence in the overall sample of men or women.

†Adjusted for age, smoking, year of baseline examination, and each of the other variables in the table.

‡PAR computed as $P_c(1-1/HR_{adj})$, where P_c is the prevalence of the risk factor among metabolic syndrome cases and HR_{adj} is the multivariable HR for metabolic syndrome associated with the specified risk factor. P_c (ordered as listed in the table) was 47.3, 15.9, 38.0, 8.6, 32.9, and 41.0 in men and 50.0, 10.7, 39.3, 8.9, 25.0, and 35.7 in women.

cardiorespiratory fitness to avoid the clustering of metabolic risk factors in young and middle-aged adulthood. The distribution of metabolic syndrome cases by fitness tertiles was not adequate for meaningful analyses in the >60-year-old age stratum; thus, additional data are needed to verify our findings in older individuals.

In our study, metabolic syndrome developed among individuals who were normal weight as well as in those who were overweight/obese at baseline. Strong inverse gradients in the adjusted HR of metabolic syndrome were seen across fitness levels in normal weight and overweight/obese men. This is contrary to findings by the CARDIA investigators, who reported an inverse association between fitness and metabolic syndrome only in participants with BMI <30 kg/m^2,[10] but consistent with data in Finnish men that indicated the association between fitness and metabolic syndrome was independent of BMI.[11] The association between fitness and metabolic syndrome in both weight categories among our women was nonsignificant perhaps because of low statistical power. Our data and those reported by others[11] suggest that higher cardiorespiratory fitness contributes to the prevention of metabolic syndrome even in individuals who are overweight or obese. Additional data on this issue are needed in women and in individuals with BMI >35 kg/m^2.

It is logical to assume that individuals with 1 or 2 of the metabolic syndrome components at baseline would be more susceptible to expressing metabolic syndrome than individuals with none at baseline. Indeed, we observed that 51% of men and 43% of women who developed metabolic syndrome had 2 baseline risk factors compared with 19% and 7% of noncases, respectively. The adjusted HRs for metabolic syndrome in men and women with 1 or 2 baseline risk factors were 3- to 16-fold higher compared with participants with no baseline risk factors. Even after adjustment for the number of baseline metabolic risk factors, fitness was a significant predictor of metabolic syndrome in women and men. Inverse associations between fitness and metabolic syndrome were also observed in subgroups of men and women with 0, 1, and 2 baseline risk factors, although the analysis in women was limited by low statistical power. Our data suggest that higher fitness levels confer protection against metabolic syndrome even in individuals with increased susceptibility because of existing metabolic risk factors. Clinicians should consider the potential benefits of greater cardiorespiratory fitness in the primary prevention of metabolic syndrome in patients who have already begun to cluster metabolic syndrome components.

When regressed simultaneously, low cardiorespiratory fitness and each metabolic syndrome risk factor were significantly associated with developing metabolic syndrome in men. Among women, a direct association was observed between low fitness and metabolic syndrome, but the association was not statistically significant after adjustment for each metabolic syndrome risk factor. Most of the predictors in the analysis were themselves components of metabolic syndrome; therefore, it is not surprising that their relative strength of association is somewhat higher than seen for low fitness, although fitness was still a significant predictor in men. Based on PAR estimates, if there were no individuals in the lowest third of fitness, the incidence of metabolic syndrome would be 15% and 20% lower in men and women, respectively. Some authors debate whether an exposure (eg, fitness) should be adjusted for risk factors that may be intermediate in the exposure-outcome causal pathway.[38,39] Therefore, we computed HRs and PARs for metabolic syndrome associated with low fitness adjusted only for age, smoking, and year of baseline examination. As expected, these PAR estimates of 27% for men and 29% for women were somewhat higher than the previously discussed PARs computed from the fully adjusted HRs. The comparable PAR estimates for metabolic syndrome associated with low fitness and the metabolic risk factors in our cohort suggest that improving population fitness levels should be given consideration similar to that given to modifying conventional metabolic risk factors for lowering the disease burden of metabolic syndrome.

Although genetics contribute to maximal cardiorespiratory fitness, the principal determinant is physical activity.[40] Cardiorespiratory fitness has been closely associated with the reported physical activity habits in the ACLS[34,41] and other studies of fitness and metabolic syndrome incidence.[10,11] For most individuals, cardiorespiratory fitness improvements can be obtained through regular participation in moderate and vigorous levels of physical activity.[33] Regular physical activity is a low-cost, safe therapy with minimal adverse side effects[33] and favorable benefits on a broad spectrum of health parameters,[28,29,34] including each metabolic syndrome component.[17–21] Pharmacological intervention for metabolic syn-

drome would require multiple agents, which increases costs and risks of adverse effects. Therefore, promoting higher population levels of cardiorespiratory fitness through greater physical activity may be the most prudent clinical and public health strategy for the primary prevention of metabolic syndrome.

Our study has limitations that should be considered. Study findings apply primarily to white men and women with higher socioeconomic affluence. Although the external validity of our data is therefore limited, the homogeneity of our population sample reduces confounding by these sociodemographic factors, which enhances internal validity. Although the overall pattern and strength of association between cardiorespiratory fitness and incident metabolic syndrome were similar in men and women, subgroup analyses in women were underpowered. Additional data are needed to better establish the influence of cardiorespiratory fitness on metabolic syndrome incidence among clinically relevant subgroups of women.

We conclude that cardiorespiratory fitness is inversely associated with metabolic syndrome incidence in women and men and that the association is strong, graded, and biologically plausible. Randomized controlled clinical trials are needed to confirm the epidemiological observations reported here and elsewhere. Still, we believe that clinicians should counsel their sedentary patients to become more physically activity and to improve their cardiorespiratory fitness as part of the primary prevention of metabolic syndrome.

Acknowledgments

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		ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象の内訳	対象	一般健常者	空白		( )		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	44(±9)歳			( )		前向き研究
	対象数	5000～10000			( )		( )
調査の方法	実測	( )					
アウトカム	予 防	高血圧症予防	肥満予防	なし	なし	高脂血症予防	糖尿病予防
	維持・改善	なし	なし	なし	なし	( )	( )

図 表

TABLE 3. HRs and 95% CIs for Metabolic Syndrome According to Cardiorespiratory Fitness and Other Predictors

	N	Cases	Follow-Up, person-y	Age-Adjusted Rate per 1000 person-y	Cardiorespiratory Fitness Tertile			Linear Trend P
					Low	Middle	High	
Men								
Total	9007	1346	92 241	25.8*	1.0 (Referent)	0.74 (0.65–0.84)	0.47 (0.40–0.54)	<0.001
BMI, kg/m²								
<25	4448	377	29 866	13.0	1.0 (Referent)	0.77 (0.59–0.99)	0.57 (0.44–0.74)	<0.001
≥25	4567	969	22 228	43.0	1.0 (Referent)	0.81 (0.70–0.93)	0.59 (0.48–0.71)	<0.001
Age, y								
20–39	3121	368	16 218	23.3*	1.0 (Referent)	0.78 (0.62–0.98)	0.48 (0.36–0.64)	<0.001
40–49	3587	500	18 311	32.9	1.0 (Referent)	0.75 (0.62–0.90)	0.46 (0.37–0.58)	<0.001
≥50	2299	358	11 256	32.5	1.0 (Referent)	0.68 (0.53–0.87)	0.47 (0.35–0.62)	<0.001
Metabolic syndrome risk factors at baseline								
0	3524	193	23 839	8.4	1.0 (Referent)	0.65 (0.46–0.92)	0.37 (0.26–0.53)	<0.001
1	3353	468	19 410	24.4	1.0 (Referent)	0.70 (0.57–0.86)	0.43 (0.34–0.54)	<0.001
2	2130	685	8841	76.1	1.0 (Referent)	0.78 (0.66–0.93)	0.57 (0.45–0.71)	<0.001
Women								
Total	1491	95	8356	6.7*	1.0 (Referent)	0.80 (0.44–1.46)	0.37 (0.18–0.80)	0.01
BMI, kg/m²								
<25	1278	31	7523	4.2	1.0 (Referent)	0.96 (0.42–2.19)	0.46 (0.18–1.24)	0.13
≥25	213	25	749	32.8	1.0 (Referent)	1.04 (0.41–2.69)	1.33 (0.29–6.22)	0.75
Age, y								
20–39	459	12	2614	4.7*	1.0 (Referent)	0.99 (0.24–4.13)	0.46 (0.07–2.79)	0.45
40–49	614	20	3122	6.4	1.0 (Referent)	1.37 (0.51–3.65)	0.24 (0.05–1.15)	0.11
≥50	418	24	1875	12.7	1.0 (Referent)	0.47 (0.17–1.28)	0.36 (0.12–1.07)	0.05
Metabolic syndrome risk factors at baseline								
0	894	13	5328	2.7	1.0 (Referent)	0.35 (0.10–1.24)	0.15 (0.03–1.24)	0.02
1	467	19	2441	7.8	1.0 (Referent)	1.17 (0.42–3.27)	0.58 (0.17–2.03)	0.45
2	130	24	512	44.3	1.0 (Referent)	0.64 (0.25–1.68)	0.34 (0.09–1.27)	0.09

The lowest third of fitness is the referent group. The HRs for the total sample of men and women and within stratum of BMI and age are adjusted for age, current smoking, alcohol intake, family history of disease, year of baseline examination, and number of baseline metabolic risk factors. The HRs within stratum of baseline metabolic syndrome risk factors are adjusted for each of these covariables except number of baseline metabolic syndrome risk factors.

*The incidence rates for the total sample of men and women and across stratum of age are crude rates.

図表掲載箇所	P509, Table3
概 要 (800字まで)	本研究は、アメリカのThe Aerobic Center Longitudinal Studyに参加した白人男女10,498名を対象に平均5.7年間の追跡調査を行い、全身持久力とメタボリックシンドローム発症リスクとの関連を検討したものである。全身持久力は、最大トレッドミルテストにより最大酸素摂取量を測定し、性年齢別に調整後、男女それぞれ低、中、高の3群に分類した。メタボリックシンドロームの発症ポイントは、次の項目に3つ以上に当てはまることを条件とした:腹囲男性102cm以上、女性80cm以上、中性脂肪150mg/dL以上、HDL男性40mg/dL未満、女性50mg/dL未満、血圧130/85以上、血糖110mg/dL。全身持久力が低の集団と比較すると、中、高の集団でメタボリックシンドローム発症リスクは男性でそれぞれ0.74(95%信頼区間:0.65-0.84)、0.47(0.40-0.54)、女性でそれぞれ0.80(0.44-1.46)、0.37(0.18-0.80)と量反応的に有意に減少することが明らかとなった(男性Ptrend<0.001、女性Ptrend=0.01)。
結 論 (200字まで)	本研究の白人コホートにおいて、全身持久力はメタボリックシンドローム発症リスクに対して強力で独立した予測因子であることが明らかとなった。
エキスパートによるコメント (200字まで)	我が国において、メタボリックシンドロームの予備群・該当者は年々増加しており、その増加は、生活習慣病発症や医療費の増大といった社会的問題にもつながっている。日本人を対象に、全身持久力とメタボリックシンドロームとの関係についても今後検討されることが期待される。

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ORIGINAL INVESTIGATION

Cardiovascular Fitness as a Predictor of Mortality in Men

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Objective: To examine the relations of cardiorespiratory fitness, as measured by maximal oxygen uptake and exercise test duration at the initiation of the study, with overall, cardiovascular disease (CVD)–related, and non–CVD-related mortality.

Methods: A population-based cohort study of 1294 men with no CVD, pulmonary disease, or cancer at baseline in Kuopio and surrounding communities in eastern Finland. During an average follow-up of 10.7 years, there were 124 overall, 42 CVD-related, and 82 non–CVD-related deaths.

Results: The relative risk of overall death in unfit men (maximal oxygen uptake <27.6 mL/kg per minute) was 2.76 (95% confidence interval, 1.43-5.33) ($P=.002$), and the relative risk of CVD-related death was 3.09 (95% confidence interval, 1.10-9.56) ($P=.05$), compared with fit men (maximal oxygen uptake >37.1 mL/kg per minute) after adjusting for age, examination years, smoking, and alcohol consumption. The relative risk of non–CVD-related death in unfit men was almost the same magnitude as for overall death. Furthermore, adjustment for serum lipid levels, blood pressure, plasma fibrinogen level, diabetes, and fasting serum insulin level did not weaken these associations significantly. Exercise test duration also had a strong inverse relation to overall, CVD-related, and non–CVD-related mortality. Poor cardiorespiratory fitness was comparable with elevated systolic blood pressure, smoking, obesity, and diabetes in importance as a risk factor for mortality.

Conclusions: Cardiorespiratory fitness had a strong, graded, inverse association with overall, CVD-related, and non–CVD-related mortality. Maximal oxygen uptake and exercise test duration represent the strongest predictors of mortality.

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PHYSICAL INACTIVITY, as measured objectively by low cardiorespiratory fitness, has been estimated to account for 12% of all deaths in the United States.[1] Thus, it is considered to be one of the most crucial public health problems. Low cardiorespiratory fitness[2-9] has consistently been associated with an increased risk of premature death in prospective population-based studies. This has been mainly due to reduced cardiovascular disease (CVD)–related mortality,[2,4,5] but also to some extent to reduced cancer-related mortality,[4] in fit individuals. Indeed, low cardiorespiratory fitness has been found to be as strong a predictor of mortality as the conventional modifiable risk factors, such as cigarette smoking, hypercholesterolemia, and hypertension.[7,9]

Recommendations concerning the specific quantity and intensity of physical activity and the level of cardiorespiratory fitness needed to reduce premature mortality are based on a few prospective population-based studies.[10,11] Maximal oxygen uptake ($\dot{V}O_2max$), as a measure of cardiorespiratory fitness, provides a quantifiable measurement of the level of physical exercise in addition to its genetic component. Directly measured $\dot{V}O_2max$ is a gold standard for assessing the amount of oxygen consumption in maximal effort.[12] Maximal oxygen uptake during exercise represents cardiac, circulatory, and respiratory function and muscle oxygen use under physiological stress conditions.

The present study examines the associations of cardiorespiratory fitness, as indicated by directly measured $\dot{V}O_2max$,[13] and exercise test duration with mortality not only from CVDs but also from other causes, in a population-based sample of men from eastern Finland.

RESULTS

BASELINE CHARACTERISTICS

At the beginning of the follow-up, the mean age of the subjects was 52.1 years (range, 42.0-61.3 years). The mean $\dot{V}O_2max$ was

SUBJECTS AND METHODS

SUBJECTS

Subjects were participants in the Kuopio Ischaemic Heart Disease Risk Factor Study.[14] This study was designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in a population-based, randomly selected sample of men in eastern Finland.[14] 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, and of the remaining men, 2682 (83%) agreed to participate in the study. Baseline examinations were conducted between March 20, 1984, and December 5, 1989.

Men who had a history of CVD, including coronary heart disease diagnosed by angina pectoris, myocardial infarction, use of medications for coronary heart disease, and myocardial ischemia in an exercise test (n=766); cardiac insufficiency (n=194); claudication (n=108); stroke (n=69); cardiomyopathy (n=55); arrhythmias (n=26); other CVDs (n=103); cancer (n=46); or pulmonary diseases, including chronic obstructive pulmonary disease (n=197), pulmonary tuberculosis (n=104), and asthma (n=96) were excluded as these conditions might have affected their physical exercise and cardiorespiratory fitness. Some men had 2 or more of these diseases. Subjects (56 men with and 13 men without disease) whose $\dot{V}O_2$max was less than 15.75 mL/kg per minute, corresponding to 4.5 metabolic equivalents (METs) (METs of oxygen consumption), were also excluded, as a low $\dot{V}O_2$max may be an indicator of an underlying but yet undiagnosed disease. An exercise capacity of 5 METs or less is related to poor prognosis in subjects younger than 65 years.[12] After these exclusions, complete data on $\dot{V}O_2$max and exercise test duration were available for 1294 of the remaining men.

ASSESSMENT OF CARDIORESPIRATORY FITNESS

Cardiorespiratory fitness was assessed with a maximal, symptom-limited exercise tolerance test on an electrically braked bicycle ergometer at the initiation of the study. For 307 men examined before May 8, 1986, the testing protocol comprised a 3-minute warm-up at 50 W followed by a step-by-step increase in the workload of 20 W/min. The remaining 987 men were tested with a linear increase in the workload of 20 W/min. The electrocardiogram was registered continuously during the exercise stress test.

Maximal oxygen uptake and exercise test duration were used as measures of cardiorespiratory fitness. A detailed description of the measurement of $\dot{V}O_2$max has been given elsewhere.[13] In short, respiratory gas exchange was measured for the first 307 men by the mixing-chamber method, and for the other 987 men by a breath-by-breath method. *Maximal oxygen uptake* was defined as the highest value for or the plateau of oxygen uptake. Maximal oxygen uptake was also expressed in METs. The *MET* is the ratio of the metabolic rate during exercise to the metabolic rate at rest. One MET corresponds to an oxygen uptake of 3.5 mL/kg per minute.

The most common reasons for stopping the exercise test were leg fatigue (n=735); exhaustion (n=207); breathlessness (n=155); and pain in the leg muscles, joints, or back (n=50). The test was discontinued because of cardiorespiratory symptoms or abnormalities in 86 men.

32.7 mL/kg per minute (range, 16.0-65.4 mL/kg per minute), and the mean exercise test duration was 9.7 minutes (range, 2.9-19.9 minutes). Maximal oxygen uptake was associated directly with serum high-density lipoprotein cholesterol level and exercise test duration and inversely with cigarette smoking, alcohol consumption, body mass index, waist-hip ratio, systolic and diastolic blood pressure, diabetes, fasting serum insulin level, plasma fibrinogen level, serum total and low-density lipoprotein cholesterol level, and triglycerides level (**Table 1**).

CARDIORESPIRATORY FITNESS AND OVERALL MORTALITY

Low cardiorespiratory fitness was related to increased risk of overall mortality (**Table 2**). Low $\dot{V}O_2$max (<27.6 mL/kg per minute) was associated with a 2.76-fold (95% CI, 1.43-5.33) (P=.002) risk of overall mortality after adjusting for age, examination years, smoking, and alcohol consumption (P<.001 for linear trend). Also, a short exercise test duration was associated with an increased risk of overall mortality (Table 2). The relative risk (RR) of overall death was 2.72 (95% CI, 1.37-5.42) (P=.004) in men whose exercise test duration was less than 8.2 minutes (lowest quartile) compared with men whose exercise test duration was more than 11.2 minutes (highest quartile) after adjusting for age, examination years, smoking, and alcohol consumption (P=.007 for linear trend). Additional adjustment for serum triglycerides level, high- and low-density lipoprotein cholesterol levels, systolic blood pressure, diabetes, fasting serum insulin level, and plasma fibrinogen level did not change the associations of $\dot{V}O_2$max and exercise test duration with overall mortality significantly.

CARDIORESPIRATORY FITNESS AND CVD-RELATED MORTALITY

Low cardiorespiratory fitness was associated with an increased risk of CVD-related mortality (Table 2). Men with a low $\dot{V}O_2$max (<27.6 mL/kg per minute) had a 3.09-fold (95% CI, 1.10-9.56) (P=.05) risk of CVD-related death after adjusting for age, examination years, smoking, and alcohol consumption compared with men with a high $\dot{V}O_2$max (>37.1 mL/kg per minute) (P=.01 for linear trend). Further adjustment for serum triglycerides level, serum low- and high-density lipoprotein cholesterol levels, systolic blood pressure, diabetes, fasting serum insulin level, and plasma fibrinogen level slightly weakened these associations (P=.05 for linear trend). There was little difference in the risk between the first and second quartiles (Table 2).

Exercise test duration was related to an increased risk of CVD-related mortality (Table 2). The RR of CVD-

These included arrhythmias (n=36), a marked change in systolic (n=8) or diastolic (n=24) blood pressure, dizziness (n=7), chest pain (n=7), or ischemic electrocardiographic changes (n=4).

ASSESSMENT OF OTHER RISK FACTORS

Assessments of smoking, alcohol consumption, physical activity, and blood pressure[13,15,16] were performed as described previously. The collection of blood specimens[15] and the measurement of serum lipids and lipoproteins,[17,18] insulin,[18] plasma fibrinogen,[19] and glucose[15] have been described elsewhere. Body mass index was computed as weight in kilograms divided by the square of height in meters, and waist-hip ratio as the ratio of the circumference of the waist to that of the hip.

ASCERTAINMENT OF FOLLOW-UP EVENTS

Deaths were ascertained by linkage to the national death registry using the Finnish social security number. There were no losses to follow-up. All deaths that occurred between study enrollment (from March 20,1984, to December 5, 1989) and December 31, 1997, were included. Deaths that were coded with the *International Classification of Diseases, Ninth Revision (ICD-9)*,[20] codes 390 to 459 were included in the analyses of CVD-related deaths. All other deaths were non–CVD-related deaths. The average time to any death or the end of follow-up was 10.7 years (range, 0.8-13.8 years). In the present sample, there were 124 deaths during the follow-up period, 42 from CVD-related causes and 82 from non–CVD-related causes.

STATISTICAL ANALYSIS

The associations of $\dot{V}O_2$max and exercise test duration with the risk factors for death were examined using covariate analysis. The levels of $\dot{V}O_2$max and exercise test duration were entered as dummy variables into forced Cox proportional hazards regression models using Statistical Package for the Social Science software (SPSS Inc, Chicago, Ill).[21] In these models, $\dot{V}O_2$max and exercise test duration were categorized according to quartiles. If possible, covariates were entered uncategorized into the Cox proportional hazards regression models. Three different sets of covariates were used: (1) age and examination years (1985, 1986, 1987, 1988, and 1989); (2) age, examination years, cigarette smoking, and alcohol consumption; and (3) in the case of overall and CVD-related mortality, age, examination years, cigarette smoking, alcohol consumption, systolic blood pressure, diabetes, fasting serum insulin level, plasma fibrinogen level, serum high- and low-density lipoprotein cholesterol levels, and triglycerides level. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariate models. Their confidence intervals (CIs) were estimated under the assumption of asymptotic normality of the estimates. All tests for statistical significance were 2-sided. The fit of the proportional hazards regression 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 analyses were performed using Statistical Package for the Social Science software for Windows. To reduce the possibility of self-selection bias, these data were reanalyzed by excluding men who had died during the first 3 years of follow-up.

related death was 3.44 (95% CI, 1.09-10.80) (P=.04) in the lowest quartile compared with men in the highest quartile after adjustment for age, examination years, smoking, and alcohol consumption (P=.01 for linear trend).

CARDIORESPIRATORY FITNESS AND NON–CVD-RELATED MORTALITY

Low cardiorespiratory fitness ($\dot{V}O_2$max of <27.6 mL/kg per minute or an exercise duration of <10.2 minutes) was also associated with an increased risk of non–CVD-related death (Table 2). The RR of non–CVD-related death in men with a low $\dot{V}O_2$max was 2.60 (95% CI, 1.16-5.83) (P=.02) after adjustment for age, examination years, smoking, and alcohol consumption (P=.005 for linear trend). Men whose exercise test duration was less than 10.2 minutes (lowest quartile) had an increased risk of non–CVD-related death (RR, 2.46; 95% CI, 1.01-5.70; P=.05) compared with men with durations that were longer than 13.2 minutes (highest quartile) after adjustment for age, examination years, smoking, and alcohol consumption.

STRONGEST RISK FACTORS FOR DEATH

The associations of other risk factors with overall and CVD-related mortality are presented in **Table 3**. High systolic blood pressure, smoking, obesity, and diabetes were associated with an increased risk of all-cause and CVD-related mortality. Men with the highest systolic blood pressure (>143 mm Hg) had a 2.32-fold risk and men with the highest waist-hip ratio (>0.98) had a 1.54-fold risk of overall death (Table 3). The RR of CVD-related death was 3.18 in hypertensive men (those with a systolic blood pressure of >143 mm Hg) and 3.74 in obese men (those with a waist-hip ratio of >0.98). Smokers had a 3.74-fold and diabetic men had a 2.38-fold risk of overall mortality, whereas the RR of CVD-related death was 2.57 in smokers and 4.09 in diabetic men (Table 3). Unfit men had RRs of 3.85 for overall and 3.97 for CVD-related death, which are at least as strong as the other risk factors presented in Table 3.

COMMENT

In the present study, in middle-aged men, $\dot{V}O_2$max and exercise test duration had a strong, graded, and inverse association with overall, CVD-related, and non–CVD-related mortality. In fact, $\dot{V}O_2$max and exercise test duration were 2 of the strongest predictors for mortality in the present unselected Finnish cohort. These findings support US cohort studies[7,9] suggesting that the risk of death associated with low cardiorespiratory fitness is compa-

Table 1. Characteristics of 1294 Men in Eastern Finland Who Reported Having No Cardiovascular or Pulmonary Disease or Cancer at Baseline According to Quartiles of Maximal Oxygen Uptake*

Characteristic	All Men	Quartile of Maximal Oxygen Uptake†				P
		1	2	3	4	
Exercise test duration, min	9.7 (2.3)	11.8 (2.0)	10.1 (1.5)	9.2 (1.5)	7.7 (1.7)	<.001
Total physical activity						
Energy expenditure, kJ/wk	10 634 (8576)	12 356 (9274)	10 370 (8551)	10 261 (8602)	9593 (8576)	<.001
Mean intensity, METs‡	4.60 (1.21)	5.21 (1.47)	4.61 (1.12)	4.37 (1.01)	4.25 (0.99)	<.001
Cigarette smoking, pack-years§	7.9 (16.0)	3.2 (8.6)	7.9 (15.1)	9.8 (15.5)	10.9 (21.3)	<.001
Alcohol consumption, g/wk	71.9 (107.6)	56.8 (83.1)	62.0 (84.2)	90.4 (131.1)	78.3 (120.4)	<.001
Body mass index‖, kg/m^2	26.6 (3.3)	24.9 (2.4)	26.4 (2.8)	26.8 (3.2)	28.3 (3.6)	<.001
Waist-hip ratio	0.94 (0.06)	0.92 (0.07)	0.94 (0.05)	0.95 (0.05)	0.97 (0.05)	<.001
Blood pressure, mm Hg						
Systolic	133.8 (16.0)	129.4 (13.7)	132.9 (15.6)	135.9 (15.9)	137.8 (17.6)	<.001
Diastolic	88.8 (10.4)	86.2 (9.2)	88.3 (10.5)	89.3 (10.0)	91.4 (11.0)	<.001
Diabetic, %	3.6	1.6	2.5	5.2	5.0	.02
Fasting serum insulin level, pmol/L	78.1 (38.7)	64.2 (27.1)	75.2 (36.5)	80.3 (37.2)	92.7 (46.0)	<.001
Blood glucose level, mmol/L‖	4.7 (0.9)	4.5 (0.7)	4.6 (0.7)	4.8 (0.9)	4.9 (1.2)	<.001
Plasma fibrinogen level, µmol/L	8.7 (1.6)	8.2 (1.6)	8.2 (1.5)	8.8 (1.5)	9.3 (1.6)	<.001
Serum cholesterol level, mmol/L¶	5.86 (1.02)	5.69 (0.95)	5.88 (1.02)	5.92 (1.03)	5.97 (1.03)	.003
LDL cholesterol	4.00 (0.97)	3.80 (0.97)	4.02 (0.97)	4.08 (0.98)	4.12 (1.00)	<.001
HDL cholesterol	1.31 (0.30)	1.42 (0.31)	1.32 (0.29)	1.27 (0.29)	1.24 (0.27)	<.001
Serum triglyceride level, mmol/L#	1.22 (0.75)	0.97 (0.53)	1.23 (0.85)	1.29 (0.87)	1.37 (0.65)	<.001

*MET indicates metabolic equivalents of oxygen consumption; LDL, low-density lipoprotein; and HDL, high-density lipoprotein. Data are given as mean (SD).

†Quartile 1 indicates greater than 37.1 mL/kg per minute; 2, 32.3 to 37.1 mL/kg per minute; 3, 27.6 to 32.2 mL/kg per minute; and 4, less than 27.6 mL/kg per minute.

‡The MET is the ratio of metabolic rate during exercise to the metabolic rate at rest. One MET corresponds to approximately 4.2 kJ/kg of body weight per hour and to an oxygen uptake of 3.5 mL/kg per minute.

§Pack-years denotes the lifelong exposure to smoking, which was estimated as the product of years of smoking and the number of tobacco products smoked daily at the time of examination.[13,14]

‖To convert glucose from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.05551.

¶To convert cholesterol from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.02586.

#To convert triglycerides from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.01129.

Table 2. Relative Risks of Overall, CVD-Related, and Non–CVD-Related Death According to Quartiles of Maximal Oxygen Uptake and Exercise Test Duration*

Variable	Overall Death (N = 124)			CVD-Related Death (n = 42)			Non–CVD-Related Death (n = 82)		
	Relative Risk (95% CI)	P	No. of Deaths	Relative Risk (95% CI)	P	No. of Deaths	Relative Risk (95% CI)	P	No. of Deaths
Maximal oxygen uptake, mL/kg per min†‡									
>37.1 (1) [>10.6]	1.00 (reference)	...	12	1.00 (reference)	...	4	1.00 (reference)	...	8
32.3-37.1 (2) [9.3-10.6]	1.47 (0.71-3.01)	.14	20	1.31 (0.37-4.69)	.68	6	1.54 (0.64-3.70)	.33	14
27.6-32.2 (3) [7.9-9.2]	2.79 (1.44-5.39)	<.001	37	2.87 (0.92-8.95)	.07	13	2.74 (1.22-6.17)	.01	24
<27.6 (4) [<7.9]	3.85 (2.02-7.32)	<.001	55	3.97 (1.31-12.0)	.01	19	3.79 (1.72-8.35)	<.001	36
P for linear trend	<.001			.002			<.001		
Exercise test duration, min†									
>11.2 (1)	1.00 (reference)	...	11	1.00 (reference)	...	4	1.00 (reference)	...	7
9.6-11.2 (2)	2.22 (1.08-4.55)	.03	24	1.33 (0.37-5.01)	.67	5	3.68 (1.13-6.45)	.03	19
8.2-9.5 (3)	2.23 (1.11-4.49)	.03	32	2.27 (0.70-7.36)	.17	12	2.22 (0.93-5.31)	.07	21
<8.2 (4)	3.94 (2.01-7.74)	<.001	57	4.54 (1.46-14.0)	.009	21	3.68 (1.59-8.55)	.002	35
P for linear trend	<.001			.002			.005		

*Relative risks are adjusted for age and examination years (1984, 1985, 1986, 1987, and 1989). CVD indicates cardiovascular disease; CI, confidence interval; and ellipses, data not applicable.

†The quartiles are given in parentheses. A description of the quartiles is given in the second footnote of Table 1.

‡The metabolic equivalents of oxygen consumption are given in brackets. A description of metabolic equivalents of oxygen consumption is given in the third footnote of Table 1.

rable with that of conventional risk factors, including smoking, hypertension, obesity, and diabetes.

Blair and coworkers[4,7] found that moderate levels of cardiorespiratory fitness, defined by quintiles of treadmill test time, were associated with reduced all-cause and CVD-related mortality, while higher levels provided only little further reduction in the risk of death. Sandvik and coworkers[5] observed that moderate levels (quartiles) of work capacity in the bicycle ergometer test were associated with reduced CVD-related mortality, but there was

Table 3. Relative Risks of Overall and CVD-Related Death According to Systolic Blood Pressure, Obesity, Smoking, and Diabetes*

Variable	Overall Death (N = 124) Relative Risk (95% CI)	*P*	% of Deaths	CVD-Related Death (n = 42) Relative Risk (95% CI)	*P*	% of Deaths
Systolic blood pressure, mm Hg†						
<123 (1)	1.00 (reference)	...	5.5	1.00 (reference)	...	1.8
123-132 (2)	1.46 (0.80-2.65)	.21	8.5	0.66 (0.18-2.33)	.52	1.3
133-143 (3)	1.62 (0.90-2.92)	.10	9.2	1.78 (0.66-4.82)	.26	3.4
>143 (4)	2.32 (1.34-4.01)	.002	14.8	3.18 (1.27-7.96)	.01	6.6
P for linear trend		.002			.001	
Smoking						
No (68.6%)	1.00 (reference)	...	6.0	1.00 (reference)	...	2.4
Yes (31.4%)	3.74 (2.43-4.96)	<.001	17.5	2.57 (1.40-4.73)	.002	5.2
Waist-hip ratio†						
<0.91 (1)	1.00 (reference)	...	6.5	1.00 (reference)	...	1.1
0.91-0.95 (2)	0.53 (0.24-1.15)	.11	4.2	1.32 (0.31-5.59)	.71	1.9
0.96-0.98 (3)	1.46 (0.79-2.72)	.23	10.3	2.55 (0.68-9.53)	.17	3.4
>0.98 (4)	1.54 (0.84-2.86)	.16	11.9	3.74 (1.06-13.4)	.04	5.4
P for linear trend		.02			.01	
Diabetes						
No (96.4%)	1.00 (reference)	...	9.1	1.00 (reference)	...	3.0
Yes (3.6%)	2.38 (1.24-4.56)	.009	21.7	4.09 (1.60-10.5)	.003	10.9

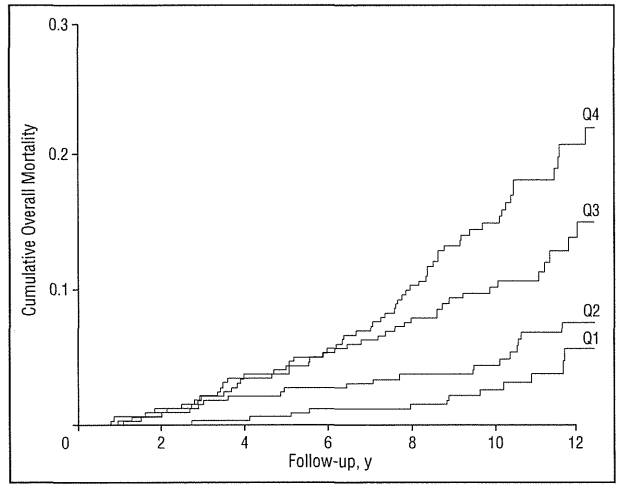
**Relative risks are adjusted for age and examination years (1984, 1985, 1986, 1987, and 1989). CVD indicates cardiovascular disease; CI, confidence interval; and ellipses, data not applicable.*

†The quartiles of systolic blood pressure and waist-hip ratio are given in parentheses.

some further reduction in the risk at the highest levels. However, Ekelund and coworkers[2] showed a marked difference in CVD-related mortality between high and low levels of cardiorespiratory fitness, assessed by heart rate at a speed of 4 km/h (2.5 miles/h) on a treadmill. In our study, $\dot{V}O_2$max had a strong, graded, and inverse association with overall, CVD-related, and non–CVD-related mortality through its whole range. The mortality curves for the quartiles of $\dot{V}O_2$max continued to diverge during follow-up (**Figure**). The greatest excess of mortality was found at the lowest level of $\dot{V}O_2$max (<27.6 mL/kg per minute or 7.9 METs).

The expert panel suggested that every US adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week to promote health and to prevent chronic diseases.[10] In a recent randomized trial,[22] researchers estimated that an increase of 10% in cardiorespiratory fitness, corresponding to a 1-MET increase in exercise capacity, can be achieved by maintaining these exercise recommendations for 2 years. However, more intense structured exercise could increase physical fitness by 1 MET in 6 months.[22] Blair and coworkers[6] reported that an increase of 2 METs in treadmill performance was related to a reduction of 30% in mortality. Previous studies[6,8] have suggested that even a small improvement in cardiorespiratory fitness can result in reduced all-cause and CVD-related mortality.

Some studies[23-27] have suggested that physical exercise reduces the risk of prostate, breast, and large-bowel cancer, but the evidence is inconclusive for other cancers. However, little is known about the relation between cardiorespiratory fitness and cancer risk. In a few previous studies, cardiorespiratory fitness has been related inversely to mortality from cancer of combined



Cumulative overall mortality up to 13.8 years of follow-up in men according to quartiles (Qs) of maximal oxygen uptake (Q4 indicates <27.6 mL/kg per minute; Q3, 27.6-32.2 mL/kg per minute; Q2, 32.3-37.1 mL/kg per minute; and Q1, >37.1 mL/kg per minute).

sites[4,23] and of the prostate.[24] In our study, cardiorespiratory fitness had a strong, graded, and inverse association with non–CVD-related mortality, primarily due to cancers and pulmonary diseases. It has been suggested that physical activity and good cardiorespiratory fitness could reduce the risk of cancer through their beneficial effects on energy balance, the digestive system (decreased intestinal transit time), hormonal concentrations (a reduced testosterone level), changes in prostaglandin levels, antioxidant enzyme activities, or body mass.[23-25] However, these mechanisms are largely speculative, whereas physiological and metabolic mechanisms underlying the association of cardiorespiratory fitness with CVD-related mortality are understood better.[10,11]

Maximal oxygen uptake, which is a product of cardiac output and maximal arteriovenous oxygen difference, is determined by age; sex; the duration, intensity, frequency, and type of physical activity; genetic factors; and clinical or subclinical disease.[2,4,7,28] The genetic component of cardiorespiratory fitness is estimated to be 25% to 40%.[28] It is proposed that low cardiorespiratory fitness reflects mainly physical inactivity. High-intensity exercise is more effective than low-intensity exercise for improving $\dot{V}O_2$max in healthy persons, but lower-intensity physical activity may be sufficient to improve $\dot{V}O_2$max in high-risk persons.[29] Therefore, the level of physical activity sufficient to improve cardiorespiratory fitness probably depends on the initial health and fitness status, the length of the previous training history, and the duration, frequency, and intensity of the exercise. Maximal oxygen uptake usually decreases by 5% to 15% per decade between the ages of 20 and 80 years, and the rate of decline in oxygen uptake is directly related to maintenance of physical activity level, emphasizing the importance of physical activity.[12]

The strength of our study is that we have a representative population-based sample of middle-aged men in Finland. Second, the participation rate was high, and there were no losses during follow-up. Third, we have reliable data on mortality because deaths were ascertained by the Finnish National Death Registry using social security number, supplemented with reliable data on health status and risk factors that permit the control of potential confounders. Our study also demonstrated that both of the measurements of cardiorespiratory fitness, $\dot{V}O_2$max and exercise test duration, were strong predictors of mortality. The exercise test is readily available from any exercise laboratory, and the duration of the test can be measured without any additional equipment. The treadmill test[2,4] and the bicycle dynamometer test[5] are useful and reliable ways to define cardiorespiratory fitness status.

In this study, we used only a single measurement of $\dot{V}O_2$max at baseline, but this is not a major limitation. Ideally, the measurement of cardiorespiratory fitness should be repeated to investigate the effect over time. However, it has been shown that the intraindividual variability of $\dot{V}O_2$max is low.[30] In fact, variation with time in cardiorespiratory fitness could underestimate the real association between $\dot{V}O_2$max and mortality. It is impossible to know whether cardiorespiratory fitness decreased or increased during follow-up because of the probable changes in the exercise and other health habits of the subjects. We have no data on changes in cardiorespiratory fitness during follow-up, which could affect mortality, as reported previously.[6,8]

This prospective population study provides evidence that $\dot{V}O_2$max is associated with an increased risk of death, although only a randomized controlled trial of thousands of subjects could prove a causal pathway between $\dot{V}O_2$max and mortality. It is difficult to distinguish an increased risk of death due to a low level of cardiorespiratory fitness from an increased risk because of prevalent asymptomatic or preexisting CVD or cancer. Thus, it is possible that the strength of the association of cardiorespiratory fitness with mortality is exaggerated by such a bias. It is unclear how long a lag time would be required to avoid any such possible selection bias. However, the importance of the lag period diminishes with longer follow-up, because any bias will be diluted by the increasing weight of the unbiased cases. We excluded men who died during the first 3 years of follow-up, but the results did not change markedly because of the few deaths occurring in the first 3 years (Figure). Furthermore, the careful exclusion of individuals with prevalent coronary heart disease, stroke, cardiac insufficiency, cardiomyopathy, arrhythmias, claudication, cancer, and pulmonary diseases and of persons with a low $\dot{V}O_2$max means that a self-selection bias is an unlikely source of bias in our study.

An increasing amount of epidemiologic data supports the measurement of cardiorespiratory fitness in clinical practice. Based on the results in our study, direct or indirect measurement of $\dot{V}O_2$max, which is available in most clinics, can provide a good estimate for cardiorespiratory fitness level and prognosis. Poor cardiorespiratory fitness is an important and independent risk factor for premature death, and can be considered to be as important as smoking, hypertension, obesity, and diabetes.

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