cardiovascular disease compared with subjects with normal or optimal blood pressure (6–8). In addition, individuals within this group have a greater incidence of progression to hypertension, especially in the presence of other cardiovascular risk factors (9–11). Although the development of hypertension can be delayed by drug therapy (12,13), lifestyle modification is currently considered the cornerstone of management strategies for individuals with high-normal blood pressure. Physical exercise, which represents an essential part of lifestyle modification, has been also shown to attenuate the progression from normal blood pressure to hypertension (14–17).

A large amount of epidemiological evidence supports that exercise capacity or cardiorespiratory fitness are strongly and inversely related to cardiovascular and all-cause mortality, even after adjustments for other confounding factors (18–22). Whether these benefits are evident in individuals with high-normal blood pressure remains uncertain, because of limited available data. We therefore sought to assess the association between exercise capacity and all-cause mortality in high-normal blood pressure individuals, and evaluate the effects of other factors on this association.

Patients and methods

In this retrospective study, we evaluated the association between exercise capacity and mortality risk in individuals with high-normal blood pressure. The cohort was selected from more than 16,000 males who underwent a symptom-limited exercise test to exclude cardiac ischemia at two sites within the Veterans Administration Health system (Washington, DC, and Palo Alto, CA).

High-normal blood pressure was defined as systolic blood pressure 130–139 mmHg and/or diastolic blood pressure 85–89 mmHg, in accordance with the 2007 European guidelines for the management of arterial hypertension (1). The selection of the cohort was based on the blood pressure reading prior to the exercise test and was confirmed by the individual's blood pressure history recorded over a period in his electronic medical records. The Veterans Administration Health System uses electronic health records that include detailed medical history and several measurements of vital signs during the regular follow-up visits. The latter permits for an accurate evaluation of blood pressure levels over time and a more precise categorization of individuals in blood pressure groups compared with a categorization based on blood pressure values at only one time point. Patients were excluded from the study if they were receiving antihypertensive drugs, had previous documented cardiovascular disease, or an ischemic response to the exercise test. In addition, the development of left bundle branch block during exercise and the need for emergency care were also considered as exclusion criteria (23). One thousand, seven hundred and twenty-seven individuals (1727) met these criteria and were included in this study. All gave informed consent before performing the exercise test, as part of standard practice in our institutions. The Internal Review Board of each participating site approved the protocol of this retrospective analysis.

The standard Bruce protocol was used for exercise testing at the Washington site and an individualized ramp protocol at the Palo Alto site (24). Peak workload was estimated in metabolic equivalents (METs), with one MET defined as the energy expenditure at rest that is equivalent to an oxygen consumption of 3.5 ml/kg of body weight per minute (25). Exercise capacity was estimated by using a common equation for the Bruce protocol (26) and the American College of Sports Medicine equation for the ramp protocol (25); both equations are based on exercise time. Age-predicted heart rate (HR) at exercise peak was determined by a standardized method (27).

Resting blood pressure and HR were assessed for all patients prior to the exercise test and after a 5-min rest in the supine position (only one measurement). During the exercise test, blood pressure was assessed at the last minute of each exercise stage, at peak exercise and during the recovery period. All blood pressure assessments were performed on the right arm by an aneroid sphygmomanometer (X018, Tycos). Diastolic blood pressure was recorded at phase V.

Demographic and clinical data as well as prior medication were extracted from the electronic files right before the exercise test, while all individuals verified relevant information. Body weight (kg) and height (m) were measured before the test, and body mass index (BMI) was calculated as weight divided by height^2 (kg/m^2). Smoking status was specifically asked and recorded before the test for all individuals. Dyslipidemia was based on abnormal blood lipid values at the time of exercise test or current use of hypolipidemic agents. Blood lipids were not assessed in all patients and thus corresponding values are not reported.

Death records were extracted from the Veterans Affairs Beneficiary Identification and Record Locator System File, which is proven to be complete and accurate, since benefits to survivors are based on this system (28). The vital status was determined as of 30 September 2008.

Determination of fitness categories

Six fitness categories were established based on the MET level achieved. Those who achieved equal to or less than 4 METs comprised the least fit group. Then sequential groups were formed based on 2-MET interval change, up to 12 METs. Those who achieved more than 12 METs comprised the highest fit category.

Table I. Demographic and clinical characteristics in the entire cohort and according to exercise capacity.

Variables	Entire cohort	≤4 METs	4.1–6.0 METs	6.1–8.0 METs	8.1–10.0 METs	10.1–12.0 METs	>12 METs	*p*-value
n	1727	108	377	440	424	195	183	–
Age (years)[a]	57±12	67±8[b]	65±10[b]	59±10	53±11	50±11	50±11	<0.001
BMI (kg/m^2)	27.8±4.8	27.0±4[b]	28.2±6	27.9±5	28.2±5	27.5±4	26.9±3	0.009
Diabetes (%)[a]	9.4	8.3	15.1	10.7	8.0	4.6	3.3	<0.001
Smoking (%)	30.7	24.1	30.5	28.0	31.1	36.9	34.4	0.12
Dyslipidemia[a]	10.7	6.5	14.3	13.0	11.6	7.7	1.1	<0.001

METs, metabolic equivalents; BMI, body mass index.
[a]Differences on all possible comparisons.
[b]Different from other fitness categories.

Statistical analysis

Continuous variables are presented as mean±standard deviation, while categorical variables are expressed as absolute and relative frequencies (%). Associations between categorical variables were tested using Pearson's chi-square test. One-way analysis of variance was applied to determine age and BMI differences among fitness categories. Interaction between the two testing sites was also performed. Post-hoc procedures were utilized to discern differences between fitness categories. The Bonferroni rule to correct for the inflation in the type-I error was applied with multiple comparisons. Equality of variances between treatment groups was tested by the Levene's test.

The relative risk of mortality was calculated for each fitness category. Individuals with an exercise capacity of ≤4 METs (least-fit category), comprised the reference group. Cox proportional hazard models were used to determine the variables that were independently and significantly associated with mortality. The analyses were adjusted for age in years, BMI, resting systolic and diastolic blood pressure, risk factors (diabetes, dyslipidemia and smoking), and race as categorical variables. Receiver-operating characteristic curves (ROC) were constructed to compare the MET level achieved, age, BMI and CV risk factors in terms of their discriminatory accuracy in predicting survival. *p*-values <0.05 using two sided tests were considered statistically significant. All statistical analyses were performed using SPSS software version 15.0, SPSS Inc., Chicago, IL, USA.

Results

A total of 1727 individuals with high-normal blood pressure were included in the final analyses. The average (±SD) follow-up period was 9.75±6 years. During this period, there were 394 deaths for an average annual mortality of 2.34%. No statistically significant interactions were observed between exercise capacity and the two different testing sites ($p=0.52$), as well as between exercise capacity and race ($p=0.68$). Approximately 80% of individuals achieved at least 85% of the age-predicted peak HR.

The demographic and clinical characteristics for the entire cohort and according to fitness categories are depicted in Table I. A significant progressive reduction of age was present in association with exercise capacity, with higher fit individuals having lower age ($p<0.001$). Significant differences were also observed in the prevalence of diabetes and dyslipidemia ($p<0.001$ for both). Therefore, adjustments for age, BMI, diabetes, dyslipidemia, use of aspirin and statins, and race were applied when probing for differences in resting HR, systolic and diastolic blood pressures, MET levels and mortality among the six fitness categories.

Table II. Exercise data in the entire cohort and according to exercise capacity.

Variables	Entire cohort	≤4 METs	4.1–6.0 METs	6.1–8.0 METs	8.1–10.0 METs	10.1–12.0 METs	>12 METs	*p*-value
n	1,727	108	377	440	424	195	183	–
Resting HR (beats/min)	75±13	79±14[b]	76±14	74±13	73±13	73±13	74±13	<0.001
Resting systolic BP (mm Hg)	131±7	132±7[b]	132±6[b]	131±6	130±7	130±6	129±8	0.009
Resting diastolic BP (mm Hg)	82±7	80±8	81±8	82±7	83±6[c]	83±7[c]	84±5[c]	<0.01
Peak HR (beats/min)[a]	148±23	120±23	132±21	146±19	158±18	162±16	163±18	<0.001
Peak systolic BP (mm Hg)	183±25	168±26[b]	174±28[b]	185±25	189±22	187±21	187±21	<0.001
Peak diastolic BP (mm Hg)	88±15	84±14	87±14	89±13[c]	88±13[c]	86±14	85±14	<0.02
Peak METs (3.5 ml O_2/kg/min)[a]	8.1±3.1	3.1±0.7	5.1±0.6	7.0±0.6	9.0±0.6	10.9±0.6	14.4±1.9	<0.001

METs, metabolic equivalents; HR, heart rate; BP, blood pressure.
[a]Differences on all possible comparisons.
[b]Different from other fitness categories.
[c]Different from the least-fit category (≤4 METs).

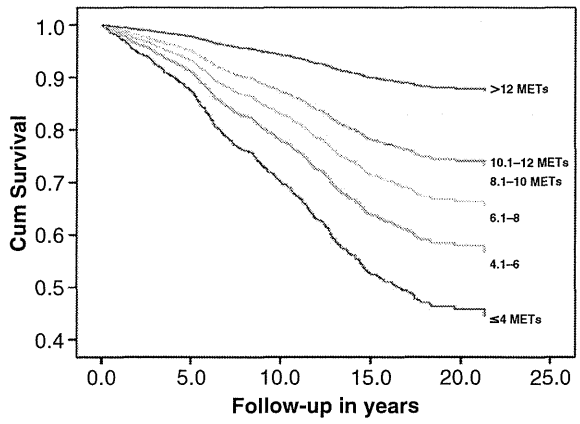

Figure 1. Survival curves according to exercise capacity.

Exercise data are presented in Table II, both for the entire cohort and for each fitness category.

ROC curves further supported the significance of exercise capacity in predicting all-cause mortality in individuals with high-normal blood pressure. Significant predictors of mortality included: exercise capacity in METs (ROC area=0.72; $p<0.001$), age (ROC area=0.70; $p<0.001$), resting systolic blood pressure (ROC area=0.54; $p=0.016$), BMI (ROC area=0.41; $p<0.001$) and resting diastolic blood pressure (ROC area=0.47; $p=0.017$).

Cox proportional hazard analysis revealed a 13% reduction in mortality risk (hazard ratio=0.87; CI 0.84–0.91; $p<0.001$) for every 1-MET increase in exercise capacity, after adjusting for age, BMI, race, diabetes, resting systolic and diastolic BP. The adjusted mortality risks for the entire cohort according to exercise capacity categories are presented in Figure 1.

When the least-fit category (peak exercise capacity ≤4 METs) was used as the referent group, a progressively lower mortality risk was noted with increased exercise capacity in individuals with high-normal blood pressure. More specifically, the mortality risk was 30% lower (hazard ratio=0.70; CI 0.51–0.95; $p=0.022$) in those who achieved 4.1–6.0 METs, whereas those who achieved 6.1–8 METs had approximately half the risk (hazard ratio=0.53; CI 0.38–0.67; $p<0.001$). The risk was about 60% lower and virtually identical for those who achieved 8.1–10 METs and 10.1–12 METs category (hazard ratio=0.39; CI 0.26–0.57; $p<0.001$, and hazard ratio=0.39; CI 0.22–0.67; $p=0.001$, respectively). An additional decline in risk was noted for those who achieved more than 12 METs (hazard ratio=0.17; CI 0.08–0.36; $p<0.001$).

It is possible that the presence of subclinical disease may be a reason for low fitness levels. If so, it is reasonable to assume that the death rate of these individuals may be substantially high within the initial follow-up period. To reduce the influence of the presence of subclinical disease on the fitness–mortality relationship, we excluded individuals who died within the first and second year of follow-up and re-analyzed the data. No substantial changes in the mortality risk reduction were observed when deaths that occurred during the initial 1 or 2 years of follow-up were included (Table III).

Discussion

The findings of our study reveal a strong, inverse and graded association between exercise capacity and all-cause mortality in Veteran male individuals with high-normal blood pressure. This association remained significant even after adjustments for other confounding factors, indicating an independent predictive value of exercise capacity on all-cause mortality. We observed 13% lower mortality risk of every one MET increase in exercise capacity. To our knowledge, this is the first study to address such an association in individuals with high-normal blood pressure.

In addition, the close scrutiny of the fitness–mortality association allowed by the small incremental changes in exercise capacity (every 2 METs), made it possible to probe for an exercise capacity threshold and plateau of health benefits. In this regard, several points are noteworthy. First, the exercise threshold appears to be at 4 METs. Beyond this threshold, the mortality risk reduction was incremental. Second, the 30% lower risk observed in those who achieved an exercise capacity just beyond this threshold (4.1–6 METs). Finally, approximately 50%–60% of the fitness-related health benefits occur at the exercise capacity between 6.1 and 10.0 METs with only additional benefits for those achieving an exercise capacity of more than 12 METs.

Table III. Hazard ratios according to fitness categories.

	Fitness categories						
Variables	≤4 METs	4.1–6.0 METs	6.1–8.0 METs	8.1–10.0 METs	10.1–12.0 METs	>12 METs	*p*-value for trend
Entire cohort	1	0.70 (0.51–0.95)	0.53 (0.38–0.73)	0.39 (0.26–0.57)	0.39 (0.22–0.67)	0.17 (0.08–0.36)	<0.001
1st year deaths excluded	1	0.71 (0.51–0.98)	0.56 (0.40–0.78)	0.42 (0.28–0.62)	0.38 (0.28–0.62)	0.17 (0.08–0.37)	<0.001
1- and 2-year deaths excluded	1	0.74 (0.53–1.0)	0.58 (0.41–0.83)	0.44 (0.29–0.76)	0.42 (0.23–0.76)	0.15 (0.06–0.56)	<0.001

Collectively, the aforementioned findings have significant clinical and public health importance. More specifically, they support that even a small shift of the fitness curve to the right (least fit individuals moving to the next fitness category) has a significant impact in mortality risk and . Furthermore, most of the risk reduction (50–60%) is realized at fitness levels between 6.1 to 10 METs with virtually no addition reduction until the exercise capacity beyond 12 METs. The amount of physical activity necessary to achieve an exercise capacity of 4.1 to 10 METs is a brisk walk to a slow jog of 30–40 min per session, 4–6 days per week. Since this level of activity is relatively safe and attainable by most middle-age or older individuals, the clinical and public health significance of this finding is immense.

Equally important however, is the substantial decline in mortality risk of individuals in the highest fitness levels (>12 METs). Therefore, the pursuit of higher fitness levels for those who are capable of such endeavor should not be discouraged.

These and similar findings reported in other large population groups (18–22,29) urge for wider implementation of physical activity in the general population, especially for sedentary individuals. The robust findings further provide healthcare professionals with a rather strong argument to motivate such individuals to adopt a more physically active lifestyle (30). To accomplish such task, it becomes imperative that governmental and other public authorities create a pleasant environment (parks, pathways, bike roads) and provide the necessary facilities (public gyms and swimming pools) that will facilitate regular physical exercise for the public. In this regard, an even small shift of the fitness curve to the right will result in considerable public health benefits.

Our study shares some unique characteristics. First, the large number of participating individuals (>1700) combined with a long follow-up period (mean of 10 years) permit for a proper evaluation of the effects of exercise capacity on all-cause mortality. Second, the equality in access to healthcare that represents an essential element of the Veterans Administration Health Care System permits for the accurate exclusion of any financial, social, or racial factors that might influence the association between exercise capacity and mortality risk, thus adding further credence to our findings. Furthermore, our study population is comprised of individuals that were referred for exercise testing to rule out exercise-induced ischemia, reflecting common real-world practice and thus rendering our findings clinically meaningful. Finally, unlike the subjective nature of questionnaires used to determine fitness, in our current study, exercise capacity was evaluated objectively by a standardized exercise test.

Given the boundaries and intrinsic limitations of epidemiological studies, a justifiable concern is that the association between the two variables of interest may be spurious. Accordingly, we raised the possibility that the higher mortality risk observed in low fit individuals was the outcome of clinical or subclinical disease that also fostered a sedentary lifestyle. Consequently, the enhanced mortality risk would be attributed to poor health and not to poor fitness levels. Although such scenario cannot be completely ruled out, several indications reduce its probability and strongly suggest of a true and independent association between poor fitness and increased mortality.

First, an important argument against it comes from the design characteristics of our study. The electronic health files used in the Veterans Administration Health Care System permit for the accurate recording of concomitant diseases, not only at baseline but during the whole follow-up period as well. Second, the graded manner of risk reduction seems to argue against the influence of subclinical disease. Theoretically, if subclinical disease is responsible for poor fitness and increased mortality, one would expect that the mortality rate would be high only in the very low fit individuals with a precipitous fall for the next fitness groups. In contrast, our findings reveal that fitness benefits follow a dose–response manner, and such benefits are evident across all fitness categories. Finally, if diseases were the impetus for the relatively high mortality rates in the low-fit, it is reasonable to assume that these individuals will die at a relatively higher rate within the initial follow-up period. Thus, the exclusion of deaths occurring within the initial follow-up period will influence mortality rates and substantially change the fitness–mortality association. We addressed this assumption by excluding deaths during the initial 1 and 2 years of follow-up and re-analyzed data. We observed similar reductions in mortality and virtually no changes in the trend (Table III).

Collectively, the aforementioned procedures and arguments strongly suggest that the association of fitness status and mortality risk is true and independent of deaths occurring as a result of subclinical diseases. However, we recognize that these statements are made within the intrinsic limitations of the epidemiological design of our study and that the association between fitness and mortality cannot be considered by itself as proof of causality. It must be emphasized, that prospective, randomized, interventional studies are needed to address the issue more definitively and prove causal relationships.

Study limitations

Several limitations can be recognized in our study that may limit the interpretation of the findings.

Our conclusions are made within the inherent limitations of epidemiological designs and the inverse association between fitness and mortality does not by itself prove causality. Interventional studies are needed to confirm such a causal relationship. The

inclusion of only male individuals that were referred for exercise testing limits the generalization of our findings to the population as a whole. Also, specific data regarding the type of death were not available, thus not permitting for a separation between cardiovascular and other cause deaths. Although all-cause mortality is widely accepted as a more accurate, objective and unbiased measure compared with cardiovascular mortality (31), it would be interesting to know the effect of fitness status on cardiovascular death.

Conclusions

We observed a strong, inverse, and graded association between exercise capacity and all-cause mortality in male individuals with high-normal blood pressure. This association was independent of traditional cardiovascular risk factors, and exercise capacity was among the strongest predictors of all-cause mortality. These findings reveal that the benefits of improved fitness apply to large population groups, are not limited in hypertensives, and are evident in individuals with high-normal blood pressure as well. These benefits create the need to surpass existing difficulties in motivating otherwise healthy individuals to adopt regular physical exercise. A shift of the fitness curve to the right in the general population might have a major impact in mortality risk, offering unprecedented benefits in public health.

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Conflicts of interest: None.

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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	境界域の者	空白		( )		コホート研究
	性別	男性	( )		( )		( )
	年齢	57(±12)歳			( )		前向き研究
	対象数	1000～5000			( )		( )
調査の方法	実測	( )					
アウトカム	予 防	高血圧症予防	な し	な し	な し	死亡	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表

Table III. Hazard ratios according to fitness categories.

	Fitness categories						
Variables	≤4 METs	4.1–6.0 METs	6.1–8.0 METs	8.1–10.0 METs	10.1–12.0 METs	>12 METs	*p*-value for trend
Entire cohort	1	0.70 (0.51–0.95)	0.53 (0.38–0.73)	0.39 (0.26–0.57)	0.39 (0.22–0.67)	0.17 (0.08–0.36)	<0.001
1st year deaths excluded	1	0.71 (0.51–0.98)	0.56 (0.40–0.78)	0.42 (0.28–0.62)	0.38 (0.28–0.62)	0.17 (0.08–0.37)	<0.001
1- and 2-year deaths excluded	1	0.74 (0.53–1.0)	0.58 (0.41–0.83)	0.44 (0.29–0.76)	0.42 (0.23–0.76)	0.15 (0.06–0.56)	<0.001

図表掲載箇所	P264, Table3
概 要 (800字まで)	本研究は、アメリカの退役軍人健康庁内で行われた運動テストに参加した1,727名の高値正常血圧(収縮期血圧130-139mmHgまたは拡張期血圧85-89mmHg)の男性を対象に平均9.75(±6)年間の追跡調査を行い、運動能力と総死亡の関連について検討したものである。最大トレッドミルテストにより全身持久力を測定した。ピーク時の代謝当量をメッツ値に換算し、4メッツ未満、4.0-6.0メッツ、6.1-8.0メッツ、8.1-10.0メッツ、10.1-12.0メッツ、12メッツ以上の6群に分類した。ピーク時の運動能力が4メッツ未満の集団と比較すると、総死亡リスクがそれぞれの集団で順に、0.70(95%信頼区間:0.51-0.95)、0.53(0.38-0.73)、0.39(0.26-0.57)、0.39(0.22-0.67)、0.17(0.08-0.36)と量反応的に有意に減少することが明らかとなった。無症候性疾患の影響を考慮し、研究開始1年目および2年目の死亡例を除外した解析においても、同様の結果が得られた。また、運動能力が1メッツ上がるごとに総死亡リスクが [illegible] 減少することが明らかとなった。
結 論 (200字まで)	高値正常血圧の白人中年男性コホートにおいて、運動能力と総死亡リスクには強力な逆相関と量反応関係が存在す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)	身体活動基準の策定に用いられた研究の1つである。高値正常血圧の人においても体力と総死亡との関係を明らかにした重要な論文である。また、本研究におけるリスク低下の程度が非常に大きい(最大で0.17のリスク低下)ことは、体力を高めることの重要性を示している。

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Exercise Capacity and Mortality in Older Men
A 20-Year Follow-Up Study

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Background—Epidemiological findings, based largely on middle-aged populations, support an inverse and independent association between exercise capacity and mortality risk. The information available in older individuals is limited.

Methods and Results—Between 1986 and 2008, we assessed the association between exercise capacity and all-cause mortality in 5314 male veterans aged 65 to 92 years (mean±SD, 71.4±5.0 years) who completed an exercise test at the Veterans Affairs Medical Centers in Washington, DC, and Palo Alto, Calif. We established fitness categories based on peak metabolic equivalents (METs) achieved. During a median 8.1 years of follow-up (range, 0.1 to 25.3), there were 2137 deaths. Baseline exercise capacity was 6.3±2.4 METs among survivors and 5.3±2.0 METs in those who died ($P<0.001$) and emerged as a strong predictor of mortality. For each 1-MET increase in exercise capacity, the adjusted hazard for death was 12% lower (hazard ratio=0.88; confidence interval, 0.86 to 0.90). Compared with the least fit individuals (≤4 METs), the mortality risk was 38% lower for those who achieved 5.1 to 6.0 METs (hazard ratio=0.62; confidence interval, 0.54 to 0.71) and progressively declined to 61% (hazard ratio=0.39; confidence interval, 0.32 to 0.49) for those who achieved >9 METs, regardless of age. Unfit individuals who improved their fitness status with serial testing had a 35% lower mortality risk (hazard ratio=0.65; confidence interval, 0.46 to 0.93) compared with those who remained unfit.

Conclusions—Exercise capacity is an independent predictor of all-cause mortality in older men. The relationship is inverse and graded, with most survival benefits achieved in those with an exercise capacity >5 METs. Survival improved significantly when unfit individuals became fit. (***Circulation.* 2010;122:790-797.**)

Key Words: aging ■ epidemiology ■ exercise ■ mortality

An inverse, graded, independent, and robust association between fitness status and mortality is supported by large epidemiological studies in apparently healthy subjects[1–6] and in patients with documented cardiovascular disease (CVD).[1,5] These health risks are particularly apparent at relatively low fitness levels but decrease with higher physical activity patterns or fitness status.[1–5] Most of this evidence is based on studies conducted among middle-aged individuals. Relatively few studies have examined the health benefits of fitness in older populations,[7–13] and most of these studies used questionnaires to estimate either fitness or physical activity patterns in their cohort.[8,10–12] Although some studies used an exercise test to more objectively assess fitness,[7,9,13] they were composed of relatively small samples of older individuals individuals[7,9] or the cohort was relatively young.[13]

Clinical Perspective on p 797

According to a recent Centers for Disease Control and Prevention report, the proportion of Americans aged 65 years and older will double by 2030.[14] This, along with the high rates of poor physical health and activity limitations among the older individuals, will contribute to a projected 25% increase in the nation's overall healthcare costs during this time. Because regular physical activity contributes substantially to healthy aging by helping to prevent or control many of the health problems that often reduce the quality and length of life in older individuals (eg, low fitness, hypertension, obesity, and diabetes mellitus), the Centers for Disease Control and Prevention report states that a physically active lifestyle in older adults should be encouraged.[14]

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In light of the sparse data available on the relationship between fitness and mortality in older individuals, the present study was undertaken to assess the extent to which exercise capacity may predict all-cause mortality among older male veterans (aged >65 years) referred for an exercise tolerance test (ETT) for clinical reasons.

Methods

Study Design and Sample

We identified 5390 male veterans (age range, 65 to 92 years) from the Veterans Exercise Testing Study (VETS) who underwent a symptom-limited ETT between January 1986 and December 2008. The tests were administered at the Veterans Affairs Medical Center, Washington, DC (n=3128), or the Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif (n=2186). All tests were performed either as a routine evaluation or to assess the possibility of exercise-induced ischemia. In addition to age (<65 years), we excluded the following subjects: (1) those with a history of an implanted pacemaker; (2) those who developed left bundle branch block during the test; (3) those with heart failure classified as New York Heart Association class II or higher and those unable to complete the test secondary to musculoskeletal or peripheral vascular issues; and (4) those who had a positive exercise test that was confirmed by additional diagnostic test (stress thallium or cardiac catheterization) or those who became unstable during the ETT or required emergent intervention.[15]

The final sample included 5314 men (3224 white and 2090 black). The mean age was 71.4±5.0 years, and the median age was 70.5 years. Participants were also divided into 2 age categories: 65 to 70 (n=2560) and >70 years (n=2754). All participants gave written consent before the ETT. The study was approved by the internal review boards at each institution.

All demographic, clinical, and medication information was obtained from patients' computerized medical records just before the ETT. Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg and or diastolic BP ≥90 mm Hg. Diabetes mellitus and dyslipidemia were defined on the basis of established criteria at the time the ETT was performed. Each individual was also asked to verify the computerized information with regard to history of chronic disease, current medications, and cigarette smoking habits. Body weight and height were recorded in the exercise stress laboratory before the test. Body mass index (BMI) was calculated as weight (kg) divided by height^2 (m^2). Individuals with CVD were defined as those with a history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary artery bypass surgery, or chronic heart failure classified as New York Heart Association class I.

The Social Security Death Index was used to match all subjects to their record according to Social Security number and death dates from the Veterans Affairs Beneficiary Identification and Record Locator System File. This system is used to determine survivors among veterans and has been shown to be complete and accurate.[16] Vital status was evaluated annually and determined as of June 30, 2009; the outcome of interest was death from any cause.

Exercise Assessments

Exercise capacity for individuals tested at the Veterans Affairs Medical Center, Washington, DC, was assessed by the standard Bruce protocol. For the individuals assessed at the Veterans Affairs Palo Alto Health Care System, an individualized ramp protocol was used, as described elsewhere,[17] Peak exercise time was recorded in seconds. Peak workload was estimated in metabolic equivalents (METs). One MET is defined as the energy expended at rest, which is equivalent to an oxygen consumption of 3.5 mL per kilogram of body weight per minute.[18] Exercise capacity (in METs) was estimated on the basis of exercise time via a commonly used equation for the Bruce protocol[19] and based on American College of Sports Medicine equations for the ramp protocol.[18] Subjects were encouraged to exercise until the occurrence of volitional fatigue in the absence of symptoms or other clinical indications for stopping the test.[15] The use of handrails during the exercise test was discouraged. Age-predicted peak exercise heart rate (HR) was determined on the basis of standardized methods.[20] Medications were not changed or stopped before testing.

Supine resting HR and BP were assessed after 5 minutes of rest. Exercise BP was recorded at 2 minutes of each exercise stage, at peak exercise, and during recovery. Indirect arm-cuff sphygmomanometry was utilized for all BP assessments. ST-segment depression was measured visually. ST depression ≥1.0 mm that was horizontal or downsloping was considered to be suggestive of ischemia.

We also established fitness categories on the basis of the MET level achieved. For the formation of fitness categories, we chose the lowest 20th percentile of METs for the entire cohort (≤4 METs), a cutoff employed in previous studies,[2] to represent the lowest fit category. Thereafter, categories were established per 1-MET incremental increase in exercise capacity (eg, 4.1 to 5; 5.1 to 6; 6.1 to 7; 7.1 to 8; 8.1 to 9; and >9 METs). Those who achieved >9 METs comprised the highest fitness category. The establishment of fitness on the basis of MET level achieved is a more objective method of fitness than self-reported physical activity habits.[2]

Statistical Analysis

Continuous variables are presented as mean and SD, and categorical variables are expressed as absolute and relative frequencies (%). Associations between categorical variables were tested with the Pearson χ^2 test. One-way ANOVA was applied to determine age, BMI, resting and exercise HR and BP, and peak MET level differences between fitness categories and age groups. Normality of the tested variables was evaluated with the Shapiro-Wilk test. Equality of variances between groups was tested by the Levene test. The mortality rates were calculated for each fitness category. We considered individuals in the lowest fitness category (exercise capacity ≤4 METs) as the reference group and individuals with exercise capacity >9 METs as the highest fitness group. Log-rank tests were calculated to evaluate significance of fitness levels on all-cause mortality. Then Cox proportional hazards models were employed to determine the variables that were significantly associated with mortality. The models were adjusted for age in years, peak METs achieved, resting systolic BP (mm Hg), and BMI as continuous variables and for ethnicity, presence of CVD, cardiovascular medications (aspirin, angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, diuretics, vasodilators, and statins), and risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking) as categorical variables. The selection of these variables was based on their clinical relevance and their significant association with mortality observed in our cohort during the exploratory analyses. Cox proportional hazards models were also utilized to determine the variables that were associated with mortality in the subgroup of individuals with repeated exercise tests. The model was adjusted for all of the aforementioned variables. The proportional hazards assumption was evaluated with the use of Schoenfeld residuals and examined graphically. P values <0.05 with 2-sided tests were considered significant. All statistical analyses were performed with the use of SPSS software (SPSS version 18.1, SPSS Inc, Chicago, Ill).

Results

Demographic and Clinical Characteristics and Follow-Up Data

The median follow-up period was 8.1 years (47 170 person-years with a range of 0.1 to 25.3 years). There were 2137 deaths during the follow-up period, with an average annual mortality of 45 deaths per 1000 person-years. The annual mortality rates for the groups aged 65 to 70 and >70 years were 40.0 per 1000 and 49.6 per 1000 person-years, respectively (P<0.001). More than 80% of the participants (n=4266) achieved a peak HR that was at least 85% of the age-predicted value (34%; 358 of those who

Table 1. Demographic and Clinical Characteristics of Study Participants

Demographic and Clinical Variables	Total (n=5314)	65–70 y (n=2560)	>70 y (n=2754)	P*
Age, y	71.4±5.0	67.3±1.6	75.3±3.9	<0.001
BMI, kg/m^2	27.5±4.7	27.9±4.9	27.0±4.5	<0.001
Resting HR, bpm	72±14	72±14	71±13	<0.001
Resting systolic BP, mm Hg	139±21	137±20	140±22	<0.001
Resting diastolic BP, mm Hg	79±11	80±11	78±11	<0.001
CVD, %	36	36	36	0.84
Previous MI, %	24	24	24	0.87
Smoking, %	24	27	22	<0.001
Hypertension, %	56	54	57	0.07
Diabetes mellitus, %	20	20	19	0.53
Dyslipidemia, %	14.0	13.0	15.0	0.02
Treatment				
β-blocker, %	17	16	17	0.21
CCB, %	25	25	25	0.31
ACE-I, %	16	15	16	0.32
Diuretics, %	10	8	11	<0.001
Aspirin, %	5	5	6	0.003
Vasodilators, %	14	15	13	0.053
Statins, %	6	5	7	0.003
Exercise data				
Peak HR, bpm	128±23	131±23	125±22	<0.001
Peak systolic BP, mm Hg	179±31	182±31	176±30	<0.001
Peak diastolic BP, mm Hg	85±16	87±15	84±16	<0.001
Peak METs, 3.5 mL O_2/kg per minute	5.9±2.3	6.3±2.5	5.4±2.0	<0.001

MI indicates myocardial infarction; CCB, calcium channel blockers; and ACE-I, angiotensin-converting enzyme inhibitors.

*Comparisons between the 2 age groups.

did not achieve this level were receiving β-blockers). Participant characteristics and exercise data for the entire cohort and the 2 age categories are presented in Table 1. Significant differences among the 2 age categories were noted in all variables examined except the prevalence of CVD, previous myocardial infarction, hypertension, diabetes mellitus, and use of β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and vasodilators (Table 1). Peak exercise HR and systolic and diastolic BP were significantly different between the 3 groups. The peak MET level was progressively and significantly lower in the older age categories (Table 1). Comparisons between fitness categories also revealed significant differences in all variables examined except resting diastolic BP and the use of β-blockers. Significant differences were also noted in all exercise variables except peak diastolic BP (Table 2).

Predictors of All-Cause Mortality for the Entire Cohort

Hazard ratios for exercise capacity for the entire cohort and for each age category are presented in Table 3. With exercise capacity introduced in the model as a continuous variable, unadjusted data analysis revealed that mortality risk was ≈13% lower for each 1-MET increase in exercise capacity and 12% lower in the fully adjusted model for the entire cohort. Additional associations with all-cause mortality were noted with diabetes mellitus (hazard ratio=1.30; confidence interval [CI], 1.1 to 1.4; $P<0.001$); smoking (hazard ratio=1.29; CI, 1.2 to 1.4; $P<0.001$); CVD (hazard ratio=1.12; CI, 1.0 to 1.2); and BMI (hazard ratio=0.96; CI, 0.95 to 0.97; $P<0.001$).

Risk of Mortality Across Fitness Categories for the Entire Cohort

Relative mortality risks across fitness categories are presented in Table 4, and survival curves are presented in the Figure. Compared with those in the lowest 20th percentile of fitness (peak MET level ≤4), the adjusted hazard ratio for those who achieved 4.1 to 5.0 METs was not statistically significant. Thereafter, the hazard ratios for mortality were progressively lower as exercise capacity increased from 5.1 to 6.0 METs (hazard ratio=0.62; CI, 0.54 to 0.71; $P<0.001$); to 6.1 to 7.0 METs (hazard ratio=0.53; CI, 0.46 to 0.62; $P<0.001$); to 7.1 to 8.0 METs (hazard ratio=0.53; CI, 0.44 to 0.64; $P<0.001$); to 8.1 to 9.0 METs (hazard ratio=0.48; CI, 0.38 to 0.60; $P<0.001$); and >9 METs (hazard ratio=0.39; CI, 0.32 to 0.49; $P<0.001$). The trend for all fitness categories and all-cause mortality was highly significant (P for trend <0.001).

No significant colinearity was noted with any of the variables chosen for the Cox proportional hazards model

Table 2. Demographic and Clinical Characteristics According to Fitness Categories

Variables	Fitness Categories Based on Peak MET Level Achieved							P for Trend
	≤4	4.1–5.0	5.1–6.0	6.1–7.0	7.1–8.0	8.1–9.0	>9.0	
n	1083	1226	866	835	486	355	463	
Age, y	72.4±5.3	72.1±5.1	71.6±5.0	70.8±4.5	70.7±5.0	70.4±4.7	69.4±4.0	<0.001
BMI, kg/m^2	27.4±5.0	27.7±5.0	28.0±4.8	27.7±4.6	27.0±4.1	27.0±4.0	26.4±3.5	<0.001
Resting HR, bpm	75±15	73±14	71±13	70±13	70±13	68±12	70±13	<0.001
Resting systolic BP, mm Hg	140±23	141±22	139±20	137±20	136±21	138±21	136±19	<0.001
Resting diastolic BP, mm Hg	79±12	78±12	79±11	80±10	79±11	79±11	80±11	0.3
CVD, %	44	41	36	34	29	29	19	<0.001
Previous MI, %	23	32	26	26	16	20	5	<0.001
Smoking, %	30	24	23	20	23	21	27	<0.001
Hypertension, %	55	57	61	55	52	54	48	<0.001
Diabetes mellitus, %	19	25	24	21	15	12	9	<0.001
Dyslipidemia, %	11	19	16	16	11	14	4	<0.001
Treatment								
β-blocker, %	17	15	19	18	14	15	19	0.09
CCB, %	29	24	26	24	24	25	21	0.02
ACE-I, %	14	16	18	17	13	16	13	0.04
Diuretics, %	8	11	12	13	7	6	4	0.02
Aspirin, %	5	7	6	6	5	5	2	0.004
Vasodilators, %	23	14	11	10	11	10	11	<0.001
Statins, %	3	5	8	8	8	5	7	<0.001
Exercise data								
Peak HR, bpm	119±23	121±25	128±21	132±19	136±19	137±18	143±20	<0.001
Peak systolic BP, mm Hg	169±33	173±33	181±29	184±28	184±28	188±27	187±24	<0.001
Peak diastolic BP, mm Hg	85±16	85±18	86±15	86±14	85±15	86±13	85±13	0.31
Peak METs, 3.5 mL O_2/kg per minute	3.2±0.7	4.7±0.3	5.6±0.3	6.6±0.3	7.6±0.3	8.6±0.3	11.0±1.8	<0.001

MI indicates myocardial infarction; CCB, calcium channel blockers; and ACE-I, angiotensin-converting enzyme inhibitors.

(highest condition index <24). There were also no significant interactions relative to site by MET level (P=0.16), site by fitness category (P=0.19), race by MET level (P=0.17), or race by fitness category (P=0.27) on mortality risk. Therefore, the analyses were not stratified by these factors.

Risk of Mortality Across Fitness Categories According to Age Groups

Age-specific hazard ratios across fitness categories are also presented in Table 4. The findings were similar to those observed for the entire cohort. More specifically, compared with those in the lowest 20th percentile (peak MET level ≤4), the adjusted relative risks across fitness categories were 32% to 63% lower in those who achieved an exercise capacity >5 METs in the group aged 65 to 70 years and 45% to 60% lower for those older than 70 years.

Accounting for Reverse Causality

To account for the possibility that the higher mortality rates observed in the low-fitness categories were the result of underlying diseases (such as cachexia) or musculoskeletal or peripheral vascular issues and not low fitness per se (reverse causality), we undertook 3 approaches: (1) we excluded those who died within the initial 2 years of follow-up; (2) we excluded those who were not treated with β-blockers but did not achieve at least 85% of their age-predicted maximal HR (to account for factors that may have impaired exercise performance); and (3) we excluded those in the 2 lowest fitness categories (≤5 METs) with BMI <20. We then repeated the survival analyses separately (for each exclusion), as well as with all exclusions combined. In all 4 scenarios, the association between exercise capacity and mortality risk remained robust, and the risk reduction did not deviate substantially from that observed in the entire cohort (Table 5).

Finally, we examined the association between change in fitness and mortality in 867 individuals who had a second exercise evaluation (ETT) at least 6 months after the initial test (Table 6). On the basis of the significant reduction in risk for >5 METs noted in the entire cohort, we classified individuals as unfit if the MET level achieved during the initial exercise test was ≤5 METs and classified as fit those who achieved >5 METs. We then reclassified unfit individuals who also achieved ≤5 METs on the follow-up exercise test (remained unfit) as unfit-to-unfit (n=133; age=71±5 years; time between evaluations=3.3±2.6 years) and those who achieved >5 METs as unfit-to-fit (n=147; age=71±4 years; time between evaluations=3.9±3.3 years). Similarly, individuals classified as fit at baseline but who achieved ≤5 METs on

Table 3. Mortality Risk Hazard Ratios for Exercise Capacity of Entire Cohort and the 2 Age Categories

Variables	No. of Deaths	Hazard Ratio	95% CI	P
All participants (n=5314)	2137			
Exercise capacity (for each 1-MET increment), unadjusted model		0.87	0.84–0.88	<0.001
Exercise capacity (for each 1-MET increment) adjusted for age, BMI, resting BP, race, cardiovascular risk factors,* cardiovascular medications,† and CVD‡		0.88	0.86–0.90	<0.001
Group aged 65–70 y (n=2560)	953			
Exercise capacity (for each 1-MET increment), unadjusted model		0.87	0.85–0.90	<0.001
Exercise capacity (for each 1-MET increment) adjusted for age, BMI, resting BP, race, cardiovascular risk factors, cardiovascular medications, and CVD		0.88	0.85–0.90	<0.001
Group aged >70 y (n=2754)	1184			
Exercise capacity (for each 1-MET increment), unadjusted model		0.86	0.83–89	<0.001
Exercise capacity (for each 1-MET increment) adjusted for age, BMI, resting BP, race, cardiovascular risk factors, cardiovascular medications, and CVD		0.88	0.85–0.91	<0.001

*Cardiovascular risk factors include hypertension, diabetes mellitus, dyslipidemia, and smoking.

†Cardiovascular medications include β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, nitrates, vasodilators, aspirin, and statins.

‡CVD includes documented coronary artery disease, cardiac surgery for coronary artery disease, myocardial infarction, stroke, heart failure, and peripheral vascular disease.

the follow-up test were reclassified as fit-to-unfit (n=134; age=70±4 years; time between evaluations=4.1±2.9 years) and those who maintained a MET level >5 METs in both tests as fit-to-fit (n=449; age=70±4 years; time between evaluations=3.9±3.0 years).

In this subgroup, there were a total of 275 deaths during a mean follow-up period of 4.0 years (range, 6 months to 16.4 years; median, 3 years). The unadjusted mortality rate was 50% for the unfit-to-unfit; 42% for the unfit-to-fit; 37% for the fit-to-unfit; and 23% for the fit-to-fit. To assess the relative mortality risk among these categories, we performed a Cox proportional hazards analysis, adjusted for the same factors used in the primary analysis, using the unfit-to-unfit category as the reference group. The mortality risk was 61% lower in the fit-to-fit group (hazard ratio=0.39; CI, 0.28 to 0.54; $P<0.001$) and 41% lower in the fit-to-unfit group (hazard ratio=0.59; CI, 0.41 to 0.85; $P=0.005$). Individuals who were unfit during the initial test but became fit by the second test (unfit-to-fit) had a 35% lower mortality risk (hazard ratio=0.65; CI, 0.46 to 0.93; $P=0.019$) compared with subjects who were unfit at both examinations.

Discussion

In the present study, the association between exercise capacity and all-cause mortality in older male veterans (65 to 92 years) was assessed. Our findings support an inverse, graded, and independent association between impaired exercise capacity and all-cause mortality risk. For every 1-MET increase in exercise capacity, the mortality risk was 12% lower for the entire cohort and for the 2 age categories.

When fitness categories were considered, comparisons between the lowest fitness category (≤4 METs) and those who achieved 4.1 to 5.0 METs (next fitness category) revealed similar risk. Mortality risk then declined significantly for the remaining fitness categories, ranging from ≈40% for those who achieved 5.1 to 6 METs to 60% for those who achieved >9 METs. We observed similar results when the mortality and exercise capacity association was examined within each age category. Collectively, these findings suggest that an exercise capacity of >5 METs may be necessary for significant health benefits for those aged ≥65 years and confirm previous reports in broader age populations.[1,2,5,9]

Table 4. Adjusted* Hazard Ratios for Mortality Risk of Entire Cohort and Within the 2 Age Groups According to Fitness Categories*

MET Level Achieved	Entire Cohort (n=5314)	No. of Deaths (%)	Age 65–70 y (n=2560)	No. of Deaths (%)	Age >70 y (n=2754)	No. of Deaths (%)
≤4	1.0	615 (57)	1.0	246 (56)	1.0	369 (58)
4.1–5	0.93 (0.83–1.04)	622 (51)	0.92 (0.77–1.1)	244 (50)	0.92 (0.79–1.06)	378 (51)
5.1–6	0.62 (0.54–0.71)	298 (34)	0.68 (0.56–0.84)	145 (36)	0.55 (0.46–0.67)	153 (33)
6.1–7	0.53 (0.46–0.62)	260 (31)	0.53 (0.42–0.85)	128 (30)	0.54 (0.44–0.66)	132 (32)
7.1–8	0.53 (0.44–0.64)	146 (30)	0.53 (0.42–0.69)	82 (30)	0.50 (0.38–0.65)	64 (30)
8.1–9	0.48 (0.38–0.60)	95 (27)	0.45 (0.33–0.62)	47 (23)	0.50 (0.37–0.67)	48 (32)
>9	0.39 (0.32–0.49)	101 (22)	0.37 (0.28–0.49)	61 (19)	0.40 (0.28–0.55)	40 (29)

Values in parentheses represent 95% CIs unless indicated otherwise.

*Adjusted for age (in years), peak METs achieved, resting systolic BP (mm Hg), BMI, ethnicity, CVD, cardiovascular medications (aspirin, angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, diuretics, vasodilators, and statins), and risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking).

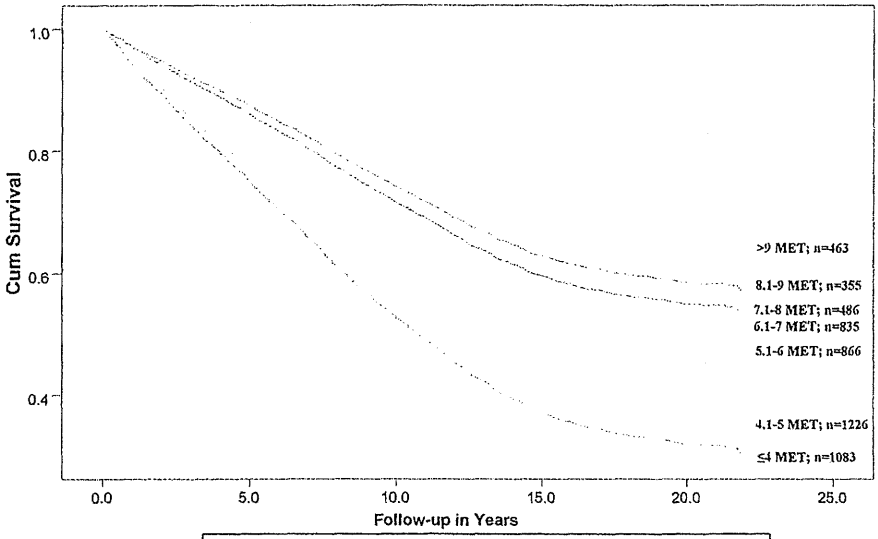

Figure. Cumulative (Cum) survival according to exercise capacity.

	Number of Cumulative Events/Number of Cases at Risk			
Fitness Categories	5 years	10 years	15 years	20 years
≤4 METs	337/724	535/379	608/186	615/63
4.1-5.0 METs	302/853	525/400	605/176	622/48
5.1-6 METs	121/656	233/330	289/122	298/36
6.1-7 METs	93/644	179/343	241/168	260/49
7.1-8.0 METs	51/386	108/180	140/72	146/22
8.1-9.0 METs	43/275	70/151	87/39	95/18
>9 METs	27/343	64/210	100/55	101/25

The inverse and graded association between exercise capacity and all-cause mortality is in accord with our previous reports among middle-aged individuals[1,5] and those from relatively small studies in older individuals.[9] However, the 12% reduction in risk for each 1-MET increase in exercise capacity is somewhat lower than the 18% reported in a smaller study among older subjects (n=514) from the Mayo Clinic.[7]

Several aspects of the present study make unique contributions to existing knowledge by providing information on the association between exercise capacity and mortality in older individuals. First, the 5314 subjects make it one of the largest studies to assess the association between fitness and mortality in a clinically referred cohort of older subjects, especially those aged 71 to 92 years (median age, 75 years; n=2754). Moreover, it allowed the formation of fitness categories per 1-MET increase in exercise capacity, which provided a more precise assessment of the association between fitness and mortality risk.

The size of our cohort also allowed us to consider the possibility that the higher mortality rates within the low fitness categories were influenced by subclinical disease and not exercise capacity per se (reverse causality). To account for this, we excluded those who died within the initial 2 years of follow-up, those who did not achieve at least 85% of age-predicted maximal HR, and those in the 2 lowest fitness categories with BMI <20. We then repeated the analysis after each exclusion and with all exclusions combined. The similarity in trends and magnitude of risk reduction observed between the findings of the entire cohort (Table 4) and these 4 separate analyses (Table 5) argue against the likelihood of reverse causality and support the validity of an association between fitness and mortality risk.

Further evidence against reverse causality is provided by the association between changes in exercise capacity over time and mortality risk in individuals with repeat exercise

Table 5. Adjusted* Hazard Ratios for Mortality Risk According to Fitness Categories (Conditional Exclusion of Study Participants)

MET Level Achieved	Excluding Deaths That Occurred During the First 2 y of Follow-Up (n=4889)	Excluding Those Who Did Not Achieve ≥85% of PMHR and Were Not Treated With β-Blockers (n=4624)	Excluding Those in the 2 Lowest Fitness Categories (≥5 METs) and BMI <20 (n=5186)	Excluding Those Who Met All 3 Conditions (n=4228)
≤4	1.0	1.0	1.0	1.0
4.1–5	0.93 (0.81–1.05)	0.88 (0.77–1.0)	0.92 (0.82–1.03)	0.86 (0.74–1.0)
5.1–6	0.67 (0.57–0.78)	0.54 (0.46–0.63)	0.62 (0.54–0.71)	0.58 (0.49–0.69)
6.1–7	0.60 (0.51–0.70)	0.51 (0.44–0.60)	0.54 (0.46–0.63)	0.57 (0.48–0.68)
7.1–8	0.55 (0.45–0.67)	0.51 (0.42–0.61)	0.53 (0.44–0.64)	0.52 (0.42–0.65)
8.1–9	0.52 (0.41–0.66)	0.45 (0.36–0.57)	0.48 (0.39–0.60)	0.49 (0.38–0.69)
>9	0.43 (0.34–0.54)	0.37 (0.30–0.46)	0.39 (0.31–0.48)	0.42 (0.33–0.54)

Values in parentheses represent 95% CIs. PMHR indicates predicted maximal HR.

*Adjusted for age (in years), peak METs achieved, resting systolic BP (mm Hg), BMI, ethnicity, CVD, cardiovascular medications (aspirin, angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, diuretics, vasodilators, and statins), and risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking).

Table 6. Clinical Characteristics of Individuals With a Follow-Up Exercise Evaluation

Variables	Baseline	Follow-Up	P
n	867	867	
Age, y*	70.3±4.3	72.6±4.6	<0.001
BMI, kg/m^2	27.5±4.7	27.3±4.3	0.56
Resting HR, bpm	70±13	71±13	0.06
Resting systolic BP, mm Hg	140±20	139±20	0.2
Resting diastolic BP, mm Hg	81±11	77±11	0.001
CVD, %	53	57	<0.001
Previous MI	30	37	<0.001
Smoking, %	37	27	<0.001
Hypertension, %	54	65	<0.001
Diabetes mellitus, %	20	30	<0.001
Dyslipidemia, %	19	29	<0.001
Treatment			
β-blocker, %	13	25	<0.001
CCB, %	24	31	<0.001
ACE-I, %	13	23	<0.001
Diuretics, %	9	17	<0.001
Aspirin, %	6	7	0.7
Vasodilators, %	15	18	<0.03
Statins, %	4	16	<0.001

MI indicates myocardial infarction; CCB, calcium channel blockers; and ACE-I, angiotensin-converting enzyme inhibitors.

tests. Compared with unfit individuals in both tests (unfit-to-unfit), mortality risk was 61% lower in those who were physically fit in both tests (fit-to-fit). The mortality risk was 34% lower in individuals defined as unfit during the initial exercise test who became fit by the second test (unfit-to-fit). This finding suggests that advancing from a low-fit to a fit status yields significant health benefits even at an advanced age. Another clinically important finding is that the fitness-related health benefits are not ephemeral but are likely to endure for some years. This notion is supported by the observation that fit individuals who drifted into the unfit category by the second test maintained 41% lower risk compared with those who were unfit on both tests. Although these findings are based on a relatively small number of participants, they are strikingly similar to findings reported by Blair and coworkers[21] in a relatively young but larger cohort.

It is also noteworthy that the Veterans Affairs Health Care System is unique in that it ensures equal access to healthcare independent of a patient's financial status.[22] In addition, the Veterans Affairs electronic healthcare database is uniquely suited to determine mortality and other outcomes accurately and facilitates risk-adjustment models to study outcomes.[23] Thus, the system provides a unique opportunity to assess the association between mortality and exercise capacity while minimizing the influence of disparities in medical care.

Study Limitations

The inverse relationship between fitness and mortality may not demonstrate cause because residual confounding may still exist. Therefore, interventional studies are needed to confirm such a causal relationship. Although similar relationships have been demonstrated for CVD mortality, we only had information on all-cause mortality and did not have data on mortality related to cardiovascular interventions. In addition, we did not have information on physical activity patterns in all subjects; the extent to which exercise capacity reflects physical activity patterns in our sample is unknown. The onset of chronic diseases, their severity, and the duration of therapy were not evaluated because of incomplete records. Dietary information was also not available in our records. The fact that 2 different exercise protocols were used to assess fitness is also a potential limitation. Our previous work suggests that the ramp protocol is somewhat more accurate in predicting measured METs.[17] However, separate analyses from the 2 locations yielded similar results. Thus, the differences in protocols did not have a substantial impact. Finally, our findings are based on men only and cannot be extrapolated to women.

Clinical Implications

The present findings strongly support an inverse and graded association between exercise capacity and mortality risk in individuals aged 65 to 92 years. Similar to previous studies, significant reductions in mortality risk are evident beyond the fitness level represented by an exercise capacity of >5 METs. This level of fitness is likely achievable by most older individuals through 20 to 40 minutes of moderate daily exercise, such as walking.[24] The findings also suggest that the health benefits associated with improved fitness are likely to endure for some years.

The association between fitness and mortality in older individuals is of particular public health significance in light of the aging of the population. Importantly, our findings suggest that fitness-related health benefits are achieved regardless of age or fitness status. Thus, these results extend the public health message on the health benefits of fitness and physical activity to older individuals.[24] Collectively, these results support the concept that exercise capacity should be given as much attention by clinicians as other major risk factors. Thus, physicians and other healthcare professionals should encourage older individuals to initiate and maintain a physically active lifestyle consisting of moderate-intensity activities (brisk walking or similar activities) at any age. Such programs are likely to improve exercise capacity and lower the risk of mortality in older individuals.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Our findings strongly support that increased exercise capacity is associated with significantly lower mortality risk in individuals aged 65 to 92 years. Most health benefits are evident at fitness levels reflected by an exercise capacity >5 METs. This level of fitness is likely achievable by most individuals regardless of age through 20 to 40 minutes of moderate daily exercise, such as brisk walking. In addition, improvement in fitness status even at this age appears to result in a significant reduction in mortality risk. The association between fitness and mortality in older individuals is of particular public health significance in light of the aging of the population. Our findings suggest that the fitness-related health benefits are achieved regardless of age or fitness status. Thus, these results extend the public health message on the health benefits of fitness and physical activity to older individuals. We urge that exercise capacity be given as much attention by clinicians as other major risk factors. Individuals should be encouraged by healthcare professionals to initiate and maintain a physically active lifestyle consisting of moderate-intensity activities (brisk walking or similar activities) at any age. Such programs are likely to improve exercise capacity and lower the risk of mortality in older individuals.

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論文名	Exercise capacity and mortality in older men: a 20-year follow-up study
著 者	Kokkinos P, Myers J, Faselis C, Panagiotakos DB, Doumas M, Pittaras A, Manolis A, Kokkinos JP, Karasik P, Greenberg M, Papademetriou V, Fletcher R.
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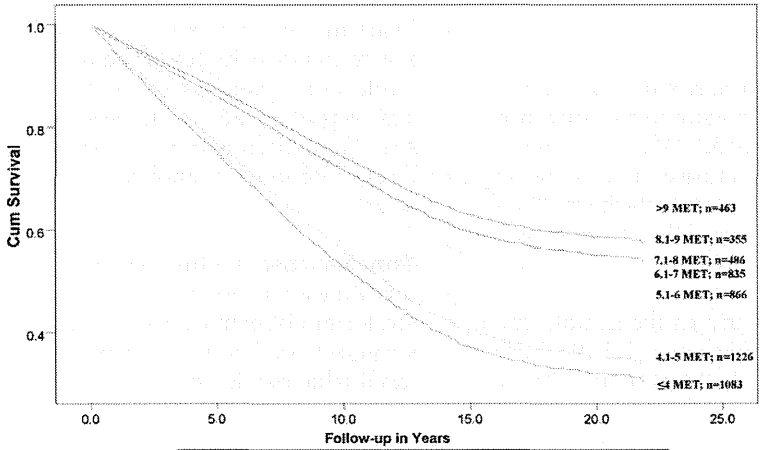
発行年	2010
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/20697029

対象の内訳	ヒト	動物	地 域	研究の種類
対象	一般健常者	空白	欧米	縦断研究
性別	男性	( )	( )	コホート研究
年齢	65-92(71.4歳)		( )	( )
対象数	5000～10000		( )	前向きコホート
			( )	( )

調査の方法						
	実測	( )				
アウトカム	予 防	なし	なし	なし	なし	(死亡) ( )
	維持・改善	な し	な し	な し	なし	( ) ( )

図 表



Fitness Categories	Number of Cumulative Events/Number of Cases at Risk			
	5 years	10 years	15 years	20 years
≤4 METs	337/724	535/379	608/186	615/63
4.1-5.0 METs	302/853	525/400	605/176	622/48
5.1-6 METs	121/656	233/330	289/122	298/36
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8.1-9.0 METs	43/275	70/151	87/39	95/18
>9 METs	27/343	64/210	100/55	101/25

図表掲載箇所	
概 要 (800字まで)	＜目的＞中年の全身持久力と死亡リスクとの間に逆相関関間があることはよく知られているが、高齢者ではどうかは十分わかっていない。この研究では、65歳以上の高齢者の全身持久力と死亡リスクとの関係を検討した。＜方法＞コホート名：the Veterans Affairs Medical Centers in Washington, DC, and Palo Alto, Calif.、対象者数：5314人、追跡期間：22年、因子評価方法詳細：最大トレッドミルテスト(Balke protocol)、因子：全身持久力、因子の単位：メッツ、分位1：(4メッツ未満)、分位2：(4.1-5メッツ)、分位3：(5.1-6メッツ)、分位4：(6.1-7メッツ)、分位5：(7.1-8メッツ)、分位6：(8.1-9メッツ)、分位7：(9メッツ以上)。＜結果＞相対危険度：分位1：1、分位2：0.93(0.83-1.04)、分位3：0.62(0.54-0.71)、分位4：0.53(0.46-0.62)、分位5：0.53(0.44-0.64)、分位6：0.48(0.38-0.6)、分位7：0.39(0.32-0.49)
結 論 (200字まで)	高齢男性において、全身持久力が高くなるほど死亡リスクは減少する量反応関係が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)	全身持久力が4メッツ未満の者と比較して、5. 1メッツ以上の持久力がある者は死亡リスクが0. 62倍で、8メッツ以上の者は0. 39倍であった。高齢者の全身持久力の基準策定に有用な貴重な研究である。

担当者 宮地元彦

ORIGINAL INVESTIGATION

Cardiorespiratory Fitness and the Risk for Stroke in Men

Sudhir Kurl, MD; Jari A. Laukkanen, MD; Rainer Rauramaa, MD, PhD, MSc; Timo A. Lakka, MD, PhD; Juhani Sivenius, MD, PhD; Jukka T. Salonen, MD, PhD, MScPH

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 ($\dot{V}O_2$max) with subsequent incidence of stroke. We also compared $\dot{V}O_2$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 $\dot{V}O_2$max was measured directly during exercise testing at baseline.

Results: The relative risk for any stroke in unfit men ($\dot{V}O_2$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 ($\dot{V}O_2$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 $\dot{V}O_2$max was one of the strongest predictors of stroke, comparable with other modifiable risk factors.

Arch Intern Med. 2003;163:1682-1688

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PREVIOUS STUDIES have shown that physical activity[1-6] and good cardiorespiratory[7-10] 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 al[17] reported a graded dose-response relation, whereas other studies[18-20] have reported a nonlinear association between physical activity and the risk for stroke. Our previous study showed that low maximum oxygen capacity ($\dot{V}O_2$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 $\dot{V}O_2$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 $\dot{V}O_2$max is that it is an objective and quantitative measure of cardiorespiratory fitness.

In this study, we investigated the association of $\dot{V}O_2$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 $\dot{V}O_2$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 $\dot{V}O_2$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 $\dot{V}O_2$max as the measure of cardiorespiratory fitness. A detailed description of the measurement of $\dot{V}O_2$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 $\dot{V}O_2$max was defined as the highest value for or the plateau on oxygen uptake. The $\dot{V}O_2$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 $\dot{V}O_2$max with the risk factors for strokes by covariate analyses and with the risk for stroke by Cox proportional hazards modeling. The levels of $\dot{V}O_2$max were entered as dummy variables into forced Cox models. In these analyses, $\dot{V}O_2$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; $\dot{V}O_2$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 $\dot{V}O_2$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*

$\dot{V}O_2$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; $\dot{V}O_2$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 $\dot{V}O_2$max was 30.2 mL/kg per minute (range, 6.36-65.4 mL/kg per minute). In our study, men with a low $\dot{V}O_2$max were older, consumed more alcohol, smoked, and had higher serum LDL cholesterol levels and SBP compared with those who had a high $\dot{V}O_2$max (**Table 1**).

RISK FACTORS FOR STROKE

As continuous variables, the strongest and statistically significant risk factors for any stroke were $\dot{V}O_2$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 $\dot{V}O_2$max (*P*<.001), SBP (*P*<.001), SES (*P*<.001), and diabetes (*P* = .003). An SD increase in $\dot{V}O_2$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 $\dot{V}O_2$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 ($\dot{V}O_2$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 (0.6801.73)	.73	.125 (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 ($\dot{V}O_2$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 ($\dot{V}O_2$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 $\dot{V}O_2$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 $\dot{V}O_2$max, and the risk for stroke. Our study shows that excessive risk for stroke was observed among men with the lowest level of $\dot{V}O_2$max (<25.2mL/kg per