

# Characterizing Differences in Mortality at the Low End of the Fitness Spectrum

SANDRA MANDIC<sup>1,2,3</sup>, JONATHAN N. MYERS<sup>1,2</sup>, RICARDO B. OLIVEIRA<sup>1,2</sup>, JOSHUA P. ABELLA<sup>1</sup>, and VICTOR F. FROELICHER<sup>1,2</sup>

<sup>1</sup>Veterans Affairs Palo Alto Health Care System, Palo Alto, CA; <sup>2</sup>Stanford School of Medicine, Palo Alto, CA; and <sup>3</sup>School of Physical Education, University of Otago, Dunedin, NEW ZEALAND

## ABSTRACT

MANDIC, S., J. N. MYERS, R. B. OLIVEIRA, J. P. ABELLA, and V. F. FROELICHER. Characterizing Differences in Mortality at the Low End of the Fitness Spectrum. *Med. Sci. Sports Exerc.*, Vol. 41, No. 8, pp. 1573–1579, 2009. **Purpose:** A graded nonlinear relationship exists between fitness and mortality with the most remarkable difference in mortality rates observed between the least-fit (first, Q1) and the next-least-fit (second, Q2) quintile of fitness. The purpose of this study was to compare clinical characteristics, exercise test responses, and physical activity patterns in Q1 versus Q2 in apparently healthy individuals. **Methods:** A total of 4384 subjects referred for clinical treadmill testing from 1986 to 2006 were followed for a mean  $\pm$  SD period of  $8.7 \pm 5.3$  yr. All subjects had normal exercise ECG responses and no history of cardiovascular disease. Subjects were classified into quintiles of exercise capacity measured in METs. Clinical characteristics, physical activity patterns, and treadmill test results were compared between the first two quintiles (Q1: METs  $<5.9$  ( $n = 693$ ); Q2: METs  $6.0\text{--}7.9$  ( $n = 842$ )). **Results:** Small differences in age ( $64 \pm 11$  vs  $60 \pm 10$  yr,  $P < 0.001$ ), use of antihypertensive medications, prevalence of diabetes (21% vs 16%,  $P = 0.02$ ), and dyslipidemia (43% vs 49%,  $P = 0.04$ ) were observed between Q1 and Q2. When the Cox proportional hazards model was adjusted for age and other clinical characteristics, the relative risk of mortality remained almost two times greater in Q1 versus Q2 (cardiovascular mortality: HR: 4.01 vs 2.01,  $P < 0.001$ ; reference group: fittest subjects (Q5)). In a subset of 802 subjects, recent recreational physical activity was significantly lower in Q1 versus Q2. **Conclusions:** Reduced physical activity patterns rather than differences in clinical characteristics contribute to the striking difference in mortality rates between the least-fit and the next-least-fit quintile of fitness in healthy individuals. **Key Words:** EXERCISE CAPACITY, PROGNOSIS, PHYSICAL ACTIVITY, HEALTHY, EXERCISE TESTING

Numerous epidemiological studies in recent years have reported an inverse, graded, and dose-dependent relationship between physical fitness and mortality in individuals with and without cardiovascular disease (2,9,18,21). Accumulating evidence suggests that this relationship is nonlinear, with the greatest decline in risk of mortality occurring between the least-fit (first, Q1) and the next-least-fit (second, Q2) quintile of fitness (2,8,18,21,24). These findings have led the current consensus statements on physical activity to emphasize that the greatest health benefits are achieved by increasing physical activity among the least-fit individuals (20,25). However, factors that may explain the steep mortality gradient at the lowest end of the fitness spectrum have not been explored. Therefore, it remains unknown whether differences in clinical characteristics (reflecting differences in severity of underlying disease), physical activity patterns, other behaviors, environmental, or

other factors such as genetics could explain the steep mortality gradient between Q1 and Q2. The purpose of this retrospective study was to compare clinical characteristics, exercise test responses, and physical activity patterns between Q1 and Q2 in apparently healthy individuals.

## METHODS

**Experimental design and approach.** The study population consisted of 4384 veterans (200 women) referred for treadmill testing for clinical reasons at the Long Beach and VA Palo Alto Health Care System (Palo Alto, CA) from 1987 to 2006. Detailed clinical history, current medications, risk factors, and cardiovascular disease were recorded prospectively on computerized forms (5,6). The study was approved by the Stanford Investigational Review Board, and all subjects signed written informed consent.

All subjects had normal exercise test results and no history of cardiovascular disease. We excluded individuals with a history of cardiovascular disease, chronic obstructive pulmonary disease, cancer, chronic renal insufficiency, endocrine, liver, or neurological disease, or abnormal exercise test results (defined as exercise-induced angina and/or ST-segment depression  $\geq 1$  mm that was horizontal or down-sloping during exercise, in recovery, or both).

The population was divided into quintiles of fitness on the basis of metabolic equivalents (METs) achieved. Cutoff

Address for correspondence: Sandra Mandic, Ph.D., Exercise Physiology, School of Physical Education, University of Otago, PO Box 56, Dunedin, New Zealand; E-mail: sandra.mandic@otago.ac.nz.

Submitted for publication October 2008.

Accepted for publication January 2009.

0195-9131/09/4108-1573/0

MEDICINE & SCIENCE IN SPORTS & EXERCISE®

Copyright © 2009 by the American College of Sports Medicine

DOI: 10.1249/MSS.0b013e31819ca063

points between the categories were set at approximately every 20th percentile of the population to yield similar sample sizes in each quintile.

**Exercise testing.** After providing written informed consent, the subjects underwent symptom-limited treadmill testing according to standardized graded (29) or individualized ramp (15) treadmill protocols. Before testing, exercise capacity was estimated by a questionnaire that allowed individualization of the ramp protocol such that maximal exercise capacity was achieved within 8 to 12 min in most subjects (16). Subjects were encouraged to exercise until volitional fatigue in the absence of symptoms or other signs of ischemia. The use of handrails during exercise was discouraged. Target heart rate (HR) were not used as predetermined end points. A 12-lead ECG was monitored throughout the test. After exercise, subjects were placed in a supine position. Medications were not changed or stopped before testing. The exercise tests were performed, analyzed, and reported according to a standardized protocol and with the use of a computerized database (22).

Peak exercise capacity (in METs) was estimated on the basis of the speed and grade of the treadmill (1). One MET is defined as the energy expended sitting quietly, which is equivalent to an oxygen consumption of approximately 3.5 mL·kg<sup>-1</sup> body weight per minute for an average adult. Normal standards for age-predicted exercise capacity were derived from regression equations developed from veterans referred for exercise testing (14) using the equation [18.0 - (0.15 × age)]. The percentage of normal exercise capacity achieved was defined as follows: [(achieved exercise capacity / predicted exercise capacity) × 100]. Age-predicted maximal HR was calculated as 187 - (0.85 × age) (14).

**Physical activity questionnaire.** Physical activity data were collected between 1993 and 2006, depending on

the availability of research assistants during that period, and were available in a subgroup of 802 subjects. Physical activity was quantified by a five-page questionnaire modified from the Harvard Alumni studies of Paffenbarger et al. (19) and has been previously described in detail (17). Examples of physical activities included walking (leisurely or briskly), jogging (slowly or briskly), swimming, gardening, carpentry, weight lifting, and playing golf (carrying clubs or using power cart, etc.). Metabolic costs of lifetime and recent recreational physical activities were computed, and energy expenditure was expressed in kilocalories per week (kcal·wk<sup>-1</sup>). Subjects were categorized as sedentary (<1000 kcal·wk<sup>-1</sup>), moderately active (1000–1999 kcal·wk<sup>-1</sup>), and active (>2000 kcal·wk<sup>-1</sup>). Cut points for categories of physical activity were determined on the basis of previously published observational studies showing that an energy expenditure of ≥1000 kcal·wk<sup>-1</sup> in physical activity (approximating 30 min or more of moderate-intensity physical activity on ≥5 d·wk<sup>-1</sup>) is widely recommended to promote health and prevent chronic disease (7,20,25). An energy expenditure of ≥2000 kcal·wk<sup>-1</sup> was considered “active” (approximating 1 h or more of moderate-intensity activity 5 to 7 d·wk<sup>-1</sup>); this amount has been used as a benchmark for risk reduction (19).

**Follow-up.** The Social Security Death Index was used to match all individuals to their records according to name and Social Security number. Vital status was determined as of October 2007. Causes of death were determined independently by two physicians, and any disagreement was resolved by consensus. Cardiovascular death was defined as death due to stroke or cardiac reasons.

**Statistical analysis.** NCSS software (Kayesville, UT) was used for all statistical analyses. ANOVA with Bonferroni *post hoc* multiple comparisons and  $\chi^2$  tests were used to compare differences between the quintiles of exercise

TABLE 1. Demographic and clinical characteristics for quintiles of fitness.

	Quintiles of Exercise Capacity (Estimated METs)						P for Main Effect	P, First vs Second
	Total (n = 4384)	Q1 (Lowest; n = 693)	Q2 (n = 842)	Q3 (n = 882)	Q4 (n = 992)	Q5 (Highest; n = 975)		
Demographics								
Age (yr)	56 ± 12	64 ± 11*	60 ± 10*†	57 ± 10*†	54 ± 10*†	48 ± 11†	<0.001	<0.001
Male gender, n (%)	4184 (95)	654 (94)	785 (93)	839 (95)	956 (96)	980 (97)	<0.001	0.358
Body mass index (kg·m <sup>-2</sup> )	28.6 ± 5.3	29.8 ± 6.7*	29.5 ± 5.5*	29.2 ± 5.2*	28.2 ± 4.6*†	27.1 ± 4.1†	<0.001	0.308
All-cause mortality, n (%)	546 (13)	170 (25)*	113 (13)*†	111 (13)*†	97 (10)*†	55 (6)†	<0.001	<0.001
Cardiovascular mortality, n (%)	109 (2.5)	37 (5.3)*	22 (2.6)*†	20 (2.3)*†	21 (2.1)*†	9 (0.9)†	<0.001	0.006
Medications, n (%)								
β-Blockers	543 (12.4)	111 (16.0)*	138 (16.4)*	121 (13.7)*	105 (10.6)*†	68 (7.0)†	<0.001	0.844
CCB	554 (12.6)	145 (20.9)*	123 (14.6)*†	128 (14.5)*†	98 (9.9)*†	60 (6.2)†	<0.001	0.001
Antihypertensive	697 (15.9)	163 (23.5)*	139 (16.5)*†	149 (16.9)*†	144 (14.5)*†	102 (10.5)†	<0.001	<0.001
ACE inhibitors	633 (14.4)	162 (23.4)*	155 (18.4)*†	135 (15.3)*†	115 (11.6)*†	66 (6.8)†	<0.001	0.017
Anticoagulant	812 (18.5)	146 (21.1)*	179 (21.3)*	170 (19.3)*	171 (17.2)†	146 (15.0)†	0.002	0.927
Statins	384 (8.8)	66 (9.5)*	98 (11.6)*	72 (8.2)*	97 (9.8)*	51 (5.2)†	<0.001	0.182
Diuretics	191 (4.4)	35 (5.1)*	60 (7.1)*	35 (4.0)*	44 (4.4)*	17 (1.7)†	<0.001	0.093
Risk factors, n (%)								
Hypertension	1980 (45.2)	422 (60.9)*	472 (56.1)*	424 (48.1)*†	399 (40.2)*†	236 (27.0)†	<0.001	0.056
Dyslipidemia	1986 (45.3)	298 (43.0)*	413 (49.0)*†	431 (48.9)*†	474 (47.8)*	370 (37.9)†	<0.001	0.018
Obesity	1407 (32.9)	278 (40.7)*	337 (41.1)*	304 (35.9)*	294 (30.4)*†	194 (20.1)†	<0.001	0.877
Diabetes mellitus	515 (11.7)	142 (20.5)*	126 (16.2)*†	105 (11.9)*†	84 (8.5)*†	48 (4.9)†	<0.001	0.028
Smoking history	2523 (57.6)	455 (65.7)*	540 (64.1)*	532 (60.3)*†	567 (56.1)*†	439 (45.0)†	<0.001	0.534

\* P < 0.05 versus fifth quintile.

† P < 0.05 versus first quintile.

CCB, calcium channel blockers.

capacity for continuous and discrete variables, respectively. Clinical characteristics of Q1 and Q2 were compared using unpaired *t*-tests and  $\chi^2$  tests where appropriate. All-cause and cardiovascular mortalities were used as the end points for Kaplan-Meier survival analysis. Cox proportional hazards analysis was used to determine which variables were independently and significantly associated with time to death in multivariate models. Analyses were adjusted for age in years as a continuous variable. The relative risks of both all-cause and cardiovascular mortalities were calculated for each fitness category. Continuous variables are presented as mean  $\pm$  SD, whereas categorical variables are expressed as absolute and relative (%) frequencies.  $P < 0.05$  were considered statistically significant.

## RESULTS

**Demographic characteristics.** During a mean  $\pm$  SD follow-up period of  $8.7 \pm 5.3$  yr, there were a total of 546 (13%) deaths from any cause and 109 (2.5%) cardiovascular deaths. Significant trends were observed for decreasing age and for both all-cause and cardiovascular mortalities from the least-fit (Q1) to the most-fit (Q5) quintiles (Table 1). Compared to the fittest subjects (fifth quintile), the least-fit subjects (Q1) had a fourfold increased risk of both all-cause and cardiovascular mortalities, and the risk was progressively reduced with increasing quintiles of fitness (Fig. 1). These trends are evident from the Kaplan-Meier survival curves (Fig. 2). However, the reduction in mortality risk between quintiles was not linear; a nearly twofold increase in age-adjusted relative risk of mortality occurred between the least-fit (Q1) and the next-least-fit (Q2) quintile of fitness, with smaller differences observed between the other quintiles (Fig. 1). Mortality remained significantly higher in Q1 compared with that in Q2 when

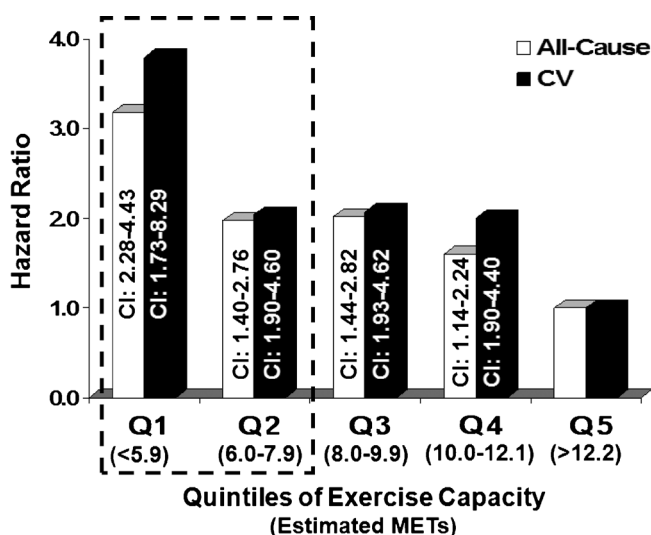


FIGURE 1—Hazard ratios for all-cause and cardiovascular mortalities across quintiles of fitness in healthy individuals. CV, cardiovascular; Q, quintile; Q1, least-fit; Q5, most-fit.

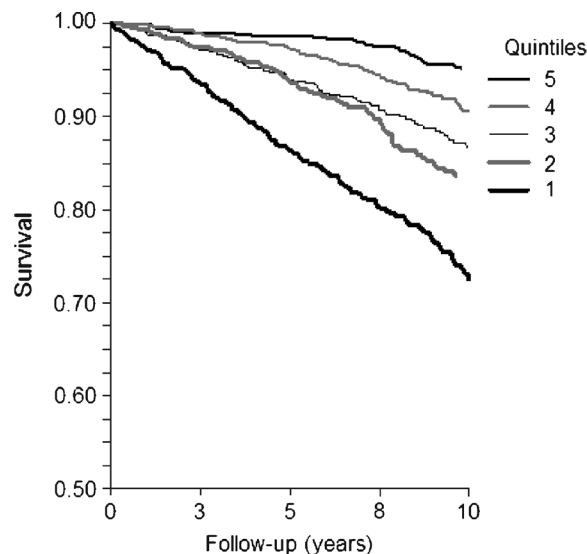


FIGURE 2—Kaplan-Meier curves for all-cause mortality across quintiles of fitness in healthy individuals. Quintile 1, least-fit; quintile 5, most-fit.

adjusted for differences in clinical characteristics or when patients with less than 3 yr of follow-up were excluded.

**Trends across quintiles of fitness.** Use of cardiovascular medications and prevalence of risk factors were significantly lower among the lowest compared with the highest quintiles of fitness (Table 1). By ANOVA, significant main effects were observed for decreased resting HR and blood pressure and increased peak exercise HR (absolute and age-predicted), systolic blood pressure, and absolute and age-predicted exercise capacity from the lowest to the highest quintile of fitness (Table 2).

The observed main effects in recreational physical activity patterns across quintiles of fitness (Fig. 3) were largely attributable to a decreased proportion of less active individuals (energy expenditure:  $<1000$  kcal·wk<sup>-1</sup>) and an increased proportion of active individuals (energy expenditure:  $>2000$  kcal·wk<sup>-1</sup>) from the first to the fifth quintile, whereas the proportion of moderately active individuals (energy expenditure: 1000–2000 kcal·wk<sup>-1</sup>) was relatively constant across quintiles of fitness (Fig. 4).

**Comparison between least-fit and next-least-fit quintiles.** Subjects in Q1 were older, had more extensive use of ACE inhibitors, calcium channel blockers, and other antihypertensive agents, and had a higher prevalence of diabetes compared with Q2 (Table 1). The prevalence of dyslipidemia was lower in Q1 versus Q2. No other differences in risk factors or medication use were found between the groups. Exercise test responses (maximum HR and systolic blood pressure, exercise capacity) were significantly lower in Q1 versus Q2 (Table 2).

Energy expenditure expressed as age-adjusted recent recreational physical activity (in the last year) was significantly lower in Q1 ( $n = 142$ ) versus Q2 ( $n = 152$ ) ( $1120 \pm 1529$  vs  $1566 \pm 1987$  kcal·wk<sup>-1</sup>, respectively,  $P = 0.03$ ).

TABLE 2. Resting, exercise, and hemodynamic data for quintiles of fitness in healthy individuals.

	Quintiles of Exercise Capacity (Estimated METs)					P for Main Effect	P, First vs Second	
	Total (n = 4384)	Q1 (Lowest; n = 693)	Q2 (n = 842)	Q3 (n = 882)	Q4 (n = 992)			Q5 (Highest; n = 975)
Resting values								
HR (bpm)	77 ± 14	80 ± 16*	78 ± 14*†	77 ± 13†	77 ± 13†	76 ± 13†	<0.001	0.029
Systolic BP (mm Hg)	131 ± 19	136 ± 22*	133 ± 20*†	132 ± 18*†	129 ± 18†	128 ± 17†	<0.001	0.021
Diastolic BP (mm Hg)	82 ± 11	81 ± 12*	82 ± 11†	83 ± 11†	82 ± 11†	83 ± 11†	<0.001	0.007
Peak exercise values								
HR (bpm)	146 ± 22	127 ± 21†	126 ± 19*†	145 ± 19*†	152 ± 18*†	163 ± 18*	<0.001	<0.001
Systolic BP (mm Hg)	182 ± 26	176 ± 30*	180 ± 28*†	182 ± 25†	184 ± 25†	185 ± 25†	<0.001	0.001
Diastolic BP (mm Hg)	85 ± 14	85 ± 14	85 ± 13	86 ± 13	85 ± 14	85 ± 14	0.935	0.811
Exercise capacity (METs)	9.4 ± 3.5	4.4 ± 1.0*	6.8 ± 0.5*†	8.7 ± 0.6*†	10.8 ± 0.7*†	14.4 ± 1.9†	<0.001	<0.001
Age-predicted METs (%)	98 ± 33	54 ± 15*	78 ± 15*†	95 ± 16*†	112 ± 19*†	134 ± 25†	<0.001	<0.001
Age-predicted HR (%)	100 ± 14	92 ± 15*	96 ± 14*†	100 ± 13*†	103 ± 12*†	107 ± 12†	<0.001	<0.001

\* P < 0.05 versus fifth quintile.

† P < 0.05 versus first quintile.

BP, blood pressure; HR, heart rate; METs, metabolic equivalents.

Lifetime adulthood recreational physical activity pattern was not different between the groups.

**Fitness as a multivariate predictor of mortality.** After adjustment for age, risk factors, and cardiovascular medications, reduced peak exercise capacity was the strongest multivariate predictor of all-cause (hazard ratio: 0.89 (95% confidence interval (CI): 0.86–0.91)) and cardiovascular mortalities (hazard ratio: 0.87 (95% CI: 0.82–0.93)). Each 1-MET increase in exercise capacity conferred an 11% risk reduction for all-cause mortality and a 13% risk reduction for cardiovascular mortality in the total population. When only Q1 and Q2 were considered, the risk reductions per MET were 21% for all-cause mortality and 24% for cardiovascular mortality.

Comparison of demographic and clinical characteristics of the cohort with physical activity data versus the entire cohort is presented in Table 3. Because physical activity data were collected on patients in more recent years, this subgroup had a significantly shorter follow-up period and lower mortality rates compared with the entire cohort. In addition, higher usage of ACE inhibitors, anticoagulants and statins, and higher prevalences of dyslipidemia and smoking were observed in the physical activity subgroup versus the remainder of the cohort. Prevalence of other risk factors and exercise capacity were not different between the cohorts.

## DISCUSSION

The overall findings of the present study are consistent with previous reports demonstrating a nonlinear gradient between fitness and both all-cause and cardiovascular mortalities (2,8,18,21,24). A unique finding was the suggestion that the striking mortality difference between the least-fit and the next-least-fit quintiles of fitness in healthy individuals are difficult to discern but may be related to a more sedentary lifestyle in the least-fit group rather than to differences in health status at the time of evaluation.

Several factors determine an individual's fitness level, including age, health status, physical activity patterns, behavioral and environmental factors, and genetics (4). We observed that older age, higher prevalence of diabetes,

lower prevalence of dyslipidemia, and more extensive use of ACE inhibitors, calcium channel blockers, and other antihypertensive agents were observed in Q1 versus Q2. No other differences in risk factors or cardiovascular medications were found between the groups. Although statistically significant, the differences in these clinical characteristics were small and are unlikely to explain the nearly twofold

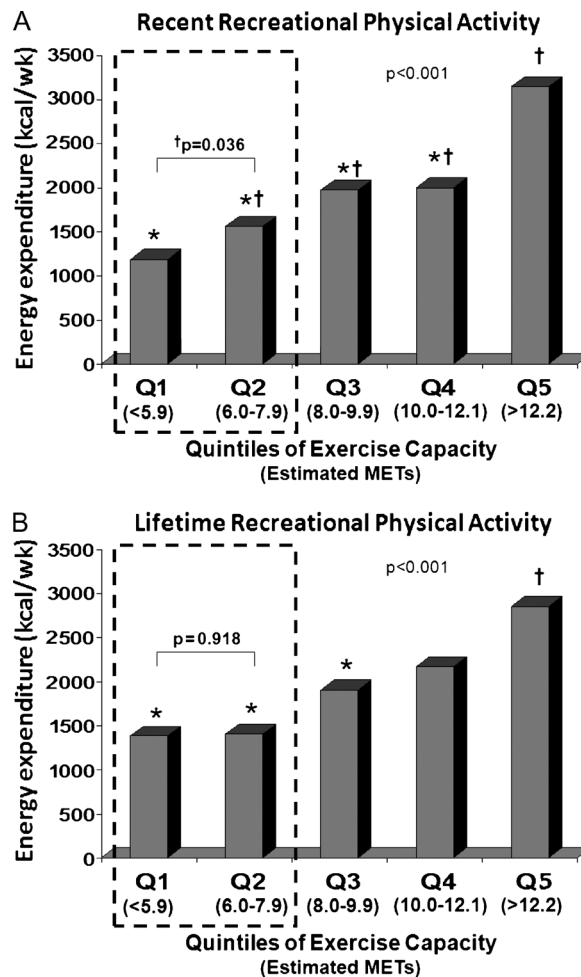
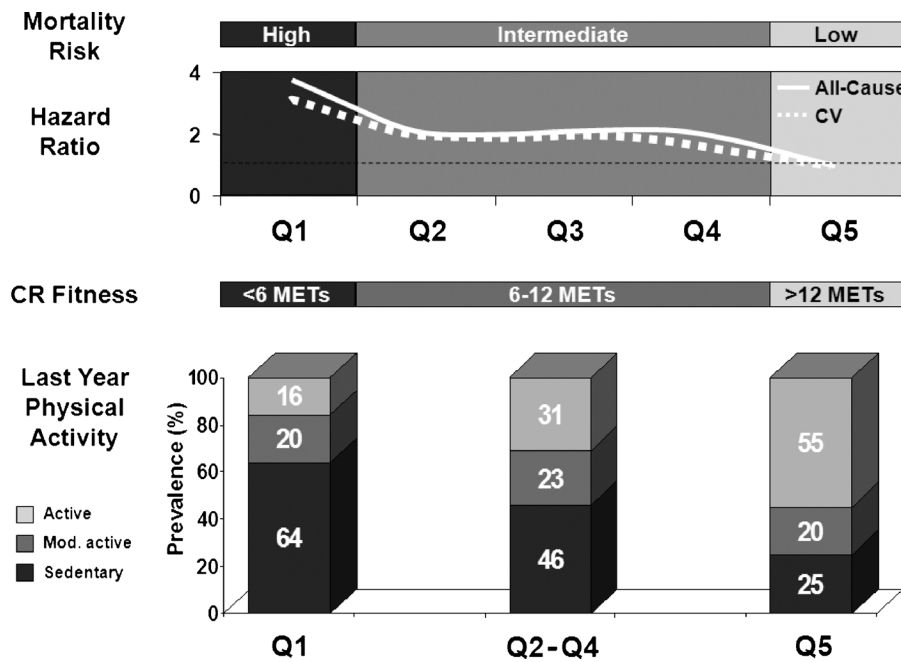


FIGURE 3—Age-adjusted weekly energy expenditure in recent (upper panel) and lifetime (lower panel) recreational physical activity for quintiles of fitness in healthy individuals. Q1, least-fit quintile; Q5, most-fit quintile. \*P < 0.05 versus Q5; †P < 0.05 versus Q1.



**FIGURE 4**—Interactions between fitness, physical activity patterns, and mortality risk in healthy individuals. All-cause, all cause mortality; CV, cardiovascular mortality; CR, cardiorespiratory; Mod. active, moderately active; Q1, least-fit quintile; Q5, most-fit quintile.

increase in mortality risk between Q1 and Q2. Therefore, other factors that are difficult to measure such as genetics (3) or lifestyle behaviors related to higher cardiovascular risk likely play a significant role.

Low levels of self-reported physical activity have been associated with an increased risk of mortality in healthy individuals (11,13,23) with the greatest survival benefits occurring between the least-active and the next-least-active category (13). Although physical fitness is a stronger predictor of mortality compared with activity pattern (17,28), physical activity is an important determinant of fitness and is an appropriate therapy for unfit individuals. In the present study, the least-fit quintile had a significantly lower level of recent recreational physical activity compared with the next-least-fit quintile after adjustment for age. Energy expenditure for lifetime (adulthood) recreational physical activity was not significantly different between the groups. Taken together, these findings provide further support for the current guidelines on physical activity and health, which emphasize the importance of maintaining modest regular physical activity throughout life.

Consistent with recent studies (2,9,10,17,18,21), we observed that exercise capacity was the strongest independent predictor of all-cause and cardiovascular mortalities after adjusting for age, medications, and cardiovascular risk factors. In addition, every 1-MET increase in exercise capacity in the lowest end of the fitness spectrum (Q1 and Q2 combined) was associated with a 21% reduction in risk of all-cause and a 24% reduction in risk of cardiovascular mortality. These risk reductions were almost two times greater than the respective values in the total population, suggesting that increasing exercise capacity is associated with the greatest survival benefit among individuals at the

low end of the fitness spectrum. In addition, mortality risk for the second, third and fourth quintiles was approximately two times greater compared with that for the fifth (the most fit) quintile (Figs. 1 and 4). Thus, these findings provide further support for the importance of encouraging individuals who are poorly fit to adopt health-promoting behaviors to improve fitness and potentially reduce their mortality risk.

According to the current public health guidelines on physical activity, all adults should attempt to accumulate  $\geq 30$  min of moderate-intensity physical activity on  $\geq 5$  d-wk<sup>-1</sup> (7,20,25). This amount of physical activity is roughly

**TABLE 3.** Comparison of demographic and clinical characteristics of the entire cohort and a subgroup with physical activity data.

	Entire Cohort (n = 4384)	Physical Activity Subgroup (n = 802)	P
<b>Demographics</b>			
Age (yr)	56 ± 12	56 ± 13	0.087
Male gender, n (%)	4184 (95)	771 (96)	0.379
Body mass index (kg·m <sup>-2</sup> )	28.6 ± 5.3	28.6 ± 5.2	0.120
Follow-up (yr)	8.7 ± 5.3	6.3 ± 4.1	<0.001
All-cause mortality, n (%)	546 (13)	50 (6)	<0.001
<b>Medications, n (%)</b>			
β-Blockers	543 (12.4)	99 (12)	0.976
CCB	554 (12.6)	108 (14)	0.518
Antihypertensive	697 (15.9)	120 (15)	0.503
ACE inhibitors	633 (14.4)	138 (17)	0.043
Anticoagulant	812 (18.5)	276 (34)	<0.001
Statins	384 (8.8)	102 (13)	<0.001
Diuretics	191 (4.4)	44 (6)	0.157
<b>Risk factors, n (%)</b>			
Hypertension	1980 (45.2)	357 (45)	0.734
Dyslipidemia	1986 (45.3)	410 (51)	<0.002
Obesity	1407 (32.9)	280 (35)	0.260
Diabetes mellitus	515 (11.7)	92 (12)	0.823
Smoking history	2523 (57.6)	514 (64)	<0.001
Exercise capacity (METs)	9.4 ± 3.5	9.5 ± 3.5	0.145

\* P < 0.05 versus fifth quintile.

† P < 0.05 versus first quintile.

CCB, calcium channel blockers.

equivalent to an energy expenditure of 1000 kcal·wk<sup>-1</sup>. In the present study, 64% of the individuals in Q1 did not meet these minimal physical activity recommendations (Fig. 4). Therefore, considerable health benefits, prolonged lifespan, and, ultimately, reduced health care costs (26) could be achieved by initiating regular physical activity including as little as 30 min of brisk walking on most days of the week in these comparatively unfit individuals. Although evidence suggests that mortality benefits could be achieved by engaging in less than recommended activity levels (12), further health outcome benefits occur at exercise levels that exceed current minimum guidelines (27).

In apparently healthy individuals, it is possible that poor fitness and a sedentary lifestyle may be due to the presence of subclinical illness. Subclinical disease could cause poor performance on an exercise test and also lead to increased mortality rates in individuals presumed to be healthy at baseline (2). In the present study, individuals with known chronic diseases, including cardiovascular and pulmonary disease, cancer, chronic renal insufficiency, and endocrine and neurologic disorders, were excluded. In addition, the gradient between fitness and mortality was not altered across quintiles after excluding individuals who died within 3 yr after baseline testing. Although an influence of subclinical disease cannot be excluded, these results suggest that the relationship between fitness and mortality was not likely due to subclinical disease.

Although the present findings were not based on the results of a prospective randomized controlled trial, a notable feature was the lack of overt differences in baseline clinical characteristics and a significant difference in the extent of recent recreational physical activity between Q1 and Q2. This observation strengthens the conclusion that the differences in energy expenditure from physical activity in the last year contribute to differences in fitness and possibly the difference in mortality risk between the least-fit and the next-least-fit quintile.

**Clinical implications.** These results extend the public health message that emphasizes the importance of increasing regular recreational physical activity, particularly in poorly fit individuals. Achieving public health recommendations for minimal physical activity can have an important impact on improving health outcomes (7,20,25). Nearly two thirds of the least-fit individuals were performing less than the minimal amount of recommended physical activity, yet this group achieves the greatest health benefits from a small increment in fitness. Thus, it is a paramount that health professionals develop strategies to encourage physical activity among patients and the public. Health professionals should

consider a sedentary lifestyle and poor fitness as treatable and major risk factors.

**Limitations.** We used a single measurement of exercise capacity and physical activity patterns at baseline. It is unknown whether changes in fitness due to changes in activity or other health behaviors influenced the results during the follow-up. Second, physical activity data were collected in more recent years and were available only in a subset of patients. Therefore, the physical activity cohort had a significantly shorter follow-up period and lower mortality rates compared with the remainder of the cohort. Despite small differences in medication use reflecting a difference in medical treatment of cardiovascular disease prevention in the last decade, the physical activity cohort was not healthier or more fit than the rest of the cohort. Moreover, information about education level and socioeconomic status between the groups was not available. Third, there are inherent limitations to self-reporting of physical activity, including potential measurement errors, recall bias, variation in the level of activity during adulthood, and how attentive subjects may have been in their responses. Fourth, aside from likely being more physically active, individuals at the high end of the fitness spectrum (Q4 and Q5) may tend to adopt other kinds of health-promoting behavior (such as healthy diet) (27) that may reduce their risk of cardiovascular disease, other illnesses, and mortality. Fifth, environmental factors and genetics affect an individual's fitness level and physical activity pattern, but their effects are difficult to quantify. Finally, our results are based on US Veterans and may not necessarily apply to the general population.

**Summary.** The present study examined the association between exercise capacity and mortality in the lowest end of the fitness spectrum in healthy individuals. Our results suggest that reduced recent physical activity rather than differences in clinical characteristics contribute to the striking difference in mortality rates between the least-fit and the next-least-fit quintile of fitness. These findings make a unique contribution to the existing literature by providing information related to factors that may explain the nonlinear gradient between fitness and mortality. Given the considerable survival benefit associated with improving fitness in the least-fit category, increasing fitness by increasing regular physical activity should be a priority in those who are unfit. Health professionals should particularly encourage unfit individuals to engage in regular physical activity.

No funding sources to be disclosed.

Conflict of interest: authors have no conflicts of interest.

The results of the present study do not constitute endorsement by ACSM.

## REFERENCES

1. American College of Sports Medicine. *Guideline for Exercise Testing and Prescription*. Lippincott Williams & Wilkins; 2006. p. 289.
2. Blair SN, Kohl HW III, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*. 1989;262:2395-401.
3. Bouchard C, Daw EW, Rice T, et al. Familial resemblance for VO<sub>2max</sub> in the sedentary state: the HERITAGE family study. *Med Sci Sports Exerc*. 1998;30(2):252-8.

4. Bouchard C, Perusse L. Heredity, activity level, fitness and health. In: Bouchard C, Shephard RJ, Stephens T, editors. *Physical Activity, Fitness and Health: International Proceedings and Consensus Statement*. Chicago (IL): Human Kinetics; 1994. p. 106–18.
5. Froelicher V, Myers J. Research as part of clinical practice: use of Windows-based relational data bases. *Veterans Health Syst J*. 1998;53–7.
6. Froelicher V, Shiu P. Exercise test interpretation system. *Phys Comput*. 1998;14:40–4.
7. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007;39(8):1423–34.
8. Hein HO, Suadicani P, Gyntelberg F. Physical fitness or physical activity as a predictor of ischaemic heart disease? A 17-year follow-up in the Copenhagen Male Study. *J Intern Med*. 1992; 232:471–9.
9. Kokkinos P, Myers J, Kokkinos JP, et al. Exercise capacity and mortality in black and white men. *Circulation*. 2008;117:614–22.
10. Laukkanen JA, Lakka TA, Rauramaa R, et al. Cardiovascular fitness as a predictor of mortality in men. *Arch Intern Med*. 2001; 161:825–31.
11. Lee IM, Hsieh CC, Paffenbarger RS Jr. Exercise intensity and longevity in men. The Harvard Alumni Health Study. *JAMA*. 1995;273:1179–84.
12. Leitzmann MF, Park Y, Blair A, et al. Physical activity recommendations and decreased risk of mortality. *Arch Intern Med*. 2007;167:2453–60.
13. Leon AS, Connett J, Jacobs DR Jr, Rauramaa R. Leisure-time physical activity levels and risk of coronary heart disease and death. The Multiple Risk Factor Intervention Trial. *JAMA*. 1987; 258:2388–95.
14. Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. *J Am Coll Cardiol*. 1993;22:175–82.
15. Myers J, Buchanan N, Walsh D, et al. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol*. 1991;17: 1334–42.
16. Myers J, Do D, Herbert W, Ribisl P, Froelicher VF. A nomogram to predict exercise capacity from a specific activity questionnaire and clinical data. *Am J Cardiol*. 1994;73:591–6.
17. Myers J, Kaykha A, George S, et al. Fitness versus physical activity patterns in predicting mortality in men. *Am J Med*. 2004; 117:912–8.
18. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793–801.
19. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med*. 1986;314:605–13.
20. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273:402–7.
21. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N Engl J Med*. 1993;328: 533–7.
22. Shue P, Froelicher V. EXTRA: an expert system for exercise test reporting. *J Noninvasive Test*. 1998;II-4:21–7.
23. Slattery ML, Jacobs DR Jr, Nichaman MZ. Leisure time physical activity and coronary heart disease death. The US Railroad Study. *Circulation*. 1989;79:304–11.
24. Sobolski J, Kornitzer M, De Backer G, et al. Protection against ischemic heart disease in the Belgian Physical Fitness Study: physical fitness rather than physical activity? *Am J Epidemiol*. 1987;125:601–10.
25. U.S. Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General*. Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996. p. 45.
26. Weiss JP, Froelicher VF, Myers JN, Heidenreich PA. Health-care costs and exercise capacity. *Chest*. 2004;126:608–13.
27. Williams PT. Relationship of distance run per week to coronary heart disease risk factors in 8283 male runners. The National Runners' Health Study. *Arch Intern Med*. 1997;157:191–8.
28. Williams PT. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc*. 2001; 33(5):754–61.
29. Wolthuis RA, Froelicher VF Jr, Fischer J, et al. New practical treadmill protocol for clinical use. *Am J Cardiol*. 1977;39: 697–700.