論文名	The association between cardiorespiratory fitness and risk of all-cause mortality among women with impaired fasting glucose or undiagnosed diabetes mellitus
著 者	Lyerly GW, Sui X, Lavie CJ, Church TS, Hand GA, Blair SN
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対象の内訳	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	境界域の者	空白		( )		コホート研究
性別	女性	( )		( )		( )
年齢	47.4(±10.1)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	なし	糖尿病予防	なし	なし	死亡	( )
アウトカム 維持・改善	なし	なし	なし	なし	( )	( )

図 表

TABLE 3. Rates and HRs (95% CIs) for All-Cause Mortality According to Baseline Cardiorespiratory Fitness and BMI[a]

Variable	Cardiorespiratory fitness			*P* for trend[b]	BMI (kg/m²)			*P* for trend[b]
	Low	Moderate	High		<25.0	25.0-29.9	≥30.0	
No. of patients	517	1041	1486		2021	677	346	
Deaths	54	62	55		120	32	19	
Woman-years of observation	9668	17,687	19,987		33,872	8991	4484	
All-cause mortality rate[c]	52.0	33.3	31.0	.01	36.3	29.8	47.4	.51
HR (95% CI) for all-cause mortality								
Adjusted for age and examination year	1.0 (referent)	0.64 (0.44-0.92)	0.60 (0.40-0.88)	.01	1.0 (referent)	0.92 (0.62-1.37)	1.30 (0.80-2.12)	.51
Adjusted for multiple variables[d]	1.0 (referent)	0.65 (0.45-0.94)	0.64 (0.43-0.95)	.03	1.0 (referent)	0.91 (0.61-1.36)	1.32 (0.80-2.18)	.51
Adjusted for multiple variables, including BMI[e]	1.0 (referent)	0.63 (0.43-0.92)	0.61 (0.39-0.93)	.03				
Adjusted for multiple variables, including continuous treadmill test duration[f]					1.0 (referent)	0.86 (0.57-1.30)	1.19 (0.70-2.03)	.84

[a] BMI = body mass index; CI = confidence interval; HR = hazard ratio.
[b] This is the *P* value for overall comparison across 3 groups.
[c] Rate is expressed per 10,000 woman-years and adjusted for baseline age and examination year.
[d] Adjusted for age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, and family history of diabetes.
[e] Adjusted for age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, family history of diabetes, and BMI.
[f] Adjusted for age, examination year, current smoking, alcohol intake, hypertension, hypercholesterolemia, family history of diabetes, and treadmill test duration.

図表掲載箇所	P784, Table3
抄録和訳	
概 要 (800字まで)	本研究は、The Aerobics Center Longitudinal Study (ACLS)に参加した耐糖能異常もしくは未診断糖尿病の女性3,044名を対象に平均15.6年の追跡調査を行い、全身持久力や肥満度と総死亡リスクの関連を検討したものである。トレッドミルテストにより最大酸素摂取量を測定し、年代別指標により全身持久力を低・中・高に分類した。全身持久力が低の集団と比較すると、中の集団、高の集団でそれぞれ総死亡のリスクが0.63(95%信頼区間:0.43-0.92)、0.61(0.39-0.93)と量反応的に有意に減少した(Ptrend=0.03)。また、体力が高く標準体重の集団と比較すると、体力が低く過体重の集団では、総死亡リスクが2.26(1.27-4.03)と有意に上昇することが明らかとなった。
結 論 (200字まで)	耐糖能異常もしくは未診断糖尿病に分類される中年女性コホートにおいて、全身持久力は総死亡リスクに対して独立して関連しているため、強力な予測因子となりうることが示唆された。
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。本研究は、糖尿病境界域や未診断の糖尿病の人においても、体力を高く保つことがその後の死亡のリスクを下げることを示した重要な研究である。また、量反応関係が認められていることから、少しでも体力を上げることが重要であることが示唆されている。

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Brief Report

Fitness and Fatness as Mortality Predictors in Healthy Older Men: The Veterans Exercise Testing Study

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Background. Low body mass index (BMI) and low cardiorespiratory fitness (CRF) are independently associated with increased mortality in the elderly. However, interactions among BMI, CRF, and mortality in older persons have not been adequately explored.

Methods. Hazard ratios (HRs) were calculated for predetermined strata of BMI and CRF. Independent and joint associations of CRF, BMI, and all-cause mortality were assessed by Cox proportional hazards analyses in a prospective cohort of 981 healthy men aged at least 65 years (mean age [±*SD*], 71 [±5] years; range, 65–88 years) referred for exercise testing during 1987–2003.

Results. During a mean follow-up of 6.9 ± 4.4 years, a total of 208 patients died. Multivariate relative risks (95% confidence interval [CI]) of mortality across BMI groups of <20.0, 20.0–25.0, 25.0–29.9, 30.0–34.9, and ≥35.0 were 2.51 (1.26–4.98), 1.0 (reference), 0.66 (0.48–0.90), 0.50 (0.31–0.78), and 0.44 (0.20–0.97), respectively, and across CRF groups of <5.0, 5.0–8.0, and >8.0 metabolic equivalents were 1.0 (reference), 0.56 (0.40–0.78), and 0.39 (0.26–0.58), respectively. In a separate analysis of within-strata CRF according to BMI grouping, the lowest mortality risk was observed in obese men with high fitness (HR [95% CI] 0.26 [0.10–0.69]; $p = .007$).

Conclusions. In this cohort of elderly male veterans, we observed independent and joint inverse relations of BMI and CRF to mortality. This warrants further investigation of fitness, fatness, and mortality interactions in older persons.

Key Words: Cardiorespiratory fitness—Body mass index—Mortality—Obesity paradox.

OBESITY, as defined by body mass index (BMI), is associated with increased mortality in the general population of U.S. adults (1). However, among older adults, the mortality risk associated with being overweight or obese is controversial (2,3). Some studies show a U-shaped BMI–mortality relationship (4,5), whereas others show an inverse association (6–9) or no association (10). Such disparate findings warrant further investigation of this relationship in the elderly.

Cardiorespiratory fitness (CRF) is a strong independent predictor of mortality in older adults (11–13). However, data on interactions among CRF, BMI, and mortality are sparse (10). Furthermore, the mortality risk of underweight may be confounded by unintentional weight loss stemming from poor health. To avoid this problem, we confined this investigation to healthy persons.

The purpose of this study was to test the hypothesis that high CRF and high BMI are independently and jointly associated with a lower risk for death among healthy elderly men.

Methods

Study Population

The Veterans Exercise Testing Study is an ongoing epidemiological investigation of more than 9,000 veteran patients referred to two university-affiliated Veterans Affairs medical centers (Long Beach, California from 1987 to 1991 and Palo Alto, California from 1992 onward) for clinical exercise testing. From this database, we identified 2,469 consecutive men aged 65 years or older who completed a baseline medical examination and maximal exercise test at least once at either Long Beach, or Palo Alto, during 1987–2003. This comprised approximately one third of all tests referred to our Cardiology Section during this time period. After excluding patients with an abnormal exercise test, documented cardiovascular disease (CVD), or both, we evaluated a total of 981 apparently healthy men aged 65–88 years. CVDs included coronary artery disease, myocardial infarction, heart failure, and stroke. Participants were classified according to five predetermined BMI groups: <20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m^2, and according to three predetermined CRF groups: <5.0, 5.0–8.0, and >8.0 metabolic equivalents (METs). Low fitness (<5.0 METs) and "normal" weight (BMI 20.0–24.9 kg/m^2) were used as the reference groups. To evaluate the interaction of BMI and CRF, we further classified participants within strata of CRF according to BMI group (for these analyses, BMI 30.0–34.9 and ≥35.0 kg/m^2 were combined). This resulted in nine crossover groups, with normal BMI–low fitness as the reference group (the group

with <20.0 BMI had too few participants and was excluded). Hazard ratios (HRs) were calculated using Cox proportional hazards analyses adjusting for age, ethnicity, current smoking, hypertension, and hypercholesterolemia. For the independent analyses of the BMI and CRF groups, we developed a second proportional hazards model that added adjustment for CRF and BMI as continuous variables, respectively. All participants gave written informed consent. Additional information on study methods and participant characteristics of this cohort has been published elsewhere (14).

Mortality Surveillance

Mortality data were gathered from the Social Security Death Index and California Death Registry. Participants in the study were those who completed their baseline examination as of December 31, 2003. Vital status was determined as of December 31, 2004. Therefore, all participants were followed for at least 1 year from baseline.

Clinical Evaluation and Exercise Testing

All participants completed a symptom-limited maximal exercise test using an individualized ramp treadmill protocol (15). Before testing, a self-administered questionnaire was used to predict target maximal METs that would be achieved within a range of 8–12 minutes (16). Immediately prior to the exercise test, height and weight were measured using standard procedures, and BMI was calculated as weight in kilograms divided by the square of height in meters. A microcomputer automatically increased workload after an individualized walking speed was established and predicted values for maximal exercise capacity were entered.

A 12-lead electrocardiogram was recorded each minute, and blood pressure was recorded on alternate minutes throughout the test. Standard clinical criteria for terminating the tests (e.g., fall in systolic blood pressure, ST-segment depression >2.0 mm, dangerous arrhythmias) were followed (17), but no heart rate or time limit was imposed, and a maximal effort was encouraged. Standardized equations were used to determine the calculated peak METs on the basis of treadmill speed and grade (17). Exercise capacity was expressed as the maximal MET value attained during the exercise test.

Statistical Analysis

The statistical software Numbers Crunching Statistical Software (Kaysville, UT) was used for all statistical analyses. The mean and standard deviation of each variable were calculated, with participants categorized as survivors or decedents. The independent effects of BMI and CRF were assessed using two proportional hazards models: first, adjusting for age, ethnicity, and CVD risk factors (hypertension, hypercholesterolemia, and current smoking), and second, by adding CRF (for BMI) and BMI (for CRF) entered as continuous variables. In joint analyses, nine CRF–BMI categories were assessed using a single proportional hazards model adjusting for age, ethnicity, and CVD risk factors. The Shoenfeld residuals were used to assess the proportional hazards assumption and the assumption was met.

Results

During a mean follow-up of 6.9 ± 4.4 years (range, 1.0–17.6 years), 208 deaths were recorded. The general characteristics of the study population, grouped by survival status, are presented in Table 1. The study population consisted of 75% non-Hispanic Whites, 9% Hispanics, 10% African Americans, and 6% Asian Americans, who ranged in age from 65 to 88 years (mean 71.3 ± 5.0). Underweight patients represented 2.1% of the cohort, normal weight 26.3%, overweight 46.6%, and obese 25.0%. In general, surviving patients were more fit, had a significantly higher BMI, and had a higher prevalence of hypercholesterolemia, and included a lower percentage of current smokers.

In the fully adjusted model, each 1-unit increase in BMI and METs was associated with reductions in mortality risks of 9% (HR [95% confidence interval {CI}] of 0.91 [0.88–0.95]; $p < .001$) and 12% (HR [95% CI] of 0.88 [0.83–0.92]; $p < .001$), respectively (Tables 2 and 3). The HRs (95% CI) for mortality associated with underweight, overweight, and obesity were 2.51 (1.26–4.98), 0.66 (0.48–0.90), and 0.48 (0.32–0.74), respectively, compared with the reference group of normal-weight men (Table 2). Compared with the reference group of men with low fitness, HRs (95% CI) for moderate and high fitness were 0.56 (0.40–0.78) and 0.39 (0.26–0.58), respectively (Table 3).

In the fully adjusted multivariate model, the association of the interaction of BMI and METs to all-cause mortality was significant ($p = .005$). Stratified results for CRF according to BMI are shown in Table 4. Among men having low CRF, multivariate risk of mortality did not differ by BMI classification. However, in the moderate CRF group, overweight and obese men were 61% and 63% less likely to die compared with the low CRF–normal BMI reference group of 56 men. Compared with this reference group, men in the high-fitness group with normal weight, overweight, and obesity had reduced mortality risks of 51%, 64%, and 74%, respectively.

Discussion

Our main finding was that both higher BMI and higher CRF reduced the risk of all-cause morality in healthy elderly men who were referred to exercise testing for clinical reasons but determined to be free of CVD. Furthermore, mortality risk was reduced as BMI increased within groups having moderate or high CRF, but BMI was not significantly associated with mortality within the low-CRF group.

Table 1. Baseline Characteristics of 981 Healthy Elderly Men According to Survival Status, Veterans Exercise Testing Study, 1987–2003

Characteristics	Total (N = 981)	Survived (N = 773)	Died (N = 208)	p
Demographic and clinical data				
Follow-up (y)	6.9 ± 4.4	6.9 ± 4.5	6.8 ± 3.9	.78
Age (y)	71.3 ± 5.0	71.3 ± 5.0	71.6 ± 4.9	.37
Non-Hispanic White ethnicity (%)	74.9	74.3	77.4	.35
BMI (kg/m^2)	27.5 ± 4.4	27.9 ± 4.4	26.2 ± 4.0	<.001
Resting systolic BP (mm Hg)	138.9 ± 19.9	138.7 ± 19.1	139.9 ± 22.5	.42
Resting diastolic BP (mm Hg)	80.3 ± 10.8	80.4 ± 10.3	79.6 ± 12.5	.31
Resting heart rate (beats/min)	73.6 ± 13.6	73.1 ± 13.0	75.6 ± 15.4	.02
BMI groups (%)				
<20.0	2.1	1.4	4.8	.003
20.0–25.0	26.3	24.2	34.1	.004
25.0–29.9	46.6	47.1	44.7	.54
≥30.0	25.0	27.3	16.3	.001
Currently smoking (%)	14.8	12.8	22.1	<.001
Hypertension (%)	57.0	57.4	55.3	.58
Hypercholesterolemia (%)*	27.9	30.1	19.7	.003
Exercise test responses				
CRF (METs)†	7.1 ± 2.9	7.2 ± 2.9	6.4 ± 2.9	<.001
<5.0 METs (%)†	23.1	21.1	30.8	.004

Notes: Data are means ± standard deviation, unless otherwise indicated. BP = blood pressure; BMI = body mass index; CRF = cardiorespiratory fitness; MET = metabolic equivalents.

*Fasting serum total cholesterol >5.6 mmol/L (>220 mg/dL).

†METs: 1 MET = 3.5 mL/kg/min oxygen uptake; CRF is maximal METs achieved during the exercise test and is calculated from treadmill speed and grade using standard equations.

Our findings on BMI accord with some (6,7,9) but not other (4,5,8) previous reports examining the relationship between BMI and mortality in elderly persons. We offer four possible explanations for our findings: (i) healthy obesity, (ii) the survival effect, (iii) increased coronary artery size, and (iv) veteran population differences. In healthy obese mice, there is preferential storage of triglycerides in adipose tissue and reduced levels in the liver (18). This may result in improved insulin sensitivity, preventing diabetes and heart disease in such animals. A similar mechanism has been proposed for obese humans (19). Furthermore, older individuals who have greater fat stores may be better able to tolerate periods of low caloric intake associated with acute illness. A second possible explanation is the well-known survival effect (3). Participants surviving until inclusion in our study were possibly less susceptible to the negative effects of overweight. Third, greater coronary artery size among patients with higher BMI has been proposed as a possible mechanism for the so-called obesity paradox (20). This may also be a factor in the better survival outcomes we observed among the healthy obese men in the present study. Finally, the possibility of a population-specific veteran effect should not be discounted. Veterans differ from other populations of patients. One of the most prominent differences is the meeting of selection criteria at the time of enlistment. These criteria include, among others, minimum height requirements, maximum weight requirements, and exclusion of recruits having certain preexisting health problems (21). Hence, obesity, when present in our population, must have developed after discharge in later life.

Moderate fitness (5.0–8.0 METs) was independently associated with lower mortality risk, and high fitness (>8.0 METs) the lowest mortality risk relative to the low-fitness group (<5.0 METs). These results are consistent

Table 2. Multivariate HRs of All-Cause Mortality According to BMI for 981 Healthy Elderly Men, Veterans Exercise Testing Study, 1987–2003

			Model 1*		Model 2†	
BMI (kg/m^2)	No. of Men	No. of Deaths (%)	HR (95% CI)	p	HR (95% CI)	p
Per 1-unit increment	981	208 (21)	0.93 (0.89–0.96)	<.001	0.91 (0.88–0.95)	<.001
<20.0	21	10 (48)	2.01 (1.02–3.98)	.045	2.51 (1.26–4.98)	.009
20.0–24.9	258	71 (28)	1 (reference)	—	1 (reference)	—
25.0–29.9	457	93 (20)	0.66 (0.48–0.90)	.009	0.66 (0.48–0.90)	.008
30.0–34.9	193	27 (14)	0.56 (0.35–0.87)	.01	0.50 (0.31–0.78)	.003
≥35.0	52	7 (14)	0.56 (0.37–0.85)	.15	0.44 (0.20–0.97)	.042

Notes: BMI = body mass index; CI = confidence interval; HR = hazard ratio.

*Adjusted for age, ethnicity, and cardiovascular disease risk factors (hypertension, hypercholesterolemia, and current smoking).

†Model 1 plus cardiorespiratory fitness.

Table 3. Multivariate HRs of All-Cause Mortality According to CRF for 981 Healthy Elderly Men, Veterans Exercise Testing Study, 1987–2003

			Model 1†		Model 2‡	
CRF (METs)*	No. of Men	No. of Deaths (%)	HR (95% CI)	*p*	HR (95% CI)	*p*
Per 1-unit increment	981	208 (21)	0.89 (0.85–0.94)	<.001	0.88 (0.83–0.92)	<.001
<5.0	227	64 (28)	1 (reference)	—	1 (reference)	—
5.0–8.0	446	93 (21)	0.59 (0.43–0.83)	<.002	0.56 (0.40–0.78)	<.001
>8.0	308	51 (17)	0.45 (0.30–0.67)	<.001	0.39 (0.26–0.58)	<.001

Notes: CI = confidence interval; CRF = cardiorespiratory fitness; HR = hazard ratio; MET = metabolic equivalents.

*METs: 1 MET = 3.5 mL/kg/min oxygen uptake; CRF is maximal METs achieved during the exercise test and is calculated from treadmill speed and grade using standard equations.

†Adjusted for age, ethnicity, and cardiovascular disease risk factors (hypertension, hypercholesterolemia, and current smoking).

‡Model 1 plus body mass index.

with the findings from previous studies on fitness and mortality in older adults (11). However, interactions among BMI, CRF, and mortality are less well studied because objective measures of CRF, such as maximal exercise testing on a treadmill, are required. From the Aerobic Center Longitudinal Study (ACLS), Sui and colleagues (10) recently reported that CRF attenuates the mortality risk of obesity. Our results are consistent with their main finding that CRF attenuates the morality risk associated with obesity. But our findings differ in that obesity was independently associated with reduced all-cause mortality and that obese patients having moderate or high fitness survived better than their normal-weight or overweight counterparts. These observed differences may be due in large part to demographics (the ACLS cohort was younger, predominately White, included women and participants not clinically referred, and comprised mainly of civilians).

Table 4. Multivariate HRs of All-Cause Mortality Within Strata of CRF Groups According to BMI for 981 Healthy Elderly Men, Veterans Exercise Testing Study, 1987–2003

Fitness Category	No. of Men	No. of Deaths (%)	HR (95% CI)*	*p*
Low, <5.0 METs				
BMI <20.0†	3	3 (100)	—	—
BMI 20.0–24.9	56	17 (30)	1 (reference)	—
BMI 25.0–29.9	103	32 (31)	0.96 (0.57–1.63)	.89
BMI ≥30.0	65	12 (19)	0.56 (0.28–1.13)	.11
Moderate, 5.0–8.0 METs				
BMI <20.0†	10	5 (50)	—	—
BMI 20.0–24.9	107	35 (33)	0.85 (0.51–1.42)	.54
BMI 25.0–29.9	205	36 (18)	0.39 (0.23–0.64)	<.001
BMI ≥30.0	124	17 (14)	0.37 (0.20–0.71)	.003
High, >8.0 METs				
BMI <20.0†	8	2 (25)	—	—
BMI 20.0–24.9	95	19 (20)	0.49 (0.27–0.91)	.03
BMI 25.0–29.9	149	25 (17)	0.36 (0.20–0.63)	<.001
BMI ≥30.0	56	5 (9)	0.26 (0.10–0.69)	.007

Notes: BMI = body mass index; CI = confidence interval; CRF = cardiorespiratory fitness; HR = hazard ratio; MET = metabolic equivalents

*Adjusted for age, ethnicity, and cardiovascular disease risk factors (hypertension, hypercholesterolemia, and current smoking); METs: 1 MET = 3.5 mL/kg/min oxygen uptake; CRF is maximal METs achieved during the exercise test and is calculated from treadmill speed and grade using standard equations.

†Too few participants for stratified analysis.

A novel finding of the present investigation was that among healthy older men, the effects of CRF and BMI were multiplicative. Specifically, our obese, highly fit participants had the lowest mortality risk of any group. Thus, among individuals with moderate or high fitness levels, those with higher BMI had better survival. To our knowledge, this has not been previously demonstrated.

Our study has several strengths, including: (i) all participants underwent an extensive physical examination, which provides thorough information on the presence or absence of baseline disease; (ii) all participants had a normal exercise test and were free of CVD, which demonstrates the apparent health of participants; (iii) CRF was determined by maximal exercise testing; and (iv) our sample size consisted of nearly 1,000 elderly patients with an average follow-up of almost 7 years.

Our study has several limitations. First, because waist circumference measures were not obtained, we were not able to evaluate body fat distribution characteristics. Second, we included only men who had prior military service and were referred for exercise testing for clinical reasons. Any effort to predict mortality by using fitness, BMI, clinical, or demographic data should be considered population specific. Though deemed "healthy," all participants were referred to exercise testing for clinical reasons. Third, CRF is a single measure that is influenced by many factors, including age, heredity, and recent and lifelong activity patterns (17). The extent to which CRF may be improved in the elderly, or the influence this may have on mortality, cannot be determined from the present investigation. Finally, because we only have baseline data on weight, exercise capacity, and other exposures, we do not know if changes in any of these variables occurred during follow-up or how this might have influenced the results.

In summary, both higher BMI and higher fitness were protective for all-cause mortality in this cohort of elderly men. Future studies should focus on the influence of fitness and fatness on mortality in diverse populations and whether changes in fitness level and/or body weight improve health outcomes in the elderly.

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論文名	Fitness and fatness as mortality predictors in healthy older men: the veterans exercise testing study
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対象の内訳	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	男性	( )		( )		( )
年齢	71.3(±5)歳			( )		前向き研究
対象数	500～1000			( )		( )

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

Table 2. Multivariate HRs of All-Cause Mortality According to BMI for 981 Healthy Elderly Men, Veterans Exercise Testing Study, 1987–2003

			Model 1*		Model 2†	
BMI (kg/m²)	No. of Men	No. of Deaths (%)	HR (95% CI)	p	HR (95% CI)	p
Per 1-unit increment	981	208 (21)	0.93 (0.89–0.96)	<.001	0.91 (0.88–0.95)	<.001
<20.0	21	10 (48)	2.01 (1.02–3.98)	.045	2.51 (1.26–4.98)	.009
20.0–24.9	258	71 (28)	1 (reference)	—	1 (reference)	—
25.0–29.9	457	93 (20)	0.66 (0.48–0.90)	.009	0.66 (0.48–0.90)	.008
30.0–34.9	193	27 (14)	0.56 (0.35–0.87)	.01	0.50 (0.31–0.78)	.003
≥35.0	52	7 (14)	0.56 (0.37–0.85)	.15	0.44 (0.20–0.97)	.042

Notes: BMI = body mass index; CI = confidence interval; HR = hazard ratio.
*Adjusted for age, ethnicity, and cardiovascular disease risk factors (hypertension, hypercholesterolemia, and current smoking).
†Model 1 plus cardiorespiratory fitness.

Table 3. Multivariate HRs of All-Cause Mortality According to CRF for 981 Healthy Elderly Men, Veterans Exercise Testing Study, 1987–2003

			Model 1*		Model 2†	
CRF (METs)‡	No. of Men	No. of Deaths (%)	HR (95% CI)	p	HR (95% CI)	p
Per 1-unit increment	981	208 (21)	0.89 (0.85–0.94)	<.001	0.88 (0.83–0.92)	<.001
<5.0	227	64 (28)	1 (reference)	—	1 (reference)	—
5.0–8.0	446	93 (21)	0.59 (0.43–0.83)	<.002	0.56 (0.40–0.78)	<.001
>8.0	308	51 (17)	0.45 (0.30–0.67)	<.001	0.39 (0.26–0.58)	<.001

Notes: CI = confidence interval; CRF = cardiorespiratory fitness; HR = hazard ratio; MET = metabolic equivalents.
‡METs: 1 MET = 3.5 mL/kg/min oxygen uptake; CRF is maximal METs achieved during the exercise test and is calculated from treadmill speed and grade using standard equations.
*Adjusted for age, ethnicity, and cardiovascular disease risk factors (hypertension, hypercholesterolemia, and current smoking).
†Model 1 plus body mass index.

図表掲載箇所	P697, Table2, P698, Table3
概 要 (800字まで)	本研究は、The Veterans Exercise Testing Studyに参加した65歳以上の男性981名を対象に平均6.9年間の追跡調査を行い、BMIと全身持久力の総死亡リスクへの関連を検討したものである。被験者集団をBMIにより20.0kg/m2未満、20.0-24.9、25.0-29.9、30.0-34.9、35.0kg/m2以上に分類し、さらに全身持久力により5.0メッツ未満、5.0-8.0、8.0メッツ以上に分類した。標準体重(BMI=20.0-24.9kg/m2)の集団と比較すると、やせ(20.0未満)の集団で総死亡リスクが2.51(95%信頼区間:1.26-4.98)に増加し、過体重(25.0-29.9、30.0-34.9)、肥満(35.0以上)の集団でそれぞれ総死亡リスクが0.66(0.48-0.90)、0.50(0.31-0.78)、0.44(0.20-0.97)と全身持久力とは独立して有意に減少した。BMIが1kg/m2増加するごとにリスクは0.91(0.88-0.95)減少することが明らかとなった。また、全身持久力の低い(5.0メッツ未満)集団と比較すると、中程(5.0-8.0メッツ)、高い(8.0メッツ以上)の集団で総死亡リスクはそれぞれ0.56(0.40-0.78)、0.39(0.26-0.58)と肥満度とは独立して有意に減少した。全身持久力が1メッツ増加するごとにリスクが0.88(0.83-0.92)減少することが明らかとなった。肥満度(BMI)と全身持久力の複合作用として、全身持久力が高く肥満度が高い集団で最も総死亡リスクが減少した0.26(0.10-0.69)。
結 論 (200字まで)	健康な高齢者の集団において、肥満度と全身持久力は互いに独立して総死亡リスクに関連しており、さらにそれらによる相乗効果も明らかとなった。
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。高齢者におけるBMIと死亡のリスクについては、議論があるところである。この研究では、BMIが高くなるほど死亡のリスク減少が認められている。この関係は、全身持久力と相互作用を持つことから非常に興味深い研究といえる。今後日本の集団においても、高齢者におけるBMIと死亡の関係を明らかにすることが必要であろう。

担当者:久保絵里子・村上晴香・宮地元彦

Obesity Paradox and Cardiorespiratory Fitness in 12,417 Male Veterans Aged 40 to 70 Years

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OBJECTIVE: **To evaluate the influence of cardiorespiratory fitness (fitness) on the obesity paradox in middle-aged men with known or suspected coronary artery disease.**

PATIENTS AND METHODS: **This study consists of 12,417 men aged 40 to 70 years (44% African American) who were referred for exercise testing at the Veterans Affairs Medical Centers in Washington, DC, or Palo Alto, CA (between January 1, 1983, and June 30, 2007). Fitness was quantified as metabolic equivalents achieved during a maximal exercise test and was categorized for analysis as low, moderate, and high (defined as <5, 5-10, and >10 metabolic equivalents, respectively). Adiposity was defined by body mass index (BMI) according to standard clinical guidelines. Separate and combined associations of fitness and adiposity with all-cause mortality were assessed by Cox proportional hazards analyses.**

RESULTS: **We recorded 2801 deaths during a mean ± SD follow-up of 7.7±5.3 years. Multivariate hazard ratios (95% confidence interval) for all-cause mortality, with normal weight (BMI, 18.5-24.9 kg/m^2) used as the reference group, were 1.9 (1.5-2.3), 0.7 (0.7-0.8), 0.7 (0.6-0.7), and 1.0 (0.8-1.1) for BMIs of less than 18.5, 25.0 to 29.9, 30.0 to 34.9, and 35.0 or more kg/m^2, respectively. Compared with highly fit normal-weight men, underweight men with low fitness had the highest (4.5 [3.1-6.6]) and highly fit overweight men the lowest (0.4 [0.3-0.6]) mortality risk of any subgroup. Overweight and obese men with moderate fitness had mortality rates similar to those of the highly fit normal-weight reference group.**

CONCLUSION: **Fitness altered the obesity paradox. Overweight and obese men had increased longevity only if they registered high fitness.**

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BMI = body mass index; BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MET = metabolic equivalent; VETS = Veterans Exercise Testing Study

Body mass index (BMI) has been widely used to evaluate the mortality risk associated with obesity. Although many large epidemiological studies of the general population report a positive association between BMI and mortality,[1-3] consistent inverse associations (the so-called obesity paradox) have been observed among patients with heart failure,[4] coronary heart disease,[5,6] hypertension,[7] peripheral artery disease,[8] type 2 diabetes,[9] and chronic kidney disease.[10] An obesity paradox has also been observed in healthier populations as diverse as San Francisco longshoremen,[11] Native American women of the Pima tribe,[12] men from rural Scotland,[13] Nauruan men,[14] and the elderly.[15]

Although substantial evidence for an obesity paradox has accumulated during the past decade,[16] including a recent examination of the influence of weight loss,[17] the influence of cardiorespiratory fitness (fitness) has not been adequately explored. Objective measures of fitness from clinical exercise testing are not readily available. Consequently, few studies have examined the combined effects of fitness and BMI on mortality, and these data come from only 2 cohorts: the Lipid Research Clinics Study[18,19] and the Aerobics Center Longitudinal Study.[20-26] Collectively, these reports provide convincing evidence that fitness is a more powerful predictor of mortality than BMI. However, these findings are from populations without an obesity paradox.

For editorial comment, see page 112

The Veterans Exercise Testing Study (VETS) affords a unique opportunity to study simultaneous measures of fitness and adiposity in a large patient population exhibiting an obesity paradox. A previous report from our group provided compelling evidence that higher levels of fitness, as well as higher BMI, reduced mortality risk in men referred for exercise testing.[27] However, this report did not examine the combined effects of fitness and BMI on mortality. Such joint analyses may identify associations obscured in independent analyses alone. To avoid bias associated with age,[28] we confined our investigation to men aged 40 to 70 years. The purpose of the current study was to examine the influence of fitness on the obesity paradox in middle-aged men with known or suspected cardiovascular disease (CVD).

PATIENTS AND METHODS

VETS is an ongoing, prospective epidemiological investigation of veteran patients that began in 1983. All patients are referred for exercise testing either as a routine evaluation or as an evaluation for exercise-induced ischemia.

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Participants in the current study were drawn from a cohort of 15,660 male veterans (excluding patients with a history of implanted pacemaker, those who developed left bundle-branch block during the test, and those who were clinically unstable or required emergent intervention) at the Veterans Affairs Medical Center, Washington, DC (n=9042) and the Veterans Affairs Palo Alto (CA) Health Care System (n=6618) who completed an exercise tolerance test at least once during 1983-2007. After patients younger than 40 (n=711) and older than 70 (n=2532) years were excluded, 12,417 patients were included in the analysis.

The 12,417 participants were either African American (n=5435) or white (n=6982) men who ranged in age from 40 to 70 years (mean ± SD, 57±8 years). Ethnicity was determined by electronic records and self-reports at the time of exercise testing. All patients gave written consent before the exercise tolerance test. The study was approved by the institutional review board at each site.

Additional information on study methods and characteristics of this cohort has been previously published.[29]

Clinical Evaluation and Exercise Testing

A standardized medical examination by a physician, including personal and family histories, was completed for all participants before exercise testing. All demographic, clinical, and medication information was obtained from patients' computerized medical records just before the exercise tolerance test. Each participant also was asked to verify the computerized information with regard to history of chronic disease, current medications, and cigarette smoking habits. Medications were not changed or stopped before testing. Body weight and height were recorded before the test. Body mass index was calculated as weight in kilograms divided by height in meters squared.

The exercise capacity of the participants at the Veterans Affairs Medical Center (Washington, DC) was assessed by the standard Bruce protocol.[30] For participants at the Veterans Affairs Palo Alto Health Care System, an individualized ramp protocol was used, as described previously.[31] Peak exercise time was recorded in minutes. Peak workload was estimated as metabolic equivalents (METs). One MET is defined as the energy expended at rest, which is equivalent to an oxygen consumption of 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$.[32] Exercise capacity (in METs) was estimated on the basis of American College of Sports Medicine equations.[32] Participants were encouraged to exercise until volitional fatigue in the absence of symptoms or other indicators of ischemia. Supine resting heart rate and blood pressure (BP) were assessed after 5 minutes of rest. Exercise BP was recorded every 2 minutes, at peak exercise, and during recovery. Indirect arm-cuff sphygmomanometry was used for all BP assessments. ST-segment depression was measured visually. ST depression of 1.0 mm or greater, horizontal or downsloping, was considered suggestive of ischemia.

Patients were classified according to 5 predetermined BMI groups: less than 18.5 (underweight), 18.5 to 24.9 (normal weight), 25.0 to 29.9 (overweight), 30.0 to 34.9 (obese I), and 35.0 or more (obese II or III). They were also classified according to 3 predetermined fitness groups: less than 5.0 (low), 5.0 to 10.0 (moderate), and more than 10.0 (high) METs. We used this approach to maintain consistency in our study methods and because a widely accepted clinical categorization of fitness does not exist. The normal-weight group (BMI, 18.5-24.9) and high-fitness group (>10.0 METs) were used as the reference groups. To evaluate the joint effects of BMI and fitness on mortality, we further classified patients within fitness strata according to BMI group.

Mortality Surveillance

We recorded death dates from the Veterans Affairs Beneficiary Identification and Record Locator System File. The Social Security Death Index was used to match all patients to their records according to Social Security number. Accuracy of deaths was reviewed by 2 clinicians blinded to exercise test results and was confirmed using the Veterans Affairs computerized medical records. Vital status was determined as of June 30, 2007.

Statistical Analyses

Continuous variables are presented as mean ± SD, and categorical variables as absolute and relative frequencies (percent). Descriptive statistics summarized baseline characteristics by BMI category.

Cox proportional hazards analyses were used to determine separate and combined associations of fitness and BMI with time to death. Continuous variables (age, BMI, and METs) were tested using analysis of variance, and categorical variables (fitness, BMI, and fitness-BMI groups) were tested using χ^2 tests. We tested models for potential interactions of BMI and race, and BMI and fitness, with all-cause mortality.

Independent effects of fitness were examined by 1 proportional hazards model, adjusting for age in years, ethnicity, examination year, test site, CVD (history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, stroke, and/or peripheral arterial disease), CVD risk factors (hypertension, dyslipidemia, diabetes mellitus, and/or current smoking), CVD medications (aspirin, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, vasodilators, and/or statins), and BMI (entered as a continuous variable). In-

TABLE 1. **Baseline Characteristics of Study Participants**[a]

Variable	BMI group					
	Underweight <18.5 (n=137)	Normal weight 18.5-24.9 (n=2885)	Overweight 25.0-29.9 (n=5187)	Obese (class) 30.0-34.9 (I) (n=2893)	35.0-39.9 (II) (n=947)	≥40.0 (III) (n=368)
Follow-up (y)	6.9±5.9	8.1±5.4	8.0±5.3	7.3±5.2	6.7±4.9	7.3±5.0
Demographics						
Age (y)	61.2±7.1	57.6±8.1	57.5±8.0	56.8±8.1	56.1±7.8	54.4±7.6
White	63 (46.0)	1636 (56.7)	2988 (57.6)	1584 (54.8)	498 (52.6)	213 (57.9)
African American	74 (54.0)	1249 (43.3)	2199 (42.4)	1309 (45.2)	449 (47.4)	155 (42.1)
BMI (kg/m^2)	17.3±1.0	22.8±1.6	27.4±1.4	32.1±1.4	37.0±1.4	44.1±4.3
Medical history						
CVD[b]	41 (29.9)	905 (31.4)	1715 (33.1)	1002 (34.6)	340 (35.9)	130 (35.3)
Hypertension	38 (27.7)	1103 (38.2)	2419 (46.6)	1684 (58.2)	616 (65.0)	231 (62.8)
Diabetes mellitus	14 (10.2)	325 (11.3)	820 (15.8)	653 (22.6)	291 (30.7)	116 (31.5)
Current smoker	62 (45.3)	1067 (37.0)	1646 (31.7)	849 (29.3)	223 (23.5)	111 (30.2)
Medications						
ACEI	8 (5.8)	248 (8.6)	639 (12.3)	494 (17.1)	202 (21.3)	88 (23.9)
β-blocker	9 (6.6)	356 (12.3)	792 (15.3)	543 (18.8)	195 (20.6)	70 (19.0)
Diuretic	9 (6.6)	190 (6.6)	391 (7.5)	307 (10.6)	130 (13.7)	68 (18.5)
Nitrate	27 (19.7)	395 (13.7)	593 (11.4)	313 (10.8)	102 (10.8)	44 (12.0)
Statin	2 (1.5)	82 (2.8)	269 (5.2)	199 (6.9)	75 (7.9)	23 (6.3)
Clinical						
SBP (mm Hg)	122.4±23.8	126.4±21.8	129.8±20.4	132.2±20.1	133.9±20.6	132.4±18.1
METs[c]	6.0±2.3	7.7±3.2	7.7±2.9	7.2±2.5	6.7±2.2	6.2±2.1
Fitness category (METs)						
Low (<5.0)	48 (35.0)	543 (18.8)	800 (15.4)	489 (16.9)	179 (18.9)	108 (29.3)
Moderate (5.0-10.0)	83 (60.6)	1779 (61.7)	3471 (66.9)	2088 (72.2)	714 (75.4)	240 (65.2)
High (>10.0)	6 (4.4)	563 (19.5)	916 (17.7)	316 (10.9)	54 (5.7)	20 (5.4)

[a] Data are presented as mean ± SD or number (percentage). ACEI = angiotensin-converting enzyme inhibitor; BMI = body mass index; CVD = cardiovascular disease; MET = metabolic equivalent; SBP = systolic blood pressure.
[b] CVD included history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, stroke, and/or peripheral arterial disease.
[c] Calculated from final treadmill speed and grade achieved on the exercise test (1 MET = 3.5 mL/kg/min).

dependent effects of BMI were assessed using 2 proportional hazards models—first, adjusting for age, ethnicity, examination year, test site, CVD, CVD risk factors, and CVD medications; second, by adding fitness entered as a continuous variable. This second model was also used to assess independent effects of hypertension, diabetes, and current smoking (except CVD risk factors were mutually adjusted). Cox proportional hazards analyses were repeated after excluding current smokers and patients who died in the first 2 years of follow-up.

Follow-up was calculated from the date of a patient's baseline exercise test and examination until the date of death or June 30, 2007. Statistical tests were 2-sided, and values of $P<.05$ were considered statistically significant. All statistical analyses were performed using NCSS 2007 software (NCSS, Kaysville, UT).

RESULTS

During a mean ± SD follow-up of 7.7±5.3 years (range, 0.08-22.92 years), 2801 deaths were recorded. Baseline characteristics grouped according to BMI category are presented in Table 1. The study population consisted of 6982 (56.2%) white and 5435 (43.8%) African American men who ranged in age from 40 to 70 years. There were 137 underweight patients (1.1%), 2885 normal-weight (23.2%), 5187 overweight (41.8%), and 4208 obese (33.9%) (2893 obese I [23.3%], 947 obese II [7.6%], and 368 obese III [3.0%]) patients. Median BMI was 28.0 (range, 13.2-65.6); ranges for quartiles 1 through 4 were 13.2 to 25.1, 25.2 to 27.9, 28.0 to 31.3, and 31.4 to 65.6, respectively. Testing of interaction models revealed a significant interaction between BMI and fitness ($P=.001$), but not BMI and race ($P=.79$).

Multivariate adjusted hazard ratio (HR) (95% confidence interval [CI]) for hypertension, diabetes mellitus, and current smoking was 1.1 (1.0-1.2), 1.3 (1.2-1.4), and 1.4 (1.3-1.5), respectively (data not shown).

Multivariate BMI-adjusted HR (95% CI) for low and moderate fitness, compared with the high-fitness reference group, was 3.6 (2.9-4.4) and 2.3 (1.9-2.8), respectively (Table 2). Multivariate fitness-adjusted HR (95% CI) for all-cause mortality associated with BMI categories of underweight, normal weight, overweight, obese I, and obese II or III was 1.9 (1.5-2.3), 1.0 (reference), 0.7 (0.7-0.8), 0.7 (0.6-0.7), and 1.0 (0.8-1.1), respectively (Table 3). These

TABLE 2. **Multivariate Proportional Mortality Hazard Ratios (HRs) by Fitness Category in Study Participants**[a]

Fitness category (METs)[b]	No. of men	No. (%) of deaths	HR (95% CI)[c]	*P* value
High (>10.0)	1875	153 (8)	1 (Reference)	
Moderate (5.0-10.0)	8375	1750 (21)	2.31 (1.90-2.82)	<.001
Low (<5.0)	2167	898 (41)	3.56 (2.88-4.40)	<.001

[a] CI = confidence interval; MET = metabolic equivalent.
[b] 1 MET = 3.5 mL/kg/min.
[c] Adjusted for age, ethnicity, examination year, test site, cardiovascular disease (CVD) (history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, stroke, and/or peripheral arterial disease), hypertension, dyslipidemia, diabetes mellitus, current smoking, CVD medications (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, nitrates, vasodilators, and/or statins), and body mass index (entered as a continuous variable in kg/m^2).

TABLE 3. **Multivariate Proportional Mortality Hazard Ratios (HRs) by Body Mass Index (BMI) Category in Study Participants**[a]

BMI category (kg/m^2)	No. of men	No. (%) of deaths	Model 1, HR (95% CI)[b]	Model 2, HR (95% CI)[c]
<18.5	137	83 (61)	2.02 (1.61-2.54)	1.86 (1.48-2.33)
18.5-24.9	2885	854 (30)	1 (Reference)	1 (Reference)
25.0-29.9	5187	1114 (22)	0.73 (0.67-0.80)	0.74 (0.68-0.81)
30.0-34.9	2893	526 (18)	0.70 (0.62-0.78)	0.65 (0.59-0.72)
≥35.0	1315	224 (17)	1.04 (0.89-1.22)	0.96 (0.82-1.12)

[a] CI = confidence interval.
[b] Adjusted for age, ethnicity, examination year, test site, cardiovascular disease (CVD), hypertension, dyslipidemia, diabetes mellitus, current smoking, and CVD medications.
[c] Adjusted for covariates listed in model 1 plus fitness (entered as a continuous variable in metabolic equivalents (METs); 1 MET = 3.5 mL/kg/min).

analyses were repeated for nonsmokers, and no substantial differences were found when compared with the entire cohort. Body mass index mortality curves, extended further in 5-unit increments from 35.0 to 50.0 or greater, with and without adjustment for fitness, are presented in the Figure.

Results of the joint effects of fitness and BMI on all-cause mortality are presented in Table 4. Compared with findings for highly fit normal-weight men, adjusted HR (95% CI) for all-cause mortality was lower for highly fit overweight men (0.4 [0.3-0.6]) and highly fit obese men

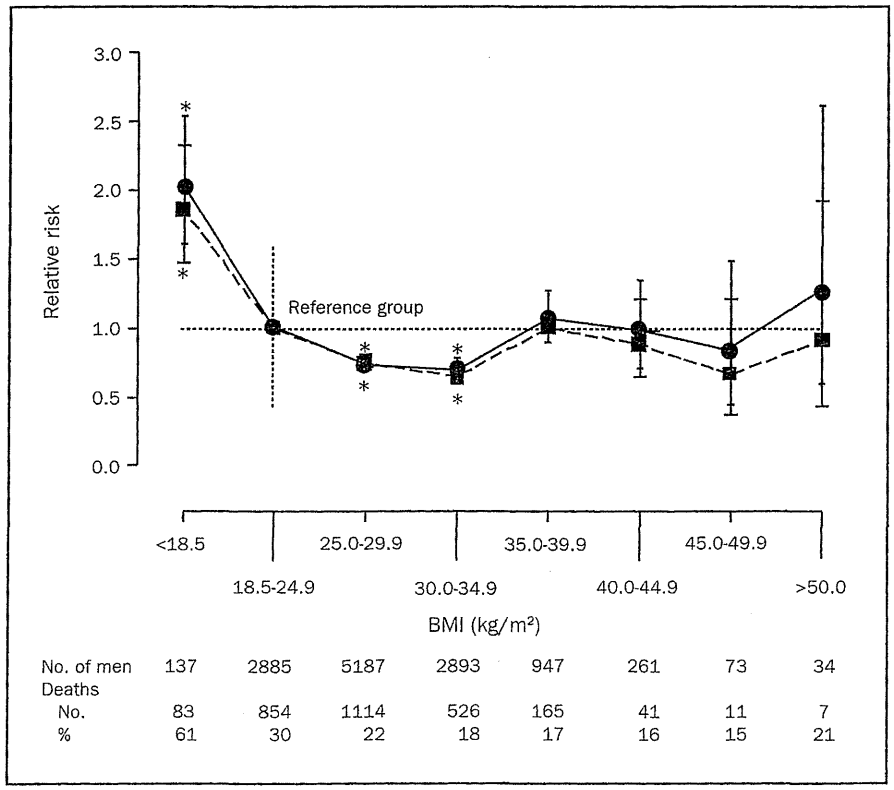

FIGURE. Multivariate hazard ratios for all-cause mortality by body mass index (BMI), adjusted for age, ethnicity, examination year, test site, cardiovascular disease, diabetes, hypertension, dyslipidemia, smoking status, and cardiovascular disease medications (solid line), and with additional adjustment for fitness, entered as a continuous variable (dashed line). Error bars are 95% confidence intervals. Number of men and number and percentage of deaths are given below each BMI category. *Differs significantly from reference group (*P*<.001).

TABLE 4. **Multivariate Proportional Mortality Hazard Ratios (HRs) by Body Mass Index (BMI) and Fitness in Study Participants[a,b]**

Fitness category	No. of men	No. (%) of deaths	HR (95% CI)[c]
BMI <18.5 (kg/m^2)			
Low fitness	48	37 (77)	4.48 (3.06-6.57)
Moderate fitness	83	46 (55)	3.09 (2.17-4.38)
High fitness[d]	6	0 (0)	...
BMI 18.5-24.9 (kg/m^2)			
Low fitness	543	259 (48)	2.03 (1.60-2.58)
Moderate fitness	1779	526 (30)	1.65 (1.34-2.04)
High fitness	563	69 (12)	1 [Reference]
BMI 25.0-29.9 (kg/m^2)			
Low fitness	800	330 (41)	1.79 (1.43-2.25)
Moderate fitness	3471	724 (21)	1.15 (0.93-1.42)
High fitness	916	60 (7)	0.43 (0.32-0.59)
BMI ≥30.0 (kg/m^2)			
Low fitness	776	272 (35)	1.61 (1.27-2.03)
Moderate fitness	3042	454 (15)	0.99 (0.80-1.23)
High fitness	390	24 (6)	0.52 (0.34-0.82)

[a] CI = confidence interval.
[b] Fitness defined as peak metabolic equivalents (METs) achieved on a maximal exercise test: low (<5.0); moderate (5.0-10.0); high (>10.0). 1 MET = 3.5 mL/kg/min.
[c] Adjusted for age, ethnicity, examination year, test site, cardiovascular disease (CVD), hypertension, dyslipidemia, diabetes mellitus, current smoking, and CVD medications.
[d] Too few participants for stratified analysis.

(0.5 [0.3-0.8]) and higher for the following groups: low-fitness underweight (4.5 [3.1-6.6]), moderately fit underweight (3.1 [2.2-4.4]), low-fitness normal-weight (2.0 [1.6-2.6]), moderately fit normal-weight (1.7 [1.3-2.0]), low-fitness overweight (1.8 [1.4-2.3]), and low-fitness obese (1.6 [1.3-2.0]). No significant differences were found for the moderately fit overweight (P=.19) and moderately fit obese (P=.96) groups compared with the reference group. Removing current smokers and patients who died during the first 2 years of follow-up from the analysis did not appreciably alter the results.

DISCUSSION

In multivariate analyses, both fitness and BMI were independently and inversely associated with mortality risk. To ascertain whether low BMI resulted from undetected illness at baseline, we excluded all patients who died during the first 2 years of follow-up and current smokers, but this did not substantially change the primary findings. In joint analyses, elevated BMI generally reduced mortality risk within each fitness category, and higher levels of fitness decreased mortality risk within each BMI category. Highly fit overweight men (n=916) had the lowest mortality risk of any fitness-BMI combination and were 57% less likely to die (HR, 0.43 [95% CI, 0.32-0.59]) as highly fit normal-weight men. Fitness altered the obesity paradox in that overweight and obese men with low fitness were less likely to survive than normal-weight men with high fitness. However, an obesity paradox persisted within fitness group strata.

Our findings that BMI and fitness are inversely associated with all-cause mortality are consistent with earlier results from the VETS[27] and extend them to joint analyses of fitness and BMI in a larger cohort of middle-aged men. Explanations for better survival with higher BMI in the current study include the following: (1) reverse causation in clinically referred patients,[33] (2) increased coronary artery size,[34] (3) the "veteran effect,"[27] (4) healthy obesity,[35] and (5) the survival effect.[36]

Several previous studies have reported an obesity paradox in specific patient populations.[4-10] First, in patient populations similar to ours, Galal et al[33] and Johnson et al[37] found significantly lower mortality in overweight and obese patients with known or suspected coronary artery disease compared with patients with normal BMI; this finding was consistent with our results.

Second, greater coronary artery size among patients with higher BMI has been proposed as a possible mechanism for the obesity paradox.[34] This may also be a factor in the favorable survival outcomes we observed among overweight and obese men in the current study of clinically referred patients, one third of whom had documented CVD.

Third, a related issue that might further explain our counterintuitive findings is the veteran effect, which we have previously noted.[27] Veterans differ from other populations in that they all must meet selection criteria at the time of enlistment. These criteria include minimum height requirements and maximum weight requirements, which must be maintained for the duration of military service. Specifically, maximum allowable weights for different branches of the service correspond to BMI of 25.9 to 29.9 for men.[38] Hence, obesity, when present in our population, must have developed after discharge from the service in later life. Some investigators have suggested that adult-onset obesity is less hazardous than obesity developing in childhood or adolescence.[39] In addition, men qualifying for military service may have greater than average muscle mass. This might explain the inverse associations between BMI and mortality found in other self-selected populations with physical attributes similar to veterans, such as longshoremen.[11]

Fourth, in the larger population of obese adults, some experience good health. This is illustrated in some of the findings from the Framingham Heart Study.[1] Participants who had a normal BMI at 40 years of age but developed obesity during 20 years of follow-up had no increased mortality risk. Moreover, in healthy obese mice, preferential storage of triglycerides in adipose tissue and reduced levels

in the liver[40] may result in improved insulin sensitivity, preventing diabetes and heart disease in such animals. A similar mechanism has been proposed for obese humans,[41] and a metabolically benign form of obesity has been recently identified.[35]

Fifth, our findings may be explained in part by the well-known survival effect,[36] which has particular relevance in epidemiological studies of older adults. Although our study patients were middle-aged, those in the upper range of this age group were possibly less susceptible to the negative effects of overweight.

Because objective measures of fitness (maximal exercise testing on a treadmill) are often unavailable, data on the joint effects of BMI and fitness on mortality are sparse. We know of 9 published studies that have specifically assessed the joint effects of fitness (as measured from standard exercise testing) and BMI on mortality.[18-26] Two studies[18,19] examined this issue by using data from the Lipid Research Clinics Study. All 7 of the remaining published studies used data from the Aerobics Center Longitudinal Study.[20-26] Collectively, these studies demonstrated that fitness was a stronger predictor of mortality than BMI and that higher fitness eliminated the mortality risk of elevated BMI (the fat-but-fit hypothesis). Our results differ from these studies in that both high fitness and higher BMI independently reduced mortality risk. The effect of higher BMI on fitness in our cohort was that it generally reduced mortality risk across fitness categories. When highly fit patients were compared by BMI category, those who were overweight and obese experienced dramatic reductions in mortality risk (HR [95% CI], 0.43 [0.32-0.59] and 0.52 [0.34-0.82], respectively). However, only 916 overweight and 390 obese men registered high fitness at baseline, which represents only 7% and 3% of our cohort, respectively. Further study of individuals having this rare phenotype is needed to confirm our findings.

Our study has several strengths. First, all participants underwent an extensive physical examination, and detailed information on medication use was obtained, providing thorough information on the presence or absence of baseline disease. Second, fitness level was determined objectively by maximal exercise testing. Third, the study had a large sample size of more than 12,000 men and an average follow-up of nearly 8 years. Fourth, when smokers and patients who died during the first 2 years of follow-up were excluded, the results were not meaningfully altered.

Our study also has limitations. First, because waist circumference measures were not obtained, we were unable to evaluate body fat distribution characteristics. Second, we included only men who had prior military service and were referred for exercise testing for clinical reasons. Any effort to predict mortality by using fitness, BMI, or clinical or demographic data should be considered population-specific. Although most men were free of CVD, all patients were referred for exercise testing for clinical reasons. Third, fitness is a single measure that is influenced by many factors, including age, heredity, and recent and lifelong activity patterns.[32,42] The extent of fitness improvement in adults, or the influence this may have on mortality, cannot be determined from the current investigation. Fourth, we had insufficient information about diet or physical activity patterns to study these factors. Fifth, because we have only baseline data on weight, exercise capacity, and other exposures, we do not know if changes in any of these variables occurred during follow-up and how this might have influenced the results.

CONCLUSION

Both higher BMI and higher fitness were protective for all-cause mortality in this cohort of white and African American middle-aged male veterans with known or suspected CVD. Fitness altered the obesity paradox such that overweight and obese men had increased longevity only if they registered high fitness. Future studies should focus on the influence of fitness and BMI on mortality in diverse populations and whether changes in fitness level and/or body weight affect health outcomes.

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対象の内訳				地　域		研究の種類	
	ヒト	動物		欧米		縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	男性	( )		( )		( )
年齢	40-70(57歳)	[redacted]		( )		前向きコホート
対象数	10000以上			( )		( )

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

TABLE 2. **Multivariate Proportional Mortality Hazard Ratios (HRs) by Fitness Category in Study Participants**[a]

Fitness category (METs)[b]	No. of men	No. (%) of deaths	HR (95% CI)[c]	*P* value
High (>10.0)	1875	153 (8)	1 (Reference)	
Moderate (5.0-10.0)	8375	1750 (21)	2.31 (1.90-2.82)	<.001
Low (<5.0)	2167	898 (41)	3.56 (2.88-4.40)	<.001

[a] CI = confidence interval; MET = metabolic equivalent.
[b] 1 MET = 3.5 mL/kg/min.
[c] Adjusted for age, ethnicity, examination year, test site, cardiovascular disease (CVD) (history of myocardial infarction, angiographically documented coronary artery disease, coronary angioplasty, coronary bypass surgery, chronic heart failure, stroke, and/or peripheral arterial disease), hypertension, dyslipidemia, diabetes mellitus, current smoking, CVD medications (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, nitrates, vasodilators, and/or statins), and body mass index (entered as a continuous variable in kg/m^2).

図表掲載箇所	
概　要 (800字まで)	＜目的＞冠状動脈疾患を有する又は疑われる中年の男性で肥満パラドックスに対する全身持久力の影響を評価すること。(肥満パラドックスとは、循環器疾患の強力な危険因子を有する肥満者の生命予後が良いという矛盾) ＜方法＞コホート名：The Veterans Exercise Testing Study (VETS)、対象者数：12417人、追跡期間：7.7年、全身持久力評価方法詳細：トレッドミルテスト(Bruce protocol)による最大負荷試験、全身持久力の単位：メッツ、全身持久力の値、分位1：10.1メッツ以上、分位2：5-10メッツ、分位3：4.9未満。＜結果＞7.7+/-5.3年のフォローアップの間、2801人の死を記録した。全身持久力と死亡リスクとの関係は、分位1：1、分位2：2.31(1.9-2.82)、分位3：3.56(2.88-4.4)であった。肥満と全身持久力との相互作用に関しては、普通体重の高体力車と比較して、低体重の低体力者のリスクは4.5(3.1-6.6)であり、高体力の過体重者で0.4(0.-0.6)と最もリスクが低かった。
結　論 (200字まで)	過体重や肥満者でも生命予後は良いのは、全身持久力が高い場合のみである。
エキスパートによるコメント (200字まで)	肥満パラドックスを解決する鍵として、全身持久力が関連することを示す研究として、肥満と独立して身体活動・運動に取り組み体力を高めることの意義を示した貴重な論文である。

担当者　宮地元彦

Ability of Exercise Testing to Predict Cardiovascular and All-Cause Death in Asymptomatic Women

A 20-Year Follow-up of the Lipid Research Clinics Prevalence Study

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Context The value of exercise testing in women has been questioned.

Objective To determine the prognostic value of exercise testing in a population-based cohort of asymptomatic women followed up for 20 years.

Design and Setting Near-maximal Bruce-protocol treadmill test data from the Lipid Research Clinics Prevalence Study (1972-1976) with follow-up through 1995.

Participants A total of 2994 asymptomatic North American women, aged 30 to 80 years, without known cardiovascular disease.

Main Outcome Measures Cardiovascular and all-cause mortality.

Results There were 427 (14%) deaths during 20 years of follow-up, of which 147 were due to cardiovascular causes. Low exercise capacity, low heart rate recovery (HRR), and not achieving target heart rate were independently associated with increased all-cause and cardiovascular mortality. There was no increased cardiovascular death risk for exercise-induced ST-segment depression (age-adjusted hazard ratio, 1.02; 95% confidence interval [CI], 0.57-1.80; $P = .96$). The age-adjusted hazard ratio for cardiovascular death for every metabolic equivalent (MET) decrement in exercise capacity was 1.20 (95% CI, 1.18-1.30; $P<.001$); for every 10 beats per minute decrement in HRR, the hazard ratio was 1.36 (95% CI, 1.19-1.55; $P<.001$). After adjusting for multiple other risk factors, women who were below the median for both exercise capacity and HRR had a 3.5-fold increased risk of cardiovascular death (95% CI, 1.57-7.86; $P=.002$) compared with those above the median for both variables. Among women with low risk Framingham scores, those with below median levels of both exercise capacity and HRR had significantly increased risk compared with women who had above median levels of these 2 exercise variables, 44.5 and 3.5 cardiovascular deaths per 10000 person-years, respectively (hazard ratio for cardiovascular death, 12.93; 95% CI, 5.62-29.73; $P<.001$).

Conclusion The prognostic value of exercise testing in asymptomatic women derives not from electrocardiographic ischemia but from fitness-related variables.

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CARDIOVASCULAR DISEASE claims the life of 1 of every 2 women in the United States,[1] with most sudden deaths in women occurring in those with no previous symptoms.[2,3] Identifying asymptomatic women who are at increased risk and who may benefit from aggressive primary prevention has the potential to reduce cardiovascular morbidity and mortality in women.[4] It is controversial whether exercise testing should be used to screen asymptomatic women for cardiovascular risk.[5,6] While several studies have found certain exercise test variables (eg, reduced exercise capacity and ischemic ST-segment depression) to be associated with increased mortality in healthy men,[7-12] it is not known if these have similar prognostic value in women. It is also unclear how other exercise test variables compare with ST-segment depression as predictors of mortality.

We investigated the role of exercise treadmill testing in predicting cardiovascular and all-cause death in a population-based cohort of asymptomatic women. We aimed to identify whether exercise test variables related to ischemia, fitness, and autonomic function were independent predictors of increased risk of all-cause or cardiovascular death and whether there were sex-related differences in the prognostic value of these exercise test variables.

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METHODS

Study Population

The study participants were enrolled in the Lipid Research Clinics Prevalence Study, which has been previously described.[13] Briefly, a 2-stage screening procedure was used. From 1972-1976, individuals were screened at 10 centers in North America (visit 1).[8] A sample consisting of 15% of eligible participants randomly selected from visit 1 and all the visit 1 participants with elevated lipid levels were invited back to visit 2 for baseline history, physical examination, fasting blood samples, and exercise tests. The women from the random sample constituted 62% of the study cohort, similar to the proportion in the original cohort at visit 2. Participants were followed up annually for vital status ascertainment until death or end of follow-up (December 31, 1995). Until 1988, deaths were identified by mail or telephone contact and confirmed using death certificates, interviews with next-of-kin or other witnesses, and review of medical records. Cause of death was classified by a committee of cardiologists masked to the identity of the deceased. From 1988-1995, deaths were identified from death certificates by trained nosologists using the National Death Index (1988-1991) and the Epidemiology Research Index (1992-1995).[14]

Participants were ineligible for exercise testing at baseline if they were pregnant, had significant cardiovascular disease, or were deemed ineligible for exercise testing by the study physicians. Of the 4006 women who came to visit 2 and were followed up, 630 did not have a baseline exercise test done. Another 382 were excluded from this analysis because they were younger than 30 years or older than 80 years; had a history of angina, claudication, myocardial infarction, stroke, heart surgery, left ventricular hypertrophy, digoxin use; exercise duration less than 1 minute; a modified Bruce exercise test; or were lost to follow-up (3 women). Thus, this study included 2994 asymptomatic women who were followed up until their death or end of follow-up (December 31, 1995). Participants gave informed written consent and the study had institutional review board approval from the University of Maryland and the Johns Hopkins Medical Institutions.

Exercise Testing

At visit 2, participants underwent exercise testing using a Bruce treadmill protocol (no cool-down period). The test was terminated when a target heart rate of 90% or more of maximal predicted heart rate for age and physical activity level was attained.[8] Target heart rates were predetermined by the investigators based on age and baseline physical activity with slightly lower target rates (approximately 5/min lower) for physically active individuals. The test was stopped prematurely if the participant was unable or refused to continue; developed significant arrhythmias, hypotension, electrocardiographic changes or angina; or due to technical difficulties. Exercise electrocardiograms were read by 2 trained coders and reviewed by a supervisor using a carefully defined visual coding system with an internal quality control system at a central coding center. Discrepancies between the coders were adjudicated by the supervisor in consultation with 1 of 2 cardiologists. The exercise electrocardiogram was also computer analyzed, and any differences between visual and computer coding were adjudicated by the supervisor and the cardiologists.

Definition of Exercise Test Variables

ST-segment depression was defined as at least 1.0 mm horizontal or downsloping depression at 0.08 seconds after the J point in the lead with the greatest abnormality (X, Y, Z [orthogonal leads], V_4, V_5, V_6) in the last stage of exercise or recovery. To compare with previous studies,[15-17] exercise-induced ventricular arrhythmia was defined as multifocal or at least 10% premature ventricular contractions in the last stage of exercise or recovery, or if the test was terminated due to ventricular tachycardia. Target heart rate was not attained if the participants failed to reach 90% or more of their maximal predicted heart rate for age and baseline physical activity. Peak exercise capacity was estimated from treadmill time and expressed in metabolic equivalents (METs).[18] Heart rate recovery (HRR) was defined as peak heart rate minus heart rate at 2 minutes postexercise (subjects were seated in a chair immediately after exercise).

Definition of Clinical Variables

The mean of 2 blood pressure measurements taken at rest prior to exercise testing was used to define hypertension (mean systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medications).[19] Participants were considered diabetic if their fasting glucose level was at least 126 mg/dL (≥7.0 mmol/L) or they were taking antidiabetic medications. Obesity was defined as body mass index of at least 30. Serum lipid values were measured after an overnight fast. High total cholesterol level was at least 240 mg/dL (≥6.22 mmol/L), high low-density lipoprotein (LDL) cholesterol level at least 160 mg/dL (≥4.14 mmol/L), low high-density lipoprotein (HDL) cholesterol level less than 40 mg/dL (<1.04 mmol/L), and a high triglyceride level of at least 200 mg/dL (≥2.26 mmol/L). Subjects were classified as current smokers if they reported smoking cigarettes at baseline. Family history of premature coronary heart disease was defined as a parent or sibling with disease onset before 60 years of age. Postmenopausal status was determined from self-reports. Medication use was assessed from questionnaires or examination of medications. Physical activity was assessed with the question: "Do you regularly engage in strenuous exercise or hard physical labor?" and participants were considered to engage in regular exercise if they answered affirmatively. The 1998 Framingham risk equation[20] was used for risk stratification based on Adult Treatment Panel III guidelines[21] that suggest an estimated 10-year total coronary heart disease event rate of less than 15% as low risk,

15% to 25% as intermediate risk, and more than 25% as high risk.

Statistical Methods

Statistical analyses were performed using STATA, 2001.[22] Survival analysis was done with Kaplan-Meier curves and log-rank tests across quintiles. Mortality rates were calculated as the number of deaths divided by person-years of follow-up. Age-adjusted Cox proportional hazards models that included the variable and age in years, and multivariable models that adjusted for other covariates, were used to estimate hazard ratios and 95% confidence intervals (CIs) for the association of variables with time to death. The proportional hazard assumption was satisfied using Schoenfeld residuals.

In the final multivariable models, the variables that were included in addition to the exercise test variables were age, smoking, diabetes, family history of premature coronary heart disease, obesity, high LDL cholesterol level, low HDL cholesterol level, high triglyceride level, and hypertension. Cardiovascular risk factors were assessed both as continuous and categorical variables. When cardiovascular risk factors were included in the models as continuous variables, no change was noted in the coefficients compared with models that had categorical variables. The addition of covariates for study site, regular exercise, and the use of lipid-lowering medications also did not change the values of the coefficients for the exercise test variables, nor were these additional covariates associated with mortality. Therefore, the final models did not include these covariates.

Peak exercise capacity and HRR were assessed as continuous variables, quintiles, and categories (≤study median vs >median). Heart rate recovery was also examined using a cut-off value (abnormal if <22/min) that has been associated with increased mortality in previous studies.[23] We tested for interaction with interaction terms and stratification. Stepwise forward and backward Cox regression analyses (at the .05 significance level) were used to statistically select which exercise test variables were independent predictors of risk. All reported *P* values were 2-sided.

RESULTS

During a mean (SD) follow-up of 20.3 (3.9) years of the 2994 women, there were 427 (14%) deaths from any cause, including 147 cardiovascular deaths

Table 1. Baseline Demographic, Clinical, and Exercise Test Characteristics According to Exercise Capacity and Heart Rate Recovery*

Variable	High METs/ High HRR (n = 822)	Low METs/ High HRR (n = 644)	High METs/ Low HRR (n = 579)	Low METs/ Low HRR (n = 940)
Demographic and clinical†				
All-cause death, No. (%)	39 (5)	78 (12)	52 (9)	257 (27)
Cardiovascular death, No. (%)	7 (1)	19 (3)	17 (3)	103 (11)
Age, mean (SD), y	42 (9)	47 (11)	44 (10)	52 (12)
White, No. (%)	780 (95)	595 (93)	553 (96)	899 (96)
Systolic blood pressure, mean (SD), mm Hg	114 (15)	122 (18)	120 (17)	129 (19)
Diastolic blood pressure, mean (SD), mm Hg	74 (10)	78 (10)	77 (10)	80 (10)
Body mass index	24.0 (4.0)	25.5 (5.0)	24.1 (4.1)	25.9 (5.1)
Total cholesterol ≥240 mg/dL (≥6.22 mmol/L), No. (%)	200 (24)	211 (33)	189 (33)	402 (43)
LDL cholesterol ≥160 mg/dL (≥4.14 mmol/L), No. (%)	204 (25)	208 (32)	193 (33)	397 (42)
HDL <40 mg/dL (<1.04 mmol/L), No. (%)	68 (8)	56 (9)	79 (14)	120 (13)
Triglycerides ≥200 mg/dL (≥2.26 mmol/L), No. (%)	58 (7)	79 (12)	63 (11)	159 (17)
Diabetes, No. (%)	8 (1)	10 (2)	17 (3)	49 (5)
Current smoking, No. (%)	280 (34)	172 (27)	240 (41)	322 (34)
Regular exercise, No. (%)	160 (19)	77 (12)	71 (12)	79 (8)
Family history, No. (%)	178 (22)	107 (17)	111 (19)	160 (17)
Exercise test‡				
Peak exercise capacity, mean (SD), METs	9.3 (1.2)	5.9 (1.4)	9.2 (1.2)	5.4 (1.6)
Resting heart rate, mean (SD), beats/min	80 (11)	83 (13)	85 (12)	90 (14)
Maximal heart rate, mean (SD), beats/min	170 (8)	166 (14)	166 (11)	156 (18)
HRR, mean (SD), beats/min	66 (8)	65 (8)	48 (7)	44 (9)
Target heart rate not attained, No. (%)	171 (21)	205 (32)	206 (36)	508 (54)
Ventricular arrhythmia, No. (%)	39 (5)	46 (7)	29 (5)	114 (12)
ST depression ≥1.0 mm, No. (%)	27 (3)	42 (7)	18 (3)	53 (6)

Abbreviations: HDL, high-density lipoprotein; HRR, heart rate recovery; LDL, low-density lipoprotein; METs, metabolic equivalents.
*High and low METs is exercise capacity above or below the study median (7.5 METs). Heart rate recovery is maximal heart rate minus rate at 2 minutes postexercise. High and low HRR is heart rate recovery above or below the study median (55/min). Numbers may not add up due to rounding.
†Regular exercise is self-reported participation in regular strenuous activity or hard labor. Family history is premature coronary heart disease in a parent or sibling. Target heart rate not attained is maximal rate less than 90% of maximal predicted rate for age and physical activity. Body mass index calculated as weight in kilograms divided by the square of height in meters.
‡Ventricular arrhythmia is multifocal or at least 10% premature ventricular contractions in exercise or recovery, or reason for test termination. ST depression is at least 1 mm of horizontal or downsloping depression in exercise or recovery. METs was available for all 2994 women, but HRR was not available for 9 women, 1 of whom died.

(34% of all deaths). Women with high levels of exercise capacity and HRR (>the study median of 7.5 METs and 55/min, respectively) had fewer all-cause and cardiovascular deaths during follow-up (TABLE 1). They were also younger, reported more regular exercise, and had more favorable clinical and exercise test profiles compared with women who had lower exercise capacity or HRR. There was a moderate difference in mean peak exercise capacity and HRR for women who reported regular exercise compared with those who did not (8.2 and 7.2 METs, 60/min and 55/min, respectively, $P<.001$ for both). At baseline, only 98 women (3%) were taking lipid-lowering medications, and only 7 (0.2%) were taking β-blockers. Peak exercise capacity and HRR were only modestly correlated ($r=0.27$).

Exercise Capacity, Heart Rate Recovery, and Mortality

Kaplan-Meier mortality curves according to quintiles of peak exercise capacity and HRR (FIGURE) diverge early and continue to diverge over the 20-year follow-up. There was a graded increase in mortality for decreasing quintiles of exercise capacity and HRR (P values from log-rank tests .001 across quintiles for both variables). Similar results were obtained for survival free of cardiovascular death.

Age-Adjusted Predictors of Mortality

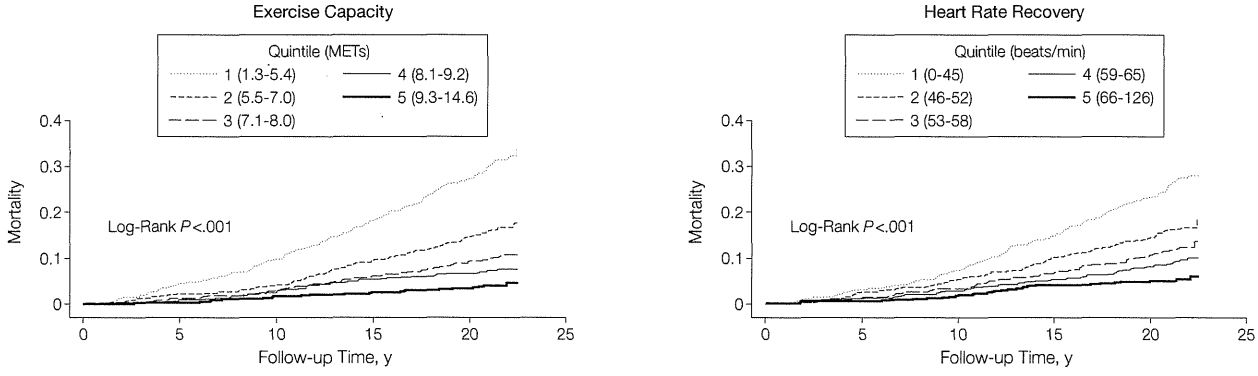
After age adjustment, the effects of exercise capacity, HRR, not achieving target heart rate, and exercise-induced ventricular arrhythmia on cardiovascular and all-cause mortality were similar in magnitude to the effects of traditional cardiovascular risk factors (TABLE 2). Neither total nor LDL cholesterol level predicted cardiovascular death after adjusting for age, similar to previous results in women from this cohort.[24] The age-adjusted hazard ratio for cardiovascular death for every MET decrement in exercise capacity was 1.20 (95% CI, 1.18-1.30), and for every 10/min-decrement in HRR, 1.36 (95% CI, 1.19-1.55). For both variables, there was a strong and graded association between decreasing quintiles and age-adjusted risk of cardiovascular and all-cause death (P values for trend <.001).

In contrast, exercise-induced ST-segment depression of at least 1 mm did not predict cardiovascular death (age-adjusted hazard ratio, 1.02; 95% CI, 0.57-1.80); neither did ST-segment depression of at least 2 mm (age-adjusted hazard ratio, 0.97; 95% CI, 0.14-6.93). In the subgroup of women who were older than 55 years at baseline (n=714), there were 104 of the 147 cardiovascular deaths during follow-up, with no predictive value for ST-segment depression (age-adjusted hazard ratio, 1.03; 95% CI, 0.55-1.93). To compare with earlier published results on the men in the Lipid Research Clinics study,[13] we analyzed the data at 10-year follow-up and again found that ST-segment depression was not associated with increased risk.

Multivariable Predictors of Mortality

We analyzed the prognostic value of exercise test variables, considered one at a time, after adjusting simultaneously for cardiovascular risk factors (age, current smoking, diabetes, family history of premature coronary heart disease, obesity, high LDL cholesterol level, low HDL cholesterol level, high triglyceride level, and hypertension). When risk factors were included in these models

Figure. Kaplan-Meier Estimates of Overall Mortality According to Quintiles of Peak Exercise Capacity Achieved and Quintiles of Heart Rate Recovery



No. at Risk					
Quintile 1	600	574	541	491	428
Quintile 2	715	700	685	645	597
Quintile 3	563	557	547	529	490
Quintile 4	528	524	514	499	484
Quintile 5	588	584	575	569	548

No. at Risk					
Quintile 1	635	614	585	536	472
Quintile 2	601	586	569	540	504
Quintile 3	566	559	547	526	489
Quintile 4	592	586	576	561	531
Quintile 5	591	585	576	562	542

Both peak exercise capacity and heart rate recovery were strongly associated with subsequent mortality, with P values <.001 obtained from log-rank tests of significance for both variables. MET indicates metabolic equivalent.

as continuous variables, similar results were obtained. Independent exercise test predictors of cardiovascular death were exercise capacity, HRR, not achieving target heart rate, and ventricular arrhythmia (TABLE 3). ST-segment depression was not associated with increased risk.

In a multivariable model for all-cause mortality that included both peak exercise capacity and HRR together in the same model with all the cardiovascular risk factors, there were trivial changes in the hazard ratios for both variables and each remained independently predictive of mortality ($P<.001$ for exercise capacity and $P=.002$ for HRR). When the study population was divided into 4 groups based on the median values for exercise capacity and HRR (TABLE 4), women who were below the median with respect to both exercise capacity and HRR had a 3.5-fold increased risk of cardiovascular death compared with women who were above the median for both variables, after controlling for cardiovascular risk factors.

Stepwise forward and backward Cox regression analysis confirmed that exercise capacity and HRR were the only 2 exercise test variables that were statistically selected as independent predictors in the same model after accounting for cardiovascular risk factors. There was no interaction between exercise capacity and HRR. There were no interactions between HRR or peak exercise capacity and any cardiovascular risk factor (including menopause status and sex) for cardiovascular or all-cause mortality.

In contrast, there was a highly statistically significant interaction between sex and ST-segment depression for all-cause mortality ($P<.001$), and a significant interaction for cardiovascular mortality ($P=.02$). Identical analyses on the 3769 asymptomatic men who were followed up for 20 years in this cohort showed that the increased risk of exercise-induced ST-segment depression that was found at 8-year follow-up[13] persisted at 20 years. Despite a similarly low prevalence of ST-segment depression in both men and women, ST-segment depression of at least 1 mm in men was predictive of both cardiovascular and all-cause mortality after multivariable adjustment for cardiovascular risk factors (adjusted hazard ratios and 95% CIs for cardiovascular death, 1.92 [1.31-2.82]; and for all-cause death, 1.44 [1.09-1.90]).

Risk Stratification by Exercise Testing and Framingham Risk Scores

Using their baseline Framingham risk scores,[20] 95% of the women were at low risk, with 4% at intermediate and 1% at high risk. Women with low risk Framingham scores (n=2817) were further subdivided into 3 categories based on their exercise capacity and HRR levels: greater than the median in the 2 exercise test variables (group 1, n=811); greater than the median in 1 of the 2 variables (group 2, n=1168); and greater than the median in the 2 variables (group 3, n=838). Cardiovascular mortality rates in these 3 groups, re-

Table 2. Age-Adjusted Risk of Cardiovascular and All-Cause Death by Clinical and Exercise Test Variables*

Variable	No.	Cardiovascular Death			All-Cause Death		
		No. of Deaths	Hazard Ratio (95% CI)	*P* Value	No. of Deaths	Hazard Ratio (95% CI)	*P* Value
Clinical							
Diabetes	84	17	3.45 (2.07-5.73)	<.001	36	2.55 (1.81-3.59)	<.001
Current smoking	1018	58	2.37 (1.68-3.36)	<.001	155	1.80 (1.47-2.21)	<.001
Total cholesterol ≥240 mg/dL (≥6.22 mmol/L)	1004	77	1.24 (0.89-1.72)	.20	212	1.18 (0.97-1.43)	.09
LDL cholesterol ≥160 mg/dL (≥4.14 mmol/L)	1004	76	1.26 (0.91-1.74)	.20	212	1.26 (1.04-1.53)	.02
Triglycerides ≥200 mg/dL (≥2.26 mmol/L)	361	40	2.37 (1.64-3.40)	<.001	81	1.49 (1.17-1.90)	.001
HDL cholesterol <40 mg/dL (<1.04 mmol/L)	323	23	1.91 (1.22-2.98)	.004	50	1.34 (1.00-1.80)	.05
Hypertension	714	78	1.82 (1.29-2.56)	.001	201	1.57 (1.29-1.93)	<.001
Body mass index ≥30†	390	29	1.79 (1.19-2.69)	.005	80	1.63 (1.28-2.08)	<.001
Exercise test							
Exercise capacity							
Categorical (≤median)	1589	123	2.04 (1.29-3.25)	.003	336	1.73 (1.35-2.22)	<.001
Continuous (per MET decrement)	...	...	1.20 (1.18-1.30)	<.001	...	1.14 (1.09-1.19)	<.001
HRR							
Categorical (<22/min)	21	4	3.02 (1.11-8.18)	.03	9	2.44 (1.26-4.73)	.008
Categorical (≤median)	1519	120	2.85 (1.85-4.39)	<.001	309	1.77 (1.42-2.20)	<.001
Continuous (per 10/min-decrement)	...	...	1.36 (1.19-1.55)	<.001	...	1.25 (1.15-1.35)	<.001
Target heart rate not attained	1091	98	1.72 (1.19-2.48)	.004	253	1.39 (1.13-1.71)	.002
Ventricular arrhythmia	229	28	1.53 (1.00-2.33)	.05	60	1.18 (0.89-1.55)	.30
ST depression ≥1.0 mm	141	13	1.02 (0.57-1.80)	.96	25	0.70 (0.47-1.05)	.09

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; HRR, heart rate recovery; LDL, low-density lipoprotein; MET, metabolic equivalent.
*Hazard ratios and 95% CIs are from Cox proportional hazards models that included the variable and age (years), comparing women with the variable to those without it. For exercise capacity and HRR, age-adjusted hazard ratios are additionally shown for every MET decrement in exercise capacity and for every 10/min-decrement in HRR.
†Calculated as weight in kilograms divided by the square of height in meters.