Greenberg PE et al. The economic burden of depression in the United States: how did it change between 1990 and 2000. Journal of Clinical Psychiatry 2003;64:1465–75.
Haringsma R, Engels GI, Beekman AT, Spinhoven P. The criterion validity of the Center for Epidemiological Studies Depression Scale (CES-D) in a sample of self-referred elders with depressive symptomatology. International Journal of Geriatric Psychiatry 2004;19:558–63.
Haskell WL et al. Cardiovascular benefits and assessment of physical activity and physical fitness in adults. Medicine and Science in Sports Exercise 1992;24:S201–20.
Heikkinen RL, Kauppinen M. Depressive symptoms in late life: a 10-year follow-up. Archives of Gerontology and Geriatrics 2004;38:239–50.
Hopko DR et al. The phenomenology and screening of clinical depression in cancer patients. Journal of Psychosocial Oncology 2008;26:31–51.
Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. Gerontology 2000;46:219–27.
Kouzis A, Eaton WW, Leaf PJ. Psychopathology and mortality in the general population. Social Psychiatry Psychiatric Epidemiology 1995;30:165–70.
Krishnan KR et al. Comorbidity of depression with other medical diseases in the elderly. Biological Psychiatry 2002;52:559–88.
Kritz-Silverstein D, Barrett-Connor E, Corbeau C. Cross-sectional and prospective study of exercise and depressed mood in the elderly: the Rancho Bernardo study. American Journal of Epidemiology 2001;153:596–603.
Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. BMJ 2001;322:763–7.
Lee I-M, Paffenbarger RSJ. Physical activity and stroke incidence: the Harvard Alumni Health Study. Stroke 1998;29:2049–54.
Lennox SS, Bedell JR, Stone AA. The effect of exercise on normal mood. Journal of Psychosomatic Research 1990;34:629–36.
Lyness JM, Noel TK, Cox C, King DA, Conwell Y, Caine ED. Screening for depression in elderly primary care patients. A comparison of the Center for Epidemiologic Studies-Depression Scale and the Geriatric Depression Scale. Archives of Internal Medicine 1997;157:449–54.
Macera CA, Jackson KL, Davis DR, Kronenfeld JJ, Blair SN. Patterns of non-response to a mail survey. Journal of Clinical Epidemiology 1990;43:1427–30.
Morgan WP. Affective beneficence of vigorous physical activity. Medicine and Science in Sports and Exercise 1985;17:94–100.
NIMH. The numbers count: mental illness in America. Science on our minds fact sheet series; 2006.
Paffenbarger RSJ, Lee IM, Leung R. Physical activity and personal characteristics associated with depression and suicide in American college men. Acta Psychiatrica Scandinavica Supplement 1994;377:16–22.
Parikh RM, Eden DT, Price TR, Robinson RG. The sensitivity and specificity of the Center for Epidemiologic Studies Depression Scale in screening for post-stroke depression. International Journal of Psychiatry in Medicine 1988;18:169–81.
Pate RR et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. Journal of the American Medical Association 1995;273:402–7.
Peluso MA, Guerra de Andrade LH. Physical activity and mental health: the association between exercise and mood. Clinics 2005;60:61–70.
Penninx BW et al. Depression and cardiac mortality: results from a community-based longitudinal study. Archieves of General Psychiatry 2001;58:221–7.
Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychosomatic Medicine 2008;70:288–97.
Pollock ML et al. A comparative analysis of four protocols for maximal treadmill stress testing. American Heart Journal 1976;92:39–46.
Pollock ML, Foster C, Schmidt D, Hellman C, Linnerud AC, Ward A. Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. American Heart Journal 1982;103:363–73.
Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 1977;1:385–401.
Ried LD, Planas LG. Aging, health, and depressive symptoms: are women and men different. Journal of Women's Health (Larchmt) 2002;11:813–24.
Rothman KJ, Greenland S. Modern epidemiology. Philadelphia, PA: Lippincott-Raven; 1998.
Russo-Neustadt AA, Beard RC, Huang YM, Cotman CW. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. Neuroscience 2000;101:305–12.
Stathopoulou G, Powers MB, Berry AC, Smits AJ, Otto MW. Exercise interventions for mental health: a quantitative and qualitative review. Clinical Psychology Science and Practice 2006;13:179–93.
Stephens T. Physical activity and mental health in the United States and Canada: evidence from four population surveys. Preventive Medicine 1988;17:35–47.
Stewart AL, Hays RD, Wells KB, Rogers WH, Spritzer KL, Greenfield S. Long-term functioning and well-being outcomes associated with physical activity and exercise in patients with chronic conditions in the medical outcomes study. Journal of Clinical Epidemiology 1994;47:719–30.
Strawbridge WJ, Deleger S, Roberts RE, Kaplan GA. Physical activity reduces the risk of subsequent depression for older adults. American Journal of Epidemiology 2002;156:328–34.
Sui X, LaMonte MJ, Blair SN. Cardiorespiratory fitness as a predictor of nonfatal cardiovascular events in asymptomatic women and men. American Journal of Epidemiology 2007;165:1413–23.
Thirlaway K, Benton D. Participation in physical activity and cardiovascular fitness have different effects on mental health and mood. Journal of Psychosomatic Research 1992;36:657–65.
Thoren P, Floras JS, Hoffmann P, Seals DR. Endorphins and exercise: physiological mechanisms and clinical implications. Medicine and Science in Sports and Exercise 1990;22:417–28.
Tolmunen T et al. Low maximal oxygen uptake is associated with elevated depressive symptoms in middle-aged men. European Journal of Epidemiology 2006;21:701–6.
Wada K et al. Validity of the center for epidemiologic studies depression scale as a screening instrument of major depressive disorder among Japanese workers. American Journal of Industrial Medicine 2007;50:8–12.
Weyerer S. Physical inactivity and depression in the community. Evidence from the upper bavarian field study. International Journal of Sports Medicine 1992;13:492–6.
Wiles NJ, Haase AM, Gallacher J, Lawlor DA, Lewis G. Physical activity and common mental disorder: results from the caerphilly study. American Journal of Epidemiology 2007;165:946–54.
Zheng H et al. Beneficial effects of exercise and its molecular mechanisms on depression in rats. Behavioural Brain Research 2006;168:47–55.

論文名	Prospective study of cardiorespiratory fitness and depressive symptoms in women and men					
著　者	Sui X, Laditka JN, Church TS, Hardin JW, Chase N, Davis K, Blair SN.					
雑誌名	Journal of psychiatric research					
巻・号・頁	43	5	546-552			
発行年	2009					
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/20141710					

		ヒト	動物	地　域	欧米	研究の種類	縦断研究
対象の内訳	対象	一般健常者	空白		(USA)		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	20-81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		( )
	維持・改善	な し	な し	な し	心理的指標改善	( )	( )

図　表

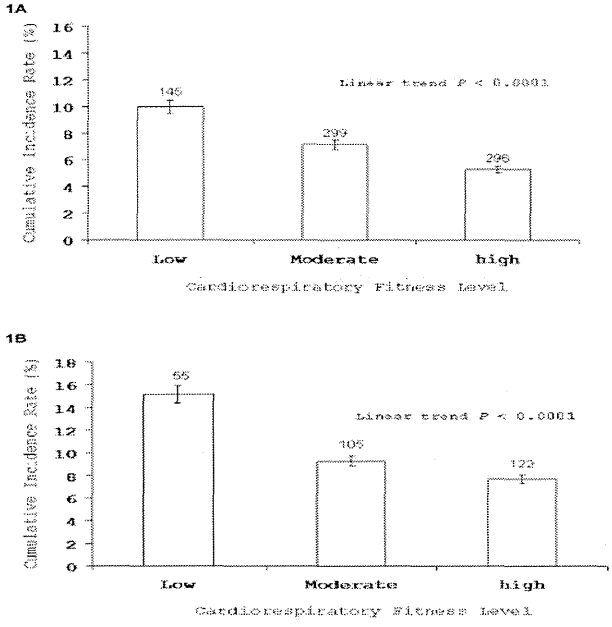

Fig. 1.
Incidence of depressive symptoms by cardiorespiratory fitness categories among men (1A) and women (1B). Bars indicate 95% confidence intervals. The number of cases is shown above the bars.

図表掲載箇所	
概　要 (800字まで)	＜目的＞全身持久力とうつ病との関係のほとんどは断面研究に限定されている。本研究の目的は、全身持久力の高いレベルの者で抑うつ症状発症のリスクが低いかどうか、縦断的に検討した。＜方法＞参加者は、テキサス州ダラスのエアロビクスセンター縦断的研究に参加した、11258人の男性と3085人の女性であった。すべての参加者はベースライン(1970年から1995年)で最大トレッドミル運動負荷試験を受け、1990年、および/または1995年にフォローアップ健康調査を完了した。精神疾患の既往、心血管疾患、または癌を持つ個人は除外した。全身持久力は、運動負荷試験によって定量化し、年齢や性別に低体力(下位20%)、中体力(中央40%)、または高体力(上位40%)に3分類された。抑うつ症状は疫学的研究抑うつ尺度(CES-D)のための20項目の質問票を使用して評価した。CES-Dで16点以上を獲得した人は抑うつ症状を持っていると判定した。＜結果＞フォローアップの12年間で、282の女性と740人の男性が抑うつ症状をと判定された。年齢、ベースライン調査年、フォローアップ健康調査応答年度の調整後、低体力の男性のうつ症状発症のオッズは中体力の男性(95%信頼区間、CI 0.56から0.85、オッズ比、OR 0.69)より31%低く、低体力の男性に比べて高体力(OR 0.49、CI 0.39から0.60)では51%低かった。女性のオッズ比は0.56(CI 0.40から0.80)と0.46(CI 0.32から0.65)であった。
結　論 (200字まで)	低い全身持久力は、他の臨床的危険予測因子とは独立した抑うつ症状発症のリスクであるが示唆された。
エキスパートによるコメント (200字まで)	全身持久力を高めることあるいは、そのために運動や身体活動に取り組むことが抑うつの予防に役立つ可能性を示唆した貴重な研究である。

担当者　　宮地元彦

American Journal of Epidemiology

Vol. 165, No. 12
DOI: 10.1093/aje/kwm031
Advance Access publication April 3, 2007

Original Contribution

Cardiorespiratory Fitness as a Predictor of Nonfatal Cardiovascular Events in Asymptomatic Women and Men

Xuemei Sui[1], Michael J. LaMonte[2], and Steven N. Blair[3]

[1] The Cooper Institute, Dallas, TX.
[2] Department of Social and Preventive Medicine, University of Buffalo, Buffalo, NY.
[3] Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC.

Received for publication August 29, 2006; accepted for publication November 20, 2006.

Prospective data relating cardiorespiratory fitness (CRF) with nonfatal cardiovascular disease (CVD) events are limited to studies in men or studies of combined fatal and nonfatal CVD endpoints. The authors examined the association between CRF and nonfatal CVD events in 20,728 men and 5,909 women without CVD at baseline. All participants performed a maximal treadmill exercise test and completed a follow-up health survey in the Aerobics Center Longitudinal Study (Dallas, Texas) between 1971 and 2004. There were 1,512 events in men and 159 events in women during an average follow-up of 10 years. Across incremental CRF groups, age- and examination year-adjusted event rates per 10,000 person-years were 107.9, 75.2, and 50.3 in men ($p_{trend} < 0.001$) and 41.9, 27.7, and 20.8 in women ($p_{trend} = 0.002$). After further adjustment for smoking, alcohol intake, family history of CVD, and abnormal exercise electrocardiogram responses, hazard ratios were 1.00 (referent), 0.82 (95% confidence interval (CI): 0.72, 0.94), and 0.61 (95% CI: 0.53, 0.71) in men, $p_{trend} < 0.001$, and were 1.00 (referent), 0.74 (95% CI: 0.49, 1.13), and 0.63 (95% CI: 0.40, 0.98) in women, $p_{trend} = 0.05$. After adjustment for other CVD predictors, the association remained significant in men but not in women.

cardiovascular diseases; cerebrovascular accident; exercise; primary prevention; women

Abbreviations: ACLS, Aerobics Center Longitudinal Study; CI, confidence interval; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; SD, standard deviation.

Cardiovascular disease (CVD) continues to exact a large economic and public health toll in the United States, accounting for nearly 1 million deaths and 6 million hospitalizations in 2003 (1). Physical inactivity is a major modifiable CVD risk factor (2) that is associated with increased risk of fatal and nonfatal CVD events in women and men (3–10). Cardiorespiratory fitness (CRF) is an objective, reproducible, physiologic measure that reflects the functional influences of physical activity habits, genetics, and disease status. Because CRF is less prone to misclassification, it may better reflect the adverse health consequences of a sedentary lifestyle than do self-reported physical activity exposures (11).

CRF is inversely associated with CVD mortality in adults (12–16). Few prospective studies have reported on CRF and nonfatal CVD risk, and those that have are limited to studies in men or to combined nonfatal/fatal endpoints (15, 17–21). Although it may be intuitive to expect that CRF would confer protection against nonfatal CVD events in women and men as is seen for fatal CVD, this conclusion can not accurately be drawn from studies of combined nonfatal/fatal events or studies only in men. We examined the prospective association between CRF and nonfatal CVD in women and men in the Aerobics Center Longitudinal Study (ACLS).

Correspondence to Dr. Xuemei Sui, Department of Exercise Science, Arnold School of Public Health, 921 Assembly Street, Columbia, SC 29208 (e-mail: msui@gwm.sc.edu).

MATERIALS AND METHODS

Study population

Participants were 20,728 men and 5,909 women aged 18–83 years who completed a baseline examination at the Cooper Clinic (Dallas, Texas) during 1971–2001. At baseline, all participants were free of known CVD, had normal resting electrocardiograms, and were able to complete an exercise stress test to at least 85 percent of their age-predicted maximal heart rate. All participants responded to at least one mail-back health survey during follow-up. Most participants were Caucasian and from middle and upper socioeconomic strata. Participants provided written consent to participate in the follow-up study.

Baseline examination

The physician's examination and clinical measurements were completed after an overnight fast of at least 12 hours (12, 13). Body mass index (weight (kg)/height $(m)^2$) was computed from measured height and weight. After a brief period of quiet sitting, blood pressure was recorded as the first and fifth Korotkof sounds by use of auscultation methods (22). Serum samples were analyzed for lipids and glucose with standardized automated bioassays. The presence of hypertension, diabetes, and dyslipidemia was based on a history of physician diagnosis or measured phenotypes that met clinical thresholds for each condition. Information on smoking habits (current smoker or not), alcohol intake (drinks per week), and physical activity habits (sedentary or active) was obtained from a questionnaire. Sedentary was defined as reporting no leisure-time physical activity in the 3 months before the examination.

CRF was quantified as the duration of a symptom-limited maximal treadmill exercise test using a modified Balke protocol (12, 23). Exercise duration on this protocol is highly correlated with measured maximal oxygen uptake ($r > 0.90$) (24, 25). The test endpoint was volitional exhaustion or termination by the supervising physician. The mean percentage of age-predicted maximal heart rate achieved during exercise was 100.3 (standard deviation (SD): 7.0) in women and was 101.2 (SD: 7.0) in men. Maximal metabolic equivalents (METs) (1 MET = 3.5 ml of oxygen uptake per kilogram/minute) were estimated from the final treadmill speed and grade (26). In previous ACLS reports that have shown low CRF to be an independent predictor of mortality and nonfatal disease (12, 13, 27), we have defined low, moderate, and high CRF exposures according to the lowest 20 percent, the middle 40 percent, and the upper 40 percent, respectively, of the age- and sex-specific distribution of treadmill duration in the overall ACLS population (table 1). To maintain consistency in our study methods and because a widely accepted clinical categorization of CRF does not exist, we used the above approach. CRF by this definition was positively associated with reported physical activity status. The percentages of participants classified as being physically active in the low, moderate, and high CRF groups were 28.8, 54.9, and 86.8 in men and were 33.5, 59.5, and 86.7 in women ($p_{trend} < 0.001$, each). Abnormal exercise electrocardiogram responses were broadly defined as rhythm and conduction disturbances and ischemic ST-T wave abnormalities as described in detail elsewhere (28). We have found 90 percent agreement between the electrocardiogram interpretation recorded in our database and that of a group of three physicians who read a random sample of 357 records of patients (28).

Assessment of outcomes

CVD events were ascertained from responses to mail-back health surveys in 1982, 1999, and 2004. The aggregate survey response rate across all survey periods in the ACLS is approximately 65 percent. Nonresponse bias is a concern in epidemiologic surveillance, and this issue has been investigated in the ACLS (29). Baseline health histories and clinical measures were similar between responders and nonresponders and between early and late responders (29). Total mortality rates also have been similar between responders and nonresponders (unpublished data). CVD endpoints were defined as diagnosis by a physician of myocardial infarction, stroke, or a coronary revascularization procedure (coronary artery bypass graft or percutaneous coronary intervention). In participants reporting multiple events, the first event was used for analysis. The primary outcome was all CVD events. Secondary outcomes were coronary heart disease events (myocardial infarction, coronary revascularization) and myocardial infarction and stroke as separate endpoints. In a random sample of these endpoints ($n = 50$ each), we applied a standard definition for defining and adjudicating myocardial infarction, revascularization, and stroke (30, 31). The percentage of agreement between reported events and participants' medical records was 88 percent, 100 percent, and 89 percent for myocardial infarction, revascularization, and stroke, respectively.

Statistical analysis

Follow-up time among noncases was computed as the difference between the date of the baseline examination and the date of the last returned survey where the participant reported being free of CVD. Follow-up time among cases was computed as the difference between the baseline examination date and the reported date of the CVD event. If a diagnosis date was not provided, we used the midpoint between the date of the case-finding survey and either the baseline examination date or the date of the last returned survey where the participant reported being free of CVD. The mean follow-up interval in years was 10.4 (SD: 8.1) for men and 10.2 (SD: 7.8) for women. Cox proportional hazards regression analysis was used to estimate hazard ratios and 95 percent confidence intervals of CVD events according to exposure categories. Multivariable analyses included six covariables: age (years), examination year, current smoker (yes/no), alcohol intake (≥5 drinks/week or not), abnormal exercise electrocardiogram responses (present or not), and family history of CVD (present or not). We conducted additional analyses that further adjusted for baseline differences in the following four factors that may be intermediate in the causal pathway between CRF and CVD: body mass index (<25 vs. ≥25 kg/m^2),

TABLE 1. Age- and sex-specific maximal treadmill exercise duration and estimated metabolic equivalent levels of cardiorespiratory fitness, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004*

Age and quintile	Men		Women	
	Duration (minutes)	METs†	Duration (minutes)	METs
20–39 years				
1	<15.0	<10.4	<10.3	<8.2
2	15.0–<18.0	10.4–<11.7	10.3–<13.0	8.2–<9.4
3	18.0–<20.3	11.7–<13.1	13.0–<15.0	9.4–<10.4
4	20.3–≤23.6	13.1–≤14.4	15.0–≤18.0	10.4–≤11.7
5	>23.6	>14.4	>18.0	>11.7
40–49 years				
1	<13.5	<9.9	<8.9	<7.6
2	13.5–<16.1	9.9–<10.8	8.9–<11.0	7.6–<8.5
3	16.1–<19.0	10.8–<12.2	11.0–<13.0	8.5–<9.4
4	19.0–≤22.0	12.2–≤13.5	13.0–≤16.0	9.4–≤10.8
5	>22.0	>13.5	>16.0	>10.8
50–59 years				
1	<11.0	<8.5	<7.0	<6.7
2	11.0–<13.3	8.5–<9.9	7.0–<9.0	6.7–<7.6
3	13.3–<16.0	9.9–<10.8	9.0–<10.7	7.6–<8.5
4	16.0–≤19.2	10.8–≤12.3	10.7–≤13.2	8.5–≤9.6
5	>19.2	>12.3	>13.2	>9.6
≥60 years				
1	<7.8	<7.2	<5.5	<5.8
2	7.8–<10.5	7.2–<8.5	5.5–<7.0	5.8–<6.7
3	10.5–<13.1	8.5–<9.5	7.0–<9.0	6.7–<7.6
4	13.1–≤16.4	9.5–≤10.8	9.0–≤11.3	7.6–≤8.6
5	>16.4	>10.8	>11.3	>8.6

* Treadmill exercise testing was performed by use of a modified Balke-Ware protocol as described in Materials and Methods. Low fitness: quintile 1; moderate fitness: quintiles 2 and 3; high fitness: quintiles 4 and 5. Among participants in the current analysis, the distribution of low, moderate, and high fitness by the above definition was 19%, 40%, and 41% in men and 15%, 35%, and 50% in women.

† METs, metabolic equivalents; 1 MET = 3.5 ml of oxygen uptake per kilogram/minute.

hypertension, diabetes, and dyslipidemia (present or not for each), although authors debate whether or not an exposure-outcome relation should be adjusted for biologic intermediates (32). To reduce the influence of ascertainment bias due to variable survey response patterns, we stratified analyses on survey year by use of the STRATA statement in Proc PHREG (SAS, version 9.1, statistical software; SAS Institute, Inc., Cary, North Carolina). Tests of linear trends across exposure categories were computed with ordinal scoring. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure; no appreciable violations were noted. The potential influence of undetected subclinical disease at baseline was evaluated by excluding events that occurred during the first year of follow-up; little change was noted. All p values are two sided, and $p < 0.05$ was regarded as statistically significant.

RESULTS

There were 1,512 CVD events (489 myocardial infarctions, 290 strokes, 733 revascularizations) during 215,984 man-years of exposure and 159 CVD events (53 myocardial infarctions, 62 strokes, 44 revascularizations) during 60,158 woman-years of exposure. Compared with noncases, individuals who developed CVD were older, had lower CRF, and had higher prevalence of sedentary habits and other major CVD risk factors (table 2).

An inverse gradient ($p_{trend} < 0.001$) of total CVD event rates was observed across CRF groups in men (table 3). After adjustment for covariables, men with moderate and high CRF had an 18 percent and 39 percent lower CVD risk than did men with low CRF ($p_{trend} < 0.001$). The inverse association remained significant after additional adjustment for body mass index, hypertension, diabetes, and

TABLE 2. Baseline characteristics of study participants by sex and cardiovascular disease event status, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004

Characteristic	Men		Women	
	Noncases (n = 19,216) (mean (SD*) or %)	Cases (n = 1,512) (mean (SD) or %)	Noncases (n = 5,750) (mean (SD) or %)	Cases (n = 159) (mean (SD) or %)
Age (years)	43.9 (9.6)	50.3 (8.7)	44.4 (10.2)	52.3 (10.0)
Body mass index (kg/m^2)	26.1 (3.6)	26.4 (3.3)	23.0 (3.8)	23.6 (3.5)
Treadmill time (minutes)	17.6 (5.0)	15.4 (4.8)	13.1 (4.6)	10.5 (4.1)
Maximal METs*	11.5 (2.5)	10.5 (2.3)	9.4 (2.1)	8.2 (1.9)
Lipids (mmol/liter)				
Total cholesterol	5.4 (1.0)	5.9 (1.0)	5.2 (1.0)	5.7 (1.0)
HDL* cholesterol	1.2 (0.3)	1.1 (0.3)	1.6 (0.4)	1.6 (0.4)
Triglycerides	1.5 (1.2)	1.8 (1.3)	1.1 (0.8)	1.3 (0.8)
Fasting blood glucose (mmol/liter)	5.6 (0.9)	5.8 (1.4)	5.2 (0.7)	5.5 (1.2)
Blood pressure (mmHg)				
Systolic	121.7 (13.7)	126.5 (14.9)	113.4 (14.5)	121.7 (15.6)
Diastolic	81.0 (9.7)	83.4 (9.7)	75.7 (9.5)	80.2 (9.5)
Sedentary (%)	36.7	42.1	30.9	34.1
Current smoker (%)	18.3	19.4	9.2	14.5
Alcohol intake (≥5 drinks/week)† (%)	40.6	39.3	18.9	24.5
Abnormal exercise ECG* (%)	4.4	14.6	4.9	13.2
Hypertension‡ (%)	30.7	45.0	17.4	40.9
Diabetes mellitus§ (%)	4.9	9.2	3.0	4.4
Hypercholesterolemia¶ (%)	18.5	34.1	13.5	25.2
Hypertriglyceridemia# (%)	14.7	21.5	4.5	11.3
Low HDL cholesterol** (%)	54.5	68.1	25.9	40.3
Dyslipidemia†† (%)	82.7	91.9	52.6	70.4
Family history of CVD* (%)	15.8	18.5	18.5	17.0

* SD, standard deviation; METs, metabolic equivalents; HDL, high density lipoprotein; ECG, electrocardiogram; CVD, cardiovascular disease.

† One unit of alcohol is defined as 12 ounces (3.41 dl) of beer, 5 ounces (1.421 dl) of wine, or 1.5 ounces (0.4262 dl) of hard liquor.

‡ Hypertension is defined as systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or previous diagnosis by a physician.

§ Diabetes mellitus is defined as a fasting plasma glucose concentration of 7.0 mmol/liter (126 mg/dl) or higher, previous diagnosis by a physician, or insulin use.

¶ Hypercholesterolemia is defined as total cholesterol of 6.20 mmol/liter (240 mg/dl) or higher or previous diagnosis by a physician.

Hypertriglyceridemia is defined as triglycerides of 2.26 mmol/liter (200 mg/dl) or higher.

** Low HDL cholesterol is defined as less than 1.03 mmol/liter (40 mg/dl).

†† Dyslipidemia is defined as the presence of one or more of the above lipid abnormalities.

dyslipidemia ($p_{trend} < 0.001$). Similar inverse patterns of association were observed between CRF and each secondary outcome.

In women (table 4), total CVD event rates were inversely associated with CRF ($p_{trend} = 0.002$). After adjustment for covariables, women with moderate and high CRF had a 26 percent and a 37 percent lower risk of CVD events than did women with low CRF ($p_{trend} = 0.05$). CRF remained inversely associated with CVD risk after additional adjustment for intermediate risk factors, although the trend was not significant ($p_{trend} = 0.30$). CRF was inversely associated with coronary heart disease event rates ($p_{trend} = 0.004$); however, significance was attenuated by adjustment for covariables ($p_{trend} = 0.09$) and intermediate risk factors

TABLE 3. Rates and hazard ratios for cardiovascular disease events by cardiorespiratory fitness groups in men, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004*

Disease event by cardiorespiratory fitness group	No. of events	Rate†	Hazard ratio‡	95% confidence interval‡	Hazard ratio§	95% confidence interval§
Total cardiovascular disease						
Low	345	107.9	1.00	Referent	1.00	Referent
Moderate	664	75.2	0.82	0.72, 0.94	0.89	0.78, 1.02
High	503	50.3	0.61	0.53, 0.71	0.75	0.64, 0.87
p for linear trend		<0.001		<0.001		0.001
Coronary heart disease						
Low	289	88.9	1.00	Referent	1.00	Referent
Moderate	533	60.5	0.81	0.70, 0.94	0.89	0.77, 1.03
High	400	40.3	0.61	0.52, 0.71	0.76	0.64, 0.90
p for linear trend		<0.001		<0.001		0.001
Myocardial infarction						
Low	123	35.6	1.00	Referent	1.00	Referent
Moderate	212	24.1	0.80	0.64, 1.01	0.87	0.69, 1.09
High	154	16.2	0.60	0.46, 0.77	0.73	0.56, 0.96
p for linear trend		<0.001		<0.001		0.02
Stroke						
Low	56	19.0	1.00	Referent	1.00	Referent
Moderate	131	14.8	0.86	0.63, 1.18	0.90	0.65, 1.24
High	103	10.0	0.63	0.45, 0.89	0.71	0.49, 1.01
p for linear trend		<0.001		0.005		0.04

* There were 66,887, 70,222, and 78,872 man-years of follow-up in the low, moderate, and high fitness groups, respectively.

† Rate per 10,000 person-years adjusted for age and examination year.

‡ Adjusted for the above plus current smoking (yes or no), alcohol intake (≥5 drinks/week or not), family history of cardiovascular disease (present or not), and abnormal exercise electrocardiogram responses (present or not).

§ Adjusted for the above plus body mass index (<25 or ≥25 kg/m^2), hypertension, diabetes, or dyslipidemia (present or not for each).

($p_{trend} = 0.49$). Lower myocardial infarction and stroke rates also were observed in women with moderate and high CRF, but these associations were not statistically significant.

We also examined whether CRF predicted CVD events independent of reported physical activity status. Age- and examination year-adjusted rates of total CVD events (per 10,000 person-years) were inversely associated with physical activity status in men (sedentary = 78.4 vs. active = 64.8; $p < 0.001$) but not in women (sedentary = 22.3 vs. active = 28.5; $p = 0.20$). After adjustment for age, examination year, and physical activity status, hazard ratios in the low, moderate, and high CRF groups were 1.00 (referent), 0.77 (95 percent confidence interval (CI): 0.68, 0.89), and 0.55 (95 percent CI: 0.47, 0.64), $p_{trend} < 0.001$, in men and were 1.00 (referent), 0.67 (95 percent CI: 0.44, 1.01), and 0.57 (95 percent CI: 0.33, 0.81), $p_{trend} = 0.005$, in women. Results were similar for secondary outcomes.

We next examined whether other risk predictors modified the association between CRF and total CVD events (tables 5 and 6). In men, after adjustment for age and examination year, each 1-minute increment of maximal exercise was, on average, associated with a 3–9 percent ($p < 0.05$) lower CVD risk in each risk factor group, adverse or not. The consistency in the direction and magnitude of association between CRF and CVD suggested that there was little effect modification across risk factor categories. Further adjustment for the other risk factors eliminated some but not all of the associations. Results were similar for coronary heart disease events and for myocardial infarction (data not shown). In women, the pattern of association between CRF and CVD risk was variable across risk factor groups, and statistical power often was limited by a small number of events.

To examine whether CRF had prognostic value beyond an individual's pretest probability of having a CVD event, we computed CVD rates by CRF levels grouped on the number of major CVD risk factors at baseline (figures 1 and 2). By convention (33), individuals with zero risk factors would be

TABLE 4. Rates and hazard ratios for cardiovascular disease events by cardiorespiratory fitness groups in women, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004*

Disease event by cardiorespiratory fitness group	No. of events	Rate†	Hazard ratio‡	95% confidence interval‡	Hazard ratio§	95% confidence interval§
Total cardiovascular disease						
Low	35	41.9	1.00	Referent	1.00	Referent
Moderate	63	27.7	0.74	0.49, 1.13	0.83	0.54, 1.28
High	61	20.8	0.63	0.40, 0.98	0.78	0.49, 1.23
p for linear trend		0.002		0.05		0.30
Coronary heart disease						
Low	22	26.6	1.00	Referent	1.00	Referent
Moderate	40	17.7	0.79	0.47, 1.35	0.93	0.54, 1.60
High	35	11.8	0.61	0.35, 1.09	0.82	0.45, 1.48
p for linear trend		0.004		0.09		0.49
Myocardial infarction						
Low	12	13.7	1.00	Referent	1.00	Referent
Moderate	24	10.5	0.92	0.45, 1.88	1.08	0.53, 2.22
High	17	6.1	0.62	0.28, 1.36	0.81	0.36, 1.82
p for linear trend		0.03		0.19		0.55
Stroke						
Low	13	15.3	1.00	Referent	1.00	Referent
Moderate	23	10.0	0.65	0.33, 1.31	0.68	0.34, 1.38
High	26	9.1	0.64	0.31, 1.30	0.69	0.33, 1.44
p for linear trend		0.18		0.28		0.40

* There were 19,808, 19,504, and 20,853 woman-years of follow-up in the low, moderate, and high fitness groups, respectively.

† Rate per 10,000 person-years adjusted for age and examination year.

‡ Adjusted for the above plus current smoking (yes or no), alcohol intake (≥5 drinks/week or not), family history of cardiovascular disease (present or not), and abnormal exercise electrocardiogram responses (present or not).

§ Adjusted for the above plus body mass index (<25 or ≥25 kg/m^2), hypertension, diabetes, or dyslipidemia (present or not for each).

classified as low risk (e.g., expected 10-year probability of <10 percent), whereas those with one or more risk factors would have an intermediate to high CVD risk (e.g., 10-year probability of ≥10 percent). In men, we observed inverse gradients of CVD rates across CRF categories within each risk factor stratum ($p < 0.01$ each). Similar inverse patterns of association were seen in women, but the rate differences were not statistically significant.

DISCUSSION

Several prospective studies have shown that CRF is inversely associated with CVD mortality in asymptomatic women and men (12–16). Only a few studies in men have reported on CRF and risk of nonfatal CVD events (17, 18). For evaluation of the true role of CRF in primary CVD prevention, it is important to determine whether CRF is related to incident events that are survived and not merely to mortality, as well as whether protection is conferred in both women and men. The present study demonstrated that higher CRF was associated with significantly lower rates of nonfatal CVD events. The inverse pattern of association was present in women and men and in those with a low or a moderate/high pretest probability of CVD. Significant associations generally persisted after considering the potential confounding or modifying effects of physical activity status and other risk factors, although some associations were attenuated in women because of low statistical power. Inverse patterns of association also were seen between CRF and nonfatal coronary heart disease events and when myocardial infarction and stroke were considered separately. This investigation is one of the largest prospective studies and, to our knowledge, the first in women to relate an objectively measured CRF exposure with the incidence of several nonfatal CVD endpoints in initially asymptomatic adults.

TABLE 5. Hazard ratios for total cardiovascular disease events per 1-minute increment in maximal exercise duration according to cardiovascular disease risk factor categories in men, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004*

Risk factor	Total no.	No. of events	Hazard ratio†	95% confidence interval†	*p* value	Hazard ratio‡	95% confidence interval‡	*p* value
Age (years)								
<55	17,532	1,025	0.94	0.92, 0.95	<0.001	0.95	0.94, 0.97	<0.001
≥55	3,196	487	0.96	0.94, 0.98	<0.001	0.98	0.96, 1.00	0.11
Current smoker								
No	16,922	1,218	0.95	0.94, 0.96	<0.001	0.97	0.96, 0.99	<0.001
Yes	3,806	294	0.93	0.90, 0.96	<0.001	0.94	0.91, 0.96	<0.001
Family history of CVD§								
No	17,411	1,233	0.95	0.94, 0.96	<0.001	0.97	0.96, 0.99	<0.001
Yes	3,317	279	0.91	0.88, 0.94	<0.001	0.93	0.90, 0.95	<0.001
Exercise ECG§ responses								
Normal	19,667	1,292	0.95	0.94, 0.96	<0.001	0.96	0.95, 0.98	<0.001
Abnormal	1,061	220	0.96	0.93, 0.99	0.007	0.97	0.94, 1.01	0.12
Body mass index (kg/m^2)								
18.5–24.9	8,701	573	0.94	0.92, 0.96	<0.001	0.96	0.94, 0.98	<0.001
≥25	12,027	939	0.95	0.94, 0.97	<0.001	0.97	0.96, 0.99	0.001
Hypertension								
No	14,143	832	0.95	0.93, 0.96	<0.001	0.96	0.95, 0.98	<0.001
Yes	6,585	680	0.95	0.94, 0.97	<0.001	0.97	0.95, 0.99	<0.001
Diabetes								
No	19,653	1,373	0.95	0.93, 0.96	<0.001	0.97	0.95, 0.98	<0.001
Yes	1,075	139	0.96	0.93, 1.00	0.048	0.98	0.93, 1.02	0.27
Total cholesterol								
<6.20 mmol/liter (<240 mg/dl)	16,668	997	0.94	0.93, 0.95	<0.001	0.96	0.94, 0.97	<0.001
≥6.20 mmol/liter (≥240 mg/dl)	4,060	515	0.97	0.95, 0.99	0.003	0.98	0.96, 1.00	0.08

* The point and interval estimates are the risk of cardiovascular disease events that are associated, on average, with each 1-minute increment in treadmill exercise duration.

† Adjusted for age and examination year.

‡ Adjusted for the above plus each of the other risk factors in the table.

§ CVD, cardiovascular disease; ECG, electrocardiogram.

Three of the study findings deserve further comment. First, CRF predicted primary CVD events independent of reported physical activity status. Because physical activity assessment was crude in the present study, caution must be taken when considering the implications of this finding. Accurate questionnaire-based assessment of physical activity habits is difficult, particularly in women (11). This may partly explain the lack of association between physical activity and CVD in the present women. Our findings suggest that assessment of CRF in asymptomatic women and men may provide important prognostic information above that obtained from self-reported physical activity habits. Clinicians should, therefore, consider the benefits and feasibility of more routine exercise testing.

In men, the inverse gradient of CVD risk across CRF groups remained significant after adjustment for confounding by age, smoking, family history of CVD, abnormal exercise electrocardiogram responses, and factors that may be intermediate in the causal pathway between CRF and CVD (body mass index, dyslipidemia, hypertension, and diabetes). The present findings of a strong independent association between CRF and nonfatal CVD in men are consistent with previous ACLS findings on CRF and CVD mortality (12, 13), with findings in Finnish men on CRF and nonfatal CVD (17), and with findings from studies that have related CRF (15, 20, 21, 34) or reported physical activity (5, 6, 8) with combined fatal/nonfatal CVD in men. Similar patterns of association generally were seen in women. Lack of

TABLE 6. Hazard ratios for total cardiovascular disease events per 1-minute increment of maximal exercise duration according to cardiovascular disease risk factor categories in women, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004*

Risk factor	Total no.	No. of events	Hazard ratio†	95% confidence interval†	*p* value	Hazard ratio‡	95% confidence interval‡	*p* value
Age (years)								
<55	4,864	93	0.94	0.89, 0.99	0.03	0.96	0.91, 1.02	0.23
≥55	1,045	66	0.96	0.89, 1.04	0.30	0.98	0.90, 1.06	0.61
Current smoker								
No	5,358	136	0.96	0.92, 1.01	0.14	0.98	0.93, 1.03	0.49
Yes	551	23	0.89	0.77, 1.01	0.07	0.87	0.75, 1.00	0.05
Family history of CVD§								
No	4,820	132	0.95	0.91, 1.00	0.05	0.97	0.92, 1.02	0.23
Yes	1,089	27	0.93	0.83, 1.04	0.22	0.97	0.85, 1.10	0.61
Exercise ECG§ responses								
Normal	5,604	138	0.95	0.90, 0.99	0.03	0.96	0.91, 1.01	0.11
Abnormal	305	21	1.00	0.85, 1.17	0.97	1.12	0.93, 1.34	0.24
Body mass index (kg/m^2)								
18.5–24.9	4,644	119	0.94	0.89, 0.94	0.01	0.95	0.90, 1.01	0.07
≥25	1,265	40	1.02	0.91, 1.14	0.80	1.03	0.92, 1.16	0.60
Hypertension								
No	4,846	94	0.97	0.92, 1.03	0.33	1.00	0.94, 1.06	0.93
Yes	1,063	65	0.94	0.87, 1.01	0.07	0.92	0.85, 0.99	0.04
Diabetes								
No	5,732	152	0.94	0.90, 0.99	0.01	0.96	0.91, 1.01	0.08
Yes	177	7	1.09	0.82, 1.44	0.57	1.15	0.73, 1.79	0.55
Total cholesterol								
<6.20 mmol/liter (240 mg/dl)	5,091	119	0.93	0.89, 0.98	0.009	0.95	0.90, 1.01	0.07
≥6.20 mmol/liter (240 mg/dl)	818	40	0.99	0.90, 1.09	0.86	1.03	0.93, 1.13	0.63

* The point and interval estimates are the risk of cardiovascular disease events that are associated, on average, with each 1-minute increment in treadmill exercise duration.

† Adjusted for age and examination year.

‡ Adjusted for the above plus each of the other risk factors in the table.

§ CVD, cardiovascular disease; ECG, electrocardiogram.

a significant association in the fully adjusted model that included biologic intermediates may be due to the small number of cases and is consistent with some (5, 8, 20) but not all (7, 9, 10, 16, 34) studies on physical activity or CRF and CVD risk in women. For example, CRF predicted CVD mortality risk in women and men in the Lipid Research Clinics study (16), whereas it was significantly associated with combined fatal/nonfatal coronary heart disease events in men but not women in the Framingham Heart Study (20). Additional prospective data on CRF exposures and nonfatal CVD events are needed in women to expand on the findings reported here and elsewhere.

A second major finding was that the inverse association between CRF and CVD generally was consistent in strata of other CVD predictors. The prognostic value of CRF is particularly noteworthy in men who were older and who had diabetes, exercise electrocardiogram abnormalities, or coexisting risk factors at baseline. A sharp rise in the risk of a first CVD event occurs in adults aged 45–60 years (1). We observed that men aged 55 years or older had a threefold higher risk of CVD events than did their younger counterparts. Diabetes and multiple coexisting risk factors now are seen as coronary risk equivalents in asymptomatic adults (33). In our study, 10-year CVD risk was 50 percent greater in men with diabetes and was threefold greater in men with two or more risk factors than in men without either condition. Abnormal exercise electrocardiogram responses also are predictive of CVD events (20, 21, 28) and were

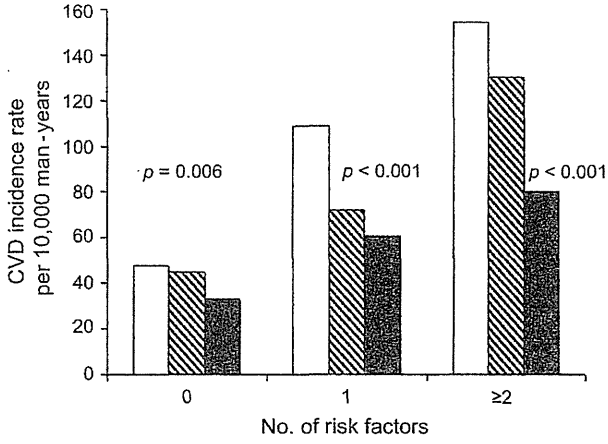

FIGURE 1. Age- and examination year-adjusted rates of total cardiovascular disease (CVD) events (per 10,000 person-years) by levels of cardiorespiratory fitness and number of major CVD risk factors (current smoking, hypertension, hypercholesterolemia, diabetes, and family history of CVD) in 20,728 men, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004. White bars represent low fitness; striped bars, moderate fitness; and black bars, high fitness. The *p* values are for a test of linear trend across cardiorespiratory fitness groups. The numbers of men (and cases) in the low, moderate, and high fitness groups were 878 ($n = 42$), 2,886 ($n = 143$), and 4,099 ($n = 154$) in those with zero risk factors; 1,548 ($n = 120$), 3,422 ($n = 266$), and 3,131 ($n = 226$) in those with one risk factor; and 1,541 ($n = 183$), 1,987 ($n = 255$), and 1,236 ($n = 123$) in those with two or more risk factors.

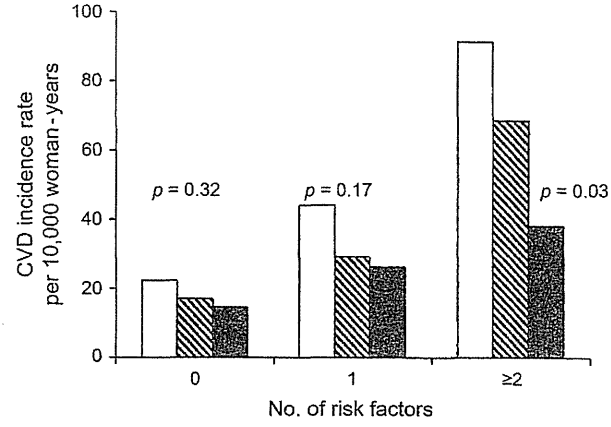

FIGURE 2. Age- and examination year-adjusted rates of total cardiovascular disease (CVD) events (per 10,000 person-years) by levels of cardiorespiratory fitness and number of major CVD risk factors (current smoking, hypertension, hypercholesterolemia, diabetes, and family history of CVD) in 5,909 women, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004. White bars represent low fitness; striped bars, moderate fitness; and black bars, high fitness. The *p* values are for a test of linear trend across cardiorespiratory fitness groups. The numbers of women (and cases) in the low, moderate, and high fitness groups were 355 ($n = 8$), 1,068 ($n = 21$), and 1,690 ($n = 25$) in those with zero risk factors; 349 ($n = 14$), 725 ($n = 22$), and 963 ($n = 24$) in those with one risk factor; and 178 ($n = 13$), 303 ($n = 20$), and 278 ($n = 12$) in those with two or more risk factors.

associated with a twofold higher risk of CVD events among men in our study. Even in these high-risk subgroups of men, higher functional capacity was associated with significantly lower CVD event rates. Stratified analyses were more variable in women; however, greater functional capacity tended to be associated with lower CVD risk across risk factor strata. CVD rates also were lower across incremental CRF groups in women with two or more risk factors. The statistical significance of these cross-tabulations in women was limited by the small number of events.

Collectively, the present results suggest that CRF is an important prognostic factor for nonfatal CVD in asymptomatic men beyond information obtained from the exercise electrocardiogram and traditional risk factors. Higher CRF is protective against CVD events in those with a moderate/high or a low pretest probability of CVD. Assessing functional capacity in asymptomatic women likely is of similar benefit to CVD risk assessment as in men (8); however, additional data are needed to confirm the suggestive findings reported here.

A third noteworthy issue is the variety of CVD endpoints that were related to baseline CRF levels. A recent review of published prospective data on physical activity, CRF, and CVD outcomes indicated that the strongest inverse associations were for CVD mortality in men, and that additional data are needed in women and on nonfatal endpoints such as myocardial infarction and stroke (35). In the current study, CRF was not only inversely related with total CVD events but also with myocardial infarction and with myocardial infarction and coronary revascularization combined. Myocardial infarction or sudden death is the first clinical manifestation in many adults, among whom risk factors often are normal or only slightly elevated (33). The findings reported herein and elsewhere (13, 16, 17, 20) suggest that low CRF is a significant predictor of atherothrombotic CVD events independent of the presence or absence of traditional risk factors. Assessment of CRF in clinical settings could, therefore, be an important tool to facilitate more effective primary CVD prevention. Effective strategies are needed to better integrate exercise testing into CVD risk assessment (36).

CRF also was inversely associated with stroke incidence in men, which is consistent with findings on CRF and stroke mortality in the ACLS (37) and in Finnish studies (19). Others have reported inverse associations between physical activity and stroke in women (4, 5). The inverse trend in stroke events across CRF groups was not significant in the present women, which may partly be due to the small number of stroke events. We were not able to differentiate between hemorrhagic and ischemic strokes, and stroke subtype modifies the association between physical activity and stroke risk (4, 38). Additional studies on activity, fitness, and stroke are needed to expand on our suggestive findings of an inverse association.

Strengths of the current study include the extensive baseline examination to detect subclinical disease, the use of measured risk factors and of maximal exercise testing to quantify CRF, the large person-years of follow-up, and the

variety of CVD endpoints. We also accounted for variable patterns of survey responses in our analyses, an approach not typically used in cohort studies such as ours (4, 9, 38). The inverse associations generally were graded and independent of traditional risk factors, which strengthens causal inferences. Biologic plausibility for these associations may, for example, be through enhanced endothelial cell function and coronary flow reserve, reduced myocardial oxygen demand under a variety of circumstances, a higher myocardial arrhythmia threshold, improved endogenous thrombolytic activity, and lower levels of circulating atherothrombotic cytokines that may promote coronary plaque stabilization (11).

The homogeneity of our population sample in sociodemographic factors enhances the internal validity of our findings by reducing confounding by these factors. Although the self-referred origin and homogeneity of our cohort also may be seen as a weakness, we believe that our data are no less meaningful than those from population samples of adults referred to exercise testing for clinical reasons (39) or data from other selected cohorts that have been influential in preventive cardiology (6, 14, 20). Our findings should be generalized carefully to other adult populations. We did not have sufficient information on medication usage, menopausal status, or dietary habits to include in our analysis. It is possible that residual confounding by these factors may exist, although it seems unlikely that it would account for all of the observed association between CRF and CVD. Future studies should include such information to expand on the findings reported here. Women tend to manifest CVD events 10 years later than men. In the present study, the age distribution in women was insufficient for grouped analysis beyond 55 years of age. Genetics clearly contribute to maximal CRF (40, 41). Nonetheless, CRF can be enhanced in most individuals through participation in moderate and vigorous physical activities, such as brisk walking, bicycling, and jogging, for 30 minutes or more on most days of the week (2).

We conclude that CRF is a significant determinant of nonfatal primary CVD events in women and men. Assessment of CRF provides important prognostic information independent of exercise electrocardiogram responses and traditional risk factors, and in those with high and low pretest probabilities of CVD. Exercise testing to assess functional capacity may enhance CVD risk stratification beyond conventional office-based methods in asymptomatic adults. We believe that clinicians should consider the benefits of assessing CRF and that they should vigilantly counsel their sedentary patients to become more physically active and to improve their CRF as a cornerstone of primary CVD prevention.

ACKNOWLEDGMENTS

Supported by National Institute of Health grants AG06945 and HL62508 and by the Communities Foundation of Texas on recommendation of Nancy Ann and Ray L. Hunt.

The authors thank Dr. Kenneth H. Cooper for establishing the Aerobics Center Longitudinal Study, the Cooper Clinic physicians and technicians for collecting the baseline data, staff at the Cooper Institute for data entry and data management, and Melba Morrow for editorial assistance.

Conflict of interest: none declared.

REFERENCES

1. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:e85–151.
2. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation 2003;107:3109–16.
3. Leon AS, Connett J, Jacobs DR Jr, et al. Leisure-time physical activity levels and risk of coronary heart disease and death. The Multiple Risk Factor Intervention Trial. JAMA 1987; 258:2388–95.
4. Hu G, Sarti C, Jousilahti P, et al. Leisure time, occupational, and commuting physical activity and the risk of stroke. Stroke 2005;36:1994–9.
5. Salonen JT, Puska P, Tuomilehto J. Physical activity and risk of myocardial infarction, cerebral stroke and death: a longitudinal study in eastern Finland. Am J Epidemiol 1982;115: 526–37.
6. Paffenbarger RS Jr, Hyde RT, Wing AL, et al. A natural history of athleticism and cardiovascular health. JAMA 1984;252: 491–5.
7. Rockhill B, Willett WC, Manson JE, et al. Physical activity and mortality: a prospective study among women. Am J Public Health 2001;91:578–83.
8. O'Connor GT, Hennekens CH, Willett WC, et al. Physical exercise and reduced risk of nonfatal myocardial infarction. Am J Epidemiol 1995;142:1147–56.
9. Lee IM, Rexrode KM, Cook NR, et al. Physical activity and coronary heart disease in women: is "no pain, no gain" passe? JAMA 2001;285:1447–54.
10. Manson JE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med 2002;347:716–25.
11. Haskell WL, Leon AS, Caspersen CJ, et al. Cardiovascular benefits and assessment of physical activity and physical fitness in adults. Med Sci Sports Exerc 1992;24(suppl 6): S201–20.
12. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, et al. Physical fitness and all-cause mortality: a prospective study of healthy men and women. JAMA 1989;262:2395–401.
13. Blair SN, Kampert JB, Kohl HW, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA 1996;276:205–10.
14. Ekelund LG, Haskell WL, Johnson JL, et al. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. N Engl J Med 1988;319:1379–84.
15. Lakka TA, Venalainen JM, Rauramaa R, et al. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. N Engl J Med 1994;330:1549–54.

16. Mora S, Redberg RF, Cui Y, et al. 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. JAMA 2003;290:1600–7.
17. Laukkanen JA, Kurl S, Salonen R, et al. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective population-based cohort study. Eur Heart J 2004;25:1428–37.
18. Miller GJ, Cooper JA, Beckles GL. Cardiorespiratory fitness, all-cause mortality, and risk of cardiovascular disease in Trinidadian men—the St James survey. Int J Epidemiol 2005; 34:1387–94.
19. Kurl S, Laukkanen JA, Rauramaa R, et al. Cardiorespiratory fitness and the risk for stroke in men. Arch Intern Med 2003; 163:1682–8.
20. Balady GJ, Larson MG, Vasan RS, et al. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. Circulation 2004;110:1920–5.
21. Bodegard J, Erikssen G, Bjornholt JV, et al. Reasons for terminating an exercise test provide independent prognostic information: 2014 apparently healthy men followed for 26 years. Eur Heart J 2005;26:1394–401.
22. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals. Part 1. Blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension 2005;45:142–61.
23. Balke B, Ware RW. An experimental study of physical fitness in Air Force personnel. U S Armed Forces Med J 1959;10: 675–88.
24. Pollock ML, Bohannon RL, Cooper KH, et al. A comparative analysis of four protocols for maximal treadmill stress testing. Am Heart J 1976;92:39–46.
25. Pollock ML, Foster C, Schmidt D, et al. Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. Am Heart J 1982; 103:363–73.
26. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000.
27. Barlow CE, LaMonte MJ, FitzGerald SJ, et al. Cardiorespiratory fitness is an independent predictor of hypertension incidence among initially normotensive healthy women. Am J Epidemiol 2006;163:142–50.
28. Gibbons LW, Mitchell TL, Wei M, et al. Maximal exercise test as a predictor of risk for mortality from coronary heart disease in asymptomatic men. Am J Cardiol 2000;86:53–8.
29. Macera CA, Jackson KL, Davis DR, et al. Patterns of nonresponse to a mail survey. J Clin Epidemiol 1990;43:1427–30.
30. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: a statement from the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute. Circulation 2003;108:2543–9.
31. Kelly-Hayes M, Robertson JT, Broderick JP, et al. The American Heart Association Stroke Outcome Classification. Stroke 1998;29:1274–80.
32. Manson JE, Stampfer MJ, Hennekens CH, et al. Body weight and longevity. A reassessment. JAMA 1987;257:353–8.
33. Greenland P, Smith SC Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. Circulation 2001;104:1863–7.
34. Roger VL, Jacobsen SJ, Pellikka PA, et al. Prognostic value of treadmill exercise testing: a population-based study in Olmsted County, Minnesota. Circulation 1998;98:2836–41.
35. Kohl HW 3rd. Physical activity and cardiovascular disease: evidence for a dose response. Med Sci Sports Exerc 2001;33(suppl 6):S472–83.
36. Lauer M, Froelicher ES, Williams M, et al. Exercise testing in asymptomatic adults: a statement for professionals from the American Heart Association Council on Clinical Cardiology, Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation 2005;112:771–6.
37. Lee CD, Blair SN. Cardiorespiratory fitness and stroke mortality in men. Med Sci Sports Exerc 2002;34:592–5.
38. Hu FB, Stampfer MJ, Colditz GA, et al. Physical activity and risk of stroke in women. JAMA 2000;283:2961–7.
39. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
40. Bouchard C, Daw EW, Rice T, et al. Familial resemblance for VO_{2max} in the sedentary state: the HERITAGE family study. Med Sci Sports Exerc 1998;30:252–8.
41. Bouchard C, An P, Rice T, et al. Familial aggregation of VO_{2max} response to exercise training: results from the HERITAGE family study. J Appl Physiol 1999;87:1003–8.

論文名	Cardiorespiratory fitness as a predictor of nonfatal cardiovascular events in asymptomatic women and men
著 者	Sui X, LaMonte MJ, Blair SN
雑誌名	Am J Epidemiol
巻・号・頁	165　1413-1423
発行年	2007
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/?term=17406007

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	男女混合	( )		( )		( )
	年齢	18-83歳			( )		前向き研究
	対象数	10000以上			( )		( )
調査の方法	実測	( )					
アウトカム	予 防	心疾患予防	なし	なし	なし	( )	( )
	維持・改善	なし	なし	なし	なし	( )	( )

図 表

TABLE 3. Rates and hazard ratios for cardiovascular disease events by cardiorespiratory fitness groups in men, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004*

Disease event by cardiorespiratory fitness group	No. of events	Rate†	Hazard ratio‡	95% confidence interval‡	Hazard ratio§	95% confidence interval§
Total cardiovascular disease						
Low	345	107.9	1.00	Referent	1.00	Referent
Moderate	664	75.2	0.82	0.72, 0.94	0.89	0.78, 1.02
High	503	50.3	0.61	0.53, 0.71	0.75	0.64, 0.87
p for linear trend		<0.001		<0.001		0.001
Coronary heart disease						
Low	289	88.9	1.00	Referent	1.00	Referent
Moderate	533	60.5	0.81	0.70, 0.94	0.89	0.77, 1.03
High	400	40.3	0.61	0.52, 0.71	0.76	0.64, 0.90
p for linear trend		<0.001		<0.001		0.001
Myocardial infarction						
Low	123	35.6	1.00	Referent	1.00	Referent
Moderate	212	24.1	0.80	0.64, 1.01	0.87	0.69, 1.09
High	154	16.2	0.60	0.46, 0.77	0.73	0.56, 0.96
p for linear trend		<0.001		<0.001		0.02
Stroke						
Low	56	19.0	1.00	Referent	1.00	Referent
Moderate	131	14.8	0.86	0.63, 1.18	0.90	0.65, 1.24
High	103	10.0	0.63	0.45, 0.89	0.71	0.49, 1.01
p for linear trend		<0.001		0.005		0.04

* There were 66,887, 70,222, and 78,872 man-years of follow-up in the low, moderate, and high fitness groups, respectively.
† Rate per 10,000 person-years adjusted for age and examination year.
‡ Adjusted for the above plus current smoking (yes or no), alcohol intake (≥5 drinks/week or not), family history of cardiovascular disease (present or not), and abnormal exercise electrocardiogram responses (present or not).
§ Adjusted for the above plus body mass index (<25 or ≥25 kg/m^2), hypertension, diabetes, or dyslipidemia (present or not for each).

TABLE 4. Rates and hazard ratios for cardiovascular disease events by cardiorespiratory fitness groups in women, Aerobics Center Longitudinal Study, Dallas, Texas, 1971–2004*

Disease event by cardiorespiratory fitness group	No. of events	Rate†	Hazard ratio‡	95% confidence interval‡	Hazard ratio§	95% confidence interval§
Total cardiovascular disease						
Low	35	41.9	1.00	Referent	1.00	Referent
Moderate	63	27.7	0.74	0.49, 1.13	0.83	0.54, 1.28
High	61	20.8	0.63	0.40, 0.98	0.78	0.49, 1.23
p for linear trend		0.002		0.05		0.30
Coronary heart disease						
Low	22	26.6	1.00	Referent	1.00	Referent
Moderate	40	17.7	0.79	0.47, 1.35	0.93	0.54, 1.60
High	35	11.8	0.61	0.35, 1.09	0.82	0.45, 1.48
p for linear trend		0.004		0.09		0.49
Myocardial infarction						
Low	12	13.7	1.00	Referent	1.00	Referent
Moderate	24	10.5	0.92	0.45, 1.88	1.08	0.53, 2.22
High	17	6.1	0.62	0.28, 1.36	0.81	0.36, 1.82
p for linear trend		0.03		0.19		0.55
Stroke						
Low	13	15.3	1.00	Referent	1.00	Referent
Moderate	23	10.0	0.65	0.33, 1.31	0.68	0.34, 1.38
High	26	9.1	0.64	0.31, 1.30	0.69	0.33, 1.44
p for linear trend		0.18		0.28		0.40

* There were 19,808, 19,504, and 20,853 woman-years of follow-up in the low, moderate, and high fitness groups, respectively.
† Rate per 10,000 person-years adjusted for age and examination year.
‡ Adjusted for the above plus current smoking (yes or no), alcohol intake (≥5 drinks/week or not), family history of cardiovascular disease (present or not), and abnormal exercise electrocardiogram responses (present or not).
§ Adjusted for the above plus body mass index (<25 or ≥25 kg/m^2), hypertension, diabetes, or dyslipidemia (present or not for each).

図表掲載箇所	P1417, Table3, P1418, Table4
概 要 (800字まで)	本研究は、アメリカのThe Aerobics Center Longitudinal Studyに参加した男性20,728名と女性5,909名を対象に平均10年間の追跡調査を行い、全身持久力と非致死性心疾患発症リスクとの関連を検討したものである。全身持久力は、最大酸素摂取量を最大トレッドミルテストにより測定し、性年齢別に調整後、男性で下位の19%をLow、次の40%をModerate、上位40%をHighに、女性で下位の15%、次の35%、上位50%をそれぞれLow、Moderate、Highの3群に分類した。男性で、全身持久力がLowの集団と比較すると、Highの集団で全心疾患発症リスク(0.75(95%信頼区間:0.64-0.87))、冠動脈性心疾患発症リスク(0.76(0.64-0.90))、および心筋梗塞発症リスク(0.73(0.56-0.96))が有意に低下した。女性ではいかなる関連もみられなかった。
結 論 (200字まで)	本研究におけるコホートでは、男性で、全身持久力の向上が非致死性心疾患発症リスクを低下させることが明らかとなった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に使用された研究である。女性で関連が見られなかったのはサンプルサイズの問題であると推測される。

担当者:久保絵里子・村上晴香・宮地元彦

ORIGINAL CONTRIBUTION

Cardiorespiratory Fitness and Adiposity as Mortality Predictors in Older Adults

Xuemei Sui, MD
Michael J. LaMonte, PhD
James N. Laditka, PhD
James W. Hardin, PhD
Nancy Chase, BS
Steven P. Hooker, PhD
Steven N. Blair, PED

Context Although levels of physical activity and aerobic capacity decline with age and the prevalence of obesity tends to increase with age, the independent and joint associations among fitness, adiposity, and mortality in older adults have not been adequately examined.

Objective To determine the association among cardiorespiratory fitness ("fitness"), adiposity, and mortality in older adults.

Design, Setting, and Patients Cohort of 2603 adults aged 60 years or older (mean age, 64.4 [SD, 4.8] years; 19.8% women) enrolled in the Aerobics Center Longitudinal Study who completed a baseline health examination during 1979-2001. Fitness was assessed by a maximal exercise test, and adiposity was assessed by body mass index (BMI), waist circumference, and percent body fat. Low fitness was defined as the lowest fifth of the sex-specific distribution of maximal treadmill exercise test duration. The distributions of BMI, waist circumference, and percent body fat were grouped for analysis according to clinical guidelines.

Main Outcome Measure All-cause mortality through December 31, 2003.

Results There were 450 deaths during a mean follow-up of 12 years and 31 236 person-years of exposure. Death rates per 1000 person-years, adjusted for age, sex, and examination year were 13.9, 13.3, 18.3, and 31.8 across BMI groups of 18.5-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0, respectively ($P=.01$ for trend); 13.3 and 18.2 for normal and high waist circumference (≥88 cm in women; ≥102 cm in men) ($P=.004$); 13.7 and 14.6 for normal and high percent body fat (≥30% in women; ≥25% in men) ($P=.51$); and 32.6, 16.6, 12.8, 12.3, and 8.1 across incremental fifths of fitness ($P<.001$ for trend). The association between waist circumference and mortality persisted after further adjustment for smoking, baseline health status, and BMI ($P=.02$) but not after additional adjustment for fitness ($P=.86$). Fitness predicted mortality risk after further adjustment for smoking, baseline health, and either BMI, waist circumference, or percent body fat ($P<.001$ for trend).

Conclusions In this study population, fitness was a significant mortality predictor in older adults, independent of overall or abdominal adiposity. Clinicians should consider the importance of preserving functional capacity by recommending regular physical activity for older individuals, normal-weight and overweight alike.

JAMA. 2007;298(21):2507-2516 www.jama.com

POPULATION AGING, OBESITY, AND physical inactivity are notable public health challenges. By 2030, 22% of the US population, or 70 million individuals, will be older than 65 years.[1] Approximately 32% of Americans are obese,[2] and the vast majority of US adults do not engage in regular physical activity.[3] A high proportion of adults have levels of functional capacity that are low enough to increase mortality risk.[4] Levels of physical activity and functional aerobic capacity each decline steadily with age,[5,6] while the prevalence of obesity tends to increase with age. Total medical expenditures associated with inactivity and obesity are greatest in the older population, a fact that underscores the significant economic burden to society posed by an aging population of inactive obese individuals.[7]

Prospective studies provide convincing evidence that obesity and physical inactivity each can produce excess mortality risk in middle-aged adults.[8-15] However, data regarding associations among obesity, physical activity, and survival in older adults are sparse and largely equivocal.[16-25] Some studies,[17,18,20-24] but not all,[19,25] have found that obesity-related mortality risk is reduced at older ages. Most of these studies have used body mass index (BMI) as a crude measure of adiposity.[17,19-21,25] Few studies have simultaneously examined physical activity levels and clinical measures of adiposity, such as waist circumference[22-24] or percent body fat,[26,27] in relation to mortality specifically in older adults.[17] Cardiorespiratory fitness (hereafter referred to as "fit-

Author Affiliations: Departments of Exercise Science (Drs Sui, Hooker, and Blair and Ms Chase) and Epidemiology and Biostatistics (Drs Laditka, Hardin, and Blair), Center for Health Services and Policy Research (Dr Hardin), and Prevention Research Center (Dr Hooker), University of South Carolina, Columbia; Department of Social and Preventive Medicine, University at Buffalo, Buffalo, NY (Dr LaMonte); and Department of Kinesiology, Health Promotion, and Recreation, University of North Texas, Denton (Dr Blair).
Corresponding Author: Xuemei Sui, MD, MPH, Department of Exercise Science, Arnold School of Public Health, University of South Carolina, 921 Assembly St, Columbia, SC 29208 (msui@gwm.sc.edu).

ness") is an objective reproducible measure that reflects the functional consequences of recent physical activity habits, disease status, and genetics.[28] To our knowledge, no study has been conducted on the independent and joint associations among fitness, various clinical measures of adiposity, and mortality in older women and men. We therefore examined these associations in a cohort of older adults enrolled in the Aerobics Center Longitudinal Study.

METHODS

Study Population

The present study comprised 2087 men and 516 women aged 60 years or older (mean, 64.4 [SD, 4.8] years; range, 60-100). All participants completed a baseline clinical examination during 1979-2001 at the Cooper Clinic (Dallas, Texas). Study participants came to the clinic for periodic preventive health examinations and for counseling regarding diet, exercise, and other lifestyle factors associated with increased risk of chronic disease. Many participants were referred by their employers for the examination; others were referred by their personal physicians or were self-referred.

Inclusion criteria for the current analysis required participants to have a maximal treadmill exercise test at baseline, during which they must have achieved at least 85% of their age-predicted maximal heart rate (220 minus age in years). We excluded participants with a BMI less than 18.5 (calculated as weight in kilograms divided by height in meters squared) at the baseline examination and those younger than 60 years at baseline. We classified participants by race/ethnicity based on their self-report when checking specific categories on the medical history. These categories are a standard part of the medical history, and we did not collect this information for the present report. The majority of the study participants were white, well-educated, and from middle to upper socioeconomic strata. All participants provided written informed consent to participate in the follow-up study, and the Cooper Institute institutional review board approved the study annually.

Clinical Data

Participants completed a comprehensive health evaluation that included self-reported personal and family health histories; a standardized medical examination by a physician; fasting blood levels of total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose; and a maximal treadmill exercise test. Body mass index was calculated from measured weight and height. Percent body fat was assessed with hydrostatic weighing, the sum of 7 skin-fold measures, or both, following standardized protocols.[29] Detailed description of our hydrodensitometry procedures has been published.[13] Fat mass (in kilograms) was calculated as weight (in kilograms) × (percent body fat ÷ 100). Fat-free mass (FFM) (in kilograms) was calculated as weight − fat mass.[13] Waist circumference was measured level with the umbilicus.

Adiposity exposure groups were based on standard clinical definitions for BMI (normal weight, 18.5-24.9; overweight, 25.0-29.9; obese class I, 30.0-34.9; and obese class II, ≥35.0), waist circumference (normal, <88.0 cm for women and <102.0 cm for men; indicating abdominal obesity, ≥88.0 cm for women and ≥102.0 cm for men), and percent body fat (normal, <30% for women and <25% for men; obese, ≥30% for women and ≥25% for men).[30] Because there is no consensus clinical categorization for FFM, groups were based on quintiles of the FFM distribution.

Blood pressure was measured with standard auscultatory methods after the participant had been seated for 5 minutes. Systolic and diastolic blood pressures were recorded as the first and fifth Korotkof sounds, respectively. Abnormal exercise electrocardiogram (ECG) responses included rhythm and conduction disturbances and ischemic ST-T wave abnormalities, as described in detail elsewhere.[31] Previously, we found 90% agreement between the ECG interpretation recorded in our database and that of a group of 3 physicians who read a random sample of 357 patient records.[31] Total cholesterol levels were determined in the Cooper Clinic clinical chemistry laboratory, which participates in and meets the quality control standards of the US Centers for Disease Control and Prevention lipid standardization program.

Baseline medical conditions, such as previous myocardial infarction, stroke, hypertension, diabetes, and hypercholesterolemia, were defined as a history of physician diagnosis, measured phenotypes that met clinical thresholds for a specific condition, or, when appropriate, the combination of both methods. Smoking habits (current smoker or not) and physical activity habits (physically inactive or not) were obtained from a standardized questionnaire.

We determined fitness using a maximal treadmill exercise test and a modified Balke protocol[32] as previously described.[12,13,33,34] Total test time correlates highly ($r \geq 0.92$) with directly measured maximal oxygen uptake in men[35] and women.[36] Participants were encouraged not to hold onto the treadmill handrails. The test end point was volitional exhaustion or termination by the physician for medical reasons.

Fitness was grouped for our primary analysis using quintiles of the sex-specific distribution of maximal exercise duration in the overall Aerobics Center Longitudinal Study population. In secondary analyses we grouped fitness into a binary variable, low fitness (the lowest 20%) compared with higher fitness (the remaining 80%).[33] Individuals in the lowest 20% within each sex group were classified as physically unfit and all others as physically fit.[33] While no consensus clinical definition of low fitness currently exists, the approach we used for defining low fitness is a standardized method in the Aerobics Center Longitudinal Study. Previous reports from that study,[12,13,33,34] including an earlier report in elderly participants,[37] have shown that low fit-

ness by this definition is an independent predictor of morbidity and mortality.

To standardize interpretation of exercise test performance, maximal metabolic equivalent tasks (METs) (1 MET = 3.5 mL O_2 uptake/kg per minute) were estimated based on the final treadmill speed and grade.[38] Exercise durations (in minutes) for the incremental fifths of fitness categories for men were less than 7.8, 7.8-10.4, 10.5-13.0, 13.1-16.4, and greater than 16.4. The corresponding durations for women were less than 5.5, 5.5-6.9, 7.0-8.9, 9.0-11.3, and greater than 11.3. In equivalent MET values, the thresholds that defined these categories were 7.2, 8.5, 9.5, and 10.8 METs for men and 5.8, 6.7, 7.6, and 8.6 METs for women.

Mortality Surveillance

Vital status was ascertained using the National Death Index and death certificates from states in which participant deaths occurred. More than 95% of mortality follow-up is complete by these methods. Causes of death were identified using *International Classification of Diseases, Ninth Revision* codes before 1999, and *International Classification of Diseases, Tenth Revision* codes (in brackets) during 1999-2003 (cardiovascular disease, 390-449.9 [I00-I78]; coronary heart disease, 410-414, 429.2 [I20-I25]; and cancer, 140-208 [C00-C97]).

Statistical Analyses

The follow-up interval was computed from the date of a participant's baseline examination until the date of death for decedents, or until December 31, 2003, for survivors. Descriptive statistics summarized baseline characteristics by survival status and by fitness levels. Groups were compared using *t* tests, χ^2 tests, and *F* tests. We used the Fisher Z transformation to examine the correlations among adiposity measures and exercise duration by assessing Pearson coefficients. We used Cox proportional hazard models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality according to fitness, adiposity, age, smoking status, abnormal exercise ECG responses, and baseline medical condition exposure categories. Multivariate analyses included the following 6 baseline covariates: age (years), sex, examination year, current smoker, abnormal exercise ECG responses, and chronic medical conditions (cardiovascular disease [myocardial infarction or stroke], hypertension, diabetes, or hypercholesterolemia). The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure; no appreciable violations were noted.

Tests of linear trends in mortality rates and risk estimates across exposure categories were computed using ordinal scoring for fitness, FFM, and age

Table 1. Baseline Characteristics by Vital Status in 2603 Older Adults—Aerobics Center Longitudinal Study, 1979-2003

Characteristic	All (n = 2603)	Survivors (n = 2153)	Decedents (n = 450)	*P* Value[a]
Women, No. (%)	516 (19.8)	464 (21.6)	52 (11.6)	<.001
Age, mean (SD), y	64.4 (4.8)	64.2 (4.7)	65.7 (5.0)	<.001
BMI, mean (SD)[b]	26.3 (3.7)	26.4 (3.7)	26.2 (3.9)	.29
BMI-defined weight groups, No. (%)				
18.5-24.9	1020 (39.2)	828 (38.5)	192 (42.7)	.10
25.0-29.9	1206 (46.3)	1010 (46.9)	196 (43.6)	.19
30.0-34.9	316 (12.1)	266 (12.4)	50 (11.1)	.46
≥35.0	61 (2.3)	49 (2.3)	12 (2.7)	.62
Waist circumference, mean (SD), cm	90.3 (19.9)	90.4 (19.3)	90.3 (22.6)	.98
Abdominal obesity, No. (%)[c]	643 (24.7)	528 (24.5)	115 (25.6)	.64
Adiposity measures, mean (SD)[d]				
Percent body fat	26.5 (5.4)	26.5 (5.4)	26.6 (5.6)	.67
Fat-free mass, kg	58.4 (9.4)	58.4 (9.5)	58.5 (8.7)	.89
Fat mass, kg	21.6 (7.2)	21.5 (7.1)	21.8 (7.8)	.40
Treadmill time, mean (SD), min	12.6 (4.8)	12.9 (4.7)	11.0 (4.8)	<.001
Maximal METs, mean (SD)	9.1 (2.2)	9.3 (2.2)	8.4 (2.2)	<.001
Abnormal exercise ECG responses, No. (%)	532 (20.4)	405 (18.8)	127 (28.2)	<.001
Lipids, mean (SD), mg/dL				
Total cholesterol	216.5 (42.2)	216.2 (41.0)	217.8 (47.6)	.51
HDL-C	50.1 (15.6)	50.8 (15.8)	47.1 (14.1)	<.001
Triglycerides	136.7 (85.9)	136.2 (86.5)	139.3 (83.4)	.49
Fasting blood glucose, mean (SD), mg/dL	106.1 (25.2)	105.7 (24.3)	107.9 (29.4)	.15
Physically inactive, No. (%)[e]	657 (25.2)	546 (25.4)	111 (24.7)	.76
Current smoker, No. (%)	235 (9.0)	175 (8.1)	60 (13.3)	<.001
Metabolic syndrome, No. (%)[f]	644 (24.7)	505 (23.5)	139 (30.9)	<.001
Chronic medical condition, No. (%)[g]				
Cardiovascular disease	139 (5.3)	93 (4.3)	46 (10.2)	<.001
Diabetes	266 (10.2)	212 (9.9)	54 (12.0)	.17
Hypertension	1241 (47.7)	993 (46.1)	248 (55.1)	<.001
Hypercholesterolemia	1034 (39.7)	881 (40.9)	153 (34.0)	.006

Abbreviations: BMI, body mass index; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; METs, maximal metabolic equivalent tasks achieved during treadmill test.
SI conversion factors: To convert total cholesterol and HDL-C values to mmol/L, multiply by 0.0259; triglycerides values to mmol/L, by 0.0113; glucose values to mmol/L, by 0.0555.
[a] For comparison of survivors and decedents.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Defined as waist circumference ≥88 cm in women and ≥102 cm in men.
[d] n = 2584 (442 deaths).
[e] Defined as reporting no leisure-time physical activity in the 3 months before the examination, as reported on the standardized medical history/health habits questionnaire.
[f] Defined as the presence of ≥3 of the 5 metabolic risk factors based on National Cholesterol Education Program Adult Treatment Panel III criteria.
[g] Defined as the presence of hypercholesterolemia (history of physician-diagnosed high cholesterol level or measured fasting total cholesterol level ≥240 mg/dL [6.20 mmol/L]) or diabetes (history of physician diagnosis, or use of insulin or measured fasting glucose level ≥126 mg/dL [7.0 mmol/L]); or hypertension (history of physician diagnosis or resting systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg); or personal history of physician-diagnosed cardiovascular disease (myocardial infarction or stroke).

groups. Models including BMI also were fitted with BMI squared to assess nonlinearity. We also examined associations between specific causes of death and fitness, BMI, waist circumference, percent body fat, and FFM. In addition, we tested joint associations of adiposity and fitness with all-cause mortality. There were no significant interactions among exposure groups.

Due to the small sample size (516) and number of deaths (52) in women, we were unable to perform a meaningful analysis in women alone. The pattern of the association between fitness, adiposity measurements, and all-cause mortality in men was similar to that observed in analyses of men and women combined. We also examined the potential interaction between sex and other covariates in the Cox regression model, and no significant interactions were observed. We therefore believe that combining women and men is an acceptable alternative. Statistical tests were 2-sided; $P < .05$ was accepted to indicate statistical significance.

RESULTS

Overall, the mean age of participants was 64.4 (SD, 4.8) years, and 20% of the study sample were women. There were 450 deaths during a mean follow-up of 12 years and 31 236 person-years of exposure. Participants' base-

Table 2. Baseline Characteristics by Cardiorespiratory Fitness (Fitness) Categories in 2603 Older Adults—Aerobics Center Longitudinal Study, 1979-2003[a]

Characteristic	All (N = 2603)	Fitness Quintile, min				
		<8.7 (n = 291)	8.7-11.2 (n = 448)	11.3-13.6 (n = 544)	13.7-18.3 (n = 668)	≥18.4 (n = 652)
Women, No. (%)	516 (19.8)	57 (11.1)	93 (18.0)	83 (16.1)	134 (26.0)	149 (28.9)
Age, mean (SD), y	64.4 (4.8)	66.1 (5.0)	65.3 (5.0)	64.4 (4.8)	63.8 (3.9)	63.7 (5.0)
BMI, mean (SD)[b]	26.3 (3.7)	29.0 (4.9)	27.3 (3.9)	27.0 (3.4)	26.0 (3.2)	24.3 (2.6)
BMI-defined weight groups, No. (%)						
18.5-24.9	1020 (39.2)	64 (6.3)	123 (12.1)	153 (15.0)	259 (25.4)	421 (41.3)
25.0-29.9	1206 (46.3)	121 (10.0)	225 (18.7)	293 (24.3)	348 (28.9)	219 (18.2)
30.0-34.9	316 (12.1)	73 (23.1)	85 (26.9)	89 (28.2)	58 (18.4)	11 (3.5)
≥35.0	61 (2.3)	33 (54.1)	15 (24.6)	9 (14.8)	3 (4.9)	1 (1.6)
Waist circumference, mean (SD), cm	90.3 (19.9)	97.8 (23.5)	94.4 (18.0)	92.9 (19.8)	89.4 (18.9)	83.1 (18.1)
Abdominal obesity, No. (%)[c]	643 (24.7)	148 (23.0)	172 (26.8)	166 (25.8)	128 (19.9)	29 (4.5)
Adiposity measures, mean (SD)[d]						
Percent body fat	26.5 (5.4)	29.9 (5.2)	28.5 (4.8)	27.6 (4.7)	26.3 (4.8)	23.1 (5.3)
Fat-free mass, kg	58.4 (9.4)	61.1 (10.5)	58.8 (9.8)	59.5 (9.0)	58.1 (8.9)	56.5 (9.0)
Fat mass, kg	21.6 (7.2)	26.8 (9.2)	23.9 (7.0)	23.1 (6.5)	20.9 (5.9)	17.1 (5.3)
Treadmill time, mean (SD), min	12.6 (4.8)	5.4 (1.6)	8.7 (1.4)	11.3 (1.6)	13.7 (2.1)	18.4 (3.6)
Maximal METs, mean (SD)	9.1 (2.2)	5.8 (0.7)	7.4 (0.6)	8.5 (0.7)	9.7 (1.0)	11.8 (1.7)
Abnormal exercise ECG responses, No. (%)	532 (20.4)	90 (16.9)	122 (22.9)	116 (21.8)	116 (21.8)	88 (16.5)
Lipids, mean (SD), mg/dL						
Total cholesterol	216.5 (42.2)	223.1 (46.9)	216.6 (42.7)	218.2 (39.9)	216.0 (40.9)	212.5 (42.6)
HDL-C	50.1 (15.6)	46.1 (13.4)	48.2 (15.7)	47.4 (14.5)	50.2 (14.6)	55.6 (16.8)
Triglycerides	136.7 (85.9)	164.3 (102.1)	147.5 (91.3)	152.7 (94.5)	134.9 (82.6)	105.1 (55.0)
Fasting blood glucose, mean (SD), mg/dL	106.1 (25.2)	119.1 (42.4)	109.5 (31.0)	105.7 (21.2)	103.6 (18.9)	100.8 (14.7)
Physically inactive, mean (SD), No. (%)[e]	657 (25.2)	142 (48.8)	179 (40.0)	165 (30.3)	113 (16.9)	58 (8.9)
Current smoker, No. (%)	235 (9.0)	43 (18.3)	55 (23.4)	54 (23.0)	50 (21.3)	33 (14.0)
Metabolic syndrome, No. (%)[f]	644 (24.7)	130 (20.2)	159 (24.7)	166 (25.8)	142 (22.1)	47 (7.3)
Chronic medical condition, No. (%)[g]						
Cardiovascular disease	139 (5.3)	30 (21.6)	35 (25.2)	38 (27.3)	20 (14.4)	16 (11.5)
Diabetes	266 (10.2)	66 (24.8)	54 (20.3)	57 (21.4)	58 (21.8)	31 (11.7)
Hypertension	1241 (47.7)	167 (13.5)	245 (19.7)	278 (22.4)	305 (24.6)	246 (19.8)
Hypercholesterolemia	1034 (39.7)	128 (12.4)	174 (16.8)	229 (22.2)	286 (27.7)	217 (21.0)

Abbreviations: BMI, body mass index; ECG, electrocardiogram; HDL-C, high-density lipoprotein cholesterol; METs, maximal metabolic equivalent tasks achieved during treadmill test.
SI conversion factors: To convert total cholesterol and HDL-C values to mmol/L, multiply by 0.0259; triglycerides values to mmol/L, by 0.0113; glucose values to mmol/L, by 0.0555.
[a] All the tests for linear trends across quintiles were significant ($P < .05$).
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] Defined as waist circumference ≥88 cm in women and ≥102 cm in men.
[d] n = 2584 (442 deaths).
[e] Defined as reporting no leisure-time physical activity in the 3 months before the examination as reported on the standardized medical history/health habits questionnaire and is likely to be a crude approximation of actual physical activity habits.
[f] Defined as the presence of ≥3 of the 5 metabolic risk factors based on National Cholesterol Education Program Adult Treatment Panel III criteria.
[g] Defined as the presence of hypercholesterolemia (history of physician-diagnosed high cholesterol level or measured fasting total cholesterol level ≥240 mg/dL [6.20 mmol/L]) or diabetes (history of physician diagnosis, or use of insulin or measured fasting glucose level ≥126 mg/dL [7.0 mmol/L]); or hypertension (history of physician diagnosis or resting systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg); or personal history of physician-diagnosed cardiovascular disease (myocardial infarction or stroke).

Table 3. Univariate Associations Between Adiposity Measures and Treadmill Exercise Duration in 2603 Older Adults—Aerobics Center Longitudinal Study, 1979-2003

	Pearson Correlation Coefficients[a]					
Adiposity Measure	BMI	Percent Body Fat	Fat Mass	Fat-Free Mass	Waist Circumference	Treadmill Test Duration
BMI	1.00	0.60	0.87	0.66	0.52	−0.30
Percent body fat		1.00	0.84	0.02	0.23	−0.50
Fat mass			1.00	0.54	0.48	−0.37
Fat-free mass				1.00	0.55	−0.09
Waist circumference					1.00	−0.10
Treadmill test duration						1.00

Abbreviation: BMI, body mass index.
[a] $P < .001$ for all, except coefficient comparing percent body fat and fat-free mass ($P = .26$).

line characteristics by vital status and by fitness categories are summarized in TABLE 1 and TABLE 2. Decedents were older, had lower fitness levels, and had more cardiovascular risk factors than survivors. However, there were no significant differences in adiposity measures across vital status. Participants in the higher fitness groups were for the most part less likely to have risk factors for cardiovascular disease, such as hypertension, diabetes, or high cholesterol levels. TABLE 3 shows that all measures of adiposity and treadmill exercise duration were significantly correlated, except for percent body fat and FFM ($r=0.02$, $P=.26$). Body mass index and fat mass were highly correlated, but BMI and waist circumference or percent body fat were only moderately correlated.

TABLE 4 presents all-cause death rates per 1000 person-years for each exposure category, adjusted for age, sex, and examination year. Death rates were 32.6, 16.6, 12.8, 12.3, and 8.1 across incremental fifths of fitness ($P<.001$ for linear trend); 20.4 and 12.1 for individuals with or without abnormal exercise ECG responses, respectively ($P<.001$); 17.7 and 12.0 for those with or without chronic medical conditions, respectively ($P<.001$); and 18.2 and 13.3 for those with or without abdominal obesity, respectively ($P=.004$). There was a J-shaped relationship between BMI and mortality (quadratic term, $P=.01$). Excluding individuals who died within 2 years of follow-up did not notably alter the association between the exposures and mortality. No relationship was found between mortality risk and percent body fat or FFM.

TABLE 5 and TABLE 6 show the estimated HRs and 95% CIs for fitness and adiposity exposure categories and all-cause mortality. After adjusting for age, sex, examination year, smoking, abnormal exercise ECG responses, and baseline health conditions (Table 5), HRs of mortality across incremental quintiles of fitness were 1.00, 0.53, 0.44, 0.43, and 0.30 ($P<.001$ for linear trend). Additional adjustment for BMI, waist circumference, percent body fat, or FFM did not meaningfully change the results (Table 5).

When the adiposity categories were adjusted for the same set of covariates (Table 6), individuals with abdominal obesity had a higher mortality risk (HR, 1.25; 95% CI, 1.00-1.56; $P=.05$), although this relationship did not persist after further adjustment for fitness (HR, 0.99; 95% CI, 0.79-1.25; $P=.95$). The J-shaped relationship between BMI and mortality remained significant after adjusting for covariates and fitness ($P=.005$), although most of the interval estimates for the BMI strata are not individually significantly different from those for the reference category. There were no significant associations between mortality and percent body fat or FFM.

Also, we examined joint associations of all-cause mortality, adiposity, and fitness, for which fitness was dichotomized as unfit and fit to preserve sample size and numbers of deaths within each adiposity stratum and to provide greater clinical meaning for physicians and other health professionals working with older populations (TABLE 7). There were no significant interactions noted in analyses that included cross-product interaction terms for each fitness-adiposity exposure combination. Fit participants had lower death rates than unfit participants within each stratum of adiposity, except for the class I and II obesity groups. In most instances, death rates for those with higher fitness were less than half of rates for those who were unfit.

COMMENT

The objective of this study was to evaluate relationships between mortality risk and well-defined measures of adiposity, fat distribution, and fitness in older adults. In age-, sex-, and examination year–adjusted analyses, both BMI and waist circumference were associated with mortality risk, but percent body fat and FFM were not related to mortality. The association between total mortality and waist circumference persisted after adjusting for baseline differences in age, sex, smoking, abnormal exercise ECG responses, and health status. Further adjustment for fitness eliminated the significant mortality risk associated with abdominal obesity. A J-shaped relationship between BMI and mortality remained significant after considering the influences of several covariates, including fitness.

Fitness had a strong inverse association with mortality, and this pattern of results was changed little by adjustments for adiposity or fat distribution.

Thus our primary finding is that both fitness and BMI were strong and independent predictors of all-cause mortality in adults 60 years or older. Other adiposity measures either did not predict mortality (percent body fat, FFM) or did not do so in models adjusted for competing risk predictors (waist circumference).

We previously demonstrated that lower levels of fitness are strongly associated with higher risk of all-cause and cardiovascular disease mortality in younger and middle-aged men with various levels of health status.[12,13,39,40] The analogous relationship is clear within adiposity subgroups.[12,13] Our findings from the current study are consistent with these earlier results from the Aerobics Center Longitudinal Study and expand them to the older segment of the cohort.

Higher levels of fitness were inversely related to all-cause mortality in both normal-weight and overweight BMI subgroups, in those with a normal waist circumference and in those with abdominal obesity, and in those who have normal percent body fat and those who have excessive percent body fat (Table 7). However, obese (BMI ≥30.0) unfit individuals were at no higher risk for mortality when compared with obese fit individuals. The obese I and II groups had relatively small sample sizes and fewer deaths;

Table 4. Risk of All-Cause Mortality Across Exposure Groups in 2603 Older Adults—Aerobics Center Longitudinal Study, 1979-2003

	Person-years	Deaths	Rate per 1000 Person-years[a]	HR (95% CI)[a]	*P* Value
BMI[b]					
18.5-24.9	13 168	192	13.9	1 [Reference]	.01[c]
25.0-29.9	14 412	196	13.3	0.95 (0.78-1.17)	
30.0-34.9	3226	50	18.3	1.31 (0.96-1.80)	
≥35.0	528	12	31.8	2.29 (1.27-4.12)	
Percent body fat					
Normal (<30 women; <25 men)	13 859	180	13.7	1 [Reference]	.51[d]
Obese (≥30 women; ≥25 men)	17 227	262	14.6	1.07 (0.88-1.30)	
Fat-free mass quintiles, kg					
<50.6	6375	72	12.9	1 [Reference]	.10[e]
50.6-56.9	6729	111	14.0	1.08 (0.73-1.60)	
57.0-61.1	6612	95	12.7	0.99 (0.65-1.49)	
61.2-65.9	5998	83	14.3	1.10 (0.72-1.68)	
≥66.0	5366	81	17.9	1.38 (0.90-2.12)	
Waist circumference, cm					
Normal (<88.0 women; <102.0 men)	24 402	335	13.3	1 [Reference]	.004[d]
Abdominal obesity (≥88.0 women; ≥102.0 men)	6925	115	18.2	1.37 (1.11-1.70)	
Fitness quintiles based on treadmill time, min[f]					
<8.7	3381	106	32.6	1 [Reference]	<.001[e]
8.7-11.2	5690	98	16.6	0.51 (0.39-0.67)	
11.3-13.6	6762	95	12.8	0.39 (0.30-0.52)	
13.7-18.3	7729	90	12.3	0.38 (0.29-0.50)	
≥18.4	7772	61	8.1	0.25 (0.18-0.34)	
Abnormal exercise ECG responses					
No	22 789	272	12.1	1 [Reference]	<.001[d]
Yes	8550	178	20.4	1.64 (1.33-2.01)	
Age, y					
60-69	28 095	358	12.4	1 [Reference]	<.001[e]
70-79	2765	82	34.4	2.78 (2.18-3.54)	
≥80	464	10	15.7	1.27 (0.67-2.38)	
Current smoker					
No	28 345	390	14.0	1 [Reference]	.08[d]
Yes	2977	60	17.9	1.28 (0.97-1.69)	
Chronic medical condition					
No	11 689	119	12.0	1 [Reference]	<.001[d]
Yes	19 645	279	17.7	1.48 (1.19-1.84)	

Abbreviations: BMI, body mass index; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio.
[a] Rates are per 1000 person-years and HRs are adjusted for age, sex, and examination year.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] For quadratic trend.
[d] For difference.
[e] For linear trend.
[f] Quintiles of cardiorespiratory fitness were based on the distribution of treadmill exercise duration standardized to the group aged ≥60 years in the overall Aerobics Center Longitudinal Study population of women and men. The tabulated values reflect the mean value for the women and men included in this analysis. Metabolic equivalent task levels of fitness associated with each quintile were <7.4, 7.4-8.4, 8.5-9.6, 9.7-11.7, and ≥11.8.