



Original Contribution

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

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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 ($p_{\text{trend}} < 0.001$) and 41.9, 27.7, and 20.8 in women ($p_{\text{trend}} = 0.002$). 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, $p_{\text{trend}} < 0.001$, and were 1.00 (referent), 0.74 (95% CI: 0.49, 1.13), and 0.63 (95% CI: 0.40, 0.98) in women, $p_{\text{trend}} = 0.05$. 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).

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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 Korotkoff 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 ($p_{\text{trend}} < 0.001$, 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/m²),

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 ($p_{\text{trend}} < 0.001$) 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 ($p_{\text{trend}} < 0.001$). 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 (<i>n</i> = 19,216) (mean (SD)* or %)	Cases (<i>n</i> = 1,512) (mean (SD) or %)	Noncases (<i>n</i> = 5,750) (mean (SD) or %)	Cases (<i>n</i> = 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 ($p_{\text{trend}} < 0.001$). 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 ($p_{\text{trend}} = 0.002$). 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 ($p_{\text{trend}} = 0.05$). CRF remained inversely associated with CVD risk after additional adjustment for intermediate risk factors, although the trend was not significant ($p_{\text{trend}} = 0.30$). CRF was inversely associated with coronary heart disease event rates ($p_{\text{trend}} = 0.004$); however, significance was attenuated by adjustment for covariables ($p_{\text{trend}} = 0.09$) 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
<i>p</i> 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
<i>p</i> 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
<i>p</i> 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
<i>p</i> 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/m²), hypertension, diabetes, or dyslipidemia (present or not for each).

($p_{\text{trend}} = 0.49$). 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), $p_{\text{trend}} < 0.001$, 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), $p_{\text{trend}} = 0.005$, 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
<i>p</i> 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
<i>p</i> 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
<i>p</i> 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
<i>p</i> 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/m²), 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 re-

lated 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

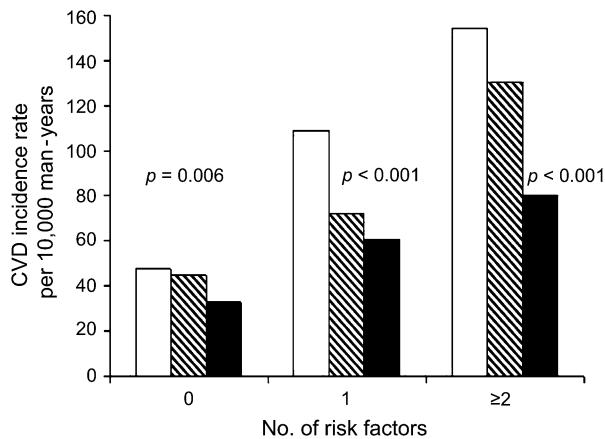


FIGURE 1. Age- and examination year-adjusted rates of total cardiovascular disease (CVD) events (per 10,000 person-years) by levels of cardiorespiratory fitness and number of major CVD risk factors (current smoking, hypertension, hypercholesterolemia, diabetes, and family history of CVD) in 20,728 men, 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.

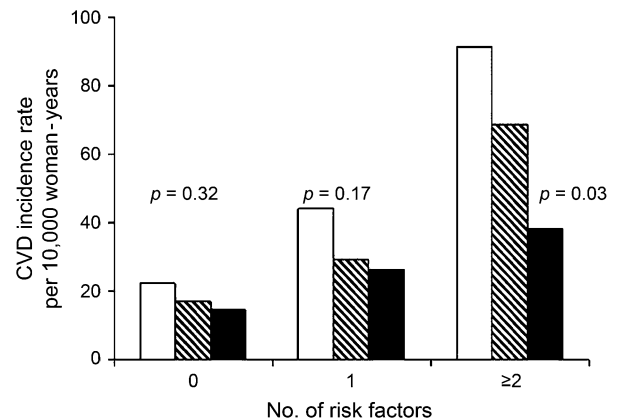


FIGURE 2. Age- and examination year-adjusted rates of total cardiovascular disease (CVD) events (per 10,000 person-years) by levels of cardiorespiratory fitness and number of major CVD risk factors (current smoking, hypertension, hypercholesterolemia, diabetes, and family history of CVD) in 5,909 women, 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.

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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 non-response 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 $\text{VO}_{2\text{max}}$ 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 $\text{VO}_{2\text{max}}$ response to exercise training: results from the HERITAGE family study. *J Appl Physiol* 1999;87:1003–8.