Cardiorespiratory Fitness as a Predictor of Fatal and Nonfatal Stroke in Asymptomatic Women and Men

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Background and Purpose—Prospective data on the association between cardiorespiratory fitness (CRF) and stroke are largely limited to studies in men or do not separately examine risks for fatal and nonfatal stroke. This study examined the association between CRF and fatal and nonfatal stroke in a large cohort of asymptomatic women and men.

Methods—A total of 46 405 men and 15 282 women without known myocardial infarction or stroke at baseline completed a maximal treadmill exercise test between 1970 and 2001. CRF was grouped as quartiles of the sex-specific distribution of maximal metabolic equivalents achieved. Mortality follow-up was through December 31, 2003, using the National Death Index. Nonfatal stroke, defined as physician-diagnosed stroke, was ascertained from surveys during 1982 to 2004. Cox regression models quantified the pattern and magnitude of association between CRF and stroke.

Results—There were 692 strokes during 813 944 man-years of exposure and 171 strokes during 248 902 woman-years of exposure. Significant inverse associations between CRF and age-adjusted fatal, nonfatal, and total stroke rates were observed for women and men ($P_{trend} \leq 0.05$ each). After adjusting for several cardiovascular disease risk factors, the inverse association between CRF and each stroke outcome remained significant ($P_{trend} < 0.05$ each) in men. In women, the multivariable-adjusted relationship between CRF and nonfatal and total stroke remained significant ($P_{trend} \leq 0.01$ each), but not between CRF and fatal stroke ($P_{trend} = 0.18$). A CRF threshold of 7 to 8 maximal metabolic equivalents was associated with a substantially reduced rate of total stroke in both men and women.

Conclusions—These findings suggest that CRF is an independent determinant of stroke incidence in initially asymptomatic and cardiovascular disease-free adults, and the strength and pattern of the association is similar for men and women. (***Stroke.*** **2008;39:2950-2957.)**

Key Words: disease prevention ■ epidemiology ■ physical activity ■ stroke

Stroke is the third leading cause of death and the leading cause of serious long-term disability in the United States, accounting for 160 000 deaths and $57 billion in annual healthcare costs.[1] It is estimated that 700 000 US adults experience an incident stroke each year and that there are 5 million stroke survivors.[1] Understanding determinants of stroke occurrence is paramount for effective primary prevention strategies to reduce the morbidity and mortality associated with stroke. Strong evidence exists in support of several biological determinants of stroke risk (eg, atrial fibrillation, hypertension), whereas comparatively less is known about the role of lifestyle risk factors such as physical inactivity.[2]

Physical inactivity is a major modifiable cardiovascular disease (CVD) risk factor[3] that has been associated in some studies with increased risk of stroke in women and men.[4–6] Cardiorespiratory fitness (CRF) is an objective reproducible physiological measure that reflects the functional influences of physical activity habits, genetics, and disease status. Because CRF is less prone to measurement error than self-reported physical activity exposures, it may better reflect the adverse health consequences of a sedentary lifestyle.[7]

Only 2 prospective studies have reported on the association between CRF and stroke risk. Each study was restricted to men, and each observed significant inverse associations between CRF and stroke mortality.[8,9] Although it seems reasonable to expect that CRF would confer protection against both nonfatal and fatal strokes in women and men, this conclusion is not warranted by evidence limited to studies of combined nonfatal/fatal strokes or studies only in men. We therefore investigated the prospective association between CRF and nonfatal, fatal, and total stroke in women and men in the Aerobics Center Longitudinal Study (ACLS).

Methods

Study Population

The ACLS is a prospective study of women and men who had a comprehensive preventive medical evaluation at the Cooper Clinic,

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Table 1. Sex-Specific Quartiles (Q) of Cardiorespiratory Fitness According to Maximal Treadmill Exercise Performance

	Men		Women	
	Exercise Duration, minutes	METs	Exercise Duration, minutes	METs
Q1	<14.2	<9.9	<10.3	<8.1
Q2	14.2–17.2	9.9–11.3	10.3–13.3	8.1–9.4
Q3	17.2–21.2	11.3–13.1	13.3–16.2	9.4–10.8
Q4	≥21.2	≥13.1	≥16.2	≥10.8

Dallas, Tex. 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 sent by their employers for the examination. Some were referred by their personal physicians. Others were self-referred. This study is reviewed and approved annually by the Cooper Institute Institutional Review Board. The current analysis includes 46 405 men and 15 282 women aged 18 to 100 years who completed a baseline examination during 1970 to 2001. Most participants were white, well-educated, and from middle and upper socioeconomic strata. At baseline, all participants were free of known myocardial infarction or stroke, had a normal resting electrocardiogram (ECG), and were able to achieve at least 85% of their age-predicted maximal heart rate (220 beats/min) during the treadmill exercise test. All participants gave their informed written consent for the follow-up study.

Baseline Examination

The clinical examination included a physical examination, anthropometry, resting and exercise ECG and blood pressure assessment, 12-hour fasting blood chemistry analyses, self-report of personal and family health histories, personal lifestyle habits (eg, smoking and alcohol intake), and demographic information.[10,11] Body mass index (kg/m^2) was computed from measured height and weight. Seated resting blood pressure was recorded as the first and fifth Korotkoff sounds using auscultation methods.[12] Fasting venous blood was analyzed for lipids and glucose using standardized automated bioassays at the Cooper Clinic Laboratory, which meets the quality control standards of the US Centers for Disease Control and Prevention Lipid Standardization Program. The presence of hypertension, diabetes, and hypercholesterolemia was based on a history of physician diagnosis or measured phenotypes that met clinical thresholds for each condition.

CRF was assessed by a maximal symptom-limited treadmill exercise test following a modified Balke protocol.[10,13] The treadmill test began with the patient walking 88 m/min at 0% grade. At the end of the first minute, elevation was increased to 2% and thereafter increased by 1% per minute until the 25th minute. Beyond 25 minutes, elevation remained constant while speed was increased each minute by 5.4 m/min until exhaustion. Patients were encouraged to give maximal effort. The test end point was volitional exhaustion or termination by the physician for medical reasons. Abnormal exercise ECG responses included rhythm and conduction disturbances and ischemic ST-T wave abnormalities as described in detail elsewhere.[14] In previous research, 3 physicians who read a random sample of 357 patient records, and who were blinded to the interpretation in the computer file, agreed with 90% of the ECG interpretations recorded in the ACLS database.[7]

Exercise duration on this protocol is highly correlated with measured maximal oxygen uptake in men ($r=0.92$)[15] and women ($r=0.94$).[16] Each participant's level of maximal metabolic equivalents (METs; 1 MET=3.5 mL O_2uptake/kg^{-1}/min^{-1}) was estimated from the final treadmill speed and grade.[17] Participants were grouped into quartiles within gender based on the maximal METs they achieved on the treadmill test. The least-fit quartile was classified as Q1 and the most-fit as Q4. Table 1 displays the treadmill duration and estimated METs according to gender-specific fitness categories in women and men for the current study.

Assessment of Stroke Outcomes

The primary outcome was total stroke (fatal and nonfatal stroke combined). Secondary end points were fatal and nonfatal strokes considered separately. Vital status was obtained from the National Death Index. Stroke, as the underlying cause of death, was identified using the International Classification of Diseases, Ninth Revision codes 430 to 434 and 436 to 438 for deaths occurring before 1999 and the Tenth Revision codes I60 to I69 for deaths occurring 1999 to 2003. The incidence of nonfatal stroke was ascertained from mail-back health surveys that were administered during the follow-up interval in 1982, 1986, 1990, 1995, 1999, and 2004. The cumulative survey response rate across all survey periods in the ACLS is approximately 70%. Nonresponse bias is a concern in epidemiological surveillance and this issue has been investigated in the ACLS cohort.[18] After eliminating decedents, the baseline health status and clinical measurements were similar between survey responders and nonresponders and between early and late survey responders. Total mortality rates also are similar between survey responders and nonresponders (unpublished data). These observations indicate that survey responders and nonresponders generally are more similar than not, although it is impossible to completely rule out potential response bias.

A case-finding question was used to identify cases of physician-diagnosed stroke. Participants were asked if a physician had ever told them that they had a stroke. If yes, respondents were asked to report the year of diagnosis. For those who reported multiple strokes, the first event was used for analysis. In a random sample of stroke end points (n=50), we applied a standard definition for defining and adjudicating stroke.[19] The percentage of agreement between reported strokes and participant medical records was 89%. This method of case ascertainment has been used in earlier ACLS reports[20,21] and in other large epidemiological studies of stroke[22] and other diseases.[23]

Statistical Analysis

Analyses were conducted separately in women and in men. Descriptive statistics were calculated for each variable stratified by CRF quartiles. Differences in baseline characteristics across CRF quartiles were examined using general linear analyses. Person-time for each participant was computed from the date of the baseline examination to the date of death, the date of a reported stroke, or December 31, 2004. The mean (SD) follow-up interval in years was 18.8 (8.0) for men and 17.4 (8.2) for women. Incidence rates were calculated as the number of cases divided by person-time follow-up separately in women and men. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs), indices of association between CRF and incident stroke, and the associated 95% CIs. The proportional hazards assumption was confirmed with log-cumulative survival plots. In multivariable analyses, adjustments were made for age (years), examination year, current smoker (yes/no), alcohol intake (≥5 drinks/week or not), abnormal exercise ECG responses (present or not), and family history of CVD (present or not). Additional analyses further adjusted for baseline differences in body mass index (kg/m^2), hypertension, diabetes, and hypercholesterolemia, each of which may be intermediate in the causal pathway between CRF and stroke. Additionally, an indicator variable was included to account for differences in the pattern of survey response. Tests of linear trends across CRF quartiles were computed using ordinal scoring. The potential influence of undetected subclinical disease at baseline was evaluated by excluding strokes that occurred during the first year of follow-up. In addition, stratified analyses were conducted for sex-specific associations between CRF and total stroke according to age (<45 versus 45 to 60 versus ≥60 years), current smoker (yes versus no), alcohol consumption (≥5 versus <5 drinks/week), overweight/obese (yes versus no), hypertension (yes versus no), diabetes (yes versus no), and hypercholesterolemia (yes versus no). Finally, to assess the dose–response relationship, the risk of total stroke incidence across increments of METs was plotted. All

Table 2. Baseline Characteristics of Study Participants by CRF Quartile (Q) Category Among Men and Women

	Men					
	Total (n=46 405)	Q1 (n=13 445)	Q2 (n=10 608)	Q3 (n=11 912)	Q4 (n=10 440)	*P* for Trend
Maximal exercise duration, mean±SD, minutes	17.6±5.2	11.5±2.5	16.1±0.9	19.6±1.1	24.8±2.4	<0.0001
Maximal metabolic equivalents, mean±SD	11.5±2.6	8.6±1.1	10.8±0.4	12.4±0.5	15.0±1.6	<0.0001
Age, mean±SD, years	43.7±10.0	48.5±10.3	44.1±9.4	41.8±8.9	39.3±8.4	<0.0001
Body mass index, mean±SD, kg/m^2	26.5±3.8	28.7±4.7	26.7±3.2	25.6±2.8	24.3±2.3	<0.0001
Total cholesterol, mean±SD, mmol/L	5.5±1.1	5.8±1.1	5.6±1.0	5.4±1.0	5.1±1.1	<0.0001
Fasting blood glucose, mean±SD, mmol/L	5.6±1.0	5.9±1.5	5.6±0.8	5.5±0.7	5.4±0.6	<0.0001
Blood pressure, mean±SD, mm Hg						
Systolic	122±14	126±15	122±13	120±13	120±12	<0.0001
Diastolic	81±10	84±10	82±9	80±9	78±9	<0.0001
Current smoker, No. (%)	8201 (17.7)	3555 (26.4)	2053 (19.4)	1727 (14.5)	866 (8.3)	<0.0001
Alcohol intake (≥5 drinks per week), no. (%)	17 098 (36.9)	4774 (35.5)	3984 (37.6)	4423 (37.1)	3917 (37.5)	0.002
Abnormal ECG during exercise, No. (%)	3938 (8.5)	2203 (16.4)	782 (7.4)	609 (5.1)	344 (3.3)	<0.0001
Hypertension,* no. (%)	14 944 (32.2)	6246 (46.5)	3563 (33.6)	3092 (26.0)	2043 (19.6)	<0.0001
Diabetes mellitus,† no. (%)	1277 (2.8)	680 (5.1)	276 (2.6)	222 (1.9)	99 (1.0)	<0.0001
High cholesterol,‡ no. (%)	8892 (19.2)	3626 (27.0)	2317 (21.8)	1915 (16.1)	1034 (9.9)	<0.0001
Family history of premature CVD, no. (%)	7530 (16.2)	2190 (16.3)	1698 (16.0)	1969 (16.5)	1673 (16.0)	0.68
	Women					
	Total (n=15 282)	Q1 (n=3606)	Q2 (n=3908)	Q3 (n=4403)	Q4 (n=3365)	*P* for Trend
Maximal exercise duration, mean±SD, minutes	13.2±4.7	7.5±1.7	11.2±0.9	14.6±1.1	20.0±2.7	<0.0001
Maximal metabolic equivalents, mean±SD	9.4±2.2	6.8±0.8	8.5±0.4	10.1±0.5	12.6±1.4	<0.0001
Age, mean±SD, years	42.9±10.8	48.8±10.9	44.2±10.3	41.1±9.7	37.4±9.0	<0.0001
Body mass index, mean±SD, kg/m^2	23.1±4.1	25.7±5.5	23.4±3.8	22.2±3.0	21.1±2.2	<0.0001
Total cholesterol, mean±SD, mmol/L	5.2±1.1	5.6±1.1	5.3±1.0	5.1±1.0	4.8±0.8	<0.0001
Fasting blood glucose, mean±SD, mmol/L	5.2±0.8	5.4±1.0	5.3±0.8	5.2±0.7	5.1±0.6	<0.0001
Blood pressure, mean±SD, mm Hg						
Systolic	113±15	119±16	113±14	110±13	109±12	<0.0001
Diastolic	75±10	79±10	76±10	74±9	73±9	<0.0001
Current smoker, no. (%)	1686 (11.0)	546 (15.1)	477 (12.2)	456 (10.4)	207 (6.2)	<0.0001
Alcohol intake (≥5 drinks per week), no. (%)	2926 (19.2)	615 (17.1)	779 (19.9)	863 (19.6)	669 (19.9)	0.004
Abnormal ECG during exercise, no. (%)	940 (6.2)	412 (11.4)	250 (6.4)	195 (4.4)	83 (2.5)	<0.0001
Hypertension,* no. (%)	2600 (17.0)	1097 (30.4)	701 (17.9)	509 (11.6)	293 (8.7)	<0.0001
Diabetes mellitus,*† no. (%)	333 (2.2)	109 (3.0)	86 (2.2)	93 (2.1)	45 (1.3)	<0.0001
High cholesterol,‡ no. (%)	1845 (12.1)	758 (21.0)	556 (14.2)	388 (8.8)	143 (4.3)	<0.0001
Family history of premature CVD, no. (%)	2898 (19.0)	652 (18.1)	780 (20.0)	859 (18.5)	607 (18.0)	0.07

*Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or a history of physician diagnosis.
†Diabetes mellitus was defined as a fasting plasma glucose concentration ≥126 mg/dL (7.0 mmol/L), a history of physician diagnosis, or insulin use.
‡High serum cholesterol was defined as serum cholesterol ≥240 mg/dL (6.2 mmol/L).

probability values were based on 2-tailed tests; $P<0.05$ was taken to indicate statistical significance.

Results

During an average follow-up of 18 years (range, 1 to 34.4 years), there were 863 strokes (241 stroke deaths, 647 nonfatal strokes). Table 2 presents baseline characteristics of the study cohort by CRF quartiles. Participants in quartiles representing higher CRF were for the most part less likely to have CVD risk factors such as hypertension, diabetes, or high cholesterol.

Table 3 presents the association between CRF and fatal, nonfatal, and total stroke in women and men. In men, age-adjusted rates of total stroke decreased across quartiles representing increasing CRF ($P_{trend}<0.0001$). This negative association remained significant after further adjusting for examination year, current smoker, alcohol intake, family

Table 3. Rates and Hazard Ratios for Fatal and Nonfatal Stroke by CRF Groups in Men and Women

	Men				
	Q1	Q2	Q3	Q4	*P* Value for Trend
Fatal stroke					
No. of cases	112	33	28	13	
No. of person-years	237 842	185 534	201 670	171 947	
Rate*	2.0	1.1	1.2	0.9	0.0007
Multivariate model 1 HR (95% CI)†	1.00 (referent)	0.56 (0.38–0.84)	0.63 (0.41–0.97)	0.48 (0.26–0.86)	0.002
Multivariate model 2 HR (95% CI)‡	1.00 (referent)	0.47 (0.30–0.74)	0.59 (0.36–0.97)	0.50 (0.25–0.97)	0.004
Nonfatal stroke					
No. of cases	257	108	113	49	
No. of person-years	170 437	133 155	144 579	116 638	
Rate*	6.5	4.9	6.0	3.9	0.006
Multivariate model 1 HR (95% CI)§	1.00 (referent)	0.70 (0.55–0.88)	0.80 (0.63–1.02)	0.51 (0.37–0.71)	0.0001
Multivariate model 2 HR (95% CI)‖	1.00 (referent)	0.78 (0.61–1.00)	0.95 (0.73–1.23)	0.62 (0.43–0.90)	0.049
Total stroke					
No. of cases	357	137	138	60	
No. of person-years	240 235	189 190	206 294	176 580	
Rate*	6.3	4.4	5.4	3.5	<0.0001
Multivariate model 1 HR (95% CI)§	1.00 (referent)	0.66 (0.54–0.81)	0.77 (0.62–0.94)	0.50 (0.38–0.94)	<0.0001
Multivariate model 2 HR (95% CI)‖	1.00 (referent)	0.70 (0.56–0.87)	0.85 (0.68–1.08)	0.60 (0.43–0.82)	0.003
	Women				
	Q1	Q2	Q3	Q4	*P* Value for Trend
Fatal stroke					
No. of cases	30	15	8	2	
No. of person-years	63 898	64 795	67 454	47 043	
Rate*	1.8	1.4	1.1	0.5	0.05
Multivariate model 1 HR (95% CI)†	1.00 (referent)	0.93 (0.44–1.57)	0.64 (0.28–1.45)	0.33 (0.08–1.44)	0.09
Multivariate model 2 HR (95% CI)‡	1.00 (referent)	0.71 (0.33–1.55)	0.62 (0.23–1.63)	0.43 (0.09–2.01)	0.18
Nonfatal stroke					
No. of cases	59	33	16	12	
No. of person-years	45 575	46 319	46 340	30 340	
Rate*	5.7	4.6	2.7	3.9	0.03
Multivariate model 1 HR (95% CI)§	1.00 (referent)	0.72 (0.47–1.12)	0.39 (0.22–0.68)	0.51 (0.27–0.98)	0.002
Multivariate model 2 HR (95% CI)	1.00 (referent)	0.75 (0.45–1.24)	0.34 (0.17–0.69)	0.56 (0.26–1.21)	0.01
Total stroke					
No. of cases	86	47	24	14	
No. of person-years	64 818	66 305	69 306	48 470	
Rate*	5.5	4.4	2.9	3.3	0.006
Multivariate model 1 HR (95% CI)§	1.00 (referent)	0.79 (0.55–1.14)	0.48 (0.30–0.77)	0.53 (0.29–0.95)	0.001
Multivariate model 2 HR (95% CI)	1.00 (referent)	0.77 (0.50–1.17)	0.43 (0.24–0.75)	0.57 (0.29–1.12)	0.007

*Rate is expressed as per 10 000 person-years and adjusted for age.

†Adjusted for age, examination year, current smoking (yes or not), alcohol intake (≥5 drinks/week or not), family history of CVD (present or not), and abnormal exercise electrocardiogram responses (present or not).

‡Adjusted for the above plus body mass index (kg/m^2) and personal history of hypertension, diabetes or hypercholesterolemia (present or not for each).

§Adjusted for age, examination year, current smoking (yes or not), alcohol intake (≥5 drinks/week or not), family history of CVD (present or not), abnormal exercise electrocardiogram responses (present or not), and survey indicator.

‖Adjusted for the above plus body mass index (kg/m^2) and personal history of hypertension, diabetes, or hypercholesterolemia (present or not for each).

history of CVD, and abnormal exercise ECG responses (P_{trend}<0.0001). Further adjustment for body mass index, hypertension, diabetes, and hypercholesterolemia did not materially change the association (P_{trend}=0.003). Similar inverse patterns of association also were seen between CRF and both nonfatal and fatal stroke.

In women (Table 3), total stroke rates were also inversely associated with CRF (P_{trend}=0.006). The inverse association

Table 4. HRs for Total Stroke per 1-MET Increment in Maximal Exercise According to Age, Smoking, Alcohol Consumption, Overweight, Hypertension, Diabetes, and Serum Cholesterol Level in Men and Women*

	Men				Women			
Risk Factor	Total No.	No. of Strokes	HR (95% CI)†	*P* Value	Total No.	No. of Strokes	HR (95% CI)†	*P* Value
Age, years								
<45	25 903	136	0.90 (0.82–0.98)	0.02	8777	32	0.82 (0.67–1.00)	0.055
45–60	17 383	387	0.88 (0.83–0.93)	<0.0001	5472	91	0.90 (0.79–1.03)	0.12
≥60	3019	169	0.94 (0.87–1.02)	0.14	993	48	0.87 (0.72–1.06)	0.16
Current smoker								
No	38 119	574	0.94 (0.90–0.98)	0.001	13 561	148	0.88 (0.80–0.96)	0.006
Yes	8186	118	0.76 (0.69–0.84)	<0.0001	1681	23	0.79 (0.61–1.04)	0.10
Alcohol consumption (≥5 drinks per week)								
No	29 238	416	0.91 (0.87–0.96)	0.0002	12 322	135	0.86 (0.78–0.95)	0.003
Yes	17 067	276	0.89 (0.84–0.95)	0.0003	2920	36	0.92 (0.76–1.12)	0.42
Body mass index, kg/m^2								
18.5–24.9	21 340	317	0.91 (0.87–0.96)	0.0002	12 282	142	0.90 (0.82–0.98)	0.02
≥25	24 965	375	0.91 (0.86–0.96)	0.0008	2960	29	0.64 (0.45–0.90)	0.01
Hypertension								
No	31 417	358	0.90 (0.85–0.95)	<0.0001	12 653	99	0.90 (0.80–1.01)	0.07
Yes	14 888	334	0.92 (0.87–0.97)	0.002	2589	72	0.83 (0.72–0.96)	0.01
Diabetes								
No	45 036	649	0.91 (0.87–0.94)	<0.0001	14 910	162	0.86 (0.78–0.94)	0.0009
Yes	1269	43	0.95 (0.81–1.12)	0.54	332	9	1.09 (0.74–1.60)	0.66
Total cholesterol								
<6.20 mmol/L (240 mg/dL)	37 437	490	0.90 (0.86–0.94)	<0.0001	13 404	133	0.87 (0.79–0.96)	0.004
≥6.20 mmol/L (240 mg/dL)	8868	202	0.94 (0.87–1.01)	0.069	1838	38	0.87 (0.69–1.09)	0.21

*The point and interval estimates are the risk of total strokes that are associated, on average, with each 1-MET increment in treadmill exercise test.
†Adjusted for examination year, survey indicator, and each of the other variables in the table.

remained significant after adjusting for the covariates (P_{trend}=0.001). Further adjustment for intermediate risk factors did not significantly alter the association (P_{trend}=0.007). A similar pattern and magnitude of the association was observed between CRF and nonfatal stroke. There was some evidence that the risk of fatal strokes for women may have decreased across increasing quartiles of CRF, although this trend was not statistically significant in either multivariate model (P_{trend}>0.05) The lack of statistical significance may be attributable to the small number of fatal strokes in women (N=55).

Additional analyses examined whether certain risk predictors modified the association between CRF and total stroke (Table 4). To provide a more clinical context to the data, the relative hazard for a stroke that is associated, on average, with a 1-MET increment in treadmill exercise performance is presented. In men, after separate adjustment for each risk factor shown in the table, each 1-MET increase in CRF was associated with a 5% to 24% lower stroke risk whether or not an adverse risk predictor was present (P<0.05 in the majority of the strata). In women, each 1-MET increase in CRF was associated with a 10% to 19% lower stroke risk without the presence of an adverse risk predictor. In women with adverse risk predictors, the pattern of association between CRF and total stroke risk was variable with significant reductions in risk noted in those with a body mass index ≥25 kg/m^2 (36%) or hypertension (17%), but not in those who smoked, consumed ≥5 alcoholic drinks per week, had diabetes, had high total cholesterol, or were ≥45 years of age.

The Figure illustrates the dose–response characteristic between CRF and rate of age-adjusted total stroke in men (solid line) and women (dashed line). Individuals with an

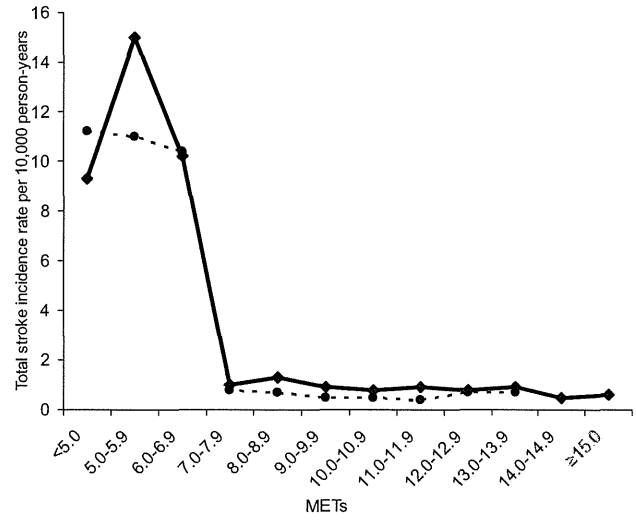

Figure. Age-adjusted rates of total stroke (per 10 000 person-years) according to 1-MET increments of cardiorespiratory fitness in men (solid line) and women (dashed line).

exercise capacity of less than 5.0 METs were the reference group. It is clear from the figure that a CRF threshold of 7 to 8 METs was associated with a substantially reduced rate of total stroke in both men and women.

Discussion

Only 2 previous studies have reported on the association between CRF and stroke. Lee and colleagues[8] conducted an earlier analysis of CRF and fatal stroke, examining 16 878 male participants in the ACLS; however, the data in that study were limited to only 32 total deaths during a 10-year follow-up. Kurl et al[24] examined the relationship between CRF and stroke in 2011 Finnish men over 11 years of follow-up. That study, however, did not provide separate risk estimates for fatal and nonfatal strokes. Neither study included women. To evaluate the precise role of CRF in primary stroke prevention, it is important to determine whether CRF is also related to incident events that are survived and not merely to mortality. It is also useful to determine whether greater CRF protects both women and men. The present study demonstrated that higher CRF was significantly associated with lower rates of nonfatal and total stroke in women and in men and with lower rates of fatal stroke in men.

The results for men in this study expand on those of the earlier ACLS analysis[8] and the Finnish[24] study as well as confirm the conclusions reached through 2 meta-analyses of physical activity and stroke risk.[4,5] The present findings in ACLS women are consistent with and expand on earlier studies reporting an inverse association between total stroke risk and self-reported occupational[25,26] and leisure-time[22,27–29] physical activity. After further adjusting for several covariates, the inverse association between CRF and 5 of the 6 stroke outcomes in the present study remained significant. This study is the first to suggest that there may be a significant independent association between CRF and fatal and nonfatal stroke in men and nonfatal stroke in women. In women, the lack of a significant independent association between CRF and fatal stroke in the fully adjusted model may be due to the small number of fatal stroke cases with only 10 such events in the top 2 CRF quartiles. Additional prospective data on CRF exposures and nonfatal and fatal stroke in women are needed to corroborate the association suggested by the current results.

The relative risk reduction in stroke mortality for men in the current study was 41% to 50% when comparing those in the highest 2 CRF quartiles with the lowest CRF quartile. This level of stroke protection is greater than that for self-reported occupational (36% lower risk) and leisure-time (20% to 25% lower risk) physical activity levels when comparing the most active and the least active men.[4,5] In ACLS women in the highest 2 CRF quartiles compared with the lowest CRF quartile, the relative risk reduction in nonfatal and total stroke was 44% to 66% and 43% to 57% lower, respectively. This level of stroke protection associated with higher CRF is greater than that reported in 6 previous cohort studies using self-reported physical activity (pooled risk reduction=43%).[22,25–29] The slightly higher strength of association between CRF and stroke risk reduction, compared with the analogous risk reduction associated with physical activity, may be attributable to less exposure misclassification in analyses that use an objective exposure measure rather than self-reported exposure.[8] These findings are consistent with those of other studies that have reported greater reductions in risk of CVD morbidity and mortality when using CRF as the criterion compared with self-reported physical activity.[10,11,21]

The present findings indicated a dramatic reduction in the incidence of total stroke for both men and women at a CRF level of 7 to 8 METs (Figure). Beyond this level of CRF, no further decreases in total stroke rate were noted for either men or women. Interestingly, in this ACLS cohort, some men and women in the lowest fitness quartile and all of them in the next highest quartile of fitness exhibited a CRF greater than 8 METs (Table 1). This finding of an apparent CRF threshold adds insight into the relationship between CRF and stroke. A functional capacity of 7 to 8 METs is rated as a low to moderate level of CRF for men and women across the adult age spectrum.[10,21] Most people can attain this level of CRF by participating in moderate and/or vigorous intensity physical activities for 30 minutes or more on most days of the week.[3,7] Therefore, healthcare providers, public health practitioners, and others should consider the potential independent cerebrovascular benefits of greater CRF and should encourage their less active patients and clients to become more physically active and improve their CRF as a strategy to considerably reduce their stroke risk.

The current findings contradict a meta-analysis[4] that examined the dose–response relationship between physical activity and stroke. The pooled results indicated that being moderately active during leisure time was associated with 15% to 20% lower total stroke incidence and mortality compared with being inactive. Being highly active during leisure time was associated with 20% to 27% lower total stroke incidence and mortality compared with being inactive. The meta-analysis findings seem to indicate an incremental dose–response relationship between self-reported physical activity and stroke rather than the threshold phenomenon between CRF and stroke observed in the present study. It is unclear what may be contributing to the differing results, although the differing approaches to measuring physical activity exposures (ie, self-reported physical activity versus CRF) likely account for some of the variability. The dose–response relationship between CRF and combined and separate rates of fatal and nonfatal stroke in men and women of varying race/ethnicity and geographic locations deserves additional investigation.

The current results further suggest a protective effect of increasing CRF regardless of the presence of known CVD risk factors (see Table 4). The results were more consistent for men than women, possibly owing to the many fewer strokes in women. However, for 2 of the more common CVD risk factors, body mass index and hypertension, a higher level of CRF was associated with a reduced risk of total stroke in men and women with or without these risk factors. Interestingly, each 1-MET increase in CRF was related to a 36% lower risk of total stroke for women classified as overweight or obese compared with a 9% lower risk for women classified

as normal weight. These results compliment those of earlier ACLS analyses revealing significantly lower risks of CVD-related morbidity and mortality in persons who have high levels of CRF despite being overweight or obese.[21,30]

Several prospective studies have shown that self-reported physical activity is inversely associated with stroke incidence or mortality in asymptomatic women and men.[10,11,31–33] However, other studies using similar self-report methods have observed a U-shaped[34–36] or a positive association[37] between physical activity and stroke risk. The reason for this discrepancy is unknown. However, it may be attributable to the use of imprecise self-reported physical activity. Self-report measures of physical activity contribute to misclassification, obscuring the relationship between physical activity and stroke risk.[8] A major strength of the ACLS is the use of CRF as an objective marker of recent physical activity patterns, thereby reducing the likelihood of any systematic bias of self-reported physical activity assessment.

It is well documented that moderate- to vigorous-intensity aerobic activities improve CRF.[17] Thus, it is reasonable to assume that CRF is a good indicator of recent physical activity habits. In ACLS, the relationship between detailed self-reports of daily physical activity recorded in a computer-based exercise log over a 3-month period and results from maximal exercise treadmill tests has been studied. It was determined that approximately 70% of the variation in CRF was accounted for by the physical activity data.[38] This is consistent with data from other sources on the genetic contribution to CRF, which is estimated in the range of 25% to 40% of the variation in an individual's aerobic power. Thus, CRF is largely a function of habitual physical activity and to a lesser extent genetic influences.

Additional strengths of the current study include the extensive baseline examination to detect subclinical disease, use of measured risk factors, large number of person-years of follow-up, and variety of stroke end points. Also, an indicator variable was used in all analyses to account for potential confounding by different patterns of survey response among participants, an approach not typically used in cohort studies such as ACLS.[21,39,40] The inverse associations generally were independent of traditional risk factors, a result that strengthens causal inferences. These associations may be biologically plausible. Mechanisms may include enhanced blood pressure control, blood lipid profile, sensitivity to insulin, blood coagulation, platelet aggregation, fibrinolysis, antioxidant defense, and body composition.[2,6] As such, moderate to high CRF attained through regular physical activity is more likely to protect against ischemic rather than hemorrhagic stroke, although to the extent that regular exercise affects blood pressure, it may also reduce risk of hemorrhagic stroke.

A limitation of the present study was the inability to adjust for diet or other potential confounding variables such as smoking intensity or duration, medication use, or menopausal status. 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 stroke. Another limitation of the present study is that stroke subtype was not considered. Given the relatively small number of strokes in each subtype, we did not examine relationships between CRF and ischemic or hemorrhagic stroke. Recent literature reviews show an inverse association between self-reported physical activity and ischemic and hemorrhagic stroke in men; these relationships in women remain unclear.[4,5] Additional research is needed to further understand the specificity of associations between CRF (or physical activity) and stroke subtypes. Due to the size of the cohort and widespread geographic distribution of patients evaluated at the Cooper Clinic, we did not have the resources to verify all reported stroke events. However, based on a random sample of verified events, it appears that an acceptable level of agreement (89%) exists between the participant's self-reported history and their medical records. The current findings are limited to white women and men in middle and upper socioeconomic strata; thus, the results may not be generalizable to other adult populations. Genetics clearly contribute to maximal CRF.[41,42] Nonetheless, as mentioned earlier, CRF can be enhanced in most adults through participation in moderate and vigorous physical activities for 30 minutes or more on most days of every week.[3,7]

This study found evidence that CRF is inversely associated with the incidence of total and nonfatal stroke in asymptomatic women and men and with fatal stroke in men. The association is biologically plausible and was observed independent of major risk factors. In addition, an apparent CRF threshold of 7 to 8 METs was observed in both men and women, at which a significant lowering of total stroke incidence was noted. Although stroke death rates have declined over the past few decades,[43] the public health burden of stroke-related disabilities continues to be large and may well increase in coming years, especially in racial/ethnic minority populations.[2] For this reason, increasing CRF should be considered a vital weapon in the arsenal to combat stroke in women and men.

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Disclosures

None.

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論文名	Cardiorespiratory fitness as a predictor of fatal and nonfatal stroke in asymptomatic women and men
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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	男女混合	( )		( )		( )
	年齢	男性43.7±10.0歳	[redacted]	10.8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	脳血管障害予防	なし	なし	なし	死亡	( )
	維持・改善	なし	なし	なし	なし	( )	( )

図 表

Table 3. Rates and Hazard Ratios for Fatal and Nonfatal Stroke by CRF Groups in Men and Women

	Men				
	Q1	Q2	Q3	Q4	P Value for Trend
Fatal stroke					
No. of cases	112	33	28	13	
No. of person-years	237 842	185 534	231 670	171 947	
Rate*	2.0	1.1	1.2	0.9	0.0007
Multivariate model 1 HR (95% CI)†	1.00 (referent)	0.56 (0.38–0.84)	0.63 (0.41–0.97)	0.48 (0.26–0.86)	0.002
Multivariate model 2 HR (95% CI)‡	1.00 (referent)	0.47 (0.30–0.74)	0.59 (0.36–0.97)	0.50 (0.25–0.97)	0.004
Nonfatal stroke					
No. of cases	257	103	113	49	
No. of person-years	170 437	133 155	144 579	116 698	
Rate*	6.5	4.9	6.0	3.9	0.005
Multivariate model 1 HR (95% CI)§	1.00 (referent)	0.70 (0.55–0.88)	0.80 (0.63–1.02)	0.51 (0.37–0.71)	0.0001
Multivariate model 2 HR (95% CI)‖	1.00 (referent)	0.78 (0.61–1.00)	0.95 (0.73–1.23)	0.62 (0.43–0.90)	0.049
Total stroke					
No. of cases	357	137	138	60	
No. of person-years	240 235	189 190	206 294	176 580	
Rate*	6.3	4.4	5.4	3.5	<0.0001
Multivariate model 1 HR (95% CI)§	1.00 (referent)	0.66 (0.54–0.81)	0.77 (0.62–0.94)	0.59 (0.38–0.94)	<0.0001
Multivariate model 2 HR (95% CI)‖	1.00 (referent)	0.70 (0.56–0.87)	0.85 (0.68–1.06)	0.69 (0.43–0.82)	0.003

	Women				
	Q1	Q2	Q3	Q4	P Value for Trend
Fatal stroke					
No. of cases	30	15	8	2	
No. of person-years	63 898	64 795	67 454	47 043	
Rate*	1.8	1.4	1.1	0.5	0.05
Multivariate model 1 HR (95% CI)†	1.00 (referent)	0.93 (0.44–1.57)	0.64 (0.28–1.45)	0.33 (0.09–1.44)	0.09
Multivariate model 2 HR (95% CI)‡	1.00 (referent)	0.71 (0.33–1.55)	0.62 (0.23–1.63)	0.43 (0.09–2.01)	0.18
Nonfatal stroke					
No. of cases	59	33	16	12	
No. of person-years	45 573	46 319	46 340	30 340	
Rate*	5.7	4.6	2.7	3.9	0.03
Multivariate model 1 HR (95% CI)§	1.00 (referent)	0.72 (0.47–1.12)	0.39 (0.22–0.68)	0.51 (0.27–0.98)	0.002
Multivariate model 2 HR (95% CI)	1.00 (referent)	0.75 (0.45–1.24)	0.34 (0.17–0.69)	0.56 (0.26–1.21)	0.01
Total stroke					
No. of cases	86	47	24	14	
No. of person-years	64 818	66 305	69 306	48 470	
Rate*	3.5	4.4	2.9	3.3	0.006
Multivariate model 1 HR (95% CI)§	1.00 (referent)	0.79 (0.55–1.14)	0.48 (0.30–0.77)	0.53 (0.29–0.95)	0.001
Multivariate model 2 HR (95% CI)	1.00 (referent)	0.77 (0.50–1.17)	0.43 (0.24–0.75)	0.57 (0.29–1.12)	0.007

*Rate is expressed as per 10 000 person-years and adjusted for age.
†Adjusted for age, examination year, current smoking (yes or not), alcohol intake (≥5 drinks/week or not), family history of CVD (present or not), and abnormal exercise electrocardiogram responses (present or not).
‡Adjusted for the above plus body mass index (kg/m²) and personal history of hypertension, diabetes or hypercholesterolemia (present or not for each).
§Adjusted for age, examination year, current smoking (yes or not), alcohol intake (≥5 drinks/week or not), family history of CVD (present or not), abnormal exercise electrocardiogram responses (present or not), and survey indicator.
‖Adjusted for the above plus body mass index (kg/m²) and personal history of hypertension, diabetes, or hypercholesterolemia (present or not for each).

図表掲載箇所	P2953, Table3
概 要 (800字まで)	本研究は、アメリカのThe Aerobics Center Longitudinal Study(ACLS)に参加した男女61,687名を対象に平均18年間の追跡調査を行い、全身持久力と脳卒中死亡および発症との関連を性別に検討したものである。ベースライン測定時の最大トレッドミルテストにより、全身持久力を男性で9.9メッツ未満、9.9-11.3メッツ、11.3-13.1メッツ、13.1メッツ以上の4群に、女性で8.1メッツ未満、8.1-9.4メッツ、9.4-10.8メッツ、10.8メッツ以上の4群に分類した。男性では、全身持久力が9.9メッツ未満の群と比較すると、それぞれの群で脳卒中死亡リスクが0.47(95%信頼区間:0.30-0.74)、0.59(0.36-0.97)、0.50(0.25-0.97)と減少し、強力な負の相関が認められた(Ptrend=0.004)。脳卒中発症リスクについては、0.78(0.61-1.00)、0.95(0.73-1.23)、0.62(0.43-0.90)と弱い負の相関がみられた(Ptrend=0.049)。全脳卒中についても、全身持久力との間に強力な負の相関がみられた(Ptrend=0.003)。女性では、全身持久力が8.1メッツ未満の群と比較すると、9.4-10.8メッツの群で脳卒中発症リスクが0.34(0.17-0.69)と有意に低下し、負の相関が認められた(Ptrend=0.01)。脳卒中死亡リスクについては明確な関連は認められなかったものの、全脳卒中に関しては、全身持久力との間に負の関連がみられた(Ptrend=0.007)。
結 論 (200字まで)	白人コホートにおいて、男女共に全身持久力と全脳卒中および脳卒中発症リスクに負の関連が認められた。また、男性のみで全身持久力と脳卒中死亡リスクとの間に強力な負の関連が認められた。さらに、全身持久力はその他のリスク因子とは独立した決定因子であることが明らかとなった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に用いられた研究の1つである。脳卒中は、日本の死因や要介護になる原因として、解決すべき問題である。本研究では、体力を高めることで脳卒中の発症や死亡が予防できることを示唆している。日本人を対象に体力と脳卒中の発症/死亡との関係についても検討されることが期待される。

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ELSEVIER

Physical Activity, Physical Fitness, and All-Cause and Cancer Mortality: A Prospective Study of Men and Women

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ABSTRACT

We studied physical fitness and physical activity in relation to all-cause and cancer mortality in a cohort of 7080 women and 25,341 men examined at the Cooper Clinic in Dallas, Texas, during 1970 to 1989. Physical fitness was assessed at baseline by a maximal treadmill exercise test, while physical activity was self-reported on the attendant health habits questionnaire. Both men and women averaged about 43 years of age at baseline (range, 20 to 88 years), and they were followed for ~ 8 years on average. Through the end of 1989, the women contributed 52,982 person-years of observation and incurred 89 deaths, including 44 deaths due to cancer. The men contributed 211,996 person-years and incurred 601 deaths, with 179 due to cancer. After adjustment for baseline differences in age, examination year, cigarette habit, chronic illnesses, and electrocardiogram abnormalities, we found a strong inverse association between risk of all-cause mortality and level of physical fitness in both men and women (P for trend < 0.001). Physically active men also were at lower risk of all-cause mortality than were sedentary ones (P for trend = 0.01). Among women, however, self-reported physical activity was not significantly related to risk of death from all causes. The risk of mortality from cancer declined sharply across increasing levels of fitness among men (P for trend < 0.001), whereas among women the gradient was suggestive but not significant (P for trend = 0.07). Physically active men also were at lower risk of death from cancer than were sedentary men (P for trend = 0.002), but among women physical activity was unrelated to cancer mortality. © 1996 by Elsevier Science Inc. Ann Epidemiol 1996; 6:452–457.

KEY WORDS: Physical fitness, physical activity, cancer, mortality, cohort study.

INTRODUCTION

Previous reports from the Aerobics Center Longitudinal Study (ACLS) show an increased risk both for development of chronic diseases and for premature mortality among study participants who were sedentary and physically unfit at baseline (1–4). This association is seen in healthy individuals as well as those who already had a chronic disease when enrolled in the follow-up study (5, 6). The findings are comparable for men and women (1), except that no association was evident between physical activity and risk of mortality in women (7). The inverse gradient of mortality risk across quintiles of physical fitness is steep, with the greatest difference in all-cause death rates observed between the first and second quintiles (1). The lower all-cause mortality rates in higher fitness categories in earlier publications are due primarily to much lower rates of cardiovascular disease and cancer mortality in the men and women who were more fit at baseline (1). Cancer rates are particularly high among less fit individuals, but the analyses are based on only 64 cancer deaths in men and 18 in women. The study population continues to grow as new participants are added, and mortality surveillance has been extended for an additional 5 years beyond the initial report on fitness and mortality.

The purpose of this report is to reexamine the association between physical activity or physical fitness and mortality risk in our expanded cohort. The preliminary analyses presented here focus on all-cause and cancer mortality.

METHODS

Study Population and Design

This is a prospective observational study of a large group of men and women who were examined at least once during 1970–1989 at the Cooper Clinic in Dallas, Texas. The study population consists of 7080 women (average age, 42.7 years; SD, 11.0 [range 20–82 years]) and 25,341 men (average age, 42.9 years; SD, 9.8 [range 20–88 years]). The cohort includes few members of minority groups (< 3%) and comes from middle and upper socioeconomic strata (~ 80% hold a college degree).

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Clinical Examination

All study participants completed a thorough health screening examination that included a personal and family health history, questionnaires on health habits and demographic characteristics, a physical examination, body composition assessment, blood chemistry analyses, blood pressure measurement, and a maximal exercise test on a treadmill. Additional details of the examination were given in previous reports (1, 5, 6).

In this study physical fitness was measured by a maximal exercise test following a standard protocol. The test begins with the participant walking on a horizontal treadmill at 88 m/min, with periodic increases in treadmill inclination, and after 25 min the speed is increased. The test continues until the participant reaches exhaustion or is stopped by the supervising physician for medical reasons. Total test duration was used as the measure of physical fitness. Because duration of the test correlates highly ($r > 0.90$) with measured maximal oxygen uptake, physical fitness as used here is analogous to aerobic power. We created age- and sex-specific treadmill time distributions and used quintile cut-points to assign participants to five fitness categories (1). In particular, the least-fit one-fifth of ACLS participants is an established high-risk category (1, 6) at one extreme of a continuum, analogous to conventional definitions of hypertension or obesity in epidemiologic work.

Physical activity was assessed by self-report on the health habits questionnaire. Subjects completed a series of questions about their usual patterns of regular physical activity in the months before the examination. Their responses allowed for creation of physical activity categories. Men and women who reported no activity were classified as sedentary. Those who walked or ran up to 10 miles per week or who participated in other sporting or leisure time activities were classified as moderately active. Total miles walked or ran per week were used to assign subjects to higher activity categories, which differed somewhat for the various analyses, due to the small number of deaths in the extreme categories. Standardized physical activity questions were not included in the examination until 1975; therefore, data on physical activity are not available from the earliest examinations.

Mortality Surveillance

Mortality surveillance in the study is current through 1989. The average length of follow-up from the date of the baseline examination to the date of death or to December 31, 1989, was $\sim$ 8 years. This observational period included 52,982 woman-years and 211,996 man-years of follow-up experience. Mortality surveillance was maintained by use of the National Death Index. The analyses reported here are based on 89 deaths among women and 601 deaths among men. Official death certificates were obtained from the departments of vital records in the 44 states in which decedents from this study had lived. An experienced nosologist coded the underlying and up to four contributing causes of death according to the *International Classification of Diseases, Ninth Edition, Revised*. There were 44 cancer deaths (*ICD-9* codes 140-208) in women and 179 cancer deaths in men. Among women these included colon cancer (seven cases), lung cancer (seven), breast cancer (12), and ovarian cancer (five). Among men these included 16 deaths that were due to colon cancer, 13 to pancreatic cancer, 43 to lung cancer, 14 to prostate cancer, 24 to lymph and blood cancer, 10 to brain cancer, and nine to skin cancer.

Statistical Procedures

Log-linear proportional hazards models were used to estimate relative risks of all-cause and cancer mortality during 1970–1989. Separate models were used for men and women. Cox's methods (8) were used to fit all models, providing point estimates, 95% confidence intervals, and hypotheses tests. Survival time in days was counted from the day of examination until either death or the end of observation on December 31, 1989. Mortality risks for grouped levels of fitness or physical activity were compared to the least-fit or the least-active category, with adjustment for baseline differences in age and year of entry (ungrouped), cigarette smoking (current or not), and presence or absence of self-reported chronic illnesses (heart attack, stroke, hypertension, diabetes) or electrocardiogram abnormalities (resting or exercising) at the baseline examination. All predictors remained fixed during follow-up. Adjusted mortality rates per 10,000 person-years of observation were computed by the indirect method. All reported P values are two-sided.

Overall trends in rates across fitness and activity levels were computed by use of ordinal scoring. The proportional hazards modeling assumption was checked by comparing empirical cumulative hazard plots grouped by categories of exposures and covariates; no appreciable violations were noted. The potential impact of subclinical morbidity at baseline was examined by discarding the first year, then the first three years, of follow-up experience; little change was noted.

RESULTS

Table 1 presents all-cause death rates among men and women by fitness categories. The low fit (least fit one-fifth) men and women had much higher death rates than did the more physically fit individuals. The test for overall trend across fitness groups was significant ($P < 0.001$) for both men and women, although there was a substantially larger difference in death rates between the first and second fitness groups than between the second and subsequent categories. Death rates appear to reach a plateau, with similar rates across the lower and upper halves of the fifth group. The

TABLE 1. All-cause mortality among ACLS participants, 1970–1989, by quintiles of fitness

Gender, fitness quintile	N	Person-years (PY)	PY%	All-cause deaths	Rate per 10,000 PY[a]	RR[a]	95% CI	P
Men								
I (low)								
622 ± 151s[b]	3436	36,114	17	197	45.9	1.00	Referent	. . .
II								
817 ± 125s	4237	40,810	19	111	25.3	0.55	(0.44–0.70)	< 0.001
III								
950 ± 122s	4560	40,610	19	110	28.0	0.61	(0.48–0.78)	< 0.001
IV								
1097 ± 133s	5765	45,510	21	102	23.8	0.52	(0.41–0.66)	< 0.001
V								
1407 ± 189s	7343	48,952	23	81	22.4	0.49	(0.37–0.64)	< 0.001
V.1[c]	3544	25,725	12	43	21.4	0.47	(0.33–0.66)	< 0.001
V.2[d]	3799	23,228	11	38	23.7	0.52	(0.36–0.74)	< 0.001
Total	25,341	211,996	100	601	28.3[e]		P for trend < 0.001	
Women								
I (low)								
377 ± 109s[b]	868	8586	16	31	33.4	1.00	Referent	. . .
II								
536 ± 107s	1047	9595	18	18	17.7	0.53	(0.30–0.95)	0.034
III								
628 ± 116s	1153	9503	18	18	18.7	0.56	(0.31–1.01)	0.054
IV								
763 ± 129s	1606	11,556	22	8	7.4	0.22	[0.10–0.49)	< 0.001
V								
1040 ± 215s	2406	13,741	26	14	12.4	0.37	(0.19–0.72)	0.003
V.1[c]	1177	7414	14	8	12.7	0.38	(0.17–0.84)	0.017
V.2[d]	1229	6327	12	6	12.1	0.36	(0.15–0.90)	0.028
Total	7080	52,982	100	89	16.8[e]		P for trend < 0.001	

[a] Adjusted for baseline differences in age, examination year, cigarette smoking, chronic illnesses, and electrocardiogram abnormalities.
[b] Mean ± SD treadmill time for category (sec).
[c] Men: lower half of fifth quintile (1278 ± 122s); women: lower half of fifth quintile (912 ± 136s).
[d] Men: upper half of fifth quintile (1528 ± 158s); women: upper half of fifth quintile (1162 ± 205s).
[e] Crude death rate per 10,000 PY.

difference in death rates is large between the lowest and highest fitness groups, with the most fit groups having a death rate that is ⩾ 50% lower than that among the less fit individuals.

Data on physical activity and all-cause mortality are shown in Table 2. Physical activity data were available only for participants examined after 1974; thus the analyses in Table 2 are limited to a subgroup of the cohort. In men the pattern of association between activity and mortality is similar to the pattern seen in the fitness analysis. Sedentary men had a higher death rate than their more active peers, and the trend across categories was statistically significant ($P = 0.01$). However, the rate estimates are more variable than those for the fitness analyses, perhaps because activity is a less precise measurement than fitness, a situation that might lead to misclassification. The death rate for the activity group V was higher than was seen for the fourth group, but group V had only 1% of the follow-up experience and only three deaths. Physical activity was not related to mortality risk for women in these analyses.

Table 3 includes data on physical fitness and cancer mortality. As for all-cause mortality, among men the greatest successive difference across fitness groups is seen between the first and second fitness categories, with a significant inverse gradient in risk ($P < 0.001$) overall. The most fit one-fifth of the men had a death rate 64% lower than that of the least-fit group. The inverse relation between fitness and cancer mortality persisted within the most-fit one-fifth of the men. The cancer death rate in the most-fit 15% of the men was only 2.8/10,000 man-years, a rate 81% lower than that for the least-fit men. Cancer mortality rates among women in the second through fifth fitness groups were lower than for the least-fit women, but the trend test was not significant ($P = 0.07$) and the 95% confidence interval (95% CI) included 1.0 for each fitness category.

Physical activity and cancer risk are shown in Table 4.

TABLE 2. All-cause mortality among ACLS participants, 1975–1989, by physical activity category

Gender, physical activity category	N	Person-years (PY)	PY%	All-cause deaths	Rate per 10,000 PY[a]	RR[a]	95% CI	P
Men								
Sedentary[b]								
855 ± 254s[c]	7920	67,546	40	256	34.6	1.00	Referent	. . .
I–II								
1072 ± 280s	11,269	77,872	46	182	24.7	0.71	(0.58–0.87)	0.001
III								
1292 ± 278s	2663	16,220	10	41	28.6	0.83	(0.59–1.16)	0.271
IV								
1453 ± 259s	1076	6,639	4	10	19.8	0.57	(0.30–1.08)	0.087
V								
1601 ± 242s	301	1895	1	3	31.7	0.92	(0.29–2.88)	0.881
Total	23,229	170,170	100	492	28.9[d]		P for trend = 0.011	
Women								
Sedentary[b]								
605 ± 224s[c]	2296	17,261	39	38	18.8	1.00	Referent	. . .
I–II								
792 ± 256s	3482	22,112	50	24	12.7	0.68	(0.39–1.17)	0.163
III								
979 ± 276s	636	3409	8	2	7.3	0.39	(0.09–1.65)	0.201
IV–V								
1158 ± 311s	260	1332	3	2	21.4	1.14	(0.27–4.80)	0.863
Total	6674	44,113	100	66	15.0[d]		P for trend = 0.217	

[a] Adjusted for baseline differences in age, examination year, cigarette smoking, chronic illnesses, and electrocardiogram abnormalities.
[b] Sedentary: no reported activities; I–II: 1–10 mi/wk of walk, jog, or run, or other activities; III: 11–20 mi/wk of walk, jog, or run; IV: 21–40 mi/wk of walk, jog, or run; V: > 40 mi/wk of walk, jog, or run.
[c] Mean ± SD treadmill time for category (sec).
[d] Crude death rate per 10,000 PY.

Cancer mortality rates among the active men were low in comparison with the rates among sedentary men. Death rates across activity classifications were variable, although the trend was significant ($P = 0.002$). There was no association between physical activity and risk of cancer in women.

DISCUSSION

The preliminary results presented here, with more than double the follow-up experience and number of deaths reported in our initial report on fitness and mortality, generally confirm and extend the earlier observations in this study (1). The strong inverse association seen in the current analyses between physical fitness and all-cause mortality in both men and women is comparable to that reported earlier, with a reduction of > 50% in risk for the most-fit one-fifth as compared with the least-fit one-fifth of the cohort. The observations for men are consistent with other reports on fitness and mortality (4, 9, 10, 11). There are no other published data on fitness and mortality in women.

We found lower all-cause death rates in the more physically active men than in the sedentary men, but this trend was not seen in women. This result is similar to our previously reported observations (7). Now, as then, we attribute the different results between men and women as being due to greater misclassification on the exposure variable. The questions on physical activity used in this study focused on running and vigorous sports. Although more adult women in the United States now participate in these activities than was the case a few decades ago, we believe that questionnaires such as the one used in this study miss many of the activities in which women frequently engage. For example, women still perform a disproportionate share of housework and childcare activities that often require substantial energy expenditure. The comparability of results for fitness and mortality in men and women leads us to believe that men and women respond similarly to an exercise stimulus. The treadmill test is an objective measure and is subject to less misclassification than physical activity questionnaires. Furthermore, exercise test performance is an excellent physiological marker for overall physical activity.

The literature on physical activity and cancer is growing rapidly, and the evidence is beginning to suggest that activity has a protective effect against colon, lung, prostate, and breast cancer (12). Our data on fitness and cancer risk show a steep inverse gradient across fitness groups for all cancers combined in men. The most-fit 15% of the men had a cancer death rate 81% lower than the least-fit one-fifth of

TABLE 3. Cancer mortality among ACLS participants, 1970–1989, by quintiles of fitness

Gender, fitness quintile	*N*	Person-years (PY)	PY%	Cancer deaths	Rate per 10,000 PY[a]	RR[a]	95% CI	*P*
Men								
I (low)								
622 ± 151s[b]	3436	36,114	17	56	14.3	1.00	Referent	. . .
II								
817 ± 125s	4237	40,810	19	34	7.8	0.54	(0.35–0.84)	0.006
III								
950 ± 122s	4560	40,610	19	32	8.0	0.56	(0.36–0.87)	0.010
IV								
1097 ± 133s	5765	45,510	21	37	8.4	0.59	(0.38–0.90)	0.016
V								
1407 ± 189s	7343	48,952	23	20	5.1	0.36	(0.21–0.61)	< 0.001
V.1[c]	3544	25,725	12	15	7.0	0.49	(0.27–0.88)	0.018
V.2[d]	3799	23,228	11	5	2.8	0.19	(0.08–0.49)	< 0.001
Total	25,341	211,996	100	179	8.5[e]		*P* for trend < 0.001	
Women								
I (low)								
377 ± 109s[b]	868	8586	16	11	13.5	1.00	Referent	. . .
II								
536 ± 107s	1047	9595	18	9	8.5	0.63	(0.26–1.54)	0.312
III								
628 ± 116s	1153	9503	18	10	10.2	0.76	(0.32–1.80)	0.528
IV								
763 ± 129s	1606	11,556	22	6	5.1	0.38	(0.14–1.03)	0.058
V								
1040 ± 215s	2406	13,741	26	8	6.4	0.47	(0.18–1.22)	0.122
V.1[c]	1177	7414	14	4	5.8	0.43	(0.13–1.37)	0.153
V.2[d]	1229	6327	12	4	7.2	0.54	(0.16–1.77)	0.305
Total	7080	52,982	100	44	8.3[e]		*P* for trend = 0.073	

[a] Adjusted for baseline differences in age, examination year, cigarette smoking, chronic illnesses, and electrocardiogram abnormalities.
[b] Mean ± SD treadmill time for category (sec).
[c] Men: lower half of fifth quintile (1278 ± 122s); women: lower half of fifth quintile (912 ± 136s).
[d] Men: upper half of fifth quintile (1528 ± 158s); women: upper half of fifth quintile (1162 ± 205s).
[e] Crude death rate per 10,000 PY.

the men. This finding may lessen concerns about high levels of exercise causing increased risk for cancer due to higher levels of free radicals produced by strenuous exercise (13). The results for activity and cancer in men were more consistent than the findings for fitness, and the reduction in risk was not as great in the fitness analysis. Overall, more active men were less likely to die of cancer than were sedentary men.

Neither activity nor fitness was significantly associated with cancer mortality in women. This result contrasts with the 1989 report (1) on fitness and cancer among women in this cohort; in those analyses fit healthy women were found to have much lower cancer death rates than were unfit healthy women. In the present analyses, cancer death rates were 53% lower among the most-fit one-fifth as compared with the least-fit one-fifth of women, but this difference was not significant ($P = 0.12$). The trend suggests a lower risk of cancer among the more-fit women, but it failed to reach statistical significance ($P = 0.07$). The small numbers of cancer deaths, however, limit these findings and warrant caution in their interpretation.

The data on fitness and cancer are intriguing, especially for men. The analyses included all cancer deaths and, while some variation across sites can be expected, this short preliminary report does not provide the opportunity to present more extensive analyses. We intend to continue these analyses and examine site-specific cancer mortality, at least in men where the numbers should be sufficient for further study, and to model the exposure-response relation using curve-fitting methods.

The data presented here support the hypothesis that an active and fit way of life delays death. The data add to the growing body of evidence that being active and fit may protect against cancer, and that high levels of activity and fitness seem unlikely to be associated with an increased risk of cancer mortality. Indeed, if moderate activity enhances the immune system response, some protection against all cancers may emerge. However, any beneficial association

TABLE 4. Cancer mortality among ACLS participants, 1975–1989, by physical activity category

Gender, physical activity category	N	Person-years (PY)	PY%	Cancer deaths	Rate per 10,000 PY[a]	RR[a]	95% CI	P
Men								
Sedentary[b]								
855 ± 254s[c]	7920	67,546	40	76	10.6	1.00	Referent	. . .
I–II								
1072 ± 280s	11,269	77,872	46	56	7.6	0.71	(0.49–1.03)	0.069
III								
1292 ± 278s	2663	16,220	10	6	4.4	0.42	(0.18–0.97)	0.042
IV–V								
1485 ± 262s	1377	8534	5	1	1.6	0.15	(0.02–1.12)	0.065
Total	23,229	170,170	100	139	8.2[d]		P for trend = 0.002	
Women								
Sedentary[b]								
605 ± 224s[c]	2296	17,261	39	14	7.2	1.00	Referent	. . .
I–II								
792 ± 256s	3482	22,112	50	13	6.1	0.84	(0.38–1.88)	0.672
III								
979 ± 276s	636	3409	8	2	6.9	0.95	(0.21–4.37)	0.948
IV–V								
1158 ± 311s	260	1332	3	2	20.6	2.85	(0.62–13.16)	0.179
Total	6674	44,113	100	31	7.0[d]		P for trend = 0.557	

[a] Adjusted for baseline differences in age, examination year, cigarette smoking, chronic illnesses, and electrocardiogram abnormalities.
[b] Sedentary: no reported activities; I–II: 1–10 mi/wk of walk, jog, or run, or other activities; III: 11–20 mi/wk of walk, jog, or run; IV–V: > 20 mi/wk of walk, jog, or run.
[c] Mean ± SD treadmill time for category (sec).
[d] Crude death rate per 10,000 PY.

between fitness and cancer risk may also be mediated through a common genetic pathway.

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	性別	男女混合	( )		( )		( )
	年齢	20-88歳（平均42.7歳）			( )		前向き研究
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図　表							
図表掲載箇所							
概　要（800字まで）	我々は、体力および身体活動と、ガンとそれ以外の死亡率との関係について、1970～1989年までの期間で、テキサス州ダラスのCooper Clinicにて、男性25341名、女性7080名を用いたコホート研究をおこなった。体力はベースラインにおいてトレッドミル運動負荷テストによって評価され、健康（運動）習慣質問紙調査に関しては自己記入式を用いた。ベースラインにおける男性と女性の平均年齢は43歳（年齢範囲：20～88歳）で、およそ8年間追跡調査された。1989年の終わりまでで、52982人年の観察が得られ、44名のガンによる死亡を含む89名の死亡を被った。男性では、年間の211996人年の観察が得られ、179名のガンによる死亡を含む601の死亡を被った。ベースラインの差を年齢、調査年数、喫煙習慣、慢性疾患、および心電図異常により補正後、男性と女性の双方で、体力とすべての死亡率との間に強い負の相関を認めた（P<0.001）。また、活動的な男性は、座業的な者に比べすべての死亡原因におけるリスクが低かった(P=0.01)。しかしながら、女性では、自己記入式質問紙による身体活動は、すべての死亡原因におけるリスクとの間に有意な関係はなかった。男性においては、ガンによる死亡リスクは、体力水準が増加していると明らかに減少するが、女性においてその傾きは、同様に予想されたものの有意ではなかった（P=0.07）。また、活動的な男性は、座業的な者に比べガンによる死亡リスクが低かった(P=0.002)が、女性においては、身体活動とガンによる死亡率との間に関係はみられなかった。						
結　論（200字まで）	男女共に、体力レベルが最も高い場合、最も低い場合に比較して全死亡リスクを約50%減らせる。男性の場合身体活動はリスク減に重要であるが、女性は不明。女性の身体活動アンケートは男性用で、女性に適していない可能性あり（家事子育てなど女性特有の活動が入っていない）。						
エキスパートによるコメント（200字まで）	体力と身体活動両面からアプローチした貴重な研究である。相互作用については検討していないが、体力が高める方が死亡リスクを減らすのに有効という論調。						

担当者　宮地 劉

ORIGINAL ARTICLE

Cardiorespiratory fitness and risk of disability pension: a prospective population based study in Finnish men

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Background: Early retiring is a major social problem in many western countries.
Aim: To investigate whether good cardiorespiratory fitness prevents disability pensioning in Finnish middle-aged men.
Methods: Subjects were a random population based sample of 1307 men who were 42–60 years old at baseline, had not retired before baseline or died during follow up, and had undergone a cycle ergometer test at baseline. Cardiorespiratory fitness was assessed at baseline with a maximal but symptom limited exercise test on an electrically braked cycle ergometer.
Results: During a follow up of 11 years on average, 790 (60.4%) men were awarded a disability pension, only 254 (19.4%) men reached the old-age pension without previous early pension, and 263 (20.1%) men were still working at the end of follow up. After adjustment for age, body mass index, alcohol consumption, smoking, education, occupation, and baseline chronic diseases, an inverse association was observed between cardiorespiratory fitness and the risk of disability pension. Men with VO_{2max} <25.98 ml/kg/min (lowest fifth) had a 3.28-fold (95% CI 1.70 to 6.32) and men with the duration of exercise test <9.54 minutes (lowest fifth) had a 4.66-fold (95% CI 2.43 to 8.92) risk of disability pension due to cardiovascular diseases compared with men in the highest fifths. Men with lowest fitness level also had an increased risk of disability pension due to musculoskeletal disorders, or all reasons combined.
Conclusions: Physical fitness is inversely associated with the risk of disability pension and especially with the risk of disability due to cardiovascular diseases.

Early retiring is a major social problem in many western countries; the situation will be worse in the near future as the mean age of the working population is increasing. Thus, there is a need to find strategies to prevent disability and to maintain working ability. Although disability pension is awarded due to a chronic disease, many other factors such as legislation, social and labour policy, work history, and individual factors intervene.[1–4] In many epidemiological studies non-medical factors have been even more important predictors of disability than medical ones.[5–9] However, few earlier studies have been longitudinal, and in few of them has disability been measured by awarded pensions.[5 10–13]

For prevention of early retirement, more information is needed about the modifiable risk factors for disability. Physical inactivity and poor cardiorespiratory fitness are potentially important modifiable risk factors for disability. It has been estimated that only one third of adult Finns exercise enough to improve their health.[14] Regular physical activity has a number of favourable cardiovascular, musculoskeletal, metabolic, hormonal, neurological, respiratory, and mental effects, and it delays many physical ageing processes and increases functional capacity.[13 15–19] Moreover, physical activity and good cardiorespiratory fitness have been associated with a reduced risk of cardiovascular diseases.[15 18 20 21] Of musculoskeletal diseases, physical activity or good physical fitness have been observed to prevent osteoporosis,[22–24] and they may also reduce the risk of low back and neck-shoulder disorders.[16 19 24 25] In osteoarthritis high dose physical activity may promote the degeneration process of the injured joint,[24 26 27] but at moderate level of activity the degeneration process of the joint may be prevented.[28 29] Physical activity has been shown to be associated with reduced symptoms of depression, but the evidence is not strong.[30]

Although there is a considerable amount of evidence about the health effects of regular physical activity and good physical fitness, there are no previous prospective population based studies concerning the association between cardiorespiratory fitness and the risk of disability pension. We therefore investigated the associations of two measures of cardiorespiratory fitness, maximal oxygen uptake from respiratory gas exchange analysis and the duration of a cycle ergometer exercise stress test, with the risk of disability pensions due to cardiovascular, musculoskeletal, and mental causes, ascertained using pension registers that cover all Finnish citizens, in a representative population based sample of middle-aged men from eastern Finland.

METHODS

Subjects

Subjects were the participants of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD),[31] an ongoing population based study, the aim of which is to investigate risk factors for chronic diseases and related outcomes. The subjects are a randomly selected sample of men living in the town of Kuopio or surrounding rural communities in eastern Finland. The men were 42, 48, 54, or 60 years old at baseline examinations between March 1984 and December 1989. Of 3235 eligible men, 2682 (82.9%) participated. Men who had retired before the baseline (n = 898), had a non-illness based pension (n = 331), had died during follow up (n = 29), or did not do the cycle ergometer test (n = 117) were excluded. Thus, the final study population included 1307 men, of whom 94.3% (n = 1233) were full time workers, 1.6% (n = 20) were part time workers, 3.2% (n = 42) were unemployed, and 0.9% (n = 12) were laid-off from work at baseline.

Assessment of cardiorespiratory fitness

Cardiorespiratory fitness was assessed at baseline between August 1986 and December 1989 with a maximal but

Main messages

- Early retiring is a significant social problem in western countries.
- Methods to prevent early retiring and to maintain working ability are needed.
- More prospective studies are needed to investigate the effect of physical activity, cardiorespiratory fitness, and exercise intervention programmes in the prevention of early retiring.
- In the present study even moderate levels of physical fitness were associated with a decreased risk of disability pension; this was most clearly seen in cardiovascular diseases.

Policy implications

- More attention should be paid to improvement of cardiorespiratory fitness by physically active lifestyle in the working aged populations.

symptom limited exercise test on an electrically braked cycle ergometer, as explained in detail previously.[15] For 318 (24.3%) men who were examined before June 1986, the testing protocol comprised a three minute warm up at 50 W followed by a step by step increase in the workload of 20 W per minute. The remaining 989 (75.7%) men were tested with a linear increase in the workload of 20 W per minute.[18] The electrocardiogram (ECG) was registered continuously during the exercise stress test. The exercise tests were supervised by an experienced physician and assisted by an experienced nurse to obtain reliable information about exercise test variables, and also for safety reasons. The exercise tests were performed between 8 and 10 am. Oxygen consumption was measured using respiratory gas exchange analysis. The maximal oxygen uptake (VO_{2max}) was defined as the highest value for or the plateau in oxygen uptake and was indexed by body weight (in ml/kg/min). The duration of exercise test was used as another measure of cardiorespiratory fitness.

Measurement of early retirement

The cohort was linked to the pension registers of the Social Insurance Institution, the Central Pension Security Institute, and some smaller pension institutions covering all the pensions of these subjects from baseline until 31 May 2000. The Social Insurance Institution is responsible for the basic social security provision for disability of every Finnish citizen from the age of 16 to 65 years. The Central Pension Security Institute is the statutory central body of the private sector pension institutions.

In Finland, when a person becomes ill and the illness causes a disability, the first step is to claim sickness allowance. The disability pension is applied if disability continues over 300 days. The individual early retirement pension is another form of a disability pension that can be applied if a person is at least 58 years old, she/he has some chronic disease reducing working capacity, and work history is long. Eligibility for both pensions requires a comprehensive medical certificate written by the attending physician and approved by an expert adviser on behalf of the Social Insurance Institution and the Central Pension Security Institute. The first diagnosis on the medical certificate made by an attending physician was regarded as the main cause of disability. In this study disability pension includes both the usual disability pensions and the individual early pensions.

Assessment of other variables

The assessment of occupation, education,[32] smoking,[33] body mass index,[34] and alcohol consumption[35] has been explained in detail previously. Chronic diseases diagnosed by a doctor were inquired in the questionnaire at baseline. The diseases were classified as follows: (1) cardiovascular diseases (coronary heart disease, cardiac insufficiency, hypertension, claudication, stroke); (2) musculoskeletal disorders (back problems, osteoarthritis); (3) mental disorders; and (4) other chronic diseases.

Statistical methods

Statistical analyses were performed using SPSS 10.0 for Windows. The associations of VO_{2max} and the duration of exercise test with the risk of disability pension were analysed using logistic regression analysis.[36] VO_{2max} and the duration of exercise test were categorised into quintiles, and men in the highest quintile were used as a reference group. Age, education, occupation, body mass index, alcohol consumption, smoking, and corresponding baseline disease (cardiovascular, musculoskeletal, mental, or other disease) were used as potential confounders.

RESULTS

Characteristics of the subjects

Table 1 shows characteristics of the subjects. Men who had been awarded disability pension had a lower VO_{2max} and a shorter duration of exercise test than men who were still working or had been at working life up to a normal old age pension. Moreover, they were older, smoked a little more, were less educated, were more likely blue collar workers, more likely had some cardiovascular disease or musculoskeletal or mental disorder, and had a slightly higher body mass index than the men in the reference group. Only 16.7% (n = 218) of the men did not have any chronic disease at baseline.

Retirement during follow up

Of 1307 men, 790 (60.4%) were awarded a disability pension during follow up, 254 (19.4%) retired at the normal pensionable age of 65 years, and 263 (20.1%) were still working at the end of follow up. The main medical diagnoses for disability were musculoskeletal disorders (n = 310, 39.2%), cardiovascular diseases (n = 226, 28.6%), and mental disorders (n = 108, 13.7%) (table 1).

Cardiorespiratory fitness and other characteristics

VO_{2max} had a strong inverse association with age, body mass index, smoking, and the prevalence of cardiovascular diseases at baseline (table 2). Moreover, the subjects with a low VO_{2max} were less likely to have a high school or middle school education than those with a high VO_{2max} The duration of exercise test was correspondingly inversely associated with age, smoking and the prevalence of cardiovascular diseases (data not shown).

Cardiorespiratory fitness and the risk of disability pension

After adjustment for age, education, occupation, alcohol consumption, smoking, and prevalent diseases at baseline, VO_{2max} and the duration of exercise test had an inverse association with the risk of all disability pensions combined (table 3). Lower VO_{2max} and shorter duration of exercise test was most strongly associated with the risk of disability due to cardiovascular diseases (odds ratio 3.58, 95% confidence

Table 1 Characteristics of the subjects

	All subjects (n = 1307)	Disability retirees (n = 790)	Working men/old age retirees (n = 517)	p value for difference between groups
Age (years)	51.3 (5.2)	52.5 (4.0)	49.4 (6.2)	<0.001
Body mass index (kg/m^2)	26.7 (3.4)	26.9 (3.5)	26.5 (3.1)	0.022
Alcohol consumption (g/week)	74.2 (110.4)	74.4 (113.6)	74.0 (105.5)	0.948
Smoking (cigarettes/day)	5.5 (10.0)	5.6 (9.9)	5.2 (10.0)	0.404
Maximal oxygen uptake (ml/kg/min)	31.8 (7.5)	30.3 (7.3)	34.0 (7.4)	<0.001
Duration of exercise test (min)	11.5 (2.5)	11.0 (2.4)	12.4 (2.4)	<0.001
Education				
High school or above (n = 120)	9.2%	5.7%	14.5%	<0.000
Middle school (n = 510)	39.1%	36.6%	42.8%	
Elementary school or less (n = 676)	51.8%	57.7%	42.6%	
Occupation				
Farmer (n = 225)	17.5%	19.1%	15,1%	<0.001
Blue collar worker (n = 467)	36.3%	39.7%	31,2%	
White collar worker (n = 593)	46.1%	41.2%	53,6%	
Diseases/disorders at baseline				
Cardiovascular diseases* (n = 653)	50.0%	58.1%	37.5%	<0.001
Musculoskeletal disorders† (n = 566)	43.3%	49.1%	34.4%	<0.001
Mental disorders‡ (n = 49)	3.7%	4.3%	2.9%	0.192
Other chronic diseases§ (n = 431)				<0.001
Reasons for disability pension				
Any reason (n = 790)	60.4%	100%	0.0%	
Cardiovascular diseases (n = 219)	16.8%	27.7%	0.0%	
Musculoskeletal disorders (n = 312)	23.9%	39.5%	0.0%	
Mental disorders (n = 108)	8.3%	13.7%	0.0%	
Other reasons¶ (n = 151)	11.6%	19.1%	0.0%	

Values are either percentages or means (standard deviations).
*Cardiovascular diseases include coronary heart disease, cardiac insufficiency, hypertension, claudication and stroke.
†Musculoskeletal disorders include back problems and osteoarthritis.
‡Mental disorders include those diagnosed by doctor or severe psychic illnesses that required hospitalisation.
§Other chronic diseases include chronic bronchitis, bronchial asthma, farmer's lung or other pneumoconiosis, lung tuberculosis, diabetes, epilepsy, thyroid illnesses, liver or pancreatic diseases, cancer, and rheumatoid arthritis.
¶Other reasons include respiratory, metabolic, dermatological, digestive tract, eye and ear diseases, injuries, cancers, malformations, and non-classifiable diseases.

interval 1.91 to 6.70, and odds ratio 4.56, 95% CI 2.40 to 8.65, respectively). Poor cardiorespiratory fitness was also associated with an increased risk of disability pension due to musculoskeletal disorders, and also showed a weak inverse association with disability due to mental disorders (table 3).

Table 2 Characteristics of the subjects in the fifths of maximal oxygen uptake

	Quintiles of maximal oxygen uptake (ml/kg/min)					p value for difference between groups
	I (low)	II	III	IV	V (high)	
Age (years)	53.9 (3.9)	52.3 (4.6)	51.2 (5.0)	50.4 (5.3)	48.5 (5.5)	<0.001
Body mass index (kg/m^2)	28.4 (4.2)	27.4 (3.3)	26.6 (3.1)	26.2 (2.7)	25.2 (2.4)	<0.001
Alcohol consumption (g/week)	79.8 (112.9)	74.8 (110.6)	83.7 (134.0)	61.3 (86.8)	71.0 (100.9)	0.177
Smoking (cigarettes/day)	7.5 (11.5)	6.3 (10.4)	5.6 (10.1)	5.0 (10.0)	3.0 (6.7)	<0.001
Education						
High school or above (n = 120)	1.0%	1.8%	2.5%	2.2%	1.7%	0.001
Middle school (n = 510)	6.6%	6.9%	8.2%	8.0%	9.3%	
Elementary school or less (n = 676)	12.6%	10.6%	9.8%	9.0%	9.7%	
Occupation						
Farmer (n = 225)	3.5%	3.6%	3.9%	4.0%	2.5%	0.096
Blue collar worker (n = 467)	8.0%	7.2%	6.4%	6.1%	8.6%	
White collar worker (n = 593)	8.9%	8.6%	9.9%	9.1%	9.7%	
Diseases/disorders at baseline						
Cardiovascular diseases* (n = 653)	15.0%	11.3%	9.9%	6.9%	6.9%	<0.001
Musculoskeletal disorders† (n = 556)	9.5%	9.0%	9.1%	7.7%	8.0%	0.163
Mental disorders‡ (n = 49)	0.7%	1.2%	0.8%	0.4%	0.7%	0.138
Other chronic diseases§ (n = 431)	8.0%	7.0%	6.4%	5.8%	5.7%	0.017
Reasons for disability pension						
Any reason (n = 790)	15.2%	12.9%	12.6%	10.7%	9.0%	<0.001
Cardiovascular diseases (n = 219)	6.4%	3.4%	2.9%	2.5%	2.1%	
Musculoskeletal disorders (n = 312)	5.0%	5.4%	5.7%	4.4%	3.4%	
Mental disorders (n = 108)	2.0%	1.9%	2.3%	1.7%	2.2%	
Other reasons¶ (n = 151)	1.8%	2.4%	1.7%	2.1%	1.3%	

Values are either means (standard deviations) or percentages.
*Cardiovascular diseases include coronary heart disease, cardiac insufficiency, hypertension, claudication, and stroke.
†Musculoskeletal disorders include back problems and osteoarthritis.
‡Mental disorders include those diagnosed by doctor or severe psychic illnesses that required hospitalisation.
§Other chronic diseases include chronic bronchitis, bronchial asthma, farmer's lung or other pneumoconiosis, lung tuberculosis, diabetes, epilepsy, thyroid illnesses, liver or pancreatic diseases, cancer, and rheumatoid arthritis.
¶Other reasons include respiratory, metabolic, dermatological, digestive tract, eye and ear diseases, injuries, cancers, malformations, and non-classifiable diseases.

Table 3 Adjusted relative risk (OR) of disability pension by disease category in fifths of maximal oxygen uptake and the duration of exercise test

	Any reason (n=790) OR (95% CI)	Cardiovascular diseases* (n=219) OR (95% CI)	Musculoskeletal disorders† (n=312) OR (95% CI)	Mental disorders‡ (n=108) OR (95% CI)	Other reasons§ (n=151) OR (95% CI)
Maximal oxygen uptake (ml/kg/min)					
7.38–25.67	2.08 (1.36–3.19)	3.58 (1.91–6.70)	2.20 (1.26–3.83)	1.44 (0.73–2.83)	2.04 (0.96–4.34)
25.68–29.47	1.72 (1.15–2.56)	2.10 (1.11–3.93)	2.03 (1.20–3.44)	1.10 (0.57–2.13)	2.23 (1.11–4.47)
29.48–33.10	1.73 (1.18–2.54)	1.93 (1.03–3.60)	2.18 (1.31–3.64)	1.41 (0.77–2.59)	1.58 (0.78–3.21)
33.11–37.61	1.54 (1.05–2.25)	1.85 (1.00–4.57)	1.71 (1.02–2.89)	0.96 (0.51–1.81)	1.89 (0.95–3.74)
37.62–65.40 (reference)	1.0	1.0	1.0	1.0	1.0
Duration of exercise test (min)					
1.50–9.54	2.33 (1.50–3.61)	4.56 (2.40–8.65)	1.98 (1.12–3.48)	2.29 (1.12–4.70)	2.07 (1.01–4.24)
9.55–10.82	1.54 (1.04–2.30)	2.14 (1.13–4.06)	1.71 (1.01–2.89)	1.29 (0.65–2.58)	1.40 (0.71–2.75)
10.83–12.06	1.73 (1.18–2.51)	2.43 (1.31–4.48)	1.96 (1.19–3.24)	1.93 (1.05–3.56)	0.95 (0.47–1.93)
12.07–13.49	1.46 (1.01–2.11)	2.00 (1.07–3.74)	1.44 (0.86–2.41)	1.33 (0.71–2.51)	1.38 (0.73–2.61)
13.50–21.85 (reference)	1.0	1.0	1.0	1.0	1.0

Adjusted for age, education, occupation, body mass index, alcohol consumption, smoking, and respective reason for retirement (cardiovascular diseases, musculoskeletal disorders, mental disorders, or other chronic diseases).
*Cardiovascular diseases include coronary heart disease, cardiac insufficiency, hypertension, claudication, and stroke.
†Musculoskeletal disorders include back problems and osteoarthritis.
‡Mental disorders include those diagnosed by doctor or severe psychic illnesses that required hospitalisation.
§Other reasons include respiratory, metabolic, dermatological, digestive tract, eye and ear diseases, injuries, cancers, malformations, and non-classifiable diseases.

DISCUSSION

The novel finding of this prospective population based study is a strong association between poor cardiorespiratory fitness and an increased risk of disability pension. A low VO_{2max} and a short duration of exercise test were associated with an increased risk of disability pension, especially due to cardiovascular diseases, but also due to musculoskeletal disorders, when other potential risk factors were controlled for.

Physical activity and cardiovascular fitness have been shown to have favourable effects on cardiovascular and musculoskeletal systems.[13 16 17 37] There is epidemiological evidence showing that regular physical activity and good cardiorespiratory fitness are effective in the prevention of cardiovascular diseases and premature mortality.[18 20 38–40] In the same population study of middle-aged Finnish men we have previously found that good cardiorespiratory fitness is associated with a reduced risk of coronary heart disease,[15] and with reduced overall, cardiovascular, and non-cardiovascular mortality.[18]

Physical exercise promotes musculoskeletal health by preventing osteoporosis,[22] and with moderate dosing probably also low back and neck-shoulder disorders[16 19 24 25] as well as osteoarthritis of non-injured joints.[24 26 27] In addition to prevention of musculoskeletal diseases, physical activity appears to be favourable in the treatment of osteoporosis,[22] chronic low back disorders,[24 41] and osteoarthritis.[14 24 27 42]

There is much less evidence of the primary and secondary prevention of mental disorders by physical activity and physical fitness. Two earlier studies showed a reduction in symptoms of depression attributable to both aerobic and resistance exercise.[30 43]

Thus, there exists relatively good evidence of the health effects of physical exercise and cardiorespiratory fitness with respect to cardiovascular and some musculoskeletal disorders. However, disability pension has multifactorial aetiology and a preceding disease explains only a part of it.[6–9] There are few earlier studies on the role of cardiorespiratory fitness or physical activity in the prevention of work disability or in maintaining work ability. In a Finnish longitudinal study, physical exercise predicted a good work ability index.[44] In the same study cardiorespiratory capacity correlated with work ability in subjects with no musculoskeletal disorders, but not in those who had musculoskeletal or cardiovascular disease.[45]

During the past decade there has been a considerable amount of effort in occupational health services to promote work ability by carrying out different exercise intervention programmes. At the moment there is a strong evidence of their positive effects on physical activity[46 47] and musculoskeletal disorders[48 49] provided that individual support is included in these programmes.[50 51]

The strengths of the present study include the representative population based sample of men at the age of high occurrence of disability pension and the long follow up time of the study. Cardiorespiratory fitness, an objective marker of physical activity, was assessed accurately at baseline by a direct measurement of VO_{2max} during a maximal symptom limited exercise stress test on a cycle ergometer, a method that is widely used in clinical practise. However, the exercise test was performed only once and it is possible that cardiorespiratory fitness may have changed during follow up. We had reliable data on disability pension decisions, since the pensions were ascertained using pension registers that cover all Finnish citizens. Extensive measurements of risk factors at baseline enabled us to control for the potential confounders comprehensively. Although we carefully adjusted for a number of possible confounders, there may still be some residual confounding. It is, however, unlikely that this would explain the observed relations. In the present study, only men were examined and these findings cannot be directly generalised to women.

Over 80% of the middle-aged men in the present cohort had at least one chronic disease at baseline, which provides one explanation for the high incidence of disability pension during follow up. Previous studies have shown that the prevalence of chronic diseases in eastern Finland is higher than in other parts of Finland[52]; on the other hand the incidence and mortality from coronary heart disease in Finland is among the highest in the world.[53] The high prevalence of chronic diseases and the high incidence of disability pension during follow up can also be explained by low educational level and heavy occupations in the present cohort. The incidence of disability pension during the follow up period in the present study is of about the same grade as in Finland generally.[1] It is, however, difficult to make international comparisons because the age of the subjects and the length of follow up varies between the studies.[13 54]