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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

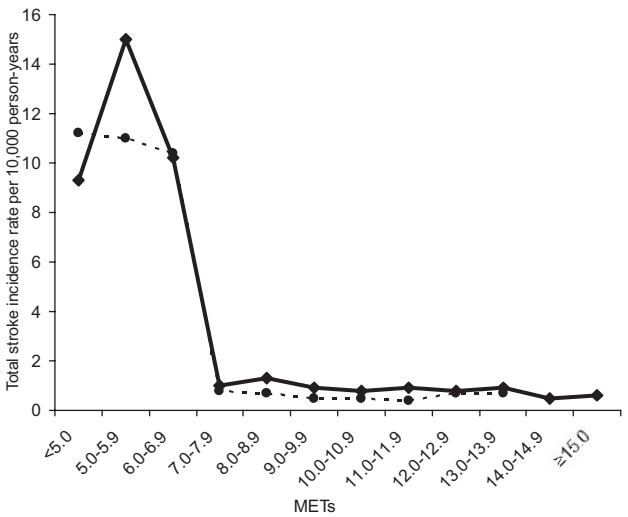

Figure. Age-adjusted rates of total stroke (per 10 000 person-years) according to 1-MET increments of cardiorespiratory fitness in men (solid line) and women (dashed line).

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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