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Cardiorespiratory Fitness and Incident Stroke Types: The FIT (Henry Ford ExercIse Testing) Project

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Abstract

Objective: To study the association between cardiorespiratory fitness (CRF) and incident stroke types.

Patients and Methods: We studied a retrospective cohort of patients referred for treadmill stress testing in the Henry Ford Health System (Henry Ford ExercIse Testing Project) without history of stroke. CRF was expressed by metabolic equivalents of task (METs). Using appropriate *International Classification of Diseases, Ninth Revision* codes, incident stroke was ascertained through linkage with administrative claims files and classified as ischemic, hemorrhagic, and subarachnoid hemorrhage (SAH). Multivariable-adjusted Cox proportional hazards models examined the association between CRF and incident stroke.

Results: Among 67,550 patients, mean ± SD age was 54±13 years, 46% (n=31,089) were women, and 64% (n=43,274) were white. After a median follow-up of 5.4 (interquartile range 2.7-8.5) years, a total of 7512 incident strokes occurred (6320 ischemic, 2481 hemorrhagic, and 275 SAH). Overall, there was a graded lower incidence of stroke with higher MET categories. Patients with METs of 12 or more had lower risk of overall stroke [0.42 (95% CI, 0.36-0.49)], ischemic stroke [0.69 (95% CI, 0.58-0.82)], and hemorrhagic stroke [0.71 (95% CI, 0.52-0.95)].

Conclusion: In a large ethnically diverse cohort of patients referred for treadmill stress testing, CRF is inversely associated with risk for ischemic and hemorrhagic stroke.

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Stroke remains a leading cause of long-term disability in the United States. The annual incidence rate of stroke is 695,000 cases per year. Stroke ranks number 5 among all causes of death, with nearly 133,000 attributable deaths.[1] Modifiable risk factors, including physical activity, account for nearly 90% of the population-attributable risk for stroke.[2] Although physical activity is self-reported and subject to measurement error, cardiorespiratory fitness (CRF) testing is an objective and reproducible marker of cardiovascular health in the general adult population.[3-5]

CRF refers to the ability of the heart and lungs to deliver oxygenated blood to the working muscles of the body to perform dynamic exercise. Importantly, it integrates the upstream effects of physical activity, genetics, risk factor, and disease burden across an individual's lifespan. CRF is typically measured by measuring peak or maximal oxygen uptake (Vo_2max, in mL/kg/min), which represents the body's maximal ability to transport and use oxygen when performing work. During this test, patients undergo a maximal graded test on a treadmill or bicycle. The exercise test becomes gradually more difficult and Vo_2max is established

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when oxygen consumption reaches its peak or levels off at the time that the patient ends the test. An alternative way of assessing CRF during a treadmill exercise stress test is based on achieved speed and elevation, whereby CRF is expressed in metabolic equivalents of task (METs) using output data from the Quinton treadmill controller.[6]

Lower CRF is associated with higher risk for cardiovascular risk factors, atrial fibrillation (AF), coronary heart disease, all-cause mortality, and cardiovascular mortality.[7-11] Previous studies have also demonstrated an inverse association between baseline and change in CRF with risk for stroke. However, these studies have included males only, lacked ethnic diversity, or exclusively assessed overall stroke outcomes rather than stroke types.[12-16] We therefore evaluated the association between CRF and risk for incident stroke in a sex-balanced and multiethnic cohort with long-term follow-up for overall stroke including stroke types (ischemic, hemorrhagic, and subarachnoid hemorrhage [SAH]). We hypothesized that CRF is inversely associated with stroke types independent of traditional risk factors.

PATIENTS AND METHODS

Study Design

We used data from the Henry Ford ExercIse Testing (FIT) Project, a retrospective cohort of patients who were referred for exercise stress testing. The methods of the FIT Project have been previously described.[17,18] The FIT Project is a single-health-system investigator-initiated study of 69,885 consecutive patients who underwent physician-referred treadmill stress testing at Henry Ford Health System—affiliated hospitals and ambulatory care centers in metropolitan Detroit, Michigan, between January 1991 and May 2009. Patients younger than 18 years at the time of stress testing or those who underwent pharmacologic stress testing, modified Bruce, and other non-Bruce protocol tests (~0.5%) were not included in the study. The FIT Project was approved by the Henry Ford Health System Institutional Review Board.[17] The data that support the findings of this study are available from the corresponding author on reasonable request.

Exclusion Criteria

Individuals with prior stroke at baseline (n=1340), missing CRF data (n=938), or lacking information for follow-up time for incident stroke (n=57) were excluded from the present analysis.

Assessment of CRF

All patients underwent symptom-limited maximal treadmill stress testing using a standard Bruce protocol.[6] Following American College of Cardiology/American Heart Association guidelines, stress testing was terminated at the discretion of the supervising clinician for potentially life-threatening reasons, including abnormal hemodynamic changes, arrhythmias, ischemic ST-segment changes, symptoms such as chest pain or shortness of breath limiting exercise, or if the patient could no longer continue.[19] CRF (expressed in METs) was assessed using output data from the Quinton treadmill controller output data based on speed and elevation achieved during stress testing.[6] METs were categorized a priori into 4 groups: less than 6, 6 to 9, 10 to 11, and 12 or more. These categories were selected because they best fit the distribution of the FIT Project and were used in all prior publications. Additionally, prior studies have demonstrated a graded association between these MET categories and risk for cardiovascular outcomes and all-cause mortality.[5,9,10,20]

Follow-up and Ascertainment of Stroke

Incident stroke was ascertained by linkage with claims files and classified using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes into ischemic stroke (433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434, 434.01, 434.11, 434.91, 436, 437, and 438), hemorrhagic stroke (431 and 432), and SAH (430). Use of *ICD-9* codes for stroke ascertainment was validated in a prior report from the Atherosclerosis

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Risk in Communities Study,[21] which showed that the codes had 76% positive predictive value and 68% sensitivity compared with 72% positive predictive value and 83% sensitivity based on the Atherosclerosis Risk in Communities adjudicated stroke diagnosis.

A diagnosis of incident stroke was considered present if the appropriate *ICD-9* code was identified in 3 or more follow-up outpatient encounters. The requirement of at least 3 follow-up encounters was chosen a priori to increase the specificity of stroke diagnosis. This was used in all outcomes in the FIT Project. This was done to primarily avoid misclassification of patients for whom "rule out stroke" could have been coded as incident stroke.

Patients who experienced more than 1 stroke type were censored after the occurrence of the first stroke. For example, if a patient had an ischemic stroke at time A and another ischemic stroke at a later time B, they were censored at both time A for overall stroke. However, in analyses of stroke type, they were censored at times A and B. This is why the sum of stroke types is greater than the number of overall stroke outcomes in this study. An incident nonstroke outcome (such as coronary artery disease [CAD]) occurring before the development of stroke did not result in censoring. Patients were censored at the time of death or at their last contact with the Henry Ford Health System when ongoing coverage with the health plan could no longer be confirmed to minimize bias from loss to follow-up.

Assessment of Covariates

Data Collection. A nurse and/or clinical exercise physiologist collected demographic information, indication for stress testing, medical history, and medication use on the day of the stress test. Other risk factors were gathered by self-report at the time of the test, then supplemented by a retrospective search of the electronic medical record and administrative databases consisting of medical records, laboratory values, and claims files. A database-verified diagnosis was considered present when the appropriate code was listed in at least 3 separate encounters within the health system. Medication use was supplemented using pharmacy claims data and classified into common indications (eg, antihypertensive, lipid or glucose lowering, and warfarin).

Covariate Definitions for Risk Factors of Interest. Race/ethnicity was defined exclusively by self-report. Obesity was self-reported and/or assessed by the clinician or defined based on height and weight data as body mass index (calculated as the weight in kilograms divided by the height in meters squared) of 30 or more kg/m^2. Current smoking was defined as self-reported active smoking at the time of stress testing. Indication for stress testing was obtained from the stress test requisition form provided by the referring physician and subsequently categorized into common indications (eg, chest pain, shortness of air, and evaluation for possible ischemia; Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Diabetes mellitus was defined as a previous diagnosis of diabetes, glucose-lowering medication use including insulin, or a database-verified diagnosis. Hypertension was defined as a previous diagnosis of hypertension, antihypertensive medication use, or a database-verified diagnosis; measured blood pressure at the time of the test was not used to diagnose hypertension. Dyslipidemia was defined as previous diagnosis of any major lipid abnormality, lipid-lowering medication use, or a database-verified diagnosis. Family history of CAD was defined as CAD in a first-degree relative. Personal history of CAD was defined as prior coronary angioplasty, myocardial infarction, coronary artery bypass surgery, or obstructive CAD on angiography. Prior AF or flutter was defined as prior clinical diagnosis of at least paroxysmal AF. Prior congestive heart failure (CHF) was defined as prior clinical diagnosis of systolic or diastolic heart failure.

Incident nonstroke outcomes (AF, hypertension, diabetes, and CAD) were

TABLE 1. Baseline Characteristics of Study Cohort By Cardiorespiratory Fitness Categories[a,b,c]

	METs <6 (n=11,389)	METs 6-9 (n=18,659)	METs 10–11 (n=23,330)	METs ≥12 (n=14,172)	Overall (N=67,550)	*P*
Demographic characteristics						
Age (y), mean ± SD	64±12	58±12	52±11	46±10	54±13	<.001
Female sex, no. (%)	6757 (59)	10,696 (57)	10,718 (46)	2898 (20)	31,089 (46)	<.001
Race/ethnicity, no. (%)						<.001
White	6387 (56)	11,252 (60)	15,288 (66)	10,347 (73)	43,274 (64)	
Black	4650 (40)	6361 (34)	6223 (27)	2569 (18)	19,713 (29)	
Other	442 (4)	1046 (6)	1819 (8)	1256 (9)	4656 (7)	
Comorbid conditions, no. (%)						
Hypertension	9854 (87)	14,091 (76)	13,977 (60)	6239 (44)	44,161 (65)	<.001
Atrial fibrillation	808 (7)	662 (3)	512 (2)	226 (2)	2208 (3)	<.001
Atrial flutter	39 (0.3)	27 (0.1)	16 (0.1)	8 (0.1)	90 (0.1)	<.001
Diabetes mellitus	3759 (33)	4617 (25)	3655 (16)	1091 (8)	13,122 (19)	<.001
Hyperlipidemia	4982 (44)	9065 (49)	10,477 (45)	5449 (38)	29,973 (44)	<.001
Obesity	2512 (22)	5725 (31)	5482 (24)	1377 (10)	15,096 (22)	<.001
Sedentary lifestyle	3853 (34)	7393 (40)	8369 (36)	3497 (25)	23,112 (34)	<.001
Family history of coronary artery disease	4800 (42)	9301 (50)	12,377 (53)	7462 (53)	33,940 (50)	<.001
History of coronary artery disease	3548 (31)	3099 (17)	2138 (9)	802 (6)	9587 (14)	<.001
History of smoking	4457 (39)	8117 (44)	10,075 (43)	5377 (38)	28,026 (41)	<.001
Body mass index (kg/m^2), mean ± SD	31.2±7.2	30.1±6.4	29.0±5.2	26.9±4.1	29.4±5.9	<.001
Laboratory measurements						
Low-density lipoprotein cholesterol (mg/dL), mean ± SD	125±40	125±38	126±37	128±36	126±38	<.001
Very low-density lipoprotein cholesterol (mg/dL), mean ± SD	30±15	30±15	29±16	28±15	29±15	<.001
High-density lipoprotein cholesterol (mg/dL), mean ± SD	49±16	51±16	50±16	49±15	50±15	<.001
Total cholesterol (mg/dL), mean ± SD	202±46	205±44	207±42	205±40	205±43	<.001
Hemoglobin A_{1c} (%), mean ± SD	7.5±1.9	7.2±1.8	6.8±1.7	6.4±1.4	7.0±1.8	<.001
Medication use, no. (%)						
β-Blockers	3677 (32)	5001 (27)	4415 (19)	1627 (11)	14,720 (22)	<.001
Angiotensin-converting enzyme inhibitors	3389 (30)	4416 (24)	3698 (16)	1304 (9)	12,807 (19)	<.001
Angiotensin receptor blockers	401 (4)	711 (4)	597 (3)	166 (1)	1875 (3)	<.001
Calcium channel blockers	2688 (24)	3214 (17)	2572 (11)	807 (6)	9281 (14)	<.001
Diabetes medications	1580 (14)	2230 (12)	1607 (7)	377 (3)	5794 (9)	<.001
Antidepressants	832 (7)	1588 (9)	1865 (8)	711 (5)	4996 (7)	<.001
Statins	2718 (24)	4820 (26)	4624 (20)	1834 (13)	13,996 (21)	<.001
Aspirin	3516 (31)	4743 (25)	4516 (19)	2042 (14)	14,817 (22)	<.001
Warfarin	431 (4)	276 (1)	171 (1)	59 (0.4)	937 (1)	<.001
Lung disease medications	1320 (12)	1853 (10)	1896 (8)	811 (6)	5880 (9)	<.001

[a]MET = metabolic equivalent of task.

[b]Continuous variables are expressed as mean ± SD, and categorical variables, as count (percentage). Differences were tested using analysis of variance or median test for continuous variables and χ^2 test for categorical variables.

[c]SI conversion factors: To convert cholesterol values to mmol/L, multiply by 0.0259.

ascertained by linkage with claims files from services delivered by the system-affiliated group practice or reimbursed by the system's health plan. Linkage was performed by use of the appropriate *ICD-9* codes (427.31, 401.XX, 410.XX, and 250.XX for AF,[10] hypertension,[22] diabetes,[9] and CAD,[11] respectively) and/or *Current Procedural Terminology* codes. Adjustment for nonstroke outcomes is important because preventive medications can be initiated or intensified following their occurrence, which may affect risk for subsequent stroke.

Statistical Analyses

Baseline characteristics were categorized by METs (<6, 6-9, 10-11, and ≥12) and differences were tested using χ^2 test for categorical variables and analysis of variance for continuous variables.

Incidence rates of overall stroke and stroke types were calculated as number of events per 1000 person-years for each MET group. Unadjusted Kaplan-Meier curves were constructed using time-to-stroke data with log-rank testing for significant differences.

Multivariable-adjusted Cox proportional hazard models were used to study the association of CRF with stroke after confirming the proportionality assumption using log-log plots. In continuous analyses, hazard ratios (HRs) were calculated per 1-unit higher MET. In categorical analyses, HRs were calculated for each MET category using METs less than 6 as the reference group, and *P* value for linear trend was calculated. Hazard ratios (95% CI) were also visualized using bar graphs.

Adjustment variables were selected a priori based on a search of the literature. Models were adjusted for age, sex, race/ethnicity, hypertension, diabetes mellitus, personal history of CAD, family history of CAD, hyperlipidemia, cigarette smoking, history of obesity, sedentary behavior, history of AF, medication use (β-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, statin, insulin, oral hypoglycemics, lung disease medication, and antidepressant), reason for stress test, adequate test (defined as achieving 85% maximal predicted heart rate), incident CAD, incident AF, incident hypertension, and incident diabetes mellitus (all occurring before the development of stroke and coded as binary).

We assessed for interaction of METs with age, sex, race/ethnicity, history of hypertension, diabetes mellitus, and hyperlipidemia. We also stratified results by warfarin use, history of CAD, history of CHF, or incident AF outcomes.

A 2-sided $P<.05$ was considered statistically significant. All analyses were performed using Stata/IC, version 13 (StataCorp).

RESULTS

Baseline Characteristics

Our study cohort consisted of 67,550 individuals without history of stroke with a mean ± SD age of 54±13 years, 46% (n=31,089) women, 64% (n=43,274) white, and 29% (n=19,713) black (Table 1). The distribution of MET categories was as follows: 17% with METs <6, 28% METs 6-9, 35% METs 10-11, and 21% METs ≥12. Compared with patients who achieved METs less than 6 on treadmill stress testing, those with METs of 12 or more were on average younger and more likely to be male and white but less likely to have hypertension, AF, diabetes mellitus, hyperlipidemia, or smoking (all $P<.05$).

Incidence Rates

During a median follow-up of 5.4 (2.7-8.5) years, there were 7512 overall stroke outcomes, including 6320 ischemic strokes, 2481 hemorrhagic strokes, and 275 SAHs. There was a stepwise lower incidence and cumulative survival of overall stroke, ischemic stroke, hemorrhagic stroke, and SAH with higher MET categories (all $P<.05$; Table 2; Figure 1).

Multivariable Analyses

In multivariable analyses (model 2), there was significantly lower risk for stroke with higher METs. For example, compared with METs less than 6, the effect estimates for those with METs of 12 or more were 0.42 (95% CI, 0.36-0.49) for overall stroke, 0.69 (95% CI, 0.58-0.82) for ischemic stroke, and 0.71 (95% CI, 0.52-0.95) for hemorrhagic stroke (Table 3; Figure 2). Effect estimates for METs 6 to 9 and 10 to 11 were only significant for overall stroke but not stroke types. Each 1-unit higher MET on treadmill stress testing was significantly associated with lower risk for overall stroke (HR, 0.91; 95% CI, 0.89-0.92). Estimates were

TABLE 2. Incidence Rates of Incident Stroke by Cardiorespiratory Fitness Categories

	No. of Events	Incidence Rate (per 1000 person-y)
Overall stroke		
METs <6	2705	41.9
METs 6-9	2377	22.0
METs 10-11	1767	12.5
METs ≥12	663	6.7
P	—	<.001
Ischemic stroke		
METs <6	2343	36.0
METs 6-9	2014	18.5
METs 10-11	1440	10.1
METs ≥12	523	5.3
P	—	<.001
Hemorrhagic stroke		
METs <6	961	14.1
METs 6-9	763	6.8
METs 10-11	533	3.7
METs ≥12	224	2.2
P	—	<.001
Subarachnoid hemorrhage		
METs <6	97	1.4
METs 6-9	84	0.7
METs 10-11	64	0.4
METs ≥12	30	0.3
P	—	<.001

MET = metabolic equivalent of task.

similar for ischemic (HR, 0.97; 95% CI, 0.95-0.99) and hemorrhagic stroke (HR, 0.97; 95% CI, 0.95-1.00), but only significant for the former. Results for SAH were not significant in all analyses.

Interaction Analyses

1. Age, Sex, and Race/Ethnicity With METs. There was a graded lower risk for overall stroke with higher METs for all age groups, though effect estimates were stronger in those younger than 40 years. Similarly, there was a graded lower risk for overall stroke for both men and women, with effect estimates slightly stronger among men. Both whites and blacks had a stepwise lower risk for overall stroke, but estimates were not significant in other race/ethnic groups. In analyses of stroke type, there was significantly lower risk for ischemic stroke only for those with METs of 12 or more who were older than 60 years, men, white or black (Supplemental Tables 2 and 3, available online at http://www.mayoclinicproceedings.org). Results for hemorrhagic stroke and SAH were both not significant.

2. Hypertension, Diabetes Mellitus, and History of AF With METs. There was an incremental lower risk for overall stroke with higher METs regardless of hypertension or diabetes mellitus status. Results for ischemic stroke were significant among those with METs of 12 or more who did not have hypertension or diabetes mellitus. Results for hemorrhagic stroke were only significant among those with METs of 12 or more and without hypertension. Results for SAH were not significant. We further adjusted for systolic and diastolic blood pressures at peak exercise and HRs remained nonsignificant among patients with baseline diabetes mellitus or hypertension. METs of 12 or more remained significantly associated with lower risk for overall stroke regardless of history of AF but only significantly associated with ischemic or hemorrhagic stroke among those without history (Supplemental Table 4, available online at http://www.mayoclinicproceedings.org).

Sensitivity Analyses

In stratified analyses, METs of 12 or more were significantly associated with lower risk for overall stroke regardless of warfarin use, history of CAD, or incident AF, but results were not significant among individuals with a history of CHF. METs of 12 or more were not significantly associated with either ischemic or hemorrhagic stroke among individuals using warfarin, with a history of CHF, or those who developed incident AF (Supplemental Table 5, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

We found that higher CRF, in particular METs of 12 or more, was associated with lower risk for overall stroke, including ischemic and hemorrhagic stroke. There was no association between CRF and SAH.

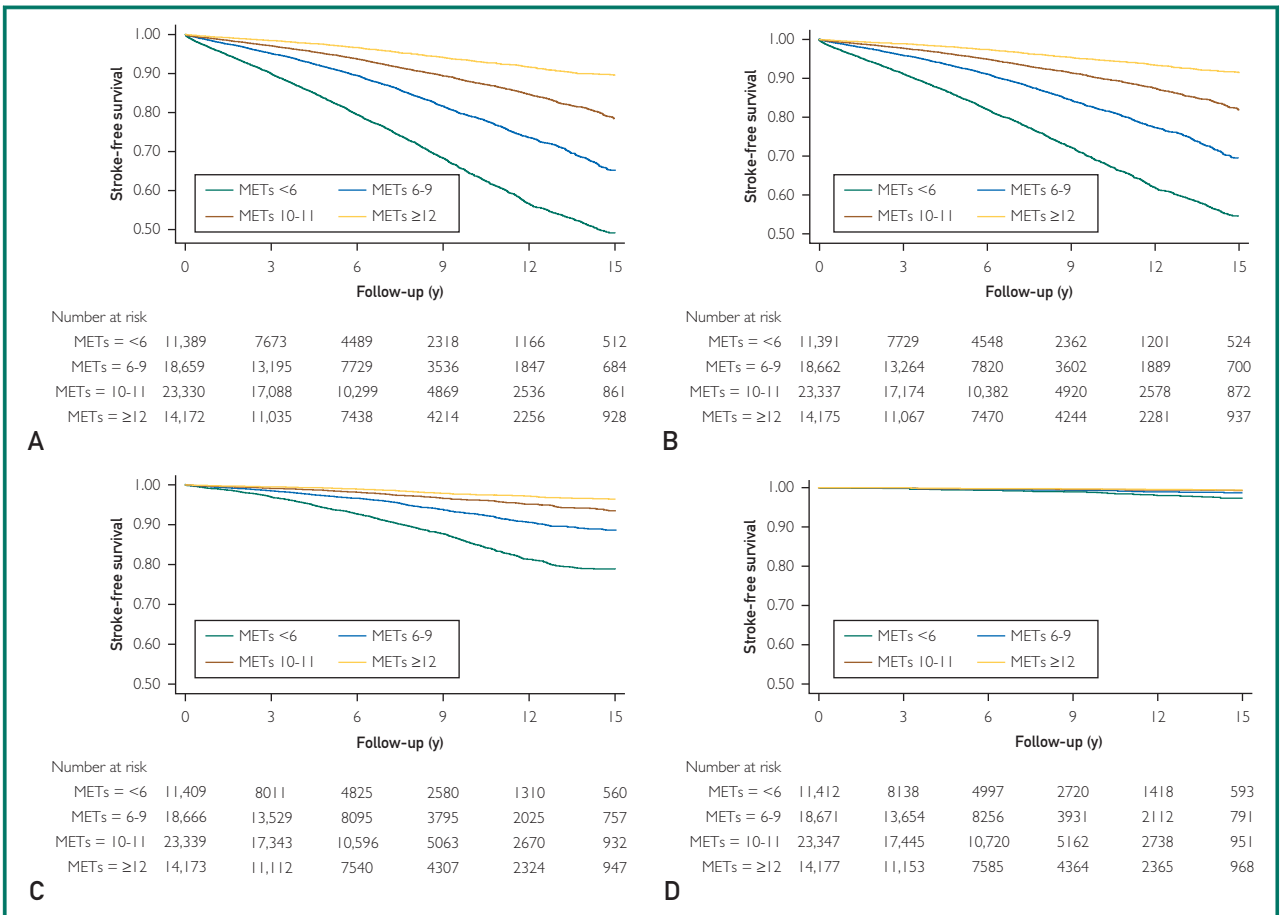

FIGURE 1. Unadjusted Kaplan-Meier graphs for the association of cardiorespiratory fitness and incident stroke. A, Overall stroke. B, Ischemic stroke. C, Hemorrhagic stroke. D, Subarachnoid hemorrhage. Log-rank testing $P<.001$ for all stroke outcomes.

Strengths of our study include a diverse sample of high-risk men and women of different race/ethnicities with long-term follow-up for stroke types.

Because exercise may be the only modifiable factor that can affect CRF,[23] engaging in at least 30 minutes or more on most days of the week of moderate to vigorous physical activity may lower risk for stroke.[2,24,25] Prior studies have established that higher CRF is associated with lower cardiovascular risk factor burden,[26] which may possibly mediate the association of CRF with incident cardiovascular disease.[27]

In the present study, we have demonstrated an inverse association between continuous METs and risk for stroke, which suggests that higher METs may be beneficial for stroke reduction. Men with METs of 12 or more had significantly lower risk for ischemic stroke (HR, 0.64; 95% CI, 0.51-0.80), but effect estimates in women were not significant (HR, 0.80; 95% CI, 0.59-1.07). Although the statistical interaction term was borderline significant ($P=.049$), it is unlikely that there are biological differences explaining this sex discrepancy. We therefore expect both men and women to derive benefit from improved CRF (particularly METs $\geq$12) for ischemic stroke reduction.

The statistically significant results among blacks and whites are likely the result of sample size because analyses in other race/ethnicities were underpowered. Similar to sex differences, there are likely no biological differences explaining the discrepant results by race/ethnicity.

TABLE 3. Multivariable-Adjusted Hazard Ratios (95% CI) for the Association of Cardiorespiratory Fitness and Incident Stroke[a]

	Model 1[b]	Model 2[c]
Overall stroke		
METs <6	1 (reference)	1 (reference)
METs 6-9	0.71 (0.65-0.77)	0.73 (0.67-0.80)
METs 10-11	0.55 (0.49-0.61)	0.58 (0.52-0.65)
METs ≥12	0.38 (0.33-0.44)	0.42 (0.36-0.49)
P for trend[d]	<.001	<.001
1-unit METs	0.90 (0.89-0.91)	0.91 (0.89-0.92)
Ischemic stroke		
METs <6	1 (reference)	1 (reference)
METs 6-9	0.72 (0.66-0.80)	1.00 (0.90-1.10)
METs 10-11	0.55 (0.49-0.61)	0.91 (0.81-1.03)
METs ≥12	0.38 (0.32-0.45)	0.69 (0.58-0.82)
P for trend[d]	<.001	<.001
1-unit higher METs	0.90 (0.89-0.91)	0.97 (0.95-0.99)
Hemorrhagic stroke		
METs <6	1 (reference)	1 (reference)
METs 6-9	0.64 (0.54-0.75)	1.03 (0.87-1.24)
METs 10-11	0.44 (0.37-0.54)	0.93 (0.75-1.14)
METs ≥12	0.32 (0.24-0.42)	0.71 (0.52-0.95)
P for trend[d]	<.001	.05
1-unit higher METs	0.88 (0.86-0.90)	0.97 (0.95-1.00)
Subarachnoid hemorrhage		
METs <6	1 (reference)	1 (reference)
METs 6-9	0.85 (0.51-1.41)	0.98 (0.48-2.03)
METs 10-11	0.71 (0.40-1.27)	0.64 (0.28-1.46)
METs ≥12	0.52 (0.23-1.19)	0.88 (0.28-2.77)
P for trend[d]	.11	.49
1-unit higher METs	0.94 (0.87-1.02)	1.97 (0.86-1.10)

[a]MET = metabolic equivalent of task.

[b]Model 1 is adjusted for demographics (age, sex, and race) plus comorbid conditions (hypertension, diabetes mellitus, personal history of coronary artery disease, family history of coronary artery disease, hyperlipidemia, cigarette smoking, obesity, sedentary behavior, atrial fibrillation, and atrial flutter) and medication use (β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, statins, insulin, oral hypoglycemics, lung disease medications, and antidepressants).

[c]Model 2 is adjusted for model 1 covariates plus stress test variables (reason for stress test and adequate test), incident disease outcomes (coronary artery disease, atrial fibrillation, hypertension, and diabetes mellitus).

[d]*P* value represents the linear trend of hazard ratio across MET categories.

CRF was not significantly associated with ischemic or hemorrhagic stroke among those with hypertension or diabetes mellitus. This could be related to competing risk for other outcomes that were unaccounted for that may have resulted in censoring. Furthermore, because hypertension and diabetes mellitus are significant risk factors for stroke, CRF may have less predictive value in the presence of these factors. Importantly, we found that CRF was inversely associated with risk for overall stroke among patients with a history of AF, an encouraging finding given the high burden of stroke in this population. Clinicians treating patients with AF should consider promoting physical activity and exercise as a heart healthy lifestyle that lowers the burden of cardiovascular risk factors and possibly risk of stroke in this high-risk population. Results for stroke subtypes were not significant, though this analysis may have been underpowered. Furthermore, there was no significant association between CRF and SAH in our study. This is likely due to the known association of SAH with other risk factors such as trauma, cerebral aneurysm rupture, or alcohol and drug abuse, which are not associated with CRF.

Few studies have examined the association between CRF and incident stroke but these were either limited to men[13,14] or did not examine stroke types.[12] In the Aerobics Center Longitudinal Study population, Lee and Blair[14] studied 16,878 men aged 40 to 87 years who underwent a maximal treadmill exercise test and were followed up for fatal strokes over a 10-year duration. Both moderate and high levels of CRF were inversely associated with stroke deaths. In a study by Prestgaard et al[15] of healthy middle-aged men, those who later became unfit had significantly higher risk for stroke.

There are important limitations to our study. The FIT Project is based on data from a single health system and therefore results may not be generalizable to other study populations. There is the potential for referral bias because most of our patients underwent a clinically indicated stress; therefore, our findings may not be generalizable to asymptomatic individuals who are otherwise healthy. There may have been misclassification of risk factors due to self-report or reliance on the medical record given the retrospective nature of our study. Inability to exclude patients based on other nonrecorded comorbid conditions may also have resulted in selection bias. Exclusive use of the Bruce protocol may have resulted in a possible selection bias because patients who could not undergo this testing modality

due to age, obesity, frailty, or physical limitations were likely tested using different methods and therefore excluded from our study. CRF may have been overestimated in some individuals who held on to the railing for support during the stress test especially given that metabolic testing for CRF (eg, Vo_2max) was not performed in our study. CRF was only assessed using METs so alternative methods of estimating or measuring CRF such as the Duke Activity Index Status or Vo_2max testing could not be used to verify our findings. To limit bias associated with loss to follow-up outside the health system, patients were censored when ongoing coverage with the health plan could no longer be confirmed, which may have resulted in a conservative bias. Although we used validated *ICD-9* codes to ascertain incident stroke, stroke outcomes in our study were not adjudicated by an independent panel of clinical experts, which may have resulted in misclassification. Furthermore, no prior study has examined the specificity and sensitivity of these codes in the FIT cohort. In addition, we do not have information for stroke-related mortality so fatal stroke outcomes could not be examined. We did not have data for the number of participants who had recurrent stroke outcomes. We were also not able to determine whether patients had concurrent stroke diagnoses; for example, an ischemic stroke with hemorrhagic conversion. Patients and physicians were unblinded to the fitness results and therefore use of preventive medications such as lipid level and blood pressure lowering may have been intensified during follow-up, which could have biased some results to the null. We only assessed CRF at baseline, but change in fitness levels over time is also important to evaluate. Although we attempted to adjust for known risk factors for stroke, information on other factors that affect CRF such as genetics was not available and therefore we cannot exclude the possibility of residual confounding. The FIT Project has higher rates of stroke compared with other cohorts, possibly related to uncontrolled hypertension in blacks[28] resulting in higher incidence of stroke in this race/ethnicity (16% in blacks vs 10% in whites in our study). This could also be related to secular changes during the follow-up period (1991-2009) in referral patterns or treatment; for example, the use of warfarin for AF anticoagulation in the 1990s was infrequent (1.2% in the FIT Project).

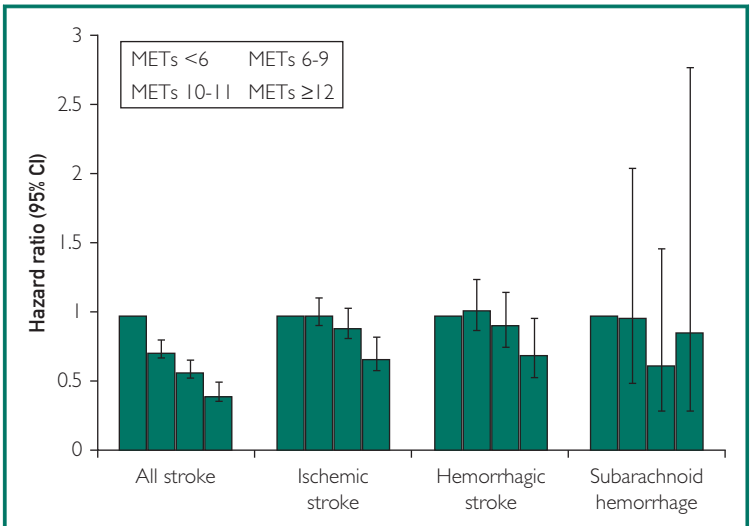

FIGURE 2. Bar graph with multivariable adjusted hazard ratios for the association of cardiorespiratory fitness and incident stroke. Model is adjusted for age, sex, race, history of hypertension, history of diabetes mellitus, personal history of coronary artery disease (CAD), family history of CAD, history of hyperlipidemia, history of cigarette smoking, history of obesity, history of sedentary behavior, history of atrial fibrillation, history of atrial flutter, β-blocker medication use, angiotensin-converting enzyme inhibitor use, angiotensin receptor blocker use, calcium channel blocker use, statin use, insulin use, oral hypoglycemic medication use, lung disease medication use, antidepressant medication use, reason for stress test, adequate test, incident CAD, incident atrial fibrillation, incident hypertension, and incident diabetes mellitus.

CONCLUSION

In conclusion, we found that higher CRF is associated with lower risk for overall stroke, including ischemic and hemorrhagic stroke. Further studies are required to demonstrate whether improvement in CRF over time is associated with lower risk for future stroke.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors

take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AF** = atrial fibrillation; **CAD** = coronary artery disease; **CHF** = congestive heart failure; **CRF** = cardiorespiratory fitness; **FIT Project** = Henry Ford Exercise Testing Project; **HR** = hazard ratio; ***ICD-9*** = *International Classification of Diseases, Ninth Revision*; **MET** = metabolic equivalent of task; **SAH** = subarachnoid hemorrhage; $\mathbf{Vo_2}$**max** = maximal oxygen uptake

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