Association Between Midlife Cardiorespiratory Fitness and Risk of Stroke
The Cooper Center Longitudinal Study

Ambarish Pandey, MD*; Minesh R. Patel, MD*; Benjamin Willis, MD, MPH; Ang Gao, MS; David Leonard, PhD; Sandeep R. Das, MD, MPH; Laura Defina, MD; Jarett D. Berry, MD, MS

Background and Purpose—Low cardiorespiratory fitness (CRF) is associated with an increased risk of stroke. However, the extent to which this association is explained by the development of stroke risk factors such as diabetes mellitus, hypertension, and atrial fibrillation is unknown. We evaluated the relationship between midlife CRF and risk of stroke after the age of 65 years, independent of the antecedent risk factor burden.

Methods—Linking participant data from the Cooper Center Longitudinal Study with Medicare claims files, we studied 19815 individuals who survived to receive Medicare coverage from 1999 to 2009. CRF estimated at baseline by Balke treadmill time was analyzed as a continuous variable (in metabolic equivalents) and according to age- and sex-specific quintiles (Q1=low CRF). Associations between midlife CRF and stroke hospitalization after the age of 65 years were assessed by applying a proportional hazards recurrent events model to the failure time data with hypertension, diabetes mellitus, and atrial fibrillation as time-dependent covariates.

Results—After 129 436 person-years of Medicare follow-up, we observed 808 stroke hospitalizations. After adjustment for baseline risk factors, higher midlife CRF was associated with a lower risk of stroke hospitalization (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.49–0.76; quintiles 4–5 versus 1). This association remained unchanged after additional adjustment for burden of Medicare-identified stroke risk factors (hypertension, diabetes mellitus, and atrial fibrillation; HR, 0.63; 95% CI, 0.51–0.79; quintiles 4–5 versus 1).

Conclusions—There is a strong, inverse association between midlife CRF and stroke risk in later life independent of baseline and antecedent burden of risk factors, such as hypertension, diabetes mellitus, and atrial fibrillation.

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Key Words: atrial fibrillation • diabetes mellitus • exercise • fitness • hypertension • Medicare • stroke

Stroke remains one of the leading causes of morbidity and mortality. In the United States, stroke remains the third leading cause of death and a common reason for hospitalization, accounting for $52 8 billion in direct medical costs annually. Several previous studies have demonstrated an inverse relationship between cardiorespiratory fitness (CRF) and both fatal and nonfatal stroke. However, the mechanism by which higher levels of CRF might lower stroke risk have not been well established, and it remains uncertain to what extent there may be a direct effect of CRF on stroke risk, independent of established stroke risk factors such as hypertension, diabetes mellitus (DM), and atrial fibrillation (AF). Although previous studies evaluating the relationship between CRF/physical activity and risk of stroke adjust for the baseline risk factors, they do not allow for the adjustment for downstream risk factors acquired after CRF/physical activity measurement. Against this background, we linked the Cooper Center Longitudinal Study (CCLS) with individual claims data from the Center for Medicare and Medicaid Services (CMS) to better characterize the association between midlife CRF and stroke risk at a later age. We sought to account for the influence of baseline and subsequent, Medicare-defined risk factors such as hypertension, DM, and AF on these associations. We hypothesized that higher midlife CRF would be associated with a lower stroke risk independent of these established stroke risk factors.

Methods
From 1970 to 2009, 73 439 participants in the CCLS underwent a full examination at the Cooper Clinic in Dallas, TX. Of these, 24 696

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*Drs Pandey and Patel contributed equally.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl doi:10.1161/STROKEAHA.115.011532/DC1.
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participants with complete baseline data available and no history of stroke were eligible to receive Medicare coverage from 1999 to 2009. From this cohort, we excluded 4010 participants lacking traditional Medicare Fee-for-Service coverage, 49 participants with early Medicare benefits (age, <65 years because of Medicare coverage for disability, end-stage renal disease, etc), and 822 individuals whose CCLS examination occurred after enrollment into Medicare Fee-for-Service. The final study sample included 19815 participants. Participants were followed up from the date of initiating Medicare coverage or 1999 (if already receiving Medicare coverage before 1999) until death or end of follow-up on December 31, 2009. No individual was excluded based on his or her performance on the exercise treadmill portion of the examination.

CCLS Clinical Examination
Details of the clinical examination and the study cohort have been published previously.12,13 CCLS participants undergo a comprehensive clinical examination that includes a self-reported personal and family history, fasting blood levels of total cholesterol, glucose, and a maximal treadmill exercise test. Body mass index was calculated from measured height and weight. Seated resting blood pressure was obtained with a mercury sphygmomanometer. Fasting venous blood was assayed for serum cholesterol and glucose using standardized, automated techniques.

CRF was measured in the CCLS by a symptom-limited maximal treadmill exercise test using a Balke protocol as detailed in the Methods in the online-only Data Supplement. The test time using this protocol has been shown to strongly correlate with directly measured maximal oxygen uptake (R=0.92).14,15

After standardized analysis of CRF data,12,13 treadmill times were compared with age- and sex-specific normative data on treadmill performance within the CCLS, allowing each individual’s treadmill time to be categorized into an age- and sex-specific quintile of CRF. These quintiles of CRF measures were then combined into 3, mutually exclusive fitness groupings: quintile 1: low fitness; quintiles 2 to 3: intermediate fitness; quintiles 4 to 5: high fitness. Furthermore, using well-established regression equations, treadmill times from the Balke protocol allow for estimation of CRF level in metabolic equivalents (METs).14,16,17

Medicare Claims Data
Medicare inpatient claims data were obtained from the CMS for CCLS participants who were 265 years of age and who were eligible for Medicare Fee-for-Service benefits from 1999—the first year CMS data are currently available for public use—to 2009. CMS data contain 100% of claims paid by Medicare for covered healthcare services. This enables participants to be tracked over time to elicit a history of all healthcare services utilized. Additional inpatient hospitalization files from CMS provide complete records for medical services billed to Medicare, the date of service, primary diagnosis with ≤8 secondary diagnoses (ie, International Classification of Diseases-Ninth Revision code), beneficiary demographic information, and other numerous data.

Stroke hospitalization was defined when listed as the primary diagnosis upon hospital discharge as indicated by International Classification of Diseases-Ninth Revision codes 430, 431, 433.x1, 434.x1, and 436. Previous work has demonstrated that when these codes are listed as the primary diagnosis, they have a positive predictive value of 92% to 100%.14–22 The presence of comorbidities, such as hypertension, DM, and AF on follow-up was also determined using data from CMS using a previously described methodology (Methods in the online-only Data Supplement).19,21

Statistical Analyses
Because patients enter the Medicare claims data at various ages and for varying durations, the data are subject to censoring on the right and left, with possibility of multiple events per patients. Therefore, we estimated the intensity of recurrent events using the conditional model of Prentice, Williams, and Peterson (PWP model).24 Briefly, this conditional modeling approach allows us to model the hazard function for outcome event beyond a participants’ first event to second and subsequent events. It assumes that a participant is not at risk for (n+1)th event until the nth event has occurred. This produces a proportional hazard model with time-dependent strata, where the dependence between event times in handled by the previous number of failures.25,26 For the present analysis, we used the PWP total time model with time for each event starting at the baseline and attained age as the dependent variable. The outcome event of interest is stroke hospitalization and the at-risk population is stratified by the number of stroke hospitalizations. Consistent with our analytic approach in previous studies from this cohort,16,23 multiple stroke events within a 30-day time interval for a participant were counted as a single event to account for repeat hospitalizations that may be related to a single index event. At the time a patient develops stroke hospitalization, they advance to the next at-risk stratum. Because only 17 participants had >2 events, the model used in the present analysis included only 2 strata: one for initial events, and the other for truly recurrent events. The presence of comorbidity (hypertension, DM, and AF) was defined when a particular condition, based on its respective aforementioned definitions, was noted before or within 365 days after a study participant’s first stroke hospitalization.

Table 1. Characteristics of Study Participants Stratified by Sex and Fitness Quintiles

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fitness Quintile 1 (n=2932)</td>
<td>Fitness Quintile 2–3 (n=6586)</td>
</tr>
<tr>
<td>Baseline age in CCLS, y</td>
<td>46.2 (8.5)</td>
<td>48.7 (8.7)</td>
</tr>
<tr>
<td>Age at Medicare entry, y</td>
<td>67.8 (4.8)</td>
<td>68.0 (5.0)</td>
</tr>
<tr>
<td>White, %</td>
<td>98.1</td>
<td>98.2</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>31.0</td>
<td>19.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.6 (4.5)</td>
<td>26.6 (3.2)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>222.3 (41.5)</td>
<td>216.4 (39.4)</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>39.8 (10.3)</td>
<td>43.3 (11.0)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>124 (14)</td>
<td>123 (14)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>5.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Fitness level, METs</td>
<td>8.3 (1.2)</td>
<td>10.3 (1.2)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD) or %; CCLS indicates Cooper Center Longitudinal Study; HDL, high-density lipoproteins; and METs, metabolic equivalents.
Unadjusted stroke hospitalization rates were analyzed separately for men and women according to CRF quintile. Risk of first stroke related hospitalization was also compared across different midlife CRF categories using the Breslow survival estimates curves for the overall population and the sex-specific subgroups. Multivariable-adjusted association between midlife CRF and stroke hospitalization was characterized according to the aforementioned mutually exclusive CRF groupings by applying a proportional hazards recurrent events model to the failure time data in 2 separate models: model 1 adjusted for age, sex, prevalent cardiovascular risk factors at baseline examination (body mass index, baseline DM [self-reported or fasting glucose >126 mg/dL, yes/no], total cholesterol, systolic blood pressure, and smoking [yes/no]), and age difference between the first and recurrent stroke events; model 2 adjusted for the variables listed in the model 1 and presence of hypertension, DM and AF observed during Medicare follow-up as time-dependent covariates. This was done to assess the evidence for a direct effect of CRF on risk of stroke that is not explained by interval development of these intermediate risks.

The proportional hazards assumption was confirmed by testing for linear interactions between covariates and the age during follow-up. Similar analyses were also performed with midlife CRF measured as a continuous variable (METs). In all analyses, death obtained from Medicare claims files was treated as a censoring event. All statistical analyses were performed using SAS for Windows (release 9.2; SAS Institute, Inc, Cary, NC).

### Results

Our study population had a low baseline prevalence of traditional risk factors at the time of entry into the CCLS (Table 1). Seventy-nine percent of the study participants were men and almost the entire study population was white (98.3%). In both men and women, higher levels of CRF were associated with lower levels of traditional cardiovascular risk factors.

After 129,436 person-years of Medicare follow-up, we observed 808 stroke hospitalizations in the study population with higher event rate in men than in women (Table 2). There were significant differences in the observed stroke hospitalization rates among the study participants according to the baseline CRF levels. Compared with low-fit participants (quintile 1), moderate- (quintile 2–3) and high-fit participants (quintiles 4–5) had a lower risk of stroke hospitalization in the overall population (Figure 1) as well as among men and women separately (Table 2; Figure I in the online-only Data Supplement). When stroke hospitalization rates were further stratified by METs achieved during maximal treadmill exercise test, a linear dose-dependent inverse relationship was observed for both men and women (Figure 2).

After adjustment for traditional cardiovascular risk factors measured at baseline examination, higher midlife CRF was associated with a lower risk for stroke hospitalization (Table 3, model 1). After adjustment for both traditional risk factors and the presence of hypertension, DM, and AF at Medicare follow-up, the association between CRF and risk of stroke hospitalization remained unchanged (Table 3, model 2). On continuous analyses, 1-MET higher midlife CRF
CRF was associated with 7% reduction in risk for stroke hospitalization (hazard ratio, 0.93; 95% confidence interval 0.98–0.97 per MET). The presence of hypertension and AF at Medicare follow-up was independently associated with a higher risk of stroke hospitalization (Table 3, model 2). In contrast, the presence of DM after the age of 65 years was not associated with increased risk of stroke in the most adjusted model (Table 3, model 2). There was no significant statistical interaction between baseline fitness and sex for the risk of stroke hospitalization on follow-up, and the association between CRF levels and stroke risk was not different between men and women (Table I in the online-only Data Supplement).

**Discussion**

In the present study, we observed 2 important findings. First, in a cohort with a low baseline prevalence of traditional risk factors, there was a dose-dependent inverse association between midlife CRF and risk of stroke later in life. Second, the inverse association between midlife CRF and risk of stroke was independent of the risk factor burden (hypertension, DM, and AF) observed on Medicare follow-up. Taken together, these findings highlight the importance of increased exercise and physical activity in midlife as a potential strategy for stroke risk reduction in older age.

Previous studies have evaluated the association between physical activity, CRF, and stroke. The relationship between physical activity and stroke risk has been shown to be inconsistent in published literature, with several studies demonstrating a nonlinear relationship between physical activity and stroke, whereas others reporting a dose-dependent inverse relationship. Furthermore, physical activity has been shown to be a less robust predictor of stroke risk than CRF, likely because of the limitations associated with self-reported measure of physical activity.

Among studies evaluating association between objective CRF measurement and stroke risk, the 2 earliest studies only included men and had limited assessments of stroke outcomes. A previous study from The Cooper Institute also examined the association between CRF and fatal/nonfatal stroke in both men and women. However, this study was limited by the use of self-reported outcome measure for nonfatal stroke. The present study with 19,815 healthy participants, objectively measured CRF levels at middle age, and objective
Our findings have important potential clinical implications. Regular exercise has previously been associated with reduction in blood pressure, decreased insulin resistance, and lower heart rates. Our study findings highlight the role of regular exercise and higher CRF in midlife as a potential stroke prevention strategy. This protective effect of higher CRF seems to go beyond risk factors modification. Previous research has suggested that exercise training and higher CRF impact carotid artery distensibility, nitric oxide availability, improving endothelial dysfunction, and thereby affecting conduit arteries and peripheral microcirculation. It has been suggested that this heightened systemic endothelial function results in improvements in cerebrovascular function by way of increased cerebral blood flow and brain volume, with a concurrent delay in naturally declining cerebral tissue density. Taken together, these findings provide further evidence in support the current guideline recommendations advocating regular physical activity for improvement in CRF and prevention of cardiovascular disease.

Several limitations should be noted. First, the study population derived from the CCLS represents a cohort that is well educated with access to preventive healthcare and a low burden of traditional risk factors. Although our findings may not generalize to the CCLS participants that were excluded from the study because of lack of Medicare coverage or the general population, our data provide a unique opportunity to characterize the health benefits of CRF in later life. In this context, the low prevalence of established risk factors at baseline represents a unique strength, allowing us to characterize the association between CRF and stroke risk independent of other comorbidities. Second, we combined individual-level data obtained from the CCLS with Medicare claims files to compare the association between CRF and stroke at the age of ≥65 years. Stroke hospitalizations that occurred between study entry and the onset of Medicare eligibility were not captured, and therefore we were not able to estimate the association between CRF and incident stroke. To accommodate this limitation, we compared the association between baseline CRF and the rate of stroke hospitalization, using attained age as the time scale. Therefore, a stroke hospitalization that occurred before Medicare enrollment would not influence our results. Third, we rely on Medicare claims files to identify stroke hospitalizations, and therefore, some events might have been missed or misclassified. However, measurement error tends to bias toward the null and encouragingly, the association between CRF and stroke hospitalizations were present despite use of administrative data. Finally, owing to the observational nature of the study, there is a potential for residual confounding, observation bias, and reverse causation in the observed associations. However, all the traditional risk factors and the stroke outcomes reported in the study are objectively measured using previously reported standardized protocols, and all participants received the same work-up regardless of their baseline cardiorespiratory fitness level. Thus, the likelihood of the confounding because of observer or selection bias is small. Furthermore, the time gap of many decades between CRF assessment and stroke diagnosis, the overall healthy nature of the cohort at baseline, and the

<table>
<thead>
<tr>
<th>Table 3. Association Between Midlife Fitness Level and Stroke Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*</td>
</tr>
<tr>
<td>Fitness as a categorical variable</td>
</tr>
<tr>
<td>Q1 (low fitness)</td>
</tr>
<tr>
<td>Q2–Q3 (moderate fitness)</td>
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<tr>
<td>Q4–Q5 (high fitness)</td>
</tr>
<tr>
<td>Model 2*</td>
</tr>
<tr>
<td>Fitness as a categorical variable</td>
</tr>
<tr>
<td>Q1 (low fitness)</td>
</tr>
<tr>
<td>Q2–Q3 (moderate fitness)</td>
</tr>
<tr>
<td>Q4–Q5 (high fitness)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Per 1 MET higher fitness</td>
</tr>
</tbody>
</table>

Model 1: adjusted for fitness, baseline age, sex, body mass index, cholesterol, baseline diabetes mellitus, smoking, systolic blood pressure, and age difference between first and recurrent stroke events. Model 2: adjusted for variables in model 1+the presence of diabetes mellitus, hypertension, and atrial fibrillation observed on Medicare follow-up. CI indicates confidence interval; HR, hazard ratio; MET, metabolic equivalent; and Q, quintiles. *P<0.05; hazards are yes vs no for diabetes mellitus, hypertension, and atrial fibrillation.
consistent inverse association between fitness measured continuously and stroke risk with no apparent threshold effect makes it less likely that the observed findings are because of reverse causation.

In summary, we observed that CRF in healthy, middle-aged adults demonstrated a dose-dependent, inverse association with stroke hospitalization in later life. This association was independent of incident hypertension, DM, and AF. Additional studies are needed to determine whether improvement in CRF among sedentary adults may reduce the risk of stroke in older age above and beyond risk factor modification.

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Disclosures
None.

References
34. Ainslie PN, Cotter JD, George KP, Lucas S, Murrell C, Shave R, et al. Elevation in cerebral blood flow velocity with aerobic fitness throughout


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/7/1720

An erratum has been published regarding this article. Please see the attached page for:
http://stroke.ahajournals.org/content/47/7/e203.full.pdf

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/06/09/STROKEAHA.115.011532.DC1

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On page 1722, in the second paragraph of the Results, “Compared with low-fit participants (quintile 1), moderate- (quintile 2–3) and high-fit participants (quintiles 4–5) had a higher risk of stroke hospitalization in the overall population (Figure 1) as well as among men and women separately (Table 2; Figure I in the online-only Data Supplement),” has been changed to read “Compared with low-fit participants (quintile 1), moderate- (quintile 2–3) and high-fit participants (quintiles 4–5) had a lower risk of stroke hospitalization in the overall population (Figure 1) as well as among men and women separately (Table 2; Figure I in the online-only Data Supplement).”

This correction has been made to the online and print version of the article, which is available at http://stroke.ahajournals.org/content/47/7/1720.
Supplemental Material
Supplemental Methods:

**Cardiorespiratory fitness testing among study participants:** Cardiorespiratory fitness was measured among the study participants by a symptom limited maximal treadmill exercise test using a Balke protocol. Using this protocol, treadmill speed is initially set at 88 m/min. At the onset of the protocol, the grade is set at 0% followed by 2% in the second minute with in an increase in grade of 1% for every minute thereafter. After 25 minutes, the grade remains unchanged but the speed is increased 5.4 m/min for each additional minute until the test is terminated. Participants were instructed not to hold onto the railing and were given encouragement to exert maximal effort. Exercise testing was terminated by volitional exhaustion reported by the participant or by the physician for medical reasons.

**Identifying co-morbidities at follow-up using CMS data:** As described previously, the presence of HTN was identified in study participants when ICD-9 codes 401.xx was listed as an outpatient claim on two occasions at least thirty days apart within two years or when listed as a single inpatient claim. The CMS Chronic Condition Warehouse (CCW) was used to identify presence of DM and AF during the Medicare follow up period. The CCW algorithm used to determine the presence of DM has been associated with a sensitivity of 69%-77% in prior studies. Similarly, the CCW algorithm used to identify the presence of AF, as determined by ICD-9 Code 427.31 when listed as two outpatient claims within 1 year or as a single inpatient claim, has also been independently validated and shown to have a sensitivity and specificity of 94% and 99% respectively.
Supplemental Figure I: Risk of stroke hospitalization after age 65 among women and men participants stratified by the mid-life cardiorespiratory fitness levels. Only the first stroke event was used to generate the survival curves due to small number the recurrent events.

Female

<table>
<thead>
<tr>
<th>Fitness category</th>
<th>Low</th>
<th>285</th>
<th>195</th>
<th>126</th>
<th>51</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>1000</td>
<td>786</td>
<td>505</td>
<td>302</td>
<td>139</td>
<td>51</td>
</tr>
<tr>
<td>High</td>
<td>1469</td>
<td>924</td>
<td>545</td>
<td>301</td>
<td>135</td>
<td>36</td>
</tr>
</tbody>
</table>

![Graph showing risk of stroke hospitalization among women and men stratified by mid-life cardiorespiratory fitness levels.](image-url)
Male

![Graph showing failure probability versus attained age (years) for different fitness categories.

<table>
<thead>
<tr>
<th>Fitness category</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1799</td>
<td>1518</td>
<td>1021</td>
</tr>
<tr>
<td>Moderate</td>
<td>4052</td>
<td>3306</td>
<td>2287</td>
</tr>
<tr>
<td>High</td>
<td>3998</td>
<td>3079</td>
<td>2040</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>174</th>
<th>555</th>
<th>523</th>
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</thead>
<tbody>
<tr>
<td>37</td>
<td>172</td>
<td>151</td>
<td></td>
</tr>
</tbody>
</table>
**Supplemental Table I**: Adjusted association between baseline cardiorespiratory fitness levels and risk of stroke hospitalization among men and women.

<table>
<thead>
<tr>
<th>Fitness as categorical variable</th>
<th>Men (N = 15,683)</th>
<th>Women (N = 3,132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (Low Fitness)</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Q2-Q3 (Moderate Fitness)</td>
<td>0.80 (0.65 – 0.98)</td>
<td>0.60 (0.37 – 0.98)</td>
</tr>
<tr>
<td>Q4-Q5 (High Fitness)</td>
<td>0.66 (0.52 – 0.84)</td>
<td>0.52 (0.31 – 0.89)</td>
</tr>
</tbody>
</table>

**Fitness as continuous variable**

| Per 1 MET higher Fitness       | 0.92 (0.88 – 0.96) | 0.97 (0.86 – 1.1) |

Separate sex specific models were created with fitness measured as categorical or continuous variable with adjustment for fitness; age; BMI; cholesterol; baseline DM; smoking; systolic BP; presence of diabetes, HTN, atrial fibrillation observed on Medicare Follow-up, and age difference between first and recurrent stroke events.
References:


