Exercise and Risk of Stroke in Male Physicians

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Background and Purpose—From a physiological perspective, physical activity might be expected to decrease the risk of developing stroke. However, epidemiological studies of physical activity and stroke risk have yielded divergent findings. We therefore sought to examine the association between exercise and stroke risk.

Methods—This was a prospective cohort study of 21,823 men, followed up for an average of 11.1 years. Participants were from the Physicians’ Health Study, a randomized trial of low-dose aspirin and beta carotene. Men, aged 40 to 84 years at baseline, were free of self-reported myocardial infarction, stroke, transient ischemic attack, and cancer. At baseline, they reported on the frequency of exercise vigorous enough to work up a sweat. Stroke occurrence was reported by participants and confirmed after medical record review (n=533). We used Cox proportional hazards regression to analyze the data.

Results—with adjustment for age, treatment assignment, smoking, alcohol intake, history of angina, and parental history of myocardial infarction, the relative risks of total stroke associated with vigorous exercise <1 time, 1 time, 2 to 4 times, and ≥5 times per week at baseline were 1.00 (referent), 0.79 (95% confidence interval [CI], 0.61 to 1.03), 0.80 (95% CI, 0.65 to 0.99), and 0.79 (95% CI, 0.61 to 1.03), respectively; P for trend=0.04. In subgroup analyses, the inverse association appeared stronger with hemorrhagic than ischemic stroke. When we additionally adjusted for body mass index, history of hypertension, high cholesterol, and diabetes mellitus, corresponding relative risks for total stroke were 1.00 (referent), 0.81 (95% CI, 0.61 to 1.07), 0.88 (95% CI, 0.70 to 1.10), and 0.86 (95% CI, 0.65 to 1.13), respectively; P for trend=0.25.

Conclusions—Exercise vigorous enough to work up a sweat is associated with decreased stroke risk in men. In the present study, the inverse association with physical activity appeared to be mediated through beneficial effects on body weight, blood pressure, serum cholesterol, and glucose tolerance. Apart from its favorable influences on these variables, physical activity had no significant residual association with stroke incidence. (Stroke. 1999;30:1-6.)

Key Words: epidemiology ■ exercise ■ risk factors ■ stroke prevention

Stroke is the third leading cause of death in the United States, after coronary heart disease and cancer.1 Every year, some 150,000 persons die from this disease.1 In addition, many survivors are left with physical and mental disabilities. Because of extended hospitalizations and productivity losses from work, this disease has a large economic impact. Further, there is limited treatment for most types of stroke. Therefore, major efforts should be focused on prevention, with emphasis directed toward modifiable predictors. Hypertension and cigarette smoking clearly increase the risk of stroke.2 Other potential risk factors include physical inactivity, obesity, glucose intolerance, dyslipidemia, diet, and use of higher-dose oral contraceptives.2

Although the association between physical activity and coronary heart disease risk has been extensively researched, fewer epidemiological studies have evaluated this factor in relation to stroke occurrence.3–23 Divergent findings have been reported, including both an inverse association between physical activity and risk of stroke3,4,7–9,12,15,17–23 as well as no decreased risk at higher levels of activity.5,6,10,11,13,14,16 In fact, the Surgeon General’s report on physical activity and health24 concluded that “it is unclear whether physical activity plays a protective role against stroke.” Additionally, few studies have examined separately the relation of physical activity to different types of stroke (eg, ischemic versus hemorrhagic).3,7,20,21 It also is unclear whether the relationship is modified by age,7,17,20,21 cigarette smoking,17,20,21 or hypertension. The Physicians’ Health Study afforded the opportunity to investigate these issues.

Subjects and Methods

Participants
The Physicians’ Health Study is a randomized, double-blind, placebo-controlled trial of low-dose aspirin and beta carotene in the
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primary prevention of cardiovascular disease and cancer.25,26 Subjects provided informed consent for participation, and the study was approved by the institutional review board at Brigham and Women’s Hospital. At study entry in 1982, 22 071 US male physicians aged 40 to 84 years were randomly assigned to aspirin alone, beta carotene alone, aspirin plus beta carotene, or bothplacebos, with use of a 2×2 factorial design. Participants were free of self-reported myocardial infarction, stroke, transient ischemic attack, and cancer (excluding nonmelanoma skin cancer) at the time of randomization. For the present analyses, we excluded 248 men who did not provide information on physical activity at baseline, leaving a total of 21 823 men.

Assessment of Physical Activity and Other Characteristics
At baseline, men completed a mailed questionnaire that included information on physical activity. Specifically, they were asked, “How often do you exercise vigorously enough to work up a sweat?” Response options were rarely/never, 1 to 3 times/mo, 1 time/wk, 2 to 4 times/wk, 5 to 6 times/wk, or daily. This method of assessing physical activity has been shown to correlate reasonably well with measures of physical fitness, such as maximal oxygen uptake and treadmill time during a maximal exercise test.27,28 Other information collected on the questionnaire included date of birth; height; weight; cigarette habit; alcohol consumption; personal history of angina, hypertension, diabetes, and high cholesterol; and parental history of myocardial infarction.

At the 36-month follow-up, we again inquired about physical activity, asking, “Do you engage in a regular program of exercise vigorous enough to work up a sweat?” For those responding affirmatively, we further queried, “How many days per week?” with the response options being <1 d/wk, 1 to 2 d/wk, 3 to 4 d/wk, or 5 to 7 d/wk.

Ascertainment of Stroke Occurrence
Every 6 months during the first year and annually thereafter, participants completed mailed questionnaires that inquired about compliance with their assigned treatment, side-effects of study agents, the occurrence of end points of interest (including stroke), and characteristics potentially predictive of chronic diseases. Nonfatal strokes were reported on these questionnaires. Deaths among physicians usually were reported by family members or postal authorities. Morbidity and mortality follow-up among physicians is more than 99% complete.

We confirmed the occurrence of a stroke only after medical records and all other relevant information were reviewed by a neurologist. Unconfirmed cases of stroke were excluded from analyses. A definite case of nonfatal stroke was defined as a typical neurological deficit that was sudden or rapid in onset, lasted >24 hours, and was attributable to a cerebrovascular event. With fatal stroke, confirmed cases were those in which clear evidence was found from all available records, including death certificate, hospital records, and eyewitness accounts, of a cerebrovascular event prior to death. With information from medical records and reports of diagnostic tests, including neuroimaging data, as well as on the basis of the neurologist’s judgment, we additionally subdivided strokes into ischemic or hemorrhagic types.29 We classified as unknown those strokes in which there was no clear documentation of stroke subtype. We analyzed only first occurrences of stroke. This report includes available data as of October 24, 1995. By then, men had been followed up for an average of 11.1 years, during which 533 confirmed first strokes (437 ischemic, 84 hemorrhagic, and 12 of unknown type) had occurred in 242 526 person-years.

Statistical Analysis
To obtain a more uniform distribution of men by activity level, we collapsed the 6 exercise categories on the baseline questionnaire into 4: <1 time/wk, 1 time/wk, 2 to 4 times/wk, and ≥5 times/wk. When computing the relative risks of stroke occurrence associated with physical activity, we used proportional hazards regression30 to analyze time to first stroke or censoring (death from causes other than stroke or October 24, 1995, whichever occurred first). The proportional hazards assumption was tested and found not to be violated. We initially modeled rate ratios (relative risks) for total stroke as a function of the 4 exercise categories at baseline and adjusted for age (in years) and randomized treatment assignment (aspirin versus placebo; beta carotene versus placebo). We then tested for trend in relative risks across physical activity categories by treating the different activity categories as a single ordinal variable.

In secondary analyses, we examined the association of physical activity, assessed at baseline and at 36 months, with total stroke incidence. Because the categorizations of exercise frequency on the baseline and 36-month questionnaires were not identical, we chose two priori to dichotomize exercise into frequency of <1 time/wk versus ≥1 time/wk at both times. In analysis, we treated physical activity as a time-varying characteristic assessed initially at baseline and updated at 36 months. We also compared the incidence rate of total stroke occurring after 36 months among men who exercised vigorously ≥1 time/wk at both baseline and 36 months with that among men who exercised vigorously <1 time/wk at both times. As before, we calculated age- and treatment-adjusted relative risks.

Next, we examined the association between physical activity assessed at baseline and total stroke incidence, with use of 2 separate multivariate models. In the first, in addition to age and treatment assignment, we also accounted for the following potential confounders: cigarette smoking (never, past, or currently smoking <20 or ≥20 cigarettes daily), alcohol consumption (rarely, monthly, weekly, or daily), history of angina (no versus yes), and parental history of myocardial infarction occurring before age 60 (in either parent; no versus yes). In the second multivariate model, besides the variables above, we additionally adjusted for the following “intermediate variables”: body mass index (kilograms per meters squared), history of hypertension (no versus yes), history of high cholesterol (no versus yes), and history of diabetes (no versus yes). We obtained similar findings when we used levels of systolic blood pressure instead of history of hypertension. The purpose of the second multivariate model was to assess whether physical activity had any effect on stroke incidence above and beyond its beneficial influences on the intermediate variables24 (ie, decreasing body weight, reducing blood pressure and serum cholesterol, and improving glucose tolerance and increasing insulin sensitivity).

We then proceeded to investigate ischemic and hemorrhagic strokes separately. Because the number of hemorrhagic strokes was small, we were unable to assess subarachnoid and intracerebral hemorrhages separately.

Finally, we examined whether age, cigarette habit, or history of hypertension modified the association between physical activity at baseline and incidence of total stroke. We did so by including an interaction term with physical activity for each of these variables in 3 separate multivariate models.

Results
Table 1 shows the characteristics of physicians at study entry, according to frequency of vigorous exercise. Twenty-eight percent of men reported such exercise <1 time/wk; 18% did so 1 time/wk; 38% exercised vigorously 2 to 4 times/wk; and 16% declared that they exercised vigorously ≥5 times/wk. Those least active tended to be somewhat older, heavier, and more likely to smoke cigarettes. Alcohol intake did not differ markedly across activity categories. The least active as well as the most active were more likely to report a history of angina. The prevalence of hypertension, diabetes, and high cholesterol generally tended to decline with increasing physical activity, while an opposite trend was noted for parental history of myocardial infarction occurring before age 60.

In age- and treatment-adjusted analyses (Table 2), we found that with increasing physical activity at baseline, risk of
developing any type of stroke declined ($P$ for trend = 0.004). The most active men experienced a significant 26% reduction in stroke risk compared with the least active men.

In a secondary analysis, we examined the association between physical activity assessed at baseline and updated at 36 months and risk of total stroke. Use of the additional physical activity information at 36 months did not change findings materially: The age- and treatment-adjusted relative risk associated with vigorous physical activity $\geq 1$ time/wk, compared with less frequent activity, was 0.77 (95% confidence interval [CI], 0.65 to 0.92). We then compared the incidence rate of total stroke occurring after 36 months among men who exercised vigorously $\geq 1$ time/wk both at baseline and at 36 months with that among men who exercised vigorously $<1$ time/wk at both times. The age- and treatment-adjusted relative risk from this analysis was 0.76 (95% CI, 0.59 to 0.97).

Next, we examined the relationship between physical activity at baseline and stroke incidence, adjusting not only for age and treatment assignment but also for the potential confounders of smoking, alcohol intake, history of angina, and parental history of early ($\leq 60$ years) myocardial infarction (Table 2). Although the association was somewhat attenuated, we continued to observe a significant inverse trend ($P$ for trend = 0.04). Men who exercised once a week had a 21% lower risk compared with less active men. All the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency of Vigorous Exercise (Times per Week)</th>
<th>No. of Events</th>
<th>RR* (95% CI)</th>
<th>Multivariate RR1† (95% CI)</th>
<th>Multivariate RR2‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 (n=6055)</td>
<td>189</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td></td>
<td>1-4 time/wk</td>
<td>87</td>
<td>0.80 (0.62–1.03)</td>
<td>0.79 (0.61–1.03)</td>
<td>0.81 (0.61–1.07)</td>
</tr>
<tr>
<td></td>
<td>2–4 times/wk</td>
<td>172</td>
<td>0.74 (0.61–0.92)</td>
<td>0.80 (0.65–0.99)</td>
<td>0.88 (0.70–1.10)</td>
</tr>
<tr>
<td></td>
<td>$\geq 5$ time/wk</td>
<td>85</td>
<td>0.74 (0.57–0.95)</td>
<td>0.79 (0.61–1.03)</td>
<td>0.86 (0.65–1.13)</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td></td>
<td></td>
<td>0.004</td>
<td>0.04</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Note:**
- RR indicates relative risk; CI, confidence interval.
- *Adjusted for age and treatment assignment.
- †Additionally adjusted for cigarette smoking, alcohol consumption, history of angina, and parental history of myocardial infarction at $< 60$ years.
- ‡Adjusted for all the variables above, plus body mass index, history of hypertension, history of high cholesterol, and history of diabetes mellitus.
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These data indicate an inverse association between physical activity at baseline and risk of stroke incidence ($P = 0.06$ and $0.07$, respectively). However, when we additionally adjusted for body mass index, history of hypertension, high cholesterol, and diabetes mellitus, the association was no longer significant. This implies that the inverse relationship was less marked for ischemic than for hemorrhagic stroke; however, this finding was based on a small number of hemorrhagic strokes.

Finally, we tested whether the association between physical activity at baseline and incidence of total stroke differed by age, cigarette smoking status, or history of hypertension. We did not find any evidence of interaction by any of these variables ($P$ for interaction terms $= 0.51, 0.07, 0.68$, respectively).

**Discussion**

These data indicate an inverse association between physical activity and risk of developing stroke. After accounting for age, smoking, alcohol intake, history of angina, and myocardial infarction in either parent, men who exercised vigorously once a week experienced a $21\%$ lower risk of total stroke than those who did so less frequently. With increasing frequency of exercise, risk did not decrease further. However, when we additionally adjusted for body mass index, history of hypertension, high cholesterol, and diabetes mellitus, the association was no longer significant. This implies that the inverse association of physical activity with stroke incidence in the present study can be explained by its favorable effects on these variables, and that physical activity does not have any significant effect above and beyond its influence on these variables. Further, the association between physical activity and stroke incidence was not modified by age, cigarette smoking, or history of hypertension. In subgroup analyses, the inverse relationship was less marked for ischemic than for hemorrhagic stroke; however, this finding was based on a small number of hemorrhagic strokes.

**TABLE 3. Relative Risks of Ischemic Stroke, According to Physical Activity**

<table>
<thead>
<tr>
<th>Frequency of Vigorous Exercise</th>
<th>No. of Events</th>
<th>RR* (95% CI)</th>
<th>Multivariate RR1† (95% CI)</th>
<th>Multivariate RR2‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 time/wk</td>
<td>148</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>1 time/wk</td>
<td>72</td>
<td>0.84 (0.64–1.12)</td>
<td>0.85 (0.64–1.13)</td>
<td>0.90 (0.66–1.22)</td>
</tr>
<tr>
<td>2–4 times/wk</td>
<td>143</td>
<td>0.79 (0.63–1.00)</td>
<td>0.84 (0.67–1.07)</td>
<td>0.95 (0.74–1.22)</td>
</tr>
<tr>
<td>≥5 times/wk</td>
<td>74</td>
<td>0.81 (0.62–1.08)</td>
<td>0.87 (0.66–1.16)</td>
<td>0.97 (0.71–1.32)</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td></td>
<td>0.06</td>
<td>0.23</td>
<td>0.81</td>
</tr>
</tbody>
</table>

$RR$ indicates relative risk; CI, confidence interval.
*Adjusted for age and treatment assignment.
†Additionally adjusted for cigarette smoking, alcohol consumption, history of angina, and parental history of myocardial infarction.
‡Adjusted for all the variables above, plus body mass index, history of hypertension, history of high cholesterol, and history of diabetes mellitus.

**TABLE 4. Relative Risks of Hemorrhagic Stroke, According to Physical Activity**

<table>
<thead>
<tr>
<th>Frequency of Vigorous Exercise</th>
<th>No. of Events</th>
<th>RR* (95% CI)</th>
<th>Multivariate RR1† (95% CI)</th>
<th>Multivariate RR2‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 time/wk</td>
<td>35</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>1 time/wk</td>
<td>13</td>
<td>0.62 (0.33–1.17)</td>
<td>0.59 (0.30–1.18)</td>
<td>0.54 (0.25–1.13)</td>
</tr>
<tr>
<td>2–4 times/wk</td>
<td>26</td>
<td>0.59 (0.35–0.98)</td>
<td>0.69 (0.41–1.16)</td>
<td>0.71 (0.41–1.23)</td>
</tr>
<tr>
<td>≥5 times/wk</td>
<td>10</td>
<td>0.48 (0.24–0.96)</td>
<td>0.55 (0.27–1.12)</td>
<td>0.54 (0.26–1.15)</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td></td>
<td>0.01</td>
<td>0.07</td>
<td>0.10</td>
</tr>
</tbody>
</table>

$RR$ indicates relative risk; CI, confidence interval.
*Adjusted for age and treatment assignment.
†Additionally adjusted for cigarette smoking, alcohol consumption, history of angina, and parental history of myocardial infarction at <60 years.
‡Adjusted for all the variables above, plus body mass index, history of hypertension, history of high cholesterol, and history of diabetes mellitus.
activity and risk of stroke, especially ischemic stroke. In contrast, other studies such as the Framingham Study, the Honolulu Heart Study, and the Northern Manhattan Stroke Study observed a benefit of physical activity even after accounting for these same factors. These differences may reflect differences in the characteristics of the populations studied.

Few investigators have examined stroke subtypes in studies of physical activity. Paffenbarger and Williams reported that male varsity athletes experienced less than half the risk of subsequently dying from stroke—whether thromboembolic or hemorrhagic—than their nonathletic classmates. In the Framingham Heart Study, physical activity also was associated with an approximate halving of the risk of stroke—whether total or nonhemorrhagic—in men. However, among older men in the Honolulu Heart Study, active men experienced a 21% nonsignificantly lower risk of thromboembolic stroke than inactive men; for hemorrhagic stroke, the risk reduction was 69%. In the NHANES I Epidemiologic Follow-up Study, findings were inconsistent for total and for nonhemorrhagic stroke. It is therefore unclear whether physical activity has a greater effect on certain types of stroke.

Although we found no significant effect modification by age, Shinton and Sagar reported that regular vigorous exercise undertaken at younger ages conferred a greater benefit. In the NHANES I Epidemiologic Follow-up Study, physical activity also was associated with greater benefit among younger white women (aged 45 to 64 years) than among those older. This did not appear to be so for white men, while findings for black subjects were not stratified by sex or age. In contrast, investigators from the Framingham Heart Study and the Honolulu Heart Study reported an inverse association between physical activity among older but not younger men. It is unclear why findings differ between studies. A possible explanation for the observation of a larger effect among those younger is that physical activity is less likely to change in this age group. Among those who are older, activity levels likely decline over time; the resulting misclassification of physical activity may bias findings to the null. Lack of statistical power is an unlikely explanation in these same factors. These differences may reflect differences in the characteristics of the populations studied.

Differences by smoking habit have been assessed in 3 studies. As in the present study, the NHANES I Epidemiologic Follow-up Study reported no clear differences by smoking status. However, Shinton and Sagar reported a greater benefit among smokers. It is possible that because of the adverse atherogenic and thrombogenic effects from smoking, physical activity is able to ameliorate these effects to a greater degree among smokers. In contrast, the Honolulu Heart Study found physical activity to be inversely associated with stroke risk only among nonsmokers. More data are required.

Strengths of the present study include detailed confirmation of stroke occurrence, including subtypes. Additionally, follow-up among subjects was very high, approaching 100%. On the other hand, limitations include a less-than-comprehensive assessment of physical activity. We did not collect information that would enable us to address specific details, such as the kinds and intensities of activity that are most beneficial. We also could not ascertain the optimum duration of exercise, or whether continuous or intermittent bouts differ in effect. A further limitation is the lack of information on diet, since diet may act as a confounder of the physical activity–stroke relationship. Finally, men in this study are not representative of the US general population. While this may limit the generalizability of findings, it does not preclude their internal validity.

In conclusion, these data add to evidence indicating that physical activity reduces the risk of developing stroke. The data further suggest that the inverse association with physical activity was mediated through beneficial effects on body weight, blood pressure, serum cholesterol, and glucose tolerance. Apart from its favorable influences on these variables, physical activity had no significant residual association with stroke incidence. Further data are needed to clarify the relationship of physical activity to stroke subtypes; the roles of age, smoking, and hypertension in modifying the association; and the optimum amount (frequency and duration) and intensity of physical activity required.

Acknowledgments
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References
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