Published in final edited form as:
*Stroke*. 2010 June ; 41(6): 1243–1250. doi:10.1161/STROKEAHA.110.584300.

# Physical Activity and Risk of Stroke in Women

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## Abstract

**Background and Purpose—**Physical activity has generally been inversely related to the risk of developing stroke, but details regarding the amount and kinds of activity required are unclear, as are associations for specific stroke subtypes.

**Methods—**Eligible subjects were 39,315 healthy US women, ≥45 years, from the Women's Health Study. Women reported physical activity at baseline (1992–1995) and at 36, 72, 96, 125, and 149 months' follow-up. During an average follow-up of 11.9 years, 579 women developed incident stroke (473 ischemic, 102 hemorrhagic, and 4 of unknown type). Proportional hazards models related physical activity, updated over time, to the risk of incident stroke.

**Results—**The multivariable relative risks (RR) associated with <200, 200–599, 600–1499, and ≥1500 kcal/wk of leisure-time physical activity were 1.00 (referent), 1.11 (95% confidence interval [CI], 0.87–1.41), 0.86 (95% CI, 0.67–1.10), and 0.83 (95% CI, 0.63–1.08), respectively; p, trend = 0.06. Similar results were observed for ischemic stroke, while no associations were observed for hemorrhagic stroke. Vigorous physical activity was not related to stroke risk (p, trend = 0.50); however walking time and walking pace were inversely related, either significantly or with borderline significance, to total, ischemic, and hemorrhagic stroke risks (p, trend between 0.002 and 0.07.

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**Conflicts of Interest/Disclosures**
Mr. Sattelmair is a part time employee at the Dossia Consortium.
Dr. Kurth has received investigator-initiated research funding from the US National Institutes of Health, the French National Research Agency (ANR, Agence Nationale pour la Recherche), the Migraine Research Foundation, and Merck. Further, he is a consultant to i3 Drug Safety and World Health Information Science Consultants, LLC; he has received honoraria from Genzyme, Merck, and Pfizer for educational lectures.
Dr. Buring has received investigator-initiated research funding from the National Institutes of Health, and has received study agents from Bayer and Natural Source Vitamin E Association for the Women's Health Study.
Dr. Lee has received investigator-initiated research funding from the National Institutes of Health. She serves as a consultant to Virgin HealthMiles, and sits on their Scientific Advisory Board.

**Conclusions—**This study shows a tendency for leisure-time physical activity to be associated with lower stroke risk in women. In particular, walking was generally associated with lower risks of total, ischemic, and hemorrhagic stroke.

### Keywords

Brain ischemia; exercise; intracranial hemorrhage; physical activity; obesity; stroke

## Introduction

Stroke is the third leading cause of death and the leading cause of adult disability in the United States.[1] It is therefore important to identify modifiable risk factors for the primary prevention of stroke. Despite progress in identifying risk factors for stroke among women (e.g. smoking, migraine with aura, postmenopausal hormone use, oral contraceptive use), continued research on other modifiable risk factors is required.[2]

A promising modifiable risk factor is physical activity, but cohort studies assessing the relation between physical activity and stroke risk, particularly early studies, have shown inconsistent results. Among more recently published reports, an inverse association between physical activity and risk of stroke has been identified in some[3–9] but not all[10–12] studies. Though recent reviews conclude that physical activity is associated with a 25–30% reduction in risk,[13] there remains a need to clarify details of the physical activity required, as well as the relation for specific stroke subtypes. Moreover, with one exception,[5] no previous studies have incorporated repeated measures of physical activity, and many studies had limited power to assess potential associations, particularly with respect to hemorrhagic stroke subtypes.

We therefore conducted the present study to examine the association of physical activity with stroke risk in a large cohort of women, addressing details of the physical activity required, and the association for specific stroke subtypes.

## Methods

### Study Population

Subjects were from the Women's Health Study (WHS), a completed randomized trial of low-dose aspirin and vitamin E for primary prevention of cardiovascular disease and cancer. The methods and results of the WHS have previously been published in detail.[14–16] In brief, between September 1992 and May 1995, female health professionals throughout the United States and Puerto Rico were asked to complete a mailed baseline questionnaire on sociodemographic characteristics, health habits, and medical history. A total of 39,876 eligible women free of heart disease, stroke, and cancer (other than non-melanoma skin cancer) were randomized to receive either active drug or placebo.

Every six months during the first year and annually thereafter, women completed follow-up surveys on treatment compliance, risk factors and endpoints of interest. Upon scheduled completion of the trial in March 2004, women were invited to continue follow-up in an observational study, and 33,796 did (88.0% of those living). The Institutional Review Board at Brigham and Women's Hospital approved this study.

For this study, we excluded women not reporting their physical activity or weight (required to estimate energy expenditure) at baseline (N=554) or who, after randomization, reported a stroke or heart disease occurring before randomization (N=7), leaving 39,315 women.

## Assessment of Physical Activity

On the baseline survey, women were asked to estimate the average time (0, 1–19 min/wk, 20–59 min/wk, 1 hr/wk, 1.5 hr/wk, 2–3 hr/wk, 4–6 hr/wk, or ≥7 hr/wk) spent on eight groups of recreational activities during the past year: walking or hiking; jogging (slower than 10-minute miles); running (10-minute miles or faster); bicycling, including use of stationary machines; aerobic exercise, aerobic dance, use of exercise machines; tennis, squash, or racquetball; lap swimming, and lower-intensity exercise, including yoga, stretching, or toning. They also reported their usual walking pace (do not walk regularly, <3.2 km/hr [2 mph; casual pace], 3.2–4.7 km/hr [2–2.9 mph; normal, average pace], 4.8–6.3 km/hr [3.0–3.9 mph; brisk pace], or ≥6.4 km/hr [4.0 mph; very brisk/striding pace]) and the number of flights of stairs climbed daily (0, 1–2, 3–4, 5–9, 10–14, or ≥15). Physical activity was updated at 36, 72, and 96 months during the trial, at trial conclusion (average follow-up, 125 months), and cycle 2 of observational follow-up (24 months after trial conclusion). We refer to these times as the 36-, 72-, 96-, 125-, and 149-month follow-up.

We assigned a multiple of resting metabolic rate (MET score) to each group of activities and stair climbing based on their energy costs,[17] and estimated the energy expended on each of these activities.18 This assessment of physical activity has been shown to be reliable and valid. 19 We summed kilocalories per week from the eight groups of recreational activities and stair climbing to estimate weekly energy expenditure, and categorized women into approximate quartiles of energy expenditure: <200, 200–599, 600–1499, or ≥1500 kcal/wk, for analyses of physical activity. We also conducted additional analyses with energy expenditure estimated in MET-hr/week, a unit independent of body weight. The results were very similar and so we present results in units of kcal/wk, a more interpretable measure.

## Assessment of Other Variables

We obtained information at baseline on potential confounders, including age, weight, height, smoking, diet (including alcohol use), parity, menopausal status, history of hypertension, history of elevated cholesterol level, history of diabetes mellitus, use of postmenopausal hormones, presence of migraine headaches, and parental history of myocardial infarction before age 60. Women were classified as being normal weight (body max index (BMI)<25 kg/m$^2$), overweight (25≤BMI<30 kg/m$^2$), or obese (30≤BMI kg/m$^2$), using World Health Organization (WHO) criteria.[20] Diet was assessed using a 131-item semi-quantitative food frequency questionnaire (FFQ).21

## Ascertainment of Stroke

Participants who reported a stroke on a follow-up questionnaire were asked for permission to review their medical records. A diagnosis of stroke was confirmed only after medical record review by an Endpoints Committee of physicians that included a neurologist. A nonfatal stroke was defined as a focal neurological deficit of sudden onset and vascular mechanism that lasted >24 hours. Cases of fatal stroke were documented by evidence of a cerebrovascular mechanism obtained from available sources, including death certificates and hospital records. Stroke was classified according to the National Survey of Stroke criteria[22] as ischemic or hemorrhagic stroke, or unknown subtype. The inter-observer agreement of the classification of stroke and its major subtypes was excellent.[23]

## Statistical Analysis

We used Cox proportional hazards regression to calculate hazard ratios as estimates for the relative risks (RR), and their associated 95% confidence intervals (CI), of stroke as a function of the different measures of physical activity. Follow-up time was calculated from study entry to the earliest of the following: stroke diagnosis, death, end of follow-up in February 2007, or loss to follow up (<3% of women).

We first estimated the relative risks of total stroke associated with the four categories of energy expended on all leisure-time activities, updated over time to represent the most recent value available. When a missing value of physical activity was encountered, the last known value was carried forward. Initial models adjusted for age and randomized treatment. A subsequent multivariable model additionally adjusted for potential confounders: smoking status (never, past, current), alcohol use (never, any), saturated fat intake (gm/day; quintiles), fiber intake (gm/day; quintiles), fruit/vegetable intake (servings/day; quintiles) hormone therapy (never, past, current), menopausal status (premenopausal, postmenopausal, unsure), migraine (no migraine, prior migraine, active migraine without aura, active migraine with aura), and parental history of myocardial infarction. A second multivariable model further adjusted for variables that likely are in the causal pathway relating physical activity to reduced stroke occurrence: body mass index, history of hypertension, history of diabetes, history of elevated cholesterol. We then separately examined the relation between total leisure-time physical activity and the risks of ischemic and hemorrhagic strokes.

To provide information on the kinds of activity required, we also examined vigorous physical activity (requiring ≥6 METs)24 and risks of total, ischemic, and hemorrhagic stroke. Women were categorized into those with no vigorous leisure-time activity plus <200 kcal/wk expended on other activities, no vigorous leisure-time activity plus ≥200 kcal/wk expended on other activities, and >0–199, 200–499, or ≥500 kcal/wk expended on vigorous leisure-time activities, based on previous analyses.25 We further examined the relation between walking, a moderate-intensity activity, and stroke risk. To prevent confounding by vigorous activities, these analyses considered only women with no vigorous activities. Women were classified according to the time spent walking (no regular walking, 1–59 min/wk, 1.0–1.5 hrs/wk, ≥2 hrs/wk) and their usual walking pace (no regular walking, <3.2 km/hr [2 mph], 3.2–4.7 km/hr [2–2.9 mph], or ≥4.8 km/hr [3.0 mph).

We also examined joint associations of physical activity and BMI (WHO categories) as well as age (≥/< 60 years at baseline) with stroke risk. Finally, we examined associations between changes in the time spent walking between baseline and 36-month follow-up and risk of stroke occurring after 36-months.

## Results

Table 1 shows the baseline characteristics of the 39,315 women by approximate quartiles of total leisure-time energy expenditure. More active women generally had a healthier profile. They also were more likely to be on postmenopausal hormone therapy, be postmenopausal, and less likely to suffer from migraine.

During a mean follow-up of 11.9 years, 579 total strokes occurred: 473 ischemic, 102 hemorrhagic, and 4 strokes of unknown type. The associations between total leisure-time physical activity and risks of total, ischemic, and hemorrhagic stroke are provided in Table 2. For total stroke, there was an inverse trend, of borderline significance, after adjusting for potential confounders (p, trend = 0.06). With additional adjustment for variables that likely are in the causal pathway, the association was further attenuated (Table 2). With ischemic stroke, the associations were similar, since these constituted the majority of strokes that women experienced. For hemorrhagic stroke, there was no trend across categories of physical activity.

The associations between specific types of leisure-time physical activity and risks of total, ischemic, and hemorrhagic stroke are shown in Table 3. There was no overall linear trend of decreased risk for total stroke across categories of vigorous activity (p, trend = 0.50). Findings for ischemic stroke again mirrored those for total stroke.

Associations of time spent walking and usual walking pace with stroke risk were next examined among women who engaged in no vigorous activity. There were inverse, dose-response relations with total stroke for both time spent walking and usual walking pace (p, trend = 0.002 and 0.007, respectively). Women who walked two or more hours per week had a 30% lower risk of any stroke than women who did not walk (multivariable-adjusted RR = 0.70; 95% CI, 0.52–0.94), while women whose usual walking pace was brisk (>4.8 km/hr) had a 37% lower risk (corresponding RR = 0.63; 95% CI, 0.44–0.91), compared with women who did not walk. Similar inverse dose-response trends were noted for ischemic stroke, that were of borderline significance (p, trend = 0.07 for both time and pace of walking). For hemorrhagic stroke, these inverse associations were significant (p, trend = 0.002 and 0.04, respectively). Compared with women who did not walk, those walking ≥2 hours/week had a 57% lower risk of hemorrhagic stroke (multivariable-adjusted RR = 0.43; 95% CI, 0.20–0.89), while women whose usual walking pace was >4.8 km/hr had a 68% lower risk (corresponding RR = 0.31; 95% CI, 0.12–0.77).

To examine the associations of change in physical activity with subsequent stroke risk, we investigated changes in walking, which was most consistently associated with lower stroke risk. We observed no clear associations, which may partly reflect the small numbers of cases, particularly for hemorrhagic stroke (Table 4).

Finally, we investigated whether age or BMI modified the physical activity-stroke relation; no significant interactions were observed (data not shown).

## Discussion

The results of this large prospective cohort study of women with updated physical activity measurements over a mean follow-up of 11.9 years generally showed results congruent with the available body of evidence. We found an inverse association of borderline significance between total leisure-time physical activity and risks of total, and ischemic, stroke. No associations were observed between vigorous-intensity activity and stroke risk. However, there were significant inverse, dose-response relations of both time spent walking and usual walking pace with risks of total and hemorrhagic strokes, and borderline significant relations with ischemic stroke.

Plausible biologic pathways support an inverse association between physical activity and risk of stroke, both ischemic and hemorrhagic.[26] Physical activity modifies risk factors for stroke such as hypertension, cardiovascular disease, type 2 diabetes, and obesity by reducing blood pressure, improving lipid profile, decelerating atherosclerosis, ameliorating endothelial dysfunction, reducing systemic inflammation, and improving insulin sensitivity. Potential effects on ischemic stroke risk may be mediated through mechanisms common to coronary heart disease (e.g. factors that modify atherosclerotic progression, especially risk of acute clot rupture), whereas potential effects on hemorrhagic stroke risk may be mediated through blood pressure and related mechanisms.

Previous cohort studies that have assessed the potential relation between physical activity and risk of stroke have varied in terms of physical activity assessment, stroke outcomes, study base (e.g. gender, age), control for confounding, and sample size, and have shown inconsistent results. Though many studies have found an inverse relation between physical activity and stroke risk,[3–9] a number of studies have observed no association.10–12 Recent reviews conclude that overall, evidence support a 25 – 30% reduction in stroke risk with physical activity,[13] though there remains ambiguous evidence for an added reduction in risk when

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moving from moderate to high levels of activity.[13] Among studies that have included three or more categories of physical activity, varying dose-response relations have been observed, including inverse monotonic,[3, 5, 6, 9] similar risk reductions for any non-referent activity level,[7] U-shaped,[8, 10] null less the most active,[4] and null.[12]

Our results are similar to those of recent studies,[3–7, 10, 12] and in general agree with a recent expert review,[13] in that we observed some inverse associations between physical activity and risk of stroke. However, unlike female cohorts from Finland,[6] Norway,3 and the United States5 where significant inverse relations were observed, our results are more similar to those from a Japanese cohort that found a non-significant inverse association12 among females. In terms of the magnitude of the inverse association, our results again are similar to the Japanese cohort12 in that we found that the most active women were 17% less likely to have any stroke than the least active, compared to analogous risk reductions of 17% in the Japanese women (fatal stroke only), but larger risk reductions of 25% in US,5 34% in Finnish,6 and 53% in Norwegian women (fatal stroke only).3

The present findings for vigorous physical activity provide little evidence for any relation with stroke risk: no inverse trend was observed, and though women in the highest category of vigorous activity were at 17% lower risk of total stroke, this was not significant. These findings are similar to those from several male or mixed-gender American cohorts,[7, 8, 10] but differ from those of other female cohorts,[5, 12] which observed a significant reduction in stroke risk among women in the highest category of vigorous-intensity physical activity.

When we examined walking, we observed consistent inverse dose-response relations between walking time or walking pace and total stroke risk that are comparable to findings from another study of US women,[5] but differ from those of the Japanese cohort discussed above,[12] which did not find an association between walking and stroke risk among women.

It is not entirely clear why we observed an association between walking, a moderate-intensity activity, and stroke risk, but no association with vigorous-intensity activity. Participation in vigorous activities was far lower than moderate activities, such as walking, in the present cohort, which may reduce our ability to observe an effect. It is unlikely that misclassification of vigorous activity is an explanation, since vigorous-intensity physical activity tends to be better reported than moderate-intensity activity.[17] Another possible explanation is that moderate-intensity physical activity may be more effective at lowering blood pressure, a strong risk factor for stroke, compared with vigorous-intensity activity as suggested by some,[27] but not all[28] randomized controlled trials.

With regard to the associations of physical activity with stroke subtypes, our results do not indicate a substantial difference similar to other studies[5, 6, 12] but the low number of hemorrhagic strokes limits the power of these analyses.

Obesity is a strong risk factor for total and ischemic stroke,[29] and no interaction was previously reported between obesity and baseline physical activity in relation to stroke risk in the WHS.[29] In the present analysis, using updated measures of physical activity, we continued to observe no effect modification between BMI and physical activity.

Strengths of our study include a large cohort, prospective design, and detailed information on physical activity, collected using a validated instrument[19] on repeated occasions. Stroke outcomes were confirmed with medical records, and ischemic and hemorrhagic sub-types were differentiated. We also controlled for many potential confounders in analyses.

Our study was limited by its observational design; thus, the potential for residual confounding remains. Physical activity was self-reported, allowing for potential misclassification. However because activity was prospectively ascertained, this bias is likely to be non-differential, causing a bias towards the null (no association). The associations among measures of physical activity and stroke risk that we observed are thus likely to under-represent the true associations. Potential confounders, including dietary intake from FFQs, were also self-reported. Physical activity measures were restricted to leisure-time activity; no household or occupational activity, or sedentary behaviors, was assessed. The numbers of ischemic and hemorrhagic stroke subtypes were too small to conduct further analyses. We had limited power to assess potential associations with hemorrhagic stroke. Finally, the WHS comprises predominantly white US female health professionals, which may limit the generalizability of findings to other populations.

In conclusion, this study shows a tendency for leisure-time physical activity to be associated with lower stroke risk in women. In particular, walking was generally associated with lower risks of total, ischemic, and hemorrhagic stroke. Future studies with larger numbers of hemorrhagic strokes will be useful. Also, studies among racial/ethnic minorities, particularly black women in whom stroke rates are almost twice that in white women, are needed.[30]

## Acknowledgments

This research was supported by grants CA047988, HL043851 and HL080467 from the National Institutes of Health. The authors would like to acknowledge the crucial contributions of the entire staff of the WHS and Eunjung Kim and Anna Klevak, PhD, for their assistance with computer programming. We are also indebted to the 39,876 dedicated and committed participants of the Women's Health Study.

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## TABLE 1

Baseline Characteristics of Participants, According to Total Leisure-Time Physical Activity*, Women's Health Study

| | Baseline Physical Activity, Kcal/wk | | | |
|---|---|---|---|---|
| **Characteristics At Baseline** | **<200 n=10,233** | **200–599 n=9855** | **600–1499 n=10,895** | **≥1500 n=8332** |
| Mean age, years | 54.7(7.1) | 54.4(7.0) | 54.7(7.1) | 54.6(7.0) |
| Mean body mass index, $kg/m^2$ | 27.0(5.8) | 26.0(4.9) | 25.5(4.6) | 25.6(4.8) |
| Smoking status, % | | | | |
| Never | 48.6 | 52.6 | 53.0 | 49.7 |
| Past | 31.6 | 34.1 | 37.0 | 41.7 |
| Current | 19.7 | 13.4 | 10.0 | 8.6 |
| Alcohol consumption, % | | | | |
| Rarely | 52.9 | 45.5 | 41.6 | 39.3 |
| 1–3 drinks/mo | 12.5 | 13.6 | 13.4 | 13.3 |
| 1–6 drinks/wk | 25.4 | 30.7 | 34.4 | 36.3 |
| ≥1 drinks/d | 9.2 | 10.2 | 10.6 | 11.1 |
| Saturated fat intake, mean(SD), gm/d | 20.5(8.7) | 20.1(8.0) | 19.4(7.8) | 18.8(7.9) |
| Fiber intake, mean(SD), gm/d | 16.5(7.3) | 18.5(7.7) | 19.7(8.1) | 21.4(9.1) |
| Fruit and vegetable consumption, mean(SD), servings/d | 5.2(3.5) | 5.9(3.2) | 6.4(3.5) | 7.3(4.0) |
| Postmenopausal hormone therapy, % | | | | |
| Never | 50.9 | 50.2 | 49.7 | 49.0 |
| Past | 10.4 | 8.8 | 8.3 | 8.8 |
| Current | 38.7 | 41.0 | 42.0 | 42.2 |
| Menopausal status, % | | | | |
| Premenopausal | 26.3 | 28.4 | 28.0 | 27.6 |
| Postmenopausal | 55.0 | 53.8 | 54.4 | 54.7 |
| Not Sure | 18.7 | 17.9 | 17.7 | 17.6 |
| Migraine, % | | | | |
| No migraine | 80.8 | 80.8 | 82.1 | 82.8 |
| Prior migraine | 5.7 | 5.6 | 5.3 | 5.1 |
| Active migraine without aura | 8.4 | 8.4 | 7.5 | 6.8 |
| Active migraine with aura | 5.2 | 5.2 | 5.0 | 5.3 |
| Parental history of myocardial infarction <60 years of age, % | 13.8 | 12.5 | 12.7 | 12.8 |
| History of hypertension, % | 29.3 | 25.6 | 24.3 | 24.0 |
| History of diabetes mellitus, % | 3.4 | 2.3 | 2.4 | 2.1 |
| History of elevated cholesterol, % | 32.0 | 30.0 | 29.0 | 26.5 |

*Physical activity levels were estimated from assessment of leisure-time activities plus stair climbing.

†P values were calculated using linear regression with an ordinal variable to test for trend across physical activity categories for continuous variables, and chi-square test for categorical variables.

## Table 2

Relative Risks (RR) of Stroke According to Total Leisure-Time Physical Activity*

| **Kcal/wk** | | | | | |
|---|---|---|---|---|---|
| **Range** | **<200** | **200–599** | **600–1499** | **≥1500** | ***p*§** |
| **No. Of Women At Baseline** | **10,233** | **9,855** | **10,895** | **8,332** | |
| Total stroke | | | | | |
| No. cases | 181 | 138 | 147 | 113 | |
| Age- and treatment-adjusted RR (95% confidence interval, CI) | 1 | 0.91 (0.73, 1.13) | 0.72 (0.57, 0.89) | 0.65 (0.51, 0.82) | <0.0001 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 1.11 (0.87, 1.41) | 0.86 (0.67, 1.10) | 0.83 (0.63, 1.08) | 0.06 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 1.16 (0.91, 1.48) | 0.93 (0.72, 1.20) | 0.89 (0.68, 1.17) | 0.21 |
| Ischemic stroke | | | | | |
| No. cases | 155 | 106 | 123 | 89 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.86 (0.68, 1.10) | 0.66 (0.52, 0.84) | 0.61 (0.47, 0.80) | <0.0001 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 1.05 (0.80, 1.38) | 0.80 (0.60, 1.06) | 0.82 (0.60, 1.10) | 0.06 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 1.11 (0.85, 1.46) | 0.87 (0.66, 1.16) | 0.88 (0.65, 1.19) | 0.22 |
| Hemorrhagic stroke | | | | | |
| No. cases | 24 | 32 | 22 | 24 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 1.29 (0.75, 2.22) | 1.04 (0.60, 1.79) | 0.93 (0.52, 1.67) | 0.64 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 1.53 (0.86, 2.71) | 1.22 (0.68, 2.19) | 0.99 (0.51, 1.91) | 0.84 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 1.55 (0.86, 2.77) | 1.28 (0.71, 2.33) | 1.04 (0.53, 2.02) | 0.98 |

* Updated over time

† Adjusted for age, randomized treatment assignment, plus smoking; alcohol; saturated fat, fruit and vegetable, and fiber intake: postmenopausal hormone therapy; menopausal status, parental history of myocardial infarction, and migraine aura

‡ Adjusted for the above variables, plus body mass index, history of diabetes, history of elevated cholesterol, and history of hypertension

§ P-value for linear trend across categories of physical activity

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**Table 3**

Relative Risks (RR) of Stroke According to Types of Physical Activity*

| Vigorous Leisure-Time Physical Activity, Kcal/wk | | | | | | |
|---|---|---|---|---|---|---|
| **Kcal/wk** | | | | | | |
| **Range** | **0 + <200§** | **0 + ≥200§** | **>0–199** | **200–499** | **≥500** | ***p*‖** |
| **No. Of Women At Baseline** | **9,326** | **13,536** | **4,100** | **4,119** | **8,234** | |
| Total stroke | | | | | | |
| No. cases | 167 | 211 | 45 | 57 | 99 | |
| Age- and treatment-adjusted RR (95% confidence interval, CI) | 1 | 0.79 (0.64, 0.96) | 1.00 (0.73, 1.37) | 0.91 (0.67, 1.23) | 0.63 (0.49, 0.83) | 0.01 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.98 (0.78, 1.24) | 1.41 (1.01, 1.97) | 1.08 (0.76, 1.52) | 0.83 (0.61, 1.12) | 0.50 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 1.04 (0.82, 1.31) | 1.51 (1.07, 2.12) | 1.21 (0.86, 1.72) | 0.90 (0.66, 1.23) | 0.99 |
| Ischemic stroke | | | | | | |
| No. cases | 143 | 166 | 38 | 45 | 81 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.75 (0.60, 0.94) | 1.01 (0.72, 1.42) | 0.77 (0.55 1.10) | 0.60 (0.45, 0.81) | 0.005 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.95 (0.74, 1.23) | 1.46 (1.01, 2.11) | 0.91 (0.61, 1.37) | 0.81 (0.58, 1.14) | 0.38 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 1.01 (0.78, 1.31) | 1.61 (1.12, 2.33) | 1.05 (0.69, 1.58) | 0.90 (0.64, 1.27) | 0.84 |
| Hemorrhagic stroke | | | | | | |
| No. cases | 22 | 44 | 7 | 12 | 17 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 1.06 (0.63, 1.78) | 1.05 (0.47, 2.36) | 1.83 (0.96, 3.48) | 0.85 (0.44, 1.64) | 0.86 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 1.27 (0.73, 2.22) | 1.34 (0.58, 3.09) | 2.04 (1.01, 4.12) | 0.94 (0.45, 1.97) | 0.71 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 1.34 (0.76, 2.37) | 1.26 (0.52, 3.05) | 2.16 (1.06, 4.41) | 1.00 (0.47, 2.12) | 0.64 |

| Time Spent Walking Per Week# | | | | | |
|---|---|---|---|---|---|
| Range | Does Not Walk Regularly | 1–59 min | 60–90 min | ≥2 hr | *p*‖ |
| No. Of Women At Baseline | 5,817 | 6,036 | 4,410 | 6,599 | |
| Total stroke | | | | | |
| No. cases | 119 | 93 | 65 | 101 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.83 (0.64, 1.07) | 0.75 (0.55, 1.01) | 0.61 (0.47, 0.80) | <0.0001 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.86 (0.65, 1.14) | 0.87 (0.62, 1.20) | 0.70 (0.52, 0.94) | 0.002 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 0.91 (0.68, 1.21) | 0.96 (0.69, 1.34) | 0.78 (0.58, 1.06) | 0.01 |

| | Vigorous Leisure-Time Physical Activity, Kcal/wk | | | | | |
|---|---|---|---|---|---|---|
| **Kcal/wk** | | | | | | |
| **Range** | **0 + <200§** | **0 + ≥200§** | **>0–199** | **200–499** | **≥500** | ***p*‖** |
| **No. Of Women At Baseline** | **9,326** | **13,536** | **4,100** | **4,119** | **8,234** | |
| Ischemic stroke | | | | | | |
| No. cases | 101 | 77 | 50 | | 81 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.89 (0.67, 1.18) | 0.70 (0.50, 0.98) | | 0.66 (0.49, 0.88) | 0.003 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.97 (0.71, 1.33) | 0.81 (0.55, 1.19) | | 0.79 (0.57, 1.10) | 0.07 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 1.04 (0.76, 1.43) | 0.92 (0.63, 1.36) | | 0.91 (0.66, 1.27) | 0.27 |
| Hemorrhagic stroke | | | | | | |
| No. cases | 17 | 15 | 15 | | 19 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.57 (0.30, 1.10) | 0.97 (0.52, 1.80) | | 0.42 (0.21, 0.84) | 0.0005 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.48 (0.24, 0.99) | 1.06 (0.56, 2.01) | | 0.42 (0.20, 0.87) | 0.002 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 0.50 (0.24, 1.02) | 1.09 (0.57, 2.08) | | 0.43 (0.20, 0.89) | 0.002 |
| | Usual Walking Pace, Km/hr# | | | | | |
| Km/hr | | | | | | |
| Range | Does Not Walk Regularly | <3.2 | 3.2–4.7 | | ≥4.8 | *p*‖ |
| No. Of Women At Baseline | 3347 | 3135 | 10,526 | | 5854 | |
| Total stroke | | | | | | |
| No. cases | 85 | 68 | 149 | | 76 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.75 (0.55, 1.03) | 0.63 (0.49, 0.82) | | 0.51 (0.37, 0.71) | <0.0001 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.82 (0.58, 1.16) | 0.72 (0.54, 0.96) | | 0.63 (0.44, 0.91) | 0.007 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 0.82 (0.58, 1.17) | 0.77 (0.57, 1.04) | | 0.75 (0.52, 1.08) | 0.09 |
| Ischemic stroke | | | | | | |
| No. cases | 71 | 55 | 117 | | 66 | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.76 (0.54, 1.07) | 0.62 (0.47, 0.83) | | 0.55 (0.39, 0.78) | 0.0002 |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.90 (0.61, 1.33) | 0.74 (0.53, 1.03) | | 0.75 (0.50, 1.12) | 0.07 |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 0.92 (0.62, 1.36) | 0.82 (0.59, 1.16) | | 0.94 (0.62, 1.42) | 0.54 |
| Hemorrhagic stroke | | | | | | |
| No. cases | 13 | 12 | 31 | | 10 | |

| | Vigorous Leisure-Time Physical Activity, Kcal/wk | | | | | |
|---|---|---|---|---|---|---|
| **Kcal/wk** | | | | | | |
| **Range** | **0 + <200**[§] | **0 + ≥200**[§] | **>0–199** | **200–499** | **≥500** | ***p***[‖] |
| **No. Of Women At Baseline** | **9,326** | **13,536** | **4,100** | **4,119** | **8,234** | |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.68 (0.31, 1.49) | 0.71 (0.39, 1.30) | | 0.39 (0.17, 0.89) | 0.04 |
| Multivariable-adjusted RR1[†] (95% CI) | 1 | 0.51 (0.22, 1.19) | 0.70 (0.38, 1.30) | | 0.32 (0.13, 0.79) | 0.04 |
| Multivariable-adjusted RR2[‡] (95% CI) | 1 | 0.50 (0.21, 1.18) | 0.66 (0.35, 1.23) | | 0.31 (0.12, 0.77) | 0.03 |

[*] Updated over time

[†] Adjusted for age, randomized treatment assignment, plus smoking; alcohol; saturated fat, fruit and vegetable, and fiber intake: postmenopausal hormone therapy; menopausal status, parental history of myocardial infarction, and migraine aura

[‡] Adjusted for the above variables, plus body mass index, history of diabetes, history of elevated cholesterol, and history of hypertension

[§] Total leisure time physical activity

[‖] P-value for linear trend across categories of physical activity

[#] Analyses are restricted to women without any vigorous leisure-time activities

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**Table 4**

Relative Risks (RR) of Stroke According to Changes in Time Spent Walking*

| **Time Spent Walking at Baseline/at 3-years, Hr/Wk** | **<2/<2** | **<2/≥2** | **≥2/<2** | **≥2/≥2** |
|---|---|---|---|---|
| **No. Of Women At Baseline** | **8235** | **2365** | **1999** | **2829** |
| Total stroke | | | | |
| No. cases | 117 | 29 | 26 | 31 |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.85 (0.57, 1.27) | 0.87 (0.57, 1.33) | 0.65 (0.44, 0.97) |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.86 (0.55, 1.34) | 0.84 (0.52, 1.37) | 0.78 (0.51, 1.19) |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 0.89 (0.57, 1.38) | 0.85 (0.53, 1.39) | 0.82 (0.54, 1.27) |
| Ischemic stroke | | | | |
| No. cases | 98 | 28 | 19 | 26 |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.98 (0.64, 1.49) | 0.76 (0.46, 1.24) | 0.64 (0.42, 0.99) |
| Multivariable-adjusted RR1† (95% CI) | 1 | 1.00 (0.63, 1.58) | 0.66 (0.37, 1.18) | 0.77 (0.48, 1.23) |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 1.04 (0.66, 1.65) | 0.68 (0.38, 1.22) | 0.85 (0.53, 1.36) |
| Hemorrhagic stroke | | | | |
| No. cases | 19 | 1 | 7 | 5 |
| Age- and treatment-adjusted RR (95% CI) | 1 | 0.18 (0.02, 1.35) | 1.48 (0.62, 3.51) | 0.70 (0.26, 1.88) |
| Multivariable-adjusted RR1† (95% CI) | 1 | 0.20 (0.03, 1.48) | 1.70 (0.70, 4.12) | 0.79 (0.28, 2.21) |
| Multivariable-adjusted RR2‡ (95% CI) | 1 | 0.20 (0.03, 1.47) | 1.62 (0.66, 3.94) | 0.74 (0.26, 2.07) |

*Analyses are restricted to women without any vigorous leisure-time activities.

†Adjusted for age, randomized treatment assignment, plus smoking; alcohol; saturated fat, fruit and vegetable, and fiber intake: postmenopausal hormone therapy; menopausal status, parental history of myocardial infarction, and migraine aura

‡Adjusted for the above variables, plus body mass index, history of diabetes, history of elevated cholesterol, and history of hypertension