Physical Activity in Primary Stroke Prevention

Just Do It!

Virginia J. Howard, PhD; Michelle N. McDonnell, PhD

Stroke is a preventable disease. Well-documented, modifiable risk factors for stroke include hypertension, diabetes mellitus, dyslipidemia, obesity and body fat distribution, cigarette smoking, atrial fibrillation, heart disease, and physical inactivity.1,2 There is a wealth of information supporting physical activity (PA) as an important component of primary stroke prevention strategies. The proposed mechanism is that PA improves vascular function and stroke risk factors.3 The well-known health benefits of regular PA include reducing the risk of hypertension, type 2 diabetes mellitus, depression, and obesity, as well as control of these risk factors.4–7 Although data from multiple clinical trials support a reduction in stroke risk factors with PA,8–11 there are no clinical trials data demonstrating the efficacy of PA in reducing stroke incidence, partially because of the long follow-up required to achieve a sufficient number of events. The next best evidence comes from nonrandomized cohort studies where the consistency of results strongly supports the benefit of PA in primary stroke prevention (Class I, Level of Evidence B).1 The purpose of this review is to summarize the terminology and measurement of PA, synthesize the results of studies of PA and stroke risk factors in men and women, and describe how PA can ameliorate the effects of stroke risk factors, such as diabetes mellitus and hypertension. The challenges with PA research will also be discussed, as well as recommendations for future research.

Terminology and Measurement of PA

PA is a complex behavior that can incorporate different elements, including occupational or leisure time PA, commuting, sport, walking, and exercise training. The accepted definition of PA used by most researchers is “any bodily movement produced by skeletal muscles that results in energy expenditure” (p. 126).12 This differs from exercise, a subset of PA defined as “PA that is planned, structured, repetitive and purposeful in the sense that improvement or maintenance of one or more components of physical fitness is an objective” (p. 128).12 Generally, epidemiological studies that rely on self-report intend to measure PA, but it is not always clear that participants understand the difference between PA and exercise when they complete surveys or questionnaires. An alternative approach is to directly measure the physiological variable cardiorespiratory fitness using maximal or submaximal exercise tests but this is not feasible in large scale studies. The approach used in many longitudinal cohort studies, such as the Framingham Heart Study (FHS), the Nurse’s Health study, and the REasons for Geographic And Racial Differences in Stroke (REGARDS), is to ask about the frequency of intense PA, enough to work up a sweat.13–15 The validity of this widely used assessment is well-established16 and correlates with objective measures of cardiorespiratory fitness.17–18 Alternatively, participants are asked about moderate intensity PA, such as walking, the most common form of PA in older adults,19 often measured in terms of frequency, duration, or total time spent walking.

Classification of PA is a significant limitation to epidemiological research. To quantify energy expenditure, it is necessary to have an estimate of the amount of time the participant spent on low intensity activities, such as domestic or occupational tasks, moderate intensity exercise (walking, playing golf), and intense physical activities (jogging or cycling).20 After this, a formula may be used to estimate the amount of energy expended on each activity. Although this approach is reported to be valid and reliable,21 the accuracy of these data is influenced by the ability of participants to accurately recall the durations spent on each activity in the period of interest. Furthermore, participants tend to overestimate the amount of time spent being physically active, leading to poor agreement between self-report and accelerometer-based measures in older adults.22 The approach to classifying participants into low, moderate, or high PA groups based on total energy expended or frequency of PA varies considerably between studies, making it impossible to quantify the specific amount and intensity of PA needed to confer significant stroke protection.

A Healthy Lifestyle (Including PA) and Risk of Incident Stroke

Adherence to a healthy lifestyle significantly reduces the risk of stroke. Table I in the online-only Data Supplement provides
an overview of the key studies that have investigated the effect of a healthy lifestyle on stroke risk. The key elements of a healthy lifestyle are avoidance of excess body weight, smoking, heavy alcohol consumption, unhealthy diet, and physical inactivity. Combined data from the US Nurse’s Health Study and the Health Professionals Follow-up Study (n=114928) showed that adult women who make healthy lifestyle choices have an 80% lower risk of total stroke when compared with those who do not; for men, the risk was 70% lower. The optimal amount of PA within a healthy lifestyle was defined as ≥30 minutes/d of moderate or vigorous activity based on a self-administered questionnaire on frequency of PA over the previous year. In the population-based Sweden Mammography Cohort of 31,696 women, the definition of a healthy level of PA included both low and moderate intensity activities, walking or cycling at least 40 minutes/d and completing at least 1 hour/wk of structured exercise. The relative risk of stroke decreased with the addition of each healthy lifestyle factor, and women who adhered to all 5 low-risk lifestyle factors had a 62% lower risk of cerebral infarction than women with no low-risk factors. Another prospective cohort study of 23,927 men and women, the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg) study, supports these findings, estimating that 38% of stroke cases in their cohort could have been prevented if participants had adhered to the same 5 healthy lifestyle factors. Specific to PA, women who engaged in any level of PA compared with being inactive had a reduced stroke risk after multivariable adjustment, but for men, the multivariable adjusted risk estimates by different levels of PA were weaker and not statistically significant. In contrast, using a health index (range, 0–20) that assigned scores of 0 to 4 to each of the 5 lifestyle components, the Women’s Health Study (n=37,636) found that an overall higher health index was associated with significantly lower stroke risk with a significant trend across the mean values of health index categories but for the individual component of PA defined by number of times per week of strenuous exercise, there was no association with stroke risk. The EPIC Norfolk study (n=20,040) used a slightly different definition of healthy lifestyle and for the unadjusted, individual component of PA, women who were physically inactive compared with not inactive had a significantly higher stroke risk, but for men there was no difference. However, for the overall healthy behavior score, in various covariate-adjusted models, both men and women had consistently higher stroke risk with worse health behavior scores. In a Finnish population survey (n=36,686) with mean follow-up of 13.7 years, there was a graded inverse association between number of healthy lifestyle factors and risks of total, ischemic, and hemorrhagic stroke. For the individual factor of moderate or high versus low PA, there was a significant association with reduced risk of stroke for total and ischemic stroke but only a trend for hemorrhagic stroke. Using 7 different health metrics (glucose, cholesterol, blood pressure, body mass index, PA, diet, and cigarette smoking), that is, Life’s Simple 7, studies have shown that increasing numbers of these optimal factors are also associated with lower stroke risk. In the large China study (n=91,686), the individual factor of PA comparing ideal (moderate or vigorous PA>80 minutes/week) versus nonideal showed a significantly lower risk of total and ischemic stroke but not hemorrhagic stroke.

Physical Inactivity as a Risk Factor for Incident Stroke

Several prospective cohort studies have collected data on PA and incident stroke (Table I in the online-only Data Supplement for details). Studies of all men or women participants have generally concurred that some PA, compared with none, offers protection against incident stroke. Studies including both men and women have also found significant risk reduction with PA, but with differing effects. Older men who were moderately active had the greatest risk reduction in the FHS, which found no such association in women. Low intensity exercise was not associated with reduced stroke risk in the Northern Manhattan Study, and moderately vigorous activity was only protective for men. This disparity was confirmed in the REGARDS study, with no association between vigorous PA and stroke risk for women when the sample was stratified by sex, despite a 20% decreased risk of stroke across the entire sample with 918 confirmed cases of stroke/transient ischemic attack. In the Spanish EPIC cohort, moderate intensity recreational PA was independently associated with reduced stroke risk in women but not in men. In all studies, the association was attenuated to some extent by multivariable adjustment for traditional stroke risk factors, such as hypertension, diabetes mellitus, alcohol, and tobacco use.

A meta-analysis of 23 studies found that moderate and high levels of activity were associated with a reduced risk of total stroke, as well as ischemic and hemorrhagic stroke. Considering only prospective cohort studies in this meta-analysis, participants who were highly active or moderately active had a 25% or 17% lower risk of stroke incidence or mortality, respectively, compared with inactive participants. Wendel-Vos et al added to this literature with several more cohort studies and confirmed that both occupational and leisure time PA were associated with reduced stroke risk. A 2012 meta-analysis confirmed these findings, with leisure-time PA reducing stroke risk by ≥20% in both men and women. A dose–response relationship was particularly evident in women, with a relative risk for high PA versus low PA of 0.78, compared with 0.89 for moderate versus low PA. A 2010 meta-analysis studying differences between men and women in the benefit of PA and stroke risk concluded that although the overall benefit was similar, women may need a higher level of PA to achieve similar reduction in stroke risk. Precisely what a higher level of PA translates to, in terms of PA duration, frequency or intensity is unknown, as these meta-analyses classified PA into low, moderate, or high based on what was reported in the studies, but without any further detail. Overall, the literature to date suggests that all participants have a reduced risk of stroke from some PA compared with none, but the PA intensity needs to be more moderate to vigorous intensity for men to gain maximal benefit, whereas women generally benefited from longer duration PA of low to moderate intensity, such as walking, for example, >3.5 hours/wk.
Few studies have examined occupational PA in men or women, but rather the majority of studies measured frequency, duration, and intensity of all types of occupational or leisure-time PA. It is important to note that the majority of participants in all studies and meta-analyses were white from the United States or Europe. Only the REGARDS study used purposeful sampling to ensure approximately equal numbers of white and black participants, with no racial differences observed in association between stroke and PA. Another important consideration in these studies is the heterogeneity of assessment of PA. All studies used self-report and differed in their questioning of PA characteristics, as well as the classification of participants into high or low PA groups. Data on the prevention of ischemic versus hemorrhagic stroke are sparse because of limited power from small numbers of hemorrhagic strokes. There are few studies that include serial assessment of PA levels during the long-term, so the cumulative benefits of PA and impact of changing behavior on stroke risk cannot be estimated. However, the evidence from several high-quality studies with large sample sizes provides a consistent message that PA, as part of a healthy lifestyle, reduces stroke risk. Future cohort studies that include stroke outcomes and objective measurement of PA using accelerometers will enable more accurate classification of PA levels and assist in clarifying the effect of intensity versus duration for men and women and dose–response relationship seen to some extent in all studies.

How Does PA Modify the Risk Factors for Stroke?

Although the mechanisms mediating the reduction in stroke risk are not fully understood, there is substantial evidence for PA to influence stroke risk factors. When measuring the impact of PA on stroke risk, it is difficult to separate the specific role of PA when it often clusters with other healthy lifestyle factors, such as healthy diet, not smoking, and maintaining a healthy weight. Indeed, PA is believed to reduce stroke risk through the positive effect it has on these other stroke risk factors. When considering the 10 modifiable risk factors that, in an international case-control study, were found to account for 90% of the risk of stroke (hypertension, smoking, waist:hip ratio, diet score, PA, diabetes mellitus, alcohol intake, psychosocial status, cardiac causes, and ratio of apolipoproteins B to A1), PA can positively influence at least 3 of these: hypertension, diabetes mellitus, and body fat.

Hypertension is considered to be the most important risk factor for primary stroke prevention. Control of blood pressure (BP) is one of the beneficial effects of PA for which specific recommendations have been made. A pilot randomized controlled trial of a simple walking intervention, using pedometers to increase step count, was effective at increasing PA and resulted in lower BP in a group of sedentary overweight and obese women. A workplace intervention conducted >1 year to increase PA in healthy office workers also resulted in a reduction in systolic BP in the PA, but not the control group. Both studies observed a reduction of >6 mm Hg in systolic BP, but larger reductions of ≤10 mm Hg are seen in studies with hypertensive participants. Individuals with treatment-resistant hypertension can also benefit from PA, with reduced incidence of stroke observed in those who were involved in vigorous PA at least 4 times per week in the REGARDS study. It is likely that these reductions in systolic BP reflect improved endothelial function after exercise.

Considerable evidence also supports the recommendation that people with type 2 diabetes mellitus should undergo structured PA because of the positive effects on glycemic control, visceral adipose tissue, and plasma triglycerides. A cohort study of individuals with newly diagnosed diabetes mellitus, followed up for 5 years, found that those who increased their PA had a relative risk of total cardiovascular disease (including stroke and myocardial infarction) of 0.53 compared with those who decreased their PA. When considering the association between stroke and PA in people with diabetes mellitus, those who participated in at least 30 minutes/d of brisk walking, or the equivalent, had a 45% reduction in stroke risk compared with those who were inactive.

Several different variables are used in studies to classify excess weight: measurement of body mass index, waist circumference, waist:hip ratio, visceral adipose tissue, and overall body fat. Randomized controlled trials of PA interventions typically result in only modest weight loss (1–2 kg), but they are often associated with improvements in body mass index, waist circumference, and body fat with PA interventions, particularly in those with diabetes mellitus. Even in the absence of significant weight loss, moderately vigorous PA improves lipid profiles through lowering low density lipoprotein-cholesterol and triglycerides and increasing high density lipoprotein-cholesterol.

Additional mediating factors, which may account for the reduction in stroke risk with regular PA, are likely to be related to inflammatory and hemodynamic factors. Blood samples from 27,055 participants of the Women’s Health Study were collected at baseline, along with data on cardiovascular risk factors including PA with follow-up of >11 years. Although this study did not examine stroke events separately from other cardiovascular events, it demonstrated that inflammatory/hemostatic biomarkers, such as high-sensitivity C-reactive protein and fibrinogen, contributed significantly to lower risk of cardiovascular disease in women who were more physically active. This is consistent with previous literature attributing the anti-inflammatory effect of PA as an important factor in preventing cardiovascular disease.

Conclusions

It is estimated that 610,000 first strokes occur in the United States each year. Worldwide, it is estimated that there were 11.6 million incident ischemic strokes and 5.3 million incident hemorrhagic strokes in 2010. Although transient ischemic attacks can precede stroke, most strokes occur without warning. Stroke is a preventable disease, and control of modifiable risk factors plays the major role in prevention strategies. There is substantial, consistent evidence from numerous, high quality studies that higher PA levels are associated with significantly lower risk of stroke, and this evidence suggests that PA has a protective benefit in stroke prevention beyond the traditional stroke risk factors. With the high prevalence
of physical inactivity in the general population, increasing PA levels could have a significant effect on reducing stroke incidence.

Given the numerous health benefits of PA, there are many public health guidelines on the recommended volume and intensity of PA for optimal health. Although separate guidelines for stroke prevention do not exist, the recommendations for primary stroke prevention are consistent with the current US guidelines: at least 40 minutes/d of moderate to vigorous intensity aerobic PA 3 to 4 days/wk. These recommendations should be stressed as part of an overall stroke prevention strategy, but even more so in persons with other risk factors. The literature suggests that men achieve a greater reduction in stroke risk when they engage in PA at a moderate to vigorous intensity, whereas women benefit from greater amounts of low intensity PA, such as walking. Further research is needed to clarify the type and intensity of PA, potential differences by race/ethnic groups, and use of more objective measurement of PA to clarify the dose-response relationship in men and women. The recommended PA level for stroke prevention is associated with a low risk within the general population, with an acceptable risk:benefit ratio. So to use the common motivational phraseology, just do it. And do it every day!

Disclosures
Dr Howard has received research funding from National Institutes of Health for studies of physical activity and stroke risk. Dr McDonnell reports no conflicts.

References
5. Marcus BH, Williams DM, Dubbert PM, Sallis JF, King AC, Yancey AK, et al; American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity); American Heart Association Council on Cardiovascular Disease in the Young; Interdisciplinary Working Group on Quality of Care and Outcomes Research. Physical activity intervention studies: what we know and what we need to know: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity); Council on Cardiovascular Disease in the Young; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research. Circulation. 2006;114:2739–2752. doi: 10.1161/CIRCULATIONAHA.106.179683.


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Howard and McDonnell

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## Table I. Summaries of Physical Activity Studies in Primary Stroke Prevention

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<td>1 Chiuve et al 2008 Health Professionals Follow-Up Study (HPFS) and the Nurses’ Health Study (NHS)</td>
<td>Prospective cohort study among 43,685 men, and 71,243 women, predominantly Caucasian. Participants were followed for incident stroke since 1976 (NHS) and 1986 (HPFS). The study determined the effect of a low risk lifestyle on stroke risk. A low-risk lifestyle was defined as not smoking, a BMI &lt;25kg/m(^2), ≥30mins/day of moderate activity, modest alcohol consumption (5-30g/day for men, 5-15g/day for women), and scoring within the top 40% of a healthy diet score.</td>
<td>1559 cases of stroke were documented in women (NHS) and 994 in men (HPFS). Women with all five low-risk factors (2% of the sample) had a relative risk of 0.21 (95% CI 0.12-0.42) for total stroke. Men with all five low-risk factors (4% of the sample) had a relative risk of 0.31 (95% CI 0.12-0.42) for total stroke. The associations between lifestyle factors and risk of ischemic/hemorrhagic stroke were similar, but the number of incident hemorrhagic strokes was low. PA was an independent predictor of total stroke in both men and women.</td>
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<td>2 Tikk 2014 EPIC-Heidelberg</td>
<td>Prospective cohort study, part of a large-scale Europe-wide study, the European Prospective Investigation into Cancer and Nutrition (EPIC). Cohort of 25,540 middle-aged men and women.</td>
<td>During an average follow up of 12.7 years, 551 incident strokes occurred. Women engaging in moderate PA showed a reduced risk of stroke (HR 0.49, 95% CI 0.33-0.73) which persisted in the multivariable model (HR 0.53, 95% CI 0.35-0.79). Women engaging in any PA had a reduced risk of stroke. In contrast, men who were moderately inactive, compared to inactive had a reduced risk of stroke (HR 0.71, 95% CI 0.51-0.98) but this did not persist after adjustment for other factors such as BMI, smoking status and diet. Higher levels of PA did not confer any benefit.</td>
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<td>3 Larsson et al 2014 Sweden Mammography Cohort</td>
<td>Population-based prospective study of 31,696 women. The effect of a low-risk lifestyle on risk of stroke was investigated. This was defined as a healthy diet (top 50% of the Recommended Food Score), moderate alcohol consumption (5-15 g/day), never smoking, PA (walking/cycling ≥ 40min/day and exercise ≥ 1hr/wk) and BMI &lt;25kg/m(^2).</td>
<td>1554 incident stroke cases were identified during 10.4 years of follow-up. The risk of stroke decreased steadily with increasing number of low-risk lifestyle factors. The multivariable relative risk of ischemic stroke for those with all five low risk factors was 0.38 (95% CI 0.20-0.73). In the univariate model, PA in isolation was inversely associated with risk of ischemic stroke, but this association did not persist in the multivariable model (RR 0.91, 95% CI 0.81-1.04).</td>
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<td>4 Kurth et al 2006 Women’s Health Study</td>
<td>Prospective cohort study of 37,636 women aged 45 years or older. The aim of the study was to investigate the effect of a healthy lifestyle, defined as never smoking, alcohol During 10 years of follow-up, 450 incident strokes were confirmed. Compared with participants with few healthy behaviors, women who reported a healthy lifestyle had multivariable-adjusted hazard ratios of 0.45 (95% CI 0.24-0.83) for total stroke and 0.29 (95% CI 0.14-0.63)</td>
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consumption between 4-10.5 drinks per week, exercise ≥ 4 times per week, BMI < 22, and a diet high in cereal fiber, folic acid and omega-3 fatty acids, with high ratio of polyunsaturated to saturated fat, and low in trans-fat and glycemic load.

PA was only weakly, and non-significantly, associated with risk of total stroke when investigated individually.

Myint EPIC-Norfolk

Population-based prospective study of 20,040 men and women, 99.5% of whom were white. Four health behaviors were investigated, with one-point each for current non-smoking, physically not inactive, moderate alcohol intake (1-14 units/wk) and at least five servings a day of fruit and vegetables/day, ascertained via plasma concentration of vitamin C ≥ 50 μmol/l.

During 229,992 person years of follow-up, 599 incident strokes occurred. The risk of stroke increased linearly with every point decrease in combined health behavior score. In the fully adjusted model, men and women who scored 0 for health behaviors had a RR of 2.31 (95% CI 1.33-4.02). When PA alone was investigated, any PA was associated with reduced risk of incident stroke in women (RR 1.37, 95% CI 1.08-1.73) but not men (RR 1.20, 95% CI 0.94-1.52). The authors acknowledge that dichotomizing PA behavior may have obscured the gradient in incidence of stroke.

Zhang

Population-based study in Finland from 1982, with five independent cross-sectional population surveys, with a total sample size of 38,737. Five healthy lifestyle factors were considered: current vs ever vs never smoking, BMI ≥ vs <25 kg/m², physical activity (low vs moderate vs high), vegetable consumption (≤ 2 vs ≥3 times/wk), and alcohol consumption (none vs ≥ 210g/wk for men/≥ 140 g/wk for women vs ≥ 1-209 g/wk for men/1-139 g/wk for women).

During a mean follow-up of 13.7 years, 1478 stroke events occurred. The multivariable-adjusted HRs associated with adherence all five healthy lifestyle indicators was 0.33 (95% CI 0.23-0.50) for total stroke. PA was inversely associated with total and ischemic stroke risk in the multivariable-adjusted model. Compared to low PA, moderate or high PA reduced the risk of stroke (HR 0.78, 95% CI 0.68-0.89) in the multivariable model. Individual lifestyle factors and effect of stroke on men versus women were not investigated.

Dong et al 2012 Northern Manhattan Study.

Prospective, multi-ethnic population based study of 2981 participants in the US. The aim of the study was to evaluate the relationship between the number of ideal cardiovascular health metrics and cardiovascular risk of myocardial infarction, stroke and vascular death.

Over a median follow-up of 11 years, 722 individuals developed an incident cardiovascular disease event, including stroke, MI and vascular death. The presence of a greater number of the ideal cardiovascular health metrics at baseline was associated with a markedly lower risk of cardiovascular disease, stroke, MI and vascular death. Ideal PA was greatest among whites, lower among blacks and lowest among Caribbean Hispanics. The greatest reduction in adjusted cardiovascular disease incidence rate was found in the comparison between 0-1 and 2 ideal health metrics, suggesting that even 2 ideal health metrics may lower CVD risk by ~27%.
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<th>Study Reference</th>
<th>Study Design and Population</th>
<th>Aim of the Study</th>
<th>Results</th>
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<td><strong>Kulshreshtha et al 2013</strong>&lt;br&gt;REGARDS</td>
<td>National population-based cohort of 30,329 blacks and whites, aged ≥45 years, sampled from the US population.</td>
<td>The aim of the study was to investigate the association between the American Heart Association’s Life’s Simple 7 (LS7) and incident stroke in black and white Americans.</td>
<td>Over a median follow up of 4.9 years, there were 432 incident strokes among 22,914 participants with data on LS7 and no previous cardiovascular disease. In the multivariable-adjusted model, each improvement in the LS7 health category was associated with 25% lower risk of stroke (95%CI 0.63-0.90). A 1-point improvement in LS7 score was associated with an 8% lower risk of stroke (95% CI 0.88-0.95). The HR for PA alone was not significantly associated with incident stroke in the multivariable adjusted model.</td>
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<td><strong>Zhang et al 2013</strong>&lt;br&gt;Large China Study</td>
<td>Prospective cohort study of 91,698 participants from the Kailuan community in China.</td>
<td>The aim of the study was to determine the relationship between ideal CVH metrics and the risks of ischemic and hemorrhagic stroke, respectively. Ideal PA was defined as moderate or vigorous PA for &gt; 80 mins/wk.</td>
<td>During a 4-year period of follow-up, 1486 incident stroke events occurred. There was a clear inverse gradient relationship between the number of ideal CVH metrics and risk of ischemic and hemorrhagic stroke in the multivariable-adjusted model. For both men and women with ideal PA levels, they had a HR of incident total stroke of 0.76 (95% CI 0.66-0.89) and ischemic stroke of 0.76 (95% CI 0.64-0.90). The relationship between PA and hemorrhagic stroke was not significant.</td>
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<td><strong>Lee et al 1999</strong>&lt;br&gt;Physicians’ Health Study</td>
<td>Prospective cohort study of 21,823 men.</td>
<td>The aim of the study was to examine the relationship between frequency of moderately-vigorous PA and stroke risk.</td>
<td>During an average follow-up of 11 years, 553 incident strokes occurred. There was a dose-dependent reduction in stroke risk with increasing PA categories: compared to the least active men, the most active men experienced a 26% reduction in stroke risk (95%CI 0.57-0.95), but this association was attenuated in the multivariable-adjusted model with adjustment for stroke risk factors.</td>
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<td><strong>Hu et al 2000</strong>&lt;br&gt;The Nurses’ Health Study</td>
<td>Prospective cohort study of 72,488 female nurses aged 40-65 years who did not have CVD or cancer at baseline.</td>
<td>PA was ascertained by questionnaire on three occasions, with questions related to average amount of time each week spent on PA and their usual walking pace, in order to calculate metabolic equivalents (METs) per week.</td>
<td>During 8 years and 560,087 person-years of follow-up, 407 incident stroke cases were observed. Increasing MET quintiles was associated with progressively lower risk of total stroke, with the highest level of PA associated with a multivariable adjusted RR of 0.56 (95% CI 0.47-0.91) and ischemic stroke 0.52 (95% CI 0.33-0.80). Walking pace was strongly associated with risk of stroke, with multivariate RR of 0.49 (95%CI 0.36-0.68) for brisk/very brisk walking, compared with an easy walking pace. Each 3.5 hr/wk increase in moderately-vigorous PA was associated with a 19% reduction in total stroke and 29% reduction in ischemic stroke.</td>
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<td>Sattelmair et al 2010 Women’s Health Study</td>
<td>Prospective cohort study of 39,315 healthy US women ≥ 45 yrs. The aim of the study was to investigate the amount and type of PA required to reduce stroke risk. Assessment of PA was done by self-report of average time per week spent on recreational activities, usual walking pace, and the number of stairs climbed daily. This information was used to calculate weekly energy expenditure into kcal/week.</td>
<td>During an average of 12 years of follow up, 579 women developed incident stroke. There was no significant relationship between total leisure-time PA and risks of total and ischemic stroke. There were significant inverse, dose-dependent relations both of time spent walking (RR 0.70, 95% CI 0.52-0.94 for women who walked ≥ 2 hrs/wk) and walking pace (RR 0.63, 95% CI 0.44-0.91) for women who reported a brisk walking pace, compared to women who did not walk.</td>
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<td>Folsom et al 1990</td>
<td>Population based prospective cohort study of 41,837 older women (aged 55-69) in Iowa, USA. The aim of the study was to investigate the association between abdominal adiposity and incidence of hypertension and stroke independent of BMI. Participants self-reported leisure PA in repeat surveys of stroke risk factors.</td>
<td>Data were analyzed as a nested case-control study investigating cases of incident hypertension and stroke. Women who reported high levels of PA had a 30% reduction in risk of hypertension. Age-adjusted stroke risk was significantly increased in those who were inactive, compared to those who reported medium levels of PA (OR 0.6, 95% CI 0.4-0.9).</td>
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<td>Kiely et al 1994 Framingham Heart Study</td>
<td>Population based prospective cohort study of 1,897 men and 2,299 women, members of the Framingham Study cohort. The aim of the study was to investigate the influence of increased levels of PA on risk of stroke. PA was ascertained with a structured questionnaire to estimate the amount of metabolic work done during a typical 24-hr period, and then organized into tertiles.</td>
<td>Over a median follow up of 32 years, multivariable-adjusted analyses revealed that increased levels of PA were protective, with the strongest effect for older members in the medium PA tertile (RR 0.41, 95% CI 0.24-0.69). Higher levels of PA in men conferred no additional benefit. There was no significant protective effect in women.</td>
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<td>Willey et al 2009 NOMAS</td>
<td>Prospective cohort study of 3,298 older, urban-dwelling, multi-ethnic individuals. PA was measured by an in-person questionnaire adapted from the National Health Interview Survey of the National Centre for Health Statistics.</td>
<td>Participants were followed for a median of 9.1 years and 238 incident strokes occurred. In the univariate analysis, moderate to heavy activity, compared to no PA, was associated with a lower risk of ischemic stroke (HR 0.65, 95% CI 0.44-0.95), but light-intensity PA was not. This association remained in the multi-variable analysis (HR 0.65, 95% CI 0.44-0.98). An interaction between PA and sex indicated that moderate to vigorous PA was protective against ischemic stroke in men (HR 0.37, 95% CI 0.18-0.77), but not in women. Light activity, such as walking, was not associated with a lower risk of ischemic stroke.</td>
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<td>McDonnell et al 2013</td>
<td>National population-based cohort of 30,329 blacks and whites, aged ≥45 years, sampled from the US population. The aim of the study was to investigate the association between self-reported moderately-vigorous PA and incident stroke in the REGARDS cohort.</td>
<td>During an average follow up of 5.7 years, 918 incident stroke cases occurred. In the univariate analysis, participants who were inactive had an increased risk of total stroke (HR 1.20, 95% CI 1.01-1.42). This association was attenuated after adjustment for traditional stroke risk factors. When data were stratified by sex, there was a trend towards a protective effect for men exercising 1-3 times a week, but this was not observed in women.</td>
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<td>Huerta et al 2013</td>
<td>Population-based prospective study of 41,438 men and women living in five different Spanish regions. The aim of the study was to investigate the risk of CVD according to PA levels, ascertained by questionnaire. The questionnaire asked about type, time or intensity of PA during a typical week, and included specific questions for work, leisure time PA and household activities.</td>
<td>A total of 652 incident stroke/TIA cases occurred over a mean follow-up of 12 years. In women, any recreational PA compared to inactivity was inversely associated with stroke risk, HR 0.45 (95% CI 0.22-0.90). Walking for ≥3.5 hrs/wk was associated with reduced risk of stroke in women (HR 0.57, 95% CI 0.35-0.92). There was no association between recreational or occupational PA and CVD in men.</td>
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<td>Lee et al 2003</td>
<td>Meta-analysis of 23 studies to examine the overall association between PA and/or cardiorespiratory fitness and stroke incidence or mortality.</td>
<td>5 case-control and 18 cohort studies were included. In the cohort studies, highly active individuals had a 25% lower risk of stroke incidence or mortality than low-active individuals (95% CI 0.69-0.82). For case-control studies, highly active individuals had a 64% lower risk of stroke incidence than low-active individuals (95% CI 0.25-0.52). Low-active individuals had a 17% (95% CI 0.76-0.89) and 48% (95% CI 0.40-0.69) reduced risk of stroke for the cohort and case-control studies, respectively.</td>
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<td>Wendel-Vos 2004</td>
<td>Meta-analysis of 31 observational studies to quantify the relationship between PA and stroke.</td>
<td>Seven case-control studies and 24 cohort studies were included. For occupational PA, being active was associated with a 43% (95% CI 0.43-0.77) and 23% (0.60-0.98) lower risk of ischemic stroke compared with being inactive and moderately active, respectively. Being moderately active at work was associated with a 36% lower risk of total stroke compared with being inactive at work. During leisure time, any PA was associated with a 22% (95% CI 0.71-0.85) lower risk of total stroke compared with being inactive.</td>
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<td>Li &amp; Siegrist 2012</td>
<td>Meta-analysis of 21 prospective studies, with a sample size of 650,000 adults free of stroke at baseline.</td>
<td>The follow-up period ranged from 5-32 years and over 20,000 incident strokes occurred. A high level of leisure time PA reduced the risk of stroke by 20-30% compared to low PA, while moderate PA decreased the risk by 10-</td>
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20%. Occupational PA offered protection from stroke at a moderate, but not high level. Compared with low PA, moderate PA resulted in an 11% reduction in risk of stroke outcome (95% CI 0.85-0.94), and high PA resulted in a 21% reduced risk (95% CI 0.74-0.85). Data were stratified by sex. Men had a 12% reduced risk (95% CI 0.82-0.94) for moderate PA and 19% reduction for high PA (95% CI 0.75-0.87). Among women, there was a 24% reduction for high PA (95% CI 0.64-0.89) but no significant difference in risk of stroke outcome for moderate PA compared to low PA.

Meta-analysis of 13 case-control studies to quantify the association between PA level and risk of stroke in healthy individuals with no history of cardiovascular disease.

**Abbreviations:** BMI = body mass index, CI = Confidence interval, CVD = cardiovascular disease, EPIC= European Prospective Investigation into Cancer and Nutrition, HPFS = Health Professionals Follow-Up Study, HR = hazard ratio, NHS = Nurses’ Health Study, NOMAS = NOrthern MAnhattan Study, OR = odds ratio, PA = physical activity, REGARDS = REasons for Geographic And Regional Differences in Stroke, RR = relative risk, TIA = transient ischemic attack.