REVIEW ARTICLE

Exercise as Stroke Prophylaxis

Carl D. Reimers, Guido Knapp, Anne K. Reimers

SUMMARY

Background: Stroke is the third most common cause of death in industrialized countries, accounting for more than 10% of deaths over age 65. Most strokes are due to arteriosclerosis. Regular physical activity lowers arterial blood pressure and body weight and improves glucose and lipid metabolism, thereby slowing the development of arteriosclerosis and its cardiovascular complications, particularly myocardial infarction. This review focuses on the question whether physical activity might also have a preventive effect on cerebral infarction and hemorrhage.

Methods: This analysis is based on 33 prospective cohort studies and 10 case-control studies that addressed the potential effect of physical activity on stroke-related morbidity and mortality.

Results: Our meta-analysis shows that physical activity reduces the risk of all types of stroke (infarction, hemorrhage, and stroke of unspecified type). The relative risk (RR) of fatal or non-fatal cerebral infarction is 0.75, while the corresponding figures for cerebral hemorrhage and stroke of unspecified type are 0.67 and 0.71, respectively. The reduction of risk is only statistically significant for men. The case-control studies show an RR of 0.32 for men and women combined.

Conclusions: When a multivariate analysis is performed that takes other vascular risk factors into account, physical activity is found to have an independent protective effect against cerebrovascular events. The effect is statistically significant only for men, not for women.

Key words: stroke, cerebral hemorrhage, risk of stroke, physical activity, health-related behavior

Stroke is the third most common cause of death in industrialized countries (1). About 30% of all deaths before age 65 and 50% of all deaths thereafter are due to cardiovascular diseases, and one-fifth of these are due to stroke (2). Every third stroke has a fatal outcome (3). Stroke is also the most important cause of disability: 15% to 30% of stroke patients have persistent deficits, which often lead them to require nursing home care (4). Despite advances in stroke treatment, including systemic clot-lysis therapy, the opportunities for treatment remain limited (1).

The risk of stroke doubles every ten years after age 55; the risk of stroke is 50% higher in men than in women from age 55 to 75, but the risk in the two sexes equalizes thereafter (4). The main treatable causes of stroke are the following (4):

- Cardiovascular diseases
- Arterial hypertension
- Smoking
- Diabetes mellitus
- Carotid stenosis
- Atrial fibrillation
- Dyslipidemia
- Overweight
- Excessive alcohol consumption
- Hypercoagulable states
- The consumption of oral contraceptive drugs.

Regular exercise lowers arterial blood pressure, reduces weight, and improves glucose and lipid metabolism, endothelial function, and the rheological properties of the blood (2, 3, 5). Accordingly, regular exercise also lowers the risk of myocardial infarction (2).

This review article concerns the question whether regular exercise can also lower the risk of suffering or dying from a stroke, and, if so, whether ischemic or hemorrhagic strokes, or both, can be prevented by exercise.

Methods

The PubMed database was searched for original articles dealing with the frequency of ischemic or hemorrhagic strokes in physically active and physically inactive persons. The search terms employed were “stroke” AND “physical activity” OR “sport” AND “prevention” (for all listed years; last update December 2008). Many of the 535 publications retrieved were experimental studies, review articles, or studies on therapeutic

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TABLE

The relative risk of a cerebrovascular event as a function of study design

Study design	Number of studies	Number of comparisons	Sex	Type of stroke	RR	Remarks
Cohort study	7	8	F	Ischemic	0.76	95% CI: 0.56–1.02, p=0.065; Q=20.54, p=0.005, I ² =65.9%
Cohort study	9	11	M	Ischemic	0.73	95% CI: 0.65–0.83, p<0.001; Q=8.71, p=0.56, I ² =0%
Cohort study	4	4	F	Hemorrhagic	0.92	95% CI: 0.44–1.93, p=0.8236; Q=6.95, p=0.073, I ² =56.9%
Cohort study	6	7	M	Hemorrhagic	0.60	95% CI: 0.43–0.83, p=0.001; Q=4.26, p=0.64, I ² =0%
Cohort study	13	14	F	Undifferentiated	0.71	95% CI: 0.58–0.88, p=0.002; Q=59.4, p<0.001, I ² =78.1%
Cohort study	18	19	M	Undifferentiated	0.72	95% CI: 0.64–0.80, p<0.001; Q=31.2, p=0.027, I ² =42.3%
Case-control study	7	7	M + F	Ischemic	0.32	95% CI: 0.17–0.59, p<0.001; Q=26.1, p<0.001, I ² =77%

M=male; F=female; CI=confidence interval; p=p-value; Q=Cochrane's homogeneity statistic; RR=relative risk; I²=Higgins' I² (a measure of the percentage of the differences between studies that is not due to chance)

aspects and the like. Thus, only a few publications were relevant to the question we sought to answer: this was the case for 33 prospective cohort studies and 10 case-control studies. In addition to these publications, all of the studies included in previously published meta-analyses (3, 6) were included in the present meta-analysis as well.

In all of the studies included in the present analysis, the level of physical activity of each person included in the study was determined from statements made by the participants themselves. The quantitative assessment of physical activity over long periods of time is impractical because of the immense amount of work it would require, and it has thus not been carried out in any study to date. Data from men and women in the cohort studies were analyzed separately as far as possible; in the case-control studies, this distinction could not be drawn, because of the relatively low number of study participants. The present study does not differentiate between occupational and leisure-time physical activity, as its goal is to determine the effect of exercise as such on stroke.

The risk of stroke in physically active persons was calculated in relation to the risk seen in the least physically active group of participants in each of the studies reviewed for the present article. Among the physically active persons, the groups that had the lowest risk of stroke in comparison to physically inactive persons were included in the calculation. The studies listed

were subjected to a meta-analysis. All calculations were performed with the aid of the “meta” packet in the “R” statistics software, version 2.8.0 (7). The cohort studies were meta-analyzed separately from the case-control studies.

More specifically, within the class of cohort studies, separate meta-analyses were performed for three subgroups—ischemic, hemorrhagic, and undifferentiated stroke—and for men and women. The “undifferentiated stroke” subgroup consisted of publications in which no diagnostic imaging was carried out, as well as those that grouped the patients with ischemic stroke together with those with intracerebral (sometimes also subarachnoid) hemorrhage. Subarachnoid hemorrhage was not considered in a separate category, as it is rare compared to other types of stroke. The studies in which subarachnoid hemorrhage was listed as an entity in its own right were not eliminated, because a small number of patients with subarachnoid hemorrhage might also be concealed in the statistics of the other studies in which no imaging was performed. The meta-analysis included only those studies whose results were available as an estimate of the strength of the effect accompanied by a confidence interval. The results from the individual studies were combined on a logarithmic scale. Because of heterogeneity among studies, a random-effects model was used consistently. In the *Figures*, the relative risk (RR) is always shown on a logarithmic

scale. The meta-analytic estimators were retransformed back onto the original RR scale.

Results

In a meta-analysis of 18 cohort and 5 case-control studies, Lee et al. (3) concluded that the RR of stroke, or of fatal stroke, is 27% lower in very physically active persons than in those whose level of physical activity is low (RR = 0.73, 95% confidence interval [95% CI]: 0.67–0.79, $p < 0.001$). Even persons who were only moderately physically active had a significantly reduced risk, with RR = 0.80. The risk of both ischemic stroke and intracerebral hemorrhage was reduced. In the cohort studies, the risk reduction for a fatal or non-fatal stroke in very active, as compared to relatively inactive, persons was 21% for ischemic events (RR = 0.79, 95% CI: 0.69–0.91, $p < 0.001$) and 34% for hemorrhagic events (RR = 0.66, 95% CI: 0.48–0.91, $p < 0.001$). The risk reduction remained significant, though of lesser magnitude, for only moderately physically active persons.

In a further meta-analysis, Wendel-Vos et al. (7) distinguished occupational physical activity from physical activity during free time. They reviewed 24 cohort and 7 case-control studies and calculated that a high level of physical activity during free time, as compared with a low one, reduced the risk of all types of stroke by 22% (RR = 0.78, 95% CI: 0.71–0.85, $p < 0.001$), the risk of ischemic stroke by 21% (RR = 0.79, 95% CI: 0.69–0.91, $p < 0.001$), and the risk of intracerebral hemorrhage by 26% (RR = 0.74, 95% CI: 0.57–0.96, $p < 0.001$). In contrast, when they studied occupational physical activity, they found that moderate physical activity on the job lowered the risk of stroke to a greater extent than a high level of physical activity on the job (36% versus 23%), although they did not state whether this difference was statistically significant. Alevizos et al. (8) also concluded in their review that exercise reduces the risk of stroke. There is as yet no definitive answer to the question whether the extent and intensity of physical activity are significantly correlated with its preventive effect (5). The literature does not even contain a uniform definition of different levels of physical activity, let alone a quantitative measure.

The authors' findings

eTables e1 and e2 show the relative risk that a physically active person will suffer a stroke or die from one, as compared to the least physically active group of study participants in each study. The *eTables* also contain further details about the level of activity in each of the groups being compared, and about the duration of observation in each study. The studies listed often give the risk of stroke in various subpopulations; in the present analysis, the two groups presented for comparison are always the group with the lowest level of physical activity as a control group, and the group with the highest level of physical activity or the one with the greatest risk reduction.

FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4

FIGURE 5

Cohort studies

28 of the 33 cohort studies were included in the meta-analysis because both effect estimators and confidence intervals were reported on.

Ischemic stroke

12 of the 14 studies in which ischemic strokes were studied were combined in a meta-analysis. These studies yielded a total of 20 individual comparisons for meta-analysis: RR = 0.75 (95% CI: 0.67–0.84, $p < 0.0001$; $Q = 30.13$, $p = 0.05$, $I^2 = 36.9\%$).

Cerebral hemorrhage

7 of the 9 studies in which the risk of cerebral hemorrhage was studied were combined in a meta-analysis. These 7 studies yielded a total of 12 individual comparisons for meta-analysis: RR = 0.67 (95% CI: 0.52–0.86, $p = 0.0013$; $Q = 13.20$, $p = 0.28$, $I^2 = 16.7\%$).

Stroke of undifferentiated type

23 of the 27 studies in which the risk of stroke was studied without any differentiation between ischemic and hemorrhagic events were combined in a meta-analysis. These studies yielded a total of 23 individual comparisons for meta-analysis: RR = 0.71 (95% CI: 0.64–0.80, $p < 0.0001$; $Q = 97.1$, $p < 0.0001$, $I^2 = 64\%$).

Case-control studies

Results for ischemic strokes were reported in 7 of the 10 case-control studies. Meta-analysis yielded the following results: RR = 0.32 (95% CI: 0.17–0.59, $p = 0.0003$; $Q = 26.1$, $p = 0.0002$, $I^2 = 77\%$). Two studies gave results for cerebral hemorrhages: one result was barely significant, the other insignificant. The results for strokes of undifferentiated type from two studies were significant.

The relative risks that were calculated separately for men and women are given in the *Table*. The results of our meta-analysis are given in *Figures 1–6* and are, in general, consistent with the findings of Lee et al. (3) and Wendel-Vos et al. (7).

16 studies in which physical activity was graded on a scale with three or more levels showed that the risk of stroke declined with increasing physical activity (9, 11, 12, 15, 18, 20, 25, e1, e2, e3, e5, e7, e10, e12, e16, e17). Eight studies revealed a U-shaped dependence, i.e., the risk of stroke was less with intermediate degrees of physical activity than with lower or higher physical activity (10, 11, 15, 18, 20, e3, e8, e11). On the other hand, five studies revealed an inverted U-shaped dependence, in which the risk of stroke was highest for an intermediate degree of activity (9, 15, 18, e5, e15). In the four studies in which physical activity was graded on a scale with at least four levels, the risk of stroke was found to depend on the level of physical activity in an unsystematic way (10, 11, 12, 21). A number of studies appear in our tables more than once, because many studies involved several different populations or types of activity (e.g., on the job

or during free time). Nonetheless, the differences in risk between the different levels of activity were mostly insignificant.

Discussion

The studies available to date show that regular exercise can lower the risk of a fatal or non-fatal stroke (infarct, cerebral hemorrhage, or—rarely—subarachnoid hemorrhage) by about 20% to 30%. There is a trend suggesting that a higher level of physical activity is more effective than a lower one for the prevention of ischemic stroke. Not all of the relevant studies yielded significant results, as is usually the case in epidemiology. Inadequate cohort size may explain this in some cases.

In the present meta-analysis, which is based on 33 cohort studies, the risk of a fatal or non-fatal ischemic stroke was lowered by 24% in women and by 27% in men, while that of a cerebral hemorrhage was lowered by 8% in women and by 40% in men. For strokes that were not radiologically classified as being either ischemic or hemorrhagic, the risk was 29% lower and 28% lower (in women and men, respectively) than in the physically inactive persons constituting the control group, but only the risk reduction in men was statistically significant. It remains an open question whether the insignificant results in women were due to the smaller number of studies including women. In the case-control studies, the risk reduction for men and women combined reached the very high figure of 68%.

As can be seen from *Figures 1–6*, there was one study for each type of stroke that actually showed the risk of stroke in physically active men to be higher than in physically inactive men. In women, a higher risk associated with physical activity was seen in two studies on ischemic stroke, one on cerebral hemorrhage, and three on undifferentiated strokes. All other studies showed that physically active persons were less likely to have a stroke. No case-control study indicated a higher risk for physically active persons.

The statistically significant preventive effect of physical activity on stroke in all of the calculations undertaken here (in agreement with two earlier meta-analyses [3, 7]) does not preclude the possibility that such an effect might be absent in certain subgroups. Thus, voluntary exercise during one's free time might conceivably have a different effect from compulsory exercise on the job. The effect might also vary from one ethnic group to another. It is known, for example, that black US-Americans suffer strokes at least twice as commonly as their white compatriots, and tend to have them at different sites and with different pathophysiological mechanisms (e28).

A clear dependence of the magnitude of risk reduction on the extent of physical activity (i.e., a dose-response effect) has not yet been demonstrated. Most studies indicate, however, that the risk is less with higher levels of activity. There may be a saturation effect, however, or even an increased risk when physical activity is very frequent or very intense.

FIGURE 6

Most of the original articles that we evaluated here to calculate the risk of a fatal or non-fatal stroke took a number of the known risk factors for vascular disease into account, e.g., high blood pressure, diabetes mellitus, lipid metabolic disorders, obesity, smoking, and alcohol consumption. Nonetheless, some publications left some risk factors out of consideration (e.g., dietary habits) and did not assess others precisely or in detail (e.g., only overall cholesterol concentrations were given, rather than subfractions), as to do otherwise would presumably have been too expensive and impractical in cohort studies involving up to 70 000 study participants. Thus, it remains conceivable that a beneficial effect of exercise on the vascular risk factors that have already been recognized accounts for at least some of the observed risk reduction. Postulated mechanisms of risk reduction that are currently under discussion include an antihypertensive effect of exercise and a beneficial effect on lipid metabolism, e.g., a reduction of elevated concentrations of HDL-cholesterol. It has also been proposed that the effect may be mediated by an improvement in endothelial function—for example, increased activity of endothelial nitric oxide synthase (eNOS) (5) and of extracellular superoxide dismutase (ecSOD) expression: nitric oxide, a potent vasodilator, inhibits platelet aggregation and adhesion (1). Other mechanisms that may play a role include a lowering of blood viscosity, a tendency toward platelet aggregation, and increased fibrinolysis (8). Further

factors include a reduction of the plasma fibrinogen concentration, increased activity of plasma tissue plasminogen activator, and a raised concentration of HDL-cholesterol (8, 17).

In view of the fact that the multivariate analyses of most of the studies reviewed here took account of the more important known cerebrovascular risk factors that can be positively influenced by exercise (obesity, glucose metabolism, arterial blood pressure, platelet aggregation tendency [e27]), one may suspect that the “gross” preventive effect of exercise is actually higher than the “net” effect on the order of 8% to 40% that is cited above. As already mentioned, the lowest risk of stroke was not always seen in the group of subjects who were most physically active; in some studies, a group with intermediate physical activity had the lowest risk. Yet, when we performed our meta-analysis, we used the data from the group whose risk was lowest in each study. It follows, therefore, that if we had compared only the (nearly) identical levels of physical activity across studies, we would have arrived at a somewhat lower figure for the reduction of stroke risk by physical activity.

The risk reduction for cerebrovascular events is of the same order of magnitude as that for coronary heart disease. The risk of coronary heart disease in men who exercise regularly in their free time is 24% lower than that of men who are physically inactive in their free time. In women, there is an analogous risk reduction of 23%. The effect is less pronounced at intermediate levels of physical activity (e29). Traveling to work on foot or by bicycle has been shown to lower the risk of cardiovascular events significantly only in women: RR = 0.87 (95% CI: 0.77–0.98, $p = 0.02$; for men, RR = 0.91, 95% CI: 0.80–1.04) (e30).

Although the description of physical activity was not quite uniform across studies, the type of activity reported in most of them corresponded to aerobic exercise. Even the types of highly intense physical activity that were named in most studies were usually leisure sports such as jogging, swimming, cycling, or the like. Walking is considered to be a mildly to moderately intense form of physical activity (3). The term “intense physical activity” in the epidemiological studies cited here thus has little to do with what an athlete would consider intense activity, i.e., an anaerobic or competitive stress. No data on this type of activity are available. Thus, regular cardiovascular exercise with moderately intense physical activity for at least 30 minutes per day is recommended (4) for persons who do not get adequate exercise on the job. Moderately intense physical activity can be provided by, for example, rapid walking, cycling, moderately fast swimming, or slow canoeing.

Conflict of interest statement

The authors declare that they have no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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KEY MESSAGES

- Physical activity, generally consisting of aerobic endurance tasks, has been found in earlier meta-analyses and in the present one to lower the risk of cerebrovascular events and the associated mortality, in a manner that is probably independent of the known risk factors for such events, at least in men.
- In men, regular physical activity reduces the risk of suffering an ischemic stroke or dying from one by 27% and the risk of a cerebral hemorrhage by 40%. In women, no significant preventive effects are seen.
- For persons whose occupations do not provide them with adequate physical activity, regular exercise for about 30 minutes per day is recommended, both to prevent cerebrovascular events and to obtain other health benefits as well.

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REVIEW ARTICLE

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eTABLE 1

The relative risk of (fatal or non-fatal) ischemic and hemorrhagic stroke depending as a function of physical exercise in prospective cohort studies

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Ischemic stroke							
Abbott et al. 1994 (15)	M, 45–68 yr 22 yr	age, arterial hypertension, smoking, alcohol consumption, glucose, cholesterol, uric acid, hematocrit, LVH	exercise	no exercise	7530	nonsmokers: 0.6 (0.3–0.9) [†] smokers: 0.8 (0.6–1.3) [†]	nonsmokers: p < 0.05 smokers: NS
Agnarsson et al. 1999 (16)	M, 45–80 yr 10.6 ± 3.6 yr	age, smoking, glucose, arterial hypertension, pulmonary function	leisure activities from age 40 onward	no sports	4484	0.62 (0.40–0.97)	p = 0.03
Chiuve et al. 2008 (11)	M, 40–75 yr 2 yr F, 30–55 yr 6 yr	Heart attack in a parent before age 60, acetylsalicylic acid, vitamin E supplementation, hormone therapy (women), arterial hypertension, hypercholesterolemia, diabetes mellitus	6 h sports/wk	no sports	43 685 M, 71 243 F	M: 0.57 (0.43–0.75) F: 0.60 (0.45–0.79)	p < 0.05
Evenson et al. 1999 (17)	F, 45–64 yr 7.2 yr	sex, age, ethnic group, education, smoking, arterial hypertension, fibrinogen, BMI, diabetes mellitus	among 4 groups, the one that was most active in sports	among 4 groups, the one that was least active in sports	8296	1.29 (0.89–1.87)	NS
Evenson et al. 1999 (17)	M, 45–64 yr 7.2 yr	sex, age, ethnic group, education, smoking, arterial hypertension, fibrinogen, BMI, diabetes mellitus	among 4 groups, the one that was most active in sports	among 4 groups, the one that was least active in sports	6279	0.74 (0.50–1.10)	NS
Gillum et al. 1996 (18)	M & F, 45–74 yr 11.6 yr	age, smoking, diabetes mellitus, coronary heart disease, education, systolic blood pressure, cholesterol, BMI, hemoglobin concentration	moderate to large amount of exercise in free time	little exercise in free time	5852	women 45–64 yr 0.35 (0.10–1.15) women 65–74yr 0.68 (0.41–1.14) men 45–64 yr 0.91 (0.45–1.85) men 65–74 yr 0.75 (0.50–1.11)	NS

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Harmsen et al. 1990 (19)	M, 47–55 yr 28 yr	blood pressure, BMI, cholesterol, smoking, emotional stress, atrial fibrillation, myocardial infarction, stroke, history of TIA	among 4 groups, the 3 groups that were more active in sports	among 4 groups, the one that was least active in sports	7495	0.83 (0.7–1.2)	NS
Hu et al. 2000 (20)	F, 40–65 yr 8 yr	age, smoking, alcohol consumption, BMI, menopausal status, aspirin consumption, family history of myocardial infarction under age 60, diabetes mellitus, hypercholesterolemia, high blood pressure	≥ 21.7 MET $\times$ h/week	≤ 2.0 MET $\times$ h/week	72 488	0.52 (0.33–0.80)	p = 0.003
Hu et al. 2005 (9)	M & F, 25–64 yr 19.0 yr	age, sex, BMI, systolic blood pressure, cholesterol, education, smoking, alcohol consumption, diabetes mellitus	Intense exercise in free time (>3 h/wk: running, swimming, intense gardening, martial arts)	Little or no exercise	474 721	0.80 (0.68–0.93)	p < 0.001
Lee et al. 1999 (21)	M, 40–84 yr 11.1 yr	age, smoking, alcohol consumption, angina pectoris, arterial hypertension, diabetes mellitus, hypercholesterolemia, myocardial infarction in a parent	intense exercise (leading to sweating) at least once a week	intense exercise (leading to sweating) less than once a week	21 823	0.90 (0.66–1.22)	NS
Mora et al. 2007 (13)	F > 45 yr 10.9 $\pm$ 1.6 yr	age, high blood pressure, diabetes mellitus, lipids, laboratory evidence of inflammation and coagulopathy, BMI, homocysteine	energy consumption 200–599 kcal/wk	energy consumption ≥ 1 500 kcal/wk	27 055	0.76 (0.58–0.99)	p < 0.05
Nakayama et al. 1997 (22)	F > 40 yr 15.5 yr	age	intense exercise	mild exercise	1469	2.10 (0.89–4.97)	NS
Nakayama et al. 1997 (22)	M > 40 yr 15.5 yr	age	intense exercise	mild exercise	1182	1.11 (0.52–2.38)	NS
Noda et al. 2005 (12)	F, 40–79 yr 9.7 yr	age, BMI, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, sleep, occupation, emotional stress, frequency of fish consumption	≥ 5 h sports/wk	1–2 h sports/wk	64 327	0.73 (0.31–1.70)	NS

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Noda et al. 2005 (12)	M, 40–79 yr 9.7 yr	age, BMI, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, sleep, occupation, emotional stress, frequency of fish consumption	≥ 5 h sports/wk	1–2 h sports/wk	31 023	0.84 (0.45–1.57)	NS
Okada et al. 1976 (23)	M & F, 40–79 yr 6 yr	age, sex	regular exercise on the job	No exercise on the job	3649	0.83	NS
Paganini-Hill & Perez Barreto 2001 (24)	F, 44–101 yr (median: 74 yr) 17 yr	arterial hypertension and its treatment, diabetes mellitus, coronary heart disease, digitalis, smoking, acetylsalicylic acid, gynecological history	exercise > 1 h/d	exercise <0.5 h/d	8532	0.81	NS
Paganini-Hill & Perez Barreto 2001 (24)	M, 44–101 yr (median: 74 yr) 17 yr	arterial hypertension and its treatment, diabetes mellitus, coronary heart disease, digitalis, smoking, acetylsalicylic acid, gynecological history	exercise > 1 h/d	exercise <0.5 h/d	4722	0.96	NS
Hemorrhagic stroke							
Abbott et al. 1994 (15)	M, 45–68 yr 22 yr	age, systolic blood pressure, smoking, alcohol consumption, glucose, uric acid, hematocrit, LVH	exercise	no exercise	7530	45–54 yr: 0.5 (0.2–1.3) [†] 55–68 yr: 0.3 (0.1–0.8) ^{††}	45–54yr: NS 55–68 yr: p < 0.05
Chiuve et al. 2008 (11)	M, 40–75 yr 2 yr F, 30–55 yr 6 yr	myocardial infarction in a parent under age 60, acetylsalicylic acid, vitamin E supplementation, hormone therapy (women), arterial hypertension, hypercholesterolemia, diabetes mellitus	≥ 6 h sports/wk	no sports	43 685 M, 71 243 F	M: 0.65 (0.39–1.09) F: 0.79 (0.50–1.26)	NS
Harmsen et al. 1990 (19)	M, 47–55 yr 28 yr	blood pressure, BMI, cholesterol, smoking, emotional stress, atrial fibrillation, myocardial infarction, stroke, history of TIA	the 3 more active of 4 groups	the least active of 4 groups	7495	0.91 (0.27–2.50)	NS

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Hu et al. 2000 (20)	F, 40–65 yr 8 yr	age, smoking, alcohol consumption, BMI, menopausal status, aspirin consumption, family history of myocardial infarction under age 60, diabetes mellitus, hypercholesterolemia, high blood pressure	4.7–10.4 MET × h/week	≤ 2.0 MET × h/week	72 488	0.72 (0.25–2.08)	NS
Hu et al. 2005 (9)	M & F, 25–64 yr 19.0 yr	age, sex, BMI, systolic blood pressure, cholesterol, education, smoking, alcohol consumption, diabetes mellitus	intense leisure activities (>3 h/wk running, swimming, intense gardening, competitive sports)	little or no exercise	47 721	0.63 (0.42–0.95)	p < 0.001
Lee et al. 1999 (21)	M, 40–84 yr 11.1 yr	age, smoking, alcohol consumption, angina pectoris, arterial hypertension, diabetes mellitus, hypercholesterolemia, myocardial infarction in a parent	intense exercise leading to sweating at least once a week	intense exercise leading to sweating less than once a week	21 823	0.54 (0.25–1.13)	NS
Nakayama et al. 1997 (22)	M > 40 yr 15.5 yr	age	mild exercise	no exercise	1182	1.38 (0.27–7.16)	NS
Nakayama et al. 1997 (22)	F, > 40 yr 15.5 yr	age, BMI, high blood pressure, smoking, alcohol consumption, albumin- and glycosuria, cholesterol, hematocrit, fundus abnormalities, ECG	mild exercise	no exercise	1469	4.13 (1.09–15.69)	p < 0.05
Noda et al. 2005 (12)	F, 40–79 yr 9.7 yr	age, BMI, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, sleep, occupation, emotional stress, frequency of fish consumption	≥ 5 h sports/wk	1–2 h sports/wk	42 242	0.40 (0.11–1.41)	NS
Noda et al. 2005 (12)	M, 40–79 yr 9.7 yr	age, BMI, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, sleep, occupation, emotional stress, frequency of fish consumption	≥ 5 h sports/wk	1–2 h sports/wk	31 023	0.67 (0.27–1.64)	NS
Okada et al. 1976 (23)	M & F, 40–79 yr 6 yr	age, sex	regular exercise on the job	no exercise on the job	3649	0.43	NS

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Paganini-Hill & Perez Barreto 2001 (24)	F, 44–101 yr (median: 74 yr) 17 yr	arterial hypertension and its treatment, diabetes mellitus, coronary heart disease, digitalis, smoking, acetylsalicylic acid, gynecological history	exercise > 1 h/d	exercise <0.5 h/d	8532	1.00	NS
Paganini-Hill & Perez Barreto 2001 (24)	M, 44–101 yr (median: 74 yr) 17 yr	arterial hypertension and its treatment, diabetes mellitus, coronary heart disease, digitalis, smoking, acetylsalicylic acid, gynecological history	exercise > 1 h/d	exercise <0.5 h/d	4722	0.69	NS
Undifferentiated stroke²							
Agnarsson et al. 1999 (16)	M, 45–80 yr 10.6 ± 3.6 yr	age, smoking, glucose, arterial hypertension, pulmonary function	leisure activities from age 40 onward	no sports	4484	0.69 (0.47–1.01)	NS
Bijnen et al. 1998 (25)	M, 64–84 yr 10 yr	age, smoking, alcohol consumption, chronic illnesses	exercise	inactive lifestyle	802	0.95 (0.52–1.74)	NS
Chiuve et al. 2008 (11)	F, 30–55 yr 6 yr	myocardial infarction in a parent under age 60, acetylsalicylic acid, vitamin E supplementation, hormone therapy (women), arterial hypertension, hypercholesterolemia, diabetes mellitus	≥ 6 h sports/wk	no sports	71 243	0.58 (0.47–0.71)	p < 0.05
Chiuve et al. 2008 (11)	M, 40–75 yr 2 yr	myocardial infarction in a parent under age 60, acetylsalicylic acid, vitamin E supplementation, hormone therapy (women), arterial hypertension, hypercholesterolemia, diabetes mellitus	≥ 6 h sports/wk	no sports	43 685	0.60 (0.49–0.74)	p < 0.05
Ellekjær et al. 2000 (e1)	F, 50–101 yr 9.0 yr	age, BMI, systolic blood pressure, antihypertensive drugs, diabetes mellitus, coronary heart disease, smoking	intense exercise	little exercise	14 101	0.52 (0.38–0.72)	p < 0.001
Folsom et al. 1990 (e2)	F, 55–69 yr 2 yr	age, arterial hypertension, diabetes mellitus	the most active among 3 groups	the least active among 3 groups	41 837	0.8 (0.5–1.1)	NS

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Gillum et al. 1996 (18)	M & F, 45–74 yr 11.6 yr	age, smoking, diabetes mellitus, coronary heart disease, education, systolic blood pressure, cholesterol, BMI, hemoglobin concentration	large amount of exercise in free time	small amount of exercise in free time	5852	women 45–64 yr 0.31 (0.10–1.05) women 65–74 yr 0.65 (0.40–1.05) men 45–64 yr 0.81 (0.41–1.59) men 65–74 yr 0.78 (0.53–1.14)	NS
Häheim et al. 1993 (e3)	M, 40–49 yr 12 yr	none	moderate to intense exercise in spare time	no exercise in spare time	14 403	0.36 (0.15–0.80)	p < 0.05
Harmsen et al. 1990 (19) (SAB)	M, 47–55 yr 28 yr	blood pressure, BMI, cholesterol, smoking, emotional stress, atrial fibrillation, myocardial infarction, stroke, TIA in the history	the 3 more active of 4 groups	the least active of 4 groups	7495	0.83 (0.56–1.25)	NS
Harmsen et al. 2006 (e4)	M, 47 – 55 yr 28 yr	age, systolic blood pressure, antihypertensive drugs, TIA, atrial fibrillation, stroke or coronary event in a parent, diabetes mellitus, angina pectoris, smoking, emotional stress, BMI, cholesterol, social status	moderate to intense exercise	little exercise	7457	0.90 (0.74–1.11) ²	NS
Hu et al. 2000 (20) (SAB)	F, 40–65 yr 8 yr	age, smoking, alcohol consumption, BMI, menopausal status, aspirin consumption, family history of myocardial infarction under age 60, diabetes mellitus, hypercholesterolemia, high blood pressure	4.7–10.4 MET × h/week	≤ 2.0 MET × h/week	72 488	0.66 (0.47–0.91)	p < 0.05
Hu et al. 2005 (9) (SAB)	F, 25–64 yr 19.0 yr	age, sex, BMI, systolic blood pressure, cholesterol, education, smoking, alcohol consumption, diabetes mellitus	intense exercise in free time (>3 h/wk running, swimming, intense gardening, competitive sports)	little or no exercise	24 880	0.77 (0.62–0.97)	p < 0.001

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Hu et al. 2005 (9) (SAB)	M, 25–64 yr 19.0 yr	age, sex, BMI, systolic blood pressure, cholesterol, education, smoking, alcohol consumption, diabetes mellitus	intense exercise in free time (>3 h/wk running, swimming, intense gardening, competitive sports)	little or no exercise	22 841	0.72 (0.60–0.87)	p < 0.001
Kiely et al. 1994 (e5)	F, 49.7 and 49.9 yr up to 32 yr	age, systolic blood pressure, cholesterol, smoking, glucose intolerance, vital capacity, BMI, LVH, atrial fibrillation, cardiac valvular defects	the most physically active of 3 groups	the least physically active of 3 groups	2873	1.21 (0.75–1.96)	NS
Kiely et al. 1994 (e5)	M, 49.7 and 49.9 yr up to 32 yr	age, systolic blood pressure, cholesterol, smoking, glucose intolerance, vital capacity, BMI, LVH, atrial fibrillation, cardiac valvular defects	the most physically active of 3 groups	the least physically active of 3 groups	2336	0.53 (0.34–0.84)	p < 0.05
Lapidus & Bengtsson 1986 (e6)	F, 38–60 yr 12 yr	age, BMI, waist-to-hip ratio, systolic blood pressure, triglycerides, cholesterol, smoking, socioeconomic status	At least a half hour walking or bicycling per day, regular exercise or competitive sports	no exercise	1462	0.1 (0.1–0.3)	p < 0.001
Lee & Blair 2002 (e7)	M, 40–87 yr 10 yr	age, smoking, alcohol consumption, BMI, arterial hypertension, diabetes mellitus, coronary heart disease in a parent	the 40% of the group that had the highest cardiovascular fitness (treadmill test)	the 20% of the group that had the lowest cardiovascular fitness	16 878	0.32 (0.12–0.82)	p < 0.05
Lee & Paffenbarger Jr. 1998 (e8)	M, 58 yr (43–88 yr) 11 yr	age, smoking, alcohol consumption, early death in a parent	weekly energy consumption by exercise <1000 kcal	weekly energy consumption by exercise 2000 to 2999 kcal	11 130	0.54 (0.38–0.76)	p < 0.05
Lindenstrøm et al. 1993 (e9)	F, >35 yr 12 yr	age, BMI, smoking, alcohol consumption, tranquilizers and hypnotics, oral contraception, hormone replacement therapy	at least 2 h of intense or 4 h of mild exercise/wk	less than 2 h of intense or 4 h of mild exercise/wk	7060	0.69 (0.48–1.00) ^{†1}	p < 0.05
Lindsted et al. 1991 (e10)	M, 49.9–54.7 ± 12.0–16.5 yr 26 yr	ethnic group, smoking, education, BMI, family status, eating habits	moderate exercise	little exercise	9484	0.78 (0.61–1.00)	NS
Menotti & Seccareccia 1985 (e11)	M, 40–59 yr up to 5 yr	age	calorie consumption >3000/d	calorie consumption <2400/d	99 029	almost 1.0	NS

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Myint et al. 2006 (10)	F, 40–76 yr 8.5 yr	age, sex, smoking, systolic blood pressure, BMI, cholesterol, diabetes mellitus	physically active	physically inactive	12 523	0.71 (0.41–1.26)	NS
Myint et al. 2006 (10)	M, 40–76 yr 8.5 yr	age, sex, smoking, systolic blood pressure, BMI, cholesterol, diabetes mellitus	physically active	physically inactive	10 079	0.67 (0.43–1.05)	NS
Nakayama et al. 1997 (22) (SAB)	F > 40 yr 15.5 yr	age, BMI, high blood pressure, smoking, alcohol consumption, albumin- and glycosuria, cholesterol, hematocrit, fundus abnormalities, ECG	mild exercise	no exercise	1469	1.95 (1.03–3.68)	p < 0.05
Nakayama et al. 1997 (22) (SAB)	M > 40 yr 15.5 yr	age	mild exercise	no exercise	1182	1.38 (0.77–2.48)	NS
Noda et al. 2005 (12) (SAB)	F, 40–79 yr 9.7 yr	age, BMI, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, sleep, occupation, emotional stress, frequency of fish consumption	≥ 5 h sports/wk	1–2 h sports/wk	42 242	1.09 (0.90–1.32)	NS
Noda et al. 2005 (12) (SAB)	M, 40–79 yr 9.7 yr	age, BMI, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, sleep, occupation, emotional stress, frequency of fish consumption	≥ 5 h sports/wk	1–2 h sports/wk	31 023	0.87 (0.59–1.27)	NS
Paffenbarger et al. 1984 (e12)	M, 49.7 ± 5.7 yr 10 yr	age, arterial hypertension, smoking	energy consumption/wk >2000 kcal	energy consumption/wk <500 kcal	16 936	0.37	p < 0.001
Paganini-Hill & Perez Barreto 2001 (24)	F, 44–101 yr (median: 74 yr) 17 yr	arterial hypertension and its treatment, diabetes mellitus, coronary heart disease, digitalis, smoking, acetylsalicylic acid, gynecological history	exercise >1 h/d	exercise <0.5 h/d	8532	0.83	p < 0.01
Paganini-Hill & Perez Barreto 2001 (24)	M, 44–101 yr (median: 74 yr) 17 yr	arterial hypertension and its treatment, diabetes mellitus, coronary heart disease, digitalis, smoking, acetylsalicylic acid, gynecological history	exercise >1 h/d	exercise <0.5 h/d	4722	0.85	NS

Source	Patient collective (sex, [median] age), median follow-up interval	Cofactors considered	Exercise group	Comparison group	n	RR	p
Panagiotakos et al. 2003 (e13)	M, 49.7 ± 5.7 yr 40 yr	age, high blood pressure, cholesterol, smoking, BMI	physically active	physically inactive	529	0.59 (0.32–0.92)	p < 0.05
Salonen et al. 1982 (e14)	F, 30–59 yr 7 yr	age, cholesterol, diastolic blood pressure, BMI, smoking	large amount of exercise in free time	small amount of exercise in free time	3688	0.8 (0.5–1.3) ^{†1}	NS
Salonen et al. 1982 (e14)	M, 30–59 yr 7 yr	age, cholesterol, diastolic blood pressure, BMI, smoking	large amount of exercise in free time	small amount of exercise in free time	3978	1.0 (0.7–1.4) ^{†1}	NS
Simonsick et al. 1993 (e15)	M and F, 65–74 yr 6 yr	age, sex, education, occupation, smoking, depression, respiratory symptoms, angina pectoris, myocardial infarction, stroke or diabetes mellitus in the history	the most physically active 16% to 26%	the most physically inactive 26% to 32%	East Boston: 1728 New Haven: 1387 Iowa: 1725	East Boston: 0.58 (0.17–1.95) New Haven: 1.06 (0.38–2.95) Iowa: 0.22 (0.08–0.61)	p < 0.05 only in Iowa, not in East Boston or New Haven
Wannamethee & Shaper 1992 (e16) ³	M, 40–59 yr 9.5 yr	age, social status, smoking, alcohol consumption, BMI	intense exercise	little or no exercise	7 735	0.3	p < 0.01
Wannamethee et al. 1998 (e17)	M, 40–59 yr 15 yr	BMI, smoking, alcohol consumption	exercise	no exercise	7 142	0.54 (0.38–0.77)	p < 0.05

BMI, body-mass index; d, day; F, female; LVH, left ventricular hypertrophy; M, male; MET, multiple of energy consumption at rest when exercising; n, number of study participants; NA, some items of (non-significant) data not mentioned because of the multiplicity of subgroups and limited space; p, level of statistical significance; PAOD, peripheral arterial occlusive disease; RR, the relative risk of having, or dying of, a stroke; SAB, including subarachnoid hemorrhage; TIA, transient ischemic attack; wk, week; yr, year;
^{†1} the original data give the relative risk of the inactive persons; the data for both sexes are given together, whenever available in the original publication
^{†2} ischemic and hemorrhagic strokes were not differentiated by imaging studies;
^{†3} not considered in the meta-analysis, because the results are incorporated in the published continuation of the same study (e17)

eTABLE 2

The relative risk of (fatal or non-fatal) ischemic and hemorrhagic stroke depending as a function of physical exercise in case-control studies

Source	Patient collective	Cofactors considered	Exercise group	Comparison group	RR	p
Ischemic stroke						
Choi-Kwon & Kim 1998 (e18)	135 F, 66 F in the comparison group, median age 65–66 yr ± 6–10 yr	age, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, eating habits, BMI, overall body fat content, subcutaneous fat	recent exercise	no recent exercise	0.2 (0.1–0.5)	p < 0.01
Ellekjær et al. 1992 (e19)	95 M, 68 F, median age 69 yr (62–75 yr) 652 in the comparison group	none	walking, skiing, bicycling or the like at least once a week	walking, skiing, bicycling or the like less than once a week	0.88 (0.58–1.39)	NS
Krarup et al. 2007 (14)	M & F, 127 in exercise group, median age 71.8 yr ± 11.7 yr 301 in the comparison group, median age 71.5 yr ± 11.6 yr	systolic blood pressure, stroke or myocardial infarction in the history, atrial fibrillation, diabetes mellitus, alcohol consumption, education, BMI, smoking	activity index for the preceding week in the highest category	activity index for the preceding week in the lowest category	0.09 (0.03–0.25)	p < 0.05
Sacco et al. 1998 (e20)	57% F, 43% M, 369 in exercise group, 678 in comparison group, 69.9 ± 12.0 yr	age, sex, ethnic group, coronary heart disease, PAOD, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, obesity, season	intense exercise (hiking, tennis, swimming, bicycling, jogging, aerobics, handball and the like)	no exercise	0.23 (0.10–0.54)	p < 0.05
Shinton & Sagar 1993 (e21)	125 M & F in exercise group, 198 M & F in control group; 35–74 yr	age, sex, cigarette smoking	walking: rapid walking, at least 1 mile/mo.; intense sports: running, swimming, bicycling and the like	less exercise than this	walking: 0.3 (0.1–0.7) intense sports: 0.61 (0.2–1.5)	walking: p < 0.05 intense sports: NS
You et al. 1995 (e22)	203 M, 203 F, 15–85 yr	sex, age, arterial hypertension, diabetes mellitus, alcohol consumption, smoking, oral contraceptives	exercise leading to sweating and shortness of breath at least three times a week	rarely, or never, exercise leading to sweating and shortness of breath	0.3 (0.1–0.7)	p < 0.05
You et al. 1997 (e23)	201 M, 201 F, 15–45 yr (median age 45.5 yr)	sex, age, arterial hypertension, diabetes mellitus, alcohol consumption, smoking, coronary heart disease, hypercholesterolemia, oral contraceptives	exercise leading to sweating and shortness of breath at least three times a week	rarely, or never, exercise leading to sweating and shortness of breath	0.6 (0.3–1.3)	NS

Source	Patient collective	Cofactors considered	Exercise group	Comparison group	RR	p
Hemorrhagic stroke						
Choi-Kwon & Kim 1998 (e18)	135 F, 66 F in the comparison group, median age 65–66 yr ± 6–10 yr	age, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, eating habits, BMI, overall body fat content, subcutaneous fat	recent exercise	no recent exercise	0.2 (0.1–1.0)	p = 0.05
Thrift et al. 2002 (e24)	331 M & F in the exercise group and 331 M & F in the control group, 63.4 ± 1.4 yr	age, sex, high blood pressure, cholesterol, coronary heart disease, diabetes mellitus, BMI, smoking, hormone replacement therapy, educational level	exercise leading to sweating at least once per month (up to the event)	no exercise leading to sweating (up to the event)	0.66 (0.39–1.11)	NS
Undifferentiated stroke *						
Herman et al. 1982 (e25)	M & F, 40–74 yr, 126 stroke patients, 212 control subjects	age	regular, intense exercise	little exercise	0.4 (0.2–0.9)	p < 0.01

BMI, body-mass index; d, day; F, female; LVH, left ventricular hypertrophy; M, male; MET, multiple of energy consumption at rest when exercising; n, number of study participants; NA, some items of (non-significant) data not mentioned because of the multiplicity of subgroups and limited space; p, level of statistical significance; PAOD, peripheral arterial occlusive disease; RR, the relative risk of having, or dying of, a stroke; SAB, including subarachnoid hemorrhage; TIA, transient ischemic attack; wk, week; yr, year; ischemic and hemorrhagic strokes were not differentiated with imaging studies