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Physical Activity and Stroke Risk
A Meta-Analysis

Chong Do Lee, EdD; Aaron R. Folsom, MD; Steven N. Blair, PED

Background and Purpose—Whether physical activity reduces stroke risk remains controversial. We used a meta-analysis to examine the overall association between physical activity or cardiorespiratory fitness and stroke incidence or mortality.

Methods—We searched MEDLINE from 1966 to 2002 and identified 23 studies (18 cohort and 5 case-control) that met inclusion criteria. We estimated the overall relative risk (RR) of stroke incidence or mortality for highly and moderately active individuals versus individuals with low levels of activity using the general variance–based method.

Results—The meta-analysis documented that there was a reduction in stroke risk for active or fit individuals compared with inactive or unfit persons in cohort, case-control, and both study types combined. For cohort studies, highly active individuals had a 25% lower risk of stroke incidence or mortality (RR=0.75; 95% CI, 0.69 to 0.82) compared with low-active individuals. For case-control studies, highly active individuals had a 64% lower risk of stroke incidence (RR=0.36; 95% CI, 0.25 to 0.52) than their low-active counterparts. When we combined both the cohort and case-control studies, highly active individuals had a 27% lower risk of stroke incidence or mortality (RR=0.73; 95% CI, 0.67 to 0.79) than did low-active individuals. We observed similar results in moderately active individuals compared with inactive persons (RRs were 0.83 for cohort, 0.52 for case-control, and 0.80 for both combined). Furthermore, moderately and highly active individuals had lower risk of both ischemic and hemorrhagic strokes than low-active individuals.

Conclusions—We conclude that moderate and high levels of physical activity are associated with reduced risk of total, ischemic, and hemorrhagic strokes. **(*Stroke*. 2003;34:2475-2482.)**

Key Words: incidence ■ meta-analysis ■ mortality ■ physical activity ■ stroke

Stroke is a leading cause of death and long-term disability in the United States. Approximately one half million US adults suffer from stroke (first attack) each year, with 100 000 recurrent attacks.[1] Of these, 160 000 are fatal.[2] Since effective treatments for stroke are limited and many stroke survivors require lengthy rehabilitation and chronic care, primary prevention of stroke is imperative to avoid the burden of this disease.

Hypertension and cardiac disease are the primary risk factors for stroke.[3,4] Physical activity may modify these risk factors for stroke and may have more direct effects to lower stroke risk as well. A systematic review reported that physical activity is inversely associated with incidence of hypertension and coronary heart disease.[5] However, whether physical activity alters stroke risk was less clear, partly because there were fewer stroke events in some studies. Some investigators found an inverse association between physical activity and stroke risk.[6–21] Other studies have shown a U-shaped association, no association, or a positive association between physical activity and stroke incidence or mortality.[22–27] To address stroke prevention strategies, it is important to investigate whether physical activity reduces stroke incidence or mortality. We therefore investigated the overall association between physical activity and stroke incidence or mortality from published studies between 1966 and 2002.

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Materials and Methods

Study Selection

We searched MEDLINE from January 1966 through July 2002, using the medical subject headings *physical activity*, *exercise*, *leisure-time activity*, *stroke*, and *cardiovascular disease*. We also searched the Surgeon General's report on physical activity and health.[28] We reviewed all relevant articles and identified 31 published epidemiological studies of physical activity and stroke, 23 of which (18 cohort and 5 case-control) met our inclusion criteria. Inclusion criteria were English language reports of any cohort or case-control study in which physical activity (leisure-time activity)[6–27] or cardiorespiratory fitness[29] was classified as low, moderate, or high[6,8–10,12–21,23–27] or was classified as the least to the highest intensity[7,11,22,26] of physical activity. We excluded 8 studies from the

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TABLE 1. Characteristics of 18 Cohort Studies of Physical Activity and the Risk of Stroke Incidence or Mortality

Study (Reference)	Year	Study Population	Exposure	Follow-Up (Y)	Outcome (No. of Events)	Covariates
Lee and Blair[29]	2002	Aerobics Center Longitudinal Study (16 878 US men; age, 40–87 y)	Low fitness	10	Stroke deaths (n=32)	Age, examination year, smoking, alcohol intake, BMI, hypertension, diabetes, and parental history of coronary heart disease
Ellekjær et al[9]	2000	Nord-Trondelag Survey (14 101 Norwegian women; age ≥50 y)	Low activity	10	Stroke deaths (n=457)	Age, smoking, diabetes, BMI, antihypertensive medication, systolic blood pressure, angina pectoris, MI, illness, and education
Hu et al[11]	2000	Nurses' Health Study (72 488 US women; age, 40–65 y)	Low activity	8	Stroke incidence (n=407)	Age, time, cigarette smoking, BMI, menopausal status, parental history of MI before age 60 years, alcohol intake, aspirin use, history of hypertension, diabetes, and hypercholesterolemia
Lee et al[26]	1999	Physicians' Health Study (21 823 US men; age, 40–84 y)	Low intensity	11.1	Stroke deaths (n=533)	Age, treatment assignment, cigarette smoking, alcohol intake, history of angina, parental history of MI at <60 years, BMI, history of hypertension, high cholesterol, and diabetes mellitus
Agnarsson et al[7]	1999	Reykjavik Study (4484 Icelandic men; age, 45–80 y)	Low intensity	10.6	Stroke incidence (n=249)	Age, blood glucose, smoking, hypertension, and ventilatory function
Evenson et al[10]	1999	ARIC Study (6279 US men and 8296 US women; age, 45–64 y)	Low activity	7.2	Stroke incidence (n=189)	Age, sex, race-center, education, and smoking
Bijnen et al[8]	1998	Zutphen Elderly Study (802 Dutch men; age, 64–84 y)	Low activity	10	Stroke deaths (n=47)	Age, baseline stroke, smoking, and alcohol consumption
Lee and Paffenbarger[22]	1998	Harvard Alumni Study (11 130 men; age, 43–88 y)	Low intensity	...	Stroke deaths (n=378)	Age, smoking, alcohol intake, and early parental death
Nakayama et al[25]	1997	Shibata Study (961 Japanese men and 1341 women; age ≥40 y)	Light activity	15.5	Stroke incidence (n=141)	Age
Gillum et al[13]	1996	NHANES I Follow-up Study (7895 white and black men and women; age, 45–74 y)	Low activity	11.6	Stroke incidence (n=623)	Age, smoking, history of diabetes, history of heart disease, education, systolic blood pressure, total cholesterol, BMI, and hemoglobin
Abbott et al[6]	1994	Honolulu Heart Program (7530 men, Japanese ancestry; age, 45–68 y)	Inactivity	22	Stroke incidence (n=537)	Age
Kiely et al[12]	1994	Framingham Study (1897 US men and 2299 US women; age, 28–62 y)	Low activity	32	Stroke incidence (n=427)	Age, systolic blood pressure, cholesterol, smoking, vital capacity, BMI, left ventricular hypertrophy, atrial fibrillation, valvular disease, history of congestive heart failure, history of ischemic heart disease, and occupation
Simonsick et al[27]	1993	Epidemiologic Studies of the Elderly (4840 US men and women; age ≥65 y)	Inactivity	6	Stroke incidence (n=?)	Age, sex, education, work status, smoking, respiratory symptoms, MI, diabetes, angina, self-rated health, and modified depression score
Haheim et al[14]	1993	Oslo Study (14 403 Norwegian men; age, 40–49 y)	Sedentary	12	Stroke incidence (n=81)	None
Wannamethee and Shaper[15]	1992	British Regional Heart Study (7735 British men; age, 40–59)	Inactivity	9.5	Stroke incidence (n=128)	Age, social class, smoking, heavy drinking, and BMI
Lindsted et al[23]	1991	Seventh-Day Adventist (9484 men; age ≥30 y)	Low activity	26	Stroke deaths (n=410)	Race, smoking, education, medical illness, BMI, marital status, and dietary pattern
Folsom et al[16]	1990	Iowa Women's Health Study (41,837 Iowa women; age, 55–69 y)	Low activity	2	Stroke incidence (n=218)	Age
Menotti and Seccareccia[24]	1985	Italian Railroad Worker (99,029 men; age, 40–59)	Sedentary	5	Stroke deaths (n=187)	Age

BMI indicates body mass index; MI, myocardial infarction.

analysis. Four studies either classified or analyzed physical activity only as low versus other[30–33]; 2 studies analyzed physical activity on a continuous scale[34,35]; and 2 studies reported death rates or relative risks (RRs) without CIs, and therefore the variances of the RRs were inestimable.[36,37]

Data Extraction

All the data were independently abstracted by 1 investigator (C.D.L.). Measures of association reported within a single study separately for different ethnic groups, sexes, age groups, or outcome measures were analyzed as separate units. For instance, in the National Health and Nutrition Examination Survey (NHANES) I epidemiological follow-up study, we included 5 different data units: white women aged 45 to 64 years, white women aged 65 to 74 years, white men aged 45 to 74 years, white men aged 65 to 74 years, and blacks aged 45 to 74 years.[13] For Honolulu Heart Study men, we used 2 data units with different age groups (aged 45 to 54 and 55 to 68 years).[6] For the Framingham Study, we separated 2 data units (men and women).[12] In the Established Populations for Epidemiologic Studies of the US Elderly, we included 3 data units: Boston (Mass) elderly, New Haven (Conn) elderly, and Iowa elderly.[27] We obtained 23 studies that met inclusion criteria, yielding a total of 31 data units. The studies' characteristics were recorded as follows: author's name, publication year, study population (sample size, age, sex, and ethnicity), physical activity classification (low, moderate, high activity intensities), activity type (leisure-time only), follow-up years (cohort studies), outcome measure (stroke incidence or mortality), RR (or odds ratio) and CI, and covariates.

Statistical Analysis

The RR or odds ratio was used to estimate the risk ratio of stroke incidence or mortality for moderately or highly active individuals

TABLE 2. Characteristics of 5 Case-Control Studies of Physical Activity and the Risk of Stroke Incidence

Study	Year	Case Patients	Controls	Exposure	Covariates
Sacco et al[17]	1998	Northern Manhattan Stroke Study (163 men and 206 women with first cerebral infarction; age ≥39 y)	678 community population	Light activity	Hypertension, diabetes, cardiac disease, smoking, alcohol use, obesity, education, and season
You et al[20]	1997	Melbourne Risk Factor Study (201 Australian men and women with cerebral infarction; age, 15–55 y)	201 community-based control subjects	Inactivity	Age, sex, smoking, hypertension, high cholesterol, heart disease, diabetes mellitus, alcohol intake, and oral contraceptive use
You et al[19]	1995	203 Australian men and women with lacunar infarction; age, 20–85 y	203 community-based control subjects	Inactivity	Age, sex, hypertension, high cholesterol, heart disease, diabetes mellitus, alcohol intake, oral contraceptive use, and smoking
Shinton and Sagar[18]	1993	English men and women (65 patients with first stroke; age, 35–74 y)	169 randomly selected general population	Inactivity	Age and sex
Herman et al[21]	1983	132 Dutch men and women with stroke; age, 40–74 y	239 patients in the same hospital	Low activity	Age, sex, education, acute myocardial infarction, cardiac arrhythmias, high blood pressure, diabetes mellitus, obesity, transient ischemic attack, and rhesus factor

versus low-active individuals. We used the general variance–based fixed effects model to analyze the cohort and case-control studies separately and then combined both study types.[38] We transformed each study's RR to natural logarithms to stabilize the variances. The variance of the RR was estimated from the CI. The overall RR was estimated as follows:

$$RR = \exp \Sigma[W_i \times \ln(RR_i)]/\Sigma\, w_i$$

where w_i is a weight for the study, which is the inverse of the variance for the study. We tested homogeneity of the association across studies using Woolf's χ^2 statistic.[39] We also tested for publication bias using a funnel plot of the sample sizes versus RRs and with the Kendall τ rank correlation method. All statistical analyses were performed with the use of STATA statistical software (Stata Corporation).

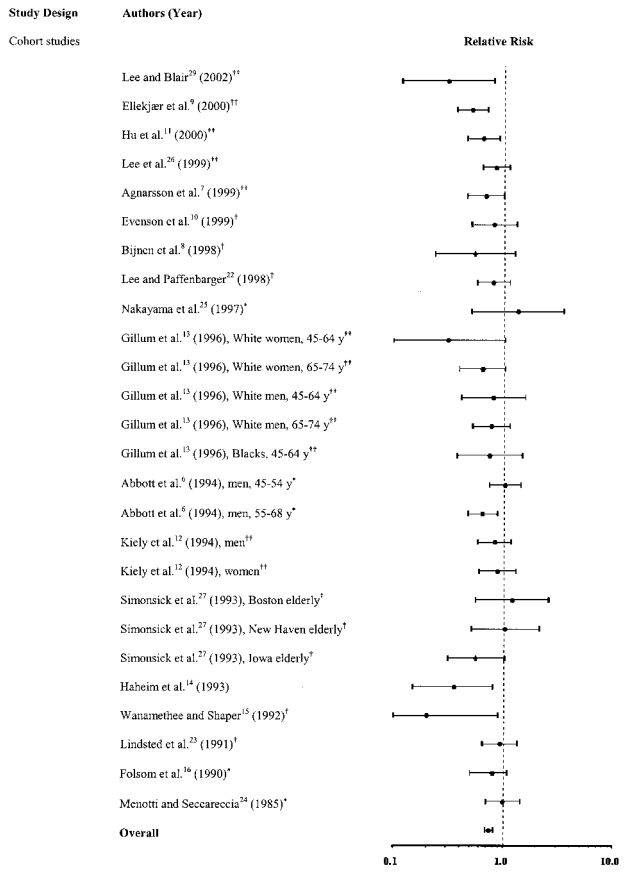

Figure 1. RRs of stroke incidence or mortality for highly active individuals vs low-active individuals in 18 epidemiological cohort studies. Error bars represent 95% CIs for each RR (*adjusted for age only; †adjusted for age and some risk factors excluding high blood pressure; ††adjusted for age and major risk factors including high blood pressure). A RR <1.0 indicates that greater physical activity levels may decrease the risk of stroke incidence or mortality.

Results

Eleven of the 18 cohort studies (Table 1) were from the United States, and 7 studies were from elsewhere, such as England, Norway, Iceland, Japan, Italy, or the Netherlands. One of the 5 case-control studies (Table 2) was from the United States (New York), and the other 4 were from England, Australia, and the Netherlands. A funnel plot (sample sizes versus RRs) and the Kendall τ correlation coefficient ($r=0.13$) suggested that there was no publication bias in the sample of reports ($P=0.30$). Associations were

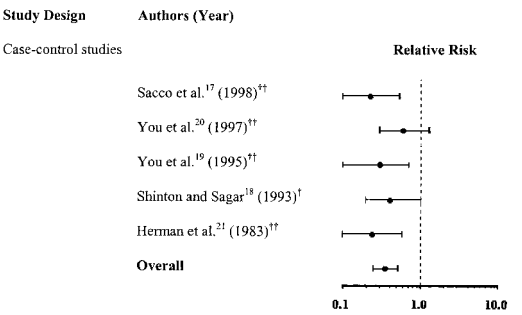

Figure 2. RRs of stroke incidence for highly active individuals vs low-active individuals in 5 epidemiological case-control studies. Error bars represent 95% CIs for each RR (†adjusted for age and some risk factors excluding high blood pressure; ††adjusted for age and major risk factors including high blood pressure). A RR <1.0 indicates that greater physical activity levels may decrease the risk of stroke incidence.

TABLE 3. Overall Relative Risks of Stroke Incidence or Mortality for Highly and Moderately Active Individuals Versus Low-Active Individuals

Activity Comparison	Stroke Type	No. of Studies	Data Units	Relative Risk (95% CI)	*P* Value	*P* for Homogeneity Test
Low, High						
All studies (cohort)	Total	18	26	0.75 (0.69, 0.82)	<0.001	0.80
All studies (case-control)	Total	5	5	0.36 (0.25, 0.52)	0.04	0.96
All studies (combined)	Total	23	31	0.73 (0.67, 0.79)	<0.001	0.78
All studies (cohort)	Ischemic	6	11	0.79 (0.69, 0.91)	<0.001	0.58
All studies (cohort)	Hemorrhagic	3	4	0.66 (0.48, 0.91)	<0.001	0.49
Low, Moderate						
All studies (cohort)	Total	15	23	0.83 (0.76, 0.89)	<0.001	0.11
All studies (case-control)	Total	4	4	0.52 (0.40, 0.69)	<0.001	0.15
All studies (combined)	Total	19	27	0.80 (0.74, 0.86)	<0.001	0.06
All studies (cohort)	Ischemic	4	9	0.91 (0.80, 1.05)	<0.001	0.90
All studies (cohort)	Hemorrhagic	3	4	0.85 (0.64, 1.13)	<0.001	0.62

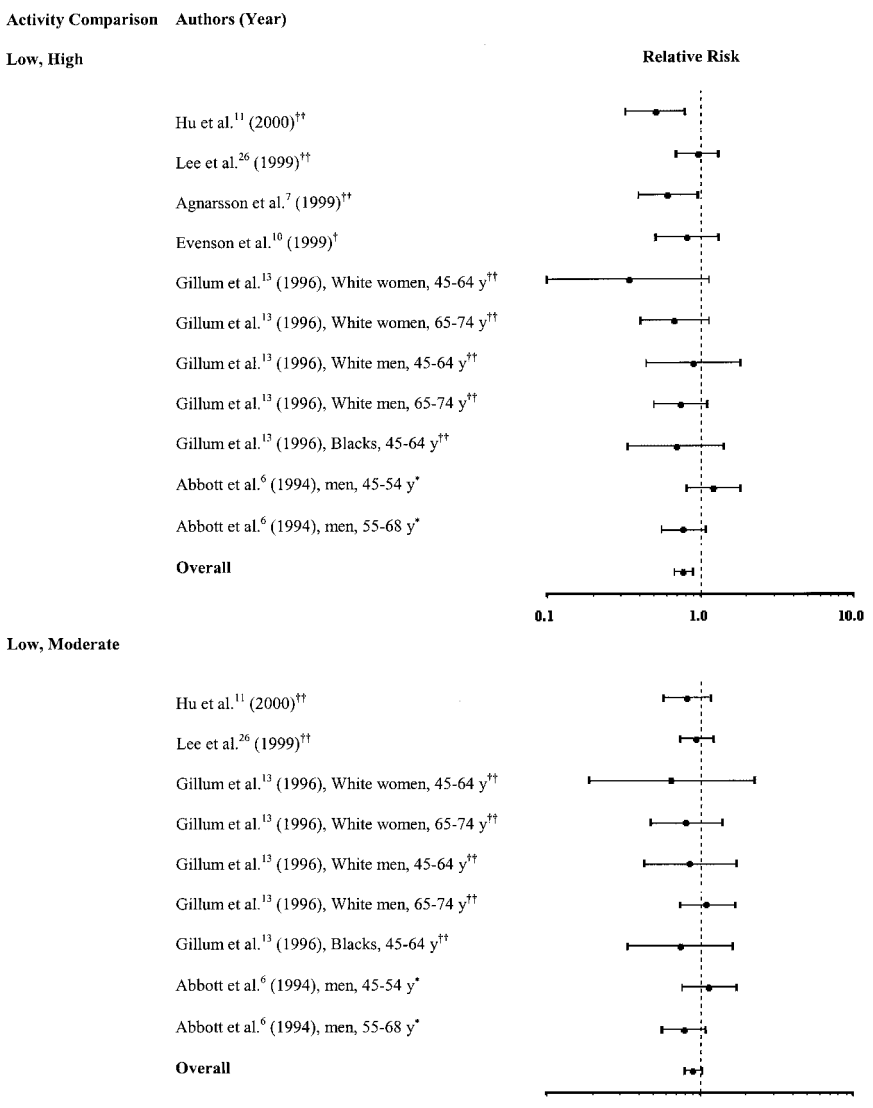

Figure 3. Overall RRs of ischemic stroke incidence or mortality for highly and moderately active individuals vs low-active individuals. Error bars represent 95% CIs for each RR (*adjusted for age only; †adjusted for age and some risk factors excluding high blood pressure; ††adjusted for age and major risk factors including high blood pressure). A RR <1.0 indicates that greater physical activity levels may decrease the risk of ischemic stroke incidence or mortality.

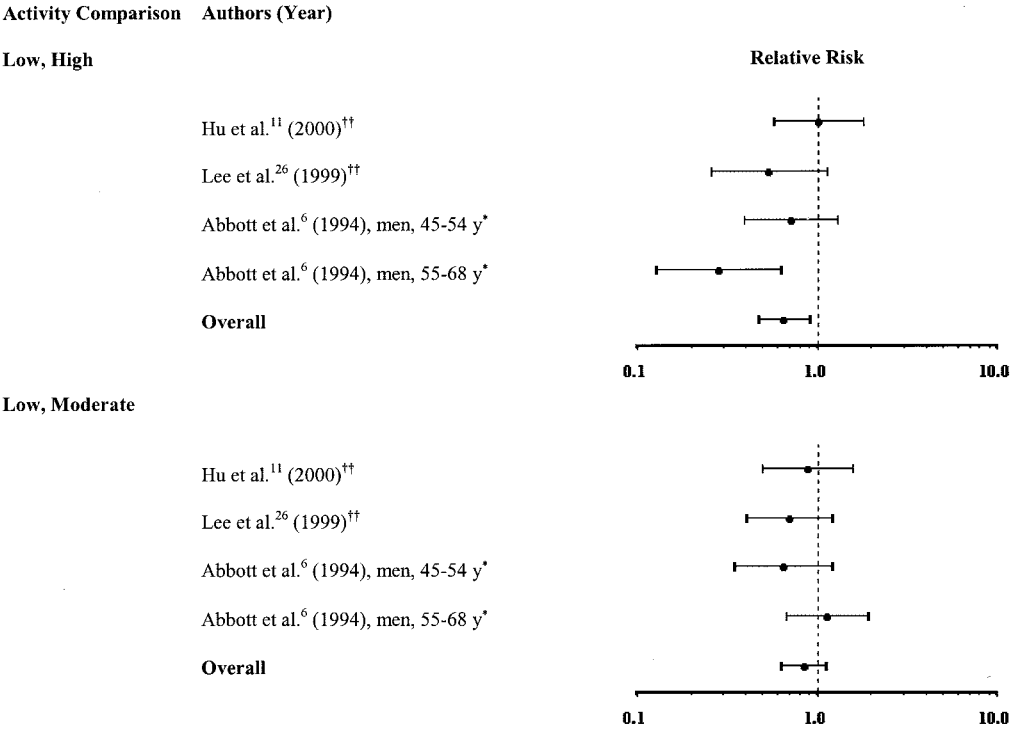

Figure 4. Overall RRs of hemorrhagic stroke incidence or mortality for highly and moderately active individuals vs low-active individuals. Error bars represent 95% CIs for each RR (*adjusted for age only; ††adjusted for age and major risk factors including high blood pressure). A RR <1.0 indicates that greater physical activity levels may decrease the risk of hemorrhagic stroke incidence or mortality.

homogeneous within cohort ($P=0.80$) and case-control ($P=0.96$) study groups and across all studies ($P=0.81$).

Figure 1 shows the RRs (and 95% CIs) of stroke incidence or mortality for highly active individuals versus low-active individuals in the cohort studies. The CIs for the RRs of many studies included 1.0. The RRs were <1.0 in 14 studies, but 4 studies had RRs >1.0. Overall, highly active individuals had a 25% lower risk of stroke incidence or mortality in the cohort studies than did low-active individuals (RR=0.75; 95% CI, 0.69 to 0.82; $P<0.001$). For case-control studies, highly active individuals had a 64% lower risk of stroke incidence than did low-active individuals (RR=0.36; 95% CI, 0.25 to 0.52; $P<0.001$) (Figure 2). When the cohort and case-control studies were combined, highly active individuals had a 27% lower risk of stroke incidence or mortality than did low-active individuals (RR=0.73; 95% CI, 0.67 to 0.79; $P<0.001$) (Table 3). We observed similar results across subtypes of stroke on the basis of 6 ischemic and 3 hemorrhagic stroke studies. Highly active individuals had a 21% lower risk of incident ischemic stroke (RR=0.79; 95% CI, 0.69 to 0.91; $P<0.001$) and a 34% lower risk of incident hemorrhagic stroke (RR=0.66; 95% CI, 0.48 to 0.91; $P<0.001$) compared with low-active individuals (Figures 3 and 4).

Table 3 also shows the RRs of stroke incidence or mortality for moderately active individuals versus low-active individuals. In cohort studies, moderately active individuals had a 17% lower risk of stroke incidence or mortality than did low-active individuals (RR=0.83; 95% CI, 0.76 to 0.89; $P<0.001$). For case-control studies, moderately active individuals had a 48% lower risk of stroke incidence compared with low-active individuals (RR=0.52; 95% CI=0.40 to 0.69; $P<0.001$). Overall, when the cohort and case-control studies were combined, moderately active individuals had a 20% lower risk of stroke incidence or mortality than did low-active individuals (RR=0.80; 95% CI, 0.74 to 0.86; $P<0.001$). Moderately active individuals also had a 9% lower risk of incident ischemic stroke (RR=0.91; 95% CI, 0.80 to 1.05; $P<0.001$) and a 15% lower risk of incident hemorrhagic stroke (RR=0.85; 95% CI, 0.64 to 1.13; $P<0.001$) than did low-active individuals (Figures 3 and 4).

Discussion

We investigated the association of physical activity with stroke risk by a meta-analysis of existing epidemiological studies. The value of meta-analysis is illustrated by the fact that most studies individually lacked precision, a problem alleviated by pooling. The major finding was that moderately or highly active individuals had lower risk of stroke incidence or mortality than did low-active individuals. Overall, moderately active individuals had a 20% lower risk and highly active individuals had a 27% lower risk of stroke incidence or mortality than the low-active individuals. Both ischemic and hemorrhagic strokes were lower in moderately and highly active individuals. Results appeared to be slightly stronger for case-control studies than for cohort studies, but there was no statistically significant evidence of heterogeneity by study type.

Our study indicates that physical activity probably reduces stroke risk. However, physical activity questionnaires tend to be imprecise and have large measurement error, and therefore

the pooled estimates of RR may have underestimated the true RR. We recently showed a strong inverse relation between cardiorespiratory fitness, an objective marker of physical activity, and stroke mortality.[29]

There are several plausible ways by which physical activity might reduce stroke risk. Hypertension and atherosclerosis of cerebral vessels are major causes of stroke.[3,4] Hypertension is a risk factor for both ischemic and hemorrhagic strokes, and there is a direct dose-response relationship between blood pressure and stroke risk.[40] Physical activity lowers blood pressure and improves lipid profiles.[41] Physical activity also improves endothelial function, which enhances vasodilation and vasomotor function in the vessels.[42] In addition, physical activity can play an antithrombotic role by reducing blood viscosity,[43] fibrinogen levels,[44] and platelet aggregability[45] and by enhancing fibrinolysis,[46–48] all of which might reduce cardiac and cerebral events.

One limitation of our meta-analysis is that few studies were available to investigate the relation of physical activity to hemorrhagic stroke,[6,11,26] although many studies have shown an inverse relationship between physical activity and ischemic stroke. More studies are needed to investigate the relation of physical activity to hemorrhagic stroke. Another limitation is that the definitions of low, moderate, and high activity varied widely among studies, making it impossible to be entirely specific about the amount and type of physical activity required to prevent stroke. The degree of control for confounding variables also varied from study to study. Most studies adjusted for some risk factors besides age; approximately one third adjusted for high blood pressure. If the causal pathway is that physical activity reduces stroke by lowering blood pressure, then not adjusting for blood pressure would be appropriate.

In conclusion, our meta-analysis documents that moderately or highly active individuals have a reduced risk of stroke incidence or mortality. Reduction of stroke risk is another reason to participate in regular and moderate- to high-intensity physical activity.

Acknowledgments

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Editorial Comment

Physical Exercise and Stroke: The Sitting Majority Has a Lesson to Learn

One of the most simple, natural, and cheapest ways of preventing a stroke is to exercise regularly. In spite of this trivial wisdom it is hard to get people to increase their cardiovascular fitness, probably because no direct gains are visible and no immediate rewards are attached. One report from Canada estimates that about two thirds of the population are inactive, and the public health burden resulting from this amounts to 2.5% of total direct health costs.[1] For this sitting majority there is now a lesson to be learned. Lee et al report in this issue of *Stroke*[2] a meta-analysis of all studies published up to mid-2002, including epidemiological as well as case-control studies, showing a clear benefit of physical activity to prevent both stroke incidence and mortality. The magnitude of the effect is considerable, homogenous, and significant: highly active individuals had a 21% lower risk of ischemic stroke and a 34% lower risk of hemorrhagic stroke when compared with low-active individuals.

What has also become evident is that no large differences exist between countries. The studies for this meta-analysis have come from North America and include data from the Framingham cohort and the Northern Manhattan Stroke Study. Other data are from the United Kingdom, Scandinavia, Netherlands, Japan, and Australia. The pooled results show unequivocally that high-level physical activity should become a global recommendation for stroke prevention. Not considering malnutrition and social impoverishment as contributing causes of stroke in less developed countries, there is no reason to assume that physical exercise should be less effective in any other social, cultural, or ethnic setting.

Physical activity has also been shown to reduce cardiovascular diseases as well as stroke in women. Although the authors have not presented a separate analysis for this, the obtainable benefits are also impressive.[3,4]

Finally, this article also compiles the evidence for a dose-response relationship: High level activity is better than moderate-level activity, but moderate activity is also effective when compared with low-level activity. When all studies are combined, the moderately active individuals had a 20% lower risk of stroke and death than did low-active persons.

This graded effect of reducing the risk of stroke with vigorous levels compared with moderate levels of physical exercise implies more than just a causal relationship. It shows that the moderate approach also is effective in a measurable, significant, and recommendable way. It shows that people inclined to exercise on moderate levels can also expect some advantage to prevent a stroke. But the role of walking compared with vigorous exercise has to be studied further for stroke prevention and has up to now has been only prospectively assessed for the prevention of cardiovascular events.[5] This is an important issue for future studies because the moderate activity approach seems to fit best for a mass approach.

A lot of the effects could be due to concomitant risk factor modification such as blood pressure lowering. Wisely, the authors argue that if the effect is via blood pressure reduction, the meta-analysis should not control for it. Still, this has been done in one third of the studies. But the major limitation of this study is that no clear working definitions for intensity of

physical exercise have been provided. Most studies use physical activity questionnaires, which are known to be imprecise and biased, especially if quantification is based on self-reported estimates. Other studies have used prespecified categories for light-moderate (such as walking) and heavy physical activity (such as jogging).[6] Usually no parallel caloric measurements or weight controls are performed, and no single laboratory marker has been shown practical for concomitant study, even if lipid profiles[7,8] and other atherogenic markers such as leukocyte count[9] or tumor necrosis factor[10]could be valuable parameters to monitor risk. On the other hand, surrogate markers such as carotid intima-media thickness cannot be measurably influenced by physical activity.[11] Others still recommend peak oxygen uptake or peak energy expenditure as a relation to oxygen uptake when a person is at rest as a robust measure of physical fitness.[12]

It is now established beyond reasonable doubt that high-level physical activity is to be strongly recommended for the prevention of stroke. Primary care physicians and stroke specialists will now be able to recommend this very effective measure with a higher level of certainty. Still, a truly randomized controlled trial assessing the prospective rates of stroke incidence (or recurrence) is needed. Only such a trial would quantify the true measures of physical activity to be recommended for stroke prevention.

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