

REVIEW

# The role of physical activity in primary stroke - prevention

EXERCISE IS MEDICINE / NEUROLOGY / PA PROMOTION



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## Summary

Physical inactivity is a known risk factor for stroke. The interaction between exercise and risk of stroke is complex. Physical activity has a beneficial effect on most risk factors for stroke, which may show reciprocal potentiation (e.g. obesity, sleep apnea, atrial fibrillation). Advice on physical activity is of importance in primary prevention of stroke. Hereby, type, amount and intensity of physical activity may be distinguished and adjusted according to comorbidities (e.g. in case of heart failure).

## Zusammenfassung

Die körperliche Inaktivität ist ein Risikofaktor für Hirnschlag. Die Zusammenhänge zwischen körperlicher Aktivität und Hirnschlag sind komplex. Die körperliche Aktivität hat einen günstigen Effekt auf die meisten Risikofaktoren für Hirnschlag, welche sich gegenseitig potenzieren können (z.B. Übergewicht, Schlafapnoe, Vorhofflimmern). Eine Beratung hinsichtlich körperlicher Aktivität nimmt in der

Primärprävention des Hirnschlags einen wichtigen Stellenwert ein. Hierbei können Art, Menge und Intensität der körperlichen Aktivität unterschieden und in Abhängigkeit der Komorbiditäten (z.B. bei Herzinsuffizienz) angepasst werden.

## Résumé

L'inactivité physique est associée avec le risque de développer un accident vasculaire cérébrale (AVC). L'interaction entre l'activité physique et un AVC est complexe. L'activité physique a un effet bénéfique sur la plupart des facteurs de risque pour un AVC, et aussi ces facteurs peuvent s'augmenter réciproquement (par exemple l'obésité, l'apnée de sommeil et la fibrillation auriculaire). Un conseil concernant l'activité physique est important dans la prévention primaire de l'AVC. Ici, on peut différencier le type, la quantité et l'intensité et adapter ces facteurs en dépendance des comorbidités (par exemple en cas d'une insuffisance cardiaque).

## Introduction

Physical inactivity is a risk factor for cerebrovascular and cardiovascular disease. [1] First observations concerning reduction of cardiovascular mortality through being physically active were published approximately 65 years ago. [2,3] The studies observed that drivers of double decker buses had fewer cardiovascular events in comparison to more sedentary drivers. It was assumed that these findings were based on the fact, that double decker bus drivers were regularly climbing and descending the bus stairs for selling travel-tickets.

Being physically active improves vascular health by different mechanisms having positive effects on risk factors for stroke. For example, there is a reduction of blood pressure and weight and an improvement of levels of blood lipids and diabetes mellitus type 2. [4]

Physical inactivity has a major socio-economic impact. In the EU, in 2015, the estimated direct costs were 71.1 billion Euro. [1] In Switzerland, in 2013, medical costs attributed to physical inactivity were 0.802 billion Swiss francs (95%CI 0.684-0.934), 35.4% of which were attributed to vascular disease (coronary heart disease, stroke and arterial hypertension). [5]

In order to understand the effects of physical activity it is crucial to elucidate its different types and proposed four dimensions. Different types are: endurance, dynamic resistance and isometric resistance training. [6] The proposed four dimensions are: mode (walking, running, cycling etc.), frequency (number of sessions per unit of time), duration and intensity. [7]

Intensity, measured as oxygen consumption, heart reserve rate, stepping rate and/or subjective rating, is classified in absolute, measured by oxygen uptake per unit of time (ml/min or L/min) or by metabolic equivalents (abr. METS), or relative, measured in relation to individual cardiovascular fitness by  $VO_2\max$  or percentage of individual maximal heart rate (%HRmax, which is 220 subtracted by age). [8] Intensity is further classified as follows into: very light, light, moderate, hard, very hard and maximal (*table 1*). [7] However, these proposed thresholds slightly vary in different studies. Also, quantity of METS/time-unit may be calculated: for example a moderate intensity of 5 METS exerted over 5 minutes would result in 25 METS.

Besides the quantity and intensity of physical activity, the cardiorespiratory fitness or exercise capacity can be used as a marker for vascular mortality. [9,10] The cardiorespiratory fitness is defined as maximal

oxygen uptake for a given task and is measured in METS and it correlates with the intensity and quantity of physical activity of one individual. [11]

Complex tools, which take the concomitant individual's medication into account, have been developed to facilitate the physician recommending physical activity as a treatment modality. [12] There are different tools assessing vascular risk: AGLA-Score, [13] SCORE-Chart, [14] risk calculator of the American heart and stroke association [15] and the ESC-heart score. [16]

relative intensity			absolute intensity	
Intensity	VO <sub>2</sub> max	maximal heart rate	intensity	METS
very light	<25%	<30%	sedentary	1-1.5
Light	25-44%	30-49%	light	1.6-2.9
Moderate	45-59%	50-69%	moderate	3.0-5.9
hard	60-84%	70-89%	vigorous	>6.0
very hard	>85%	>90%		
maximal	100%	100%		

Table 1: Proposed classification of the intensity of physical activity, modified after Strath et al. [7]

## Physical activity and risk of stroke overall

In a meta-analysis of 23 studies (18 cohort, 5 case-control), highly active individuals had a reduction of 25% (RR 0.75, 95%CI, 0.69-0.82, p=0.001) of risk of stroke compared to individuals with low activity in cohort studies and of 64% (RR 0.36, 95%CI, 0.25-0.52, p=0.001) in case-control studies. [17]

Another meta-analysis of observational studies (31 publications, 24 cohort, 7 case-control) demonstrated a benefit of high intensity physical activity on risk of stroke compared to moderately intense physical activity (RR 0.77, 95%CI 0.6-0.98) and to inactivity (RR 0.57, 95%CI 0.43-0.77). [18]

A prospective study (n=47,721, follow-up of 19 years) analyzed the effect of occupational physical activity, leisure time physical activity and commuting on the risk of stroke. Occupational physical activity was defined as physical activity performed at the working place (e.g. sitting office work, standing and walking and lifting or heavy manual labor). Examples for leisure time physical activity are: reading, watching television, walking, cycling, light gardening, running, jogging, swimming, heavy gardening or regular exercise or competitive sports several times per week. The association between occupational activity and risk of stroke was not significant (p=0.060). The HR associated with low, moderate and high leisure time physical activity was 1, 0.77 and 0.63 respectively (p<0.001). The effect remained significant even after adjusting for the major risk factors. Also, commuting protected against stroke: the HRs associated with 0, 1-29, and ≥30 minutes of active commuting were 1, 0.92, and 0.89 respectively (p=0.043). [19]

The protective effect of physical activity is also evident in advanced age. In a prospective cohort analysis of 4,207 men and women (mean age of 73 years), physical activity was inversely associated with stroke, especially with ischaemic stroke, coronary heart disease and total cardiovascular (fatal or nonfatal myocardial infarction, coronary death or stroke) mortality. This study analyzed walking pace, walking distance/week and leisure time activity and showed that greater values of all these variables are inversely associated with the risk of stroke. [20]

A prospective cohort study in Japan (n=74,913, 698,946 person-years follow up) demonstrated a J-shaped curve concerning the quantity of physical activity (measured in MET-hours per day) for ischaemic stroke. There was highest benefit for the second and third MET-hours/day quartile (5.4 and 13 MET-hours/day respectively). However, although not statistically significant, individuals with levels of activity of >30-35 MET-hours/day were likely to have increased risk of subarachnoid haemorrhage. Furthermore, individuals who performed vigorous physical activity (in the 90th percentile, range 18.8-68.4 MET-hours/day) had an increased risk of haemorrhagic stroke. Of note, blood pressure is increasing during physical activity and might be triggering subarachnoid haemorrhage and/or haemorrhagic stroke. [21]

A recent meta-analysis of 14 cohort studies with 1,409,340 participants (23,894 strokes) showed an inverse dose-relationship between cardiorespiratory fitness and ischaemic but also haemorrhagic stroke, including subarachnoid haemorrhage, demonstrating that every increment of 5 METS reduces the risk of stroke by 15% (RR 0.85, 95%CI 0.79-0.91). [22]

Another meta-analysis included 80 studies with 1,338,143 participants and found a clear inverse dose-response relationship between all-cause mortality and physical activity. Comparing highest with lowest activity levels for total activity the RR was 0.65 (95%CI, 0.6-0.71), for leisure activity 0.74 (95% CI 0.70-0.77), for activities of daily living 0.64 (95%CI 0.55-0.75) and for occupational activity 0.83 (95%CI 0.71-0.97). [23] In another prospective study of healthy women (n=27,055) the risk of vascular disease decreased linearly with more physical activity. The investigators studied the impact of physical activity on known risk factors. 59% of the inverse association turned out to be explained by the favorable effect on known risk factors, with the strongest correlation with systemic inflammation/haemostatic markers (32.6%) and blood pressure (27.1%). [24]

## Primary stroke prevention overall

The INTERSTROKE-Study (n=13,447, case-control study, 32 countries) included 10,388 patients with ischaemic stroke and 3,059 with intracerebral haemorrhage and 13,472 controls. The population attributable risk (PAR) of physical activity for stroke turned out to be 35.8%. Regular physical activity, defined as moderate to strenuous activity  $\geq 4$  hours/week, reduced the overall risk of (ischaemic and haemorrhagic) stroke (OR 0.41, 95%CI 0.35-0.48). [25] The same study showed that 10 potentially modifiable risk factors (i.e. arterial hypertension, physical inactivity, dyslipidaemia, unhealthy diet, obesity, psychosocial stress, smoking, cardiac arrhythmia and causes, alcohol overconsumption and diabetes mellitus) were associated with 90% of the PAR for stroke. [25]

In Switzerland, there were 15,254 hospitalizations because of stroke in 2016. [26] Taking these as well as the data of the INTERSTROKE-Study into account, up to 12-14,000 strokes/year could potentially be prevented in Switzerland. This by optimal management of risk factors for stroke. However, this extrapolation is assuming that the distribution of risk factors between the Swiss population and the patients in the INTERSTROKE-Study is roughly comparable.

## Effects of physical activity on risk factors for stroke

### *Blood pressure*

Arterial hypertension is one of the most important risk factors for stroke. [25] It induces remodeling of the vessel wall, atherosclerosis, disturbed endothelial function and loss of autoregulation. [27]

The prevalence of high blood pressure increases with age; 26.1% among those 20-44 years of age and 78.2% among those >65 years of age suffer from arterial hypertension. [4] Advancing age is weakening the association between arterial hypertension and stroke. [28]

There is strong evidence that physical activity has an antihypertensive effect, even in individuals with resistant arterial hypertension. [29,30] The exact mechanisms are still unclear, postulated is an endothelial gain of function, a decrease of inflammation, autonomic modulation, angio- and arteriogenesis, intima-media thickness and an increase of insulin sensitivity, arterial compliance and luminal diameter. [31] A meta-analysis (n=5,223, 3,401 exercise and 1,822 sedentary controls) showed a significant reduction for systolic blood pressure (abr. SBP) after endurance, dynamic resistance and isometric resistance training, but not after combined training. The diastolic blood pressure (abr. DBP) was significantly reduced after endurance, isometric resistance and after combined training. [6]

An intervention study (207 subjects with stage 1 and 2 hypertension, 8-week exercise intervention) has demonstrated a clear relationship between the duration of physical activity per week and blood pressure in people with essential arterial hypertension, with the greatest effect at 61-90 min/week of moderate intensity exercise. Higher duration of physical activity did not seem to be of further benefit. [30]

### *Dyslipidaemia*

A high Apolipoprotein (Apo) B/ApoA1 ratio is associated with an elevated risk of ischaemic stroke. [25] ApoB are contained in LDL-particles. ApoB-containing particles, including triglycerides and LDL are able to cross the endothelial barrier and may provoke the initiation and subsequent growth of an atheroma. [14] One meta-analysis of prospective studies (n=352,033, 2 million person-years) has found a 25% (95%CI 13-40%) increased risk of ischaemic stroke with every increase of the total cholesterol level of 1mmol/l on the one hand, but on the other hand a 20% (95%CI: 8-30%) decreased risk of fatal haemorrhagic stroke. [32] Cholesterol has an important role in maintaining the membrane integrity [33] and lower levels may trigger vessel-wall rupture.

Physical activity has a favorable effect on plasma lipid levels regardless of the diet and of the body weight. [34] Exercise increases the ability of muscle tissue to take up and oxidize non-esterified fatty acids and increases the activity of lipoprotein lipase in muscles. [35]

A prospective study (n=384, follow-up duration of 6 months) demonstrated a higher reduction of LDL-cholesterol levels the higher the exercise intensity. [34] The group with the highest reduction of LDL-cholesterol levels did 20 miles (aprox. 32 km) a week at 65-80% max-VO<sub>2</sub>max. Physical activity is supposed to reduce plasma lipid levels through weight loss. [36]

### *Obesity*

Obesity increases the risk of stroke by increased plasma cholesterol, arterial hypertension, heart disease, diabetes, atrial fibrillation, sleep apnea, psychosocial factors and economic difficulties. [25,37]

The favorable effect of physical activity on the body-mass-index (abr. BMI) and waist circumference in morbid obese people is well known. Multiple conducted prospective studies have shown reduced BMI in obese individuals after a period of sustained aerobic and dynamic resistance training. [38] However, a significant difference between high intensity interval/sprint interval training and moderate intensity continuous training has not been found. [39]

Weight loss is beneficial by decreasing blood pressure, inflammatory markers, LDL-cholesterol and triglycerid levels, by increasing HDL-cholesterol levels and by improving glucose tolerance. [37]  
The amount of physical activity recommended by the American College of Sports Medicine and current evidence category is presented in table 2. [37]

Evidence Statement	Evidence Category
Physical activity (PA) of 150-250 min/week will prevent weight gain greater than 3% in most adults.	A
PA 150 min/week promotes minimal weight loss, PA of 150 min/week results in modest weight loss of 2-3 kg, PA of 225-420 min/week results in 5-7.5 kg weight loss and a dose-response exists.	B
Some studies support a 200-300 min/week PA for weight maintenance to reduce weight regain after weight loss, and it seems that "more is better". However, there are no correctly designed, adequately powered, energy balance studies to provide evidence for PA to prevent weight regain after weight loss.	B
Lifestyle PA is an ambiguous term and must be carefully defined to evaluate the literature. Given this limitation, it seems lifestyle PA may be useful to counter the small energy imbalance responsible for obesity in most adults.	B
PA will increase weight loss if diet restriction is modest but not if diet restriction is severe.	A
Research evidence does not support resistance training (RT) as effective for weight loss with or without diet restriction. There is limited evidence that RT promotes gain or maintenance of lean mass and loss of body fat during energy restriction.	B

Table 2: Amount of physical activity recommended by the American College of Sports Medicine and current evidence category [38]

### *Psychosocial stress*

A meta-analysis of 17 prospective studies showed an increase in risk of stroke of 34% (95%CI 17-54%; p=0,003) in individuals with depression. [40] Possible explanations are medication malcompliance, unhealthier lifestyle, increased systemic inflammation, associated arterial hypertension, diabetes mellitus and increased platelet activity. [40,41]

Physical inactivity increases the odds of having depression (OR 3.15). [42] In a population-based study (n=19,288) exercisers were less anxious, depressed, neurotic and more extroverted and sensation seeking. [43]

### *Smoking*

Smoking is associated with increased vascular mortality. In people who smoke, there is a twofold increased risk of ischaemic stroke. [44] Moreover, the risk grows exponentially with more cigarettes smoked per day. [25] Smoking is strongly associated with subarachnoidal haemorrhage (SAH). About 1 in 3 SAHs is attributed to current smoking. Possible mechanisms are increased systemic coagulability, inflammation within arterial walls, increased blood pressure, endothelial dysfunction and degradation of elastin. [45] Moderate to heavy smoking is also associated with intracerebral haemorrhage. However, the association of mild smoking and intracerebral haemorrhage is less clear. [25,46,47]

Physical activity has a favorable effect on cigarette craving, prolonging the delay to ad libitum smoking. [48] Smoking cessation is facilitated by physical activity. In an intervention study including female smokers (n=236, medium age 43, medium cigarettes/day 17), physical activity was associated with a higher chance of achieving complete cessation (targeted quit date week 4). [48] For persons who already quit

smoking, engaging in physical activity increased the overall-sense of well-being. [50]

Physical activity reduces smoking-induced systemic inflammation by reducing surface markers on T-cells and decreasing inflammatory cytokines and improves the structure and function of muscles by inhibition of catabolism and by stimulating anabolic pathways. [51]

### *Atrial fibrillation*

Atrial fibrillation is a known risk factor for stroke. [25,52–54]

After analyzing the available evidence, Elliot et al. [55] concluded, that a reduction of approx. 12% of relative risk of developing atrial fibrillation could be achieved at a dose of approx. 1000-1500 MET-minutes/week. However, this analysis should be interpreted with caution. In the available studies, quantity of physical activity was self-reported in all and atrial fibrillation in some studies.

In an observational study participants who performed any vigorous physical activity in the upper tertile (i.e. >19.575 MET-minutes/week), showed a reduction of incidence of atrial fibrillation (upper tertile HR 0.46, 95%CI 0.22-0.98, p=0.045) after adjusting for cigarette smoking, resting heart rate, systolic blood pressure, use of antihypertensives, low density lipoprotein, high density lipoprotein, body mass index, diabetes mellitus and left ventricular hypertrophy. [56]

However, in a cohort-study of 52,755 long-distance cross-country skiers a higher incidence of cardiac arrhythmias, including atrial fibrillation, was observed. [57]

Also, inflammation of the heart tissue and in the systemic circulation is associated with initiation and recurrence of atrial fibrillation. [58] Physical activity reduces the subclinical systemic inflammation, which could have a favorable effect on the incidence of atrial fibrillation. [59]

Moreover, obesity is a risk factor for atrial fibrillation through multiple mechanisms such as left atrial enlargement and increased inflammation. Therefore, weight loss achieved through physical activity reduces the incidence, severity and morbidity of atrial fibrillation. [60]

Furthermore, it was shown that physical activity improves the autonomic modulation of cardiac rhythm control. [61] Autonomic dysbalance has a putative role in the genesis of atrial fibrillation. So, the modulation of autonomic balance through physical activity may have a positive effect on incident atrial fibrillation. [62]

Last but not least, in a cohort-study of sleep-clinic patients those with obstructive sleep apnea (defined as AHI >5/h) had a two-fold increased risk of incident atrial fibrillation after an average follow-up of 4.7 years. [63] Physical activity has been shown to be a simple to implement treatment option for sleep apnea. [64] Multiple beneficial mechanisms of physical activity on sleep apnea have been postulated which are: increased upper airway dilator muscle tone, reduced fluid accumulation in the neck, increased slow-wave sleep, reduced body weight and reduced systemic inflammatory response. [60,64]

### *Heart attack*

Although many risk factors for heart attack are the same as for ischaemic stroke, heart attack is an independent risk factor for ischaemic stroke by inducing cardiac arrhythmia and intra-cardiac thrombus formation. [65]

Physical activity has beneficial effects on coronary heart disease by improving heart function, increasing exercise capacity and reducing rate, recurrence and mortality of coronary heart disease. [66]

### *Alcohol overconsumption*

Alcohol overconsumption is another risk factor for stroke. [25] A recent meta-analysis (n=599,912) showed that >100g ethanol/week increased the risk of stroke (HR 1.14, 95%CI 1.10-1.17). [67] Light alcohol consumption is associated with higher HDL-cholesterol levels, reduced platelet-activity, lower fibrinogen concentration and increased insulin-sensitivity, whereas heavy alcohol consumption is associated with arterial hypertension, hypercoagulability, reduced cerebral blood flow and atrial fibrillation. [45]

A survey study with US-participants (n=230,856) showed a positive correlation between alcohol consumption and physical activity up to a certain upper quantity of alcohol consumed (i.e. light and moderate drinking). However, the probability of a physically active lifestyle decreased with heavy drinking. [68]

A systematic review of 5 studies, which examined the interaction between alcohol consumption disorders and physical activity concluded that alcohol dependence, diagnosed according to DSM IV-criteria, is not related to physical activity. Also, this study speaks about a “ceiling effect”, up to which alcohol consumption is positively associated with physical activity. [69]

There are multiple possible explanations of the apparently paradoxical positive association between alcohol consumption and physical activity: sensation-seeking behavior, socializing and drinking after participation in organized group sports, willing to compensate for the weight gain after drinking by being physically active, especially in women. [70,71]

In experimental studies in mice physical activity as a naturally rewarding activity induced expression of various molecules in mesolimbic reward pathways. The same phenomenon has been observed after illicit drug consumption. [70]

Physical activity is increasingly recognized as a treatment option for alcohol overconsumption. A meta-analysis of 22 prospective studies investigated the effect of physical activity on substance use disorders. 3 studies studied alcohol overconsumption alone and 4 polytoxicomania, including alcohol overconsumption. The studies showed a significant benefit of physical activity on abstinence for alcohol (OR 1.65, 95%CI 1.14-2.39, p=0.0032) regardless of the type, i.e. mind-body exercise (Tai Chi Quan, Qigong and Yoga) or aerobic exercise and intensity. A significant effect of physical activity also has been observed (SMD -0.77, 95%CI 1.73-0.19, p=0.0165) on the associated depression. A benefit of physical activity in patients with alcohol use disorders, although not statistically significant, was shown for anxiety (SMD -0.21, 95%CI -0.58-0.16, p=0.5975) and withdrawal symptoms (SMD -1.67, 95%CI -3.51-0.17, p=0.399). [72]

### *Diabetes mellitus*

Diabetes mellitus is a risk factor for stroke. [25] It is associated with arterial hypertension, overweight (diabetes mellitus type 2), dyslipidemia and atrial fibrillation. It causes endothelial dysfunction, thickening of basal membrane and systemic inflammation. [73,74]

The role of physical activity in diabetes mellitus has been described in detail elsewhere. [75]

The evidence of a favorable effect of physical activity on diabetes mellitus type 2 is strong. A meta-analysis of 47 randomized trials (n=8,538) showed that a significant HbA1c reduction can be achieved by structured aerobic, resistance or combined physical activity and that greater HbA1c reduction was observed in the subgroup performing >150 min/week of supervised physical activity, without serious adverse effects being reported. High intensity exercise was not associated with significant reduction of HbA1c. The favorable



effect of physical activity on diabetes mellitus is explained by improved resistance to insulin. [76] However, the benefit of physical activity on diabetes mellitus type 1 is less clear because of an associated potential complication of hypoglycaemia linked to high intensity exercise. The glycemic variability is greater during physical activity. [77] However, knowing the glycemic index of different foods, adapting the required insulin-dose and usage of continuous glucose monitoring, physical activity can be performed safely. [75]

## Conclusions

Even small amounts of physical activity are decreasing the risk of stroke according to one meta-analysis. Authors found a linear relation between the quantity of physical activity and risk for ischaemic stroke. Only very high amounts have been associated with higher risks of subarachnoid haemorrhage and/or haemorrhagic stroke. However, an increase of cardiorespiratory fitness through exercise has been demonstrated not only to protect against ischaemic but also against haemorrhagic stroke in another meta-analysis. Also a dose-response relationship between physical activity and all-cause mortality was found. Physical activity is a simple to implement treatment option in primary prevention of stroke. The INTER-STROKE-Study identified the 10 most relevant potentially modifiable risk factors for stroke: arterial hypertension, physical inactivity, dyslipidaemia, unhealthy diet, obesity, psychosocial stress, smoking, cardiac arrhythmia and causes, alcohol overconsumption and diabetes mellitus. Physical activity has been shown to have beneficial effects on these risk factors. Every patient should get enlightened about this. Current guidelines on primary prevention in stroke prevention recommend moderate to high intensity physical activity in healthy individuals for 40 min/day, 3-4 days/week. [45] Examples of modes of physical activity include walking, jogging, swimming, cycling, gardening etc. The proposed thresholds for moderate intensity are 3-5.9 METS,  $VO_2$ max 45-59% and HRmax 50-69% and for high intensity are >6 METS,  $VO_2$ max 60-84%, HRmax 70-89%.

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