REVIEW

ACCEPTED: February 2019
PUBLISHED ONLINE: March 2019
DOI: 10.5960/dzsm.2019.372
Reimers CD. Physical activity and sports as primary prevention of neurological diseases: a narrative review. Dtsch Z Sportmed. 2019; 70: 57-66.

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Physical Activity and Sports as Primary Prevention of Neurological Diseases: a Narrative Review

Körperliche Aktivität und Sport als Primärprävention neurologischer Erkrankungen: ein narrativer Überblick

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Summary

- **Cerebral infarcts and haemorrhages,** dementia, Parkinson´s disease, sarcopenia, falls, and insomnia have in common that they frequently occur in higher ages, may considerably impair quality of life and cannot be primarily prevented by medication. Regular physical activity and sports however have the ability to reduce the risk of these diseases. In this review, mainly the results of corresponding meta-analyses are presented. The current knowledge indicates that the risk of ischaemic or haemorrhagic strokes can by reduced by about one fifth to one fourth, that of cognitive decline by about one fifth to one third, and that of Parkinson´s disease by about one third.
- **The effective risk reduction** probably is somewhat higher, since in the meta-analyses of the prospective cohort studies the known so-called vascular risk factors such as arterial hypertension, diabetes mellitus, and dyslipidaemia, which also profit by physical activity, have been taken into account. The question of possible reverse causality has been discussed.
- **The risk of a sarcopenia** may be reduced by one third to almost a half. Regular exercise, especially balance training, reduces the risk of falls by one fifth to one half. Also sleep disturbances are less frequent in physical active as compared to inactive individuals.

KEY WORDS:
Stroke, Dementia, Parkinson´s Disease, Sarcopenia, Falls, Insomnia

Zusammenfassung

- **Den Schlaganfällen,** Demenz-Erkrankungen, Stürzen und Schlafstörungen sowie der Parkinson-Krankheit und Sarkopenie sind gemeinsam, dass sie vor allem im höheren Lebensalter häufig sind, die Lebensqualität erheblich beeinträchtigen können und bisher keine medikamentöse Primärprävention existiert. Regelmäßige körperliche Aktivität und Sport sind jedoch in der Lage, das Risiko dieser Erkrankungen zu verringern.
- **In der vorliegenden Übersicht** werden vor allem die Ergebnisse entsprechender Metaanalysen vorgestellt. Diese zeigen, dass sich das Risiko eines Schlaganfalls um etwa ein Fünftel bis Viertel, das eines kognitiven Abbaus um etwa ein Fünftel bis Drittel und das einer späteren Parkinson-Krankheit um etwa ein Drittel reduzieren lässt.
- **Die tatsächliche Risikoreduktion** dürfte sogar noch höher ausfallen, da bei den den Metaanalysen zugrunde liegenden prospektiven Kohortenstudien multivariate Analysen vorgenommen wurden, bei denen die diesen Erkrankungen teilweise zugrunde liegenden sog. vaskulären Risikofaktoren (arterielle Hypertonie, Diabetes mellitus, Dyslipidämien), die ihrerseits durch Sport positiv beeinflusst werden, als Kofaktoren berücksichtigt wurden. Die Frage einer möglicherweise umgekehrten Kausalität wird diskutiert.
- **Das Risiko einer späteren Sarkopenie** lässt sich um ein Drittel bis fast die Hälfte reduzieren. Regelmäßiges sportliches Training, insbesondere Gleichgewichtstraining, vermindert das Sturzrisiko um ein Fünftel bis zur Hälfte. Auch Schlafstörungen sind bei körperlich aktiven Personen deutlich seltener als bei inaktiven.

SCHLÜSSELWÖRTER:
Schlaganfall, Demenz, Parkinson-Krankheit, Sarkopenie, Stürze, Schlafstörungen

GERMAN JOURNAL OF SPORTS MEDICINE VOLUME 70
Deutsche Zeitschrift für Sportmedizin

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Introduction

One of the most important goals of the health system is to increase life expectancy, improve health and make healthy aging possible by limiting illnesses to the shortest possible time at the end of life (65). Age-related neurodegenerative diseases (Parkinson's Disease (56) and dementias (55)) are of increasing importance to the quality of life as well as to mortality due to the demographic change (average life expectancy in Germany in 2016 was 81.53 years for women, 75.19 years for men; in 1966 the figures were 65.26 resp. 70.03 years, or more than 10 years shorter (8). From a neurological point of view, stroke is of particular relevance as an age-associated disease.

The risk factors are in part identical for dementias and stroke. The most important risk factor is age. Common risk factors of vascular dementia and Alzheimer-type dementia as well as stroke are ›

Table 1

Meta-analyse of the risks of developing a stroke in the most physically or sports-active persons compared to the least active persons in prospective cohort studies (from: Reimers et al. (51)). CI=confidence interval; n=number of original studies.

TYPE OF STROKE AND GENDER OF THE STUDY PARTICIPANT	RELATIVE RISK OF A STROKE IN PHYSICALLY ACTIVE PERSONS COMPARED TO INACTIVE PERSONS.	RELATIVE RISK OF A STROKE IN SPORTS-ACTIVE PERSONS COMPARED TO INACTIVE PERSONS
Cerebral infarct	0.69 (95%-CI: 0.57-0.84)	0.61 (95%-CI: 0.47-0.80)
Women	n=7	n=2
Cerebral infarct	0.74 (95%-CI: 0.65-0.84)	0.76 (95%-CI: 0.52-1.12)
Men	n=10	n=3
Cerebral infarct	0.77 (95%-CI: 0.70-0.85)	0.90 (95%-CI: 0.61-1.33)
Women and Men	n=8	n=3
Cerebral hemorrhage	0.85 (95%-CI: 0.62-1.17)	0.73 (95%-CI: 0.47-1.13)
Women	n=4	n=2
Cerebral hemorrhage	0.58 (95%-CI: 0.42-0.79)	0.62 (95%-CI: 0.42-0.91)
Men	n=6	n=3
Cerebral hemorrhage	0.72 (95%-CI: 0.56-0.92)	-
Women and Men	n=3	-
Not specified strokes	0.77 (95%-CI: 0.68-0.89)	0.87 (95%-CI: 0.53-1.45)
Women	n=17	n=3
Not specified strokes	0.79 (95%-CI: 0.68-0.84)	0.73 (95%-CI: 0.57-0.92)
Men	n=25	n=7
Not specified strokes	0.72 (95%-CI: 0.63-0.82)	0.73 (95%-CI: 0.57-0.92)
Women and Men	n=10	n=7

arterial hypertension, insulin resistance, diabetes mellitus, adiposity, hyperhomocysteinemia, and hyperlipidemia (69). Common to the diseases cited is also a lack of possibility for influencing by medicational primary-preventive means – apart from treatment of the vascular risk factors. For this reason, interest in a possibly non-medication prevention measure is especially great. The overview below deals with the primary-preventive effects of regular physical activity and of sports on the diseases cited. While there are controlled randomized studies on sports on various disease entities, prospective cohort studies usually limit themselves to recording overall physical activity. In addition sarcopenia, falls and sleep disorders will be addressed, since they are also age-associated.

Basically, two variants of the way in which physical activity could influence the risk of neurological diseases are plausible: on the one hand directly and on the other via the so-called vascular risk factors.

Effect of Physical Activity on the Vascular Risk Factors

There are various meta-analyses available on the influence of sports training on blood pressure. For example, regular training in water reduces the systolic blood pressure on average by 8.4mmHg, the diastolic pressure by 3.3mmHg (24). Dancing reduces the systolic blood pressure by 12.01mmHg (95% confidence interval (CI): 16.08-7.94mmHg) and the diastolic pressure by 3.38 mmHg (95% CI: 4.81-1.94mmHg) (5). Strength training reduces systolic blood pressure on average by 5.20 mmHg (95%-CI: 6.08-4.33mmHg) and diastolic pressure by 3.91mmHg (95%-CI: 5.68-2.14mmHg) (25) resp. 8.2mmHg (CI: 10.9-5.5) and 4.1mmHg (CI: 6.3-1.9) (6). Tai Chi reduces systolic blood pressure by 13.00mmHg (95%-CI: 21.24-4.77), the diastolic pressure by 6.13mmHg (95%-CI: 11.20-1.07) (75). Our own meta-analyses in persons who were healthy, apart from possible arterial hypertension and adiposity, brought mostly smaller effects, depending on the type of sport. These were, however, overproportionally associated with the baseline blood pressure, so that especially persons with arterial hypertension profit from regular training (47).

The risk of developing diabetes mellitus type 2 was found in the meta-analysis by Smith et al. (61) to be reduced by 26% (95%-CI: 20%-31%) in those who spent 11.25 MET h/week (=150 minutes/week moderate physical activity), compared to physically inactive persons. Bellou et al. (3) report a risk reduced by 25% (95%-CI: 21%-30%) in physical leisure activity.

Unlike earlier meta-analyses which produced a heterogeneous picture of the effects of regular physical training on lipid metabolism, our own meta-analyses showed slight, sometimes significantly reduced triglyceride and LDL cholesterol as well as increased HDL cholesterol concentrations, independent of the type of sport (48).

At least with respect to blood pressure and glucose metabolism, probably with respect to lipid metabolism as well, sports activity thus shows significant positive effects, which may express – depending on the initial situation – as primary or secondary-preventive on the risk of neurological diseases (stroke, dementia, Parkinson's Disease).

Strokes

The annual incidence of cerebral infarcts is cited in Europe with 141.3 (95%-CI: 118.9-166.6) per 100,000 men and 94.6 (95%-CI: 76.5-115.7) per 100,000 women; the corresponding frequencies for cerebral hemorrhage are 16.9 (95%-CI: 9.8-27.1) and 12.4 (95%-CI: 6.5-21.4) per 100,000 persons (12). The stroke prevalence has not changed in the past two decades in Germany, the stroke mortality has, however, decreased (4, 22), similar to the situation for ischemic heart diseases (55).

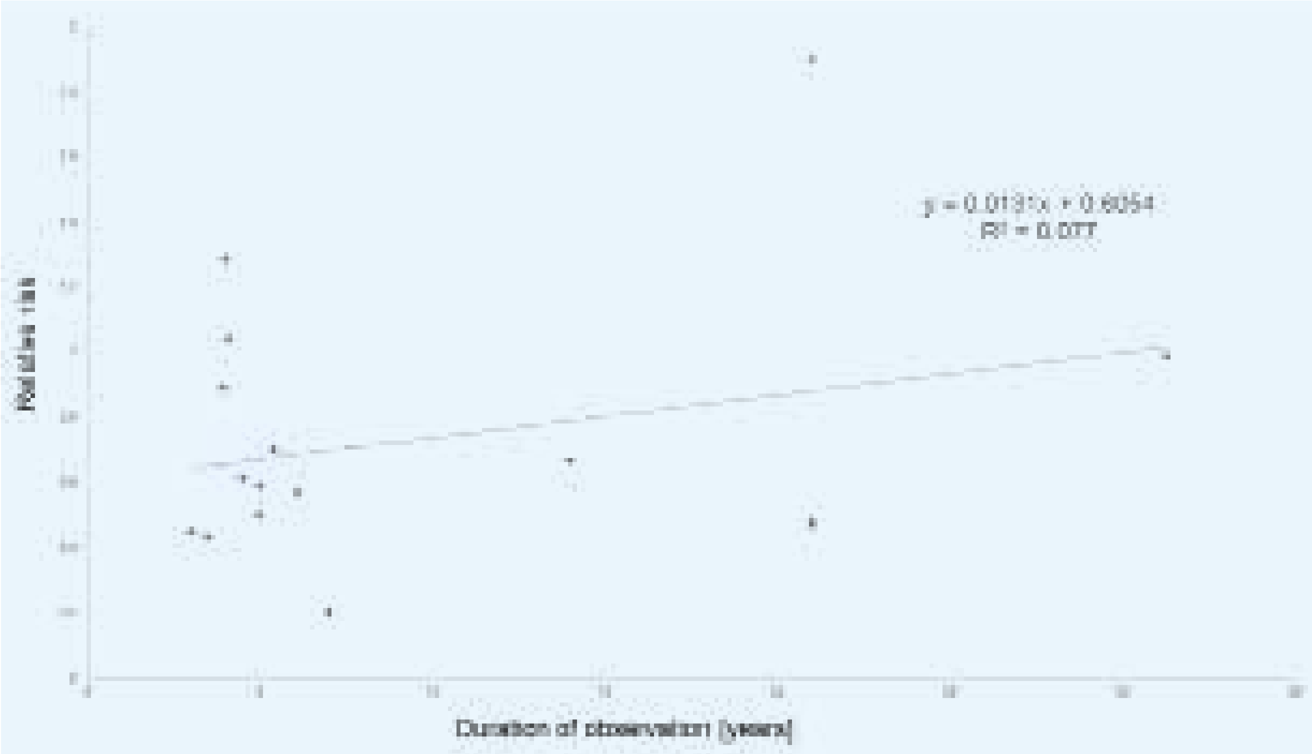

Figure 1

Correlation between the observation period and the risk of later developing an Alzheimer-type dementia (Data from Felbecker et al. (13)).

In a meta-analysis of seven studies, Li and Siegrist (32) calculated a relative risk of later stroke of 0.80 (95-CI: 0.74-0.87) in men with moderate physical leisure sport activity compared to those with low activity level. The analogous meta-analysis of six studies on women showed a relative risk of 0.82 (95%-CI: 0.76-0.88). Wendel-Vos et al. (71) calculated a relative risk of cerebral infarct among people engaging in leisure sports of RR=0.79 (95%-CI: 0.69-0.91, 11 studies), for cerebral hemorrhage of RR=0.76 (95%-CI: 0.57-0.96, 9 studies). Our own meta-analyses of prospective cohort studies also showed significantly reduced risks (Table 1). The risk thus decreases on the order of about one-quarter. Sports activity does not appear to have more primary-preventive effect than any other physical activity (51).

Remembering that the known risk factors were already taken into account in the multivariate analyses on which the meta-analyses are based, it can be assumed that the actual risk decrease is even greater. A decrease in blood pressure of 10 mmHg above 115/75mmHg reduces the risk of stroke by about one-third. In younger persons, the effects are somewhat clearer (31). In other words: The reduction of elevated blood pressure by only 5 mmHg reduces the risk of stroke by about 15%.

Dementias

According to the Deutscher Alzheimer-Gesellschaft [German Alzheimer Society] (7) it is estimated that in 2016 there were just over 1.6 million people with dementia living in Germany. There is evidence that the number of dementia sufferers in countries with high income is stabilizing or even decreasing (52).

Meta-analyses of prospective cohort studies have brought partially diverging preventive effects of regular physical training on the risk of later developing cognitive deficits. A current meta-analysis of five studies with a total of 2,878 randomized participants showed no significant preventive effect (2). Another current meta-analysis of 15 studies with 3,436 participants, by contrast, showed that per 500 kcal or 10 MET*h physical leisure activity per week decreased the risk of a not specified dementia by 10%. An analogous assessment of eight studies on Alzheimer-type dementia with 25,031 participants showed a risk reduction of 13%. In their meta-analysis of ten studies with 23,345 participants between 70 and 90 years of age and an observation time of 3.9 to 31 years, Santos-Lozano et al. (54) calculated a mean relative risk of developing Alzheimer-type dementia of 0.65 (95%-CI: 0.56-0.74) among physically active versus inactive persons. Guure et al. (20) assessed 45 studies with a total of 117,410 participants and observation periods up to maximal 28 years. For persons with high physical activity compared to lower activity they calculated a relative risk of developing a later, not specified dementia of 0.79 (95%-CI: 0.69-0.88), for Alzheimer-type dementia correspondingly a risk of 0.62 (95%-CI: 0.49-0.75), for cognitive deterioration of 0.67 (95%-CI: 0.55-0.78), and for the vascular dementias of 0.92 (95%CI: 0.62-1.30, not significant). No preventive effect for vascular dementia was found in this or in another meta-analysis of four studies with 16,797 participants (76). This may be due to the fact that there are only relatively few studies on vascular dementias thus far. Apparently, however, vascular aspects also play no particularly great role in the development of dementia. Similar results were found in our own meta-analytical combinations of 14 prospective cohort studies on unspecified dementias (18% risk reduction in every form of physical activity compared to inactive persons), of 12 studies on Alzheimer-type dementia (26% risk reduction), five studies on vascular dementias (31% risk reduction, however barely not significant) and nine studies on so-called mild cognitive deficit (47% risk reduction) (13). Norton et al. (39) calculated ›

Table 2

Selection of possible mechanisms of dementia-preventive effects in physical activity. BDNF=brain-derived neurotrophic factor, h=human-biological finding, a=animal-experimental finding.

DEMENTIA FACTOR	EFFECT OF REGULAR PHYSICAL ACTIVITY
Cerebral volume	Physical activity possibly associated with greater volume of the prefrontal gray matter and the hippocampus (11) (however, Frederiksen et al. (14) report no significant influence on hippocampus volume. (h)
Neurotrophines	The peripheral and cerebral concentrations of neurotrophines, e.g. BDNF and IGF-1, are increased by acute and chronic physical activity (1, 9, 23, 36, 43, 64). (h, a)
Cerebral blood flow	acute and regular physical activity increases cerebral blood flow (27, 42).
Neurogenesis/-plasticity	Physical activity improves the neuronal plasticity, e.g. the neurogenesis (1, 36, 37). (a)
β-Amyloid-precursor-Proteins (β-APP- and Aβ-Peptides)	Physical activity reduces the cerebral concentration of these proteins (43). (a)
β-Amyloid-Plaques	Physical activity reduces the number of hippocampal formation of β-Amyloid-Plaques (36). (a)
Tolerance to oxidative stress	Physical activity reduces the damaging effects of oxidative stress, among other things by increased production of antioxidative enzymes (primarily hydrogensuperoxiddismutase) (42, 43). (a)

that 12.7%, resp. 20.3% of the Alzheimer diseases worldwide and in Europe in 2010 could be mathematically attributed to physical inactivity. Since the known dementia risk factors, such as lower education and the so-called vascular risk factors cited above were taken into account in most of the multivariate studies (details in Felbecker et al. (13)), other factors than these must be the basis of dementia prevention. Possible mechanisms are presented in Table 2. The author knows of no prospective cohort studies on primary prevention of dementia diseases especially through sports.

Moreover, favorable effects of physical activity on vascular risk factors could play an important dementia-preventive role. Glucose intolerance and diabetes mellitus, arterial hypertension, hyperlipidemia, and adiposity play a causal role not only in the development of a vascular dementia, but also in Alzheimer-type dementia. For example, diastolic blood pressure increased by 10 mmHg is associated with a 7% greater risk of cognitive deficit, systolic blood pressure elevated by 1 mmHg in middle age increases the risk of a cognitive impairment later in life by 1% (10). Thus, regular physical activity alone can reduce the risk of later cognitive impairment by up to more than 10% due to the blood pressure-reducing effect.

A combination of cognitive and physical training significantly improves the cognitive performance capacity in healthy persons. This combination is significantly more effective than purely physical training (15). Additional physical training does not significantly increase the effect of purely cognitive training in the meta-analyses by Gheysen et al. (15). However this statement is based only on the assessment of few studies. Elderly persons capable of physical performance (measured as maximum oxygen uptake) do, however, show greater cognitive performance capacity than persons less capable of physical performance (1).

Alzheimer-type dementia, like practically all dementias, is associated with Parkinson-like impairments. Even in early stages of the disease, the gait is slower which becomes more pronounced over the course of the disease (41). The clinically-manifest disease is preceded by a subclinical phase lasting at least a decade (62). It is thus logical that an inverted causality between physical activity and the risk of dementia is under discussion, i.e. persons in whom there is already a subclinical dementia development may be less physically active and thus simulate a protective effect of physical activity (53). An indication toward a preclinically-reduced physical performance capacity and thus possibly also physical activity could be the reduced walking speed of persons later suffering dementia. This correlates with the cognition; the slower the walking speed, the more likely there will be a later cognitive deficit (44), the quicker the walking tempo, the lower the risk of later suffering dementia (21, 29). Kuate-Tegueu et al. (29) found a relative risk of developing Alzheimer-type dementia after 12 years of 1.2 (95%-CI: 1.02-1.32) per standard deviation of additional walking time. Welmer et al. (70) came to a very similar conclusion. They found a relative risk of developing dementia of 1.45 (95-CI: 1.17-1.80) per standard deviation of low baseline speed. However, the reduced walking speed and later dementia could both be the result of insufficient physical activity.

The results of intervention studies which show improved cognitive performances in trained versus untrained persons argue against inverted causality (16, 33, 38). Sports interventions with aerobic, strength or combined training and Tai Chi have significant positive effects, as long as training sessions of 45 to 60 minutes are performed at at least moderate intensity. In the meta-analyses by Northey et al. (38), contrary to those by Li et al. (33), the training frequency had no influence on the effects. Physically active rats also show improved cognitive performance compared to inactive rats (46). In the case of inverted causality, it would be expected that the relative risk of developing a cognitive deficit would be reduced less in physically active persons in studies with longer observation periods than in studies with shorter observation periods. This is, in fact, the case (Fig. 1 and Fig. 2). However, the trend is not statistically significant. In the end, no definitive proof can be found for either a direct dependency of the risk of dementia on physical activity or for an inverted relationship. It may be that both dependencies exist at the same time.

Parkinson's Disease

The prevalence of Parkinson's disease, according to Savica et al. (56) increases from 41 in 100,000 (0.04%) in persons between 40 and 49 years of age to 1,903 in 100,000 (1.9%) in persons aged at least 80 years. The risk of developing a Parkinson´s syndrome is lower by 34% (95%-CI: 22%-43%) in the persons with the highest level of physical activity compared to the least active, as found in a meta-analysis of six

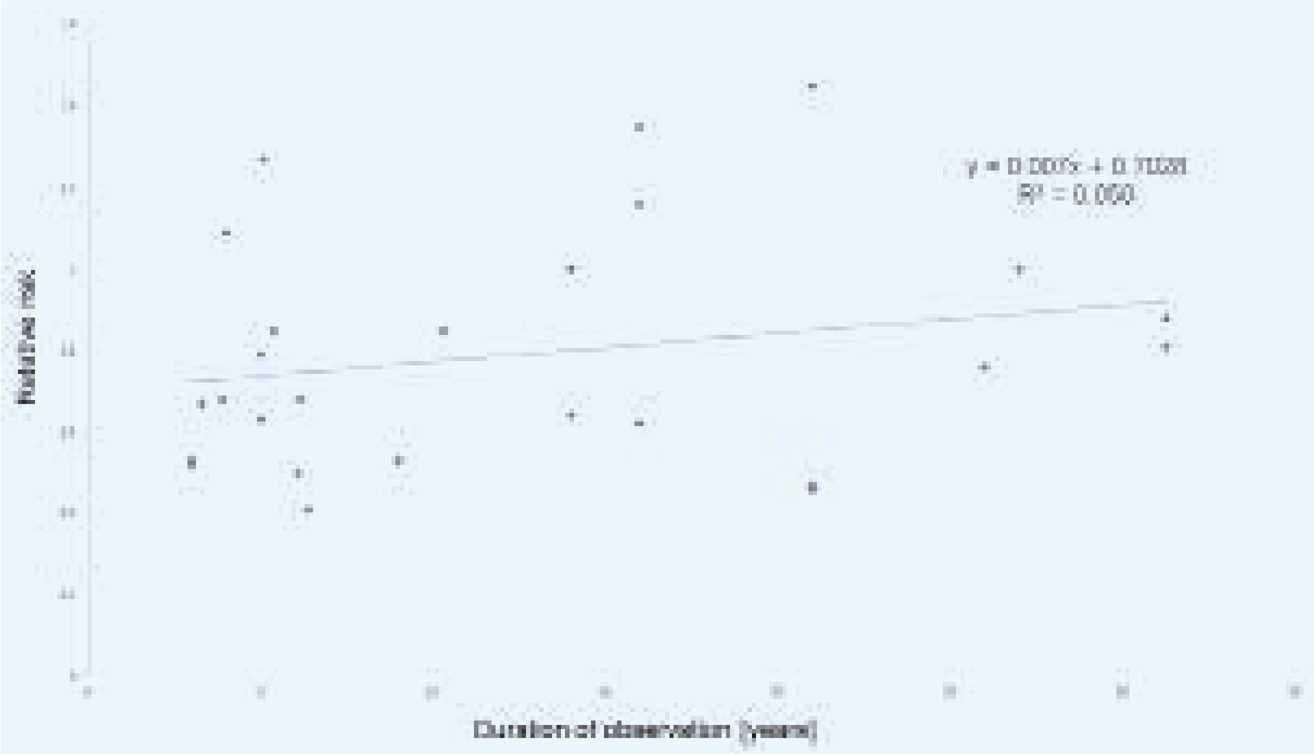

Figure 2

Correlation between the observation period and the risk of later developing an unspecified dementia (Data from Felbecker et al. (13), supplemented by Sabia et al. (53) and Zhou et al. (79))

prospective cohort studies. Sports activity alone was not found to have a significant preventive effect (77). Physically active Parkinson's patients have better cognitive performance capacity than inactive patients (1). Adiposity is a risk factor for later development of a Parkinson´s syndrome, probably also diabetes mellitus type 2 (78). Physical activity might also have a Parkinson-preventive effect in this way. Unlike in Alzheimer-type dementia, high blood pressure appears rather to have something of a protective effect for the later development of a Parkinson´s syndrome (40). Parkinson's disease is also preceded by a preclinical phase. Since Parkinson's disease is primarily characterized by hypokinesis, an inverted causality between physical activity and disease development could play an even greater role than in Alzheimer-type dementia.

Sarcopenia

The total muscle mass decreases per year during life by about 0.37% in women and 0.47% in men starting in young adulthood. After about the age of 75, the percentual loss is even greater (67). Sarcopenia is understood as low muscle mass and muscular strength, the combination of low muscle mass with reduced physical performance capacity or a combination of all three factors in advanced age (50). Sarcopenic adiposity denotes the combination of reduced muscle mass with a high proportion of body fat.

The meta-analyses by Steffl et al. (63) showed that various physical activities by persons older than 40 reduced the risk of later sarcopenia by 54% (95%-CI: 42%-63%, 6 studies, 2,186 participants) in men, 35% (95%-CI: 19%-48%, 6 studies, 2,598 participants) in women, and 55% (95%-CI: 45%-63%, 7 studies, 2,732 participants) in the studies on men and women together. Another meta-analysis of 49 studies with a total of 1,328 participants aged at least 50 showed an increase in muscle mass of 1.1 kg (95%-CI: 0.9-1.2) after a mean of 20.5 weeks of strength training two to three times per week (45). A further meta-analysis of 1,079 elderly subjects showed a strength increase of up to 33% after an average 17.6 weeks of strength training (SE: 2%) depending on the muscle type (67).

Falls

Every year, more than 30% of all people at least 65 years of age and more than 50% of all 80-year-olds living outside nursing homes fall (34, 60). Half of these persons fall several times a year (17). 55 to 70% of the falls result in injury, of which in turn 20% require medical treatment (34). Falls are the most frequent reason for elderly persons to be taken to emergency admission (60).

Various systematic studies show a reduced risk of falling in physically active compared to inactive people. In the meta-analysis by Tricco et al. (66), there was a risk reduction of 49% (95%-CI: 21%-67%, 39 studies, 41,596 participants). Physical training reduces the risk of falling by 21% (95%-CI: 15%-27%, 19,478 participants) in mobile persons at least 65 years of age according to results of the meta-analysis by Sherrington et al. (59). Targeted balance and walking training of at least three hours per week reduces the risk by 39% (95%-CI: 28%-47%). In another meta-analysis, physical training in elderly persons results in a 19% reduction (95% CI: 10%-27%, 4,622 participants) of falls leading to injury (19). Tai Chi training reduces the risk of falling by up to 50% (35).

Sleep Disorders (Insomnia)

In a survey of 8,152 representative adult residents in Germany, about one-third of those questioned reported that a potentially clinically relevant problem falling asleep and sleeping through the night had been present during the preceding four weeks, about one-fifth additionally reported poor quality of sleep. Women were twice as affected by insomnia as men. With advancing age, sleep disorders, except trouble falling asleep in men, increase significantly (57).

As early as 1998, Sherrill et al. (58) published that regular physical training at least once a week, or rapid walking around at least six blocks per day reduces the risk of all kinds of sleep disorders (increased fatigue during the day, trouble falling asleep and nightmares). The prospective cohort study by Tsunoda et al. (68) confirmed a preventive effect of moderate and intensive physical activity on the quality of sleep in persons aged 65 ±- 4.7 years. Moderate physical activity at least once a week reduces the risk of insomnia by 42% (95%-CI: 19%-58%). Moreover, the sleep of physically active persons is more efficient than that of inactive persons (18). Trouble sleeping through the night especially was significantly less frequent in persons who engaged in sports at least five times a week in the study by Inoue et al. (26). The meta-analysis by Kredlow et al. (28) also showed that regular physical activity shortens the time to falling sleep, prolongs the duration of sleep and increases sleep efficiency.

The Restless Legs Syndrome is a frequent cause of insomnia, with a prevalence of 10% to15% in the general population, whereby only every fourth or fifth person requires medication therapy (30). Women who engage at least four times a week in sports have a 16% (95% CI: 5%-26%) lower risk of developing a Restless Legs Syndrome (73). In men who engage in sports five to seven times a week, the risk is reduced by 22% (95%-CI: 9%-33%) (74). The preventive effect was even more pronounced in the prospective cohort study by Tsunoda et al. (68).

Conclusion

Numerous prospective cohort studies substantiate a clearly reduced risk of later suffering stroke, developing Parkinson´s syndrome or dementia for people who are regularly physically active compared to physically inactive persons. Even though both human-biological and animal-experimental study results support the hypothesis of a preventive effect, the argument of inverted causality, namely already preclinically-reduced physical activity, for dementia diseases and Parkinson's Disease cannot be definitively rejected as long as there is no long-term intervention study on healthy subjects with a physically active intervention group and an inactive control group. Such studies are, however, hardly feasible for a variety of reasons (such as the immense expenditure, ethical considerations).

The Sport Medical Societies (72) recommend at least 150 minutes of moderate (3 to 6 MET) or 75 minutes of intensive physical activity (>6 MET) or combinations of the two per week. The meta-analyses presented show that physical activity is also very effective in the primary prevention of neurological diseases. However, with respect to neurological diseases, they have not as yet demonstrated a superiority of sports versus general physical activity. In elderly persons, strength training should additionally be performed to prevent sarcopenia (and osteoporosis). Especially in dementia prevention, regular training sessions of about one hour duration with aerobic or strength training, so-called body-mind techniques (e.g. Tai Chi) or combinations of sports types are recommended at least once per week, since these probably improve the cognitive performance capacity in cognitively-healthy and already afflicted elderly persons (16). Recommendations for sport-practical implementation of primary and, if needed secondary and tertiary prevention as well, by means of sport can be found in Reimers et al. (49).

Conflict of Interest

The author has no conflict of interest.

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