

ACCEPTED: September 2021

PUBLISHED ONLINE: October 2021

Hemmeter U, Ngamsri T, Henkel K. The role of exercise for prevention and treatment of depression and cognitive decline in the elderly. *Dtsch Z Sportmed.* 2021; 72: 300-306.
doi:10.5960/dzsm.2021.500

The Role of Exercise for Prevention and Treatment of Depression and Cognitive Decline in the Elderly

Körperliche Aktivität in der Prävention und Behandlung der Depression und kognitiver Störungen im Alter

Summary

- › **Depression and dementia disorders** are associated with cardiovascular and somatic co-morbidities, which are closely related to physical inactivity.
- › **Physical exercise** can improve these cardiovascular and metabolic co-morbidities. In addition, physical activity and training are effective in the prevention and treatment of affective and cognitive disorders. These effects were also found in the elderly.
- › **Because of limited effectiveness** and tolerance of pharmacological standard treatment options, the relevance of physical exercise as a therapeutic tool should be recognized. In a multifactorial way psychological, neurobiological as general somatic (e.g. cardiovascular and metabolic) aspects are involved in the effectiveness of exercise on brain structure and function.
- › **Hence assessment of exercise habits** and individual recommendations for physical activity should be implemented as a standard procedure in the therapy of affective disorders and dementia, beginning as early as possible but also at higher ages.

KEY WORDS:

Aerobic Exercise, Add-On Therapy, Lifelong Training, Neurobiologic Effects, Somatic Co-Morbidities

Zusammenfassung

- › **Depressionen und Demenzerkrankungen** gehen häufig mit kardiovaskulären und metabolischen Erkrankungen einher und sind -krankheitsbedingt- auch oft mit Bewegungsmangel verbunden.
- › **Bewegung und körperliches Training** haben eine wissenschaftlich nachgewiesene Effektivität in der Prophylaxe und Behandlung kardiovaskulärer und metabolischer, aber auch affektiver Erkrankungen und kognitiver Störungen.
- › **Eine besondere Bedeutung** erhält körperliches Training als Therapieoption aufgrund begrenzter Effektivität und Verträglichkeit pharmakologischer Standardbehandlungen im höheren Alter. Multifaktorielle psychologische, neurobiologische und allgemein somatische (z.B. kardiovaskuläre und metabolische) Effekte von körperlicher Aktivität auf die Struktur und Funktion des Gehirns wurden nachgewiesen.
- › **Die Erhebung körperlicher Aktivität** und individuelle Bewegungsempfehlungen sollten zum Standard ärztlichen Handelns werden, auch und insbesondere bei Älteren. Diese Interventionen sind am effektivsten, wenn sie spätestens im mittleren Alter begonnen werden, sie wirken aber auch noch im höheren Alter.

SCHLÜSSELWÖRTER:

Aerobes Training, Zusatztherapie, lebenslange körperliche Aktivität, neurobiologische Auswirkungen, somatische Komorbiditäten

Introduction

Worldwide 10-20% of the population suffer from a psychiatric disorder with a lifetime prevalence of 18.1-36.1% (28). Although mental disorders decrease in the senium, still a 12 month prevalence of about 20 % is found at the ages of 65 to 79 years (26).

Besides anxiety disorders depression is the most common psychiatric disorder, in particular among the elderly. Likewise also cognitive decline and dementia disorders increase while aging, becoming most important in old age.

Diagnosis and treatment of both disorders (dementia and late life depression) are challenging, because symptomatology can be very similar.

Despite depressed mood and loss of interest somatic symptoms, such as loss of energy, appetite, pain-syndroms, sleep disturbance and, in particu-

lar, disturbed cognitive performance and memory decline may be prominent symptoms. In addition, both disorders share cardiovascular morbidity as risk factors (66).

Recurrent depressive episodes increase the risk for the development of dementia in later life (35). Therefore, also in patients with already known recurrent depressive disorder, dementia can additionally develop. Consequently, the diagnostic process should include neurobiologic and functional dementia testing in any case for reasons of exclusion.

Treatment of both disorders is mainly based on psychopharmacologic (antidepressant and anti-dementive drugs), psychotherapeutic and further non-pharmacologic interventions, aiming on an improvement of cognitive and social interactions (38)



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and modification of life-style. Pharmacotherapy of depression in the elderly is less effective and associated with more side effects when compared to younger patients (2) and has limited efficacy in cognitive decline. Therefore, prevention and non-pharmacologic strategies are eligible.

Sedentary behaviour is associated with depression and dementia (63, 65). Physical training, as one of the possible non-pharmacologic interventions, has been proven to be effective preventing the development and even as (add on-) therapy of both diseases in the elderly (22).

This selective review will focus on the preventive and therapeutic properties of physical activity (physical exercise and training) in depression, particularly late life depression and dementia disorder.

Somatic Co-Morbidities in Late Life Depression and Dementia, Effect of Physical Activity

In the elderly co-morbidities as cardiovascular diseases, hypertension, diabetes and others are frequent. Furthermore, in depression an increased incidence of these diseases has been described, which is thus associated with an increased mortality (14, 26).

Behavioural and lifestyle factors, which are present in patients with major depression, can increase the chance for developing a chronic heart disease (27). Among other factors, such as smoking and obesity, they include physical inactivity (51).

Depression may also increase the risk of dementia because of its association with a higher number of behavioural risk factors, for instance the consumption of alcohol and fatty meals, sedentary lifestyle (obesity) and vascular risk factors (hypertension, hyperlipidemia and diabetes) (59).

Furthermore, diabetes for itself is a risk factor for the development of vascular dementia and may accelerate cognitive decline in Alzheimer's disease (AD) (37). The risk of AD and vascular dementia ranged from 40% to two-fold higher in patients with diabetes compared to controls without diabetes (8, 30, 37).

Multiple aspects including inflammatory factors, hyperglycemia-induced tissue damage, vascular complications, hypoglycemic episodes, insulin resistance, which are related to diabetes, might further increase the risk of dementia (60).

For maintaining cardiorespiratory and muscular fitness and flexibility the recommendation for exercise in healthy individuals is to engage in at least 150 minutes of moderate aerobic exercise or 75 minutes of vigorous intensity per week (18).

Therefore, physical training may also reduce the development of cardiovascular disease and diabetes in dementia and depression.

Nevertheless, exercise as an efficient treatment option is neglected or underused by therapists and patients in praxis especially with older age (9).

Physical Activity, Physical Exercise and Physical Training

This manuscript provides a review of studies concerning the relationship between physical activity, physical exercise and physical training on late life depression and/or dementia.

In the literature, the three terms have been applied not systematically and seem to be sometimes interchangeable. The American College of Sports Medicine (ACSM) defines physical training as intended structured and repetitive physical activity applied for the maintenance or improvement of one or more areas of physical fitness (3). In the EPA guidance of physical activity as treatment for severe mental illness physical

Table 1

Effects of physical training on depression (modified from (25)):

DEPRESSIVE SYMPTOMS
General reduction of depressive core symptoms
Improvement of executive cognition and attention
Improvement of sleep and appetite
Reduction of restlessness
LONG TERM SOMATIC MORBIDITY
Improvement of somatic parameters
Reduction of somatic (e.g. cardiovascular, neoplastic) morbidity and mortality
RECOMMENDATIONS
60-85% of maximal heartrate (in cardiologic healthy subjects, otherwise with cardiologic supervision like heart sports groups)
45+ minutes per unit
3-5 times a week, at least 10 weeks (continuous training recommended for recurrence prophylaxis)
Mild to moderate intensity
alternatively or combined, daily stretching exercise up to 30 Min. (33)
Group interventions or professional supervision

exercise is defined in the same manner as planned, structured and repetitive with a final or intermediate objective, the improvement of physical fitness (10, 53). In contrast, physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (10, 53). In this manuscript we follow these definitions. According to the ACSM and the EPA definition physical training or physical exercise reflect some kind of training activity, which is planned and systematically and repetitively applied to increase the training status of the patients. Therefore, physical exercise and physical training in our understanding can be used as synonyms and can be regarded as a specific aspect of physical activity. A different aspect between physical exercise and training according to the ACSM-definition might be that exercise can be defined as one activity within a physical training program. Therefore, physical training may be regard as a spectrum of different single exercises.

Exercise and Depression

Prevention

The beneficial effect of physical activity on depression is already well described (46, 54). Results from a meta-analysis including 49 studies with in total n=266.939 subjects show a clear protective effect of physical activity on the development of a depressive disorder (46).

In contrast, lacking physical activity and increased sedentary behaviour was associated with an increased risk for developing depression (65). The HUNT cohort study assessed prospectively the effect of physical exercise on the development of depression. The authors found that regular exercise during leisure time was associated with reduced incidence of future depression but not anxiety. Most of the protective effect was observed with a dosage of 1 hour of exercise/week with no additional benefit beyond this weekly hour of exercise. According to these results the authors suggest that an intensification of everyday activities such as walking or cycling may be sufficient to get this protective effect (20).

This association seems to follow a general rule, as comparable associations have been observed in different regions of the world (North-America, Asia) as well as in different countries of Europe (Germany, Austria, the UK, Netherlands, Denmark, Spain und Iceland). In addition, this relationship seems to work across the life span as well (from adulthood, to old age) without gender differences (20, 46).

Therapeutic Effects of Physical Training:

Gaining a therapeutic effect in depressed patients a more intense dosage of physical training -in contrast to the preventive capacity- is necessary. This efficiency is documented in several meta-analyses showing that endurance training of about three times a week for 40 to 60 minutes reaches comparable effect sizes to a pharmaco- or psychotherapy in mild to moderate depression (23, 31, 39). Most of the studies evaluated long term effects (over several months), but also short term effects (up to 4 weeks) showing a moderate to large effect on depression have been reported (39). Aerobic endurance training was applied in the majority of studies, which also worked in severely depressed patients, when applied several times a week as add on therapy to an antidepressant medication (24, 48), but also other forms of physical training have shown beneficial effects (walking, jogging, stretching a.o.) (33).

Physical Training in Late Life Depression:

These observations have also been reported in elderly inpatients with depression (Bridle et al. 2012). Physical exercise has proven to be efficient, since aerobic endurance training several times a week as add on therapy showed positive effects in this age group as well (6). A meta-analysis in depressed patients with the age of over 60 years has also revealed strong and significant effects of physical training (47).

But also physical training affecting flexibility, tonus and balance training performed over six months led to a reduction of depression in the elderly (1). Another study showed that even walking with moderate intensity (40 Min. three times a week) was related to a significant reduction in depression scores (7).

Based on these results the Swiss recommendations for the treatment of late life depression underline the positive effects of physical training as part of the treatment options. The recommendation for the application of physical training is based on the ACSM-Guidelines, (American College of Sports Medicine), which –according to the recommendations of the WHO recommend independent of age for healthy subjects 150 min. of moderate aerobic exercise as well as resistance and balance training (13, 18). This dosage and intensity has been applied in most of the reported studies.

For elderly depressed patients currently no clearly evidence based recommendations are available. The English NICE-guideline „Depression“ (2009) recommends for light to moderate depression in adults, systematically applied and supervised training-programs three times a week for 45 to 60 minutes over 10 bis 14 weeks (41). No specific recommendations have been described for late life depression. The WHO's Global recommendations on physical activity for Health (61) recommend for elderly subjects above 65 in contrast to people of younger age physical training units in order to enhance balance and prevent falls on three or more days per week and muscle-strengthening activities involving major muscle groups, on two or more days per week. Probably elderly patients do not achieve the dosage (intensity recommended for younger depressed patients. However a higher relief from depression has been reported for elderly depressed by physical exercise (49).

The Swiss guidelines for late life depression follow these suggestions, but additionally emphasize that these units should be performed under the supervision of a professional therapist/coach, requiring that there are no contraindications (co-morbidities which do not allow physical activity or will be worsened by it) are present (21).

The effects and the recommendations of physical training on depression are shown in the table derived from Imboden et al. 2016 (25) added with the recommendation of stretching exercise, which has been shown to be effective in particular in elderly depressed (33). It has to be kept in mind, that for elderly the intensity recommended here cannot always be achieved and, therefore, it has to be adapted individually and therefore, there is the recommendation for the professional supervision..

Physical Activity and Cognition (Mild Cognitive Impairment (MCI), Dementia)

A number of studies show a close and dose dependant association between neuroprotective effects of physical activity and cognitive performance in the elderly (29). Physical inactivity at higher age is associated with the relative risk of developing dementia (34).

Prevention

Studies concerning this topic have been predominantly examined patients with AD. Data from a meta-analysis of 24 studies show that the risk to develop AD is substantially reduced, if subjects performed physical activities, especially in leisure time. In contrast, physical activity during worktime was much less effective (52). This may be due to better achieve the required duration and intensity in planned training sessions or other adverse effects with exercise during worktime. Based on these findings an inverse proportional relationship between physical activity during leisure time and at work has been proposed. Subjects with inactivity (sedentary behaviour) at work perform more physical activity during leisure time. This additional activity may exert the beneficial risk-reducing effect (45).

A further important aspect to mention is that physical activity and sports during leisure time are closely related to social and cognitive stimulation, which both are protective factors for themselves (56).

In a population-based study neuroprotective effects of physical activity have been reported, if exercise is continuously performed during leisure time over a long period beginning at the middle age with increasing intensity (55).

Therapeutic Aspect

Several reviews underline the therapeutic property of physical training to improve reduced cognitive performance in MCI and -in part-also in dementia.

In particular, aerobic exercise shows moderate effects on cognition, such as attentional functions, psychomotor speed and executive functions in MCI (42, 50, 67). Predominantly resistance training was effective in improving cognitive performance (11).

In particular, an improvement of executive and memory functions in MCI and beginning dementia and an improvement of psychological and emotional stability in dementia has been described (42, 64).

The physical training applied in these studies mainly followed the recommendations of the WHO, which suggests aerobic training of at least 150 min./week with moderate or 75 min. with strong intensity for staying healthy in old age (42, 62).

Another meta-analysis in patients with different chronic disorders of the brain (e.g. AD, Huntington's disease (HD), Parkinson's disease (PD)) found positive associations between physical training and different cognitive domains, which include significantly better attention and working memory, if patients were physically active (12). In addition, also better executive functions and memory performance were found to be related to physical activity.

This positive association was mainly observed with patients consequently performing clearly structured aerobic training units.

The ACES-study, which included 220 patients showed that a combination of physical training and cognitive stimulation (virtual bike-tour) leads to better results concerning executive and memory functions. In addition, a parallel stimulation of Brain derived neurotrophic factor (BDNF) and an increase of hippocampal volume after physical training has also been observed in this study (4).

In patients already suffering from clinically manifest dementia results on the effects of physical training on cognitive performance, especially memory performance, are not unanimous.

However, there are some findings pointing to an improvement of daily function and behavioural and psychological symptoms (BPSD) in dementia after physical training (5, 15, 17, 40). These beneficial effects exert also positive effects on the burden of caregivers (17).

Neurobiological Effects Underlying the Beneficial Effect of Physical Activity on Depression and Dementia

The neurobiological effects of exercise on the central nervous system are diverse and include modifications in synaptic plasticity, neurotrophins, glial cells, blood volume, growth factors, inflammation, DNA-polymorphisms and metabolic parameters (57). Only some of these aspects were explicitly studied in patients with depression and dementia. Physical exercise resp. physical training can reduce neuronal cell loss; thus, brain volume in AD-sensitive regions may be preserved for longer (16).

An increase of cerebral perfusion and stimulation of neurogenesis, synaptogenesis and angiogenesis by exercise are discussed as possible mechanism of the effects of exercise on cognition and dementia. These effects reduce loss of neurons and, thus may prevent the reduction of brain volume, especially in AD sensitive regions, for instance the hippocampus (4, 16).

Moreover, physical training can modify neuropathological processes typical for AD such as beta-amyloid aggregation and tau-phosphorylation (19).

BDNF-secretion, which is stimulated by physical training seems to play a core role in these observed effects (16). Animal studies show that exercise-stimulated BDNF secretion in parallel improves spatial memory in rats, while Inhibition of BDNF reverses this effect (58). Also human studies were able to show, that BDNF secretion is enhanced in the elderly by physical training, especially performing resistance exercises (36).

In major depression BDNF secretion is also reduced and can be stimulated by antidepressant medication and physical exercise (43). It is supposed that BDNF enhancement in depression also stimulates brain plasticity and prevents or reverses reduction of hippocampal volume.

While for BDNF independent enhancement a moderate intensity of physical activities appears to be essential, positive effects on neuroinflammation could be achieved also in mild to moderate exercise levels (44), e.g. by walking.

In conclusion, physical training has various beneficial effects on the central nervous system as shown in animal studies and studies with healthy subjects. Findings of these effects in patients with dementia and depression are still limited to date.

Nevertheless, the still available evidence concerning these beneficial neurobiological effects should encourage for the application of physical training as add-on therapy in the patients with depression and cognitive decline, as well as for the recommendation for prophylactic purpose.

Discussion

Depression and dementia have an increased risk for cardiovascular and metabolic disorders. In addition, both disorders are associated with physical inactivity, which further increases the risk for the development of cardiovascular and metabolic co-morbidities. Physical training can reduce the risk for the development of these comorbidities.

Moreover, several studies show that physical activity and training have also specific disease related effects concerning reduction of depressive symptoms, improvement of cognitive performance and behavioural and psychological symptoms of dementia. In addition, preventive effects of physical activity on the development of depression and dementia have been observed.

Therefore, a consequent implementation of physical training in multimodal therapy- and prevention programs of both disorders is recommended.

Concerning the prevention and treatment of comorbidities, which may contribute to the development and maintenance of depression and dementia, the WHO Guidelines for elderly patients should be applied, if possible. With respect to the direct effects of physical training on depression and dementia, aerobic exercise and to a minor degree resistance training have been examined the most, but also other exercises (stretching, walking etc.) have been proven to be effective. In most of the studies the recommendations of the ACSM have been used, although not all subjects were able to reach this level.

Therefore, at the current knowledge on this topic, we recommend to apply physical training either endurance training or a multicomponent training (more frequently applied in MCI and dementia) with a moderate level, added by balance and muscle strengthening activities to prevent falls in the elderly. If possible, the level recommended by the ACSM/WHO should be achieved, but supervised and personally adapted by a professional team (physician, physio/sports therapist, psychologist).

This is especially important considering the motivational aspects in implementation and the physical and mental restrictions of the older population requiring a multi-professional cooperation. ■

Conflict of Interest

The authors have no conflict of interest.

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