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Review Article

Effect of Physical Exercise on Cognitive Performance in Older Adults with Mild Cognitive Impairment or Dementia: A Systematic Review

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Key Words
Cognition · Dementia · Exercise · Mild cognitive impairment · Systematic review

Abstract
Numerous studies have shown that physical exercise has positive effects on cognition in healthy adults. Less is known about the effectiveness of exercise interventions in older individuals already suffering from mild cognitive impairment (MCI) or dementia. The aim of this study was to systematically review the evidence from randomized controlled trials (RCTs) of the effects of physical exercise on cognition in older subjects with MCI or dementia. PubMed, Cochrane and DARE databases were systematically searched for RCTs using terms related to cognition and physical exercise. Altogether, 22 trials were found. The studies on older subjects with MCI reported some positive effects of physical exercise on cognition, mainly on global cognition, executive function, attention and delayed recall. However, most studies performed on older subjects with dementia showed no effect of exercise on cognition. The studies had methodological problems in defining dementia/MCI diagnosis, blinding, inadequate sample sizes and not reporting dropouts, compliance or complications. More studies of good quality on older adults with dementia are needed.

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Introduction

A number of longitudinal cohort studies have suggested that physical activity in middle age protects against cognitive decline and dementia in old age [1, 2]. A recent systematic review of 15 cohort studies (n = 33,816) showed that physical activity may protect against cognitive impairment in initially cognitively healthy individuals [2]. Another systematic review (16 studies with 163,797 cognitively healthy participants) of prospective epidemiological studies yielded similar findings with respect to dementia [1].

The first intervention study to examine the effect of physical exercise on cognition was performed in 1990 [3]. It suggested that aerobic walking has a positive effect on executive function in cognitively healthy older individuals. Reviews including randomized controlled trials (RCTs) examining the effect of physical exercise on healthy older subject's cognition support this proposition [4–6]. According to the Cochrane review with 11 RCTs of cognitively healthy individuals, aerobic exercise improves cognitive performance in tests measuring attention, delayed recall and reaction time [6]. Two other reviews have indicated that the most pronounced effect of exercise is on executive function [4, 5].

Although evidence of the effect of exercise on cognition of cognitively healthy older individuals is fairly consistent, less is known about the effectiveness of exercise interventions in subjects who suffer from mild cognitive impairment (MCI) or dementia. The need for interventions to preserve cognitive function in subjects with dementia is great since the current possibilities of prevention or pharmacological treatment of dementia are inadequate [7]. The aim of this study was to systematically review the evidence from RCTs of the effects of physical exercise on cognition in individuals with MCI or dementia.

Methods

Search Strategy

PubMed, Cochrane, DARE and Ovid Nursing databases were systematically searched for RCTs using terms related to cognition and physical exercise (cogniti* OR demen* OR Alzheimer* OR memory decline OR memory disorder OR mild cognitive impairment) AND (physical activity OR physical exercise OR exercise OR fitness OR training OR aerobic OR strength OR functional training OR walk*). The search was performed in January 2013 and repeated in May 2014. Additional trials were found from the reference lists of articles and the authors' own literature databases. Previous systematic reviews on this topic and references from the review papers were also examined [1, 2, 4–6, 8–13].

Inclusion Criteria

The trials selected in this review had to meet the following inclusion criteria: RCTs, participants were subjects with MCI or dementia, physical exercise was the main intervention and cognitive function, assessed using neuropsychological or cognitive tests, was the outcome measure. Articles not written in English were excluded.

Methodological Quality

Three reviewers (K.H.P., N.S. and H.Ö.) independently evaluated the included studies according to 13 criteria of methodological quality, and disagreements were discussed between the reviewers until a consensus was reached. We used a modified rating system for evaluation. In this rating system, we applied the criteria for randomized intervention trials used by Cochrane and collaborators [14, 15] as well as the PEDro scale, which is a tool for measuring the methodological quality of clinical trials related to physiotherapy interventions [16]. In addition, we included the criteria developed by the Evidence-Based Medicine Working Group [17, 18]. We added one more criterion to these because compliance is often low in exercise studies, and this may dilute the effects of intervention. The criteria are described in table 1. Each criterion was considered to be worth 1 point. The quality of the research was considered high when a study scored 11–13 points. Scores of 7–10 indicated moderate quality and <7 poor quality.

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Table 1. Evaluation of the quality criteria fulfillment in RCTs examining the effects of exercise interventions on cognition

Study	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
Study population with mild cognitive impairment (MCI)													
Suzuki et al., 2013 [41]	+	+	+	+	+	+	+	+	+	+	+	+	+
Nagamatsu et al., 2012, 2013 [42, 43]	+/–	+	+	+	+	+	+	+	+	+	+	+/–	+
Varela et al., 2012 [35]	–	+	+	–	+	+	+	+	–	+	–	+	+
Lam et al., 2011 [32]	+	+	+	+	-	+	–	–	–	+	+	+	+
Baker et al., 2010 [30]	+	+	+	–	–	+	+	+	–	?	–	+	+
van Uffelen et al., 2008, 2009 [26, 27]	+	+	+	+	+	+	+	+	+	+	+	+	+
Lautenschlager et al., 2008 [25]	+	+	+	+	+	+	+	+	+	+	+	+	+
Scherder et al., 2005 [22]	+	+	+	–	–	+	+	–	–	–	–	+	+
Study population with dementia													
Vreugdenhil et al., 2012 [36]	+	+	+	–	–	+	+	–	–	–	–	+	+
Venturelli et al., 2011 [33]	+	+	+/–	–	–	+	+/–	+	–	+/–	+	+	+
Yágüez et al., 2011 [34]	+	+	+	–	–	+	+	+	–	–	–	+	–
Kemoun et al., 2010 [31]	+	+	–	–	–	+	+	+	–	–	–	+	–
Eggermont et al., 2009 [29]	–	+	+	+	+/–	+	+	–	–	+/–	+	+	+
Steinberg et al., 2009 [28]	+	+	+	–	–	+	+	+	+	–	+	+	+
Burgener et al., 2008 [37]	+/–	–	+	–	–	+	+	+/–	–	–	–	+	–
Christofoletti et al., 2008 [38]	+/–	+	–	–	+	+	+	–	–	–	–	+	–
Kwak et al., 2008 [24]	+/–	+	–	–	–	–	+	?	–	?	?	–	–
Miu et al., 2008 [39]	+	+	+/–	+	–	+	+	–	–	+/–	–	+	+
Stevens and Killeen, 2006 [23]	?	?	–	+	–	+	+	–	–	–	–	–	?
van de Winckel et al., 2004 [21]	+	+	+/–	–	–	+	+	–	–	+/–	–	+	–
Cott et al., 2002 [20]	–	+	+	–	+	+	+	–	–	+/–	–	–	+
Friedman and Tappen, 1991 [19]	+	+	+	–	+/–	+	+	–	–	?	–	+	–

(1) The diagnosis of dementia is based on the DSM-IV or NINCDS-ADRDA criteria or is made by a geriatrician or a neurologist. (2) Inclusion and exclusion criteria are satisfactorily described. (3) Groups are comparable at baseline. (4) The study has sufficient statistical power to detect an effect (n ≥ 25/group). (5) The randomization method is adequately described and the method is valid (a computerized randomization program or a separate randomization center). (6) The measurements and outcome measures are valid and well defined. (7) The intervention is adequately described. (8) The compliance of participants is described. (9) Complications are reported. (10) The dropouts are described and the analyses take them into account. (11) Intention-to-treat analysis is applied. (12) A comparison is made in relation to outcome variables between the groups. (13) The group assignment is blinded when assessing the outcomes.

+ = Criterion fulfilled; – = criterion not fulfilled; +/– = criterion partly fulfilled; ? = unclear.

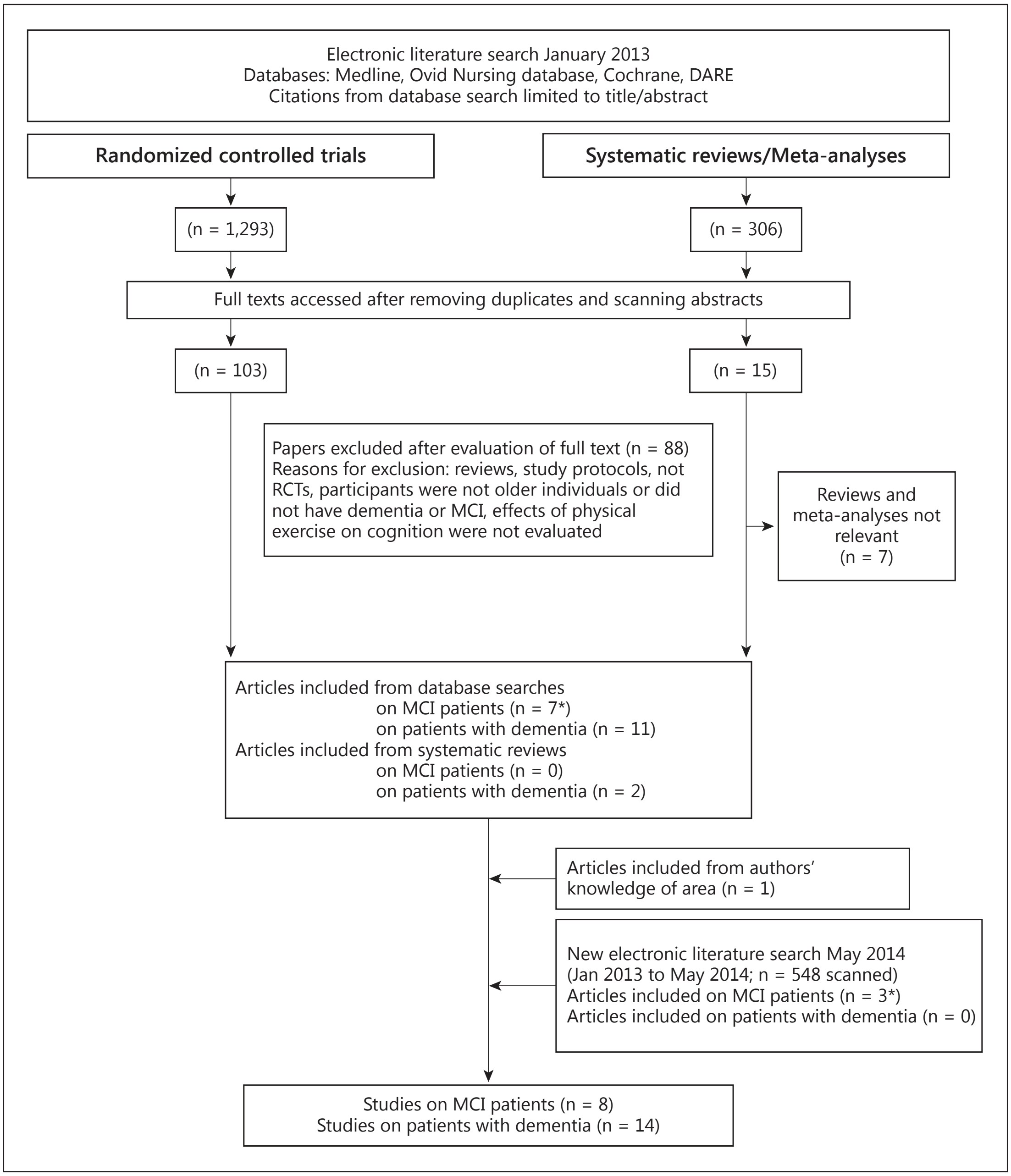

Fig. 1. Results of the research strategy using the terms cogniti* or demen* or Alzheimer* or mild cognitive impairment and physical activity or physical exercise or exercise or aerobic or strength or walk*. *One study was reported in two publications.

Results

Identification and Selection of Studies

Altogether, we found 22 RCTs that examined the effects of physical exercise on cognition in subjects with MCI or dementia. Of these, 17 [19–36] were found directly from database searches and 2 additional articles [37, 38] were mentioned in a systematic review [11]. One study [39] was known to the authors from a previous review [40]. The original database search was repeated in May 2014, and 2 more studies were found [41–43] (fig. 1).

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Table 2. Summary of the data of included studies

a Participants with MCI

Study	Participants	Interventions	Outcomes	Methodological quality
Suzuki et al., 2013 [41] (n = 100)	women 45%, mean age 75.4 years, mean MMSE 27 inclusion criteria: community dwelling, age >65 years exclusion criteria: other psychiatric, neurological disease, severe cardiac disease, impairment in ADL, use of donepezil	exercise group, n = 50 (25 amnestic MCI, 25 other MCI): aerobic exercise, strength training, balance, dual tasking 2 × 90 min/week, 24 weeks Control group, n = 50 (25 amnestic MCI, 25 other MCI): education about health promotion group intervention	MMSE improved in the exercise group in participants with amnestic MCI; WMS-LM I improved in the exercise group in both types of MCI	good 13/13
Nagamatsu et al., 2012/2013 [42, 43] (n = 86)	women 100%, mean age 75 years, mean MMSE 27 inclusion criteria: community dwelling women with MMSE >23, MoCA <26/30, subjective memory problems IADL Lawton >5/8 exclusion criteria: psychiatric or neurodegenerative disease, estrogen replacement therapy, medical condition contraindicated participation in exercise	RT, n = 28 2 × 60 min/week, 26 weeks AT (walking), n = 30 2 × 60 min/week, 26 weeks BT, n = 28 2 × 60 min/week, 26 weeks group training	RT improved in the Stroop Test and test for associative memory compared to BT AT improved verbal memory compared to BT AT and RT improved reaction times in spatial memory tasks compared to BT	good 11/13
Varela et al., 2012 [35] (n = 48)	women 56%, mean age 78.3 years, mean MMSE 20 inclusion criteria: confirmed dg of MCI, age >65 years, able to walk for 30 m without shortness of breath, independent of the assistance of another person for walking, residing in a care home	group A, n = 17: aerobic exercise (cycling) 40% of the heart rate reserve, 3 × 30 min/week, 12 weeks group B, n = 16: aerobic exercise (cycling) 60% of the heart rate reserve, 3 × 30 min/week, 12 weeks group C, n = 15: recreational activity, 3 × 30 min/week, 12 weeks group intervention	changes between groups A, B and C in MMSE were not statistically significant	moderate 9/13

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Table 2 (continued)

Study	Participants	Interventions	Outcomes	Methodological quality
Lam et al., 2011 [32] (n = 389)	women 54%, mean age 72 years, mean MMSE 24 inclusion criteria: age >65 years, CDR 0.5 or dg of amnestic MCI, CDR <1, physically fit exclusion criteria: dg of dementia, dementia medication, impaired communication, regular Tai Chi practice	Tai Chi group, n = 171: Tai Chi exercise, ≥3 × 30 min/week, 12 weeks control group, n = 218: stretching ≥3 × 30 min/week, 12 weeks group intervention	MMSE, ADAS-Cog, delayed recall, trial A, verbal fluency, subjective cognitive complaints were improved in both groups improvements in attention and the CDR-SOB scores in the exercise group	moderate 10/13
Baker et al., 2010 [30] (n = 33)	women 52%, mean age 70 years, mean MMSE 28 (women), 25 (men) inclusion criteria: MCI, sedentary exclusion criteria: musculoskeletal impairment, unstable cardiac disease, significant cerebrovascular disease	exercise group, n = 23: high-intensity exercise (treadmill, stationary bicycle, elliptical trainer), 4 × 45–60 min/week, 24 weeks control, n = 10: stretching 4 × 45–60 min/week, 24 weeks group intervention	Symbol digit, verbal fluency, Stroop and task switching improved for women in the exercise group trails B improved in men and women in the exercise group delayed recall: no difference	moderate 8/13
van Uffelen et al., 2008, 2009 [26, 27] (n = 152)	women 44%, mean age 75 years, mean MMSE 29 inclusion criteria: community dwelling, age 70–80 years, MMSE ≥24, able to perform moderate physical activity, no other psychiatric or neurologic condition, no alcohol abuse, not using vitamin B supplements	group 1, n = 71: aerobic walking, 2 × 60 min/week and vitamin B supplementation, 52 weeks group 2, n = 75: placebo activity, 2 × 60 min/week and vitamin B supplementation, 52 weeks group 3, n = 78: walking 2 × 60 min/week and placebo supplementation, 52 weeks group 4, n = 74: placebo activity, 2 × 60 min/week and placebo supplementation, 52 weeks group intervention	no improvement in MMSE or verbal fluency Women with good attendance in aerobic walking improved in attention men with good attendance in aerobic walking improved in delayed recall	good 13/13

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Table 2 (continued)

Study	Participants	Interventions	Outcomes	Methodological quality
Lautenschlager et al., 2008 [25] (n = 170)	women 43%, mean age 68 years inclusion criteria: age >50 years, subjective cognitive complaints exclusion criteria: e.g. MMSE <24, GDS ≥6, alcohol >4 units/day, chronic mental illness, unstable general health	physical activity program, n = 85 walking, strength training 3 × 50 min/week, 24 weeks usual care control, n = 85: participants received educational material individual intervention	intervention group improved in ADAS-Cog scores, improvement in delayed recall and CDR-SUB scores was lower no improvement in verbal fluency	good 13/13
Scherder et al., 2005 [22] (n = 43)	women 88%, mean age 86 years, mean MMSE 9/12 inclusion criteria: resident in a home for the elderly, MMSE >7/12 exclusion criteria: dementia, history of alcoholism, cerebral trauma, hydrocephalus, neoplasm or epilepsy	walking group, n = 15: walking 3 × 30 min/week, 6 weeks hand and face exercises, n = 13: bending and stretching the fingers, producing different facial expressions 3 × 30 min/week, 6 weeks control group, n = 15, social visits or normal social activities individual intervention	category naming, trails A and B were better in the walking group and the hand/face group	moderate 7/13

b Participants with dementia

Study	Participants	Interventions	Outcomes	Methodological quality
Vreugdenhil et al., 2012 [36] (n = 40)	women 60%, mean age 74.1 years, MMSE 10–28 (mean 22) inclusion criteria: dementia, community dwelling, living with a carer exclusion criteria: e.g., physical disability, already exercising ≥1 ×/week	exercise group, n = 20: daily home-based exercises and walking under the supervision of their carer, 16 weeks control group, n = 20: usual treatment individual intervention	MMSE: exercise group increased by 2.6 points ADAS-Cog: exercise group decreased by 7.1 points	moderate 7/13

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Table 2 (continued)

Study	Participants	Interventions	Outcomes	Methodological quality
Venturelli et al., 2011 [33] (n = 21)	mean age 84 years, mean MMSE 15 (walking group) and 12 (control group) inclusion criteria: age >65 years, dependent of assistance in ADL, MMSE 5–15, ambulatory SpO_2 >85% during walking, nursing home resident	walking group, n = 12: 4 × 30 min/week, 24 weeks control group, n = 12: usual treatment individual intervention	walking group: no difference in MMSE control group: slight decrease in the MMSE scores	moderate 7/13
Yágüez et al., 2011 [34] (n = 27)	women 59%, mean age 73.1 years, mean MMSE 22.1–26.3 inclusion criteria: AD dg, MMSE between 12–29 exclusion criteria: FTD, LBD	exercise group, n = 15: brain gym® training 1 × 2 h/week, 6 weeks control group, n = 12: psychological support	exercise group improved in visual memory, sustained attention and working memory measured with CANTAB	moderate 7/13
Kemoun et al., 2010 [31] (n = 38)	women 74%, mean age 81.8 years, mean MMSE 12 inclusion criteria: MMSE <23, ability to walk 10 m, nursing home resident	intervention group, n = 20: walking, ergocycling, dancing 3 × 60/week, 15 weeks control group, n = 18: no physical activities group intervention	ERFT score increased in the intervention group	poor 6/13
Steinberg et al., 2009 [28] (n = 27)	women 70%, mean age 75 years exercise group: mean MMSE 20, control group: mean MMSE 15 inclusion criteria: probable AD, MMSE ≥10, community residing, stable general health, ambulatory, caregiver	intervention group, n = 14: daily exercise program (aerobic fitness, strength training, balance and flexibility training), 12 weeks control group, n = 13: home safety assessments individual intervention	MMSE, BNT, HVLT no differences between groups	moderate 10/13

Table 2 (continued)

Study	Participants	Interventions	Outcomes	Methodological quality
Eggermont et al., 2009 [29] (n = 97)	women 81%, mean age 85.4 years, mean MMSE 17.7 nursing home residents inclusion criteria: age >70 years, dg of dementia, ambulatory exclusion criteria: e.g., MMSE <10 or >24, personality disturbances, various diseases	exercise group, n = 51: walking 5 × 30 min/week, 6 weeks control group, n = 46: social visits in the same frequency and during the same period individual intervention	memory domain (face recognition, picture recognition, eight words test): no difference executive functions domain (digit span, category and letter fluency): no difference	moderate 8/13
Burgener et al., 2008 [37] (n = 43)	women 47%, mean age 77 years CDR mean 1.15/1.22 inclusion criteria: confirmed dg of dementia (AD, LBD, VD, FTD, mixed), CDR <2	treatment group, n = 24: Tai Chi exercises 3 × 60 min/week + CBT 90 min bi-weekly + support group 90 min bi-weekly, 40 weeks control group, n = 19: usual treatment group intervention	intervention group: MMSE score increased by 0.4 points at 20 weeks, at 40 weeks scores remained stable control group: MMSE decreased by 0.5 points at 20 weeks	poor 4/13
Christofoletti et al., 2008 [38] (n = 54)	women 69%, mean age 74.3 years, mean MMSE 13–19 inclusion criteria: primary dg of dementia, no other neurological or neuropsychiatric dg, medically fit to participate, no antidepressant with anticholinergic or sedative actions, nursing home resident	group 1, n = 17: physiotherapy, occupational therapy and physical education 5 × 2 h/week, 24 weeks group 2, n = 17: physiotherapy 3 × 60 min/week, 24 weeks group 3, n = 20: no motor intervention individual intervention	group 1 improved in verbal fluency and Clock Drawing Test compared to group 3 group 2 did not show changes compared to control group	poor 5/13
Kwak et al., 2008 [24] (n = 30)	women 100%, mean age 80 years, mean MMSE 14 inclusion criteria: ≥60 years, caregiver for relative with dementia, stable general health, stable medication, no regular physical activity in the previous 6 months	exercise group, n = 15: restorator, strength training 2 or 3 × 30–60 min/week, 52 weeks control group, n = 15 individual intervention	exercise group: MMSE score increased 20 and 30% at 24 and 52 weeks, respectively control group: no change	poor 2/13

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Table 2 (continued)

Study	Participants	Interventions	Outcomes	Methodological quality
Miu et al., 2008 [39] (n = 85)	women 54%, mean age 76 years, mean MMSE 20 mean ADAS-Cog 24 AD 61%, VaD 20%, mixed dementia 17%, PD 2% inclusion criteria: mild-to-moderate dementia, age >60 years, community dwelling, ambulatory, caregiver exclusion criteria: MMSE <10	exercise group, n = 36: treadmill, bicycle, arm ergometry, flexibility training 2 × 60 min/week, 12 weeks control group, n = 49: conventional medical treatment group intervention follow-up: 52 weeks	MMSE: no differences between groups ADAD-Cog: no differences between groups	moderate 9/13
Stevens and Killeen, 2006 [23] (n = 120)	women 75%, mean age 80.5 years, MMSE 10–22 inclusion criteria: mild-to-moderate dementia, able to respond to verbal requests, physically capable of regular exercise, nursing home resident	group 1, n = 24: strength-training 3 × 30 min/week, 12 weeks group 2, n = 21: social visits/interactive group discussion 3 × 30 min/week, 12 weeks group 3, n = 30: control, no intervention group intervention, follow-up: 12 weeks	average score in Clock Drawing Test increased in the exercise group	poor 3/13
van de Winckel et al., 2004 [21] (n = 25)	women 100%, mean age 81 years, mean MMSE 11 inclusion criteria: AD or multiple infarct dementia, MMSE <24, able to hear music, able to respond to commands, to mimic movements exclusion criteria: apathy, unable to sit	exercise group, n = 15: music-based dance therapy 30 min daily, 12 weeks control group, n = 10: daily one-to-one conversations, 3 months group intervention follow-up: 12 weeks	mean MMSE scores and the subset ‘fluency’ (ADS6) improved in the exercise group picture recognition, orientation, draw alternating sequences, copying figures, free recall: no differences	poor 5/13

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Table 2 (continued)

Study	Participants	Interventions	Outcomes	Methodological quality
Cott et al., 2002 [20] (n = 86)	women 53%, mean age 82 years, mean MMSE 6 (0–21) inclusion criteria: MMSE <20, stable health, ability to walk 5 m or more	walk and talk group, n = 30: walk and talk sessions 5 × 30 min/week, 16 weeks talk only group, n = 30: conversation with the research assistant 5 × 30 min/week, 16 weeks control group, n = 26: no intervention individual intervention follow-up: 16 weeks	no effect on communication skills	poor 6/13
Friedman and Tappen, 1991 [19] (n = 30)	women 43%, mean age 72.8 years, mean MMSE 7 inclusion criteria: AD, MMSE <19, stable health, nursing home resident exclusion criteria: history of mental illness, mental retardation, stroke or head injury	walking group, n = 15: walking and conversation with the investigator 3 × 30 min/week, 40 weeks conversation group, n = 15: conversation only 3 × 30 min/week, 10 weeks individual intervention follow-up: 40 weeks	communication performance improved in the planned walking group	poor 6/13

ADL = Activities of daily living; WMS-LM I = Wechsler Memory Scale-Logical Memory I; MoCA = Montreal Cognitive Assessment; IADL = instrumental activities of life; RT = resistance training; AT = aerobic training; BT = balance and tone training; dg = diagnosis; SpO_2 = oxygen saturation; FTD = frontotemporal dementia; AD = Alzheimer's disease; CBT = cognitive behavioral therapy; BNT = Boston Naming Test; HVLT = Hopkins Verbal Learning Test; ERFT = Rapid Evaluation of Cognitive Function Test (French version); CANTAB = Cambridge Neuropsychological Test Automated Battery; VaD = vascular dementia; PD = Parkinson's disease.

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The 22 studies incorporated into this systematic review included 1,699 participants. The number of participants in the trials varied from 21 [33] to 389 [32]. Of these studies, 8 were performed in subjects with MCI (n = 1,021) [22, 25–27, 30, 32, 35, 41–43] and 14 in patients with dementia (n = 678) [19–21, 23, 24, 28, 29, 31, 33, 34, 36–39]. The duration of the physical intervention varied from 6 weeks [22, 29] to 12 months [24, 26, 27]. The most frequently used exercise in the interventions was walking, but Tai Chi, ergocycling and strength training were also practiced. There was a wide range of cognitive measurement tools used in the studies, and the interventions were heterogeneous (table 2a, b).

All studies on MCI turned out to be of at least moderate quality. Most studies on dementia were found to be of poor quality, 6 were of moderate quality and none was rated as good quality. The most common methodological problems were poor definition of the diagnosis of dementia or MCI, inadequate blinding and low statistical power. The dropouts were rarely included in the analyses, the compliance and complications were often not described and the intention-to-treat analysis was infrequently used.

Effects of Exercise

Global Cognition

In total, 13 studies examined the effect of physical exercise on global cognition using the Mini-Mental State Examination (MMSE) [21, 24, 26–28, 33, 35, 37, 41], ADAS-Cog (Alzheimer's Disease Assessment Scale cognitive subscale) [10, 32, 36, 39, 41] and CDR-SOB (Clinical Dementia Rating Sum of Boxes) [25, 32] as the most common outcome measures (table 3).

Of the trials examining the effect of exercise on global cognition, 5 were performed on subjects with MCI. A positive effect was observed in 3 of these studies [25, 32, 41]. The pooled effect size for ADAS-Cog improvement in 2 of these studies [25, 32] was small [0.29 (95% CI 0.09–0.48)]. An Australian study of good methodological quality [25] randomized 170 participants with MCI for either a 24-week home-based physical activity program or an education group. The intervention group exercised with moderate intensity for 50 min three times a week. At the end of the intervention, the physical activity group showed an improvement of 0.26 points (95% CI 0.32–1.82) on ADAS-Cog, whereas the control group showed a deterioration of 1.04 points (95% CI –2.38 to –0.22). Suzuki et al. [41] studied the effects of a multicomponent exercise program on cognition in patients with MCI. The program consisted of 90-min training sessions (aerobic exercise, strength training, balance and dual tasking) twice weekly and the intervention lasted for 12 months. After the intervention, the participants with amnestic MCI showed an improvement on MMSE but not on ADAS-Cog, which is slightly surprising since the ADAS-Cog test is considered more sensitive to change than the MMSE. However, a Dutch intervention study of good methodological quality [26, 27] found no positive effect on global cognition in subjects with MCI (n = 152) after a 12-month walking intervention. The intervention was group-based, and the participants exercised twice weekly for 1 h.

All these studies were of good quality with sufficient statistical power, but there were small differences that may explain the results [25–27, 41]. The positive outcome in the Australian study may be explained by the better compliance with the exercise program and the higher intensity of the exercise [25]. Japanese researchers suggest that the use of a multicomponent exercise program including dual tasking could be the explanation for the positive outcomes in their study [41].

One study yielded positive effects with the CDR-SOB, but not with ADAS-Cog or MMSE [32]. This is somewhat surprising since CDR-SOB might have a ceiling effect in this patient group, whereas ADAS-Cog should be sensitive to change. This study used Tai Chi in groups as exercise intervention, which is not aerobic but may have socializing effects, thus having an impact on daily functioning in CDR.

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Table 3. Effects of physical exercise on different domains of cognition

Study	Global cognition	Executive function	Attention	Working memory	Delayed recall	Declarative memory	Communi-cation
Study population with MCI							
Suzuki et al., 2013 [41]	+[a]			+[a]	+[a]		
Nagamatsu et al., 2012, 2013 [42, 43]		+[b]	+		+		
Varela et al., 2012 [35]	0						
Lam et al., 2011 [32]	+	0	+		0		
Baker et al., 2010 [30]		+	+		0	0	
van Uffelen et al., 2008, 2009 [26, 27]	0	0	+[c]		+[d]		
Lautenschlager et al., 2008 [25]	+	0		0	0		
Scherder et al., 2005 [22]		+		0	0		
Study population with dementia							
Vreugdenhil et al., 2012 [36]	+						
Venturelli et al., 2011 [33]	0						
Yágüez et al., 2011 [34]			+	0			
Kemoun et al., 2010 [31]	+						
Steinberg et al., 2009 [28]						0	
Eggermont et al., 2009 [29]		0		0	0	0	
Burgener et al., 2008 [37]	+						
Christofoletti et al., 2008 [38]	0	+[e]		0	0	0	
Kwak et al., 2008 [24]	+						
Miu et al., 2008 [39]	0						
Stevens and Killeen, 2006 [23]		+					
van de Winckel et al., 2004 [21]	+	+		0		+	
Cott et al., 2002 [20]							0
Friedman and Tappen, 1991 [19]							+

+ = Improvement; 0 = no difference between intervention and control groups.
[a] Amnestic MCI; [b] reaction time improved in Spatial Memory Test; [c] female; [d] male; [e] group 1.

Two studies of moderate quality [33, 39] performed on participants with dementia did not find a positive association between exercise and global cognition. Venturelli et al. [33] studied nursing home patients with moderate dementia with very low statistical power and using insensitive MMSE as an outcome measure. Similarly, Miu et al. [39] used MMSE as an outcome measure but could not show any effect on the more sensitive ADAS-Cog. The intervention lasted for 12 weeks, and the participants adhered well to aerobic training. However, 1 study of moderate quality on 40 Alzheimer patients showed positive effects on global cognition [36]. In the present study, the participants in the intervention group performed daily home-based exercises and walking under the supervision of their carer for 4 months. The intervention group showed improvements both in MMSE and ADAS-Cog scores. The effect size for ADAS-Cog improvement in this study was medium (EF 0.59). The recommended intensity of exercise was lower in the two negative studies [33, 39] than in the Vreugdenhill study [36], but the latter did not report the true compliance of the participants. Several studies evaluated as being of poor quality suggested positive effects of exercise on global cognition despite having a low statistical power [21, 24, 31, 37]. None of these studies described their randomization method nor did they use blinded outcome assessors or intention-to-treat analyses, thus exposing them to a high risk of bias.

Executive Function

The effect of exercise on executive functioning was evaluated in 10 studies, and 6 of them found modest positive effects. Most intervention studies used the verbal fluency test (also referred to as category fluency test) [21, 22, 25–27, 29, 30, 32, 38] as an outcome measure to assess the effect of physical exercise on executive function. Additionally, the Clock Drawing Test [23, 38], Trail Making Tests A and/or B [22, 30, 32], Symbol-Digit Substitution test [30] and Task Switching [30] were used, often together with the verbal fluency test.

Two studies on participants with MCI with a moderate quality found a positive effect of exercise on executive functioning [22, 30]. Baker et al. [30] examined the effects of high-intensity aerobic exercise (treadmill, elliptical trainer) on executive function. The intervention lasted for 6 months, and the exercises were carried out four times a week for 45–60 min. Favorable effects of physical exercise were found in all outcome measures (verbal fluency, Trail Making Test B and Task Switching). However, there were sex differences in cognitive response as females tended to benefit more. Scherder et al. [22] measured executive functioning with the verbal fluency and Trail Making Tests A and B, and all showed positive outcomes. The intervention of this study was 6 weeks of slow walking three times a week for 30 min. Three other studies of good or moderate quality measuring effects of exercise on executive functioning in participants with MCI [25–27, 32] with the verbal fluency test found no effect. In one of these studies, the authors discussed that including noncompliant participants in the intention-to-treat analysis may have diluted the effects [26, 27].

Only poor-quality studies of participants with dementia showed some improvements in executive function after exercise intervention [21, 23, 38]. Stevens and Killeen [23] evaluated nursing home residents (n = 120) with moderate stage dementia and found some improvement in the Clock Drawing Test after a 12-week intervention (30 min of group exercise three times a week) compared with controls. In a Brazilian study [38], participants (n = 54) with mixed dementia were randomized into three groups receiving a 6-month intervention: group 1 received a multidimensional intervention (physiotherapy, occupational therapy, physical education), group 2 only physiotherapy and group 3 was the control group. The first group trained for 2 h five times a week and the physiotherapy group three times a week for 60 min. Group 1 improved in both the verbal fluency test and the Clock Drawing Test relative to the control group. There was, however, no statistical differ-ence between group 2 (physiotherapy only) and the control group. Thus, it is difficult to determine whether the improvement detected in the multidimensional intervention was due to the high intensity of exercise or its multidimensionality. A study of moderate methodological quality [29] reported no changes in executive function measured by verbal fluency after a 6-week walking intervention in participants with dementia (n = 97). The authors speculated that the duration of the exercise program might have been too short to improve cognition.

Attention

Some researchers consider attention to be a dimension of executive function, while others treat it as a separate concept. Attention was measured as a specific cognitive domain in 4 studies [26, 27, 30, 34, 42] in which Stroop colour and word test was most commonly used to assess attention [26, 27, 30, 42]. The Digit Span Test is generally also used as a test for attention [45]. However, some studies using the Digit Span Test defined it as a test for working memory [22, 29].

In participants with MCI, 3 studies showed positive findings [26, 27, 30, 42]. High-intensity exercise intervention was associated with improvements in the Stroop Effect Test in females but not in males according to the study by Baker et al. [30], in which 37 patients with MCI were randomized to a high-intensity exercise group for 6 months or to a stretching control group. Similar sex-specific findings of the effect of aerobic exercise on attention were reported by van Uffelen et al. [26, 27]. In a Canadian study, 86 participants with probable MCI were randomized into resistance, aerobic or balance exercise interventions. After 26 weeks of intervention, the participants in the resistance training group improved their performance in the Stroop Effect Test [42]. In addition, this study also suggests that the reaction time in spatial memory tasks improved in the aerobic training and resistance training groups [43]. A small study with 27 dementia patients found no effect of a Brain Gym® exercise intervention on attention [34].

Memory

Nine studies evaluated the effects of physical exercise on delayed recall; 5 of them were performed in subjects with MCI. Delayed recall was most commonly examined with an auditory verbal learning test [22, 25–27, 29, 30].

One large study of good methodological quality [26, 27] found a positive association between physical exercise intervention and delayed recall in participants with MCI. van Uffelen et al. [26, 27] tested the efficacy of a walking program and vitamin B supplementation in patients with MCI (n = 152). Participants with good adherence to the walking program improved their performance on the auditory verbal learning test. However, Lautenschlager et al. [25] did not show improvement in delayed recall measured with a word list in the CERAD (Cognitive Battery of the Consortium to Establish a Registry for Alzheimer Disease). In a Japanese study, the multicomponent exercise intervention was associated with improved results on the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II [44] measuring delayed recall [41]. Another good quality study suggested improved delayed recall in the aerobic training group compared with the balance training group [43].

The effect of exercise on delayed recall in demented subjects was examined in 3 studies [28, 29, 38], and no significant effect was observed. Working memory was studied in 6 trials and measured most often with the Digit Span Test. None of the studies [21, 22, 28, 29, 34, 38] showed any positive effects of exercise on working memory. Declarative memory was examined with the Story Recall Test [30], Boston Naming Test [28] and Rivermead Behavioural Memory Test [29]; no significant improvements with exercise were seen.

Communication

Effects of physical activity on communication skills have been examined only in 2 studies on patients with dementia. A small study with 30 participants compared the effects of walking and conversation with conversation-only on communication skills in demented subjects [19]. The results revealed improvement in communication performance in the walking and conversation group compared to the conversation-only group. However, a larger Canadian study with 86 participants with Alzheimer's disease did not find a positive association between a walk-and-talk intervention and communication skills [20]. The participants in these 2 studies were in the advanced stage of Alzheimer's disease in long-term care facilities with a mean MMSE score of 6.5 [19] and 6 [20].

Discussion

We found 22 RCTs examining the efficacy of physical exercise on cognition in individuals with MCI or dementia. The studies performed on participants with MCI were generally of better quality than those performed on patients with dementia. All except one of the studies on participants with MCI demonstrated some positive effects on one or several domains of cognition, global cognition, executive function or attention. However, the effect of exercise on cognition was not as clear in subjects with dementia. Four of 6 studies of moderate methodological quality showed no improvements in any domain of cognition. Studies of poorer quality found some efficacy on global cognition or executive function.

Only 5 [25–27, 41–43] of the 22 studies included in this review met most of the quality criteria presented in table 1 and were rated as being of good methodological quality. Ten studies were rated as moderate quality and 8 as poor quality. The methodological problems were generally related to defining the diagnoses of dementia and MCI, blinding and inadequate statistical power. Dropouts were rarely included in the analyses, compliance and possible side-effects of the interventions were inadequately described and intention-to-treat analysis was infrequently used.

In many studies, the duration of the exercise intervention was relatively short, from 6 weeks to 3 months. The exercise intensity was quite high in several studies, but the attendance to the training sessions was rarely described. Compliance was reported in only 6 of the studies on MCI subjects [25–27, 30, 41–43] and in 4 of those with dementia [28, 31, 33, 34]. In these papers, the reported compliance was generally fairly good, varying between 71% [26, 27] and 94% [30].

All MCI studies of good quality showed some positive effects of aerobic exercise on cognition [25–27, 41–43]. They all used a long-term and intense exercise. However, the effect sizes of exercise that we were able to calculate on cognitive measures appeared to be only mild. A large study among community-dwelling subjects with MCI [26, 27] suggested a stepwise effect of exercise on cognitive performance. An increase in attendance to the exercise sessions led to a better performance in the attention test among females and in delayed recall among males. In a large Australian study of good quality, participants were followed for 12 months after a 24-week exercise intervention. The benefits of the intervention were observed at the end of the intervention and they persisted for at least 12 months [25].

A high degree of heterogeneity existed between different types of physical exercises in the studies. The most commonly used exercise types were walking, Tai Chi, dancing and strength training combined with aerobic training. Multicomponent and dual tasking interventions were also used. A long duration of the intervention, a high intensity and a good adherence to the program seemed to be essential for positive outcome [19, 21, 25–27, 30, 38, 41–43]. In some of the trials, the control group was offered conversation, social visits [19–22, 29] or low-intensity activity such as stretching [30, 32] or balance training [42, 43] at the same frequency as the intervention group participated in the physical exercise, but most often the control group continued with normal care.

The neurocognitive tests used to measure the effect of exercise on cognition were numerous and heterogeneous. This finding is consistent with the results of a recent review article on neuropsychological tests used in studies investigating treatment effects on cognition in older patients with dementia [45].

Tests measuring global cognition were more frequently used than tests covering a specific cognitive domain. Global cognition was generally measured with MMSE, which has a good reliability but is insensitive to change [46, 47]. The verbal fluency test was most commonly chosen to assess the effect of exercise on executive function. However, results on the verbal fluency test depend not only on executive function but also on semantic memory [48]. This can dilute the impact of exercise since the effectiveness on executive function has been found to be stronger than that on memory in previous studies [4].

The changes in neuropsychological tests were generally small and the clinical significance can be questioned. The studies performed on subjects with MCI usually had more participants and the exercise interventions were more intensive and longer lasting than studies on patients with dementia. Measuring the effectiveness of exercise on cognition is often challenging in patients with an advanced stage of dementia. Furthermore, comorbidity and disability might diminish the efficacy of the intervention.

The mechanisms by which physical exercise can affect the aging brain are numerous. Physical exercise improves cerebral circulation by increasing the blood flow and oxygen supply to the brain [49]. Regular exercise lowers the blood pressure and lipids, prevents metabolic syndrome, has a positive effect on inflammatory markers and improves endothelial function, all of which are risk factors for vascular diseases and Alzheimer's disease [49]. These mechanisms may explain why exercise might not have as many marked effects in cognitively impaired subjects as in their cognitively healthy peers. Animal studies have revealed that exercise stimulates neuron proliferation in hippocampal areas [50], and exercise may even increase the volume of the hippocampus in humans [51].

Conclusions

The effect of physical exercise has been studied in 22 RCTs, but especially the studies on patients with dementia were mainly underpowered and of poor quality. Seven RCTs of good or moderate quality examining the efficacy of exercise in subjects with MCI showed some positive cognitive outcomes, mainly on global cognition, executive function or attention. The results of exercise intervention studies among participants with dementia are, however, inconsistent, and there is a need for more studies of good quality on subjects with dementia to determine the effect of physical exercise on cognition. These studies should have larger sample sizes, random allocation should be sound and assessments blinded. Preferably, they should focus separately on patients with mild, moderate and severe dementia to evaluate whether all stages benefit of exercise. Alzheimer's disease and vascular dementia should be examined separately since they probably respond differently to intervention. Furthermore, the training should be aerobic, sufficiently intense and long-term.

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