Effects of physical exercise on cognitively impaired older adults: a systematic review and meta-analysis of randomized control trials

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Abstract

Objectives: The main aim of this study was to compare the effects of different physical activities on cognitive functions in older adults divided according to cognitive impairment levels.

Methods: We searched Web of Science, Scopus, and PubMed for randomized control trials (RCT). A standardized mean difference (SMD) of the pre-post intervention score of global cognitive function tests was calculated by the random model in the Cochrane meta-analyses for people with cognitive impairment generally and across three levels - mild, mild to moderate, and moderate to severe cognitive impairment separately. Additionally, an unstandardized coefficient beta (B) was calculated in generalized linear models to estimate the effects of exercise, cognitive impairment severity, age, female ratio, length of intervention, and time of exercise a week on the global cognitive function.

Results: Data from 26 studies involving 1,137 participants from intervention groups and 1,187 participants from control groups were analyzed. Physical exercise had a positive effect on cognitive functions in people across all levels of cognitive impairments SMD (95 % confidence interval [CI]) = 1.19 (0.77 - 1.62); however, heterogeneity was considerably high $I^2 = 95\%$. Aerobic (B = 8.881) and resistance exercise (B = 4.464) was significantly associated with better results in global cognitive functions when compared to active control. A higher number of female participants in intervention groups had a statistically significant effect on the global cognitive function (B = 0.229).

Conclusions: Physical exercise was associated with cognitive function improvement in older people with cognitive impairments. Aerobic exercise was more strongly associated than resistance exercise to combat cognitive decline.

Background

The number of older adults with dementia is on the rise due to global population ageing. Current estimates suggest that more than 131.5 million people will be affected by dementia by the year 2050 [1]. Dementia is generally characterized by a progressive decline in cognitive and physical functions, often leading to a loss of independence and in some cases, institutionalization [2]. Thus, dementia impacts not only the daily lives of individuals diagnosed with the condition but also their families and broader society.

During the past two decades, epidemiological research has highlighted the link between modifiable lifestyle factors and cognitive function. For example, current evidence has demonstrated that a physically active lifestyle may help to delay the onset of cognitive decline and slow down disease progression [3], and physically active individuals have been shown to have a smaller risk of developing dementia or mild cognitive impairment than those who do not take part in any regular physical activity [4]. Moreover, results from several prospective studies have shown that exercise and physical fitness seem to have a positive effect on brain health [5, 6]. In particular, it has been demonstrated that regular physical activity in mid-life is associated with a lower risk of dementia in later life [7], as well as that one of the most effective protections against neurodegenerative or vascular dementia is to be sufficiently physically active from mid-life [3]. In addition, it is now well known that exercise interventions increase the functional performance and activities of daily living in patients with cognitive impairments [8, 9, 10, 11, 12]. A positive effect of physical exercise on global cognition in individuals with mild cognitive impairments was partly confirmed [13, 14, 15, 16, 17, 18]. Nevertheless, the effects of exercise on global cognitive function in people taking into account the level of cognitive impairment has still not been clearly elucidated. Likewise, the effects of aerobic and resistance exercise require further investigations too.

Therefore, the main aim of this study was to generally analyze the effects of exercise on cognitive functions in older adults divided according to cognitive impairment severity, taking into consideration the effects of resistance exercise and aerobic exercise separately. Additionally, we aimed to investigate the association between selected factors including the passive or active control, cognitive impairment severity, age, sex, frequency of exercise per week, and length of interventions on global cognitive function. We hypothesized that there exists a difference between aerobic and resistance exercise in terms of the effect on cognitive functions and that the effect might vary across different levels of cognitive impairment. We also hypothesized that different activity programs in control groups might influence the results. For example, a social program without physical activities may be beneficial for older adults with cognitive impairment. We also assumed that social or education activities in control groups might be more helpful against the cognitive decline rather than inactivity in passive control groups.

Methods

This study assessed the effects of physical exercise programs on people with cognitive impairment. It is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19]. A compiled PRISMA checklist is included in **Table 1**.

Table 1 Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, Table 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7, Fig 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 Table 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 3, 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

The PICO (population, intervention, comparisons, and outcomes) framework was used for framing the inclusion criteria (see below).

- Participants: people with a cognitive impairment being diagnosed with one of the standardized tools with a closed scale
- Intervention: activities requiring increased energy output excluding interventions combining both physical and cognitive training
- Comparisons: active or passive controls according to reported activities
- Outcomes: cognitive performance; focus on: type of exercise or control group activities, age and sex of participants, length of interventions, frequency of exercise, and severity of impairment

Inclusion criteria for this study

Based on the above-mentioned PICO framework, the following inclusion criteria were applied: only data from randomized trials (RCT) were used, and the participants had to be diagnosed with a cognitive impairment according to one of the standardized tools with a closed scale written in the English language. Following global cognitive function tests were considered appropriate: Cambridge Cognitive Examination (CAMCOG) [20], the Mini-Mental State Examination (MMSE) [21], the Rapid Evaluation of Cognitive Function (ERFC) [22], the Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) [23], and the Montreal Cognitive Assessment (MoCA) [24].

Concerning the exercise programs, only exercise activities that required increased energy output without taking frequency or intensity into account were included. All intervention groups from studies with a combination of physical exercise and cognitive training were excluded. However, their control groups were included if they met our search criteria.

Exercise intervention and control group classification

Walking, stretching, toning, kinesiotherapeutic exercise, music-based dance therapy, ergometer cycling, as well as generally specified “aerobic exercise” were classed as aerobic exercise. When the intervention program included high-intensity functional exercise, strengthening exercise with own body weight, or exercise with dumbbells, we classed it as resistance exercise.

According to the activities that were prescribed, we divided the control groups into two categories - active and passive control groups. All the control groups with activities that could have potentially been beneficial for cognitive functions (for example, attention-control educational programs, social visits, or recreational activities such as card playing or home craftwork) were categorized as the active control groups. Control groups asked to maintain their usual activities were categorized as the passive control groups.

We also analysed information about the length of intervention, the duration of exercise per week, and female ratios.

Search strategy

The analysis was conducted by identifying relevant papers referenced in the Web of Science, Scopus, and PubMed. Search terms used in all databases are presented in **Table 2**.

Table 2 Search results in electronic databases

DATABASE	KEY	NUMBER
Web of Science	TITLE: (dementia) OR TITLE: ("Alzheimer disease") OR TITLE: ("cognitive function") OR TITLE: ("cognitive impairment") AND TITLE: ("physical activity") OR TITLE: (exercise) OR TITLE: (training) AND TOPIC: (randomized) OR TOPIC: (trial)	489
Scopus	((TITLE (dementia) OR TITLE ("Alzheimer disease") OR TITLE ("cognitive impairment") OR TITLE ("cognitive function"))) AND ((TITLE ("physical activity") OR TITLE (exercise) OR TITLE (training))) AND ((TITLE-ABS-KEY (randomized) OR TITLE-ABS-KEY (trial)))	612
PubMed	Search ((((((dementia[Title]) OR "Alzheimer disease"[Title]) OR "cognitive impairment"[Title]) OR "cognitive function"[Title]))) AND (((("physical activity"[Title]) OR exercise[Title]) OR training[Title]))) AND ((randomized[Title/Abstract]) OR trial[Title/Abstract])	329

Data extraction and quality assessment

All potential papers were first downloaded into EndNote. Then, our three reviewing authors (LS, AT, and MS) deleted all the duplicates and scanned the titles and abstracts of the papers in order to identify studies that had the potential to meet the eligibility criteria. Full texts were subsequently assessed for eligibility. Any disagreements among the reviewers (KD, and IH) were resolved through discussions. We used the Physiotherapy Evidence Database (PEDro) scale to assess the methodological quality of the included studies [25].

We collected the following data for both the exercise groups and control groups separately: baselines and after intervention means with 95% confidence interval (CI) and/or standard deviation (SD); and if described, also the mean of post-pre intervention score with SD or 95% CI were collected. Additionally, for factors or covariates for general linear models, we collected information about the type of exercise or control group activities, age of participants, sex of participants, length of interventions, and frequency of exercise.

Cognitive impairment classification

We divided the participants into three categories according to the level of their cognitive impairment: mild, mild to moderate, and moderate to severe impairment. In the classification, we used a 95% CI of the baseline mean in the standardized 100 points scale. Mild cognitive impairment = the lower 95% CI > 65.0 points, mild to moderate cognitive impairment = the lower 95% CI > 57 to points, and moderate to severe impairment = the upper 95% CI < 60 points. This division was in concordance with the standard diagnostic of cognitive impairment according to MMSE [26]. We could say with 95% certainty that in the mild impairment group there were not participants with less than 20.1 points, in the mild to moderate impairment group there were not participants with less than 17.1 points and in the moderate to severe impairment group, there were not any participants with higher than 18 points.

Data analysis

The sample size and mean post-pre intervention score with standard deviation (SD) from intervention as well as control groups were used to calculate the standardized mean differences (SMD). The random effect models were used for all the analyses [27]. To assess the heterogeneity I^2 was considered. A rough guide to the interpretation of I^2 is as follows: 0 to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent considerable heterogeneity, and 75% to 100% represents substantial heterogeneity [28]. Additionally, we standardized all the mean of the baseline score and post-pre intervention score from all the groups separately onto the 100 points scale. Then generalized linear models were used to estimate the influences of selected factors and covariates to the standardized post-pre intervention score as the continual dependent variable. We calculated an unstandardized coefficient beta (B), standard error (SE) and 95% CI. B represents the amount by which dependent variable changes if we change independent variable by one unit keeping other independent variables constant. If 95 % CI does not cross the 0 then the result is statistically significant. Statistics were calculated using RevMan 5.3 and IBM SPSS Statistics 24.

Results

Description of studies

We included 26 randomized controlled trials in the final analysis out of the 785 publications resulting from the database search. These were controlled trials on physical activity and its effect on cognitive performance in people with cognitive impairment. **Figure 1** shows the PRISMA flow diagram. Across the studies, we extracted data from 2,324 participants, all being over 50 years of age (60.1 % females). The standardized baseline mean of cognitive function tests in all the groups included was 66.9 (95 % CI 62.3-71.5), which corresponded to 20.1 (95 % CI 18.7-24.5) points of the MMSE classed as a mild to moderate cognitive impairment according to the standard interpretation of MMSE [26]. Interventions were mostly aerobic exercise and walking, and the amount of exercise varied between 60 minutes to 420 minutes per week. The shortest duration period of the intervention was 6 weeks, and the longest was 60 weeks. As the main outcome, the following were used: 21x MMSE [21], 1x CAMCOG [20], 1x MoCA [24], 1x ERFC [22], and 2x ADAS-Cog [23]. 16 out of the 26 control groups took part in additional activities such as education, one-to-one conversation or recreational activities. The other participants in control groups were instructed to maintain their normal physical activities, or they

had standard care in nursing homes. 10 out of 24 intervention groups presented a statistical beneficial effect while only 2 presented a significant harmful effect. There was no significant effect found in 12 studies involving intervention groups. While more than one-third of the interventions were beneficial, 14 out of 26 controls showed significant decrease in cognitive functions. Descriptions of intervention and control groups included in the review are presented in **Table 3** [29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54]. All of the included studies were considered to have had a good methodological quality, scoring between 7 and 9 points according to the PEDro. The methodological quality of the included studies according to the PEDro scale is presented in **Table 4**.

Table 3 Studies included in the analyses

Intervention groups					
Study	Main parts of interventions	Group size	Settings	Main Outcome	Statistically significant effect
Arcoverde, 2014	30 min treadmill walking at 60% of VO ₂ max; 2x a week; 16 weeks	10	H	CAMCOG	Beneficial
Bademli, 2018	40 min aerobics exercise 4x a week and 40 min walking 3x a week; 20 weeks	30	N	MMSE	Beneficial
Bossers, 2015	30 min walking; 36 individualized sessions in 9 weeks	36	N	MMSE	No
	30 min of strength sessions or walking sessions; 18 and 18 individualized sessions in 9 weeks	37	N	MMSE	No
Cancela, 2016	15 min cycling ergometer; 7x a week; 60 weeks	51	H	MMSE	No
Holthoff, 2015	30 min home-based motor-assisted or active resistive training of the legs; 3x a week; 12 weeks	15	H	MMSE	No
Hong, 2018	60 min exercise with an elastic band at 15-repetition maximum (65% of 1RM); 2x a week; 12 weeks	10	H	MoCA	No
Christofolletti, 2008	60 min kinesiotherapeutic exercises; 3x a week; 6 months	17	N	MMSE	Beneficial
Kemoun, 2010	60 min articular mobilization, muscle stimulation, and walking; 3x a week; 15 weeks	16	N	ERFC	Beneficial
Kwak, 2008	30 - 60 min chair exercises max. 60% VO ₂ max; 2-3x a week; 12 months	15	H	MMSE	Beneficial
Lam, 2015	60 min stretching and toning exercise, one mind body exercise (e.g. Tai Chi) and one aerobic exercise session (e.g. static bicycle riding); 3x a week; 12 months	147	H	MMSE	No
Lamb, 2018	70 min aerobic and strengthening exercise program of moderate to high intensity; 2x a week; 16 weeks	298	C	ADAS-Cog	No
Langoni, 2018	60 min exercise with elastic bands, balls, ankle weights, own body weight, and dumbbells; 2x a week; 24 weeks	26	H	MMSE	Beneficial
Lautenschlager, 2008	50 min walking, light strength training exercise, circuit gym exercise; 3x a week; 24 weeks	85	H	ADAS-Cog	No
Miu, 2008	60 min aerobic exercise training with treadmill, bicycle, arm ergometry and flexibility exercises; 2x a week; 12 weeks	36	H	MMSE	Harmful
Muscari, 2009	60 min cycle ergometer, treadmill and free-body activity at intensity 70% of maximal heart rate; 3x a week; 12 months	60	C	MMSE	No
Toots, 2017	40 min high-intensity functional exercises performed in weight bearing positions; 5x per two-week; 16 weeks	93	N	MMSE	Harmful
Van de Winkel, 2004	30 min music-based dance therapy and a conversational session; 7x a week; 6 weeks	15	Hos	MMSE	No
Varela, 2012	30 min exercise on 60% of participant's heart rate reserve; 3x a week; 12 weeks	16	N	MMSE	Beneficial
	30 min exercise on 40% of participant's heart rate reserve; 3x a week; 12 weeks	17	N	MMSE	Beneficial
Venturelli, 2011	30 min walking; 4x a week; 6 months	12	N	MMSE	No
Vreugdenhil, 2012	30 min upper and lower body strength and balance training in addition to at least 30 minutes of brisk walking; daily; 16 weeks	20	C	MMSE	Beneficial
Williamson, 2009	60 min combination of aerobic, strength, balance, and flexibility exercises; 3x a week; 12 months	50	H	MMSE	No
Yang, 2015	40 min cycling training at 70% of maximal intensity; 3x a week; 12 weeks	25	Hos	MMSE	Beneficial

Control groups					
Study	Activities	Group size	Settings	Main Outcome	Statistically significant effect
Arcoverde, 2014	-	10	H	CAMCOG	Harmful
Bademli, 2018	-	30	N	MMSE	Harmful
Bossers, 2015	Four social visits each week	36	N	MMSE	No
Burgener, 2008	Attention-control educational programs	19	H	MMSE	No
Cancela, 2016	Recreational activities - card-playing, reading, craftwork	63	H	MMSE	Harmful
Holthoff, 2015	-	15	H	MMSE	No
Hong, 2018	-	12	H	MoCA	No
Christofolletti, 2008	-	20	N	MMSE	No
Kemoun, 2010	Manual and intellectual activities organized by the nursing home (pottery, painting, soft gymnastics, outings, etc.)	15	N	ERFC	Harmful
Kwak, 2008	-	15	H	MMSE	No
Lam, 2015	At least three one-hour social activity sessions per week	131	H	MMSE	No

Lamb, 2018	-	145	C	ADAS-Cog	No
Langoni, 2018	-	26	H	MMSE	Harmful
Lautenschlager, 2008	Educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking	85	H	ADAS-Cog	Harmful
Miu, 2008	-	49	H	MMSE	Harmful
Muscari, 2009	Educational materials about suggestions to improve lifestyle, including individualized self-administered programs to increase physical activity	60	C	MMSE	Harmful
Shimada, 2017	90-minute health promotion classes thrice over the 40-week trial period	154	C	MMSE	Harmful
Suzuki, 2013	2 education classes about health promotion during the 6-month study period	50	C	MMSE	No
Suzuki, 2012	3 education classes about health promotion during the 12-month study period	25	C	MMSE	No
Toots, 2017	Participants conversed, sang, listened to music or readings, and/or looked at pictures and objects	93	N	MMSE	Harmful
Van de Winckel, 2004	One-to-one conversation	10	Hos	MMSE	No
Varela, 2012	Recreational activities - playing cards, reading newspapers, handicrafts	15	N	MMSE	Harmful
Venturelli, 2011	Organized activities like bingo, patchwork sewing, and music therapy	12	N	MMSE	Harmful
Vreugdenhil, 2012	-	20	C	MMSE	Harmful
Williamson, 2009	Health education - a session per week included health topics relevant to older adults such as nutrition, medications, foot care, and recommended preventive services at different ages	52	H	MMSE	No
Yang, 2015	Health education	25	Hos	MMSE	Harmful

Note: CAMCOG: Cambridge Cognitive Examination; MMSE: Mini-Mental State Examination; ERFC: Rapid Evaluation of Cognitive Function; ADAS-Cog: Alzheimer Disease Assessment Scale-Cognitive Subscale; MoCA: Montreal Cognitive Assessment; C: community; H: home; N: nursing home; Hos: hospital

Table 4 PEDro scores of the included studies

Study	Eligibility criteria	Randomization	Concealed allocation	Similar group baselines	Blinding of all subjects	Blinding of all therapists	Blinding of all assessors	Drop out < 15%	Intention- to-treat method	Statistical between- group comparison	Point measures and measures of variability	Score
Arcoverde, 2014	1	1	1	1	1	0	0	1	1	1	1	9
Bademli, 2018	1	1	1	1	0	0	0	1	1	1	1	8
Bossers, 2015	1	1	1	1	0	0	0	1	1	1	1	8
Burgener, 2008	1	1	1	1	0	0	0	1	1	1	1	8
Cancela, 2016	1	1	1	1	0	0	1	0	1	1	1	8
Holthoff, 2015	1	1	1	1	0	0	0	1	1	1	1	8
Hong, 2018	1	1	1	1	0	0	0	0	1	1	1	7
Christofoletti, 2008	1	1	1	1	0	0	1	1	1	1	1	9
Kemoun, 2010	1	1	1	1	0	0	0	0	1	1	1	7
Kwak, 2008	1	1	1	1	0	0	0	1	1	1	1	8
Lam, 2015	1	1	1	1	0	0	0	1	1	1	1	8
Lamb, 2018	1	1	1	0	0	0	0	1	1	1	1	7
Langoni, 2018	1	1	1	1	1	0	0	1	1	1	1	9
Lautenschlager, 2008	1	1	1	1	1	0	0	1	1	1	1	9
Miu, 2008	1	1	1	0	0	0	0	1	1	1	1	7
Muscari, 2009	1	1	1	1	0	0	0	1	1	1	1	8
Shimada, 2017	1	1	1	1	0	0	0	0	1	1	1	7
Suzuki, 2013	1	1	1	1	0	0	1	1	1	1	1	9
Suzuki, 2012	1	1	1	1	0	0	1	1	1	1	1	9
Toots, 2017	1	1	1	1	1	0	0	1	1	1	1	9
Van de Winckel, 2004	1	1	1	0	0	0	0	1	1	1	1	7
Varela, 2012	1	1	1	1	0	0	0	0	1	1	1	7
Venturelli, 2011	1	1	1	1	0	0	0	0	1	1	1	7
Vreugdenhil, 2012	1	1	1	1	0	0	1	1	1	1	1	9
Williamson, 2009	1	1	1	1	0	0	1	1	1	1	1	9
Yang, 2015	1	1	1	1	0	0	0	1	1	1	1	8

Exercise effect

In general, physical exercise had a positive effect on cognitive functions in people with cognitive impairment SMD (95 % CI) = 1.19 (0.77 - 1.62); however, heterogeneity was considerably high $I^2 = 95\%$. In separate groups according to the cognitive impairment severity, the only aerobic exercise had statistically significant effect SMD (95 % CI) = 2.42 (0.86 - 3.99) in mild and 1.73 (1.08 - 2.38) in moderate to severe impairment respective. Nevertheless, the heterogeneity was considerably high as well. A forest plot with a graphical representation of individual effects is presented in **Figure 2**.

In the generalized linear models, when we used the active control groups as a reference category, its change on the aerobic exercise group caused an increase in the post-pre intervention score estimate by more than 8 times ($B = 8.881$) and the change on resistance group by 4 times ($B = 4.464$), both significantly. When comparing passive groups to active groups there was found a negative trend for the passive controls, nevertheless, not significant. Cognitive impairment level, as well as age and length of intervention, were not significantly associated with the post-pre intervention score. The result of the generalized linear model of intervention and control groups together is presented in **Table 5**.

Table 5 Generalized linear model for both groups

	B	SE	95% CI	
			Lower	Upper
Physical activity				
Aerobic exercise	8.881*	1.677	5.594	12.167
Resistance exercise	4.464*	1.779	0.978	7.951
Passive control	-0.170	1.839	-3.774	3.434
Active control	0 ^a			
Cognitive impairment				
Mild to moderate	2.519	2.163	-1.720	6.758
Mild	2.625	2.624	-2.518	7.769
Moderate to severe	0 ^a			
Length of intervention				
Less than half a year	2.750	1.487	-0.163	5.663
More than half a year	0 ^a			
Age	-0.146	0.214	-0.565	0.274

Note: B: standardised coefficient beta; SE: standard error; CI: Wald confidence interval; ^aSet to zero because this parameter is redundant;
*Statistically significant

For the intervention groups, aerobic exercise was significantly strongly associated with better results in the post-pre intervention score estimate (B = 4.326) compared to resistance exercise. Shorter interventions had significantly better effect compared to the lengthier ones (B = 4.798). In addition, age played a significant negative role (B = -0.708), and a higher number of women in intervention groups had a statistically significant effect as well (B = 0.229). Cognitive impairment level, as well as time of exercise weekly, were not significantly associated with the post-pre intervention score. The result of the generalized linear model of intervention groups separately is presented in **Table 6**.

Table 6 Generalized linear model for intervention groups

	B	SE	95% CI	
			Lower	Upper
Physical activity				
Aerobic exercise	4.326*	1.730	0.936	7.716
Resistance exercise	0 ^a			
Cognitive impairment				
Mild to moderate	1.974	2.751	-3.430	7.365
Mild	0.315	3.008	-5.580	6.210
Moderate to severe	0 ^a			
Length of intervention				
Less than half a year	4.798*	1.867	1.129	8.449
More than half a year	0 ^a			
Time a week				
> 2 hours	0.118	1.989	-4.017	3.780
≤ 2 hours	0 ^a			
Age	-0.708*	0.318	-1.332	-0.084
Female ratio	0.229*	0.064	0.103	0.355

Note: B: standardised coefficient beta; SE: standard error; CI: Wald confidence interval; ^aSet to zero because this parameter is redundant;
*Statistically significant

Discussion

It is well-established that cognitive functions decline gradually over time as part of the natural ageing process [55]. The overall results of this meta-analysis indicate that physical exercise and specifically aerobic exercise may have the power to mitigate cognitive decline process even in people with cognitive impairment.

According to our results, aerobic exercise had twice higher impact on cognitive functions than resistance exercise when compared to active controls, and 4 times when compared only the intervention groups. Previous studies partly confirmed a positive effect of physical exercise on executive functions [14, 15], and global cognition [16, 17, 18] in individuals with mild cognitive impairments. However, we found that aerobic exercise also had a statistically significant positive effect in moderate to severe cognitively impaired people. Probably the positive effect of aerobic exercise on brain health seems to lie in the proposed mechanisms behind aerobic

exercise such as neovascularization, synaptogenesis and angiogenesis, hippocampal high-affinity choline uptake and upregulation of muscarinic receptor density, increasing of mitochondrial volume in Purkinje cells, inhibition of the apoptotic biochemical cascades, identified primarily through animal research [56, 57, 58, 59].

Moreover, a higher number of female participants in intervention groups had a positive effect on global cognitive function. This result could be explained by both different cognitive responses to exercise between men and women as well as by the different ratios in elderly females suffering dementia. As described by Baker et al. (2010), aerobic exercise improved performance on multiple tests of executive function, increased glucose disposal during the metabolic clamp, and reduced fasting plasma levels of insulin, cortisol, and brain-derived neurotrophic factor in women but not in men [60]. They also found that peak oxygen consumption was associated with improved executive function in women. It turns out that gender differences in cognitive functions can be related to the metabolic effects of physical activity. However, there are several other reasons that sex may influence trial results. For instance, women have a higher lifetime risk of dementia [61], greater vulnerability to certain risk factors such as sex specific chromosomes, *APOE ε4*, sex differences in hormone levels etc. [62], and they demonstrate higher differential associations between biomarkers and cognitive impairment than men [63]. Moreover, there was a higher percentage of female participants in the intervention studies (19 of 24 intervention studies had a majority of female participants). One reason for this fact could be higher life expectancy in females [64] although the gender gap has been narrowing in Europe recently [65]. Another explanation could be greater adherence to health-related exercise programs in older women [66]. Thus, it would be of interest to explain which of the above-mentioned proposed factors is responsible for gender differences.

Studies included in this meta-analysis varied in terms of length of interventions. In fifteen studies, the duration of interventions was less than half a year, and in another nine, the duration of the interventions was for more than half a year. According to our analysis, it seems that the length of the intervention was associated with cognitive decline. We may hypothesize that this was probably caused by the natural ageing process. Surprisingly, the frequency of exercise per week did not play any significant role in global cognition.

It should be noted that several limitations are involved in this study. There was considerable heterogeneity in all the analyses. Unfortunately, it could not be controlled for by the sensitivity analysis otherwise more than half of the studies would have to be excluded. In fact, heterogeneity is a common problem when conducting meta-analyses on this topic [14, 18], so the standard approach is not always the best. Nevertheless, using general linear models involved some limitations too. For example, we used only individual standardized post-pre mean difference and not the total amplitude such as 95% CI. Therefore, the statistical significance of individual studies could not be drawn. Moreover, it was almost impossible to create a category with similar cognitive impairment because it varied considerably among the studies. The same is true for exercise interventions because the interventions included many different activities with different durations and intensities.

Conclusion

Despite the numerous above-mentioned limitations this study has shown that physical exercise and especially aerobic exercise may have the power to influence cognitive functions in people with cognitive impairment. Such findings could have practical implications such as to recommend physical activity as a nonpharmacologic treatment to combat the progression of cognitive decline in patients with dementia. Future research based on longitudinal epidemiological studies is needed to confirm such findings further.

List Of Abbreviations

ADAS-Cog	Alzheimer Disease Assessment Scale–Cognitive Subscale
B	Standardized Coefficient Beta
CAMCOG	Cambridge Cognitive Examination
CI	Confidence Interval
ERFC	Rapid Evaluation of Cognitive Function
MMSE	Mini Mental State Examination

MoCA	Montreal Cognitive Assessment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PEDro	Physiotherapy Evidence Database
RCT	Randomized Control Trials
SE	Standard Error
SMD	Standardized Mean Difference
VO ₂ max	the maximum amount of oxygen the body can utilize during a specified period of usually intense exercise.
WA	Weighted Averages

Declarations

Our results have not been published previously and are not under submission elsewhere. Co-authors are cognizant of the submitted text and agree to its publication in BMC Public Health.

Ethics approval and consent to participate

N/A

Consent for publication

N/A

Availability of supporting data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

LS, AB, and MS have screened the literature and selected papers for inclusion in the review LS, MS, KD, and IH have contributed to data extraction. All authors read and approved the final manuscript.

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Figures

Figure 1

Flowchart illustrating the different phases of the search and study selection

Figure 2

Effects meta-analysis of physical activities on cognitive function in people divided according to their cognitive impairment severity