 AUC Kinanthropologica, Vol. 57, No. 1, pp. 51–78

Effects of physical exercise on cognitively impaired older adults: a systematic review

Lenka Sontáková[1], Alžběta Bártová[2], Klára Daďová[1,*], Iva Holmerová[2], Michal Šteffl[1]

[1] Faculty of Physical Education and Sport, Charles University, Prague, Czech Republic
[2] Faculty of Humanities, Charles University, Prague, Czech Republic
* Corresponding author: dadova@ftvs.cuni.cz

ABSTRACT

Background. The main aim of this study was to estimate the effect of physical activities (PA) on cognitive functions (CF) in cognitively impaired older adults divided according to the impairment severity.

Methods. We searched Web of Science, Scopus, and PubMed for randomized controlled trials (RCT). We focused on the effect of exercise on CF in intervention groups and control groups separately in people with cognitive impairment across three levels - borderline intact, mild, and moderate cognitive impairment separately.

Results. Data from 40 studies involving 1,780 participants from intervention groups and 1,508 participants from control groups were analyzed. 37.0% of intervention groups presented a statistically significant beneficial effect of PA on CF, while 5% presented a statistically significant harmful effect of PA on CF. 40.0% of the control groups showed a significant decrease in CF. 54.3% interventions had a statistically significant beneficial effect (Hedges' $g > 0$). However, there was a great variability between the studies in terms of exercise program description and cognitive impairment of the subjects.

Conclusions. Physical exercise was associated with cognitive function improvement in older people with cognitive impairment. The positive effect is stronger in people with a mild level of cognitive impairment.

KEYWORDS

physical activity; dementia; ageing; aerobic exercise; resistance exercise; cognitive function

DOI

10.14712/23366052.2021.5

BACKGROUND

The number of older adults with dementia is on the rise due to ageing of the global population. Current estimates suggest that more than 131.5 million people will be affected by dementia by the year 2050 (Sha et al., 2016). Dementia is generally characterized by a progressive decline in cognitive and physical function, often leading to a loss of independence, and institutionalization in some cases (Winblad et al., 2016). 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 functions. For example, current evidence has demonstrated that a physically active lifestyle may help to delay the onset of cognitive decline and to slow down disease progression (Rolland et al., 2008). Also, 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 (Rockwood & Middleton, 2007). Moreover, results from several prospective studies have shown that exercise and physical fitness seem to have a positive effect on brain health (Blondell et al., 2014; Stephen et al., 2017). In particular, it has been demonstrated that regular physical activity in mid-life is associated with a lower risk of dementia in later life (Chen et al., 2016), as well as that one of the most effective protections against neurodegenerative or vascular dementia is to be sufficiently physically active from mid-life (Rolland et al., 2008). In addition, it is now well known that exercise interventions increase the functional performance and activities of daily living in patients with cognitive impairment (Garuffi et al., 2013; Hauer et al., 2012; Pitkala et al., 2013; Schwenk et al., 2014; Steinberg et al., 2009). Partial confirmation of a general positive effect of physical exercise was seen as well as stratified effect according to the type of exercise undertaken on executive function, memory (Gates et al., 2013), and global cognition (Groot et al., 2016; Song et al., 2018; Wang et al., 2014) in individuals with mild cognitive impairment. However, there are other important variables that may influence results; for example the effects of exercise on cognitive function in people in relation to the level of cognitive impairment, frequency of sessions or duration of interventions. It is necessary to focus attention on these variables to better understand this complex issue.

Therefore, the main aim of this study was to investigate which type of exercise interventions work effectively in the prevention of cognitive decline in older adults stratified according to the level of cognitive impairment. Additionally, we aimed to investigate the association between other factors, e.g. whether there is a difference between passive and active controls. We hypothesized that there is a difference between exercise programs (mainly from the duration point of view) 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 review 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 (Moher et al., 2019). 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.	51
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.	51
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	52
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	52
		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.	55
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.	56, 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).	58, Figure 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.	56
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	–

Section/topic	#	Checklist item	Reported on page #
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.	59 Table 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	57–58
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.	57–58
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.	–
		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.	57–60, 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.	Tables 3, 4, 5
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).	–
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.	Tables 6, 7, 8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	–
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]).	–
		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).	70–71
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).	71
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	71
		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.	72

The PICO (population, intervention, comparisons, and outcomes) framework was used for framing the inclusion criteria (see below) (Higgins et al., 2019).

- Participants: people >50 years of age with a cognitive impairment
- Intervention: physical exercise interventions
- Comparisons: active or passive controls with no additional physical activities
- Outcomes: cognitive function

Inclusion criteria for this study

Based on the above-mentioned PICO framework, the following inclusion criteria were applied:

- only data from randomized controlled trials (RCT)
- the participants had to be diagnosed with any stage of cognitive impairment by one of the standardized tools
- written in the English language

Exercise intervention

We considered only exercise programs that require increased energy output such as aerobic, resistance exercise, walking, dancing, various types of combat activities or sports games. The intervention programs involving a combination of physical exercise and cognitive training were not included. In addition to the program itself, we focused on the duration of exercise program and exercise frequency. Regarding exercise program duration and frequency of exercise per week, we used the same classification as Forbes et al (2015) in the Cochrane systematic review – "up to three times per week" or "more than three times per week" and "up to 12 weeks" or "more than 12 weeks" (Forbes et al., 2015).

According to activities that were prescribed, we have also divided control groups into two categories – active and passive control groups. All control groups where extra 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 "active control groups". Control groups asked to maintain their usual activities were categorized as "passive control groups".

Cognitive function

The following global cognitive function tests were considered appropriate:

- Mini-Mental State Examination (MMSE) (Folstein et al., 1983)
- Rapid Evaluation of Cognitive Function (ERFC) (Gil et al., 1986)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (Mohs et al., 1997)
- Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005)
- Cambridge Cognitive Examination (CAMCOG) (Roth et al., 1998)

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	TOPIC: (training) OR TOPIC: (exercise) OR TOPIC: (physical) OR TOPIC: (activit*) AND TOPIC: ("Mini-Mental State Examination") OR TOPIC: (MMSE) OR TOPIC: ("Cambridge Cognitive Examination") OR TOPIC: (CAMCOG) OR TOPIC: ("Montreal Cognitive Assessment") OR TOPIC: (MoCA) OR TOPIC: ("Alzheimer's Disease Assessment Scale-Cognitive Subscale") OR TOPIC: (ADAS-Cog) OR TOPIC: ("Rapid Evaluation of Cognitive Functions test") OR TOPIC: (ERFC) AND TITLE: (dementia) OR TITLE: (Alzheimer*) OR TITLE: (cognitive) OR TITLE: (MCI) AND TITLE: (randomized) OR TITLE: (randomised) OR TITLE: (trial) OR TITLE: (intervention)	425
Scopus	((TITLE (training) OR TITLE (exercise) OR TITLE (physical) OR TITLE (activit*))) AND ((TITLE-ABS-KEY ("Mini-Mental State Examination") OR TITLE-ABS-KEY (mmse) OR TITLE-ABS-KEY ("Cambridge Cognitive Examination") OR TITLE-ABS-KEY (camcog) OR TITLE-ABS-KEY ("Montreal Cognitive Assessment") OR TITLE-ABS-KEY (moca) OR TITLE-ABS-KEY ("Alzheimer's Disease Assessment Scale-Cognitive Subscale") OR TITLE-ABS-KEY ("Rapid Evaluation of Cognitive Functions test") OR TITLE-ABS-KEY (erfc))) AND ((TITLE (dementia) OR TITLE (alzheimer*) OR TITLE (cognitive) OR TITLE (mci))) AND ((TITLE-ABS-KEY (randomized) OR TITLE-ABS-KEY (randomised) OR TITLE-ABS-KEY (trial) OR TITLE-ABS-KEY (intervention))) AND NOT ((TITLE-ABS-KEY (review) OR TITLE-ABS-KEY (meta-analysis) OR TITLE-ABS-KEY (protocol)))	460
PubMed	Search ((((((((training[Title/Abstract]) OR exercise[Title/Abstract]) OR physical[Title/Abstract]) OR activit*[Title/Abstract])) AND (((((((((("Mini-Mental State Examination") OR MMSE) OR "Cambridge Cognitive Examination") OR CAMCOG) OR "Montreal Cognitive Assessment") OR MoCA) OR "Alzheimer's Disease Assessment Scale-Cognitive Subscale") OR ADAS-Cog) OR "Rapid Evaluation of Cognitive Functions test") OR ERFC)) AND ((((dementia[Title]) OR Alzheimer*[Title]) OR cognitive[Title]) OR MCI[Title])) AND ((((randomized[Title/Abstract]) OR randomised[Title/Abstract]) OR trial[Title/Abstract]) OR intervention[Title/Abstract])) NOT (((review[Title/Abstract]) OR meta-analysis[Title/Abstract]) OR protocol[Title/Abstract])	830

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 by reviewers KD, MS and IH who extracted the data. Any disagreements among reviewers were resolved through discussions.

We used the Physiotherapy Evidence Database (PEDro) scale to assess the methodological quality of the included studies (Maher et al., 2003).

Data collection

We collected the following data for both exercise groups and control groups separately: the post/pre-intervention mean of the cognitive function test with a 95% confidence interval (CI) and/or standard deviation (SD), if they were not described, we collected means of the cognitive function tests from baselines and after intervention. Additionally, we collected information about the type of exercise and control group activities, age of participants, female ratio, exercise program duration, and frequency of exercise.

Cognitive impairment classification

We divided the participants according to the level of their cognitive impairment into three categories – borderline intact, mild, and moderate cognitive impairment. In the classification, we used the mean of the baseline cognitive function test using the standard classification of each diagnostic tool from which it was calculated.

Data analysis

To see the effect of physical activity on cognitive function of participants, we calculated Hedges' g (Hedges, 1981) for intervention groups and control groups separately as well as for both groups together as follows:

$$Hedges' \ g = \frac{M_{IG} - M_{CG}}{SD_{pooled}} \times \left(\frac{N-3}{N-2.25}\right) \times \sqrt{\frac{N-2}{N}}$$

where $M_{IG} - M_{CG}$ is the difference in mean changes in intervention and control groups and SD_{pooled} is the pooled and weighted standard deviation. Hedges' g is interpreted as:

– Small Effect = 0.2
– Medium Effect = 0.5
– Large Effect = 0.8

Negative values represented a harmful effect (i.e. decrease of cognitive functions) of intervention. To test statistical significance we calculated 95% Confidence Interval (CI) for each study as follows:

$$95\ \%\ CI = g \pm SE \times 1.96$$

where SE is standard error calculated as:

$$SE = \sqrt{\frac{n_1 + n_2}{n_1 \times n_2} + \frac{g^2}{2(n_1 + n_2)}}$$

If the post-pre intervention mean and SD were not available in the paper, we calculated the post-pre intervention mean as the post-intervention mean minus the pre-intervention mean and SD was estimated as:

$$SD_{dif} = \sqrt{SD_{pre}^2 + SD_{post}^2 - (2 \times Corr \times SD_{pre} \times SD_{post})}$$

We used Corr = 0.8 based on the assumption of a relatively high correlation between pre and post-measurements.

The statistics were calculated using Microsoft Excel.

RESULTS

We included 40 RCT in the final analysis out of the 1,258 publications resulting from the database search. These were controlled trials on physical activity and its effect on cognitive functions in people with cognitive impairment. Figure 1 shows the PRISMA flow diagram.

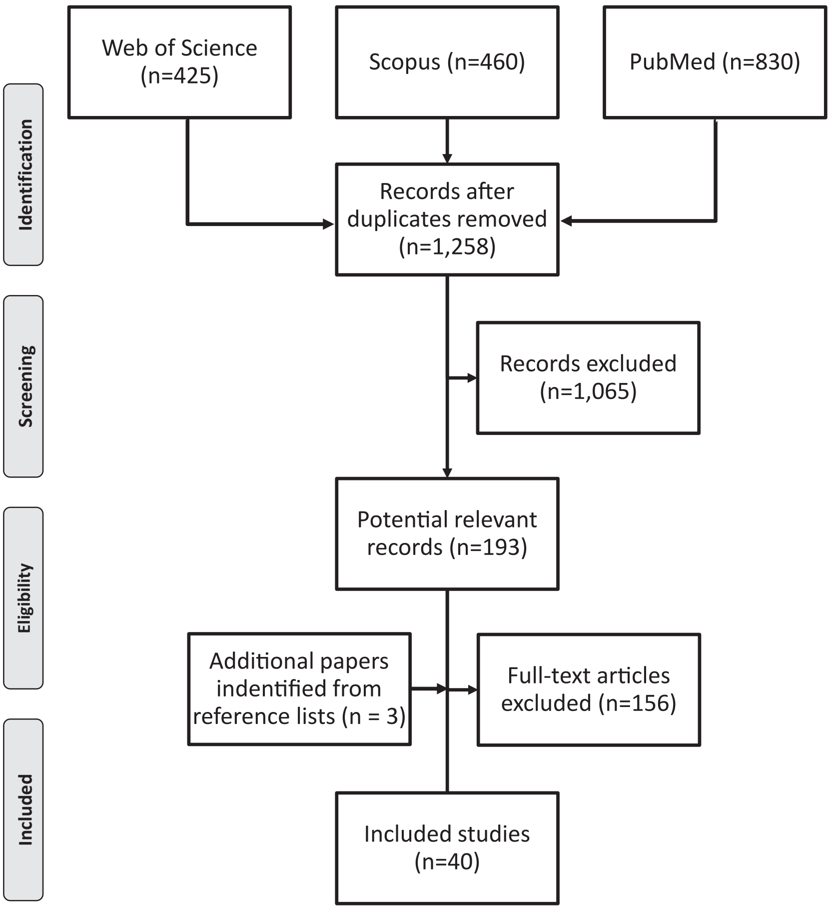

Figure 1 Flowchart illustrating the different phases of the search and study selection

Across the studies, we extracted data from 3,288 participants, the average age was 77.1 years and the average female ratio was 69.1%. The shortest duration of the exercise program was 6 weeks, and the longest was 60 weeks. As the main outcome, the following were used: 31× MMSE (Folstein et al., 1983), 5× MoCA (Nasreddine et al., 2005), 1× ERFC (Gil et al., 1986), and 3× ADAS-Cog (Mohs et al., 1997). The majority of participants lived in their own homes (21 studies). 19 studies came from Europe, 14 from Asia, 4 from South America, 2 from North America and 1 from Australia. The basic data on studies included in the analyses are presented in Table 3. All of the included studies were considered to have 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 The basic data on studies included in the analyses

Study	Year	Country	Duration (weeks)	Settings	N	Mean Age	Females (%)	Main Outcome
Arcoverde	2014	Brazil	16	H	20	78.5	60	MMSE
Arrieta	2020	Spain	36	N	88	84.8	71	MoCA
Bademli	2018	Turkey	20	N	60	72.2	60	MMSE
Bossers	2015	Netherlands	9	N	109	85.5	78	MMSE
Cancela	2016	Spain	60	H	114	80.6	43	MMSE
de Souto Barreto	2017	France	24	N	91	88.3	93	MMSE
Dorner	2007	Austria	10	LTC	30	86.8	77	MMSE
Enette	2020	France	9	Hos	52	77.0	65	MMSE
Fiatarone	2014	Australia	26	H	49	–	–	ADAS-Cog
Harris	2017	Canada	12	LTC	16	83.3	63	MMSE
Henskens	2018	Netherlands	26	N	44	85.1	77	MMSE
Holthoff	2015	Germany	12	H	30	72.4	53	MMSE
Hong	2018	South Korea	12	H	22	77.2	73	MoCA
Cheng	2014	Hong Kong	12	N	74	81.8	64	MMSE
Christofoletti	2008	Brazil	26	N	37	72.9	71	MMSE
Kemoun	2010	France	15	N	31	81.8	73	ERFC
Kwak	2008	South Korea	12	H	30	79.7	100	MMSE
Lam	2015	Hong Kong	52	H	278	75.5	77	MMSE
Lamb	2018	UK	26	Hos	443	77.0	55	ADAS-Cog
Langoni	2018	Brazil	24	H	52	72.6	77	MMSE
Lautenschlager	2008	Australia	24	H	170	68.7	50	ADAS-Cog
Miu	2008	Hong Kong	12	H	85	75.0	53	MMSE
Mollinedo Cardalda	2019	Spain	12	N	77	85.4	70	MMSE
Muscari	2009	Italy	52	H	120	69.6	50	MMSE

Study	Year	Country	Duration (weeks)	Settings	N	Mean Age	Females (%)	Main Outcome
Nascimento	2015	Brazil	26	H	45	66.7	80	MoCA
Qi	2019	China	12	H	32	70.6	69	MMSE
Sanders	2020	Netherlands	24	H	69	81.7	54	MMSE
Siu	2018	China	16	H	160	77.7	75	MMSE
Song	2019	China	16	H	120	75.8	75	MoCA
Sun	2015	China	26	H	138	68.3	81	MMSE
Tao	2019	China	24	H	57	65.5	68	MoCA
Toots	2017	Sweden	16	N	166	84.4	75	MMSE
Van de Winckel	2004	Belgium	6	Hos	25	81.3	100	MMSE
Varela	2012	Spain	12	N	48	76.2	56	MMSE
Venturelli	2011	Italy	26	N	24	83.0	83	MMSE
Vreugdenhil	2012	Australia	16	H	40	73.5	45	MMSE
Wei	2014	China	26	N	60	66.7	30	MMSE
Williamson	2009	US	52	H	102	76.8	72	MMSE
Yang	2015	China	12	Hos	50	72.6	60	MMSE
Yoon	2017	South Korea	12	H	30	75.0	100	MMSE

Note: MMSE – Mini-Mental State Examination; ERFC – Rapid Evaluation of Cognitive Function; ADAS-Cog – Alzheimer Disease Assessment Scale-Cognitive Subscale; MoCA – Montreal Cognitive Assessment; H – home; N – nursing home; Hos – hospital; LTC – long-term care facility.

Many types of exercise such walking, cycling, exercising with pneumatic resistance machines or therabands were used in the studies. Altogether 62.5% of control groups were enrolled in some additional activities such as education, one-to-one conversation, handicrafts, drinking tea with the nursing staff, watching videos or recreational activities. The other participants in the control groups were instructed to maintain their normal physical activities, or they were given standard care in nursing homes. The shortest session was only 15 minutes and the longest was 75 minutes, 60 minutes was the most usual (19×). The frequency of exercise program started at 2 sessions a week, and 3 sessions a week was the most frequent (21×). Four intervention programs required participants to exercise daily. Descriptions of intervention and control groups included in the review are presented in Table 5.

When we divided interventions according to cognitive impairment severity, duration of program, frequency of program, type of exercise, and activities in control groups we created 27 different categories. In general, 37.0% of intervention groups presented a statistically significant beneficial effect of physical activity, while only two presented a statistically significant harmful effect on cognitive functions. Nevertheless, 40.0% of control groups showed a significant decrease in cognitive functions and no group showed an increase. 54.3% of interventions had a statistically significant beneficial effect (Hedges' g significantly > 0). No intervention demonstrated a statistically significant harmful effect (Hedges' g significantly < 0). A statistically significant bene-

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	1	1	1	1	1	0	0	1	1	1	1	9
Arrieta	1	1	1	1	0	0	0	0	1	1	1	7
Bademli	1	1	1	1	0	0	0	1	1	1	1	8
Bossers	1	1	1	1	0	0	0	1	1	1	1	8
Cancela	1	1	1	1	0	0	1	0	1	1	1	8
de Souto Barreto	1	1	1	1	0	0	0	0	1	1	1	7
Dorner	1	1	1	1	1	0	0	1	1	1	1	9
Enette	1	1	1	1	0	0	0	0	1	1	1	7
Fiatarone	1	1	1	1	1	0	0	1	1	1	1	9
Harris	1	1	1	1	0	0	0	1	1	1	1	8
Henskens	1	1	1	1	0	0	1	0	1	1	1	8
Holthoff	1	1	1	1	0	0	0	1	1	1	1	8
Hong	1	1	1	1	0	0	0	0	1	1	1	7
Cheng	1	1	1	1	1	0	0	1	1	1	1	9
Christofoletti	1	1	1	1	0	0	1	1	1	1	1	9
Kemoun	1	1	1	1	0	0	0	0	1	1	1	7
Kwak	1	1	1	1	0	0	0	1	1	1	1	8
Lam	1	1	1	1	0	0	0	1	1	1	1	8
Lamb	1	1	1	0	0	0	0	1	1	1	1	7
Langoni	1	1	1	1	1	0	0	1	1	1	1	9

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
Lautenschlager	1	1	1	1	1	0	0	1	1	1	1	9
Miu	1	1	1	0	0	0	0	1	1	1	1	7
Mollinedo Cardalda	1	1	1	1	0	0	0	0	1	1	1	7
Muscari	1	1	1	1	0	0	0	1	1	1	1	8
Nascimento	1	1	1	1	1	0	0	1	1	1	1	9
Qi	1	1	1	1	0	0	0	0	1	1	1	7
Sanders	1	1	1	1	0	0	0	1	1	1	1	8
Siu	1	1	1	1	1	0	0	1	1	1	1	9
Song	1	1	1	1	0	0	0	0	1	1	1	7
Sun	1	1	1	1	1	0	0	1	1	1	1	9
Tao	1	1	1	1	1	0	0	1	1	1	1	9
Toots	1	1	1	1	1	0	0	1	1	1	1	9
Van de Winckel	1	1	1	0	0	0	0	1	1	1	1	7
Varela	1	1	1	1	0	0	0	0	1	1	1	7
Venturelli	1	1	1	1	0	0	0	0	1	1	1	7
Vreugdenhil	1	1	1	1	0	0	1	1	1	1	1	9
Wei	1	1	1	1	0	0	0	0	1	1	1	7
Williamson	1	1	1	1	0	0	1	1	1	1	1	9
Yang	1	1	1	1	0	0	0	1	1	1	1	8
Yoon	1	1	1	1	1	0	0	1	1	1	1	9

Table 5 Detailed description of intervention and control groups included in the review

	Intervention groups	
Study	**Main parts of interventions**	**Frequency (weekly)**
Arcoverde	30 min treadmill walking at 60% of VO_2max	2
Arrieta	25 min strength training – arm curl, chair stand, leg flexion and abduction	2
Bademl	40 min aerobics exercise 4× a week and 40 min walking 3× a week	7
Bossers	30 min walking	4
Bossers	30 min of strength sessions or walking sessions	4
Cancela	15 min cycling ergometer	7
de Souto Barreto	10–15 min of muscle strengthening (e.g., weight lifting), 20 minutes of aerobic exercise (mostly walking)	2
Dorner	25 min of strength training, 10 minutes of balance training	3
Enette	30 min of continuous aerobic training	2
Enette	30 min of interval aerobic training	2
Fiatarone	75 min on pneumatic resistance machines	3
Harris	15–30 min walking	3
Henskens	30–45 min combined strength and walking	3
Holthoff	30 min home-based motor-assisted or active resistive training of the legs	3
Hong	60 min exercise with an elastic band at 15-repetition maximum (65% of 1RM)	2
Cheng	60 min Tai Chi 12-form yang-style	3
Christofoletti	60 min kinesiotherapeutic exercises	3
Kemoun	60 min articular mobilization, muscle stimulation, and walking	3
Kwak	30–60 min chair exercises max. 60% VO_2 max	2–3
Lam	60 min stretching and toning exercise, one mind body exercise (e.g. Tai Chi) and one aerobic exercise session (e.g. static bicycle riding)	3

Lamb	70 min aerobic and strengthening exercise program of moderate to high intensity	2
Langoni	60 min exercise with elastic bands, balls, ankle weights, own body weight, and dumbbells	2
Lautenschlager	50 min walking, light strength training exercise, circuit gym exercise	3
Miu	60 min aerobic exercise training with treadmill, bicycle, arm ergometry and flexibility exercises	2
Mollinedo Cardalda	60 min strength training with therabands	2
Mollinedo Cardalda	60 min multi-calisthenics performed mostly in the seated position	2
Muscari	60 min cycle ergometer, treadmill and free-body activity at intensity 70% of maximal heart rate	3
Nascimento	60 min program aimed to stimulate aerobic metabolism	3
Qi	35 min dance with a target heart rate	3
Sanders	30 min walking and lower limb strength training program with 12 weeks low- and 12 weeks high-intensity training	3
Siu	60 min Tai Chi 24 yang-style simple form	2
Song	60 min aerobic stepping exercise program	3
Sun	60 min Tai Chi 24 yang-style simple form	2
Tao	60 min Baduanjin training	3
Tao	60 min brisk walking	3
Toots	40 min high-intensity functional exercises performed in weight bearing positions	5
Van de Winckel	30 min music-based dance therapy	7
Varela	30 min exercise on 60% of participant's heart rate reserve	3
Varela	30 min exercise on 40% of participant's heart rate reserve	3
Venturelli	30 min walking	4
Vreugdenhil	30 min upper and lower body strength and balance training in addition to at least 30 minutes of brisk walking	7
Wei	30 min handball training	5
Williamson	60 min combination of aerobic, strength, balance, and flexibility exercises	3

Yang	40 min cycling training at 70% of maximal intensity	3
Yoon	60 min elastic band training (tension: very low)	2
Yoon	60 min elastic band training (tension: high)	2

Control groups		
Study	**Activities**	**Frequency (weekly)**
Arcoverde	–	–
Arrieta	Activities will be low intensity: memory workshops, reading, singing, etc.	–
Bademli	–	–
Bossers	Four social visits each week	–
Cancela	Recreational activities - card-playing, reading, craftwork	–
de Souto Barreto	Social activity 60 min	2
Dorner	–	–
Enette	Interactive information sessions around multiple-choice questionnaires	1
Fiatarone	Watching 5 short National Geographic videos + tests and stretching and seated calisthenics	–
Harris	30–45 minute social visits from a student volunteer	1
Henskens	Drink tea with the nursing staff	3
Holthoff	–	–
Hong	–	–
Cheng	60 min simple handicrafts	3
Christofoletti	–	–
Kemoun	Manual and intellectual activities organized by the nursing home (pottery, painting, soft gymnastics, outings, etc.)	–
Kwak	–	–
Lam	At least three one-hour social activity sessions per week	–

Lamb	–	–
Langoni	–	–
Lautenschlager	Educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking	–
Miu	–	–
Mollinedo Cardalda	60 min crafts, reading comprehension and cognitive stimulation activities	2
Muscari	Educational materials about suggestions to improve lifestyle, including individualized self-administered programs to increase physical activity	–
Nascimento	–	–
Qi	–	–
Sanders	Flexibility exercises and recreational activities	–
Siu	–	–
Song	Health education program included eight bi-weekly educational classes (45 min/each session)	–
Sun	Playing cards or singing at the activity center	–
Tao	Health education every 8 weeks for 30 min per session	–
Toots	Participants conversed, sang, listened to music or readings, and/or looked at pictures and objects	–
Van de Winckel	One-to-one conversation	–
Varela	Recreational activities – playing cards, reading newspapers, handicrafts	–
Venturelli	Organized activities like bingo, patchwork sewing, and music therapy	–
Vreugdenhil	–	–
Wei	–	–
Williamson	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	–
Yang	Health education	–
Yoon	Static and dynamic stretching once a week for 60 min	–

Table 6 Effect of physical exercise on cognitively impaired older adults – borderline intact

	Exercise program		Intervention groups		Control groups		Effect size		
	Duration (weeks)	**Frequency (weekly)**	**Physical activity**	**Statistically significant effect**	**Control**	**Statistically significant effect**	**Hedges' g**	**95% CI lower**	**95% CI upper**
Hong, 2018	≤ 12	≤ 3	Resistance	No	Passive	No	0.23	−0.61	1.07
Qi, 2019	≤ 12	≤ 3	Dance	**Beneficial**	Passive	No	0.41	−0.29	1.11
Kemoun, 2010	> 12	≤ 3	Aerobic	**Beneficial**	Active	**Harmful**	**1.80**	**0.96**	**2.63**
Lam, 2015	> 12	≤ 3	Aerobic	No	Active	No	0.20	−0.03	0.44
Muscari, 2009	> 12	≤ 3	Aerobic	No	Active	**Harmful**	**0.43**	**0.06**	**0.79**
Song, 2019	> 12	≤ 3	Aerobic	No	Active	No	**1.87**	**1.44**	**2.30**
Tao, 2019	> 12	≤ 3	Aerobic	No	Active	No	−0.11	−0.76	0.53
Fiatarone, 2014	> 12	≤ 3	Resistance	No	Active	No	**0.83**	**0.25**	**1.42**
Lautenschlager, 2008	> 12	≤ 3	Combined	No	Active	**Harmful**	0.28	−0.02	0.58
Williamson, 2009	> 12	≤ 3	Combined	No	Active	No	−0.17	−0.56	0.22
Sun, 2015	> 12	≤ 3	Tai Chi	**Beneficial**	Active	No	**0.84**	**0.49**	**1.19**
Tao, 2019	> 12	≤ 3	Tai Chi	No	Active	No	0.52	−0.11	1.15
Nascimento, 2015	> 12	≤ 3	Aerobic	**Beneficial**	Passive	No	**0.70**	**0.10**	**1.30**
Siu, 2018	> 12	≤ 3	Tai Chi	No	Passive	No	**0.52**	**0.20**	**0.83**
Wei, 2014	> 12	> 3	Other	**Beneficial**	Passive	No	**1.37**	**0.81**	**1.93**

Table 7 Effect of physical exercise on cognitively impaired older adults – mild cognitive impairment

	Exercise program		Intervention groups		Control groups		Effect size		
	Duration (weeks)	Frequency (weekly)	Physical activity	Statistically significant effect	Control	Statistically significant effect	Hedges' g	95% CI lower	95% CI upper
Enette, 2020	≤ 12	≤ 3	Aerobic	No	Active	No	**2.23**	**1.38**	**3.08**
Enette, 2020	≤ 12	≤ 3	Aerobic	No	–	–	0.57	–0.08	1.22
Mollinedo Cardalda, 2019	≤ 12	≤ 3	Aerobic	No	Active	**Harmful**	0.41	–0.15	0.96
Yang, 2015	≤ 12	≤ 3	Aerobic	**Beneficial**	Active	**Harmful**	**1.03**	**0.44**	**1.62**
Yoon, 2017	≤ 12	≤ 3	Resistance	**Beneficial**	Active	**Harmful**	**3.66**	**2.23**	**5.09**
Yoon, 2017	≤ 12	≤ 3	Resistance	**Beneficial**	–	–	**1.89**	**0.71**	**3.08**
Cheng, 2014	≤ 12	≤ 3	Tai Chi	No	Active	No	**0.53**	**0.06**	**0.99**
Miu, 2008	≤ 12	≤ 3	Aerobic	**Harmful**	Passive	**Harmful**	–0.42	–0.85	0.02
Dorner, 2007	≤ 12	≤ 3	Resistance	**Beneficial**	Passive	No	**0.92**	**0.17**	**1.68**
Holthoff, 2015	≤ 12	≤ 3	Resistance	No	Passive	No	0.45	–0.27	1.18
Mollinedo Cardalda, 2019	≤ 12	≤ 3	Resistance	No	–	–	**0.94**	**0.38**	**1.51**
Varela, 2012	≤ 12	> 3	Aerobic	**Beneficial**	Active	**Harmful**	**1.58**	**0.78**	**2.37**
Varela, 2012	≤ 12	> 3	Aerobic	**Beneficial**	–	–	**1.47**	**0.68**	**2.27**
Arrieta, 2020	> 12	≤ 3	Resistance	No	Active	**Harmful**	**0.65**	**0.22**	**1.08**
Sanders, 2020	> 12	≤ 3	Combined	No	Active	No	–0.09	–0.57	0.38
Arcoverde, 2014	> 12	≤ 3	Aerobic	BENEFICIAL	Passive	**Harmful**	0.46	–0.43	1.35
Bademli, 2018	> 12	≤ 3	Aerobic	BENEFICIAL	Passive	**Harmful**	**3.93**	**3.07**	**4.80**
Langoni, 2018	> 12	≤ 3	Resistance	BENEFICIAL	Passive	**Harmful**	**2.96**	**2.17**	**3.74**
Lamb, 2018	> 12	≤ 3	Combined	No	Passive	No	–0.14	–0.34	0.06
Vreugdenhil, 2012	> 12	> 3	Resistance	**Beneficial**	Passive	**Harmful**	0.55	–0.08	1.18

Table 8 Effect of physical exercise on cognitively impaired older adults – moderate cognitive impairment

	Exercise program		Intervention groups		Control groups		Effect size		
	Duration (weeks)	**Frequency (weekly)**	**Physical activity**	**Statistically significant effect**	**Control**	**Statistically significant effect**	**Hedges´g**	**95% CI lower**	**95% CI upper**
Harris, 2017	≤ 12	≤ 3	Aerobic	No	Active	No	–0.31	–1.30	0.67
Bossers, 2015	≤ 12	> 3	Aerobic	No	Active	No	0.33	–0.14	0.79
Bossers, 2015	≤ 12	> 3	Combined	No	–	–	**0.77**	**0.29**	**1.24**
Van de Winckel, 2004	≤ 12	> 3	Dance	No	Active	No	0.79	–0.04	1.62
de Souto Barreto, 2017	> 12	≤ 3	Combined	No	Active	No	–0.15	–0.56	0.26
Henskens, 2018	> 12	≤ 3	Combined	No	Active	No	0.08	–0.51	0.67
Christofoletti, 2008	> 12	≤ 3	Other	**Beneficial**	Passive	No	**1.79**	**1.03**	**2.56**
Kwak, 2008	> 12	≤ 3	Aerobic	**Beneficial**	Passive	No	**1.41**	**0.61**	**2.20**
Cancela, 2016	> 12	> 3	Aerobic	No	Active	**Harmful**	**0.68**	**0.30**	**1.06**
Venturelli, 2011	> 12	> 3	Aerobic	No	Active	**Harmful**	**3.95**	**2.58**	**5.33**
Toots, 2017	> 12	> 3	Resistance	**Harmful**	Active	**Harmful**	–0.08	–0.39	0.22

ficial effect was found in: 52.7% of interventions with frequency ≤ 3 sessions weekly, 60% of interventions with frequency > 3 sessions weekly, 61.1% of aerobic exercise, 63.3% of resistance exercise, 35.3% of other exercise interventions, 50% of bordeline intact participants, 60% of participants with mild cognitive impairment, and 45.5% of participants with moderate cognitive impairment. The highest effect was found in Bademli (Bademli et al., 2018) in participants with mild cognitive impairment where the duration was > 12 with frequency ≤ 3 of aerobic exercise against a passive control Hedges' g = 3.82 (95% CI 2.97–4.67). On the other hand, an almost statistically significant harmful effect was found in the Miu study (Miu et al., 2008) with a similar design where the only difference was in the duration that was ≤ 12 weeks Hedges' g = −0.41 (95% CI −0.84–0.03). The effect of physical exercise on cognitively impaired older adults according to impairment severity is presented in Tables 6, 7 and 8.

DISCUSSION

It is well-established that cognitive functions decline gradually over time as part of the natural ageing process (Harada et al., 2013). The findings of this systematic review partly indicate that physical exercise may have the power to mitigate the cognitive decline process even in people with cognitive impairment. The similar findings were found in previous reviews where physical exercise had a positive effect on executive function (Gates et al., 2013; Song et al., 2018), and on global cognition (Groot et al., 2016; Wang et al., 2014; Ohman, 2014) in individuals with mild cognitive impairment. However, the new knowledge from this study is that the positive effect is stronger in people with a mild level of cognitive impairment and, above all, it points to a very strong negative effect of physical inactivity on cognitive function in the control groups.

However, it was practically impossible to merge the studies together into one analysis because so many different approaches were used regarding physical exercise activities, control group activities as well as the frequency of exercise program. Studies included in this review varied in terms of duration of exercise programs. In twenty-seven studies, the duration of interventions was less than half a year, and in another nineteen, the duration of the interventions was for more than or equal to half a year. According to our analysis, it seems that the duration of the exercise program was associated with cognitive decline, which may be caused by the natural cognitive decline during ageing. Surprisingly, the frequency of exercise per week did not play any significant role in global cognition.

It has been well described that the positive effect of aerobic exercise on brain health lies in the 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 (Black et al., 1990; Fordyceet al., 1991; Isaacs et al., 1992; Um et al., 2008).

Moreover, a higher number of female participants in intervention groups experienced 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 (Baker et al., 2010). 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 why gender may influence trial results. For instance, women have a higher lifetime risk of dementia (Chene et al., 2015), greater vulnerability to certain risk factors such as gender-specific chromosomes, APOE ε4, gender differences in hormone levels etc. (Snyder et al., 2016), and they demonstrate higher differential associations between biomarkers and cognitive impairment than men (Koran et al., 2017). Moreover, there was a higher percentage of female participants in the intervention studies (32 of 36 intervention groups had a majority of female participants). One reason for this fact could be higher life expectancy in females (Samaras et al., 2018) although the gender age gap has been narrowing in Europe recently (Kolip & Lange, 2018). Another explanation could be greater adherence to health-related exercise programs in older women (Aartolahti et al., 2015). Thus, it would be of interest to explain which of the above-mentioned proposed factors is responsible for gender differences.

It should be noted that one of the biggest limitations of this study was considerable heterogeneity in all the analyses which hampered the meta-analysis. In fact, heterogeneity is a common problem of meta-analyses on this topic (Gates et al., 2013; Ohman et al., 2014). Moreover, it was almost impossible to create a category with similar cognitive impairment because it varied considerably among the studies so the classification has some limitations, because if the variability was high then we could not be sure that all the participants were allocated correctly. The same is true for exercise interventions because the interventions included many different activities with different durations and intensities.

CONCLUSION

Despite the numerous limitations mentioned above, this study has shown that physical exercise may have the power to influence cognitive functions in people with cognitive impairment especially in people with a mild level of cognitive impairment. Such findings could have practical implications for recommending physical activity as a non-pharmacologic 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_{2max}	the maximum amount of oxygen the body can utilize during a specified period of usually intense exercise
WA	Weighted Averages

DECLARATIONS

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
This manuscript has not been previously submitted or published and is not under consideration in any other peer-reviewed media. To the best of our knowledge, no conflict of interest, financial or other, exists.

Funding
This research was supported by the Alzheimer Endowment Fund – AVAST, the project Q41, the AZV research project NV18-09-00587 of the Ministry of Health and project SVV 260466.

The funding agencies played no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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.

ACKNOWLEDGEMENTS

N/A

REFERENCES

Aartolahti, E., Tolppanen, A. M., Lonnroos, E., Hartikainen, S., Hakkinen, A. (2015). Health condition and physical function as predictors of adherence in long-term strength and balance training among community-dwelling older adults. *Archives of Gerontology and Geriatrics*, *61*(3), 452–457.

Arcoverde, C., Deslandes, A., Moraes, H., Almeida, C., de Araujo, N. B., Vasques, P. E., Silveira, H., Laks, J. (2014). Treadmill training as an augmentation treatment for Alzheimer's disease: A pilot randomized controlled study. *Arquivos de Neuro-Psiquiatria*, *72*(3), 190–196.

Arrieta, H., Rezola-Pardo, C., Kortajarena, M., Hervas, G., Gil, J., Yanguas, J. J., Iturburu, M., Gil, S. M., Irazusta, J., Rodriguez-Larrad, A. (2020). The impact of physical exercise on cognitive and affective functions and serum levels of brain-derived neurotrophic factor in nursing home residents: A randomized controlled trial. *Maturitas*, *131*(3), 72–77.

Bademli, K., Lok, N., Canbaz, M., Lok, S. (2019). Effects of Physical Activity Program on cognitive function and sleep quality in elderly with mild cognitive impairment: A randomized controlled trial. *Perspect Psychiatr Care*, *55*(3), 401–408.

Baker, L. D., Frank, L. L., Foster-Schubert, K., Green, P. S., Wilkinson, C. W., McTiernan, A., Plymate, S. R., Fishel, M. A., Watson, G. S., Cholerton, B. A. et al. (2010). Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Archives of Neurology*, *67*(1), 71–79.

Black, J. E., Isaacs, K. R., Anderson, B. J., Alcantara, A. A., Greenough, W. T. (1990). Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats *Proceedings of the National Academy of Sciences of the USA*, *87*(14), 5568–5572.

Blondell, S. J., Hammersley-Mather, R., Veerman, J. L. (2014). Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. *BMC Public Health*, *14*(1), 510.

Bossers, W. J., van der Woude, L. H., Boersma, F., Hortobagyi, T., Scherder, E. J., van Heuvelen, M. J. (2015). A 9-week aerobic and strength training program improves cognitive and motor function in patients with dementia: A randomized, controlled trial. *The American Journal of Geriatric Psychiatry*, *23*(11), 1106–1116.

Cancela, J. M., Ayan, C., Varela, S., Seijo, M. (2016). Effects of a long-term aerobic exercise intervention on institutionalized patients with dementia. *Journal of Science and Medicine in Sport*, *19*(4), 293–298.

de Souto Barreto, P., Cesari, M., Denormandie, P., Armaingaud, D., Vellas, B., Rolland, Y. (2017). Exercise or social intervention for nursing home residents with dementia: A pilot randomized, controlled trial. *Journal of the American Geriatrics Society*, *65*(9), E123–E129.

Dorner, T., Kranz, A., Zettl-Wiedner, K., Ludwig, C., Rieder, A., Gisinger, C. (2007). The effect of structured strength and balance training on cognitive function in frail, cognitive impaired elderly long-term care residents. *Aging clinical and experimental research*, *19*(5), 400–405.

Enette, L., Vogel, T., Merle, S., Valard-Guiguet, A. G., Ozier-Lafontaine, N., Neviere, R., Leuly-Joncart, C., Fanon, J. L., Lang, P. O. (2020). Effect of 9 weeks continuous vs. interval aerobic training on plasma BDNF levels, aerobic fitness, cognitive capacity and quality of life among seniors with mild to moderate Alzheimer's disease: a randomized controlled trial. *European Review of Aging and Physical Activity*, *17*, 2.

Fiatarone Singh, M. A., Gates, N., Saigal, N., Wilson, G. C., Meiklejohn, J., Brodaty, H., Wen, W., Singh, N., Baune, B. T., Suo, C. et al. (2014). The Study of Mental and Resistance Training (SMART) study-resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *Journal of the American Medical Directors Association*, *15*(12), 873–880.

Folstein, M. F., Robins, L. N., Helzer, J. E. (1983). The mini-mental state examination. *Archives of General Psychiatry*, *40*(7), 812.
Forbes, D., Forbes, S. C., Blake, C. M., Thiessen, E. J., Forbes, S. (2015). Exercise programs for people with dementia. *Cochrane Database Syst. Rev.*, Apr. 15, (4).
Fordyce, D. E., Farrar, R. P. (1991). Enhancement of spatial learning in F344 rats by physical activity and related learning-associated alterations in hippocampal and cortical cholinergic functioning. *Behavioural Brain Research*, *46*(2), 123–133.
Garuffi, M., Costa, J. L., Hernandez, S. S., Vital, T. M., Stein, A. M., dos Santos, J. G., Stella, F. (2013). Effects of resistance training on the performance of activities of daily living in patients with Alzheimer's disease. *Geriatrics & Gerontology International*, *13*(2), 322–328.
Gates, N., Fiatarone Singh, M. A., Sachdev, P. S., Valenzuela, M. (2013). The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. *American Journal of Geriatric Psychiatry, 21*(11), 1086–1097.
Gil, R., Toullat, G., Pluchon, C., Micheneau, D., Cariou, B., Rivault, L., Sicot, I., Boissonnot, L. (1986). Une méthode d'évaluation rapide des fonctions cognitives (ERFC), son application à la démence sénile de type Alzheimer. *Semin Hop Paris, 62*(27), 2127–2133.
Groot, C., Hooghiemstra, A. M., Raijmakers, P. G., van Berckel, B. N., Scheltens, P., Scherder, E. J., van der Flier, W. M., Ossenkoppele, R. (2016). The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing Research Reviews*, Jan, *25*, 13–23.
Harada, C. N., Natelson Love, M. C., Triebel, K. L. (2013). Normal cognitive aging. *Clin. Geriatr. Med.*, *29*(4), 737–752.
Harris, J. B., Johnson, C. S. (2017). The Impact of Physical versus Social Activity on the Physical and Cognitive Functioning of Seniors with Dementia. *Act. Adapt. Aging*, *41*(2), 161–174.
Hauer, K., Schwenk, M., Zieschang, T., Essig, M., Becker, C., Oster, P. (2012). Physical training improves motor performance in people with dementia: a randomized controlled trial. . *Journal of the American Geriatrics Society*, *60*(1), 8–15.
Hedges, L. (1981). Distribution Theory for Glass's Estimator of Effect Size and Related Estimators. *J. Educ. Behav. Stat.*, *6*(2), 107–128.
Henskens, M., Nauta, I. M., Van Eekeren, M. C. A., Scherder, E. J. A. (2018). Effects of Physical Activity in Nursing Home Residents with Dementia: A Randomized Controlled Trial. *Dementia and Geriatric Cognitive Disorders*, *46*(1–2), 60–80.
Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., Welch, V. A. (2019). *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd Edition. Chichester (UK): John Wiley & Sons.
Holthoff, V. A., Marschner, K., Scharf, M., Steding, J., Meyer, S., Koch, R., Donix, M. (2015). Effects of physical activity training in patients with Alzheimer's dementia: results of a pilot RCT study. *PLoS One*, *10*(4), e0121478.
Hong, S. G., Kim, J. H., Jun, T. W. (2018). Effects of 12-Week Resistance Exercise on Electroencephalogram Patterns and Cognitive Function in the Elderly With Mild Cognitive Impairment: A Randomized Controlled Trial. *Clinical Journal of Sport Medicine*, *28*(6), 500–508.
Chen, W. W., Zhang, X., Huang, W. J. (2016). Role of physical exercise in Alzheimer's disease. *Biomedical Reports*, *4*(4), 403–407.
Chene, G., Beiser, A., Au, R., Preis, S. R., Wolf, P. A., Dufouil, C., Seshadri, S. (2015). Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *The Journal of the Alzheimer's Association*, *11*(3), 310–320.

Cheng, S. T., Chow, P. K., Song, Y. Q., Yu, E. C., Chan, A. C., Lee, T. M., Lam, J. H. (2014). Mental and physical activities delay cognitive decline in older persons with dementia. *The American Journal of Geriatric Psychiatry*, *22*(1), 63–74.

Christofoletti, G., Oliani, M. M., Gobbi, S., Stella, F., Bucken Gobbi, L. T., Renato Canineu, P. (2008). A controlled clinical trial on the effects of motor intervention on balance and cognition in institutionalized elderly patients with dementia. *Clinical Rehabilitation*, *22*(7), 618–626.

Isaacs, K. R., Anderson, B. J., Alcantara, A. A., Black, J. E., Greenough, W. T. (1992). Exercise and the brain: angiogenesis in the adult rat cerebellum after vigorous physical activity and motor skill learning. *Journal of Cerebral Blood Flow & Metabolism*, *12*(1), 110–119.

Kemoun, G., Thibaud, M., Roumagne, N., Carette, P., Albinet, C., Toussaint, L., Paccalin, M., Dugue, B. (2010). Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. *Dementia and Geriatric Cognitive Disorders*, *29*(2), 109–114.

Kolip, P., Lange, C. (2018). Gender inequality and the gender gap in life expectancy in the European Union. *European Journal of Public Health*, *28*(5), 869–872.

Koran, M. E. I., Wagener, M., Hohman, T. J. (2017). Alzheimer's Neuroimaging, I. Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging Behavior*, *11*(1), 205–213.

Kwak, Y. S., Um, S. Y., Son, T. G., Kim, D. J. (2008). Effect of regular exercise on senile dementia patients. *International Journal of Sports Medicine*, *29*(6), 471–474.

Lam, L. C., Chan, W. C., Leung, T., Fung, A. W., Leung, E. M. (2015). Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. *PLoS One*, *10*(3), e0118173.

Lamb, S. E., Sheehan, B., Atherton, N., Nichols, V., Collins, H., Mistry, D., Dosanjh, S., Slowther, A. M., Khan, I., Petrou, S. et al. (2018). Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. *British Medical Journal*, *16*.

Langoni, C. D. S., Resende, T. L., Barcellos, A. B., Cecchele, B., Knob, M. S., Silva, T. D. N., Rosa, J. N. D., Diogo, T. S., Silva Filho, I. G. D., Schwanke, C. H. A. (2018). Effect of Exercise on Cognition, Conditioning, Muscle Endurance, and Balance in Older Adults With Mild Cognitive Impairment: A Randomized Controlled Trial. *Journal of Geriatric Physical Therapy*, May 4, 0000000000000191.

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J. G., Greenop, K. R., Almeida, O. P. (2009). Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease: A Randomized Trial. *Jama-Journal of the American Medical Association*, *301*(1), 276–276.

Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., Elkins, M. (2003). Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther*, *83*(8), 713–721.

Miu, D., Szeto, S. L., Mak, Y. F. (2008). A randomised controlled trial on the effect of exercise on physical, cognitive and affective function in dementia subjects. *Asian Journal of Gerontology & Geriatrics*, *3*, 8–16.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.*, *6*(7), e1000097.

Mohs, R. C., Knopman, D., Petersen, R. C., Ferris, S. H., Ernesto, C., Grundman, M., Sano, M., Bieliauskas, L., Geldmacher, D., Clark, C. et al. (1997). Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease

Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. *Alzheimer Disease & Associated Disorders, 11* (Suppl. 2), S13–21.
Mollinedo Cardalda, I., López, A., Cancela Carral, J. M. (2019). The effects of different types of physical exercise on physical and cognitive function in frail institutionalized older adults with mild to moderate cognitive impairment. A randomized controlled trial. *Archives of Gerontology and Geriatrics*, *83*, 223–230.
Muscari, A., Giannoni, C., Pierpaoli, L., Berzigotti, A., Maietta, P., Foschi, E., Ravaioli, C., Poggiopollini, G., Bianchi, G., Magalotti, D. et al. (2010). Chronic endurance exercise training prevents aging-related cognitive decline in healthy older adults: a randomized controlled trial. *International Journal of Geriatric Psychiatry*, *25*(10), 1055–1064.
Nascimento, C. M., Pereira, J. R., Pires de Andrade, L., Garuffi, M., Ayan, C., Kerr, D. S., Talib, L. L., Cominetti, M. R., Stella, F. (2015). Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different bdnf Val66Met genotypes. *Journal of Alzheimer's Disease*, *43*(1), 81–91.
Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699.
Ohman, H., Savikko, N., Strandberg, T. E., Pitkala, K. H. (2014). Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review. *Dementia and Geriatric Cognitive Disorders*, *38*(5–6), 347–365.
Pitkala, K. H., Poysti, M. M., Laakkonen, M. L., Tilvis, R. S., Savikko, N., Kautiainen, H., Strandberg, T. E. (2013). Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. *JAMA Internal Medicine*, *173*(10), 894–901.
Qi, M., Zhu, Y., Zhang, L., Wu, T., Wang, J. (2019). The effect of aerobic dance intervention on brain spontaneous activity in older adults with mild cognitive impairment: A resting-state functional MRI study. *Experimental and Therapeutic Medicine*, *17*(1), 715–722.
Rockwood, K., Middleton, L. (2007). Physical activity and the maintenance of cognitive function. *Alzheimer's Dementia*, *3*(Suppl. 2), S38–44.
Rolland, Y., Abellan van Kan, G., Vellas, B. (2008). Physical Activity and Alzheimer's Disease: From Prevention to Therapeutic Perspectives. *Journal of the American Medical Directors Association*, *9*(6), 390–405.
Roth, M., Huppert, F. A., Mountjoy, C. Q., Tym, E. (1998). *CAMDEX-R: The Cambridge Examination for Mental Disorders of the Elderly*. Cambridge: Cambridge University Press.
Samaras, T., Marson, S., Lillis, J. (2018). The close inverse relationship between male and female height and life expectancy. *Innovation in Aging*, *2*(Suppl. 1), 888–889.
Sanders, L. M. J., Hortobagyi, T., Karssemeijer, E. G. A., Van der Zee, E. A., Scherder, E. J. A., van Heuvelen, M. J. G. (2020). Effects of low- and high-intensity physical exercise on physical and cognitive function in older persons with dementia: a randomized controlled trial. *Alzheimer's Research & Therapy*, *12*(1), 28.
Shah, H., Albanese, E., Duggan, C., Rudan, I., Langa, K. M., Carrillo, M. C., Chan, K. Y., Joanette, Y., Prince, M., Rossor, M. et al. (2016). Research priorities to reduce the global burden of dementia by 2025. *Lancet Neurology*, *15*(12), 1285–1294.
Schwenk, M., Zieschang, T., Englert, S., Grewal, G., Najafi, B., Hauer, K. (2014). Improvements in gait characteristics after intensive resistance and functional training in people with dementia: a randomised controlled trial. *BMC Geriatrics*, *14*(1), 73.
Siu, M. Y., Lee, D. T. F. (2018). Effects of tai chi on cognition and instrumental activities of daily living in community dwelling older people with mild cognitive impairment. *BMC Geriatrics*, *18*(1), 37.
Snyder, H. M., Asthana, S., Bain, L., Brinton, R., Craft, S., Dubal, D. B., Espeland, M. A., Gatz, M., Mielke, M. M., Raber, J. et al. (2016). Sex biology contributions to vulnerability

to Alzheimer's disease: A think tank convened by the Women's Alzheimer's Research Initiative. *Alzheimer's Dementia*, *12*(11), 1186–1196.

Song, D., Yu, D. S. F. (2019). Effects of a moderate-intensity aerobic exercise programme on the cognitive function and quality of life of community-dwelling elderly people with mild cognitive impairment: A randomised controlled trial. *International Journal of Nursing Studies*, *93*, 97–105.

Song, D., Yu, D. S. F., Li, P. W. C., Lei, Y. (2018). The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis. *International Journal of Nursing Studies*, *79*, 155–164.

Steinberg, M., Leoutsakos, J. M., Podewils, L. J., Lyketsos, C. G. (2009). Evaluation of a home-based exercise program in the treatment of Alzheimer's disease: the Maximizing Independence in Dementia (MIND) study. *International Journal of Geriatric Psychiatry*, *24*(7), 680–705.

Stephen, R., Hongisto, K., Solomon, A., Lonnroos, E. (2017). Physical Activity and Alzheimer's Disease: A Systematic Review. *Journals of Gerontology Series A Biological Sciences and Medical Sciences*, *72*(6), 733–739.

Sun, J., Kanagawa, K., Sasaki, J., Ooki, S., Xu, H., Wang, L. (2015). Tai chi improves cognitive and physical function in the elderly: a randomized controlled trial. *Journal of Physical Therapy Science*, *27*(5), 1467–1471.

Tao, J., Liu, J., Chen, X., Xia, R., Li, M., Huang, M., Li, S., Park, J., Wilson, G., Lang, C. et al. (2019). Mind-body exercise improves cognitive function and modulates the function and structure of the hippocampus and anterior cingulate cortex in patients with mild cognitive impairment. *NeuroImage: Clinical*, *23*, 101834.

Toots, A., Littbrand, H., Bostrom, G., Hornsten, C., Holmberg, H., Lundin-Olsson, L., Lindelof, N., Nordstrom, P., Gustafson, Y., Rosendahl, E. (2017). Effects of Exercise on Cognitive Function in Older People with Dementia: A Randomized Controlled Trial. *Journal of Alzheimer's Disease*, *60*(1), 323–332.

Um, H. S., Kang, E. B., Leem, Y. H., Cho, I. H., Yang, C. H., Chae, K. R., Hwang, D. Y., Cho, J. Y. (2008). Exercise training acts as a therapeutic strategy for reduction of the pathogenic phenotypes for Alzheimer's disease in an NSE/APPsw-transgenic model. *International Journal of Molecular Medicine*, *22*, 529–539.

Van de Winckel, A., Feys, H., De Weerdt, W., Dom, R. (2004). Cognitive and behavioural effects of music-based exercises in patients with dementia. *Clinical Rehabilitation*, *18*(3), 253–260.

Varela, S., Ayan, C., Cancela, J. M., Martin, V. (2012). Effects of two different intensities of aerobic exercise on elderly people with mild cognitive impairment: a randomized pilot study. *Clinical Rehabilitation*, *26*(5), 442–450.

Venturelli, M., Scarsini, R., Schena, F. (2011). Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. *American Journal of Alzheimer's Disease & Other Dementias*, *26*(5), 381–388.

Vreugdenhil, A., Cannell, J., Davies, A., Razay, G. (2012). A community-based exercise programme to improve functional ability in people with Alzheimer's disease: a randomized controlled trial. *Scandinavian Journal of Caring Sciences*, *26*(1), 12–19.

Wang, C., Yu, J. T., Wang, H. F., Tan, C. C., Meng, X. F., Tan, L. (2014). Non-pharmacological interventions for patients with mild cognitive impairment: a meta-analysis of randomized controlled trials of cognition-based and exercise interventions. *Journal of Alzheimer's Disease*, *42*(2), 663–678.

Wei, X. H., Ji, L. L. (2014). Effect of handball training on cognitive ability in elderly with mild cognitive impairment. *Neuroscience Letters*, *566*, 98–101.

Williamson, J. D., Espeland, M., Kritchevsky, S. B., Newman, A. B., King, A. C., Pahor, M., Guralnik, J. M., Pruitt, L. A., Miller, M. E., Investigators, L. S. (2009). Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. *Journals of Gerontology Series A Biological Sciences and Medical Sciences*, *64*(6), 688–694.

Winblad, B., Amouyel, P., Andrieu, S., Ballard, C., Brayne, C., Brodaty, H., Cedazo-Minguez, A., Dubois, B., Edvardsson, D., Feldman, H. et al. (2016). Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurology*, *15*(5), 455–532.

Yang, S. Y., Shan, C. L., Qing, H., Wang, W., Zhu, Y., Yin, M. M., Machado, S., Yuan, T. F., Wu, T. (2015). The Effects of Aerobic Exercise on Cognitive Function of Alzheimer's Disease Patients. *CNS & Neurological Disorders-Drug Targets*, *14*(10), 1292–1297.

Yoon, D. H., Kang, D., Kim, H. J., Kim, J. S., Song, H. S., Song, W. (2017). Effect of elastic band-based high-speed power training on cognitive function, physical performance and muscle strength in older women with mild cognitive impairment. *Geriatrics & Gerontology International*, *17*(5), 765–772.