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

Lenka Sontakova  
Univerzita Karlova Fakulta telesne vychovy a sportu

Alzbeta Bartova  
Univerzita Karlova Fakulta humanitnich studii

Klara Dadova (dadova.klara@gmail.com)  
Univerzita Karlova Fakulta telesne vychovy a sportu  https://orcid.org/0000-0003-3164-2236

Iva Holmerova  
Univerzita Karlova Fakulta humanitnich studii

Michal Steffl  
Univerzita Karlova Fakulta telesne vychovy a sportu

Research article

Keywords: Physical activity, Dementia, Aging, Meta-analysis, Aerobic exercise, Cognitive function

DOI: https://doi.org/10.21203/rs.3.rs-15634/v3

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
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 - borderline intact, mild, and moderate 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, duration and frequency of exercise program on the global cognitive function.

Results: Data from 40 studies involving 1,780 participants from intervention groups and 1,508 participants from control groups were analyzed. After sensitivity analysis, physical exercise had a positive effect on cognitive functions in people across all levels of cognitive impairments, SMD (95% confidence interval [CI]) = 0.41 (0.29 - 1.54). All the activities were significantly associated with better results in global cognitive functions when compared to active control (B = 0.538 in aerobic, 0.999 in resistance, 0.640 in combined exercise and 0.746 in Tai Chi). Age was significantly associated with global cognitive functions decreasing and a higher number of female participants in intervention groups had a statistically significant effect on the global cognitive function (B = 0.021).

Conclusions: Physical exercise was associated with cognitive function improvement in older people with cognitive impairments. Cognitive impairment severity was not associated with cognitive functions changes after exercise interventions.

Background

The number of older adults with dementia is on the rise due to a 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 institutionalization in some cases [2]. Thus, dementia impacts not only 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 [3]. 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 [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 and duration of exercise program. We hypothesized that there is 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.

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, exercise program duration, 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)
• the participants had to be diagnosed with a cognitive impairment according to one of the standardized tools
• written in the English language

Following global cognitive function tests were considered appropriate:

• Cambridge Cognitive Examination (CAMCOG) [20]
• Mini-Mental State Examination (MMSE) [21]
• Rapid Evaluation of Cognitive Function (ERFC) [22]
• Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) [23]
• Montreal Cognitive Assessment (MoCA) [24].

Concerning the exercise programs, only exercise activities that required increased energy output were included. All intervention groups from studies with a combination of physical exercise and cognitive training were excluded.

Exercise intervention and control group classification

We divided interventions into four categories accordingly:

1. Aerobic exercise - walking, stretching, ergometer cycling, as well as activities generally specified as “aerobic exercise”
2. Resistance exercise - strengthening exercise with elastic bands, balls, ankle weights, own body weight, dumbbells, resistance machines training, strength training, and activities generally specified as “resistance exercise”
3. Combined exercise - if the intervention program included both aerobic and resistance exercise, then music-based dance therapy, kinesiotherapeutic exercise, and handball training
4. Tai Chi - for significant similarity baduanjin was also included

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”.

We also analyzed the duration of exercise program, frequency of exercise, and female ratios. For exercise program duration and frequency of exercise per week, we used the same classification as Forbes at al (2013) in 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” [25].

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.
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 [26].

We collected the following data for both 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, 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 a mean of the baseline using the standard classification of each diagnostic tools.

Data analysis

The standardized mean difference (SMD) was calculated from the sample size, mean post-pre intervention score with SD from intervention and control groups. The random effect models were used for all the analyses [27]. If there were no available data, we calculated the mean of post-pre intervention score as a mean of the post-intervention score - a mean of the pre-intervention score. The SD we estimated as: See formula 1 in the supplementary files.

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

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]. We made a sensitivity analysis using funnel plots to eliminate heterogeneity. Additionally, we calculated SMD for intervention as well as control groups separately. Then generalized linear models were used to estimate the influences of selected factors and covariates to the SMD as the continuous 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 the 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

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 impairments. Figure 1 shows the PRISMA flow diagram. Across the studies, we extracted data from 3,288 participants, all being over 50 years of age (69.1% females). The majority of interventions was aerobic exercise (18 out of 46) and the frequency of exercise varied between two and seven sessions per week. The shortest duration of the exercise program was 6 weeks, and the longest was 60 weeks. As the main outcome, the following were used: 31x MMSE [21], 5x MoCA [24], 1x ERFC [22], and 3x ADAS-Cog [23]. 25 out of the 40 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. 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, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68]. 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.

17 out of 46 intervention groups presented a statistically significant beneficial effect of physical activity, while only two presented a significant harmful effect on cognitive functions. While more than one-third of the interventions were beneficial, 16 out of 40 controls showed a significant decrease in cognitive functions. However, in moderate cognitive impairment, only combined exercise was statistically beneficial (Table 5).
In general, and after sensitivity analysis, physical exercise had a positive effect on cognitive functions in people with cognitive impairment SMD (95 % CI) = 0.41 (0.29 - 0.54); heterogeneity was low $\hat{\eta}^2 = 24 \%$. In separate groups and according to the cognitive impairment severity, the exercise had statistically significant effect SMD (95 % CI) = 0.32 (0.18 - 0.47) $\hat{\eta}^2 = 0\%$ in borderline intact and 0.64 (0.44 - 0.84) $\hat{\eta}^2 = 0\%$ in mild cognitive impairment respective. Nevertheless, there was not significant effect in moderate cognitive impairment SMD (95 % CI) = 0.20 (-0.18 - 0.58) $\hat{\eta}^2 = 53\%$. 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 any type of exercise caused a significant increase in SMD estimate. Aerobic exercise $\beta = 0.538$, resistance exercise $\beta = 0.999$, combined exercise $\beta = 0.640$, and Tai Chi $\beta = 0.746$. When comparing the passive groups to the active groups, no significant effect was found $\beta = 0.038$. Age was significantly negatively associated with global cognitive functions $\beta = -0.026$. Cognitive impairment level, as well as the duration of exercise program, were not significantly associated with SMD estimate. The result of the generalized linear model of intervention and control groups is presented in Table 6.

For the intervention groups, there was not any significant association between SMD estimate and type of exercise, cognitive impairment, as well as the frequency of exercise. Age played a significant negative role ($\beta = -0.048$), and a higher number of women in intervention groups had a statistically significant positive effect ($\beta = 0.021$). The result of the generalized linear model of intervention groups separately is presented in Table 7.

**Discussion**

It is well-established that cognitive functions decline gradually over time as part of the natural ageing process [69]. 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 a twice higher impact on cognitive functions than resistance exercise when compared to active controls, which was four times higher when only the interventions groups were compared. Previous studies partly confirm these results demonstrating a positive effect of physical exercise on executive functions [14, 15], and on 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 [70, 71, 72, 73].

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 [74]. 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 [75], greater vulnerability to certain risk factors such as sex-specific chromosomes, APOE ε4, sex differences in hormone levels etc. [76], and they demonstrate higher differential associations between biomarkers and cognitive impairment than men [77]. Moreover, there was a higher percentage of female participants in the intervention studies (40 of 46 intervention groups had a majority of female participants). One reason for this fact could be higher life expectancy in females [78] although the gender gap has been narrowing in Europe recently [79]. Another explanation could be greater adherence to health-related exercise programs in older women [80]. 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 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 should be noted that several limitations are involved in this study. Before the sensitivity analysis, there was considerable heterogeneity in all the analyses. In fact, heterogeneity is a common problem when conducting meta-analyses on this topic [14, 18]. Nevertheless, using general linear models involved some limitations too. For example, we used only individual SMD 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 so the classification has some limitations, because if the variability was
high then we could not be sure that all the participants were allocated rightly. 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 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.

**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.

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

**List Of Abbreviations**

| Abbreviation | Description |
|--------------|-------------|
| 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 |
References

1. Shah H, Albanese E, Duggan C, et al. Research priorities to reduce the global burden of dementia by 2025. Lancet Neurol. 2016;15(12):1285-1294.

2. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. Lancet Neurol. 2016;15(5):455-532.

3. Rolland Y, Abellan van Kan G, Vellas B. Physical activity and Alzheimer’s disease: from prevention to therapeutic perspectives. J Am Med Dir Assoc. 2008;9(6):390-405.

4. Rockwood K, Middleton L. Physical activity and the maintenance of cognitive function. Alzheimers Dement. 2007;3(2 Suppl):S38-44.

5. Stephen R, Hongisto K, Solomon A, Lonroos E. Physical activity and Alzheimer’s disease: a systematic review. J Gerontol A Biol Sci Med Sci. Jun 1 2017;72(6):733-739.

6. Blondell SJ, Hammersley-Mather R, Veerman JL. Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. BMC Public Health. 2014;14:510.

7. Chen WW, Zhang X, Huang WJ. Role of physical exercise in Alzheimer’s disease. Biomed Rep. 2016;4(4):403-407.

8. Hauer K, Schwenk M, Zieschang T, Essig M, Becker C, Oster P. Physical training improves motor performance in people with dementia: a randomized controlled trial. J Am Geriatr Soc. 2012;60(1):8-15.

9. Schwenk M, Zieschang T, Englert S, Grewal G, Najafi B, Hauer K. Improvements in gait characteristics after intensive resistance and functional training in people with dementia: a randomized controlled trial. BMC Geriatrics. 2014;14(1):73.

10. Garuffi M, Costa JL, Hernandez SS, et al. Effects of resistance training on the performance of activities of daily living in patients with Alzheimer's disease. Geriatr Gerontol Int. 2013;13(2):322-328.

11. Pitkala KH, Poysti MM, Laakkonen ML, et al. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. JAMA Intern Med. 2013;173(10):894-901.

12. Steinberg M, Leoutsakos JM, Podewils LJ, Lyketsos CG. Evaluation of a home-based exercise program in the treatment of Alzheimer's disease: the Maximizing Independence in Dementia (MIND) study. Int J Geriatr Psychiatry. 2009;24(7):680-685.

13. Karssemeijer EGA, Aaronson JA, Bossers WJ, Smits T, Olde Rikkert MGM, Kessels RPC. Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis. Ageing Res Rev. 2017;40:75-83.

14. Gates N, Fiatarone Singh MA, Sachdev PS, Valenzuela M. The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. Am J Geriatr Psychiatry. 2013;21(11):1086-1097.

15. Song D, Yu DSF, Li PWC, Lei Y. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis. Int J Nurs Stud. 2018;79:155-164.

16. Groot C, Hooghiemstra AM, Rajmakers PG, et al. The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Res Rev. 2016;25:13-23.

17. Wang C, Yu JT, Wang HF, Tan CC, Meng XF, Tan L. Non-pharmacological interventions for patients with mild cognitive impairment: a meta-analysis of randomized controlled trials of cognition-based and exercise interventions. J Alzheimers Dis. 2014;42(2):663-678.

18. Ohman H, Savikko N, Strandberg TE, Pitkala KH. Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review. Dement Geriatr Cogn Disord. 2014;38(5-6):347-365.

19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
20. Roth M, Huppert FA, Mountjoy CQ, Tym E. CAMDEX–R: The Cambridge Examination for Mental Disorders of the Elderly. Cambridge: Cambridge University Press; 1998.

21. Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. Archives of General Psychiatry. 1983;40(7):812-812.

22. Gil R, Toullat G, Pluchon C, et al. Une méthode d'évaluation rapide des fonctions cognitives (ERFC), son application à la déméline séniile de type Alzheimer. Semin Hop Paris. 1986;62:2127–2133.

23. Mohs RC, Knopman D, Petersen RC, et al. 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 Dis Assoc Disord. 1997;11 Suppl 2:S13-21.

24. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-699.

25. Forbes D, Thiessen EJ, Blake CM, Forbes SC, Forbes S. Exercise programs for people with dementia. Cochrane Database Syst Rev. 2013;12.

26. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83(8):713-721.

27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 6 2003;327(7414):557-560.

28. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97-111.

29. Holthoff VA, Marschner K, Scharf M, et al. Effects of physical activity training in patients with Alzheimer's dementia: results of a pilot RCT study. PLoS One. 2015;10(4):e0121478.

30. Hong SG, Kim JH, Jun TW. Effects of 12-week resistance exercise on electroencephalogram patterns and cognitive function in the elderly with mild cognitive impairment: a randomized controlled trial. Clin J Sport Med. 2018;28(6):500-508.

31. Cheng ST, Chow PK, Song YQ, et al. Mental and physical activities delay cognitive decline in older persons with dementia. Am J Geriatr Psychiatry. 2014;22(1):63-74.

32. Christoforetti G, Oliani MM, Gobbi S, Stella F, Bucken Gobbi LT, Renato Canineu P. A controlled clinical trial on the effects of motor intervention on balance and cognition in institutionalized elderly patients with dementia. Clin Rehabil. 2008;22(7):618-626.
44. Kemoun G, Thibaud M, Roumagne N, et al. Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord. 2010;29(2):109-114.

45. Kwak YS, Um SY, Son TG, Kim DJ. Effect of regular exercise on senile dementia patients. Int J Sports Med. 2008;29(6):471-474.

46. Lam LC, Chan WC, Leung T, Fung AW, Leung EM. 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. 2015;10(3):e0118173.

47. Lamb SE, Sheehan B, Atherton N, et al. Dementia and physical activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. BMJ. 2018;16(361).

48. Langoni CDS, Resende TL, Barcellos AB, et al. Effect of exercise on cognition, conditioning, muscle endurance, and balance in older adults with mild cognitive impairment: a randomized controlled trial. J Geriatr Phys Ther. 2019;42(2):E15-E22.

49. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2009;301(3):276-276.

50. Miu D, Szeto SL, Mak YF. A randomised controlled trial on the effect of exercise on physical, cognitive and affective function in dementia subjects. Asian J Gerontol Geriatr. 2008;3:8-19.

51. Mollinedo Cardalda IA, López A, Cancela Carral JM. 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. Arch Gerontol Geriatr. 2019;83:223-230.

52. Muscani A, Giannoni C, Pierpaoli L, et al. Chronic endurance exercise training prevents aging-related cognitive decline in healthy older adults: a randomized controlled trial. Int J Geriatr Psychiatry. 2010;25(10):1055-1064.

53. Nascimento CM, Pereira JR, Pires de Andrade L, et al., Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different bdnf Val66Met genotypes. J Alzheimers Dis. 2015;43(1):81-91.

54. Qi M, Zhu Y, Zhang L, Wu T, Wang J. The effect of aerobic dance intervention on brain spontaneous activity in older adults with mild cognitive impairment: A resting-state functional MRI study. Exp Ther Med. 2019;17(1):715-722.

55. Sanders LMJ, Hortobagyi T, Karssemeijer EGA, Van der Zee EA, Scherder EJA, van Heuvelen MJG. Effects of low- and high-intensity physical exercise on physical and cognitive function in older persons with dementia: a randomized controlled trial. Alzheimer Dis. 2020;12(1):28.

56. Siu MY, Lee DTF. Effects of tai chi on cognition and instrumental activities of daily living in community dwelling older people with mild cognitive impairment. BMC Geriatr. 2018;18(1):018-0720.

57. Song D, Yu DSF. 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. Int J Nurs Stud. 2019;93:97-105.

58. Sun J, Kanagawa K, Sasaki J, Ooki S, Xu H, Wang L. Tai chi improves cognitive and physical function in the elderly: a randomized controlled trial. J Phys Ther Sci. 2015;27(5):1467-1471.

59. Tao J, Liu J, Chen X, et al. Mind-body exercise improves cognitive function and modulates the function of the hippocampus and anterior cingulate cortex in patients with mild cognitive impairment. Neuroimage Clin. 2019;23:101834.

60. Toots A, Littbrand H, Bostrom G, et al. Effects of Exercise on Cognitive Function in Older People with Dementia: A Randomized Controlled Trial. J Alzheimers Dis. 2017;60(1):323-332.

61. Van de Winckel A, Feys H, De Weerdt W, Dom R. Cognitive and behavioural effects of music-based exercises in patients with dementia. Clin Rehabil. 2004;18(3):253-260.

62. Varela S, Ayan C, Cancela JM, Martin V. Effects of two different intensities of aerobic exercise on elderly people with mild cognitive impairment: a randomized pilot study. Clin Rehabil. 2012;26(5):442-450.

63. Venturelli M, Scarsini R, Schena F. Six-month walking program changes cognitive and ADL performance in patients with Alzheimer. Am J Alzheimer Dis Other Demen. 2011;26(5):381-388.

64. Vreugdenhil A, Cannell J, Davies A, Razay G. A community-based exercise programme to improve functional ability in people with Alzheimer's disease: a randomized controlled trial. Scand J Caring Sci. 2012;26(1):12-19.

65. Wei XH, Ji LL. Effect of handball training on cognitive ability in elderly with mild cognitive impairment. Neurosci Lett. 2014;566:98-101.

66. Williamson JD, Espeland M, Kritchevsky SB, et al. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. J Gerontol A Biol Sci Med Sci. 2009;64(6):688-694.

67. Yang SY, Shan CL, Qing H, et al. The effects of aerobic exercise on cognitive function of Alzheimer's disease patients. CNS Neurol Disord Drug Targets. 2015;14(10):1292-1297.

68. Yoon DH, Kang D, Kim HJ, Kim JS, Song HS, Song W. Effect of elastic band-based high-speed power training on cognitive function, physical performance and muscle strength in older women with mild cognitive impairment. Geriatr Gerontol Int. 2017;17(5):765-772.
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).                                                                                                                                                                                                                                                                                                      | 5                 |
| 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.                                                                                                                                                                                                                                                          | 5-7               |
| 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.                                                                                                                                                                                                                                                  | 7, 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).                                                                                                                                                                                                                                                                                                                                      | 8                 |
| Synthesis of results  | 14 | Describe the methods of handling                                                                                                                                                                                                                                                                                                                                                                                   | 8-9               |
data and combining results of studies, if done, including measures of consistency (e.g., \( I^2 \)) for each meta-analysis.

**Risk of bias across studies**

Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).

**Additional analyses**

Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

---

**RESULTS**

**Study selection**

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.

**Study characteristics**

For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.

**Risk of bias within studies**

Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

**Results of individual studies**

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.

**Synthesis of results**

Present results of each meta-analysis done, including confidence intervals and measures of consistency.

**Risk of bias across studies**

Present results of any assessment of risk of bias across studies (see item 15).

**Additional analysis**

Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).

---

**DISCUSSION**

**Summary of evidence**

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).

**Limitations**

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).

**Conclusions**

Provide a general interpretation of the results in the context of other evidence, and implications for future research.

---

**FUNDING**

**Funding**

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

---

**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: (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 ( 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]) | 830    |
Table 3 Studies included in the analyses
| Study                | Year | Main parts of interventions, frequency and duration of exercise program | Group size | Main Outcome  |
|---------------------|------|------------------------------------------------------------------------|------------|---------------|
| Arcoverde [29]      | 2014 | 30 min treadmill walking at 60% of VO₂max; 2x a week; 16 weeks          | 10         | MMSE          |
| Arrieta [30]        | 2020 | 25 min strength training - arm curl, chair stand, leg flexion and abduction; 2x a week; 20 weeks | 45         | MoCA          |
| Bademli [31]        | 2018 | 40 min aerobics exercise 4x a week and 40 min walking 3x a week        | 30         | MMSE          |
| Bossers [32]        | 2015 | 30 min walking; 36 individualized sessions in 9 weeks                  | 36         | MMSE          |
| Bossers [32]        | 2015 | 30 min of strength sessions or walking sessions; 18 and 18 individualized sessions in 9 weeks | 37         | MMSE          |
| Cancela [33]        | 2016 | 15 min cycling ergometer; 7x a week; 60 weeks                           | 51         | MMSE          |
| de Souto Barreto [34]| 2017 | 10-15 min of muscle strengthening (e.g., weight lifting), 20 minutes of aerobic exercise (mostly walking); 2x a week; 24 weeks | 44         | MMSE          |
| Dorner [35]         | 2007 | 25 min of strength training, 10 minutes of balance training; 3x a week; 10 weeks | 15         | MMSE          |
| Enette [36]         | 2020 | 30 min of continuous aerobic training 2x a week; 9 weeks               | 14         | MMSE          |
| Enette [36]         | 2020 | 30 min of interval aerobic training 2x a week; 9 weeks                 | 17         | MMSE          |
| Fiatarone [37]      | 2014 | 75 min on pneumatic resistance machines; 3x a week; 6 months          | 22         | ADAS-Cog      |
| Harris [38]         | 2017 | 15-30 min walking; 3x a week; 12 weeks                                 | 8          | MMSE          |
| Henskens [39]       | 2018 | 30-45 min combined strength and walking; 3x a week; 6 months          | 22         | MMSE          |
| Holthoff [40]       | 2015 | 30 min home-based motor-assisted or active resistive training of the legs; 3x a week; 12 weeks | 15         | MMSE          |
| Hong [41]           | 2018 | 60 min exercise with an elastic band at 15-repetition maximum (65% of 1RM); 2x a week; 12 weeks | 10         | MoCA          |
| Cheng [42]          | 2014 | 60 min tai chi 12-form yang style; 3x a week; 12 weeks                | 39         | MMSE          |
| Christofoletti [43]| 2008 | 60 min kinesitherapeutic exercises; 3x a week; 6 months               | 17         | MMSE          |
| Kemoun [44]         | 2010 | 60 min articular mobilization, muscle stimulation, and walking; 3x a week; 15 weeks | 16         | ERFC          |
| Kwak [45]           | 2008 | 30 - 60 min chair exercises max. 60% VO₂ max; 2-3x a week; 12 months   | 15         | MMSE          |
| Lam [46]            | 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        | MMSE          |
| Lamb [47]           | 2018 | 70 min aerobic and strengthening exercise program of moderate to high intensity; 2x a week; 6 months | 298        | ADAS-Cog      |
| Langoni [48]        | 2018 | 60 min exercise with elastic bands, balls, ankle weights, own body weight, and dumbbells; 2x a week; 24 weeks | 26         | MMSE          |
| Lautenschlager [49]| 2008 | 50 min walking, light strength training exercise, circuit gym exercise; 3x a week; 24 weeks | 85         | ADAS-Cog      |
| Miu [50]            | 2008 | 60 min aerobic exercise training with treadmill, bicycle, arm ergometry and flexibility exercises; 2x a week; 12 weeks | 36         | MMSE          |
| Mollinedo Cardalda [51] | 2019 | 60 min strength training by means of Therabands; 2x a week; 12 weeks | 25         | MMSE          |
| Mollinedo Cardalda [51] | 2019 | 60 min multi-calisthenics performed mostly in the seated position; 2x a week; 12 weeks | 23         | MMSE          |
| Muscari [52]        | 2009 | 60 min cycle ergometer, treadmill and free-body activity at intensity 70% of maximal heart rate; 3x a week; 12 months | 60         | MMSE          |
| Nascimento [53]     | 2015 | 60 min program aimed to stimulate aerobic metabolism; 3x a week; 6 months | 24         | MoCA          |
| Study                  | Year | Activities                                                                 | Control groups Group size | Main Outcome |
|-----------------------|------|----------------------------------------------------------------------------|---------------------------|--------------|
| Qi [54]               | 2019 | 35 min dance with a target heart rate; 3x a week; 12 weeks                | 16 MMSE                  |              |
| Sanders [55]          | 2020 | 30 min walking and lower limb strength training program with 12 weeks low- and 12 weeks high-intensity training; 3x a week; 24 weeks | 39 MMSE                  |              |
| Siu [56]              | 2018 | 60 min tai chi 24 yang-style simple form; 2x a week; 16 weeks             | 80 MMSE                  |              |
| Song [57]             | 2019 | 60 min aerobic stepping exercise program; 3x a week; 16 weeks             | 60 MoCA                  |              |
| Sun [58]              | 2015 | 60 min tai chi 24 yang-style simple form; 2x a week; 12 weeks              | 72 MMSE                  |              |
| Tao [59]              | 2019 | 60 min Baduanjin training; 3x a week; 24 weeks                            | 20 MoCA                  |              |
| Tao [59]              | 2019 | 60 min brisk walking; 3x a week; 24 weeks                                 | 17 MoCA                  |              |
| Toots [60]            | 2017 | 40 min high-intensity functional exercises performed in weight bearing positions; 5x per two-week; 16 weeks | 81 MMSE                  |              |
| Van de Winckel [61]   | 2004 | 30 min music-based dance therapy; 7x a week; 6 weeks                      | 15 MMSE                  |              |
| Varela [62]           | 2012 | 30 min exercise on 60% of participant’s heart rate reserve; 3x a week; 12 weeks | 16 MMSE                  |              |
| Varela [62]           | 2012 | 30 min exercise on 40% of participant’s heart rate reserve; 3x a week; 12 weeks | 17 MMSE                  |              |
| Venturelli [63]       | 2017 | 30 min walking; 4x a week; 6 months                                       | 12 MMSE                  |              |
| Vreugdenhil [64]      | 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 MMSE                  |              |
| Wei [65]              | 2014 | 30 min handball training; 5x a week; 6 months                             | 30 MMSE                  |              |
| Williamson [66]       | 2009 | 60 min combination of aerobic, strength, balance, and flexibility exercises; 3x a week; 12 months | 50 MMSE                  |              |
| Yang [67]             | 2015 | 40 min cycling training at 70% of maximal intensity; 3x a week; 12 weeks  | 25 MMSE                  |              |
| Yoon [68]             | 2017 | 60 min elastic band training (tension: very low); 2x a week; 12 weeks     | 14 MMSE                  |              |
| Yoon [68]             | 2017 | 60 min elastic band training (tension: high); 2x a week; 12 weeks         | 9 MMSE                   |              |
| Study                | Year | Interventions                                                                 | PEDro Score | Outcome Measure |
|---------------------|------|-------------------------------------------------------------------------------|-------------|-----------------|
| Lautenschlager [49] | 2008 | Educational material about memory loss, stress management, healthful diet, alcohol consumption, and smoking | 85          | ADAS-Cog        |
| Miu [50]            | 2008 | -                                                                             | 49          | MMSE            |
| Mollinedo Cardalda [51] | 2019 | 60 min crafts, reading comprehension and cognitive stimulation activities; 2x a week; 12 weeks | 29          | MMSE            |
| Muscari [52]        | 2009 | Educational materials about suggestions to improve lifestyle, including individualized self-administered programs to increase physical activity | 60          | MMSE            |
| Nascimento [53]     | 2015 | -                                                                             | 21          | MoCA            |
| Qi [54]             | 2019 | -                                                                             | 16          | MMSE            |
| Sanders [55]        | 2020 | Flexibility exercises and recreational activities                             | 30          | MMSE            |
| Siu [56]            | 2018 | -                                                                             | 80          | MMSE            |
| Song [57]           | 2019 | Health education program included eight bi-weekly educational classes (45 min/each session) | 60          | MoCA            |
| Sun [58]            | 2015 | Playing cards or singing at the activity center                              | 66          | MMSE            |
| Tao [59]            | 2019 | Health education every 8 weeks for 30 min per session                         | 20          | MoCA            |
| Toots [60]          | 2017 | Participants conversed, sang, listened to music or readings, and/or looked at pictures and objects | 85          | MMSE            |
| Van de Winckel [61] | 2004 | One-to-one conversation                                                       | 10          | MMSE            |
| Varela [62]         | 2012 | Recreational activities - playing cards, reading newspapers, handicrafts      | 15          | MMSE            |
| Venturelli [63]     | 2011 | Organized activities like bingo, patchwork sewing, and music therapy          | 12          | MMSE            |
| Vreugdenhil [64]    | 2012 | -                                                                             | 20          | MMSE            |
| Wei [65]            | 2014 | -                                                                             | 30          | MMSE            |
| Williamson [66]     | 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          | MMSE            |
| Yang [67]           | 2015 | Health education                                                             | 25          | MMSE            |
| Yoon [68]           | 2017 | Static and dynamic stretching once a week for 60 min                          | 7           | MMSE            |

**Table 4** PEDro scores of the included studies

*Note: MMSE: Mini-Mental State Examination; ERFC: Rapid Evaluation of Cognitive Function; ADAS-Cog: Alzheimer Disease Assessment Scale–Cognitive Subscale; MoCA: Montreal Cognitive Assessment*
| 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 | Statistically significant between-group comparison | Point measures and measures of variability | Score |
|-----------------------|----------------------|---------------|----------------------|-------------------------|-------------------------|---------------------------|--------------------------|----------------|---------------------------|---------------------------------------------|-------------------------------------------|--------|
| Arcoverde [29] Arrieta [30] | 1 1 1 1 1 0 0 0 1 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Bademli [31]          | 1 1 1 1 1 0 0 0 1 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Boskers [32]          | 1 1 1 1 1 0 0 0 1 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Cancela [33]          | 1 1 1 1 1 0 0 1 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| de Souto Barreto [34] | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Dorner [35]           | 1 1 1 1 1 0 0 0 1 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Enette [36]           | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Fiatarone [37]        | 1 1 1 1 1 0 0 1 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Harris [38]           | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Hensken s [39]        | 1 1 1 1 1 0 0 1 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Holthoff [40]         | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Hong [41]             | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Cheng [42]            | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Christofletti [43]    | 1 1 1 1 1 0 0 1 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Kemoun [44]           | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Kwak [45]             | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Lam [46]              | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Lamb [47]             | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Langoni [48]          | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Lautenschlager [49]   | 1 1 1 1 1 0 0 1 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Miu [50]              | 1 1 1 1 0 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Mollinedo Cardalda [51] | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Muscari [52]          | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Nascimento [53]       | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Qi [54]               | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Sanders [55]          | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Siu [56]              | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Song [57]             | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Sun [58]              | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Tao [59]              | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Toots [60]            | 1 1 1 1 1 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Van de Winckel [61]   | 1 1 1 1 0 0 0 0 0 1 1 1 1 |               |                       |                         |                         |                           |                           |                |                           |                                             |                                           |        |
| Author               | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 7 |
|---------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| Varela [62]         | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 7 |
| Venturelli [63]     | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 7 |
| Vreugdenhil [64]    | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 9 |   |
| Wei [65]            | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 7 |
| Williams on [66]    | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 9 |   |
| Yang [67]           | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 8 |
| Yoon [68]           | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 9 |   |

**Table 5** Effect of physical exercise on cognitively impaired older adults
| Study                  | Cognitive impairment | Intervention groups | Control groups | Study                  | Cognitive impairment | Intervention groups | Control groups |
|-----------------------|----------------------|---------------------|----------------|-----------------------|----------------------|---------------------|-----------------|
| Kemoun [44]           | Borderline intact    | Aerobic             | Beneficial     | Muscari [52]         | Borderline intact    | Aerobic             | Active          |
|                       |                      |                     |                |                       |                      |                     | Harmful         |
| Nascimento [53]       | Borderline intact    | Aerobic             | Beneficial     | Song [57]            | Borderline intact    | Aerobic             | Passive No      |
|                       |                      |                     |                | Tao [59]             | Borderline intact    | Aerobic             | Active No       |
| Arcoverde [29]        | Mild                 | Aerobic             | Beneficial     | Bademli [31]         | Mild                 | Aerobic             | Passive          |
|                       |                      |                     |                | Enette [36]          | Mild                 | Aerobic             | Active No       |
|                       |                      |                     |                | Enette [36]          | Mild                 | Aerobic             | No              |
|                       |                      |                     |                | Miu [50]             | Mild                 | Aerobic             | Passive          |
|                       |                      |                     |                | Mollinedo Cardalda [51] | Mild              | Aerobic             | Active          |
|                       |                      |                     |                | Varela [62]          | Mild                 | Aerobic             | Active          |
|                       |                      |                     |                | Yang [67]            | Mild                 | Aerobic             | Active          |
| Bossers [32]          | Moderate             | Aerobic             | No             | Cancela [33]         | Moderate             | Aerobic             | Active          |
|                       |                      |                     |                | Harris [38]          | Moderate             | Aerobic             | Active No       |
|                       |                      |                     |                | Venturelli [63]      | Moderate             | Aerobic             | Active          |
| Fiatarone [37]        | Borderline intact    | Resistance          | No             | Hong [41]            | Borderline intact    | Resistance          | Passive No      |
|                       |                      |                     |                |                      |                      |                     |                 |
| Arrieta [30]          | Mild                 | Resistance          | No             | Dorner [35]          | Mild                 | Resistance          | Passive No      |
|                       |                      |                     |                | Holthoff [40]        | Mild                 | Resistance          | Passive No      |
|                       |                      |                     |                | Langoni [48]         | Mild                 | Resistance          | Passive          |
|                       |                      |                     |                | Mollinedo Cardalda [51] | Mild              | Resistance          | No              |
|                       |                      |                     |                | Vreugdenhil [64]     | Mild                 | Resistance          | Passive          |
|                       |                      |                     |                | Yoon [68]            | Mild                 | Resistance          | Active          |
|                       |                      |                     |                | Yoon [68]            | Mild                 | Resistance          | No              |
| Toots [60]            | Moderate             | Resistance          | Harmful        | Lam [46]             | Borderline intact    | Combined            | No              |
|                       |                      |                     |                | Lautenschlag er [49] | Borderline intact    | Combined            | No              |
|                       |                      |                     |                | Qi [54]              | Borderline intact    | Combined            | Passive No      |
|                       |                      |                     |                | Wei [65]             | Borderline intact    | Combined            | Passive No      |
|                       |                      |                     |                | Williamson [66]      | Borderline intact    | Combined            | Active No       |
|                       |                      |                     |                | Lamb [47]            | Mild                 | Combined            | No              |
|                       |                      |                     |                | Sanders [55]         | Mild                 | Combined            | No              |
|                       |                      |                     |                | Bossers [32]         | Moderate             | Combined            | No              |
|                       |                      |                     |                | de Souto Barreto [34]| Moderate             | Combined            | No              |
| Reference                  | Stage | Treatment     | Intervention | Activeness | Passiveness |
|----------------------------|-------|---------------|--------------|------------|-------------|
| Henskens [39]              | Moderate | Combined       | No           |            | No          |
| Christofoletti [43]        | Moderate | Combined       | Beneficial   | Passive    | No          |
| Kwak [45]                  | Moderate | Combined       | Beneficial   | Passive    | No          |
| Van de Winckel [61]        | Moderate | Combined       | No           |            | Active      |
| Siu [56]                   | Borderline intact | Tai Chi     | No           | Passive    | No          |
| Sun [58]                   | Borderline intact | Tai Chi     | Beneficial   | Active     | No          |
| Tao [59]                   | Borderline intact | Tai Chi     | No           | - -        |             |
| Cheng [42]                 | Mild   | Tai Chi       | No           |            | Active      |

Table 6 Generalized linear model for both groups
|                                | B   | SE   | Lower | Upper |
|--------------------------------|-----|------|-------|-------|
| Physical activity              |     |      |       |       |
| Aerobic exercise               | 0.538| 0.168| 0.210 | 0.897 |
| Resistance exercise            | 0.999| 0.203| 0.601 | 1.397 |
| Combined exercise              | 0.640| 0.200| 0.248 | 1.032 |
| Tai Chi                        | 0.746| 0.298| 0.162 | 1.330 |
| Passive control                | 0.038| 0.184| -0.323| 0.399 |
| Active control                 | 0a  |      |       |       |
| Cognitive impairment           |     |      |       |       |
| Mild                           | -0.202| 0.169| -0.533| 0.130 |
| Moderate                       | -0.169| 0.203| -0.517| 0.279 |
| Borderline intact              | 0a  |      |       |       |
| Duration of exercise program   |     |      |       |       |
| > 12 weeks                     | -0.227| 0.138| -0.497| 0.043 |
| ≤ 12 weeks                     | 0a  |      |       |       |
| Age                            | -0.026| 0.012| -0.050| -0.003|
|                                | B   | SE  | Lower  | Upper  |
|--------------------------------|-----|-----|--------|--------|
| **Physical activity**          |     |     |        |        |
| Aerobic exercise               | -0.015 | 0.274 | -0.552 | 0.521  |
| Resistance exercise            | 0.208 | 0.290 | -0.360 | 0.776  |
| Combin ed exercise             | 0.144 | 0.297 | -0.439 | 0.726  |
| Tai Chi                         | 0a   |     |        |        |
| **Cognitive impairment**       |     |     |        |        |
| Mild                            | 0.247 | 0.199 | -0.142 | 0.636  |
| Moderate                       | -0.152 | 0.250 | -0.642 | 0.337  |
| Borderline intact              | 0a   |     |        |        |
| **Frequency of exercise program** |     |     |        |        |
| ≤ 3 sessions                   | -0.072 | 0.182 | -0.422 | 0.285  |
| > 3 sessions                   | 0a   |     |        |        |
| Age                            | -0.048 | 0.014 | -0.074 | -0.021 |
| Female ratio                   | 0.021 | 0.005 | 0.011  | 0.032  |

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

**Figures**
Figure 1

Flow diagram
Figure 2

Present results of each meta-analysis done, including confidence intervals and measures of consistency.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- formula.docx