Effects of exercise training on the cognitive function of older adults with different types of dementia: a systematic review and meta-analysis

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ABSTRACT

Objectives  To assess the effect of exercise training on the cognitive function of older adults living with different types of dementia, as well as potential moderators of exercise efficacy.

Design  Systematic review and meta-analysis.

Data sources  Cochrane Central, PsycINFO, Embase, Medline and CINAHL.

Eligibility criteria  Peer-reviewed, randomised controlled trials, in English (1990–present), which examined the effects of exercise training on the cognitive function of older adults living with dementia.

Study appraisal and synthesis  Risk of bias and study quality were assessed (Cochrane Risk of Bias Tool 2.0 and Physiotherapy Evidence Database Scale). We performed random-effects models using robust variance estimation and tested moderators using the approximate Hotelling-Zhang test.

Results  Twenty-eight studies (n=2158) were included in the qualitative review and 25 in the meta-analysis. For all-cause dementia, a small effect of exercise training on cognitive function was observed (g=0.19, 95% CI 0.05 to 0.33; p=0.009). Type of dementia and exercise training characteristics did not moderate the effects of exercise training on cognitive function (p=0.05). Adherence to the intervention moderated the cognitive outcome effect size such that greater mean adherence was associated with greater cognitive outcome effect sizes (β=0.02; SE=0.01; p=0.005).

Conclusion  Exercise training showed small benefits for the cognitive function of older adults living with all-cause dementia. More research and standardised reporting of exercise training characteristics can strengthen the evidence for what works best for which types of dementia.

PROSPERO registration number  CRD42020198716.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exercise training is a promising non-pharmaceutical therapy to promote cognitive function in older adults living without cognitive impairment.

⇒ Most of the evidence of exercise training efficacy improving cognitive function in people living with dementia comes from Alzheimer’s disease.

WHAT THIS STUDY ADDS

⇒ Exercise training interventions have a small effect on cognitive function of older adults living with all-cause dementia independent of cognitive domain.

⇒ The beneficial effects of exercise training on cognitive function are not moderated by type of dementia.

⇒ There is not enough information to conclude what exercise training prescription (eg, type, intensity, volume and intervention length) will yield the best results for older adults living with all-cause and specific types of dementia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Future research must include older adults living with different types of dementia other than Alzheimer’s disease. Our study highlights the need to adequately report exercise training interventions to strengthen the evidence of what works best for which types of dementia.

⇒ Health practitioners should recommend exercise to older adults living with dementia.

INTRODUCTION

Over 50 million people worldwide are living with dementia, and this number is projected to grow to more than 150 million by 2050.1 Dementia is a syndrome of cognitive impairment that affects several domains of cognitive function (eg, memory and executive function) beyond what might be expected from normal ageing, resulting in the loss of independence and poorer quality of life.4 Combating dementia is a public health priority, and thus effective non-pharmaceutical strategies that can delay dementia progression are an exciting line of research inquiry.

Exercise training is one promising non-pharmaceutical therapy to promote cognitive health in older adults living with all-cause dementia,5,6 mild cognitive impairment (MCI) and early stages of dementia,7 and Alzheimer’s disease (AD).8–12 Broadly, exercise is any type of planned, structured and repetitive physical activity done for the purpose of improving or maintaining physical fitness.13 The current evidence of the effects of exercise training on the cognitive function of older adults living with dementia has some key limitations, such as heterogeneity in study design, lack of appropriate reporting intervention parameters and wide variability in cognitive tests used.14 It is also reported limitations when delivering and measuring exercise training interventions effectiveness in older adults living with dementia.15 Exercise training is not a one-size-fits-all answer.16 Our study highlights the need to adequately report exercise training interventions to strengthen the evidence of what works best for which types of dementia.
adults with later stages of dementia due to comorbidities and disabilities.15

Of note, it is not clear how the effects of exercise training on cognitive function may vary as a function of type of dementia (eg, vascular dementia, frontotemporal dementia, mixed dementias, etc) or specific exercise characteristics. Specifically, there is a lack of knowledge regarding how exercise training characteristics (ie, type, intensity, volume, and intervention length) influence the effects of exercise training on the cognitive function of older adults living with dementia. Furthermore, different types of dementia present specific neuropsychological and neuropsychopathological profiles, which could elicit differential effects of exercise training. Precise recommendations require a better understanding of exercise training characteristics that either attenuate or amplify their efficacy depending on the type of dementia.

Thus, we performed a systematic review and meta-analysis of exercise training randomised controlled trials (RCTs) to answer the following questions: (1) in older adults living with dementia (ie, all-cause and specific types), what are the effects of exercise training on cognitive function?; (2) what are the treatment-level (ie, exercise training characteristics and exercise adherence), individual-level (ie, sex and age), study-level (ie, type of dementia and risk of bias) and outcome-level (ie, global cognition and domain specific) moderators of exercise efficacy in older adults living with dementia?

METHODS
Summary of the search strategy
We conducted our systematic review and meta-analysis according to the Cochrane Handbook for Systematic Reviews and Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements.16 17 Our protocol was registered with PROSPERO on 18 August 2020, and updated on 3 December 2020 (CRD42020198716) to reflect the updated set of databases and search terms used. Between 29 July and 6 August 2020, searches were performed in the Cochrane Central Register of Controlled Trials, PsycINFO, Embase, Medline and CINAHL for articles published between 1 January 1990 and 1 July 2020. Reference lists from identified studies and previous relevant systematic reviews5 8 9 13 18 19 were examined to identify additional articles not captured by the database search. An updated search was conducted on 15 April 2021 to capture studies published between 1 July 2020 and 15 April 2021.

The terms used in the database searches were divided into four categories: dementia, older adults, exercise training and cognitive function. All terms were searched as keywords in addition to each database-specific subject headings and MeSH terms. The complete search strategy can be found in online supplemental material 1). We exported all initial records into Covidence,20 wherein we excluded duplicates and screened references (both title/abstract and full text).

Study selection
We selected peer-reviewed, published RCTs in English that examined the effect of exercise training interventions (ie, aerobic training [AT], resistance training [RT], multicomponent training [MT] or alternative forms of exercise) on the cognitive function of older adults (>60 years old) living with dementia. If a given inclusion criterion was not sufficiently described by the authors, we contacted the corresponding author for further clarification. Our criteria for consideration of exercise training programmes were: (A) AT interventions that included exercise aiming to improve cardiovascular fitness, including walking, running, or cycling; (B) RT interventions that aimed to increase muscular strength, power or endurance using resistance bands, weight machines, free weights or bodyweight; (C) MT interventions that incorporated a combination of AT, RT and other forms of exercise training such as balance or agility; (D) other structured exercise interventions included alternative form of exercise such as tai chi, qigong, yoga and dance.

After excluding duplicate records, titles and abstracts were screened independently by two of three authors (GMB, SYS and AB). Full texts of eligible studies were then reviewed by the same authors. Details are presented in online supplemental material 2. Three studies used combined interventions (ie, exercise training + cognitive training or exercise training + activities of daily living),20 21 and we extracted data for the exercise training-only intervention and the control group. Disagreements were resolved as a committee between the three authors (GMB, SYS and AB). A fourth author (CKB) resolved disagreements not solved as a committee.

Inclusion and exclusion criteria
Articles were included if they met the following inclusion criteria: (1) RCTs; (2) published in a peer-reviewed journal in English language; (3) participants were older adults (≥60 years old) living with dementia (AD, vascular dementia, frontotemporal dementia, Lewy body dementia, mixed dementia or unspecified dementia) regardless of stage of dementia; (4) the exercise intervention was AT, RT, MT or alternative form of exercise of any intensity that was at least 8 weeks in duration and occurred at least once weekly; and (5) included at least one cognitive function outcome as measured by a valid neuropsychological test. Studies that included older adults living with MCI or subjective memory complaints were excluded. Two studies22 23 included participants living with MCI but allocated them in separate groups or presented independent data analysis for those living with MCI. We included these studies and did not extract data on MCI participants. Studies were not included in the meta-analysis if they did not provide enough data (eg, sample size, means, and SD for outcomes at preintervention and postintervention data collection) even after contacting the authors.

Data extraction
Data extraction was conducted independently by three authors (GMB, SYS and AB) using a standardised data abstraction form developed by our team. Extracted information included: author, year, study characteristics (eg, randomisation and type of analysis), type and severity of dementia, cognitive domain, neuropsychological test, sample size, participant characteristics (eg, % female, age), intervention characteristics (eg, type, intensity, volume and intervention length), intervention adherence, comparison group characteristics (ie, type, frequency and volume) and adherence, measurement time-points and results by time-points (ie, mean and SD at baseline and postintervention).

We defined cognitive function as a broad set of thinking abilities measured using performance-based tasks.22 We classified cognitive function into global cognition and three specific domains: (1) executive function; (2) memory; and (3) processing speed. The specific classification criteria can be found in online supplemental material 3.

Data on potential moderators (ie, treatment, individual, study and outcome levels) were extracted according to predefined categories or units of measure. Treatment-level moderators included: (1) intervention type (AT, RT, MT or alternative forms of...
exercise); (2) intervention intensity using the following parameters: (A) high intensity: the goal was to achieve a heart rate >75% of age-predicted maximum, or >70% heart rate reserve, or a Borg rating of perceived exertion >14 or RT with a percentage of repetition maximum (%RM) >80%; (B) moderate intensity: the heart rate was kept between 55% and 75% of age-predicted maximum, or a heart rate reserve between 55% and 70%, or a Borg rating between 11 and 14, or RT with %RM between 60% and 80%; (C) low intensity: the heart rate was kept <55% of age-predicted maximum, or a heart rate reserve <55%, or a Borg rating <11 or RT with %RM less than 60%.26 None of the included studies had a low-intensity only programme; (D) mixed intensities: those interventions that proposed gradual increases from light to moderate or moderate to high intensities within the intervention period; (E) unspecified intensities: those interventions that did not report a specific targeted exercise training intensity; (3) intervention weekly volume (ie, min/week [weekly frequency*session duration]); (4) intervention length, defined by Colcombe and Kramer27 and Northey et al28 as short (8–12 weeks), medium [13–26 weeks], and long (>26 weeks); and (5) adherence to intervention programme (percentage of sessions attended). Individual-level moderators included: (1) mean age of the sample; and (2) the percentage of female participants (≤65% low proportion of females and >65% high proportion of females based on median split). Study-level moderator included: (1) type of dementia (ie, AD, vascular dementia, multiple types of dementia and unspecified dementia). Multiple types of dementia refer to studies that included older adults with several types of dementia (eg, AD, vascular dementia, mixed dementia or others). Unspecified dementia refers to studies that included older adults without specifying their diagnosis. In these cases, the authors only reported the inclusion of participants living with dementia without further specifications; and (2) overall risk of bias (ie, low, some concerns and high). Finally, the outcome-level moderator included global cognition and domain-specific cognitive function (ie, executive function, memory and processing speed).

Statistical analysis

We used Hedges’ g effect sizes and variances, which provides a small sample bias correction to Cohen’s d.29 We first computed Cohen’s d and its variance for each outcome using the preintervention and postintervention mean scores for the treatment and control groups, the preintervention SD for each group and the sample size for each group:

\[
\text{Effect Size} = \frac{(M_{PostInt} - M_{PreInt}) - (M_{PostCtrl} - M_{PreCtrl})}{\sqrt{\left(\frac{(n_{PostInt} - 1) \times SD_{PostInt}^2}{n_{PostInt}} + \frac{(n_{PostCtrl} - 1) \times SD_{PostCtrl}^2}{n_{PostCtrl}}\right) \times V\left(\frac{1}{n_{PostInt}} + \frac{1}{n_{PostCtrl}}\right)}}
\]

Separate effect sizes were computed for each outcome measure reported in the study. Cohen’s d was calculated with the above formula in 80.1% of the outcomes. One study provided median data,30 for which we estimated mean and SD,11 32 and then calculated effect sizes according to the formula previously. The estimations from median and interquartile range to mean and SD were carried out according to Luo et al31 and Wan et al12 formulas: \(X \approx \frac{Q_3 + M + q_i}{3}\) and \(SD \approx \frac{Q_3 - Q_1}{\eta(n)}\).

Where, \(Q_1\) and \(Q_3\) are the 25th and 75th quartiles, and \(M\) is the median (for details on \(\eta(n)\), please see Wan et al12). One study computed Cohen’s d for each outcome of interest.31 Six studies reported means and SD for preintervention and change scores,34–39 which were used in the numerator of the formula previously. Finally, for one outcome of one study,34 we first transformed data from median data and then used change score. For studies with multiple treatment or control groups, effect sizes were computed separately. We coded effect sizes so that positive estimates indicate a favourable change for the intervention group compared with the control group. Effect sizes were interpreted as proposed by Brydges,40 with Hedge’s g=0.15, 0.40 and 0.75 corresponding to small, medium and large effects, respectively.

A previous meta-analysis guided our analysis protocol.26 Analyses were conducted in the statistical package R V.4.0.3 using the packages of robumeta and clubSandwich.41–43 We conducted the meta-analyses performing random-effects models to account for the heterogeneity between studies. Most meta-analytic packages assume that effect sizes are statistically independent; however, as we included multiple effect sizes from the same study, this assumption was violated. Robumeta implements robust variance estimation to account for the dependency of within-study effect sizes by weighting those effect sizes based on a prespecified within-study correlation. The default setting of within-study correlation was 0.8. The robumeta package weights each individual effect size according to Hedges et al44 method for estimating the inverse variance weights:

\[
W_i = \frac{1}{\kappa_i (\eta_i + 2)}
\]

Where, \(\eta_i\) is the mean of the within-study sampling variances for the \(\kappa_i\) effect sizes in study \(j\), \(\eta^2\) is the estimate of the between-study variance component and \(\kappa_i\) is the number of effect sizes within each study \(j\). Next, we conducted sensitivity analyses in which the correlation varied from 0.0 to 1.0 by increments of 0.2.

The overall summary effect was computed for the overall effects of exercise training on cognitive function (ie, all measures of cognitive function regardless of domain) in all-cause dementia by fitting intercept-only random-effects robust variance estimation models to the set of dependent effect sizes. Subsequently, we performed models testing the effects of exercise training on cognitive function by type of dementia (ie, AD, vascular dementia, multiple types of dementia and unspecified dementia). Due to few studies and robust variance estimation models with \(df < 4\) being untrustworthy, we only present data as a function of type of dementia for cognitive function regardless of domain.

We present \(\eta^2\) as the estimate of true heterogeneity of the effects in the same metric as the original effect sizes45 and \(I^2\) as the estimate of true heterogeneity expressed as a proportion of the total observed variance in effect sizes.17 To account for potential outliers, we performed leave-one-out analyses in which each effect size was sequentially removed to determine whether doing so significantly altered the summary effect size.

We tested the potential moderators using mixed-effects robust variance estimation models. Continuous (eg, mean age and mean Mini-Mental State Examination (MMSE)) and categorical moderators (eg, type of dementia and type of exercise training) were separately entered as predictors into regression equations using robust variance estimation. For continuous and binary moderators (ie, proportion of females), t-tests determined whether the moderator predicted changes in cognitive function. For categorical moderators with three or more levels (eg, type of exercise training), Hotelling Zhang tests were performed to produce an F-value that indicated whether different levels of the moderator led to differential effects on cognitive function.46 This approach is an extension of multiple-contrast hypothesis tests specifically developed to test moderation effects in meta-analyses using random effects models with robust variance estimation. They were developed as generalisations from Tipton’s47 methods to determine if effect sizes are moderated by categorical...
variables with multiple levels (details in Tipton and Pustejovsky). The significance level was set at p ≤0.05. The R code is available in online supplemental material 7.

Risk of bias and quality assessment
Three authors (GMB, SS and AB) independently assessed the risk of bias of included studies following the Cochrane Risk of Bias tool 2.0 for randomised trials. The same three authors evaluated methodological quality using the Physiotherapy Evidence Database (PEDro) Scale. Details are presented in online supplemental material 2.

RESULTS
Search results and study characteristics
Figure 1 shows a summary of the study selection and screening process. The original search yielded 12,918 articles. Thirty additional records were identified through the bibliographic review and 726 were identified in an updated search. After deduplication, 8358 records remained. Titles and abstracts screening resulted in 110 full-text articles assessed based on the inclusion criteria. The online supplemental material 1 presents studies excluded after full-text review along with its reasons for exclusion. Twenty-eight studies were included in the qualitative review, and 25 studies were included in the quantitative review (meta-analysis).

Study characteristics
Study characteristics are described in online supplemental material 4. The final systematic review included 24 original parent trials and 4 secondary outcome articles. Sample sizes ranged from 20 to 204, with a total of 2158 participants included. Participants were 81.3±3.4 years old and majority female (65.3%±11.9%). Nine studies included participants living with AD, two with vascular dementia, and 11 with multiple types of dementia and 6 with unspecified dementia. Global cognition was assessed in 26 studies, executive function in 15, memory in 10, and processing speed in 8. The online supplemental material 3 describes the measures of cognitive function used. We examined 12 AT interventions, one RT intervention, 13 MT interventions and 4 alternative forms of exercise interventions. Online supplemental material 5 presents a summary of exercise training interventions and comparison group characteristics.

Effects of exercise training on cognitive function in all-cause dementia
We calculated 185 effect sizes (41 for global cognition, 94 for executive function, 31 for memory and 19 for processing speed) from 25 studies with a Hedges’ g range of −1.56 to 2.4. A forest plot with effects sizes of exercise training on cognitive function regardless of domain in all-cause dementia can be seen in online supplemental material 6. The meta-analytic summary effect was g = 0.19 (95% CI 0.05 to 0.33; p = 0.009). More than three-quarters of the variance was estimated to be true effect size heterogeneity (I² = 69.26%, T² = 0.13).

Sensitivity analyses altering the assumed within-study correlation from 0.0 to 1.0 had no substantial impact on the summary effect (g = 0.19 with r = 0.0 and g = 0.19 with r = 1.0).
Leave-one-out analysis suggested that similar results could be obtained after excluding any single study, no single effect size disproportionately influenced the summary effect or heterogeneity estimate ($\Delta g_{\text{min}} = -0.04$, $\Delta g_{\text{max}} = 0.02$; $\Delta I^2_{\text{min}} = 4.62\%$, $\Delta I^2_{\text{max}} = 2.79\%$).

**Moderators of the effects of exercise training on cognitive function for all-cause dementia**

Table 1 displays results for moderator analyses of categorical moderators along with point estimates of each level and its respective number of studies. Due to models with df < 4 being considered untrustworthy, the estimates for such instances are not presented. None of the treatment-level, individual-level, study-level or outcome-level moderators significantly moderated the effects of exercise on cognitive function in older adults living with all-cause dementia (all Hotelling Zhang tests $p > 0.05$).

Table 2 displays results for continuous moderators. Adherence to the intervention moderated the cognitive outcome effect size such that each percentage point increase in mean adherence was associated with a 0.02 increase in cognitive outcome effect sizes ($b = 0.02$; $SE = 0.01$; $p = 0.005$). Specifically, considering the meta-regression equation is $y = b_0 + b_1 \times x$. Where $y$ is the meta-analytic summary Hedges’ $g$ (ie, 0.19), $b_0$ is the intercept (ie, $-1.61$), $b_1$ is the slope (ie, 0.02) and $x$ is % adherence to the

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**Table 1** Results of moderation analyses for categorical moderators

<table>
<thead>
<tr>
<th>Moderator</th>
<th>Summary effect</th>
<th>Test of moderation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$g$</td>
<td>LL</td>
</tr>
<tr>
<td>Treatment level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of intervention</td>
<td></td>
<td></td>
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<tr>
<td>Aerobic training</td>
<td>0.35</td>
<td>0.02</td>
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<td>Resistance training</td>
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<td>--</td>
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<tr>
<td>Multicomponent</td>
<td>0.16</td>
<td>--0.08</td>
</tr>
<tr>
<td>Alternative forms</td>
<td>0.02</td>
<td>--0.08</td>
</tr>
<tr>
<td>Intervention length</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short</td>
<td>0.14</td>
<td>--0.03</td>
</tr>
<tr>
<td>Medium</td>
<td>0.21</td>
<td>--0.11</td>
</tr>
<tr>
<td>Long</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Exercise training intensity</td>
<td></td>
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</tr>
<tr>
<td>Moderate</td>
<td>0.13</td>
<td>--0.24</td>
</tr>
<tr>
<td>High</td>
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<td>--</td>
</tr>
<tr>
<td>Mixed</td>
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<td>--0.02</td>
</tr>
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<td>Unspecified</td>
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<td>--0.12</td>
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<tr>
<td>Study level</td>
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<td></td>
</tr>
<tr>
<td>Type of dementia</td>
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<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
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<td>0.03</td>
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<tr>
<td>Vascular dementia</td>
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<td>--</td>
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<tr>
<td>Multiple types</td>
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<td>--0.08</td>
</tr>
<tr>
<td>Unspecified</td>
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<td>--0.09</td>
</tr>
<tr>
<td>Overall risk of bias</td>
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<td></td>
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<tr>
<td>Low</td>
<td>0.14</td>
<td>--0.003</td>
</tr>
<tr>
<td>Some concerns</td>
<td>0.17</td>
<td>--0.08</td>
</tr>
<tr>
<td>High</td>
<td>0.28</td>
<td>--0.07</td>
</tr>
<tr>
<td>Comparison group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual care</td>
<td>0.16</td>
<td>--0.16</td>
</tr>
<tr>
<td>Other activities</td>
<td>0.31</td>
<td>0.06</td>
</tr>
<tr>
<td>Physically active</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cognitive training</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Individual level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low proportion</td>
<td>0.22</td>
<td>--0.01</td>
</tr>
<tr>
<td>High proportion</td>
<td>0.103</td>
<td>--0.04</td>
</tr>
<tr>
<td>Unspecified</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Outcome level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global cognition</td>
<td>0.31</td>
<td>0.05</td>
</tr>
<tr>
<td>Memory</td>
<td>0.09</td>
<td>--0.08</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.10</td>
<td>--0.06</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.14</td>
<td>--0.18</td>
</tr>
</tbody>
</table>

df, Degrees of freedom; LL, Lower limit of the 95% confidence interval; UL, Upper limit of the 95% confidence interval.
intervention. The solution of this equation demonstrates that high attendance (ie, 90% attendance) is necessary to elicit a small effect on cognitive function.

**Effects of exercise training on cognitive function for specific types of dementia**

Although the Hotelling Zhang test did not indicate a moderator effect of type of dementia on cognitive function (table 1), we present the estimates for each type of dementia. For AD, we calculated 30 effect sizes within seven studies demonstrating a medium effect of exercise training on cognitive function of older adults living with AD ($g=0.56; 95\% CI 0.03$ to $1.09; p=0.040$). Importantly, although $p<0.05$, the Hotelling Zhang test was non-significant, suggesting the lack of moderation as a function of different types of dementia. Nine effect sizes within two studies demonstrated a negligible effect for older adults living with vascular dementia ($g=-0.10; 95\% CI -0.62$ to $0.45; p=0.257$). These effects are not trustworthy since $df<4$. We calculated 106 effect sizes within 10 studies showing a negligible effect in studies including older adults living with multiple types of dementia ($g=0.10; 95\% CI -0.08$ to $0.27; p=0.248$). Forty effect sizes within six studies indicated no effect of exercise training on cognitive function of older adults living with unspecified of dementia ($g=0.09; 95\% CI -0.09$ to $0.27; p=0.256$). Forest plots of these analyses are available in online supplemental material 6.

**Publication bias and risk of bias**

There is some degree of publication bias (online supplemental material 2). Risk of bias assessment rendered 7 studies with low risk of bias, 11 with some concerns and 10 with a high risk of bias (online supplemental material 2). Importantly, risk of bias was not a significant moderator of exercise training’s effect on cognitive function. Risk of bias assessment by type of dementia revealed that among the studies that included only participants living with AD, one had a low risk of bias (14.2%), three a moderate risk of bias (42.9%) and three a high risk of bias (42.9%). However, risk of bias assessment of studies that included participants living with vascular dementia, multiple types of dementia and unspecified dementia revealed that six trials had a low risk of bias (33.33%), eight a moderate risk of bias (44.44%) and four a high risk of bias (22.22%). Among the included trials, 3.6% were classified as poor quality, 14.3% as fair quality, 53.6% as good quality and 28.5% as optimal quality (PEDro scale). A detailed scoring is presented in online supplemental material 2.

**DISCUSSION**

We found a small effect of exercise training on cognitive function of older adults living with all-cause dementia. This effect was independent of type of dementia and was not moderated by exercise training type, intensity, volume, intervention length, sex or age. Furthermore, studies with higher participants’ adherence to the intervention showed greater effects on cognitive function.

**The effects of exercise training on different types of dementia**

Previous meta-analyses of prospective longitudinal studies have demonstrated that engagement in physical activity across the lifespan has a protective role against all-cause dementia and AD. Our moderation analyses of RCTs did not demonstrate that the effects of exercise training on cognitive function were moderated by different types of dementia. This result is similar to the previous meta-analysis of RCTs that included people living with different types of dementia. The authors compared the impact of exercise training on cognitive function in older adults living with AD versus older adults living with non-AD dementia. The results revealed that there were no differences on the effect of exercise training between individuals living with AD and those with other types of dementia.

Of the 25 RCTs included in the meta-analysis, 9 RCTs included only participants with AD and other types of dementia. Among the 11 RCTs with AD and non-AD participants, most participants were living with AD. While AD is the leading cause of dementia worldwide, accounting for 60%–80% of all dementia cases, more research is needed in older adults with non-AD dementia, such as vascular dementia, Lewy body dementia, frontotemporal dementia and mixed dementia. Understanding the effects of exercise training in different dementia types will help to refine ‘exercise as medicine’ for dementia.

Although beyond the scope of our study, some underlying mechanisms of action through which exercise might affect cognitive function needs to be considered. Two recent systematic reviews and meta-analyses speculated potential mechanisms of action contributing to the effects of exercise training on cognitive function of older adults living with MCI, AD and all-cause dementia. Stigger et al demonstrated that exercise significantly increased serum concentrations of brain-derived neurotrophic factor (BDNF) and significantly decreased interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) (both proinflammatory cytokines). Another systematic review and meta-analysis stratified the effects on potential mechanisms of action by type of exercise (ie, AT, RT and MT). The results suggested...
a non-significant trend of AT and MT increasing concentrations of BDNF and RT increasing the concentrations of insulin-like growth factor 1. The authors recognised divergent results and a lack of studies investigating the role of exercise on inflammatory markers (eg, IL-6 and TNF-α). Noticeably, both meta-analyses included only eight studies, which hinders the ability to detect robust effects. Future studies must explore the mechanisms that may drive neuroplasticity, molecular and cellular dynamics and its moderator and/or mediator roles in cognitive function of older adults living with different types of dementia.

The moderator role of exercise training characteristics

Exercise training characteristics did not moderate the effects of exercise on cognitive function. These results do not concur with previous meta-analyses that included people with AD. Panza et al found AT was more beneficial than RT and MT among those at risk for AD (eg, people living with MCI, APOE4 carriers, biological parents with AD) and living with AD. Jia et al found AT interventions that were greater than 16 weeks, and up to three training sessions per week for ≤30 min per session were more effective than interventions with shorter intervention length, higher frequency and longer exercise training sessions. Groot et al demonstrated that MT and AT interventions had greater effects on cognition in older adults living with all-causes dementia than non-aerobic interventions.

The discrepancy between current and prior results may be due to differences in inclusion criteria. The previously published meta-analyses included RCTs published in non-English languages, non-RCTs, physical activity interventions, and adults aged 19 years and older at risk of or diagnosed with AD. Consequently, several studies included in prior meta-analyses were not eligible for our meta-analysis. Current evidence regarding the moderating effects of exercise training characteristics in older adults with dementia is equivocal and is mainly among those with AD. Thus, more research is needed to determine exercise training characteristics (ie, type, intensity, volume and intervention length) that are most effective for older adults living with different types of dementia. We lack RCTs designed specifically to compare different types of exercise training, intensity, volume and intervention length in older adults living with or without dementia, highlighting need for more research.

In addition, to advance the application of exercise as therapy for dementia, trial descriptions of exercise training interventions need to be improved, as recommended by the Consensus on Exercise Reporting Template (CERT). For example, exercise intensity is pivotal when considering the quality and strength of the evidence on the benefits of exercise on cognitive function and health. Even though, exercise intensity was poorly reported in several RCTs included in our systematic review and meta-analysis. Eight (29.7%) trials did not report exercise intensity at all, and five (18.5%) reported incomplete aspects of intensity measurement (eg, only reported the target intensity without presenting details about whether and how the target intensity was measured and achieved during exercise sessions). This inconsistency in describing key intervention characteristics poses barriers for the quality and strength of the evidence.

The moderating role of biological sex and adherence

Past meta-analyses with cognitively healthy older adults suggest that females benefit more from exercise training interventions than males. However, biological sex was not a significant moderator in our meta-analysis, which concurs with the findings of a prior meta-analysis that included individuals at risk for or diagnosed with AD. Minimal research has examined sex differences in exercise efficacy among older adults living with dementia. However, it is critical for future RCTs to do so as two-thirds of dementia and AD cases are among females.

Higher intervention adherence was associated with greater improvements in cognitive performance, which is consistent with prior findings. Thus, it is important to implement evidence-based strategies that promote exercise adherence, including multiple contacts, discussing barriers and developing coping strategies and action plans, setting implementation intentions and concrete plans and encouraging individuals to continually self-monitor their progress. Noticeably, the moderator effect of adherence to the intervention should be interpreted with caution. We did not investigate potential characteristics of exercise training interventions (eg, social engagement, quality of instructions, easiness of access to intervention facilities, etc) that could promote or hinder participants’ adherence.

Suggestions for future RCTs

Given our results and those from past studies, we suggest that future exercise training RCTs that include older adults living with dementia should: (1) describe the target population (eg, age, type of dementia, sex, gender); (2) take into account that the diagnosis of dementia often is not definite and may vary according to diagnostic and referral protocols. It is necessary to clearly report the protocol for the diagnosis of dementia; (3) include people living with vascular dementia, since it is the second most common type of dementia and significantly contributes to AD pathology and mixed dementia; (4) follow the CERT instructions to adequately report the exercise training intervention characteristics; (5) identify the primary outcome(s) and the sample size necessary to achieve adequate power a priori (eg, publication of trial protocol and statistical plan); (6) clearly identify, describe and report the neuropsychological tests and cognitive domains used to measure cognitive function; (7) examine the effects of exercise on cognitive function for males and females on the individual level, presenting individual preintervention and postintervention cognitive scores for males and females, rather than treating sex as a descriptive of the sample; and (8) investigate the effects of exercise training on physical function, performance of activities of daily life, quality of life and well-being.

Limitations

Our inclusion criteria, although broader than past meta-analyses in some respects (eg, the inclusion of different types of dementia other than AD, inclusion of cognitive training as comparison group), were more stringent in other aspects (eg, the inclusion of studies with participants >60 years and exclusion of MCI). The inclusion of cognitive training as a comparison while more inclusive also needs to be recognised as a limitation, since it is not a true control group and can elicit changes in cognitive function. Likely, it led to the exclusion of articles that were once eligible for similar previous meta-analyses. Furthermore, only one RT intervention was eligible for our meta-analysis, which hampered our ability to explore the moderating role of exercise type.

Echoing the conclusions of Falck et al our approach to categorising different cognitive measures into cognitive domains might limit our findings. First, some cognitive measures could be categorised into multiple cognitive domains. For example, digit symbol coding can be classified as a measure of executive function, global cognition or processing speed. Second, our classification scheme included a range of cognitive processes under single a cognitive domain. For example, immediate recall, delayed recall, episodic
memory, verbal and non-verbal memory were all classified under a single domain—memory. While each of these cognitive processes are broadly related to memory, they could be categorised under more specific cognitive domains (eg, episodic memory, verbal memory) that could be impacted differently by exercise.

The neuropsychological tools used to measure cognitive function varied widely between the studies, and in some instances, were poorly described, which made it difficult to categorise them into cognitive domains. For example, Huang et al\(^9\) reported using the Trail Making Test but did not specify if they adopted part A, part B, both parts separately or part B – part A. Other examples of poorly reported measures were Stroop, verbal fluency and digit span tests. Although we strived to accurately categorise the neuropsychological tests into our predefined cognitive domains, poor reporting could have led to inaccurate categorisation.

CONCLUSION
In summary, our meta-analysis suggests that exercise training has a small effect on cognitive function in older adults living with all-cause dementia. The effects seem to be more pronounced in people with AD, even though moderation analysis did not confirm this result. It is also important to consider that studies including only participants living with AD presented a higher risk of bias compared with studies with other types of dementia or unspecified dementia. We did not find exercise training characteristics (eg, type, intensity, volume and intervention length) or type of dementia to be moderators of the effects of exercise training on cognitive function. Future RCTs should focus on clearly defining participant inclusion criteria, neuropsychological tests and exercise training characteristics. Furthermore, more research is needed to determine the effects of exercise on a range of dementia types other than AD and to elucidate the mechanisms of action.

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