

# A meta-analysis of randomised controlled trials of physical activity in people with Alzheimer's disease and mild cognitive impairment with a comparison to donepezil

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## Abstract

**Objectives:** Physical exercise may benefit people with Alzheimer's disease (AD) and mild cognitive impairment (MCI). However, randomised controlled trials (RCTs) of exercise have shown conflicting findings and it is unclear if positive outcomes are comparable to a commonly used cholinesterase inhibitor, donepezil.

**Methods:** Embase, Medline, PsycINFO, PsycARTICLES, SCOPUS were searched for RCTs of physical activity compared to a control condition, and donepezil compared to placebo in people with AD and MCI. Effect sizes were calculated from pre- and post-MMSE and ADAS-Cog scores and pooled using a random effects meta-analysis.

**Results:** Nineteen RCTs were included in the exercise meta-analysis (AD, N = 524; MCI, N = 1269). Physical exercise improved MMSE scores in AD (Hedges'  $g = 0.46$ ) and MCI groups ( $g = 0.63$ ). For the MCI group, exercise appeared to have a stronger effect for those with lower MMSE scores at baseline ( $p = 0.022$ ). 18 RCTs were included in the donepezil meta-analysis (AD, N = 2984, MCI, N = 1559). In people with AD, donepezil improved cognition (MMSE  $g = 0.23$ ; ADAS-Cog,  $g = -0.17$ ) but there was no evidence of improved cognition in MCI.

**Conclusions:** Physical exercise improved cognition in both AD and MCI groups. Where comparisons were possible, the effect size for physical exercise was generally comparable to donepezil. These results strengthen the evidence base for exercise as an effective intervention in AD and MCI, and future clinical trials should examine exercise type, intensity and frequency, in addition to cholinesterase inhibitors to determine the most effective interventions for AD and MCI.

## KEYWORDS

Alzheimer's disease, cognition, donepezil, mild cognitive impairments, physical activity

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### Key points

- Randomised controlled trials have suggested that physical activity has beneficial effects in Alzheimer's disease (AD) and Mild cognitive impairment, however it is not known how efficacious this intervention is compared to medication
- To our knowledge this is the first meta-analysis to compare the effects of physical activity to donepezil (a commonly used medication in AD) in these two clinical populations
- Where direct comparisons were possible, the effects of physical activity were comparable to those exerted by donepezil

## 1 | INTRODUCTION

A growing number of studies have investigated the effects of exercise in people with Alzheimer's disease (AD) and Mild cognitive impairment (MCI). AD is characterised by severe progressive memory impairments which are associated with deposition of amyloid plaques (A $\beta$ ) in extracellular spaces leading to cortical dysfunctions and neuronal loss.<sup>1,2</sup> These deficits can be detected throughout late lifespan and often in individuals with MCI<sup>3</sup> which may be a prodrome to AD. There is an increasing interest in non-pharmaceutical interventions due to the current lack of disease-modifying drugs and long-term effective treatments.<sup>4-7</sup> A common class of medications used to treat dementia are acetylcholinesterase inhibitors. One of the most commonly prescribed cholinesterase inhibitors is donepezil which has been found to ameliorate cognitive symptoms in AD<sup>8,9</sup> but it is not recommended for the treatment of MCI.<sup>10</sup> After 6 months from the administration of these drugs in dementia, cognition tends to decline further<sup>11</sup> and it is acknowledged that these medications primarily exert a palliative effect without counteracting neurodegeneration.<sup>6,12</sup>

Moderate and high intensity exercise has been demonstrated to diminish the progression of neuropsychological deficits in both AD and MCI.<sup>13-15</sup> Recent findings show that exercising increases levels of brain-derived neurotrophic factor (BDNF), an essential component for neuronal growth and neuronal plasticity.<sup>16</sup> Research in transgenic mice mimicking AD pathology has demonstrated that pharmacologically-induced neurogenesis in the mice's adult hippocampus ameliorates AD symptoms only if the mice had been physically active.<sup>17</sup> These promising findings suggest that exercising could alleviate or delay cognitive impairments by increasing neurogenesis. Results from the large Dementia and Physical Activity (DAPA) randomised controlled trial reported no benefits of physical activity on any cognitive domain<sup>18</sup>; whilst other studies have suggested small to moderate positive effects on cognitive functions.<sup>19</sup> Previous meta-analyses examining the effect of physical activity on people with AD and MCI,<sup>20-26</sup> have shown that exercise compared to a control arm has beneficial effects, but it is not clear how this compares to pharmacological treatments. A recent meta-analysis examining the impact of both exercise and medications in AD and MCI revealed that medications have a small impact on cognition primarily in AD, whilst physical activity was shown to improve cognition in both clinical groups.<sup>27</sup> While this meta-analysis had a number of important strengths its main focus was on drug studies and it included a relatively small number of

exercise RCTs ( $n = 10$ ) and specifically combined cognitive measures (MMSE, ADAS-Cog, etc.) into a single outcome variable. This makes comparisons between the two types of intervention problematic because of the possible confound of different cognitive measures used in the medication and exercise literature.

The aim of this meta-analysis is to strengthen the existing knowledge on the effects of physical activity on cognition in AD and MCI and to compare this to the effect of a common acetylcholinesterase inhibitor medication (i.e., donepezil). There has been an expanding interest in non-pharmacological interventions for these conditions since the study by Ströhle and colleagues<sup>27</sup> and this meta-analysis intends to provide at present a comparison between physical activity and donepezil. We also aim to address some of the weaknesses in the design of previous meta-analyses. Only randomized controlled trials (RCTs) are included to reduce the effects of bias and confounding. In line with prior research,<sup>14,15,20-22</sup> strict diagnostic criteria for both groups and a specific definition of physical activity<sup>28</sup> are applied to reduce heterogeneity. The quality of the included studies is assessed according to established scale of Gates et al.<sup>15</sup> The results from specific cognitive scales are analysed separately rather than combined to reduce heterogeneity and to allow a comparison between exercise and donepezil for each reported measure where available. We have applied a method of calculating effect sizes recommended by Morris<sup>29</sup> who has systematically examined the accuracy and stability of effect sizes from repeated measures designs. As cognitive decline may be associated with age,<sup>1,20</sup> and poor cognitive abilities at baseline<sup>30</sup> we have examined these potential moderators in a meta-regression. In line with prior research, we hypothesized that physical activity would be beneficial for cognition in people with AD and that exercise would be particularly effective in people with MCI as this disorder is earlier in the disease process. In comparison with medication we predicted the beneficial effect of exercise would be of a similar magnitude to the effects of donepezil.

## 2 | METHODS

### 2.1 | Identification of exercise and donepezil randomised controlled trials

The PRISMA guidelines were followed for this meta-analysis.<sup>31</sup> Two systematic searches of randomised controlled trials (RCTs) for

exercise and for donepezil were conducted on Medline, Embase, PsycINFO, PsycARTICLES Full Text through the OVID database and also SCOPUS in October 2019. Free-text words and subject headings were employed.

To identify RCTs that examined the effects of physical activity broad search terms were used: 'Alzheimer's disease' or 'Alzheimer's\*' or 'Mild cognitive impairment\*' and 'physical activity' or 'physical exercise' or 'aerobic fitness' and 'randomized controlled trial.' To identify RCTs that examined the effects of donepezil the following broad search terms were used: 'Alzheimer's disease' or 'Alzheimer\*' or 'Mild cognitive impairment\*' and 'donepezil' or 'Aricept' and

'randomized controlled trial.' Full search strategies can be found in Supplementary Material 1 (S1). Two PRISMA flowcharts were created for each search strategy (Figure 1, Figure 2).

## 2.2 | Inclusion and exclusion criteria

Only RCTs were included. Longitudinal, cross-sectional, case-control studies, systematic reviews, meta-analyses, cross-over randomized controlled trials and non-randomized controlled trials were excluded. Studies were included if they provided evidence of AD diagnosis

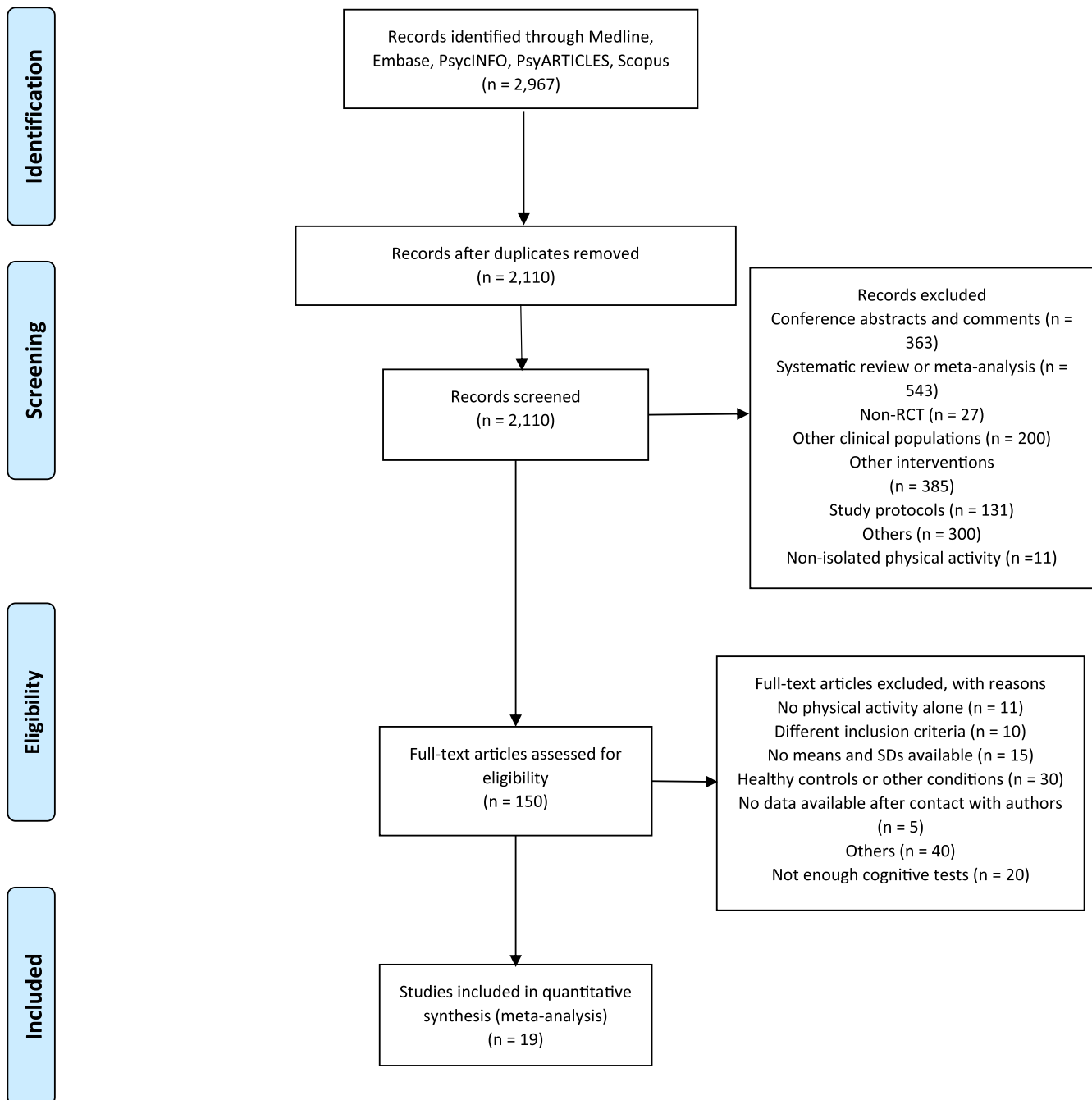


FIGURE 1 PRISMA flowchart of the study selection process for physical activity randomised controlled trials (RCTs) [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

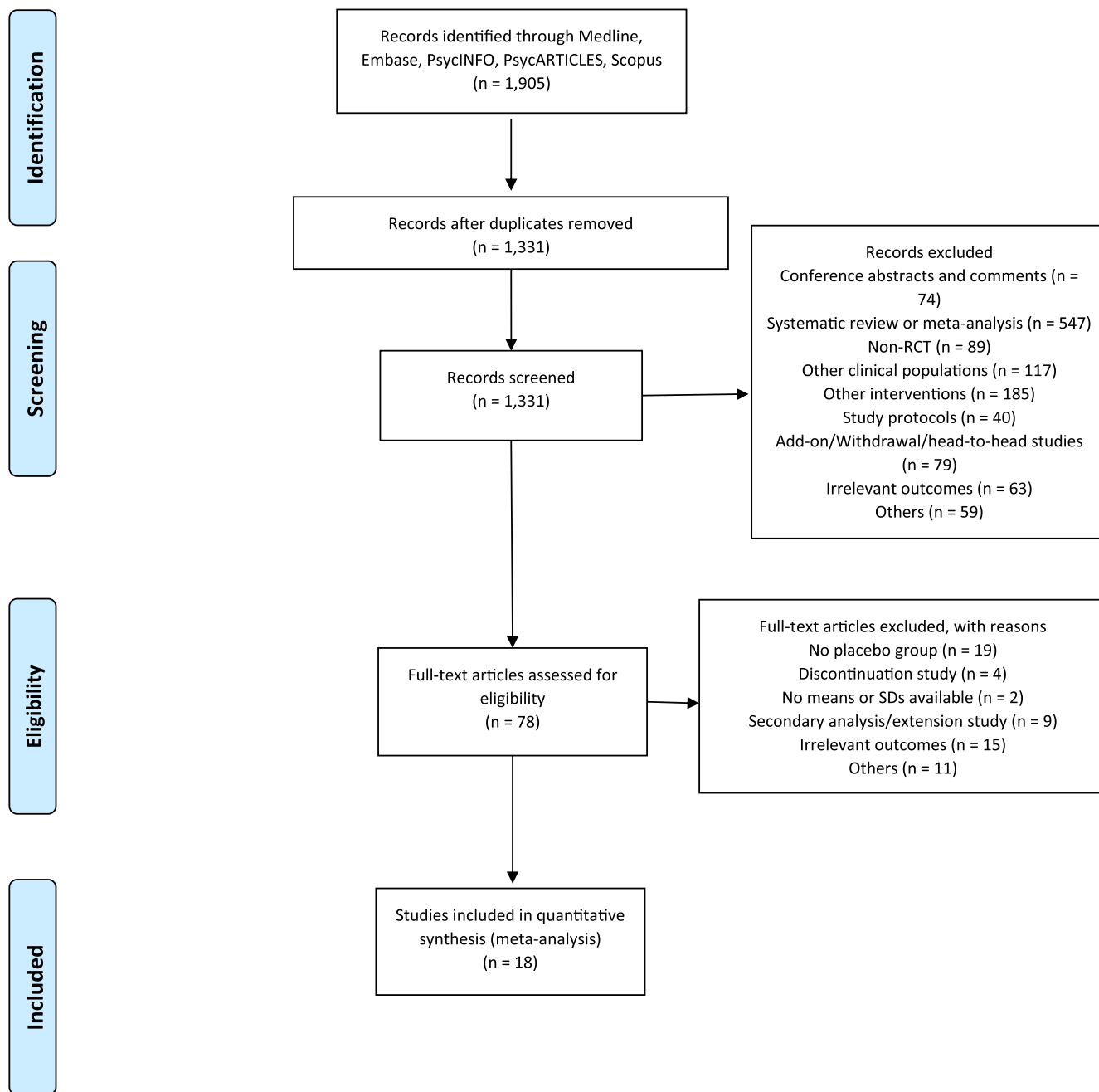


FIGURE 2 PRISMA Flowchart of study selection process of donepezil randomised controlled trials (RCTs) [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

(definite, probable and/or possible) following the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Associations (NINCDS-ADRDA),<sup>32</sup> the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-V) or International Statistical Classification of Diseases and Related Health Problems (ICD-10). MCI studies had to provide relevant evidence of a clinical diagnosis following Petersen's criteria,<sup>33</sup> or Albert et al. criteria,<sup>3</sup> and/or a score of 0.5 on the Clinical Dementia Rating scale.

**Physical activity:** Physical activity was defined according to the American College of Sports Medicine (ACSM)<sup>15,28</sup> whereby exercise

entails the investment of energy due to body movement and planned, repetitive exercise leading to improved physical fitness.<sup>28</sup> Studies were included if they compared an exercise-only intervention to a control group. For studies that compared different interventional arms, for example cognitive training, physical activity, music therapy, combined cognitive and physical training, the group with isolated physical exercise was compared to a control group. Multimodal interventions that included exercise plus additional component(s) were excluded.

**Donepezil:** Studies were included if they evaluated the effectiveness of donepezil compared to a control group receiving placebo.

## 2.3 | Outcome measures

The mini-mental state examination (MMSE) and Alzheimer's disease assessment scale—cognitive subscale (ADAS-Cog) were chosen as the outcome measures because they were most commonly reported by studies. To ensure the different meta-analyses were sufficiently powered, outcomes were included if there were three or more independent studies that reported a mean and SD in both the control, donepezil and exercise groups. Where follow-up means and SDs were not available authors were contacted for this information.

## 2.4 | Data extraction

Sample characteristics (e.g., gender, age and diagnosis), type and details of interventions, (i.e. length, dosage and intensity of exercise), control conditions and outcome measures were extracted from each study. Any disagreements were resolved via consensus of three authors (SP, CM and MJK). Pre- and post-intervention means and standard deviations (SD) were extracted from each study and each cognitive assessment for both intervention and control groups. Where confidence intervals or standard errors were provided, these were converted into SD.

## 2.5 | Quality assessment of studies

The Physiotherapy evidence database scale (PEDro)<sup>15,34</sup> is an 11-item quality rating scale of RCTs where each item is marked 0 or 1, with 1 indicating higher quality. The scale assesses eligibility criteria (item 1); internal validity (items 2–9) which include concealed allocation (item 3), blinding of participants (item 5), and of the assessor (item 7); and the appropriate outcome reported (items 10–11). Item 6 is blinding of the therapist, which is relevant for exercise studies, but is not applicable for pharmacological studies. Therefore, for RCTs of donepezil this item was removed, hence not coded, to indicate no additional risk of bias.

## 2.6 | Calculation of effect size

Investigators have applied different methods when calculating effect sizes from repeated measure designs. Morris<sup>29</sup> has extensively investigated these different methods in terms of precision, robustness and bias, and has proposed the optimal methodology uses the pre and post intervention means and pre-intervention SD from both the treatment and control groups. Thus, we calculated the Hedges effect size (which is the Cohen effect size with a correction for bias from small sample sizes) and its variance from equations provided by Morris<sup>29</sup> (equations 8 and 25, respectively) for each study (S2). This effect size is approximately equal to the

difference between the treatment and control change score divided by the pooled baseline standard deviation of the treatment and control group. The effect size variance requires an estimate of the correlation coefficient ( $\rho$ ) between pre and post intervention measures.  $\rho$  is not usually given in publications, but can be calculated if pre, post and change values are presented. These data were available in 5 of the included RCTs and mean weighted  $\rho$  was determined as 0.70 (95% CI 0.59–0.81). Thus,  $\rho$  was set to 0.7 for each meta-analysis but varied in the sensitivity analysis (see below). In some studies outcome measures were given at multiple time points during the intervention; in these cases, the final outcome values at end the intervention were used as the post-intervention value.

## 2.7 | Meta-analysis

Effect sizes were pooled using a random-effects inverse-weighted variance model.<sup>35</sup> When conducting a meta-analysis there is balance between maximising the number of studies to increase power and being more selective to reduce heterogeneity. In this meta-analysis we performed separate meta-analyses for AD and MCI where there was a sufficient number of studies. Between-study heterogeneity was analysed using Cochran Q test and  $I^2$  which indicates the percentage of total variation across studies due to heterogeneity.<sup>36,37</sup> Publication bias was assessed using Egger's regression<sup>38</sup> when at least five studies were included to ensure that the test was sufficiently powered. The calculation of effect sizes was performed using meta-analytical equations entered into Excel. These equations are identical to the METAN<sup>39</sup> command in STATA,<sup>40</sup> which is commonly used in meta-analyses publications. In terms of validation, the method has been used in parallel with STATA in a number of meta-analyses<sup>41,42</sup> and produced the same results.

## 2.8 | Meta-regression of mini-mental state examination

A random effects meta-regression was conducted on MMSE change in the AD and MCI groups using METAREG<sup>43</sup> in STATA<sup>40</sup> to investigate the contribution of age, baseline MMSE, on physical activity and donepezil. MMSE change was chosen because it was the most commonly reported outcome variable.

## 2.9 | Sensitivity analysis

To examine the strength of the results in relation to the variability of meta-analysis methods, a sensitivity analysis was conducted adjusting  $\rho$  from the standard value of 0.7 to a lower value of 0.5 and a higher value of 0.9.

TABLE 1 Descriptions of the studies which examined the effect of physical activity in Alzheimer's disease and mild cognitive impairment included in the meta-analysis

Authors	Clinical group	Baseline cognitive scores, mean (SD)	Mean Age (SD); Gender (M, F)	Physical activity (N)	Control group (N)	Additional group (N)	Outcome measure included in analysis	Intervention characteristics		
								Length	Frequency	Intensity
De Oliveira et al. (2019) <sup>44</sup>	MCI (N = 17); AD (N = 27)	MCI, exercise 29, control 29; AD, exercise 25.70, control 27.68	Exercise MCI 71.85 (5.69), exercise AD 81.22 (8.88), control MCI 78.20 (5.26), control AD 77.54 (8.05); 19M, 27F	Aerobic exercises, strength and balance training (N = 28)	No physical activity (N = 28)	None	MMSE	12 weeks	Twice per week	60 min
Langoni et al. (2019) <sup>45</sup>	MCI	Exercise 21.9 (4.8), control 23.7 (3.7)	Exercise 72.6 (7.8), control 71.9 (7.9); 12M, 40F	Aerobic and strength exercises (N = 26)	Life as usual (N = 26)	None	MMSE	24 weeks	Twice per week	60 min
Ohman et al. (2016) <sup>46</sup>	AD	Exercise (home-based) 17.8 (6.6), exercise (group based) 18.5 (6.3), control 17.7 (6.2)	Exercise 78, control 78.1 (5.3); 129M, 81F	Aerobic exercises, strength exercises and balance and toning training (home-based exercise) (N = 70)	Usual care (N = 70)	Aerobic exercises, strength exercises and balance and toning training (group-based exercise) (N = 70)	MMSE	12 months	Twice per week	60-min class
Lazarou et al. (2017) <sup>47</sup>	MCI	Exercise 27.60 (2.19), control 26.88 (2.10)	Exercise 65.89 (10.76), control 67.92 (9.47); 28M, 101F	International ballroom dance classes (N = 66)	Life as usual (N = 63)	None	MMSE	10 months	Twice per week	60-min class
Hoffmann et al. (2016) <sup>48</sup>	AD	Exercise 23.8 (3.4), control 24.1 (3.8)	Exercise 69.8 (7.4), control 71.3 (7.3); 113M, 87F	Aerobic and strength building exercises (N = 107)	Treatment as usual (N = 93)	None	MMSE	16 weeks	3 times per week	60-min class
Lu et al. (2015) <sup>49</sup>	MCI	Exercise 27.23 (1.63), control 26.43 (2.00)	Exercise 69 (3.83), control 70.43 (5.53); 13M, 32F	Dumbbell-training sessions (N = 22)	Treatment as usual (N = 23)	None	ADAS-cog	12 weeks	3 times per week	60-min class
Holthoff et al. (2015) <sup>50</sup>	AD	Exercise 22.05 (0.5), control 21.95 (0.54) <sup>a</sup>	Exercise 72.40 (4.43), control 70.67 (5.41); 15M, 15F	Lower-body movement training (N = 15)	Counselling sessions without physical activity (N = 15)	None	MMSE	12 weeks	3 times per week	30 min
Lam et al. (2015) <sup>51</sup>	MCI	Exercise 25.8 (2.3), control 25.6 (2.4)	Exercise 75.5 (6.7), control 75.4 (6.1); 63M, 215F	Stretching and toning exercises, Tai Chi sessions and aerobic exercise (i.e. static bicycle riding) (N = 147)	Social group (social activities, e.g. tea gathering, film watching) (N = 131)	Cognitive exercises (N = 145); cognitive-physical training (N = 132)	ADAS-cog; MMSE	12 months	At least once per week	60-min class

TABLE 1 (Continued)

Authors	Clinical group	Baseline cognitive scores, mean (SD)	Mean Age (SD); Gender (M, F)	Physical activity (N)	Control group (N)	Additional group (N)	Outcome measure included in analysis	Intervention characteristics		
								Length	Frequency	Intensity
Arcoverde et al. (2014) <sup>52</sup>	AD	Exercise 20.4 (2.7), control 19.9 (3.4)	Exercise 78.5, control 79; 9M, 11F	Treadmill training (N = 10)	Routine medical care (N = 10)	None	MMSE	3 months	Twice per week	30 min
Wei and Ji (2014) <sup>53</sup>	MCI	Exercise 24.33 (1.65), control 25.00 (1.29)	Exercise 66.73 (5.48), control 65.27 (4.63); 40M, 20F	Handball training (N = 30)	Life as usual (N = 30)	None	MMSE	6 months	5 days per week	30 min
Suzuki et al. (2013) <sup>54</sup>	MCI	Exercise 26.8 (2.3), control 26.3 (2.7)	Exercise 74.8 (7.4), control 75.8 (6.1); 51M, 49F	Aerobic exercises and strength and balancing exercises (N = 50)	Educational classes (N = 50)	None	MMSE; ADAS-Cog	6 months	Twice per week	90 min
Varela et al. (2012) <sup>55</sup>	MCI	Exercise (group A) 19.86 (5.12), exercise (group B) 20.81 (4.69), control (group C) 21.80 (3.23)	Exercise 77.88, control 79.40 (6.72); 21M, 27F	Aerobic exercise at 40% HR (group A) (N = 17)	Recreational activities (no physical activity) (N = 15)	Aerobic exercise at 60% HR (group B) (N = 16)	MMSE	6 months	3 times per week	30 min
Vreugdenhil et al. (2012) <sup>56</sup>	AD	Exercise 22.9, control 21.10	Exercise 73.5, control 74.7; 16M, 24F	Upper and lower muscle building exercises, balance training and brisk walking (community-based home exercise) (N = 20)	Usual care (N = 20)	None	MMSE	4 months	Daily	30 min
Van Uffelen et al. (2008) <sup>57</sup>	MCI	Exercise 22.9 (5.00), control 21.00 (6.3)	Exercise 74.97, control 74.97; 78M, 73F	Walking programme (N = 86)	Placebo pill (N = 89)	Placebo activity programme [relaxation, posture exercises, low intensity] (N = 93); vitamin B (N = 90)	MMSE	12 months	Twice per week	60 min

(Continues)

TABLE 1 (Continued)

Authors	Clinical group	Baseline cognitive scores, mean (SD)	Mean Age (SD); Gender (M, F)	Physical activity (N)	Control group (N)	Additional group (N)	Intervention characteristics			
							Outcome measure included in analysis	Length	Frequency	Intensity
Yoon et al. (2017) <sup>58</sup>	MCI	Exercise (high speed) 21.00 (1.04), exercise (low speed) 21.56 (0.73), control 22.29 (1.11)	Exercise 75.61, control 78.00 (2.77); NR	High-speed training with elastic band (N = 14)	Life as usual (N = 7)	Low-speed physical activity training (N = 9)	MMSE	12 weeks	Twice per week	60-min class
Nakatsuka et al. (2015) <sup>59</sup>	MCI	Exercise 23.5 (2.4), control 25.1 (2.7)	Exercise 81.3 (3.8), control 81.2 (4.0); 36M, 46F	Walking and step aerobics (N = 38)	Conversation classes (N = 44)	Cognitive exercises (N = 45)	MMSE	12 weeks	Once per week	60-min class
Venturelli et al. (2011) <sup>60</sup>	AD	Exercise 13.00, Control 12.00	Exercise 83 (6.0), control 85 (5.0); NR	Walking group (N = 12)	Routine medical care (N = 12)	None	MMSE	24 weeks	4 times per week	30 min
Bademli et al. (2018) <sup>61</sup>	MCI	Exercise 23.27 (2.17), control 23.42 (1.07)	Exercise 72.24 (7.16), control 70.67 (8.34); 25M, 37F	Physical activity programme (N = 30)	Life as usual (N = 30)	None	MMSE	20 weeks	4-7 days per week	40 min
Doi et al. (2017) <sup>62</sup>	MCI	Exercise 26.0 (2.6), control 25.8 (2.4)	Exercise 75.7 (4.1), control 76.0 (4.9); 70M, 64F	Dance programme (N = 67)	Health education programme (N = 67)	Music programme (N = 67)	MMSE	40 weeks	Weekly sessions	60 min

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease Assessment Scale – Cognitive subscale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

<sup>a</sup>Standard error reported between brackets.



### 3 | RESULTS

#### 3.1 | Study characteristics

**Physical activity:** 2110 articles were initially identified, and after applying inclusion and exclusion criteria, 19 RCTs were included (Figure 1; AD,  $n = 7$ ; MCI,  $n = 13$ ). One study included both people with AD and MCI and conducted their analyses separate for each clinical group.<sup>44</sup> In total, 1793 individuals took part in these 19 RCTs, 970 allocated to physical activity and 823 to control arms (Table 1). Of the studies that reported gender there were a total of 949 females and 738 males. The mean of age in the intervention arm was 74.52 years (AD, 76.63 years; MCI, 73.39 years), whilst the mean of age in the control group was 75.07 (AD, 76.62 years; MCI, 74.24 years). The interventions entailed aerobic (e.g. Nordic walking, bicycle riding, dancing, handball training and others) and non-aerobic activities (stretching and toning, dumbbell training, weightlifting, and others). Studies examining combined interventions, for example physical activity and cognitive training, or cognitive activity and virtual reality, were included in the analysis where they had an arm of isolated physical activity comparable to a control group that did not include any physical exercise. Control arms included treatment as usual or routine medical care, educational classes and social activities, and relaxation with light movement (Table 1). The average length of the intervention was 25.26 weeks, with a mean of 51.05 min of physical activity, conducted between twice per week to everyday.

**Donepezil:** 1,331 articles were initially identified, and after applying inclusion and exclusion criteria, 18 RCTs were included in the analysis (Figure 2; AD,  $n = 15$ ; MCI,  $n = 3$ ). 4,543 people took part in these studies, 2,219 were allocated to donepezil, whilst 2,324 were assigned to control (placebo) arm (Table 2). There were 2,690 females and 1,853 males, the mean age of those allocated to donepezil was 74.21 (AD, 74.69 years; MCI, 71.80 years), the mean age of those in the control arm was 74.23 (AD, 74.71 years; MCI, 71.80 years). Four studies administered donepezil at 10 mg/day, three studies administered it at 5 mg/day, whilst in 11 studies donepezil dosage started at 5 mg/day and then gradually increased to maximum of 10 mg/day in 11 studies. Studies examining other medications in addition to donepezil were included in the analysis where they had an arm of isolated donepezil. The average length of the intervention was 25.36 weeks.

#### 3.2 | Quality assessment of exercise randomised controlled trials

**Physical activity:** Across the 19 RCTs, the average PEDro score was 7.58 out of a maximum of 11 with a range between 6 and 9 points. A common reason for reduced scores was the lack of blinding participants and professionals administering the physical activity to the sample; as blinding of participants was deemed not feasible due to the nature of the intervention. Blinding of the researchers conducting the cognitive assessments was present in 14 (73%) out of the 19 studies (Table 4).

**Donepezil:** Across 18 RCTs, the average PEDro score was 9.33 out of a maximum of 10, after removing the item that assessed the blinding of the therapist (see methods). The range was between 8 and 10 points. Methodological weaknesses were primarily related to concealed allocation. Studies were double-blinded and always randomised (Table 5).

#### 3.3 | Meta-analysis—physical activity

In AD, physical activity was associated with an improvement in MMSE compared to the control arm ( $g = 0.458$ ,  $p = 0.013$ ; Figure 3), however this result was associated with small sample bias ( $p = 0.02$ ). Only two studies employed the ADAS-Cog, precluding a meta-analysis. Physical activity also had a significant beneficial effect on cognitive functions assessed with the MMSE compared to the control condition for MCI ( $g = 0.631$ ,  $p = 0.001$ ) (S5, Figure 4). There was no significant effect of physical activity on the ADAS-Cog ( $p = 0.399$ ) (Figure 5; Table 3).

#### 3.4 | Meta-regression

In the AD group, there were no significant moderating effect of age ( $n = 7$ ,  $p = 0.082$ ) or baseline MMSE ( $n = 7$ ,  $p = 0.081$ ) on the effect of exercise on MMSE. Baseline MMSE scores moderated the effects of exercise on MMSE in MCI ( $n = 15$ ,  $t = -2.59$ ,  $p = 0.022$ ), the direction of the findings indicated that lower MMSE baseline scores were associated with a stronger beneficial effect of physical activity. There was no significant moderating effect of age ( $n = 15$ ,  $p = 0.798$ ; Table 6).

#### 3.5 | Sensitivity analysis

There was no change in results classified as significant or non-significant when  $\rho = 0.9$ , or when  $\rho = 0.5$ .

#### 3.6 | Meta-analysis—donepezil

Full details of the results are given in Table 3. For people with AD, those taking donepezil had improvements in MMSE ( $g = 0.233$ ,  $p < 0.001$ ; Figure 7) and ADAS-Cog ( $g = -0.174$ ,  $p < 0.001$ ; Figure 6). For people with MCI, there was a trend towards significance for improved cognition assessed with the ADAS-Cog ( $g = -0.130$ ,  $p = 0.059$ ; Figure 8).

#### 3.7 | Meta-regression

There were no significant moderating effects of age or baseline MMSE scores for AD or MCI groups (all  $p > 0.05$ ; Table 6).

TABLE 2 Descriptions of the studies which examined the effect of donepezil in Alzheimer's disease and mild cognitive impairment included in the meta-analysis

Study	Clinical group	Baseline cognitive scores, mean (SD)	Mean Age (SD); Gender (M, F)	Donepezil (N)	Control group (N)	Additional groups (N)	Intervention length	Dosage	Outcome measure included in analysis
Petersen et al. (2005) <sup>63</sup>	MCI	Donepezil 27.25 (1.8), control 27.35 (1.8)	Donepezil 73.1 (7.1), placebo 72.9 (7.6); 279M, 233F	Donepezil (N = 253)	Placebo (N = 259)	Vitamin E (2000 IU/day, N = 257)	36 months	5 mg/day to 10 mg/day	ADAS-cog
Doody et al. (2009) <sup>64</sup>	MCI	Donepezil 83.9%, control 83.2% <sup>a</sup>	Donepezil 70.2 (9.71), placebo 69.8 (10.32); 424M, 354F	Donepezil (N = 391)	Placebo (N = 387)	None	48 weeks	5 mg/day to 10 mg/day	ADAS-cog
Salloway et al. (2004) <sup>65</sup>	MCI	Donepezil 27.5 (2.2), control 27.4 (2.0)	Donepezil 72.1 (8.0), placebo 72.7 (8.0); 155M, 114F	Donepezil (N = 132)	Placebo (N = 137)	None	24 weeks	5 mg/day to 10 mg/day	ADAS-cog
Moraes et al. (2006) <sup>66</sup>	AD	Donepezil 35.6 (13.7), control 39 (18.5) <sup>b</sup>	Donepezil 77.4 (6.66), placebo 74.5 (9.8); 11M, 24F	Donepezil (N = 17)	Placebo (N = 18)	None	12 weeks	5 mg/day to 10 mg/day	ADAS-cog
Frolich et al. (2011) <sup>67</sup>	AD	Donepezil 61.4%, control 60.7% (mild severity) <sup>c</sup> ; donepezil 38.6%, control 39.3% (moderate severity) <sup>c</sup>	Donepezil 73.9 (6.48), placebo 73.5 (6.42); 127M, 194F	Donepezil (N = 158)	Placebo (N = 163)	AZD3480 (5 mg/day, N = 77) versus AZD3480 (20 mg/day, N = 78) versus AZD3480 (35/100 mg/day, N = 82)	12 weeks	5 mg/day to 10 mg/day	MMSE; ADAS-Cog
Mazza et al. (2005) <sup>68</sup>	AD	Donepezil 18.55 (3.47), control 18.80 (3.63)	Donepezil 64.5 (6.00), placebo 69.8 (3.00); 23M, 28F	Donepezil (N = 25)	Placebo (N = 26)	Ginkgo biloba (160 mg/day, N = 25)	24 weeks	5 mg/day	MMSE
Howard et al. (2007) <sup>69</sup>	AD	Donepezil 8.1 (5.9), control 8.2 (6.8)	Donepezil 84.9 (7.73), placebo 84.4 (8.2); 40M, 219F	Donepezil (N = 128)	Placebo (N = 131)	None	12 weeks	5 mg/day to 10 mg/day	MMSE
Winbald et al. (2006) <sup>70</sup>	AD	Donepezil 6.0 (3.0), control 6.2 (3.0)	Donepezil 84.5 (6.60), placebo 85.3 (5.9); 58M, 190F	Donepezil (N = 128)	Placebo (N = 120)	None	6 months	5 mg/day to 10 mg/day	MMSE
Maher-Edwards et al. (2015) - study 1 <sup>71</sup>	AD	Donepezil 26.2 (11.41), control 18.2 (3.88)	Donepezil 71.1 (7.49), placebo 73.3 (6.80); 100M, 182F	Donepezil (N = 147)	Placebo (N = 135)	SB-742457 (15 mg/day, N = 142) versus SB-742457 (35 mg/day, N = 130)	24 weeks	5 mg/day to 10 mg/day	ADAS-cog
Haig et al. (2014) <sup>72</sup>	AD	Donepezil 18.1 (4.1), control 18.2 (3.9)	Donepezil 70.5 (8.31), placebo 70.3 (7.84); 48M, 75F	Donepezil (N = 60)	Placebo (N = 63)	ABT-288 (1 mg/day, N = 63) versus ABT-288 (3 mg/day, N = 56)	12 weeks	10 mg/day	MMSE; ADAS-Cog

TABLE 2 (Continued)

Study	Clinical group	Baseline cognitive scores, mean (SD)	Mean Age (SD); Gender (M, F)	Donepezil (N)	Control group (N)	Additional groups (N)	Intervention length	Dosage	Outcome measure included in analysis
Gold et al. (2010) <sup>73</sup>	AD	Donepezil 24.9 (9.68), control 25 (10.26)	Donepezil 72.9 (7.97), placebo 72.5 (8.56); 92M, 143F	Donepezil (N = 76)	Placebo (N = 159)	RSG XR (2 mg/day, N = 162) versus RSG XR (8 mg/day, N = 156)	24 weeks	10 mg/day	ADAS-cog
Vila-castellar et al. (2019) <sup>74</sup>	AD	Donepezil 24.3 (3.5), control 25.4 (1.7)	Donepezil 79.3 (7.74), placebo 81.7 (3.8); 8M, 15F	Donepezil (N = 12)	Placebo (N = 11)	None	6 weeks	5 mg/day	MMSE; ADAS-Cog
Homma et al. (2000) <sup>75</sup>	AD	Donepezil 17.8 (3.9), control 16.6 (3.9)	Donepezil 70.1 (7.76), placebo 69.4 (8.8); 75M, 153F	Donepezil (N = 116)	Placebo (N = 112)	None	24 weeks	5 mg/day	ADAS-cog
Gault et al. (2016) <sup>76</sup>	AD	Donepezil 18.4 (4.42), control 19.1 (4.00)	Donepezil 75.1 (7.75), placebo 73.2 (7.39); 74M, 105F	Donepezil (N = 75)	Placebo (N = 104)	ABT-126 (25 mg/day, N = 77) versus ABT-126 (50 mg/day, N = 107) versus ABT-126 (75 mg/day, N = 73)	24 weeks	10 mg/day	MMSE; ADAS-Cog
Rogers et al. (1998b) <sup>77</sup>	AD	Donepezil 19 (0.4), control 19.2 (0.4) <sup>d</sup>	Donepezil 72.9 (8.39), placebo 72.6 (8.04); 120M, 196F	Donepezil (N = 154)	Placebo (N = 162)	Donepezil (10 mg/day, N = 157)	24 weeks	5 mg/day or 10 mg/day	ADAS-cog
Black et al. (2007) <sup>78</sup>	AD	Donepezil 7.5 (3.25), control 7.4 (3.57)	Donepezil 78.0 (8.04), placebo 78.0 (8.20); 102M, 241F	Donepezil (N = 176)	Placebo (N = 167)	None	24 weeks	10 mg/day	MMSE
Jia et al. (2017) <sup>79</sup>	AD	Donepezil 7.6 (3.36), control 7.0 (3.4)	Donepezil 71.6 (8.56), placebo 70.0 (9.57); 110M, 203F	Donepezil (N = 157)	Placebo (N = 156)	None	24 weeks	5 mg/day to 10 mg/day	MMSE
Tune et al. (2003) <sup>80</sup>	AD	Donepezil 20.8 (3.7), control 21.4 (4.1)	Donepezil 73.7, placebo 72.2; 7M, 21F	Donepezil (N = 14)	Placebo (N = 14)	None	24 weeks	5 mg/day to 10 mg/day	ADAS-cog

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease Assessment Scale—Cognitive subscale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RSGXR, Rosiglitazone extended release.

<sup>a</sup>MMSE scores  $\leq 28$ .

<sup>b</sup>Cognitive functions measured at baseline with ADAS-Cog.

<sup>c</sup>MMSE severity divided according to two ranges of scores, mild severity (21–26) and moderate severity (12–20).

<sup>d</sup>Standard error reported between brackets.

**TABLE 3** Meta-analysis of physical activity and donepezil against control condition in AD and MCI. Effects sizes, 95% confidence intervals and *p* value are here shown, as well as heterogeneity values and publication bias analysis

Studies	Intervention participants (n)	Control/placebo participants (n)	Comparison of Intervention to Control group				Heterogeneity			S.S. Bias <sup>a</sup>	
			Effect size	95% CI	Effect size <i>p</i> -value	Q	I <sup>2</sup> %	<i>p</i> -value	<i>p</i> -value		
<b>Alzheimer's disease</b>											
MMSE—physical activity	288	213	0.458	0.097 To 0.819	0.013	27.16	77.90	<0.001	0.021		
MMSE—Donepezil	843	875	0.233	0.159 To --- (not enough studies) --	<0.001	3.26	0.00	0.917	0.757		
ADAS-cog—physical activity											
ADAS-cog—donepezil	728	813	-0.174	-0.253 To -0.095	<0.001	8.41	0.00	0.494	0.173		
<b>Mild cognitive impairment</b>											
MMSE—physical activity	621	535	0.631	0.244 To 1.018	0.001	185.04	92.40	<0.001	0.065		
MMSE—donepezil				--- (not enough studies) ---							
ADAS-cog—physical activity	216	199	-0.208	-0.692 To 0.276	0.399	14.17	85.90	0.001	0.636		
ADAS-cog—donepezil	764	774	-0.130	-0.266 To 0.005	0.059	5.54	63.90	0.063	0.620		

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease Assessment Scale—Cognitive subscale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

<sup>a</sup>Publication bias was only examined when there were at least 5 studies included to ensure the test was appropriately powered. Significant findings are in bold. The negative effect size from ADAS-Cog is a consequence of the scoring, with higher scores indicating greater cognitive impairment.

### 3.8 | Sensitivity analysis

There were no changes in the results except when  $\rho = 0.09$  for ADAS-Cog in people with MCI only where scores on ADAS-Cog in the donepezil group changed from a trend to becoming significant ( $p = 0.059$  to  $p = 0.045$ ).

## 4 | DISCUSSION

This meta-analysis examined the effect of physical activity and donepezil on cognitive abilities measured by the MMSE and ADAS-Cog in AD and MCI. Both people with AD and MCI in the exercise group showed moderate improvement in MMSE. The meta-analyses of donepezil showed that the medication improved cognition measured by ADAS-Cog and MMSE in the AD group. No improvements were reported in people with MCI who took donepezil.

For the AD group, exercise was associated with nominally larger effect sizes than donepezil for MMSE, however the exercise meta-analysis also showed evidence of small sample bias which may include publication bias, so additional studies will be needed to confirm the difference in effect size. In the MCI group, exercise was associated with a robust improvement in MMSE, but there was no evidence that donepezil had a beneficial effect on cognition in this clinical group.

Our findings are in line with previous research but are arguably more robust as the meta-analysis was limited to only RCTs,<sup>14,15,20,21,24,25</sup> pre- and post-treatment measures have been taken into account using Morris' recommendations<sup>29</sup> and the cognitive measures were meta-analysed using the same scales rather than pooling different instruments. There was a significant impact of baseline MMSE scores for people with MCI, whereby those whose MMSE scores were low experienced more benefit from practising physical activity. An alternative explanation for these results could be due to a compensation effect,<sup>81</sup> whereby individuals who are cognitively poor may benefit more from physical activity, that is the effect of this intervention is stronger on this population because of the extent of their cognitive impairment (compensation).<sup>81</sup> This should be further investigated as it could provide insight on the appropriate approach to maximise the benefits of physical activity. There was no significant influence of age so additional longitudinal studies may be required to pinpoint the optimum age after a diagnosis of MCI or AD to administer physical activity interventions. A beneficial effect of exercise on MMSE was seen in the MCI group but not on ADAS-Cog although the latter measure showed a strong trend ( $p = 0.059$ ). This could be because of the small number of papers ( $n = 3$ ) and because the ADAS-Cog is more commonly used in AD and may be more sensitive to more advanced cognitive deficits which are more observable in people with AD. Our results contrast with those reported in the DAPA RCT trial of 494 people with dementia<sup>18</sup> where Lamb and colleagues observed a greater reduction in ADAS-Cog scores after 12 months in the exercise intervention group

compared to the control group. We were not able to include this study because there were fewer than 3 studies reporting the ADAS-Cog score in people with AD precluding a meta-analysis. This raises the need to further investigate the relationship between exercise and cognition in neurodegenerative disorders. Nevertheless, our results show moderate effect sizes in both AD and MCI group meta-analyses indicating that physical activity is an efficacious and potentially complementary intervention to pharmacological therapies. Only three donepezil RCTs with MCI participants included the MMSE and had data available pre- and post-intervention; in this analysis, donepezil had no significant effect on cognition. The results from the analyses on donepezil trials were in line with previous research,<sup>8-10</sup> showing that donepezil may have limited effects on cognitive functions in people with MCI. Exercise may therefore be beneficial in such a group to improve cognitive function and can be easily added to home care settings and to people's routine. People with MCI experienced greater benefits from physical exercise than people with AD, highlighting the need for follow up studies that examine whether exercise could reduce the progression of MCI to AD.

### 4.1 | Strengths, limitations and future directions

There are a number of limitations to this study. Significant heterogeneity was present across most of the physical exercise analyses. Heterogeneity is expected with different clinical populations and differences in clinical characteristics between studies. It is well-known that both AD and MCI have diverse speeds of progression which may vary according to age of onset, family history, gender and onset of treatment.<sup>1,12,31,39</sup> Pharmacological studies did not report as much heterogeneity as that observed in exercise studies. This may be because administering one medication entails a more homogeneous procedure compared to different types of physical activities (i.e., Tai Chi, Nordic walking). Physical activity RCTs generally had smaller sample sizes than pharmacological studies which is likely due to greater financial investment in pharmacological therapies. Future studies could consider a three-arm design for an RCT examining the effect of cholinesterase inhibitors against aerobic activity and a control or could consider combining both exercise and a cholinesterase inhibitor to see if the beneficial effects are additive. Control arms of some studies that examined physical activity in AD and MCI included treatment as usual. As clinical care in neurological disorders can include a combination of different medications (e.g., cholinesterase inhibitors), occupational therapy and other treatment, it was challenging to differentiate medication-only control groups. Some studies did not report the specific medications participants took, whilst others reported general statements or listed in a table the number of participants undergoing treatment for AD or cholinesterase inhibitors.<sup>48,56</sup> The presence of these medications in participants within the control group could affect the effect sizes observed in this meta-analysis. Although interrupting necessary routine medical care in a clinical trial would be not be ethical, there is the need in future studies to account for this aspect by statistical approaches, by clarifying the

medical treatments involved, or by direct comparison of physical activity to medication for AD. One other limitation relates to the search strategy: although applying randomised controlled trial as key words can be considered a more conservative way of identifying this specific research design during literature searches, this strategy might have restricted the breadth of studies that could be included. Although the use of physical activity and similar terms was applied to be inclusive, this search might not have picked up specific or modern types of exercises. Similarly, we tried to be as inclusive as possible with terms indicating global cognitive functions, however future meta-analyses could also consider specific cognitive domains such as executive function and working memory as search terms. Blinding participants to either physical activity or control is generally not feasible, given the nature of exercise. This might have inflated the effect sizes, as people were not blind to the intervention. However, for the majority of the included studies the researchers assessing participants' post-intervention were blinded to their condition, preventing observer bias. Blinding of both participants and assessors was achieved in all donepezil trials. The application of the ACSM definition of physical activity<sup>15,28</sup> is a strength of our study as it specified a consistent criterion for including RCTs, providing a less biased framework. Nevertheless, the meta-analysis included varied types of physical exercise: resistance training, aerobic and non-aerobic exercises, sports and specific activities. Future research may be able to determine whether there are specific exercises or an optimum frequency of physical exercise to reduce neuropsychological decline in MCI and AD. In addition, future RCTs could be conducted using a precision medicine approach where participants are stratified according to key clinical variables or the presence of predictive biomarkers (e.g., APOE genotype), assigned to different physical activities.

## 5 | CONCLUSION

In conclusion, this meta-analysis provided confirmation of the efficacy of physical activity as an intervention in the treatment of Alzheimer's disease and Mild cognitive impairment and where comparisons were possible that the effect was comparable to donepezil. There remain unanswered questions regarding the most effective specific activity type, adherence to the intervention and the heterogeneity of symptom severity between AD and MCI, thus warranting explorations to shed further light on this complementary intervention.

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## DECLARATION OF INTEREST

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## STATEMENT ON ETHICS APPROVAL, EXPERIMENTATION ON HUMANS, AND TRIAL REGISTRATION

For this study, no experiments on human subjects was conducted. This is a meta-analysis on data provided by randomised controlled trials examining Alzheimer's disease and Mild cognitive impairment. No experimentation on animal subject was conducted or involved in this study. This study was not registered on any clinical trial registry.

This meta-analysis has not been published before nor is being considered for publication in another journal.

## DATA AVAILABILITY STATEMENT

This publication is a meta-analysis and as such it includes data that has already been published. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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