Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis


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A R T I C L E   I N F O

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A B S T R A C T

Combined cognitive and physical exercise interventions have potential to elicit cognitive benefits in older adults with mild cognitive impairment (MCI) or dementia. This meta-analysis aims to quantify the overall effect of these interventions on global cognitive functioning in older adults with MCI or dementia. Ten randomized controlled trials that applied a combined cognitive-physical intervention with cognitive function as an outcome measure were included. For each study effect sizes were computed (i.e., post-intervention standardized mean difference (SMD) scores) and pooled, using a random-effects meta-analysis. The primary analysis showed a small-to-medium positive effect of combined cognitive-physical interventions on global cognitive function in older adults with MCI or dementia (SMD[95% confidence interval] = 0.32[0.17;0.47], p < 0.00). A combined intervention was equally beneficial in patients with dementia (SMD = 0.36[0.12;0.60], p < 0.00) and MCI (SMD = 0.39[0.15;0.63], p < 0.05). In addition, the analysis showed a moderate-to-large positive effect after combined cognitive-physical interventions for activities of daily living (ADL) (SMD = 0.65[0.09;1.21], p < 0.01) and a small-to-medium positive effect for mood (SMD = 0.27[0.04;0.50], p < 0.01). These functional benefits emphasize the clinical relevance of combined cognitive and physical training strategies.

1. Introduction

Due to the aging population, the number of people with mild cognitive impairment (MCI) or dementia is expected to grow (World Health Organisation and Alzheimer’s Disease International, 2012). Currently there are about ten million new cases of dementia each year, a number which will increase to approximately 131.5 million prevalent dementia cases in 2050 (Alzheimer’s Disease International, 2015). These rapidly growing numbers will have a large societal impact, placing a high economic burden on health care (Alzheimer’s Disease International, 2015; Winblad et al., 2016). Therefore, the World Health Organization (WHO) stresses to take global action against cognitive decline and dementia, encouraging governments worldwide to focus on prevention, disease-modifying therapies and improving health care services (World Health Organization, 2015).

Mild cognitive impairment (MCI) is the transitional phase between normal cognitive functioning and dementia, characterized by cognitive decline that is larger than expected considering a person’s age and education, though without notably interference in daily-life activities (Gauthier et al., 2006). The annual conversion rates from MCI to dementia ranges from 5 to 20%, depending on the sample studied and the follow-up duration (Langa and Levine, 2014). Dementia is characterized by progressive and severe cognitive decline, motor deficits and/or behavioural problems causing a decline in activities of daily living (ADL) (Alzheimer’s Association, 2014). A variety of neuropathologies underlie dementia syndromes, with Alzheimer’s disease being the most common cause in older adults, accounting for 60–80% of all dementia cases, followed by vascular dementia (Alzheimer’s Association, 2014). Thus far, pharmacological therapies solely alleviate dementia symptoms, but fail to modify disease progression (Feldman et al., 2007; Kivirajar and Schneider, 2007; Versijpt, 2014).

Recent meta-analyses show that physical exercise may help to
preserve or even improve cognitive function in healthy older adults (Angevaren et al., 2008; Colcombe and Kramer, 2003; Smith et al., 2010; Voss et al., 2011). There is evidence that exercise increases the volumes of the prefrontal cortex (Colcombe and Kramer, 2006) and the anterior hippocampus (Dieitch et al., 2008; Erickson et al., 2011), and may enhance neurogenesis (Nokia et al., 2016) and angiogenesis (Lange-Asschenfeldt and Kojda, 2008). Furthermore, exercise reduces cardiovascular risk factors (Rovio et al., 2005). In contrast, research on the effects of physical exercise in older adults with MCI or dementia are less abundant and vary in efficacy (Forbes et al., 2015; Gates et al., 2013; Groot et al., 2016; Heyn et al., 2004). The large variability in exercise protocols, study populations and treatment compliance complicate interpretation of the results (Forbes et al., 2015; Groot et al., 2016; Heyn et al., 2004).

Possibly, the neural and cognitive benefits elicited by physical activity can be enhanced by adding exposure to a cognitively challenging environment (Fabel and Kempermann, 2008; Fabel et al., 2009; Olson et al., 2006). Experimental animal studies have shown that physical activity and environmental enrichment induce hippocampal neurogenesis via different pathways, and a combination results in greater benefits than either physical activity or an enriched environment alone (Fabel et al., 2009; Olson et al., 2006). In line, a meta-analysis of Zhu et al. (2016) revealed significant benefits of combined cognitive and physical interventions, compared with both single exercise training and a control group, on overall cognitive function in healthy older adults. A qualitative review of Law et al. (2014) shows some benefits of combined interventions in cognitively impaired populations, however the evidence was limited when the evaluation included comparison with active control groups. Moreover, conclusions drawn from this qualitative review were based on reported levels of statistical significance without considering the magnitude of the observed effects. Therefore, a quantitative meta-analysis including the most recent studies is needed to clarify the efficacy of combined cognitive and physical exercise interventions on global cognitive function in older adults with MCI or dementia.

The primary objective of this meta-analysis is to quantify the overall effect of combined cognitive and physical exercise interventions on global cognitive function in older adults with MCI or dementia. Secondary objectives are to (1) assess the effect of combined cognitive and physical exercise interventions on the cognitive domains of memory and executive function/attention, (2) determine whether combined interventions positively influence activities of daily living (ADL) and (3) evaluate the efficacy of combined interventions on mood.

2. Methods

The review was registered in the International prospective register of systematic reviews (PROSPERO, https://www.crd.york.ac.uk/PROSPERO/: CRD42016051342) and the work was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2009) guidelines.

2.1. Search strategy

In February 2017 systematic searches were conducted in the databases PUBMED, PsyCINFO, Embase and Cochrane Library. This search was updated in May 2017. We used a combination of terms for cognitive impairment (“dementia” OR “cognitive impairment” OR “Alzheimer”), AND cognitive/physical intervention terms (“exercise” OR “physical activity” OR “aerobic therapy” OR “resistance training” OR “cognitive therapy” OR “memory training” OR “cognitive stimulation”), AND combined intervention terms (“multimodal” OR “combined” OR “cognitive-motor” OR “dual–task”) (See Supplementary A for full search terms). To identify additional potentially relevant articles, the reference lists of the selected articles were screened.

2.2. Eligibility criteria and study selection

Studies were eligible if they met the following inclusion criteria: (1) inclusion of a sample of patients diagnosed with MCI or dementia not caused by traumatic brain injury or space-occupying lesion; (2) intervention consisting of a combined cognitive and physical training; (3) peer-reviewed articles with a randomized controlled trial (RCT) design including an active or passive control group and (4) reporting at least one measure for global cognitive function to calculate an effect size. Studies were excluded if they were: (1) prospective or retrospective cohort studies; (2) case reports; (3) conference abstracts or (4) not written in English. When articles reported an overlap in the sample of participants the article with the largest sample was included. Two reviewers (E.K. and T.S.) screened the title/abstracts and subsequently full text articles separately. Disagreements were discussed with a third researcher (J.A.) and adjusted after reaching consensus.

2.3. Interventions and outcome measures

Only RCTs with a combined cognitive and physical exercise intervention group, that also included an active or passive control group, were included. If the RCTs consisted of two or more intervention groups (i.e., also single physical and single cognitive training), only data of the combined intervention and control group were used for analyses. Global cognitive function, evaluated with a global cognitive screening instrument, was used as the primary outcome measure. Secondary outcome measures were performance on the domains of memory and executive function/attention, ADL and mood. All outcome measures had to be administered at baseline and directly after the intervention period. Corresponding authors of eligible studies were contacted and asked to provide missing data in case of insufficient reporting of statistics.

2.4. Risk of bias assessment

The Cochrane Collaboration’s tool (Higgins and Green, 2011) for assessing risk of bias was used as a measure of quality assessment. Risk of bias was reported in six domains; selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Each bias domain was rated as low, high, or unclear. Two researchers (E.K. and T.S.) independently performed the risk of bias assessment. Differences in outcome were discussed with a third researcher (J.A.) until consensus was reached. A total risk of bias judgment was based on the assessment of all domains.

2.5. Statistical analysis

The statistical analysis was conducted using Comprehensive Meta-analysis (CMA) Version 2.0 (Englewood, NJ, USA, 2005). A random-effects meta-analysis was used to correct for variable effect sizes across the studies and because studies showed heterogeneity in the intervention methods (e.g., intervention type, duration, outcome measures) (Borrenstein et al., 2009). The intervention effect was measured by the standardized mean difference (SMD) estimated as follows (Borrenstein et al., 2009)

\[
SMD = \frac{X_e - X_c}{S_{within}}
\]

\(X_e\) is the sample mean of the experimental group and \(X_c\) is the sample mean of the control group. \(S_{within}\) is the within the group standard deviation, pooled across groups:

\[
S_{within} = \sqrt{\frac{(n_e - 1)S_e^2 + (n_c - 1)S_c^2}{n_e + n_c - 2}}
\]

where, \(S_e\) is the standard deviation of the experimental group, \(S_c\) is the
standard deviation of the control group and $n_c$ and $n_t$ the numbers of participants in the experimental and control group (Borrenstein et al., 2009). Pooled-SMDs were computed for all three cognitive domains, ADL and mood, weighted for the sample size of the individual studies (Borrenstein et al., 2009). These pooled effect sizes were classified as small (0.2), moderate (0.5) and large (0.8) in accordance with convention (Cohen, 1992). If studies used more than one measure in a cognitive domain, an average effect size was computed to avoid one study over influencing the results.

A 95% confidence interval was used to determine the efficacy of combined interventions versus control on cognitive function, mood and ADL. In addition, Orwin’s fail safe N was calculated for significant results to assess how many studies were needed in order to reduce the effect size to less than 0.1 (Borrenstein et al., 2009).

The Q-statistic and $I^2$ index were calculated to report the level of heterogeneity. The Q-statistic is a measure of the true variance within studies. A significant Q-statistic indicates heterogeneity among studies. The $I^2$ index reflects the proportion of true heterogeneity in the observed variance and is calculated using the equation $\frac{Q - df}{df} \times 100\%$, where $df$ symbolizes the degrees of freedom ($= \text{number of studies} - 1$). A $I^2$ value of 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity (Borrenstein et al., 2009).

Publication bias was assessed by visual inspection of funnel plots. These funnel plots display the relationship between sample size and effect size. In absence of publication bias, studies should be distributed symmetrically around the mean effect size in a funnel shape. Smaller studies with a relatively large variance scatter at the bottom and larger studies appear towards the top clustering around the mean effect size. Studies that fall outside the funnel shape have high risk of bias (Borrenstein et al., 2009).

3. Results

3.1. Identification of studies

Fig. 1 shows the flow diagram of the study selection. The initial search yielded 1687 articles (published between June 1976 and February 2017). Based on titles and abstracts 1597 papers were excluded. The remaining 90 articles were screened full text, leading to exclusion of 81 articles. An updated search in May 2017 identified one additional study.

Fig. 2 shows the risk-of-bias profile for the ten included studies. The final judgment was low in six studies and unclear in four studies. The criterion of blinding of patients/personnel was disregarded for this total judgment, since participants were aware of the content of the training. Risk of bias due to insufficient information regarding allocation concealment, random sequence generation and incomplete outcome data was our highest concern in the studies. Risk of bias data per study is provided in Supplementary Fig.A and Table A.

3.2. Participant and study characteristics

Table 1 summarizes the characteristics of the included studies. Five RCTs included patients with dementia ($N = 271$) (Burgener et al., 2008; Graessel et al., 2011; Holthoff et al., 2015; Santos et al., 2015; Venturelli et al., 2016), three RCTs included patients with MCI ($N = 267$) (Fiatarone Singh et al., 2014; Suzuki et al., 2013; Train the Brain Consortium, 2017) and two RCTs included both MCI and dementia patients ($N = 204$) (Han et al., 2016; Olazaran et al., 2004). Global cognitive function data were available for 391 patients who participated in a combined cognitive-physical intervention and for 351 patients who participated as controls. The mean age of the total sample was 72.1 and 41% of the patients were men. All studies consisted of a combined cognitive-physical exercise intervention, with widely varying intervention components. In the majority of studies the mode of combination of the physical and cognitive intervention component was separate (7 studies). Intervention periods ranged between two to twelve months. The training frequency varied between two to six sessions per week and the duration per session varied between thirty to 120 min.

Table 2 gives an overview of the used outcome measures in the different studies. To measure global cognitive function four studies used the Mini-Mental State examination (MMSE) (Folstein et al., 1975), three studies used the Alzheimer’s Disease Assessment Scale-Cognitive subscale (ADAS-Cog) (Graham et al., 2004) and three studies used both MMSE and ADAS-Cog. Measures of executive function and attention included Verbal Fluency (3 studies) (Moms et al., 1989; Strauss et al., 2006), Symbol Digit Modalities Test (1 study) (Strauss et al., 2006), Matrices and Similarities from the Wechsler Adult Intelligence Scale Third Edition (1 study) (Kaufman and Lichtenberg, 1999; Wechsler, 1997), Digit Span Forward (1 study) (Wechsler, 1997), Corsi Span Forward (1 study) (Lezak, 2004), Trail Making Test (1 study) (Reitan and Wolfson, 2004), Raven Coloured Progressive Matrices (1 study) (Lezak, 2004), Attentional matrices (1 study) (Lezak, 2004), Copy of Rey-Osterrieth Complex Figure Test (1 study) (Lezak, 2004) and the Reaction Time Ruler Test (1 study) (Davis, 2000). Memory was assessed using the Logical Memory I and II subs tests from the Wechsler Memory Scale Third Edition (2 studies) (Wechsler, 1997), the Benton Visual Retention Test Fifth Edition (1 study) (Benton, 1992), Rey Auditory Verbal Learning Task (1 study) (Lezak, 2004), Babcock Short Story test (1 study) (Lezak, 2004) and Rey-Osterrieth Complex Figure Test (1 study) (Lezak, 2004). Four studies included measures of ADL; The Bayer ADL (Erzigkeit et al., 2001), Erlangen ADL (Graessel et al., 2009), Alzheimer Disease Cooperative Study (ADCS) (Galasko et al., 1997) ADL and the Disability Assessment for dementia (DAD) ADL scale (Feldman et al., 2001). As a measure of mood the Geriatric Depression Scale (GDS) (Yesavage et al., 1983) was used in four studies.

3.3. Primary and secondary analyses

The primary analysis showed a positive small-to-medium effect of combined cognitive-physical exercise interventions on global cognitive function in older adults with MCI or dementia ($SMD = 0.32[0.17;0.47], p < 0.00$, Fig. 3). There was no significant heterogeneity across the studies ($Q = 5.87, > 0.05, I^2 0\%, \text{Table 3}$). This effect remained for the subgroup analysis of dementia patients ($SMD = 0.36[0.12;0.60], p < 0.00, 5 \text{ studies}$) and MCI patients ($SMD = 0.39[0.15;0.63], p < 0.05, 3 \text{ studies}$), without significant heterogeneity. Visual inspection of the funnel plot did not reveal risk of publication bias (Fig. 4). Domain-specific analyses did not show any significant differences between the intervention and control groups for the domains executive function/attention ($SMD = 0.38[-0.21;0.97], p > 0.05, \text{Table 3}$) and memory ($SMD = 0.02[0.35;0.39], p > 0.05, \text{Table 3}$). The domain executive function/attention showed significant heterogeneity across studies ($Q = 7.15, p < 0.05, I^2 72\%, \text{Table 3}$).

Secondary analyses revealed a moderate-to-large positive effect of combined interventions on ADL ($SMD = 0.65[0.09;1.21], p < 0.01, 4 \text{ studies}$, Table 3) with significant heterogeneity across the studies ($Q = 15.29, p = 0.00, I^2 80\%, \text{Table 3}$). Based on visual inspection of the funnel plot two studies were excluded for further analyses due to considerable risk of bias (Supplementary Figure B.1) (Han et al., 2016; Holthoff et al., 2015). After removal of these studies, the effect size remained moderate-to-large ($SMD = 0.75[0.42;1.08], p < 0.01$) without heterogeneity ($Q = 0.00, p = 0.97, I^2 0\%$). Furthermore, a small-to-medium overall effect of combined interventions on mood ($SMD = 0.27[0.04;0.50], p < 0.01, 4 \text{ Table 3}$) was found, without significant heterogeneity ($Q = 1.71, p = 0.64, I^2 0\%$, Table 2). The symmetrical funnel plot showed that there was no risk of publication bias (Supplementary Fig. B.2).

Orwin’s fail-safe N was calculated only for the measures that showed significant differences between treatment and control. For
Fig. 1. Flow diagram of study selection process.

Fig. 2. Risk of bias assessment per domain across studies with domains of bias on the Y-axis and % of studies having a high, unclear or low risk of bias in each domain on the X-axis. The total score is the final author judgment of the total risk of bias.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample</th>
<th>Combined Intervention Design</th>
<th>Cognitive Intervention Component</th>
<th>Physical Exercise Component</th>
<th>Mode of Combination</th>
<th>Setting</th>
<th>Frequency</th>
<th>Duration (weeks)</th>
<th>No. of sessions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burgener et al. (2008)</td>
<td>USA</td>
<td>43 (24 IG/19 CG)</td>
<td>Mixed</td>
<td>CBT</td>
<td>Taiji</td>
<td>Separate</td>
<td>240 min/session, bi-weekly, PT: 60 min/session, 3 x/wk</td>
<td>26</td>
<td>65</td>
<td>Share cognitive impairment, AD = Alzheimer's disease, MCI = mild cognitive impairment, AD = activities of daily living (ADL)</td>
<td>Cross over design with 4 weeks washout period</td>
</tr>
<tr>
<td>Fiatarone Singh et al. (2014)</td>
<td>USA</td>
<td>54 (27 IG/27 CG)</td>
<td>Separate</td>
<td>Computer-based cognitive exercises, progressive resistance training</td>
<td>Separate</td>
<td>No</td>
<td></td>
<td>8</td>
<td>8</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Graessel et al. (2011)</td>
<td>Germany</td>
<td>96 (50 IG/46 CG)</td>
<td>Separate</td>
<td>Cognitive tasks, physical exercises</td>
<td>Separate</td>
<td>Music and reminiscence therapy</td>
<td>120 min/session, 2 x/wk</td>
<td>26</td>
<td>52</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Han et al. (2016)</td>
<td>Korea</td>
<td>120 (60 IG/60 CG)</td>
<td>Separate</td>
<td>Cognitive training, cognitive stimulation and reality orientation</td>
<td>Separate</td>
<td>Music and reminiscence therapy</td>
<td>120 min/session, 2 x/wk</td>
<td>52</td>
<td>104</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Holhöfer et al. (2015)</td>
<td>Germany</td>
<td>30 (15 IG/15 CG)</td>
<td>Separate</td>
<td>Computer-assisted cognitive training and cognitive simulation</td>
<td>Separate</td>
<td>Physical therapy</td>
<td>120 min/session, 2 x/wk</td>
<td>36</td>
<td>12</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Ibanez et al. (2016)</td>
<td>Spain</td>
<td>96 (48 IG/48 CG)</td>
<td>Separate</td>
<td>Computer-based cognitive exercises</td>
<td>Separate</td>
<td>Physical therapy</td>
<td>240 min/session, 2 x/wk</td>
<td>52</td>
<td>104</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Ishikawa et al. (2017)</td>
<td>Japan</td>
<td>100 (50 IG/50 CG)</td>
<td>Separate</td>
<td>Computer-assisted cognitive training and cognitive simulation</td>
<td>Separate</td>
<td>Physical therapy</td>
<td>240 min/session, 2 x/wk</td>
<td>52</td>
<td>104</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Santoros et al. (2015)</td>
<td>Brazil</td>
<td>54 (27 IG/27 CG)</td>
<td>Separate</td>
<td>Computer-assisted cognitive exercises</td>
<td>Separate</td>
<td>Physical therapy</td>
<td>240 min/session, 2 x/wk</td>
<td>52</td>
<td>104</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Suzuki et al. (2013)</td>
<td>Japan</td>
<td>50 (25 IG/25 CG)</td>
<td>Separate</td>
<td>Computer-assisted cognitive training and cognitive simulation</td>
<td>Separate</td>
<td>Physical therapy</td>
<td>240 min/session, 2 x/wk</td>
<td>52</td>
<td>104</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Train the Brain (Train the Brain)</td>
<td>Italy</td>
<td>50 (25 IG/25 CG)</td>
<td>Separate</td>
<td>Computer-assisted cognitive exercises</td>
<td>Separate</td>
<td>Physical therapy</td>
<td>240 min/session, 2 x/wk</td>
<td>52</td>
<td>104</td>
<td>Education control group</td>
<td></td>
</tr>
<tr>
<td>Venturelli et al. (2016)</td>
<td>Italy</td>
<td>50 (25 IG/25 CG)</td>
<td>Separate</td>
<td>Computer-assisted cognitive exercises</td>
<td>Separate</td>
<td>Physical therapy</td>
<td>240 min/session, 2 x/wk</td>
<td>52</td>
<td>104</td>
<td>Education control group</td>
<td></td>
</tr>
</tbody>
</table>

Notes: IG = intervention group; CG = control group; CT = cognitive training; PT = physical training; − = no data available; N = number of participants; AD = Alzheimer’s disease; MCI = mild cognitive impairment; AD = activities of daily living (ADL).
Table 2

<table>
<thead>
<tr>
<th>Article</th>
<th>Memory</th>
<th>Executive function &amp; attention</th>
<th>ADL</th>
<th>Mood</th>
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<tbody>
<tr>
<td>Burgener et al. (2008)</td>
<td>-</td>
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<td>Fiatarone Singh et al. (2014)</td>
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<td>Graessel et al. (2011)</td>
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<td>Han et al. (2016)</td>
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<td>Holtho et al. (2015)</td>
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<td>Suzuki et al. (2013)</td>
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<tr>
<td>Train the Brain Consortium (2017)</td>
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<tr>
<td>Venturelli et al. (2016)</td>
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</tr>
</tbody>
</table>

Notes: (−) = no data available. MMSE = Mini-Mental State Examination; ADAS-Cog = Alzheimer’s Disease Assessment Scale-Cognitive Subscale; WAIS-III = Wechsler Adult Intelligence Scale Third Edition; WMS-III = Wechsler Memory Scale Third Edition; COWAT = Controlled Oral Word Association Test; WAIS-III Matrices and Similarities = Wechsler Adult Intelligence Scale Third Edition: Matrices and Similarities; ADAS-Cog Digit Span Forward = Alzheimer’s Disease Assessment Scale-Cognitive Subscale: Digit Span Forward; WAIS-III Logical Memory = Wechsler Memory Scale Third Edition: Logical Memory; Rey-Osterrieth Complex Figure Test = Rey-Osterrieth Complex Figure Test; Raven Coloured Progressive Matrices = Raven Coloured Progressive Matrices; DAD-ADL = Disability Assessment for Dementia subscale Activities of Daily Living; DAD; E-ADL = Erlangen test of Activities of Daily Living; GDS = Geriatric Depression Scale.

4. Discussion

This meta-analysis examined the efficacy of combined cognitive and physical exercise interventions on global cognitive functioning in older adults with MCI or dementia. Secondary, the effects on memory, executive function/attention, ADL and mood were explored. Ten RCTs published between 2004 and 2017 were included in the meta-analysis.

The results of this meta-analysis emphasize the potential of combined cognitive and physical interventions to positively affect global cognitive function, ADL and mood in older adults with MCI or dementia. A positive small-to-medium effect of combined cognitive and physical exercise interventions on global cognitive function in older adults with MCI or dementia was found. In addition, the analysis showed a moderate-to-large effect of combined interventions on ADL and a small-to-medium effect on mood. These results may suggest a mediating effect of improved global cognitive function to improved function in ADL and mood, indicating the potential clinical relevance of combined interventions. Furthermore, the current results did not show a significant effect of combined interventions on the specific cognitive domains of executive function/attention and memory.

4.1. Interpretation of results and comparison with previous research

To the best of our knowledge, this is the first meta-analysis examining the effect of combined cognitive and physical exercise interventions on cognitive function in older adults with MCI or dementia. Law et al. (2014) investigated the cognitive benefits of combined interventions in older adults with cognitive impairment in a systematic review. Five studies were included of which three studies showed significant improvements in global cognitive functions, memory, executive functions or attention. Importantly, only three out of five included studies were RCTs and two studies compared the results with an active control group (Law et al., 2014). This meta-analysis adds to the qualitative review of Law et al. (2014) because only RCTs were included, and we were able to quantify the magnitude of the overall effect, confirming the efficacy of combined interventions in MCI or dementia patients.

The current results are comparable with a recently published meta-analysis of Zhu et al. (2016), who reported a small-to-moderate positive effect on overall cognitive function after combined cognitive and physical interventions in healthy older adults (SMD = 0.29 [0.12;0.46]). In their study, domain-specific analyses showed that combined interventions induced significant improvements with moderate effect sizes for global cognitive function and visuospatial ability, and small effects for memory, executive function and attention (Zhu et al., 2016). The domain-specific effects are in contrast with our current data that did not show any significant effects in the domains executive function/attention and memory. However, our results should be interpreted with some caution, since the combined effect sizes were based on two studies only. Furthermore, the measures of cognition used varied across the studies that included cognitive tests, limiting its comparability. This stresses the need for further research on specific cognitive domains in order to draw definite conclusions.

A recent meta-analysis of Groot et al. (2016) showed that physical exercise interventions—without a cognitive component—positively influence global cognitive function in patients with dementia. They found a small-to-medium positive overall effect of physical exercise interventions on global cognitive function (SMD = 0.42[0.23;0.62]), which is comparable to the effect sizes observed in the current meta-analysis. Although no direct comparison can be made, these findings may question whether a combined intervention is indeed superior to a single physical intervention. In contrast, a meta-analysis of the Cochrane Library reported that the effect of physical exercise on cognitive function...
in older adults with dementia could not be determined due to inconsis-
tent results and low methodological quality of the studies (Forbes
et al., 2015). Moreover, Zhu et al. (2016) found superiority of combined
cognitive and physical exercise interventions compared with single
physical exercise in healthy older adults, with a large effect size on
global cognitive function (SMD = 0.87[0.31; 1.44]). Assessing this
possible additional benefit of combined interventions versus single
physical exercise in older adults with dementia should be a focus of
future research.

The moderate-to-large effect of combined interventions on ADL
(SMD = 0.65[0.09; 1.21]) is in accordance with the efficacy of single
physical exercise interventions on ADL found by Groot et al. (2016)
(SMD = 1.18[0.57; 1.79]) and the Cochrane Library (SMD = 0.68[0.08; 1.27]) (Forbes et al., 2015). These changes in ADL
may be mediated by improvement in motor and cognitive function
(Bossers et al., 2016). ADL disability leads to increased dependency in
daily life, which may result in a lower quality of life (Andersen et al.,
2004) and larger long-term care costs (World Health Organisation and
Alzheimer’s Disease International, 2012). Interventions that slow de-
cline in ADL function are therefore of high clinical relevance. In addi-
tion, three out of four studies only used proxy-reported ADL measures,
which are, compared to performance-based ADL tests, less valid (e.g.
prone to social desirability bias) and less sensitive to detect change
(Fisher, 1993; Puente et al., 2014). Future studies should therefore in-
clude both proxy- and performance-based ADL measures to study the
effect of intervention on ADL. The current meta-analysis also showed a
small-to-moderate positive effect of combined interventions on mood
(SMD = 0.27[0.04; 0.50]), suggesting that combined cognitive-physical
interventions may be helpful in preventing or treating depressive
symptoms. Depressive symptoms are key determinants for increased
distress and therewith an important target for interventions (McKeith
and Cummings, 2005).

4.2. Strengths and limitations

A strength of this meta-analysis is that only studies with an RCT
design were included for review analyses. Furthermore, we were able to
obtain cognitive data from all eligible studies that were not reported in
the primary paper by contacting the authors. Therefore, no RCTs were
excluded due to missing data. There are also some limitations that need
to be addressed when interpreting the current results. First, there is
considerable heterogeneity in the included studies regarding the in-
tervention characteristics (e.g., type of training, separate or dual-task,
treatment period, frequency, duration). Therefore, the optimal in-
tervention design for eliciting beneficial effects remains unclear.
Second, due to the limited number of included studies (N = 10) it was
statistically inappropriate (Borenstein, 2008) to analyze the impact of
different intervention components or to calculate the efficacy for dif-
ferent causes of neurodegeneration or disease severity using a mod-
erator analysis. However, moderation analyses are very useful in de-
veloping preventive strategies and designing appropriate interventions.
Third, the majority of studies (N = 7) used the MMSE as a measure of
global cognitive function. The MMSE was originally developed as a
screening method for cognitive impairment and not as an outcome
measure, since sensitivity to change over time is low (Hensel et al.,
2007; Tangalos et al., 1996). This makes the MMSE an inappropriate
outcome measure to assess the effect of interventions. Thus, another,
more sensitive, method for measuring global cognition in MCI and
dementia patients is needed. Fourth, in all included studies the ad-
herence to the intervention and intensity of the physical exercise pro-
gramme was not reported in detail, which could have in-
fluenced the study results. Also, data about adherence and intensity of intervention
programmes are essential to gain insight in doses-response ratio’s. Fi-
nally, only studies reported in English were included in the current
meta-analyses. This could have introduced language-bias, since this

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Outcome</th>
<th>K</th>
<th>N</th>
<th>SMD</th>
<th>95% CI</th>
<th>Q</th>
<th>p (Q)</th>
<th>I²</th>
<th>Fail-safe N</th>
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<tr>
<td>Burgener</td>
<td>Dementia</td>
<td>MMSE</td>
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<td>0.106–1.116</td>
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<td>-0.250–0.823</td>
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<tr>
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<tr>
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<td>MCI or dementia</td>
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<td>0.128</td>
<td>-0.222–0.484</td>
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Table 3

Mean weighted effect sizes, confidence interval and heterogeneity for primary and secondary outcome measures.

Notes: k = number of studies, N = number of patients, CI = confidence interval, Q = within domain heterogeneity, p(Q) = p-value for heterogeneity, I² = percentage of heterogeneity due to true differences within studies, Fail-safe N = number of studies needed to nullify the effect, AD = activities of daily living, p < 0.01
may not cover all potential eligible studies.

4.3. Implications for future research

To investigate the different intervention combinations, future research is warranted. We suggest to use a multi-arm design, including a combined cognitive and physical training, single physical training, single cognitive training and a control group to distinguish the contribution of different components of the intervention. Also, additional studies are needed to explore the most effective training characteristics in combined interventions specifically aiming at duration, frequency, intervention type and mode of combination. Furthermore, future research should focus on investigating physiological mechanisms that underlie the positive effect by including neuro-imaging measures and molecular markers as an outcome. Moreover, long-term effects of combined interventions should be studied to gain insight into possible maintenance effects. Zhu et al. (2016) found that combined interventions had advantages over single training for long term maintenance in healthy older adults. It would be important to investigate whether this is also the case in older adults with MCI or dementia. Finally, the identification of individual predictors for a beneficial outcome is also important in order to personalize multi-modal interventions. To conclude, selecting appropriate outcome measurements is essential in future research. The use of a more comprehensive neuropsychological assessment is needed to assess which domains of cognitive function benefit most from a combined intervention.

5. Conclusion

Results of the present meta-analysis showed that combined cognitive and physical exercise interventions improve global cognitive function, ADL and mood in older adults with MCI or dementia. Studies show a large methodologically heterogeneity in intervention characteristics and the included study samples and thus, the current results should be interpreted with caution. Despite these methodological limitations the current meta-analysis illustrates the importance of combined interventions to help delay the progression of MCI or dementia. There is a need for future well-designed RCT’s with a multi-arm design and long-term follow-up assessment to investigate the potential superiority of combined interventions over single interventions in older adults with MCI or dementia, including extensive neuropsychological assessments to gain more insight in the beneficial effects for the different domains.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.arr.2017.09.003.

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