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Review

The effects of aerobic exercise and transcranial direct current stimulation on cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis

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ABSTRACT

Background: Aerobic exercise (AE) may slow age-related cognitive decline. However, such cognition-sparing effects are not uniform across cognitive domains and studies. Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation and is also emerging as a potential alternative to pharmaceutical therapies. Like AE, the effectiveness of tDCS is also inconsistent for reducing cognitive impairment in ageing. The unexplored possibility exists that pairing AE and tDCS could produce synergistic effects and reciprocally augment cognition-improving effects in older individuals with and without cognitive impairments.

Previous research found such synergistic effects on cognition when cognitive training is paired with tDCS in older individuals with and without mild cognitive impairment (MCI) or dementia.

Aim: The purpose of this systematic review with meta-analysis was to explore if pairing AE with tDCS could augment singular effects of AE and tDCS on global cognition (GC), working memory (WM) and executive function (EF) in older individuals with or without MCI and dementia.

Methods: Using a PRISMA-based systematic review, we compiled studies that examined the effects of AE alone, tDCS alone, and AE and tDCS combined on cognitive function in older individuals with and without mild cognitive impairment (MCI) or dementia. Using a PICOS approach, we systematically searched PubMed, Scopus and Web of Science searches up to December 2021, we focused on 'MoCA', 'MMSE', 'Mini-Cog' (measures) and 'cognition', 'cognitive function', 'cognitive', 'cognitive performance', 'executive function', 'executive process',

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'attention', 'memory', 'memory performance' (outcome terms). We included only randomized controlled trials (RTC) in humans if available in English full text over the past 20 years, with participants' age over 60. We assessed the methodological quality of the included studies (RTC) by the Physiotherapy Evidence Database (PEDro) scale.
Results: Overall, 68 studies were included in the meta-analyses. AE (ES = 0.56 [95% CI: 0.28–0.83], p = 0.01) and tDCS (ES = 0.69 [95% CI: 0.12–1.26], p = 0.02) improved GC in all three groups of older adults combined (healthy, MCI, demented). In healthy population, AE improved GC (ES = 0.46 [95% CI: 0.22–0.69], p = 0.01) and EF (ES = 0.27 [95% CI: 0.05–0.49], p = 0.02). AE improved GC in older adults with MCI (ES = 0.76 [95% CI: 0.21–1.32], p = 0.01). tDCS improved GC (ES = 0.69 [90% CI: 0.12–1.26], p = 0.02), all three cognitive function (GC, WM and EF) combined in older adults with dementia (ES = 1.12 [95% CI: 0.04–2.19], p = 0.04) and improved cognitive function in older adults overall (ES = 0.69 [95% CI: 0.20–1,18], p = 0.01).
Conclusion: Our systematic review with meta-analysis provided evidence that beyond the cardiovascular and fitness benefits of AE, pairing AE with tDCS may have the potential to slow symptom progression of cognitive decline in MCI and dementia. Future studies will examine the hypothesis of this present review that a potentiating effect would incrementally improve cognition with increasing severity of cognitive impairment.

1. Introduction

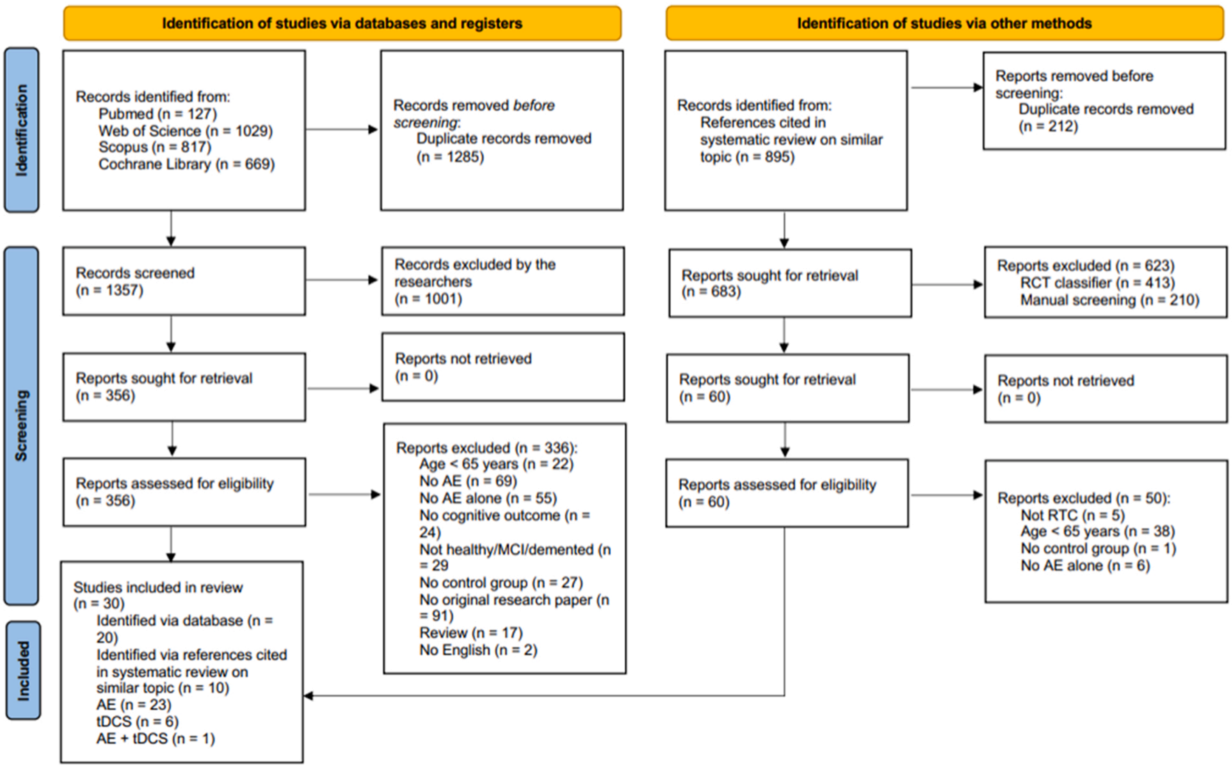
Normal cognitive function is a quintessential element of healthy ageing (Morley et al., 2015). Cognitive impairment starting in late mid-life is associated with functional dependence, morbidity, and mortality (Calderón-Larrañaga et al., 2019). Brain injury or disease can cause dementia, characterized by a set of related symptoms involving a progressive deterioration of global cognition (GC), working memory (WM), and executive function (EF) (Duong et al., 2017). The World Health Organization (WHO) predicts that the number of dementia patients will reach 82 million in 2030 and 152 million in 2050 (WHO, 2020). With no cure in sight and drug trials ending with disappointing (Cummings et al., 2016; Rice, 2014) or controversial results (Walsh et al., 2021), non-pharmaceutical interventions are needed. Low-cost, side effects-free, and logistically simple treatments should be applied that have the potential to delay the onset age of dementia and slow disease progression to its full form. Of the many non-pharmaceutical interventions such as cognitive and behavioural training, diet, social facilitation, and music therapy singularly or in combination (Duplantier and Gardner, 2021; Gavelin et al., 2021; Lissek and Suchan, 2021; Mansky et al., 2020; Whitty et al., 2020), exercise as a lifestyle modifier represents an increasingly advocated alternative to pharmaceutical treatments of dementia (Baranowski et al., 2020; Bhatti et al., 2020; Falck et al., 2019; Gupta et al., 2021; Herold et al., 2019; Intzandt et al., 2021; Kraal et al., 2021; Macaulay et al., 2020; McGurran et al., 2019; Ruiz-González et al., 2021; Siddappaji et al., 2021; Zhang et al., 2020). Perhaps due to the complexity of the disease (Ferrari and Sorbi, 2021), exercise interventions like other single modality treatments, can be of low efficacy (Sanders et al., 2020), improve symptoms inconsistently (Sanders et al., 2019), or can be even controversial (Diamond and Ling, 2019). Ineffectiveness of aerobic exercise (AE) for improving cognition with increasing disease severity is especially striking (Sanders et al., 2019), as long-term interventions with presumably the most effective form of exercise failed to improve cognitive outcomes in mild cognitive impairment (MCI) and dementia (Hall et al., 2021; Sanders et al., 2019).

In animal models and humans, AE activates brain areas known to be involved in GC, WM, and EF such as the medial prefrontal, perirhinal cortex, striatum, hippocampus, and raphe nuclei in animals, and the dorsal anterior cingulate cortex, supplementary motor area, superior and middle frontal gyrus, right inferior frontal gyrus, middle temporal gyrus, anterior white matter tracts, and hippocampus in humans (Colcombe et al., 2006; Jonasson et al., 2017; Pietrelli et al., 2018; Terjung, 2011; Voss et al., 2013). AE can induce neuroplasticity and neuroprotection activated in cognitive processes (Constans et al., 2016; McDonnell et al., 2013; Mellow et al., 2020), an effect that is less likely to arise from neurogenesis (Hvid et al., 2021). One potential mediator of AE-induced neuroplasticity is brain-derived neurotrophic factor (BDNF) (Szuhany et al., 2015), which can increase even after just a single session of AE, causing adaptive plasticity (Huang et al., 2017).

One option to augment AE-induced neuroplasticity and neuroprotection for the betterment of cognitive function could be its pairing with non-invasive brain stimulation (NIBS) (Cantone et al., 2021; Clark et al., 2021; Indahlastari et al., 2021; Koch et al., 2020; Lee et al., 2021; Reinhart and Nguyen, 2019; Steinberg et al., 2019; Suarez-García et al., 2020; Thomas et al., 2021; Vaqué-Alcázar et al., 2021; Velioglu et al., 2021). Transcranial direct current stimulation (tDCS) is a form of NIBS. Through surface electrodes affixed to the scalp, tDCS delivers constant, low-amplitude electrical currents (0.5 – 2 mA) to the targeted brain area and lastingly modulates neuronal excitability and connectivity (Huang et al., 2017; Nitsche et al., 2005; Nitsche and Paulus, 2000; Wagner et al., 2007). Placing the positive electrode (anode) pair over the target area increases cortico-neuronal excitability, while placing the negative electrode (cathode) over the target area decreases cortico-neuronal excitability, producing an inhibitory effect (hyperpolarization) (Nitsche and Paulus, 2001, 2000; Romero Lauro et al., 2014; Utz et al., 2010). In animal experiments, tDCS induces neurogenesis and activates processes associated with neuronal repair in the brain (Fritsch et al., 2010; Kronberg et al., 2017; Lopes et al., 2020; Podda et al., 2016; Ranieri et al., 2012; Rohan et al., 2015). In humans, tDCS can lastingly alter cortico-neuronal excitability in the primary motor cortex, dorsolateral prefrontal cortex, posterior parietal cortex, inferior frontal cortex, and network connectivity, underlying cognition-improving effects (Polanía et al., 2018). Repetitive administration of tDCS can favourably modify dysfunctional brain states and networks (Bandeira et al., 2021) and can modify maladaptive neuroplasticity underlying symptoms of cognitive impairment (Flöel, 2014; Fregni et al., 2005; Kuo et al., 2014). Indirect evidence suggests that anodal tDCS-generated long-term potentiation (LTP) and cathodal tDCS-induced long-term depression (LTD) accompanied cognitive improvements in healthy older individuals (Nitsche et al., 2003; Nitsche and Paulus, 2001; Rioult-Pedotti, 2000). Compensatory neuroplasticity induced by tDCS underlies the effects of motor, affective and cognitive training, memory, speech therapy, perception, and attention training, but establishing a direct link between tDCS effects and behavioural modifications is complex. Indeed, tDCS, like AE, might need boosting for increased efficacy (Semmler and Opie, 2021; Song and Yu, 2019).

Because AE and tDCS share common neural substrates, it is conceivable that pairing of the two methods could produce synergistic effects on cognitive function and lead to a higher efficacy rate than what is achieved with each intervention singularly. Indeed, combining AE with NIBS improved cognitive function in healthy young individuals, but whether such boosting effect would occur in older individuals with and without cognitive impairment has not yet been systematically reviewed (Hendrikse et al., 2017; Moreau et al., 2015; Thomas et al., 2020, 2021; Steinberg et al., 2019; Clark et al., 2021; Manor et al., 2018, 2016; Nissim et al., 2019; Manenti et al., 2014; Wrightson et al., 2015; Ma et al., 2020; Schneider et al., 2021; Zhou et al., 2014; Tahtis et al., 2014).

A. Healthy older adults.



B. Older adults with mild cognitive impairment (MCI).

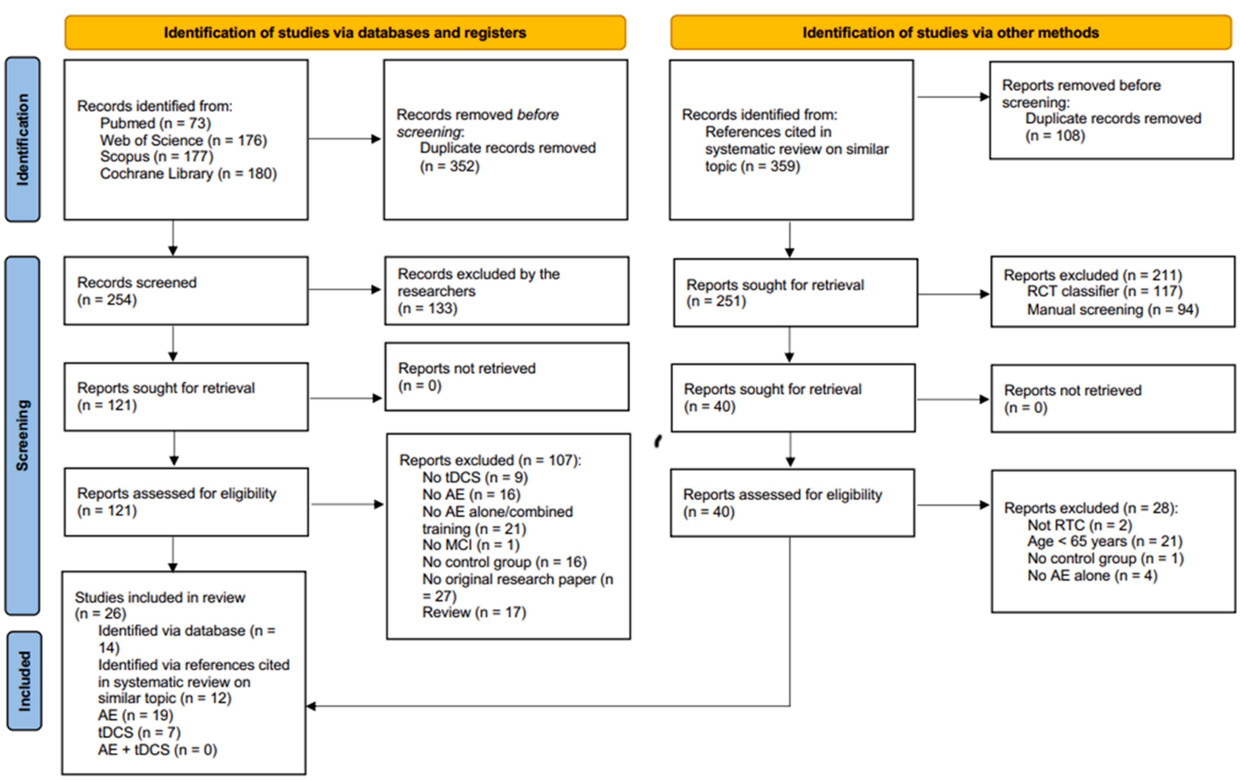


Fig. 1. Study retrieval process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.

C. Older adults with dementia.

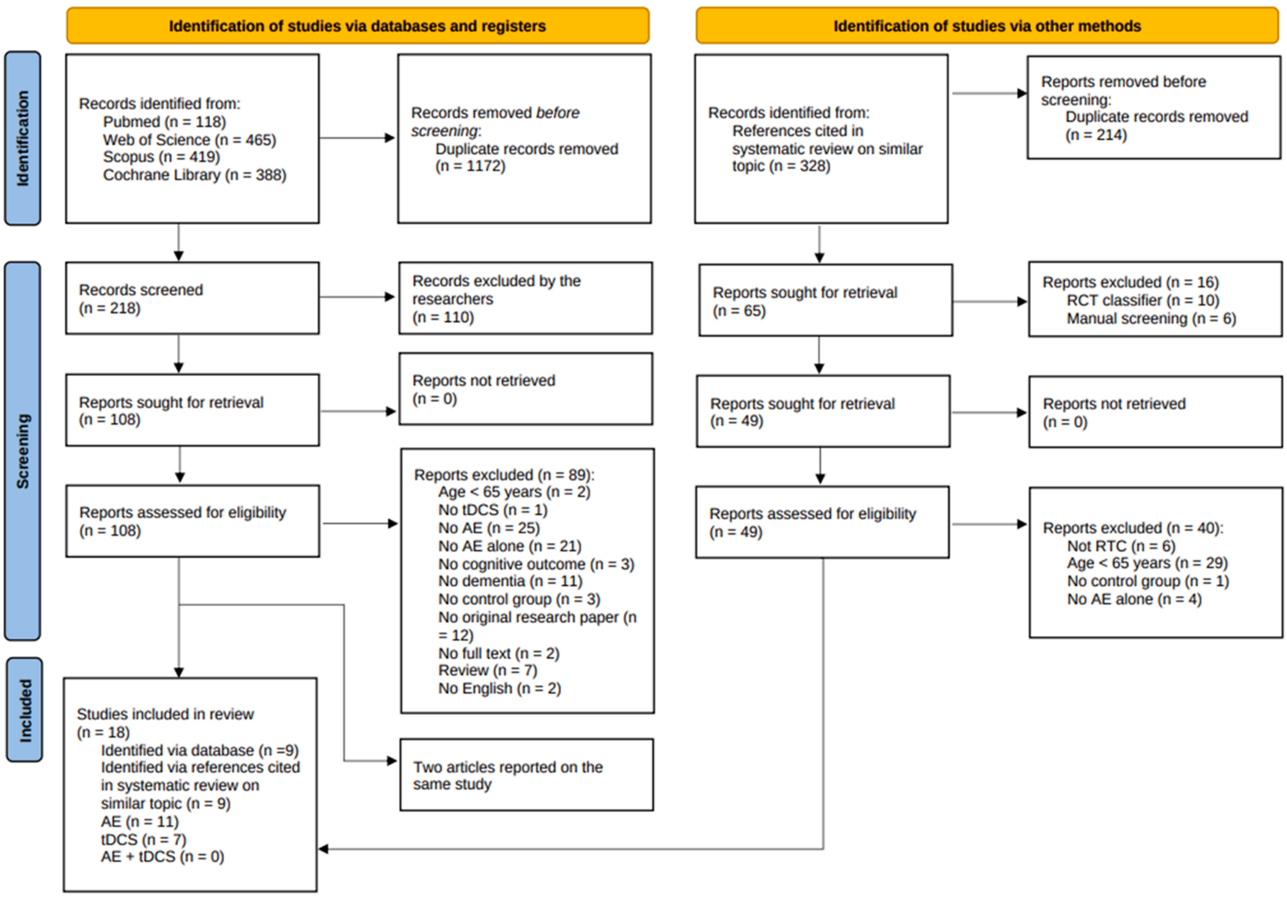


Fig. 1. (*continued*).

While the most effective order for sequencing AE and tDCS remains to be determined, it seems that AE could potentiate subsequent NIBS-induced plasticity under certain conditions (Mellow et al., 2020). It remains unclear if such combined treatment would, in fact, have behavioural effects. Therefore, we aimed to systematically and meta-analytically review existing data to determine the effects of AE and tDCS on selected cognitive functions (GC, WM, EF) and see if pairing the two treatments would potentiate the singular effects in older individuals with and without MCI or dementia. We hypothesized that the individual effects of AE and tDCS would decrease with increase in cognitive impairment (Sanders et al., 2019). Further, we expected that the combination of the two methods would potentiate the individual effects and cognitive function would improve in individuals with MCI and dementia.

2. Methods

2.1. Registration of the systematic review protocol

The protocol of the investigation was registered in the International Prospective Register of Systematic Reviews PROSPERO (ID: CRD42021240644). This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) (PRISMA checklist, Fig. 1).

2.2. Search strategy

A search from January 2000 up to and including December 2021 was conducted in the following databases: PubMed, Scopus, Web of Science and Cochrane Library. A combination of keywords related to aerobic exercise, transcranial direct current stimulation, global cognition, working memory, and executive function was used with Boolean conjunction AND, OR, NOT (see Appendix S1 for the full search terms). Moreover, the reference lists of the previous reviews were screened to identify additional studies for inclusion in the current review (Barha et al., 2017; Biazus-Sehn et al., 2020; Bruderer-Hofstetter et al., 2018; Chen et al., 2020; Colcombe and Kramer, 2003; Cruz Gonzalez et al., 2018; de Souto Barreto et al., 2018; Etnier et al., 2006; Gheysen et al., 2018; Heyn et al., 2004; Hindin and Zelinski, 2012; Hsu et al., 2015; Huo et al., 2021; Kelly et al., 2014; Law et al., 2020; Li et al., 2019; Ludyga et al., 2016; McSween et al., 2019; Northey et al., 2018; Sáez de Asteasu et al., 2017; Sanders et al., 2019, 2020; Steinberg et al., 2019; Summers et al., 2016; Wollesen et al., 2020; Xiong et al., 2021; Xu et al., 2019a; Young et al., 2015; Zheng et al., 2016; Zhou et al., 2020; Zhu et al., 2016). The titles and abstracts of the screened articles were evaluated for eligibility (JN, MV). If any disagreement occurred, another co-author (KT) was consulted for clarification.

2.3. Inclusion and exclusion criteria

The inclusion criteria were determined according to the PICOS (P = population, I=intervention, C=comparator, O=outcome, S=study design) approach: (1) participants that were older individuals ($\geq$ 60 years of age). Individuals aged ≥ 60 years are considered older according to WHO (WHO, 2021); participants were healthy, diagnosed with MCI or dementia, (2) the intervention consisted of AE of intensity > 40% of heart rate reserve (HRR) (as moderate intensity occurs at 40–60% of HRR) (Karvonen et al., 1957) or tDCS (anodal, cathodal), (3) passive controls; (4) with the outcomes for cognitive function (GC, WM and EF), (5) randomized controlled trial (RTC) as study design, (6) manuscripts that were published in English. The exclusion criteria were as follow: (1) other intervention than aerobic exercise or tDCS, (2) active control group (i.e., comprising AE/strength training; studies with stretching, toning, tDCS sham or cognitive training as a control were included), (3) participants aged below 60 years, with (4) no outcomes for cognitive function, and (5) no randomized controlled trail. (6) Master or PhD theses as well as conference proceedings were excluded.

2.4. Data extraction

The following data from the included studies were extracted: (1) characteristics of the study (publication year, geographical area), (2) the sample size and patient characteristics (age, gender, size, cognitive health status), (3) intervention parameters (exercise program, session duration, frequency, intensity), (4) outcome measures and (5) overall effect of the outcome of interest. For quantitative analyses (meta-analyses) the group size and mean differences of the outcomes of interest with a 95% confidence interval (CI) or standard deviation (SD) for intervention and control group were collected. The data were tabulated in an Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA). In case of missing data, the original authors were reached.

2.5. Study quality assessment

To evaluate the quality of included studies the 11-item Physiotherapy Evidence Database (PEDro) scale was used (de Morton, 2009). The PEDro scale assesses the methodological quality of randomized controlled trials in evidence-based physical therapy (Herbert et al., 1998). The scores ≤ 3 indicate poor study quality, 4 − 5 fair quality and ≥ 6 good to excellent quality (Maher et al., 2003). Items were scored as either present (1) or absent (0) and the sum of 10 scores was obtained. The first item (eligibility criteria) was not included in the total score due to external validity.

2.6. Statistical Analysis

The effect sizes (ES) were computed as the standardized mean difference between the AE group and the control group or tDCS and the sham group. In addition to the meta-analyses exploring the overall effects of AE and tDCS on cognitive outcomes, the subgroup analyses were performed exploring the effects of both interventions on (a) cognitive outcomes in healthy, MCI and demented older adults separately, (b) individual outcome categories (WM, EF, GC) regardless of the participant health status. The subgroup analyses were not performed for individual outcomes in healthy, MCI and demented older adults separately were not performed due to the low number or non-existent studies for these subgroups. A random-effects meta-regression method called robust variance estimation (RVE) for multilevel data structures was used in all analyses, because it allows for the inclusion of the multiple dependent outcomes from the same study. RVE assesses the variance of meta-regression coefficient estimates with the use of the observed residuals and does not require the weights or distributional assumptions (Hedges et al., 2010; Tipton, 2015). To account for the correlated effects within the studies the study was used as the clustering variable. The observations were weighted with the use of the inversion of the sampling variance. They ensure that the choice of correlational values does not impact the results of the meta-analysis, the sensitivity analysis was performed using alternative correlational values to calculate the standard error (SE). Between-study heterogeneity was evaluated using I^2 statistics. The values of I^2 > 25% indicate the low, > 50% moderate and > 75% high heterogeneity (Melsen et al., 2014). All analyses were performed using the robumeta (version 2.0) and metaphor (version 3.0–2) packages in R version 4.41.42 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study selection

To assess the effect of AE and tDCS on cognition and behavioural outcomes, expert librarians constructed a syntax for older adults without and with MCI, dementia, respectively (Appendix, S1). In healthy older adults, the search yielded 2642 articles and 30 were included in the analyses. In older adults with MCI, the search yielded 606 articles and 26 were included in the analyses. In older adults with dementia, the search yielded 1390 articles and 19 were included. As one study reported its results in two separate articles, 18 studies were included in this review (Fig. 1).

3.2. Methodological quality

Table S2 shows the methodological quality of the studies, revealing a score ranging from 5 to 10, with a median 8 (Appendix, S2).

3.3. Study characteristics

3.3.1. Aerobic exercise studies

In 53 RCTs with AE intervention, there were 3427 participants (n = 2120 women) in the three groups (healthy older adults: n = 23 studies, MCI: n = 19 studies, dementia: n = 11 studies). Participants' age ranged from 65 to 86 years, with mean age increasing with disease severity (healthy: 79, MCI: 73, dementia: 82 years). Mean AE programs duration was 19 weeks (range 1–60 weeks, median 16 weeks, and mode 24 weeks, n = 20 studies), and the mean frequency was 3 times per week (range 1 – 7 times per week), session duration varied between healthy older adults (range 1 – 60 weeks, mean duration 40 min, n = 23 studies), MCI (range 8 – 48 weeks, mean duration 46 min, n = 19 studies) and dementia (range 6 – 24 weeks, mean duration 34 min, n = 13 studies). AE intensity in healthy older adults was 59% of HRR (range 40 – 75% of HRR), in MCI 66% of HRR (range 40 – 80% of HRR) and in demented 58% of HRR (range 40 – 75% of HRR).

Table 1 presents cognitive and behavioural outcomes and measures of the 53 studies (Table 1). Table 1 shows the characteristics of the studies examining the effects of aerobic exercise training on 3 measures of cognition and behavioral outcomes in older adults (Supplement 1, Table 1).

3.3.2. tDCS studies

In 20 RTCs with tDCS intervention in the three groups combined (healthy, MCI, dementia), there were 772 participants (443 women). The mean age ranged from 61 to 82 years. Three groups were varied in age (healthy: 68 years, MCI: 75, dementia: 72). The mean duration of tDCS program was 3 weeks (range 1–10 weeks, median 2 weeks, and mode 1 and 2 weeks, n = 12 studies), and the mean frequency was 3 times per week. tDCS stimulation intensity was similar in the three groups (healthy: 2.0 mA, MCI: 1.8 mA, dementia: 2.0 mA) and mean session duration varied (healthy: 32 min, MCI: 28 min, dementia: 26 min). Table 2 presents the effects of tDCS on 3 measures of cognition and behavioural outcomes of the 20 studies included (healthy older adults: n = 6, MCI: n = 7, dementia: n = 7, Table 2). Table 2 presents the study characteristics concerning the effects of tDCS on 3 measures of cognition (Supplement 1, Table 2).

3.3.3. Dose-parameters for AE and tDCS

Table 4. presents the weighted descriptive statistics (mean and total

Table 1
The effects of aerobic exercise training on 3 measures of cognition and behavioural outcomes in healthy, MCI and demented older adults.

Study	Cognitive outcome	Cognitive measure	Overall cognitive effect	Behavioural outcome	Overall behavioural effect
Healthy older adults					
(Albinet et al., 2010)	Global cognition, Executive function	MMSE, WCTS	↑ Errors (number) in IG and CG	HRV (RMSSD)	↑ short-term HRV (RMSSD) in IG and CG
(Albinet et al., 2016)	Global cognition, Executive function, Working memory	MMSE, Stroop task, 2-back task	↑ Stroop task in IG and CG ↑ 2-back task in IG and CG	Vo2max, HRV (RMSSD)	↑ Vo2max in IG and CG ↑ RMSSD in IG and CG
(Alghadir et al., 2016)	Global cognition	LOTCA	↑ LOTCA in IG and CG	Vo2max	No data about the change of Vo2max
(Antunes et al., 2015)	Working memory, Executive function	Digit span forwards, Digit span backwards, WCST	↑ Digit span forward in IG, ↓ Digit span forward in CG, ↑ Digit span backward in IG and CG, ↑ WCST in IG and CG	peak Vo2, HR max, Vo2 at VT-1 intensity, HR at VT-1 intensity, maximum ventilation, workload at VT-1 intensity	↑ peak Vo2 in IG, ↓ peak Vo2 in CG, ↑ HR max in IG, ↓ HR in CG, ↑ Vo2 at VT-1 intensity in IG and CG, ↑ HR at VT-1 intensity in IG and CG, ↑ maximum ventilation in IG, ↓ maximum ventilation in CG, ↑ workload at VT-1 intensity in IG and CG
(Barella et al., 2010)	Executive function	Stroop task	↑ Stroop task interference in IG and CG ↑ Stroop task inhibition in IG and CG	N/A	N/A
(Bouaziz et al., 2019)	Executive function	TMT B	↓ TMT B (−13.3%) in IG, ↑ TMT B (+0.9%) in CG	TUG, SPPB, 6MWT	↑ TUG (−16.5%) in IG, ↓ TUG (+5.4%) in CG, ↑ SPPB (14.6%) in IG, ↓ SPPB (−3.2%) in CG, ↑ 6MWT (11.5%) in IG, ↓ 6MWT (−3.2%) in CG
(Eggenberger et al., 2016)	Global cognition, Executive function	MoCA, TMT B, Stroop task, Executive control	↑ MoCA in IG and CG, ↑ TMT B in IG and CG, ↑ Stroop task in IG and CG, ↑ Executive control in IG and CG	SPPB, 4 m walk, 5 chair rises	↓ SPPB in IG, ↑ SPPB in CG, No significant difference in 4 m walk in IG and CG, ↑ 5 chair rises in IG and CG
(Esmail et al., 2020)	Global cognition	MOCA, MMSE	↑ MoCA in IG, ↓ MoCA in CG	resting HR, 10-m walking speed, TUG, VO2max	↑ 10-m walking speed in IG and CG, ↑ TUG in IG and CG
(Fabre et al., 2002)	Working memory	Digit span forwards, logical memory I, memory quotient	↑ Digit span forward in IG, No significant change in digit span forward in CG, ↑ Logical memory I in IG and CG, ↑ Memory quotient in IG and CG	Vo2max, max o2 pulse, Vo2, o2 pulse	↑ Vo2max in IG and CG, ↑ max o2 pulse in IG, ↓ max o2 pulse in CG, ↑ Vo2 in IG and CG, ↑ o2 pulse in IG, ↓o2 pulse in CG
(Ferreira et al., 2015)	Working memory	Digit span forwards, digit span backwards, logical memory I	↓ Digit span forward in IG and CG, ↑ Digit span backward in IG, ↓ Digit span backward in CG, ↑ Logical memory I in IG and CG	resting HR, SPO2	↓ resting HR in IG, ↑ resting HR in CG, ↑ SPO2 in IG and CG
Franco et al. (2020)	Executive function, Global cognition	TMT B-A, MoCA	↑ TMT B-A in IG, ↓ TMT B-A in CG, ↑ MoCA in IG and CG	Sit-to-stand, 4 m walk	↓ Sit-to-stand in IG and CG, ↑ 4 m walk in IG and CG
Hardman et al. (2020)	Executive function, Working memory	Stroop task, Spatial span	↓ Stroop task in IG, ↑ Stroop task in CG, ↓ Spatial span in IG, ↓ Spatial span in CG	6MWT	↑ 6MWT in IG, ↓ 6MWT in CG
Hars et al. (2014)	Global cognition	MMSE	↑ MMSE in IG and CG	TUG	↑ TUG in IG and CG
Legault et al. (2011)	Global cognition, Executive function, Working memory	MMSE, 1-Back, 2-Back, Flanker task, Task switching test, Self-ordered pointing task	↑ 1-Back in IG and CG, ↑ 2-Back in IG and CG, ↑ Flanker task in IG, ↓ Flanker task in CG, ↑ Task switching test in IG and CG, ↑ Self-ordered pointing task in IG and CG	400 m walk	no data about the change of 400 m walk
(Lopes Filho et al., 2019)	Working memory, executive function, Global cognition	Digit span forwards, digit span backwards, TMT B, MMSE	No significant difference in Digit span forward in IG, ↑ Digit span forward in CG, ↑ Digit span backward in IG and CG,	N/A	N/A

(continued on next page)

Table 1 (*continued*)

Study	Cognitive outcome	Cognitive measure	Overall cognitive effect	Behavioural outcome	Overall behavioural effect
			↑ TMT B in IG, ↓ TMT B in CG		
(Maki et al., 2012)	Global cognition, Executive function	MMSE, TMT B	↑ TMT B in IG and CG	TUG	↑ TUG in IG and CG
(Mortimer et al., 2012)	Executive function	Stroop task, TMT B	↑ Stroop task in IG and CG, ↑ TMT B in IG and CG	N/A	N/A
(Muscari et al., 2009)	Global cognition	MMSE	↓ MMSE in IG and CG	Vo2max	↑ Vo2max in IG, ↓ Vo2max in CG
(Prehn et al., 2019)	Global cognition, Working memory, Executive function	MMSE, TMT B, digit span backward, Stroop task	↑ TMT B in IG, ↓ TMT B in CG, ↓ Digit span backward in iG, ↑ Digit span backward in CG, ↑ Stroop task in IG, ↓ Stroop task in CG	Vo2 peak	↑ Vo2 peak in IG and CG
(Raichlen et al., 2020)	Global cognition	MMSE	No data about the change of MMSE	N/A	N/A
(Schoene et al., 2015)	Global cognition, Executive function	Mini-Cog, TMT B, Stroop task	↑ TMT B in IG, ↓ TMT B in CG, ↑Stroop stepping test in IG and CG	N/A	N/A
(Tsai et al., 2017)	Global cognition	MMSE	↑ MMSE in IG and CG	Vo2max, chair sit-and-reach, 8-foot up-and-go, chair stand	↑ Vo2max in IG, ↓ Vo2max in CG, No significant difference in chair sit-and-reach in IG, ↓ chair sit-and-reach in CG, ↑ 8-foot up-and-go in IG, ↓ 8-foot up-and-go in CG, ↑ chair stand in IG, ↓ chair stand in CG
(Varela et al., 2018)	Global cognition	MEC	↑ MEC in IG, ↓ MEC in CG	TUG	↑ TUG in IG, ↓ TUG in CG
Older adults with MCI					
(Anderson-Hanley et al., 2012)	Executive function, Working memory	Stroop task, color trials, digit span backwards	↑ Stroop task in IG, ↓ Stroop task in CG, ↑ Color trials in IG, ↓ Color trials in CG, ↑ Digit span backwards in IG, ↓ Digit span backwards in CG	N/A	N/A
(Baker et al., 2010)	Global cognition, Executive function	MMSE, Stroop task, TMT B	↑ Stroop task in IG, ↓ Stroop task in CG, ↑ TMT B in IG, ↓ TMT B in CG	Vo2 peak	No data about the change of Vo2 peak
(Brydges et al., 2020)	Global cognition, Executive function, Working memory	MMSE, MoCA, 1-Back, Task switching test, Spatial span	↓ 1-Back in IG and CG, No significant difference in Task switching test in IG, ↓ Task switching test in CG, ↓ Spatial span in IG and CG	N/A	N/A
(Davis et al., 2013)	Global cognition, Executive function	MoCA, Stroop task	↑ Stroop task in IG and CG	N/A	N/A
(Hsu et al., 2018)	Global cognition, Executive function	MMSE, MoCA, Flanker task	↓ MMSE in IG, No significant difference in MMSE in CG, ↑ MoCA in IG, ↓ MoCA in CG, ↑ Flanker task in IG and CG	6MWT	↑ 6MWT in IG and CG
(Hu et al., 2014)	Working memory	Immediate memory	↑ Immediate memory in IG and CG	N/A	N/A
(Law et al., 2019)	Executive function	TMT B	↑ TMT B in IG, ↓ TMT B in CG	N/A	N/A
(Lazarou et al., 2017)	Global cognition, Executive function	MMSE, MoCA, ROCFT (copy), ROCFT (delay)	↑ MMSE in IG and CG, ↑ MoCA in IG and CG, ↑ ROCFT (copy) in IG and CG, ↑ ROCFT (delay) in IG and CG	N/A	N/A
(Liu-Ambrose et al., 2016)	Global cognition, Executive function, Working memory	ADAS-Cog, MMSE, MoCA, TMT B-A, Stroop task, Digit span forward-backward	↑ ADAS-Cog in IG, ↓ ADAS-Cog in CG, ↑ TMT B in IG and CG, ↓ Stroop task in IG and CG, ↑ Digit span forward-backwards in IG and CG	6MWT, resting HR, TUG	↑ 6MWT in IG, ↓ 6MWT in CG, ↑ resting HR in IG and CG
(Nagamatsu et al., 2013)	Global cognition	MoCA, MMSE	No data about the change of MoCA and MMSE	N/A	N/A
(Rojasavastera et al., 2020)	Global cognition	MoCA	↑MoCA in IG and CG	GS, Chair stand test, Single-leg stand test	↑ GS in IG, ↓ GS in CG, No data about the

(*continued on next page*)

Table 1 (*continued*)

Study	Cognitive outcome	Cognitive measure	Overall cognitive effect	Behavioural outcome	Overall behavioural effect
					change of Chair stand test and Single-leg stand test
(Scherder et al., 2005)	Global cognition, Executive function, Working memory	MMSE, TMT A+B, Category naming, Digit span, Visual memory span	↑ TMT A+B in IG, ↓ TMT A+B in CG, ↑ Category naming in IG, ↓ Category naming in CG, ↑ Digit span in IG, ↓ Digit span in CG, ↓ Visual memory span in IG, ↑ Visual memory span in CG	N/A	N/A
(Shimada et al., 2018)	Global cognition, Executive function, Working memory	MMSE, TMT B, Immediate word memory, Immediate logical memory	↑ MMSE in IG, ↓ MMSE in CG, ↓ TMT B in IG, ↑ TMT B in CG, ↑ Immediate word memory in IG and CG, ↑ Immediate logical memoy in IG, ↓ Immediate logical memory in CG	HGS, GS	↑ HGS in IG and CG, ↓GS in IG, ↑GS in CG
(Song and Yu, 2019)	Global cognition	MoCA	↑ MoCA in IG, ↓ MoCA in CG	N/A	N/A
(ten Brinke et al., 2015)	Global cognition	MMSE, MoCA	No data about the change of MoCA and MMSE	N/A	N/A
(Varela et al., 2012)	Global cognition	MMSE	↑ MMSE in IG, ↓ MMSE in CG	TUG	↑ TUG in IG, ↓ TUG in CG
(van Uffelen et al., 2009)	Global cognition, Executive function	MMSE, Stroop task	↓ MMSE in men in IG and CG, No signifficant difference in MMSE in women in IG and CG, ↓ Stroop task in men in IG, ↑ Stroop task in men in CG, ↓ Stroop task in women in IG, ↑ Stroop task in women in CG	N/A	N/A
(Wei and Ji, 2014)	Global cognition	MMSE	↑ MMSE in IG, ↓ MMSE in CG	N/A	N/A
(Zhu et al., 2018)	Global cognition, Executive function, Working memory	MoCA, TMT B, Digit span forwards-backward, Logical Memory I – WMS	↑ MoCA in IG, ↓ MoCA in CG, ↑ TMT B in IG and CG, ↑ Digit span forwards-backward in IG, ↓ Digit span forward-backward in CG ↑ Logical Memory I (WMS) in IG, ↓ Logical Memory I (WMS) in CG	6MWT, 10-m walk test	No data about the change of 6MWT and 10-m walk test
Older adults with dementia					
(Arcoverde et al., 2014)	Global cognition, Executive function, Working memory	MMSE, CAMCOG, Stroop task, Digit span forward, Digit span backward	↑ MMSE in IG, ↓ MMSE in CG, ↑ CAMCOG in IG, ↓ CAMCOG in CG, ↓ Stroop task in IG, ↑ Stroop task in CG, ↓ Digit span forward in IG and CG, ↓ Digit span backward in IG and CG	TUG, Chair stand test	↓ TUG in IG, ↑ TUG in CG, ↑ Chair stand test in IG, ↓ Chair stand test in CG
(Barnes et al., 2013)	Global cognition, Executive function	modified MMSE, TMT B, EFT congruent RT, EFT incongruent RT	↑ TMT B in IG and CG, ↓ EFT congruent RT in IG, ↑ EFT congruent RT in CG, ↑ EFT incongruent RT in IG and CG	N/A	N/A
(Bossers et al., 2016, 2015)	Global cognition, Working memory, Executive function	MMSE, Digit span forward, Digit span backward, Stroop task	↑ MMSE in IG, ↓ MMSE in CG, ↑ Digit span forward in IG, ↓ Digit span backward in CG, ↓ Digit span backward in IG and CG, ↑ Stroop task in IG and CG	Walking endurance, leg muscle strength, balance	↑ Walking endurance in IG, ↑ Leg muscle strength in IG, ↑ Balance in IG, ↑ Mobility in IG
(Cancela et al., 2016)	Global cognition	MMSE	↑ MMSE in IG, ↓ MMSE in CG	TUG	↑TUG in IG and CG
(Eggermont et al., 2009)	Working memory	Digit span forward, Digit span backward	↓ Digit span forward in IG and CG, ↓ Digit span backward in IG and CG	N/A	N/A
(Enette et al., 2020)	Global cognition, Working memory	MMSE, Digit span forward, Digit span backward	↑ Digit span forward in IG, No significant change in Digit span forward in CG, ↑ Digit span backward in IG, No significant change in Digit span backward in CG,	6MWT	↑ 6MWT in IG and CG

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Table 1 (*continued*)

Study	Cognitive outcome	Cognitive measure	Overall cognitive effect	Behavioural outcome	Overall behavioural effect
(Karssemeijer et al., 2019)	Global cognition, Executive function, Working memory	MMSE, TMT B, Stroop task, Digit span, Spatial span	↑ MMSE in IG, ↓ MMSE in CG No data about the change of MMSE, ↑ TMT B in IG and CG, ↑ Stroop task in IG and CG, ↑ Digit span in IG and CG ↑ Spatial span in IG, ↓ Spatial span in CG	resting HR	No data about the change of resting HR
(Kim et al., 2016)	Global cognition	MMSE, ADAS-Cog	↑ MMSE in IG, No significant difference in MMSE in CG, ↓ ADAS-Cog in IG, No significant difference in ADAS-Cog in CG	N/A	N/A
(Miu et al., 2008)	Global cognition	MMSE, ADAS-Cog	↓ MMSE in IG and CG, ↑ ADAS-Cog in IG and CG	6MWT	↑ 6MWT in IG, ↓ 6MWT in CG
(Swinnen et al., 2021)	Global cognition	MoCA	↑ MoCA in IG, ↓ MoCA in CG	SPPB	↑ SPPB in IG, ↓ SPPB in CG
(Yu et al., 2021)	Global cognition, Executive function	MMSE, TMT B, ADAS-Cog	↓ MMSE in IG and CG, ↑ TMT B in IG and CG, ↑ ADAS-Cog in IG and CG	N/A	N/A

IG: intervention group; CG: control group; MMSE: Mini-mental state examination test; WCTS: Wisconsin card sorting test; HRV: heart rate variability; RMSSD: toot-mean-square of successive R-R; LOTCA: Loewenstein Occupational Therapy Cognitive Assessment; VT-1: Ventilatory threshold 1; HR: heart rate; HR max: maximum heart rate; Vo2max: maximal oxygen consumption; 6MWT: 6 min walk test; HGS: handgrip strength; GS: gait speed; TMT: Trial Making Test; ROCFT: Rey-Osterrieth Complex Figure Test; MEC: Mini-Examen Cognoscitivo (Spanish version of MMSE); WMS: Wechsler Memory Scale; CAMCOG: Cambridge Cognitive Examination; N/A: Non applicable.

program duration, session duration, frequency, and intensity) for dose-parameters (Table 4).

3.4. The effect of AE on cognitive function

Figs. 2 - 4 show that AE improved GC (ES = 0.56 [95% CI: 0.28–0.83], p = 0.01), WM (ES = 0.26 [95% CI: −0.01 to 0.53], p = 0.05) and EF (ES = 0.20 [95% CI: 0.04–0.36], p = 0.01) in all three groups combined. Heterogeneity ranged from 53% to 84% (Figs. 2–4).

Figs. 1 – 3 show that AE improved cognitive function in healthy older adults (ES = 0.40 [95% CI: 0.23–0.57], p = 0.01) and MCI (ES = 0.59 [95% CI: 0.24–0.93], p = 0.01), but not in dementia (ES = 0.08 [95% CI: −0.10 to 0.26], p = 0.32). Heterogeneity ranged from 43% to 83% (Supplement 2, Figs. 1–3).

Figs. 1 – 3 show that AE improved GC (ES = 0.46 [95% CI: 0.22–0.69], p = 0.01) and EF (ES = 0.27 [95% IC: 0.05–0.49], p = 0.02) in healthy, in MCI (ES = 0.76 [95% CI: 0.21–1.32], p = 0.01), but not in dementia. Heterogeneity ranged from 0% to 90% (Supplement 3, Figs. 1–3).

In sum, AE improved GC in healthy, and MCI older adults and in the three groups combined but the results were inconsistent for WM and EF.

3.5. tDCS effects on cognitive function

tDCS improved cognitive function in the three outcomes and the three groups combined (ES = 0.69 [95% CI: 0.20–1.18], p = 0.01, I^2 = 81%).

Figs. 1 – 3 show that tDCS improved GC (ES = 0.69 [95% CI: 0.12–1.26], p = 0.02), but not WM (ES = 0.30 [95% CI: −0.31 to 0.92], p = 0.24) or EF (ES = 0.16 [95% CI: −0.46 to 0.78], p = 0.50) in the three patient groups combined, with the range of heterogeneity between 53% and 81% (Supplement 4, Figs. 1–3).

In the three cognitive outcomes combined, Figs. 1 – 3 show that tDCS had no effects on cognition in healthy older adults (ES = 0.88 [95% CI: −5.51 to 7.27], p = 0.33) or MCI (ES = 0.20 [95% CI: −0.04 to 0.44], p = 0.08), but had an effect in dementia (ES = 1.12 [95% CI: 0.04–2.19], p = 0.04) with heterogeneity between 27% and 85% (Supplement 5, Figs. 1–3).

Specifically, tDCS improved GC in dementia (ES = 1.12 [95% CI: 0.04–2.19], p = 0.04, I^2 = 85%, Fig. 5).

3.6. Pairing AE with tDCS in the three groups

There was one study (n = 13 participants, 9 women, age: 73 years) concurrently delivering tDCS during AE in healthy older adults in 18 sessions over 6 weeks (Clark et al., 2021). Table 3 presents the characteristics of this study (Supplement 1, Table 3). There were no studies in older adults with MCI and dementia.

Moreover, Fig. 6 summarizes the effects of AE and tDCS on three measures of cognition (GC, WM, EF) in the three patient groups (healthy, MCI and demented older adults).

4. Discussion

4.1. Summary of results

For the first time, we aimed to systematically and meta-analytically review existing data to determine the effects of AE and tDCS on selected cognitive function (GC, WM, EF) and see if pairing the two treatments would potentiate the singular effect of AE with tDCS in older adults with and without MCI or dementia. While suggested repeatedly (Hendrikse et al., 2017; Moreau et al., 2015; Steinberg et al., 2019), there are currently insufficient data to examine the hypothesis and to conclude that pairing AE and tDCS would produce a potentiated effect on cognition in ageing. Against the hypothesis, we found significant effects of individually delivered AE and tDCS on GC independent of cognitive status (healthy, MCI, demented). In agreement with the hypothesis, the severity of cognitive impairment affected the efficacy of AE to improve cognition so that AE did not improve cognition in dementia. tDCS was effective in a pooled analysis of cognition (GC, WM, EF) in older adults with dementia. Moreover, tDCS intervention improved global cognition in the three groups combined.

We discuss these data with a perspective on the potential of pairing AE with tDCS in an effort to reciprocally boost the effects of these individual treatments on cognition and provide individualized and disease-specific treatment options for reducing symptom evolution of

Table 2
The effects of transcranial direct current stimulation intervention on 3 measures of cognition and behavioural outcomes in healthy, MCI and demented older adults.

Study	Outcome	Measure	Overall effect (mean±SD)
Healthy older adults			
(Boggio et al., 2010)	Global Cognition	MMSE	No data for MMSE after intervention
(Firouzkouhi Moghadam et al., 2020)	Global cognition, Executive Function, Working memory	MMSE, 2-back, Forward digit span, Backward digit span	No change in MMSE (both IG's and CG), ↑ 2-back in IG F3, No change 2-back in IG F4 and CG, ↑ Forward digit span in IG F3, No change forward digit span in IG F4 and CG, ↑ Backward digit span IG F3, IG F4 and CG
(Krebs et al., 2021)	Global cognition	Learning sum wordlist, delayed recall, d prime word recognition, Corsi blocks, d prime figural recognition, Semantic fluency, Lexical fluency, d prime divided attention, d prime selective attention, Number connection test, 5 point test	↑ significant effect of session on divided and selective attention in tDCS, ↑ significant interaction between pre-assessment MoCa and stimulation. No significant effect of stimulation on the composite score differences
(Leach et al., 2016)	Working memory	Recognition test, Cued recall test	↓ recognition test in IG, No significant change in recognition in CG, No significant change in recall in IG and CG
(Nilsson et al., 2017)	Working memory, Executive function	Running span, N-back task, Task switching, Rule switching	No significant change in Running span in IG and CG, No significant change in N-back task in IG and CG, No significant change in Task switching in IG and CG, No significant change in Rule switching in IG and CG
(Saldanha et al., 2020)	Working memory	N-back Task	No significant change in N-back Task in elderly IG
Older adults with MCI			
(Fileccia et al., 2019)	Global cognition, Executive Function	MMSE, BMDB, Immediate Visual Memory, Barrage test, Stroop test, Figure naming	↑ MMSE, ↑ BMDB, ↑ Immediate Visual Memory, ↑ Barrage test, ↑ Stroop test, ↑ Figure naming
(Gomes et al., 2019)	Global cognition, Executive function, Working memory	CAMCOG, MMSE, TMT A, TMT B, Forward digit span, Backward digit span, N-back test, WLMT	↑ CAMCOG, ↑ MMSE, ↑ Trail making Test, ↑ Forward digit span, ↑ Backward digit span, ↑ N-back test, ↑ Word list memory test (WLMT)
(He et al., 2021)	Global cognition	MMSE, MoCA	↑ MMSE in IG, ↑ MMSE in CG, ↑ MoCA in IG, ↑ MoCA in CG
(Kim et al., 2021)	Global cognition, Executive function	MMSE, TMT A, TMT B, Stroop-Word, Stroop-Color	No data for MMSE after intervention, ↑ TMT A in IG and CG, ↑ TMT B in IG and CG, ↓ Stroop-Word in IG and CG, ↑ Stroop-Color in IG and CG
(Lu et al., 2019)	Global cognition, Executive function, Working memory	N-back task, ADAS-Cog, Logical memory, TMT, MMSE (Cantonese), forward digit span	↑ N-back task, ↑ ADAS-Cog, ↑ Logical memory, ↑ TMT, ↑ MMSE (Cantonese), ↑ Forward digit span
(Manor et al., 2018)	Global cognition, Executive Function	TMT-B, MoCA	↑ TMT-B, ↑ MoCA
(Yun et al., 2016)	Working memory	MMQ	↑ MMQ
Older adults with dementia			
(André et al., 2016)	Global cognition, Executive function, Working memory	ADAS-Cog, 2-back task, Go/no-go	↑ ADAS-Cog, ↑ 2-back task, ↑ Go/no-go
(Boggio et al., 2012)	Global cognition	MMSE, ADAS-Cog, VRT, VAT	↑ for VRT, No change for MMSE, No change for ADAS-Cog, No change for VAT
(Gangemi et al., 2021)	Global cognition	MMSE, MODA	↑ MMSE in IG and CG, ↑ MODA in IG and CG
(Inagawa et al., 2019)	Global cognition	ADAS-Cog, MMSE	No significant difference in ADAS-Cog and MMSE
(Khedr et al., 2014)	Global cognition, Working memory	MMSE, Digit span	↑ MMSE, ↑ digit span
(Khedr et al., 2019)	Global Cognition	MMMSE, MoCA, Clock drawing test	↑ MMMSE, ↑ MoCA, ↑ Clock drawing test
(Suemoto et al., 2014)	Global cognition	MMSE, ADAS-Cog	N/A

IG: intervention group; CG: control group; MMSE: Mini-mental state examination test; TMT: Trial Making Test; ROCFT: Rey-Osterrieth Complex Figure Test; RMSSD: toot-mean-square of successive R-R; LOTCA: Loewenstein Occupational Therapy Cognitive Assessment; DLPFC: the dorsolateral prefrontal cortex; ADAS-Cog: The Alzheimer's Disease Assessment Scale–Cognitive Subscale; MoCA: Montreal Cognitive Assessment; MMQ: Multifactorial Memory Questionnaire; tDCS – transcranial direct current stimulation; WM: Working memory; VRT: visual recognition task; VAT: Visual attention task; WLMT: Word list memory test; BMDF: Brief mental deterioration battery; CAMCOG: the Cambridge Cognitive Examination; N/A: Non applicable.

Table 4
Weighted[a] descriptive statistics for dose-parameters.

	AE healthy	AE MCI	AE dementia	tDCS healthy	tDCS MCI	tDCS dementia	Total
Mean # participants (SD)	57.1 (37.0)	70.1 (49.6)	73.9 (46.0)	32.7 (19.1)	55.9 (65.8)	28.6 (11.0)	58.1 (44.0)
Mean age (SD)	69.7 (5.3)	73 (7.6)	82 (3.0)	67.5 (4.9)	75.5 (2.1)	71.7 (6.3)	72.7 (6.6)
Mean program duration in weeks (SD)	19.8 (13.7)	21.3 (9.04)	13.4 (6.02)	3.3 (3.5)	5.4 (6.0)	1.6 (0.5)	14.6 (12.0)
Mean session duration in minutes (SD)	39.6 (13.3)	46.3 (17.1)	33.6 (13.8)	32 (13.5)	27.8 (9.1)	26.4 (7.5)	37.5 (15.0)
Mean frequency (#/week, SD)	3.1 (1.6)	2.8 (1.1)	3.4 (1.6)	2.5 (1.9)	3.4 (1.1)	5.3 (0.9)	3.2 (1.6)
Mean intensity (% of HRR in AE, # mA in tDCS, SD)	59.3 (11.3)	66.1 (12.2)	58.3 (11.2)	2.0 (0)	1.8 (0.4)	2.0 (0)	61.8 (11.7) % 1.9 (0.2) mA

[a] Descriptive statistics weighted for n per study.

cognitive impairment in ageing.

4.2. Effects of AE combined with tDCS on three measures on cognition in older adults with and without MCI or dementia

Notwithstanding repeated calls and conceptual frameworks, our systematic search identified little to no data concerning the synergistic effects of pairing chronic AE with chronic tDCS on CG, WM, and EF in the three populations. Synergistic effects between concurrent AE and tDCS could arise because cognition and walking and running, activities often used in AE and rehabilitation, share common neural substrates (Dougherty et al., 2021; Kikkert et al., 2016; Moreau et al., 2015; Morris et al., 2016; Steinberg et al., 2019; Verlinden et al., 2014). In particular, the frontal lobe, where circuits controlling EF reside, becomes increasingly activated as the speed and complexity of walking increase (Clark et al., 2014; Wagshul et al., 2019). Conversely, impaired EF is associated with gait slowing and a reduced ability to perform complex gait tasks (Nutt, 2013; Steinberg et al., 2019). Intervention variables to produce dose effects on cognition are unclear from single-session cross-sectional studies, as cognitive, motor skill, sports skill, and AE training at varying intensities, duration, and complexity all seemed to improve cognition in combination with tDCS (Ma et al., 2020; Manenti et al., 2014; Manor et al., 2018, 2016; Moreau et al., 2015; Nissim et al., 2019; Schneider et al., 2021; Tahtis et al., 2014; Wrightson et al., 2015; Zhou et al., 2014).

A combination of tDCS at 1 mA (below the 2-mA maximal stimulator output) with a moderate level of AE in a single session appeared effective to immediately improve healthy young adults' EF (Thomas et al., 2021). In the context of the current review, the only study that combined and concurrently delivered real and sham tDCS with complex walking ('AE') chronically in 18 sessions over 6 weeks in healthy older adults age ≤ 65 y, cautiously concluded that there is a potential for improving EF by adding frontal tDCS to walking rehabilitation (Clark et al., 2021). While this study administered complex walking tasks and tDCS concurrently (Clark et al., 2021), there is also evidence that AE could potentiate subsequent NIBS-induced plasticity under certain conditions, requiring additional studies to determine the most effective order for sequencing AE and tDCS (Mellow et al., 2020). While tDCS and AE act on overlapping brain areas, each method acts via different molecular mechanisms. tDCS presumably improves cognition by modifying the levels of acetylcholine, dopamine, and GABA and cortical activation, whereas AE modifies levels of growth factors (IGF-1, BDNF, VEGF), dopamine, glutamate, serotonin, and norepinephrine, promoting vascularization and neurogenesis (Hendrikse et al., 2017; Moreau et al., 2015; Steinberg et al., 2019). Our search identified no studies that examined the synergistic effects of pairing AE and tDCS on CG and WM in MCI and dementia. A potentiating effect might still occur between these two interventions to improve CG, WM, and EF because pairing cognitive training combined with tDCS can improve selected measures of cognition in older adults with and without MCI or dementia and in selected psychiatric conditions (Ciullo et al., 2021; Gonzalez et al., 2021; Lu et al., 2019; Siegert et al., 2021).

In sum, the strong conceptual framework of dual application of chronic AE and tDCS for augmenting the individual treatment effects on cognition is juxtaposed with scant experimental evidence. Future studies will need to examine the hypothesis of this present review that such a potentiating effect would incrementally improve cognition with increasing severity of cognitive impairment. In addition, sequencing effects of AE and tDCS should be elucidated.

4.3. Effects of AE on three measures of cognition in older adults with and without MCI or dementia

AE is considered as a highly effective strategy to improve cognition in older adults (Gheysen et al., 2018). Neuroplasticity, the mechanism responsible for creating and modifying synaptic connections improves cognitive function with AE in older people (Quigley et al., 2020). Chapman et al. study of shorter duration of AE (12 weeks) observed improvement in healthy older people's hippocampal size and blood flow (Chapman et al., 2013). Similarly, Voss et al. presented increase in temporal lobe connectivity after AE training for 48 weeks in older adults (Voss, 2010). Considering that each of the above-mentioned studies suggests the upregulation of growth factors and neuroplasticity as a key biological mechanism that appears to underline exercise-induced cognitive improvement in older individuals (Liang et al., 2021; Vecchio et al., 2018), future studies should focus on identifying the role of BDNF, vascular endothelial growth factor (VEGF), and insulin-like growth factor-1 (IGF-1) following exercise-induced adaptations.

In healthy older adults, previous reviews show that AE has medium effects on GC and small effects on EF and WM (Angevaren et al., 2008; Barha et al., 2017; Bruderer-Hofstetter et al., 2018; Chen et al., 2020; Colcombe and Kramer, 2003; Gheysen et al., 2018; Hindin and Zelinski, 2012; Kelly et al., 2014; Ludyga et al., 2016; Northey et al., 2018; Sanders et al., 2019; Xiong et al., 2021; Young et al., 2015; Zhu et al., 2016). Our results partially support these data, as we found medium pooled effects of AE on CG (ES = 0.46, p = 0.01), small effects of AE on EF (ES = 0.27, p = 0.02) and non-significant medium effect of AE on WM (ES = 0.49, p = 0.16). The source of discrepancy could be the number of studies being substantially higher in the present review (Supplement 2, Fig. 1, n = 17 studies) than in the previous reviews ((Angevaren et al., 2008; Barha et al., 2017; Bruderer-Hofstetter et al., 2018; Chen et al., 2020; Colcombe and Kramer, 2003; Gheysen et al., 2018; Hindin and Zelinski, 2012; Kelly et al., 2014; Ludyga et al., 2016; Northey et al., 2018; Sanders et al., 2019; Xiong et al., 2021; Young et al., 2015; Zhu et al., 2016), n = up to 9 studies). Our results indicated that different domains of cognition (GC, EF, WM) respond differently to the same exercise stimulus (AE) in the healthy segment of the population, mainly due to the brain structures primarily controlling a given cognitive function that vary in their microstructure, sensitivity to blood flow, and level of decline (Oschwald et al., 2019).

In mildly cognitively impaired older adults, AE carried beneficial effects for CG (ES = 0.76, p = 0.01) and cognition overall (ES = 0.59, p = 0.01), but there were no statistically significant effects of AE on WM and EF. These results are partially in line with previous meta-syntheses which suggest medium effect of AE on GC and a small effect on EF and WM in older adults with MCI (Biazus-Sehn et al., 2020;

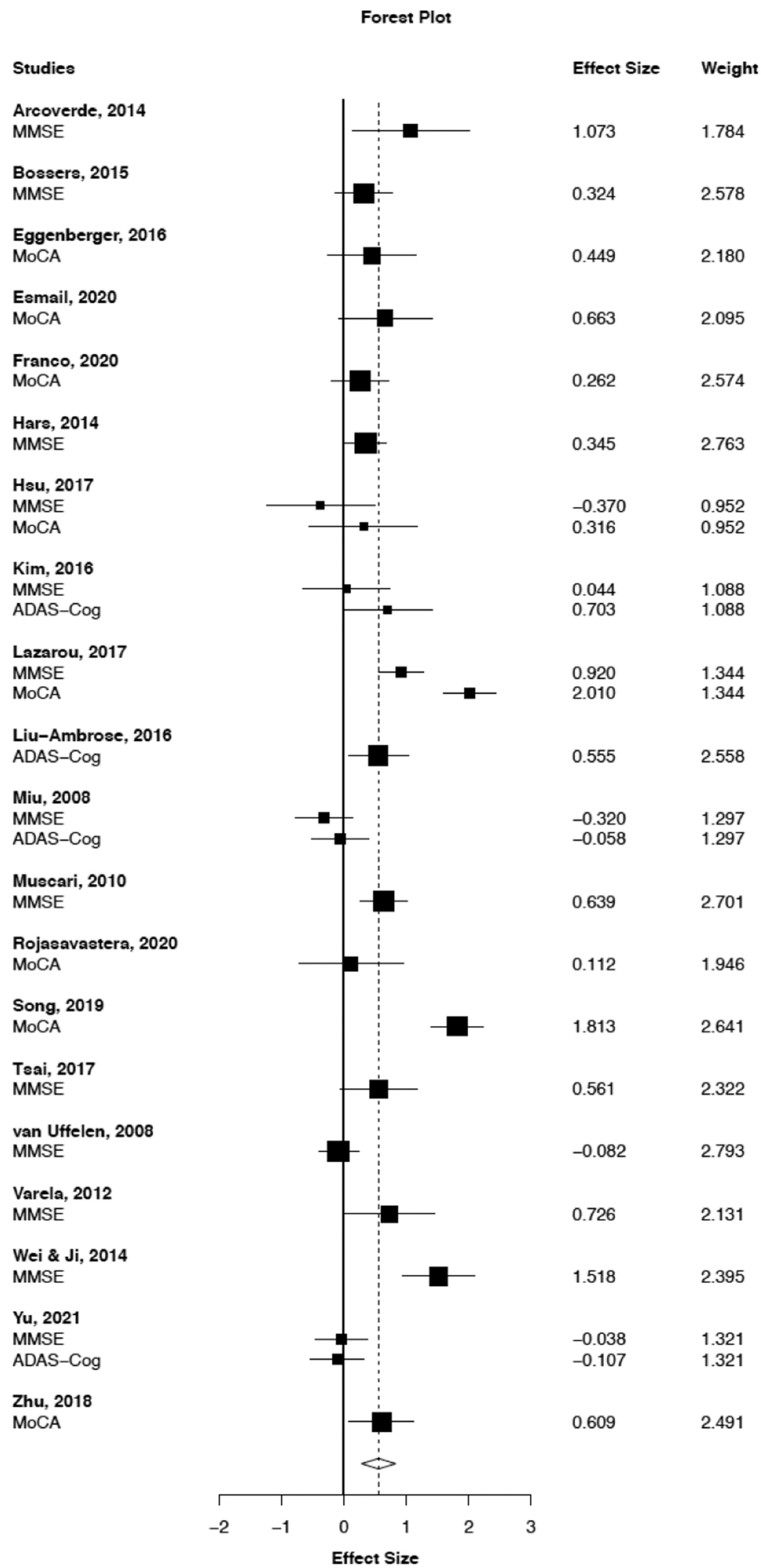

Fig. 2. The effects of aerobic exercise intervention on global cognition in healthy, MCI and demented older adults. Effect sizes greater than zero favour aerobic exercise (ES = 0.56 [95% CI: 0.28–0.83], n = 20, p = 0.01, I^2 = 53%).

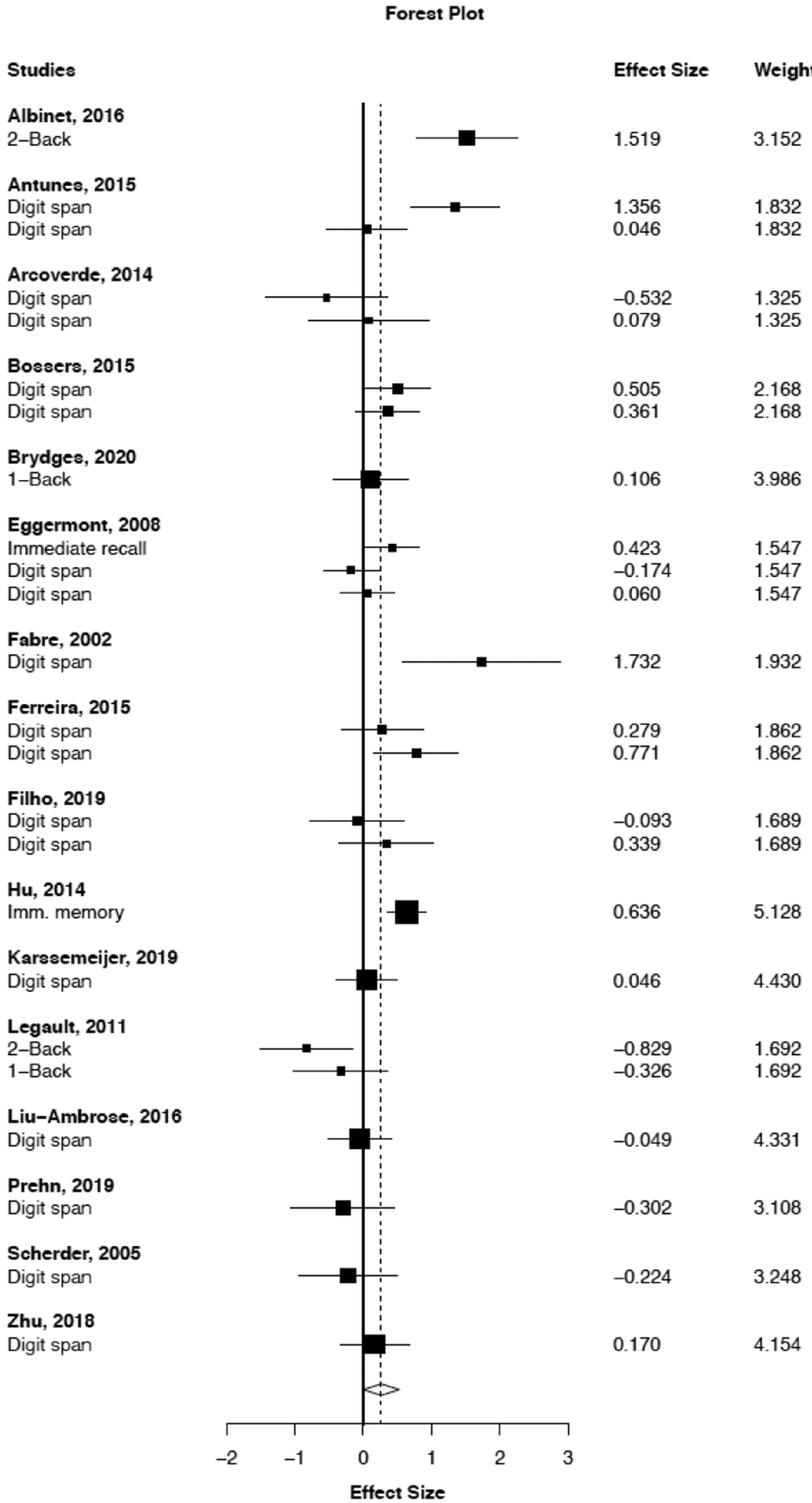

Fig. 3. The effects of aerobic exercise on working memory in healthy, MCI and demented older adults. Effect sizes greater than zero favour aerobic exercise (ES = 0.26 [95% CI: −0.01 to 0.53], n = 16, p = 0.05, I^2 = 69%).

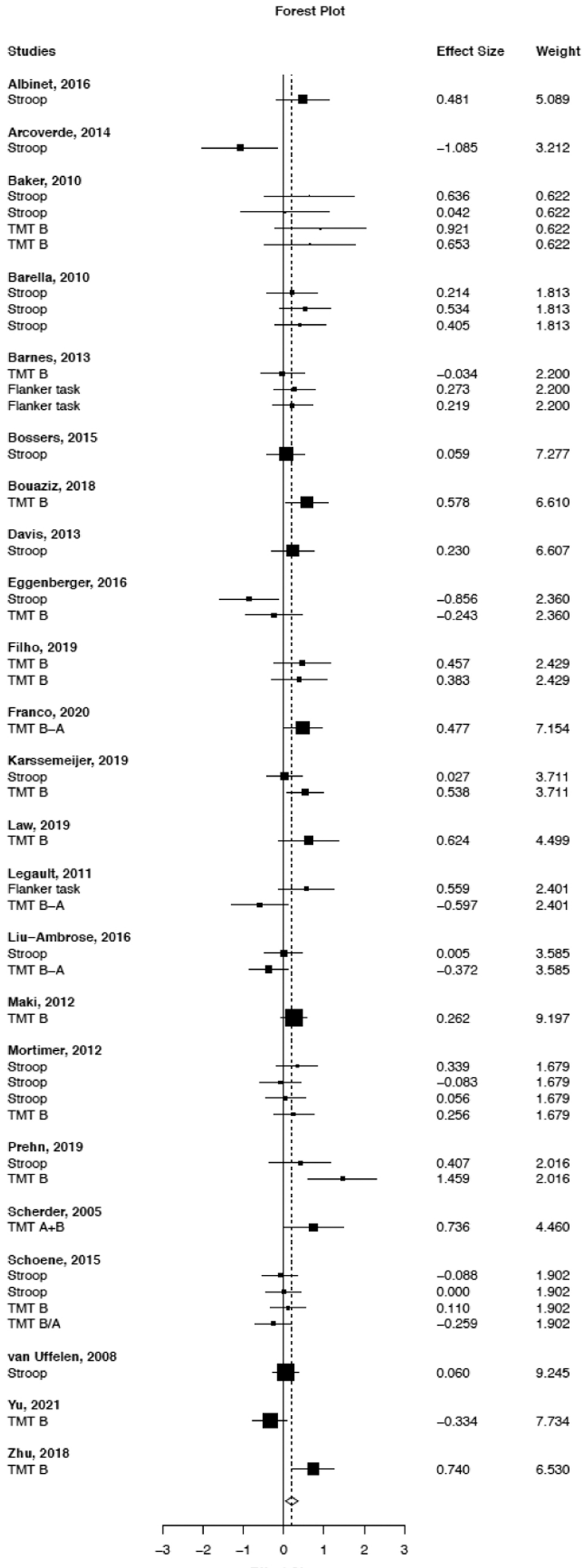

Fig. 4. The effects of aerobic exercise on executive function in healthy, MCI and demented older adults. Effect sizes greater than zero favor aerobic exercise (ES = 0.20 [95% CI: 0.04–0.36], p = 0.01, n = 23, I^2 = 53%).

Bruderer-Hofstetter et al., 2018; Chen et al., 2020; Northey et al., 2018; Sanders et al., 2019; Zheng et al., 2016; Zhou et al., 2020). The reason for such differences could be the number of studies being substantially higher in the present review (Supplement 2, Fig. 2, n = 15 studies) than in previous reviews (n = up to 9 studies). Beneficial effects of AE on cognition in older adults with MCI may be caused by exercise-induced increases in cortical excitability, motor evoked potential (MEP) responses (Dai et al., 2013; McGregor et al., 2018), up-regulation of BDNF (Allard et al., 2017), increased left hippocampal volume (ten Brinke et al., 2015) and prevention of brain volume loss (Frodl et al., 2020). Another factor could be that the mean program duration of AE (Table 4, ~21 weeks) was relatively shorter than in the previous reviews (~23 weeks) and the mean session duration lasted for ~46 min, while in the other studies for ~51 min. Northey et al. recommended a session duration of 45 min that is beneficial for cognition (Northey et al., 2018). We suspect that GC, EF and WM responded differently to the exercise stimulus due to the significantly varying level of cognitive deterioration among the studies (decline measured objectively over time or subjective assessment of decline by the participant) (Winblad et al., 2004).

In demented older people, previous metasyntheses showed that AE has medium effects on GC and small effects on EF and WM (Heyn et al., 2004; Law et al., 2020). Our results do not support these data, as we found statistically non-significant small effects of AE on CG (ES = 0.19, p = 0.34) and small, non-significant effects of AE on cognition overall (ES = 0.08, p = 0.32). Moreover, there were no statistically significant results of AE on WM and EF. The source of discrepancy could be the number of studies being substantially higher in the present review (Figure 9, n = 8 studies) than in previous reviews (n = up to 7 studies). Another factor could be that the mean program duration of AE (Table 7, ~13 weeks) was shorter than in the previous studies (~17 weeks) and the mean session duration lasted for ~34 min, while in the other studies for 45 min. Also, the mean age was higher (Table 7, 82 years) than in the previous studies (~79 years).

In conclusion, we found robust evidence for a decrease in the effectiveness of AE on three measures of cognition (CG, WM, EF) with increasing severity of cognitive impairment. In the spirit of discussion under 4.2, future studies will need to seek alternatives to singular treatments by blending interventions that are conceptually expected to produce a synergistic effect. We also found a positive effect of tDCS on GC individually and all cognitive function (GC, WM, EF) in the three groups combined. Moreover, AE was effective to improve GC individually in older adults with MCI and when the three cognitive measures were combined (GC, WM and EF).

4.4. *Effects of tDCS on three measures of cognition in older adults with and without MCI or dementia*

The increasing popularity of tDCS in sport science is observed due to the evidence of regulation of exertion markers, eg. RPE, HR (Thomas et al., 2021). The effect of NIBS is measured using the change in motor evoked potentials (MEPs) when applied over the primary motor cortex (M1) (Huang et al., 2017). MEPs are the electrical signals recorded from the muscles via electromyography (EMG) that respond to the direct stimulation as an index of the motor cortex excitability (Legatt, 2014). It is recommended to measure MEPs with TMS before using tDCS due to the high variability of corticospinal excitability (CSE) in tDCS protocols (Bashir et al., 2019; Horvath et al., 2016, 2015). The reasons of occurrence of variability are still unknown (Laakso et al., 2019). MEPs can be evoked by the paired pulse techniques: the short interval intracortical inhibition (SICI), obtained while giving 2 pulses close to each other (2 ms) to condition and test stimuli or by the long interval intracortical inhibition (LICI), when 2 pulses are distal to themselves (800 ms) or intracortical facilitation (ICF), when during the inter-stimulus intervals (ISI) (10 ms) the conditioned MEP is greater than the test MEP (Chen et al., 1998; Huang et al., 2017; Udupa et al., 2009; Ziemann, 1999). Study of Indahlastari et al. proposes tDCS method that improves

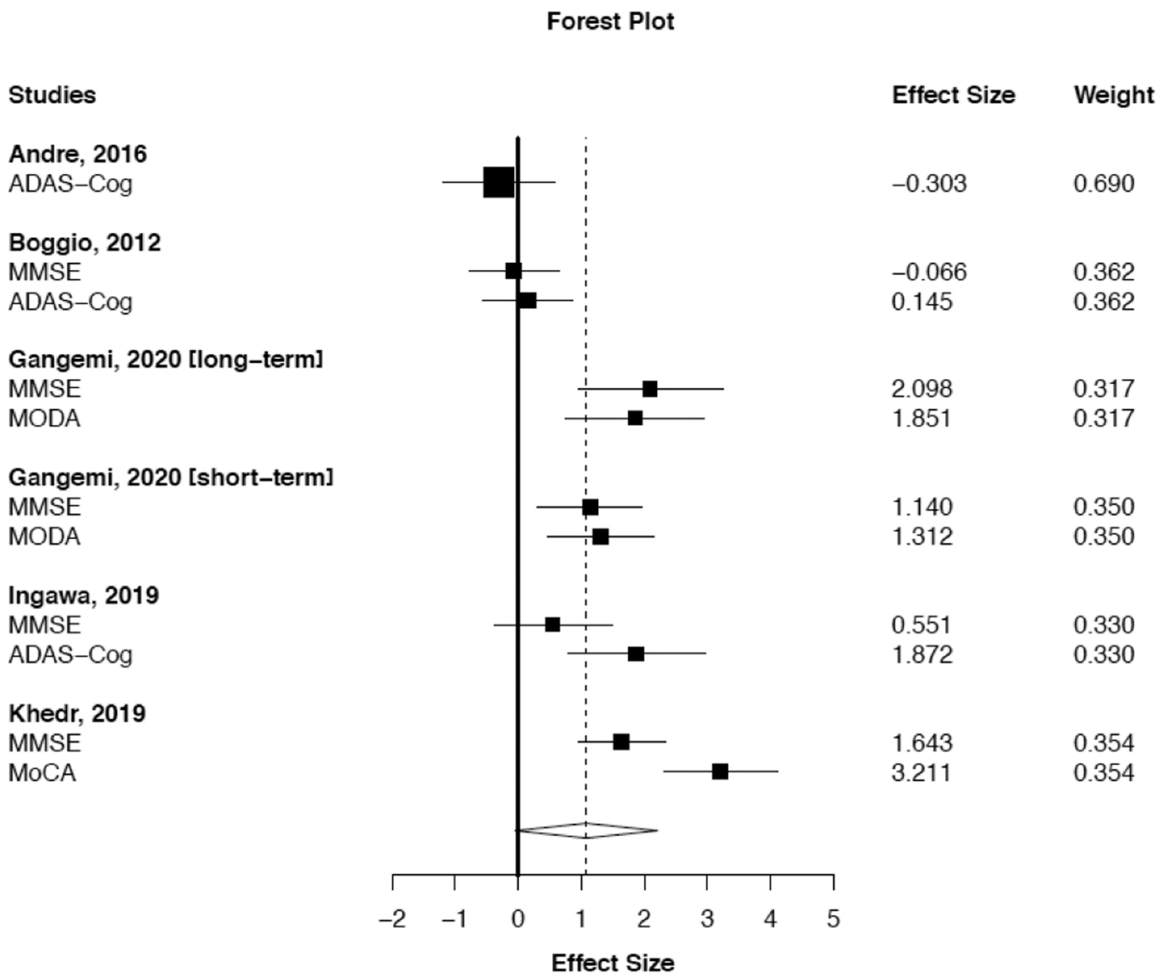

Fig. 5. The effects of transcranial direct current stimulation on global cognition in demented older adults. Effect sizes greater than zero favour transcranial direct current stimulation (ES = 1.08 [95% CI: −0.05 to 2.21], p = 0.06, n = 6, I^2 = 86%).

Table 3
The effects of aerobic exercise training combined with transcranial direct current stimulation intervention on cognition and behavioural outcomes in healthy older adults.

Study	Cognitive outcome	Cognitive measure	Overall cognitive effect	Behavioural outcome	Overall behavioural effect
Healthy older adults					
(Clark et al., 2021)	Executive function	TMT B, EXAMINER WM Score, EXAMINER Composite Score	↑ TMT B in IG and CG, ↑ EXAMINER WM Score in IG, ↓ EXAMINER WM Score in CG, ↑ EXAMINER Composite Score in IG and CG	↑ Typical Walk speed (m/s) in IG and CG, ↑ Fastest Walk speed (m/s) in IG and CG, ↑ Obstacle Walk Speed (m/s) in Ig and CG, ↑ Figure-8 Walk Time (s) in IG and CG	↑ Typical Walk speed (m/s) in IG and CG, ↑ Fastest Walk speed (m/s) in IG and CG, ↑ Obstacle Walk Speed (m/s) in Ig and CG, ↑ Figure-8 Walk Time (s) in IG and CG

IG: intervention group; CG: control group; TMT: Trial Making Test; WM: working memory.

cognition and delays cognitive decline in healthy older people (Indahlastari et al., 2021).

Contrary to the previous results that tDCS has medium effects on GC, large effects on EF and medium effects on WM in healthy older adults (Hsu et al., 2015; Huo et al., 2021; Summers et al., 2016), present study shows large but non-significant effects on all cognitive function combined (ES = 0.88, p = 0.33). The source of discrepancy could be the small number of studies included in our meta-analysis (Supplement 5, Figure 16, n = 2 studies) than in the previous reviews (Hsu et al., 2015; Huo et al., 2021; Summers et al., 2016), up to 11 studies. Such difference in the number of the included studies occurred due to the different outcome measures (e.g., motor outcome) used in the meta-analysis (Summers et al., 2016), different non-invasive brain stimulation techniques (Hsu et al., 2015) or proposed by Gavelin et al., 2021 classification of cognitive outcomes (Gavelin et al., 2021). This last is critical factor as there is not a generic classification of cognitive processes (Harvey, 2019; Hay et al., 2017) and differences in cognitive categories could lead to different assessment.

Moreover, previous studies showed that tDCS has large effects on GC, small effects on EF and medium effects on WM in older adults with MCI (Chu et al., 2021; Cruz Gonzalez et al., 2018; Xu et al., 2019b). Again, our results do not support these data, as we found no significant effects

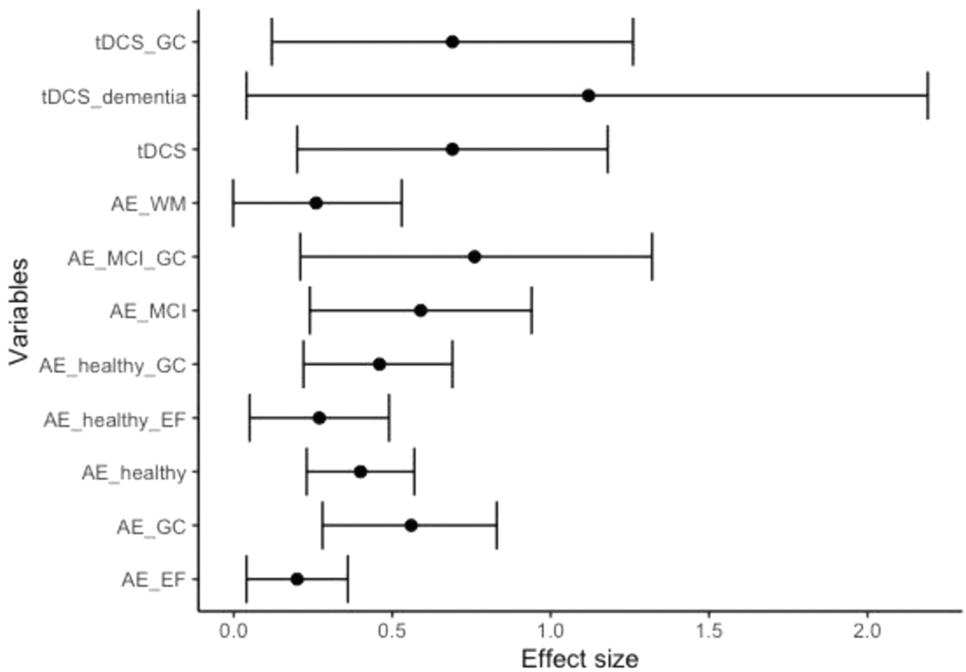

Fig. 6. The effects of aerobic exercise and transcranial direct current stimulation training on global cognition, working memory, executive function in healthy, MCI and demented older adults. Pooled effect size greater than zero favour intervention (AE, tDCS training) vs. passive control and were computed using Random Variance Estimate meta-analytical modelling. Note that the figure does not contain any data on the combined effects of AE and tDCS on cognition, as only one study has examined such combined effects. Horizontal brackets denote confidence intervals ($p < 0.05$). AE, aerobic exercise; GC, global cognition; WM, working memory; MCI, mild cognitive impairment; EF, executive function.

on GC, EF, and WM in older adults with MCI. We included small number of studies in our meta-analysis (Supplement 5, Fig. 2, n = 6 studies), similarly to other authors in the previous reviews (Chu et al., 2021; Cruz Gonzalez et al., 2018; Xu et al., 2019b), n = up to 4 studies). The difference in the obtained results occurs due to the different non-invasive brain stimulation techniques (Xu et al., 2019b) or division of short-term and long-lasting effects of tDCS on cognitive function (Chu et al., 2021; Cruz Gonzalez et al., 2018).

Cruz Gonzalez et al. suggested that tDCS had small effects on WM in older adults with dementia (Cruz Gonzalez et al., 2018). Our results partially support these data, as we found large and significant effects on cognitive function (GC, WM, and EF) in older adults with dementia after tDCS intervention (ES = 1.12, p = 0.04). The source of discrepancy could be the number of studies being substantially higher in the present review (Supplement 5, Fig. 3, n = 6 studies) than in the previous (up to 4 studies). Moreover, to our knowledge, there were no reviews examining the effects of tDCS on WM and EF in demented older adults. Therefore, it is recommended to experimentally and systematically investigate the effect of tDCS on cognition in older people with dementia.

In summary, tDCS was effective on all three cognitive function combined (GC, WM and EF) in older adults with dementia. We found no statistically significant effects of tDCS on cognitive function in older adults with MCI.

4.5. Interaction of AE and tDCS with disease severity

The emerging picture supports the idea that the effectiveness of AE and tDCS differs with disease severity. While AE improves cognitive function in healthy (ES = 0.40, p = 0.001), and MCI (ES = 0.59, p = 0.003) older adults, tDCS is effective in demented older people (ES = 1.12, p = 0.04). Moreover, the present study found that older people overall (healthy, MCI, demented) significantly improved in GC after tDCS (ES = 0.69, p = 0.02) and AE (ES = 0.56, p = 0.01) interventions. Hence, a combination of the two methods (AE + tDCS) appears to be a promising non-pharmacological intervention to delay in midlife the onset age of clinical dysfunction and slow progression of cognitive impairment with ageing, which can possibly reduce the dependency of older adults and, improve quality of life (Fusco et al., 2012) and decrease care costs (Guralnik et al., 2002; Hazra et al., 2018).

4.6. Strengths and limitations

In this study, the RVE meta-regression was used to be able to include multiple dependent outcomes from the same study. This is an important strength of the present meta-analyses, as many of the included studies reported multiple cognitive outcomes, with the substantially varying effect of the intervention, sometimes even in the opposite direction (André et al., 2016; Arcoverde et al., 2014; Eggenberger et al., 2016; Legault et al., 2011; Miu et al., 2008; Prehn et al., 2019; Scherder et al., 2005; Schoene et al., 2015; Yu et al., 2021). Using a standard meta-analytical approach would require choosing just one outcome and discarding others, leading to a potential selection bias. Thus, similarly to other meta-analyses of physical interventions (Pallarés et al., 2021; Talar et al., 2021), the use of RVE is better suited for the purpose and can also explain the discrepancies between our results and the results of some previous reviews (Chen et al., 2020; Law et al., 2020; Xiong et al., 2021; Y. Xu et al., 2019; Young et al., 2015; Zhu et al., 2016).

This systematic review has limitations. First, except for AE on GC in healthy older adults and tDCS on GC, WM in older people with MCI, most meta-analyses presented moderate to high levels of heterogeneity. This fact could be explained by the different methodologies (e.g., volume, intensity, type of AE intervention, stimulation tool, protocol, stimulation position, program duration, session duration and frequency), different variables included in the quantitative analysis (i.e., clinical diversity), as well as by the inconsistent statistical analyses performed in two studies (André et al., 2016; Yu et al., 2021) that affected our results and the interpretation.

Second, only one study met the inclusion criteria for the combination of tDCS and AE intervention in older people (Clark et al., 2021). For this reason, future systematic reviews are encouraged to examine the effects of pairing AE with tDCS on GC, WM and EF in older people with or without MCI or dementia.

Third, the cognitive tools used by included studies, could assess the level of cognitive impairment, not measure GC. The studies where MMSE, MoCA and ADAS-Cog were measured only at baseline were excluded from our meta-analysis (Albinet et al., 2016, 2010; Barnes et al., 2013; Brydges et al., 2020; Cancela et al., 2016; Davis et al., 2013; Esmail et al., 2020; Ferreira et al., 2015; Karssemeijer et al., 2019; Khedr et al., 2014; Legault et al., 2011; Liu-Ambrose et al., 2016; Lopes Filho et al., 2019; Maki et al., 2012; Nagamatsu et al., 2013; Raichlen et al., 2020; Scherder et al., 2005; Shimada et al., 2018; Suemoto et al., 2014; ten Brinke et al., 2015; van Uffelen et al., 2008). Similarly to Arevalo-Rodriguez et al., 2015 we recommend using additional and extensive cognitive tests to observe the disease severity from MCI stages to dementia. That could be achieved by MMSE, MoCA and ADAS-Cog changes over time instead of a single measurement (Arevalo-Rodriguez et al., 2015).

Fourth, dementia as a clinical syndrome is not a single disease, covers many medical conditions: Alzheimer's disease (60–80% cases), vascular dementia (5–10% cases) and dementia with Lewy bodies (5–10% cases) (Anon, 2021; Sheehan, 2012). For this reason, the studies in the dementia category included the above-mentioned diseases. Although it could be considered as a strength of this article, it is possible that such division influenced our results in older adults with dementia.

4.7. Recommendations for future research

The low number of studies with dual AE and tDCS (only 1 study found for healthy older adults) suggests the need for more studies examining the synergistic effects of AE and tDCS on cognitive function in older people. Future studies and reviews should also address the limitations of the present review (duration, timing, frequency, intensity of AE). It should be noted, that both techniques have similarities except separate mechanisms and modulating ability of brain functions. Moreover, both techniques may be used in a direct combination (i.e., tDCS can stimulate the brain while exercising). Moreover, other non-invasive brain stimulation techniques are recommended, e.g., TMS and tACS during exercise (Ross et al., 2018). These methods are relatively easy to apply, safe (no known severe side effects) and cost-effective. Lastly, the long-term effect of pairing tDCS and AE should be examined in future studies.

5. Conclusions

Beyond the cardiovascular and fitness benefits of AE, pairing AE with tDCS may have the potential to slow symptom progression of cognitive decline in MCI and dementia. Future studies will need to examine the hypothesis of this present review that a potentiating effect would incrementally improve cognition with increasing severity of cognitive impairment.

Conflicts of Interest

The authors declare no conflict of interest.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2022.101738.

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