






Review

A Systematic Study into the Effects of Long-Term Multicomponent Training on the Cognitive Abilities of Older Adults with Neurodegenerative Disorders

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Abstract: Cognition includes all processes through which a person becomes aware of their situation, needs, goals, and necessary actions. Regular specialized cognitive and neuromotor simulation exercises have improved various cognitive processes, including memory, speed of reasoning, and problem-solving skills. This review focuses on understanding the efficacy of long-term multicomponent exercise interventions to mitigate and delay the effects on cognitive abilities in older adults with neurodegenerative disorders. The main criteria for final studies were randomised controlled trials with a minimum of a 24-week intervention. The Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS, B-On, Sport Discus, Scielo, APA PsycINFO, Psychology and Behavioural Sciences, Academic Search Complete, Medline (PubMed), ERIC, and Google Scholar databases were checked. The search occurred between April 2022 and July 2022. A total of 19 studies were used in this review. The initial search identified 6.835 studies. In the first screening, a total of 6474 studies were excluded. After this, 361 studies were analysed by co-authors and did not meet the specific final criteria and were excluded. In total, 19 studies were included in the final analysis, and 14 papers met all requirements previously defined.

Keywords: cognition; physical exercise; older adults

1. Introduction

The relationship between physical and cognitive performance changes is not yet fully understood [1]. The aging process diminishes the ability to learn new information, as well as preserve more established knowledge [2]. Recently, an attempt was made to understand changes between cognitive and physical status [3]. Physical and mental dysfunction represent two of the most feared states among older adults because they can lead to physical dependence and social isolation [4]. However, the relationship between several cognition abilities and performance-based measures of physical functioning has seldom been analysed. Thus, the link between cognition and improvement of physical conditions still needs to be explored [5].

Cognitive decline is a negative outcome associated with aging [6]. Indeed, cognition includes all processes through which a person becomes aware of their situation, needs, goals, and necessary actions, using this information to implement problem-solving strategies [7]. The different brain capacities and the respective aspects of cognition allow us to interact with others and the world [8]. When a progressive cognitive incapacity sets in, it translates into the collapse of our identity that distinguishes us as rational thinking individuals [9]. Several studies related to cognition focus on sustained attention, response inhibition, information processing speed, cognitive flexibility and control, simultaneous multiple attention, working memory, category formation, and pattern recognition [10].

Executive functions (EFs), the most important of the cognitive skills, are a set of mental skills that include working memory, flexible thinking, and self-control. These are skills that are used all the time in our daily lives to learn, work, and manage daily life [11]. Problems in EFs can make it difficult to focus, follow directions, and switch emotions, among other things [12]. The core EFs are known as response inhibition (self-control) and interference control (problems solving, creative adaptation, and working memory) [11].

Several rating scales have been developed to assess executive functions, both in general and specific functions. Some of these functions are included in scales that assess cognition's global dimension [13]. To assess global cognition, we use the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) [10]. The MMSE can assess Spatio-temporal, orientation, retention, attention and calculation, language semantics, comprehension, and constructive ability. The MoCA assesses executive function, visuospatial ability, working memory, attention, and concentration, as well as language and orientation [14].

Age-related neurodegenerative disorders increased over the past ten years because of an aging population [15]. The major factorial causes are genetic predispositions, environmental triggers, and endogenous variables [16]. The beginning and progression of neurodegenerative disorders are correlated with nutritional inadequacies, hypertension, diabetes, hypercholesterolemia, obesity, and inflammation [17]. There is still no definitive treatment that can cure or reverse the deterioration of cognitive function, such as Alzheimer's disease (AD), Parkinson's disease (PD), or Mild Cognitive Impairment (MCI) [18]. Currently, two possibilities to prevent these diseases exist, non-pharmacological treatment or pharmacological conduct (drugs) [19].

Brain function in some conditions is directly compromised, affecting neuromotor areas related to large muscle groups [20]. Non-pharmacological interventions, such as physical exercise alone or multifactorial programmes, have attenuated cognitive decline and improved behavioural disorders in patients [21]. The multicomponent exercise program (MEP) that involves stretching-balance, aerobic conditioning, neuromotor stimulation, or a combination of the two [22], may be related to this process and has been shown to improve various cognitive processes, including memory, reasoning speed, and problem-solving skills [23,24].

The MEP practice can be classified as adjuvant therapy, which benefits patients with neurodegenerative disorders [25]. Aerobic training in older people improved cognitive functioning, especially in executive functions [26]. Several studies highlighted a significant improvement in global cognitive functions with the practice of regular MPE in individuals with mild cognitive decline or dementia [27]. On the other hand, other studies present unsatisfactory results and claim that the intervention time or program characteristics can be changed to seek more consistent and promising results [28].

Solid evidence has demonstrated the neuroprotective effects of exercise over the last decade. Regular physical exercise has been proposed as one of the most effective lifestyle interventions for both healthy aging and patients suffering from neurodegenerative disorders such as AD, PD, or MCI [29]. Furthermore, physical exercise appears to be an "entity" capable of mitigating some cognitive losses in people suffering from neurodegenerative disorders [30].

In terms of molecular and cellular processes, exercise can induce a cascade that promotes angiogenesis, neurogenesis, and brain synaptogenesis [31]. Aerobic exercise effectively increases the brain-derived neurotrophic factor (BDNF) in older populations [32], which may explain the improvement in various cognitive abilities. Furthermore, cognitive functions sensitive to early dementia and age-related cognitive declines, such as memory, executive functions, and processing reaction times, have been shown to respond and be liable to the effects of exercise in PD patients [33].

This review will look at how long-term MEP interventions affect cognitive abilities in older adults with neurodegenerative disorders. In addition, we look at MEP used as non-pharmacological therapy to mitigate, delay, and reverse the impairment of cognitive disorders. Furthermore, we aimed to identify the most recent studies that bring the best innovative practices and consistent results in MEP long-term exercise programs.

2. Materials and Methods

This research followed a pre-determined Systematic Review (SR) procedure, registered in the PROSPERO database under CRD42022309712. The guidelines to stratify, analyse, and select the scientific publications used in this SR follow the Preferred Reporting Items for Systematic Reviews (PRISMA) [34].

2.1. Research Procedures/Strategies

Two independent reviewers conducted reproducible scientific literature research in the following online databases: The Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS, B-On, Sport Discus, Scielo, APA PsycINFO, Psychology and Behavioural Sciences, Academic Search Complete, Medline (PubMed), ERIC, and Google Scholar. The search occurred between April 2022 and July 2022. Original papers that contained relevant data regarding exercise's effect on cognitive abilities in older adults with neurodegenerative disorders were primarily selected in English. To improve the search in the selected databases, we used the combination of the descriptors indexed in the Medical Subjects Headings [35]. Studies conducted in the last 10 years, with the abstract/full text available, that involved older adult participants of more than 65 years of both genders were included.

2.2. Study Selection Criteria

Published papers on multicomponent exercise interventions evaluating the long- and medium-term effects on cognitive abilities were primarily included. Physical exercise programs that were not explicitly stated as fully supervised were excluded. Older participants in the included studies had to have a clinical outcome of one of the three major neurodegenerative disorders (Alzheimer's, Parkinson's, and Mild Cognitive Impairment) or other neurodegenerative disorders that are encompassed by the concept [36]. Notwithstanding the use of the PRISMA flowchart and its respective phases (identification, screening, included) [37], the steps used for the final selection of the articles in this SR were: (i) One or more keywords must be present in the title or abstract; (ii) initial selection carried out through the title/abstract; and (iii) reading the full text to final selection. The following MESH descriptors, considering the pilot meta-search on PubMed, were used:

(((("physical exercise"[All Fields]) OR ("exercise 1"[All Fields] OR "exercise"[All Fields])) OR (multicomponent)) OR ("cognitive abilities"[All Fields])) OR ("cognition"[All Fields])) AND ("neurodegenerative diseases"[All Fields])

Following this initial search, the key terms were used in the remaining databases, considering their entry specificities. The exclusion criteria adopted for this study were (i) the elimination of all systematic reviews articles; (ii) exclusion of opinion articles, letters to editors, study protocol papers, master's dissertations, doctoral theses, and final course works; (iii) exclusion of articles whose participants were not classified as older adults; and (iv) papers that report short-term exercise interventions.

2.3. Main Concepts

We assume that particular concepts must be provided clearly and directly to clarify the specific goals of our SR study. In this perspective, we leave the significance in the following lines.

2.4. Data Extraction

The Table 1 shows the initial research for the preparation of this SR study was carried out by two researchers independently, following the final criterion for the selection of articles, whose definition was based on the methodology already partly described. Any report that raised doubts was discussed among the specialists to decide the inclusion or exclusion, considering the pre-established selection criteria.

Table 1. Central concepts that guided the SR.

| Key-Terms | Concepts |
|------------------------------------|---|
| Cognition | Involves the entire process through which a person becomes aware of their situation, requirements, goals, and required activities, and then applies this knowledge to problem-solving tactics in everyday life [38] |
| Cognitive abilities | The concept of skill can be broadly defined as a method of action and generalized strategy for coping with situations and difficulties. These can be of various types, and the conceptual field to solve the problem is not uniform. Cognitive talents are the abilities that enable an individual to be competent and engage symbolically with his environment [39]. |
| Neurocognitive disorders | It is characterized as a group of conditions frequently leading to impaired brain functioning due to a medical disease other than a psychiatric illness. It is often used synonymously (but incorrectly) with dementia [40]. |
| Older adults | According to the World Health Organization, the older are defined as people who are 60 years or older in developing nations and 65 years or older in industrialized countries [41]. |
| Physical Exercise | Comprises all the conscious, systematic, and planned practice of physical activity, performed with a specific objective (e.g., to improve health) and well delineates the time of practice, duration, intensity, and type. It can be performed with or without a prescription [42]. |
| MulticomponentExercise | It is a type of physical exercise intervention designed to improve muscle strength, balance, and walking retraining, respecting a set of exercises conducted usually in the same session [43]. |
| Long-term (exercise) interventions | Considering the recent scientific literature, we assume that long-term interventions (with physical exercise) have 24 weeks (6 months) or more since the definition is still not wholly clear [44]. |

2.5. Method of Analysis of Results

After the search and final selection of the articles, a qualitative analysis of the discussion and presentation of the results was performed considering the impact of the exercise on the different areas of cognition described in detail in the subtopic “operationalization of concepts” and previously defined by the authors of this proposal.

2.6. Quality of Information

The guidelines of PRISMA positioning were followed to assist in the methodological design of this study [45]. These guidelines circumscribe the four phases (identification, screening, eligibility, and final selection) to be covered to conduct research and the selection of articles, with a graphical option for the elaboration of a flowchart [46]. It presents the acronym PICOS (patient, problem, or population; intervention; comparison or control; outcomes; and study design), which directs the refinement of the systematic search, making the process more efficient [45].

3. Results

3.1. Study Selection

Figure 1 shows the PRISMA flow diagram of the systematic search and study selection. The initial search using the previously selected key terms yielded 6835 studies. After excluding duplicates and studies that did not meet the general inclusion criteria, 6474 studies remained in the screening phase. In the next step of screening, a total of 34 studies were excluded. This stage was analysed by co-authors, and 200 did not meet the specific final criteria and were excluded. In total, 19 studies were included in the final analysis, and five papers did not meet the criteria previously defined. A total of 14 studies were identified.

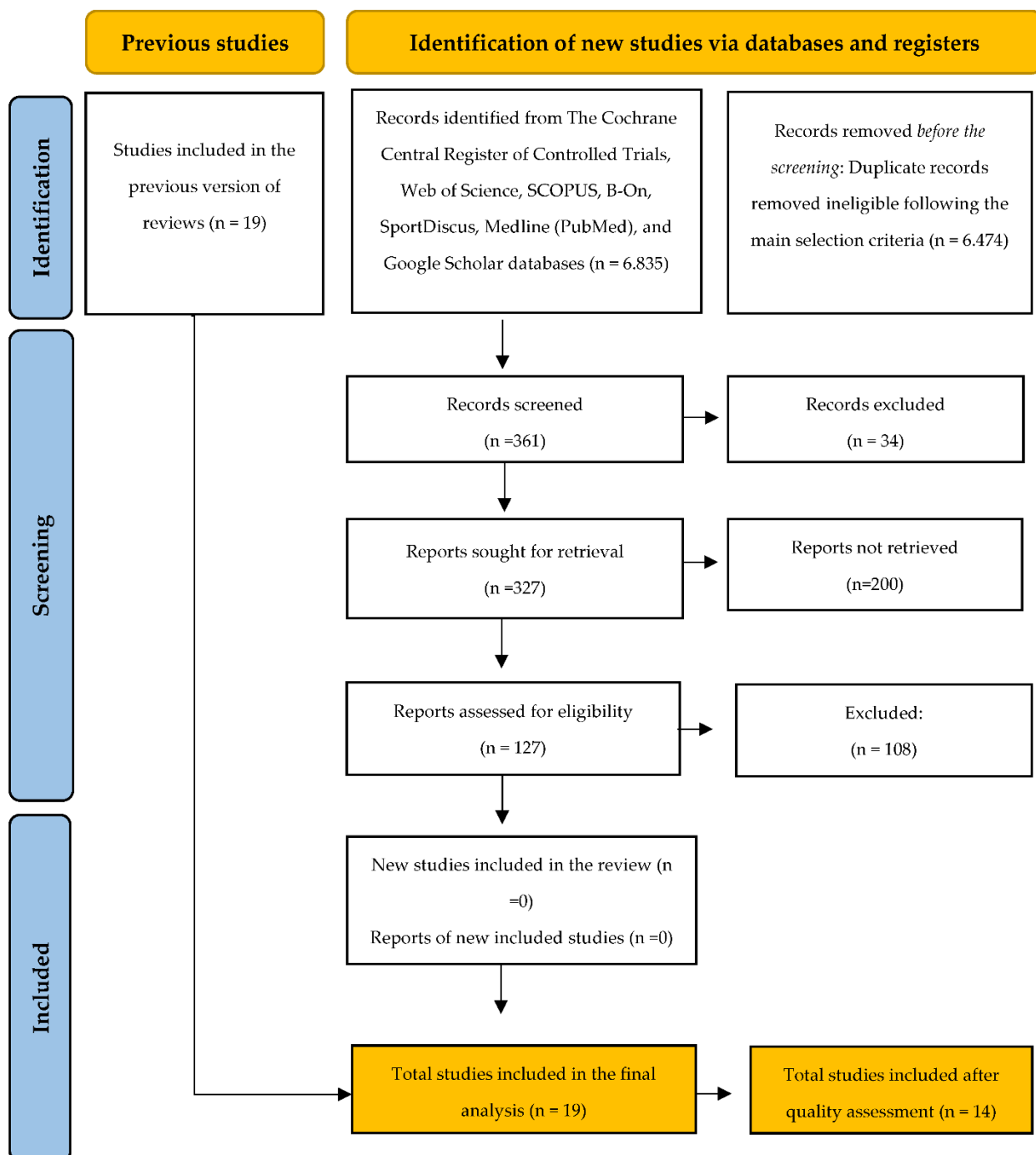


Figure 1. PRISMA of each stage of the study selection.

3.2. General Characteristics of Studies

Table 2 shows the general characteristics of all included studies according to the PICOS statement. The 14 studies incorporated in this SR included 1432 participants (Table 2). Of these studies, two were performed in subjects with AD (n = 301) [47–49], three studies were carried out with PD (n = 269) patients [50–52], and nine studies involved older adults with MCI (n = 862), [53–59]. The duration of the MEP intervention varied from 24 weeks [48] to 40 weeks [49]. Interventions targeting the comparison or control group varied in content and format. A total of two studies used a control group without an intervention [48]. Other interventions included a social intervention [47], Irish dance [51], functional mobility and mental leisure activities [50], and a home-based education intervention [49]. Considering this type of exercise, all selected studies presented a multicomponent intervention that met the initial criteria.

Table 2. Presentation of the study target following the acronym PICOS.

| | |
|---|---|
| P | Older adults with neurodegenerative disorders |
| I | Group class, supervised, and long-term MEP. |
| C | No contact, attention control, sham (placebo) physical exercise, or alternative active management |
| O | Any validated neuropsychological cognition test was used to assess at least one cognition abilities outcome measured at baseline and follow-up. |
| S | Randomized controlled trials |

3.3. Cognitive Performance Assessments

An assessment of the global cognitive profile was carried out in five studies, using the Mini-Mental State Exam [47–51], and one study used the Clinical Dementia Rating Test [49]. Other tests related to the assessment of cognitive skills included the Clock Design Test (spatial dysfunction and neglect) [49] and the Verbal Fluency Test (executive functioning and language ability) [42]. Other assessments, namely in studies with AD, assessed neuromotor areas such as the Unified Parkinson’s Disease Rating Scale, and the Hoehn and Yahr Stage scale [50] that assesses neuromotor performance related to PD. The PDQ-39 assesses the quality of life of Parkinson’s disease patients, and despite being a self-completion questionnaire, some questions assess cognition abilities [51]. The studies including MCI participants used the MMSE [53–55,58–61], Montreal Cognitive Assessment (MoCA) [55,62], Chinese version Mini-Physical Performance Test [55], and Gerontology-Functional Assessment Tool [56].

3.4. Multicomponent Interventions Effects

Table 3 shows the results of the studies found. Only one study comprising community-dwelling AD participants (n = 301) had statistically significant results in cognitive performance after the MEP intervention [49]. In another study involving AD patients, the authors did not show satisfactory results in the cognitive skills after MEP, despite the effects on the other variables analysed (improvement in activities of daily living and physical function) [47].

In studies involving PDs, they also did not find satisfactory results; however, the authors left interesting clues for future studies. In the first study, the authors suggest that task specificity may be a mediating factor in the progression of cognitive dysfunction; however, after MPE, patients did not present specific results in cognitive aspects [50]. In the second and third studies, the authors also did not promise results in the cognitive dimension assessments [51], although both programs registered great adherence of the participants [52].

Table 3. Characterization of the studies included in the review, according to PICOS statement.

| Authors | Population | Characteristics of MET Intervention | Comparison | Outcomes | Main Results |
|---|------------|-------------------------------------|---|--|--|
| <i>Alzheimer's disease</i> | | | | | |
| de Souto Barreto et al. (2017) [47] France | (n = 91) | Twice a week, for 24 weeks | Social intervention | MMSE | No improvements in cognitive performance |
| Öhman et al. (2016) [49] Finland | (n = 210) | Twice a week for 1 year | Home-based health literacy intervention | Clock Design Test, Verbal Fluency, Clinical Dementia rating test, and MMSE | Modest effects on executive function |
| <i>Parkinson's disease</i> | | | | | |
| Gobbi et al. (2021) [32] Brazil | (n = 107) | Twice a week, for 32 weeks | Functional Mobility Mental/Leisure | MMSE, Hoehn and Yahr Stage scale, UPDRS, Baecke Questionnaire. | A short delay in the decline of global cognitive function |
| Volpe et al. (2013) [51] Italy | (n = 24) | Once a week for 24 weeks. | Irish set dancing | MMSE and PQD—39. | Improvements in neuromotor tasks related to balance and motor disability |
| Mavrommatiet al. (2017) [63] United Kingdom | (n = 138) | Twice a week for 24 weeks | Control group(non-exercise) | UPDRS | No improvements in cognitive performance |
| <i>Mild Cognitive impairment</i> | | | | | |
| Makizako et al. (2012) [60] Japan | (n = 50) | Twice a week for 24 weeks | Control group (non-exercise) | MMSE | No significant difference in the MMSE score. |
| Suzuki et al. (2013) Japan [53] | (n = 100) | Twice a week for 24 weeks | Control group (non-exercise) | MMSE and Alzheimer's Disease Assessment Scale | No improvements in cognitive performance |
| Doi et al. (2013) Japan [61] | (n = 50) | Twice a week for 24 weeks | Control group (non-exercise) | MMSE | No significant difference in the MMSE score. |
| Tarazona-Santabalbina et al. (2016) Spain [54] | (n = 100) | Five days per week for 24 weeks | Control group (non-exercise) | MMSE | Increase in the global cognition |

Table 3. Cont.

| Authors | Population | Characteristics of MET Intervention | Comparison | Outcomes | Main Results |
|--------------------------------------|--------------|-------------------------------------|---|--|--|
| Li et al. (2021) China [55] | (n = 84) | 5 times a week for 24 weeks | The Control group received regular educational health instruction | MMSE, MoCA, CM-PPT; Mini-Physical Performance Test | No improvements in cognitive performance |
| Bae et al. (2020) Japan [56] | (n = 280) | Once a week 40 weeks | Control group (non-exercise) | Gerontology-Functional Assessment Tool (NCGG-FAT) | No improvements in cognitive performance |
| Yang et al. (2021) China [62] | (n = 112) | Twice a week for 24 weeks | Control group (non-exercise) | MoCA | No improvements in global cognitive performance |
| Murukesu et al. (2020) Malaysia [58] | (n = 42) | Twice a week for 24 weeks | Control group (non-exercise) | MMSE | No improvements in global cognitive performance |
| Uemura et al. 2013 (Japan) [59] | MCI (n = 44) | Twice a week for 24 weeks | Pre and post-physical exercise program | MMSE, Trail Making Test Part B, | No improvements in global cognitive performance. |

Notes: MET = Multicomponent exercise training; PQD-39 = Parkinson Disease Q questionnaire; MMSE = Mini-Mental State Exam; GDS = Geriatric Depressive Scale; CM-PPT Chinese version Mini-Physical Performance Test; NCGG-FAT Gerontology-Functional Assessment Tool; UPDRS = Unified Parkinson's disease rating scale (UPDRS).

The researchers involving MCI patients [53,55,56,58–62] reported no significant differences related to cognitive assessments, except in one study where the authors found significant results in global cognition [54].

On the other hand, all studies showed satisfactory responses in components of functional physical fitness related to diseases [47,49–56,58–62]. Although some studies do not point to good results for the performance indicators of cognitive performance, some of them recommend that longer trials are required to determine whether physical exercise has more significant health and cognitive benefits [47,48].

3.5. Short Description of Excluded Studies

Out of 127 records screened, the full text of 19 studies was examined, and 4 of these studies were excluded because they did not meet all the inclusion criteria for the review (see Table 4). Despite fulfilling all other requirements, two studies provided an aquatic variation of the multi-component training [64,65]. Two other studies that evaluated the effect of exercise on ALS patients were excluded because the psychometric tools used in the study did not evaluate one or more cognitive abilities [66,67]. However, one study that met the above criteria investigated the effects of MEP in the elderly with MCI [60,68].

Table 4. Characterization of the excluded studies.

| Authors | Population | Characteristics of MET Intervention | Comparison | Outcomes | Outcomes/Main Results |
|----------------------------------|--|--|------------------------------|---------------------------------|---|
| Ferri et al. 2019 [67] (Italy) | Amyotrophic lateral sclerosis (n = 11) | 12 weeks 3 times a week | The Usual Care control group | UPDRS, ALSFRS-R | Tailored moderate-intensity exercise is not detrimental for patients with ALS and can counteract muscle disuse. |
| Kalron et al. 2021 [66] (Israel) | Amyotrophic lateral sclerosis (n = 32) | Twice a week for 12 weeks | Flexibility training group | ALSFRS-R | The ALSFRS-R is in favour of the aerobic-strength group. Exercise is far superior to flexibility and well-being in ambulatory ALS patients. |
| Siega et al. 2021 [65] (Brazil) | Parkinson disease (n = 22) | MET aquatic twice a week for 12 weeks | Control group (non-exercise) | UPDRS | Exercise program was capable increasing UPDRS scores |
| Siega et al. 2022 [64] (Brazil) | Adults with Parkinson | Multicomponent aquatic training 12 weeks, twice a week | Control group (non-exercise) | Parkinson Disease Questionnaire | Exercise program provides positive results in terms of controlling the progress of PD symptoms with the parameters assessed. |

Notes: MMSE = Mini-Mental State Exam; ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; UPDRS = Unified Parkinson's disease rating scale.

4. Discussion

This study aimed to verify the impact of physical exercise on the different areas of cognitive performance in older adults with neurodegenerative disorders. After a systematic search of studies conducted over the last 10 years, our SR identified only 14 trials of long-term MEP training for three major negative cognitive outcomes (AD, PD, and MCI), half of which were RCTs of moderate quality with significant heterogeneity. Indeed, the number of articles chosen according to the previously established criteria, with a primary focus on long-term exercise programs, influenced the results. Despite these limitations, the systematic search yielded some interesting results, as well as other issues that could be discussed in light of the prospects.

In general, the results revealed that global cognition assessments (i.e., MMSE and MoCA) were the most used to assess “cognitive abilities”, regardless of the characteristics of the study participants of all cognitive disorders. In contrast to the study that used

the global assessment of cognition [47], one of the two studies involving AD participants found satisfactory results in other cognitive skills [49]. Different outcomes were exposed in the three studies involving people with PD. A short delay in the decline of global cognitive function after 32 weeks of the MEP was found in the first study [50]. The authors of the second study exposed that there were improvements in neuromotor functions affected by PD [51]. In contrast, the third study with PD participants found no significant improvements in cognitive abilities following MEP [52]. Except for the study conducted in Spain [54], all authors reported no significant improvements in the screening of cognitive abilities after MEP in the nine studies involving participants with MCI [53–56,58–62]. The presentation of global cognition results does not allow for the verification of whether or not specific functions (e.g., executive function, numerical memory) improved after exercise. Although the MMSE is widely used and evaluates various aspects of cognition, it was not designed to present the results in a fragmented manner [69]. In one of the studies included in the review, which included AD patients [49], a significant improvement in executive function was found, and in this study, the authors used different tests to assess each cognitive ability separately.

Although the relationship between MPE and cognitive functions is unclear, previous reviews indicated that MPE is shown to improve cognition in older adults with cognitive disorders such as dementia and MCI [70]. However, some authors claim that MEP combined with a significant amount of continuous aerobic exercise is the most promising type of exercise [71]. Most studies support a substantial impact of aerobic training in the different areas of cognitive abilities in older adults [72]. In the studies involving patients with MCI undergoing a long-term aerobic exercise program, changes in brain plasticity (e.g., neurochemical, neuroplasticity, and neuro-structural modifications) were verified [72].

The authors hypothesized that the complex biochemical cascades are responsible for the formation of new vascular and neural structures in the brain, and the Brain-Derived Neurotrophic Factor (BDNF) plays an important role in the maintenance of synaptic plasticity in learning and memory [73]. Furthermore, BDNF plays a vital role in facilitating nerve growth and maturation through the developmental stages and the regulation of synaptic transmission and flexibility in adulthood. In this sense, it is clear that BDNF levels change in patients with cognitive disorders, especially PD and AD patients [74]. Aerobic exercise improves synaptic plasticity, new cell survival, neuronal differentiation, and neurogenesis. Moreover, exercise induces a beneficial effect on memory via decreasing inflammation, and combined with BDNF expression modulation [75]. In summary, the literature showed that even if deteriorated by the effect of some syndromes or diseases, some functions can be (re)activated through the action of regular exercise [26].

Some authors also claim that the MEP's greatest challenge is quantifying the components used to prepare the program, which may follow the ACSM's recommendations (aerobic, muscle strength, and balance) [43] or may include some variations involving different volumes, intensities, and other types of exercises [68,73]. However, the results of the present SR showed that, in general, the MEP had a positive impact on all functional fitness variables studied [47,49–56,58–62]. Some cognitive abilities (and their respective areas) related to exercise, for example, may not be affected in MCI patients [74]. On the other hand, regular exercise promotes improvements, whereas detraining periods promote fast regression in physical-functional fitness [75].

Neurocognitive diseases such as PD and AD are characterized by a loss of neuromotor functions, resulting in a decline in movement of "course" and mobility tasks such as walking and picking up objects, among other movements [75]. In the case of MCI, the outcomes may be following a similar pathway, but some brain areas responsible for motor activity may be preserved [76]. However, as with older patients with MCI, when the exercise program is interrupted, it causes rapid deterioration of neuromotor functions in AD and PD patients [76].

In this review, some limitations were observed, such as the number of articles, due to the quality criteria and inclusion standards chosen in this review, thus contributing to the

small number of studies analysed. These studies should have larger sample sizes, random allocation, and blinded assessments. Preferably, they should focus separately on patients with mild, moderate, and severe dementia to evaluate whether all stages benefit from regular exercise. The solution for future research involves valid tests that assess different cognitive abilities separately, because some cognitive abilities appear to be more sensitive to the effects of regular exercise. Despite the paucity of evidence on MEP's effects, the contrast with the recent state of the art leads us to believe that this type of exercise program should include a significant component of continuous aerobic exercise.

5. Conclusions

However, the results of long-term MEP interventions among participants with MCI, AD, and PD are inconsistent. For this reason, further studies are required to determine the effect of physical exercise on cognition. Analysing the results of each study, we conclude that the impact of MEP on the overall assessment of cognition and working memory has poor effects. However, as studies in this specific area of intervention and characteristics are still small, further studies and further research will be needed to try to understand whether the positive effect of the impact of MEP extends to other cognitive abilities.

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References

1. Tolea, M.I.; Morris, J.C.; Galvin, J.E. Longitudinal Associations between Physical and Cognitive Performance among Community-Dwelling Older Adults. *PLoS ONE* **2015**, *10*, e0122878. [[CrossRef](#)] [[PubMed](#)]
2. Murman, D.L. The Impact of Age on Cognition. *Semin. Heart* **2015**, *36*, 111–121. [[CrossRef](#)] [[PubMed](#)]
3. Fechine, B.; Vasconcelos, O.; Botelho, M.; Trompieri, N.; Carvalho, J. Memória, exercício físico e envelhecimento: Um estudo sobre a relação existente entre a memória visuomotora e idosos praticantes e não praticantes de atividade física. *InterScience Place* **2013**, *1*, 170–192. [[CrossRef](#)]
4. Maffei, L.; Picano, E.; Andreassi, M.G.; Angelucci, A.; Baldacci, F.; Baroncelli, L.; Begenisic, T.; Bellinvia, P.F.; Berardi, N.; Biagi, L.; et al. Randomized trial on the effects of a combined physical/cognitive training in aged MCI subjects: The Train the Brain study. *Sci. Rep.* **2017**, *7*, 39471.
5. Schure, M.B.; Borson, S.; Nguyen, H.Q.; Trittschuh, E.H.; Thielke, S.M.; Pike, K.C.; Adams, S.G.; Fan, V.S. Associations of cognition with physical functioning and health-related quality of life among COPD patients. *Respir. Med.* **2016**, *114*, 46–52. [[CrossRef](#)]
6. Klimova, B.; Valis, M.; Kuca, K. Cognitive decline in normal aging and its prevention: A review on non-pharmacological lifestyle strategies. *Clin. Interv. Aging* **2017**, *ume 12*, 903–910. [[CrossRef](#)]
7. Borson, S. Cognition, Aging, and Disabilities: Conceptual Issues. *Phys. Med. Rehabil. Clin. North Am.* **2010**, *21*, 375–382. [[CrossRef](#)]
8. Raichlen, D.A.; Alexander, G.E. Adaptive Capacity: An Evolutionary Neuroscience Model Linking Exercise, Cognition, and Brain Health. *Trends Neurosci.* **2017**, *40*, 408–421. [[CrossRef](#)]
9. Cieza, A.; Sabariego, C.; Bickenbach, J.; Chatterji, S. Rethinking Disability. *BMC Med.* **2018**, *16*, 14. [[CrossRef](#)]
10. Uehara, E.; Fichman, H.; Landeira-Fernandez, J. Funções executivas: Um retrato integrativo dos principais modelos e teorias desse conceito / Executive functions? An integrative portrait of the main models and theories of this concept. *Rev. Neuropsicol. Latinoam.* **2013**, *5*, 25–37.
11. Diamond, A. Executive functions. *Annu. Rev. Psychol.* **2013**, *64*, 135–168. [[CrossRef](#)] [[PubMed](#)]
12. Blader, J. Review of Executive Functions: What They Are, How They Work, and Why They Evolved, by Russell A. Barkley. *J. Child Adolesc. Psychopharmacol.* **2014**, *24*, 362–363. [[CrossRef](#)]

13. Lu, W.; Chen, G.; Li, W. RETRACTED ARTICLE: Melanin-based biomimic photothermal nanoparticles for therapeutic application in diabetic nephropathy. *J. Drug Target.* **2021**, *29*, i–viii. [[CrossRef](#)] [[PubMed](#)]
14. Hobson, J. The Montreal Cognitive Assessment (MoCA). *Occup. Med.* **2015**, *65*, 764–765. [[CrossRef](#)]
15. Erkkinen, M.G.; Kim, M.-O.; Geschwind, M.D. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases. *Cold Spring Harb. Perspect. Biol.* **2017**, *10*, a033118. [[CrossRef](#)]
16. Von Bernhardi, R.; Eugenin-von Bernhardi, L.; Eugenin, J. Microglial cell dysregulation in Brain Aging and Neurodegeneration. *Front. Aging Neurosci.* **2015**, *7*, 124. [[CrossRef](#)] [[PubMed](#)]
17. Anjum, I.; Fayyaz, M.; Wajid, A.; Sohail, W.; Ali, A. Does Obesity Increase the Risk of Dementia: A Literature Review. *Cureus* **2018**, *10*, e2660. [[CrossRef](#)]
18. Sun, C.; Armstrong, M. Treatment of Parkinson’s Disease with Cognitive Impairment: Current Approaches and Future Directions. *Behav. Sci.* **2021**, *11*, 54. [[CrossRef](#)]
19. Weller, J.; Budson, A. Current understanding of Alzheimer’s disease diagnosis and treatment [version 1; peer review: 2 approved]. *F1000Research* **2018**, *7*, 1161. [[CrossRef](#)]
20. Orsini, M.; Ferreira, A.C.A.D.F.; De Assis, A.C.D.; Magalhães, T.; Teixeira, S.; Bastos, V.H.; Marinho, V.; Oliveira, T.; Fiorelli, R.; Oliveira, A.B.; et al. Cognitive Impairment in Neuromuscular Diseases: A Systematic Review. *Neurol. Int.* **2018**, *10*, 3–12. [[CrossRef](#)]
21. Mendonça, D.C.B.; Fernandes, D.R.; Hernandez, S.S.; Soares, F.D.G.; de Figueiredo, K.; Coelho, F.G.D.M. Physical exercise is effective for neuropsychiatric symptoms in Alzheimer’s disease: A systematic review. *Arq. De Neuro-Psiquiatr.* **2021**, *79*, 447–456. [[CrossRef](#)] [[PubMed](#)]
22. Amaro-Gahete, F.J.; De-La-O, A.; Jurado-Fasoli, L.; Espuch-Oliver, A.; Robles-Gonzalez, L.; Navarro-Lomas, G.; de Haro, T.; Femia, P.; Castillo, M.J.; Gutierrez, A. Exercise training as S-Klotho protein stimulator in sedentary healthy adults: Rationale, design, and methodology. *Contemp. Clin. Trials Commun.* **2018**, *11*, 10–19. [[CrossRef](#)]
23. Kirk-Sanchez, N.J.; McGough, E.L. Physical exercise and cognitive performance in the elderly: Current perspectives. *Clin. Interv. Aging* **2014**, *9*, 51–62. [[CrossRef](#)] [[PubMed](#)]
24. Yu, F.; Lin, F.V.; Salisbury, D.L.; Shah, K.N.; Chow, L.; Vock, D.; Nelson, N.W.; Porsteinsson, A.; Jack, C. Efficacy and mechanisms of combined aerobic exercise and cognitive training in mild cognitive impairment: Study protocol of the ACT trial. *Trials* **2018**, *19*, 700. [[CrossRef](#)] [[PubMed](#)]
25. Luan, X.; Tian, X.; Zhang, H.; Huang, R.; Li, N.; Chen, P.; Wang, R. Exercise as a prescription for patients with various diseases. *J. Sport Health Sci.* **2019**, *8*, 422–441. [[CrossRef](#)] [[PubMed](#)]
26. Kramer, A.F.; Colcombe, S. Fitness Effects on the Cognitive Function of Older Adults: A Meta-Analytic Study—Revisited. *Perspect. Psychol. Sci.* **2018**, *13*, 213–217. [[CrossRef](#)]
27. Heyn, P.; Abreu, B.C.; Ottenbacher, K.J. The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. *Arch. Phys. Med. Rehabil.* **2004**, *85*, 1694–1704. [[CrossRef](#)]
28. Haeger, A.; Costa, A.S.; Romanzetti, S.; Kilders, A.; Trautwein, C.; Haberl, L.; Beulertz, M.; Hildebrand, F.; Schulz, J.B.; Reetz, K. Effect of a multicomponent exercise intervention on brain metabolism: A randomized controlled trial on Alzheimer’s pathology (Dementia-MOVE). *Alzheimer’s Dement. Transl. Res. Clin. Interv.* **2020**, *6*. [[CrossRef](#)]
29. Vecchio, L.M.; Meng, Y.; Xhima, K.; Lipsman, N.; Hamani, C.; Aubert, I. The Neuroprotective Effects of Exercise: Maintaining a Healthy Brain Throughout Aging. *Brain Plast.* **2018**, *4*, 17–52. [[CrossRef](#)]
30. Esnigdh, S.; Rivera, C.E.; Milgram, N.W.; Cotman, C.W. Exercise enhances memory consolidation in the aging brain. *Front. Aging Neurosci.* **2014**, *6*, 3. [[CrossRef](#)]
31. Gomez-Pinilla, F.; Hillman, C. The Influence of Exercise on Cognitive Abilities. *Compr. Physiol.* **2013**, *3*, 403–428. [[CrossRef](#)] [[PubMed](#)]
32. Frederiksen, K.S.; Gjerum, L.; Waldemar, G.; Hasselbalch, S.G. Effects of Physical Exercise on Alzheimer’s Disease Biomarkers: A Systematic Review of Intervention Studies. *J. Alzheimer’s Dis.* **2018**, *61*, 359–372. [[CrossRef](#)] [[PubMed](#)]
33. Mudò, G.; Mäkelä, J.; Di Liberto, V.; Tselykh, T.V.; Olivieri, M.; Piepponen, P.; Eriksson, O.; Mälkiä, A.; Bonomo, A.; Kairisalo, M.; et al. Transgenic expression and activation of PGC-1 α protect dopaminergic neurons in the MPTP mouse model of Parkinson’s disease. *Cell. Mol. Life Sci.* **2012**, *69*, 1153–1165. [[CrossRef](#)] [[PubMed](#)]
34. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [[CrossRef](#)]
35. Huang, M.; Névéol, A.; Lu, Z. Recommending MeSH terms for annotating biomedical articles. *J. Am. Med. Inform. Assoc.* **2011**, *18*, 660–667. [[CrossRef](#)]
36. Mulasso, A.; Roppolo, M.; Rainoldi, A.; Rabaglietti, E. Effects of a Multicomponent Exercise Program on Prevalence and Severity of the Frailty Syndrome in a Sample of Italian Community-Dwelling Older Adults. *Healthcare* **2022**, *10*, 911. [[CrossRef](#)]
37. Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gotzsche, P.C.; Ioannidis, J.P.A.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions: Explanation and Elaboration. *BMJ* **2009**, *339*, b2700. [[CrossRef](#)]
38. Thomas, A.J.; O’Brien, J.T. Depression and cognition in older adults. *Curr. Opin. Psychiatry* **2008**, *21*, 8–13. [[CrossRef](#)]

39. Darling-Hammond, L.; Flook, L.; Cook-Harvey, C.; Barron, B.; Osher, D. Implications for educational practice of the science of learning and development. *Appl. Dev. Sci.* **2019**, *24*, 97–140. [[CrossRef](#)]
40. Hugo, J.; Ganguli, M. Dementia and cognitive impairment: Epidemiology, diagnosis, and treatment. *Clin. Geriatr. Med.* **2014**, *30*, 421–442. [[CrossRef](#)]
41. Awuah, R.B.; Aikins, A.D.-G.; Doodoo, F.N.-A.; Meeks, K.A.; Beune, E.J.; Klipstein-Grobusch, K.; Addo, J.; Smeeth, L.; Bahendeka, S.K.; Agyemang, C. Psychosocial stressors among Ghanaians in rural and urban Ghana and Ghanaian migrants in Europe. *J. Health Psychol.* **2020**. [[CrossRef](#)] [[PubMed](#)]
42. Lucini, D.; Pagani, M. Exercise Prescription to Foster Health and Well-Being: A Behavioral Approach to Transform Barriers into Opportunities. *Int. J. Environ. Res. Public Health* **2021**, *18*, 968. [[CrossRef](#)] [[PubMed](#)]
43. Baker, M.K.; Atlantis, E.; Singh, M.A.F. Multi-modal exercise programs for older adults. *Age Ageing* **2007**, *36*, 375–381. [[CrossRef](#)] [[PubMed](#)]
44. Ashton, R.; Tew, G.; Aning, J.J.; Gilbert, S.E.; Lewis, L.; Saxton, J.M. Effects of short-term, medium-term and long-term resistance exercise training on cardiometabolic health outcomes in adults: Systematic review with meta-analysis. *Br. J. Sport. Med.* **2018**, *54*, 341–348.
45. Panic, N.; Leoncini, E.; de Belvis, G.; Ricciardi, W.; Boccia, S. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS ONE* **2013**, *8*, e83138. [[CrossRef](#)]
46. de Souto Barreto, P.; Cesari, M.; Denormandie, P.; Armaingaud, D.; Vellas, B.; Rolland, Y. Exercise or Social Intervention for Nursing Home Residents with Dementia: A Pilot Randomized, Controlled Trial. *J. Am. Geriatr. Soc.* **2017**, *65*, E123–E129. [[CrossRef](#)]
47. de Oliveira Silva, F.; Ferreira, V.; Plácido, J.; Sant’anna, P.; Araújo, J.; Marinho, V.; Laks, J.; Deslandes, A.C. Three months of multimodal training contributes to mobility and executive function in elderly individuals with mild cognitive impairment, but not in those with Alzheimer’s disease: A randomized controlled trial. *Maturitas* **2019**, *126*, 28–33. [[CrossRef](#)]
48. Öhman, H.; Savikko, N.; Strandberg, T.E.; Kautiainen, H.; Raivio, M.M.; Laakkonen, M.L.; Tilvis, R.; Pitkälä, K.H. Effects of Exercise on Cognition: The Finnish Alzheimer Disease Exercise Trial: A Randomized, Controlled Trial. *J. Am. Geriatr. Soc.* **2016**, *64*, 731–738. [[CrossRef](#)]
49. Gobbi, L.T.B.; Pelicioni, P.H.S.; Lahr, J.; Lirani-Silva, E.; Teixeira-Arroyo, C.; Dos Santos, P.C.R. Effect of different types of exercises on psychological and cognitive features in people with Parkinson’s disease: A randomized controlled trial. *Ann. Phys. Rehabil. Med.* **2021**, *64*, 101407. [[CrossRef](#)]
50. Volpe, D.; Signorini, M.; Marchetto, A.; Lynch, T.; Morris, M.E. A comparison of Irish set dancing and exercises for people with Parkinson’s disease: A phase II feasibility study. *BMC Geriatr.* **2013**, *13*, 54–56. [[CrossRef](#)]
51. Mavrommati, F.; Collett, J.; Franssen, M.; Meaney, A.; Sexton, C.; Dennis-West, A.; Betts, J.F.; Izadi, H.; Bogdanovic, M.; Tims, M.; et al. Exercise response in Parkinson’s disease: Insights from a cross-sectional comparison with sedentary controls and a per-protocol analysis of a randomised controlled trial. *BMJ Open* **2017**, *7*, e017194. [[CrossRef](#)] [[PubMed](#)]
52. Suzuki, T.; Shimada, H.; Makizako, H.; Doi, T.; Yoshida, D.; Ito, K.; Shimokata, H.; Washimi, Y.; Endo, H.; Kato, T. A Randomized Controlled Trial of Multicomponent Exercise in Older Adults with Mild Cognitive Impairment. *PLoS ONE* **2013**, *8*, e61483. [[CrossRef](#)] [[PubMed](#)]
53. Tarazona-Santabalbina, F.J.; Gómez-Cabrera, M.C.; Pérez-Ros, P.; Martínez-Arnau, F.M.; Cabo, H.; Tsaparas, K.; Salvador-Pascual, A.; Rodríguez-Mañas, L.; Viña, J. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. *J. Am. Med. Dir. Assoc.* **2016**, *17*, 426–433. [[CrossRef](#)] [[PubMed](#)]
54. Li, L.; Liu, M.; Zeng, H.; Pan, L. Multi-component exercise training improves the physical and cognitive function of the elderly with mild cognitive impairment: A six-month randomized controlled trial. *Ann. Palliat. Med.* **2021**, *10*, 8919–8929. [[CrossRef](#)]
55. Bae, S.; Harada, K.; Lee, S.; Harada, K.; Makino, K.; Chiba, I.; Park, H.; Shimada, H. The Effect of a Multicomponent Dual-Task Exercise on Cortical Thickness in Older Adults with Cognitive Decline: A Randomized Controlled Trial. *J. Clin. Med.* **2020**, *9*, 1312. [[CrossRef](#)]
56. Sacks, D.; Baxter, B.; Campbell, B.C.V.; Carpenter, J.S.; Cognard, C.; Dippel, D.; Eesa, M.; Fischer, U.; Hausegger, K.; Hirsch, J.A.; et al. Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke. *Int. J. Stroke* **2018**, *13*, 612–632. [[CrossRef](#)]
57. Murukesu, R.R.; Singh, D.K.A.; Shahar, S.; Subramaniam, P. A Multi-Domain Intervention Protocol for the Potential Reversal of Cognitive Frailty: “WE-RISE” Randomized Controlled Trial. *Front. Public Health* **2020**, *8*. [[CrossRef](#)] [[PubMed](#)]
58. Uemura, K.; Shimada, H.; Makizako, H.; Doi, T.; Yoshida, D.; Tsutsumimoto, K.; Anan, Y.; Suzuki, T. Cognitive function affects trainability for physical performance in exercise intervention among older adults with mild cognitive impairment. *Clin. Interv. Aging* **2013**, *8*, 97–102. [[CrossRef](#)]
59. Makizako, H.; Shimada, H.; Yoshida, D.; Tsutsumimoto, K.; Uemura, K.; Suzuki, T. Does a multicomponent exercise program improve dual-task performance in amnesic mild cognitive impairment? A randomized controlled trial. *Aging Clin. Exp. Res.* **2012**, *24*, 640–646. [[CrossRef](#)]

60. Doi, T.; Makizako, H.; Shimada, H.; Yoshida, D.; Tsutsumimoto, K.; Sawa, R.; Misu, S.; Suzuki, T. Effects of multicomponent exercise on spatial–temporal gait parameters among the elderly with amnesic mild cognitive impairment (aMCI): Preliminary results from a randomized controlled trial (RCT). *Arch. Gerontol. Geriatr.* **2013**, *56*, 104–108. [[CrossRef](#)]
61. Yang, Q.-H.; Lyu, X.; Lin, Q.-R.; Wang, Z.-W.; Tang, L.; Zhao, Y.; Lyu, Q.-Y. Effects of a multicomponent intervention to slow mild cognitive impairment progression: A randomized controlled trial. *Int. J. Nurs. Stud.* **2021**, *125*, 104110. [[CrossRef](#)] [[PubMed](#)]
62. Siega, J.; Lucksch, D.D.; Israel, V.L. Multicomponent Aquatic Training (MAT) Program for People with Parkinson’s Disease: A Protocol for a Controlled Study. *Int. J. Environ. Res. Public Health* **2022**, *19*, 1727. [[CrossRef](#)] [[PubMed](#)]
63. Siega, J.; Lucksch, D.D.; Da Silva, A.Z.; Zotz, T.G.G.; Israel, V.L. Parkinson’s disease and multicomponent aquatic exercise: Effects on motor aspects, functional mobility, muscle function and aquatic motor skills. *J. Bodyw. Mov. Ther.* **2021**, *27*, 314–321. [[CrossRef](#)] [[PubMed](#)]
64. Kalron, A.; Mahameed, I.; Weiss, I.; Rosengarten, D.; Balmor, G.R.; Heching, M.; Kramer, M.R. Effects of a 12-week combined aerobic and strength training program in ambulatory patients with amyotrophic lateral sclerosis: A randomized controlled trial. *J. Neurol.* **2021**, *268*, 1857–1866. [[CrossRef](#)] [[PubMed](#)]
65. Ferri, A.; Lanfranconi, F.; Corna, G.; Bonazzi, R.; Marchese, S.; Magnoni, A.; Tremolizzo, L. Tailored Exercise Training Counteracts Muscle Disuse and Attenuates Reductions in Physical Function in Individuals With Amyotrophic Lateral Sclerosis. *Front. Physiol.* **2019**, *10*, 1537. [[CrossRef](#)] [[PubMed](#)]
66. Estrada-Orozco, K.; Bonilla-Vargas, K.; Cruz, F.; Mancera, O.; Ruiz, M.; Alvarez, L.; Pardo, R.; Arboleda, H. Cognitive Assessment Test: Validation of a Short Cognitive Test for the Detection of Mild Cognitive Disorder. *Int. J. Alzheimer’s Dis.* **2018**, *2018*, 3280621. [[CrossRef](#)]
67. Borges-Machado, F.; Silva, N.; Farinatti, P.; Poton, R.; Ribeiro, Ó.; Carvalho, J. Effectiveness of Multicomponent Exercise Interventions in Older Adults With Dementia: A Meta-Analysis. *Gerontologist* **2020**, *61*, e449–e462. [[CrossRef](#)]
68. Venegas-Sanabria, L.C.; Cavero-Redondo, I.; Martínez-Vizcaino, V.; Cano-Gutierrez, C.A.; Álvarez-Bueno, C. Effect of multicomponent exercise in cognitive impairment: A systematic review and meta-analysis. *BMC Geriatr.* **2022**, *22*, 617. [[CrossRef](#)]
69. Farhani, F.; Shahrbani, S.; Auais, M.; Hekmatikar, A.H.A.; Suzuki, K. Effects of Aerobic Training on Brain Plasticity in Patients with Mild Cognitive Impairment: A Systematic Review of Randomized Controlled Trials. *Brain Sci.* **2022**, *12*, 732. [[CrossRef](#)]
70. Girotra, P.; Behl, T.; Sehgal, A.; Singh, S.; Bungau, S. Investigation of the Molecular Role of Brain-Derived Neurotrophic Factor in Alzheimer’s Disease. *J. Mol. Neurosci.* **2021**, *72*, 173–186. [[CrossRef](#)]
71. Amidfar, M.; de Oliveira, J.; Kucharska, E.; Budni, J.; Kim, Y.-K. The role of CREB and BDNF in neurobiology and treatment of Alzheimer’s disease. *Life Sci.* **2020**, *257*, 118020. [[CrossRef](#)] [[PubMed](#)]
72. Ebrahimnejad, M.; Azizi, P.; Alipour, V.; Zarrindast, M.-R.; Vaseghi, S. Complicated Role of Exercise in Modulating Memory: A Discussion of the Mechanisms Involved. *Neurochem. Res.* **2022**, *47*, 1477–1490. [[CrossRef](#)]
73. Venegas-Sanabria, L.C.; Martínez-Vizcaino, V.; Cavero-Redondo, I.; Chavarro-Carvajal, D.A.; Cano-Gutierrez, C.A.; Álvarez-Bueno, C. Effect of physical activity on cognitive domains in dementia and mild cognitive impairment: Overview of systematic reviews and meta-analyses. *Aging Ment. Health* **2020**, *25*, 1977–1985. [[CrossRef](#)] [[PubMed](#)]
74. Chang, Y.-T. Physical Activity and Cognitive Function in Mild Cognitive Impairment. *ASN Neuro* **2020**, *12*. [[CrossRef](#)] [[PubMed](#)]
75. Biduski, G.M.; Bertoli, J.; Sousa, M.V.; Diefenthaler, F.; Freitas, C.D.L.R. Effects of 6-weeks of detraining on functional capacity and rapid torque production in older women. *J. Bodyw. Mov. Ther.* **2021**, *29*, 167–173. [[CrossRef](#)]
76. Ilardi, C.R.; Chieffi, S.; Iachini, T.; Iavarone, A. Neuropsychology of posteromedial parietal cortex and conversion factors from Mild Cognitive Impairment to Alzheimer’s disease: Systematic search and state-of-the-art review. *Aging Clin. Exp. Res.* **2021**, *34*, 289–307. [[CrossRef](#)]