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REVIEW ARTICLE

Effects of physical activities on dementia-related biomarkers: A systematic review of randomized controlled trials

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Abstract

Introduction: Physical activities (PA) may lead to improved cognition in mild cognitive impairment (MCI), Alzheimer's disease (AD), and dementia. The mechanisms mediating potential PA effects are unknown. Assessment of PA effects on relevant biomarkers may provide insights into mechanisms underlying potential PA effects on cognition.

Methods: We systematically reviewed randomized controlled trials (RCTs) that studied PA effects on biomarkers in MCI, AD, and dementia populations. We examined whether biological mechanisms were hypothesized to explain associations among PA, biomarkers, and cognitive functions. We used the PubMed database and searched for RCTs with PA until October 31, 2019.

Results: Of 653 studies examining changes in biomarkers in PA trials, 18 studies met inclusion criteria for the present review. Some studies found favorable effects of PA on neurotrophic and inflammatory biomarkers. AD pathological markers were rarely investigated, with inconclusive results. Most studies were relatively small in sample size, of limited duration, and not all studies compared the changes in biomarkers between the control and experimental groups.

Discussion: There is only limited use of potentially informative biomarkers in PA trials for MCI, AD, and dementia. Most studies did not examine the role of biomarkers to study associations between PA and cognitive functions in their analyses. Several potential biomarkers remain uninvestigated. Careful use of biomarkers may clarify mechanisms underlying PA effects on cognition. Our review serves as a useful resource for

developing future PA RCTs aimed at improving cognitive functions in MCI, AD, and dementias.

KEYWORDS
Alzheimer's disease, biomarkers related to dementia, brain health, dementia, exercise, mild cognitive impairment, neurobiological biomarkers, physical activity, underlying mechanism

1 | INTRODUCTION

Physical activity (PA) is a promising neuroprotective lifestyle intervention, with emerging evidence supporting beneficial effects on brain health.[1–4] Because of rapid population aging, age-related cognitive disorders including mild cognitive impairment (MCI), Alzheimer's disease (AD), and dementias are major global public health threats.[5,6] The absence of curative treatments[7,8] for these disorders led to interest in nonpharmacological interventions, such as PA, to prevent or mitigate these age-related cognitive disorders.[9,10]

Recent evidence suggests that PA, in combination with cognitive training, has beneficial or protective effects on brain health, improving cognitive functions among healthy adults as well as subjects with MCI, AD, and other dementias.[1–3,11–20]

Putative biomarkers examined in animal models and cognitively intact humans may provide insight into the underlying mechanisms through which PA may exert cognitive benefits.[21–24] Among these are neurotrophic factors, including brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), fibroblast growth factor 21 (FGF21), and nerve growth factor (NGF). Other potentially informative biomarkers include a variety of inflammatory markers, as well as measures of cerebral blood flow (CBF), irisin, salivary and serum cortisol, cathepsin B, myostatin, kynurenic acid, tau protein metabolism, and amyloid beta ($A\beta$) metabolism.

The effects of PA on these putative biomarkers in subjects with MCI, AD, or dementias are largely unknown. A prior systematic review investigating the biochemical effects of PA in subjects with MCI and dementia used a low sensitive search strategy[25] and reported results on a limited spectrum of potential biomarkers. Additional studies examining a wider range of biomarkers were subsequently published. To clarify the status of research on PA effects on potentially relevant biomarkers, we systematically summarized past randomized controlled trials (RCTs) that assessed changes in potentially relevant biomarkers in MCI, AD, and other dementias.

2 | METHODS

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, we systematically reviewed published RCTs which aimed to improve cognitive functions through PA interventions among patients with MCI, AD, or dementias. We selected RCTs which examined changes in potential biomarkers (either as primary, secondary, or exploratory outcomes of RCTs) for this review.

2.1 | Search strategies to identify relevant RCTs

We performed a literature search in the PubMed database to identify relevant RCTs published from PubMed inception to October 31, 2019, limited to publications in English, using three separate search terms (a, b, and c). Search terms under "a" were explicitly built for identifying relevant RCTs targeted for patients with dementias, whereas "b" and "c" were built to identify RCTs which included patients with AD and MCI, respectively.

(a). ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]) AND ("dementia"[MeSH Terms] OR "dementia"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]) AND "humans"[MeSH Terms];

(b). ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]) AND ("alzheimer disease"[MeSH Terms] OR ("alzheimer"[All Fields] AND "disease"[All Fields]) OR "alzheimer disease"[All Fields] OR ("alzheimer's"[All Fields] AND "disease"[All Fields]) OR "alzheimer's disease"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]) AND "humans"[MeSH Terms]; and

(c). (("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]) AND ("cognitive dysfunction"[MeSH Terms] OR ("cognitive"[All Fields] AND "dysfunction"[All Fields]) OR "cognitive dysfunction"[All Fields] OR ("mild"[All Fields] AND "cognitive"[All Fields] AND "impairment"[All Fields]) OR "mild cognitive impairment"[All Fields])) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]) AND "humans"[MeSH Terms].

2.2 | Selection criteria and data extraction

First, we retrieved all papers from the above-mentioned searches, and then removed duplicates to compile an exhaustive list of papers. Second, we screened the titles and abstracts of all papers to identify the relevant papers for full-text reviews. We performed screening based on two criteria: (1) title or abstract mentioned any interventions related to PA or exercise, and (2) changes in any biomarker(s) examined. Third, we collected full text for all relevant papers, identified from the initial screening, and reviewed them thoroughly for final eligibility.

Eligibility criteria included: (1) papers must be PA RCTs targeting participants with MCI, AD, or dementias, and (2) papers must report results on PA-induced changes in biomarker(s). We excluded papers if they: (1) used other study designs such as observational studies including cross-sectional, case-control, or cohort; (2) were RCT protocols (did not have results); (3) were RCTs and reported results but targeted healthy population (ie, cognitively intact) or special population groups (eg, nonagenarians or with other clinical conditions or disorders such as diabetes, Parkinson's disease, multiple sclerosis, cancer survivors, etc.); and (4) were animal models. We also retrieved and reviewed relevant papers, if any, from the reference lists of retrieved papers.

Fourth, we extracted necessary information (presented in Table 1) from the eligible papers. Two independent reviewers (MM and MSA) conducted data extraction. When discrepancies arose between the two reviewers, they were resolved by consensus and, in case of uncertainty, we contacted study authors to clarify uncertainties. We used a reference manager program—EndNote X8—for retrieving, reviewing, and removing duplications of references for this systematic review.[26]

We also calculated, where possible, the percent (%) change(s) in biomarker(s) in response to intervention using this formula: (follow-up – baseline)/baseline*100 (Table 1).

RESEARCH IN CONTEXT

1. **Systematic review**: We systematically reviewed (using PubMed) published randomized controlled trials (RCTs) that examined the effects of physical activities (PA) on relevant biomarkers among mild cognitive impairment, Alzheimer's disease, or dementia populations. We summarized the changes in PA biomarkers and their mediating effects on cognitive functions, which are yet to be clarified.
2. **Interpretation**: Our systematic review concludes an overall favorable effect of PA on neurotrophic and inflammatory biomarkers. None of the included RCTs examined the potential mediating effects of biomarkers between PA and cognition. Some concerns for the methodology were raised, and potential candidate biomarkers uninvestigated. Currently, there are no guidelines on PA RCTs in terms of the intensity, frequency, and duration of intervention.
3. **Future directions**: We believe that our review will serve as a useful resource for developing future PA RCTs aimed to improve cognitive functions and clarify their underlying mechanisms.

3 | RESULTS

3.1 | Search results

We identified 653 papers after removal of duplicates. From these, we selected 58 papers for full-text assessment. Eighteen papers fulfilled our inclusion criteria for this review.[27–44] The detailed selection process is shown in Figure 1.

3.2 | Characteristics of included RCTs

Of the included 18 RCTs, 11 studies recruited participants with MCI and 7 with AD. Of note, six papers were published from two RCTs; the ADEX study[35,40,41,44] and the Train the Brain study.[37,43]

Included studies were from nine countries: United States (4), Denmark (4), Italy (2), Japan (2), Brazil (2), Canada (1), China (1), Iran (1), and Saudi Arabia (1). All studies targeted participants aged > 50 years. Sample size (n) used in these studies ranged from 22 to 113 (n < 50 [8 studies], between 50 and 100 [8 studies], and n > 100 [n = 113 in 2 studies from the same RCT]) as shown in Table 1.

The duration of PA interventions included: single bout of acute exercise in 2 studies,[29,31] < 3 months in 3 studies,[28,36,42] 3 to 6 months in 11 studies,[27,30,32–35,38–41,44] and as long as 7 months in 2 studies from the same RCT.[37,43]

Twelve studies used moderate- or moderate-to-high–intensity aerobic exercise as an intervention;[27,29,31–33,35,36,38–41,44] five studies used aerobic exercise in combination with other types of training or stimulation (multidomain), including cognitive, social, and music;[30,34,37,42,43] and one study investigated the influence of high-intensity PA on diet-induced effects (diet intervention) on cerebrospinal fluid (CSF) amyloid levels.[28]

The frequency of PA intervention performed in the included studies varied from two to four times a week and the duration of sessions varied from 40 minutes to 90 minutes. The most commonly reported frequency and duration of a session was three times a week and 60 minutes per session, respectively. Three studies included a single bout of acute exercise[29,31] and a diet intervention.[28]

TABLE 1 Summary of the included papers (n = 18)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
1	27	Baker LD et al., 2010. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. –Conducted in the USA. –Targeted for participants with aMCI. –Executed high-intensity aerobic exercise for 45 to 60 minutes per session, 4 times a week for 6 months.	**Primary**: Cognitive function, particularly executive processing. **Secondary**: Biomarkers associated with AD pathology including plasma levels of insulin, cortisol, Aβ42 and Aβ40, BDNF, and IGF-I. –Examined intervention effects on AD-related biomarkers to explore putative mechanisms linking exercise with improved cognitive function.	Total n = 33. Adults (men, 16; women, 17) with aMCI aged 55 to 85 years (mean age = 70 years). Participants were randomized using a 2:1 ratio into either aerobic exercise group (n = 23) or stretching control group (n = 10).	Six months of aerobic exercise relative to stretching control improved cognitive functions, particularly executive control abelites assessed by Symbol-Digit Modalities, Verbal Fluency, Stroop, Trails B, Task Switching, Story Recall, and List Learning, in older adults with MCI ($P < 0.05$). These effects were more pronounced for women than men.	After 6 months of intervention, sex-specific effects of aerobic exercise vs control were observed for plasma levels of cortisol (ANOVA, group x sex interaction, F = 6.00; $P = 0.02$) and BDNF (ANOVA, group x sex interaction, F = 4.68; $P = 0.04$). Relative to controls, aerobic exercise reduced cortisol and BDNF levels in women (cortisol, $P = 0.05$; BDNF, $P = 0.06$) but increased in men (cortisol, $P = 0.04$; BDNF, $P = 0.10$). Plasma IGF-I was higher at baseline and increased in men ($P = 0.02$) after aerobic exercise. Mean plasma levels of Aβ42 decreased in aerobic group (−6%) and increased in the control group (24%). However, this difference failed to reach statistical significance ($P = 0.13$).	Uninvestigated.
2	28	Baker LD et al., 2012. Hi-PA modulates diet effects on CSF Aβ levels in normal aging and MCI. –Conducted in the USA. –Targeted for participants both with normal aging and aMCI. –Executed diet intervention (high fat, high glycemic index diet [HIGH] versus a low fat, low glycemic index diet [LOW]) for 1 month.	**Primary:** Whether hi-PA modulated diet-induced changes in CSF Aβ42. **Secondary:** cross-sectional associations, at baseline, of hi-PA with CSF Aβ42, total tau, and IL-8. –Hypothesized that hi-PA would potentiate the effect of LOW diet on CSF Aβ42 yet attenuate the effect of the HIGH diet.	Total n = 41. Of them, 18 normal older adults (mean age = 68.6 ± 7.4 years) and 23 adults with aMCI (mean age = 68.0 ± 6.5 years).	Uninvestigated.	Baseline hi-PA significantly modulated the diet-induced effects on CSF Aβ42 during the intervention (three-way ANOVA, diet [HIGH, LOW] by diagnosis [normal, aMCI] by hi-PA [min/week] interaction, F = 3.13, $P = 0.039$), which differed for normal and aMCI. That is, for normal adults, increased hi–PA tended to attenuate the negative effect of the HIGH diet on CSF Aβ42 (r = - 0.61, $P = 0.11$), whereas in aMCI, increased hi–PA potentiated the beneficial effect of the LOW diet (r = 0.64, $P = 0.034$). For adults with aMCI, baseline hi-PA was not associated with CSF Aβ42 ($P = 0.9$), total tau ($P = 0.60$) or IL-8 ($P = 0.98$).	Uninvestigated.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
3	29	Segal Sk et al., 2012. Exercise-induced noradrenergic activation enhances memory consolidation in both normal aging and patients with aMCI. –Conducted in the USA. –Targeted for participants both with normal aging and aMCI. –Executed a single bout of acute exercise for 6 minutes.	**Primary**: Endogenous noradrenergic response measured by sAA levels. **Secondary**: Explored whether exercise-induced noradrenergic activation could enhance memory storage. –Hypothesized that exercise could function as a natural stimulus to enhance memory consolidation through activating the locus coeruleus and increasing brain norepinephrine.	Total n = 53. Of them, 30 healthy adults (mean age = 69 ± 2 years) and 23 patients with aMCI (mean age = 71.4 ± 2.4 years). All participants were randomly assigned to either exercise condition group (15 control and 11 aMCI) or sedentary condition group (15 controls and 12 aMCI).	After an acute aerobic exercise for 6 minutes, exercise group enhanced recall memory, assessed by 20 images presentation, in both aMCI (aMCI exercise vs aMCI non-exercise, $P < 0.001$) and healthy (control exercise vs control non-exercise, $P < 0.01$) participants.	After an acute aerobic exercise, sAA levels significantly increased relative to baseline in both healthy adults (control exercise vs control non-exercise) and aMCI (aMCI exercise vs aMCI non-exercise) groups ($P < 0.001$). Exercise-induced sAA increase did not differ between aMCI and control exercise participants ($P > 0.1$).	There was a significant positive correlation between changes in recall and changes in sAA levels in the aMCI subjects ($r = 0.716$, $P < 0.001$).
4	30	Suzuki T et al., 2013. A randomized controlled trial of multicomponent exercise in older adults with MCI. –Conducted in Japan. –Targeted for participants with MCI. –Executed multicomponent exercise intervention, including aerobic exercise, muscle strength training, postural balance retraining, and dual-task training, for 90 minutes per session, 2 times a week for 6 months.	**Primary**: Rate of cognitive decline, especially in memory function, and reduce the rate of brain volume decline. **Secondary**: Biomarkers (total cholesterol, HbA1c, BDNF, and VEGF) at baseline used potential predictors for identifying improvement of cognitive functions. –Identified biomarkers associated with improvement of cognitive functions.	Total n = 100. Older adults with MCI aged 65 to 95 years (mean age = 75.4 ± 7.1 years). Participants were classified to an aMCI (n = 50) and other MCI (n = 50) group and then randomized to either a multicomponent exercise or an educational control group using a ratio of 1:1.	Six months of multicomponent exercise improved cognition in aMCI compared to aMCI control, with pronounced effects on logical memory ($P = 0.04$) and general cognitive functions ($P = 0.04$) assessed by WMS-LM I scores and MMSE scores, respectively.	Multiple logistic regression analysis revealed that low total cholesterol level before the intervention was associated with improvement in WMS-LM I (OR 0.98, 95% CI 0.96–1.00, $P = 0.02$). Higher serum BDNF level, but not VEGF, at baseline was significantly associated with improvement in ADAS-cog (OR 1.07, 95% CI 1.02–1.13, $P = 0.01$) independent of age, sex, educational level, and intervention.	Baseline low total cholesterol was associated with improvement in improvement in WMS-LM I. Higher serum BDNF level, but not VEGF at baseline was associated with improvement in ADAS-cog.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
5	31	Coelho FG et al., 2014. Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with AD. –Conducted in Brazil. –Targeted for participants with AD. –Executed a single bout of acute aerobic exercise for 17 to 22 minutes.	**Primary:** Plasma BDNF levels.**Secondary:** Explored associations among BDNF levels, aerobic fitness, and level of physical activity. –Investigated, for the first time, the effects of acute exercise on plasma BDNF levels in both elderly with AD and matched healthy controls.	Total n = 39. Of them, 21 patients with AD (mean age = 76.3 ± 6.2 years) and 18 healthy older adults (mean age = 74.6 ± 4.7 years).	Uninvestigated.	After an acute aerobic exercise, plasma BDNF significantly increased in both AD patients (22%, 255.2 ± 11.6 to 311.6 ± 110.7 pg/mL, $P < 0.05$) and healthy controls (16%, 353.3 ± 169.9 to 411.0 ± 172.8 pg/mL, $P < 0.05$). Two-way ANOVA showed a significant effect of time ($P = 0.001$, $F = 13.63$, df = 37, power = 0.94) but no interaction of group x time ($P < 0.05$). There was a significant moderate correlation (Pearson correlation, $r = 0.33$; $P = 0.04$) between BDNF levels and the level of physical activity.	Uninvestigated.
6	32	Nascimento CM et al., 2014. Physical exercise in MCI elderly promotes reduction of pro-inflammatory cytokines and improvements on cognition and BDNF peripheral levels. –Conducted in Brazil. –Targeted for participants with MCI. –Executed multimodal aerobic exercise for 60 minutes per session, 3 times a week for 4 months.	**Primary**: Peripheral BDNF levels and TNF-α, IL-6, and cognitive functions by MoCA. **Secondary:** Non-Exercise can help reduce pro-inflammatory cytokines levels and improve BDNF concentrations and cognitive functions.	Total n = 67. Older adults aged ≥ 60 years (30 cognitively normal subjects and 37 CI subjects). Of 30 normal subjects (15 in intervention group [mean age = 66.6 ± 7.9 years] and 15 in control group [mean age = 68.1 ± 5.7 years]). Of 37 MCI subjects, (20 in intervention group [mean age = 67.3± 5.3 years] and 17 in control group [mean age = 68.5 ± 5.9 years]).	Four months of aerobic exercise significantly improved cognitive functions in only MCI trained group, increased median MoCA scores from 19 to 23 points ($P = 0.03$).	After 4 months of intervention, mean plasma BDNF significantly increased in both training groups (TG; TG_{MCI} [20.4%, 2.85 ± 1.9 to 3.43 ± 2.2 pg/mL, $P < 0.05$]; TG_{normal} [26.7%, 2.81 ± 1.5 to 3.56 ± 1.8 pg/mL, $P < 0.05$]). The between-subject factors for two-way ANOVA indicated to the significant improvement for these groups for BDNF levels ($F_{3,64} = 7.98$, $P < 0.001$), compared to control. Regarding the inflammatory cytokines, mean plasma TNF-α significantly reduced in both TG (TG_{MCI} [−14.4%, 1.74 ± 0.5 to 1.49 ± 0.5 pg/mL, $P < 0.05$]; TG_{normal} [−12.9%, 1.48 ± 0.3 to 1.29 ± 0.3 pg/mL, $P < 0.05$]). Mean plasma IL-6 also significantly reduced in both TG (TG_{MCI} [−11.1%, 1.53 ± 0.3 to 1.36 ± 0.3 pg/mL, $P < 0.05$]; TG_{normal} [−12.8%, 1.17 ± 0.2 to 1.02 ± 0.2 pg/mL, $P < 0.05$]). The between-subject factors for two-way ANOVA indicated to the significant reductions for these groups for both TNF-α levels ($F_{3,64} = 6.43$, $P = 0.001$) and IL-6 ($F_{3,64} = 10.02$, $P < 0.001$), compared to control. No significant changes were observed for these variables for both control groups (CG) (CG_{MCI} and CG_{normal})	Uninvestigated.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
7	33	Yang SY et al., 2015. The effects of aerobic exercise on cognitive function of AD patients. –Conducted in China. –Targeted for participants with AD. –Executed moderate-intensity aerobic exercise (cycling training) for 40 minutes per session, 3 times a week for 3 months.	**Primary**: Cognitive functions. **Secondary**: Plasma apo a1, triglycerides, low-density lipoprotein, and total cholesterol. –Not mentioned about biological theory.	Total n = 50. Patients with mild AD (cognitive impairment) aged 65 to 80 years. Of them, 25 in intervention group (mean age = 72.0 ± 6.7 years) and 25 in control group (mean age = 71.9 ± 7.3 years)	Three months of aerobic exercise increased (pre vs post intervention) MMSE scores ($P < 0.001$) and QoL-AD scores ($P = 0.013$) in AD participants. On the other hand, ADAS-Cog and NPI scores decreased ($P = 0.004$). These results are limited to the changes in the intervention group (no comparison with the control group).	After 3 months of intervention, mean plasma apo a1 significantly increased (8.0%, 1.38 ± 0.20 to 1.49 ± 0.34, $P = 0.041$) in aerobic group but decreased non-significantly (–5.7%, 1.58 ± 0.45 to 1.49 ± 0.27, $P = 0.270$) in control group.	Uninvestigated.
8	34	Yokoyama H et al., 2015. The effect of cognitive-motor dual-task training on cognitive function and plasma Aβ42/40 ratio in healthy elderly persons: a randomized controlled trial. –Conducted in Japan. –Targeted for participants both with healthy and cognitive impairment. –Executed dual-task training (DT) vs single-task training (ST) group. Both groups received exercise training for 60 minutes per session, 3 times a week for 3 months. For the DT group, concurrent cognitive tasks were performed during the resistance and aerobic exercise.	**Primary**: Cognitive function (executive functions) and Plasma Aβ 42/40 ratio. **Secondary**: None. –Hypothesized that the intervention by dual-task training improved cognitive functions via modulating the metabolism of Aβ peptide.	Total n = 25. Sedentary healthy and cognitive impaired elders aged ≥ 65 years, with no habit of regular exercise for more than 1 hour per week. Of them, 13 in ST group (mean age = 74.2 ± 3.4 years) and 12 in DT group (mean age = 74.2 ± 4.3 years).	Three months of interventions improved attention, verbal fluency and understanding, and similarities assessed by 3MS, with the higher beneficial effects of DT than ST group ($P < 0.05$ between the groups). Neither group showed improvements in the results of Trail-Making Test.	After 3 months of intervention, plasma Aβ 42/40 ratio decreased in both groups (ST group: –74.6%, 0.63 ± 0.13 to 0.16 ± 0.03, $P = 0.001$; DT group: –58.3%, 0.60 ± 0.12 to 0.25 ± 0.06, $P = 0.044$), although the pre- and post-intervention values were not different between the groups for either measure.	Uninvestigated.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
9	35	Jensen CS et al., 2016. Cerebrospinal fluid Aβ and tau concentrations are not modulated by 16 weeks of moderate- to high-intensity physical exercise in patients with AD. –Conducted in Denmark. –Targeted for participants with AD. –Executed moderate-to-high intensity aerobic exercise for 60 minutes per session, 3 times a week for 4 months.	**Primary**: Biomarkers of AD—CSF Aβ and tau load (Aβ38/40/42, t-tau, p-tau, soluble amyloid precursor protein species sAPPα, and sAPPβ). Also ratio between sAPPβ and sAPPα (sAPPβ/α), and ratio between Aβ42 and Aβ40 (Aβ42/40). **Secondary**: Effects of APOE ε4.Hypothesized that exercise would increase the CSF levels of sAPPα and less aggregation-prone Aβ species and reduce CSF markers of neurodegeneration (t-tau and p-tau) in patients with clinically diagnosed mild AD.	Total n = 53. Clinically diagnosed mild AD. Of them, 26 in intervention group (mean age = 69.2 ± 3.9 years) and 27 in control group (mean age = 68.1 ± 6.8 years).	Uninvestigated.	Non-significant results. After 4 months of intervention, there was no significant difference in changes from baseline to follow-up between the control and intervention groups in any of the selected biomarkers (Aβ38, Δ [95% CI], −68 [−271; 135], $P = 0.50$; Aβ40, −404 [−879; 71], $P = 0.094$; Aβ42, −21 [−53; 11], $P = 0.20$; Aβ42/40, −0.0026 [−0.0062; 0.001], $P = 0.16$; t-tau, 78 [−134; 290], $P = 0.46$; p-tau, −4.8[−12.8; 3.3], $P = 0.24$; sAPPα, −34 [−142; 75], $P = 0.53$; sAPPβ, 15 [−198; 228], $P = 0.89$; and sAPPβ/α, −0.28 [−0.84; 0.28], $P = 0.32$). Dividing the intervention group into low- and high-exercise subjects did not alter the results. At follow-up, the high-exercise subjects (n = 18) did not differ from the control group in any of the outcome measures.	Uninvestigated.
10	36	Abd El-Kader SM et al., 2016. Aerobic exercise improves quality of life, psychological well-being and systemic inflammation in subjects with AD. –Conducted in Saudi Arabia. –Targeted for participants with AD. –Executed treadmill aerobic exercise for 45 minutes per session, 3 times a week for 2 months.	**Primary**: Quality of life, systemic inflammation (TNF-α, IL-6) and psychological well-being. **Secondary**: None. –Hypothesized that exercise improved the systematic (neuro)inflammation in AD.	Total n = 40. AD elderly subjects aged 65 to 75 years. Of them, 20 in intervention group (mean age = 68.94 ± 5.76 years) and 20 in control group (mean age = 69.13 ± 6.12 years).	Uninvestigated	After 2 months of intervention, mean changes significantly reduced in serum TNF-α (−25.3%, 4.87 ± 1.65 to 3.64 ± 1.32 pg/mL, $P < 0.05$) and IL-6 (−19.4%, 2.63 ± 0.84 to 2.12 ± 0.75 pg/mL, $P < 0.05$) in aerobic exercise group (A). No significant change was found in no-exercise training group (B).	Uninvestigated.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
11	37	Train the Brian Consortium, 2017. Randomized trial on the effects of a combined physical/cognitive training in aged MCI subjects: the Train the Brain study. –Conducted in Italy. –Targeted for participants with MCI. –Executed multidomain training, including cognitive, physical exercise, and music therapy. Aerobic exercise training for 60 minutes session 3 times a week for 7 months.	**Primary**: Cognitive decline assessed by ADAS-Cog. **Secondary**: Modifications in blood oxygen level dependent (BOLD) signal, loss of gray and white matter in the cortex and the hippocampus, and modifications in cerebral blood flow (CBF). –Hypothesized that the physical/cognitive training would modify CBF in hippocampus and parahippocampus areas in MCI participants.	Total n = 113. Elderly subjects with MCI aged 65 to 89 years (mean age = 74.5 ± 4.6 years). Of them, 55 in intervention group (mean age = 74.0 ± 4.8 years) and 58 in control group (mean age = 74.9 ± 4.4 years).	Seven months of intervention significantly improved global cognitive status assessed by ADAS-Cog in MCI-training subjects, while decreased in MCI-nontraining subjects. The mean difference between groups in changes in ADAS-Cog was -2.17 ($P < 0.001$).	After 7 months of intervention, CBF, assessed by MRI, increased in the hippocampal (+ 3.2 ± 1.4%) and parahippocampal (+ 4.1 ± 1.2%) regions of MCI-training subjects, but statistical significance was reached only for parahippocampal regions (two-way mixed model ANOVA, interaction time x treatment $P < 0.05$). No significant change was found in MCI-nontraining subjects.	Uninvestigated.
12	38	Barha CK et al., 2017. Sex difference in aerobic exercise efficacy to improve cognition in older adults with vascular cognitive impairment: Secondary analysis of a randomized controlled trial. –Conducted in Canada. –Targeted for participants with vascular cognitive impairment. –Executed aerobic exercise training for 60 minutes per session, 3 times a week for 6 months.	**Primary**: Executive functions. **Secondary**: Serum BDNF levels. –Investigated the possible role of BDNF in the sex difference in exercise efficacy (neurobiological mechanism).	Total n = 58. Participants with subcortical ischemic vascular cognitive impairment (SIVCI) aged ≥ 55 years. Of them, 31 in intervention group (men, 14 [mean age = 74.2 ± 9.3 year]; women, 17 [mean age = 73.4 ± 6.8 years]) and 27 in control group (men, 15 [mean age = 75.3 ± 9.1 years]; women, 12 [mean age = 72.3 ± 4.9 years]).	Compared to control, 6 months of exercise improved executive functions from baseline to follow-up, specifically the set-shifting ability assessed by Trail Making Test, in females ($P < 0.013$) in the intervention group, but not in males ($P > 0.122$). There were no significant main or interaction effects for Stroop or Digits Forward and Backward tests at trial completion or follow-up.	After 6 months of intervention, women showed mean increases in serum BDNF levels (1.57 ± 1.01 ng/mL) but men showed decreases (–2.55 ± 1.01 ng/mL). Women showed significantly greater increases in BDNF levels compared to men in the intervention group (4.12 ng/mL difference, 95% CI 1.07 to 7.16, $P < 0.012$).	Uninvestigated.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
13	39	Allard JS et al., 2017. APOEε4 impacts upregulation of brain-derived neurotrophic factor after a six-month stretch and aerobic exercise intervention in MCI elderly African Americans: A pilot study. –Conducted in USA. –Targeted for participants with MCI. –Executed Aerobic exercise group performed aerobic exercise for 40 minutes per session, 3 times a week for 6 months. Also added unsupervised low intensity walking on weekends for 45 to 60 minutes after first 4 weeks of training. Stretching group performed static stretch activity of joints for 40 minutes per session, 3 times a week for 6 months.	**Primary**: Serum BDNF levels. **Secondary**: Effects of APOEε4 carrier status on changes in BDNF. –Hypothesized that an increase in aerobic capacity would result in a parallel increase in BDNF levels.	Total n = 22. African Americans diagnosed with MCI aged ≥ 55 years (mean age = 72.0 ± 7.2 years). Of them, 13 in aerobic exercise group (mean age = 73.1 ± 7.8 years) and 9 in stretching group (mean age = 70.41 ± 6.3 years).	Uninvestigated.	Non-significant results. After 6 months of intervention, both stretch and aerobic groups showed mean increases in serum BDNF (stretch = 46.29%; aerobic = 15.12%). However, these increases were not significantly different from baseline values (stretch, $P = 0.24$; aerobic, $P = 0.82$). Median percent changes in serum BDNF were similar for the two groups (stretch = 6.82; aerobic = 0.415; $P = 0.950$, U = 51). There was no sex (men vs women) effects on changes in serum BDNF levels ($P = 1.0$, U = 52.0). There was no correlation between changes in BDNF and changes in $VO2_{Max}$ (R = 0.292, $P = 0.20$).	Uninvestigated.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
14	40	Jensen CS et al., 2017. Effect of physical exercise on markers of neuronal dysfunction in cerebrospinal fluid in patients with AD. –Conducted in Denmark. –Targeted for participants with AD. –Executed moderate-to-high intensity aerobic exercise for 60 minutes per session, 3 times a week for 4 months.	**Primary**: Biomarkers of neuronal and synaptic integrity—CSF concentrations of neurofilament light (NFL), neurogranin (Ng), visinin-like protein-1 (VILIP-1), and chitinase-3–like protein 1 (YKL-40). **Secondary**: None. –Hypothesized that the concentrations of markers of neuronal and synaptic damage would decrease in CSF in patients with AD as an effect of exercise.	Total n = 51. Clinically diagnosed mild AD. Of them, 25 in intervention group (mean age = 68.9 ± 8.05 years) and 26 in usual care (control) group (mean age = 68.2 ± 6.94 years).	Uninvestigated.	Non-significant results. After 4 months of intervention, there were no significant differences in CSF concentrations of NFL, Ng, VILIP-1, and YKL-40 comparing mean change from baseline between the exercise and control groups ($P > 005$).	Uninvestigated.
15	41	van der Kleij LA et al., 2018. The effect of physical exercise on cerebral blood flow in AD. –Conducted in Denmark. –Targeted for participants with AD. –Executed moderate-to-high intensity aerobic exercise for 60 minutes per session, 3 times a week for 4 months.	**Primary:** Cerebral blood flow (CBF).**Secondary:** Non~~d~~-Hypothesized that increasing cardiorespiratory fitness may aid in preventing or slowing pathological cognitive decline by increasing CBF.	Total n = 51. Patients with mild-to-moderate AD aged 50 to 90 years. Of them, 27 in intervention group (mean age = 68.0 ± 7.0 years) and 24 in control group (mean age = 69.0 ± 7.0 years).	Uninvestigated.	Non-significant results. After 4 months of intervention, the median difference in whole brain CBF was −6 (IQR, −1 to 3) mL/100/min for the control group and −4 (IQR, 0 to 3) mL/100/min for the intervention group. The change in CBF (whole brain, frontal regions, anterior cingulate cortex, posterior cingulate cortex, superior parietal gyrus, and precuneus) over the study period did not differ either in within or between (control vs intervention) group ($P > 0.05$).	Uninvestigated.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
16	42	Damirchi A et al., 2018. Mental training enhances cognitive function and BDNF more than either physical or combined training in elderly women with MCI: A small-scale study. –Conducted in Iran. –Targeted for participants with MCI. –Executed multicomponent exercise, including physical and mental training. Aerobic exercise for 55 minutes per session, 3 times a week for 2 months.	**Primary**: Cognitive performance and serum BDNF and irisin levels. **Secondary**: None. –Hypothesized that the combined (physical and mental) training would lead to improvements in cognitive functions and BDNF elevation.	Total n = 44. Women diagnosed with MCI aged 60 to 85 years. Of them, 11 in physical training (PH) group (mean age = 68.81 ± 3.68 years), 11 in mental training (ME) group (mean age = 67.90 ± 3.75 years), 13 in PH + ME group (mean age = 67.76 ± 4.69 years), and 9 in control group (mean age = 69.11 ± 4.93 years).	After 2 months of intervention, PH group showed no significant change in cognitive functions.	Non-significant results. After 2 months of intervention, the PH group showed non-significant within-group reduction in mean serum BDNF (−3.8%, 1167.46 ± 473.91 to 1122.41 ± 542.66 pg/mL; t [10] = 0.266, $P = 0.795$). The PH group also showed non-significant within group change in serum irisin level (2.1%, 11.23 ± 2.77 to 11.47 ± 3.08 ng/mL, $P > 0.05$). Between-group (PH vs other groups) differences either in BDNF or Irisin were also non-significant ($P > 0.05$).	In PH group, no correlations were found between changes in serum BDNF/irisin and changes in score of working memory, processing speed, reaction time, and error number.
17	43	Bruno RM et al., 2018. Vascular function is improved after an environmental enrichment program: The Train the Brain-Mind the Vessel study. –Conducted in Italy. –Targeted for participants with MCI. –Executed multidomain training, including cognitive, physical exercise, and music therapy. Aerobic exercise training for 60 minutes session 3 times a week for 7 months.	**Primary**: Cognitive and vascular function. **Secondary**: Circulating hematopoietic CD34+ cells, endothelial progenitor cells (EPC). –Investigated the efficacy of multidomain training on vascular and cognitive outcomes (vascular roots of dementia).	[Same as Ref.36] Total n = 113. Elderly subjects with MCI aged 65 to 89 years (mean age = 74.5 ± 4.6 years). Of them, 55 in intervention group (mean age = 74.0 ± 4.8 years) and 58 in control group (mean age = 74.9 ± 4.4 years).	Seven months of intervention significantly improved cognitive status assessed by ADAS-Cog (MCI-training, 14.0 ± 4.5 to 13.1 ± 5.5; MCI-nontraining, 12.1 ± 3.9 to 13.2 ± 4.8; P for interaction time × training = 0.02).	After 7 months of training, circulating hematopoietic CD34+ cells (30.8%, 1.17 ± 0.7 to 1.53 ± 0.6 per μL, $P = 0.004$), but not in EPC (−16.7%, 0.06 ± 0.08 to 0.05 ± 0.08 per μL, $P = 0.26$), significantly increased only in MCI-training group, suggesting a favorable effect of the training on the hematopoietic cell mobilization. No significant changes in either CD34+ cells or EPC were found in MCI-nontraining group.	Uninvestigated.

(Continues)

TABLE 1 (Continued)

S/N	Ref.	First author with year and title, study setting, target population, and intervention methods	Outcome(s), and hypothesized biological theory	Sample size and sample characteristics	Results related to cognition	Results related to biomarkers	Results on the associations between changes in biomarkers and changes in cognition
18	44	Frederiksen KS et al., 2019. Moderate- to high-intensity exercise does not modify cortical Aβ in AD. –Conducted in Denmark. –Targeted for participants with AD. –Executed moderate-to-high intensity aerobic exercise for 60 minutes per session, 3 times a week for 4 months.	**Primary**: Cortical Aβ deposition assessed by PET imaging. **Secondary**: None. —-Hypothesized that the concentrations of markers of neuronal and synaptic damage would decrease in CSF in patients with AD as an effect of exercise.	Total n = 36. Patients with mild-to-moderate AD aged 50 to 90 years. Of them, 20 in intervention group (mean age = 68.7 ± 7.6 years) and 16 in usual care (control) group (mean age = 70.4 ± 7.4 years).	Uninvestigated.	Non-significant results. After 4 months of intervention, there was no significant difference in mean levels of cortical Aβ, measured using SUVRs, within the two groups from baseline to follow-up (intervention group = 0.85%, 2.35 ± 0.37 to 2.37 ± 0.37, $P = 0.46$; usual care group = −1.47%, 2.07 ± 0.46 to 2.04 ± 0.47, $P = 0.68$). Furthermore, exercise load did not correlate with change in SUVR.	Uninvestigated.

Abbreviations: 3MS, Modified Mini-Mental State; Aβ, amyloid beta; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; aMCI, amnestic mild cognitive impairment; ANOVA, analysis of variance; apo a1, apolipoprotein a1; APOE, apolipoprotein E ε4; BDNF, brain-derived neurotrophic factor; CI, confidence interval; CSF, cerebrospinal fluid; HbA1c, glycated hemoglobin; hi-PA; high-intensity physical activity; IGF-I, insulin-like growth factor I; IL-6, interleukin-6; IL-8, interleukin 8; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; OR, odds ratio; PET, positron emission tomography; QoL-AD, Quality of Life in Alzheimer's Disease; sAA, salivary alpha-amylase; SUVR, standardized uptake value ratio; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; WMS-LM I, Weschler Memory Scale-Logical Memory I.

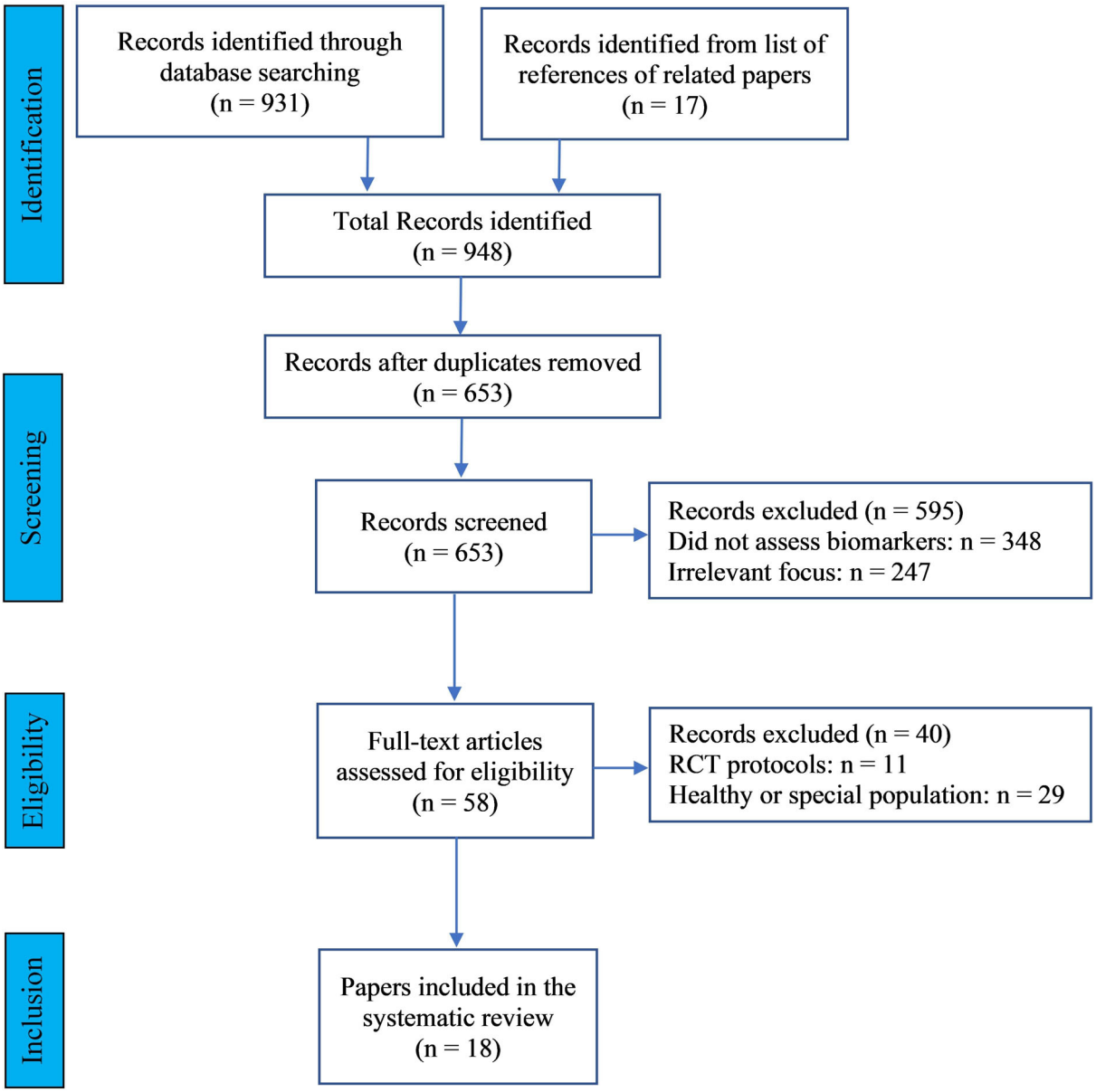

FIGURE 1 Flowchart of study selection

3.3 | Biomarkers investigated in the included studies

More than two thirds of these studies (66.7%) examined dementia-related biomarker(s) as a primary outcome and the rest as a secondary outcome. Studies included in this review examined the effect of PA on several biomarkers. These include:

1. **Neurotrophic factors**: Seven studies investigated neurotrophic factors including BDNF,[27,30–32,38,39,42] IGF-1,[27] and VEGF[30] based on either plasma[27,31,32] or serum[30,38,39,42] levels;
2. **Inflammatory markers**: Three studies investigated inflammatory markers based on plasma,[32] serum,[36] and CSF[28] levels. These include interleukin-6 (IL-6),[32,36] IL-8,[28] and tumor necrosis-alpha (TNF-α);[32,36]
3. **AD pathological markers**: Two studies investigated AD pathological markers using blood samples and examined plasma-based Aβ40,[27] Aβ42,[27] and Aβ42/Aβ40 ratio,[34] whereas another two studies investigated CSF Aβ38,[35] Aβ40,[35] Aβ42,[28,35] total tau (t-tau),[28,35] phosphorylated tau (p-tau),[35] and soluble amyloid precursor protein α and β (sAAP α and sAAP β).[35] A single study investigated cortical Aβ burden assessed by positron emission tomography (PET) imaging;[44]
4. **Other biomarkers**: One study investigated biomarkers of neuronal and synaptic integrity measured by CSF concentrations of neurofilament light chain (NFL), neurogranin (Ng), visinin-like protein-1 (VILIP-1), and chitinase-3–like protein 1 (YKL-40).[40] One study investigated plasma cortisol;[27] one study investigated salivary alpha-amylase (sAA);[29] one study investigated circulating hematopoietic CD34+ and endothelial progenitor cells

(EPC);[43] two studies investigated CBF;[37,41] and four studies also investigated markers of cardiovascular health including insulin sensitivity,[27] total cholesterol,[27,30,33] triglyceride,[27,33] low density lipoprotein,[27,33] high density lipoprotein,[27] apolipoprotein a1 (apo-a1),[33] irisin,[42] and glycated hemoglobin (HbA1c).[30]

3.4 | Effects of PA on neurotrophic factors (BDNF, IGF, and VEGF)

3.4.1 | Effects on BDNF

Five of seven studies reported PA-induced effects on increasing plasma/serum BDNF.[27,31,32,38,39] An acute aerobic exercise intervention study by Coelho et al.[31] found significantly increased plasma BDNF in AD patients (22%) and also healthy controls (16%). They also found moderate correlation between plasma BDNF and level of physical activity (Pearson correlation, r = 0.33, $P = 0.04$). In a 4-month multimodal aerobic exercise intervention study by Nascimento et al.,[32] plasma BDNF significantly increased in both MCI trained (20.4%) and cognitively normal trained (26.7%) groups, compared to MCI and healthy controls, respectively ($P < 0.001$). In a 6-month intervention study with amnestic MCI (aMCI) participants by Baker et al.,[27] aerobic exercise increased plasma BDNF levels in men relative to stretching controls but reduced levels in women. Another 6-month intervention study with vascular cognitive impairment (VCI) participants by Barha et al.[38] reported that aerobic training significantly increased serum BDNF levels in women but reduced serum BDNF levels in men among those in the aerobic training group. A 6-month intervention study in MCI participants by Allard et al.[39] reported mean increases in serum BDNF, albeit non-significant and possibly due to small sample size (total n = 22), in both stretch (46.3%) and aerobic (15.1%) groups compared to baseline measures. These trends were similar in men and women.

Conversely, a study by Damirchi et al.[42] reported non-significant reduction of serum BDNF compared to baseline in the physical training group after a 2-month duration aerobic exercise intervention targeted at women with MCI. This study also showed non-significant between-group changes (PA vs control group) in serum BDNF. The sample size was relatively small (44 participants).

One study by Suzuki et al.[30] showed significant beneficial effects of exercise intervention for cognitive function in aMCI participants. This study did not report PA-induced changes in serum BDNF but did report that higher serum BDNF at baseline significantly associated with improved general cognitive functions in the MCI participants.

3.4.2 | Effects on IGF-1

Only one study investigated IGF-1, which showed a significant increase in plasma IGF-1 in men ($P = 0.02$) after a 6-month aerobic exercise intervention, compared to stretching controls.[27]

3.4.3 | Effects on VEGF

In a single study, serum VEGF levels at baseline were used in multiple logistic regression models for determining the potential predictors of improvements in cognitive function. This study reported a non-significant relationship.[30]

3.5 | Effects of PA on inflammatory markers (IL-6, IL-8, and TNF-α)

Two studies showed significant reduction of IL-6 levels; plasma IL-6 in MCI participants (−11.1%; $P < 0.001$),[32] and serum IL-6 in AD participants (−19.4%; $P < 0.05$)[36] in response to aerobic exercise, compared to MCI and AD controls, respectively. These two studies[32,36] also showed a significant reduction of plasma and serum TNF-α ($P < 0.05$), respectively.

Another study examined cross-sectional associations at baseline and showed high-intensity PA significantly associated with lower CSF levels of IL-8 in participants with normal cognition ($P = 0.025$) but not in participants with MCI ($P = 0.98$).[28]

3.6 | Effects of PA on AD pathological markers

3.6.1 | Plasma amyloid-beta species

In a 6-month intervention study in aMCI participants by Baker et al.,[27] mean plasma levels of Aβ42 decreased in the aerobic exercise group (−6%) whereas levels increased in the control group (+24%). This difference was not statistically significant. Total sample size was 33 participants. This study also assessed plasma Aβ40 but did not report any results on this measure.

One study assessed the plasma Aβ42/Aβ40 ratio in a mixture of cognitively healthy and impaired participants. Both groups received 60 minutes of aerobic training for 4 months[34] with a single-task group performing only exercise and a dual-task group performing exercise and concurrent cognitive tasks. Results showed significant decreases in the Aβ42/Aβ40 ratio in both single-task (−74.6%, 0.63 ± 0.13 to 0.16 ± 0.03, $P = 0.001$) and dual-task (−58.3%, 0.60 ± 0.12 to 0.25 ± 0.06, $P = 0.044$) training groups. This study was targeted at sedentary subjects.

3.6.2 | CSF Aβ species, t-tau, p-tau, sAAP α, and sAAP β, and PET cortical Aβ

In a 1-month dietary intervention study by Baker et al.,[28] baseline levels of high-intensity PA modulated diet-induced effects on CSF Aβ42. There were differential effects on participants with normal cognition and MCI (analysis of variance, $P = 0.039$). In the MCI group, increased minutes/week of high-intensity PA significantly potentiated (r = 0.64, $P = 0.034$) the effects of a LOW diet (low saturated fat/low glycemic

index) in increasing CSF Aβ42 levels. In cognitively normal participants, PA tended to attenuate (r = −0.61, $P = 0.11$) the negative effect of a HIGH diet (high saturated fat/high glycemic index) on increasing CSF Aβ42 levels. No effects were observed for CSF t-tau.

Two reports, by Jensen et al.[35] and Frederiksen et al.,[44] from the parent ADEX study that investigated the PA-induced changes in CSF biomarkers of AD (Aβ38, Aβ40, Aβ42, Aβ42/40, t-tau, p-tau, sAAPα, sAAPβ, and sAAPβ/α) and PET cortical Aβ, showed no effects of a 4-month aerobic exercise program on these biomarkers.

3.7 | Effects of PA on other biomarkers

3.7.1 | CBF

In a 7-month combined physical/cognitive intervention study,[37] CBF, measured by magnetic resonance imaging, increased in the hippocampal (+ 3.2 ± 1.4%) and parahippocampal (+ 4.1 ± 1.2%) regions of the MCI-experimental group with the latter parahippocampal finding showing a statistically significant difference from the MCI-nontraining group ($P < 0.05$). Another study[41] failed to find detectable PA-induced changes in either whole brain or regional CBF in patients with AD after a 4-month moderate-to-high–intensity aerobic exercise program. CBF also did not differ between the control (usual care) and exercise group ($P > 0.05$) at the end of the study.

3.7.2 | CSF concentrations of NFL, Ng, VILIP-1, and YKL-40

A single study investigated markers of neuronal dysfunction in patients with AD, and it showed null effects of 4-month aerobic exercise program on CSF concentrations of NFL, Ng, VILIP-1, and YKL-40 comparing mean change from baseline between AD-intervention and AD-usual care (control) groups ($P > 005$).[40]

3.7.3 | Plasma cortisol

One study is available and it showed sex-specific effects of 6-month aerobic exercise on plasma cortisol levels in aMCI participants. Relative to stretching controls, the aerobic exercise group exhibited reduced cortisol levels in women ($P = 0.05$) but increased in men ($P = 0.04$).[27]

3.7.4 | Salivary alpha-amylase (sAA)

A single study of an acute 6-minute aerobic exercise intervention showed significant increases in sAA levels ($P < 0.001$), relative to baseline, in all participants (both cognitively intact control and aMCI groups) in the exercise condition but not in participants in the sedentary condition.[29] This study also reported a significant positive correlation relationship between recall test scores and sAA levels in the MCI participants (aMCI: r = 0.716, $P < 0.001$).

3.7.5 | Circulating hematopoietic $CD34^+$ and EPC

The results of one study showed a significant increase in $CD34^+$ cells (30.8%, 1.17 ± 0.7 to 1.53 ± 0.6 per μL; $P = 0.004$). This effect was found in the MCI-training group after a 7-month combined training, but not in MCI-nontraining group. No effect was found in EPC.[43]

3.7.6 | Markers of cardiovascular health

Four studies analyzed markers of cardiovascular health including insulin sensitivity,[27] total cholesterol,[27,30,33] triglyceride,[27,33] low density lipoprotein,[27,33] high density lipoprotein,[27] apo-a1,[33] irisin,[42] and HbA1c.[30] One study showed significant beneficial effects of aerobic exercise on total cholesterol ($P = 0.04$) in MCI participants compared to stretching controls, and insulin sensitivity for women, measured by glucose disposal ($P = 0.005$) and homeostasis model assessment ($P = 0.04$), in the aerobic group.[27] In another study, mean apo-a1 levels significantly increased (8%, 1.38 ± 0.20 to 1.49 ± 0.34, $P = 0.041$) in patients with AD in the aerobic group but decreased non-significantly (−5.7%, 1.58 ± 0.45 to 1.49 ± 0.27, $P = 0.270$) in the control group.[33] One study investigated PA-induced changes in irisin in elderly women with MCI and showed non-significant change.[42]

3.8 | Association between biomarkers and cognitive functions

Although biomarkers are often hypothesized as mediating factors to explain the effects of PA on cognitive functions, only three studies[29,30,42] examined the potentially mediating role of biomarkers. None performed formal mediation analysis. One study of acute aerobic exercise for 6 minutes showed a significant positive correlation between changes in recall, assessed by 20 positive images presentation, and changes in sAA levels in aMCI participants.[29] In another 6-month multicomponent exercise study, baseline low total cholesterol was associated with improved logical memory assessed by the Wechsler Memory Scale-Logical Memory I in MCI participants. This study also showed higher serum BDNF level at baseline was associated with improved general cognitive functions assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale.[30] On the other hand, in a 2-month multicomponent exercise study, MCI participants in the physical training group reported no correlation between changes in either serum BDNF or irisin and changes in scores of working memory, processing speed, reaction time, and error number.[42]

4 | DISCUSSION

Although a large number of RCTs investigated the effects of PA on cognitive health in patients with MCI, AD, or dementia, there is a dearth of evidence addressing potential mechanisms of PA effects. Incorporating appropriate biomarker studies into PA RCTs would be a useful way to

address this evidence gap. To date, however, few PA RCTs incorporated a biomarker(s) appropriately. Only 18 studies met our inclusion criteria for the present review, with very heterogeneous use of biomarkers, varying intervention designs, and generally small study Ns.

Most studies aimed to demonstrate the effects of PA on changes in neurotrophic and inflammatory biomarkers among patients with MCI and AD. BDNF was the most frequently investigated biomarker among the included studies (seven),[27,30–32,38,39,42] and most of these studies showed effects on increasing BDNF, either in response to both a single bout of acute aerobic exercise (less than 25 minutes) or long-term aerobic exercise (over a few weeks/months) interventions. The null effect found in one study[42] could be explained by its small sample size (total n = 44). Alternatively, a null effect could be due to the sample characteristics; only women aged 60 to 85 years old were included. Because estrogen regulates BDNF expression,[45] age-related decline in estrogen levels in elderly women may result in larger variability in BDNF expression, which could make it harder to observe a group difference. Although this study showed a null effect, the direction of this result was consistent with other studies. Study results, overall, support PA effects of increasing plasma/serum BDNF levels.[46–49] Recent comprehensive reviews, integrating knowledge from the molecular level, animal models, and clinical and epidemiological studies, indicate that increased BDNF production is a plausible mediator of exercise benefits on cognitive health in healthy individuals and those with cognitive impairments.[24,50,51]

One included study investigated IGF-1 and reported a significant effect of PA on increasing plasma IGF-I in male but not in female subjects.[27] Although IGF-1 is best characterized as regulating muscle growth, it is produced in the brain and may affect brain health by modulating neuronal growth, survival, and function.[52] Circulating levels of IGF-1 are upregulated by exercise and were shown to augment BDNF concentrations.[53,54] Well-designed biomarker components of PA RCTs in cognitively impaired subjects would be useful in addressing the potential mediating roles of these neurotrophins in PA effects.

A small number of studies showed that aerobic exercise significantly reduced IL-6 and TNF-α levels in MCI[32] as well as AD participants.[36] These findings are analogous to previous results of healthy individuals as well as patients with schizophrenia.[55,56] Among the proinflammatory cytokines, IL-6 and TNF-α are the most frequently investigated. They may contribute to neuroinflammatory processes hypothesized to be important in AD pathogenesis.[57–59] Increased plasma and serum levels of IL-6 and TNF-α were reported in patients with MCI and AD compared to controls and are negatively correlated with cognitive function.[60,61]

PA effects on pathological biomarkers of AD/dementia, such as plasma/CSF Aβ species, t-tau, p-tau, sAAP α, and sAAP β, and Aβ42/40 ratio,[62,63] were rarely investigated and showed inconsistent results. Two studies showed decreases in plasma Aβ42[27] and Aβ42/40 ratio[34] after aerobic exercise intervention, but another two studies, from the ADEX study, showed null effects on CSF Aβ38, Aβ40, Aβ42, t-tau, p-tau, sAAP α, and sAAP β,[35] and PET cortical Aβ.[44] In one study, increased PA potentiated the effects of the LOW diet in increasing CSF Aβ42 levels in MCI participants.[28] Findings were also inconsistent for CBF; one study showed PA-induced increases in CBF in the hippocampal and parahippocampal regions of MCI participants,[37] but another study failed to detect changes in either whole brain or regional CBF in subjects with AD.[41]

The three studies with null effects were from the parent ADEX study, with a small number of AD subjects and a relatively short intervention (4-month) period.[35,41,44] In addition, overtly demented individuals may have too advanced disease to respond to these types of interventions.

A few studies investigated the effects of PA on other biomarkers including CSF concentrations of NFL, Ng, VILIP-1 and YKL-40,[40] plasma cortisol,[27] sAA,[29] circulating hematopoietic CD34$^+$ and EPC,[43] and markers of vascular health (eg, insulin sensitivity, total cholesterol, triglyceride, low density lipoprotein, apo-a1, irisin, HbA1c)[27,30,33,42] in MCI and AD participants. Little can be said about these potential biomarkers because of insufficient number of studies with inconsistent results, and variable sex-specific effects. Recent novel findings from a well-designed longitudinal study suggest that interventions aimed at improving cardiovascular health could delay or prevent dementia.[64] Future PA RCTs aiming to improve brain health should consider incorporating relevant vascular disease biomarkers to study underlying mechanisms.[65]

Our review found that 15 of 18 studies did not examine the role of biomarkers in explaining the association between PA and cognitive functions. Out of three studies that examined both cognitive outcomes and biomarkers, one study analyzed the association between PA biomarkers at baseline and cognitive functions at the end of intervention.[30] Another study did not find any association between changes in PA biomarkers and changes in cognitive scores.[42] The third study showed a significant positive correlation between changes in recall and changes in sAA levels in the aMCI participants.[29] sAA levels are generally used as a measure of acute stress and it is not surprising that the sympathetic activation accompanying acute PA is associated with increased sAA.

No study examined potential mediating roles that biomarkers play in potential associations between cognition and PA. Numerous potential candidate biomarkers remain uninvestigated, including platelet-derived growth factor (PDGF), FGF21, NGF, myostatin, cathepsin B, and kynurenic acid.

Several RCT protocols were published recently aiming to investigate the PA effects on cognition and incorporating different dementia-related biomarkers of participants with MCI, AD, or dementia.[66–71] Completion of these studies should significantly expand the knowledge base about PA and biomarkers.

The present review has some limitations. First, although we used comprehensive search strategies, our literature search was limited to one online database— PubMed. Our search strategy might have left out some relevant papers. Second, we could not perform a meta-analysis for biomarker(s) because only a limited number of studies assessed several biomarkers.

TABLE 2 Recommendations for future PA RCTs

Key features	Recommendations
Include appropriate biomarkers in PA studies	We suggest incorporating appropriate biomarkers in PA RCTs to illuminate mechanisms underlying PA effects.
Postulate pre-specified, mechanistic hypothesis related to biomarker(s)	Hypotheses involving biomarkers should be based on mechanistic concepts of biomarker effects. Potentially useful biomarkers are of 2 main types; those addressing PA effect mediating mechanisms and those addressing effects on underlying neurodegenerative pathologies.
Require rigorous statistical plan for biomarker(s)	Biomarker evaluations should be based on clear, pre-specified hypotheses and with rigorous statistical planning.
Plan to relate biomarker(s) to relevant cognitive outcome(s)	PA RCTs should explicitly plan to assess associations between PA interventions and cognitive outcomes.
Perform formal mediation analysis	Formal mediation analyses should be performed to demonstrate mediating potential PA effects on cognitive outcome(s).
Standardize PA intervention	We propose to standardize PA intervention trials with moderate- to high-intensity exercise for 45 to 60 minutes per session, at least 3 times a week for 6-12 months to assess meaningful effects.

Abbreviations: PA, physical activity; RCT, randomized controlled trials.

5 | CONCLUSIONS

Our principal finding is that there has been only limited use of biomarkers in PA RCTs enrolling cognitively impaired subjects. A very modest amount of data suggests favorable effects of PA on neurotrophic and inflammatory biomarkers. Several biomarkers were studied infrequently, some in only one study. Several potential candidate biomarkers remain uninvestigated. We identified some RCT methodological shortcomings, particularly small sample sizes, low frequency of PA, and short intervention periods. Only three studies attempted to address potential roles of biomarkers in the associations between PA and cognition.

There are no guidelines for PA RCTs in terms of the intensity, frequency, and duration of PA interventions, let alone for associated biomarker studies. Because of their potential to illuminate mechanisms underlying PA effects, we suggest that appropriate biomarkers should be incorporated into PA RCTs. Whenever used, biomarker evaluations should be based on clear, prespecified hypotheses and with rigorous statistical planning to allow assessments of associations between PA interventions and cognitive outcomes, if not formal mediation analyses. Hypotheses involving biomarkers should be based on mechanistic concepts of biomarker effects. Potentially useful biomarkers are of two main types: those addressing PA effect mediating mechanisms and those addressing effects on underlying neurodegenerative pathologies. Measurements, for example, of inflammatory biomarkers are an example of the former. Measurements of CSF NFL would be an example of the latter. There should also be efforts to standardize PA intervention trials. Based on our review, we suggest that interventions with moderate- to high-intensity exercise for 45 to 60 minutes per session, at least three times a week for 6 to 12 months, are required to assess meaningful effects. Our review serves as a useful resource for developing future PA RCTs aimed at improving cognitive functions and clarifying their underlying mechanisms. Our recommendations are summarized in Table 2.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Rolland Y, Abellan van Kan G, Vellas B. Healthy brain aging: role of exercise and physical activity. *Clin Geriatr Med*. 2010;26:75-87.
2. Gallaway PJ, Miyake H, Buchowski MS, et al. Physical activity: a viable way to reduce the risks of mild cognitive impairment, Alzheimer's disease, and vascular dementia in older adults. *Brain Sci*. 2017;7:22.
3. Macpherson H, Teo WP, Schneider LA, Smith AE. A life-long approach to physical activity for brain health. *Front Aging Neurosci*. 2017;9:147.
4. Lautenschlager NT, Cox K, Cyarto EV. The influence of exercise on brain aging and dementia. *Biochim Biophys Acta*. 2012;1822:474-481.
5. Prince M, Guerchet M, Prina M. *The epideMiology and Impact of Dementia: Current State and Future Trends*. Geneva: World Health Organization; 2015.
6. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:88-106.
7. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimer Res Ther*. 2014;6:37.
8. Cooper C, Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: systematic review. *Br J Psychiatry*. 2013;203:255-264.
9. Coley N, Andrieu S, Gardette V, et al. Dementia prevention: methodological explanations for inconsistent results. *Epidemiol Rev*. 2008;30:35-66.

10. Yaffe K, Hoang T. Nonpharmacologic treatment and prevention strategies for dementia. *Continuum (Minneapolis, Minn)*. 2013;19:372-381.
11. Cammisuli DM, Innocenti A, Franzoni F, Pruneti C. Aerobic exercise effects upon cognition in Mild Cognitive Impairment: a systematic review of randomized controlled trials. *Arch Ital Biol*. 2017;155:54-62.
12. Bherer L, Erickson KI, Liu-Ambrose T. A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *J Aging Res*. 2013;2013:657508.
13. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *Am J Geriatr Psychiatry*. 2009;17:179-187.
14. Strohle A, Schmidt DK, Schultz F, et al. Drug and exercise treatment of alzheimer disease and mild cognitive impairment: a systematic review and meta-analysis of effects on cognition in randomized controlled trials. *Am J Geriatr Psychiatry*. 2015;23:1234-1249.
15. Farina N, Rusted J, Tabet N. The effect of exercise interventions on cognitive outcome in Alzheimer's disease: a systematic review. *Int Psychogeriatr*. 2014;26:9-18.
16. Groot C, Hooghiemstra AM, Raijmakers PG, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. *Ageing Res Rev*. 2016;25:13-23.
17. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Arch Phys Med Rehabil*. 2004;85:1694-1704.
18. Du Z, Li Y, Li J, Zhou C, Li F, Yang X. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. *Clin Interv Aging*. 2018;13:1593-1603.
19. Karssemeijer EGA, Aaronson JA, Bossers WJ, Smits T, Olde Rikkert MGM, Kessels RPC. Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: a meta-analysis. *Ageing Res Rev*. 2017;40:75-83.
20. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement (N Y)*. 2015;11:718-726.
21. Barber SE, Clegg AP, Young JB. Is there a role for physical activity in preventing cognitive decline in people with mild cognitive impairment?. *Age Ageing*. 2012;41:5-8.
22. Pedersen BK. Physical activity and muscle-brain crosstalk. *Nat Rev Endocrinol*. 2019;15:383-392.
23. Foster PP, Rosenblatt KP, Kuljis RO. Exercise-induced cognitive plasticity, implications for mild cognitive impairment and Alzheimer's disease. *Front Neurol*. 2011;2:28.
24. Tari AR, Norevik CS, Scrimgeour NR, et al. Are the neuroprotective effects of exercise training systemically mediated? *Prog Cardiovasc Dis*. 2019;62:94-101.
25. Jensen CS, Hasselbalch SG, Waldemar G, Simonsen AH. Biochemical markers of physical exercise on mild cognitive impairment and dementia: systematic review and perspectives. *Front Neurol*. 2015;6:187.
26. Bramer WM. Reference checking for systematic reviews using Endnote. *J Med Libr Assoc*. 2018;106:542-546.
27. Baker LD, Frank LL, Foster-Schubert K, et al. Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol*. 2010;67:71-79.
28. Baker LD, Bayer-Carter JL, Skinner J, et al. High-intensity physical activity modulates diet effects on cerebrospinal amyloid-beta levels in normal aging and mild cognitive impairment. *J Alzheimers Dis*. 2012;28:137-146.
29. Segal SK, Cotman CW, Cahill LF. Exercise-induced noradrenergic activation enhances memory consolidation in both normal aging and patients with amnestic mild cognitive impairment. *J Alzheimers Dis*. 2012;32:1011-1018.
30. Suzuki T, Shimada H, Makizako H, et al. A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment. *PLoS One*. 2013;8:e61483.
31. Coelho FG, Vital TM, Stein AM, et al. Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *J Alzheimers Dis*. 2014;39:401-408.
32. Nascimento CM, Pereira JR, de Andrade LP, et al. Physical exercise in MCI elderly promotes reduction of pro-inflammatory cytokines and improvements on cognition and BDNF peripheral levels. *Curr Alzheimer Res*. 2014;11:799-805.
33. Yang SY, Shan CL, Qing H, et al. The effects of aerobic exercise on cognitive function of Alzheimer's disease patients. *CNS Neurol Disord Drug Targets*. 2015;14:1292-1297.
34. Yokoyama H, Okazaki K, Imai D, et al. The effect of cognitive-motor dual-task training on cognitive function and plasma amyloid beta peptide 42/40 ratio in healthy elderly persons: a randomized controlled trial. *BMC Geriatr*. 2015;15:60.
35. Jensen CS, Portelius E, Siersma V, et al. Cerebrospinal fluid amyloid beta and tau concentrations are not modulated by 16 weeks of moderate- to high-intensity physical exercise in patients with Alzheimer disease. *Dement Geriatr Cogn Disord*. 2016;42:146-158.
36. Abd El-Kader SM, Al-Jiffri OH. Aerobic exercise improves quality of life, psychological well-being and systemic inflammation in subjects with Alzheimer's disease. *Afr Health Sci*. 2016;16:1045-1055.
37. 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.
38. Barha CK, Hsiung GR, Best JR, et al. Sex difference in aerobic exercise efficacy to improve cognition in older adults with vascular cognitive impairment: secondary analysis of a randomized controlled trial. *J Alzheimers Dis*. 2017;60:1397-1410.
39. Allard JS, Ntekim O, Johnson SP, et al. APOEepsilon4 impacts up-regulation of brain-derived neurotrophic factor after a six-month stretch and aerobic exercise intervention in mild cognitively impaired elderly African Americans: a pilot study. *Exp Gerontol*. 2017;87:129-136.
40. Jensen CS, Portelius E, Høgh P, et al. Effect of physical exercise on markers of neuronal dysfunction in cerebrospinal fluid in patients with Alzheimer's disease. *Alzheimers Dement (N Y)*. 2017;3:284-290.
41. van der Kleij LA, Petersen ET, Siebner HR, et al. The effect of physical exercise on cerebral blood flow in Alzheimer's disease. *NeuroImage Clin*. 2018;20:650-654.
42. Damirchi A, Hosseini F, Babaei P. Mental training enhances cognitive function and BDNF more than either physical or combined training in elderly women with MCI: a small-scale study. *Am J Alzheimers Dis Other Demen*. 2018;33:20-29.
43. Bruno RM, Stea F, Sicari R, et al. Vascular function is improved after an environmental enrichment program: the train the brain-mind the vessel study. *Hypertension (Dallas, Tex : 1979)*. 2018;71:1218-1225.
44. Frederiksen KS, Madsen K, Andersen BB, et al. Moderate- to high-intensity exercise does not modify cortical β-amyloid in Alzheimer's disease. *Alzheimers Dement (N Y)*. 2019;5:208-215.
45. Sohrabji F, Lewis DK. Estrogen-BDNF interactions: implications for neurodegenerative diseases. *Front Neuroendocrinol*. 2006;27:404-414.
46. Zoladz JA, Pilc A. The effect of physical activity on the brain derived neurotrophic factor: from animal to human studies. *J Physiol Pharmacol*. 2010;61:533-541.
47. Huang T, Larsen KT, Ried-Larsen M, Moller NC, Andersen LB. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: a review. *Scand J Med Sci Sports*. 2014;24:1-10.
48. Dinoff A, Herrmann N, Swardfager W, Lanctot KL. The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: a meta-analysis. *Eur J Neurosci*. 2017;46:1635-1646.

49. Coelho FG, Gobbi S, Andreatto CA, Corazza DI, Pedroso RV, Santos-Galduroz RF. Physical exercise modulates peripheral levels of brain-derived neurotrophic factor (BDNF): a systematic review of experimental studies in the elderly. *Arch Gerontol Geriatr*. 2013;56:10-15.
50. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain. *Front Cell Neurosci*. 2019;13:363.
51. Alkadhi KA. Exercise as a positive modulator of brain function. *Mol Neurobiol*. 2018;55:3112-3130.
52. Aleman A, Torres-Aleman I. Circulating insulin-like growth factor I and cognitive function: neuromodulation throughout the lifespan. *Prog Neurobiol*. 2009;89:256-265.
53. Frystyk J. Exercise and the growth hormone-insulin-like growth factor axis. *Med Sci Sports Exerc*. 2010;42:58-66.
54. Berg U, Bang P. *Exercise and circulating insulin-like growth factor I. Horm Res*. 2004;62(suppl 1):50-58.
55. Cronin O, Keohane DM, Molloy MG, Shanahan F. The effect of exercise interventions on inflammatory biomarkers in healthy, physically inactive subjects: a systematic review. *QJM*. 2017;110:629-637.
56. Gómez-Rubio P, Trapero I. The effects of exercise on IL-6 levels and cognitive performance in patients with schizophrenia. *Diseases*. 2019;7:11.
57. Rosenberg PB. Clinical aspects of inflammation in Alzheimer's disease. *Int Rev Psychiatry*. 2005;17:503-514.
58. Finch CE, Morgan TE. Systemic inflammation, infection, ApoE alleles, and Alzheimer disease: a position paper. *Curr Alzheimer Res*. 2007;4:185-189.
59. Brosseron F, Krauthausen M, Kummer M, Heneka MT. Body fluid cytokine levels in mild cognitive impairment and Alzheimer's disease: a comparative overview. *Mol Neurobiol*. 2014;50:534-544.
60. Kim YS, Lee KJ, Kim H. Serum tumour necrosis factor-α and interleukin-6 levels in Alzheimer's disease and mild cognitive impairment. *Psychogeriatrics*. 2017;17:224-230.
61. Swardfager W, Lanctot K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry*. 2010;68:930-941.
62. Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. *J Intern Med*. 2018;284:643-663.
63. Counts SE, Ikonomovic MD, Mercado N, Vega IE, Mufson EJ. *Biomarkers for the early detection and progression of Alzheimer's Disease*. Neurotherapeutics. 2017;14(1):35-53.
64. Shaaban CE, Jia Y, Chang CH, Ganguli M. Independent and joint effects of vascular and cardiometabolic risk factor pairs for risk of all-cause dementia: a prospective population-based study. *Int Psychogeriatr*. 2019;31:1421-1432.
65. Gustafson DR. Epidemiology informs randomized clinical trials of cognitive impairments and late-onset, sporadic dementias. *J Neurol Neuromedicine*. 2018;3:13-18.
66. Ho RT, Cheung JK, Chan WC, Cheung IK, Lam LC. A 3-arm randomized controlled trial on the effects of dance movement intervention and exercises on elderly with early dementia. *BMC Geriatr*. 2015;15:127.
67. Devenney KE, Sanders ML, Lawlor B, Olde Rikkert MGM, Schneider S. The effects of an extensive exercise programme on the progression of Mild Cognitive Impairment (MCI): study protocol for a randomised controlled trial. *BMC Geriatr*. 2017;17:75.
68. Makizako H, Tsutsumimoto K, Doi T, et al. Effects of exercise and horticultural intervention on the brain and mental health in older adults with depressive symptoms and memory problems: study protocol for a randomized controlled trial [UMIN000018547]. *Trials*. 2015;16:499.
69. Gates NJ, Valenzuela M, Sachdev PS, et al. Study of Mental Activity and Regular Training (SMART) in at risk individuals: a randomised double blind, sham controlled, longitudinal trial. *BMC Geriatr*. 2011;11:19.
70. Montero-Odasso M, Almeida QJ, Burhan AM, et al. SYNERGIC TRIAL (SYNchronizing Exercises, Remedies in Gait and Cognition) a multi-Centre randomized controlled double blind trial to improve gait and cognition in mild cognitive impairment. *BMC Geriatr*. 2018;18:93.
71. Li D, Thomas R, Tsai MY, et al. Vascular biomarkers to predict response to exercise in Alzheimer's disease: the study protocol. *BMJ Open*. 2016;6:e011054.

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