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The Effect of Aerobic Exercise on Brain-Derived Neurotrophic Factor (BDNF) in Individuals with Mild Cognitive Impairment: a Systematic Review and Meta-Analysis of a Randomized Controlled Trials

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Objective: Mild cognitive impairment (MCI) is a condition in which cognitive and executive functions are reduced, and older adults with MCI are ten times more likely to develop dementia than healthy older adults.
Expression of brain-derived neurotrophic factor (BDNF) through aerobic exercise is associated with increased cognitive and executive functions. in this review, randomized controlled trials (RCTs) on the effects of aerobic exercise on BDNF in individuals with mild cognitive impairment are summarized and qualitatively and quantitatively analyzed to suggest the necessity of aerobic exercise.

Design: a systematic review and meta-analysis.

Methods: RCTs were searched for changes in BDNF through aerobic exercise using four international databases. Quality assessment and quantitative analysis were performed using RevMan 5.4. Quantitative analysis was quantified with a standardized mean difference (SMD) and presented as a random effect model.

Results: Three RCTs evaluated BDNF in 123 patients with MCI. There was a significant improvement in the experimental group that performed aerobic exercise compared to the control group. The results analyzed using the random effects model were SMD = 0.48.

Conclusions: In this review, we reported the effects and mechanisms of aerobic exercise in individuals with MCI. As a result of synthesizing RCTs that performed aerobic exercise, a significant increase in BDNF was confirmed.

Key Words: Aerobic exercise, Brain-derived neurotrophic factor, ederly, mild cognitive impairment

Introduction

Older adults with mild cognitive impairment (MCI) are likely to deteriorate functional agility, cognitive function, and social engagement, and the incidence of MCI progressing to dementia in the same age group is 10-fold [1-3]. Therefore, improving cognitive decline and disability is important [4].

The beneficial effects of various exercises on cognitive function have been demonstrated in an increasing number of clinical studies in animal models and the older adults [5-7]. Brain imaging studies have shown that aerobic exercise improves executive control and memory processes in healthy older adults, which is associated with reduced atrophy through improved blood circulation in the brain [8].

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Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic family of proteins found in the peripheral and central nervous systems known to play important roles in neuronal development, plasticity, differentiation, and survival [9-11]. Neurotrophic factor, an important factor in the formation of long-term reinforcement [12], which significantly influences memory and learning processes, protects brain from neurodegeneration and neuronal damage that causes Alzheimer's disease. There is growing evidence that it is linked to protection [13]. Besides, it has been suggested that aerobic exercise may enhance synaptic plasticity by inducing the expression of BDNF throughout the central nervous system [14].

Therefore, in this review, a randomized controlled trials (RCTs) of the effect of aerobic exercise on BDNF in individuals with MCI is synthesized and qualitatively and quantitatively analyzed to present the need for aerobic exercise.

Methods

Study design

This review is a systematic review and meta-analysis to synthesize and analyze studies on the effects of aerobic exercise on BDNF in older adults with MCI. This review was conducted in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Search strategy and selection of studies

This reviewed the literature after searching the database according to PICOSD (Participants [P], Intervention [I], Comparison [C], Outcomes [O], Study design [SD]) as a search strategy.

Inclusion criteria

The PICOSD of this review is as follows. Includes studies that provided aerobic exercise (I) to older adults with MCI (P); Comparison (C) is inactivity or other exercise except aerobic exercise; The outcome (O) variables were BDNF, and the study design (SD) included only RCTs within 10 years to reflect the latest research trend.

Exclusion criteria

Although BDNF was evaluated, studies that included participants who were not older adults with MCI, and studies that included aerobic exercise as a control group were excluded from the review.

Literature-search strategy

The literature search was searched and collected in February 2022, and the data were independently searched by two researchers with meta-analysis experience. The searched terms were constructed by merging terms representing P, I, and S.

Pre-identified keywords (aerobic exercise AND [mild cognitive impairment OR elderly OR older adult] AND brain-derived neurotrophic factor AND Randomized Controlled Trial) and a database containing index terms Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), Cumulative Index of Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro).

Study selection and data extraction

For studies retrieved from four international electronic databases, duplicate data were removed using Reference Manager (EndNote 20, Thomson Reuters, NY, USA). According to the selection criteria, two researchers checked the title and abstract and selected them. The researchers then discussed the reasons for the exclusion. Finally, the selected studies were classified and features were extracted. All selections and extractions of data retrieved from the database were performed independently by three researchers.

Quality assessment

The quality assessment of the studies selected for this review was assessed using a seven-item Cochrane risk of bias (RoB) tool developed by the Cochrane Bias Method Group. RoB was rated as low (+), uncertain (?) or high (−) by three researchers with experience in meta-analysis studies. Similarly, for research selection and data extraction, if there were inconsistencies, the original text was reviewed and re-evaluated.

Strategy for Data Synthesis

Data synthesis was performed through RevMan 5.4 provided by Cochrane Collaboration. When there are identical variables that can be analyzed or there are three or more quantitative variables in the pre- and post-intervention tests, they were included in the meta-analysis. For the effect size, standardized mean difference (SMD) was used for the same variable. It was analyzed using a random effects model that resets the weights [15]. The homogeneity of the selected studies is confirmed through I2 and chi-squared test. The result of I2 is interpreted as follows. less than 40%, low heterogeneity; 50% to 75% heterogeneity is medium; More than 75% is highly heterogeneous [16].

Publication bias of the analyzed studies is analyzed through a funnel plot. It is not conducted if there are fewer than 10 selected studies [17].

Results

Literature search and characteristics of the randomized controlled trials

A total of 75 studies were searched through international databases, and 6 studies were additionally searched through Google scholar, resulting in a total of 81 studies. Four duplicate studies were excluded, and 67 studies were excluded after the title and abstract were reviewed. As a result of reviewing the full text of 10 studies selected according to the study eligibility criteria, 7 studies were excluded from the selection criteria (participants, intervention, and study design), and qualitative and quantitative analysis of 3 studies was possible [18-20] (Figure 1).

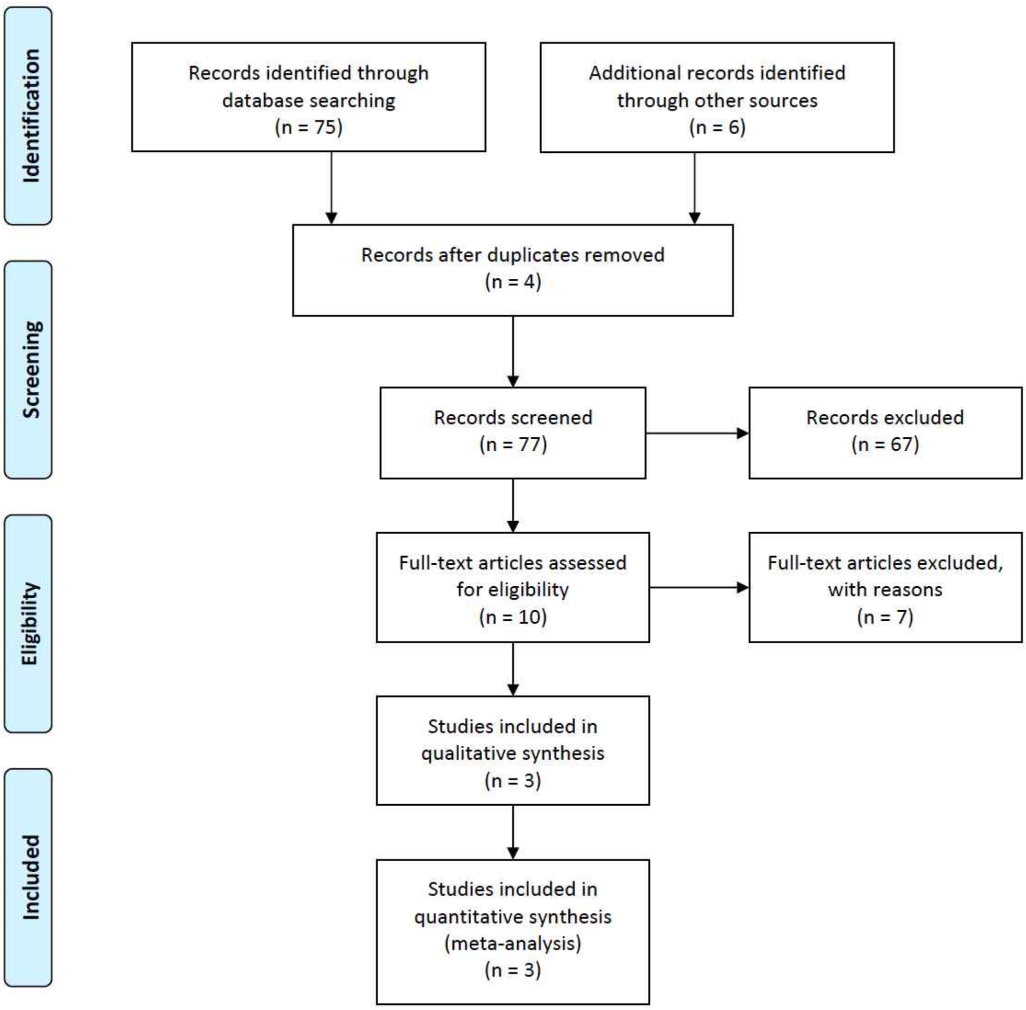

Figure 1. Flow diagram.

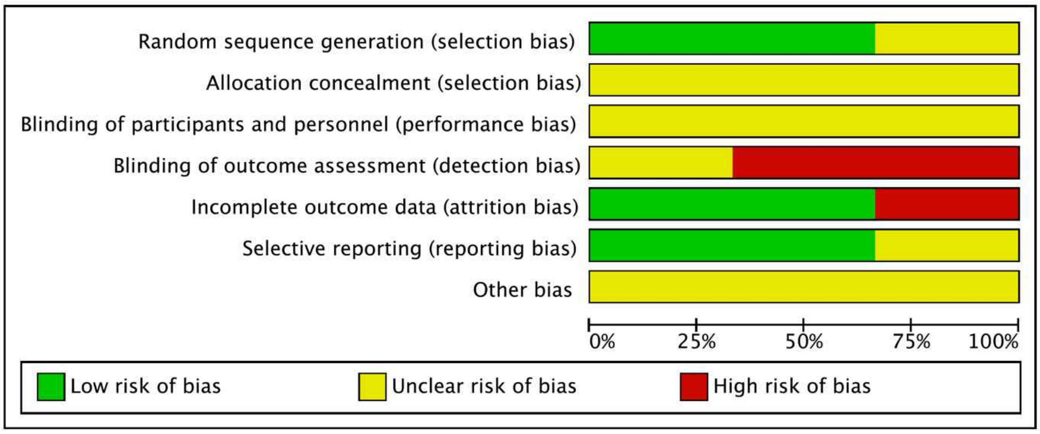

Figure 2. Risk of bias graph.

Quality assessment

RoB was used for methodological quality assessment of 3 studies. Each of the 7 items was random sequence generation (+: 2, −: 0, ?: 1), allocation concealment (+: 0, −: 0, ?: 3), blinding of participants and personnel (+: 0, −: 0, ?: 3), blinding outcome assessment (+: 0, −: 2, ?: 1), incomplete outcome data (+: 2, −: 1, ?: 0), selective reporting (+: 0, −: 2, ?: 1), and other biases (+: 0, −: 0, ?: 3) was evaluated as (Figure 2).

Aerobic exercise on BDNF in patients with MCI

In this review, 123 individuals with MCI were included in the three selected studies. In each study, combined exercise including aerobic exercise was also included. Control groups had no physical activity or were in usual care. For Outcome, only BDNF was evaluated, and the characteristics of the selected studies are shown in Table 1.

Table 1. Characteristics of included studies

Study	Sample size	Duration	Therapeutic intensity	Authors conclusion
Damirchi, et al. 2018	PT=11 PT+MT=13 CG=9	Eight weeks	MT: Modified My Better Mind PT: 5-minute warm-up followed by 6-minute walking with 55% heart rate reserve in the first session, incrementally reaching to 20 minutes with 75% heart rate reserve at the eighth week; and muscular strength, range of movement Silver Sneakers.	Positive effects of mental training on cognitive-related variables, such as increased BDNF, are useful interventions to slow the progression of MCI.
Nascimento, et al. 2015	EG=24 CG=21	Six months	Multimodal physical exercise program Three one-hour sessions per week	The BDNF genotype was shown to affect BDNF secretion in the effect of physical exercise, but the effect on cognitive function was insignificant.
Tsai, et al. 2018	EG=25 CG=20	One day	A five min warm-up, the participant performed a 30 min bout of exercise at moderate intensity, corresponding to 65–75% of the individual target heart rate reserve, as determined for everyone from the heart rate (rest) and heart rate (max), and then a five min cool down was performed.	In individuals with aMCI, acute AE and RE produces beneficial alterations in neuro-protective growth factors and neurocognitive performances.

AE: aerobic exercise, aMCI: amnestic mild cognitive impairment, CG: control group, EG: experimental group, MT: mental training, PT: physical training, RE: resistance exercise.

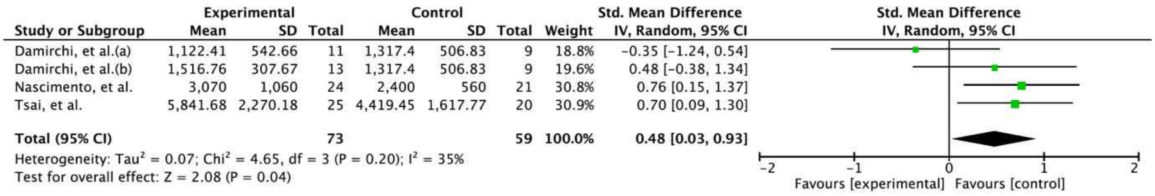

Figure 3. Forest plot on the effect of aerobic exercise on brain-derived neurotrophic factor. Damirchi, et al. (a): physical training, Damirchi, et al. (b): mental training plus physical training.

Effectiveness of aerobic exercise on BDNF

Three RCTs evaluated BDNF in 123 patients with MCI. There was a significant improvement in the experimental group that performed aerobic exercise compared to the control group. The results analyzed using the random effects model were SMD = 0.48; 95% CI: 0.03 to 0.93; heterogeneity (x^2 = 4.65, df = 3, I^2 = 35%); overall effect (Z = 2.08, $p < 0.05$) (Figure 3).

Discussion

This systematic review and meta-analysis were conducted to quantify the effect by synthesizing and analyzing a RCTs that investigated the changes in BDNF through aerobic exercise in individuals with MCI.

In the three studies we analyzed, individuals with MCI showed significant improvement in BDNF through aerobic exercise (SMD = 0.48; 95% CI: 0.03 to 0.93). In Nascimento, et al. [19] study, a multimodal physical exercise program was performed instead of the traditional aerobic exercise. Although there was a significant improvement after the intervention compared to the control group ($p < 0.05$), only participants with the BDNF-Met genotype showed significant improvement in peripheral BDNF levels. Tsai, et al. [20] compared the acute effects of aerobic exercise and resistance exercise. Both exercises similarly affected neurocognitive performance, and aerobic exercise was more effective at increasing exerkin levels compared to resistance exercise. Damirchi, et al. [18] reported that the combination of mental training, which showed a significant improvement in BDNF, was more effective than physical training alone.

These results are similar to those reported that exercise has a positive benefit in improving cognitive function and executive function [21, 22] and that it is effective in cognitive function in older adults with MCI [23]. In addition, a study by Suzuki, et al. [24] reported that exercise in older with amnestic MCI contributes to the improvement of logical memory and maintenance of cognitive function and might slow the atrophy of the cerebral cortex.

Therefore, it should be noted that the improvement of cognitive function and executive function is important for MCI and the relevance of BDNF. It has been reported that decreased hippocampal volume and decreased executive function of MCI are related to low serum levels of BDNF [25]. This is because BDNF, the neurotrophic family of proteins, is concentrated in the hippocampus and cortex and supports nerve growth and survival and synaptic plasticity [26-28]. In other words, an intervention is required for the increase of BDNF, which is an important factor in the formation of long-term reinforcement [12]. In interventions, neurophysiological mechanisms through exercise induce molecular and cellular processes that promote angiogenesis, neurogenesis, and brain synapse formation through increased cerebral blood flow [29], thereby increasing the synthesis and use of neurotransmitters, leading to increased BDNF synthesis and release [30]. As for the related evidence, a correlation between serum and cortical BDNF levels was reported in rodent studies [31], and BDNF expression in the hippocampus and cortical regions was reported to increase due to exercise [32, 33]. As such, the positive effects of exercise are related to an increase in cognitive function and BDNF [34-36].

In this review, we reported the effects and mechanisms of aerobic exercise in individuals with MCI. As a result of synthesizing RCTs that performed aerobic exercise, a significant increase in BDNF was confirmed. However, there were several limitations in this review. First, it is difficult to generalize because only three RCTs were extracted. Second, since the therapeutic intensity of aerobic exercise was not matched, an appropriate aerobic exercise protocol was not presented. In further studies, many RCTs should be studied, and an appropriate aerobic exercise protocol should be suggested.

Conclusion

From our results, it should be concluded that aerobic exercise contributes to a significant increase in BDNF in individuals with MCI. Results might vary with various aerobic exercise protocols. In the future, RCTs in which chronic exercise effects as well as acute exercise effects were studied should be included.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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