Meta analysis of aerobic exercise improving intelligence and cognitive function in patients with Alzheimer’s disease

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Abstract

Objective: Alzheimer’s disease (AD) is a neurodegenerative disease. This study aims to explore the intervention and treatment effects of aerobic exercise and different exercise modes on AD through meta-analysis.

Methods: Using the set inclusion and exclusion criteria, retrieve the China national knowledge infrastructure (CNKI), Wanfang Data Knowledge Service Platform, China Science and Technology Journal Database, Cochrane Library, and PubMed were searched from January 1, 2012, to December 31, 2021. Cochrane risk bias assessment tool was used to evaluate the quality of the included articles, and ReMan5.4.1 was used for forest plot analysis of mini-mental state exam (MMSE) score indicators included in the included articles.

Results: Twelve randomized controlled trials and 795 samples were included. Meta analysis of all articles: \( I^2 = 91\% \), \( P = .000001 \). Meta analysis of five fit aerobic groups: \( I^2 = 4\% \), \( P = .02 \). Meta analysis of three spinning groups: \( I^2 = 3\% \), \( P = .36 \). Meta analysis of five spinner groups: \( I^2 = 4\% \), \( P = .38 \). Meta analysis of five fit anaerobic groups: \( I^2 = 3\% \), \( P = .09 \). Meta analysis of five mixed aerobic and anaerobic groups: \( I^2 = 3\% \), \( P = .02 \).

Conclusion: Aerobic exercise can effectively improve intellectual and cognitive impairment in AD patients, and for different forms of aerobic exercise, the therapeutic effect of spinning aerobic exercise is better than that of fit aerobic.

Abbreviations: AD = Alzheimer’s disease, CI = confidence interval, CNKI = China national knowledge infrastructure, MMSE = mini-mental state exam.

Keywords: aerobic exercise, Alzheimer’s disease, cognition, intelligence, meta-analysis

1. Introduction

Alzheimer’s disease (AD) is characterized by occult onset and progressive development. The clinical symptoms are mainly cognitive impairment and memory decline.[1] The pathological manifestations of AD mainly include the inflammation of nerve cells effects deposition of amyloid \( \beta \) protein (A\( \beta \)) and the neurofibrillary tangles caused by the hyperphosphorylation of tau protein.[2] However, the newly published articles believe that the onset of AD is related to poorly acidified autolysosomes.[3]

As many countries enter into an aging society, the proportion of patients with Alzheimer’s disease will increase in the future. If a unified diagnosis and treatment standard for Alzheimer’s disease can not be formulated, the treatment and care of dementia patients will cause a serious economic pressure on their families and society.[4] The number of patients with dementia in China accounts for approximately 5% of the total population and 25% of the total number of patients with dementia world.[5] Dementia is commonly referred to as Alzheimer’s disease. More than 50 million people suffering from Alzheimer’s disease in the world, and AD has become the fifth leading cause of death world.[6] However, most drugs for treating AD in clinics have only a single target, which can only relieve the disease, but can not be cured.[9,10] In view of this, many scholars have conducted extensive research on the intervention and improvement of clinical symptoms related to AD by aerobic exercise.[11-15] Many animal experiments in mice have also demonstrated the effect of aerobic exercise on the brains of AD mice A\( \beta \) deposition, neurological tangles and cognitive memory function have obvious therapeutic effects. This article aims to prove the effect of aerobic exercise in the clinical treatment of AD through the data analysis of the included literature to provide a theoretical basis for the clinical treatment of AD by aerobic exercise in the future.

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2. Methods

2.1. Literature retrieval

The China national knowledge infrastructure (CNKI), Wanfang Data Knowledge Service Platform, China Science and Technology Journal Database, Cochrane Library and PubMed database were searched. From January 1, 2012, to December 31, 2021, a total of 2774 related articles were collected (220 articles in the CNKI database, 214 articles in the Wanfang database, 14 articles in the China Science and Technology Journal Database, 234 articles in the Cochrane library, and 2092 articles in PubMed).

The following combinations of key terms were employed for literature search: “Alzheimer’s disease” and “aerobic exercise” or “intelligence”, “cognition” and “aerobic exercise”. According to the inclusion and exclusion criteria, the data were extracted by two authors independently. First, by reading the abstract, the articles were initially included, and then the full text of the articles that met the inclusion requirements was read, and the included articles were screened. If there were differences in opinions between both reviewers, the third author was consulted for resolving the discrepancy.

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria: Participants meet the AD diagnostic criteria stipulated by the National Institute of Stroke Neurological Disorders and AD and Related Disorders Association of the United States[19] or have the risk of memory and cognitive decline; The ending indicator is the Mini-Mental State Exam (MMSE). Aerobic exercise was the intervention method for the experimental group. All the documents that meet these above conditions can be included.

Exclusion criteria: Repeatedly published literature; The subjects of this study were patients suffering from nervous system diseases, such as vascular dementia and mixed dementia with cognitive or memory disorders other than AD; Clinical interventions were not randomized controlled trials; On the basis of aerobic exercise, addition of drugs, music therapy and other therapeutic interventions; The original documents were incomplete, so it was impossible to analyze. Literature that met any of the above requirements were excluded.

2.3. Data extraction

Data were collected in the form of self-made Excel tables, including the title of the article, publication year, author information, sample size, age, MMES score, aerobic exercise form, intensity and frequency. It was estimated by drawing the scores of MMSE into the forest plot. In the process of literature inclusion and data collection, if there are differences, the third author will reach a consensus.

2.4. Literature quality evaluation

The quality of the included literature was evaluated using the evaluation criteria in the Cochrane Risk Assessment Tool for bias, which included seven evaluation items, random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The evaluation of literature quality is carried out by two authors independently, if there are different opinions, the third author will decide whether to include the article.

2.5. Detect the publication bias

We used ReMan 5.4.1 statistical software to make funnel plot to determine whether there was publication bias in the included literature. In the funnel plot, the log odds ratio was taken as the abscissa, and the ordinate was the standard error. Smaller samples had larger dispersion, so it was usually located at the

Figure 1. Literature screening process.
3.4. Funnel plot results analysis

The funnel plot was plotted from the included articles, and the results showed a symmetrical distribution. The presence of publication bias was generally judged by whether the funnel plot showed symmetry, the publication bias being small if the funnel plot was symmetrical and large if it was asymmetrical. The heterogeneity of the included literature was considered large if the funnel plot was located at the bottom, while smaller samples had smaller dispersion, so it was located at the top.

2.6. Statistical analysis

ReMan 5.4.1 statistical software was used to import the data and scale scores of randomized controlled trials in various studies into the software to create a forest plot for the meta-analysis. For continuous data, the standardized mean difference was used as the effect value. If standardized mean difference >0, the intervention is proved to be effective. The interval estimation used a 95% confidence interval (CI).

3.1. Literature retrieval results

The retrieval period was from January 1, 2012, to December 1, 2021. The retrieval databases included CNKI, Wanfang, China Science and Technology Journal Database, Cochrane Library, and PubMed, with 2774 retrieved articles. There were 448 articles in Chinese (220 in CNKI, 214 in Wanfang and 14 in China Science and Technology Journal Database), and 2326 articles in English (234 in The Cochrane Library and 2092 in PubMed).

3.2. Basic features of the included literature

A total of 12 articles were included and published between January 1, 2012, and December 1, 2021. All the intervention measures in the experimental group were aerobic exercises, and the subjects were diagnosed with Alzheimer's disease. MMSE scores were used to test the experimental results (Table 1).

Table 1

| Author | Control/ experimental (sample) | Control/ experimental (age) | Intervention measures | Motion | Exercise time (min/time) | Exercise frequency (times/wk) | MMSE score | Control group baseline | Experimental group baseline | Results of control group | Results of experimental group |
|--------|-------------------------------|----------------------------|-----------------------|--------|-------------------------|----------------------------|------------|-----------------------|-----------------------------|-----------------------------|-----------------------------|
| Wang Y[20] | 2014 26/13 | 70.6/71.6 | Spinning | 12 wk | 45 | 3 | 19.8 ± 3.8 | 20.3 ± 2.8 | 19.0 ± 5.0 | 21.4 ± 5.4 |
| Wang W[21] | 2014 28/26 | 70.0/71.2 | Spinning | 3 mo | 40 | 3 | 19.4 ± 4.1 | 20.2 ± 3.6 | 18.6 ± 4.1 | 21.3 ± 4.1 |
| Yan YL[22] | 2015 18/18 | 70.6/72.1 | Spinning | 6 mo | 40 | 3 | 20.5 ± 1.6 | 19.1 ± 3.1 | 18.3 ± 1.4 | 24.2 ± 1.8 |
| Wang W[23] | 2015 21/21 | unclear | Treadmill or spinning | 12 wk | 60–90 | 3 | 19.7 ± 3.3 | 18.4 ± 4.5 | 18.7 ± 3.1 | 19.1 ± 4.7 |
| Yang SY[24] | 2016 25/25 | 72.4/70.7 | Fit aerobics | 3 mo | 40 | 3 | 22.0 ± 2.9 | 22.4 ± 2.9 | 22.1 ± 4.1 | 24.2 ± 3.6 |
| Mu HY[25] | 2016 39/39 | 73.7/72.9 | Walk | 16 wk | >60 | ≥3 | 18.3 ± 2.5 | 18.4 ± 2.4 | 17.9 ± 2.4 | 19.1 ± 12.1 |
| Liu Y[26] | 2017 24/24 | 70.3/70.9 | Fit aerobics | 3 mo | 30 | 3 | 22.6 ± 1.9 | 22.8 ± 2.7 | 23.3 ± 2.0 | 24.4 ± 3.2 |
| Qi MP[27] | 2017 18/18 | 71.8/76.4 | Fit aerobics | 3 mo | 35 | 3 | 23.0 ± 1.6 | 22.9 ± 3.0 | 23.7 ± 1.5 | 24.4 ± 3.5 |
| Wang W[28] | 2019 18/18 | 71.1/68.7 | Fit aerobics | 3 mo | 40 | 3 | 24 ± 2.5 | 24 ± 1.0 | 23 ± 3.0 | 26 ± 4.0 |
| He Q[29] | 2020 30/30 | 74/70 | Fit aerobics | 6 mo | 10–20 | 3 | 14.9 ± 3.5 | 14.9 ± 3.6 | 17.7 ± 2.9 | 23.8 ± 3.0 |
| Wang JJ[30] | 2021 63/63 | 65.6666 | Walking or fit aerobic | 16 wk | 60 | 3 | 24.1 ± 3.8 | 23.8 ± 3.4 | 23.9 ± 3.9 | 23.9 ± 3.4 |

MMSE = mini-mental state exam.
the bottom of the plot, suggesting a large degree of dispersion in the included papers. There was asymmetry between the samples, suggesting high heterogeneity and possible publication bias. But there is not sufficient evidence of publication bias.

After removing two papers, Yan YL 2015 and Wang JJ 2021, the remaining ten papers were used to draw a funnel plot (Fig. 5). The samples were in the middle of the funnel plot, suggesting an average dispersion level. The funnel plot showed that the samples were more symmetrical than Figure 4. This may be caused by the long experimental protocol designed by Yan YL 2015 and Wang JJ 2021, which led to the final MMSE results being too different from other studies.

3.5. Meta-analysis results

3.5.1. Intervention analysis of aerobic exercise on intelligence and cognitive function in patients with Alzheimer’s disease Meta-analysis was conducted using ReMan5.4.1, $I^2 \geq 50\%$, and $P \leq .1$, so the forest plot of the random effect model was adopted (Fig. 6). From $I^2 = 91\%$, it can be seen that the 12 included articles have high heterogeneity, mainly from Yan YL 2015 and Wang JJ 2021. The reasons for this heterogeneity may be the publication year and experimental scheme design. MD = 2.95, indicating that aerobic exercise has significant effects on the intelligence and cognitive ability of patients with Alzheimer’s disease.

3.6. Effect of different aerobic exercise forms on intelligence and cognitive function of patients with Alzheimer’s disease

Eight articles had the same intervention time, or the difference in intervention days was <10 days. They were divided into the fit aerobic group and the spinning group.

Five articles were included in the fit aerobic group: He Q 2020, Liu Y 2017, Yang SY 2016, Wang W 2019, and QI M 2017. The total sample size was 230, and the average exercise time was $23.84 \pm 2.92$ hours. Through ReMan5.4.1 analysis of
the fit aerobics group, $I^2 = 4\%$, $P = .38$, indicating that there was no heterogeneity, the forest plot of the fixed effect model (Fig. 7) was adopted. Showing $95\% \text{CI} (0.72, 2.33)$, $\text{MD} = 1.53$, $P = .0002$, the results show that aerobic exercise in the form of fit aerobics can effectively improve the intellectual and cognitive dysfunction of AD patients.

Three articles were included in the spinning group, Wang Y 2014, Wang W 2014, Wang W 2015. The total sample size was 135, and the average exercise time was $32.57 \pm 10.79$ hours. Through ReMan5.4.1 analysis of the spinning group, $I^2 = 3\%$, $P = .36$, indicated that there was no heterogeneity. Therefore, the forest plot of the fixed effect model was adopted (Fig. 8). Showing $95\% \text{CI} (0.29, 3.29)$, $\text{MD} = 1.79$, $P = .02$. The results showed that aerobic exercise in the form of spinning can effectively improve intellectual and cognitive dysfunction of AD patients.

By analyzing the forest plot of the two groups, the therapeutic effect of aerobic exercise in the form of spinning was better than that of aerobic exercise in the form of fit aerobics for AD patients.
4. Discussion

The clinical symptoms of Alzheimer’s disease are mainly Aβ amyloid plaque deposition in the brain and neurological tangles caused by hyper phosphorylation of tau protein.[29] Many researchers treat AD with Aβ as the target, but eventually the drug research and development have failed.[30] Therefore, researchers suspect that Aβ amyloid plaques are only an accompanying phenomenon in the process of AD, rather than the cause of AD. Therefore, researchers started from the perspectives of Tau protein, ferroptosis and exercise[31–37] in order to find the original target for the treatment of AD.

Compared with previous meta-analyses,[18,19] this meta-analysis included three new articles published in 2019 by Wang Wei, 2020 by He Qing and 2021 by Wang Junjun, and compared the therapeutic effects of different forms of exercise. Studies have shown that aerobic exercise can improve the intelligence and cognitive impairment of AD patients. The advantages of aerobic exercise in the prevention and treatment of AD include: First, high feasibility, and it can be carried out anytime and anywhere; Second, the cost is low, and the therapeutic effect can be achieved by simple running or gymnastics without purchasing equipment; Third, high flexibility. Different forms of aerobic exercise therapy can be designed according to different patient conditions. However, aerobic exercise has many limitations in the treatment of AD. For example, there is no unified standard for the form, spinning, time, frequency and exercise intensity of aerobic exercise, and different AD patients have different tolerances to exercise, which increases the difficulty of clinical treatment of AD. At the same time, some scholars have studied the mechanism by which aerobic exercise improves AD symptoms,[40–44] but the specific mechanism is not clear. In the future, a large number of experiments and studies will be needed to determine the aerobic exercise treatment scheme and mechanism of AD.

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Author contributions

X-PZ proposed the theme of the article and completed the editing and writing of the paper; L-MZ sorted and screened the data of the paper; G-QC, S-WW and J-FH have strictly revised the important knowledge content; B-SZ and Z-L decided the controversial issues in the paper; All authors contributed to the editorial changes of the manuscript. All authors have read and approved the final manuscript.

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