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Comparison of the effects of different exercise interventions on cognitive function in patients with Alzheimer's disease: A systematic review and network meta-analysis

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Review question / Objective: **Exercise is an effective therapy that can improve cognitive performance in people with Alzheimer's disease, but no studies have yet explored which types of exercise are most effective.**
Condition being studied: **We conducted a systematic review and network meta-analysis using previously published randomized controlled trials in patients with AD by comparing the relative efficacy of different types of exercise interventions based on indirect evidence. The aim was to identify the best exercise measures to improve cognitive function in patients with AD and to provide a clinical basis for the rehabilitation of clinical ADpatients.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 March 2023 and was last updated on 18 March 2023 (registration number INPLASY202330066).

INTRODUCTION

Review question / Objective: **Exercise is an effective therapy that can improve cognitive performance in people with Alzheimer's disease, but no studies have yet explored which types of exercise are most effective.**

Rationale: **This study searched Pubmed, EMBASE, SPORT Discus, Cochrane Library, and Web of Science databases written in English only up to November 30, 2022, and identified by title and abstract to include randomized controlled trials of exercise interventions for patients with Alzheimer's disease that met set criteria. The primary outcomes analyzed included global cognition, executive function, and memory function, and effect sizes were estimated using standardized mean differences (SMDs) and 95% confidence intervals (95%**

CIs) using random effects models for pairwise analyses and Network Meta-analysis. To compare the effects of different types of exercise interventions, we divided the exercise interventions into the following categories: aerobic exercise, resistance exercise, multicomponent exercise and mind-body exercise. The exercise interventions were ranked by using the surface under the cumulative ranking curve (SUCRA) and mean rank.

Condition being studied: We conducted a systematic review and network meta-analysis using previously published randomized controlled trials in patients with AD by comparing the relative efficacy of different types of exercise interventions based on indirect evidence. The aim was to identify the best exercise measures to improve cognitive function in patients with AD and to provide a clinical basis for the rehabilitation of clinical ADpatients.

METHODS

Search strategy: The research process follows PRISMA guidelines,Search Pubmed, EMBASE, SPORTDiscus, Cochrane Library and Web of Science databases for literature written in English only, identified by title and abstract, using the keywords "Alzheimer's disease" or "AD" or "dementia" and "exercise" or "physical activity" or "aerobic exercise" or "resistance training" or "cognitive function" or "systematic review" or "Meta-analysis" and any possible combination of these terms. The search strategy was determined by three investigators, two of whom completed the search independently and a third involved in resolving any searchdisputes.

Participant or population: Participants must have at least one group diagnosed with AD-type dementiaparticipants must have at least one group diagnosed with AD-type dementia; (3) intervention includes any type of motor exercise; (4) study must report one of the following outcomes, including the presence of global cognition, executive function, memory function.

Intervention: In the process of data extraction,we referred to the Physical Activity Guidelines for Americans and previous systematic reviews for the classification of exercise interventions, In order to compare the effects of different types of exercise interventions, we divided them into the following categories: aerobic exercise (AE, exercise aimed at improving cardiovascular health, including walking, running, cycling), resistance exercise (RE, aimed at increasing muscle strength building), multicomponent exercise(ME, a combination of at least two exercise types, such as AE, RE and balance training) and mind-body exercise (MBE, exercises that aim to improve the coordination and awareness of participants by having them practice a series of exercises that focus on the interactions between the brain, body, mind and behavior, such as Gymnastics and yoga).

Comparator: Other neurodegenerative disorders and did not report AD-independent outcomes.Studies excluded non-randomized controlled trials and studies that included other neurodegenerative disorders and did not report AD-independent outcomes. If multiple articles were from the same study and reported the same or duplicate results, we included only the most recently published article.

Study designs to be included: Search Pubmed, EMBASE, SPORTDiscus, Cochrane Library and Web of Science databases for literature written in English only, identified by title and abstract, using the keywords "Alzheimer's disease" or "AD" or "dementia" and "exercise" or "physical activity" or "aerobic exercise" or "resistance training" or "cognitive function" or "systematic review" or "Meta-analysis" and any possible combination of these terms.

Eligibility criteria: (1) randomized controlled trial; (2) participants must have at least one group diagnosed with AD-type dementia; (3) intervention includes any type of motor exercise; (4) study must report one of the following outcomes, including the presence

of global cognition, executive function, memory function. Studies excluded non-randomized controlled trials and studies that included other neurodegenerative disorders and did not report AD-independent outcomes. If multiple articles were from the same study and reported the same or duplicate results, we included only the most recently publishedarticle.

Information sources: Pubmed, EMBASE, SPORTDiscus, Cochrane Library and Web of Science database.

Main outcome(s): A total of 24 randomized controlled trials were included in this study, and the results showed that exercise improved global cognition, executive function, and memory function in patients with Alzheimer's disease. Resistance exercise had the highest probability (72.4%) of being the most effective intervention to slow down the overall cognitive decline in patients with Alzheimer's disease. the SUCRA value was 90.1; Multicomponent exercise was most likely to be an effective measure to improve executive function (30.4%) with a SUCRA value of 68.5. Memory function is the cognitive domain least sensitive to exercise, and only resistance exercise would have a significant effect on memory function.

Quality assessment / Risk of bias analysis: Risk of bias was assessed by 2 pairs of authors according to the Cochrane Collaboration's risk of bias tool. Considering the characteristics of exercise intervention, it was impossible to blind the participants in the included studies. Thus, we only assessed the other 6 categories of risk bias, which included random sequence generation, allocation concealment, blinding of the outcome assessor, incomplete data, selective reporting, and other sources of bias. Any differences will be resolved by the third researcher.

Strategy of data synthesis: Paired Meta-analyses were first performed in the results to explore the effects of different exercise interventions separately compared with controls by random effects models, with standardized mean differences (SMDs) and 95% confidence intervals (95% CIs) to estimate effect sizes. Network meta-analyses for the primary outcomes were conducted based on the frequentist framework using Stata software (Verson 15.0; StataCorp, College Station,TX, USA). The data were analyzed using a random effects model, which takes into account heterogeneity due to various factors and provides more conservative confidence intervals for the combined point estimates.The exercise interventions were ranked by using the surface under the cumulative ranking curve (SUCRA) and mean rank.

Subgroup analysis: The results assessed by the studies and the heterogeneity of intervention types (different frequencies, durations, and exercise types) were not developed for subgroup analysis.

Sensitivity analysis: No sensitivity analysis was conducted.

Language restriction: The search is in English only.

Country(ies) involved: China.

Other relevant information: This systematic review and network meta-analysis has been registered in PROSPERO (CRD42023400432) and in INPLASY (INPLASY202330066).

Keywords: exercise; cognitive; Alzheimer's disease; systematic review; network meta-analysis.

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