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Physical activity interventions as neuroprotective measures against neurodegeneration, cognitive impairment, and neurological aging: A systematic review of randomized controlled trials

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective This review aims to systematically review the literature of randomized controlled trials using physical activity interventions as neuroprotective measures in healthy older human adults and investigate how the possible neurological and cognitive benefits of physical activity differ between healthy older adults and neurodegenerative (i.e., Alzheimer's disease, Parkinson's disease, multiple sclerosis) or cognitively impaired (i.e., mild cognitive impairment, amnesic mild cognitive impairment) human populations. Furthermore, this review aims to investigate (a) the anti-inflammatory and neuroplastic mechanism(s) induced by physical activity across brain structure and function; and (b) their association with specific cognitive domains (i.e., memory, executive function, attention) across healthy older adults and neurodegenerative or cognitively impaired human populations.

Rationale The broad clinical implications for PA-induced improvements are vast; however, despite sedentary behavior's role as a risk factor for cognitive decline, the neurological and cognitive effects of PA have not been clearly elucidated. The upregulation of BDNF and reduction of inflammation is thought to have a neuroprotective effect through promoting synaptogenesis and neurogenesis, stimulating physiological resilience and cognitive processes such as learning and memory, against cerebral atrophy and degeneration. Furthermore, the literature has demonstrated associations between PA and brain regions (e.g., medial temporal lobes, basal ganglia, gray/white matter, frontal cortex) and cognitive domains (e.g., memory, executive function, global cognition) often targeted by normal age-related changes and clinical cognitive impairment and neurodegeneration. However, there is no consensus among the literature regarding the most effective dosages or types of PA, whether the effectiveness of PA varies between populations, or the underlying mechanisms, and the true nature of this relationship in neurodegenerative or

cognitively impaired populations may be obscured due to extreme heterogeneity.

Condition being studied This study includes healthy older adults and neurodegenerative (i.e., Alzheimer's disease, Parkinson's disease, multiple sclerosis) or cognitively impaired (i.e., mild cognitive impairment, amnesic mild cognitive impairment) human populations.

METHODS

Search strategy A systematic review of three relevant databases (PsycINFO, PubMed, Web of Science) was conducted. Database search terms were developed in collaboration with a Pennsylvania State University librarian, and databases were searched using the terms with Boolean logic operators "OR" and "AND". These terms included all variations of "(Mild Cognitive Impairment OR Alzheimer's Disease OR Parkinson's Disease OR Multiple Sclerosis OR Dementia OR Memory Impairment OR Healthy Aging) AND (Exercise Intervention OR Exercise Training OR Exercise Testing OR Metabolic Equivalent of Task) AND (Biomarker Analysis OR Amyloid OR Tau Protein OR Magnetic Resonance Imaging OR Functional Magnetic Resonance Imaging OR Diffusion Tensor Imaging OR Positron Emission Tomography OR Disease Progression OR Functional Outcomes OR Quality of Life) AND (Randomized Controlled Trials)".

Participant or population This review included studies of human adult participants healthy or diagnosed with Alzheimer's disease, Parkinson's disease, multiple sclerosis, amnesic mild cognitive impairment, or mild cognitive impairment.

Intervention Physical activity interventions (i.e., aerobic exercise, resistance training, stretching exercise, multicomponent exercise, and vestibular exercise) were evaluated. Multicomponent interventions were defined as interventions utilizing more than one form of physical activity, such as an intervention that combines aerobic exercise and resistance training.

Comparator There was no comparative intervention used.

Study designs to be included Peer-reviewed scholarly journal articles reporting primary research findings and planned sub-analyses from randomized controlled trials.

Eligibility criteria Inclusion criteria

- Language: Papers available in English
- Publication type: Peer-reviewed scholarly journal articles reporting primary research findings and planned sub-analyses from randomized controlled trials
- Population/Age: Adult (greater than or equal to 18 years) human studies
- Physiological phenomenon of study: Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI) and Amnesic Mild Cognitive Impairment (aMCI), Parkinson's Disease (PD), Multiple Sclerosis (MS), selective memory complaints/memory issues, or non-demented healthy aging
- Physical activity intervention: Includes a physical activity intervention program
- Physiological measure: Structural magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), positron emission tomography (PET), cytokine, blood-biomarker, cerebrospinal fluid, or saliva analysis
- Behavioral measure: Includes behavioral, cognitive, neurocognitive, psychological, and/or neuropsychological assessment or battery
- Specificity of brain region analysis: Any, all brain region
- Outcomes: Any behavioral, cognitive, imaging, or exercise data which meets inclusion criteria

Exclusion criteria

- Language: Papers in non-English
- Publication type: Secondary reporting of research, research reviews, magazine articles, abstracts
- Population: Non-human, animal, or theoretical models
- Age: Youth (less than 18 years)
- Physiological phenomenon of study: All other neurological disorders, cardiovascular disorders, or metabolic disorders
- Physical activity intervention: No presence of physical activity measurement or intervention
- Physiological measure: No presence of structural magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), positron emission tomography (PET), cytokine, blood biomarker, cerebrospinal fluid, or saliva analysis
- Behavioral measure: Does not include any behavioral, cognitive, neurocognitive, psychological, or neuropsychological measure
- Specificity of brain region analysis: Spinal cord, peripheral nervous system, facial nerves
- Outcomes: Any behavioral, cognitive, imaging, or exercise data which do not meet inclusion criteria.
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Information sources A systematic review of three relevant databases (PsycINFO, PubMed, Web of Science) was conducted.

Main outcome(s) The main outcome of this study is to systematically review physical activity interventions as neuroprotective measures in healthy older human adults and investigate how the possible neurological and cognitive benefits of physical activity differ between healthy older adults and neurodegenerative (i.e., Alzheimer's disease, Parkinson's disease, multiple sclerosis) or cognitively impaired (i.e., mild cognitive impairment, amnesic mild cognitive impairment) human populations.

Additional outcome(s) The additional outcome of this study is to investigate (a) the anti-inflammatory and neuroplastic mechanism(s) induced by physical activity across brain structure and function; and (b) their association with specific cognitive domains (i.e., memory, executive function, attention) across healthy older adults and neurodegenerative or cognitively impaired human populations.

Quality assessment / Risk of bias analysis The Cochrane Risk of Bias 2 (RoB2) was utilized to evaluate the risk of bias of the studies included in the present analysis. The RoB2 is a widely used and validated tool for assessing the risk of bias in randomized controlled trials included in systematic reviews. This tool assesses the risk of bias in five domains: randomization, deviation from intended interventions, missing outcome data, measurement of the outcome, and selective reporting of results. Based on responses to signaling questions in each domain, the tool's algorithm generates outcomes of "low," "some concerns" of, or "high" risk of bias. The tool then generates an overall risk of bias based on the domain-level judgements. Authors M.M. and Z.N. reviewed included studies independently using the RoB2. If conflicting judgements arose, the authors thoroughly discussed disagreements. If a consensus could not be reached, a third independent reviewer arbitrated the conflict. If necessary information could not be identified in the text and the methodological protocol was referenced in the text, the authors extracted information from the protocol; however, if the protocol was not referenced in the text, the authors did not utilize any supplementary papers or information. The Jadad scale for reporting randomized controlled trials was utilized to evaluate the methodological quality of the studies included in the present analysis. The Jadad scale is a widely used valid measure of internal validity for randomized controlled trials that evaluates randomization, double-blinding, and a description of dropouts on a zero to five scale. Scores of zero to two indicate low-quality results, and scores of

three to five indicate high-quality results. Within the randomization domain, one point is allocated for mentioning randomization; an additional point is allocated for appropriate randomization methods, and a point is subtracted for inappropriate methods. Similarly, in the double-blinding category, one point is allocated for mentioning a double-blinding procedure; an additional point is allocated for appropriate procedures, and a point is subtracted for inappropriate procedures. If necessary information could not be identified in the text and the methodological protocol was referenced in the text, the authors extracted information from the protocol; however, if the protocol was not referenced in the text, the authors did not utilize any supplementary papers or information.

Strategy of data synthesis Systematic coding of relevant data fields was recorded and summarized by the authors to compare key findings between included articles. Physiological and cognitive-behavioral outcomes were either plainly stated or inferred from the data for each article. Data were also extracted for non-intervention controls from studies of neurodegenerative and cognitively impaired populations.

Interventions were coded as either aerobic exercise (AE), resistance exercise (RES), stretching exercise (STR), vestibular exercise (VEST), or multicomponent exercise (MIX). Multicomponent exercise interventions were characterized by multiple intervention categories (i.e., AE, RES, STR, VEST) employed under the same protocol. For instance, a protocol including aerobic exercise training and balance training was coded as a multicomponent intervention. Several studies utilized active control conditions. In these conditions, however, participants were still given an exercise program to follow that deviated from their normal daily activities and level of physical activity; therefore, active control conditions utilizing exercise programs were also treated as intervention programs.

Subgroup analysis Comparisons were made between physical activity intervention types at the level of the whole sample and at the level of neurodegeneration type. Additionally, comparisons were made between neurodegeneration types to investigate the effectiveness of physical activity interventions as a whole without specifying the type of intervention.

Sensitivity analysis No statistical analyses were performed as part of this review; therefore, there are no subsequent sensitivity analyses.

Country(ies) involved United States.

Keywords physical activity; exercise; neurodegeneration; aging; imaging; cognition; biomarkers.

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