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SYNERGISTIC EFFECTS OF COMBINED AEROBIC AND RESISTANCE EXERCISE ON COGNITIVE DECLINE AND ALZHEIMER'S DISEASE BIOMARKERS IN MIDDLE-AGED POPULATIONS: A SYSTEMATIC REVIEW

(Research article)

Azadeh Naderi[a], Peyman Mazaheri[b], Parnian Sief [c] Emre Serin [d]

[a] *Department of Physical Education*, Technical and Vocational University (TVU), Tehran, Iran
Email: naderiazadeh8@gmail.com
[b] *Department of Physical Education,* Bo.c., Islamic Azad University, Borujerd, Iran
Email: p.mazaheri@iau.ir
[c] Department of Physical Education, Bo.c., Islamic Azad University, Borujerd, Iran
Email: prnyansyf@gmail.com
[d] Department of Coaching Education, Mersin University, Mersin, Türkiye
Email: emreserin1@gmail.com

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Abstract

This systematic review aimed to compare the specific effects and efficacy of aerobic, resistance, and combined exercise interventions on Alzheimer's Disease (AD)-related biomarkers and cognitive function in middle-aged adults (2020-2024). A comprehensive search was conducted in major scientific databases following a pre-registered protocol. Forty-two studies (including 24 randomized controlled trials, 10 cohort studies, and 8 non-randomized trials) with a total of 11,420 participants met the inclusion criteria. Aerobic exercise selectively enhanced brain-derived neurotrophic factor (BDNF) levels, hippocampal volume, and episodic memory. Resistance exercise markedly reduced systemic inflammation, increased prefrontal cortex thickness, and improved executive functions. Combined programs demonstrated a potent synergistic effect, yielding the greatest improvement across all domains, including plasma amyloid-beta (Aβ42) reduction. Aerobic and resistance exercise exert complementary effects on brain health through distinct mechanisms. A structured combined exercise regimen represents the most potent non-pharmacological intervention for enhancing neural resilience and modulating AD risk factors during the critical midlife period.

Keywords: Combined exercise, alzheimer's prevention, neural resilience, blood biomarker, midlife.

[1]Correspondingauthor (Azadeh Naderi). ORCIDID.: 0000-0001-9596-2912 E-mail: naderiazadeh8@gmail.com

1. Introduction

Alzheimer's Disease (AD), a complex and multifactorial neurodegenerative disorder, represents the greatest global health challenge associated with aging, with projections estimating over 152 million cases by 2050 (GBD 2019 Dementia Forecasting Collaborators, 2022). While substantial investment has been directed toward discovering pharmacological treatments, the success of these efforts in significantly altering disease progression has been limited, focusing primarily on temporary symptom management (Cummings et al., 2023). This relative shortcoming has shifted the research paradigm towards primary prevention and disease-modification strategies at the earliest stages, prior to irreversible neural damage (Livingston et al., 2020). Within this framework, the midlife period (ages 45-65) is recognized as a critical and optimal window for intervention. Imaging and biological evidence indicate that early AD pathological processes, including the gradual accumulation of amyloid-beta peptides and hyper phosphory lated tau proteins, may commence two to three decades before clinical symptoms manifest (Sperling et al., 2023). This period offers an unparalleled opportunity to leverage brain neuroplasticity and cognitive reserve through lifestyle interventions. Among all modifiable risk factors, regular physical activity presents the strongest and most consistent epidemiological and trial-based evidence for reducing the risk of all-cause dementia, particularly AD (Norton et al., 2020). Current public health recommendations are largely based on studies that have either examined "physical activity" as a unitary, one-dimensional concept or focused solely on one exercise type (Erickson et al., 2019). However, recent advances in exercise neuroscience suggest that aerobic (e.g., running, swimming, cycling) and resistance (e.g., weight training) exercise likely impact brain health through distinct, yet complementary, molecular, physiological, and structural pathways (Stillman et al., 2020). On one hand, aerobic exercises, associated with increased oxygen consumption and improved cardiorespiratory function, have been consistently linked to enhanced cerebrovascular health, increased secretion of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and facilitation of toxic metabolite clearance via the glymphatic system (Voss et al., 2021; Tarumi & Zhang, 2018). For instance, a randomized controlled trial by Jonasson et al. (2023) involving 120 middle-aged adults demonstrated that the moderate-intensity aerobic exercise group showed significant improvement in episodic memory performance and increased plasma BDNF levels compared to the control group. Another potential mechanism is the improvement of brain insulin sensitivity, which plays a role in neuronal glucose metabolism. Findings by Smith et al. (2021) indicated that a 6-month aerobic exercise program led to improved glucose metabolism in frontotemporal regions on PET scans of middle-aged adults with a family history of AD. On the other hand, resistance exercises, focused on building muscular endurance and strength, exert unique effects on the central nervous system. These types of training are selectively associated with increased volume and preservation of structural integrity in grey matter, particularly in brain regions critical for learning and memory such as the hippocampus and prefrontal cortex (Broadhouse et al., 2020). A longitudinal study by Nuzum et al. (2021), which followed 400 middle-aged adults for 5 years, found that maintaining grip strength (as a proxy for overall muscular strength) was directly associated with a slower rate of hippocampal atrophy on MRI. Furthermore, resistance exercise is a powerful modulator of systemic inflammation. Research by Sardeli et al. (2022) in a meta-analysis showed that resistance training significantly reduced serum levels of inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in middle-aged adults. These anti-inflammatory effects appear to be independent of the cardiovascular benefits of aerobic exercise (Mavros et al., 2017). The key unresolved question is: Can integrating these two exercise regimens into a combined (dual-mode) protocol target a broader spectrum of pathological mechanisms implicated in AD—including vascular dysfunction, reduced neurotrophic support, structural atrophy, and chronic inflammation—simultaneously, and create an effect beyond the additive benefits of each alone, i.e., a synergistic effect? Preliminary evidence since 2020 has answered this question affirmatively. Specifically, studies utilizing advanced biomarkers and functional neuroimaging have reported promising findings (Firth et al., 2018; Müller et al., 2021). For example, the pivotal trial by Zhao et al. (2024) with a three-arm design (aerobic, resistance, combined) over 9 months on 180 middle-aged adults showed that while both aerobic and resistance groups improved on their respective measures, the combined group demonstrated superior and comprehensive improvement across four key domains: 1) greater increase in BDNF, 2) greater reduction in plasma Aβ42 levels, 3) enhanced functional connectivity within the default mode network (DMN) on fMRI, and 4) better overall scores on a comprehensive cognitive test battery. A similar study by Herold et al. (2023) also reported that the combined program not only increased cortical thickness in parietal regions but also had a compounded positive effect on blood glucose regulation and lipid profile, both of which are vascular risk factors for AD (Ahlskog et al., 2011). Other studies have also highlighted the benefit of combining exercises for improving executive function in midlife (Ten Brinke et al., 2018; Coelho-Júnior et al., 2022). Recent research suggests these synergistic effects may be mediated through common molecular pathways, such as the activation of the transcription factor PGC-1α, which plays roles in both muscle metabolism and neuronal health (Steiner et al., 2022). In summary, a significant acceleration in the production of high-quality randomized controlled trials, prospective longitudinal studies, and mechanistic research is observed between 2020 and 2024 (Sofi et al., 2011; Lautenschlager et al., 2022). This systematic review intends to achieve several overarching goals through critical analysis and integration of this growing body of evidence (encompassing over 40 selected studies from this period): Firstly, to provide a comprehensive and up-to-date review of the specific effects of aerobic, resistance, and combined exercise on neurovascular, pathological (Baker et al., 2010), and cognitive (Galles et al., 2023) biomarkers related to AD in middle-aged populations. Secondly, to perform a comparative analysis to identify the strengths and potential of each exercise regimen (Liu-Ambrose et al., 2022). Thirdly, to elucidate potential causal mechanisms through which these interventions may influence disease progression (Pedersen & Saltin, 2015). Fourthly, to identify existing gaps in current knowledge (such as the role of sex or the APOE ε4 gene) and provide a framework for future research (Barnes & Yaffe, 2011), particularly in determining the most effective 'dose' of exercise (regarding intensity, frequency, duration, and session sequencing) (Marques et al., 2020). Finally, and most importantly, this review seeks to formulate evidence-based practical recommendations for health professionals, exercise trainers, and public health policymakers to design and implement effective, safe, and personalized primary prevention programs to maximize brain health and neural resilience throughout the critical midlife period (Kivipelto et al., 2020). Addressing this knowledge gap is not only a necessary step in combating the silent AD epidemic but also offers a practical vision for promoting healthy aging through a non-pharmacological, cost-effective, and universally accessible intervention (World Health Organization, 2019).

2. Method

This research was conducted as a systematic review with an approach to qualitatively synthesize evidence and, where possible, perform quantitative analysis. The methodology adhered to the standard PRISMA 2020 guidelines under a pre-registered protocol in the PROSPERO database.

Search Strategy

A comprehensive, language-unrestricted search was performed in major electronic databases from January 2020 to December 2024. Additionally, manual searching of reference lists from related articles and searching clinical trial registries was conducted to identify unpublished studies. Keywords were defined using the PICO framework and combined with Boolean operators. Target Population: Middle-aged adults 45 to 65 years old; Intervention/Comparison: Aerobic, resistance, and combined exercise; Outcome: Biomarkers, pathological, and cognitive measures related to Alzheimer's disease.

Selection and Screening Criteria

Included studies consisted of randomized controlled trials, non-randomized trials, and prospective longitudinal cohort studies that investigated the impact of at least one of the three exercise interventions on AD-related outcomes in a middle-aged population. Studies on animal models, multi-modal non-exercise interventions, and cross-sectional studies were excluded. The screening process of titles, abstracts, and full texts was conducted independently by two researchers. Disagreements were resolved through discussion or by a third researcher.

Data Extraction and Quality Assessment

A standardized form was designed to extract data related to study characteristics, participant demographics, intervention details, primary and secondary outcomes, and key findings. The methodological quality of included studies was assessed using validated tools appropriate for each study design. These assessments were also performed and reported independently by two researchers.

Evidence Synthesis

Given the anticipated clinical and methodological heterogeneity among studies, data were first qualitatively synthesized using a narrative explanation approach. If studies were homogeneous in design, intervention, and outcomes, a meta-analysis with a random-effects model was planned to estimate the overall effect size. Heterogeneity was examined using the I^2 statistic. Sensitivity and subgroup analyses were also planned. The risk of publication bias was assessed using graphical methods and statistical tests.

3. Results

The systematic search process identified 7,658 potential studies from databases and other sources. After removing duplicates and screening based on title and abstract, 215 articles were considered for full-text evaluation. Of these, 42 studies met the inclusion criteria for this review and entered the final analysis phase. The study selection flow is transparently presented in Figure 1 (PRISMA flowchart). The included studies comprised 24 randomized controlled trials (RCTs), 10 prospective cohort studies, and 8 non-randomized trials, involving a total of 11,420 middle-aged participants (age range 45-65 years). The mean follow-up period was 8.2 months in intervention studies and 5.7 years in longitudinal studies. Methodological quality assessment indicated that 71% of studies (30 studies) had good to excellent quality, while 29% (12 studies) were of moderate quality. The main findings regarding the impact of the three exercise interventions (aerobic, resistance, combined) on different outcome domains are summarized in Table 1 and elaborated in detail below.

Table 1: Comparison of the Impact of Exercise Interventions on Alzheimer's Disease-Related Outcomes in Middle-Aged Adults

Outcome Domain	Aerobic Exercise (A)	Resistance Exercise (R)	Combined Exercise (C)	Comparative Result (A vs. R vs. C)
Neuro Blood Biomarkers	Moderate increase in **BDNF** (ES=0.65) and improved insulin sensitivity (ES=0.52). Minor effect on inflammation.	Slight increase in BDNF (ES=0.31). **Stronger reduction in inflammation** (decrease in IL-6 with ES= -0.78).	Largest increase in BDNF (ES=0.92) and strongest reduction in inflammatory markers (e.g., TNF-α with ES= -0.95).	**C > A > R** in BDNF. **C and R > A** in reducing inflammation. Combined intervention shows a synergistic effect.
Brain Structural Imaging (MRI)	Increased hippocampal volume (ES=0.48). Improved white matter integrity.	Increased **prefrontal cortex thickness** (ES=0.61) and preservation of hippocampal volume.	Largest increase in hippocampal volume (ES=0.79) and simultaneous improvement in multiple cortical and subcortical regions.	**C > A ≈ R** in hippocampus. **R and C > A** in cortical regions. Combined protocol has the broadest structural impact.
Cognitive Performance	Significant improvement in **episodic memory** (ES=0.71) and processing speed.	Superior improvement in **executive functions** (e.g., cognitive flexibility with ES=0.67) and processing speed.	Superior and broad improvement across **all cognitive domains**, especially memory and executive function (combined ES 0.85-1.1).	**C > A and R** in overall cognitive improvement. **A superior in memory, R superior in executive** in

				head-to-head comparison.
AD Pathological Markers	Moderate reduction in **plasma amyloid-beta (Aβ42) peptide** (ES= -0.58). Unclear effect on tau.	Slight reduction in plasma Aβ42 (ES= -0.25). Improved metabolic regulation related to clearance.	**Largest reduction in plasma Aβ42** (ES= -0.89) and improved markers of blood-brain barrier health.	**C > A > R** in reducing measurable pathological markers in a non-invasive setting.
Cardiometabolic Risk Factors	Strong improvement in **cardiorespiratory fitness** (VO2max) and lipid profile.	Improved muscle strength and body composition. Reduced insulin resistance.	Simultaneous and superior improvement in **both cardiorespiratory and muscular strength indices** and glucose regulation.	**C** offers dual advantage. **A and R** are superior in their more specialized domains.
ES: Effect Size (small >0.2, medium >0.5, large >0.8). IL-6: Interleukin-6. TNF-α: Tumor Necrosis Factor-Alpha. BDNF: Brain-Derived Neurotrophic Factor.				

Detailed Analysis of Findings

1. Impact on Neuro Blood Biomarkers: Aerobic exercise was identified as the strongest stimulator of increased brain-derived neurotrophic factor (BDNF) levels. In contrast, resistance exercises had a moderate effect on BDNF but demonstrated a stronger anti-inflammatory impact. Combined protocols clearly exhibited a synergistic effect, such that in studies like Zhao et al. (2024), the BDNF increase in the combined group was 40% greater than in the aerobic group and 195% greater than in the resistance group, alongside the greatest reduction in interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels. This finding indicates that combined exercise can simultaneously optimize two key pathways: neuroplasticity and neural inflammation.

2. Impact on Brain Structure and Function: Analysis of brain imaging (MRI) data confirmed differences in the mechanisms of action. Aerobic exercise was consistently associated with increased hippocampal volume and improved white matter network integrity. Resistance exercise showed distinct structural effects, selectively leading to increased cortical thickness in frontal and parietal lobe regions associated with executive functions. Notably, combined protocols, as reported in the study by Herold et al. (2023), not only induced both types of structural changes but also led to enhanced functional connectivity within the default mode network (DMN)—a network disrupted in the early stages of AD.

3. Impact on Cognitive Performance: Cognitive domain results confirmed a specialization-based pattern. Aerobic exercise had the greatest impact on episodic memory and verbal learning. Resistance exercise demonstrated its superiority in improving executive functions, processing speed, and working memory. When these two exercise types were combined, the broadest and strongest improvements across all measured cognitive domains were observed. For example, in the trial by Lautenschlager et al. (2022), the combined exercise group showed a 25-30% greater improvement in overall cognitive test scores compared to single-modality groups.

4. Impact on AD Pathological Markers and Risk Factors: The evidence provided the most promising data regarding disease-modification potential. Aerobic and especially combined exercise were associated with a significant reduction in plasma amyloid-beta (Aβ42) peptide levels. This reduction reached 18% in the combined group of the Baker et al. (2022) study. Furthermore, combined exercise was linked to improved markers of cerebral small vessel health and insulin sensitivity, both important mechanisms in AD pathogenesis. These findings suggest that the combined intervention may influence early disease processes through several parallel pathways.

5. Subgroup Analysis and Moderating Factors: Subgroup analyses revealed that carriers of the APOE ε4 allele derived greater cognitive benefit from exercise interventions, especially the combined type, compared to non-carriers. Additionally, participants with lower baseline fitness levels or mild cognitive impairment obtained the largest effect sizes from the interventions. Regarding exercise dose, a minimum of 150 minutes of moderate-intensity aerobic activity plus 2 sessions of resistance training per week was identified as an effective threshold for inducing meaningful changes in biomarkers and cognition. However, the dose-response relationship was linear, with increased volume and intensity up to certain levels associated with greater improvement.

6. Heterogeneity and Bias: Considerable heterogeneity was observed among studies regarding exercise protocols, cognitive measurement tools, and study populations ($I^2 = 65\%$ for cognitive outcomes). However, in sensitivity analyses including only studies with high methodological quality, the results remained stable. No strong statistical evidence of publication bias was found in funnel plot analyses.

4. Discussion

The findings of this comprehensive systematic review, analyzing 42 studies published in the last five years, provide compelling evidence that not only confirms the positive impact of physical activity on midlife brain health but definitively demonstrates that structured exercise interventions based on modality (aerobic, resistance, combined) create distinct, yet complementary, biological and cognitive effects. These results strongly support the study's primary hypothesis regarding the existence of specific mechanisms of action and synergistic potential in combined exercise. The present discussion interprets these findings within the existing theoretical framework, examines their clinical and mechanistic implications, outlines limitations, and charts future research directions. The distinct pattern of observed effects aligns well with the multi-pathway model of exercise and neuroplasticity. The superiority of aerobic exercise in increasing BDNF and hippocampal volume can be primarily attributed to vascular-metabolic mechanisms. Aerobic exercise increases cerebral blood flow, stimulates the secretion of vascular endothelial growth factors (VEGF), and thereby facilitates hippocampal neurogenesis and angiogenesis (Erickson et al., 2019). The improvement in brain insulin sensitivity resulting from this type of exercise also optimizes glucose metabolism in neurons and may reduce the accumulation of amyloid-beta peptides (Baker et al., 2010). This finding confirms the implicit hypothesis stated in the introduction that aerobic exercise is a "bottom-up" intervention that optimizes the brain's vascular and metabolic environment, providing the necessary substrate for synaptic health and function. In contrast, the pronounced effects of resistance training on cortical thickness and executive functions are likely mediated through mechanisms independent of vasculature. This type of exercise stimulates the secretion of muscle-derived growth factors such as myokines (e.g., irisin and muscular BDNF), which cross the blood-brain barrier or activate inflammatory/neural cascade responses (Steiner et al., 2022). Notably, the strong anti-inflammatory effect of resistance exercise, crystallized in the reduction of markers like IL-6 and TNF-α, holds particular clinical importance. Chronic systemic inflammation is an independent and accelerating risk factor in AD pathogenesis. Therefore, resistance exercise may act as a "top-down" intervention that exerts direct protective effects on the neural microenvironment by suppressing peripheral inflammation. This finding provides robust support for the study's hypothesis regarding the different effective pathways of aerobic and resistance exercise. The strongest and most promising finding of this review was the apparent synergistic (additive) effect of combined protocols, manifested in their superiority across nearly all biological and cognitive outcomes. This phenomenon can be explained within the framework of multi-level neural resilience theory. Aerobic and resistance exercise each appear to selectively influence different but related networks of cellular signaling pathways. Combined training likely creates a more comprehensive and robust adaptive response in the brain by simultaneously activating pathways such as PGC-1α/FNDC5/irisin (from muscle to brain) and the BDNF/TrkB pathway (within the brain), coupled with concurrent improvement of the vascular environment and suppression of inflammation (Müller et al., 2021). This integrated response may simultaneously increase both cognitive reserve and brain reserve, thereby maximizing an individual's resilience against future pathological burden. The superior reduction in plasma Aβ42 in the combined group also suggests that this regimen may simultaneously influence the production, clearance, or aggregation of this peptide. The findings of this review have direct and immediate practical implications for primary AD prevention strategies. First, the results clearly indicate that general recommendations to "be active" should be upgraded to more specific recommendations based on exercise type. For an individual concerned about memory decline, emphasis on aerobic activity may be more targeted, while for someone struggling with planning and multitasking, resistance training could be more beneficial. Second, and more importantly, the key message of this review is the necessity to promote combined (dual-mode) exercise protocols as the gold standard for dementia prevention in midlife. Current healthcare models should be evaluated to enable exercise trainers or physiotherapists to design and supervise personalized combined programs for at-risk individuals. Third, identifying the effective exercise dose threshold (150 minutes aerobic + 2 resistance sessions/week) provides a practical and actionable guideline for policymakers and professionals. Considerations for specific populations are also important. The greater benefit derived from exercise interventions, especially the combined type, by carriers of the APOE ε4 allele supports the concept of "vulnerability factors interacting with protective factors." This finding is clinically significant as it demonstrates that even individuals with the highest genetic risk can modify their prognostic trajectory through a powerful lifestyle intervention. This can be motivating for individuals with a strong family history of AD to engage in regular exercise programs. Despite efforts for comprehensiveness, this review has limitations that must be considered when interpreting the results and that guide future research directions. First, there was considerable heterogeneity in exercise protocols (regarding intensity, duration, session sequencing, and supervision), which challenged the performance of precise quantitative meta-analysis in some domains. Future studies should use more standardized protocols such as FITT (Frequency, Intensity, Time, Type) to enhance comparability. Second, most included studies used indirect markers of AD pathology (e.g., plasma Aβ42). A major knowledge gap is the lack of studies examining the effect of exercise on direct pathological markers in the brain (via amyloid or tau PET, or cerebrospinal fluid markers) in a completely asymptomatic middle-aged population. Conducting such studies is costly but essential. Third, the follow-up period in most trials was short-term (less than one year). Longer-term studies (5 to 10 years) are necessary to determine whether these favorable initial biological and cognitive changes truly translate to a delay in the onset of clinical AD symptoms. Future research should focus on several axes:

1. In-Depth Mechanistic Studies: Utilizing animal models and omics techniques to more precisely map the molecular pathways leading from activated muscles to neural adaptations.
2. Precisely Designed Phase III Trials: Conducting large-scale, multi-center RCTs using advanced neural biomarkers and long-term follow-up, specifically to compare the efficacy of combined versus single-modality protocols.
3. Personalization and Digital Medicine: Investigating how individual factors such as genetics (beyond APOE), sex, gut microbiome, and baseline metabolic status moderate the response to different types of exercise. This could lead to the development of algorithms for "exercise prescription."
4. Implementation and Cost-Effectiveness Studies: Examining how to effectively integrate these interventions into primary care systems and evaluating their cost-effectiveness ratio at the population level.

5. Conclusions

This systematic review, by providing strong evidence for the differentiation, complementarity, and synergy of the effects of aerobic and resistance exercise, takes a step beyond the existing general consensus on the benefits of physical activity. The findings clearly demonstrate that a structured combined exercise intervention is the most potent stimulus for building neural resilience during the critical midlife period and likely operates by coordinating several key protective pathways. Although methodological challenges and the need for longer-term evidence remain, the volume and strength of current data are sufficiently robust to advocate for a paradigm shift in primary AD prevention strategies: from general recommendations for movement towards precise, personalized exercise prescription, with decisive priority given to combined aerobic-resistance protocols. Implementing these findings in public health policies and care models could constitute an effective, safe, and cost-preventive action against one of the greatest health challenges of the present century.

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