QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

Cite as: KARBOWNIK, Liwia, KASTERKA, Natalia, KOLASA, Magdalena, FIGWER, Agnieszka, FIGWER, Krzysztof, DZITKOWSKA, Kinga, CZARNY, Norbert, BRONIECKA, Anna, ŚMIGIELSKI, Michał and GARBACIAK, Jędrzej. Physical Exercise and Neuroinflammation in Alzheimer's Disease and Mild Cognitive Impairment: Molecular Mechanisms and Clinical Relevance. Quality in Sport. 2026;59:72815. https://doi.org/10.12775/QS.2026.59.72815

ARTICLE TIMELINE
Received: 29.05.2026. Revised: 20.06.2026. Accepted: 20.06.2026. Published: 25.06.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines: Medical Sciences; Health Sciences.
Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Nauki medyczne; Nauki o zdrowiu.

Physical Exercise and Neuroinflammation in Alzheimer's Disease and Mild Cognitive Impairment: Molecular Mechanisms and Clinical Relevance

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Abstract

Background

Alzheimer's disease (AD) and mild cognitive impairment (MCI) are associated with neuroinflammatory, vascular, and metabolic alterations beyond amyloid-beta and tau pathology. Physical exercise has attracted growing interest as a non-pharmacological intervention, although evidence linking exercise-induced changes in inflammatory pathways to clinical outcomes remains limited.

Aim of the Study

This narrative review critically examines the evidence on whether physical exercise influences neuroinflammatory processes in AD and MCI, with particular attention to biological mechanisms, biomarker interpretation, clinical outcomes, safety, and current research limitations.

Materials and Methods

A structured literature search was conducted using PubMed/MEDLINE, PubMed Central, selected publisher databases, and relevant clinical guidelines. Priority was given to randomized controlled trials, systematic reviews, meta-analyses, consensus statements, and key mechanistic studies. As this was a narrative review rather than a registered systematic review, formal PRISMA reporting, quantitative meta-analysis, and GRADE assessment were not performed.

Conclusion

Physical exercise may be considered a supportive intervention for individuals with MCI and early AD, with potential benefits for physical function, overall health, and possibly cognition. However, current evidence does not support its classification as a disease-modifying anti-neuroinflammatory therapy. Future studies should focus on well-defined patient populations, appropriate active comparators, supervised multimodal exercise programmes, standardized safety reporting, and combined clinical and biomarker outcomes.

Keywords: Alzheimer's disease; mild cognitive impairment; physical exercise; neuroinflammation; biomarkers; dementia.

Introduction

Alzheimer's disease (AD) is the most common cause of dementia and is often preceded by mild cognitive impairment (MCI). Current diagnostic frameworks increasingly define AD using biological markers such as amyloid, tau, and neurodegeneration, while acknowledging that disease progression is also influenced by vascular, inflammatory, and metabolic factors [1–4]. In clinical practice, cognitive decline in older adults rarely results from a single pathological mechanism. Patients often present with multiple overlapping contributors, including hypertension, insulin resistance, physical inactivity, sleep disturbances, frailty, and depressive symptoms, all of which may interact with underlying AD pathology.

Neuroinflammation is now recognized as an important component of AD pathophysiology. Microglia, astrocytes, complement activation, inflammasome signaling, endothelial dysfunction, and blood–brain barrier impairment all interact with amyloid-beta and tau pathology throughout disease progression [1,5–7]. However, these processes are complex and not exclusively harmful. Glial activation may support amyloid clearance and tissue repair in some contexts, whereas chronic or dysregulated activation may contribute to synaptic dysfunction, oxidative stress, and neuronal injury [1,5,6]. This complexity makes neuroinflammation a challenging therapeutic target. Physical exercise is of growing interest as a non-pharmacological intervention because it affects multiple pathways relevant to AD, including blood pressure regulation, insulin sensitivity, endothelial function, skeletal muscle metabolism, sleep quality, and neurotrophic signaling [8–10]. At the same time, interpreting these effects remains difficult. Improvements in cognition or daily functioning following exercise may reflect better cardiovascular health, mood, mobility, or social engagement rather than direct modulation of neuroinflammatory processes.

This review examines the extent to which physical exercise influences neuroinflammatory processes in AD and MCI. Given the complexity of proposed mechanisms, it is important to distinguish biological hypotheses from effects that have been demonstrated in clinical studies.

Neuroinflammation as a therapeutic target: complexity beyond inflammation alone

Current evidence supports neuroinflammation as an important component of AD pathophysiology, involving microglia, astrocytes, complement activation, cytokine signaling, endothelial dysfunction, and interactions between peripheral and central immune systems [1,5–7]. Genetic studies further support the role of immune and microglial pathways in AD susceptibility, particularly mechanisms related to lipid metabolism, phagocytosis, and innate immune regulation [4]. However, this does not mean that broadly suppressing inflammation is necessarily beneficial. The effects of neuroinflammatory processes likely depend on disease stage, timing, cellular phenotype, and regional brain context.

This complexity is particularly relevant when considering exercise as an intervention. Physical activity may reduce chronic low-grade systemic inflammation, improve vascular and metabolic health, and support neuroplasticity, but these effects are systemic rather than specific to the central nervous system. In individuals with MCI, where neuronal damage may be less advanced, such effects could still influence disease progression indirectly. In established AD, exercise may provide meaningful clinical benefits by preserving mobility, reducing frailty, and supporting daily functioning, even without measurable changes in core AD pathology. This broader interpretation is consistent with multidomain dementia prevention strategies and observational evidence linking physical activity with lower risk of cognitive decline and dementia [34–36].

Interpreting mechanistic claims requires caution. Improvements in cognition or physical function after exercise do not necessarily indicate direct modulation of neuroinflammatory pathways. For example, improved insulin sensitivity, vascular function, or cerebral perfusion may contribute to better cognitive outcomes without directly altering glial activation. For this reason, the term *neuroinflammation* should be used carefully and should refer specifically to central immune and glial processes rather than broader systemic inflammatory or metabolic changes.

Clinical outcomes in MCI and AD

Randomized trials and systematic reviews suggest that physical exercise may provide modest clinical benefits in older adults with MCI or dementia, although findings remain heterogeneous. The EXERT trial is particularly relevant because it evaluated a structured exercise intervention in individuals with amnestic MCI using biomarker assessment and an active stretching/balance comparator [11]. The lack of clear superiority of higher-intensity

aerobic exercise over the comparator does not necessarily indicate lack of benefit. Instead, it suggests that factors such as supervision, regular social interaction, structured routines, and even low-intensity physical activity may contribute meaningfully to observed outcomes.

Earlier trials have similarly reported modest improvements in cognitive or functional outcomes in at-risk older adults and individuals with MCI, particularly when interventions were sustained and supervised [12–15]. Meta-analyses in MCI and dementia populations also suggest potential benefits for global cognition, activities of daily living, and behavioral symptoms, although substantial heterogeneity exists in exercise type, intensity, duration, diagnostic definitions, and outcome measures [16–20]. Taken together, current evidence supports exercise as a useful supportive intervention, but not as a proven disease-modifying treatment for AD.

Comparator selection is an important methodological issue when interpreting this literature. Sedentary control groups may overestimate the apparent effect of exercise, as intervention participants also receive increased attention, supervision, routine, and social engagement. Conversely, active comparators such as stretching, balance training, or health education may reduce between-group differences because they are not biologically inert. This does not weaken the clinical relevance of exercise, but it does make attribution of specific biological effects more difficult.

In established dementia, treatment priorities often shift from disease modification to preservation of function and quality of life. Preventing deconditioning, sarcopenia, falls, sleep disruption, and caregiver burden may be more realistic clinical goals than measurable biomarker-defined neuroprotection. For many patients and caregivers, maintaining mobility, reducing falls, and preserving daily functioning may be as clinically meaningful as small changes in cognitive test performance. These benefits are important, but they should not be conflated with direct evidence of anti-neuroinflammatory disease modification.

Interpretation of clinical outcomes is further complicated by the limitations of neuropsychological assessment itself. Cognitive performance in older adults may vary for reasons unrelated to disease progression or the intervention being studied, including fatigue, poor sleep, mood, anxiety, intercurrent illness, or simple day-to-day fluctuations in attention and motivation. Repeated exposure to the same cognitive tests may also introduce practice effects, particularly in individuals with milder impairment, making small changes more

difficult to interpret. At the same time, conventional neuropsychological measures may not be sensitive enough to capture subtle but clinically meaningful changes in areas such as executive functioning, dual-task performance, or everyday adaptive abilities.

Ceiling and floor effects present an additional challenge. Patients with very mild impairment may show little measurable improvement simply because baseline performance remains relatively preserved, whereas those with more advanced dementia may have limited capacity to demonstrate detectable gains despite potential functional benefit. For this reason, a lack of statistically significant improvement in standard cognitive endpoints should not automatically be taken as evidence that an intervention lacks clinical value.

The duration of intervention studies is another important limitation. Alzheimer's disease develops over many years, often long before overt clinical symptoms appear, whereas exercise trials are typically conducted over months rather than extended follow-up periods. As a result, shorter studies may be better suited to detecting symptomatic or functional changes than any meaningful influence on long-term disease progression. Conversely, if exercise does exert biologically relevant protective effects, shorter intervention periods may simply be too brief to capture them.

Challenges in defining clinically meaningful outcomes

Interpreting clinical benefit in exercise studies involving patients with MCI and Alzheimer's disease remains challenging. Cognitive test scores are commonly used as primary outcomes, but modest numerical changes do not necessarily reflect noticeable differences in everyday functioning, independence, caregiver burden, or quality of life. At the same time, the absence of statistically significant cognitive improvement does not automatically mean that an intervention lacks clinical relevance. In progressive neurodegenerative disease, preserving mobility, maintaining daily function, reducing fall risk, or simply slowing further decline may represent outcomes of genuine clinical importance.

Comparison across studies is made more difficult by the wide variation in selected endpoints. Some trials focus mainly on neuropsychological measures, while others place greater emphasis on functional performance, behavioural symptoms, physical capacity, or biomarker-based outcomes. Benefit in one domain does not necessarily translate into measurable improvement in another. For example, better cardiovascular fitness or gait stability may improve day-to-day functioning without producing a clear cognitive signal during a relatively

short follow-up period. This likely contributes to some of the inconsistency seen across the literature and makes the definition of treatment success less straightforward.

Microglia, astrocytes and glial biomarkers

Microglia play a central role in AD pathophysiology through their involvement in amyloid clearance, synaptic remodeling, and inflammatory signaling. PET imaging, post-mortem studies, and transcriptomic analyses suggest that microglial activation may interact with tau pathology in anatomically vulnerable brain regions [6]. Astrocytes are also important, given their roles in glutamate homeostasis, metabolic support, maintenance of the blood–brain barrier, and inflammatory signaling. In human studies, plasma and CSF GFAP have emerged as clinically relevant markers of astroglial activation across the AD continuum [21–24].

The main challenge lies in biomarker interpretation rather than biological relevance. Elevated GFAP does not indicate whether astrocytic activation is protective, compensatory, or harmful. Similarly, sTREM2 may reflect microglial activity, but this activity may represent phagocytosis, tissue repair, inflammatory signaling, or mixed cellular states. YKL-40 and circulating cytokines are also relatively non-specific. For this reason, changes in a single biomarker following an exercise intervention should not be interpreted as direct evidence of reduced neuroinflammation unless supported by broader biomarker, imaging, or clinical findings. Interpretation of neuroinflammatory biomarkers is further complicated by the fact that their biological significance may change over the course of disease progression. Microglial and astrocytic activation are dynamic processes, and the same biomarker may not reflect the same underlying mechanism at different disease stages. In earlier phases, glial activation may be linked to compensatory responses such as immune surveillance, amyloid clearance, or tissue repair, whereas in more advanced disease it may be associated with chronic inflammatory signalling and ongoing neurodegeneration. This makes interpretation of exercise-related biomarker changes particularly difficult, especially in studies with short follow-up or clinically heterogeneous populations. An increase in a biomarker after intervention cannot automatically be assumed to indicate harm, just as a reduction should not automatically be interpreted as evidence of benefit. Without longitudinal assessment and meaningful clinical correlation, isolated biomarker changes may be difficult to interpret reliably. Interpretation is further complicated by the fact that biomarker dynamics and clinical outcomes may evolve on different timescales. Biological changes may precede measurable

functional improvement, whereas short-term clinical benefits may occur through symptomatic mechanisms without detectable biomarker change.

This issue is particularly relevant in MCI, where biomarker abnormalities may appear before clear clinical symptoms. A biomarker associated with future disease risk is not necessarily suitable as a treatment-response marker. For example, plasma GFAP may help identify amyloid-associated astroglial activation, but a reduction following intervention could reflect multiple factors, including altered glial activity, assay variability, changes in comorbidity burden, or regression to the mean. Neurofilament light chain should also be interpreted cautiously, as it primarily reflects axonal injury rather than neuroinflammation itself. While it may provide useful context regarding neuronal damage, it does not demonstrate direct modulation of microglial or astrocytic processes by exercise [24].

Interpretation is further complicated by the marked biological and anatomical heterogeneity of neuroinflammatory processes within the brain. Microglial activation does not occur uniformly across brain regions, and its relationship with amyloid accumulation, tau propagation, synaptic dysfunction, and neurodegeneration may vary depending on disease stage and anatomical context. Consequently, biomarkers measured in plasma or cerebrospinal fluid provide only an indirect and substantially simplified representation of processes occurring within the central nervous system. Biologically relevant regional effects of exercise may therefore remain undetected when assessment relies solely on circulating biomarkers.

Methodological limitations add further uncertainty. Plasma biomarkers are clinically attractive because of their accessibility and scalability, but their concentrations may be influenced by multiple non-neurological factors, including renal function, systemic inflammatory states, assay variability, and common age-related comorbidities. In older adults, chronic cardiovascular disease, diabetes, obesity, infection, and frailty may all affect inflammatory signalling independently of Alzheimer-related pathology. This reduces specificity when attempting to attribute biomarker changes directly to exercise-induced modulation of central neuroinflammatory pathways.

Neuroimaging approaches may offer more direct mechanistic insight, but they also present important limitations. PET imaging targeting neuroinflammatory pathways, including TSPO-based tracers, has improved understanding of glial activation in research settings, yet currently available tracers have limited cellular specificity, and interpretation may be

influenced by genetic variability affecting ligand binding. In addition, microglial activation should not be viewed as a simple binary phenomenon. Microglia may adopt a range of functional states, including potentially protective, adaptive, or maladaptive responses, which complicates simplified interpretation. Current imaging techniques are not always able to distinguish these biologically distinct states with sufficient precision.

Temporal variability represents another important challenge. Neuroinflammatory biomarkers may fluctuate over time in response to disease progression, acute illness, medication changes, sleep disturbance, or recent physical activity. Exercise itself can transiently alter inflammatory signalling, particularly shortly after exertion, meaning that biomarker levels may reflect short-term physiological responses rather than sustained biological adaptation. Without standardized sampling protocols and repeated longitudinal assessment, distinguishing transient variation from clinically meaningful mechanistic change remains difficult.

Taken together, these limitations suggest that isolated biomarker changes should be interpreted with caution. A reduction in a single marker does not necessarily indicate therapeutic benefit, just as an increase does not automatically imply harm. More informative mechanistic studies will likely require multimodal approaches combining fluid biomarkers with neuroimaging, cognitive assessment, and clinically meaningful functional outcomes, rather than relying on individual surrogate markers alone.

Peripheral inflammation, vascular biology, and blood–brain barrier function

Physical exercise may reduce cardiometabolic risk, chronic low-grade inflammation, and endothelial dysfunction, while improving overall physiological resilience [8,9,25]. These mechanisms are relevant because vascular injury, hypertension, diabetes, obesity, and physical inactivity are all associated with an increased risk of cognitive decline and dementia [3,26–29]. Improved vascular health may also indirectly influence neuroinflammatory processes by supporting cerebral perfusion and maintaining blood–brain barrier integrity. Improved sleep may be one of the indirect mechanisms through which exercise influences cognitive health. Better sleep quality could affect cognitive performance, inflammatory regulation, and possibly glymphatic function, although direct evidence in Alzheimer's disease populations remains limited.

At the same time, peripheral inflammatory markers should be interpreted with caution. Cytokines such as IL-6, TNF-alpha, and IL-1beta are influenced by multiple factors,

including recent physical activity, infection, adiposity, sleep quality, medication use, and methodological differences between assays. A reduction in post-intervention IL-6, for example, may reflect changes in systemic metabolic or adipose inflammation rather than direct modulation of central immune activity. For this reason, isolated peripheral cytokine changes are insufficient to support claims of reduced neuroinflammation.

Blood–brain barrier dysfunction represents one possible link between systemic vascular disease and central inflammatory processes. Hypertension, diabetes, and chronic vascular injury may increase endothelial dysfunction and barrier permeability, potentially altering communication between peripheral and central immune systems. Exercise could plausibly improve this environment through better blood pressure control, improved insulin sensitivity, and vascular adaptation. However, this remains a mechanistic hypothesis unless directly evaluated in human studies using appropriate imaging or biomarker-based assessment of vascular and blood–brain barrier function. Interpretation of exercise-related effects is further complicated by the fact that vascular and neurodegenerative mechanisms often overlap in older adults with cognitive impairment. Patients diagnosed clinically with MCI or Alzheimer's disease frequently also present with small vessel disease, hypertension-related cerebral injury, endothelial dysfunction, or mixed pathological changes. Given the established cardiovascular and metabolic effects of exercise, some improvements in cognition or functional performance may reflect better vascular health rather than direct modulation of neuroinflammatory pathways specific to Alzheimer's disease. This is particularly relevant in studies without biomarker-based diagnostic characterization, where the underlying contribution of vascular versus neurodegenerative pathology may be difficult to define. In this context, interpreting clinical benefit as evidence of direct disease-specific neuroinflammatory modification may be overly simplistic.

Muscle–brain crosstalk and exerkines

Skeletal muscle is increasingly recognized as an endocrine organ that releases signaling molecules in response to contraction. Proposed mediators such as BDNF-related pathways, IGF-1, lactate, irisin/FNDC5, cathepsin B, and other exerkines may contribute to communication between peripheral exercise and brain function [8,30–33]. Experimental and human studies suggest that exercise may influence hippocampal structure, neuroplasticity-related pathways, and memory performance [30–33].

However, translating these findings into clinical practice remains challenging. Peripheral BDNF concentrations do not reliably reflect central BDNF activity, and biomarkers such as irisin or cathepsin B have not been validated as treatment-response markers in AD. Their levels may vary according to age, sex, APOE genotype, baseline fitness, exercise intensity, sampling conditions, and comorbidities. For this reason, exerkines are better viewed as mechanistic candidates than clinically actionable biomarkers.

Current evidence suggests that muscle–brain signaling may contribute to the biological rationale for exercise in cognitive disorders, but these mechanisms are not yet sufficiently defined to guide clinical decision-making. Biomarkers such as peripheral BDNF, irisin, or cathepsin B may be useful in mechanistic research, particularly when interpreted alongside imaging, cognitive outcomes, and functional measures, but they should not be considered established markers of neuroprotection in AD or MCI.

Exercise modality and individualized prescription

Aerobic exercise has the strongest evidence base in older adults with cognitive impairment, largely because of its established cardiovascular and metabolic benefits [12,17–20]. Resistance training is also clinically relevant, particularly given the high prevalence of frailty, sarcopenia, and insulin resistance in this population [14]. In practice, multimodal programmes may be the most appropriate, as they combine endurance, strength, balance training, and fall prevention.

For individuals with MCI or early AD, exercise programmes commonly include moderate-intensity aerobic activity combined with progressive resistance and balance training, adapted to baseline fitness and comorbidity. In more advanced dementia, supervision, environmental safety, and caregiver involvement become increasingly important. Mind–body and balance-based interventions may also be beneficial, particularly for adherence and fall prevention, although their effects are more difficult to interpret mechanistically because they involve multiple active components, including social interaction, attention, and cognitive engagement.

Exercise prescription should not be defined solely by duration or weekly frequency. Intensity, progression, supervision, adherence, baseline functional status, and recovery capacity are equally important. Interventions that are appropriate for physically independent individuals with MCI may be unsuitable or unsafe for frailer patients with advanced dementia, orthostatic

symptoms, or recurrent falls. This clinical heterogeneity makes direct comparison between studies difficult and supports an individualized rather than protocol-driven approach. An unresolved question concerns the dose-response relationship between exercise and cognitive outcomes in neurodegenerative disease. Although physical activity is generally associated with health benefits, it remains unclear whether greater exercise intensity or volume consistently translates into superior cognitive or biological effects in patients with MCI or Alzheimer's disease. Higher-intensity interventions may offer stronger cardiovascular or metabolic adaptation, but they may also reduce tolerability, increase dropout risk, or be impractical for frailer patients with multimorbidity or impaired mobility. Conversely, lower-intensity interventions may be easier to sustain and still provide clinically relevant benefit through improved routine, movement, and functional preservation. Current evidence does not clearly define an optimal exercise "dose," which limits the ability to make precise prescription-based recommendations for different stages of cognitive impairment.

From a practical perspective, regular physical activity should be considered as part of a broader multidomain care strategy, with exercise type selected according to the patient's functional status and clinical priorities. Aerobic exercise may be particularly relevant when cardiometabolic risk factors predominate, whereas resistance and balance training may be more important in patients with frailty, sarcopenia, or fall risk. In some cases, multimodal rehabilitation may offer the most clinically relevant approach.

A practical issue that deserves attention is the role of supervision in exercise interventions for cognitively impaired patients. Supervision may be more than a simple logistical component of programme delivery and could itself influence outcomes. In this population, regular participation often depends not only on the prescribed type of exercise, but also on reminders, external structure, reassurance, behavioural guidance, and safety monitoring. Patients with apathy, executive dysfunction, impaired judgment, or limited insight may have difficulty maintaining consistent engagement in unsupervised programmes, regardless of the theoretical benefits of exercise itself. This raises an important interpretative question, as some positive effects reported in structured intervention studies may partly reflect the benefits of routine, social interaction, behavioural activation, and supervised engagement rather than exercise-specific physiological mechanisms alone. This issue becomes particularly relevant when considering implementation in routine clinical practice, where comparable levels of supervision and support may be difficult to provide consistently.

Safety and adverse-event reporting

Exercise is generally safe when appropriately individualized, but older adults with cognitive impairment require specific precautions. Pre-intervention assessment should consider cardiovascular symptoms, orthostatic hypotension, arrhythmia risk, polypharmacy, neuropathy, visual impairment, osteoporosis, gait instability, delirium risk, wandering behaviour, and the availability of caregiver support. Potential adverse events include falls, syncope, musculoskeletal injury, excessive fatigue, and behavioural distress. Exercise safety in cognitively impaired patients may be affected by challenges not commonly encountered in the broader older adult population. Poor judgment, difficulty following instructions, limited awareness of potential hazards, or unreliable symptom reporting may increase the risks of unsupervised activity. Behavioural symptoms such as agitation, anxiety, or wandering may further complicate participation.

A limitation of the current literature is inconsistent reporting of adverse events, particularly when compared with pharmacological trials. This is relevant because exercise studies often enroll healthier and more motivated participants, while frailer individuals with advanced cognitive impairment may be underrepresented. As a result, findings from controlled trials may not fully reflect the realities of routine dementia care.

Implementation barriers and long-term adherence

Evidence from clinical trials suggests that structured exercise programmes may benefit individuals with MCI and early-stage Alzheimer's disease, but applying these interventions in routine clinical practice is considerably more challenging. Trial participants are typically selected according to eligibility criteria, monitored closely, and supported within structured programmes, which may not reflect everyday care. In routine settings, sustained participation in exercise may be limited by apathy, cognitive impairment, reduced mobility, frailty, behavioural symptoms, or practical dependence on caregivers. Access to transport, supervised programmes, and local rehabilitation resources may also influence feasibility, particularly in older or more functionally impaired patients. Practical implementation may also be limited by cost, programme availability, and healthcare system resources, particularly in settings where supervised exercise is not routinely incorporated into dementia care. These issues are important because populations included in intervention studies may not fully represent

patients encountered in routine dementia care. As a result, benefits observed under research conditions may be more difficult to reproduce consistently in real-world settings.

Discussion

Current evidence supports physical exercise as a clinically relevant supportive intervention in MCI and AD, particularly for cardiovascular, metabolic, musculoskeletal, and functional health, with possible modest benefits for cognition [3,11–20,26–29]. However, available data do not support the conclusion that exercise acts as a proven disease-modifying anti-neuroinflammatory therapy in AD.

Several methodological issues complicate interpretation of the literature. Improvements in symptoms or functional outcomes do not necessarily indicate direct modification of AD pathophysiology. Exercise may improve cognition indirectly through better vascular health, sleep, mood, or physical conditioning rather than through specific neuroinflammatory mechanisms. Similarly, changes in peripheral inflammatory markers do not automatically reflect changes in central immune activity. The EXERT trial illustrates another important challenge: lack of superiority over an active comparator does not necessarily indicate treatment failure, particularly when the comparator itself includes structured movement, supervision, and social interaction [11].

Interpretation of biomarker findings also requires caution. Although modern AD research increasingly relies on biological markers, no single biomarker captures the full complexity of disease progression. Amyloid, tau, GFAP, neurofilament light chain, cytokines, and neuroinflammatory PET imaging each provide only partial information. Because exercise is a complex systemic intervention, its effects may be distributed across multiple pathways rather than reflected in a single measurable biomarker. As a result, isolated biomarker changes should not be overinterpreted as evidence either for or against disease modification. Exercise may provide benefit not only through biological mechanisms, but also by supporting cognitive resilience. Better physical conditioning, sleep, mood, social engagement, and preserved functional capacity may help patients maintain cognitive and day-to-day functioning despite underlying pathology, even in the absence of clear biomarker change.

Another important distinction is the difference between dementia prevention, early intervention, and established dementia care. Observational studies linking physical activity with lower dementia risk are informative, but they remain susceptible to reverse causation and

healthy-user bias. Randomized trials in MCI and AD provide stronger evidence for intervention effects, although these studies often include shorter follow-up and more selected populations. Biological effects may be easier to detect earlier in the disease course, whereas the most clinically meaningful outcomes in established dementia may relate to function, mobility, and quality of life rather than biomarker-defined neuroprotection. Frailty may also be an important modifier of treatment response, influencing tolerability, adherence, and the range of clinically achievable outcomes.

Future studies should use clearer mechanistic hypotheses, appropriate active comparators, and integrated outcome assessment rather than relying on isolated biomarkers. Trials in biomarker-characterized MCI or early AD populations, with objective adherence monitoring, standardized adverse-event reporting, and combined clinical, imaging, and biomarker endpoints, would provide more informative evidence. A potential precision-medicine perspective should also be considered, as response to exercise is unlikely to be uniform across biologically heterogeneous populations. Patients with predominant vascular pathology, different APOE genotypes, varying frailty burden, or biomarker-confirmed early Alzheimer pathology may not respond similarly to the same intervention.

Overall, exercise should be viewed as a supportive component of multidomain dementia care rather than a replacement for diagnostic evaluation, vascular risk management, pharmacological treatment when indicated, or caregiver support. Its clinical value is meaningful even if the precise neurobiological mechanisms remain incompletely defined.

Table 1 presents selected considerations relevant to the interpretation of exercise intervention studies in patients with MCI and Alzheimer’s disease. Observed effects may arise from multiple overlapping mechanisms and should be interpreted cautiously, particularly when drawing conclusions about disease modification.

Study finding	Possible interpretation	Points requiring cautious interpretation
Improvement in cognitive test scores	May reflect better cognitive performance, improved neuroplasticity, or indirect benefits related to sleep, mood, cardiovascular fitness, or daily activity	Practice effects, day-to-day variability, motivation, and limited sensitivity of standard cognitive tests
Improvement in mobility or physical performance	Suggests functional benefit, improved physical conditioning, reduced frailty, or lower fall risk	Functional improvement does not necessarily indicate direct modification of neurodegenerative processes
Reduction in peripheral inflammatory markers (e.g. IL-6, TNF-α)	May indicate reduced systemic inflammation or improved metabolic status	Peripheral markers do not provide direct evidence of reduced central neuroinflammation
Changes in biomarkers such as GFAP or NfL	May reflect biological changes associated with disease processes or response to intervention	Biomarkers remain non-specific and may be influenced by disease stage, comorbidities, and methodological variability
No significant difference compared with an	May suggest benefit in both groups or limited added value of	Active comparators such as stretching, balance training, or supervised activity are not

active control group	the tested intervention	biologically inert
No measurable cognitive improvement despite functional gains	Clinical benefit may be present outside conventional cognitive endpoints	Short follow-up, ceiling or floor effects, and mismatch between selected outcomes and clinically meaningful change
High dropout rates or poor adherence	May reflect limited feasibility or tolerability in cognitively impaired populations	Results may be less generalizable to routine clinical practice if only highly selected participants complete the intervention

Table 1. *Practical interpretation of selected findings from exercise intervention studies in patients with MCI and Alzheimer's disease. Source: own elaboration based on the literature discussed in this review [11,16–20,25–29,34].*

Practical clinical interpretation

In individuals with MCI, exercise programmes may follow a prevention-oriented model, including aerobic activity such as walking or cycling, progressive resistance training, balance exercises, and reduction of sedentary behaviour. Similar strategies may be appropriate in early AD, although simpler routines and greater caregiver involvement are often needed. In moderate dementia, preserving mobility, reducing fall risk, and maintaining daily function may be more realistic clinical goals than improvements in cognitive test scores. In patients with more advanced cognitive impairment, practical feasibility and safety considerations may be more important than optimizing exercise intensity, with regular participation and appropriate supervision often being the more clinically relevant priorities.

Across disease stages, exercise should be viewed as part of a broader multidomain care strategy that also addresses vascular risk factors, hearing impairment, sleep, mood disorders, medication burden, nutrition, and social engagement [3,26–29,34].

Research priorities

A clearer methodological direction is needed in this field, with study designs that are both more consistent and closer to real clinical practice. One recurring problem in exercise trials is the gap between prescribed interventions and what participants actually complete. More objective monitoring, for example through wearable devices, heart-rate monitoring, or activity tracking, could improve interpretation, particularly in cognitively impaired populations where adherence may be difficult to assess accurately.

Greater emphasis should also be placed on outcomes with direct clinical relevance. Conventional cognitive scales remain useful, but they may not fully capture benefits that matter most to patients and caregivers, especially in more advanced stages of disease. Measures such as mobility, fall risk, daily functioning, caregiver burden, and quality of life may provide a more realistic picture of clinical benefit in some settings.

Longer follow-up is also needed, particularly if exercise is expected to influence disease progression rather than only short-term symptomatic or functional outcomes. The choice of comparator remains another methodological challenge, since both inactive control groups and active comparators introduce different interpretative limitations. Study designs that better reflect the complexity of patients seen in routine clinical practice would also improve the generalizability of future findings.

Future research should focus less on whether exercise is broadly beneficial and more on identifying which patients are most likely to benefit, at what stage of disease, and through which biological mechanisms. Studies in biomarker-characterized MCI and early AD populations may be particularly informative, as they reduce diagnostic heterogeneity and may better capture early disease-related effects. Objective monitoring of adherence, standardized adverse-event reporting, and clearly defined mechanistic hypotheses would strengthen study design. Sex differences may also influence response to exercise and deserve greater attention in future studies, particularly given differences in hormonal status, body composition, inflammatory biology, and dementia risk profiles.

Biomarker strategies also require greater methodological consistency. Assessing neuroinflammatory effects based on isolated peripheral cytokine measurements is unlikely to provide robust evidence. More informative studies would combine markers of astroglial and microglial activity, neurodegeneration biomarkers, core AD biomarkers, vascular or perfusion measures, and clinically meaningful outcomes. Ideally, proposed biological changes should be linked to measurable effects on cognition, functional status, or disease progression. Until such evidence becomes available, claims regarding direct anti-neuroinflammatory effects of exercise should remain cautious.

Limitations

This review has several limitations. First, its narrative design does not provide the methodological rigor of a registered systematic review or meta-analysis. No formal protocol, duplicate study screening, quantitative pooling, or structured risk-of-bias assessment was performed, and conclusions should therefore be interpreted accordingly. The duration of many exercise intervention studies should also be considered when interpreting the available evidence. Alzheimer's disease develops over many years, often long before clinical symptoms become apparent, whereas intervention trials typically evaluate outcomes over months rather than prolonged follow-up periods. This makes it difficult to determine whether observed effects reflect short-term functional improvement or any meaningful influence on the underlying disease process. Improvements in mobility, cardiovascular fitness, or day-to-day functioning may be clinically valuable without necessarily altering the long-term course of neurodegeneration. At the same time, if exercise does have disease-modifying potential, shorter studies may simply be unable to capture it.

A further limitation is the nature of the available mechanistic evidence. Much of the biological literature is derived from animal models, broader aging research, or studies in healthy adults rather than biomarker-confirmed AD populations, which limits direct clinical translation. Interpretation is also complicated by substantial heterogeneity across exercise studies, including differences in intervention type, intensity, duration, supervision, comparator design, and adherence. One practical challenge in interpreting exercise trials is that prescribed interventions do not always reflect what participants actually complete. This is particularly relevant in cognitively impaired populations, where motivation, caregiver involvement, frailty, and behavioural symptoms may substantially affect adherence. In some cases, neutral results may therefore reflect insufficient exposure to the intervention rather than true biological

inefficacy. Better objective monitoring of adherence would strengthen interpretation of future studies.

The biomarker field presents an additional challenge. Plasma and CSF markers such as GFAP, phosphorylated tau species, and neurofilament light chain are increasingly relevant in both research and clinical practice, but their value as treatment-response markers for lifestyle interventions remains uncertain. Neuroinflammatory PET imaging may provide useful mechanistic information, but its clinical application remains limited by cost, technical complexity, and availability. For these reasons, direct mechanistic conclusions regarding exercise-induced modulation of neuroinflammatory pathways should be interpreted cautiously.

The characteristics of participants included in exercise intervention studies also limit interpretation and generalizability. Trial populations are often healthier, more motivated, and less functionally impaired than the patients typically encountered in routine clinical practice. Individuals with advanced dementia, marked frailty, behavioural disturbances, severe mobility limitations, or substantial dependence on caregivers may be less likely to participate because of practical barriers to recruitment and continued engagement. This means that findings from controlled studies may not fully reflect the feasibility, tolerability, or adherence that could be expected in broader real-world clinical populations.

Publication bias should also be considered. Positive or clinically encouraging findings may be more likely to appear in the published literature than neutral or negative results, particularly in lifestyle intervention research, where exercise is often viewed favourably from both clinical and public health perspectives. Interpretation is further complicated by differences in study design, intervention protocols, selected outcomes, and reporting quality, all of which make direct comparison between studies more difficult and increase the potential for selective interpretation of the evidence.

Conclusions

Physical exercise represents a clinically relevant supportive intervention for individuals with MCI and early AD. The most consistent evidence relates to benefits in physical function, vascular and metabolic health, and quality of life, with possible modest cognitive benefit. Although exercise may influence biological pathways relevant to neuroinflammation, current human evidence is insufficient to support its classification as a proven disease-modifying anti-neuroinflammatory therapy in AD.

In clinical practice, exercise should be individualized and incorporated into broader multidomain prevention and care strategies, with supervision when appropriate. Future research should focus on adequately powered studies in biomarker-characterized populations, with clearer mechanistic hypotheses and integrated clinical and biomarker outcomes. A more precise understanding of how exercise dose, biological mechanisms, and clinical response interact will be necessary to define its role in disease modification. Clinical relevance should not be judged solely by the question of disease modification. Even without clear evidence that exercise directly alters the biological course of Alzheimer's disease, maintaining mobility, preserving independence, reducing frailty, and supporting overall physical function remain meaningful therapeutic goals in patients with cognitive impairment. For this reason, the value of exercise in dementia care may extend beyond biomarker-based interpretations of treatment effect.

Disclosure

Supplementary Materials: Not applicable

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All of the authors read and agreed with the final version of the manuscript.

Financing statement:

This research received no external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Conflict of interest:

The authors deny any conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies the writing process.

In preparing this work, the authors used Claude (Anthropic) for the purpose of language editing and improving the readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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