OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

The Effects of Aerobic Exercise on Amyloid-β and Tau Pathology in APOE ε4 Carriers

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ABSTRACT

Background/Objective: The APOE ε4 allele is the strongest genetic risk factor for late-onset Alzheimer's disease (AD), accelerating both amyloid-β (Aβ) accumulation and tau hyperphosphorylation. Aerobic exercise is a promising strategy for reducing AD pathology. However, its effects on Aβ and tau biomarkers specifically in APOE ε4 carriers remain poorly characterized. By examining both Aβ and tau outcomes exclusively in APOE ε4 carriers, this study evaluates whether aerobic exercise is associated with AD pathology in those at the highest genetic risk.

Methods: A PubMed and Google Scholar search of articles published between January 2021 and December 2025 identified 50 studies. Using a modified PRISMA 2020 approach, studies were screened in two stages with predefined inclusion criteria and a structured rubric assessing APOE ε4 stratification, biomarker specificity, and methodological rigor. The 12 highest scoring studies were included.

Results: Physically active APOE ε4 carriers consistently demonstrated lower cortical amyloid burden compared to inactive peers in observational and cross-sectional studies. Short-term randomized trials relying on blood-based biomarkers produced null results for both amyloid and tau. Evidence for tau modification associated with exercise in humans is absent, as mechanistic support comes almost entirely from animal studies. Analyses suggest that ε4 carriers may exhibit stronger neuroprotective responses to aerobic exercise than non-carriers.

Conclusion: Observational studies consistently associate exercise with reduced amyloid burden in APOE ε4 carriers, but there lacks direct evidence for tau modification in humans. Longer randomized trials using sensitive central biomarkers, stratified by APOE genotype, are needed to determine whether exercise can meaningfully alter AD progression in ε4 carriers.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder(1,2). It is also the leading cause of dementia worldwide, with no treatment currently capable of stopping the progression of AD(3,4). At its

core, AD is defined by two pathological features: the accumulation of amyloid-β (Aβ) plaques, which is the buildup of toxic protein between neurons, and abnormal accumulations of hyperphosphorylated tau protein inside neurons(5–8). Together, these processes contribute to the progressive and irreversible cognitive decline observed in the disease(9,10). Pharmacological interventions have failed at altering the trajectory of this disease, leading to increasing research for accessible and low-cost preventive strategies(3).

Among the most promising preventive strategies is aerobic exercise. It has well-established cardiovascular and metabolic benefits, but research has also shown regular physical activity may influence the brain through metabolic and vascular pathways in ways that are relevant to AD pathology(11,12). It remains unclear whether these neurological effects are strong or specific enough to influence the molecular processes underlying AD, especially in high-risk individuals(13). Epidemiological data have also consistently associated higher levels of physical activity with reduced dementia(14). However, the relationship between exercise and AD pathology is less consistent and varies across individuals(15).

The apolipoprotein E 4 allele (APOE ε4) is the strongest genetic risk factor for the onset of AD and is carried by roughly 25% of the general population(8,16). APOE ε4 impairs the brain's ability to clear deposits of AB and promotes tau hyperphosphorylation(7,8). This causes carriers to accumulate amyloid earlier and more aggressively than non-carriers(8). Some studies suggest that the relationship between physical activity and lower amyloid burden may be more pronounced in APOE ε4 carriers, though this relationship is not yet fully understood(17).

There is a clear discrepancy in the current literature between findings from observational imaging studies and short-term clinical trials examining the effects of exercise on AD pathology. It remains unclear whether the associations observed in imaging studies reflect a genuine reduction in amyloid burden caused by exercise(10,18). Furthermore, no long-term randomized trial has examined both amyloid and tau outcomes together in the APOE ε4 population. As a result, the current evidence base may overstate the extent to which exercise influences the processes directly tied to AD progression(18). This review synthesizes the available literature across both pathological biomarkers, specifically in APOE ε4 carriers. Clarifying this relationship is essential for informing future trials and refining exercise as a targeted intervention, especially for individuals who carry the APOE ε4 variant.

METHODS

This review was conducted using modified PRISMA 2020 guidelines to improve transparency in study identification and selection. Modifications include the use of a single-reviewer screening process and the absence of protocol pre-registration.

This literature review search utilized PubMed and Google Scholar. The search was restricted to articles published between January 2021 and December 2025 to ensure only the recent advancements in biomarker sensitivity and exercise protocols. The search terms included concepts related to the method of

intervention (aerobic exercise, physical activity, cardiovascular training), the biomarkers of interest (Aβ, p-tau), and genotype (APOE ε4). This initial search resulted in 50 relevant articles. Studies eligible for inclusion included randomized controlled trials, observational and cross-sectional studies, systematic reviews, and animal studies.

The next selection process followed a two-step approach. First, titles and abstracts were reviewed to remove studies that were clearly outside the scope of this review, including those focused exclusively on non-aerobic interventions or dietary modifications and those that did not measure Aβ or tau biomarkers. Studies that did not report APOE genotype data were also excluded at this stage, as genotype stratification is essential to the central aim of this review. Without this information, it is not possible to determine whether the effects of exercise on Alzheimer's disease biomarkers are specific to ε4 carriers or reflect broader population trends. This resulted in 30 studies for the next step.

In the second step, a structured scoring rubric was applied to evaluate the remaining articles and identify the highest-quality subset for inclusion. Quality was assessed across three domains: APOE ε4 stratification, biomarker specificity, and methodology. Each domain was scored on a scale from 0 to 2 (Table 1). Equal weighting of the criteria was used to prevent any single factor from disproportionately influencing study selection, ensuring that methodological rigor, population relevance, and biomarker validity were considered equally. This approach was chosen for transparency and reproducibility rather than introducing additional judgment through unequal weighting, especially since there is no established framework for weighting domains in APOE ε4 biomarker research.

The final number of included studies was limited by the narrow date range and the requirement for APOE ε4 genotype stratification alongside dual biomarker measurement. The selection process resulted in 12 studies for inclusion, as only these achieved consistently high composite scores across the evaluated domains. The final included studies had a mean composite quality score of 5.09 out of 6.0, reflecting strong overall performance on the applied criteria. A formal meta-analysis and standardized risk-of-bias assessment were not performed due to the limited number of eligible studies and heterogeneity in study design.

A single reviewer conducted all screening and scoring. Research indicates that single-reviewer abstract screening misses, on average, 13% of relevant studies compared to approximately 3% with dual-reviewer screening(19). To partially mitigate this risk, a structured two-stage selection process was implemented(20), with inclusion criteria applied at both the title-and-abstract stage and the full-text scoring stage. The use of a rubric-based approach reduces the role of subjective judgment relative to unstructured screening. Nevertheless, the possibility of selection bias cannot be excluded, and this should be considered when interpreting the findings of this review.

Data from each included study were extracted and summarized in Table 2. For each study, the table lists the key results, methods, population, and overall takeaway. This table provides a structured overview of the included literature to support the results and discussion sections.

Table 1: Scoring Criteria

Domain	Score: 2	Score: 1	Score: 0
Population Relevance	Human study with APOE ε4 stratification	Mixed population or indirect APOE analysis	Limited APOE detail or unclear stratification
Biomarker Specificity	Direct measurement using PET, CSF, or high-sensitivity blood biomarkers (p-tau217)	Standard or less validated blood-based biomarkers	No biomarker measurement
Methodology	Randomized controlled trial or large prospective cohort	Observational or smaller-scale study	Small sample size

Table 2: Summary of Included Studies

Study	**Results**	**Methods**	**Population**	**Takeaway**
Sevilay Tokgöz et al., 2021	Exercise reduced Aβ, protected the brain, and improved cognition in APOE ε4 carriers.	Systematic Review	Older adults who are APOE ε4 carriers	Exercise is a non-pharmacological treatment option for APOE ε4 carriers, potentially improving cognitive function and reducing Aβ load.
Kelsey R. Sewell et al., 2024	Six months of exercise did not change blood biomarkers related to AD.	Controlled experimental study with exercise intervention and biomarker analysis	Cognitively normal older adults	Exercise does not significantly affect blood-based biomarkers of AD in cognitively unimpaired older adults.
R. Pedrero-Chamizo et al., 2024	Low physical activity combined with APOE ε4 genotype increased Aβ burden but did not affect its accumulation over	Prospective cohort study	Cognitively normal older adults with and without ApoE4 genotype	Low physical activity and APOE ε4 genotype are associated with increased Aβ deposition in healthy older

	time.			adults, but this effect is insufficient to modulate the change in Aβ accumulation over time.
Jaisalmer de Frutos Lucas et al., 2023	Physical activity influences multiple molecular pathways to reduce risk of AD, even in APOE ε4 carriers.	Comprehensive Review	APOE ε4 carriers	Physical activity can reduce AD risk by influencing various molecular targets.
Rosalía Fernández-Calle et al., 2022	APOE ε4 carriers face a higher risk of late-onset AD compared to other genotypes, as it worsens Aβ buildup and tau pathology	Comprehensive Review	APOE ε4 carriers	APOE ε4 genotype is a significant risk factor for late-onset AD and neuroinflammation. APOE genotype influences AD pathology
Longfei Xu et al., 2023	Physical exercise improves key metabolic pathways linked to AD pathology.	Comprehensive Review	Adults with AD	Regular physical exercise can improve metabolic dysfunction in AD, potentially contributing to the development of non-pharmacological interventions.
Maria Francesca Astorino et al., 2025	Aerobic exercise may reduce AD pathology by	Comprehensive Review	Adults with AD	Structured physical activity may delay AD

	improving amyloid clearance and reducing neuroinflammation.			progression through modulation of amyloid-metabolism, gene expression, and neuroinflammation.
Larissa Fischer et al., 2024	Higher precuneus activity predicted greater Aβ burden in APOE ε4 carriers and worse memory over time.	Longitudinal observational neuroimaging study	Cognitively normal older adults with family history of AD	In normal ε4 carriers, higher precuneus activity during memory retrieval is associated with increased amyloid burden, while low precuneus activity is associated with better future cognitive outcomes.
Francheska Delgado-Peraza et al., 2023	Exercise increased neuroprotective protein BDNF in neuron-derived vesicles.	Randomized Controlled Trial	Patients with mild to moderate AD	Exercise in AD patients may improve cognitive benefits by upregulating neuroprotective factors, particularly in APOE ε4 carriers.
M. Lozupone et al., 2024	APOE ε4 increases risk of AD by 4 to 12 times. Influenced by epigenetic DNA methylation.	Comprehensive Review	APOE ε4 carriers	Epigenetics plays a significant role in aging and AD, APOE variants potentially increasing or decreasing the risk of developing AD.

E. Roccati et al., 2025	Higher physical activity was linked to lower serum GFAP.	Cross-sectional observational study	Cognitively healthy adults aged 50-83 years	Higher physical activity levels are associated with lower blood-based biomarkers of neurodegeneration, with APOE ε4 and activity intensity impacting this relationship.
Vidoni et al., 2021	Aerobic exercise improved cardiorespiratory fitness by 11%. No significant effect on amyloid accumulation compared to control group.	52-week supervised aerobic exercise randomized controlled trial	117 underactive, cognitively normal older adults	One year exercise intervention is insufficient to reduce amyloid burden in individuals with amyloid pathology.

RESULTS

3.1 Effects of Aerobic Exercise on Amyloid-β Pathology

Across many studies and systematic reviews, higher levels of physical activity were consistently associated with a lower cortical Aβ burden in APOE ε4 carriers. Physical inactivity was also linked to greater Aβ deposition(15,17,21,22). This relationship was mainly observed in PET imaging studies that directly measure Aβ burden. Studies relying on blood-based biomarkers have produced less consistent findings(15,17).

3.2 Effects of Aerobic Exercise on Tau Pathology

Across all human intervention trials reviewed, no study showed significant reductions in plasma tau following aerobic training programs, even when analyses were stratified by the APOE genotype(21,23). In animal studies, aerobic exercise was associated with reduced tau phosphorylation through improved glucose metabolism and suppressed kinase activity.(24,25). This relationship has not been validated in human populations.

3.3 Genotype-Specific Responses

APOE ε4 not only exacerbates amyloid aggregation and impairs its clearance but also accelerates tau hyperphosphorylation and neurodegeneration(21,26). Several studies have found that the protective effects of physical activity on reducing amyloid accumulation are stronger in ε4 carriers than in non-carriers(15,17,22). Further evidence also suggests that aerobic exercise may induce greater increases in neuroprotective factors such as BDNF in ε4 carriers(25). However, markers of neurodegeneration such as GFAP and NfL showed no genotype-specific differences following short-term exercise interventions(23,27).

DISCUSSION

This review shows two clear patterns when looking at aerobic exercise and AD in APOE ε4 carriers. First, across observational and cross-sectional studies, there is consistent evidence that exercise is associated with amyloid levels(15,17). Second, no human intervention study has detected a significant reduction in tau biomarkers associated with exercise. This lack of effect is consistent across studies regardless of genotype stratification.(28). An evaluation of these patterns, including quality of evidence, sources of inconsistency, and the difference between association and causation, is necessary before drawing conclusions about whether exercise can meaningfully alter AD pathology in ε4 carriers.

Before interpreting these findings further, we must note a series of important limitations. First, a substantial portion of the evidence linking aerobic exercise with lower levels of amyloid accumulation in APOE ε4 is derived from observational studies, rather than long-term randomized experiments. Observational designs cannot completely control lifestyle and other variables, making it difficult to establish evidence for physical activity and biomarker changes(29). This distinction should be maintained when interpreting the conclusions. Second, several randomized trials reported no significant changes in blood-based or cerebrospinal fluid biomarkers such as Aβ, tau, or GFAP after six months of moderate to high intensity aerobic training(23,27). This heterogeneity limits the strength of conclusions regarding biomarker responsiveness to exercise. Third, the reliance on animal models for mechanistic tau data limits the direct translation of these findings to human clinical populations. Fourth, the use of a custom scoring rubric for study selection introduces subjectivity, and the rubric has not been formally validated. Fifth, restricting included studies to those published between 2021 and 2025 may have excluded earlier foundational work. Finally, all screening and scoring were conducted by a single reviewer, increasing the risk of selection bias and the possibility of missed relevant studies.

Notwithstanding these limitations, this review has several strengths. First, this review provides a focused synthesis that examines aerobic exercise in relation to both Aβ and tau pathology, specifically in APOE ε4 carriers. By focusing only on individuals carrying the ε4 allele, this review highlights patterns that may not be noticeable when genetic vulnerability is not considered. Second, the review uses findings from multiple types of evidence, including observational studies and intervention trials. This allows for a more comprehensive understanding. This study also directly addresses the limited understanding of genotype-specific responses to lifestyle interventions. By combining studies that analyzed physical

activity, biomarker levels, and APOE genotype, this review helps characterize potential relationships between genetic risk and behavioral factors in AD.

The association between physical activity and lower cortical amyloid burden in APOE ε4 carriers is one of the most consistent findings in this review(15,17,22). This pattern was most reliably observed in PET imaging studies. These studies provide a direct and validated measure of amyloid deposition and are considered the gold standard for in vivo amyloid quantification(38). However, most of this evidence comes from observational and cross-sectional study designs, which do not support causal conclusions(29). Observational designs cannot fully account for confounding variables such as diet, sleep quality, or baseline health. All of these factors may influence both physical activity levels and amyloid accumulation. Furthermore, cross-sectional designs may be subject to reverse causation. Individuals starting with a lower amyloid burden may be overall healthier and therefore more capable of aerobic activity, rather than exercise having reduced their amyloid levels.

The one large randomized controlled trial in this review found no significant difference in amyloid accumulation between aerobic exercise and control groups after 52 weeks(18). This null result from a long term, randomized controlled trial directly challenges the causal interpretation suggested by observational data. However, this trial was not stratified by APOE genotype, and the one year duration may have also been insufficient to detect change in amyloid pathology due to the multi-decade progression of amyloid accumulation. Despite these limitations, the findings still highlight the gap between association and causation. The observational data reviewed here support two possible interpretations. Exercise may directly influence amyloid clearance through mechanisms such as neprilysin upregulation or improved blood–brain barrier integrity(17,21,32). Alternatively, the observed differences may reflect broader cerebrovascular and metabolic health advantages that are associated with more active lifestyles. The current evidence cannot clearly distinguish between these explanations.

A notable inconsistency across the included studies is the difference between PET imaging findings and results from studies using blood-based biomarkers. Observational PET studies consistently show lower amyloid burden in active ε4 carriers. In contrast, studies measuring plasma Aβ, p-tau181, GFAP, and NfL have mainly reported null results following structured exercise interventions(23,27). This difference likely reflects methodological limitations rather than a true contradiction between studies. Blood-based biomarkers can be influenced by factors outside the brain. Changes caused by exercise in metabolism, muscle turnover, and inflammation can affect protein levels in the blood even if brain pathology has not changed(33). This could potentially mask brain-specific effects. In addition, although assays such as SIMOA are an improvement over earlier methods, plasma biomarkers, especially p-tau181, remain less sensitive and specific than CSF or PET measures for detecting subtle amyloid changes(33). As a result, null findings in blood-based studies may reflect measurement limitations rather than a true absence of biological effect and should be interpreted with caution.

Across all human intervention trials included in this review, there is a consistent lack of evidence for changes caused by exercise in tau biomarkers(28,31). This represents a gap in the literature rather than a delay in translating findings from animal models. Animal studies suggest that aerobic exercise can reduce tau phosphorylation by improving glucose metabolism and inhibiting specific kinase pathways(24).

However, these models rely on genetic modifications that produce rapid and artificially accelerated pathology. They are also conducted under tightly controlled conditions with exercise intensities that may not be feasible in humans. These differences limit the direct applicability of animal findings to clinical populations. In human trials, the absence of tau effects may also be due to study duration. Tau pathology develops over decades, and interventions lasting six months to one year are unlikely to produce measurable changes in plasma tau, even if a biological effect exists(18). It is also possible that changes in tau require prior reductions in amyloid burden, but this has not been tested in long-term trials in ε4 carriers. Current evidence neither confirms nor rules out an effect of exercise on tau pathology. However, it does highlight the lack of studies.

Several included studies reported that the association between physical activity and reduced amyloid accumulation was more pronounced in ε4 carriers than in non-carriers(15,17,22). ε4 carriers start with a more impaired amyloid clearance environment, so they may experience greater relative benefit from exercise-related improvements in cerebrovascular and metabolic function(17). Some supporting evidence aligns with this idea. Exercise-related BDNF upregulation may be more pronounced in ε4 carriers(25), and aerobic training has been shown to improve hippocampal blood flow specifically in hypertensive ε4 carriers(35). Together, these findings suggest a potential interaction between exercise and genotype.

However, this interpretation has some important limitations. These observations come from secondary outcomes of observational studies, which carry an increased risk of false-positive findings due to multiple comparisons. Spencer et al. (2025), a meta-analysis of randomized controlled trials stratified by APOE genotype, concluded that evidence quality was very low to moderate and that it remains unclear whether ε4 carriers consistently benefit more than non-carriers across physical and cognitive outcomes(31). Contradictory findings also exist. Some studies report no genotype-specific differences in neurodegeneration markers such as GFAP and NfL following exercise(23,27), and a randomized trial found that APOE ε4 status did not significantly influence exercise related improvements in physical function(39). Overall, a genotype-specific response to exercise remains plausible but unconfirmed.

A key limitation of the available evidence is the heterogeneity in study design, population characteristics, and biomarker methodology across included studies. The 12 studies reviewed here range from large prospective cohorts using PET imaging to short-term randomized trials with blood-based assays, as well as comprehensive reviews. Exercise protocols also varied widely in type, intensity, duration, and level of supervision, making it difficult to identify whether a specific exercise dose is needed to produce measurable biological effects. Population characteristics were similarly inconsistent, with studies including cognitively normal older adults, individuals with mild AD, and patients with AD dementia. Age ranges and ε4 carrier proportions were not standardized. These differences limit direct comparability across studies. Furthermore, a substantial portion of the included literature consists of comprehensive reviews. While these provide useful context, they may introduce inherited bias from their source studies and do not independently verify causal claims. Overall, the evidence is heterogeneous. There are strong observational associations but limited support for causality.

CONCLUSION

Higher levels of aerobic exercise is consistently associated with lower Aβ burden in APOE ε4 carriers across observational and cross-sectional imaging studies. This suggests that a modifiable lifestyle behavior can interact with one of the strongest known genetic risk factors for Alzheimer's disease. However, this association is not established as causal. The randomized trial did not replicate the pattern of amyloid reduction and blood-based biomarker studies consistently produce null results. Whether the observational associations reflects a reduction in amyloid accumulation caused by aerobic exercise remains to be established through longer randomized trials that take into account different variants of the APOE gene and the use of carefully monitored aerobic exercise protocols. As biomarker technology improves and longitudinal studies become more accessible, future research may be better able to determine whether a low-cost and widely accessible behavioral change can meaningfully reduce the risk of Alzheimer's disease in high-risk individuals.

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