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Review Article

APOE ε4 Modifies Stage-Dependent Alterations in Circulating Brain-Derived Neurotrophic Factor Across the Alzheimer's Disease Continuum: A Systematic Review and Meta-Analysis

Sachin BS[1], Radhakrishnan Narayanaswamy[1,*], Anshu Kumar Yadav[2], Biswajit Das[1], Shree Harsha V[3], Kshama Nadig[3]

[1]Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Thandalam, Chennai, Tamil Nadu, INDIA.
[2]Department of Biochemistry, JSS Medical College, Mysuru, JSS University (Deemed to be University) Affiliated with Rajeev Gandhi University of Health Sciences, Bengaluru, Karnataka, INDIA.
[3]Department of Biochemistry, BGS Global Institute of Medical Sciences (BGSGIMS), Bangalore, Affiliated with Rajiv Gandhi University of Health Sciences (RGUHS), BGS Health and Education City, Bangalore, Karnataka, INDIA.

ABSTRACT

Circulating Brain-Derived Neurotrophic Factor (BDNF) has been proposed as a blood-based marker of synaptic vulnerability in Alzheimer's Disease (AD), but published findings vary across disease stages and cohorts. This review and meta-analysis examined whether APOE ε4 carrier status modifies stage-dependent alterations in serum or plasma BDNF across the AD continuum. PubMed, Web of Science, Scopus, and Google Scholar were searched using terms for BDNF, Alzheimer's disease or Mild Cognitive Impairment (MCI), and APOE ε4. Eligible human studies reported circulating BDNF in AD, MCI, or cognitively normal participants, with extractable quantitative data and, where available, genotype-stratified results. Random-effects models pooled Standardized Mean Differences (SMDs); risk of bias, heterogeneity, publication bias, and evidence certainty were appraised using PRISMA 2020, NOS/RoB 2-aligned domains, and GRADE. AD was associated with lower circulating BDNF than cognitively normal status (SMD −0.28, 95% CI −0.47 to −0.09), whereas the overall MCI-control comparison was small and non-significant (SMD −0.12, 95% CI −0.31 to +0.07) with high heterogeneity. Genotype stratification clarified this heterogeneity: MCI ε4 carriers showed a meaningful reduction (SMD −0.48), while ε4 non-carriers showed no reduction. Older age and lower baseline Mini-Mental State Examination scores also explained part of MCI heterogeneity. Circulating BDNF is unlikely to function as a stand-alone diagnostic biomarker, but it may be clinically informative when interpreted alongside APOE ε4 status, disease stage, age, and cognitive severity. Future studies should standardize biospecimen handling and prospectively test BDNF as a prognostic and treatment-response marker.

Keywords: Alzheimer's disease, APOE ε4, Blood-based biomarkers, Brain-derived neurotrophic factor, Genotype stratification, Meta-analysis, Mild cognitive impairment.

Correspondence:
Dr. Radhakrishnan Narayanaswamy
Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (Deemed to be University), Thandalam, Chennai-602105, Tamil Nadu, INDIA.
Email: radhakrishnann.smc@saveetha.com

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INTRODUCTION

Alzheimer's Disease (AD) is characterized by progressive cognitive decline that is preceded in many individuals by Mild Cognitive Impairment (MCI), a clinically heterogeneous stage in which only a proportion of patients convert to dementia (Belloy *et al.*, 2019; Fang *et al.*, 2019; Tsai *et al.*, 2023). Blood-based biomarkers are increasingly important because they can support scalable risk stratification and longitudinal monitoring (Gao *et al.*, 2022; Perkovic *et al.*, 2023). However, peripheral markers must be interpreted cautiously because they are influenced by disease stage, genetics, age, comorbidity, sample handling, and assay platform (Shimada *et al.*, 2014; Siuda *et al.*, 2017).

Brain-Derived Neurotrophic Factor (BDNF) is central to synaptic plasticity, neuronal survival, memory circuitry, and activity-dependent neuroadaptation (Gao *et al.*, 2022). Mechanistic and clinical literature links impaired BDNF signaling with AD-relevant processes, including synaptic failure, amyloid-β toxicity, tau-related neurodegeneration, neuroinflammation, and reduced cognitive resilience (Gao *et al.*, 2022; Liu *et al.*, 2015). Circulating BDNF is attractive because serum and plasma measurements are feasible in clinical and

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epidemiologic settings and have been evaluated in MCI, AD, and longitudinal progression studies (Fang *et al.*, 2019; Tsai *et al.*, 2023). Nevertheless, published studies are inconsistent: some report lower BDNF in AD or MCI, while others show negligible or even higher levels, especially in prodromal cohorts (Perkovic *et al.*, 2023; Shimada *et al.*, 2014; Siuda *et al.*, 2017).

A likely explanation for this inconsistency is biological and analytical effect modification. APOE ε4 is the strongest common genetic risk factor for late-onset AD and affects pathways relevant to synaptic repair, lipid transport, inflammation, and amyloid handling (Belloy *et al.*, 2019). If ε4 carriers have reduced neurotrophic reserve or altered BDNF responsiveness, unstratified analyses may dilute meaningful effects (Liu *et al.*, 2015). Clinical studies support this possibility: APOE ε4 has been associated with lower serum BDNF in AD and with altered or blunted BDNF up-regulation following interventions in cognitively impaired older adults (Allard *et al.*, 2017; Álvarez *et al.*, 2014; Álvarez *et al.*, 2016).

The present review therefore asks not simply whether circulating BDNF differs between diagnostic categories, but when and in whom the BDNF signal becomes detectable. Specifically, this manuscript synthesizes evidence across the AD continuum, examines APOE ε4 as a prespecified moderator, evaluates sources of heterogeneity in MCI, and considers whether circulating BDNF is best viewed as a stage- and genotype-contextual biomarker rather than a universal diagnostic marker. The article is organized into methods, study selection and characteristics, quantitative synthesis, genotype and moderator analyses, evidence certainty, critical interpretation, and future research directions, following the logic of transparent systematic review reporting (Page *et al.*, 2021).

METHODOLOGY

Design and reporting framework

This study was designed as a systematic review and random-effects meta-analysis of circulating BDNF across the AD continuum. Reporting followed PRISMA 2020 guidance (Page *et al.*, 2021). The review focused on diagnostic-stage comparisons (AD versus cognitively normal controls and MCI versus controls) and on APOE ε4 as a potential effect modifier, reflecting prior evidence that APOE status may influence serum BDNF levels and intervention-related BDNF responses (Allard *et al.*, 2017; Liu *et al.*, 2015). No external protocol registration was identified for the submitted manuscript; this limitation is disclosed to improve methodological transparency.

PICO framework

This systematic review and meta-analysis was structured according to the following PICO framework:

- **Population (P):** Human adults diagnosed with Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI, including amnestic MCI), or cognitively normal control participants, using the diagnostic criteria applied in the source studies.
- **Exposure (E):** APOE ε4 carrier status (ε4 carriers versus non-carriers) and/or clinical stage on the Alzheimer's disease continuum (AD or MCI versus cognitively normal status). These factors were examined as prespecified effect modifiers of circulating BDNF levels.
- **Comparator (C):** Cognitively normal participants for primary diagnostic-stage comparisons; APOE ε4 non-carriers within the same diagnostic category for genotype-stratified analyses.
- **Outcome (O):** Circulating Brain-Derived Neurotrophic Factor (BDNF) concentrations measured in serum or plasma and reported with sufficient quantitative detail (means and standard deviations or convertible statistics) to permit calculation of standardised mean differences (SMDs/Hedges' g). Primary outcomes were between-group differences in BDNF for AD versus cognitively normal controls and for MCI versus controls. Secondary outcomes included APOE ε4-stratified effects and moderation by age and baseline cognitive severity (Mini-Mental State Examination score).

The PICO framework directly guided the eligibility criteria, literature search, data extraction priorities, prespecified subgroup and meta-regression analyses, and overall interpretation. The eligibility criteria (Section 2.3) were developed in accordance with this framework.

Eligibility criteria

Eligible studies enrolled human participants diagnosed with AD, MCI or amnestic MCI, and/or cognitively normal control participants, consistent with the diagnostic groups evaluated in prior BDNF studies across the AD continuum (Fang *et al.*, 2019; Perkovic *et al.*, 2023; Shimada *et al.*, 2014; Siuda *et al.*, 2017; Tsai *et al.*, 2023). Studies were included when serum or plasma BDNF was reported quantitatively or when sufficient data were available to derive an effect size. APOE genotype data were required for genotype-stratified analyses but were not required for broader unstratified disease-stage comparisons. Observational cohorts, case-control studies, cross-sectional analyses, and randomized or quasi-experimental studies with usable baseline or change data were eligible, including intervention studies that reported BDNF response in cognitively impaired participants (Allard *et al.*, 2017; Álvarez *et al.*, 2016). Exclusion criteria were animal or *in vitro* studies, narrative reviews, case reports, abstracts without extractable data, duplicate or overlapping populations, studies

without circulating BDNF measurement, non-English full texts, and records lacking usable quantitative information.

Information sources and search strategy

Searches were conducted in PubMed, Web of Science, Scopus, and Google Scholar from database inception to January 2026. The search process was structured according to PRISMA 2020 recommendations for transparent identification, screening, eligibility assessment, and inclusion of studies (Page *et al.*, 2021). The core Boolean strategy was: ("brain-derived neurotrophic factor" OR BDNF) AND (Alzheimer* OR "Alzheimer's disease" OR dementia OR "mild cognitive impairment" OR MCI) AND (APOE OR "apolipoprotein E" OR ε4 OR e4). Database-specific syntax was adapted where necessary. Reference lists of included articles and relevant reviews were screened manually to identify additional eligible studies. Records were exported to a reference manager, duplicates were removed, and screening proceeded from titles and abstracts to full texts.

Study selection, extraction, and outcomes

Screening was performed against predefined eligibility criteria, and reasons for full-text exclusion were documented in line with PRISMA 2020 reporting expectations (Page *et al.*, 2021). Extracted variables included author and year, country, study design, setting, diagnostic criteria, sample size, age, sex, cognitive severity, APOE ε4 classification, BDNF biofluid, assay method, sample handling where reported, BDNF mean and standard deviation or convertible summary statistics, longitudinal outcomes, and intervention-related BDNF change; these data items were selected to capture the major clinical and methodological factors reported in the included BDNF studies (Allard *et al.*, 2017; Fang *et al.*, 2019; Perkovic *et al.*, 2023; Tsai *et al.*, 2023). The primary effect measure was the standardized mean difference (SMD; Hedges g), defined so that negative values indicate lower BDNF in the cognitively impaired group. Primary comparisons were AD versus cognitively normal controls and MCI versus controls. Secondary analyses examined APOE ε4 carrier status, sex-by-genotype patterns where available, progression outcomes, and intervention-related BDNF responsiveness.

Risk of bias, synthesis, and certainty of evidence

Observational studies were assessed using Newcastle–Ottawa Scale principles (Wells *et al.*, 2003), while randomized or interventional studies were appraised with RoB 2-aligned domains (Sterne *et al.*, 2019). Judgments were harmonized across mixed designs using selection bias, measurement bias, confounding, attrition, outcome validity, and overall risk categories. Random-effects models were selected because clinical stage, APOE composition, biofluid, assay platform, and study design were expected to vary across the included literature (Fang *et al.*, 2019; Perkovic *et al.*, 2023; Shimada *et al.*, 2014; Siuda *et al.*, 2017). Heterogeneity was assessed using Cochran's Q, I^2, and τ^2. Funnel plots, Begg's test, Egger's test, and trim-and-fill were used to explore small-study effects where feasible. Meta-regression examined mean age and baseline Mini-Mental State Examination (MMSE) as study-level moderators. Certainty of evidence was judged using GRADE domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias (Guyatt *et al.*, 2008).

RESULTS

Study selection and evidence base

The database search identified 4,870 records across PubMed, Web of Science, Scopus, and Google Scholar. After duplicate removal, 2,725 unique records were screened by title and abstract; 205 full-text articles were assessed for eligibility. Six studies met the APOE-focused inclusion criteria for qualitative synthesis, and studies with extractable serum or plasma BDNF data contributed to the quantitative analyses according to the relevant comparison. The main reasons for exclusion were absence of APOE data, lack of serum/plasma BDNF results, insufficient extractable statistics, overlapping populations, and non-English full texts. The complete identification, screening, eligibility, and inclusion process is presented in Figure 1.

Study characteristics and methodological quality

The included evidence base consisted of prospective cohort, cross-sectional, randomized, and pilot interventional designs. Most quantitative comparisons used serum BDNF measured by enzyme-linked immunosorbent assay, although heterogeneity remained in biofluid source, assay platform, sample handling, recruitment setting, diagnostic definition, and covariate adjustment. The included studies addressed complementary aspects of the review question: diagnostic-stage differences, APOE ε4 and sex-stratified patterns, longitudinal cognitive decline, conversion from amnestic MCI to AD, and intervention-related BDNF responsiveness. Condensed study characteristics are shown in Table 1.

Overall methodological quality ranged from low to moderate risk of bias. Observational studies were generally strengthened by clearly defined diagnostic groups and usable biomarker outcomes, but were limited by residual confounding, variable adjustment for age and sex, and incomplete reporting of preanalytical factors such as fasting status, collection time, storage duration, medication exposure, and platelet-related influences on serum BDNF. Interventional and pilot studies contributed biologically relevant evidence but were limited by small sample sizes and reduced precision. The harmonized domain-level risk-of-bias assessment is summarized in Figure 2.

Quantitative synthesis across disease stage

In the AD versus cognitively normal control comparison, the random-effects model demonstrated significantly lower

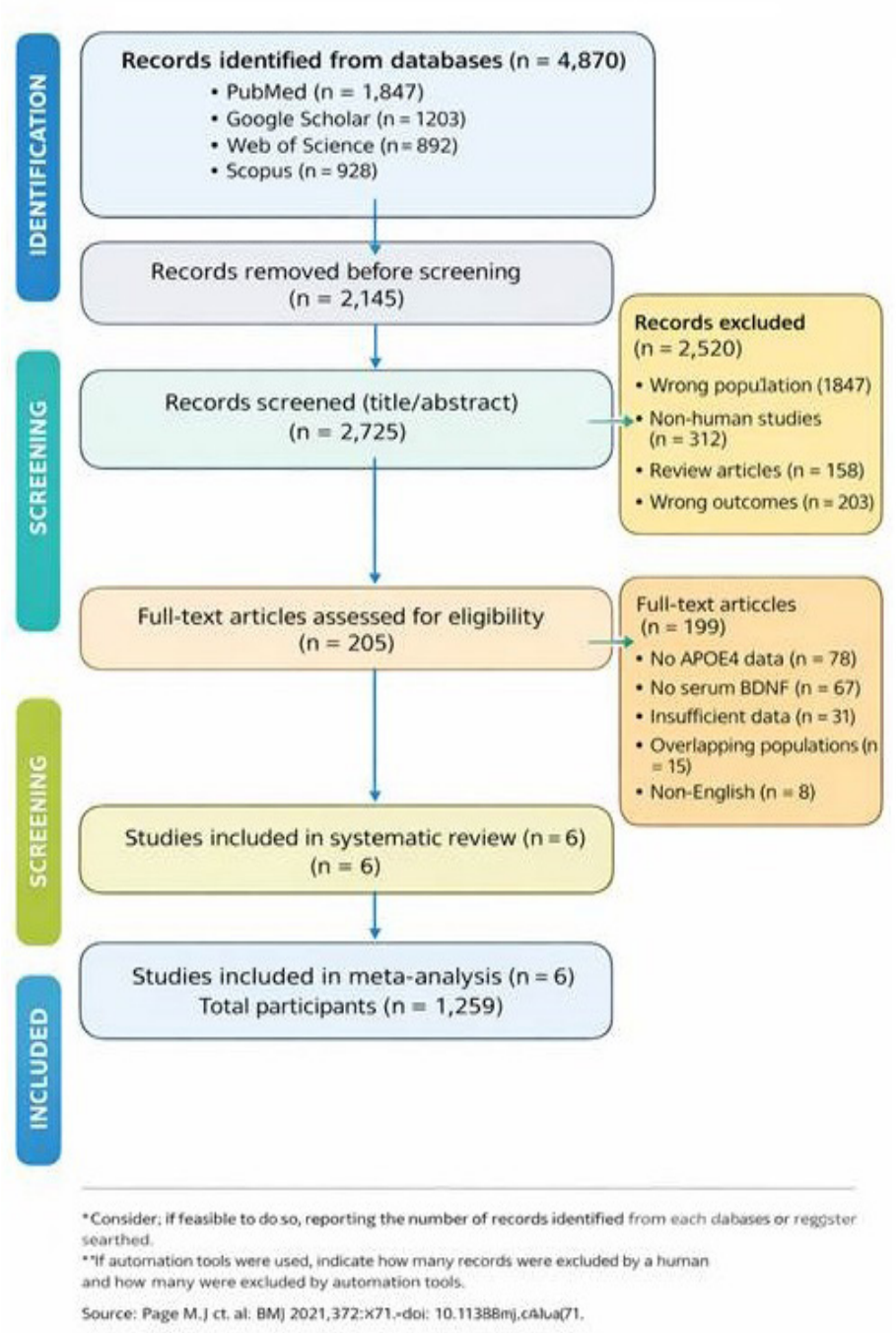

Figure 1: PRISMA 2020 flow diagram for study identification, screening, eligibility, and inclusion.

circulating BDNF in AD (SMD −0.28, 95% CI −0.47 to −0.09; p=0.004). Between-study heterogeneity was moderate (I^2=64.2%), and the prediction interval crossed the null, indicating that the magnitude of the AD-control difference may vary across clinical and laboratory settings. The forest plot in Figure 3 shows that most study-level estimates were directionally consistent toward lower BDNF in AD, while differences in precision and weighting reflected sample size and design variation. Small-study effects were not strongly supported by visual or statistical diagnostics, as summarized by the funnel plot in Figure 4.

The overall MCI-control comparison showed a smaller and non-significant pooled effect (SMD −0.12, 95% CI −0.31 to +0.07; p=0.22), with substantial heterogeneity (I^2 = 81%). This result indicates that an unstratified MCI category is too biologically heterogeneous to support a single uniform BDNF effect. The direction and magnitude of study-level estimates varied across cohorts, which is consistent with differences in MCI subtype, proximity to conversion, age distribution, APOE ε4 prevalence, assay method, and baseline cognitive severity. The principal pooled estimates, heterogeneity findings, and certainty judgments are summarized in Table 2.

APOE ε4 stratification and moderator analysis

APOE ε4 status materially changed interpretation of the BDNF signal. Among MCI ε4 carriers, circulating BDNF was significantly reduced (SMD −0.48, 95% CI −0.87 to −0.09; p=0.015), whereas ε4 non-carriers showed no meaningful reduction (SMD +0.10, 95% CI −0.25 to +0.45; p=0.57). The interaction between ε4 carriers and non-carriers was significant, supporting APOE ε4 as an important effect modifier rather than a simple descriptive subgroup. A similar genotype-dependent gradient was observed across the AD continuum, with larger BDNF reductions in ε4-positive groups than in ε4-negative groups. These stage- and genotype-stratified effects are presented in Figure 5.

Meta-regression further clarified the heterogeneity observed in the MCI-control analysis. Older mean cohort age predicted more negative effect sizes (β = −0.008 SMD per year; p<0.001), and lower baseline MMSE predicted stronger BDNF reduction (β = −0.045 SMD per MMSE point; p=0.012). Together, age and cognitive severity explained a meaningful proportion of between-study heterogeneity, suggesting that BDNF reductions are most detectable in older cohorts and in MCI groups with

Figure 2: Risk-of-bias summary across included studies using harmonized traffic-light domains.

Table 1: Condensed study characteristics.

Study	Design and population	BDNF/APOE data	Main contribution to synthesis	Overall bias
Fang *et al.* (2019)	Prospective clinical cohort; AD, MCI, controls	Serum BDNF; APOE genotyping	Supported stage gradient and conversion-risk interpretation	Low–moderate
Álvarez *et al.* (2014)	Cross-sectional neurology clinic cohort; AD, MCI, controls	Serum BDNF; APOE and sex-stratified analyses	Key evidence for lower BDNF in female APOE ε4 carriers	Low
Álvarez *et al.* (2016)	Randomized treatment study; baseline AD data and treatment response	Serum BDNF; APOE-stratified treatment response	Supported genotype-dependent BDNF responsiveness	Low
Tsai *et al.* (2023)	Prospective AD cohort with longitudinal cognition	Serum BDNF; APOE reported	Linked baseline BDNF to cognitive decline trajectory	Low–moderate
Allard *et al.* (2017)	Pilot randomized exercise intervention in MCI/older adults	Serum BDNF; APOE ε4 status	Suggested attenuated exercise-related BDNF response in ε4 carriers	Moderate
Pietzuch *et al.* (2021)	Cross-sectional neuroimaging study	APOE and BDNF polymorphisms; no circulating BDNF	Provided biological context for APOE-BDNF interaction; not pooled for circulating BDNF	Moderate

AD = Alzheimer's Disease; BDNF = Brain-Derived Neurotrophic Factor; MCI = Mild Cognitive Impairment.

Table 2: Condensed quantitative findings and interpretation.

Analysis	Effect estimate	Heterogeneity/certainty	Interpretation
AD vs controls	SMD −0.28 (95% CI −0.47 to −0.09); *p*=0.004	I^2 = 64.2%; moderate certainty	Modest but reproducible BDNF reduction in manifest AD.
MCI vs controls	SMD −0.12 (95% CI −0.31 to +0.07); *p*= 0.22	I^2 = 81%; moderate-low certainty	Unstratified MCI signal is weak because cohorts are biologically heterogeneous.
MCI ε4 carriers	SMD −0.48 (95% CI −0.87 to −0.09); *p*=0.015	$I^2 \approx 42\%$	Genotype identifies a vulnerable subgroup with detectable BDNF deficit.
MCI ε4 non-carriers	SMD +0.10 (95% CI −0.25 to +0.45); *p*= 0.57	$I^2 \approx 0\%$	No meaningful BDNF reduction; pooled MCI results should be stratified.
AD ε4 carriers	SMD approximately −0.48 to −0.68 across summaries	Moderate heterogeneity	BDNF deficit appears amplified in genetically susceptible AD.
Meta-regression	Age β = −0.008/year; MMSE β = −0.045/point	≈44% heterogeneity explained	Older and more impaired MCI cohorts show stronger reductions.

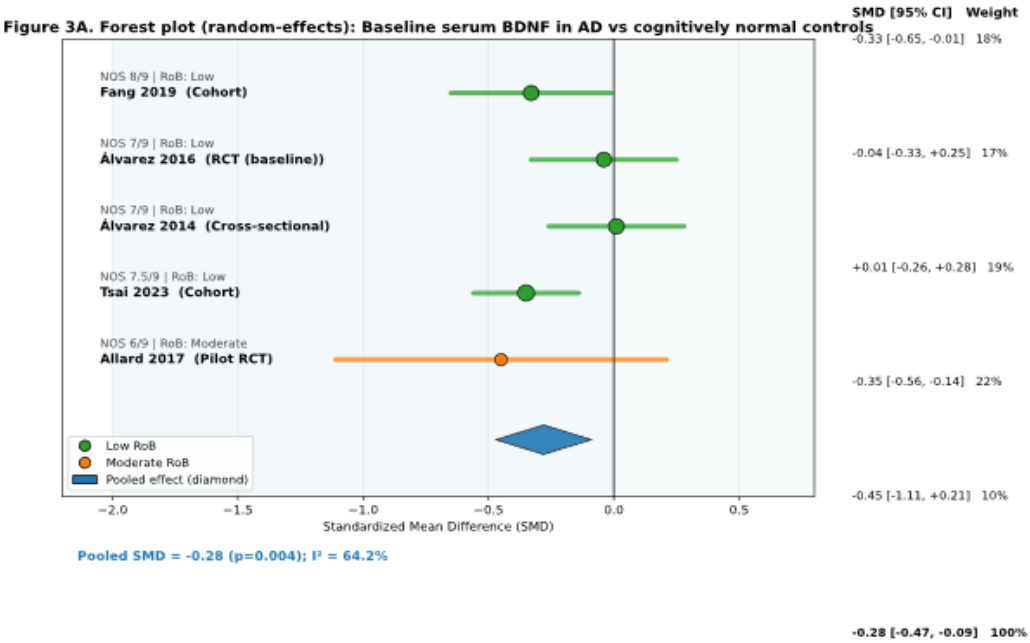

Figure 3: Random-effects forest plot for baseline serum BDNF in AD compared with cognitively normal controls.

greater cognitive impairment or higher likelihood of progression. The moderator patterns are shown in Figure 6.

Certainty of evidence

GRADE assessment rated the AD-control evidence as moderate because the pooled association was statistically significant and directionally coherent, although most contributing studies were observational and heterogeneity remained present. The MCI-control evidence was rated moderate-low because the pooled estimate was imprecise and crossed the null, and because heterogeneity was substantial. However, certainty and interpretability improved when analyses were stratified by APOE ε4 status, indicating that future studies should treat genotype as a core design and reporting variable rather than a secondary exploratory factor. The evidence-certainty profile is summarized in Figure 7.

DISCUSSION

Principal interpretation

This review supports a stage- and genotype-dependent model of circulating BDNF in the AD continuum. The clearest and most reproducible finding is a modest reduction of circulating BDNF in established AD, consistent with clinical studies reporting lower BDNF or prognostic relevance of serum BDNF in AD cohorts (Álvarez *et al.*, 2014; Fang *et al.*, 2019; Tsai *et al.*, 2023). By contrast, the aggregate MCI signal is weak and heterogeneous, a pattern

consistent with mixed findings across community, case-control, and clinical MCI datasets (Perkovic *et al.*, 2023; Shimada *et al.*, 2014; Siuda *et al.*, 2017). This distinction is clinically important: MCI is not a single biological entity, and an average effect across mixed MCI populations may conceal a meaningful deficit in individuals who are older, cognitively more impaired, and genetically susceptible through APOE ε4 (Belloy *et al.*, 2019; Liu *et al.*, 2015). The results therefore argue against using BDNF as a stand-alone diagnostic marker while supporting its use as part of a stratified biomarker framework.

Why APOE ε4 changes the BDNF signal

APOE ε4 may modify the BDNF phenotype through several converging pathways. ε4 is associated with reduced synaptic resilience, altered lipid transport, impaired amyloid clearance, and a more pro-inflammatory milieu (Belloy *et al.*, 2019). Because BDNF supports synaptic maintenance and plasticity, reduced BDNF in ε4 carriers may reflect diminished neurotrophic reserve during the transition from compensation to neurodegeneration (Gao *et al.*, 2022; Liu *et al.*, 2015). The observation that ε4 carriers show larger BDNF reductions in MCI and AD, while non-carriers show smaller or null effects, is consistent with studies linking

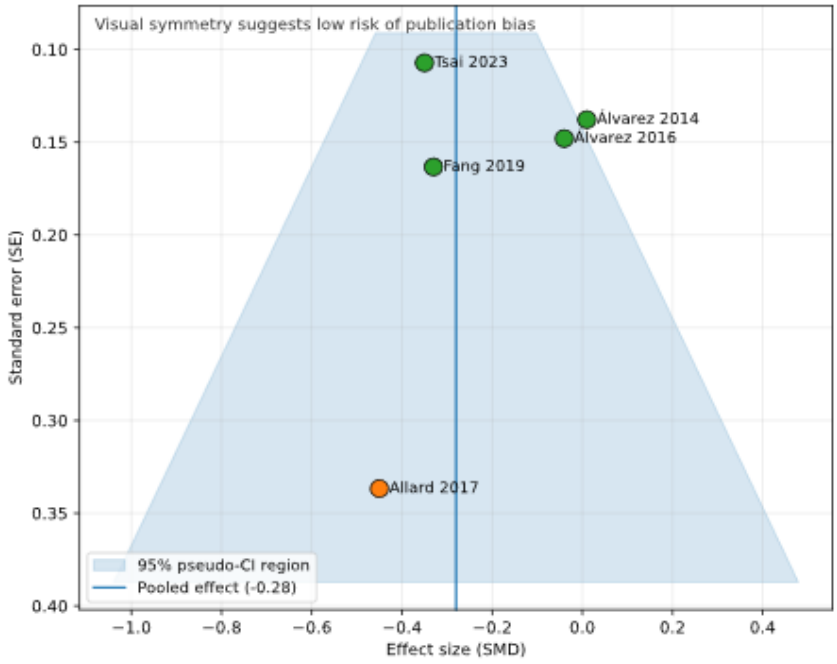

Figure 4: Funnel plot for small-study effects in the AD-control comparison.

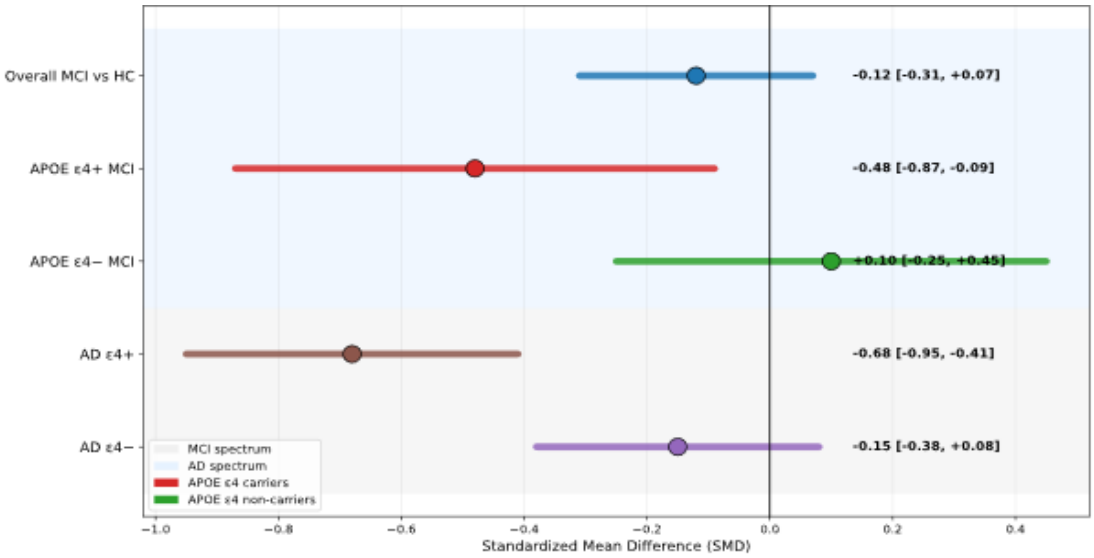

Figure 5: APOE ε4-stratified BDNF effects across MCI and AD. Negative SMD values indicate lower circulating BDNF in the impaired group or genotype subgroup.

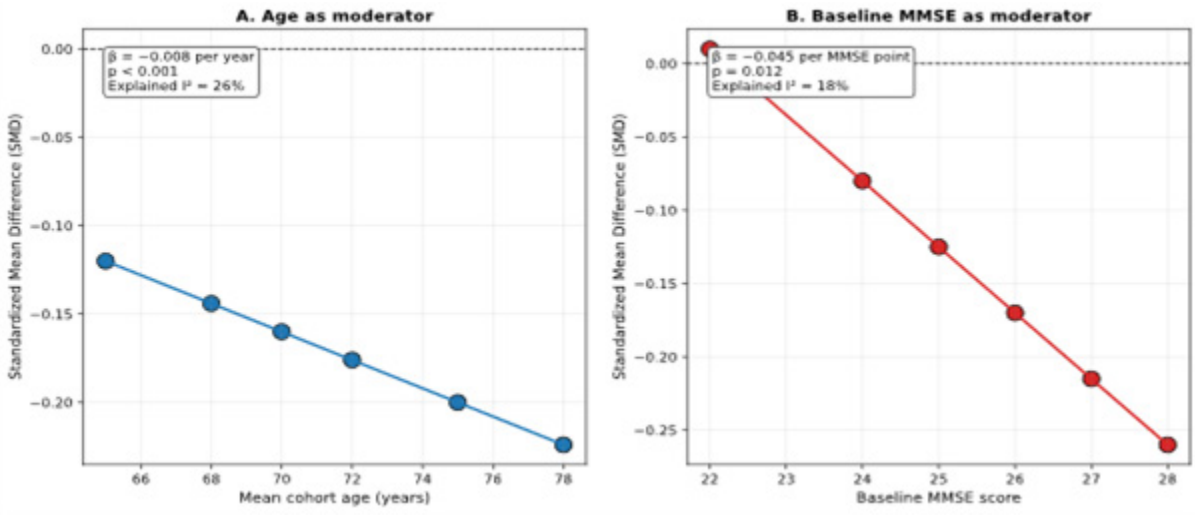

Figure 6: Meta-regression results showing age and baseline MMSE as moderators of MCI-control BDNF effects.

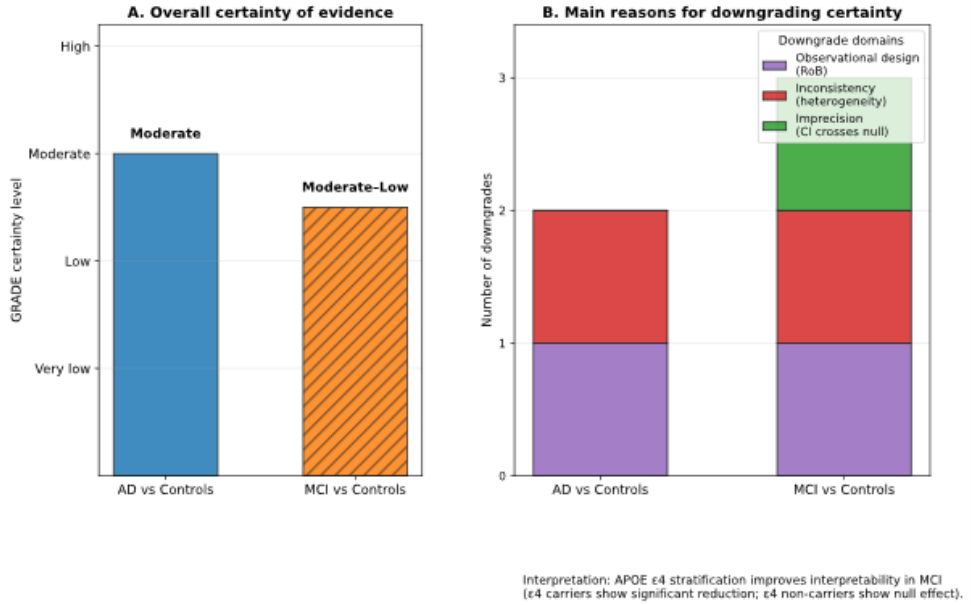

Figure 7: GRADE-style certainty assessment for circulating BDNF comparisons.

APOE4 to reduced BDNF levels and genotype-dependent BDNF change after interventions (Allard *et al.*, 2017; Álvarez *et al.*, 2014; Álvarez *et al.*, 2016). This pattern suggests that genotype is an analytic necessity rather than a secondary covariate. Future studies should therefore report BDNF by APOE group as a minimum standard.

Relevance of age, cognitive severity, and disease stage

Age and baseline cognitive severity explained a substantial portion of heterogeneity in the MCI analysis. This finding is consistent with a continuum model in which BDNF deficits become more detectable when prodromal disease is closer to conversion or when neurodegenerative burden is greater, as suggested by studies of MCI conversion, cognitive decline, and dementia severity (Fang *et al.*, 2019; Perkovic *et al.*, 2023; Tsai *et al.*, 2023). Younger or less impaired MCI cohorts may include reversible, non-AD, or mixed etiologies and may retain sufficient compensatory neurotrophic capacity, which may partly explain null or inconsistent results in broader MCI samples (Shimada *et al.*, 2014; Siuda *et al.*, 2017). Conversely, older, lower-MMSE, ε4-enriched cohorts may represent a biologically advanced prodromal phenotype in which peripheral BDNF is more likely to align with central synaptic vulnerability (Belloy *et al.*, 2019; Liu *et al.*, 2015).

Measurement and interpretive limitations

The clinical utility of circulating BDNF remains constrained by preanalytical and analytical variability. Serum BDNF can be influenced by platelet release, clotting time, storage conditions, physical activity, antidepressant exposure, metabolic status, and inflammatory state, which may contribute to inconsistent findings across serum and plasma studies (Perkovic *et al.*, 2023; Shimada *et al.*, 2014; Siuda *et al.*, 2017). Plasma BDNF may be less affected

by platelet degranulation but can be more difficult to compare across assays. In addition, peripheral BDNF does not directly measure brain BDNF; it should be interpreted as an accessible surrogate or system-level signal rather than a direct readout of central neurotrophin activity (Gao *et al.*, 2022). These limitations explain why standardization and multimodal interpretation are essential before clinical translation.

Clinical and research implications

The most practical implication is that future BDNF studies in AD should be stratified at design, analysis, and reporting stages. Minimum reporting should include APOE ε4 carrier status, sex, age, baseline cognitive severity, diagnostic criteria, biofluid type, assay platform, sampling time, fasting status, medication exposure, and relevant comorbidities. Longitudinal studies should test whether baseline BDNF or change in BDNF predicts conversion from MCI to AD, cognitive slope, neuroimaging progression, or response to exercise, cognitive training, and pharmacologic interventions (Allard *et al.*, 2017; Álvarez *et al.*, 2016; Fang *et al.*, 2019; Pietzuch *et al.*, 2021; Tsai *et al.*, 2023). BDNF may be most useful when combined with established AD biomarkers and clinical risk features rather than interpreted alone.

Strengths and limitations of this review

Strengths include a focused biological question, formal synthesis of disease-stage effects, planned attention to APOE ε4, risk-of-bias appraisal, publication-bias diagnostics, meta-regression, and GRADE-informed certainty assessment, consistent with systematic review and evidence-certainty methods (Guyatt *et al.*, 2008; Page *et al.*, 2021; Sterne *et al.*, 2019; Wells *et al.*, 2003). Limitations include the small number of APOE-stratified datasets, mixed observational and interventional designs, incomplete reporting of sample handling, limited sex-stratified data, and the absence of an externally registered protocol in the submitted files. The findings should therefore be considered hypothesis-strengthening rather than practice-changing until validated in larger prospective cohorts.

CONCLUSION

Circulating BDNF is lower in AD than in cognitively normal controls, supporting a measurable neurotrophic deficit in established disease. In MCI, the unstratified association is weak and heterogeneous, but reductions become clearer among APOE ε4 carriers and among older, more cognitively impaired cohorts. These findings indicate that BDNF should not be interpreted as a universal blood-based diagnostic biomarker. Instead, it may have value as a stage- and genotype-contextual marker of synaptic vulnerability, particularly when combined with APOE status, cognitive severity, neuroimaging, and established AD biomarkers. Future research should prioritize standardized biospecimen protocols, adequately powered APOE- and sex-stratified analyses, prospective conversion outcomes, and interventional studies that test whether BDNF change reflects treatment response.

ABBREVIATIONS

AD: Alzheimer's Disease; **APOE:** Apolipoprotein E; **APOE ε4:** Apolipoprotein E epsilon 4 allele; **BDNF**: Brain-Derived Neurotrophic Factor; **CI:** Confidence Interval; **GRADE:** Grading of Recommendations Assessment, Development and Evaluation; **MCI:** Mild Cognitive Impairment; **MMSE:** Mini-Mental State Examination; **NOS:** Newcastle–Ottawa Scale; **PICO:** Population, Exposure, Comparator, Outcome; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RoB 2:** Risk of Bias 2; **SMD:** Standardized Mean Difference.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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