

Fluid Proteostasis-Related Biomarkers In Alzheimer's Disease And Mild Cognitive Impairment: A Systematic Review And Meta-Analysis

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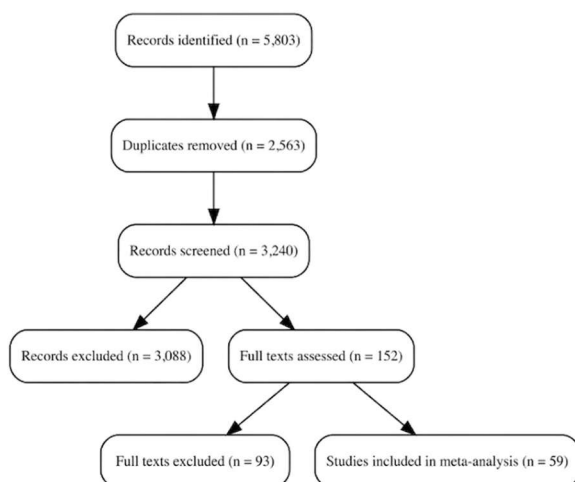
Background

- Alzheimer's disease (AD) pathogenesis involves a systemic failure of cellular quality-control mechanisms that lead to early protein misfolding which precedes clinical symptom onset
- Extracellular chaperones target A β aggregation, while intracellular heat-shock proteins manage hyperphosphorylated tau
- Prior clinical findings across cerebrospinal fluid (CSF) and peripheral blood are highly discordant, masking their utility as reliable biomarkers

Methods

- Medline, Scopus, Embase, and PubMed were systematically searched from inception through May 2026 using a PICO framework in collaboration with an information specialist
- Original, peer-reviewed clinical articles measuring fluid concentrations of CLU, A2M, Hp, HSP60, HSP70, or HSP90
- Two reviewers independently assessed eligibility, resolving discrepancies via consensus with a third rater

Figure 1. PRISMA flow diagram



- Hedges' g standardized mean differences (SMDs) were pooled using random-effects models (REML method) to evaluate central (CSF) and peripheral (plasma/serum) compartment concentrations
- Variance was explored via mixed-effects meta-regressions and subgroup analysis ($I^2 > 50\%$), with publication bias verified via non-parametric trim-and-fill algorithms

Results

Figure 2. Random-effects meta-analysis of peripheral blood clusterin (CLU) concentrations. Panel A: Forest plot contrasting individuals with Alzheimer's disease (AD) versus healthy controls, demonstrating a significant pooled CLU elevation in AD across 21 independent cohorts ($k = 21$, $p = 0.005$). **Panel B:** Forest plot contrasting individuals with mild cognitive impairment (MCI) versus healthy controls, showing a consistently preserved, significant pooled CLU elevation in prodromal stages across 15 independent cohorts ($k = 15$, $p = 0.013$). Individual study effect sizes are represented by black squares, with sizes proportional to their relative weight in the model. Horizontal lines denote 95% confidence intervals (CIs). The black diamonds represent the overall pooled standardized mean differences (SMD) calculated via Restricted Maximum Likelihood (REML) estimation. High cross-study heterogeneity was observed in both fluid pools ($I^2 > 92\%$).

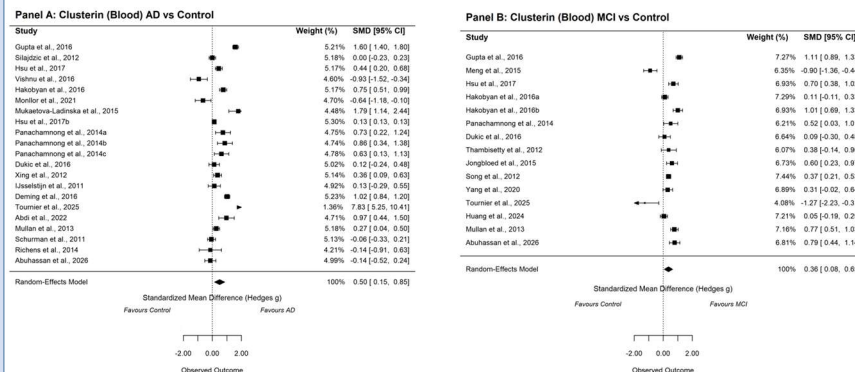
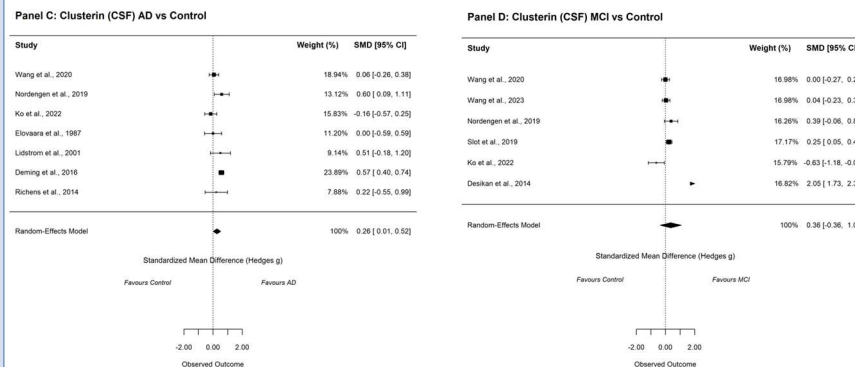


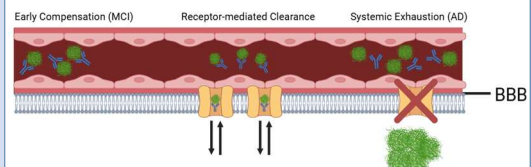
Figure 3. Random-effects meta-analysis of central nervous system (CSF) clusterin (CLU) concentrations. Panel C: Forest plot contrasting CSF CLU concentrations in individuals with Alzheimer's disease (AD) versus healthy controls, showing a significant central elevation across 7 distinct datasets ($k = 7$, $p = 0.045$). **Panel D:** Forest plot contrasting CSF CLU concentrations in individuals with mild cognitive impairment (MCI) versus healthy controls across 6 datasets ($k = 6$), demonstrating a positive directionality that did not reach statistical significance ($p = 0.327$). Individual study effect sizes are represented by black squares (sized by relative weight), and horizontal lines represent 95% confidence intervals (CIs). Black diamonds indicate the aggregated pooled standardized mean differences (SMD) derived using Restricted Maximum Likelihood (REML) random-effects modeling. Moderate heterogeneity was observed in the central AD contrast ($I^2 = 61.7\%$).



Discussion

- Clusterin (CLU) is robustly elevated in peripheral blood across both prodromal (MCI) and dementia (AD) stages, whereas CSF changes are less pronounced and localized primarily to symptomatic AD
- Systemic accumulation suggests an early, upregulated proteostatic response to counter mounting A β misfolding long before clinical dementia manifests

Figure 4. Conceptual model of stage-specific clusterin (CLU) clearance kinetics across the blood-brain barrier. Chronically elevated levels of CLU in the periphery may signal a state of systemic receptor saturation or compromised clearance pathways, where the chaperone can no longer effectively prevent or clear toxic protein aggregates



- Broad variance in blood compartments ($I^2 > 92\%$) likely reflects diverse clinical cohorts, mixed assay types, and variable stages of systemic vascular inflammation

Conclusion

- Blood CLU holds clinical promise as an accessible, minimally invasive upstream screening tool for early risk stratification
- Characterizing stage-specific fluid chaperone dynamics shifts the clinical paradigm toward early, proactive therapeutic windows aimed at stabilizing proteostasis before irreversible neurodegeneration begins

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