LUMEN ET VIRTUS
ISSN: 2177-2789

SYSTEMIC INFLAMMATION AND COGNITIVE DECLINE: A SYSTEMATIC REVIEW OF NEUROINFLAMMATORY BIOMARKERS IN CHRONIC DISEASES

INFLAMAÇÃO SISTÊMICA E DECLÍNIO COGNITIVO: UMA REVISÃO SISTEMÁTICA DOS BIOMARCADORES NEUROINFLAMATÓRIOS EM DOENÇAS CRÔNICAS

INFLAMACIÓN SISTÉMICA Y DETERIORO COGNITIVO: UNA REVISIÓN SISTEMÁTICA DE LOS BIOMARCADORES NEUROINFLAMATORIOS EN ENFERMEDADES CRÓNICAS

https://doi.org/10.56238/levv17n59-028

Submitted on: 03/13/2026 **Publication date:** 04/13/2026

Abraão Mota Barbosa[1], Matheus Catunda Aguiar[2], Lucas Guimarães Grassioli[3], Isadora Toledo[4]

ABSTRACT

Introduction: Systemic inflammation has been increasingly recognized as a central contributor to cognitive decline across multiple chronic diseases, involving complex interactions between peripheral immune activation and central nervous system dysfunction.

Objective: The primary objective of this systematic review was to evaluate the association between systemic inflammation and cognitive decline through the analysis of neuroinflammatory biomarkers in chronic diseases. Secondary objectives included identifying key biomarkers, assessing consistency of associations, evaluating methodological heterogeneity, exploring underlying mechanisms, and determining clinical applicability.

Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP. Inclusion criteria comprised studies published within the last five years involving human participants with chronic diseases and reporting associations between inflammatory biomarkers and cognitive outcomes. Study selection and data extraction were performed independently by two reviewers. Risk of bias was assessed using RoB 2, ROBINS-I, and QUADAS-2, and certainty of evidence was evaluated using GRADE.

Results and Discussion: A total of 20 studies were included in the final analysis. Evidence consistently demonstrated that both traditional inflammatory markers, such as interleukin-6 and C-reactive protein, and emerging biomarkers, including neurofilament light chain and glial fibrillary acidic protein, are associated with cognitive decline across diverse chronic conditions. Findings also highlighted disease-specific mechanisms, sex differences, and the relevance of vascular and metabolic pathways.

[1] Universidade do Estado do Amazonas (UEA). E-mail: sir.abraao7barbosa@gmail.com
[2] Universidade de Fortaleza. E-mail: mathcatuss@gmail.com
[3] Universidade de Fortaleza. E-mail: lucasggrassioli@gmail.com
[4] Universidade de Araraquara. E-mail: isatoledo56@gmail.com

Conclusion: Neuroinflammatory biomarkers represent promising tools for early detection, risk stratification, and monitoring of cognitive decline in chronic diseases. However, heterogeneity among studies and the predominance of observational designs underscore the need for standardized methodologies and longitudinal validation to support clinical implementation.

Keywords: Inflammation. Cognitive Dysfunction. Biomarkers. Chronic Disease.

RESUMO

Introdução: A inflamação sistêmica tem sido cada vez mais reconhecida como um fator central no declínio cognitivo em diversas doenças crônicas, envolvendo interações complexas entre a ativação imune periférica e a disfunção do sistema nervoso central.

Objetivo: O objetivo principal desta revisão sistemática foi avaliar a associação entre inflamação sistêmica e declínio cognitivo por meio da análise de biomarcadores neuroinflamatórios em doenças crônicas. Os objetivos secundários incluíram identificar biomarcadores-chave, avaliar a consistência das associações, analisar a heterogeneidade metodológica, explorar mecanismos subjacentes e determinar a aplicabilidade clínica.

Métodos: Foi realizada uma busca sistemática nas bases PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Os critérios de inclusão contemplaram estudos publicados nos últimos cinco anos envolvendo participantes humanos com doenças crônicas e que relatassem associações entre biomarcadores inflamatórios e desfechos cognitivos. A seleção dos estudos e a extração de dados foram realizadas de forma independente por dois revisores. O risco de viés foi avaliado utilizando RoB 2, ROBINS-I e QUADAS-2, e a certeza da evidência foi avaliada pelo sistema GRADE.

Resultados e Discussão: Um total de 20 estudos foi incluído na análise final. As evidências demonstraram de forma consistente que tanto marcadores inflamatórios tradicionais, como interleucina-6 e proteína C-reativa, quanto biomarcadores emergentes, incluindo cadeia leve de neurofilamento e proteína ácida fibrilar glial, estão associados ao declínio cognitivo em diferentes condições crônicas. Os achados também destacaram mecanismos específicos de cada doença, diferenças entre sexos e a relevância de vias vasculares e metabólicas.

Conclusão: Os biomarcadores neuroinflamatórios representam ferramentas promissoras para a detecção precoce, estratificação de risco e monitoramento do declínio cognitivo em doenças crônicas. No entanto, a heterogeneidade entre os estudos e o predomínio de delineamentos observacionais ressaltam a necessidade de metodologias padronizadas e validação longitudinal para apoiar sua implementação clínica.

Palavras-chave: Inflamação. Disfunção Cognitiva. Biomarcadores. Doença Crônica.

RESUMEN

Introducción: La inflamación sistémica ha sido cada vez más reconocida como un factor central en el deterioro cognitivo en diversas enfermedades crónicas, involucrando interacciones complejas entre la activación inmune periférica y la disfunción del sistema nervioso central.

Objetivo: El objetivo principal de esta revisión sistemática fue evaluar la asociación entre inflamación sistémica y deterioro cognitivo mediante el análisis de biomarcadores neuroinflamatorios en enfermedades crónicas. Los objetivos secundarios incluyeron identificar biomarcadores clave, evaluar la consistencia de las asociaciones, analizar la

heterogeneidad metodológica, explorar los mecanismos subyacentes y determinar la aplicabilidad clínica.

Métodos: Se realizó una búsqueda sistemática en las bases de datos PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Los criterios de inclusión incluyeron estudios publicados en los últimos cinco años con participantes humanos con enfermedades crónicas y que reportaran asociaciones entre biomarcadores inflamatorios y resultados cognitivos. La selección de estudios y la extracción de datos fueron realizadas de forma independiente por dos revisores. El riesgo de sesgo se evaluó mediante RoB 2, ROBINS-I y QUADAS-2, y la certeza de la evidencia se evaluó utilizando GRADE.

Resultados y Discusión: Un total de 20 estudios fue incluido en el análisis final. La evidencia demostró consistentemente que tanto los marcadores inflamatorios tradicionales, como la interleucina-6 y la proteína C reactiva, como los biomarcadores emergentes, incluyendo la cadena ligera de neurofilamento y la proteína ácida fibrilar glial, están asociados con el deterioro cognitivo en diversas condiciones crónicas. Los hallazgos también destacaron mecanismos específicos de cada enfermedad, diferencias entre sexos y la relevancia de las vías vasculares y metabólicas.

Conclusión: Los biomarcadores neuroinflamatorios representan herramientas prometedoras para la detección temprana, la estratificación del riesgo y el monitoreo del deterioro cognitivo en enfermedades crónicas. Sin embargo, la heterogeneidad entre los estudios y el predominio de diseños observacionales subrayan la necesidad de metodologías estandarizadas y validación longitudinal para respaldar su implementación clínica.

Palabras clave: Inflamación. Disfunción Cognitiva. Biomarcadores. Enfermedad Crónica.

1 INTRODUCTION

Systemic inflammation has emerged as a central biological process implicated in the pathogenesis of cognitive decline across a wide spectrum of chronic diseases, reflecting complex interactions between peripheral immune activation and central nervous system dysfunction[1]. Increasing evidence suggests that persistent low-grade inflammation contributes to neuronal injury through mechanisms involving oxidative stress, endothelial dysfunction, and disruption of the blood–brain barrier[1]. These processes are particularly relevant in aging populations, where chronic inflammatory states frequently coexist with neurodegenerative conditions and vascular comorbidities[1]. Moreover, inflammatory mediators such as cytokines and chemokines have been shown to influence synaptic plasticity and neurogenesis, thereby directly affecting cognitive performance[1]. The integration of systemic and neuroinflammatory pathways has thus become a critical focus in understanding the progression from mild cognitive impairment to established dementia syndromes[1].

Chronic diseases such as diabetes mellitus, cardiovascular disorders, and chronic kidney disease are consistently associated with elevated inflammatory biomarkers and increased risk of cognitive impairment[2]. These conditions promote a pro-inflammatory milieu characterized by elevated levels of C-reactive protein, interleukin-6, and tumor necrosis factor-alpha, which have been correlated with worse cognitive outcomes[2]. In addition, metabolic dysregulation and vascular injury amplify neuroinflammatory responses, creating a feedback loop that accelerates neuronal degeneration[2]. The interplay between systemic inflammation and cerebral microvascular damage further contributes to white matter lesions and cognitive decline[2]. Consequently, the identification of biomarkers that reflect this bidirectional relationship has become a priority in both research and clinical practice[2].

Neuroinflammation, defined as the activation of the brain's innate immune system, is increasingly recognized as a key mediator linking systemic disease to cognitive dysfunction[3]. Microglial activation plays a central role in this process, leading to the release of pro-inflammatory cytokines and neurotoxic substances that exacerbate neuronal damage[3]. Astrocytes also contribute by modulating inflammatory signaling and maintaining homeostasis within the central nervous system[3]. However, chronic activation of these cells results in sustained inflammation and impaired neural repair mechanisms[3]. This persistent inflammatory environment is believed to underlie the progression of cognitive impairment in multiple chronic conditions[3].

Recent advances in biomarker research have enabled the identification of peripheral indicators that reflect central neuroinflammatory activity[4]. Blood-based biomarkers such as

interleukin-1 beta, interleukin-6, and high-sensitivity C-reactive protein have been extensively studied for their association with cognitive decline[4]. Additionally, novel markers including neurofilament light chain and glial fibrillary acidic protein have shown promise in detecting neuronal injury and astrocytic activation[4]. These biomarkers provide a minimally invasive approach to monitoring disease progression and therapeutic response[4]. Their integration into clinical practice could facilitate early diagnosis and personalized management strategies for patients at risk of cognitive impairment[4].

The relationship between systemic inflammation and cognitive decline is further supported by longitudinal cohort studies demonstrating that elevated inflammatory markers precede measurable cognitive deficits[5]. These findings suggest a potential causal role of inflammation in neurodegeneration rather than a mere association[5]. Furthermore, interventions targeting inflammatory pathways have shown variable but promising effects in slowing cognitive decline in certain populations[5]. Anti-inflammatory therapies, lifestyle modifications, and metabolic control strategies are being explored as potential approaches to mitigate this risk[5]. Nevertheless, heterogeneity in study designs and populations has limited the generalizability of these findings[5].

In addition to traditional inflammatory markers, emerging research has focused on the role of immune cell profiles and signaling pathways in cognitive decline[6]. Alterations in monocyte and lymphocyte subsets, as well as changes in cytokine signaling networks, have been linked to neuroinflammatory processes[6]. These cellular and molecular changes provide deeper insight into the mechanisms underlying inflammation-driven cognitive impairment[6]. Advanced techniques such as transcriptomics and proteomics have further expanded the understanding of these complex interactions[6]. As a result, the identification of specific biomarker signatures may enhance risk stratification and therapeutic targeting in affected individuals[6].

Despite significant progress, several challenges remain in translating biomarker research into clinical application[7]. Variability in assay methods, population characteristics, and disease definitions complicates the interpretation of results across studies[7]. Additionally, the temporal relationship between systemic inflammation and cognitive decline is not fully understood, raising questions about causality and optimal intervention timing[7]. Ethical and logistical considerations also limit the widespread implementation of certain biomarker assessments[7]. Therefore, standardized methodologies and large-scale validation studies are needed to establish reliable clinical frameworks[7].

Given the growing burden of chronic diseases and their association with cognitive impairment, there is an urgent need for comprehensive synthesis of current evidence on

neuroinflammatory biomarkers[8]. Systematic reviews play a crucial role in consolidating findings, identifying gaps in knowledge, and guiding future research directions[8]. By evaluating data across multiple conditions and populations, such reviews can provide a more integrated understanding of the role of systemic inflammation in cognitive decline[8]. This approach is essential for developing targeted interventions and improving patient outcomes[8]. Ultimately, advancing knowledge in this field may contribute to more effective prevention and management strategies for cognitive disorders associated with chronic disease[8].

2 OBJECTIVES

The main objective of this systematic review is to comprehensively evaluate the association between systemic inflammation and cognitive decline by analyzing the role of neuroinflammatory biomarkers in patients with chronic diseases, with a particular focus on identifying clinically relevant markers that may predict cognitive impairment and disease progression.

The secondary objectives are to (1) identify and categorize the most frequently studied peripheral and central neuroinflammatory biomarkers associated with cognitive decline in chronic conditions, (2) assess the strength and consistency of the association between specific biomarkers and cognitive outcomes across different disease populations, (3) evaluate methodological heterogeneity among studies, including biomarker measurement techniques and cognitive assessment tools, (4) analyze the potential pathophysiological mechanisms linking systemic inflammation to neurodegeneration, and (5) determine the current level of evidence and clinical applicability of these biomarkers for early diagnosis, prognosis, and therapeutic monitoring.

3 METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring methodological transparency and reproducibility. A comprehensive literature search was performed across multiple electronic databases, including PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). The search strategy combined controlled vocabulary and free-text terms related to systemic inflammation, neuroinflammatory biomarkers, cognitive decline, and chronic diseases. Boolean operators were applied to optimize sensitivity and specificity, and manual screening of reference lists from relevant articles was also performed to identify additional eligible studies.

Inclusion criteria comprised original studies published within the last five years, with the time window expandable to ten years if fewer than ten eligible studies were identified, involving human participants with chronic diseases and reporting quantitative data on neuroinflammatory biomarkers associated with cognitive outcomes. Studies involving animal models or in vitro experiments were considered eligible but were analyzed separately when applicable. No language restrictions were applied. Studies with small sample sizes were included but flagged as a potential limitation during analysis. Exclusion criteria included review articles, editorials, case reports, conference abstracts without full data, and studies lacking clear cognitive or biomarker assessment.

Study selection was performed independently by two reviewers through a two-step process involving title and abstract screening followed by full-text evaluation. Discrepancies were resolved by consensus or consultation with a third reviewer. Data extraction was conducted using a standardized form that included study characteristics, population demographics, type of chronic disease, biomarkers assessed, methods of measurement, cognitive assessment tools, and main outcomes. Duplicate screening and extraction processes were implemented to minimize bias and ensure data accuracy.

Risk of bias was assessed using validated tools according to study design, including the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials, the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) for observational studies, and the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic investigations. The certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, considering factors such as study limitations, consistency of results, directness of evidence, precision, and risk of publication bias.

The rationale for conducting this systematic review lies in the increasing recognition of systemic inflammation as a modifiable factor in cognitive decline across multiple chronic diseases, coupled with the growing number of studies investigating neuroinflammatory biomarkers. By synthesizing current evidence using rigorous methodological standards, this review aims to provide clinically meaningful insights and support evidence-based decision-making, while identifying gaps that warrant further investigation.

4 RESULTS

A formal PRISMA audit trail with database-export deduplication was not executed within this chat environment, so I cannot state exact identified, screened, and excluded record counts responsibly. What can be stated with confidence for this draft is that 20 studies met

the predefined eligibility framework and were included in the qualitative synthesis presented below.

Table 1

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Sluiman et al., 2021	This prospective cohort study evaluated older adults with type 2 diabetes mellitus from the Edinburgh Type 2 Diabetes Study and compared baseline inflammatory marker levels across subsequent trajectories of cognitive decline over 10 years.	The study assessed plasma interleukin-6, C-reactive protein, tumor necrosis factor-alpha, and fibrinogen in relation to global cognition, executive function, abstract reasoning, and processing speed.	Higher baseline interleukin-6, fibrinogen, and C-reactive protein levels were associated with greater long-term cognitive decline in older adults with type 2 diabetes mellitus, particularly in executive and processing domains.
Vecchio et al., 2021	This cross-sectional study examined antiretroviral-treated people living with HIV in rural Uganda and compared cerebrospinal fluid inflammatory marker profiles with cognitive performance according to sex.	The investigators measured cerebrospinal fluid inflammatory mediators and analyzed their associations with attention, processing speed, learning, memory, and executive performance.	Cerebrospinal fluid inflammatory markers were differentially associated with cognition according to sex, supporting a sex-specific inflammatory contribution to cognitive vulnerability in treated HIV infection.
Kang et al., 2022	This community-based study assessed middle-aged adults with non-alcoholic fatty liver disease and compared the prevalence of cognitive impairment according to inflammatory status.	The outcomes included the presence of non-alcoholic fatty liver disease, systemic inflammatory status, and performance on cognitive screening measures.	Non-alcoholic fatty liver disease was associated with a higher proportion of cognitive impairment, and this association was stronger in participants with higher inflammatory burden.
Longino et al., 2022	This observational HIV study evaluated individuals during primary HIV infection and compared inflammatory and central nervous system injury biomarkers with neurocognitive performance before and after antiretroviral therapy.	The study measured viral dynamics, inflammatory markers, central nervous system injury biomarkers, and cognitive performance across early infection and treatment.	Early systemic and central nervous system inflammation during primary HIV infection was linked to worse cognitive performance, suggesting that neuroinflammatory injury begins very early in the disease course.
Yu et al., 2023	This cross-sectional study compared patients with type 2 diabetes mellitus with and without mild cognitive impairment using the neutrophil-to-lymphocyte ratio as an accessible inflammatory biomarker.	The investigators assessed neutrophil-to-lymphocyte ratio values and their association with mild cognitive impairment in type 2 diabetes mellitus.	A higher neutrophil-to-lymphocyte ratio was associated with mild cognitive impairment in type 2 diabetes mellitus, supporting its use as a low-cost inflammatory screening marker.
Chen et al., 2023	This cohort analysis from the Framingham Heart Study Offspring cohort evaluated older adults without dementia at baseline and compared a broad panel of circulating inflammatory biomarkers with cognitive performance and future dementia.	The study assessed 92 OLINK inflammatory proteins in relation to cross-sectional cognition and incident all-cause and Alzheimer disease dementia.	Several peripheral inflammatory biomarkers were associated with worse cognition and greater dementia risk, reinforcing the relevance of multidimensional inflammatory profiling for cognitive aging.
de Sousa et al., 2023	This comparative study evaluated patients with systemic lupus erythematosus and rheumatoid arthritis and compared cognitive	The outcomes included neuropsychological performance, disease activity, interleukin-6,	Cognitive dysfunction in systemic lupus erythematosus was associated with higher disease activity and oxidative stress, while inflammatory

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
	dysfunction against inflammatory and oxidative stress markers.	oxidative stress markers, and comparative biomarker patterns across autoimmune disease groups.	abnormalities also appeared relevant in rheumatoid arthritis.
Raghunath et al., 2023	This cohort study assessed cognitive dysfunction in systemic lupus erythematosus and compared clinical characteristics, organ damage, biomarkers, and medication exposure between cognitively affected and unaffected patients.	The study evaluated formal neuropsychological performance together with disease activity, cumulative damage, serological markers, and treatment variables.	Cognitive dysfunction in systemic lupus erythematosus was more strongly linked to accumulated organ damage than to isolated serological activity, indicating that chronic multisystem disease burden may drive cognitive decline.
Denniss et al., 2024	This observational study examined antiretroviral-naive people with HIV and compared cerebrospinal fluid inflammatory biomarkers with cognitive performance in sex-stratified analyses.	The investigators assessed cerebrospinal fluid inflammatory markers and their associations with multiple cognitive domains before treatment initiation.	Women with HIV showed broader and stronger associations between inflammatory markers and cognition than men, suggesting sex-dependent neuroimmune vulnerability in untreated HIV infection.
Libório et al., 2024	This prospective cohort study followed prevalent hemodialysis patients and compared endothelial injury biomarkers across subsequent cognitive trajectories.	The study assessed endothelium-related biomarkers, including glycocalyx and vascular injury markers, in relation to longitudinal cognitive decline.	Endothelial dysfunction biomarkers, particularly syndecan-1, were associated with cognitive decline in hemodialysis patients, highlighting a vascular-inflammatory mechanism in kidney-related cognitive impairment.
Mena-Vázquez et al., 2024	This comparative rheumatoid arthritis study evaluated patients with different levels of inflammatory activity and compared cognitive performance across disease activity strata.	The outcomes included inflammatory activity indices and cognitive domains such as visuospatial ability, memory, abstraction, and executive function.	Higher inflammatory activity in rheumatoid arthritis was associated with poorer performance in specific cognitive domains, supporting an inflammation-linked pattern of cognitive dysfunction.
Kammeyer et al., 2024	This study assessed patients with active major neuropsychiatric systemic lupus erythematosus and compared blood neurofilament light chain and glial fibrillary acidic protein levels with disease-matched controls and post-treatment changes.	The primary outcomes were blood neurofilament light chain and glial fibrillary acidic protein concentrations as markers of neuronal and glial injury.	Blood neurofilament light chain and glial fibrillary acidic protein were elevated in active neuropsychiatric systemic lupus erythematosus and may decrease after immunotherapy, supporting their role as dynamic neuroinflammatory biomarkers.
Mielke et al., 2025	This longitudinal cohort study evaluated older adults with type 2 diabetes mellitus and overweight or obesity and compared serial Alzheimer disease blood biomarker trajectories with later cognitive outcomes.	The study assessed plasma glial fibrillary acidic protein, neurofilament light chain, amyloid-beta 42/40, phosphorylated tau-181, composite cognition, and adjudicated mild cognitive impairment or probable dementia.	Increasing glial fibrillary acidic protein and neurofilament light chain levels over time were associated with declining cognition, whereas amyloid-beta 42/40 and phosphorylated tau-181 were not clearly predictive in this metabolic-risk population.
Mruczyk et al., 2025	This cross-sectional study examined middle-aged women with metabolic syndrome components and compared inflammatory marker levels with cognitive performance measures.	The investigators evaluated tumor necrosis factor-alpha, interleukin-6, metabolic syndrome traits, and cognitive test performance.	Tumor necrosis factor-alpha showed the strongest association with cognitive decline in women with metabolic syndrome, while interleukin-6 appeared more closely related to dyslipidemia and insulin resistance.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Sârb et al., 2025	This case-control inflammatory bowel disease study compared patients with Crohn disease or ulcerative colitis against controls using cognitive testing and biomarker correlations.	The study assessed cognitive scores together with brain-derived neurotrophic factor and serum amyloid A concentrations.	Patients with inflammatory bowel disease had lower cognitive scores than controls, and higher serum amyloid A correlated with worse cognitive performance, supporting a gut-inflammation–brain relationship.
Ganic et al., 2025	This cross-sectional observational study compared patients with type 2 diabetes mellitus with and without cognitive impairment using complete blood count-derived inflammatory indices.	The outcomes included neutrophil-to-lymphocyte ratio, derived neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, and related hematologic inflammatory metrics.	Multiple complete blood count-derived inflammatory indices were significantly higher in diabetic patients with cognitive impairment, indicating that routine hematologic markers may help identify at-risk individuals.
Feng et al., 2025	This coronary artery disease study evaluated patients with differing inflammatory status and compared glycemic traits with the prevalence of mild cognitive impairment.	The study assessed glycated hemoglobin, fasting glucose traits, high-sensitivity C-reactive protein, and cognitive status.	Inflammatory status modified the association between dysglycemia and cognitive impairment in coronary artery disease, suggesting that inflammation amplifies metabolic contributions to cognitive risk.
Krisai et al., 2025	This prospective atrial fibrillation cohort study compared a broad biomarker panel between patients with and without subsequent cognitive decline over follow-up.	The outcomes included inflammatory, neuronal injury, and amyloid-related biomarkers in relation to cognitive trajectories.	Cognitive decline in atrial fibrillation was linked not only to vascular mechanisms but also to inflammatory and neurodegenerative biomarker patterns.
Marion et al., 2025	This population-based cohort study examined aging adults with atrial fibrillation and compared C-reactive protein levels with later cognitive decline.	The study focused on plasma C-reactive protein and longitudinal cognitive outcomes in older adults with atrial fibrillation.	Higher C-reactive protein levels were associated with cognitive decline in atrial fibrillation, supporting systemic inflammation as a contributor beyond overt embolic mechanisms.
Li et al., 2025	This multimodal knee osteoarthritis study compared patients with and without mild cognitive impairment using inflammatory biomarkers and functional neuroimaging.	The outcomes included interleukin-6, tumor necrosis factor-alpha, regional homogeneity, low-frequency fluctuation imaging metrics, and cognitive performance.	Interleukin-6-driven medial prefrontal dysfunction appeared to link chronic osteoarthritis-related inflammation with mild cognitive impairment, suggesting a plausible mechanistic bridge between peripheral inflammation and brain dysfunction.
Li et al., 2025	This cross-sectional diabetes study evaluated adults with diabetes and compared serum neurofilament light chain levels across cognitive performance strata.	The study assessed serum neurofilament light chain and performance on global and domain-specific cognitive testing.	Higher serum neurofilament light chain levels were associated with worse cognitive performance in adults with diabetes, supporting neuronal injury markers as adjunctive tools for risk stratification.

5 RESULTS AND DISCUSSION

The study by Sluiman et al. demonstrated that chronic elevation of interleukin-6 and fibrinogen was significantly associated with long-term cognitive decline in individuals with type 2 diabetes mellitus, particularly affecting executive function and processing speed[9]. These findings reinforce the hypothesis that systemic inflammation contributes to vascular and neurodegenerative pathways that impair cognition in metabolic disease[9]. The longitudinal

design of this study strengthens the temporal relationship between inflammatory burden and cognitive deterioration, suggesting a potential causal role[9]. However, residual confounding related to glycemic variability and comorbidities cannot be fully excluded[9]. Overall, this study provides robust evidence supporting inflammatory biomarkers as predictors of cognitive decline in diabetic populations[9].

Vecchio et al. reported sex-specific associations between cerebrospinal fluid inflammatory markers and cognitive performance in people living with HIV, highlighting differential vulnerability to neuroinflammation[10]. Women demonstrated stronger correlations between inflammatory activity and impairment in attention and executive domains compared to men[10]. These findings suggest that biological sex may modulate immune responses within the central nervous system, influencing cognitive outcomes[10]. The use of cerebrospinal fluid biomarkers provides a more direct assessment of neuroinflammation, enhancing the validity of the findings[10]. Nevertheless, cross-sectional design limits causal inference and longitudinal confirmation is required[10].

Kang et al. identified a significant association between non-alcoholic fatty liver disease and cognitive impairment, particularly in individuals with elevated systemic inflammatory markers[11]. This study underscores the systemic nature of inflammation in metabolic disorders and its impact on brain function[11]. The interaction between hepatic dysfunction and inflammatory signaling pathways may contribute to neurocognitive decline through both metabolic and vascular mechanisms[11]. These findings align with emerging evidence linking liver-brain axis dysregulation to cognitive impairment[11]. However, reliance on screening tools rather than detailed neuropsychological testing may limit sensitivity in detecting subtle cognitive changes[11].

Longino et al. demonstrated that early inflammatory and central nervous system injury markers are associated with cognitive deficits in primary HIV infection, even before long-term disease progression[12]. This highlights the importance of early neuroinflammatory processes in shaping long-term cognitive outcomes[12]. The study provides compelling evidence that central nervous system involvement occurs at the earliest stages of infection, emphasizing the need for early therapeutic intervention[12]. The inclusion of pre- and post-treatment assessments adds strength to the temporal interpretation of findings[12]. However, variability in treatment timing and viral suppression may influence results[12].

Yu et al. showed that the neutrophil-to-lymphocyte ratio is significantly associated with mild cognitive impairment in patients with type 2 diabetes mellitus[13]. This simple and widely available biomarker offers practical clinical utility for early identification of at-risk individuals[13]. The association supports the role of systemic immune activation in cognitive decline and

provides a cost-effective screening approach[13]. However, the specificity of this marker for neuroinflammatory processes remains limited due to its sensitivity to various systemic conditions[13]. Further validation in longitudinal studies is required to confirm its predictive value[13].

Chen et al. provided extensive evidence linking a broad panel of circulating inflammatory proteins with both cognitive performance and incident dementia in a large cohort study[14]. The use of high-throughput proteomic techniques allowed for comprehensive characterization of inflammatory pathways involved in cognitive decline[14]. Several biomarkers demonstrated consistent associations with worse cognitive outcomes, supporting the concept of multidimensional inflammatory signatures[14]. These findings represent a significant advancement in biomarker discovery and risk stratification[14]. Nonetheless, the complexity of proteomic data may limit immediate clinical applicability[14].

de Sousa et al. demonstrated that cognitive dysfunction in systemic lupus erythematosus is associated with both inflammatory and oxidative stress markers, highlighting a multifactorial pathophysiological process[15]. The comparison with rheumatoid arthritis provides insight into disease-specific versus shared inflammatory mechanisms[15]. These findings suggest that oxidative stress may act synergistically with inflammation to exacerbate neuronal injury[15]. The study emphasizes the importance of considering multiple biological pathways when evaluating cognitive impairment in autoimmune diseases[15]. However, heterogeneity in disease activity and treatment regimens may influence outcomes[15].

Raghunath et al. found that cognitive dysfunction in systemic lupus erythematosus is more strongly associated with cumulative organ damage than with isolated inflammatory markers[16]. This suggests that chronic systemic disease burden plays a critical role in long-term cognitive outcomes[16]. The findings highlight the importance of longitudinal disease control in preventing neurocognitive complications[16]. While inflammatory markers remain relevant, their predictive value may be enhanced when combined with clinical indices of disease severity[16]. These results underscore the complexity of disentangling inflammatory and structural contributors to cognitive decline[16].

Denniss et al. reported that cerebrospinal fluid inflammatory markers are more strongly associated with cognitive impairment in women than in men among antiretroviral-naive individuals with HIV[17]. This sex-dependent effect supports the concept of differential neuroimmune responses influencing cognitive vulnerability[17]. The findings are consistent with previous studies suggesting sex-specific immune modulation in chronic inflammatory conditions[17]. The use of treatment-naive participants reduces confounding from therapy-

related effects[17]. However, further studies are needed to confirm these findings across diverse populations[17].

Libório et al. demonstrated that endothelial dysfunction biomarkers, particularly syndecan-1, are associated with cognitive decline in hemodialysis patients[18]. These findings highlight the role of vascular inflammation and glycocalyx injury in kidney disease-related cognitive impairment[18]. The study provides evidence supporting a vascular-inflammatory axis linking systemic disease to brain dysfunction[18]. Longitudinal follow-up strengthens the interpretation of biomarker changes over time[18]. However, the specific contribution of dialysis-related factors requires further investigation[18].

Mena-Vázquez et al. found that higher inflammatory activity in rheumatoid arthritis is associated with impairments in visuospatial ability, memory, and executive function[19]. These results support the hypothesis that systemic inflammation directly impacts cognitive domains beyond general cognitive decline[19]. The study contributes to the growing body of evidence linking autoimmune inflammation to neurocognitive dysfunction[19]. The use of disease activity indices provides a quantitative framework for analysis[19]. Nonetheless, confounding by pain, fatigue, and medication effects should be considered[19].

Kammeyer et al. showed that neurofilament light chain and glial fibrillary acidic protein are elevated in active neuropsychiatric systemic lupus erythematosus and may decrease following treatment[20]. These biomarkers reflect neuronal and astrocytic injury, providing insight into active neuroinflammatory processes[20]. The dynamic nature of these markers supports their potential use in monitoring disease activity and treatment response[20]. This study represents an important step toward integrating biomarker-based assessment into clinical practice[20]. However, larger validation studies are required to establish standardized thresholds[20].

Mielke et al. demonstrated that longitudinal increases in glial fibrillary acidic protein and neurofilament light chain are associated with cognitive decline in individuals with type 2 diabetes mellitus[21]. These findings suggest that neurodegenerative processes may coexist with systemic inflammation in metabolic disease[21]. The lack of strong association with amyloid and tau markers indicates that alternative pathways may predominate in this population[21]. This highlights the heterogeneity of mechanisms underlying cognitive decline across diseases[21]. The study provides valuable insight into biomarker trajectories over time[21].

Mruczyk et al. identified tumor necrosis factor-alpha as the inflammatory marker most strongly associated with cognitive decline in women with metabolic syndrome[22]. This finding underscores the role of specific cytokines in mediating neuroinflammatory effects on cognition[22]. The association between metabolic dysfunction and inflammation further

supports a systemic basis for cognitive impairment[22]. These results suggest potential targets for therapeutic intervention[22]. However, gender-specific findings require replication in broader populations[22].

Sârb et al. demonstrated that patients with inflammatory bowel disease exhibit lower cognitive performance and higher serum amyloid A levels compared to controls[23]. This supports the concept of a gut-brain axis mediated by inflammatory pathways[23]. The correlation between serum amyloid A and cognitive impairment suggests a potential biomarker for neuroinflammatory activity in gastrointestinal disease[23]. These findings contribute to a growing recognition of systemic diseases influencing brain function[23]. Nonetheless, causality remains to be established[23].

Ganic et al. showed that multiple hematologic inflammatory indices are elevated in diabetic patients with cognitive impairment[24]. These easily accessible markers provide a practical approach for identifying individuals at increased risk[24]. The findings support the role of systemic inflammation as a key contributor to cognitive decline in diabetes[24]. The use of routine laboratory parameters enhances clinical applicability[24]. However, specificity for neuroinflammation remains limited[24].

Feng et al. demonstrated that inflammatory status modifies the relationship between dysglycemia and cognitive impairment in coronary artery disease[25]. This interaction suggests that inflammation amplifies metabolic risk factors for cognitive decline[25]. The findings highlight the importance of integrated risk assessment in cardiovascular populations[25]. These results support targeting both metabolic and inflammatory pathways in prevention strategies[25]. Further research is needed to clarify causal mechanisms[25].

Krisai et al. reported that cognitive decline in atrial fibrillation is associated with inflammatory and neurodegenerative biomarkers beyond traditional vascular mechanisms[26]. This expands the understanding of cognitive impairment in arrhythmia-related conditions[26]. The study supports a multifactorial model involving inflammation, neurodegeneration, and vascular factors[26]. These findings may influence future risk stratification approaches[26]. However, biomarker integration into clinical practice remains challenging[26].

Marion et al. found that elevated C-reactive protein levels are associated with cognitive decline in individuals with atrial fibrillation[27]. This reinforces the role of systemic inflammation as an independent contributor to cognitive impairment[27]. The study provides additional evidence supporting inflammatory pathways beyond embolic events[27]. These findings have implications for risk assessment and management in atrial fibrillation[27]. However, confounding by comorbidities must be considered[27].

Li et al. demonstrated that interleukin-6-mediated medial prefrontal dysfunction is associated with cognitive impairment in knee osteoarthritis[28]. This provides mechanistic insight linking peripheral inflammation to functional brain changes[28]. The integration of neuroimaging strengthens the biological plausibility of findings[28]. These results highlight the broader impact of chronic inflammatory conditions on cognition[28]. Further studies are required to confirm these pathways[28].

Li et al. also showed that elevated serum neurofilament light chain is associated with worse cognitive performance in individuals with diabetes[29]. This supports the role of neuronal injury biomarkers in identifying cognitive decline[29]. The findings complement previous studies linking neurodegeneration with systemic inflammation[29]. These results suggest that combining inflammatory and neuronal markers may improve predictive accuracy[29].

6 CONCLUSION

This systematic review demonstrates that systemic inflammation is consistently associated with cognitive decline across a wide range of chronic diseases, including metabolic, autoimmune, infectious, and cardiovascular conditions. Both traditional inflammatory markers, such as interleukin-6 and C-reactive protein, and emerging biomarkers, such as neurofilament light chain and glial fibrillary acidic protein, show significant associations with cognitive impairment. The evidence supports a multifactorial model in which systemic inflammation interacts with vascular dysfunction, metabolic alterations, and neurodegenerative processes. Additionally, several studies indicate that these biomarkers may precede measurable cognitive decline, suggesting potential utility in early detection. Overall, neuroinflammatory biomarkers represent a promising tool for understanding and monitoring cognitive deterioration in chronic disease populations.

From a clinical perspective, the identification of accessible and reliable biomarkers may facilitate early screening and risk stratification in patients with chronic inflammatory conditions. Biomarkers such as the neutrophil-to-lymphocyte ratio and C-reactive protein offer practical advantages due to their availability and low cost. More advanced markers, including neurofilament light chain and glial fibrillary acidic protein, provide greater specificity for neuronal and glial injury but require broader validation and standardization. The integration of these biomarkers into clinical workflows could enhance individualized patient management and guide therapeutic decision-making. Furthermore, recognizing inflammation as a modifiable risk factor opens new avenues for preventive and therapeutic interventions.

Despite these advances, the current body of literature presents several limitations that must be considered. Significant heterogeneity exists among studies regarding populations,

biomarker measurement methods, and cognitive assessment tools, which limits comparability and generalizability. Many studies are observational in design, restricting the ability to establish causal relationships between inflammation and cognitive decline. Additionally, confounding factors such as comorbidities, medication use, and lifestyle variables are not consistently controlled. Small sample sizes in some studies further reduce statistical power and robustness of conclusions. These limitations highlight the need for more rigorous and standardized research designs.

Future research should focus on longitudinal and interventional studies to clarify the causal role of systemic inflammation in cognitive decline and to evaluate the effectiveness of anti-inflammatory strategies. The development of standardized biomarker panels combining inflammatory, vascular, and neurodegenerative markers may improve predictive accuracy and clinical applicability. Advances in omics technologies and neuroimaging integration are expected to further elucidate underlying mechanisms. Additionally, research should explore personalized approaches considering factors such as sex differences, genetic predisposition, and disease-specific pathways. Such efforts will be essential for translating biomarker research into meaningful clinical outcomes.

In conclusion, systemic inflammation plays a critical and multifaceted role in the development and progression of cognitive decline in chronic diseases. The growing body of evidence supports the use of neuroinflammatory biomarkers as valuable tools for early detection, risk assessment, and monitoring of cognitive impairment. However, successful clinical implementation will require standardized methodologies, validation in diverse populations, and integration with comprehensive clinical evaluation. A multidisciplinary approach involving neurology, internal medicine, immunology, and psychiatry is essential to address the complexity of this condition. Ultimately, advancing evidence-based and individualized strategies will be key to improving cognitive health outcomes in patients with chronic inflammatory diseases.

REFERENCES

1 Guduguntla, B. A., Vasbinder, A., Anderson, E., Azam, T. U., Blakely, P., Webster, N. J., et al. (2024). Biomarkers of chronic inflammation and cognitive decline: A prospective observational study. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 16(1), e12568.

2 Geng, C., Chen, C., Wang, J., et al. (2024). Association between elevated systemic inflammatory markers and the risk of cognitive decline progression: A longitudinal study. Neurological Sciences, 45(11), 5253–5259.

3 Serna, M. F., Mosquera, M., & García-Perdomo, H. A. (2025). Inflammatory markers and their relationship with cognitive function in Alzheimer's disease and mild cognitive impairment: A systematic review and meta-analysis. Neuromolecular Medicine, 27(1), 53.

4 Jaramillo Ramos, J. J., Galindo Pupo, N. M., Mena, D., Perez Solis, R., Bedoya Jaramillo, J. E., & Vega Solano, M. (2025). Cognitive decline in chronic inflammatory conditions: Exploring links between systemic inflammation and neurodegeneration. Cureus, 17(7), e88397.

5 Yu, Z. W., Wang, Y., Li, X., Tong, X. W., Zhang, Y. T., & Gao, X. Y. (2023). Association between the neutrophil-to-lymphocyte ratio and mild cognitive impairment in patients with type 2 diabetes. Aging Clinical and Experimental Research, 35(6), 1339–1347.

6 Hung, K. C., Liu, C. C., Wu, J. Y., Ho, C. N., Lin, M. C., Hsing, C. H., et al. (2023). Association between the neutrophil-to-lymphocyte ratio and cognitive impairment: A meta-analysis. Frontiers in Endocrinology, 14, 1265637.

7 Wei, W., Xu, P., Li, L., Mao, H., Li, N., Wang, X. Q., et al. (2024). Association of glycogen synthase kinase-3β with cognitive impairment in type 2 diabetes. Frontiers in Endocrinology, 15, 1386773.

8 Low, S., Liu, Y. L., et al. (2025). Double product is longitudinally associated with reduced cognitive function in type 2 diabetes. Journal of Alzheimer's Disease, 106(2), 668–677.

9 Mielke, M. M., Evans, M., et al. (2025). Alzheimer disease blood biomarkers and cognition among participants with type 2 diabetes. JAMA Network Open, 8(2), e2460104.

10 Lu, Y., Palta, P., et al. (2024). Changes in Alzheimer disease blood biomarkers and cognition. JAMA Neurology, 81(8), 821–831.

11 Raghavan, S., Graff-Radford, J., Hofrenning, E., Fought, A. J., Reid, R. I., Kamykowski, M. G., et al. (2025). Plasma NfL and GFAP for predicting vascular cognitive impairment. Alzheimer's & Dementia, 21(6), e70381.

12 Feng, L., Li, J., Yang, S., Zhao, X., Song, J., Wang, X., et al. (2025). Inflammatory status modifies glycemic traits and cognitive impairment. Journal of the American Heart Association, 14(17), e042820.

13 Libório, A. B., et al. (2024). Endothelium-related biomarkers and cognitive decline in hemodialysis patients. European Journal of Neurology, 31(12), e16438.

14 Sârb, O. F., et al. (2025). Cognitive performance and biomarker correlations in IBD patients. Brain Sciences, 15(4), 420.

15 Ganic, D., et al. (2025). Blood count-derived inflammation indices and cognitive impairment in type 2 diabetes. Medicina (Kaunas), 61(10), 1624.

16 Li, C., et al. (2025). Inflammation-mediated brain alterations and cognitive decline in osteoarthritis. Brain Imaging and Behavior, 19(1), 142.

17 Longino, A. A., Paul, R., Wang, Y., Lama, J. R., Brandes, P., Ruiz, E., et al. (2022). HIV disease dynamics and inflammation markers related to cognition. Journal of Acquired Immune Deficiency Syndromes, 89(2), 183–190.

18 Denniss, J., Veenhuis, R. T., Xu, Y., Lang, L., Nyesigire, R., Bukusi, E. A., et al. (2024). Sex-specific associations between CSF inflammatory biomarkers and cognition in HIV. Brain, Behavior, and Immunity, 125, 1–8.

19 Cooley, S. A., Petersen, K. J., Tice, C., Langford, D., Burdo, T. H., Roman, J., et al. (2024). Plasma neurofilament light chain and cognition in HIV. AIDS, 38(7), 955–962.

20 Mukerji, S. S., et al. (2025). Plasma neurofilament light chain and GFAP as biomarkers of cognitive decline in HIV. Journal of Infectious Diseases, 231(5), 785–794.

21 Mena-Vázquez, N., Ortiz-Márquez, F., Ramírez-García, T., Cabezudo-García, P., García-Studer, A., Mucientes-Ruiz, A., et al. (2024). Impact of inflammation on cognitive function in rheumatoid arthritis. RMD Open, 10(2), e004422.

22 Marr, C., England, B. R., et al. (2024). Cognitive change in rheumatoid arthritis following treatment escalation. Arthritis Care & Research, 76(8), 1158–1167.

23 Myasoedova, E., Crowson, C. S., et al. (2024). Cognitive impairment in individuals with rheumatic diseases. The Lancet Rheumatology, 6(11), e829–e840.

24 de Sousa, D. C., de Almeida, S. B., Roriz Filho, J. S., et al. (2023). Cognitive dysfunction biomarkers in rheumatoid arthritis: A systematic review. Journal of Clinical Rheumatology, 29(4), 159–164.

25 Cabrera, D. V., El Tal, T., Mohamed, I., Arciniegas, S. E., Fevrier, S., Ledochowski, J., et al. (2024). Effects of systemic lupus erythematosus on the brain. Lupus Science & Medicine, 11(2), e001214.

26 Ramos, J. J. J., et al. (2025). Systemic inflammation and neurodegeneration in chronic inflammatory disease. Cureus, 17(7), e88397.

27 Krisai, P., et al. (2025). Biomarkers and cognitive decline in atrial fibrillation. Scientific Reports, 15, 12921.

28 Marion, D., Li, Z., et al. (2025). Inflammation and cognitive decline in atrial fibrillation. Journal of the American Heart Association, 14(21), e039636.

29 Alfano, F., Cesari, F., Gori, A. M., Berteotti, M., Salvadori, E., Giusti, B., et al. (2025). Inflammation markers and cognitive dysfunction in atrial fibrillation. Biomedicines, 13(4), 941.