Review

Blood Biomarkers of Alzheimer's Disease and Cognition: A Literature Review

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Blood Biomarkers of Alzheimer's Disease and Cognition: A Literature Review

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Abstract: Blood biomarkers represent a promising future for studying cognitive impairment, particularly in Alzheimer's Disease (AD), as they offer a non-invasive alternative to cerebrospinal fluid tests and have potential as population screening tools. However, the relationships between these biomarkers and specific cognitive functions, as well as their utility in predicting longitudinal cognitive decline, are not yet fully understood. This descriptive review surveys the literature from 2018 to 2023, focusing on the associations between Amyloid-β, Total Tau, Phosphorylated Tau (p-tau), Neurofilament Light (Nfl), and Glial Fibrillary Acidic Protein (GFAP) with cognition. The reviewed studies are heterogeneous, varying in design and population (mixed, cognitively impaired, or unimpaired), and show results that are sometimes conflicting. Generally, cognition positively correlates with Aβ levels, especially when evaluated through the Aβ42/Aβ40 ratio. In contrast, Tau, Nfl, and GFAP levels typically show a negative correlation with cognitive performance. While p-tau measures tend to show stronger associations with cognitive functions than other biomarkers, no single blood marker has emerged as predominantly associated with a specific cognitive domain. These findings add to our understanding of the complex relationship between blood biomarkers and cognitive performance and underscore their potential utility in clinical evaluations of cognition.

Keywords: Alzheimer's disease; cognitive impairment; blood biomarkers; cognitive functions; cognition

1. Introduction

Alzheimer's disease (AD) is the main cause of dementia, and the World Health Organization recognizes it as a public health priority. It is extensively described the main clinical manifestations of AD as a progressive memory impairment and other cognitive domains such as language, attention, executive functions (EF), and visuospatial abilities [1] which leads a decline in daily life activities and usually accompanied by neuropsychiatric symptoms. An objective cognitive and functional impairment is determined by neuropsychological assessments which consists of objective standardized tests of multiple cognitive domains which obtained scores are compared with normative scales according to relevant demographics (ex. patient's age and education) to quantify how the patient's performances diverges from that which is expected [2]. These examinations remain essential in the classification of the different diagnoses within neurodegenerative diseases. AD pathology is defined by the accumulation of abnormally conformational proteins, on the one hand, extracellular senile plaques formed by amyloid-β (Aβ) fibrils derived from the precursor protein, and on the other hand, intracellular neurofibrillary tangles of tau protein[3]. Initially, the diagnosis of AD was based on the stage of dementia explained by these cognitive, functional, and behavioral symptoms [4] but the advances in the biomarker field have enabled to detect *in-vivo* the pathophysiological characteristics of the disease and to contribute to a more accurate diagnosis criterion of AD. Current criteria for AD proposed by National Institute on Aging and Alzheimer's

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Association (NIA-AA) are only based in biomarkers evidence of amyloid, phosphorylated tau (p-tau) and neurodegeneration [5]. Cerebrospinal fluid (CSF) can reflect pathological changes in brain tissue due to its direct contact. Although CSF is considered as an optimal measure, it requires an invasive technique of acquisition (lumbar puncture), and this underlies the need for less invasive techniques [6,7].Plasma biomarkers are promising fluid biomarkers due to their less invasive and less costly extraction and commonly used in multiple diseases [8]. This underlies the importance of research on the applicability of plasma biomarkers in memory units. Thus, together with an adequate exploration of neurological and cognitive symptoms, it will contribute to a more accurate diagnosis of AD.

We aim to conduct a descriptive review of the literature from the last five years (2018-2023) concerning the main plasma AD biomarkers (Amyloid-β, Total tau (t-tau) and p-tau) as well as two other promising plasma AD biomarkers (Neurofilament Light (Nfl) and Glial Fibrillary Acidic Protein (GFAP)) and their association with cognition.

2. Material and Methods

For this review, we conducted a PubMed search using the strategy: "Plasma biomarkers" AND "Alzheimer's disease" AND "Cognitive change." We included all relevant studies identified from the reference lists of articles initially found during the search. This article systematically explores five plasma biomarkers associated with AD: Amyloid-β, t-tau, p-tau, Nfl, and GFAP. Each section begins with an introductory overview and proceeds to examine findings from both longitudinal and cross-sectional population-based studies. The review then focuses on samples with cognitive impairment before concluding with studies that involve cognitively unimpaired (CU) individuals for each biomarker. Summary information on the association between different neuropsychological tests and blood biomarkers of Aβ and Tau proteins are presented in Tables 1 and 2 respectively.

Table 1. Summary of Studies Examining the Association Between Plasma Amyloid Levels and Neuropsychological Tests.

Author	Population	Study	Neuropsychological test	Correlated
Xiao et al., 2021	Mixed sample	cross-sectional	MMSE; single-domain composites	Yes ($A\beta_{42}$, $A\beta_{42}/A\beta_{40}$)
Sun et al., 2022	Mixed sample	cross-sectional	MMSE; Story recall; CDT	Yes ($A\beta_{42}/A\beta_{40}$)
Sapkota et al., 2022	Mixed sample	longitudinal	Single-domain composites	Yes ($A\beta_{42}/A\beta_{40}$)
Tsai et al., 2019	Mixed sample	cross-sectional longitudinal	MMSE MMSE	No ($A\beta_{42}/A\beta_{40}$)
Pereira et al., 2021	Mixed sample	longitudinal	MMSE	No ($A\beta_{42}/A\beta_{40}$)
Chen et al., 2022	Mixed sample	longitudinal	MMSE, AdasCog13	No ($A\beta_{42}/A\beta_{40}$)
Chen et al., 2019	AD AD and MCI MCI	cross-sectional cross-sectional longitudinal	Single and multi-domain composites Multi-domain composites Single-domain composites	Yes ($A\beta_{42}$) Yes ($A\beta_{42}$) Yes ($A\beta_{42}/A\beta_{40}$)
Tsai et al., 2020	Amnestic MCI CU	longitudinal longitudinal	MMSE MMSE	Yes ($A\beta_{42}$) No ($A\beta_{42}$)
Chouliaras et al., 2022	MCI with positive AD biomarkers	cross-sectional and longitudinal	ACE-R	Yes ($A\beta_{42}/A\beta_{40}$)
Pascual-Lucas et al., 2023	CU	cross-sectional	The Face-Name Associative Memory Exam	Yes ($A\beta_{42}/A\beta_{40}$)
Cullen et al., 2021	CU	longitudinal	PACC	Yes ($A\beta_{42}/A\beta_{40}$)
Giudici et al., 2020	CU	longitudinal	Multi-domain composite	Yes ($A\beta_{42}/A\beta_{40}$)
Aschenbrenner al., 2022	CU	longitudinal cross-sectional	Multi-domain composite Multi-domain composite	Yes ($A\beta_{42}/A\beta_{40}$) No($A\beta_{42}/A\beta_{40}$)
Hong et al., 2023	CU	longitudinal	Verbal Learning Test scores; TMT	Yes ($A\beta_{42}/A\beta_{40}$)
Simrén et al., 2021	CU	longitudinal	MMSE	No ($A\beta_{42}/A\beta_{40}$)
Ashton et al., 2022	CU	longitudinal	MMSE, PACC	No ($A\beta_{42}/A\beta_{40}$)
Saunders et al., 2023	CU	longitudinal	WAIS-III subtests	No ($A\beta_{42}/A\beta_{40}$)

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Wang et al., 2022	CU	longitudinal	MMSE	Yes ($A\beta_{42}$) No ($A\beta_{42}/A\beta_{40}$)

CU, Cognitively Unimpaired,; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; Mini-Mental State Examination (MMSE); Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADASCog), Auditory Verbal Learning Test (AVLT); Clock Drawing Test (CDT); Word List Learning (WLL); Trail Making Test (TMT); Modified Rey-Osterrieth Complex Figure Test (MROCFT); Addenbrooke's Cognitive Examination Revised version (ACE-R); Preclinical Alzheimer's Cognitive Composite (PACC); Wechsler Adult Intelligence Scale (WAIS)

Table 2. Summary of Studies Examining the Association Between Different Plasma Tau proteins and Neuropsychological Tests.

Author	Population	Study	Neuropsychological test	Correlated
Tsai et al., 2019	Mixed sample MCI and AD	cross-sectional longitudinal	MMSE MMSE	Yes (p-tau181; t-tau) Yes (t-tau); No (p-tau)
Karikari 2020	Mixed sample	Cross-sectional longitudinal	MMSE	Yes (p-tau181)
Xiao et al., 2021	Mixed sample	cross-sectional	MMSE, single-domain composites	Yes (p-tau181; t-tau)
Wang et al., 2022	Mixed sample MCI with positive AD biomarkers AD	cross-sectional longitudinal	MMSE; MoCA, ADNI single- domain composites ADNI-memory composite	Yes (p-tau181)
Sun et al. 2022	Mixed sample	cross-sectional	Story Recall, CDT	Yes (p-tau181; t-tau)
Weigand et al. 2023	Mixed sample	cross-sectional	AVLT	Yes (p-tau181)
Pereira et al. 2021	Mixed sample	longitudinal	MMSE	Yes (p-tau181, p-tau217)
Chen et al. 2022	Mixed sample	longitudinal	Adas-Cog13	Yes (p-tau181)
Smirnov et al. 2022	Mixed sample	longitudinal	DRS	Yes (p-tau181; p-tau231)
Tsai et al. 2020	Mixed sample	longitudinal	MMSE	No (p-tau181; t-tau)
Groot et al. 2023	Mixed sample	longitudinal	MMSE	Yes (p-tau217)
Pase et al. 2019	Mixed sample	Cross-sectional	HVOT, Logical memory, Paired Associate Learning, Visual reproductions, TMT	Yes (t-tau)
Marks et al. 2021	Mixed sample	Cross-sectional longitudinal	AVLT, Logical Memory (WMS-R) AVLT, Logical Memory, TMT, Digit Symbol (WAIS-R)	Yes (t-tau)
Sapkota et al. 2022	Mixed sample	longitudinal	Single-domain composites	Yes (t-tau)
Rajan et al. 2020	Mixed sample	longitudinal	Multi-domain composite	Yes (serum t-tau)
Smirén et al. 2021	AD	Cross-sectional longitudinal	MMSE MMSE	Yes (p-tau181)
Saloner et al 2023	MCI CU	Longitudinal longitudinal	single-domain composites CVLT	Yes (p-tau217)
Chouliaras et al 2022	MCI and AD	longitudinal	ACE-R	Yes (p-tau181)
Moscoso et al 2021	CU MCI and AD	Longitudinal Longitudinal	PACC ADASCog	Yes (p-tau181) Yes (p-tau181)
Thomas et al 2021	CU	Longitudinal	PACC, CDR-SOB, FAQ	Yes (p-tau181)
Saunders et al 2023	CU	Longitudinal	WAIS-III subtests	Yes (p-tau181)

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Ashton et al 2022	CU	Longitudinal	MMSE, PACC, RAVL	Yes (p-tau217)
Cullen et al 2021	CU	Longitudinal	PACC	Yes (p-tau217)
Mattsson-Carlgren et al 2023	CU	Longitudinal	MMSE, PACC	Yes (p-tau217)
Snellman et al. 2023	CU	Cross-sectional	MMSE	No (p-tau181)
Baldacci et al 2020	CU	Cross-sectional	MMSE, FCSRT	No (t-tau)
		Longitudinal	MMSE	Yes (t-tau)
Rübsamen et al 2021	CU	Cross-sectional	Single-domain composite	No (t-tau)

CU, Cognitively Unimpaired,; MCI, Mild Cognitive Impairment; AD, Alzheimer's disease; Mini-Mental State Examination (MMSE); MoCA, Montreal Cognitive Assessment; ADNI, Alzheimer's Disease Neuroimaging Initiative Auditory Verbal Learning Test (AVLT); Clock Drawing Test (CDT);) Trail Making Test (TMT); Addenbrooke's Cognitive Examination Revised version (ACE-R); Preclinical Alzheimer's Cognitive Composite (PACC); Clinical Dementia Rating Scale (CDR)- Sum Of Boxes (CDR-SOB), Functional Assesment Questionnaire (FAQ); Hooper Visual Organization Test (HVOT); Dementia Rating Scale (DRS); California Verbal Learnig Test (CVLT); Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADASCog), Wechsler Adult Intelligence Scale (WAIS), Wechsler Memory Scale (WMS), Free and Cued Selective Reminding Test (FCSRT)

A. Plasma Amyloid-β

It is well known that accumulation of Aβ peptides is closely associated with AD pathophysiological changes, which can be detected within 20-30 years of developing dementia [9]. The most evaluated types are $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{42/40}$ ratio. Lower levels of Aβ in fluid biomarkers are associated with AD pathology. Several studies have found lower plasma Aβ levels in AD patients and with regarding CU individuals and other diagnostic [10] however, these plasma measures seem to differ less than CSF ones [11]. In addition, plasma Aβ levels can differentiate AD from Mild Cognitive Impairment (MCI) patients [12]. MCI is classically defined as those who present cognitive impairment but without meeting dementia criteria [13]. On the other side, some studies have reported that $A\beta_{42/40}$ ratio has better correlation with Aβ pathology than $A\beta_{42}$ and $A\beta_{40}$ measures alone [14,15].

Association between plasma Aβ and cognition

Some cross-sectional studies in mixed samples, including CU and cognitive impairment subjects, have found a significant positive association between the plasma $A\beta_{42}/A\beta_{40}$ ratio or plasma $A\beta_{42}$ and Mini-Mental State Examination (MMSE); as well as with verbal memory tests such as the Auditory Verbal Learning Test (AVLT) and Story Recall; and a visuospatial task, the Clock Drawing Test (CDT) [16,17]. Moreover, a longitudinal study involving mixed samples found that lower baseline plasma $A\beta_{42}/A\beta_{40}$ ratio levels were associated with poorer performance in a verbal memory task (Word List Learning) and an attention/EF composite score, which included semantic fluency (SF), letter fluency (LT), digit span, and visual span; and a steeper cognitive decline was observed over approximately 1.5 years [18].

Conversely, other cross-sectional studies failed to show a correlation between $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ ratio and the MMSE [19] and an attention/EF task, the Trail Making Test (TMT) [17] , in mixed samples. Similarly, several other findings did not find an association between baseline plasma $A\beta_{42}/A\beta_{40}$ and the longitudinal decline in MMSE [19–21].

Regarding only cognitively impaired samples, a study conducted by Chen et al. 2019 [22] revealed a significant positive cross-sectional association in AD patients between plasma $A\beta_{42}$ and attention/EF composite scores. These composite scores included tests such as the Stroop Color-Word Test (SCWT), TMT Part B, SF, as well as Digit Span (DS) recall. Additionally, they found a correlation with a multi-domain composite score observed in both MCI and AD patients. Furthermore, they observed a significant positive association between the plasma $A\beta_{42}/A\beta_{40}$ ratio and memory composite scores among individuals with MCI during a 3-year follow-up period. These composite scores included verbal memory tests like the AVLT and Story recall, as well as a visual memory task,

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the Modified Rey-Osterrieth Complex Figure Test (MROCFT), and attention/EF scores (forward/backward DS recall). Consistent with this finding, Tsai et al. (2020) [23] demonstrated a significant negative correlation between plasma $A\beta_{42}$ levels and the annual changes in MMSE scores in the amnestic MCI group. However, another study did not find a cross-sectional association or a longitudinal decline between the plasma $A\beta_{42}/A\beta_{40}$ ratio and a brief multi-domain cognitive battery, the Addenbrooke's Cognitive Examination Revised version (ACE-R), in MCI and AD patients [24].

Concerning CU samples, a cross-sectional study revealed a positive association between CU participants with subjective cognitive decline (SCD) and lower plasma $A\beta_{42}/A\beta_{40}$ ratio, which correlated with poorer performance on a novel episodic memory task called the Face-Name Associative Memory Exam [25]. Additionally, in a recent longitudinal study by Cullen et al. (2021) [26] they predicted that CU individuals with SCD would experience a more pronounced decline in scores on the Preclinical Alzheimer's Cognitive Composite (PACC) over a period of approximately 4 years. Other studies have corroborated this trajectory in multi-domain composite cognitive scores, which incorporate tasks related to verbal memory (e.g., Free and Cued Selective Reminding Test, FCSRT) and executive function/attention (e.g., Digit Symbol Substitution Test, DSST). These studies compared individuals classified as Aβ+ CU and Aβ- CU, based on plasma $A\beta_{42}/A\beta_{40}$ ratio levels. Specifically, Giudici et al. (2020) [27] observed this trend over a follow-up period of 3.9 years, while Aschenbrenner et al. (2022) [28] noted a more rapid decline over an extended follow-up period of approximately 12 years. Similarly, Aβ positive- SCD participants showed a decline in verbal memory (as measured by Verbal Learning Test scores) and in an attention/EF task (as measured by TMT Part B) after 2 years [29]. However, it is worth noting that some studies involving CU samples did not report a cross-sectional association between the plasma $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio and cognitive composite scores [28] or a longitudinal decline over time on measures such as MMSE[23,30,31], PACC [31] and a multi-domain cognitive composite comprising Wechsler Adult Intelligence Scale-III (WAIS-III) subtests [32] . In line with this, another recent study found that a significant decline in MMSE scores at the two-year follow-up was not based on the baseline plasma $A\beta_{42}/A\beta_{40}$ ratio but rather on baseline plasma $A\beta_{42}$ levels [33].

B. Plasma Total Tau and Phosphorylated Tau

Tau pathology is the other main element involved in AD. P-tau aggregated into neurofibrillary tangles is more specific to AD pathology and has a precipitant role of neurodegeneration and cognitive decline of the disease [34]. Literature has shown that plasma t-tau is increased in AD compared with a control group but there is a large an overlap between normal aging and in patients without dementia which prevents it from being considered as a diagnostic tool [11,35,36]. On the other hand, phosphorylation at threonine 181 (p-tau181) is the most widely used p-tau biomarker in the clinical setting and increases in early phases of AD [11]. Phosphorylation at threonine 217 and threonine 213 (p-tau217, p-tau231) are other phosphorylated tau species are increased in AD and current assays are focusing on them [37]. It has been reported that plasma p-tau181 levels are increased in AD versus controls [38]. A recent study has shown that plasma p-tau181 and p-217 can differentiate patients with an AD CSF profile (defined by CSF $A\beta_{42}$/p-tau ratio) from the non-AD CSF profile group in a memory unit [39]. Literature have reported higher levels of plasma p-tau181, p-tau217 and p-tau231 in AD patients regarding CU individuals [7,40] and MCI patients [7,41]. It has also shown that plasma p-tau217 showed better distinguishing accuracy than plasma p-tau181 and plasma p-tau231 in early stages [7,42] and discriminated AD from other neurodegenerative diseases [43]. Other recent studies also show plasma p-tau231 can identify AD patients with other non-AD neurodegenerative diseases [44] and abnormal levels of plasma p-tau231 are reached in preclinical AD stages [11]. A recent systematic review reported that plasma p-tau231 increased from CU to MCI to AD and showed an excellent diagnostic accuracy for asymptomatic Aβ pathology [45].

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Association between plasma t-tau and p-tau and cognition

Some cross-sectional studies of mixed samples have reported significant negative correlation between higher plasma p-tau181 levels and MMSE [16,19,33,46] and Montreal Cognitive Assessment (MoCA) [33]. In addition, other studies have found this association with verbal memory tests such as AVLT and Story Recall [17,47] a visuospatial task (CDT) [17] and with single-domain composites. These composites include memory, as measured by The AD Neuroimaging Initiative (ADNI)-Memory [48] visuospatial abilities, assessed through overlapping imaging in MoCA-B, MROCFT copy, and the copy form Stick test [16] ; language, measured by ADNI-Language [33]; and naming abilities assessed in MMSE and MoCA, Boston Naming Test (BNT), and Objects naming [16] ; as well as EF, as measured by ADNI-EF [33]. In addition, longitudinal studies have found various associations regarding p-tau measures. Higher plasma p-tau181 levels have been linked to a faster decline in MMSE scores [20,46], in scores of a multi-domain cognitive battery Disease Assessment Scale–Cognitive Subscale with 13 tasks (ADAS-Cog 13) [21] , and Dementia Rating Scale (DRS) scores [49]. In contrast, Tsai et al. (2020) [23] did not find an association between plasma p-tau181 and the decline in MMSE scores. On the other hand, higher plasma p-tau217 has been shown to predict declines and annual changes in MMSE scores [20,50] with a larger effect size observed in the prediction of plasma p-tau217 compared to p-tau181 [20]. Furthermore, in the study conducted by Smirnov et al. (2022) [49], higher plasma p-tau231 has also been associated with a more rapid cognitive decline, as measured by the DRS, over time. Regarding plasma t-tau measures, higher levels have been also associated with poorer performance on the MMSE [17,19] a visuospatial task, the Hooper Visual Organization Test (HVOT) [36], some memory tasks such as AVLT, WMS memory subtests and a word list learning test [18,36,51], as well as attention/EF tasks like the TMT [36] and an EF composite that included SF, LF, verbal and visual span backwards [18]. Continuing with mixed samples, a study showed that a higher concentration of serum t-tau was correlated with a longitudinal decline in multi-domain cognitive composite scores, which included MMSE, memory, and attention/EF tasks, over a span of 16 years [52]. Another study also reported longitudinal associations between higher t-tau levels and declines in memory, attention, and global cognitive scores [51]. On the other hand, some findings have concluded that plasma t-tau levels did not predict changes in MMSE scores [23].

In samples involving only cognitively impaired subjects, a cross-sectional study showed that also MMSE scores are negatively associated with plasma p-tau181 in AD patients [30]. Longitudinal data revealed a significant correlation between plasma p-tau181 concentration and longitudinal declines in MMSE, MoCA, and ADNI battery cognitive composite in individuals with Aβ+ MCI Additionally, a significant decrease was observed in ADNI-Memory scores in individuals at the AD dementia stage [33]. A negative association has also been found between plasma p-tau181 levels and prospective decline in ADASCog 13 scores [53] as well as with ACE-R slopes [24] in MCI and AD subjects. Furthermore, higher baseline plasma p-tau217 levels have also been associated with a steeper cognitive decline across language tasks (SF and BNT), and attention/EF tasks (DS backwards, TMT, SCWT, LT, and Design fluency) in individuals with MCI. This association was also observed across memory tasks, the California Verbal Learning Test (CVLT) and Benson Figure but only in male MCI subjects [54]. Regarding plasma t-tau levels in MCI subjects, a study has reported a decrease in MMSE scores during the first few years [19].

Regarding CU samples, some longitudinal studies have reported that higher plasma p-tau181 levels are longitudinally associated with lower PACC scores in CU individuals [53]. A study conducted by Thomas et al. (2021) [55] also showed a faster decline in PACC, CDR-Sum Of Boxes (CDR-SOB) and the Functional Activities Questionnaire (FAQ) scores was related to higher plasma p-tau181 levels in objectively defined subtle cognitive decline (Obj-SCD) subjects. Moreover, a recent finding showed that elevated baseline plasma p-tau181 levels significantly predicted greater decline in a multi-domain cognitive composite score (encompassed by WAISS-III subtest) over 10 years in an ageing cohort [32]. However, in a recent finding, plasma p-tau181 levels did not correlate with MMSE scores [56]. Regarding plasma p-tau217 levels in CU participants, a study also identified a significant inverse relationship with longitudinal worsening in MMSE, PACC, and verbal memory (RAVLT

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scores) [31]. Similarly, Saloner et al. (2023) [54] observed a strong correlation between higher plasma p-tau217 levels and verbal memory decline (CVLT scores) in female CU individuals. Another finding described a strong association between plasma p-tau217 levels and annual change in PACC scores in SCD participants [26]. In this line, a recent study has stated that plasma p-tau217 predicted MMSE and PACC scores decline among Aβ-positive CU participants [57].

Concerning t-tau measures, Baldacci et al. (2020) [58] suggested that changes in plasma t-tau levels might serve as predictors of longitudinal decline in MMSE scores among individuals with SCD at a 3-year follow-up but they did not found cross-sectional associations with MMSE and FCSRT scores. Additionally, no correlation was found between serum t-tau and other memory measures such as word recall, motor function such as Purdue Pegboard Test (PPT) scores, and attention/EF scores assessed by the SCWT and Letter Digit Substitution test (LDST) [59].

Other plasma biomarkers

In addition to the core biomarkers of AD pathology (Aβ and p-tau proteins), there are several biomarkers involving other concomitant pathological mechanisms (i.e., synaptic dysfunction, vascular damage, or inflammation) that are being assessed in AD since they have an important role in the disease and its progression. Among them, plasma Nfl and GFAP biomarkers are commonly evaluated.

C. Neuronal injury: Plasma Neurofilament light

Nfl is a component of neural cytoskeleton, and it is a well-stablished marker of neuroaxonal injury and neurodegeneration [10,60]. Higher levels of Nfl are present in multiple neurological conditions such as traumatic brain injury, atypical parkinsonian disorders, and amyotrophic lateral sclerosis among others [61]. Increased plasma Nfl levels have found in MCI and AD compared with a control group [62–64]. A study also found increased rates according to a positive Aβ status within CU and MCI groups, thus associating plasma Nfl also with AD pathology [63]. In addition, this biomarker has also demonstrated the ability to predict progression of the disease in familial AD [65,66].

Association between plasma Nfl and cognition

Some findings have reported a significant cross-sectional negative correlation in mixed samples between higher plasma Nfl levels and poorer MMSE scores [16,17,67,68]. Additionally, specific attention/EF scores, such as TMT, DSST, LT Delis Kaplan Executive Function System subtests, have shown similar correlations [17,51,68–70]. Visuospatial tasks (CDT, HVOT), memory tasks (logical memory, AVLT, and visual memory), and language tasks (BNT and SF) have also exhibited such associations [16,17,51,69,70] as well as the multi-domain cognitive composite score [68]. In addition, some longitudinal research has shown that elevated plasma Nfl levels were also associated with a faster decline in follow-up assessments in global cognitive scores [49,51,52,71]. PACC scores [72] and in composite scores of memory, EF, language and visuospatial tasks [18,72] DRS scores [49] and everyday functioning assessed by The FAQ [72]. In another mixed-sample study it was reported that MMSE scores, ADAS-Cog-11 scores, and CDR-SOB scores were associated with higher baseline levels and a more rapid increase in plasma NfL, regardless of the diagnostic group [63]. Nevertheless,a study conducted by Mielke et al. (2019) [71] did not find any significant cross-sectional associations between plasma Nfl and global cognition score and either with memory scores (WMS subtests and AVLT); attention/EF scores (TMT and DSST); visuospatial scores (Picture Completion and Block Design) and language scores (SF and BNT). In this line, a study did not show that plasma NfL was associated with longitudinal decline in cognition assessed by MMSE [20].

Regarding cognitively impaired samples, higher plasma Nfl levels were also associated with lower performances in multi-domain cognitive composite scores [68] (He 2021), ACE-R scores [24], attention/EF scores, and memory scores [69,70]. Additionally, correlations were found in language scores such as SF and visuospatial function scores like HVOT [69] in individuals with MCI. Lin et al.

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(2018) [67] found a trend toward a significant negative correlation between plasma Nfl levels and MMSE scores in the MCI group, but the correlation was significant in AD patients. Furthermore, a study conducted in an autosomal dominant AD cohort reported significant negative associations between serum Nfl levels and MMSE scores, memory tasks (FSCRT), attention/EF (DS and TMT part B), and language tasks (BNT) in mutation carrier subjects [65]. Some longitudinal data are also available such as a study conducted by Moscoso et al (2021) [53] that reported an association with cognitive decline measured by ADAS-Cog scores in cognitive impaired subjects. In other samples exclusively composed of MCI patients, some studies have shown a relationship between higher plasma NfL and a cognitive decline over time assessed by MMSE [30,63], ADAS-Cog, and CDR-SOB scores [63], ADNI-memory composite and PACC scores [72] as well as in global cognitive scores [68]. In AD groups, higher plasma NfL and longitudinal worsening in ADAS-Cog scores have been found [63,73]. Li et al. (2021) [73] also reported that higher baseline plasma NfL was associated with a faster decline in activities of daily living functionality, assessed by the Disability Assessment for Dementia (DAD), from baseline to 12 months in a sample with mild-to-moderate AD dementia. Another recent study pointed out that a combination of higher plasma NfL levels and changes in MMSE scores is a strong predictor of progression from MCI to AD dementia within 5 years [74]. Nevertheless, a study did not find an association between plasma Nfl and cognition assessed by ACE-R slopes in MCI with positive AD biomarkers [24].

When examining CU samples, a cross-sectional association has also been found between higher plasma Nfl levels and worse multi-domain composite cognitive scores [28,75]. This association has also been reported in relation to attention/EF measures such as SCWT and LDST, as well as motor speed tasks like PPT, and memory tests such as the 15-Word Learning Test [70,75]. Additionally, Nfl serum levels were found to be associated with a multi-domain cognitive composite score and attention/executive function (SCWT and LDST scores) and motor performance (PPT scores), but not with the memory domain [59]. In CU individuals with SCD, Chatterjee et al. (2018)[76] also observed a significant inverse correlation between plasma Nfl and attention/EF composite scores (DS backward, DSST), as well as the multi-domain cognitive score. There is also longitudinal research that has reported a negative correlation between baseline serum Nfl levels and the annual change in MMSE scores [77]. Other longitudinal findings have suggested an association between higher baseline plasma Nfl levels and a decline over time in global cognitive composite scores [28,32] as well as in specific cognitive tests such as memory (CVLT). Furthermore, this trajectory has also been observed in MMSE, memory composites, and PACC scores in SCD subjects 26,58,72] and in memory tasks among Aβ+ CU individuals [78]. In contrast, some studies have found no cross-sectional association between plasma Nfl and MMSE scores [58] , as well as memory and EF composite scores measured by ADNI-Memory and ADNI-EF [78] , or with any cognitive scores across different domains [68,69] in CU individuals. Additionally, some longitudinal studies have not reported any association between baseline plasma Nfl levels and a subsequent decline in cognitive scores, including those measured by the MMSE, ADASCog-11, and specific domain tasks such as episodic memory or SF[63,75,79]. This association was not found to be statistically significant for MMSE and PACC scores in individuals with Aβ+ who are CU [31].

D. Inflammation: Plasma Glial Fibrillary Acid Protein

GFAP is a marker of astrogliosis and plays a critical role in maintaining cell structure as one of the cytoskeletal proteins within astrocytes [80]. Astrogliosis is a pathological process commonly associated with Aβ pathology in AD [69,81]. A recent study found that CSF GFAP levels are associated with Aβ [82], potentially indicating a link between Aβ and Tau pathology [10]. Firstly, Oeckl et al 2019 [83] discovered that serum GFAP is a valuable tool for distinguishing AD patients from controls and those with frontotemporal dementia and it could also serve as a CSF-independent marker. More recently, it has been reported that plasma GFAP levels are elevated in AD patients compared to CU individuals [64]. A recent meta-analysis has confirmed that astrocyte biomarkers are altered in AD, thus supporting their inclusion in clinical research on AD [84].

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Association between plasma GFAP and cognition

A recent study comprising mixed cohorts showed that higher plasma GFAP was associated with lower language tests such as SF and BNT but also with lower cognitive scores as attention/EF scores (LT, Design Fluency, SCWT, TMT and DS), visual memory scores (Benson Figure) and visuospatial scores (Benson Figure copy and Number Location of subtest of the Visual Object and Space Perception battery) [85]. Oeckl et al. (2019) [83] showed that elevated serum GFAP levels were also associated with lower MMSE scores but not with CDR-SOB scores. Furthermore, longitudinal data found that plasma GFAP levels were associated with greater decline in annual MMSE [30] and multi-domain composites scores [52]. In samples involving only cognitively impaired subjects, a recent study with familial AD subjects showed a significant inverse cross-sectional association between plasma GFAP with MMSE, a cognitive composites score (composed by Logical Memory, Word List Learning, Digit Symbol and MMSE) and CDR-SOB scores. They also found that plasma GFAP was predictive of longitudinal decline in MMSE and CDR-SOB scores in mutation carriers [86]. In this line, another study, involving MCI with positive AD biomarkers, found that higher plasma GFAP was associated with annual ACE-R scores slopes [24]. However, a recent study conducted by Saloner et al. (2023) [32] showed weaker associations between GFAP and cognitive trajectories in MCI subjects.

Considering CU individuals, a longitudinal study discovered that baseline plasma GFAP significantly predicted a lower cognitive composite score in an ageing cohort [32]. Another recent cross-sectional study found that lower scores on both MMSE and PACC were correlated with higher plasma GFAP levels [56]. Otherwise, a study showed no longitudinal association with MMSE and PACC scores in Aβ+ CU subjects [31].

3. Discussion

We summarize the main findings from recent literature through a descriptive review. Studies have shown the following associations between blood biomarkers and cognitive variables: Plasma Aβ measures, primarily assessed through the $A\beta_{42}/A\beta_{40}$ ratio, show a positive association with cognition. Conversely, measures of plasma Tau assessed by plasma p-tau181, p-tau217, p-tau231, and t-tau—as well as plasma Nfl and plasma GFAP, demonstrate a negative association with cognition. This suggests that individuals with higher levels of plasma Aβ and/or lower levels of plasma tau pathology, plasma Nfl, and plasma GFAP tend to achieve higher scores on neuropsychological tests. Although this trend has been observed in both CU and subjects with cognitive impairment, the results are heterogeneous. Some studies, despite lacking statistical significance, have still observed the expected trend.

Among the various cognitive domains studied, no single blood biomarker has shown a predominant association with a specific domain. One reason for this could be that many studies use a multi-domain composite score to measure cognitive performance, which prevents a more specific analysis. On the other hand, studies within our review suggest that plasma p-tau measures show stronger associations with cognition than other plasma biomarkers [16,21,22,30–32,53,54,57]. Regarding the cognitive measures employed, classical neuropsychological tests are still widely used. Global cognition is primarily assessed using the MMSE. The memory domain is evaluated through verbal tasks such as the AVLT or FCSRT, and visual tasks like the Modified MROCFT. Language abilities are examined using the SF and BNT, while the visuospatial domain is often measured with the CDT. The attention / executive function (EF) domain is assessed using well-known tests such as Digit Span, TMT, or SCWT. This underlines the ongoing validity of these neuropsychological tests in both routine clinical practice and research settings.

Limitations

The search for this review was conducted exclusively using PubMed, which may have resulted in the omission of significant studies published in databases not indexed there. While the review incorporates all relevant studies identified from the reference lists of initially retrieved articles, it is

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possible that some pertinent studies may have been overlooked. It should also be noted that this is a descriptive review, not a systematic review or meta-analysis; therefore, the conclusions drawn may lack the statistical power that could be achieved with more rigorous methodologies. These limitations should be considered when interpreting the findings of this review.

4. Conclusions

In summary, our findings, along with recent studies, have revealed associations between blood AD biomarkers and cognitive performances along the AD continuum. Further research is needed, but this study can provide data that support the future clinical applicability of blood AD biomarkers. The future incorporation of more extensive neuropsychological assessments could yield more precise conclusions concerning the association between blood biomarkers and specific cognitive functions.

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