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Review Article

Associations between plasma beta amyloid and cognitive decline: A systematic review and meta-analysis

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Abstract

Alzheimer's disease is a leading neurodegenerative disorder characterized by progressive cognitive decline. Early prediction is crucial for enabling timely interventions. Plasma amyloid β-peptides (Aβ), particularly the Aβ-42/Aβ-40 ratio, have been proposed as potential non-invasive biomarkers for cognitive decline and Alzheimer's disease risk. However, conflicting findings and methodological variability have hindered consensus regarding their clinical utility. The aim of this study was to evaluate whether the plasma Aβ levels predict dementia, Alzheimer's disease, and cognitive decline. Studies were eligible for inclusion if they measured at least one plasma Aβ species (Aβ-40, Aβ-42, or the Aβ-42/Aβ-40 ratio) and reported outcomes related to dementia, Alzheimer's disease, or cognitive change. Only human studies published in peer-reviewed journals were included. A comprehensive search of six databases (PubMed, PMC, SSRN, Scopus, BioRxiv, and MedRxiv) was conducted up to December 1, 2024. Risk of bias was assessed using the ROBINS-E tool, and pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a random-effects meta-analysis. A total of 25 studies were included in the systematic review, with four contributing to the meta-analysis. Lower plasma Aβ-42/Aβ-40 ratio was not significantly associated with Alzheimer's disease risk (pooled HR=0.8; 95%CI: 0.62–1.04), and substantial heterogeneity was observed (I^2=70%, p=0.02). Individual studies varied in their findings: while some reported that lower Aβ-42/Aβ-40 ratio predicted increased Alzheimer's disease risk, others found no association or even opposing trends. Methodological heterogeneity—including differences in sample handling, measurement techniques, and study designs—likely contributed to these inconsistencies. Overall, this review suggests that plasma Aβ-42/Aβ-40 ratio is not reliable predictors for the onset of Alzheimer's disease or dementia. However, the substantial heterogeneity observed underscores the need for further research to clarify the potential of plasma Aβ as a preclinical biomarker.

Keywords: Alzheimer's disease, cognitive decline, plasma amyloid beta, biomarkers, meta-analysis

Introduction

Alzheimer's disease is a prevalent neurodegenerative disorder and the leading cause of dementia in older adults, posing a major global public health challenge [1,2]. Alzheimer's disease follows a

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progressive course, beginning with pathophysiological changes such as amyloid-β accumulation, tau protein tangles, and neurodegeneration due to chronic microglial activation years before clinical symptoms appear [3,4]. These changes lead to cognitive decline, memory loss, and neuropsychiatric symptoms like agitation, confusion, and, in advanced stage, hallucinations [3,5]. Epidemiological evidence reveal the increasing incidence and prevalence with age, with rates as high as 48.2% among individuals aged 95–99 in China [6]. The impact of Alzheimer's disease's extends beyond cognitive impairment, as it significantly diminishes quality of life and is associated with increases level of depression, anxiety, and stress. These factors contribute to dementia being the fifth leading global cause of death, with mortality rates doubling between 1990 and 2016, due to aging populations [7,8].

Advancements in early detection methods are crucial for improving outcomes by enabling timely interventions prior to the full onset of dementia [9]. Early diagnosis not only benefits patients and their caregivers by delaying the progression of dementia. but also yields significant cost savings for healthcare systems [10]. Access to appropriate services and support after an early diagnosis empowers individuals to take control of their condition, maintain independence in their own homes for longer, and preserve quality of life [10]. Furthermore, early intervention allows individuals to plan while they still have the capacity to make informed decisions about their legal, financial, and future care options [11].

Despite these important advancements, current challenges in Alzheimer's disease diagnostics and therapeutics persist, primarily due to conventional methods that often identify the condition only after substantial neurodegeneration and cognitive decline have occurred [12,13]. Traditional diagnostic techniques can be subjective and vary widely based on clinician experience, leading to potential biases and inconsistent diagnoses [14]. Moreover, procedures such as neuroimaging and cerebrospinal fluid (CSF) analysis can be expensive and invasive, limiting their accessibility and practicality in routine clinical settings [15]. Considering these limitations, there is a growing interest in exploring blood-based biomarkers as a more affordable and less invasive diagnostic approach. While recent studies have drawn attention to the potential of plasma amyloid β-peptides (Aβ) as predictive markers for dementia, results have varied widely, leading to conflicting interpretations [16-20]. To address this gap in knowledge, the aim of this study was to review and analyze existing literature to evaluate the efficacy of plasma Aβ levels in predicting dementia and cognitive decline.

Methods

Study design and setting

This systematic review and meta-analysis included human studies that were published in peer-reviewed journals, focusing on the predictive value of plasma Aβ for dementia, Alzheimer's disease (AD), and cognitive decline. The study involved a comprehensive search of six databases (PubMed, PMC, SSRN, Scopus, BioRxiv, and MedRxiv) as of December 1, 2024. Risk of bias was assessed using the ROBINS-E tool, and a random-effects meta-analysis was conducted to calculate pooled hazard ratios (HRs) with 95% confidence intervals (CIs).

Information sources and search strategy

To identify relevant studies, a comprehensive search was conducted across six databases: PubMed, PMC, SSRN, Scopus, BioRxiv, and MedRxiv. The search strategies were tailored to each database using terms related to amyloid beta-protein, plasma, and dementia-related conditions. The full search terms are listed in **Table 1**. The last search was performed on December 1, 2024. Additional studies were identified through citation tracking of selected papers.

Eligibility criteria

Studies included in this systematic review and meta-analysis should met the following criteria: (1) focused on human subjects; (2) published in peer-reviewed journals in English; and (3) reported the association between plasma Aβ and dementia, Alzheimer's disease, or cognitive decline. Only studies presenting effect sizes or providing sufficient data to calculate effect sizes, with a minimum sample size of 30 participants, were eligible for meta-analysis.

Table 1. Search terms used for the search strategy

Database	Search terms
PubMed	("Amyloid Beta-Protein" OR "beta-amyloid") AND ("plasma" OR "blood") AND ("Dementia" OR "Alzheimer Disease" OR "Senile Dementia" OR "Presenile Dementia"[Title/Abstract] OR "Presenile Dementia" OR "Alzheimer Dementia" OR "cognitive impairment" OR "cognitive decline"[Title/Abstract] OR "mci")
PMC	#1 Amyloid Beta-Protein #2 Plasma #3 Dementia #4 Alzheimer Disease #5 Senile Dementia #6 Presenile Dementia #7 (Presenile Dementia): ti,ab,kw #8 Alzheimer Dementia #9 Cognitive Impairment #10 (Cognitive Decline): ti,ab,kw #11 MCI #12 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 #13 #1 AND #2 AND #12 Trials only
SSRN	("Amyloid Beta-Protein" OR "Amyloid Beta-Protein/blood") AND ("plasma") AND ("Dementia" OR "Alzheimer Disease" OR "Senile Dementia" OR "Presenile Dementia" OR "Alzheimer Dementia" OR "cognitive impairment" OR "cognitive decline" OR "mci")
Scopus	(TITLE-ABS-KEY (“Amyloid beta-Protein”)) AND (TITLE-ABS-KEY ("plasma")) AND (TITLE-ABS-KEY ("Dementia" OR "Alzheimer Disease" OR "Senile Dementia" OR "Presenile Dementia" OR "Alzheimer Dementia" OR "cognitive impairment" OR "cognitive decline" OR "mci"))
BioRxiv	("Amyloid beta-protein") AND (plasma) AND (Dementia OR Alzheimer OR "cognitive impairment" OR "cognitive decline" OR "mci")
MedRxiv	("Amyloid beta-protein") AND (plasma) AND (Dementia OR Alzheimer OR "cognitive impairment" OR "cognitive decline" OR "mci")

Selection and data collection process

Two investigators independently (CC and RD) screened titles and abstracts to identify studies meeting the inclusion criteria. Full texts of potentially relevant studies were reviewed, and disagreements were resolved through discussion with a third investigator (JN). The screening process adhered to predefined criteria to ensure consistent and unbiased study selection.

Extracted data included author and publication year, study design, measured outcomes, number of subjects, number of events, mean age of participants, percentage of female participants, follow-up duration (in years), and details of Aβ levels, including the specimen type and measurement methods. Effect sizes with 95% confidence intervals (CIs) were also extracted. Discrepancies were resolved through consensus with a third investigator.

Risk of bias assessment

The risk of bias in included studies was assessed using the ROBINS-E tool, evaluating the following domains: (1) bias due to confounding; (2) bias in selection of participants; (3) bias in classification of interventions; (4) bias due to deviations from intended interventions; (5) bias due to missing data; (6) bias in measurement of outcomes, and (7) bias in selection of the reported result [21]. Two investigators independently (CC and RD) assessed each study, with disagreements resolved by a third investigator (JN). The Risk-of-bias VISualization tool (robvis) was used to summarize and visualize the results [22].

Statistical analysis

Meta-analyses were conducted if at least three studies reported comparable effect sizes (e.g., HRs, odds ratios, or relative risks). Pooled effect estimates were calculated using a random-effects model to account for variability between studies. Statistical heterogeneity was assessed using the I^2 statistic and Cochran’s Q test. Subgroup and sensitivity analyses were performed to explore potential sources of heterogeneity. All analyses were conducted using the meta package in R v4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), and forest plots were generated with the ggplot2 package in R [23].

Results

Search results

Our systematic search identified a total of 9,472 records across six databases. After removing 1,087 duplicate records, 8,385 records were screened based on titles and abstracts. A total of 8,349 were excluded after titles and abstracts screening due to unrelated articles. The remaining 36 articles were retrieved for full-text. Out of these 36 articles, 11 were excluded due to some reasons: (1) inappropriate exposure (n=2); (2) inappropriate measured outcomes (n=10); and inappropriate study design (n=1). Ultimately, 23 studies were included in the systematic review, with four of them were included in the meta-analysis (**Figure 1**).

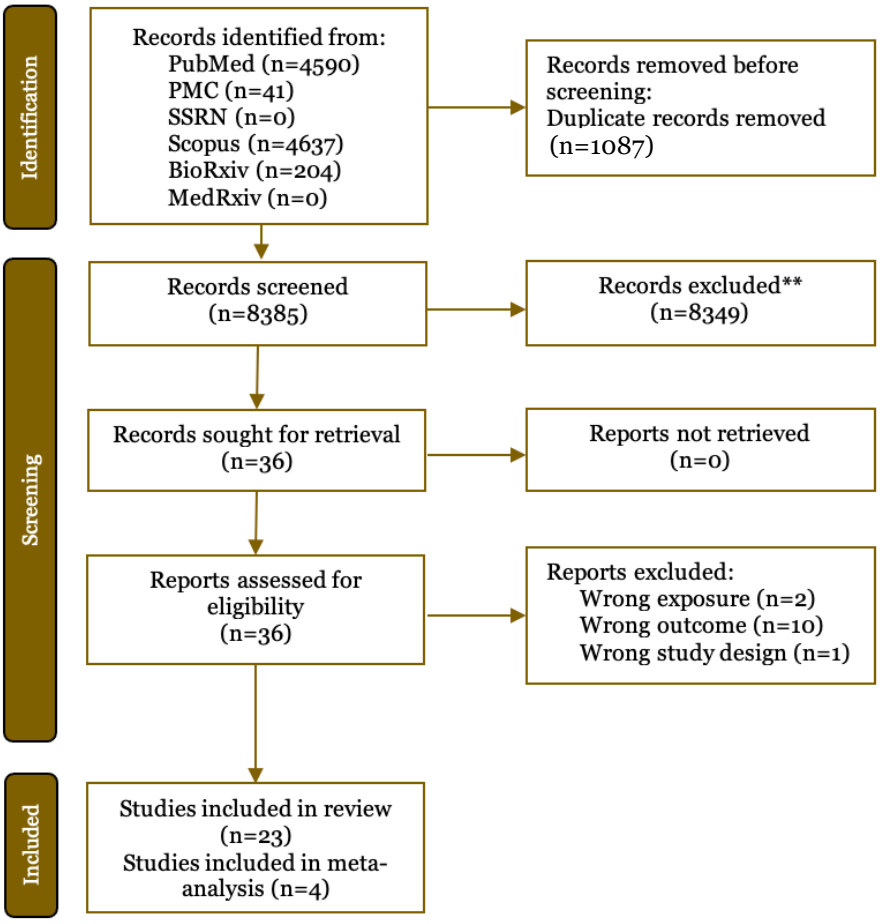

Figure 1. PRISMA 2020 flow diagram showing the study selection process.

Quality assessment

The risk of bias assessment revealed that 11 studies [17,24-30] were judged to have an overall low risk of bias, ten studies [31-40] had some concerns, and four studies [41-44] were found to have a high risk of bias (**Figure 2**). The highest frequency of bias was observed in domains related to the measurement of outcomes and missing data. Notably, among the four studies included in the meta-analysis, three studies [17,25,45] were judged to have a low risk of bias, and only one study[31] had some concerns. This indicated that the studies contributing to the meta-analysis were of generally high methodological quality, minimizing the potential impact of bias on the pooled estimates and strengthening the reliability of the meta-analytic findings.

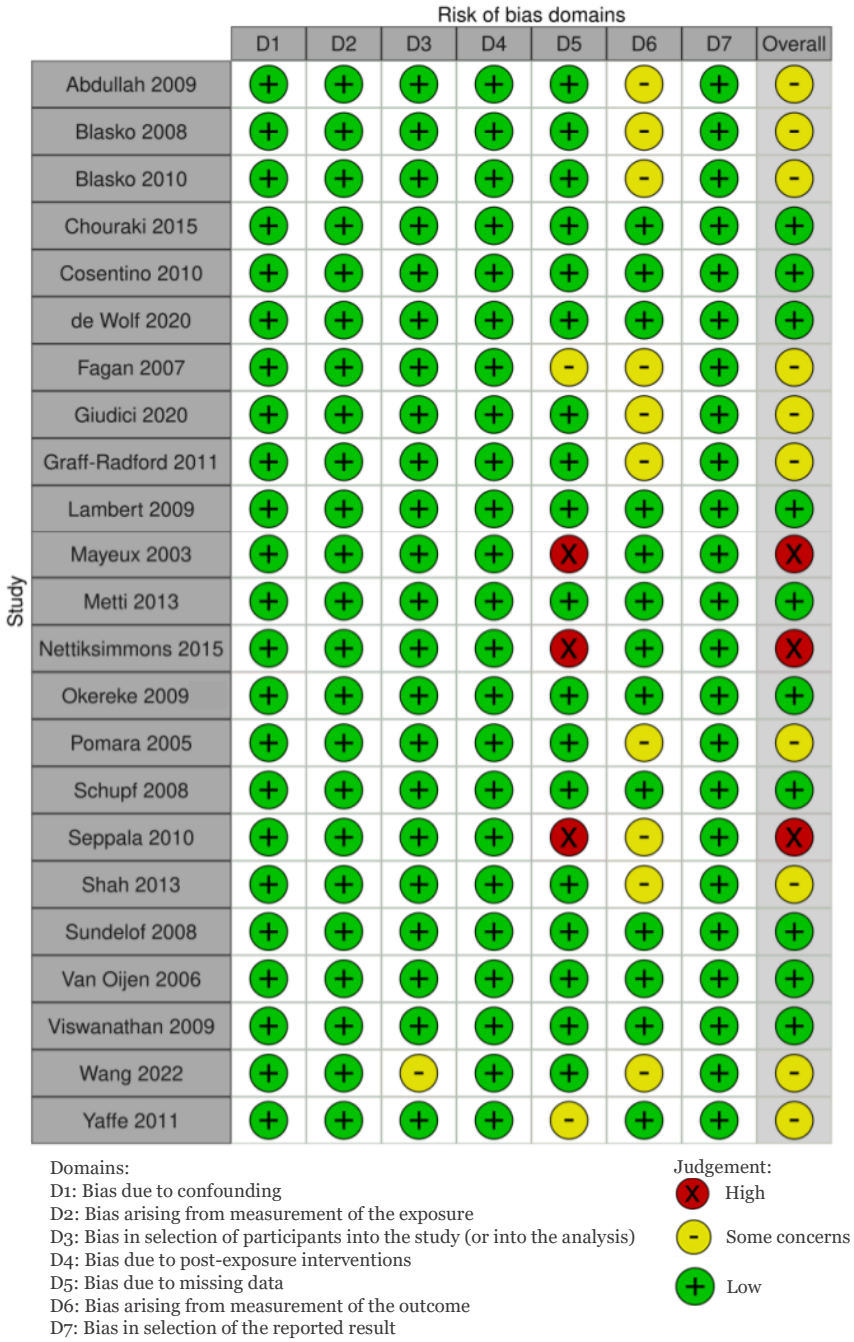

Figure 2. Traffic light plot of risk of bias assessment across included studies.

Characteristics of the studies

Detailed characteristics of all included studies are presented in **Table 2**. All analyses were based on cohort studies involving patients older than 60 years. Four articles did not report the sex distribution [37,38,43,46], one study included only female patients [29], and the rest reported that females comprised 48.3% to 73.3% of the study populations [17,24-28,30-33,37-47]. Follow-up durations ranged from a single year in one study to 2.1 to 15.8 years in the others. A total of 33,158 samples were included in the analysis. The sample types varied, including one article used serum[31]; three articles used KEDTA [32,33,47]; three studies used K3EDTA [17,24,30]; four articles used used EDTA [25,34,39,44]; three articles used heparin [29,37,44]; one article sodium used citrate[45]; and ten studies used plasma [26-28,35,38,40-43,46]. The assays used to measure plasma Aβ levels included 18 articles employed ELISA [19,24,27,29-34,36-39,41,43-47]; five studies used Multiple xMAP-INNOBIA [17,26,28,40,42]; one article used Single Molecule Array/Simoa [25]; and a study used immunoprecipitation [35].

Table 2. Summary of the studies included in the review

First author, year (ref)	Design	Observed outcome	Follow-up time (years)	Study population				Findings	Amyloid-β level specimen/method
				Subjects, mean age (n, years)	Events (n)	Sex (females, %)	Parameters		
Abdullah, 2009 [31]	Cohort	Alzheimer's Disease (AD)	2.1	203, 76.8	24	48.3	Plasma Aβ-42 levels Plasma Aβ-40 levels	Elevated Aβ levels are associated with vascular risk factors, which may reflect presymptomatic Alzheimer's disease pathology.	Serum/ELISA
Blasko, 2008 [32]	Cohort	AD, Dementia	2.5	606, 75.8	98	59.4	Plasma Aβ-42 levels	Higher plasma Aβ-42 levels independently predicts development of LOD and possible Alzheimer's disease	KEDTA/double-antibody sandwich enzyme linked immunosorbent
Blasko, 2010 [33]	Cohort	AD, Dementia	5	406, 75.8	33	56.5	Plasma Aβ-42 levels	Plasma Aβ42 levels may provide insight into cognitive decline, but they are not sufficient as standalone biomarkers for Alzheimer's disease.	KEDTA/double-antibody sandwich enzyme linked immunosorbent
Chouraki, 2015 [17]	Cohort	AD, Dementia	7.6	2189, 72	194	56	Plasma Aβ-42 levels Plasma Aβ-42:Aβ-40 ratio	Lower plasma Aβ levels are associated with a higher risk of developing clinical Alzheimer's disease and dementia.	Nonfasting K3EDTA/multiple xMAP-INNO-BIA
Cosetino, 2010 [24]	Cohort	Cognitive Change	4.5	880, 76.1	70	68	Plasma Aβ-42 levels Plasma Aβ-40 levels	Plasma Aβ-42 levels may serve as significant biomarkers for cognitive decline.	K3EDTA/double-antibody sandwich ELISA+K10:K14
de Wolf, 2020 [25]	Cohort	AD, Dementia	14	4444, 71.9	374	57.50	Plasma Aβ-42 levels	Low Plasma Aβ-42 levels are strongly associated with increased risk of Alzheimer's disease & all-cause dementia	EDTA/Quanterix, single molecule array (Simoa)
Fagan, 2007 [34]	Cohort	Cognitive Decline	8	139, 73.3	49	69	CSF tau/Aβ42 ratio ptau181/Aβ42	CSF tau/Aβ42 and ptau181/Aβ42 ratios may be used to predict future cognitive decline in cognitively normal older adults for distinguishing early-stage Alzheimer's disease and nondemented aging.	Fasted EDTA/ELISA
Giudici, 2020 [35]	Cohort	Cognitive Decline	5	483, 80	161	59.20	Plasma Aβ-42:Aβ-40 ratio	low plasma Aβ 42/40 is associated with a more	Plasma/Immunoprecipitation

First author, year (ref)	Design	Observed outcome	Follow-up time (years)	Study population				Findings	Amyloid-β level specimen/method
				Subjects, mean age (n, years)	Events (n)	Sex (females, %)	Parameters		
Abdullah, 2009 [31]	Cohort	Alzheimer's Disease (AD)	2.1	203, 76.8	24	48.3	Plasma Aβ-42 levels Plasma Aβ-40 levels	Elevated Aβ levels are associated with vascular risk factors, which may reflect presymptomatic Alzheimer's disease pathology. pronounced decline in cognitive function	Serum/ELISA
Graff-Radford, 2007 [36]	Cohort	AD, Cognitive Change	3.7	563, 78	17	62	Plasma Aβ-42:Aβ-40 ratio	Plasma Aβ42/Aβ40 ratio may be a useful biomarker for identifying cognitively normal elderly individuals at increased risk for developing MCI or Alzheimer's disease.	Nonfasting EDTA/enzyme-linked immunosorbent
Lambert, 2009 [26]	Cohort	Dementia	4	8414, 74.6	154	60.4	Plasma Aβ-42:Aβ-40 ratio	Higher Aβ1–42/Aβ1–40 were linked to a lower risk of developing dementia.	Nonfasting EDTA/ multiple xMAP-INNO-BIA
Mayeux, 2003 [41]	Cohort	AD	5	451, 76,2	86	69	Plasma Aβ-42 levels	Elevated plasma Aβ-42 levels are associated with an increased risk of developing Alzheimer's disease.	Plasma/double-antibody sandwich enzyme-linked immunosorbent
Metti, 2013 [28]	Cohort	Depression	9	988, 74.0	51	55.2	Plasma Aβ-42:Aβ-40 ratio	Low plasma Aβ42/Aβ40 is a potential biomarker for increased risk of depression.	Plasma/multiple xMAP-INNO-BIA
Nettiksimmons, 2015 [42]	Cohort	Cognitive Decline	11	865, N/A	N/A	53	Plasma Aβ-42:Aβ-40 ratio	Plasma Aβ-42:Aβ-40 ratio may be utilized to evaluate cognitive decline, particularly using the 3MS tool.	Plasma/multiple xMAP-INNO-BIA
Okereke, 2009 [29]	Cohort	Cognitive Change	10	481, 63.6	N/A	100	Plasma Aβ-42:Aβ-40 ratio	Mid-life levels and changes in the Aβ-40:Aβ-42 ratio are significant predictors of cognitive decline	Heparin/Sandwich ELISA
Pomara, 2005 [37]	Cohort	Cognitive decline	4	34, 65.4	NA	N/A	Plasma Aβ-42 levels	Higher initial plasma Aß42 levels and greater reductions in Aß42 during follow-up were significantly associated with declines in cognitive performance as measured by the Mini-Mental State Exam (MMSE).	Heparin (9-11am)/double-antibody sandwich enzyme-linked immunosorbent
Schupf, 2008 [30]	Cohort	AD	4.6	1125, 76.9	104	68.3	Plasma Aβ-42 levels	Plasma levels of Aβ42, particularly when measured	K3EDTA/double-antibody sandwich ELISA

First author, year (ref)	Design	Observed outcome	Follow-up time (years)	Study population				Findings	Amyloid-β level specimen/method
				Subjects, mean age (n, years)	Events (n)	Sex (females, %)	Parameters		
Abdullah, 2009 [31]	Cohort	Alzheimer's Disease (AD)	2.1	203, 76.8	24	48.3	Plasma Aβ-42 levels Plasma Aβ-40 levels Plasma Aβ-40 levels Plasma Aβ-42:Aβ-40 ratio	Elevated Aβ levels are associated with vascular risk factors, which may reflect presymptomatic Alzheimer's disease pathology. longitudinally, can serve as significant biomarkers for the risk of Alzheimer's disease in elderly populations.	Serum/ELISA
Seppala, 2010 [44]	Cohort	Cognitive Decline	3	269, 70	52	55	Plasma Aβ-42 levels Plasma Aβ-42:Aβ-40 ratio	Low or decreasing plasma Aβ42 levels are associated with cognitive decline.	Heparin/ELISA
Shah, 2012 [38]	Cohort	AD	15.8	667, 58.9	77	N/A	Plasma Aβ-40 levels Plasma Aβ-42 levels	Plasma Aβ levels are related to Alzheimer's disease risk.	Plasma/Sandwich ELISA Eli Lily
Sundelof, 2008 [46]	Cohort	AD	11.2	1045, 71	82	0	Plasma Aβ-42 levels Plasma Aβ-40 levels	Plasma Aβ levels may be utilized as biomarkers for Alzheimer's disease risk in elderly men.	Fasting plasma/enzyme-linked immunosorbent
van Oijen, 2006 [45]	Cohort	AD	8.6	6713, 68.6	289	61	Plasma Aβ-42:Aβ-40 ratio Plasma Aβ-40 levels	Individuals with a higher ratio of Aβ1–42/Aβ1–40 had a reduced risk of dementia. High plasma concentrations of Aβ1–40 were associated with an increased risk of dementia.	Sodium citrate and EDTA/double-antibody sandwich enzyme-linked immunosorbent
Viswanathan, 2009 [47]	Cohort	Cognitive Decline	2	150, 67.2	N/A	53.8	Plasma Aβ-42:Aβ-40 ratio Plasma Aβ-42 levels Plasma Aβ-40 levels	although there is a correlation between tHcy and Aβ40, the interventional treatment did not alter Aβ levels.	KEDTA/Sandwich ELISA
Wang, 2018 [39]	Cross-sectional	Cognitive Decline	1	1180, 55.1	134	59.6	Plasma Aβ-42:Aβ-40 ratio Plasma Aβ-42 levels	Elevated levels of plasma Aβ42 and the Aβ42/Aβ40 ratio were more pronounced in the early stages of cognitive impairment, which may serve as biomarkers of early cognitive decline.	Fasting EDTA/Sandwich ELISA

First author, year (ref)	Design	Observed outcome	Follow-up time (years)	Study population				Findings	Amyloid-β level specimen/method
				Subjects, mean age (n, years)	Events (n)	Sex (females, %)	Parameters		
Abdullah, 2009 [31]	Cohort	Alzheimer's Disease (AD)	2.1	203, 76.8	24	48.3	Plasma Aβ-42 levels Plasma Aβ-40 levels	Elevated Aβ levels are associated with vascular risk factors, which may reflect presymptomatic Alzheimer's disease pathology.	Serum/ELISA
Yaffe, 2011 [40]	Cohort	Cognitive Change	10	997, 74	N/A	55.1	Plasma Aβ-42: Aβ-40 ratio	Lower plasma β-amyloid 42/40 levels were significantly associated with greater cognitive decline over a 9-year period.	Plasma/multiple xMAP-INNO-BIA

Role of Aβ on predicting cognitive decline and cognitive impairment

Numerous studies have examined the relationship between plasma Aβ peptides, Aβ-40 and Aβ-42, and cognitive decline or mild cognitive impairment (MCI). A study found that higher Aβ-40/Aβ-42 ratio in midlife and subsequent increases in this ratio were associated with greater cognitive decline (p=0.04) [43] Another study demonstrated that lower plasma Aβ-42/Aβ-40 ratios were significantly associated with pronounced cognitive decline over time (adjusted β=5.51; 95%CI: 1.35–9.67; p=0.009) [35] Abdullah *et al.* identified low Aβ-42 levels and low Aβ-42/Aβ-40 ratios as predictors of MCI [31]. Lower Aβ-42/Aβ-40 ratios significantly increased the risk of MCI (RR=3.1; 95%CI: 1.1–8.3; p=0.01) [36]. Furthermore, a study reported that high baseline plasma Aβ-42 levels (p=0.01) and decreasing levels over time (p=0.02) were significantly associated with accelerated cognitive decline in elderly individuals.

Role of Aβ on predicting dementia

Early elevations in plasma Aβ-42 were associated with an increased risk of dementia, while later reductions in plasma Aβ-42 level was indicative of disease progression [24,25,27,38,41] A study reported that higher baseline plasma Aβ-42 level was significantly predictive of dementia onset (OR=1.7; 95%CI: 1.1–2.7), supporting their role in early risk stratification. Similarly, another study demonstrated that each standard deviation increase in plasma Aβ-42 levels was associated with a 21% reduction in dementia risk (HR=0.79; 95%CI: 0.69–0.90; p<0.001), while a higher Aβ-42/Aβ-40 ratio was also linked to reduced dementia incidence (HR=0.83; 95%CI: 0.72–0.96; p=0.012) [17]. A study reported that a higher Aβ-42/Aβ-40 ratio was associated with lower dementia risk, particularly in the short term [26]. Conversely, elevated Aβ-40 levels alone were associated with increased dementia risk [45]. A study also found that lower plasma Aβ-42 levels significantly increased the risk of dementia (HR=2.20; 95%CI: 1.51–3.20), reinforcing the biomarker's prognostic potential in preclinical populations [25].

Role of Aβ on predicting Alzheimer's disease

Several studies have demonstrated the potential of plasma Aβ levels in predicting the progression to Alzheimer's disease. However, there is no consensus on whether higher levels of Aβ are consistently associated with increased or decreased Alzheimer's disease risk. Three articles reported that a higher risk of Alzheimer's disease was associated with higher levels of Aβ [27,30,32], while two studies found the opposite, linking higher Aβ levels with a lower risk of Alzheimer's disease [17,25]. Additionally, three articles reported no statistically significant association between Aβ levels and Alzheimer's disease risk [41,43,47].

A previous study identified low Aβ-42 levels and low Aβ-42/Aβ-40 ratios as strong predictors of Alzheimer's disease (HR=2.93; 95%CI: 1.02–8.32 and HR=3.53; 95%CI: 1.24–10.07), emphasizing their utility in early risk detection [31]. Another study found that lower Aβ-42/Aβ-40 ratios significantly increased the risk of Alzheimer's disease (RR=3.1; 95%CI: 1.1–8.3; p=0.01) [36]. A study reported that elevated Aβ-42 level was initially associated with increased Alzheimer's disease risk, although the level declined as the disease progressed [30]. Higher baseline Aβ-42 levels predicted the onset of late-onset dementia and Alzheimer's disease (OR=1.7; 95%CI: 1.1–2.7), while a follow-up study found that Aβ-42 levels alone were not predictive of disease development, suggesting time-dependent variability in biomarker utility [32,33]. Another further highlighted significant associations between low plasma Aβ-42 levels and increased Alzheimer's disease risk (HR=2.46; 95%CI: 1.60–3.78) [17].

The predictive value of Aβ markers, however, varies across studies. A study found that low plasma Aβ-40 level was associated with a higher incidence of Alzheimer's disease in elderly men, while Aβ-42 level was not predictive [46]. Another study observed that declining Aβ-42 levels correlated with cognitive decline, independent of genetic risk factors [37]. Further studies reported elevated plasma Aβ-42 levels several years before Alzheimer's disease onset, followed by a decline with disease progression [27,41]. A study found that higher Aβ-42/Aβ-40 ratio was associated with a reduced risk of Alzheimer's disease (HR=0.76; 95%CI: 0.62–0.92; p=0.006), whereas another study found no significant association between plasma Aβ levels and vascular dementia [26,38]. Viswanathan *et al.* also reported no correlation between plasma Aβ-40 and cognitive outcomes [47].

Integrating Aβ measurements with other biomarkers appears to enhance diagnostic accuracy. For example, a study found that low CSF Aβ-42 level was strongly associated with early-stage Alzheimer's disease [34] while another study showed that combining low plasma Aβ-42 with high neurofilament light chain level provided the strongest predictive correlation for dementia [25].

Meta-analysis

Only four studies [17,25,31,45] reported HRs as the effect size for the association between the Aβ-42/Aβ-40 ratio and Alzheimer's disease as the clinical outcome, all of which presented adjusted HRs. Two additional studies [31,36] reported relative risks as the effect size, but one study [38] stratified Aβ levels into quartiles, making meta-analysis for these studies unsuitable. The pooled HR for the Aβ-42/Aβ-40 ratio was not statistically significant (HR=0.8, 95%CI: 0.62–1.04) (**Figure 3**). Evidence of heterogeneity was observed between study estimates, with an I^2 of 70% (restricted likelihood ratio test for heterogeneity p=0.02).

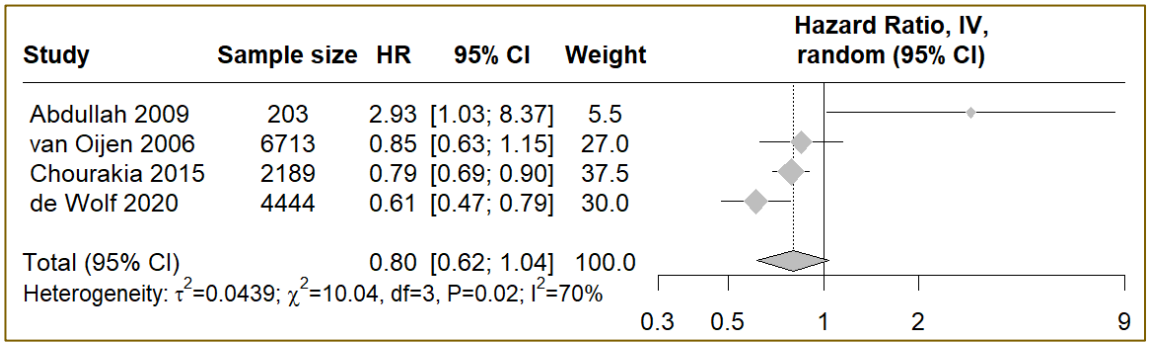

Figure 3. Associations between ratio of amyloid beta 42 and amyloid beta 40 (Aβ-42/Aβ-40 ratio) and Alzheimer's disease. Estimates are expressed as adjusted hazards ratio (HRs) and 95% confidence intervals (CIs) pooled using a random-effects meta-analysis.

Discussion

The studies provided a variety of insights into the role of plasma Aβ levels as biomarkers for Alzheimer's disease [17,24-47]. Many studies reported that lower baseline concentrations of Aβ-42, or a decline over time, were associated with cognitive decline and the onset of Alzheimer's disease [24,44]. Conversely, some studies identified higher plasma Aβ-42 levels as an early indicator of increased Alzheimer's disease risk, although these levels tended to decrease as the disease progressed [25,30,32]. This decrease may result from Aβ peptides accumulating in the brain, leading to reduced plasma levels, supporting the hypothesis that Aβ aggregation and deposition in the brain occur years before clinical symptoms emerge.

Plasma Aβ-42 levels alone are not consistently strong predictors of Alzheimer's disease. Higher Aβ-42 levels might signify early disease risk but decline over time, likely due to deposition in plaques. Some studies suggested this reflected the dynamic equilibrium between Aβ deposition in the brain and its clearance into peripheral circulation [30,39]. Aβ-42, which selectively deposits in the Alzheimer's disease brain, shows reduced levels in both CSF and plasma as the disease progresses [30,39]. A longitudinal analysis further supported this dynamic, indicating that elevated baseline Aβ-42 level was predictive of late-onset Alzheimer's disease (OR=1.7; 95%CI: 1.1–2.7), while their follow-up study in 2010 showed that Aβ-42 levels alone no longer predicted disease progression, highlighting the temporal complexity of Aβ dynamics [48,49]. These findings underscored the importance of monitoring temporal changes in Aβ levels rather than relying on single measurements to assess Alzheimer's disease risk and progression.

Evidence for the utility of the Aβ-42/Aβ-40 ratio as a biomarker remains inconclusive due to conflicting findings across studies. Several studies have suggested that lower Aβ-42/Aβ-40 ratios, or increased Aβ-40/Aβ-42 ratios, are associated with a higher risk of MCI and Alzheimer's disease, while higher ratios may be protective, reflecting better brain health. However, some studies found no significant associations [26,30,31,36,40,43]. A study proposed that plasma Aβ-40 and Aβ-42 levels might be more useful as prognostic markers than diagnostic tools for

Alzheimer's disease [41]. Evidence regarding the independent role of Aβ-40 in Alzheimer's disease risk is also mixed, with some studies linking low Aβ-40 levels to higher Alzheimer's disease incidence [46,47], while others found no significant association [27,41,47]. These findings highlighted the distinct roles of Aβ-40 and Aβ-42, with Aβ-42 being more neurotoxic and closely associated with cognitive impairment, whereas Aβ-40 may contribute to cerebral vascular dysfunction. Van Oijen *et al.* further implicated plasma Aβ levels in microvascular pathology, noting associations with white-matter hyperintensity and lacunar infarcts, supporting the hypothesis that vascular factors mediate the relationship between plasma Aβ levels and Alzheimer's disease risk [45].

The relationship between plasma Aβ dynamics and Alzheimer's disease risk is further complicated by the interplay of brain-derived and peripheral Aβ production. While amyloid precursor protein is produced in both brain and peripheral tissues, the relative contributions of these sources to plasma Aβ levels remain unclear. Abdullah et al. found that even after adjusting for confounders such as vascular factors and medications, low Aβ-42 levels and low Aβ-42/Aβ-40 ratios remained strong predictors of conversion to MCI or Alzheimer's disease [31]. Additionally, the presence of the apolipoprotein E (APOE) ε4 allele appears to modify the relationship between plasma Aβ levels and cognitive outcomes, suggesting a genetic interaction [31].

Depression in older adults has also been associated with an increased risk of cognitive decline, dementia, and MCI [28,48-50]. Studies suggested that depression may influence the development of amyloid plaques and neurofibrillary tangles, hallmark features of Alzheimer's disease [51-53]. The hypothesis that depression linked to low plasma Aβ-42/Aβ-40 ratios represents a prodromal dementia subtype is supported by evidence that depression in the earliest preclinical phases of dementia has distinct pathologies and etiologies [54]. The presence of the APOE ε4 allele in individuals with low plasma Aβ-42/Aβ-40 ratios may further increase the risk of both depression and Alzheimer's disease. Potential mechanisms include amygdala atrophy and reduced brain volume, both implicated in depression and dementia, as well as hippocampal atrophy, which has been associated with high Aβ-40/Aβ-42 ratios. Chronic stress is another possible factor, as it is linked to increased glucocorticoid levels, which in animal models have been associated with altered Aβ-42/Aβ-40 ratios. Finally, shared genetic risk factors, such as APOE ε4, may also underlie the connection between depression and dementia, with at least one longitudinal study reporting an increased risk of dementia in individuals with depression and the APOE ε4 allele [28].

The question remains, however, what underlies the association between plasma Aβ concentrations and risk of dementia? The brain is generally considered the primary source of the Aβ deposited in plaques in patients with Alzheimer's disease. Since CSF and plasma Aβ concentrations are thought to exist in dynamic equilibrium, increased production of Aβ in the brain may correspond to elevated plasma levels. Additionally, changes in the peripheral clearance of plasma Aβ, potentially influenced by renal function, could also affect plasma Aβ concentrations, as evidenced by strong associations between plasma Aβ levels and serum creatinine.

One of the major challenges in interpreting the findings across studies is the significant heterogeneity in methods and results. Differences in measurement techniques, with studies employing various tests that yield a wide range of Aβ levels, contribute to this variability. Standardizing these methodologies is critical for future research to produce more consistent and interpretable results. Furthermore, plasma Aβ levels may hold different implications depending on the stage of dementia, and inconsistent follow-up durations across studies likely contribute to the observed variation. Tracking changes in Aβ levels over time, rather than relying on single measurements, has been suggested as a more reliable approach, as declining Aβ-42 levels or Aβ-42:Aβ-40 ratios have been linked to cognitive decline in several studies.

Methodological variations across studies are another significant source of variability. Differences in study design, population demographics (e.g., age, ethnicity, genetic background), follow-up duration, and technical protocols—including sample collection, handling, and storage—pose challenges for data interpretation. Technical factors, such as freeze-thaw cycles, choice of anticoagulant (heparin vs. EDTA), and assay sensitivity, can also influence plasma Aβ measurements. Heparin tubes, used in some studies may interfere with Aβ measurements due to

binding [55,56] whereas EDTA tubes, preferred in other studies reduce potential interference [17,26,30,32,36]. Blood samples are typically stored at temperatures ranging from -70°C to -130°C, with protocols emphasizing immediate centrifugation and aliquoting to minimize the effects of freeze-thaw cycles, as highlighted in some studies [30,35]. These measures are critical to maintaining sample integrity, particularly when considering factors such as fasting versus nonfasting states.

The presence of the APOE ε4 allele significantly modifies the association between plasma Aβ levels and Alzheimer's disease risk, highlighting the potential for tailored interventions. In addition to genetic modifiers, specific plasma Aβ profiles, such as low Aβ-42 levels and decreased Aβ-42/Aβ-40 ratios, have demonstrated predictive value even after adjusting for vascular risk and APOE status, as shown in Abdullah et al.'s findings. Depression and vascular factors, such as elevated plasma homocysteine, also influence plasma Aβ levels and their relationship with cognitive decline. Variability in follow-up periods and confounding factors, including renal function, medication use, and comorbidities like vascular disease, further complicate the interpretation of plasma Aβ as a biomarker, limiting its diagnostic specificity. Many studies rely on single time-point measurements, which fail to capture the dynamic changes in Aβ levels over the course of the disease, further contributing to inconsistent findings.

To address these challenges, future research must prioritize the standardization of plasma Aβ measurement protocols to improve comparability across studies. A study found differences between absolute levels in 70 samples measured twice 4 years apart, highlighting the need for consistency in testing [44]. Longitudinal studies that track changes in plasma Aβ levels over time are needed to gain deeper insights into its role in disease progression. Early exploration of preclinical and prodromal stages of Alzheimer's disease may clarify the relationship between plasma Aβ and cognitive decline. Moreover, integrating plasma Aβ biomarkers with other modalities, such as neuroimaging or genetic data, could enhance predictive accuracy and diagnostic value.

Despite its limitations, plasma Aβ remains an attractive biomarker due to its simplicity, affordability, and non-invasive nature, making it ideal for large-scale screening. Plasma Aβ biomarkers are particularly promising as (1) many current Alzheimer's disease treatments target Aβ, enabling these biomarkers to identify candidates likely to benefit from these therapies; (2) Aβ accumulation is an early pathological event in Alzheimer's disease, allowing for earlier detection; and (3) plasma-based assays provide a practical alternative to more invasive CSF or imaging techniques.

Conclusion

The meta-analysis supports the potential of the plasma Aβ-42/Aβ-40 ratio as a promising biomarker for Alzheimer's disease risk. While elevated plasma Aβ-42 levels may indicate early risk, their decline over time could signify disease progression. The Aβ-42/Aβ-40 ratio appears more informative than absolute levels of Aβ-42 or Aβ-40 alone. However, current evidence is insufficient to establish plasma Aβ as a definitive diagnostic tool. Combining these measurements with other biomarkers and refining sample collection and assay protocols may enhance their diagnostic utility. Standardized methodologies, longitudinal research, and consideration of genetic and environmental factors are critical for improving risk stratification, early detection, and treatment optimization in Alzheimer's disease.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used artificial intelligence (AI) tools and methodologies of which AI-based language model, ChatGPT, was employed in language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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