Systematic Review

Plasma Aβ biomarker for early diagnosis and prognosis of Alzheimer's disease – a systematic review

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ABSTRACT

INTRODUCTION. Alzheimer's disease (AD) is the most common cause of dementia worldwide and a cost-effective diagnostic biomarker is needed. This systematic review provides an overview of the current research on plasma amyloid beta (Aβ) as a biomarker of AD and explores the clinical implications of this line of research.

METHODS. PubMed was searched using the keywords plasma Aβ and AD from 2017 to 2021. Only clinical studies involving amyloid PET (aPET) or cerebrospinal fluid (CSF) biomarker analysis (or both) were included. A meta-analysis of CSF Aβ42/40 ratio, aPET and plasma Aβ42/40 ratio was conducted when possible.

RESULTS. A total of 17 articles were identified. Plasma Aβ42/40 ratio was inversely correlated with aPET positivity r = –0.48 (95% confidence interval (CI): –0.65-–0.31). In numerous studies, plasma Aβ42/40 ratio was also found to be directly correlated with CSF Aβ42 and CSF Aβ42/40 ratio r = 0.50 (95% CI: 0.30-0.69). Three studies found plasma Aβ42 to be positively associated with aPET positivity and CSF Aβ42; however, four other studies found no significant association between these variables. Seven studies reported no significant association of plasma Aβ40 with aPET or CSF Aβ40.

CONCLUSION. Plasma Aβ42/40 ratio seems as a promising plasma biomarker as it significantly correlates inversely with aPET positivity and directly with CSF Aβ42 and CSF Aβ42/40 ratio. However, more research is warranted, including validation studies, longitudinally clinical studies, studies comparing measurement methods and studies of Aβ kinetics.

KEY POINTS

- Plasma beta amyloid plaques (Aβ) 42/40 ratio is inversely associated with amyloid PET positivity and directly associated with cerebrospinal fluid (CSF) Aβ42/40 and CSF Aβ42.
- Aβ42/40 can predict Alzheimer's disease (AD) pathology progression.
- The multiple different measurement methods, considerable clinical variation within the AD continuum and incomplete knowledge of Aβ kinetics hamper the validation of plasma Aβ as a biomarker for AD diagnosis and prognosis.

Premorbid pathophysiological changes in Alzheimer's disease (AD) precede symptom onset by decades [1-3]. The amyloid cascade hypothesis states that the earliest pathology and hallmark of AD is beta amyloid plaques (Aβ) in the brain [4]. The inter-neuronal pathological change is thought to induce the intra-neuronal tau pathology of tau fibrils. These events induce additional inflammation leading to synaptic dysfunction and ultimately dementia [5, 6].

Aβ originates from cleavage of the amyloid precursor protein, which is a transmembrane protein partially embedded in the plasma membrane [7, 8]. Aβ is denoted by a number referring to the number of amino acids that the isoform consists of. How exactly Aβ is distributed from the brain to the blood stream is not completely understood. However, it seems increasingly evident that Aβ is cleared into the plasma through cerebrospinal fluid (CSF) or via the blood-brain barrier [9].

CSF biomarker analyses and amyloid PET (aPET) may be used to track AD pathology and thus have diagnostic applicability [10]. However, CSF analysis is a time-consuming and invasive procedure and an aPET is expensive and less available outside academic hospitals [11]. Diagnosing solely based on clinical assessments is less accurate so a cost-effective plasma biomarker has been extensively sought after.

CSF Aβ42 levels have been robustly shown to be lower in AD patients than in cognitively unimpaired elderly [12]. The pathophysiology of this phenomenon is thought to be that Aβ42 is sequestered in the insoluble plaques of the brain in AD, which lowers the amount secreted to the CSF [13]. Indeed, it was shown that antemortem CSF Aβ42 correlates inversely with the amount of senile amyloid plaques measured both postmortem [14] and antemortem [15] (by aPET).

Many studies have shown that CSF Aβ40 (which is found at around ten times higher concentrations than CSF Aβ42 [16, 17]) exhibits only minor or no changes in AD [12], whereas the CSF Aβ42/40 ratio was proven to be superior in identifying AD compared with isolated CSF Aβ42 [18-20]. It is hypothesised that the CSF Aβ42/40 ratio lessens the interindividual variance as CSF Aβ40 is seen as a proxy for total Aβ, which may differ between individuals [21].

This systematic review investigates the biomarker potential of plasma Aβ. The focus is on Aβ42, Aβ40 and the Aβ42/40 ratio and their respective association with already established biomarkers of AD pathology; aPET positivity and CSF Aβ levels.

METHODS

PubMed was searched for articles for the systematic review using the terms listed in **Table 1**. The publication types of *Reviews* and *Clinical Trials* were excluded and only articles published from 2017-2021 with human species in English were included. This search yielded 185 articles.

TABLE 1 Terms used in PubMed for the searching of articles: "All fields", 15 November 2021.

Search	Filter	Reference
No. 1		
Alzheimer's disease *Or* Alzheimer's disease *Or* Alzheimer* *Or* AD	-	307284
No. 2		
abeta42 *Or* a beta 42 *Or* abeta-42 *Or* abeta40 *Or* a beta 40 *Or* abeta-40 *Or* abeta42/40 *Or* abeta42/40 ratio *Or* APP669-711 *Or* APP669-711/abeta42	-	7193
No. 3		
plasma	-	989687
No. 4		
No. 1 *And* No. 2 *And* No. 3	-	749
No. 5		
No. 4	((y_5[Filter]) *And* (humans[Filter]) *And* (English[Filter])) *Not* (Review[Publication Type]) *Not* (Clinical Trial[Publication Type])	185

After excluding articles about other biomarkers than Aβ and articles with no relevance to Aβ in plasma, 50 articles remained. The methods used in these 50 articles were reviewed and only articles in which the population of interest had undergone either lumbar puncture for the biomarker analyses of CSF or aPET (or both) were included in the current systematic review. This procedure left 14 articles for review. Apart from these 14 articles, three more were added by the reviewers during peer review, yielding a total of 17 included articles.

The PubMed search was conducted according to the PRISMA guidelines and a flow diagram including further exclusion reasons is presented in **Figure 1**.

FIGURE 1 PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only [22]. For more information, please see [23].
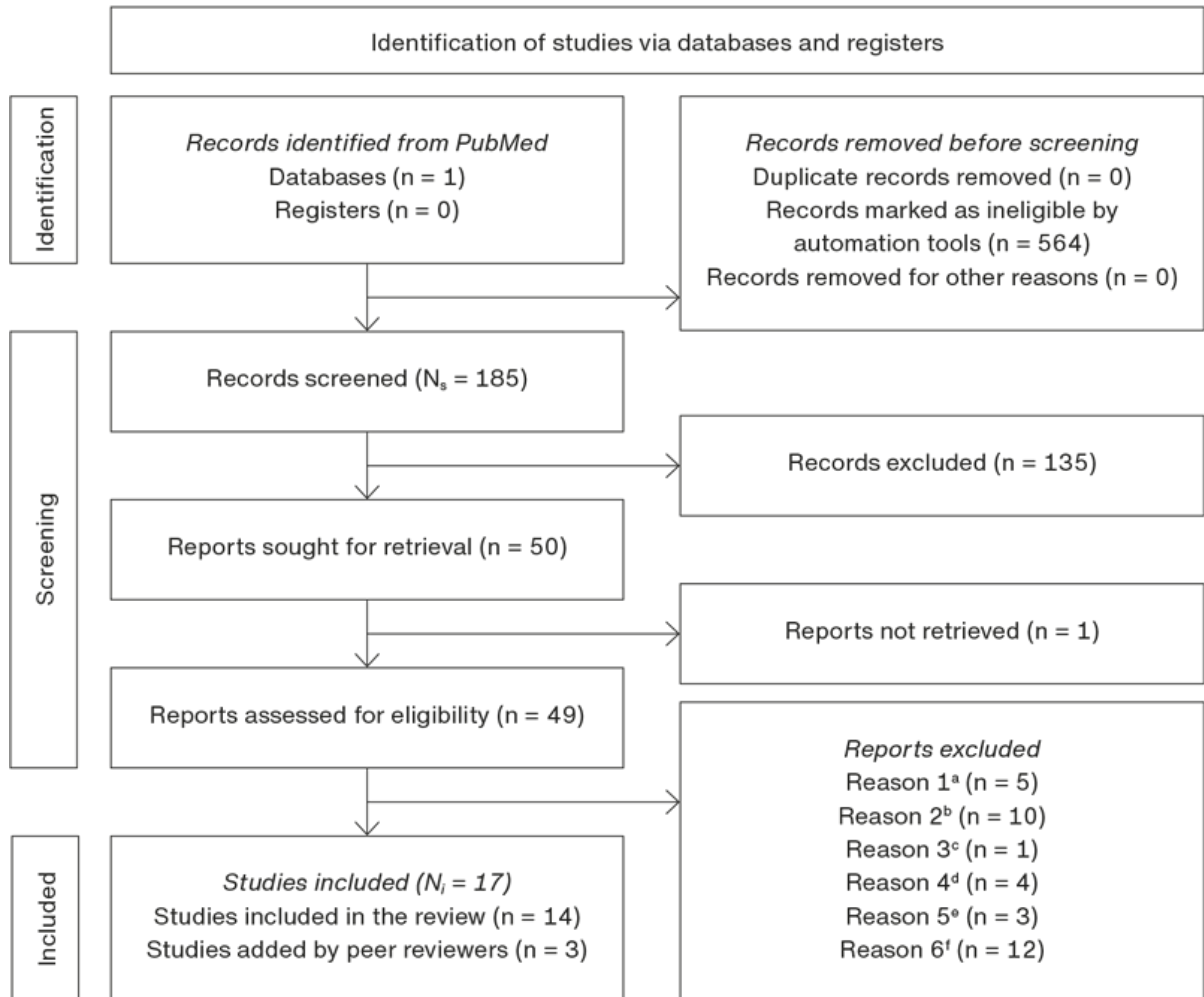
AD = Alzheimer's disease; aPET = amyloid PET; CSF = cerebrospinal fluid.
a) Other patient groups.
b) Not using either aPET or CSF.
c) Not published.
d) Mainly focused on assay technicalities.
e) Mainly focused on genetic aspects.
f) Inferior quality studies with unclear methods of AD diagnosis; mixtures of different cohorts; with a primary neuropsychological perspective, etc.

A meta-analysis was conducted including the studies reporting correlation coefficients describing the relationship between the Aβ42/40 ratio in plasma and the Aβ42/40 ratio in CSF or aPET. The meta-analysis was conducted in R version 4.2.1 using the *meta* package.

RESULTS

Plasma Aβ as an amyloid PET surrogate

Increased standardised uptake value ratio of the Aβ binding isotope demonstrated by aPET is a gold standard biomarker of AD [10]. Several studies have investigated the relationship between plasma Aβ and aPET.
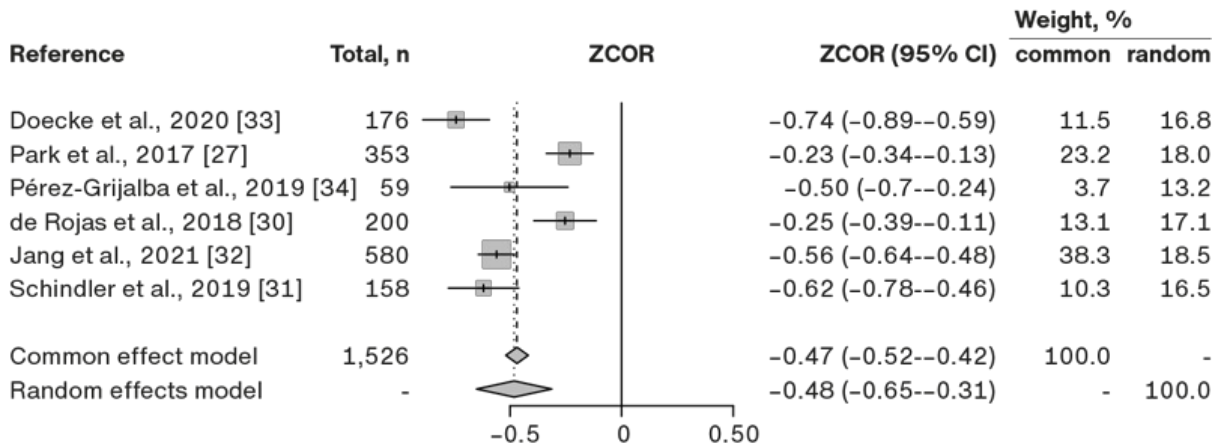
Plasma Aβ42 and Aβ40

It has been proposed that abnormal levels of isolated Aβ42 in plasma is the first detectable biomarker in AD [24]. Multiple studies have investigated both Aβ42 in CSF and plasma, and beta amyloid in senile plaques with aPET. In a study by Verberk et al., no relation was found between plasma Aβ40 and aPET; however, plasma Aβ42 levels were shown to be lowered in subjective cognitive decline (SCD: Subjects with a "self-perceived decline in any cognitive domain over time" [25]) patients (n = 69) with positive aPET compared with patients with negative aPET [26]. Contradicting this, in a study by Park et al. where plasma was treated with a mixture of phosphatase inhibitors and protease inhibitors (MPP-treated), MPP-treated plasma Aβ42 and Aβ40 levels were found to be higher in mild cognitive impairment (MCI: Subjects meeting the following criteria: a) memory complaints by oneself, an informant or a clinician; b) objective memory impairment; c) having largely intact functional activities; d) no dementia; e) No other cognitive disorder or medical condition affecting mental status [27]) patients with positive aPET scans compared with MCI patients with negative aPET scans [27]. Furthermore, aPET-positive subjects (consisting of cognitively normal subjects, MCI patients and AD patients) had significantly higher levels of MPP-treated plasma Aβ40 [27]. Other studies have found no association between Aβ42 and aPET [28-30].

Plasma Aβ42/40 ratio

Six studies conducted a correlation analysis between aPET positivity and low plasma Aβ42/40 ratio. The results of a meta-analysis of the correlation coefficients is shown in **Figure 2**, giving a random-effects model estimate of r = −0.48 (95% confidence interval (CI): −0.65-−0.31) with an of 90%. The substantial heterogeneity is underscored by the fact that point estimates differ much between studies with Doecke et al. and Schindler et al. reporting moderately negative correlations below −0.5 and de Rojas et al. and Park et al. reporting small negative correlations. Pérez-Grijalba et al. had the smallest sample of only 59 cases and thus reported wide CIs. The overall sample is too small for analysis for a possible publication bias.

FIGURE 2 Correlation between plasma beta amyloid plaques 42/40 ratio and amyloid PET positivity.

Reference	Total, n	ZCOR	ZCOR (95% CI)	Weight, % common	Weight, % random
Doecke et al., 2020 [33]	176		−0.74 (−0.89−−0.59)	11.5	16.8
Park et al., 2017 [27]	353		−0.23 (−0.34−−0.13)	23.2	18.0
Pérez-Grijalba et al., 2019 [34]	59		−0.50 (−0.7−−0.24)	3.7	13.2
de Rojas et al., 2018 [30]	200		−0.25 (−0.39−−0.11)	13.1	17.1
Jang et al., 2021 [32]	580		−0.56 (−0.64−−0.48)	38.3	18.5
Schindler et al., 2019 [31]	158		−0.62 (−0.78−−0.46)	10.3	16.5
Common effect model	1,526		−0.47 (−0.52−−0.42)	100.0	-
Random effects model	-		−0.48 (−0.65−−0.31)	-	100.0

CI = confidence interval; ZCOR = Fisher's z transformed correlation.
Heterogeneity: I^2 = 90%, τ^2 = 0.0383, $p < 0.01$.

In cognitively normal people, Schindler et al. found that aPET-positive subjects had a significantly lower level of plasma Aβ42/40 ratio than aPET negative subjects [31]. The correlation between low plasma Aβ42/40 ratio and aPET positivity is also seen in patients with SCD [26, 30] and in MCI patients [32, 35].

A single study found no significant difference in plasma Aβ42/40 ratio between aPET positive and negative patients [28].

Plasma Aβ as a cerebrospinal fluid Aβ surrogate
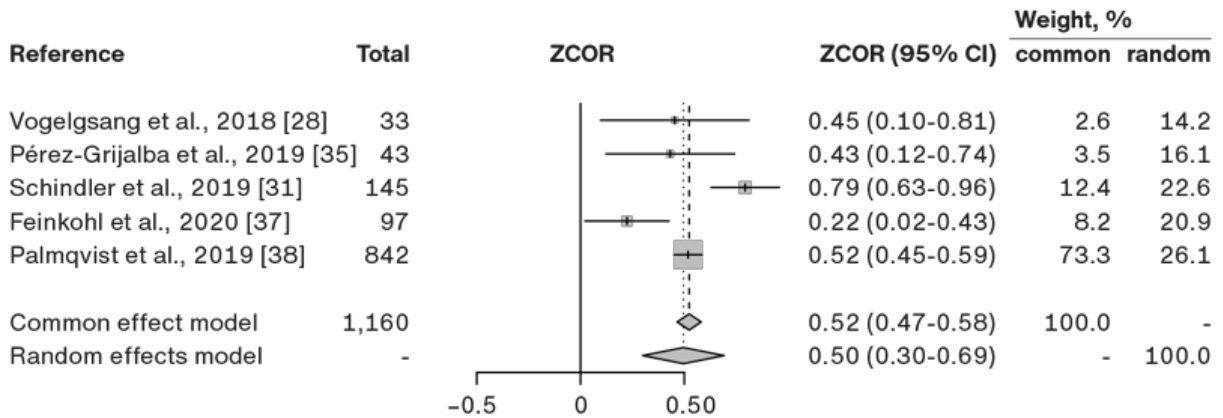
Plasma Aβ42 and Aβ40

In a study by Hanon et al. comparing subjects diagnosed with MCI and AD, a significant association was found between plasma and CSF levels of Aβ42 in both MCI patients and AD patients [36]. A positive association (r = 0.18, p < 0.001) was also found between plasma Aβ42 and CSF Aβ42 in SCD patients in a study by Verberk et al. They did not find a statistically significant association between plasma Aβ40 and CSF Aβ40 in the same study [26]. Feinkohl et al. found a significant but small association in AD patients and controls combined between plasma Aβ42 and CSF Aβ42 but an insignificant association with regards to Aβ40 [37]. In a study by Palmqvist et al. of cognitively unimpaired subjects with MCI and AD, both plasma Aβ42 and plasma Aβ40 were shown to be directly associated with CSF Aβ42/40 ratio [38].

In contrast, no significant correlation was found between either plasma Aβ42 or plasma Aβ40 and CSF levels in a combined study of patients with AD and demented controls without AD pathology [28].

Plasma Aβ42/40 ratio

Five studies reported correlations between Aβ42/40 ratio in plasma and CSF [28, 31, 35, 37, 38], and the results of the meta-analysis are shown in **Figure 3**. The random-effects model estimate is r = 0.50 (95% CI: 0.30-0.69) with an of 79%. Heterogeneity is high, but the largest study by Palmqvist et al. is more than five times larger than the second-largest study, and the smaller studies are more different from each other (Feinkohl et al. and Schindler et al.) or exhibit low precision (Vogelgsang et al. and Pérez-Grijalba et al.) so we may assign a higher confidence to the study by Palmqvist et al.; but considering only the Palmqvist et al. study, estimate r = 0.52 (95% CI: 0.45-0.59) is not significantly different from the meta-analytical estimate.

FIGURE 3 Correlation between plasma beta amyloid plaques 42/40 ratio and cerebrospinal fluid beta amyloid plaques 42/40 ratio.

Reference	Total	ZCOR	ZCOR (95% CI)	Weight, % common	Weight, % random
Vogelgsang et al., 2018 [28]	33		0.45 (0.10-0.81)	2.6	14.2
Pérez-Grijalba et al., 2019 [35]	43		0.43 (0.12-0.74)	3.5	16.1
Schindler et al., 2019 [31]	145		0.79 (0.63-0.96)	12.4	22.6
Feinkohl et al., 2020 [37]	97		0.22 (0.02-0.43)	8.2	20.9
Palmqvist et al., 2019 [38]	842		0.52 (0.45-0.59)	73.3	26.1
Common effect model	1,160		0.52 (0.47-0.58)	100.0	-
Random effects model	-		0.50 (0.30-0.69)	-	100.0

−0.5   0   0.50

CI = confidence interval; ZCOR = Fisher's z transformed correlation.
Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0373$, $p < 0.01$.

A positive correlation between plasma Aβ42/40 ratio and CSF Aβ42/40 ratio was seen in cognitively normal subjects [31] (r = 0.66 (95% CI: 0.56-0.75)) and in a group comprising AD patients and demented patients without AD pathology (r = 0.425, p = 0.014) [28].

Feinkohl et al. found positive associations between plasma Aβ42/40 ratio and CSF Aβ42/40 ratio, Aβ42 and Aβ40 in subjects with AD and in cognitively normal subjects [37]. The association between plasma Aβ42/40 ratio and CSF Aβ42 was also found in SCD subjects r = 0.38, p < 0.001 [26]. In the study by Pérez-Grijalba et al. of cognitively normal subjects and patients with probable MCI, it was also shown that plasma Aβ42/40 ratio is positively correlated to CSF Aβ42 levels (r = 0.549, p < 0.001) and negatively correlated to CSF tau levels (tTau r = −0.314, p = 0.031; pTau r = −0.329, p = 0.040) [35].

Plasma Aβ as a biomarker in Alzheimer's disease

Many studies investigating whether clinical AD and aPET positivity may be predicted by plasma Aβ have used different methodologies and analyses. The study of patients with MCI by Pérez-Grijalba et al. showed that during a follow-up time of two years, 52.4% of the MCI patients with a low plasma Aβ42/40 ratio (baseline below the median of the cohort) progressed to AD compared with 28.8% of the MCI patients with a high plasma Aβ42/40 ratio (baseline above the median of the cohort) [35]. The level of plasma Aβ42/40 ratio of the progressors was significantly lower than the level of non-progressors. This low plasma Aβ42/40 ratio level resulted in an approx. 70% increased risk among MCI patients of progressing to AD (hazard ratio (HR) = 1.687 (95% CI: 1.058-2.691), p = 0.028). Plasma Aβ42/40 ratio for discrimination between MCI progressors or non-progressors had a sensitivity and specificity above 70%, and a receiver-operating characteristic curve for the sensitivity/specificity trade-off had an area under the curve (AUC) of 0.857 [35].

Verberk et al. found an increased risk that SCD patients progressed clinically to MCI or AD if they had low levels of plasma Aβ42/40 ratio (HR = 2.31 (95% CI: 1.55-3.43)) or Aβ42 (HR = 1.74 (95% CI: 1.19-2.56)). Isolated plasma Aβ40 levels did not predict higher risk of progression from SCD to MCI or AD [26]. During a follow-up period, Schindler et al. found that cognitively normal patients who converted from aPET negative to aPET positive had lower baseline levels of plasma Aβ42/40 ratio (0.117 ± 0.008) than non-converters (0.128 ± 0.009), p < 0.01. A logistic regression model showed that aPET negative subjects with a low plasma Aβ42/40 ratio had a 15 times

increased risk of converting to aPET positivity than subjects with a high plasma Aβ42/40 ratio [31].

Several studies have investigated models combining plasma Aβ42/40 ratio and other covariates. In cognitively normal subjects (including SMC subjects), a model combining age, APOE &;4 allele and plasma Aβ42/40 ratio predicted current aPET positivity with an AUC of 0.776 [29]. Furthermore, an AUC of 0.855 was found (in a cohort of patients with AD, MCI, young and old controls, n = 510) by Jang et al. combining the same covariates. Interestingly, AUC rose to 0.916 when further adding the cognitive stage as a covariate [32]. Pérez-Grijalba et al. found AUCs of 0.957 and 0.814 in controls and MCI patients, respectively, when investigating the ability of unadjusted plasma Aβ42/40 ratio to predict aPET positivity. In the study by Feinkohl et al. comprising AD patients and controls, plasma Aβ42/40 ratio, Aβ42 and Aβ40 discriminated poorly between AD and controls with AUC values ≤ 0.58 [37].

DISCUSSION

Plasma Aβ as a future biomarker

Currently, the clinical diagnosis of probable AD relies on a combination of clinical examination and neuropsychological test batteries standardised by a revised version of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's criteria [11]. However, even experienced clinicians will occasionally reach incorrect diagnoses. Hence, a study by Li et al. found that 22.64% of the study subjects who were diagnosed with probable AD according to the NINCDS-ADRDA Alzheimer's criteria were aPET negative [11].

Different methods of measurement, diverse study populations and an incomplete knowledge of Aβ kinetics may complicate the united research on the subject. However, some patterns have been consistently demonstrated:

Plasma Aβ40: With the exception of an association between high MPP-treated plasma Aβ40 levels and aPET positivity in the study by Park et al. [27], the studies included in this systematic review all found no significant association of plasma Aβ40 with either aPET [26, 28-30] or CSF Aβ40 [26, 28, 37].

Plasma Aβ42: This biomarker has been suggested as the first detectable biomarker in plasma [24]. Some studies included in the present work have suggested an association between low plasma Aβ42 and low CSF Aβ42 [26, 36] or aPET positivity [26]. Other studies reported no association between plasma Aβ42 and aPET [28-30] or CSF Aβ42 [28].

Plasma Aβ42/40 ratio: The majority of results extracted from the included articles of this systematic review reported of an inverse association between plasma Aβ42/40 ratio and aPET positivity [11, 26, 27, 29, 30-35]. Only one of the included articles reported no association between plasma Aβ42/40 ratio and aPET positivity [28].

A direct association between plasma Aβ42/40 ratio and CSF Aβ42/40 ratio has been noted in some studies [28, 31]. However, other studies show a direct association between plasma Aβ42/40 ratio and CSF Aβ42 [26, 35, 37]. Plasma Aβ42/40 ratio has further been inversely associated with CSF tau levels. The high CSF tau levels combined with low CSF Aβ42 together constitute a typical AD profile [35].

Methods of measurement

The laboratory handling of measurements of plasma Aβ partly explains the observed variation in concentrations and ratios since detected differences in plasma Aβ are very small and not all processes have been automated [33]. The great variation in assays and technical methods of measuring plasma Aβ may hinder consistent validation of its potential as a plasma biomarker.

Study populations

The study populations in the included studies have comprised the entire spectrum of the AD continuum from cognitively normal controls to dementia. Plasma Aβ levels vary between cognitive stages, leading to different between-study concentrations and ratios. To validate the concept of plasma Aβ as an early biomarker predicting progression to AD, longitudinal studies of cognitively normal elderly people are warranted.

Aβ kinetics

It seems evident that Aβ originates from brain tissue. However, some portion of Aβ is also thought to originate from peripheral tissue [39]. In plasma, Aβ is met by several components such as protein-binding albumin, proteases, phosphatases, etc. [27]. These plasma components may very well be responsible for some of the conflicting results on plasma Aβ reported by different studies.

Summary, limitations and strengths

The forest plots on Figure 2 and Figure 3 illustrate the overall strength of the correlation between plasma Aβ42/40 ratio and aPET positivity ($r = -0.48$ (95% CI: -0.65--0.31)), and plasma Aβ42/40 ratio and CSF Aβ42/40 ratio ($r = 0.50$ (95% CI: 0.30-0.69)).

The studies included in the meta-analysis exhibited substantial heterogeneity, which limits the generalisability of the results and lowers the confidence in the meta-analytic model estimates. This may be due to the considerable variance in studies partly produced by the many different included subjects; cognitively unimpaired, MCI, AD patients, etc. However, the forest plots provide a visual summary of the individual studies and from a statistical point of view we can assign higher confidence in the more strongly powered and more precise studies and lower confidence in the smaller studies. The direction of the effects is consistent; plasma Aβ42/40 ratio is positively correlated with CSF Aβ42/40 ratio and negatively correlated with aPET.

None the less, even though the association between amyloid pathology and plasma Aβ42/40 ratio is generally solid, the robustness of Aβ42/40 ratio as a marker for AD pathology may be questioned due to the small fold changes between amyloid positivity versus negativity. Also, it should be mentioned that emerging methods for biomarker detection such as mass spectrometry have shown a potentially better performance than conventional immunoassays [40, 41], and several other biomarkers and biomarker combinations warrant further investigation. For instance, Janelidze et al. found that a combination of plasma Aβ42/40 ratio and plasma phosphorylated-tau217 in cognitively unimpaired subjects resulted in an AUC in the 0.83-0.86 range [42].

This systematic review has some weaknesses. The different study designs of the included studies prevent direct comparisons. The cognitive stages referred to in the studies are very similar. However, different definitions and cut-offs have been used. Measurements of plasma Aβ have been interchangeably referred to as plasma Aβ in this review even though some articles refer to the measures of total plasma Aβ (e.g., TP42/40 [35]). Lastly, the term aPET has been used interchangeably about PET assessing brain amyloidosis regardless of the cut-off values and type of tracer being used.

The greatest strength of this systematic review lies in the strict inclusion of studies in which subjects had been either examined by aPET or CSF biomarker analysis (or both).

The potential of a plasma biomarker

If a plasma biomarker of AD can be validated, it will probably reduce societal costs markedly as the need for aPET and CSF biomarker analyses will diminish, whereas the usage of these methods may be targeted where most relevant. It would potentially identify subjects with prodromal AD eligible for clinical trials, thus inducing a faster development of new treatments for AD. Lastly, it will enable general practitioners to identify patients at

risk of developing AD much earlier than is currently the case, using a simple blood sample. Given the epidemiology of AD and calculated risk of double prevalence within the next decades [43, 44], the importance of a valid, early and cost-efficient biomarker is high.

CONCLUSION

Most studies have found no significant association between plasma Aβ40 and aPET or CSF Aβ40. The studies of plasma Aβ42 have yielded somewhat contradictory results with some studies indicating an association with aPET and CSF Aβ42 and other studies showing no association.

The predictive potential of plasma Aβ42/40 ratio seems more promising. Plasma Aβ42/40 ratio is positively correlated with CSF Aβ42/40 ratio at r = 0.50 and negatively correlated with aPET at r = –0.48. There was substantial between-study heterogeneity, but the overall direction of these effects remains consistent. Some of the heterogeneity stems from differences in study population, laboratory and assay parameters.

Some studies have longitudinal follow-up and investigated how low CSF or plasma Aβ42/40 ratio predicts conversion to AD and report AUCs up to 0.86. However, larger longitudinal studies are required to fully characterise the diagnostic utility of plasma Aβ.

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