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A systematic review and meta-analysis of plasma amyloid 1-42 and tau as biomarkers for Alzheimer's disease

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Abstract

Objective: Amyloid 1-42 (Aβ42) and tau in cerebrospinal fluid are currently used as markers for diagnosis of Alzheimer's disease. Conflicting reports exist regarding their plasma levels in Alzheimer's disease patients. A meta-analysis was performed to statistically validate the use of plasma Aβ42 and tau as biomarkers for Alzheimer's disease.

Methods: Different databases were searched using the search key: (amyloid OR amyloid1-42 OR Aβ42) AND (tau OR total tau) AND plasma AND (alzheimer's OR alzheimer's disease), and for databases not accepting boolean search, records were retrieved using the search key: plasma + amyloid + tau + alzheimer's. A total of 1880 articles for Aβ42 and 1508 articles for tau were shortlisted. The abstracts were screened, and 69 articles reporting plasma Aβ42 levels and 6 articles reporting plasma tau were identified. After exclusion, 25 studies reporting plasma Aβ42 and 6 studies reporting total tau were analysed in Review Manager version 5.2 using weighted mean difference method, and the bias between studies was assessed using the funnel plot.

Results: Plasma Aβ42 and tau did not vary significantly between Alzheimer's disease patients and controls. The funnel plot showed that there was no bias between studies for Aβ42, while possible bias existed for tau due to availability of limited studies.

Conclusion: This analysis pinpoints that plasma Aβ42 and tau could not serve as reliable markers independently for diagnosis of Alzheimer's disease and a cohort study with age, sex and apolipoprotein E correction is warranted for their possible use as Alzheimer's disease markers.

Keywords

Meta-analysis, plasma Aβ42, plasma tau, tau-to-amyloid ratio, Alzheimer's disease, Review Manager

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Introduction

Alzheimer's disease (AD) is the most common form of dementia characterised by progressive decline in cognitive abilities of the affected individuals. The sporadic form of AD is the most common form constituting up to 98% of the total AD patients.[1] Amyloid 1-42 (Aβ42) plaques and neurofibrillary tangles (NFT) play a pivotal role in the aetiology of AD, and it has been identified that pathological changes in AD manifest decades before appearance of clinical symptoms.[2] Hence, biological markers are essential to identify individuals at early stages of the disease for timely therapeutic intervention.

The current methods that are used in AD diagnosis are magnetic resonance imaging (MRI), positron emission tomography (PET) and biomarkers in cerebrospinal fluid (CSF) via lumbar puncture. The validity of these methods is very limited since they are expensive, invasive or time-consuming. Thus, there is an urgent need for less invasive and affordable blood-based biomarker that can aid in large-scale screening of AD patients. CSF Aβ42 and total tau are used as biomarkers for AD. Several longitudinal studies and meta-analysis reports have indicated decreased Aβ42 and elevated tau levels in CSF of AD patients compared to healthy controls.[3–7] Conflicting reports exist on plasma Aβ42 levels,[1,8,9] and only few studies report the status of plasma

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tau in AD patients.[10–12] Therefore, using the experimental reports available in the literature, a meta-analysis on plasma levels of Aβ42 was performed, along with plasma tau, in AD patients and compared with age-matched healthy controls. The study would help to validate the potential use of plasma Aβ42 and tau as biomarkers for AD diagnosis.

Methods

Source of data

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) protocol.[13] An extensive literature search on journal databases (PUBMED, Oxford, Science Direct, Cell, HighWire, PNAS, Springer, Nature, IOS, Wiley and Google Scholar) for articles published during 1975–2014 was performed using keywords: (amyloid OR amyloid1-42 OR Aβ42) AND (tau OR total tau) AND plasma AND (alzheimer's OR alzheimer's disease). For databases not accepting Boolean search, articles were retrieved using search key: plasma + amyloid + tau + alzheimer's and Plasma, Alzheimer's disease, Biomarkers, Amyloid, tau. The articles were analysed and included for meta-analysis based on the following inclusion criteria:

- Cross-sectional studies and longitudinal studies reporting the first time point values
- Studies reporting mean, median and range ± SD or SE for both control and Alzheimer's patients;
- Total sample size >20.

If a study reported the levels of Aβ42 and tau through other means of central tendency (Median, quartile, percentile), the values were converted to mean ± standard deviation using formulas specified by Hozo et al.[14] and included for the analysis

Statistical analysis

Analysis was performed using Review Manager (RevMan) version 5.2 with weighted mean difference (WMD) and random effect model to calculate the consolidated outcome of the included studies. WMD accounts for the pooled difference of mean values between AD and controls of different studies on a weighted scale of measurement. The funnel plot was used to calculate the bias among studies. An approximate symmetrical plot indicates lack of bias while an asymmetrical plot indicates a difference between the studies. The I^2 value was used to assess the heterogeneity between the different studies.

Results

This review describes the overall status of plasma Aβ42 and tau level in AD patients when compared to healthy controls reported in the literature. To further validate their use as biomarkers, baseline levels in AD cross-sectional studies and initial (first time) data of longitudinal studies were included in the study, and follow-up data from the longitudinal study were excluded. Since the objective of the study is to analyse AD-specific biomarkers, data from studies reporting other types of dementia were excluded.

A total of 6,102,294 articles were retrieved from different databases using the specified key word search for Aβ42 and total tau (Figure 1). Screening of the titles of retrieved articles resulted in short-listing of 1880 records pertaining to amyloid and 1508 records for tau in AD. The abstracts and full texts of these articles were further screened, and a total of 69 studies for Aβ42 and 6 studies for tau were identified. Based on the inclusion criteria, a total of 25 articles for Aβ42 (AD: n = 1542; Controls: n = 2142; Table 1) and 6 for total tau (AD: n = 279; Controls: n = 322; Table 2) were included for the analysis.

Plasma Aβ42 and Tau did not vary significantly between AD and controls

In the present meta-analysis, no significant difference was observed for plasma Aβ42 (Figure 2(a)) between AD patients and controls (WMD: 0.80, 95% confidence interval (CI): −1.89 to 3.50, z = 0.58 and p = 0.56). The funnel plot indicated no bias between the studies (Figure 3(a)). The I^2 value of 98% indicates that the studies are highly heterogeneous. Plasma tau levels also did not vary significantly (Figure 2(b)) in AD patients (WMD: −7.21, 95% CI: −28.91 to 14.49, z = 0.65 and p = 0.51) compared to controls. The funnel plot had an asymmetrical shape indicating bias between the studies (Figure 3(b)) with a high heterogeneity (I^2 value) of 98%.

Discussion

β-amyloid (Aβ) peptides play a key role in the aetiology of AD. Two predominant forms of Aβ peptides (Aβ40 and Aβ42) are generated from the cleavage of amyloid precursor protein (APP) by the action of β and γ secretases.[35] Aβ42 is more pathogenic than Aβ40 since it aggregates more rapidly and deposits much earlier than Aβ40.[36] Hence, Aβ42 would serve as a better diagnostic marker for AD. Evidences also indicate that Aβ40 and Aβ42 are rapidly cleared from the central brain into peripheral circulation.[1,24,37] Therefore, valuating their plasma levels would also help in identifying the severity of the disease.

A meta-analysis of this study revealed an insignificant variation in plasma Aβ42 levels between AD patients and controls. Conflicting reports exist regarding the status of plasma Aβ42 in AD with many studies reporting an increase,[2,10,15] decrease[22] or no change[4,24,28] when compared to controls. A meta-analysis of plasma Aβ40 and Aβ42 reported by Song et al.[9] concluded that patients with mild

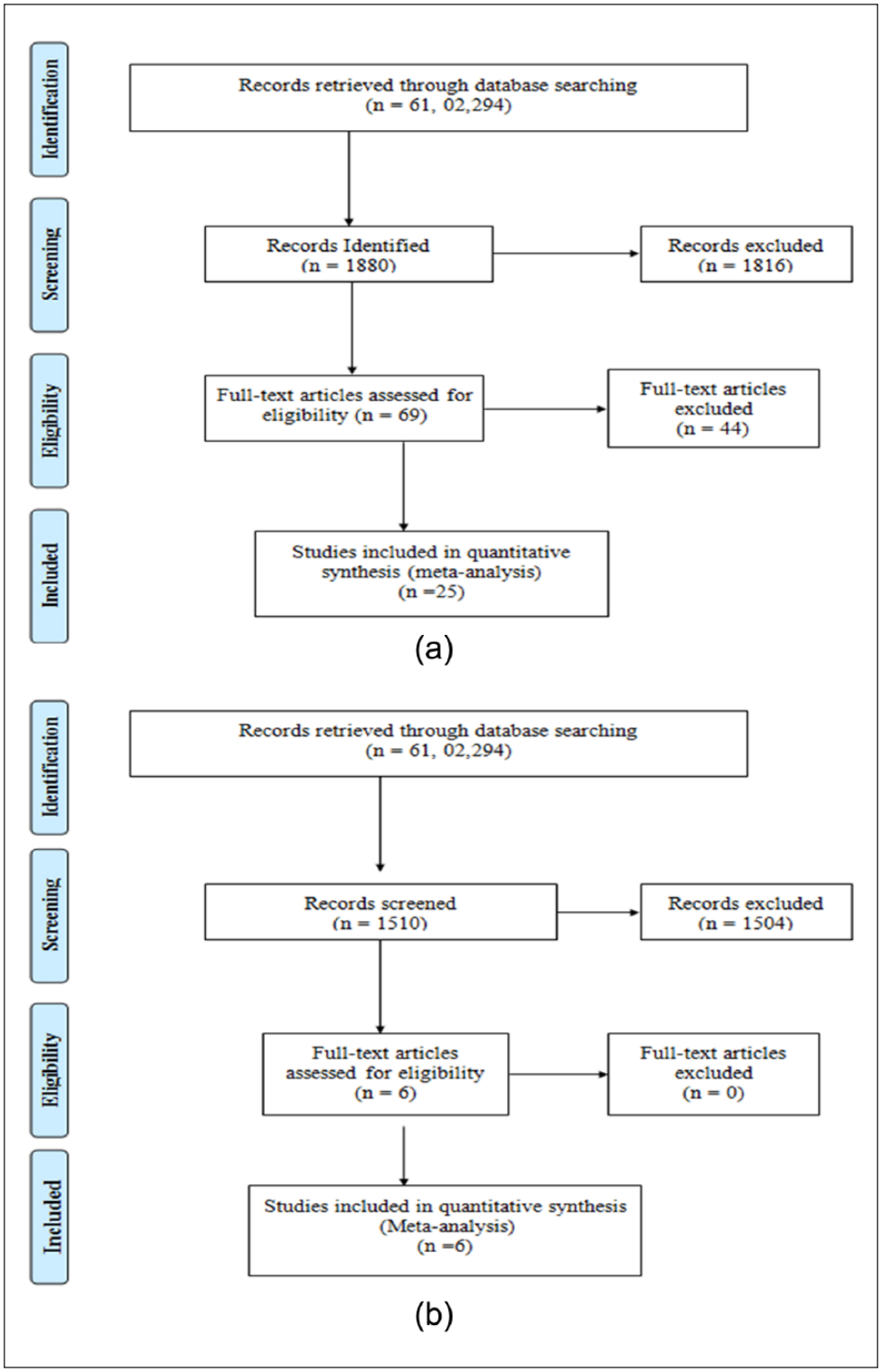

Figure 1. Data retrieval process for meta-analysis of (a) plasma Aβ42 and (b) total tau as markers for AD diagnosis.

AD-like symptoms had higher baseline Aβ42 levels, while AD patients reported marginally lower Aβ42 levels. Many studies have also reported that lower plasma Aβ42/Aβ40 ratio[24,38–40] and elevated oligomeric Aβ[28] could increase the risk of development of AD.

The status of Aβ peptides in plasma is governed by various factors. Age, sex and apolipoprotein E (APO E) status are reported to regulate the levels of Aβ peptides in plasma.[1,18,20] Fukumoto et al.[20] indicated that the elevation of Aβ levels in plasma is mainly due to age and is irrespective

Table 1. Characteristics of studies used for analysis of plasma Aβ42 levels in AD.

Study	Subjects (N)	Male	Female	Age[a]	Plasma Aβ42 levels[a] (pg/mL)	APO E (%)	MMSE[a]	Method
Tamaoka et al.[15]	AD (28)	#	#	73.8 ± 8.9	276.7 ± 115.1	#	#	ELISA (antibody: BAN50/BC05)
	Controls (25)			64.5 ± 9.2	194.6 ± 106.1			
Kosaka et al.[16]	AD (44)	#	#	71.9	44.2 ± 14.9	#	#	ELISA (antibody: BNT77/BC05)
	Controls (15)			72.3	48.3 ± 9.5			
Mayeux et al.[17]	AD (64)	#	#	77.4 ± 5.9	82.4 ± 68.8	#	#	ELISA (antibody: 6E10/R165)
	Controls (105)			73.4 ± 5.3	51.5 ± 42.1			
Mehta et al.[18]	AD (78)	39	39	74 ± 11	262.7 ± 270.1	66.6	15 ± 7.8	ELISA (antibody: 6E10/R226)
	Controls (61)	27	34	67 ± 12	273.0 ± 277.2	21.3	29.5 ± 0.9	
Arvanitakis et al.[19]	AD (220)	#	#	74.9 ± 7.8	92.5 ± 106.1	#	#	ELISA (antibody: BAN50/BC05)
	Controls (59)			77.7 ± 7.6	85.3 ± 88.5			
Fukumoto et al.[20]	AD (146)	66	80	76.0 ± 8.2	33.4 ± 24.2	3.8	#	ELISA (Takeda Pharmaceuticals, Japan)
	Controls (92)	37	55	69.4 ± 10.3	31.6 ± 14.0	1.1		
Sobów et al.[21]	AD (54)	17	37	77.5 ± 4.4	37.8 ± 10.3	#	17.5 ± 3.4	ELISA (Biosource International Inc., USA)
	Controls (35)	11	24	75.0 ± 2.9	36.3 ± 6.3		29.5 ± 0.6	
Pesaresi et al.[22]	AD (146)	35	111	73.7 ± 7.6	38.0 ± 13.0	29.0	18.0 ± 5.1	ELISA (Innogenetics Ltd, Belgium)
	Controls (89)	32	57	68.2 ± 12.0	52.0 ± 22.0	5.5	27.1 ± 2.4	
Kulstad et al.[23]	AD (59)	#	#	71.4 ± 1.0	31.2 ± 25.3	#	#	ELISA (Signet Laboratories, USA)
	Controls (50)			70.5 ± 1.1	41.8 ± 25.4			
Abdullah et al.[24]	AD (67)	32	35	76.1 ± 7.8	24.5 ± 4.2	#	18.0 ± 8.2	ELISA (Invitrogen, USA)
	Controls (146)	64	82	74.1 ± 8.3	5.6 ± 3.7		29.0 ± 1.0	
Giedraitis et al.[25]	AD (39)	22	17	65.9	97.5 ± 86.2	44.5	#	ELISA (Takeda Pharmaceuticals)
	Controls (18)	5	13	65.9	114.7 ± 124.6	27.8		
Fagan et al.[6]	AD (16)	28	62	75.2	36.0 ± 37.2	#	#	ELISA (antibody: m266/m21F12)
	Controls (65)	8	8	73.3	36.0 ± 29.4			
Sedaghat et al.[26]	AD (29)	11	18	71.0 ± 9.0	17.6 ± 2.6	#	15.0 ± 9.0	ELISA (Innogenetics Ltd)
	Controls (16)	5	11	64.0 ± 8.0	13.4 ± 1.4			
Bastard et al.[27]	AD (48)	17	32	82.0 ± 2.3	41.1 ± 5.2	#	16 (13–19)	ELISA (Innogenetics Ltd)
	Controls (29)	21	18	66.0 ± 6.3	38.7 ± 4.3		28 (27–30)	
Roher et al.[1]	AD (17)	7	10	81.3 ± 5.2	139.9 ± 77.8	#	22.2 ± 3.7	ELISA (Innogenetics Ltd)
	Controls (21)	7	14	75.8 ± 7.1	124.7 ± 42.3		28.9 ± 1.4	
Buerger et al.[4]	AD (17)	#	#	70.2 ± 10.6	20.0 ± 8.0	#	23.0 ± 3.3	ELISA (Innogenetics Ltd)
	Controls (15)				24.0 ± 7.0		29.0 ± 0.7	
Cosentino et al.[8]	AD (70)	23	47	80.8	46.3 ± 29.1	#	#	(Antibodies: 6E10/R165) ELISA
	Controls (481)	159	322	74.5	43.8 ± 27.3			
Zhou et al.[28]	AD (44)	9	35	77.5 ± 9.2	10.9 ± 5.5	29.5	16.5 ± 7.2	ELISA (Invitrogen)
	Controls (22)	12	10	72.5 ± 8.0	9.6 ± 4.0	18.2	27.7 ± 2.1	
Uslu et al.[29]	AD (28)	10	18	68.3 ± 6.7	10.3 ± 2.3	#	19.0 ± 1.1	ELISA (Biosource International Inc.)
	Controls (26)	10	13	66.6 ± 9.7	29.4 ± 10.2		26.2 ± 1.3	
Pesini et al.[2]	AD (15)	8	8	70.3 ± 4.1	186.3 ± 227.3	62	#	ELISA (Araclon Biotech, Spain)
	Controls (16)	8	8	78.8 ± 4.7	98.8 ± 24.4	6		
Rembach et al.[30]	AD (125)	#	#	78.0 ± 7.8	34.3 ± 10.9	#	19.3 ± 5.3	INNO-BIA plasma Ab forms assays (Innogenetics NV, Belgium
	Controls (577)			69.0 ± 6.8	33.8 ± 10.0		28.9 ± 1.1	
Krishnan and Rani[10]	AD (30)	16	14	71.0 ± 8.7	164.6 ± 66.7	#	4.0 ± 3.8	ELISA (CUSABIO, China)
	Controls (40)	22	18	65.2 ± 9.3	86.1 ± 43.7		28.1 ± 1.6	
Wang et al.[31]	AD (122)	54	43	73.7 ± 8.4	47.5 ± 1.9	#	28.5 ± 1.3	Invitrogen, number: KHB3442
	Controls (97)	56	66	73.7 ± 9.4	47.1 ± 2.2		17.8 ± 7.5	
Swaminathan et al.[32]	AD (22)	15	7	74.0 ± 9.0	36.0 ± 9.1	63.0	#	#
	Controls (22)	14	8	77.1 ± 6.1	36.0 ± 9.1	27.0		
Tzen et al.[33]	AD (14)	10	4	64.9 ± 11.5	18.9 ± 0.3	64.2	20.7 ± 4.6	Immunomagnetic
	Controls (20)	10	10	63.7 ± 7.9	15.9 ± 0.3	25.0	29.0 ± 1.1	Reduction

AD: Alzheimer's disease; APO E: apolipoprotein E; MMSE: mini–mental state examination.
[a]Values are expressed as mean ± standard deviation.
#Data not reported.

Table 2. Characteristics of studies used for analysis of plasma tau levels in AD.

Study	Subjects (N)	Male	Female	Age[a]	Plasma tau levels[a] (pg/mL)	APO E	MMSE[a]	Method
Sparks et al.[11]	AD (49)	26	23	84.4 ± 7.7	530.4 ± 193.6	#	#	ELISA, (Invitrogen, USA) Western blot (antibodies: Tau7/Tau12)
	Controls (110)	4	6	78.5 ± 7.3	819.5 ± 294.4			
Zetterberg et al.[12]	AD (54)	17	37	75 ± 6.5	8.8 ± 10.1	#	19 ± 4.9	Digital Array Technology (antibodies: Tau5/BT5-HT7)
	Controls (25)	6	19	74 ± 6.7	4.4 ± 2.8		29 ± 1.4	
Krishnan and Rani[10]	AD (30)	16	14	71.0 ± 8.7	458.6 ± 253.8	#	4.0 ± 3.8	ELISA (CUSABIO, China)
	Controls (40)	22	18	65.2 ± 9.3	879.1 ± 389.5		28.1 ± 1.6	
Wang et al.[31]	AD (122)	54	43	73.7 ± 8.4	214.9 ± 43.2	#	28.5 ± 1.3	Invitrogen, number: KHB0042
	Controls (97)	56	66	73.7 ± 9.4	213.9 ± 44.5		17.8 ± 7.5	
Chiu et al.[34]	AD (10)	6	4	69.3 ± 9.4	53.9 ± 11.7	50	22.7 ± 3	Immunomagnetic
	Controls (30)	17	13	64.4 ± 9.5	15.6 ± 6.9	27	28.8 ± 1.6	Reduction
Tzen et al.[33]	AD (14)	10	4	64.9 ± 11.5	46.7 ± 2.0	64.2	20.7 ± 4.6	Immunomagnetic
	Controls (20)	10	10	63.7 ± 7.9	13.5 ± 5.5	25	29.0 ± 1.1	Reduction

AD: Alzheimer's disease; APO E: apolipoprotein E; MMSE: mini–mental state examination.
[a]Values are expressed as mean ± standard deviation.
#Data not reported.

of the disease stage. All the studies in this analysis (Table 1) used age-matched controls, representing both males and females. Hence, the observed variation and heterogeneity in some studies included in the analysis could not be due to ageing and may be associated with other factors involved in the disease pathogenesis. APO E isoforms also play a role in the clearance of Aβ peptides across the blood–brain barrier (BBB) and transport of Aβ peptides between different brain compartments.[41,42] Although many reports indicate that plasma Aβ levels are higher in people with APO E ε4 allele, Mehta et al.[18] observed that the plasma Aβ42 levels were similar in controls and AD patients with ε4 and other allelic forms of APO E. In most of the studies included in the analysis, the plasma Aβ levels with respect to APO E allelic variation were not reported. The difference in the levels of Aβ in the studies included in the analysis could also be attributed to variability in sample storage and processing, sensitivity and specificity of the antibodies and kits employed for analysis. Buerger et al.[4] reported that frozen plasma and CSF samples render greater diagnostic accuracy than fresh samples in a multi-centric context, and Abdullah et al.[24] reported the presence of high intra- and inter-person variability, possibly due to factors that influence peripheral Aβ levels.

Apart from the brain, the source for Aβ peptides in plasma are skeletal muscles, platelets and vascular walls.[43–45] The other tissues that express APP include pancreas, kidney, spleen, heart, liver, testis, aorta, lung, intestines, skin, as well as the adrenal, salivary and thyroid glands which contribute to the peripheral pool of Aβ peptides.[1] The transport of Aβ peptides from brain to blood and vice versa, across the BBB also influences the plasma Aβ levels. The Aβ peptides present in the brain are cleared into the systemic circulation by low-density lipoprotein receptor–related protein (LRP1) at the BBB.[46] Down-regulation of LRP1 can cause abnormal build up of Aβ peptides in the brain, thereby promoting aggregation and neurodegeneration. Also, Aβ42 is cleared less efficiently than Aβ40 peptides by LRP1,[47] increasing the level of Aβ40 in plasma compared to Aβ42.

The Aβ peptides are also transported into the brain through the receptor for advanced glycation end products (RAGE).[46] Hence, the transport of Aβ peptides across the BBB is governed by the synergistic expression of LRP1 and RAGE. Studies have reported that the expression of RAGE is increased and LRP1 is decreased in patients with AD,[46,48,49] favouring increased transport of the peptides from blood to the brain and promoting aggregation. Moreover, the G82S polymorphism in the RAGE ligand–binding domain increases BACE1 expression, leading to overproduction of Aβ42 in the brain.[50] The amino acid change also increases glycosylation of RAGE at N81 residue which in turn increases the affinity of Aβ towards RAGE,[51] thereby decreasing Aβ42 levels in plasma and further alleviating AD pathology. The hepatic clearance of Aβ peptides by LRP1 also reduces the levels of the peptides in blood.[52] Faulty clearance of these peptides by LRP1 may also increase its levels in blood and contribute to Aβ accumulation in brain.

Since these factors influence plasma Aβ status, the use of plasma Aβ as a diagnostic marker for AD is limited and has to be accompanied with its corresponding levels in CSF. In a meta-analysis of plasma Aβ by Song et al.,[9] plasma Aβ levels were reported to be marginally lower, but statistically insignificant, in AD patients compared to controls. The study also indicated that cognitively normal individuals with higher baseline Aβ levels in plasma are at increased

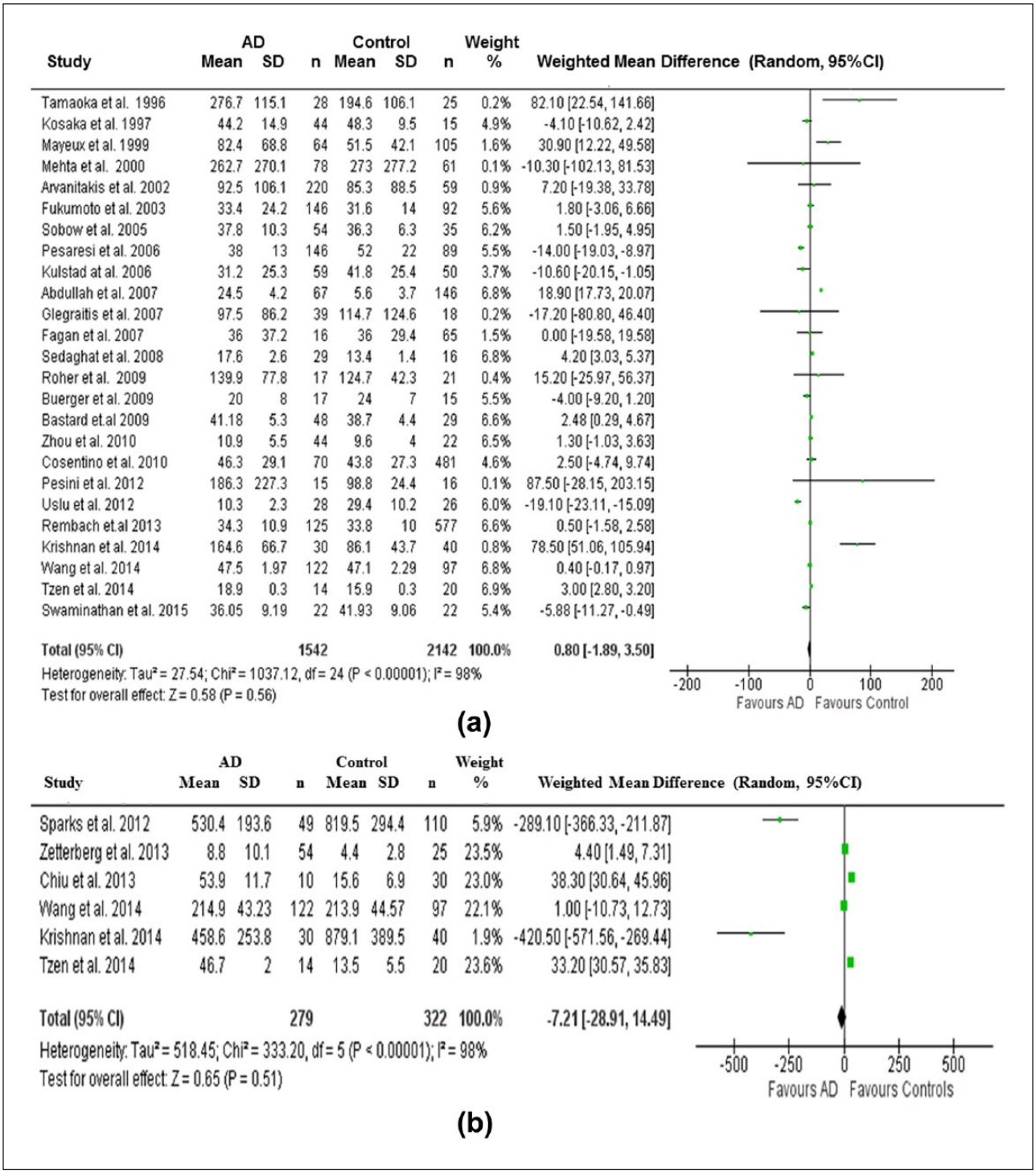

Figure 2. Forest plots for (a) plasma Aβ42 and (b) total tau in AD patients compared to controls. The figure indicates the mean and SD (pg/mL) along the weighted mean difference and 95% confidence interval of each study included in the meta-analysis.

risk of developing AD in later stages of life. This analysis also indicates a statistically insignificant variation in plasma Aβ levels in AD patients compared to controls which indicate that baseline plasma Aβ levels may not be a good indicator of the disease condition.

NFT is also a characteristic feature of AD which occurs due to abnormal phosphorylation of tau protein. While several studies report elevated CSF levels of total tau and phosphorylated tau in AD patients[3,53,54] compared to controls, limited reports exist on plasma levels of tau in AD. Hence, a meta-analysis was done to validate the use of plasma tau as

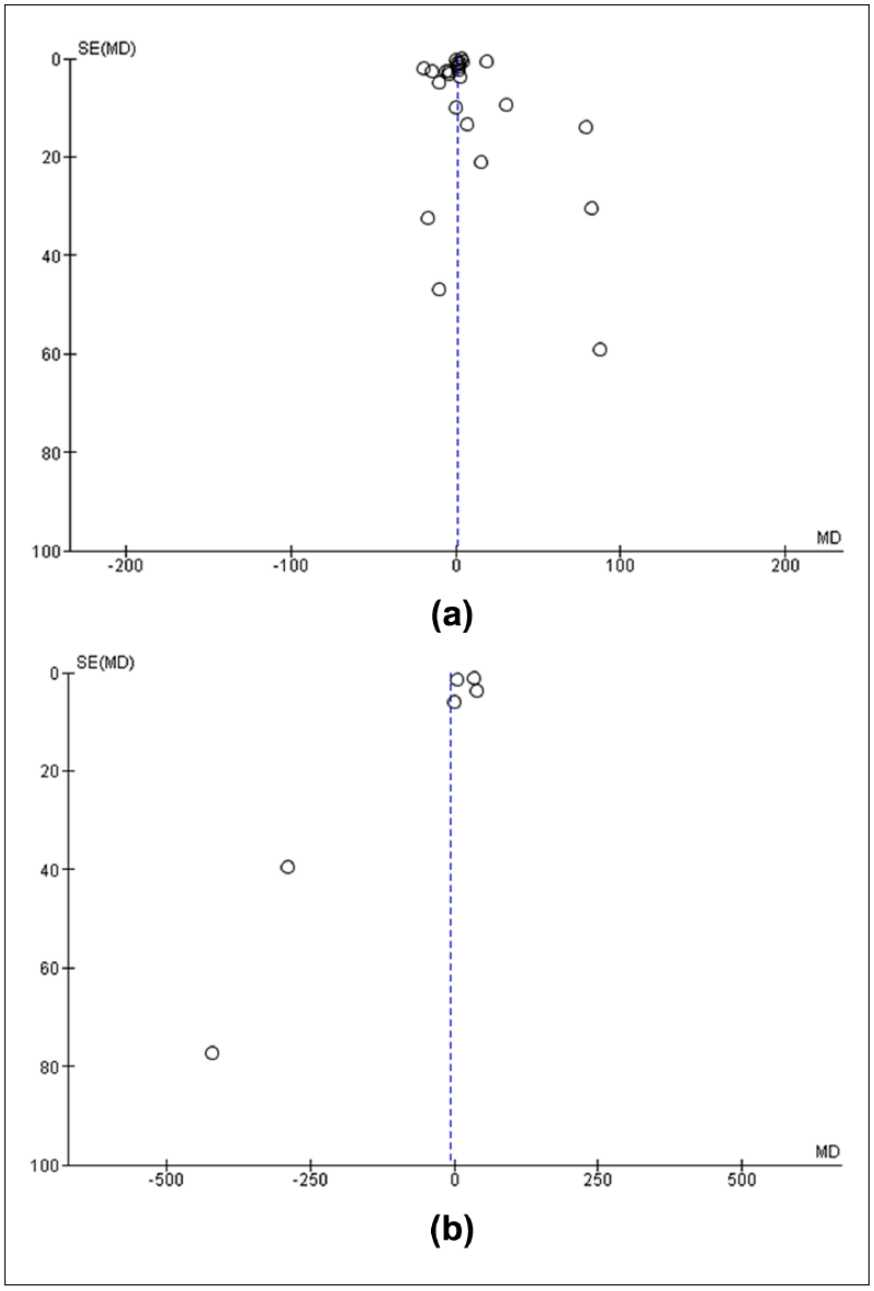

Figure 3. Funnel plots of (a) plasma Aβ42 and (b) total tau in AD patients.

AD marker. The result of the analysis revealed an insignificant variation in plasma tau levels in AD patients indicating that plasma tau may not be used as an AD marker.

The measurement of Aβ and tau in plasma poses an immense challenge than their measurement in CSF. Since Aβ levels in plasma is almost 10-fold lower than the CSF,[9] methods with high sensitivity, specificity and reproducibility should be employed for quantification. For plasma Aβ measurement, most studies utilised ELISA-based methods with sensitivity in the range of 10–70 pg/mL and specificity <0.1%. The funnel plot (Figure 3) also indicated that there is minimal bias between the studies used in the analysis. However, possible bias and heterogeneity for plasma tau were observed (Figure 3(b)) between the different studies, with some studies reporting an increase,[12,33,34] decrease[10,11] and no change[31] in AD patients. The difference in plasma tau levels between the studies could be primarily attributed to the sensitivity of the analytical method employed. Plasma tau was estimated using different immunoassays like ELISA, digital array technology and immunomagnetic reduction technology wherein the sensitivity of detection ranges from 0.02 to 12 pg/mL. In this analysis, when studies that used ELISA-based quantification were considered, plasma tau was decreased in AD patients

(WMD: −228.91, 95% CI: −488.67 to 30.89, z = 1.73, p = 0.08) compared to controls. However, after incorporation of reports which employed a more sensitive method for detecting plasma tau, no significant variation was observed between AD and controls. This meta-analysis clearly indicates that a large-scale study employing methods with high sensitivity to measure plasma tau is warranted, and reports also indicate that estimation of tau in plasma is still in its experimental stage.[11,12]

The results of this analysis indicate that both plasma Aβ42 and tau independently cannot be used as a marker to diagnose AD. In our previous study, we reported receiver operator characteristic (ROC) curves for Aβ42 and tau, indicating that they may not serve as markers for AD diagnosis independently, whereas their ratio (tau-to-amyloid) could serve as a potential marker for the diagnosis of AD.[10] Kapaki et al.[7] and Fagan et al.[6] also reported the use of CSF tau-to-amyloid ratio as a useful marker for the diagnosis of AD. Since the levels of Aβ and tau are also influenced by factors like age, sex, APO E status and method of analysis, a thorough validation taking the baseline correction of these factors into account would help in determining the usefulness of Aβ, tau and tau-to-amyloid ratio as possible markers for AD.

Conclusion

This review using meta-analysis reveals a statistically insignificant variation in plasma Aβ42 and tau in AD patients compared to controls indicating that both plasma Aβ42 and tau may not be used as a marker for AD diagnosis. A cohort study, with age, sex and APO E correction, is warranted for their possible use as markers for AD diagnosis.

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Declaration of conflicting interests

The authors declare no conflict of interest in preparing this article.

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