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Medical Histories of Control Subjects Influence the Biomarker Potential of Plasma Aβ in Alzheimer's Disease: a Meta-analysis

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Abstract

Whether blood amyloid-β (Aβ) could be a peripheral biomarker of Alzheimer's disease (AD) remains in dispute. In the present study, we conducted a meta-analysis with 19 citations searched from Embase, PubMed, and the Cochrane Library database. Weighted mean difference (WMD) with 95% confidence intervals (CIs) was used to estimate the effect size. We firstly analyzed the plasma $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{42}/A\beta_{40}$ ratio in AD and control group subjects. However, only a lower level of plasma $A\beta_{42}$ was figured out in AD group subjects with weak statistical significance (WMD 1.82; 95% CI 0.59, 3.06; $P = 0.004$; $I^2 = 84\%$). We considered that the medical histories of control subjects could influence the biomarker ability of plasma Aβ. Therefore, subgroup analyses were then carried out based on a new recruiting criterion for control subjects, defining as no afflictions of any Aβ-related diseases. Surprisingly, AD group subjects showed a significant decrease in plasma $A\beta_{42}/A\beta_{40}$ ratio with low heterogeneity among studies (WMD 0.02; 95% CI 0.02, 0.02; $P < 0.00001$; $I^2 = 0\%$). Moreover, not only the $A\beta_{42}/A\beta_{40}$ ratio but also $A\beta_{42}$ and $A\beta_{40}$ were indifferent between AD and pseudo-control subjects which might be afflicted with Aβ-related diseases. This meta-analysis demonstrated that medical histories of control subjects were interference factors impeding plasma Aβ to be a biomarker of AD.

Keywords Alzheimer's disease (AD) · Biomarker · Amyloid-β · Meta-analysis

Introduction

It was estimated that about 131.5 million people would suffer from dementia worldwide by 2050 from 46 million at present, in which Alzheimer's disease (AD) patients is the most common cohort (Fei et al. 2011). However, finding a peripheral biomarker to diagnose and estimate the development of AD is still a challenge. Amyloid-β (Aβ) is the principal pathogenic factor of AD (Rissman et al. 2012). It can be detected in various body fluids including cerebrospinal fluid (CSF) and plasma (Mehta et al. 2000; Nascimento et al. 2015). Thus, Aβ is considered as a promising candidate for AD biomarkers (Andreasen and Zetterberg 2008; Frankfort et al. 2008).

Although some clinical trials have been performed to evaluate the biomarker potential of plasma or CSF Aβ in AD (Shoji and Kanai 2001; Waragai et al. 2012), the controversy was still unsettled (Guo et al. 2013; Chouraki et al. 2015). The failure of monoclonal Aβ antibodies treatment even adversely affected the Aβ hypothesis of AD (Doody et al. 2014). These problems increase the difficulty of biomarker research focusing on Aβ peptide. However, how can we explain the pathological changes and toxic effects of Aβ aggregation in the brain of AD patients? Are there any other factors influencing the fact of Aβ peptide as a biomarker?

Imaging studies demonstrated that Aβ production had occurred long before the onset of cognitive impairment (de Leon et al. 2007). Also, some diseases can increase the production of amyloid precursor protein (APP) and Aβ, such as epilepsy (Sima et al. 2014), multiple sclerosis (Augutis et al. 2013), cerebrovascular diseases (ElAli et al. 2013; Liang et al. 2015), chronic heart failure (Greco et al. 2017), chronic hepatic (Wang et al. 2017), and renal insufficiency (Gronewold et al. 2016). However, the definition of control subjects was still not comprehensive in some clinical studies of AD biomarkers. Some subjects affected by Aβ-overproduced diseases were classified into the control group because of their normal cognitive phenotype. Based on these phenomena, we hypothesized that the medical history of control subjects

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might be a determinant confusing the results of AD biomarker studies.

Compared with CSF testing and other methods like functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), plasma detection is more acceptable because of its lower cost and less trauma. Thus, we collected 19 clinical trials of plasma Aβ for meta-analysis (Tamaoka et al. 1996; Fukumoto et al. 2003; Sobow et al. 2005; Abdullah et al. 2007; Corzo et al. 2007; Fagan et al. 2007; Giedraitis et al. 2007; Ait-ghezala et al. 2008; Lui et al. 2010; Akatsu et al. 2011; Chiu et al. 2012; Han et al. 2012; Zhang et al. 2013; Rembach et al. 2014; Richens et al. 2014; Tzikas et al. 2014; Wang et al. 2014; Janelidze et al. 2016, and Poljak et al. 2016). The aim was to clarify whether the Aβ-related medical histories of control subjects obstructed the plasma Aβ to be a biomarker of AD.

Methods

Search Strategy

Studies were identified by searching online in Embase (via OvidSp), Medline (via PubMed), and the Cochrane Library database, using the keywords "Alzheimer's disease", "amyloid-beta protein", "plasma", "biomarker", and "diagnosis" in English. The searching deadline was February 2019.

Study Selection

By reading titles, abstracts and full texts of the search results, the letters, case-control studies, case reports, reviews, and duplicated articles were excluded.

Qualitative Analysis

To ensure the validity of the assessment, two reviewers independently assessed the quality of each included study according to the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). When there was any disagreement in quality assessment, a consensus was reached by discussion.

Data Extraction

The author, journal, title, and date of publication were extracted as the basic information of each study. Study design, inclusion or exclusion criterion, and methods utilized for diagnosing AD and healthy persons were also extracted. For all included studies, the mean value of plasma $A\beta_{40}$ and $A\beta_{42}$, the number of participants and standard deviation (SD) were selected for statistical analysis.

Statistical Analysis

The mean and SD of continuous variate were extracted to conduct the meta-analysis by using weighted mean difference (WMD) methodology to perform this process in Review Manager 5.3 (http://tech.cochrane.org/revman/download). The equation $SD = SE^*\sqrt{n}$ was used to calculate SD when articles provided the SE of continuous variate. According to the molecular weight of plasma Aβ (Aβ40, 4329.86 g/mol; Aβ42, 4514.1 g/mol), plasma Aβ reported as pmol/l was converted into pg/ml. I^2-statistic was used to assess the presence of heterogeneity among trials. When I^2 was less than 50%, the fixed effect model was chosen to calculate the confidence intervals (CIs), otherwise, the random effect model would be chosen. A Funnel plot was used to address publication bias. Forest plot was used to describe the characteristics of data distribution indicated by 95% CIs. The area of each square reflected the weight contributed to the study. The horizontal line across each square represented the 95% CI. All statistical tests were two-sided and expressed a significance level of $P < 0.05$. The diamond was regarded as the total effect of width representing 95% CI which overlapped the invalid line suggested no difference between two groups.

Results

Study Assortments and Characteristics

Firstly, 852 relevant papers were identified during the initial searching. After reading the titles and abstracts, articles non-associated with human plasma Aβ nor AD were excluded. Then, 76 papers were selected for full-text review and 57 were excluded for the reasons detailed in Fig. 1: (1) not cohort study, (2) no comparison, (3) improper outcomes, (4) not for old patients, (5) not about Aβ monomer, and (6) duplicated reports from the same population. Finally, 19 papers were selected for the meta-analysis and systemic review, among them 4 papers from the USA (Fukumoto et al. 2003; Abdullah et al. 2007; Fagan et al. 2007; Ait-ghezala et al. 2008), 4 from China (Chiu et al. 2012; Han et al. 2012; Zhang et al. 2013; Wang et al. 2014), 3 from Australia (Lui et al. 2010; Rembach et al. 2014; Poljak et al. 2016), 2 from Japan (Tamaoka et al. 1996; Akatsu et al. 2011), 2 from Sweden (Giedraitis et al. 2007; Janelidze et al. 2016), and the other 4 from Spain (Corzo et al. 2007), Poland (Sobow et al. 2005), Germany (Tzikas et al. 2014), and the UK (Richens et al. 2014).

For the source of control subjects in the selected 19 studies: 6 studies recruited the control subjects through institutes and hospitals (Abdullah et al. 2007; Ait-ghezala et al. 2008; Han

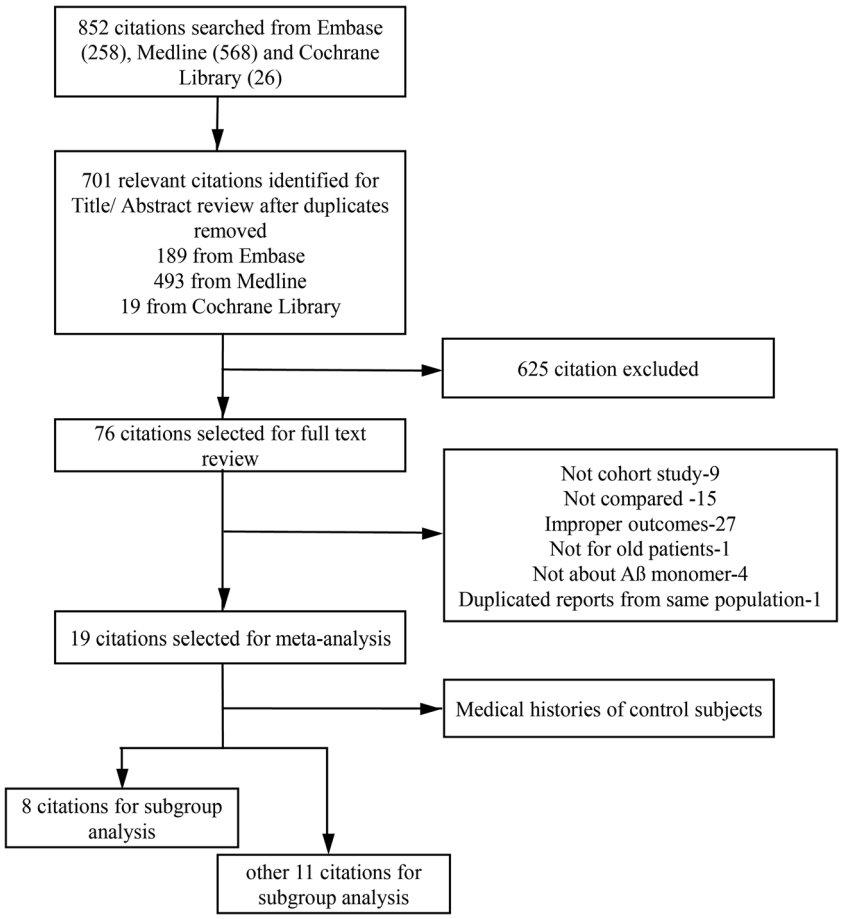

Fig. 1 The flowchart of study selection

et al. 2012; Zhang et al. 2013; Richens et al. 2014; Wang et al. 2014); 5 studies from community volunteers or staff volunteers (Fagan et al. 2007; Lui et al. 2010; Akatsu et al. 2011; Wang et al. 2014; Poljak et al. 2016); 1 study from media advertising (Rembach et al. 2014); 1 study from spouses of the patients (Giedraitis et al. 2007); and the other six studies did not have complete description of the source of control subjects (Tamaoka et al. 1996; Fukumoto et al. 2003; Sobow et al. 2005; Corzo et al. 2007; Chiu et al. 2012; Tzikas et al. 2014).

The basic characteristics of recruited subjects in the selected 19 studies were described in Table 1. Fifteen studies recruited AD subjects referring to the criteria of the National Institute of Neurological Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCSD-ADRDA) (Tamaoka et al. 1996; Sobow et al. 2005; Abdullah et al. 2007; Corzo et al. 2007; Fagan et al. 2007; Giedraitis et al. 2007; Ait-ghezala et al. 2008; Lui et al. 2010; Chiu et al. 2012; Zhang et al. 2013; Rembach et al. 2014; Tzikas et al. 2014; Wang et al. 2014; Janelidze et al. 2016; Poljak et al. 2016). Two studies collected AD subjects based on the criteria of CERAD (Akatsu et al. 2011; Richens et al. 2014). One trial collected AD subjects based on the Blessed Dementia Scale–Information-Memory-Concentration Score (Fukumoto et al. 2003). The other one had no detail description (Han et al. 2012). A total of 1395 AD patients and 3160 control subjects were included for the meta-analysis. The mean age of participants varied from 60.1 (Akatsu et al. 2011) to 82.8 (Akatsu et al. 2011) years old and the female members occupied 40.7% (Tzikas et al. 2014) to 76.2% (Akatsu et al. 2011) in selected studies. To better control the comparability of the level of the plasma $A\beta_{40}$ and $A\beta_{42}$ among different studies, only the data detected by the method of ELISA, Lumi-nex xMAP, or ultrasensitive Simoa immunoassay was used to analysis.

AD Patients Possess a Similar $A\beta_{42}/A\beta_{40}$ Ratio to Control Subjects

We then performed meta-analysis and found that, compared with control subjects, AD patients possessed a slightly higher plasma $A\beta_{40}$ without statistical significance (WMD −4.00; 95% CI −9.87, 1.87; $P = 0.18$; $I^2 = 86\%$; Fig. 2a) and significantly lower plasma $A\beta_{42}$ level (WMD 1.82; 95% CI 0.59, 3.06; $P = 0.004$; $I^2 = 84\%$; Fig. 2b). However, the absolute concentrations of plasma Aβ levels were dramatically variable in different trials. The mean plasma $A\beta_{42}$ level of control subjects ranged from 2.82 (Chiu et al. 2012) to 260.012

Table 1 Basic characteristics of included citations

Study	Diagnosis (n)	Female%	Age (mean±SD)	Aβ40 (pg/ml) (mean±SD)	Aβ42 (pg/ml) (mean±SD)	Aβ42/Aβ40 (mean±SD)	Exclusion	AD Diagnosis	Method
Abdullah et al. (2007)	Control (146)	56.16	74.43 ± 8.10	80.66 ± 22.47	5.66 ± 3.75	0.061 ± 0.072	Yes	NINCDS–ADRDA	ELISA
	AD (67)	52.14	76.04 ± 8.02	103.38 ± 34.95	4.53 ± 4.26	0.053 ± 0.434			
Ait-Ghezala et al. (2008)	Control (102)	56.9	75.35 ± 8.18	81.04 ± 29.69	2.82 ± 3.55	0.032 ± 0.042	Yes	NINCDS–ADRDA	ELISA
	AD (73)	45.2	76.61 ± 8.12	91.99 ± 42.89	1.91 ± 4.97	0.015 ± 0.07			
Akatsu et al. (2011)	Control (529)	63.5	60.1 ± 21.2	316.513 ± 292.699	25.279 ± 175.147	0.033 ± 0.072	No	CERAD	ELISA
	AD (147)	76.2	82.8 ± 9.3	480.614 ± 545.562	78.997 ± 428.388	0.055 ± 0.111			
Chiu et al. (2012)	Control (26)	50	66.3 ± 9.3	65.84 ± 13.47	15.79 ± 0.56	0.2464 ± 0.037	No	NINCDS-ADRDA	ELISA
	AD (18)	55.6	72.9 ± 12.0	53.21 ± 34.69	34.22 ± 31.62	0.6906 ± 0.3363			
Corzo et al. (2007)	Control (55)	45	66.7 ± 6.9	–	18 ± 10.5	–	No	NINCDS-ADRDA	ELISA
	AD (42)	62	69.8 ± 7.2		17.9 ± 7.4				
Fagan et al. (2007)	Control (65)	69	73.3 ± 8.4	191 ± 61.3	36 ± 29.4	–	Yes	NINCDS-ADRDA	ELISA
	AD (16)	50	75.2 ± 5.8	214 ± 90.3	36 ± 37.2				
Fukumoto et al. (2003)	Control (92)	60	69.4 ± 10.3	211.73 ± 74.474	31.599 ± 13.994	–	No	BDS-IMC	ELISA
	AD (146)	55	76.0 ± 8.2	226.885 ± 75.773	33.404 ± 24.376				
Giedraitis et al. (2007)	Control (18)	72.2	65.9 ± 8.6	280.575 ± 73.608	114.658 ± 124.589	–	No	NINCDS–ADRDA	ELISA
	AD (39)	43.6	65.9 ± 7.9	260.658 ± 56.721	97.505 ± 86.219				
Han et al. (2012)	Control (116)	64.7	71 ± 4	92.4 ± 13	37.7 ± 7.6	0.41 ± 0.09	No	–	ELISA
	AD (112)	47.3	70 ± 8	90.7 ± 8.7	32.1 ± 3	0.29 ± 0.07			
Janelidze et al. (2016)	Control (274)	61	73 ± 5	276.7 ± 66.1	19.6 ± 5.2	0.073 ± 0.023	Yes	NINCDS–ADRDA	Lumi-nex xMAP
	AD (57)	60	76 ± 5	244.3 ± 105.8	13.2 ± 7.3	0.057 ± 0.022			
Lui et al. (2010)	Control (724) AD (186)	57.7 62.9	70 ± 7 78.6 ± 8.5	124.7 ± 64.3 128.3 ± 71.0	48.1 ± 33.7 44.8 ± 20.0	0.414 ± 0.152 0.424 ± 0.259	No	NINCDS–ADRDA	ELISA
Poljak et al. (2016)	Control (129)	66.7 43.6	77.25 ± 4.66	254.85 ± 145.72	65.63 ± 217.04	0.26 ± 0.59	No	NINCDS–ADRDA	ELISA
	AD (39)		75.35 ± 7.73	155.82 ± 75.11	18.34 ± 32.10	0.20 ± 0.64			
Rembach et al. (2014)	Control (577)	58.3	69 ± 6.8	157.772 ± 31.069	34.88 ± 9.432	0.223 ± 0.055	Yes	NINCDS–ADRDA	Ultrasensitive Simoa immunoassay
	AD (125)	60.8	78 ± 7.8	172.244 ± 40.884	34.566 ± 10.764	0.202 ± 0.047			
Richens et al. (2014)	Control (18)	–	–	40.527 ± 7.144	22.164 ± 4.063	–	Yes	CERAD	ELISA
	AD (10)			38.969 ± 4.763	15.980 ± 1.851				
Sobow et al. (2005)	Control (35) AD (54)	68.5 68.5	75.0 ± 2.9 77.5 ± 4.4	160.1 ± 15.2 168.7 ± 32.2	36.3 ± 6.3 37.8 ± 10.3	–	No	NINCDS-ADRDA	ELISA
Tamaoka et al. (1996)	Control (40)	–	67.7 ± 10.2	274.513 ± 110.411	260.012 ± 162.508	–	No	NINCDS–ADRDA	ELISA
	AD (28)		73.8 ± 8.97	305.688 ± 182.287	276.714 ± 182.821				
Tzikas et al. (2014)	Control (27)	40. 57.1	67.6 ± 9.7	36.30 ± 6.68	3.39 ± 2.64	–	No	NINCDS–ADRDA	ELISA
	AD (28)		72.9 ± 9.0	39.65 ± 8.08	3.38 ± 2.34				
Wang et al. (2014)	Control (122)	54.1 44.3	73.7 ± 8.4	43.14 ± 22.57	47.53 ± 1.97	–	Yes	NINCDS–ADRDA	ELISA
	AD (97)		73.7 ± 9.4	9.1 ± 20.3	47.1 ± 2.29				
Zhang et al. (2013)	Control (120)	56.7 57.5	70.2 ± 7.1	92.6 ± 26.7	13.3 ± 3.7	0.14 ± 0.01	Yes	NINCDS–ADRDA	ELISA
	AD (153)		71.6 ± 9.2	97.7 ± 30.6	11.5 ± 2.9	0.12 ± 0.03			

Exclusion: exclusion of dementia-related diseases in control subjects

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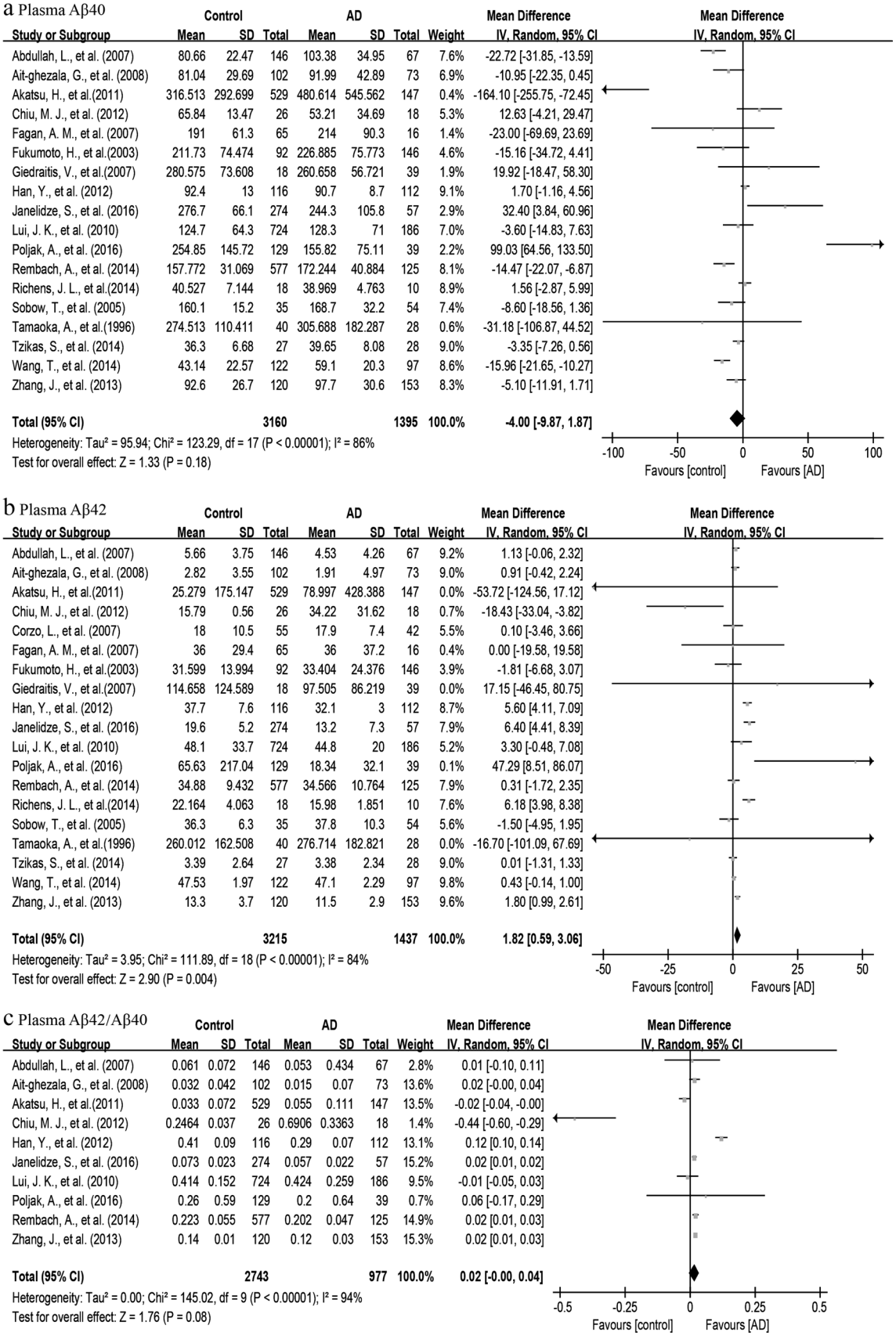

Fig. 2 Forest plots for plasma $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{42}$/ $A\beta_{40}$ ratio levels in control and AD subjects. **a** Forest plots for plasma $A\beta_{40}$ analysis. **b** Forest plots for plasma $A\beta_{42}$ analysis. **c** Forest plots for plasma $A\beta_{42}/A\beta_{40}$ ratio analysis

(Tamaoka et al. 1996) pg/ml in the selected studies. This will present challenges to define the diagnostic criteria in clinics. The $A\beta_{42}/A\beta_{40}$ ratio was more reliable and less variable because it eliminates the errors of absolute concentrations in different trails. Thus, the assessment of plasma $A\beta_{42}/A\beta_{40}$ ratio seems to be a better choice. Unexpectedly, control and AD subjects did not show significant different plasma $A\beta_{42}/A\beta_{40}$ ratios (WMD 0.02; 95% CI − 0.00, 0.04; $P = 0.08$; $I^2 = 94\%$; Fig. 2c). Obvious publication bias of $A\beta_{40}$ (Fig. 3a), $A\beta_{42}$ (Fig. 3b), and $A\beta_{42}/A\beta_{40}$ (Fig. 3c) were figured out by the analysis of the funnel plots.

Medical Histories of Control Subjects Influence Biomarker Potential of Plasma Aβ

We next wondered the other factors influencing the analytic results and considered that the medical histories of control subjects should be a key point. To verify this issue, we reviewed all the collected papers again and found 8 studies clearly described that the recruited control subjects were free of any dementia-related diseases including active neurologic illness, psychiatric disorders or other medical conditions such as congestive heart failure, subdural hematoma, severe hepatic, or renal insufficiency (Abdullah et al. 2007; Fagan et al. 2007; Ait-ghezala et al. 2008; Zhang et al. 2013; Rembach et al. 2014; Richens et al. 2014; Wang et al. 2014; Janelidze et al. 2016), while the other 11 trials had no detail descriptions. Therefore, we first conducted a subgroup analysis with the 8 papers with clear descriptions of control subjects. As predicted, relative to control subjects, AD patients possessed significantly higher plasma $A\beta_{40}$ (WMD − 8.90; 95% CI − 16.96, − 0.85; $P = 0.03$; $I^2 = 85\%$, Fig. 4a) and lower plasma $A\beta_{42}$ levels (WMD 2.24; 95% CI 0.89, 3.59; $P = 0.001$, $I^2 = 87\%$; Fig. 4b). Importantly, the $A\beta_{42}/A\beta_{40}$ ratio of AD subjects was significantly lower than that in control subjects (WMD 0.02; 95% CI 0.02, 0.02; $P < 0.00001$; $I^2 = 0\%$, Fig. 4c).

We then performed the subgroup analysis for the other 11 trials without clear medical history descriptions of control subjects (pseudo-control subjects) (Tamaoka et al. 1996; Fukumoto et al. 2003; Sobow et al. 2005; Corzo et al. 2007; Giedraitis et al. 2007; Lui et al. 2010; Akatsu et al. 2011; Chiu et al. 2012; Han et al. 2012; Tzikas et al. 2014; Poljak et al. 2016). Interestingly, different from the results from the subgroup analysis of the 8 studies, the forest plots showed that all of the plasma $A\beta_{40}$ (WMD 1.56; 95% CI − 7.20, 10.32; $P = 0.73$; $I^2 = 84\%$; Fig. 5a), $A\beta_{42}$ (WMD 0.60; 95% CI − 2.50, 3.70; $P = 0.70$; $I^2 = 82\%$; Fig. 5b), and $A\beta_{42}/A\beta_{40}$ ratio (WMD − 0.04; 95% CI − 0.14, 0.06; $P = 0.43$; $I^2 = 97\%$; Fig. 5c) failed to differentiate AD from the pseudo-control subjects.

Discussion

Aβ deposition is the principal pathological sign of AD. Lots of imaging and clinical studies have been performed to evaluate the amyloid pathology of AD patients (Arvanitakis et al. 2002; Maji et al. 2010). According to the definition, a biomarker should be diagnosed with a high degree of accuracy, cost-effectiveness, and easily translated into general use (Schneider et al. 2009). Therefore, blood-based biomarkers are highlighted because of the inexpensive and convenient screening procedure in both clinics and labs. In contrast, CSF collection is invasive and currently far from realistic, especially in communities and developing countries. However, whether the blood-based Aβ level could be a biomarker of AD is still under debate due to inconsistent results from different reports (Abdullah et al. 2007; Ait-ghezala et al. 2008).

To clarify the potential reason, in this study, we collected 19 studies for the meta-analysis. We found that, although a reduction of plasma $A\beta_{42}$ in AD group subjects, no significant

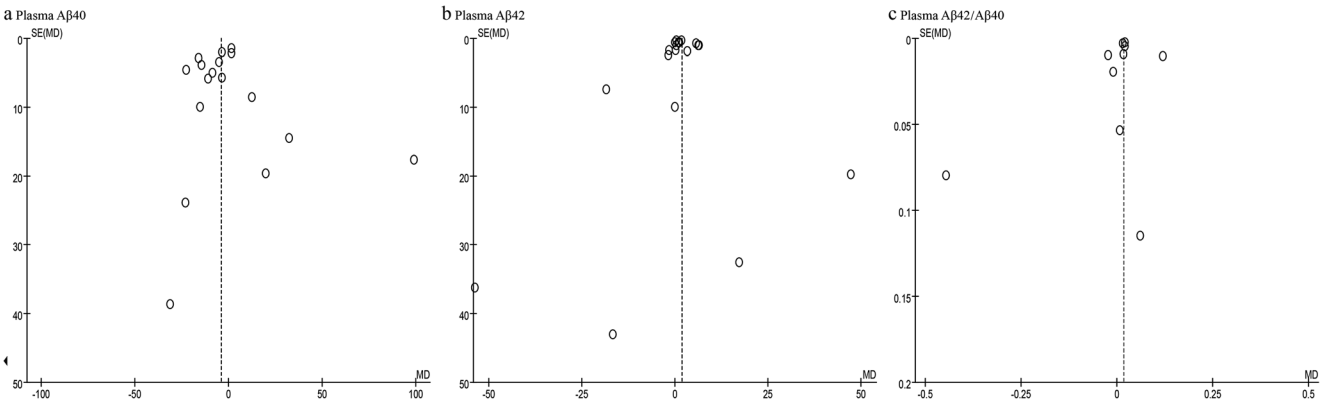

Fig. 3 Funnel plots for plasma $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{42}/A\beta_{40}$ ratio levels in control and AD subjects. **a** Funnel plots for plasma $A\beta_{40}$ analysis. **b** Funnel plots for plasma $A\beta_{42}$ analysis. **c** Funnel plots for plasma $A\beta_{42}/A\beta_{40}$ ratio analysis

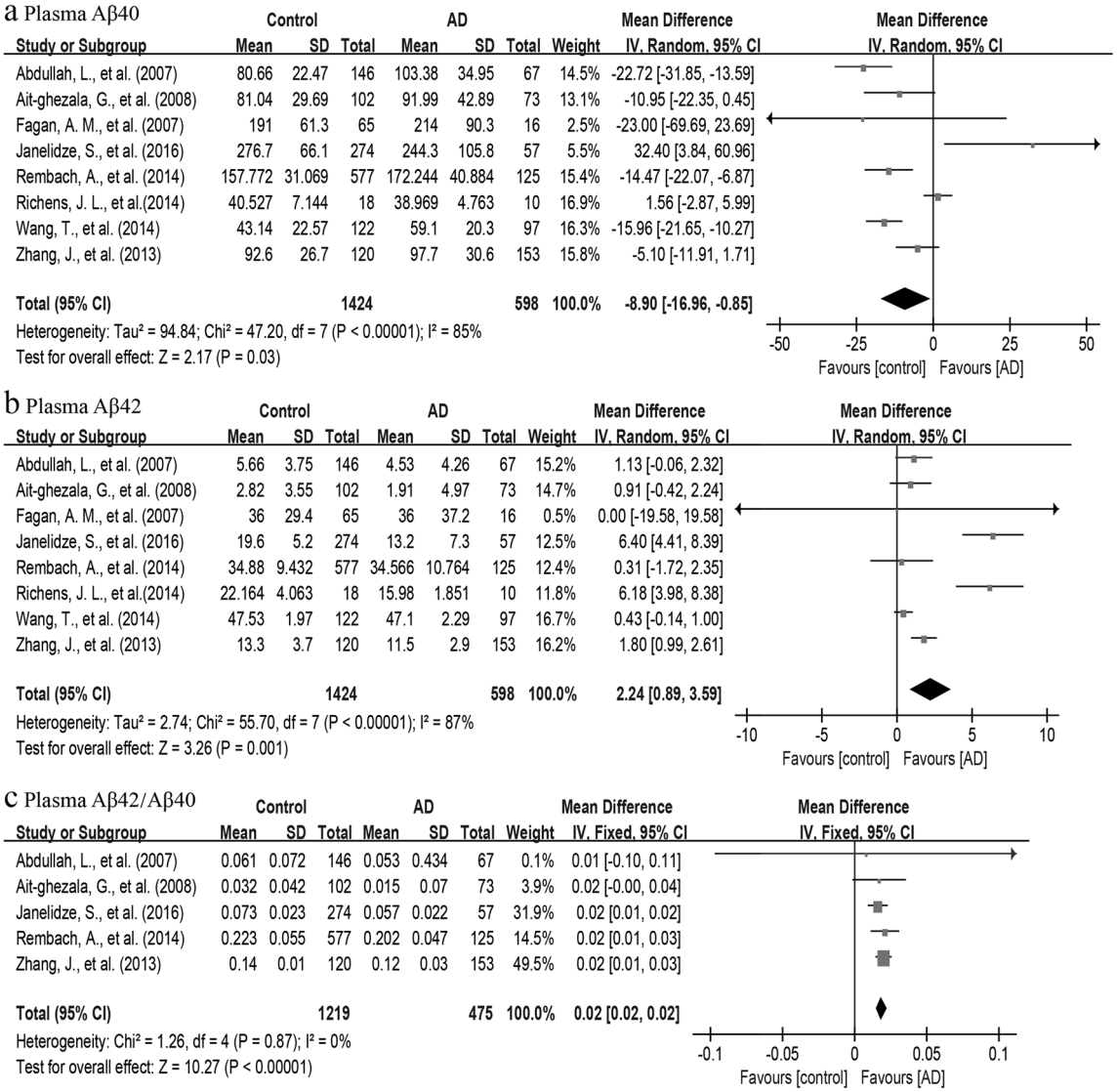

Fig. 4 Forest plots for subgroup analyses of plasma $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{42}/A\beta_{40}$ ratio levels in AD and control subjects with a clear medical history description. **a** Forest plots for subgroup analysis of plasma $A\beta_{40}$. **b** Forest plots for subgroup analysis of plasma $A\beta_{42}$. **c** Forest plots of subgroup analysis for plasma $A\beta_{42}/A\beta_{40}$ ratio

differences were demonstrated in plasma $A\beta_{40}$ and $A\beta_{42}/A\beta_{40}$ ratio between control and AD subjects. To identify the interference factors of the analytic results, we re-reviewed the included studies and found that only part of the papers clearly described the medical histories of control subjects. The medical histories of patients, including active neurological illness, psychiatric disorders, and other medical conditions such as congestive heart failure, subdural hematoma, and severe hepatic or renal insufficiency, were reported dramatically influence the plasma Aβ levels (Toledo et al. 2011). According to the recent studies, 0.86%, 5.83%, 0.49%, and 6.9% of the 65–74-year old population were suffered from epilepsy, stroke, multiple sclerosis, and chronic heart failure, respectively (Benjamin et al. 2019; Christina et al. 2019). Approximately 10% of the adult US population has chronic kidney disease (Knutson et al. 2018). Fifteen to 30% of the western general population are affected by chronic liver disease (Hsu et al. 2016). Therefore, about 35% of aging subjects are affected by some Aβ-related chronic disease, but they may have a higher plasma Aβ level with normal cognition. We hence speculated that the medical histories of normal cognitive control subjects would impede the biomarker ability of plasma Aβ. As predicted, when extracting the 8 studies, which described that control subjects were free from those Aβ-related diseases, for subgroup meta-analysis, we remarkably found that plasma $A\beta_{42}/A\beta_{40}$ displayed a high ability to differentiate AD from control subjects with narrow 95% CI and low heterogeneity. In contrast, the meta-analysis of the left 11 papers demonstrated that none of plasma $A\beta_{42}/A\beta_{40}$, $A\beta_{42}$, and $A\beta_{40}$ levels could discriminate AD group from pseudo-

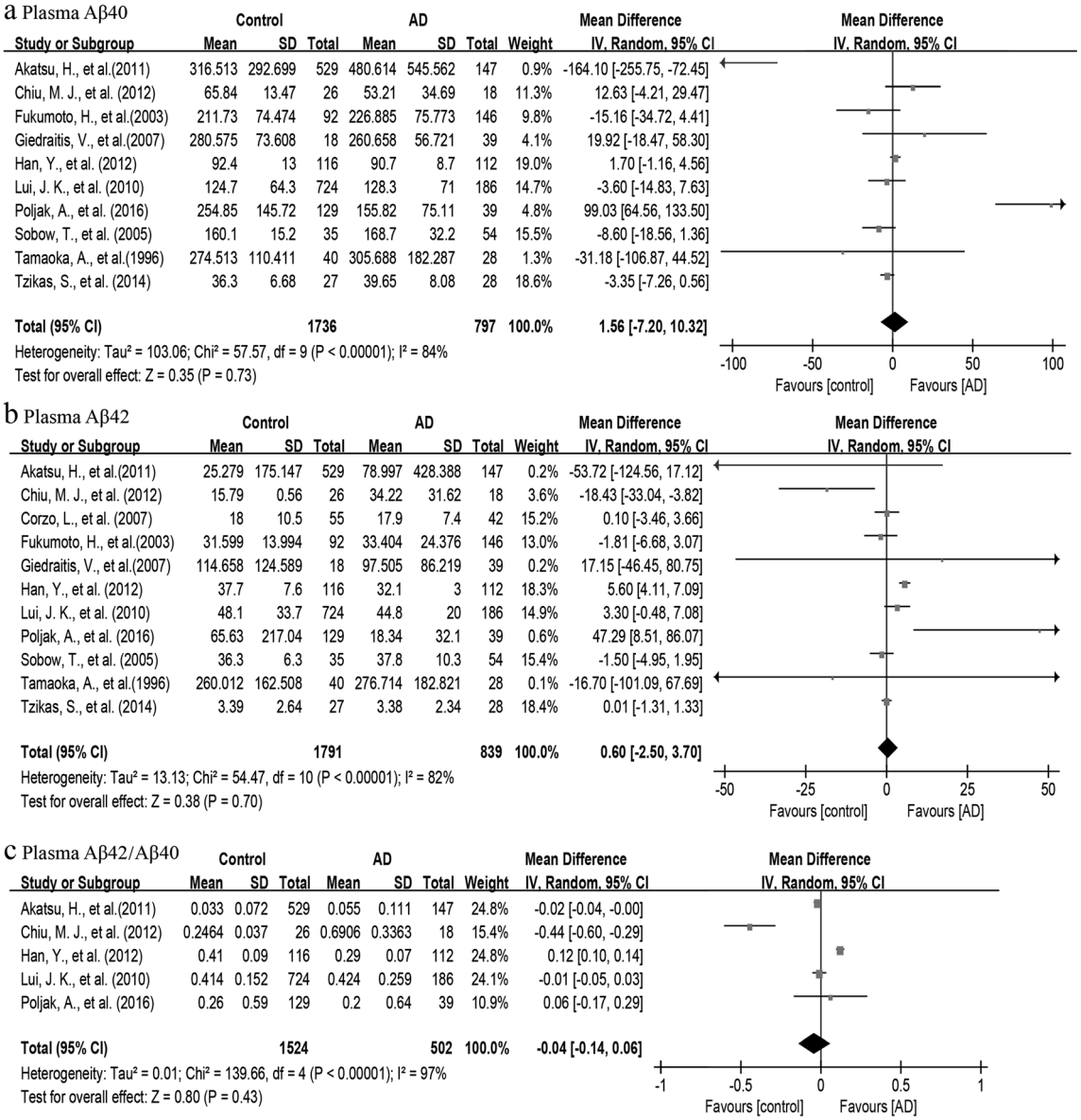

Fig. 5 Forest plots for subgroup analyses of plasma $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{42}$/ $A\beta_{40}$ ratio levels in AD and pseudo-control subjects. **a** Forest plots for subgroup analysis of plasma $A\beta_{40}$. **b** Forest plots for subgroup analysis of plasma $A\beta_{42}$. **c** Forest plots for subgroup analysis of plasma $A\beta_{42}/A\beta_{40}$ ratio

control subjects. These analyzed results fully illustrated that medical histories of the cognitively normal pseudo-control subjects impede plasma Aβ to be a biomarker of AD.

Notably, our conclusion based on the present meta-analysis is slightly different from the previous meta-analysis (Song et al. 2011). We thought that two reasons could account for this result: (1) newly published literatures were involved in this study; (2) we reset the recruitment criteria and excluded all of the pseudo-control subjects. On the other hand, based on the result from this meta-analysis, we deem that the $A\beta_{42}$/ $A\beta_{40}$ ratio could eliminate the differences of absolute plasma $A\beta_{40}$ and $A\beta_{42}$ concentrations in different researches. And the $A\beta_{42}/A\beta_{40}$ ratio does not vary with the ApoE genotype (Kim et al. 2015). Therefore, it might be a more convincing peripheral biomarker for AD diagnosis and prediction.

In the present study, although the analyzed literatures covered all of the clinical trial studies from Embase, PubMed, and the Cochrane Library database, not all of these literatures provided the detail medical history information of the recruited control samples. The clinical design limited the accuracy of the present meta-analysis. We look forward to more high-quality clinical trials in the future, which will help us to get a more accurate conclusion of the impact of medical histories of control subjects on the biomarker potential of plasma Aβ in AD.

In conclusion, we found that AD patients possess lower plasma $A\beta_{42}$, $A\beta_{42}/A\beta_{40}$ ratio, and higher $A\beta_{40}$ levels than

control subjects without any kind of Aβ-related chronic disease. While plasma $A\beta_{42}/A\beta_{40}$ ratio, unlike the variable Aβ levels in different trials, is more stable and has unique superiority to distinguish AD and control subjects. This meta-analysis supports the plasma $A\beta_{42}/A\beta_{40}$ ratio as a biomarker of AD. Also, it highlights the importance of medical history information for clinical studies.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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