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CSF tau and amyloid β_{42} levels in Alzheimer's disease—A meta-analysis

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ABSTRACT

Alzheimer's disease International (ADI) estimates that there are currently 30 million people with dementia in the world. The main objective was to perform meta-analysis of studies of CSF tau and Amyloid β_{42} (Aβ_{42}) levels in Alzheimer's disease (AD) patients and controls. In the present study MEDLINE was reviewed from 1995 to 2009, supplemented by citation analysis from retrieved articles to select case control studies. Descriptive statistics showed that median effect size (raw mean difference) of CSF tau and Aβ_{42} levels were 301 pg/ml (Range: 22 to 614 pg/ml) and –352 pg/ml (Range: –969 to 203 pg/ml) respectively. The pooled effect size CSF tau and Aβ_{42} was 289.14 pg/ml (95% CI 253.278 to 325.013 pg/ml) and –329.02 pg/ml (95% CI –387.740 to –270.445 pg/ml) respectively. Heterogeneity in effect size of selected studies was present for both parameters (CSF tau: Q statistics = 1816.596, DF = 40, P = 0.000 and CSF Aβ_{42}: Q-statistics = 1259.358, DF = 24, p < 0.001). Based on the findings of meta-analysis in the present study, CSF tau and Aβ_{42} levels in AD and controls may be considered as potential biomarker along with the clinical phenotype to perform them during high quality diagnostic testing in dementia.

Keywords: Alzheimer's Disease; Dementia; CSF Amyloid β_{42}; CSF Tau; Meta-Analysis

1. INTRODUCTION

Alzheimer's disease International (ADI) estimates that there are currently 30 million people with dementia in the world and will increase to be over 100 million by 2050 [1]. Due to increased life expectancy, aging population is increasing in developed and developing countries, adding burden to societal costs each year for chronic care and lost productivity [2]. As per National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's disease and Related Disorders Association (ADRDA) criteria for diagnosis of Alzheimer's disease (AD), convened in 1983 is based on medical history, clinical examination, neuropsychological testing have been quite successful and being in used over 27 years. However, a broad consensus now exists to revise these criteria owing to the advances occurring in our understanding of AD, development of biomarkers to detect the pathophysiological process of AD and changes in conceptualization regarding the clinical spectrum of the disease in the intervening 27 years [3]. The National Institute on aging (NIA) and the Alzheimer's Association sponsored a series of advisory round table meetings in 2009 for revising the diagnostic and research criteria for AD in three stages-preclinical phase, predementia phase and symptomatic phase of AD. The most notable differences from the AD criteria published in 1984 are incorporation of the biomarkers of the underlying disease state and formalization of different stages of disease in the diagnostic criteria. The biomarkers were divided into two major categories [3]: 1) the biomarkers of Amyloid β accumulation, which are abnormal tracer retention on amyloid PET imaging and low CSF Aβ_{42}, and 2) the biomarkers of neuronal degeneration or injury, which are elevated CSF tau (both total and phosphorylated tau); decreased flourodeoxyglucose uptake on PET involving temperoparietal cortex and atrophy on structural magnetic resonance in medial, basal and lateral temporal lobes and medial and lateral parietal cortices. In the preclinical phase, biomarkers are used to establish the presence of AD pathophysiology in research subjects with no or very subtle overt symptoms. In the symptomatic predementia MCI phase, biomarkers are used to establish the underlying etiology responsible for the clinical deficit and biomarker severity indicates likelihood of imminent progression to AD dementia. In dementia phase, biomarkers are used to increase or decrease the level of certainty that AD pathophysiology

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underlines the dementia in an individual. In last two phases, clinical diagnosis is paramount and biomarkers are complimentary [3-6].

The biomarkers of AD that have been investigated most extensively are levels of tau and Aβ_{42} in CSF and have sensitivities between 81% (for tau) and 86% (for Aβ_{42}), both at 90% specificity with respect to distinction between AD and normal aging [7]. The rationale for including these biomarkers in the diagnostic criteria of probable AD is that it increases the certainty that the basis of the clinical dementia syndrome is the AD pathophsiological process [8]. Most Amyloid peptide is extracellularly and is cleaved to Aβ_{40} (90%) and Aβ_{42} (10%). As per amyloid cascade hypothesis β_{42} peptide aggregatees as amyloid fibrils in the brain more rapidly than β_{40}. Overproduction of β_{42} or failure to clear this peptide leads to AD [2]. Several studies have found increased CSF tau [9,10] and reduced CSF Aβ_{42} [11-13] levels in AD to be a pathological CSF biomarker signature that is diagnostic of AD heralding the onset of AD before it becomes clinically manifest [7,14-16].

However, before comparing CSF tau and Aβ_{42} levels in cases of dementia patients who had AD and controls for diagnosis of AD can be established, it is crucial to assess whether effect size of published studies reported in last fifteen years shows consistent trends in their levels or not in AD cases as compared to controls. The consistency in effect size of tau & Aβ_{42} levels of the studies can be explored by advanced statistical method, which is known as meta-analysis. Typically, meta-analysis has three main goals [17]: 1) to test whether the studies results are homogeneous, 2) to obtain a global index about the effect magnitude of the studied relation, joined to a confidence interval and its significance and 3) to identify possible variables or characteristics moderating the results obtained if there is heterogeneity among studies. Among published studies, a considerable variability has been observed in levels of these biomarkers as well as their diagnostic sensitivity and specificity. In the present study, studies conducted from 1995 till 2009 were taken and meta-analysis was performed to compare the CSF tau and Aβ_{42} level in AD and control in published studies and also whether these trends are consistent.

2. METHODS

2.1. Search Strategy

We searched the data base MEDLINE for English language publications from 1995 to 2009 with key words Biomarkers in Alzheimer's disease, Amyloid β_{42} and tau. Additional articles were also obtained from references citations within retrieved articles. The search revealed 60 publications on CSF tau studies in AD and 41 publications on CSF Aβ_{42} studies in AD. Studies were sorted out as per predefined inclusion criteria: 1) case control studies in which the cases were defined as clinically diagnosed confirmed AD; 2) studies where tau and Aβ_{42} were measured by Enzyme linked Immunosorbant assay using Innotest kit from Innogenetics, Belgium; 3) studies in which quantitative measurement of CSF tau and Aβ_{42} levels were done (expressed as pg/ml and mean ± SD).

2.2. Statistical Analysis

All the values were expressed in pg/ml. Hence, the raw mean difference (unstandardized) was used for calculating the effect size of each study. The heterogeneity in effect size of both parameters (tau & Aβ_{42}) in the studies was explored with the help of three statistical tools: 1) Test of significance (Q statistics); 2) Between studies variance (T^2); 3) Degree of heterogeneity (I^2) to select the appropriate model (Fixed effect vs. Random effect model) for meta-analysis. In the present study, DerSimonian-Laird random effect model was used for analysis because of high variability between the studies. Under random effect model, all studies considered for meta-analysis have random samples of hypothetical population of studies and true effect is allowed to vary from study to study as well as within study.

The graphical method (Forest plot) has also been applied for presenting the results of meta-analysis. In Forest plot, each study's effect size and respective confidence interval (CI) are plotted on one set of axis along with pooled estimate of effect size, together with its CI.

One of the major problems with meta-analysis is possibility of presence of "publication bias" and it must be explored before concluding the meta-analysis [18].While a meta-analysis will yield a mathematically accurate synthesis of the studies included in the analysis, if these studies are a biased sample of all relevant studies, then the mean effect computed by the meta-analysis will reflect this bias. There are many methods to examine the publication bias. In the present study, we applied funnel plot and sensitivity analysis. Former is a graphical method, to examine the publication bias. Traditionally, the funnel plot is plotted with effect size on the X-axis and sample size or variance on the Y-axis. But in present study, we used precision on Y-axis in place of variance and effect size on X-axis as usual. Sensitivity analysis was carried out to examine the effectiveness of overall effect size in present meta-analysis. It is performed by repeating the meta-analysis after systematically excluding each individual study in turn. This assessment can indicate which studies are more influential.

All the statistical analysis was done using the Meta-analysis report soft ware Meta Analyst [Version: Beta 3.13] downloaded from the web site on 05. 01. 10.

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3. RESULTS

3.1. Meta-Analysis of Tau Level

Out of 60 publications retrieved from the MEDLINE search, 19 studies were excluded as in 10 studies SD was not expressed in their tau mean value, in 5 studies controls were not provided in the data whereas in 2 studies each immunoblotting technique was used to measure tau and tau was expressed in pmol/L. 41 case-control published studies of Alzheimer's disease that were meeting the inclusion criteria for meta-analysis, were identified (**Table 1** & **Figure 1**) [9,10,12,13,16,19-55]. In only 01 studies, controls were age and gender matched with cases [42] and 6 studies had equal or more number of controls than cases [16,25,30,49,53,55] (**Table 1**). All the studies report a significant difference in CSF tau levels between AD subjects and controls.

Median sample size in 41 studies of tau level was 66 (case + control) and its range was 26 - 479 where as median effect size (raw mean difference) was 301 pg/ml (range: 22 to 614 pg/ml). The overall effect size (CSF tau level difference between AD and control subjects) of the meta-analysis of published studies was 289.14 pg/ml (95% CI 253.278 to 325.013 pg/ml) (**Table 2** & **Figure 1**).

Heterogeneity in effect size across the selected studies of CSF tau level was found statistically significant (Q statistics: 1816.596, DF: 40, P: 0.000). Between studies variance (T^2) was 10773.390 and the contribution of between study variance in total heterogeneity of effect sizes was real (I^2: 97.798%, 95% CI of I^2: 97.452% - 98.098%).

3.2. Meta-Analysis of Amyloid β_{42} Level

As in tau 25 case-control published studies of AD meeting the inclusion criteria for meta-analysis were taken from 40 studies retrieved after MEDLINE search (**Table 3** & **Figure 3**) [12,13,16,19,20,34,35,41,42,47-53,56, 57-64]. Rest 15 studies were excluded as SD was not given in 8, control was not included in 3, immunoblotting technique was used in 2 and in 2 studies Aβ_{42} was expressed as pmol/L (**Table 1**).

23 studies of the 25 studies in the meta-analysis showed reductions in CSF Aβ_{42} levels in AD as compa- red to controls whereas in 2 studies [58,63] values were higher than controls. The overall effect size CSF Aβ_{42} level (difference between AD and control subjects) of the meta-analysis of published studies was –329.02 pg/ml (95% CI –387.740 to –270.445 pg/ml).

Heterogeneity in effect size across the selected studies of CSF Aβ_{42} level was found statistically significant (Q-statistics: 1259.358, DF: 24, P: 0.000). Between studies variance (T^2) was 17723.932 and the contribution of between study variance in total heterogeneity of effect sizes was real (I^2: 98.094%, 95% CI of I^2: 97.717% - 98.407%).

Visual inspection of the funnel plot for CSF tau and Aβ_{42} levels (**Figures 2** & **4**) indicates asymmetrical distribution, suggesting publications bias. Publication bias had also been examined in different regions *i.e.* America, Asia (Japan), Scandinavian countries (Sweden, Finland) and Western Europe (UK, France, Germany, Austria, Netherlands, Italy, Belgium) for both tau and Aβ_{42} levels in CSF and it was observed that the same was in all the four regions (Funnel plot not shown).

Sensitivity analysis of 41 studies undertaken for CSF tau levels in AD showed that one by one exclusion of 07 studies [21,26-29,49,54] led to significant change in overall effect size and the confidence interval (**Figure 5**). Similarly, in case of CSF Aβ_{42} levels in AD, the overall effect size and the confidence interval showed drastic change with one by one exclusion of 09 studies [13,34, 35, 50,54,58,60,61,63].

4. DISCUSSION

The results of this meta analysis show that there was significantly increase in CSF tau levels and decrease in CSF Aβ_{42} levels in AD compared to controls (**Figures 1** & **3**). Despite the uniform patterns of raised CSF tau levels in AD as compared to controls, there was wide range of effect size among 41 articles under study (22 to 614 pg/ml) with pooled estimate of 289.146. Sunderland *et al.* [19] have also reported the pattern of uniform change in CSF tau levels in AD with higher CSF tau levels vs controls. Similarly, van Harten *et al.* [65] reported that increased CSF concentration of tau can be interpreted as evidence for a diagnosis of AD with specificity exceeding 85% as compared to Dementia with Lewy Bodies (DLB) and Vascular Dementia (VaD), in their meta-analysis on tau and p-tau as CSF biomarkers in Dementia, confirming that increased concentration of tau serves as potential biomarker for AD. In this meta-analysis 23 out of 25 studies show significant reductions in CSF Aβ_{42} levels in AD as compared to control subjects, the results of meta analysis were unequivocal and the range of effect size was quite large (–969 to 203 pg/ml). Studies by Sunderland *et al.* [19] reported considerable variability in mean valueos among studies undertaken by them for the meta-analysis.

Before general conclusions can be drawn, we are required to consider several points, which could not be addressed in this study. First, each biomarker was not presented in association with the clinical presentation. In clinical practice, the diagnosis of probable AD is not based on single parameters, but on a number of signs and symptoms like insidious presentation, history of worsening of cognition, amnestic and non amnestic presentation (Language presentation, visuospatial presentation, executive dysfunction). Hence, at present to make a diagnosis of AD with biomarker support, the core clinical diagnosis of AD must first be satisfied [4].

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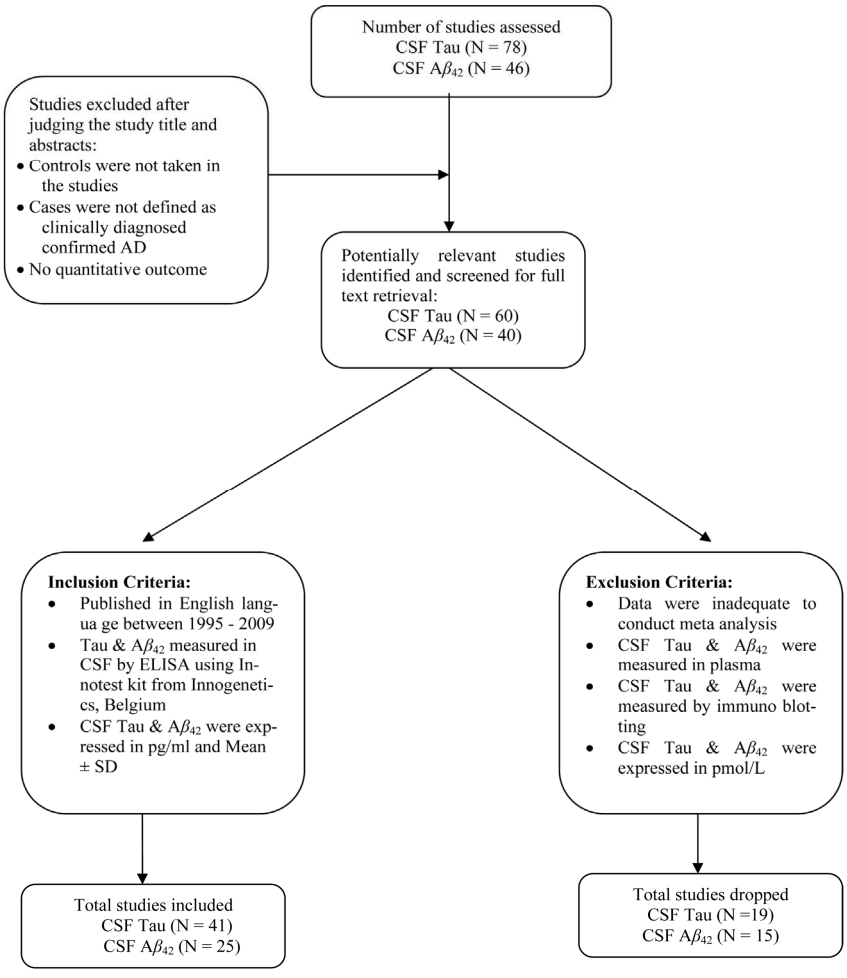
Second, the cited studies include clinically diagnosed cases of AD only. The rationale for including biomarkers representing the pathophysiological process of AD in the diagnostic criteria is that these changes begin more than four decades before the appearance of clinical symptoms [3-6]. But in the present meta analysis, we did not select the studies in which these biomarkers were studied in preclinical and mild cognitive impairment (MCI) phases of AD.

Third, use of CSF biomarkers as diagnostic criteria for AD depends on a quantitative interpretation in compareson to normal standards. In cases where biomarkers test values are abnormal (high/low), interpretation will be the presence of the underlying AD pathophysiological process *i.e.* "positive" findings. However, in some cases ambiguous or indeterminate results will be obtained. Although, sophisticated quantitative method does exist, at present accepted "cut off" for these biomarkers is not available. This is further complicated by the variability introduced during sample collection and storage like using glass or polysterene tubes [66] than polypropylene tubes, prolonged storage of CSF samples in frozen state, repeated freezing and thawing of CSF or lack of standardisation of assay methods [61].

Fourth, with the general consistency in the literature for CSF tau and Aβ_{42}, it is not surprising that the combination of high CSF tau and low Aβ_{42} are being considered useful in screening out the suspected cases of AD from other types of dementias [25,49,72-74]. However, the studies undertaken have reported wide variation in values of CSF biomarkers in AD and controls. Sensitivity analysis was performed to examine the robustness of the finding of present meta-analysis. This sensitivity assessment indicated the studies which are most influential.

Sensitivity analysis of CSF tau studies in AD showed that inclusion of 07 studies [21,26-29,49,54] in CSF tau studies and 09 studies [13,34,35,50,54,58,60,61,63] for CSF Aβ_{42} led to significant change in the total effect size and CI **(Figures 5** and **6**). The pooled effect size varied from 281 to 301 pg/ml for CSF tau and –354.49 to –307.13 pg/ml for CSF Aβ_{42} on exclusion of these influential studies indicating that CSF tau biomarker is highly sensi-

Table 1. Flow chart for considered and included studies.



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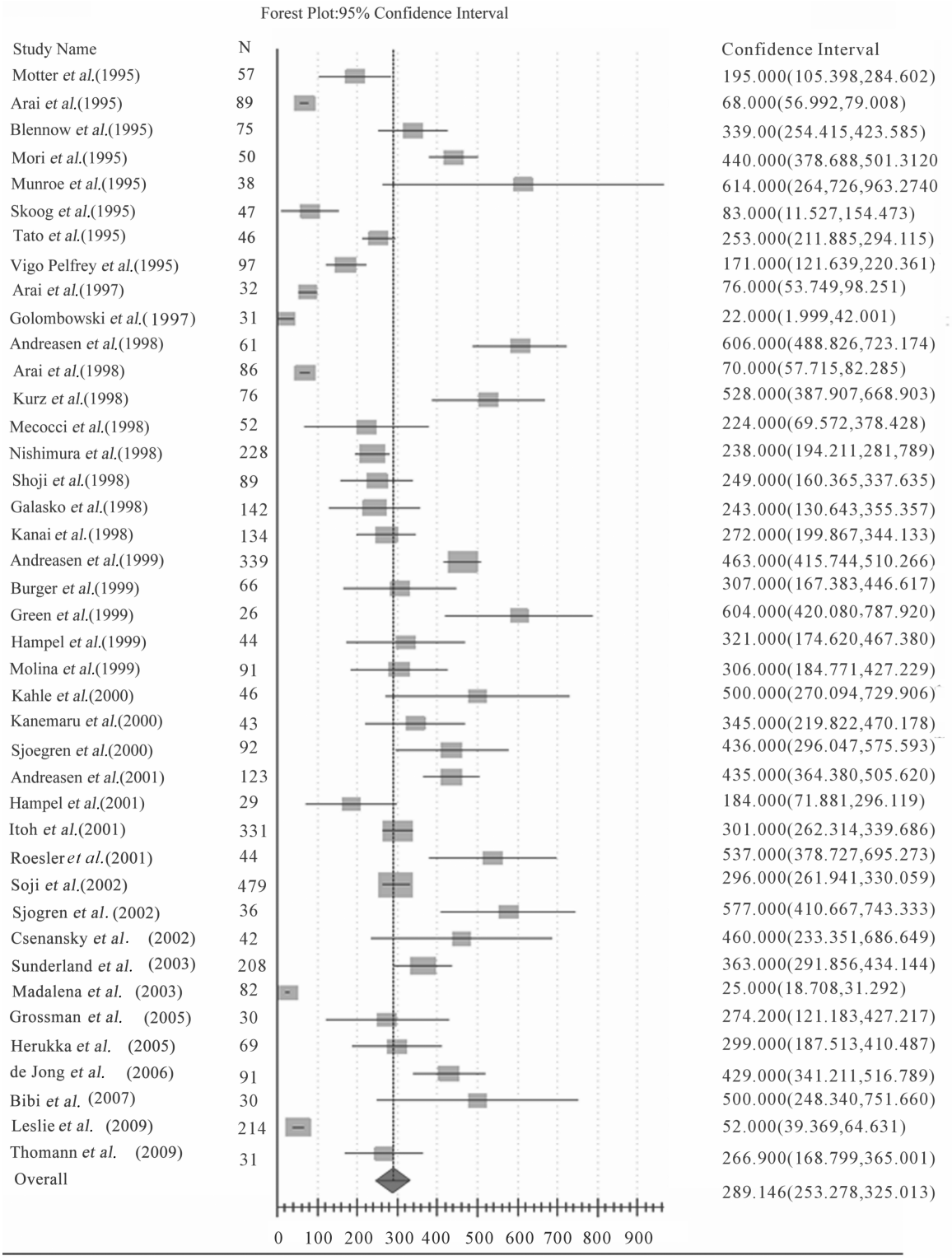

Figure 1. CSF tau levels in Alzheimer's disease (total studies).

tive as compared to CSF Aβ_{42}. In previous studies sensitivity for CSF Aβ_{42} in AD versus control varied from 78% to 94% whereas specificity ranged from 47% to 93% [13, 34,52]. De Jong *et al.* [52] found CSF Aβ_{42} as highly sensitive (93%) and specific (93%) marker, when comparing AD with healthy subjects, whereas Kanai *et al.* [34] reported it as highly sensitive but non specific marker for diagnosis of AD. Similarly, sensitivity and

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Table 2. Effect size, its 95% CI & weight calculations for each selected studies of the CSF tau in Alzheimer's disease.

Sr. No.	Author's name & year	Country of study	Tau level (pg/ml)				Effect size (pg/ml)	95% CI	Weight
			Diseased		Control				
			N	Mean (SD)	N	Mean (SD)	RMD* (SE)		
1	Motter *et al.* (1995)	USA	37	407 (241)	20	212 (102)	195.00 (45.72)	105.40, 284.60	0.00
2	Arai *et al.* (1995)	Japan	70	77 (46)	19	9 (5)	68.00 (5.62)	56.99, 79.01	0.15
3	Blennow *et al.* (1995)	Sweden	44	524 (280)	31	185 (50)	339.00 (43.16)	254.42, 423.59	0.00
4	Mori *et al.* (1995)	Japan	14	820 (90)	36	380 (120)	440.00 (31.28)	378.69, 501.31	0.01
5	Munroe *et al.* (1995)	USA	24	1430 (739)	14	816 (355)	614.00 (178.20)	264.73, 963.27	0.00
6	Skoog *et al.* (1995)	Sweden	11	254 (113)	36	171 (78)	83.00 (36.47)	11.53, 154.47	0.00
7	Tato *et al.* (1995)	Spain	23	279 (100)	23	26 (11)	253.00 (20.98)	211.89, 294.12	0.01
8	Vigo-Pelfrey *et al.* (1995)	USA	71	361 (166)	26	190 (80)	171.00 (25.19)	121.64, 220.36	0.01
9	Arai *et al.* (1997)	Japan	17	95 (44)	15	19 (15)	76.00 (11.35)	53.75, 98.25	0.04
10	Golombowski *et al.* (1997)	Switzerland	19	53 (39)	12	31 (17)	22.00 (10.21)	211.89, 294.12	0.04
11	Andreasen *et al.* (1998)	Sweden	43	796 (382)	18	190 (57)	606.00 (59.78)	488.83,723.17	0.00
12	Arai *et al.* (1998)	Japan	69	90 (45)	17	20 (13)	70.00 (6.27)	57.72, 82.29	0.12
13	Kurz *et al.* (1998)	Germany	40	697 (447)	36	169 (64)	528.00 (71.48)	387.91, 668.09	0.00
14	Mecocci *et al.* (1998)	Italy	29	436 (360)	23	212 (200)	224.00 (78.79)	69.57, 378.43	0.00
15	Nishimura *et al.* (1998)	Japan	163	426 (234)	65	188 (103)	238.00 (22.34)	194.21, 281.79	0.01
16	Shoji *et al.* (1998)	Japan	55	467 (285)	34	218 (139)	249.00 (45.22)	160.37, 337.64	0.00
17	Galasko *et al.* (1998)	USA	82	630 (481)	60	387 (167)	243.00 (57.33)	130.64, 355.36	0.00
18	Kanai *et al.* (1998)	Japan	93	489 (298)	41	217 (128)	272.00 (36.80)	199.87, 344.13	0.00
19	Andreasen *et al.* (1999)	Sweden	274	690 (341)	65	227 (101)	463.00 (24.11)	415.74, 510.26	0.01
20	Burger *et al.* (1999)	Germany	38	580 (370)	28	273 (203)	307.00 (71.24)	167.38, 446.62	0.00
21	Green *et al.* (1999)	UK	17	802 (381)	9	198 (49)	604.00 (93.84)	420.08, 787.92	0.00
22	Hampel *et al.* (1999)	Germany	25	566 (329)	19	245 (154)	321.00 (74.69)	174.62, 467.38	0.00
23	Molina *et al.* (1999)	France	83	522 (290)	8	216 (150)	306.00 (61.85)	184.77, 427.23	0.00
24	Kahle *et al.* (2000)	USA	30	840 (560)	16	340 (230)	500.00 (117.30)	270.09, 729.91	0.00
25	Kanemaru *et al.* (2000)	Japan	24	460 (301)	19	115 (76)	345.00 (63.87)	219.82, 470.18	0.00
26	Sjoegren *et al.* (2000)	Sweden	60	743 (503)	32	307 (168)	436.00 (71.41)	296.05, 575.95	0.00
27	Andreasen *et al.* (2001)	Sweden	105	699 (275)	18	264 (102)	435.00 (36.03)	364.38, 505.62	0.00
28	Hampel *et al.* (2001)	Germany	17	496 (205)	12	312 (98)	184.00 (57.21)	71.88, 296.12	0.00
29	Itoh *et al.* (2001)	Japan	236	450 (252)	95	149 (107)	301.00 (19.74)	262.31, 339.69	0.01
30	Roesler *et al.* (2001)	Austria	27	761 (407)	17	224 (81)	537.00 (80.75)	378.73, 695.27	0.00
31	Soji *et al.* (2002)	Japan	366	482 (271)	113	186 (107)	296.00 (17.38)	261.94, 330.06	0.02
32	Sjogren *et al*. (2002)	Sweden	19	919 (349)	17	342 (116)	577.000 (84.87)	410.67, 743.33	0.00
33	Csenansky *et al.* (2002)	Sweden	32	1260 (460)	10	800 (260)	460.00 (115.64)	233.35, 686.65	0.00
34	Sunderland *et al.* (2003)	USA	136	587 (365)	72	224 (156)	363.00 (36.30)	291.86,434.14	0.00
35	Madalena *et al.* (2003)	Switzerland	51	52 (19)	31	27 (10)	25.00 (3.21)	18.71, 31.29	0.44
36	Grossman *et al.* (2005)	USA	17	534.6 (303.50)	13	260.4 (93.80)	274.20 (78.07)	121.18, 427.22	0.00
37	Herukka *et al.* (2005)	Finland	23	608 (239)	46	309 (186)	299.00 (56.88)	187.51, 410.49	0.00
38	de Jong *et al.* (2006)	Netherlands	61	613 (326)	30	184 (89)	429.00 (44.79)	341.21, 516.79	0.00
39	Bibl *et al.* (2007)	Germany	15	700 (480)	15	200 (130)	500.00 (128.40)	248.34, 750.66	0.00
40	Leslie *et al.* (2009)	USA	100	122 (58)	114	70 (30)	52.00 (6.45)	39.37, 64.63	0.11
41	Thomann *et al.* (2009)	Germany	16	455.63 (198.96)	15	188.73 (21.62)	266.90 (50.5)	168.80, 365.00	0.00

Abbreviations: SD: Standard Deviation; SE: Standard Error; RMD: Raw Mean Difference; CI: Confidence Interval.

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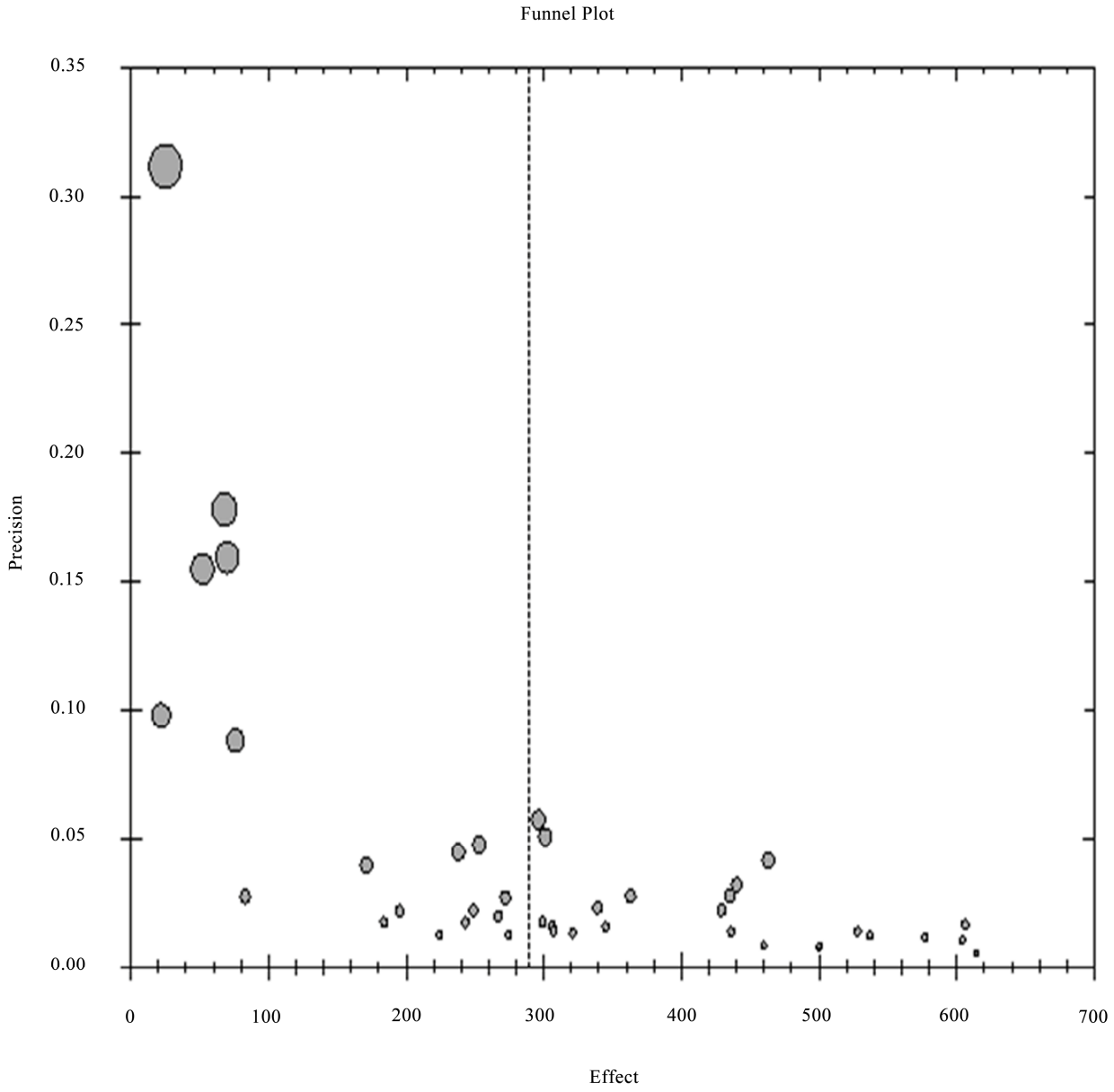

Figure 2. Funnel plot of CSF tau (Total studies).

specificity for CSF tau in AD versus controls varied from 40% to 98.6% and 83% to 100% [13,21,28,34,52]. Arai *et al.* [21] found CSF tau as most sensitive (98.6%) and specific (100%) biomarker to separate from normal subjects. Thus with such considerable variance in the data for CSF tau and Aβ_{42} along with reported wide range of their sensitivity and specificity, it is currently unclear whether tau and Aβ_{42} can be used alone to separate AD from MCI and other dementias like vascular dementia and neurological disorders. This leads to reduction in their clinical diagnostic utility and this drawback, at least partly can be overcome by using them in conjunction with the characteristics symptoms pertaining to memory disturbances and characteristic brain imaging findings in AD [34].

Fifth, there can be two sources of variability leading to heterogeneity in the set of studies undertaken in present meta-analysis [67-71]. One, variability introduced by sampling error (within-study). This occurs due to different samples used in every single study. Second source of variation, between-studies variability, is introduced due to influence of an indeterminate number of characteristics that vary among the studies. It includes heterogeneity introduced by inadequate plan like small sample size [71], less number of controls taken in the study as compared to cases or case and controls are not age and sex matched. Also, variability may also be introduced during sample collection and storage like using glass or polysterene

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tubes [71] than polypropylene tubes, prolonged storage of CSF samples in frozen state, repeated freezing and thawing of CSF or lack of standardisation of assay methods [61].

Sixth, one of the major problems with this meta-analysis study was the presence of "publication bias". Several lines of evidence show [67] that studies that report relatively high effect sizes are more likely to be published than studies that report lower effect sizes. Since published studies are more likely to find their way into meta-analysis and such meta-analysis do not truly represent all studies on the topic of interest. In present meta-analysis, average tau level in cases was significantly different than control for all 41 studies ($p < 0.001$), whereas, for Aβ_{42} parameter, only 02 studies were showing not significant results. This observation supports the hypothesis that any bias in the literature is likely to be reflected in the meta-analysis study as only statistically sig-

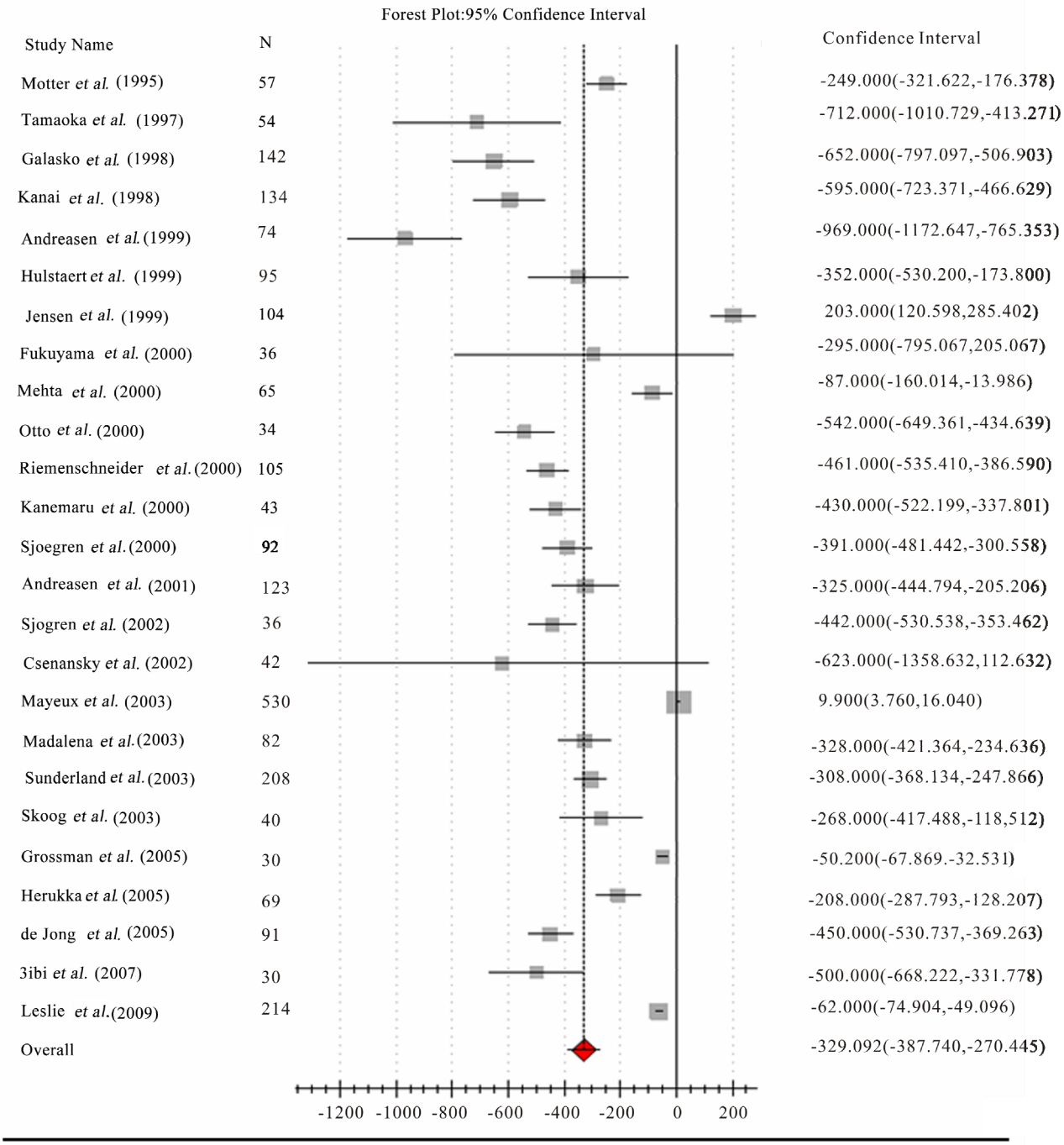

Figure 3. CSF Aβ_{42} levels in Alzheimer's disease (total studies).

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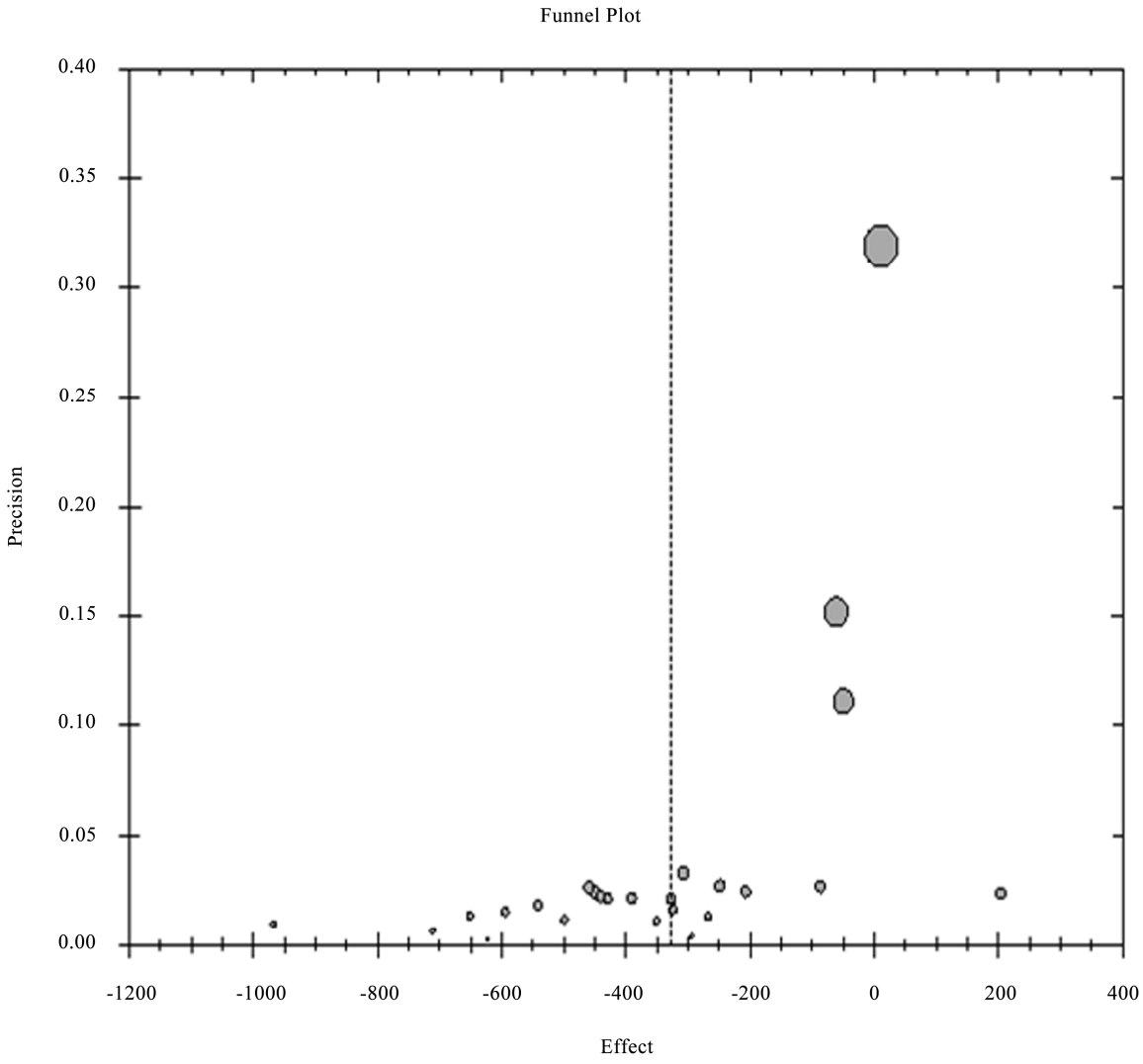

Figure 4. 4 Funnel plot of CSF Aβ_{42} (total studies).

nificant results are more likely to be published. Also, in the present study, funnel plot analysis shows the presence of publication bias for both parameters.

In the present meta-analysis, CSF tau levels showed uniform increased pattern in AD as compared to controls. However, the mean CSF tau levels varied in AD from 52 pg/ml [49] to 1430 pg/ml [23] as compared to controls (9 - 816 pg/ml). Similarly, CSF Aβ_{42} level showed decline in AD as compared to control with variation of their levels from 45 pg/ml [50] to 17,777 pg/ml [48] in AD and control (58.8 - 1485 pg/ml). Such wide variation in CSF tau and Aβ_{42} levels in AD among the studies is due to lack of standardization from one locale to another. Also, it makes it difficult to decide the cut-off values for the same. Hence, at present these biomarkers can not be used to diagnose AD in earlier stages and also can not be used to assess the progress of disease. Meta-analysis performed by Grossman et al [50] also showed wide variation in CSF tau levels (53 - 1260 pg/ml) and Aβ_{42} (60 - 1777 pg/ml) in AD.

The recommendation that together low CSF Aβ_{42} and elevated tau provide a high likelihood of progression of AD in patients with mild cognitive impairment (MCI) [4] requires these CSF biomarker levels to be standardized from one locale to another with defined cut off and access of these biomarkers to different settings. The results from the present meta-analysis suggest that once the results of CSF Aβ_{42} and tau are negative, dementia is unlikely to be due to AD. As the diagnostic accuracies of

CSF biomarkers increase with time from diagnosis, our analysis suggests that longitudinal studies in non demented subjects having MCI with long term follow up are needed to decide whether the prognostic accuracy of CSF biomarkers does increase much earlier than the moment of diagnosis. The current meta-analysis can not answer this as this review only has included the studies in

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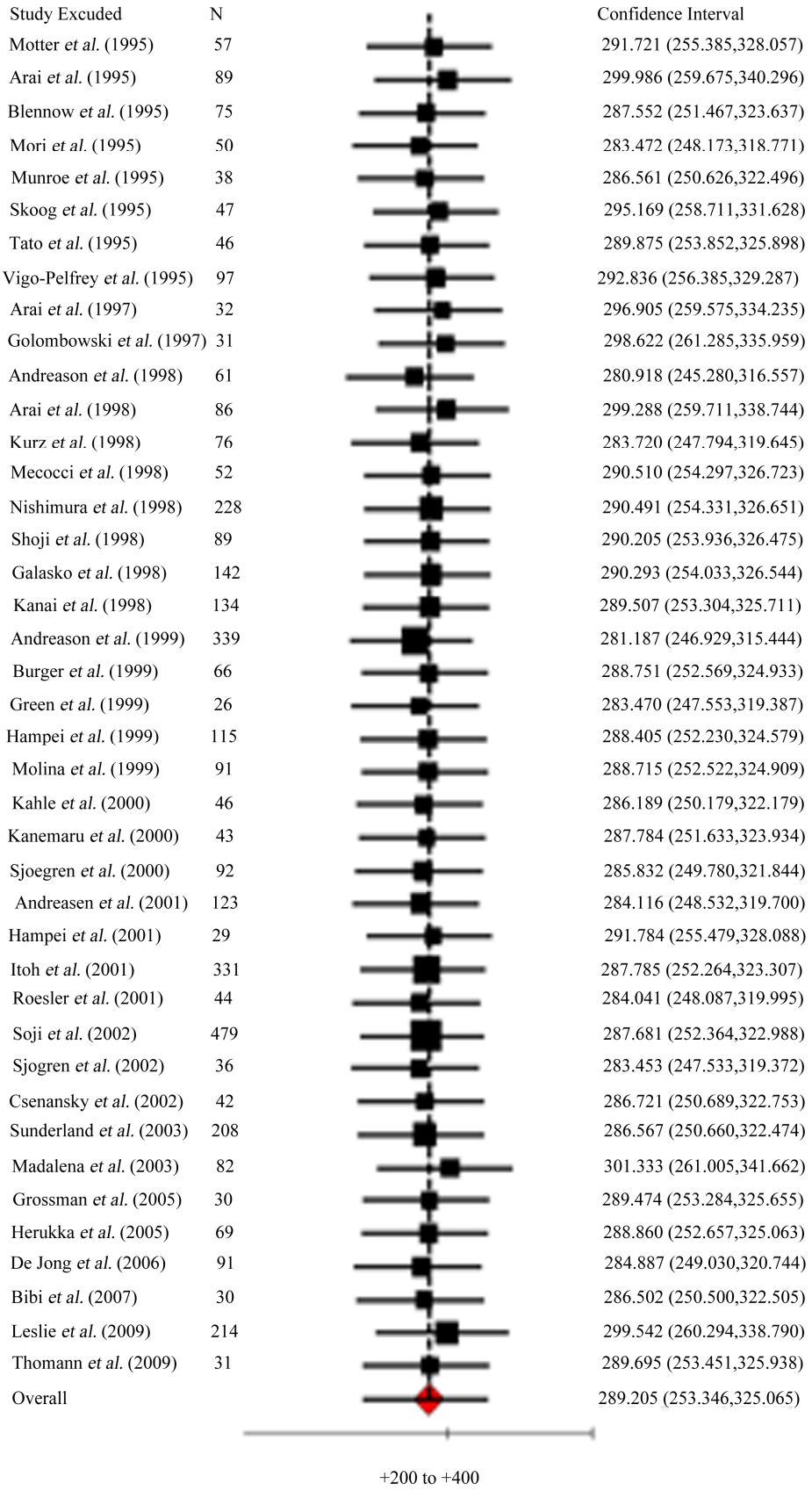

Figure 5. Sensitivity analysis of CSF tau studies.

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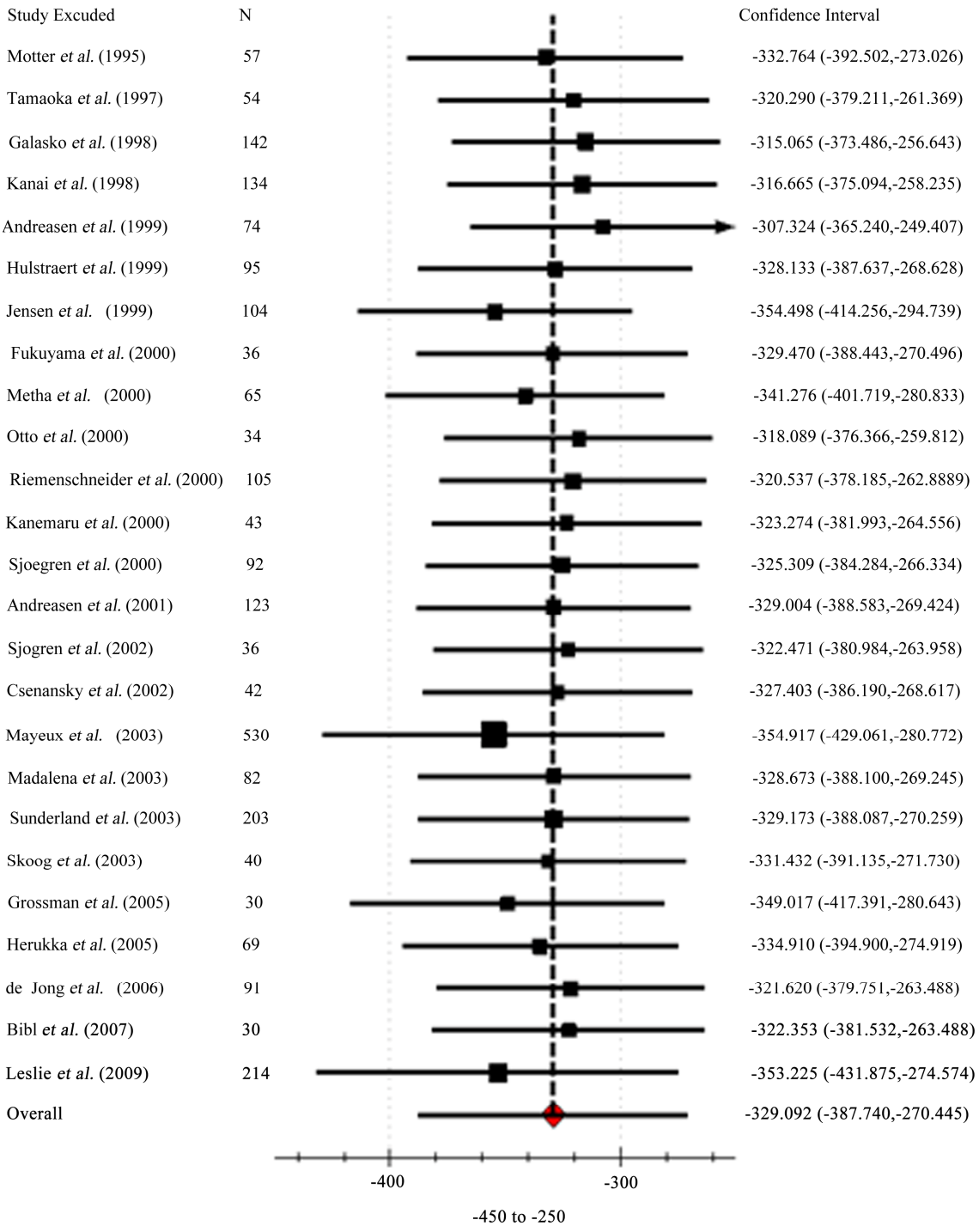

Figure 6. Sensitivity analysis of CSF amyloid β_{42} studies.

which cases of probable AD were taken. However, CSF tau/Aβ_{42} ratio follow up done by Fagan *et al.* [5] to predict cognitive decline in non-demented older adults observed that CSF biomarkers tau and Aβ_{42} were not related to follow up diagnosis. Irrespective of present scenario, it is not very likely that CSF biomarkers along with MRI and PET will ever be the sole object for choosing the correct therapy, when effective preventive and disease modifying treatments are available because treatment of biomarkers abnormality associated with AD will have the drawback that many persons will be treated unnecessarily who may never have the probability of reaching the dementia stage [75]. It should be noted that increased Aβ_{42} deposition is seen in disorders other than AD (e.g

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amyloid angiopathy) and elevated tau levels also occur in other neurodegenerative disorders (e.g. prion disease) [3].

Limitation

Meta-analysis is not without disadvantages and it is the subject of harsh criticism from some quarters [76]. One disadvantage of meta-analysis is simply the amount of effort and expertise it takes. There was lack of complete information in some studies and we obtained full data in 60% studies only. There was high level of heterogeneity in individual study effect size for both parameters (Tau & Aβ_{42}), although appropriate statistical model has been applied for reaching at conclusive results.

At present use of AD biomarkers for routine diagnostic purposes has many limitations [8]: 1) the core clinical criteria provide very good diagnostic utility in most patients; 2) more research needs to be done to ensure that criteria that include the use of biomarkers have been appropriately designed; there is limited standardization of biomarkers from one locale to another, and 3) access to biomarkers is limited to varying degrees in community settings.

There are number of challenges to be addressed before applying CSF tau and Aβ_{42} as part of a prospective clinical evaluation of participants who are at risk for developing AD. The studies undertaken were case control studies which are known to exaggerate the test performance leading to introduction of bias in the study. The cases in the published studies included in the present meta-analysis were diagnosed with probable AD and not MCI, preclinical AD and possible AD. The one of the limiting factor is collection of CSF sample as lumbar puncture required for CSF collection is a moderately invasive procedure and must be done after patients'/ relatives' consent. Another limiting factor is inconsistency in standardization of procedures for sample collection, storage and analysis in different laboratories and distinct cut-off which can be used from one laboratory to another.

5. CONCLUSION

Based on the findings of present meta-analysis, it can be concluded that tau increase alone or an Aβ_{42} decrease is not specific of AD, the combination of high tau and low Aβ_{42} might be useful in ensuring that AD pathophysiology underlines the dementia in an individual, thereby helping in differentiating AD from other types of dementia in addition to the characteristic symptoms pertaining to memory disturbances and characteristic brain imaging findings in AD. In view of the heterogeneous findings and publication bias in the present meta-analysis, the present conclusion is not strong enough to generalize the findings. Hence, at present they may be useful in investigational studies, clinical trials and as additional tools in addition to clinical diagnosis.

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