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# Plasma and cerebrospinal fluid amyloid-β levels in late-life depression: a systematic review and meta-analysis

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## Abstract

This study aimed to evaluate differences in plasma and cerebrospinal fluid (CSF) levels of Aβ peptides in older adults with late-life depression compared to non-depressed older controls. We conducted a systematic review and meta-analysis of the literature using PubMed, Web of science and Scopus databases with no search limits for publication dates or languages. Two independent reviewers extracted data and assessed quality. Six hundred references were retrieved, and we included 12 studies in the meta-analysis after eligibility screening. Older adults with late-life depression (LLD) had a higher plasma $A\beta_{40}$:$A\beta_{42}$ ratio compared to non-depressed participants (SMD= 1.10, $CI_{95\%}$ [0.28; 1.96], p=0.01), and marginally significant reduction of CSF $A\beta_{42}$ levels (SMD= −1.12, $CI_{95\%}$ [−2.47; 0.22], p=0.1). The present results evidence that older adults with depression have significant differences in Aβ metabolism, in the same direction observed in individuals with AD. These differences in the Aβ metabolism may help identify a subgroup of subjects with LLD at higher risk of developing AD.

### Keywords

Late-Life Depression; dementia; amyloid-β; plasma; cerebrospinal fluid; meta-analysis

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**CONFLICT OF INTEREST**

The authors do not have any conflict of interest to report regarding this manuscript.

**AUTHOR AND CONTRIBUTORS**

All authors contributed with the study design, data analysis, interpretation of results, drafting and revising the manuscript.

## Introduction

Late-life depression (LLD) is a common disorder in the elderly and is associated with cognitive impairment and a higher risk of dementia, especially Alzheimer's disease (AD) and vascular dementia (Byers and Yaffe, 2011; da Silva et al., 2013; Diniz *et al.*, 2013). The mechanisms linking depression and the risk of dementia are unknown, but may involve abnormalities in multiple biological cascades, including the metabolism of amyloid-β (Aβ) peptide in the brain (Butters et al., 2008a). Neuroimaging studies using *in vivo* brain amyloid ligands show higher Aβ load in older adults with LLD, in particular, those with late-onset depression, compared with healthy controls (Butters *et al.*, 2008b; Tateno et al., 2014). Nonetheless, other studies reported no significant differences in Aβ burden between LLD and healthy controls (Madsen et al., 2012) what is in line with recent neuropathological studies (Royall and Palmer, 2013; Wilson et al., 2014).

The metabolism of the amyloid precursor protein (APP) yields two common Aβ peptides, the $A\beta_{40}$ and $A\beta_{42}$, that can be readily measured in the cerebrospinal (CSF) and plasma (Blennow et al., 2010). Reduced CSF $A\beta_{42}$ levels is associated with an increased risk of progression of mild cognitive impairment (MCI) to AD (Diniz et al., 2008). Previous clinico and epidemiological studies have reported that increased $A\beta_{42}$ levels and lower plasma $A\beta_{42}$:$A\beta_{40}$ ratio can be an indicator of a higher risk of progression from MCI to AD; though other studies have also found no association between plasma Aβ biomarkers and increased risk of progression (Hansson et al., 2012; Fei et al., 2011; Koyama *et al.*, 2012; Gabelle et al., 2013). Previous studies investigated the levels of Aβ peptides in the CSF and plasma of LLD patients. Pomara and colleagues (2006) showed that the CSF $A\beta_{42}$ levels are reduced in older adults with depression compared to healthy controls. In contrast, other studies did not find significant differences or even found increased CSF $A\beta_{42}$ levels in older depressed individuals (Gudmundsson *et al.*, 2007; Kramberger *et al.*, 2012; Reis *et al.*, 2012). Other studies evaluated the plasma levels of Aβ peptides. Most studies found a significant reduction of plasma $A\beta_{42}$ and increased $A\beta_{40}$:$A\beta_{42}$ ratio in LLD; although non-significant results have also been reported (Sun *et al.*, 2008; Baba *et al.*, 2012; Benitez *et al.*, 2009; Kita *et al.*, 2009).

The current knowledge about the dynamics of Aβ peptides in the CSF and plasma of LLD patients are limited by the small sample size of individual studies that are generally underpowered to detect small, but significant, group differences. Due to the importance of understanding the role of abnormalities of Aβ metabolism in LLD, and the lack of power of individual studies, we aim to carry out a meta-analysis on the levels of CSF and plasma Aβ peptides in LLD.

## Methods

### Search Strategy

This study followed the guidelines for conducting and reporting systematic reviews and meta-analysis methods proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) working group (Moher *et al.*, 2009). We conducted a comprehensive literature search for potentially relevant studies in the electronic databases

PubMed, Scopus and Web of Science. There were no search limits for publication language. We used the following string term for the literature search: "(depression OR depressive disorder OR major depressive disorder) AND (amyloid)". Additionally, we carried out a manual search for relevant articles in the references of the original articles included in the meta-analysis, as well as in review articles about this subject. We conducted the literature search in January 2015, and all papers published until December 31, 2014 were included.

## Study Selection, Data Extraction and Quality Assessment

We selected studies for data extraction and analysis based on the following criteria: (a) identification of depression "caseness"; (b) age over 50 years at baseline assessment for participants with major depression and controls; (c) assessment of human plasma and/or CSF of Aβ peptide levels ($A\beta_{40}$, $A\beta_{42}$, and/or $A\beta_{40}$:$A\beta_{42}$ ratio) in participants with depression as compared with participants without depression (regarded as controls in the original studies). Two investigators (K.K.F.N and K.S.P) independently reviewed the title and abstract of each article retrieved from the literature search to identify potentially relevant studies. The selected articles were revised to verify whether they fulfilled the inclusion criteria for data extraction. If there was any disagreement in study selection, a third investigator (B.S.D.) made the final decision on the inclusion of the selected article. If different publications reported data from the same population, we included data from the publication with the larger sample size.

Data was extracted by two independent investigators (K.K.F.N and K.S.P) using a standardized data extraction form. The following data were extracted for each study: year of publication, country, study design, depression assessment method, demographic variables, sample size and mean and standard deviation, or median and interquartile range, for each analyte. When the study provided only the median and interquartile range, we transformed these values into mean and standard deviation (Hozo *et al.*, 2005). We used the Newcastle–Ottawa Scale (NOS) to assess the scientific method quality of each study selected for inclusion in the meta-analysis (Wells *et al.*, 2013). This scale assesses methodological aspects of non-randomized observational studies such as selection criteria for inclusion of cases and controls, comparability of population ascertainment of exposure to risk, quality of case ascertainment and outcome assessment.

## Statistical Analysis

We carried out the meta-analysis using the standardized mean difference (SMD) method with a Hedges' correction for bias in small samples to evaluate differences between LLD and control subjects for plasma $A\beta_{40}$, $A\beta_{42}$ levels, and $A\beta_{40}$:$A\beta_{42}$ ratio; and for CSF $A\beta_{40}$, $A\beta_{42}$ levels (Hedges and Olkin 1985). We assessed heterogeneity in the analysis with the Q-test and $I^2$ index. If the p-value was equal to or below 0.05 in the Q-test and/or the $I^2$ index was higher than 50%, the pooled analysis was considered significantly heterogeneous. Random- or fixed-effect model was used based on the statistical evidence of heterogeneity. We performed sensitivity analyses by excluding one study at a time and recalculating the summary effect (i.e. 'leave-one-out' technique) to evaluate whether any individual study biased the result of the meta-analysis. Publication bias was ascertained by visual inspection of a funnel plot. All analyses were carried with the statistical software RevMan 5.1 for

Windows 7 (The Nordic Cochrane Centre, Copenhagen, Denmark, http://ims.cochrane.org/revman/download).

## Results

### Study Selection and Description of Studies

Two hundred forty-eight studies were retrieved from PubMed, 591 from the Web of Science and 143 from Scopus databases. After removing duplicate studies, we included 600 studies for revision. Twelve studies met all inclusion criteria and were included in the meta-analysis. The flowchart shows all steps for the study assessment and selection (figure 1). The main characteristics of studies included are summarized in Tables 1 and 2.

### Plasma Aβ peptides ($A\beta_{40}$, $A\beta_{42}$, and $A\beta_{40}$:$A\beta_{42}$ ratio)

The LLD group had a higher Aβ40:Aβ42 ratio compared to non-depressed participants (SMD= 1.10, $CI_{95\%}$ [0.28, 1.96], z=2.52, p=0.01; Q=92.50, p<0.00001; I2 =97%). We found no significant differences in plasma $A\beta_{42}$ (SMD= −0.44, $CI_{95\%}$ [−1.00, 0.11], z=1.57, p=0.1; Q=42.8, p<0.001; I2=91%) or plasma $A\beta_{40}$ levels (SMD= −0.10, $CI_{95\%}$ [−0.45, 0.25], z=0.54, p=0.59; Q=20.82, p=0.00003; I2 =81%) between groups.

Sensitivity analysis showed no significant effect of individual studies on results for plasma Aβ40:Aβ42 ratio or $A\beta_{40}$ levels. On the other hand, sensitivity analysis showed that after the exclusion of Blasko et al. (2010) study, plasma $A\beta_{42}$ levels were significantly reduced in the LLD group (SMD= −0.68 $CI_{95\%}$ [−1.07, −0.29], z=3.42, p<0.001). This result suggests that the data from Blasko et al. (2010) is biasing the meta-analysis results for plasma $A\beta_{42}$ levels.

### CSF peptide ($A\beta_{40}$ and $A\beta_{42}$)

As there were only two studies that evaluated CSF $A\beta_{40}$ levels, we did not carry out a meta-analysis for this peptide. There was no significant difference in the CSF $A\beta_{42}$ levels between groups (SMD= −1.12, $CI_{95\%}$ [−2.47; 0.22], z=1.64 p=0.10; Q=130.83, p<0.00001; I2 =96%, figure 3). Nonetheless, sensitivity analysis revealed that after excluding one study (Gudmundsson *et al.*, 2007) depressed participants had a marginally significant lower level of CSF $A\beta_{42}$ compared to non-depressed participants (SMD= −1.51, $CI_{95\%}$ [−3.00; −0.01], z=1.97, p=0.05, Q=107.32, p=0.00001; $I^2$=96%). The visual inspection of funnel plots showed no evidence of publication bias for the CSF $A\beta_{40}$ and $A\beta_{42}$.

### Additional Analysis

Age is one of the most important risk factor for AD, and there is evidence of a positive correlation between age and increased deposition of Aβ peptide in the brain of non-demented older adults. We carried out additional analysis to assess whether there were significant differences in the age of depressed and non-depressed subjects that could bias the results of the analyses. We found no significant differences in the age of depressed and non-depressed participants in the studies included in the meta-analysis of plasma Aβ peptides (SMD= 0.44, $CI_{95\%}$ [−0.35; 1.22], z=1.09, p=0.28) or CSF Aβ (SMD= −0.67, $CI_{95\%}$ [−1.40; 0.06], z=1.79, p=0.07).

Cognitive impairment is also an important risk factor for the development of AD in older adults with depression (Modrego and Ferrández, 2004; Aizenstein *et al.*, 2011). However, only one study included in this meta-analysis specifically evaluated whether cognitive impairment in subjects with LLD was associated with differences in the AD-related biomarker in plasma or CSF (Diniz *et al.*, 2014). Thus, it was not possible to carry out a meta-analysis on the influence of this risk factor.

## Discussion

This present study showed that older adults with LLD have significantly different Aβ peptide metabolism, identified by a significantly lower level of plasma $A\beta_{42}$ level and higher $A\beta_{40}$:$A\beta_{42}$ ratio. This pattern of differences in plasma Aβ peptides is similar to those observed in subjects with AD and those with MCI, who progress to AD upon follow-up (Forlenza *et al.*, 2010). However, the magnitude of change in individuals with LLD is less than that observed in individuals with AD. Therefore, we can hypothesize that abnormalities in the Aβ metabolism may be one of the possible mechanisms by which a depressive episode in the elderly increases the risk of AD.

The measurement of Aβ in the plasma and CSF is a potential biomarker for the diagnosis of AD (Blennow et al., 2010). Low CSF levels of $A\beta_{42}$, along with high total and phosphorylated tau protein may be helpful in differentiating AD from other dementia syndromes and can predict the conversion to from MCI to AD (Diniz *et al.*, 2008). As depression in older adults may increase the risk of AD on follow-up, the systematic evaluation of AD-related biomarkers can help identify a subgroup of depressed older adults, perhaps over and above the presence of cognitive impairment, that are at increased risk of developing AD. It should be noted that depression is also a common feature of other dementia syndromes, as vascular dementia or Lewy body dementia (Ballard et al., 2000; Klatka et al., 1996). These syndromes have also been associated with altered levels of Aβ peptides in the CSF, though at a lesser degree compared to AD (Schoonenboom et al., 2012; Kaerst et al., 2014). Therefore, the current results can in part explain the increased association between depression and other dementia syndromes like vascular dementia or Lewy body dementia.

The Aβ peptides are the result of sequential proteolytic cleavage of the type I transmembrane amyloid precursor protein (APP) by β and γ secretase, producing various peptides with different lengths. The concentration of Aβ species in human plasma and CSF is $A\beta_{40}$ (~90%) followed by $A\beta_{42}$ (~10%). Despite the higher concentration of $A\beta_{40}$, $A\beta_{42}$ is a major constituent of amyloid plaques, what suggest that $A\beta_{42}$ aggregation plays a critical role in plaque formation in AD (Iwatsubo *et al.*, 1994; Tamaoka *et al.*, 1994; Gravina *et al.*, 1995; Mcgowan *et al.*, 2005). The dynamics of Aβ peptides in the CSF is better understood than in plasma. CSF Aβ peptides have large diurnal variability, and its metabolism is significantly influenced by sleep-wake cycle disruptions (Bateman *et al.*, 2006; Kang *et al.*, 2009). Nonetheless, the dynamics and the pathological relevance of circulating Aβ species are less understood. Plasma Aβ peptides can be derived from CSF clearance or from APP metabolism in the platelets as they have the full biological machinery to cleave APP into Aβ peptides (Smith *et al.*, 2009; Zainaghi *et al.*, 2012). Plasma and CSF

$A\beta_{40}$ and $A\beta_{42}$ have a weak to moderate correlation, though it is not clear whether plasma Aβ peptides can cross the blood-brain barrier (reverse transport), influencing CSF levels and deposit into neuritic plaques (Barten *et al.*, 2005; Toledo *et al.*, 2011; Huang *et al.*, 2012). Thus, additional studies are necessary to improve knowledge about the dynamics and biological significance of plasma Aβ peptides in physiological and pathological conditions, to improve its use as diagnostic and prognostic markers in AD or LLD.

Depression and AD often co-occur and share some clinical symptoms such as memory impairment, executive dysfunction, and behavioral symptoms as apathy, suggesting that these disorders may share common pathophysiologic changes. A recent animal study showed that the injection of amyloid-β oligomers leads to depressive-like phenomena in mice (Ledo *et al.*, 2013). Also, the deposition of Aβ in the brain leads to microglial activation, increased pro-inflammatory markers, and reduced neurotrophic support (Azevedo *et al.*, 2013). These changes are observed in both AD and LLD subjects (Thorsell *et al.*, 2010; Naismith *et al.*, 2012). On the other hand, long-term antidepressant treatment can modulate Aβ metabolism (Sheline *et al.*, 2014). Thus, the changes in Aβ metabolism may not only reflect the emergence of neurodegenerative changes in older adults with depression, but also, may reflect a primary pathophysiologic event in a subgroup of LLD subjects, i.e. the amyloid-related depression (Sun *et al.*, 2008).

Other neurobiological abnormalities, in addition to abnormalities in the Aβ metabolism, can contribute to the higher risk of AD in older adults with major depression. Pomara and colleagues (Pomara *et al.*, 2012) found higher F2-isoprostane CSF levels indicating pro-oxidative stress status in LLD. Kern and colleagues (Kern *et al.*, 2014) found higher CSF levels of IL-6 and IL-8 in older adults with LLD suggesting older adults with LLD present with pro-inflammatory status. In a recent study, we found that despite no significant differences in AD-related biomarkers, older adults with LLD had significantly lower CSF BDNF levels compared to non depressed control subjects (Diniz *et al.*, 2014). The reduction in CSF BDNF levels was greater in those with LLD and MCI. Finally, a recent data-driven proteomic-based study showed that cognitive impairment in LLD was associated with abnormalities in multiple biological pathways, e.g., regulation of the immune-inflammatory processes, lipid and protein metabolism, metabolic control, cell survival and neurotrophic support (Diniz *et al.*, 2015). These changes have been reported in AD and may help to explain why LLD increases the risk of AD and other dementias in the elderly.

The present results should be viewed in light of some limitations. The individual study samples were very heterogeneous with relatively small samples of depressed and non-depressed subjects, with methodological difference in the diagnosis of depression, recruitment settings, and the laboratorial methods used to measure plasma and CSF Aβ peptides. Moreover, depression in older adults has a very heterogeneous clinical presentation that may reflect abnormalities in multiple biological pathways. These factors may have introduced significant heterogeneity in the meta-analysis, influencing its results. Nonetheless, we addressed study heterogeneity by using random effects models in all analyses. Also, due to the cross-sectional design of the included studies we could not evaluate whether plasma or CSF Aβ peptides can predict the risk of AD among older adults with depression. Some studies did not find a significant correlation between plasma and CSF

Aβ peptides concentration or brain amyloid deposition (Mehta *et al.*, 2001; Fagan *et al.*, 2006), which limits the interpretation of the role of plasma in AD or LLD. Finally, the studies included in the meta-analysis, except one (Diniz *et al.*, 2014), did not specifically address the impact of cognitive impairment co-occurring with depression on CSF or plasma levels of Aβ peptides. This is important since the comorbidity of depression and MCI significantly increases the risk of developing AD in older adults (Modrego and Ferrández, 2004; Aizenstein *et al.*, 2011).

In conclusion, the present meta-analysis provides additional evidence that LLD is associated with significant changes in the metabolism of plasma and CSF Aβ peptide. The findings also provide insights into the potential role for Aβ in the pathophysiology of LLD. Population-based studies with systematic assessment of cognitive performance, are necessary to determine whether the systematic measurement of plasma and CSF Aβ peptides can identify a subgroup of older adults with major depression that are at increased risk for developing AD and the possibility to adjust for future dementias.

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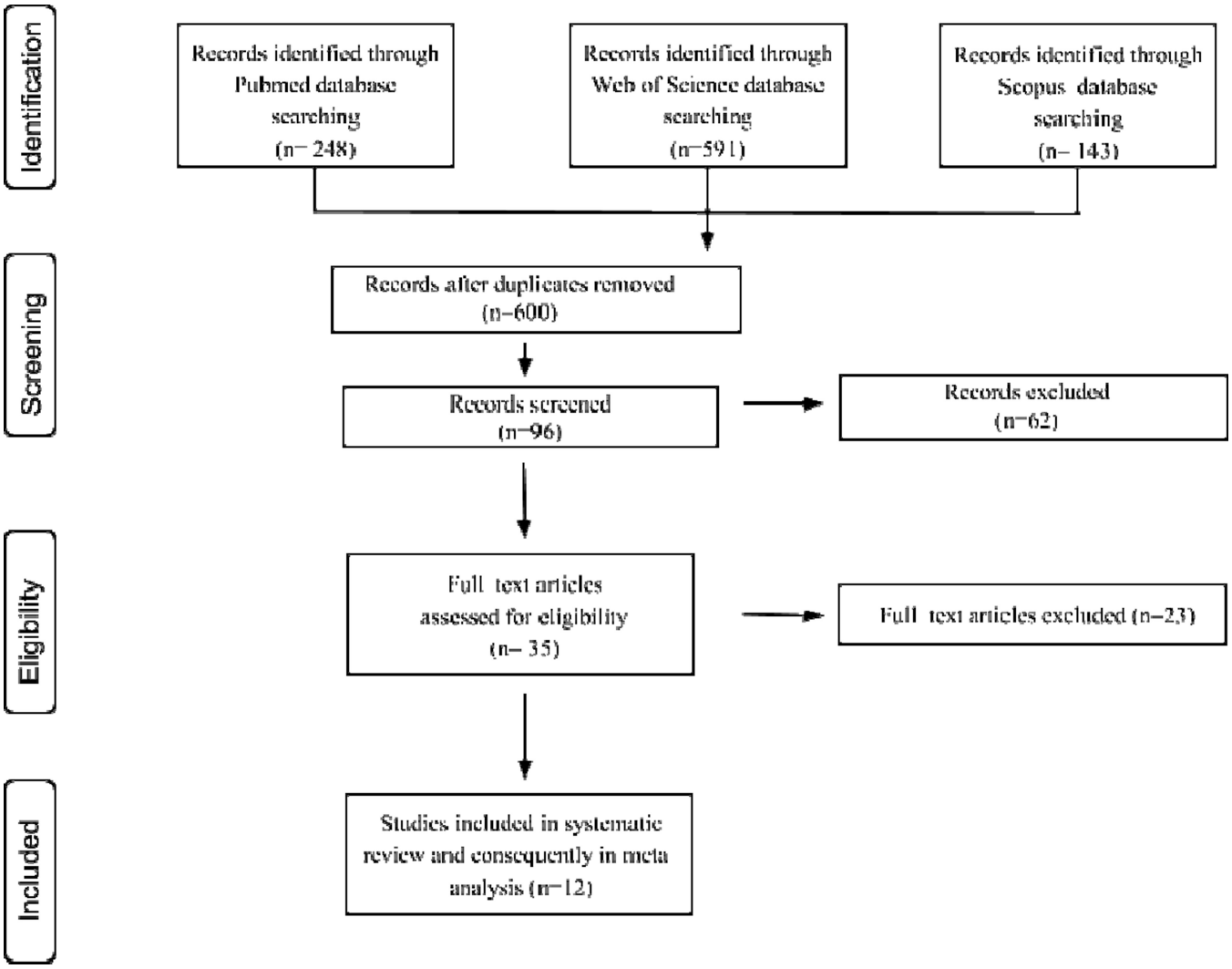


**Figure 1.**
Flow diagram of study search and selection for inclusion in the meta-analysis.

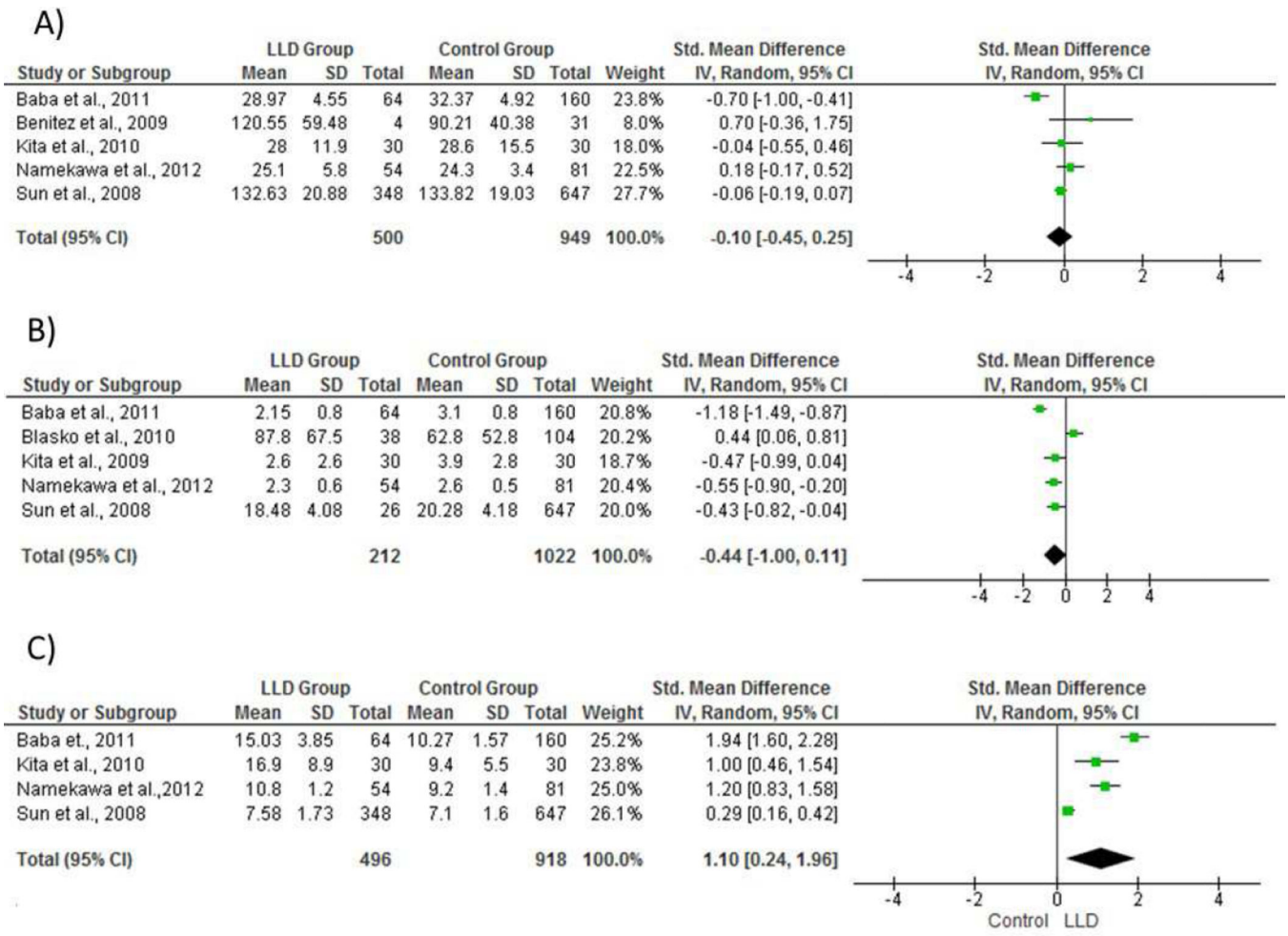


**Figure 2.**

Forest plot of plasma amyloid-β levels for individual studies and its respective weight for (A) $A\beta_{40}$ levels (B) $A\beta_{42}$ levels and (C) $A\beta_{40}$:$A\beta_{42}$ ratio levels

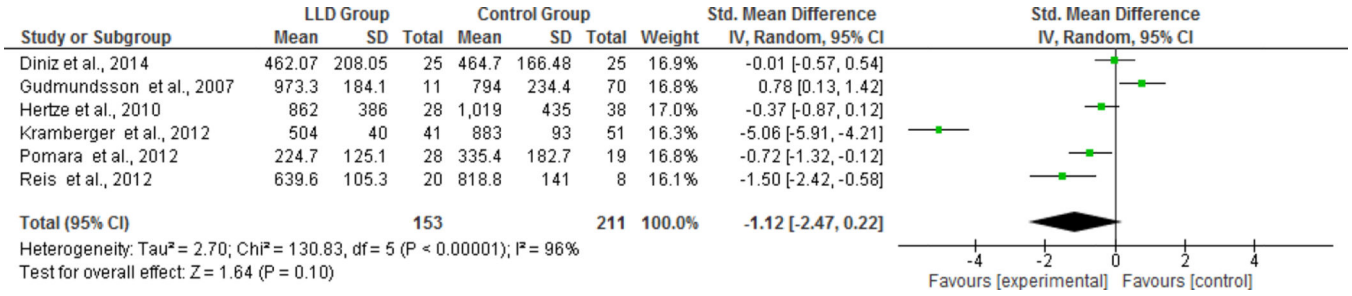


**Figure 3.**

Forest plot of CSF for individual studies and its respective weight for $A\beta_{42}$ levels for all individual studies and its respective weight.

**Table 1**

Characteristics of included studies in systematic review for plasma Aβ peptides levels.

| Study | Control Group (n) | Mean Age ± SD | $A\beta_{40}$ (pg/mL) | $A\beta_{42}$ (pg/mL) | $A\beta_{40}A\beta_{42}$ ratio | LLD Group (n) | Mean Age ± SD | $A\beta_{40}$ (pg/mL) | $A\beta_{42}$ (pg/mL) | $A\beta_{40}A\beta_{42}$ ratio | Method | DSM criteria | Study setting |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Baba *et al.*, 2012 | 160 | 69.7 ± 3.8 | 32.4 ± 4.9 | 3.1 ± 0.8 | 10.3 ± 1.6 | 64 | 72.0 ± 5.5 | 29.0 ± 4.6 | 2.2 ± 0.8 | 15.0 ± 3.9 | Elisa | yes | Clinical |
| Benitez *et al.*, 2009 | 31 | 73.7 ± 6.6 | 90.2 ± 40.4 | - | - | 4 | 73.7 ± 6.6 | 120.6 ± 59.5 | - | - | Elisa | no | Clinical |
| Blasko *et al.*, 2010 | 104 | 75.8 ± 0.5 | - | 62.8 ± 52.8 | - | 38 | 75.8 ± 0.5 | - | 87.8 ± 67.5 | - | Elisa | yes | Clinical |
| Kita *et al.*, 2009 | 30 | 69.7 ± 4.7 | 28.6 ± 15.5 | 3.9 ± 2.8 | 9.4 ± 5.5 | 30 | 68.2 ± 5.6 | 28.0 ± 11.9 | 2.6 ± 2.6 | 16.9 ± 8.9 | Elisa | yes | Clinical |
| Namekawa *et al.*, 2013 | 81 | 66.9 ± 4.9 | 24.3 ± 3.4 | 2.6 ± 0.5 | 9.2 ± 1.4 | 54 | 68.3 ± 5.0 | 25.1 ± 5.8 | 2.3 ± 0.6 | 10.8 ± 1.2 | Elisa | no | Clinical |
| Sun *et al.*, 2008 | 647 | 76.0 ± 8.3 | 133.8 ± 19.0 | 20.3 ± 4.2 | 7.1 ± 1.6 | 348 | 73.8 ± 8.5 | 132.6 ± 20.9 | 18.5 ± 4.1 | 7.6 ± 1.7 | Elisa | yes | Clinical |
| Total number | 1052 | | | | | 538 | | | | | | | |

Abbreviations: LLD: Late-Life Depression; ELISA: Enzyme-Linked Immunosorbent Assay; DSM: Diagnostic and Statistical Manual of Mental Disorders; CES-D: Centre for Epidemiological Studies - Depression Scale; HDRS: Hamilton Depression Rating Scale; GDS: Geriatric Depression Scale; PRIME-MD: Primary Care Evaluation of Mental Disorders

**Table 2**

Characteristics of included studies in systematic review for CSF Aβ peptides levels.

| Study | Control Group (n) | Mean Age ± SD | $A\beta_{40}$ (pg/mL) | $A\beta_{42}$ (pg/mL) | LLD Group (n) | Mean Age ± SD | $A\beta_{40}$ (pg/mL) | $A\beta_{42}$ (pg/mL) | Method | DSM criteria | Study setting |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Diniz *et al.*, 2014 | 25 | 71.0 ± 3.7 | - | 464.7 ± 166.5 | 25 | 69.2 ± 5.5 | - | 462.1 ± 208.0 | Luminex | yes | Clinical |
| Gudmundsson *et al.*, 2007 | 70 | 72.6 ± 3.1 | - | 794.0 ± 234.4 | 11 | 72.6 ± 3.1 | - | 973.3 ± 184.1 | Elisa | yes | Population-based |
| Hertze *et al.*, 2010 | 38 | 77.0 ± 8.2 | 11036.0 ± 2613.0 | 1019.0 ± 435.0 | 28 | 58.0 ± 8.4 | 8235.0 ± 2535.0 | 862.0 ± 386.0 | Luminex | yes | Population-based |
| Kramberger *et al.*, 2012 | 51 | 70.7 ± 6.3 | - | 883.0 ± 93.0 | 41 | 71.3 ± 6.1 | - | 504.0 ± 40.0 | Elisa | no | Clinical |
| Pomara *et al.*, 2012 | 19 | 68.1 ± 7.3 | 6518.0 ± 2687.0 | 335.4 ± 182.7 | 28 | 66.5 ± 5.4 | 5146.0 ± 2369.0 | 224.7 ± 125.1 | Luminex | yes | Population-based |
| Reis *et al.*, 2012) | 8 | 65.0 ± 5.6 | - | 818.8 ± 141.0 | 20 | 62.7 ± 3.0 | - | 639.6 ± 105.3 | Elisa | yes | Clinical |
| Total number | 211 | | | | 153 | | | | | | |

Abbreviations: LLD: Late-Life Depression; ELISA: Enzyme-Linked Immunosorbent Assay; DSM: Diagnostic and Statistical Manual of Mental Disorders; CES-D: Centre for Epidemiological Studies - Depression Scale; HDRS: Hamilton Depression Rating Scale; MADRS: Montgomery–Asberg Depression Rating Scale; CPRS: Comprehensive Psychopathological Rating Scale.