Meta-analysis of Cerebrospinal Fluid Neuron-specific Enolase Levels in Alzheimer's Disease, Parkinson's Disease, Dementia With Lewy Bodies, and Multiple System Atrophy

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Research

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Abstract

Background: To investigate the usefulness of cerebrospinal fluid (CSF) neuron-specific enolase (NSE) levels as a candidate biomarker of neurodegeneration in Alzheimer's disease (AD), Parkinson's disease (PD), PD with dementia (PDD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA).

Methods: We performed a systematic search of PubMed, the Cochrane Library, SCOPUS, and Google Scholar to find studies that investigated the CSF levels of NSE in AD, PD, DLB, and/or MSA. For each disease, we pooled all available data and performed a meta-analysis, and meta-regression analyses of age and sex were conducted when significant in the main analysis.

Results: Twenty studies were included (13 for AD, 8 for PD/PDD/DLB, and 4 for MSA). Significantly elevated CSF NSE levels were detected in AD (Hedges' g = 0.822, 95% confidence interval [95%CI]: 0.332 to 1.311, p = 0.0010), but the data exhibited high heterogeneity (I^2 = 88.43%, p<0.001). The meta-regression analysis of AD showed that age (p<0.001), but not sex, had a significant effect on NSE. A meta-analysis of all the pooled data for PD/PDD/DLB did not show any significant changes in the CSF NSE level, but a sub-group analysis of PDD/DLB revealed significantly elevated CSF NSE levels (Hedges' g = 0.507, 95%CI: 0.020 to 0.993, p = 0.0412). No significant changes in CSF NSE levels were detected in MSA.

Conclusions: This study provided evidence about the usefulness of CSF NSE levels as a biomarker in AD and PDD/DLB, and age was found to affect the CSF NSE levels of AD patients.

Introduction

Neuron-specific enolase (NSE) (or γ-enolase) is abundantly and ubiquitously expressed in neurons, and it is considered to be a candidate cerebrospinal fluid (CSF) biomarker for neurological disorders.

It is widely accepted to be a useful biomarker of Creutzfeldt-Jakob disease [1], hypoxic encephalopathy [2], epilepsy [3], and brain injuries [4].

The CSF level of NSE has also been studied in neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), Lewy body disease (LBD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). However, these previous studies reported inconclusive or even conflicting results.

Herein, we report the first meta-analysis of the CSF levels of NSE in AD, PD, DLB, and MSA.

Methods

We adopted the PRISMA 2009 system for the meta-analysis. We performed a search of PubMed, the Cochrane Library, Google Scholar, and SCOPUS for articles published on or before September 22, 2020. The keywords used for the search were as follows: "neuron-specific enolase" AND "cerebrospinal fluid" AND ("Alzheimer" OR "Parkinson" OR "Lewy" OR "multiple system atrophy"). Non-human studies,

irrelevant studies, non-English articles, and review articles were excluded. All available articles were retrieved, and the mean and standard deviation (SD) values they reported were pooled. If an article reported median, quartile, or standard error values, the data were converted to mean and standard deviation values using a previously reported method [5].

Effect sizes (ES) were generated based on the sample size, mean CSF NSE level, and the associated SD values. Detailed data from our previous study (Katayama et al., 2020a) are also reported in this article. The significance of differences in the pooled ES was estimated using 95% confidence intervals (95%CI).

We combined the data for PD, PDD, LBD, and DLB and analyzed it under the heading “PD/PDD/DLB” because these conditions share common mechanisms; i.e., they are all synucleinopathies involving Lewy bodies [6], and we analyzed the data for AD and MSA separately.

All statistical analyses were performed using the STATA software, version 16 (StataCorp LLC, TX, USA), and a random effects model (the DerSimonian-Laird method) was adopted. Heterogeneity was assessed with Cochran’s Q test, and the Higgins I^2 index was used to determine heterogeneity across studies. I^2 indexes of 0–25%, 26–50%, 51–75%, and 76–100% were regarded to indicate low, medium, high, and very high levels of heterogeneity, respectively. Forest plots and funnel plots were drawn with the software. Egger’s test was used to check for publication bias. Sensitivity analyses were performed by removing the data for one study at a time to test whether the outcomes of the meta-analysis were significantly influenced by a single study. When significantly altered CSF NSE levels were detected in the main analysis, meta-regression analysis was performed to assess the effects of age and sex.

P-values of < 0.05 ($p < 0.05$) were considered statistically significant. We did not adjust the level of significance for multiple comparisons because of the exploratory aims of our analyses.

Results

We found 41 relevant articles in PubMed, 21 in the Cochrane Library, 127 in SCOPUS, and 576 in Google Scholar. We scrutinized their titles, abstracts, and contents and eliminated the articles that met the exclusion criteria. Finally, 20 studies (13 for AD, 8 for PD/PDD/DLB, and 4 for MSA) were included [7–26]. Five studies reported data for two or more diseases (Fig. 1).

1. Analysis of AD

The pooled data for AD are summarized in Additional file 1. One study reported early and late AD (e-AD and l-AD) separately [11], and we combined the mean and SD data for these conditions into a single group.

The meta-analysis detected significantly elevated CSF NSE levels in AD (Hedges’ g = 0.822, 95%CI: 0.332 to 1.311, p = 0.0010), but the data exhibited very high heterogeneity (Cochran’s Q = 103.74, df = 12, I^2 = 88.43%, p < 0.001; Fig. 2).

The sensitivity analysis, which involved the removal of the data for each study in turn, did not identify any study that significantly affected the result, and therefore, the consistency of the conclusion was confirmed. A funnel plot is shown in Fig. 3, and Egger's test did not produce a significant result (z = 1.87, p = 0.0608); i.e., no publication bias was observed.

The meta-regression analysis showed that age (coefficient = 0.1626, standard error = 0.0407, 95%CI: 0.0828 to 0.2424, z = 3.99, p < 0.001), but not sex (p > 0.05) had a significant effect on the CSF NSE levels of AD patients.

2. Analysis of PD, PDD, LBD, and DLB

The pooled data for these diseases are summarized in Additional file 2. The meta-analysis did not show any significant changes in the CSF NSE levels in PD/PDD/DLB (Hedges' g = 0.343, 95%CI: -0.027 to 0.713, p = 0.0694), although the data exhibited very high heterogeneity (Q = 48.85, df = 7, I^2 = 81.58%, p < 0.0001). However, a sub-group analysis showed significantly elevated CSF NSE levels in PDD/DLB (Hedges' g = 0.507, 95%CI: 0.020 to 0.993, p = 0.0412; Fig. 4). A funnel plot is shown in Fig. 5, and Egger's test did not produce a significant result (z = 1.52, p = 0.1280); i.e., there was no publication bias.

In the sensitivity analysis, the results were only affected when the data from the study by Abdo et al. [21] were removed (Hedges' g = 0.494, 95%CI: 0.179 to 0.810). In a meta-regression analysis of PDD/DLB, neither age nor sex exhibited a significant effect on the CSF NSE level (p > 0.05).

3. Analysis of MSA

The pooled data for MSA are summarized in Additional file 3.

Two studies examined MSA with predominant Parkinsonism (MSA-P) and MSA with cerebellar features (MSA-C) separately [21, 26]. We combined the mean and SD data for these conditions to create a single group for the main analysis.

A meta-analysis did not show any significant changes in CSF NSE levels in MSA (Hedges' g = 0.387, 95%CI: -0.293 to 1.067, p = 0.2648; Fig. 6), although the data displayed very high heterogeneity (Q = 20.63, df = 3, p = 0.0001, I^2 = 85.46%). Furthermore, sub-group analyses of MSA-C and MSA-P without the data from the study by Santaella et al. [24] were performed because sub-group data were not reported in the latter study, but no significant changes in CSF NSE levels were detected in either group (MSA-C: Hedges' g = 0.412, 95%CI: -0.654 to 1.479; MSA-P: Hedges' g = -0.006, 95%CI: -0.577 to 0.566; see Additional file 4). No sensitivity analysis was performed because of the small size of the data sample.

A funnel plot is shown in Fig. 7, and Egger's test produced a statistically significant result (z = 3.19, p = 0.0014), which suggested that our data for MSA were affected by publication bias.

Discussion

This is the first reported meta-analysis of the CSF NSE levels of AD, PD, DLB, and MSA patients, and it provided evidence about the significance of CSF NSE levels in AD and PDD/DLB.

1. CSF NSE levels in AD

This study detected significantly elevated CSF NSE levels in AD patients, which are considered to reflect the neurodegenerative processes that occur in AD, and the sensitivity analysis of the AD-related data confirmed the consistency of the results. Therefore, this study indicated that the CSF NSE level might be useful as an objective surrogate biochemical marker of AD-related neuronal damage. T-tau is widely accepted as a biomarker of AD-related neurodegeneration [27], and the current study suggested that NSE could also be used for such purposes.

Meta-regression analysis revealed that age contributed to the high heterogeneity of the data, and this point should be considered when interpretating the CSF NSE levels of AD patients. However, a previous study reported CSF NSE levels were not correlated with age or sex in a normal population [28]. Other possible causes of the heterogeneity include sex, the spatial distribution of pathological changes, disease activity/rapidity, disease stage, genotypes (e.g., apolipoprotein ε4), and confounding vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, etc.). Indeed, a previous study detected a significant correlation among NSE, Aβ42, and total tau levels [13]. Generally, NSE is seen as a marker of neurodegeneration, whereas amyloid and tau are regarded as markers of upstream changes in AD. Further studies are needed to examine these points.

The high heterogeneity observed in the CSF NSE levels of the AD patients in this study raises other possibilities, such as the effects of diagnostic accuracy. The clinical diagnosis of AD is based on the relevant criteria, but post-mortem pathological verification has demonstrated the difficulty of achieving an accurate pre-mortem diagnosis and differentiating AD from non-Alzheimer's dementias, such as argyrophilic grain disease, primary age-related tauopathy, and other AD-mimicking disorders, pre-mortem [29]. A previous set of diagnostic criteria (NINCDS-ADRDA) exhibited high sensitivity (93%) for diagnosing AD and frontotemporal dementia, but low specificity (23%) [30]. However, a study of the latest criteria for AD (the IWG-2 criteria), which include criteria relating to CSF biomarkers and amyloid positron emission tomography (PET), reported that the use of this combination of biomarkers resulted in a sensitivity value of 90–95% and a specificity value of about 90% for diagnosing AD, and the agreement between florbetapir amyloid PET images and post-mortem results reached 96% [31]. Therefore, the updating of diagnostic criteria to account for new methodologies could have contributed to the heterogeneity observed in this study. Other possible reasons for the heterogeneity include variations in the disease duration, stage, or activity of AD, and differences among the subtypes of AD [32]. The meta-regression analysis of AD conducted in this study showed that age contributed to the heterogeneity in the CSF NSE levels of the AD patients. Many previous studies did not stratify their data according to disease duration or stage. In addition, another study did not detect a clear difference between the CSF NSE levels of early-onset and late-onset AD patients [11], but further studies with larger samples are needed to examine this

issue. Moreover, technical factors, such as sampling procedures or assay methods, should be evaluated to clarify whether they can explain the heterogeneity of the results.

2. CSF NSE levels in PD, PDD, and DLB

This study revealed significantly elevated CSF NSE levels in PDD/DLB, but not in PD.

The detection of significant changes in CSF NSE levels in both AD and DLB reminds us that AD and DLB share common amyloid β- and tau-related pathologies [6], but examining the effects of these pathologies on CSF NSE levels would require further studies, such as studies involving amyloid or tau PET. The meta-regression analysis of PDD/DLB did not show significant effects of age or sex on CSF NSE levels, but these results were inconclusive because of the small number of studies included.

3. NSE levels in MSA

This study did not reveal any significant changes in the CSF NSE level in MSA, and significant evidence of publication bias relating to this topic was detected. Recent studies have identified other potentially useful biomarkers of MSA, such as α-synuclein, neurofilament light chain, DJ-1, 8-hydroxyguanosine (8OHG), Flt3 (Fms-related tyrosine kinase) ligand, YKL-40 (CHI3L1), and ubiquitin carboxy-terminal hydrolase L1 (UCHL-1) [33]. Further studies are needed to identify the optimal molecular biomarkers of MSA.

This study had some limitations. First, the CSF NSE level data exhibited high heterogeneity, and there were quite large overlaps between the disease groups and controls. Therefore, the application of this biomarker to clinical practice should be performed cautiously. Second, elevated CSF NSE levels reflect neuronal damage, but are not disease-specific. Several of the studies included in this study adopted panels of biomarkers (amyloid β, total tau, phosphorylated tau, α-synuclein, and neurofilament light chain, etc.) to detect combinations of molecular pathological changes.

Nevertheless, measuring CSF NSE levels could be useful because NSE assays are available in many laboratories.

In conclusion, this meta-analysis revealed significantly elevated CSF NSE levels in AD and PDD/DLB, but not in MSA. This study will aid our understanding of the pathological mechanisms underlying these diseases and support further investigations, more accurate diagnosis, and evaluations of therapeutic interventions.

Abbreviations

Aβ: Amyloid beta; AD: Alzheimer’s disease; CI: confidence interval; CSF: cerebrospinal fluid; DLB: dementia with Lewy bodies; ES: effect size; LBD: Lewy body disease; MSA: multiple system atrophy; MSA-C: multiple system atrophy with cerebellar features; MSA-P: multiple system atrophy with predominant Parkinsonism; NSE: neuron specific enolase; PD: Parkinson’s disease; PDD: Parkinson’s disease with

dementia; PET: positron emission tomography; p-tau: phosphorylated tau; SD: standard deviation; t-tau: total tau

Declarations

Ethics approval and consent to participate

Ethical approval was not required because all work was carried out using previously published studies.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None

Authors' contributions

The statistical analyses and data interpretation were conducted by TK. The study was designed by TK. The manuscript was drafted by TK. The literature search was conducted by TK and JS, and the manuscript was revised by TK, JS, KT, OS, and NH. All authors read and approved the final manuscript.

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Not applicable

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Figures

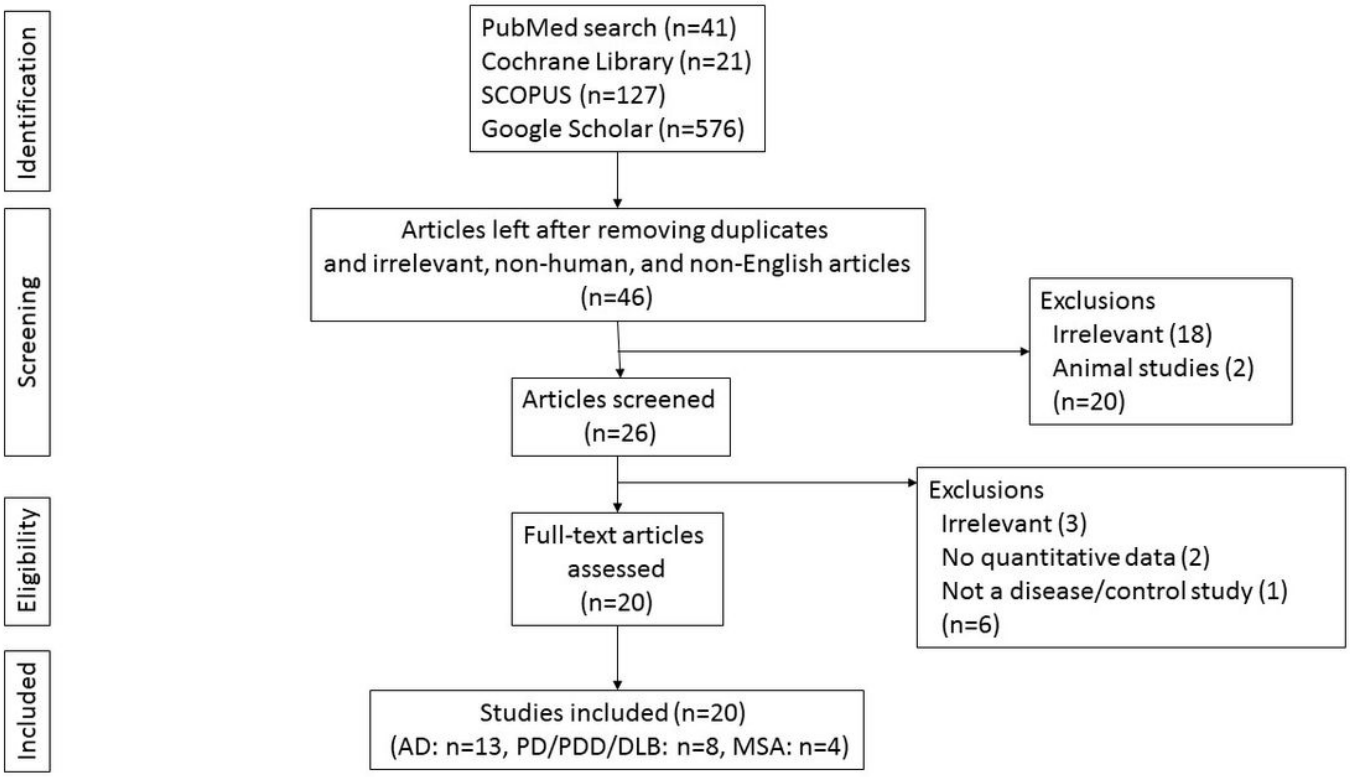

Figure 1

Study design AD, Alzheimer’s disease; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PD, Parkinson’s disease The figures in parentheses indicate the numbers of articles.

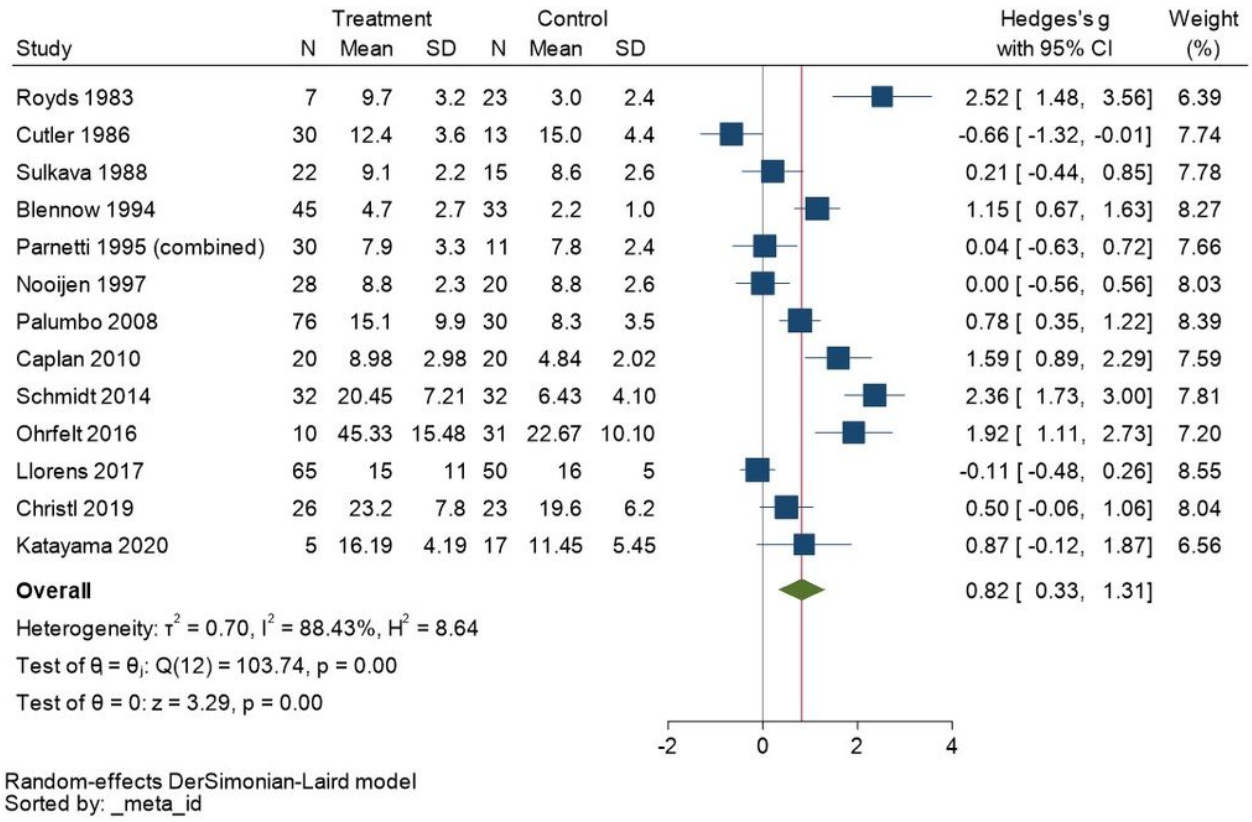

Figure 2

Forest plot for Alzheimer's disease CI, confidence interval; SD, standard deviation

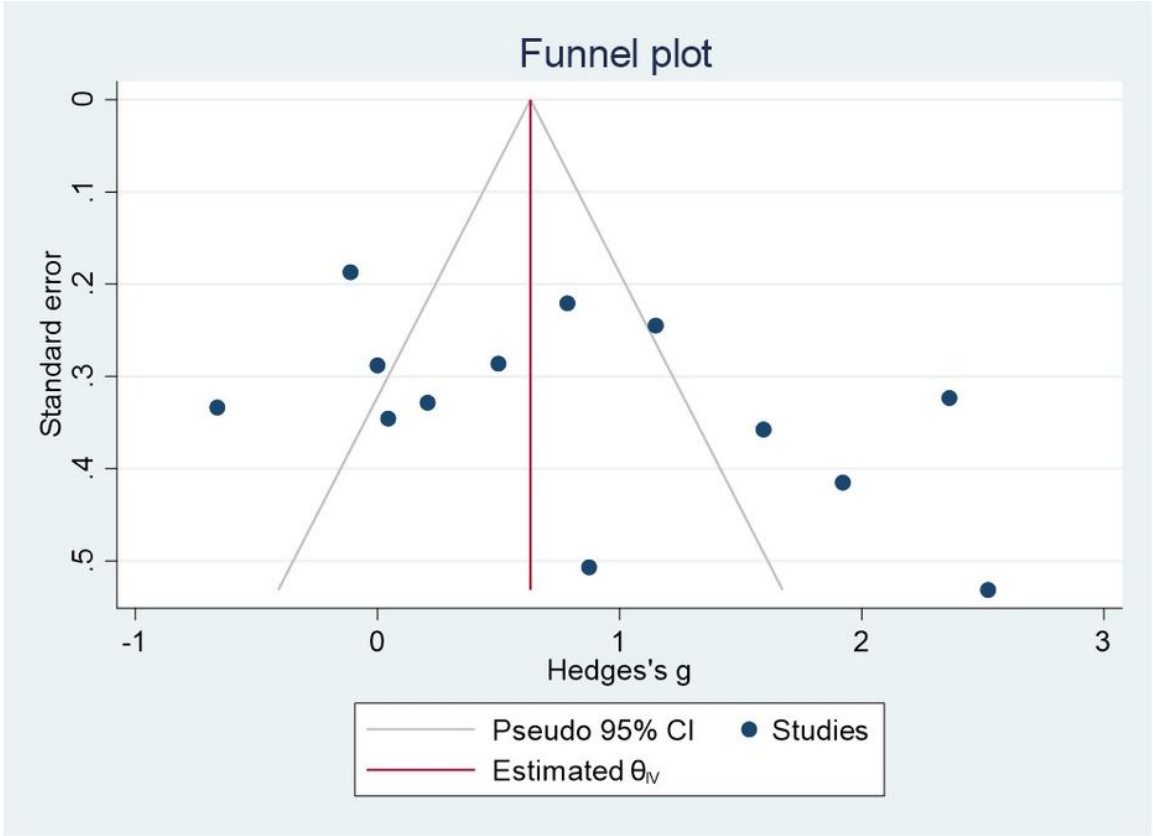

Figure 3

Funnel plot for Alzheimer's disease

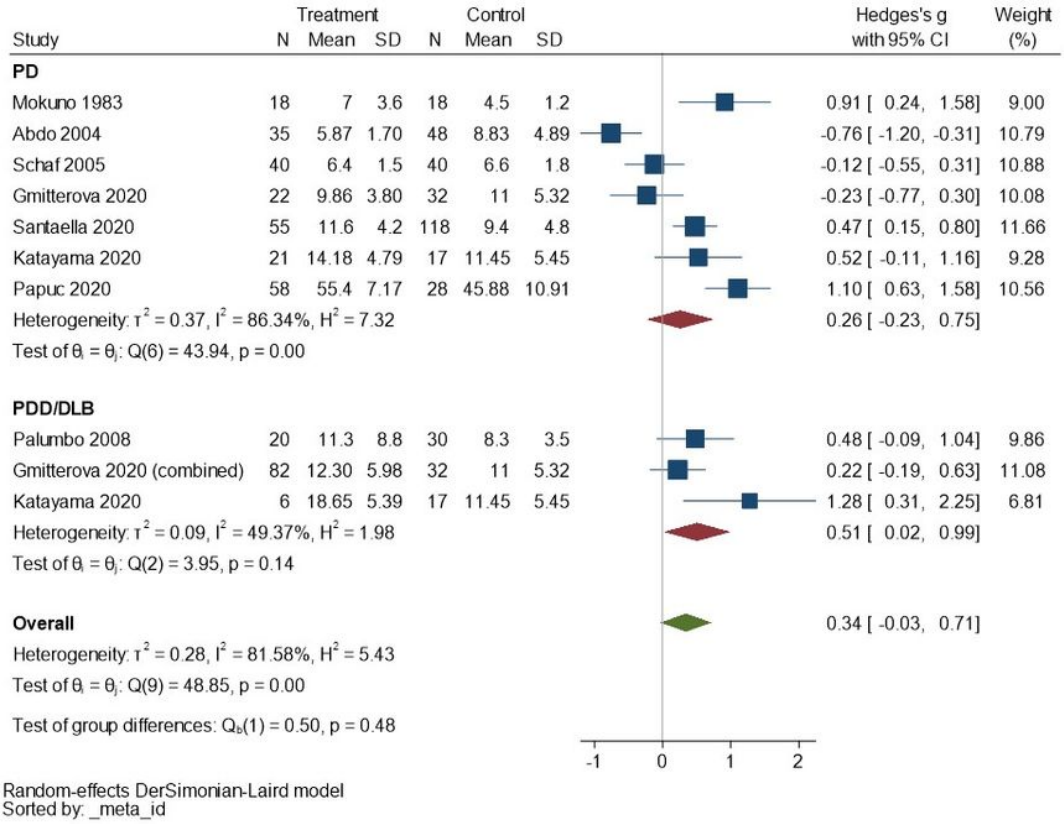

Figure 4

Forest plot for Parkinson's disease (PD), PD with dementia, dementia with Lewy bodies, and the overall analysis CI, confidence interval; SD, standard deviation

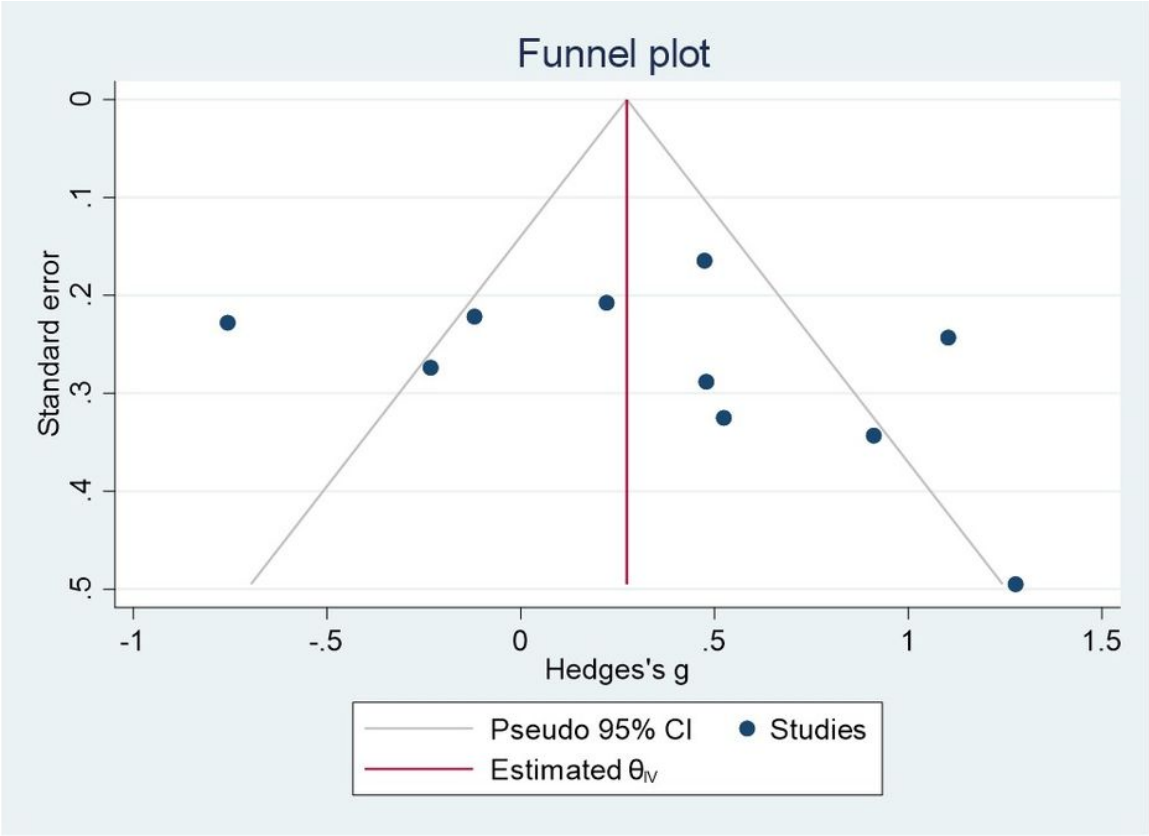

Figure 5

Funnel plot for Parkinson's disease (PD), PD with dementia, and dementia with Lewy bodies

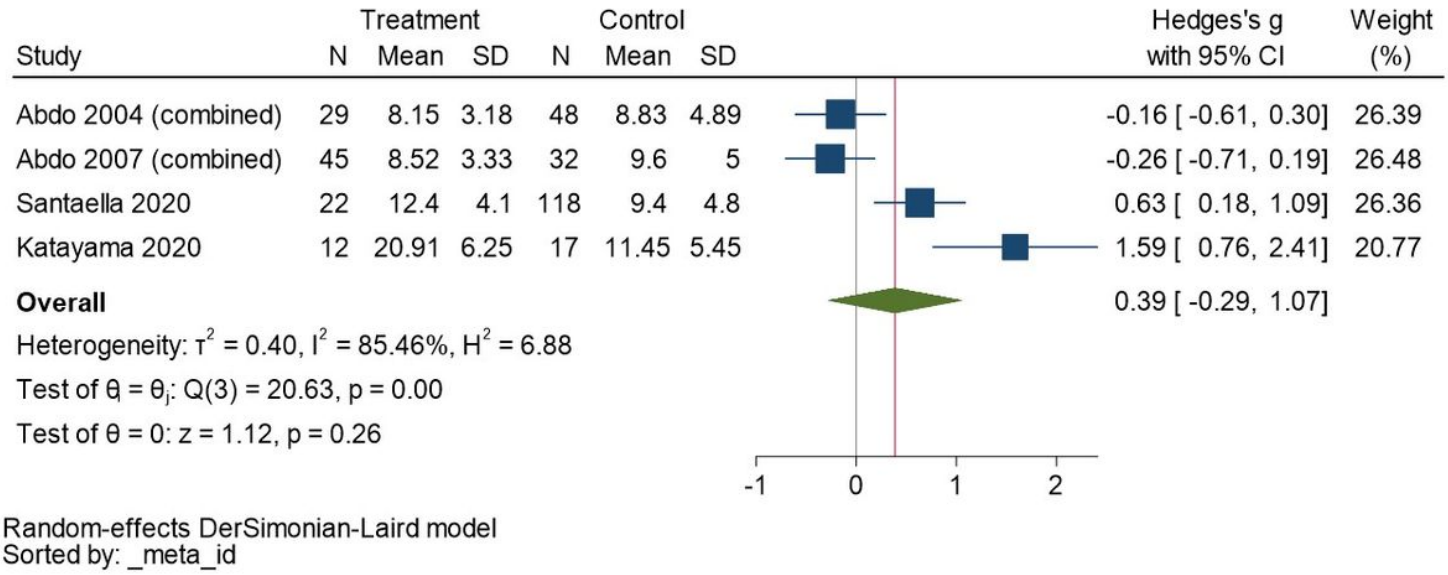

Figure 6

Forest plot for multiple system atrophy CI, confidence interval; SD, standard deviation

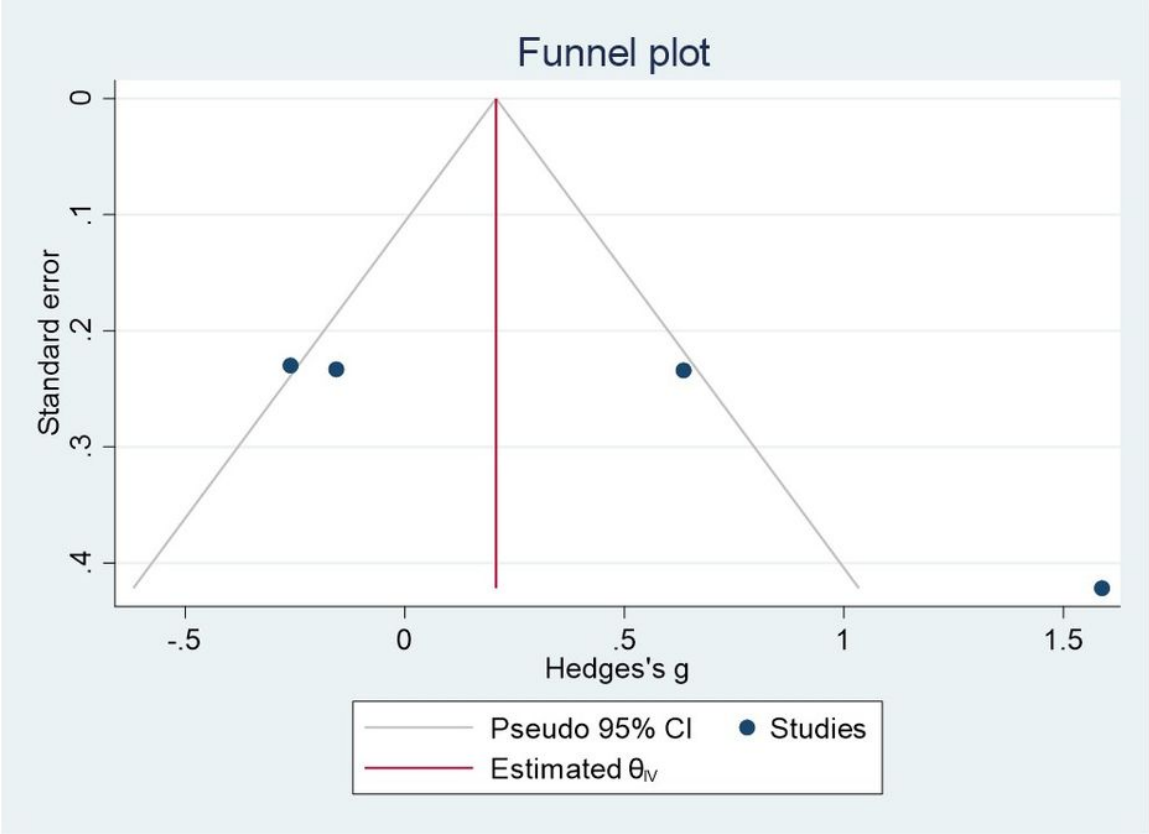

Figure 7

Funnel plot for multiple system atrophy

Supplementary Files

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