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## Prevalence of TDP-43 proteinopathy in cognitively normal older adults: systematic review and meta-analysis

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### Ethical Approval

Only ethically approved articles were included in our systematic review and meta-analysis.

### Author Contributions

Camila Nascimento, study concept and design, acquisition and interpretation of data

Ana Tereza Di Lorenzo Alho, acquisition of data

Caroline Bazan Conceição Amaral, acquisition of data

Renata Elane Paraizo Leite, critical revision of the manuscript for important intellectual content and study supervision

Ricardo Nitrini, critical revision of the manuscript for important intellectual content

Wilson Jacob-Filho, study supervision

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Suvi Rosa Kastehelmi Hokkanen, acquisition of data and critical revision of the manuscript for important intellectual content and study supervision

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Lea Tenenholz Grinberg, critical revision of the manuscript for important intellectual content

Claudia Kimie Suemoto, analysis and interpretation of data, critical revision of the manuscript for important intellectual content and study supervision

### Units of measurement

Symbols and abbreviations were used in conformity with the guidelines laid down in Baron D.N. (1988) *Units, Symbols and Abbreviations*, 4th ed. published and supplied by the Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE.

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## Abstract

**Objective**—To perform a systematic review and meta-analysis on the prevalence of TDP-43 proteinopathy in cognitively normal older adults.

**Methods**—We systematically reviewed and performed a meta-analysis on the prevalence of TDP-43 proteinopathy in older adults with normal cognition, evaluated by the Mini-Mental State Examination or the Clinical Dementia Rating. We estimated the overall prevalence of TDP-43 using random-effect models, and stratified by age, sex, sample size, study quality, antibody used to assess TDP-43 aggregates, analyzed brain regions, Braak stage, CERAD score, hippocampal sclerosis, and geographic location.

**Results**—A total of 505 articles were identified in the systematic review, and seven were included in the meta-analysis with 1,196 cognitively normal older adults. We found an overall prevalence of TDP-43 proteinopathy of 24%. Prevalence of TDP-43 proteinopathy varied widely across geographic location (North America: 37%, Asia: 29%, Europe: 14%, and Latin America: 11%). Estimated prevalence of TDP-43 proteinopathy also varied according to study quality (quality score >7: 22% vs. quality score <7: 42%), antibody used to assess TDP-43 proteinopathy (native: 18% vs. hyperphosphorylated: 24%), and presence of hippocampal sclerosis (without 24% vs. with hippocampal sclerosis: 48%). Other stratified analyses by age, sex, analyzed brain regions, sample size, and severity of AD neuropathology showed similar pooled TDP-43 prevalence.

**Conclusions**—Different methodology to assess TDP-43, and also differences in lifestyle and genetic factors across different populations could explain our results. Standardization of TDP-43 measurement, and future studies about the impact of genetic and lifestyle characteristics on the development of neurodegenerative diseases are needed.

## Keywords

TDP-43 proteinopathy; brain aging; elderly; dementia; postmortem

## Introduction

Abnormal accumulation of transactive response DNA-binding protein 43 (TDP-43) is found in several age-related diseases, including frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD) [1, 2]. Indeed, expression of clinical symptoms during disease progression follows regional and cell-specific patterns of pathological TDP-43 accumulation [3]. For example in FTD behavioral variant, TDP-43 inclusions are present in brain regions that play a central role in emotional control, such as in the orbitofrontal cortex and the amygdala, while in ALS the encephalic regions responsible for motor control are primarily affected [4, 5]. In the semantic variant of FTD, left lateral temporal cortex atrophy is associated with frontotemporal lobar degeneration with accumulation of TDP-43 (FTLD-TDP). TDP-43 pathology has been also associated with aggravated memory loss and medial temporal atrophy in AD, which are major features of the

disease [6]. Furthermore, TDP-43 proteinopathy have been independently associated with more rapid cognitive decline and impairment of episodic memory in older adults [7].

Pathological changes in the brain may be present decades before the onset of clinical symptoms [8, 9]. Early detection of neurodegenerative diseases is crucial to better understand their pathophysiology and improve the diagnosis and treatment of these diseases. Tools to assess pathological accumulation of proteins related to other neurodegenerative diseases in patients, such as tau and  $\beta$ -amyloid [10–12], are now possible to be used in patients. However, approaches to detect TDP-43 accumulation *in vivo* in humans are not yet available [13]. A way to better understand the early changes in TDP-43 protein is studying its prevalence through post-mortem neuropathological evaluation in cognitively normal older adults. These studies have shown a wide variation in TDP-43 frequency, ranging from 8 to 52% [14–17]. In this study, we performed a systematic review of the literature on the prevalence of TDP-43 proteinopathy in cognitively normal older adults.

## Methods

The systematic review and meta-analysis were performed based on the guidelines of both the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [18–20] and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) [21].

### Selection of studies

We conducted a systematic review of the literature from January 2006 to November 2015 on the prevalence of TDP-43 proteinopathy, using the search terms: "TDP-43 AND cognitively normal elderly" OR "TDP-43 AND health aging" OR "TDP-43 AND normal aging" OR "TDP-43 AND controls". All search terms were used across three different databases: Pubmed (which comprises MEDLINE, Mesh, and NLM), EMBASE, and Web of Science. Three investigators conducted the search independently of each other (ATA, CB, and CN).

We included studies that had data on the prevalence of TDP-43 proteinopathy in cognitively normal subjects without FTLTDP. Normal cognition was evaluated by the Clinical Dementia Rating (CDR=0) [22] or by the Mini-Mental State Examination [23]. To be included in this meta-analysis, articles had to state ethical approval, and the assessment of TDP-43 inclusions had to be performed using immunohistochemistry in post-mortem brain tissue, which is the gold-standard method to diagnose TDP-43 proteinopathy [24]. Because TDP-43 proteinopathy can be found widespread in the brain [1, 4, 17, 25], we considered studies that analyzed these inclusions in any encephalic region. Since TDP-43 proteinopathy in neurodegenerative diseases was first described in 2006, we included studies published from 2006 to 2015. Only articles published in English were included.

Duplicate articles among the databases were excluded and the remaining articles were organized in numeric codes. Two blinded investigators (ATA and CN) screened the titles and the abstracts of all articles and selected those that were considered eligible to this study. We also checked the references of these articles for additional eligible studies. Subsequently, ATA and CN read the entire content of the eligible articles and reached a consensus on those that met the inclusion criteria. For data extraction, authors consulted all available

information in the included articles, such as figures and tables, as well as the main text. Besides the sample size and the number of subjects with TDP-43 proteinopathy, we also included information about other variables that could explain heterogeneity among studies. These variables were age, sex, where the study was conducted, type of antibody used to assess TDP-43 inclusions, and the brain regions in which TDP-43 proteinopathy was analyzed. If any variable of interest was missing, CN contacted the corresponding authors of the articles to request the missing data by e-mail.

### Quality control

Quality control of the included studies was performed based on a guideline for the evaluation of prevalent studies [26]. We used nine of the ten original guideline questions to assess the quality of the included studies. One question was excluded because it was regarding recruitment of the patients and our study focused on post-mortem neuropathological data. A score from 0 to 9 was given independently by each one of the investigators (ATA and CN), according to sample size, reliability of the study, and quality of the statistical analysis. Higher scores indicate better study quality. The final score was achieved by consensus between the two investigators when necessary.

The minimum required sample size to be included in this meta-analysis was calculated, according to the formula [26]:  $n = \frac{Z^2 * P(1 - P)}{d^2}$ , where n= sample size, Z= Z-statistic for the level of confidence, P= expected prevalence or proportion, and d=precision.

We considered an overall prevalence of 40%, since this was the average prevalence found in studies with larger sample sizes and good quality control scores [15, 17]. Therefore, the minimum sample size required to be included in this study was 47.

### Data analysis

Meta-analytic methods enable the quantitative integration of data across multiple observational studies in order to derive pooled prevalence estimates stratified across key variables, such as different diagnostic criteria for TDP-43 diagnosis or the geographical region of the population sampling [18–21]. Data analysis was carried out using Stata software (version 12, StataCorp, College Station, TX, USA). We used the following user-defined procedures: *metaprop*, *metafunnel*, and *metabias* [27, 28].

The level of statistical heterogeneity was reported using the I<sup>2</sup> statistic [(Q statistic—degree of freedom) /Q statistic) × 100%], which is a measure of the percentage of variability in the pooled prevalence estimate due to inter-study heterogeneity (tau-squared:  $\tau^2$ ) [29]. Since significant heterogeneity was present in all analyses, a random-effects model was used. In random-effects models, the inverse variance is corrected by a measure of between-study variation ( $\tau^2$ ), thus reducing the effects of sample size. Because prevalence is a proportion, study estimates were combined using a log transformation to help normalize the data. Confidence intervals were calculated using the exact method [30], which is the gold-standard method for binomial data [28].

We performed sensitivity analyses to explore possible explanations for variations in TDP-43 prevalence: (1) sample size (<300 and ≥300); (2) mean age (<80 and ≥80 years old); (3) sex; (4) antibody used to assess TDP-43 aggregates (antibody that recognizes total TDP-43 protein, or antibody that recognizes its hyperphosphorylated form, with a specific site of phosphorylation at serine 409/410, mentioned throughout the text as pSer409/410); (5) analyzed brain regions (limbic and non-limbic); and (6) geographic location (North America, Europe, Asia, and Latin America), (7) geographic location, but considering only studies that analyzed limbic brain regions; and (8) study quality (quality score ≥7 versus quality score <7).

In addition, we requested additional data from all included studies to investigate TDP-43 prevalence according to Braak & Braak stage and CERAD scores [31, 32]. Braak & Braak classification was categorized in Braak stage II and III, and CERAD score in A and B [33]. Similarly, we investigated TDP-43 prevalence among participants with and without hippocampal sclerosis (HS).

Funnel plots of the prevalence logit plotted against the standard error were assessed for asymmetry to look for evidence of publication bias. Begg's rank correlation test and Egger's asymmetry test were also conducted to provide a formal assessment of publication bias across studies [34, 35].

## Results

We identified a total of 505 abstracts regarding the prevalence of TDP-43 accumulation in cognitively normal subjects throughout all databases. From these, 202 abstracts were suitable according to the inclusion criteria, and 18 articles were selected for full-text assessment. After this step, we contacted authors from these studies to retrieve missing data. We finally included seven studies in the systematic review and meta-analysis that included data from 1,196 participants (Figure 1).

Characteristics of the subjects from these seven studies are shown in Table 1. The mean age at death was  $80.2 \pm 8.5$  years. Two studies were from North America, two from Europe, two from Asia, and one from Latin America. The mean quality score of the studies was  $6.5 \pm 2.0$  (with minimum score of 2.5 and maximum of 8.0).

Our meta-analysis of pooled prevalence of TDP-43 in cognitively normal subjects showed an overall prevalence of 24% (effect size [ES] = 0.24, 95% confidence interval [CI] = 0.13–0.34, Figure 2), with a high heterogeneity across studies (ES varying from 0.08 to 0.40,  $I^2 = 126\%$ ,  $p = 0.001$ ).

When pooled prevalence was stratified across geographical region, the highest prevalence found was in North America at 37%, followed by Asia at 29%. Europe and Latin America showed the lower prevalence, 14% and 11% respectively (Figure 3A). Interestingly, effect sizes were similar within studies from the same geographic location, except for Asia, where prevalence varied from 16% to 40%. In the case of North America, TDP-43 prevalence was 36% [15] and 37% [36], while TDP-43 prevalence in Europe was lower and varied from 8% [14] to 18% [37]. Because previous studies [16, 17] showed that limbic brain regions

(including hippocampus and amygdala) are preferentially affected in cognitively normal subjects, we performed a sensitivity analysis of the pooled prevalence of TDP-43 proteinopathy, considering neuropathological findings only in hippocampus and amygdala (Figure 3B). While a slight difference was found in the pooled prevalence, the variation across geographic location remained similar.

Pooled TDP-43 prevalence among cognitively normal subjects were similar regarding mean age at death (<80 years old: ES = 0.21, 95% CI = 0.06–0.41; and 80 years old: ES = 0.24, CI = 0.13–0.39; Supplementary Figure 1), sex (Male: ES = 0.24, 95% CI = 0.11 – 0.38; and Female: ES = 0.24, 95% CI = 0.13 – 0.36, Supplementary Figure 2A and B, respectively) and brain regions analyzed (limbic ES = 0.25, 95% CI = 0.12–0.41; and non-limbic: ES = 0.17, 95% CI=0.05 – 0.50, Supplementary Figure 3A).

Regarding the type of antibody used to identify the TDP-43 protein, the antibody against the pser409/410 showed pooled prevalence of 24% (95%CI = 0.12 – 0.37), while the one that recognizes the native form of the protein 18% (95%CI = 0.12 – 0.26, Supplementary Figure 2B). Higher quality studies (quality control = 7) showed a TDP-43 prevalence of 21%, while lower quality studies had a prevalence of 32% (quality control <7, Supplementary Figure 2C). We find similar TDP-43 prevalence when we pooled studies with sample size ≥ 300 (ES = 0.23, 95%CI = 0.20 – 0.27), and <300 participants (ES = 0.23, 95%CI = 0.12 – 0.35; Supplementary Figure 2D).

Five out of seven studies provided additional data about TDP-43 prevalence in participants with lower AD neuropathology and higher AD neuropathology (Supplementary Figures, 4 and 5). The prevalence of TDP-43 among participants with Braak II was 20% (ES=0.20, 95%CI=0.06–0.34, Supplementary Figure 4A) and 23% in Braak III (ES=0.23, 95%CI=0.08–0.38, Supplementary Figure 4B). Similarly, TDP-43 prevalence was 23% in participants with CERAD A (ES=0.23, 95%CI=0.08–0.37, Supplementary Figure 5A) and CERAD B (ES=0.23, 95% CI=0.08–0.37, Supplementary Figure 5B). Four out of seven studies had information on TDP-43 and HS. Among these four studies, only 2 studies had participants with HS pathology in the brain. The prevalence of TDP-43 was 24% in participants without HS (ES=0.24, 95%CI=0.07–0.40, Supplementary Figure 6A) and 48% in participants with HS (ES=0.48, 0.28–0.68, Supplementary Figure 6B); however this last estimate varied widely between the two available studies (27% in Nascimento et al. to 75% in Yu et al.).

We looked for evidence of publication bias using the funnel plot, and the Egger's and Begg's tests. Figure 4 shows the funnel plot of the logit prevalence of TDP-43, plotted against the logit standard error. Egger's test for small-study effects was not significant ( $t = -0.35$ ,  $p = 0.74$ ). The Begg's adjusted rank correlation test for funnel plot asymmetry also did not show evidence of publication bias ( $z=0.90$ ,  $p=0.37$ ).

## Discussion

In a meta-analysis of seven studies with 1,196 cognitively normal older adults, we found an overall prevalence of TDP-43 proteinopathy of 24%. We observed high heterogeneity with a

wide range of TDP-43 prevalence across studies. We also found large differences in the pooled prevalence estimation of TDP-43 when we stratified the meta-analysis by geographic location, with higher prevalence in North America and lower prevalence in Europe and Latin America. Higher TDP-43 prevalence values were found in subjects with HS. We found similar prevalence estimations of TDP-43 among cognitively normal subjects when we stratified the meta-analysis by age, sex, analyzed brain regions, and Braak and CERAD scores.

Unfortunately, there is a lack of systematic reviews and meta-analysis studies to estimate overall prevalence of misfolded proteins in cognitively normal older adults with neurodegenerative diseases. The available data are from post-mortem neuropathological studies, and only a few originally focused on cognitively normal subjects. A previous neuropathological study on these subjects showed a prevalence of 23% of  $\alpha$ -synuclein, which is another misfolded protein present in the brain of patients with Parkinson's disease [38]. This result is similar to what we observed for TDP-43 proteinopathy overall prevalence after meta-analysis (24%). On the other hand, the reported prevalence of other misfolded proteins, such as tau and  $\beta$ -amyloid found in cognitively normal elderly adults is twice as high compared to what was found for TDP-43 or  $\alpha$ -synuclein. Up to 45% of non-demented subjects meet neuropathological criteria for AD based on the National Institute on Aging (NIA)-Reagan, which means they have considerable neuropathological burden of two misfolded proteins (tau and  $\beta$ -amyloid) without manifestation of clinical symptoms [39–42]. The relationship between the presence of protein aggregates in the brain and the clinical manifestation in neurodegenerative diseases is not completely understood. Since in cognitively normal subjects TDP-43 and  $\alpha$ -synuclein were less frequent than tau and  $\beta$ -amyloid, we may speculate that TDP-43 and  $\alpha$ -synuclein protein aggregates seem to be more toxic than tau and  $\beta$ -amyloid, since less burden of pathology is found in cognitively normal subjects who present these types of aggregates in the brain. Tau protein aggregates may be influenced by environmental/ lifestyle factors [43]. In the case of TDP-43 pathology, several underlying genetic factors have been identified [44], but little is known about the role of environmental/ lifestyle factors. These factors should receive more attention, since TDP-43 functions are particularly important under cellular stress conditions [45–48].

Other important factor to be considered is the co-occurrence of different types of aggregates [14]. Because misfolded protein clearance systems may not be able to cope with the amount of malformed proteins that are produced during the aging process, a combination of these protein aggregates in the aged brain has been verified [14, 15, 49]. However, when we performed sensitivity analyses by AD neuropathology severity (considering Braak II or Braak III, and CERAD A or CERAD B), we did not find differences in the pooled prevalence of TDP-43 proteinopathy. Likewise, Arnold et al. also showed lack of association between AD neuropathology and TDP-43 proteinopathy in cognitively normal subjects. On the other hand, association between TDP-43 proteinopathy and AD neuropathology is consistently found in cognitively impaired subjects [14, 49]. Interestingly, TDP-43 stage showed a dose-response relationship with clinical Alzheimer's disease [49]. We found higher TDP-43 prevalence values in individuals with HS (48%) than in those without HS (27%). Association between HS and TDP-43 has been consistently found in the literature [49–51]. However, we could only investigate this association in four studies.



Previous post-mortem neuropathological studies focusing on TDP-43 proteinopathy in cognitively normal elderly adults had found wide range prevalence [14–17]. For this reason, we sought to conduct a systematic review of the literature and present results obtained by a meta-analysis to estimate an overall pooled prevalence of TDP-43 proteinopathy and understand factors that could explain the high heterogeneity across studies. Primarily, we would assume that differences in study design and methodology would explain these variations. Indeed, our results showed variations in the pooled prevalence estimations according to the quality of the studies and the antibody used to assess TDP-43 proteinopathy. In fact, one study that assessed concordance of 25 independent evaluators on the diagnosis of AD-related hyperphosphorylated-tau pathology showed poor agreement (50%) for mild burden of lesions [52]. Standardized methods across different brain banks regarding the use of the same antibodies [53] and guidelines to assess lesions (including the number of evaluators) could make results more comparable. We found higher pooled prevalence values in studies that used antibody against the phosphorylated TDP-43 (24%), when compared to non-phosphorylated TDP-43 (18%). In agreement with our findings, the study that classified pathological FTLN-TDP subtypes using antibodies against phosphorylated (pTDP43) and non-phosphorylated TDP-43 (iTDP-43) showed that pTDP43 identified a greater severity of pathological inclusions in comparison to iTDP43, as well as a higher inter-observer agreement of subtype classification [54]. Indeed, previous published data using immunoblot analysis showed phosphorylation as the major component of TDP-43 inclusions in FTLN an ALS, but not in AD subjects [55]. In our meta-analysis, we included older adults that had normal cognition at the time of death. For this reason, it is not clear whether these subjects would evolve to FTLN-TDP or AD with TDP-43 inclusions [1]. The use of antibodies against the phosphorylated TDP-43 may contribute to the uniformity of TDP-43 proteinopathy classification across brain banks. Additionally, immunoblot analysis using antibodies that can recognize different epitopes of the protein, may contribute to our understanding of biochemical modification along the formation of TDP-43 aggregates in aging and neurodegenerative disease. When we examined other variables related to the study design (e.g. sample size and analyzed brain regions), we did not observe differences in the prevalence estimations.

Although we did not find changes in the pooled prevalence of TDP-43 proteinopathy when individuals were grouped by age or sex, similar prevalence estimations were found within the same geographic locations, except for Asia. The reason why the two studies from Asia showed variations in prevalence estimations may be because the distribution of TDP-43 varies across brain regions [56, 57]. While one study from Asia [17] analyzed TDP-43 changes in the limbic system, Mizuno et al. only analyzed a specific brainstem nucleus, the oculomotor nucleus. We performed a sensitivity analysis to certify that difference in geographic location were not due to differences in studied brain region. After this analysis, the different prevalence estimations across geographic location still remained. Our hypotheses is, that differences in population characteristics due to environmental and genetic factors could influence the neural microenvironment, and modify the presence of TDP-43 aggregates in the brain. Epidemiological studies have shown that changes in lifestyle can modify the chance of developing dementia in older ages [58]. These lifestyle changes include enrollment in social and physical activities, changes in dietary habits, as well as

control of vascular risk factors [59–62]. Indeed, this is particularly important for TDP-43 since cerebral vascular changes may play a role [63]. Ethnicity also impacts the prevalence of age-related diseases, such as hypertension, cardiovascular disease [64, 65], and dementia [66]. Interestingly, our recently published data showed that cognitively normal Asians were more prone to exhibit TDP-43 proteinopathy, when compared to Caucasians, even after we controlled for age, sex, and education [16].

The high heterogeneity across studies included in our meta-analysis is a clear limitation, as reported previously in meta-analysis studies of prevalence [29, 67]. However, we conducted a funnel plot analysis accompanied by Egger's and Begg's tests that did not show evidence of publication bias. We also did not have individual participant data, which could have allowed for more comprehensive analyses. Additionally, the investigation of the coexistence of other neurodegenerative diseases and TDP-43 proteinopathy was limited to five out of seven studies that agreed to share the data for this meta-analysis.

In conclusion, we found a wide range of estimates when we examined the prevalence of TDP-43 proteinopathy in cognitively normal older adults from different geographic locations. Different methodology used across brain banks to access TDP-43 may explain these results. Another possible explanation for these results is the difference in lifestyle and genetic factors in different populations. Investigating the ethnical, genetic, and lifestyle factors that could affect the presence of TDP-43 related neuropathological findings, as well as standardization of the methods to measure TDP-43 protein, are of extreme importance to move forward our understanding of TDP-43 pathophysiology.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## List of abbreviations

<b>TDP-43</b>	transactive response DNA-binding protein 43
<b>ALS</b>	amyotrophic lateral sclerosis
<b>AD</b>	Alzheimer's disease
<b>FTLD-TDP</b>	Frontotemporal lobar degeneration with transactive response DNA-binding protein 43
<b>PRISMA</b>	Preferred Reporting Items for Systematic reviews and Meta-Analyses

<b>MOOSE</b>	Meta-analyses of Observational Studies in Epidemiology
<b>CDR</b>	Clinical Dementia Rating
<b>AD</b>	Alzheimer's disease
<b>CERAD</b>	Consortium to Establish a Registry for Alzheimer's Disease
<b>ES</b>	effect size
<b>CI</b>	confidence interval

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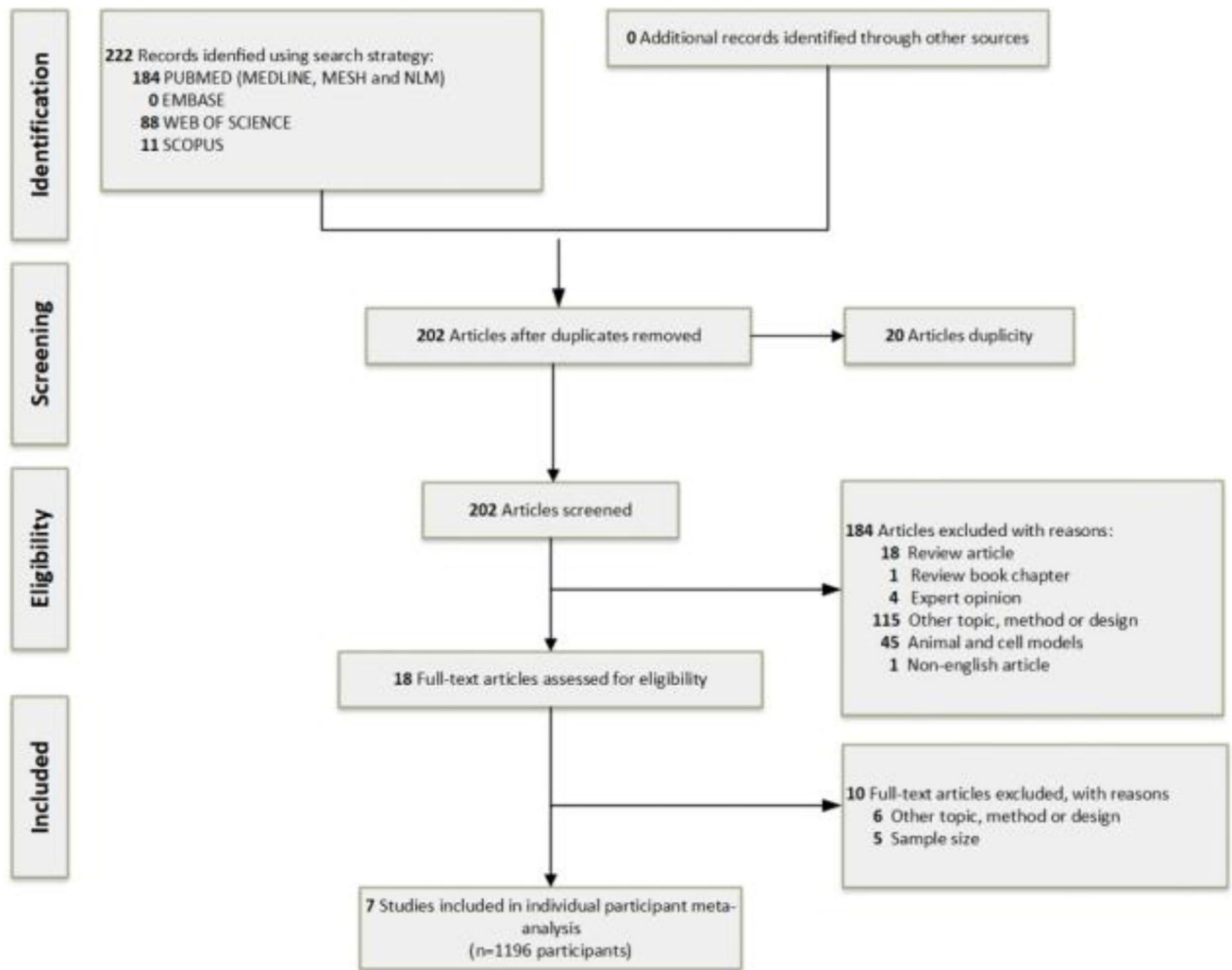
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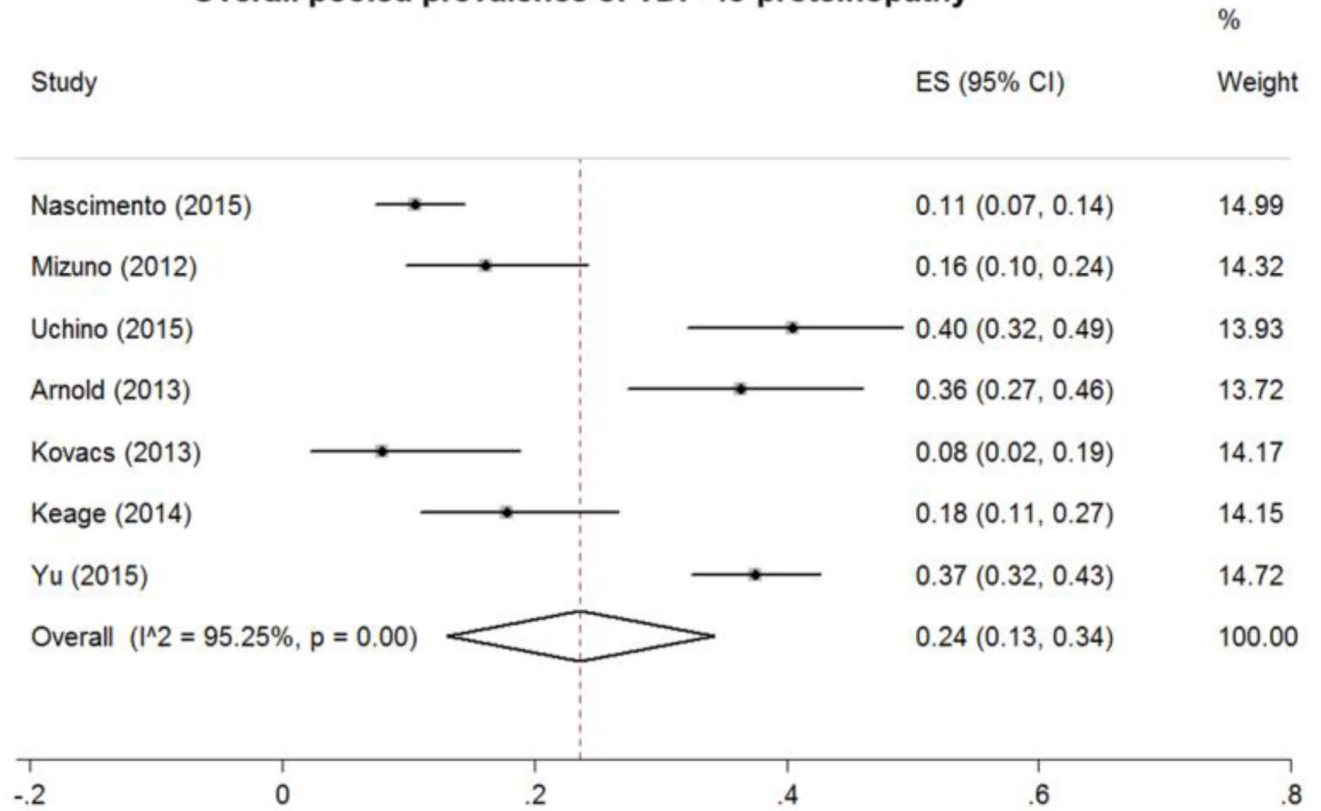
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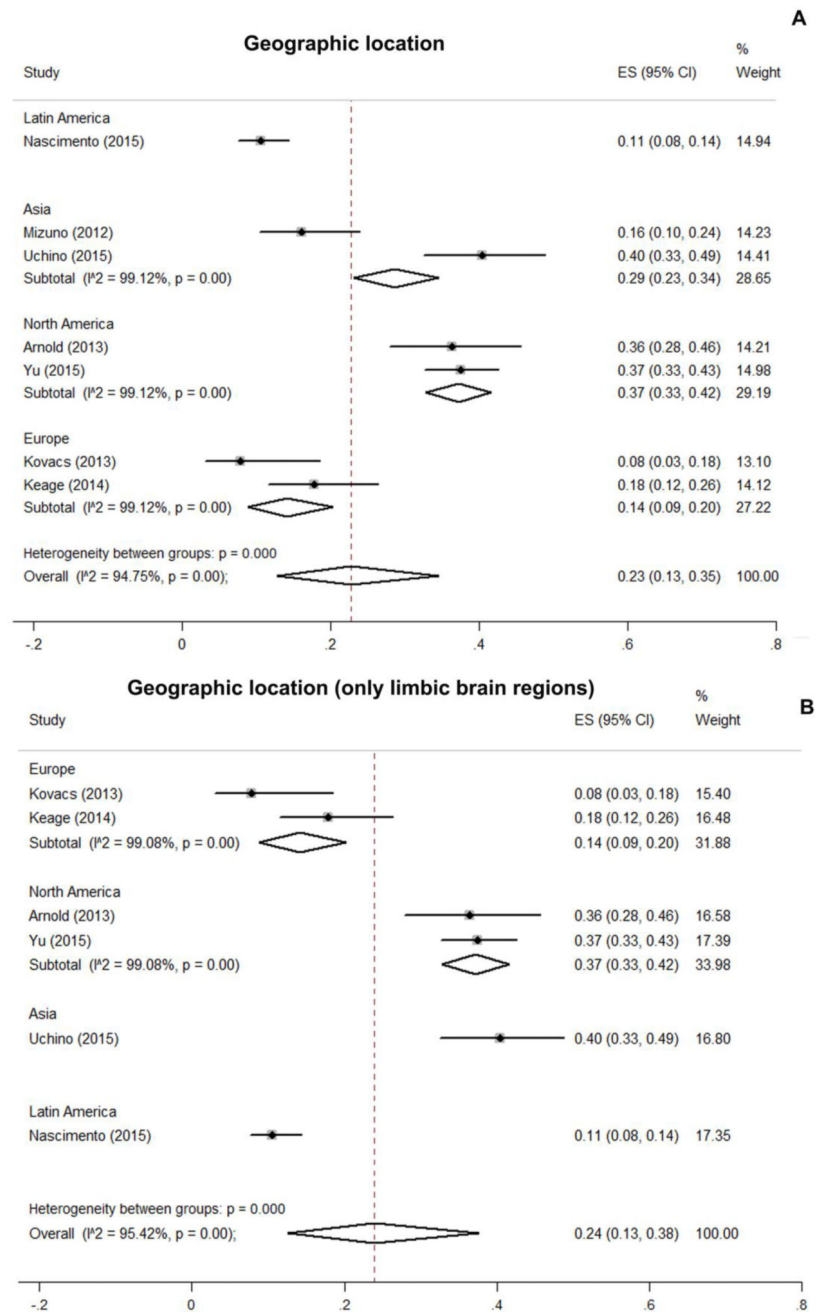
**Figure 1.** Flow diagram of the literature search and study selection through the different phases of the systematic review.



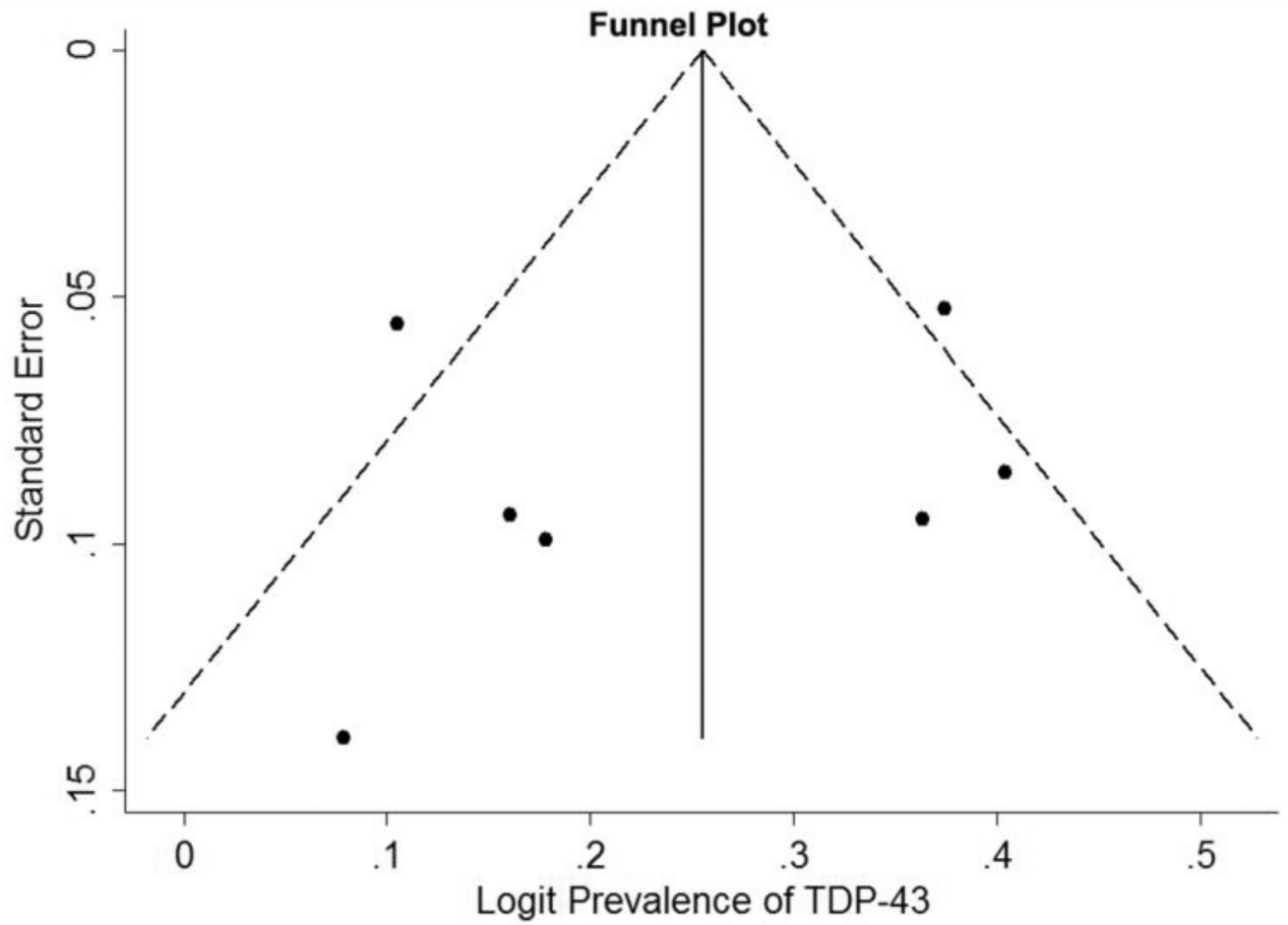
**Overall pooled prevalence of TDP-43-proteinopathy**



**Figure 2.** Estimated prevalence of transactive response DNA-binding protein 43 (TDP-43) proteinopathy of the included articles and overall meta-analysis pooled prevalence



**Figure 3.** Estimated prevalence values of transactive response DNA-binding protein 43 proteinopathy of the included articles grouped by geographic location (all brain regions, A vs. only limbic brain regions, B).



**Figure 4.** Publication bias assessed by the funnel plot of the logit prevalence of transactive response DNA-binding protein 43 (TDP- 43) proteinopathy plotted against the standard error

**Table 1**

Studies selected for meta-analysis according to the inclusion criteria (n = 7)

Author, year	sample size (n)	TDP-43 proteinopathy (n)	Mean (SD) age at death	Male (n)	Geographic location	Brain regions analyzed	Quality control score
Yu et al., 2015	363	136	86.6 (6.9)	41	North America	Limbic and neocortex	5
Keage et al., 2014	101	18	90.6 (4.6)	40	Europe	Only Limbic	8
Kovacs et al., 2013	51	4	81.8 (2.8)	26	Europe	Limbic and neocortex	8
Mizuno et al., 2012	112	18	74 (n/a)	72	Asia	Brainstem	2.5
Nascimento et al 2015	323	34	69.9 (11.7)	155	Latin America	Limbic, neocortex and other regions (subcortical nuclei and brainstem)	7
Arnold et al., 2013	110	40	86 (6)	54	North America	Limbic and neocortex	7
Uohino et al 2015	136	55	78.5 (9.7)	95	Asia	Limbic, neocortex and other regions (subcortical nuclei and brainstem)	8

SD=standard deviation; INA = Information not available