The associations between Enlarged Perivascular Spaces and partial Clinical symptoms: a meta-analysis

Keywords
Meta-analysis, Enlarged Perivascular Spaces, Clinical symptoms

Abstract

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Material and methods
Relevant studies up to April 2022 were extracted from PubMed, Embase, Cochrane, OVID, and Web of Science. Odds ratios (ORs) and 95% confidence interval (CI) were used to estimate the strength of the correlation.

Results
Of the 6622 articles identified, 32 studies were eligible, enrolling a total of 19987 people. EPVS was associated with the risk of cognitive impairment (OR: 1.60, 95 % CI: 1.39- 1.81), motor impairment (OR: 2.24, 95 % CI: 1.22- 3.25), sleep disturbance (OR: 1.81, 95% CI: 1.34-2.28), depressive symptoms (OR: 1.54, 95 % CI: 1.14- 1.95), but was not significantly associated with the occurrence of stroke (OR: 0.97, 95 % CI: 0.74-1.21). Results of subgroup analysis showed that basal ganglia (BG) EPVS were more associated with cognitive impairment (OR: 2.19, 95% CI: 1.72- 2.65) and sleep disturbance(OR: 1.74, 95 % CI: 1.20- 2.29).

Conclusions
Our findings suggested that people with EPVS may be at a greater risk for cognitive impairment, motor impairment, sleep disturbance, and depressive symptoms. This will inform future treatments.

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Keywords: Enlarged Perivascular Spaces; Clinical symptoms; Meta-analysis

Introduction

The importance of enlarged perivascular spaces (EPVS, also known as Virchow–Robin spaces) as an imaging marker of cerebral small vessel disease (CSVD) has been recognized [1]. With age, the number and volume of EPVS gradually increase [2], and more than 80% of people over the age of 70 have enlarged perivascular spaces [3]. The normal perivascular space (PVS) is important for maintaining brain health and functions as a lymphoid system in the brain, serving as a pathway for fluid transport, cerebrospinal fluid-interstitial fluid exchange (CSF-ISF), and clearance of metabolic wastes in the brain. At present, the PVS that can be observed on MRI is considered to be EPVS, and its diameter is usually less than 3 mm [4]. EPVS has a smooth and clear boundary on MRI, which is round, oval, or linear, consistent with the course of perforating arteries, and has the same signal as CSF on T2WI, T1WI, and FLAIR sequences [4]. PVS expansion, suggests brain microcirculation disorders and brain clearance mechanism dysfunction [5]. EPVS are mainly distributed in the basal ganglia (BG), center semiovale (CS), midbrain, and hippocampus (HP) [6]. At present, visual semi-quantitative methods are often used to assess the severity of EPVS, but the methods are not uniform. The most commonly used method now is the Potter assessment method [7]. The basal ganglia and the center of the semiovale of the cerebral hemisphere on the side with heavier EPVS load were assessed with a score of 0-4, and the midbrain was assessed with a score of 0-1.

In recent years, research on EPVS and clinical symptoms has gradually increased, such as cognitive impairment, movement disorders, depressive symptoms, sleep disorders, and stroke [8-13], which bring huge social and economic burdens [14]. EPVS is closely related to age and the aging of society is a growing problem [15], so understanding what it means to see many EPVS on MRI has important clinical implications. However, EPVS has the characteristics of insidious onset of cerebral small vessel disease, and its imaging manifestations are easily confused with lacunar; some scholars believe that EPVS is a pathological manifestation of the result of brain tissue loss during aging and is an incidental phenomenon, and the current research on neurological dysfunction such as dementia and stroke focuses on blood vessels or neurons/glial cells, these reasons make EPVS not easy to attract the attention of clinicians [1, 16]. It should still be noted that the relevance and importance of EPVS to neurological disorders is still controversial [3, 17]. For example, Thomas [18] showed that EPVS was significantly associated with the appearance of depressive symptoms over time. However, Zhang et al. [19] found no significant correlation between EPVS and depressive symptoms in the study of CSVD and post-stroke depression. Similarly, in the study of EPVS and sleep disorders, Shuna Yang et al. [20] and Melinda et al. [12] found opposite results; in the study of EPVS and cognitive impairment, Francesco Arba et al. [21] and Jae Eun Sim et al. [22] also showed inconsistent results. In addition, the generation mechanism of EPVS in different regions and its possible consequences are also controversial issues [23]. Based on this, we decided to conduct a meta-analysis of the association of EPVS with clinical symptoms in different regions.

Methods

Search strategy for the literature

The meta-analysis was reported according to the PRISMA guidance. We searched PubMed, Embase, Cochrane, OVID, and Web of Science databases from the date of establishment to April 2022 using predefined search terms, and checked the reference list of relevant articles. The study was conducted by 3 independent investigators and disagreements were resolved by discussion. See Table 1 for search keywords.

Table 1. The search strategy of PubMed

Table 1	The search strategy of PubMed
Search	**Query**
#1	(((((((Enlarged Perivascular Space[MeSH Major Topic]) OR (Enlarged Virchow-Robin Spaces[Title/Abstract])) OR (Perivascular Spaces Enlargement[Title/Abstract])) OR (Virchow-Robin Spaces Enlargement[Title/Abstract])) OR (perivascular spaces[Title/Abstract])) OR (Virchow-robin spaces[Title/Abstract]))) OR (Enlarged Perivascular Spaces[Title/Abstract])
#2	((Clinical[Title/Abstract]) OR (Clinical Symptoms[Title/Abstract])) OR (Clinical Manifestation[Title/Abstract])
#3	((((Magnetic Resonance Imaging[Title/Abstract]) OR (Imaging[Title/Abstract])) OR (MR Tomography[Title/Abstract])) OR (MRI[Title/Abstract])) OR (fMRI[Title/Abstract])
#4	#2 OR #3
#5	#1 And #4

Inclusion and exclusion criteria

We aimed to include all papers reporting EPVS related to cognitive impairment, motor impairment, sleep disturbance, depressive symptoms, and stroke. We excluded studies without effect estimates such as odds ratios (ORs), relative risks (RRs), hazard ratios (HRs), and confidence intervals (CI), and excluded case reports, animal studies, and reviews. We also excluded studies where EPVS occurs in inflammatory conditions (eg, multiple sclerosis, lupus) and inherited CSVD (eg, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL). Exclude nervous system diseases (such as traumatic brain injury, brain tumor, hydrocephalus, encephalitis, secondary and inherited Parkinson's syndrome) that may cause relevant clinical symptoms of the participant.

Data extraction

We removed duplicate articles, deleted irrelevant articles based on titles and abstracts, and included eligible articles by reading the full text. The extracted data were as follows: first author name, year of publication, country or region of publication, study type, study samples, main clinical symptoms, follow-up time, EPVS location, association outcomes (ORs or RRs or HRs and corresponding 95% CI).

Quality score assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the study [24]. On this scale, a score of 9 is considered high quality, a score of 7-8 is considered moderate quality, and a score below 7 is considered low quality. Two reviewers independently assess quality and differences are resolved through discussion with a third reviewer.

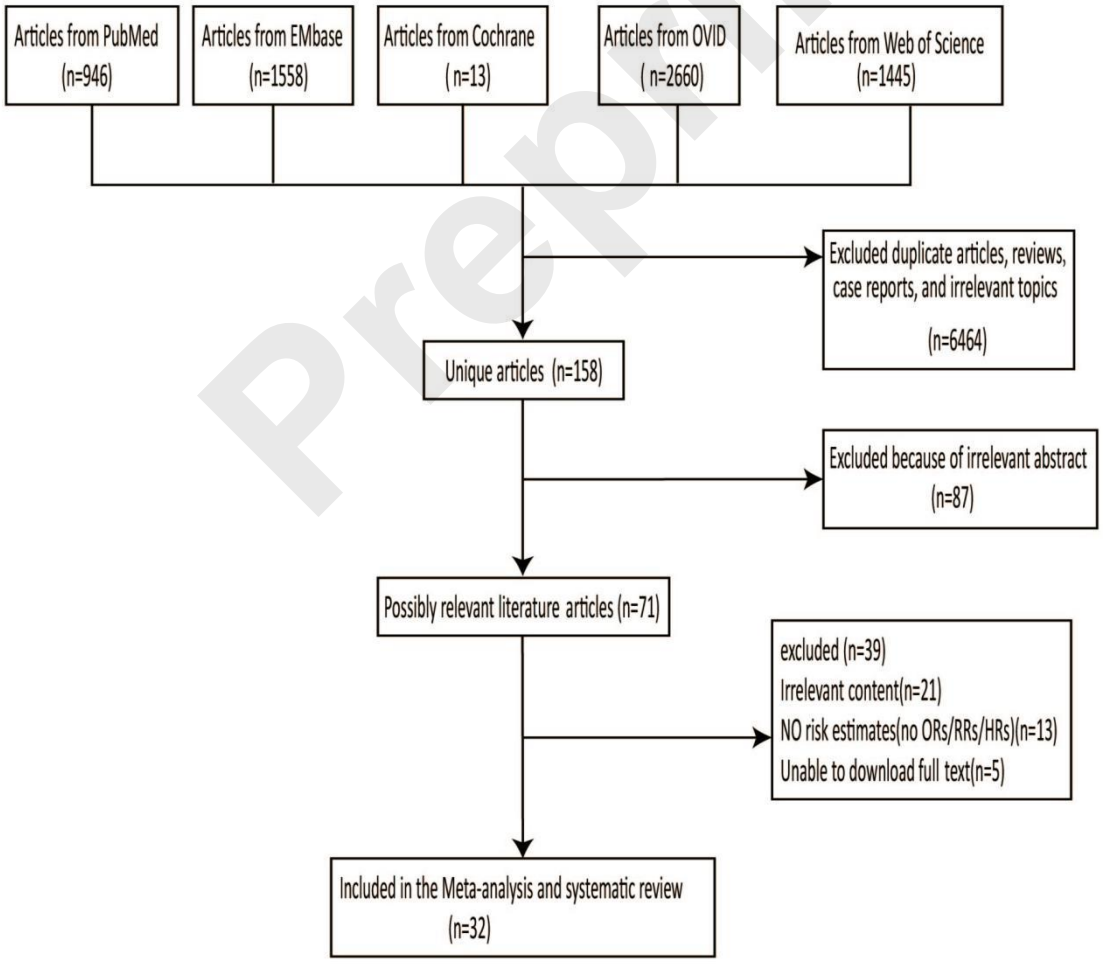
Statistical analysis

We performed meta-analyses using Stata software version 15.1. Multivariate-adjusted ORs and 95% CI were plotted, and summary ORs were generated. Inter-study heterogeneity was assessed using the I^2 test, with a random-effects model when I^2 >50%, and a random-effects model when I^2 <50% [25]. The z-test was used to summarize the significance of ORs, and a $P < 0.05$ was considered statistically significant. Sensitivity analysis was performed to evaluate the stability of the results. Potential publication bias was investigated using Beeg's test. Subgroup analyses were performed to explore heterogeneity.

Results

The initial search in PubMed, Embase, Cochrane, OVID, and Web of Science identified 6622 articles. 32 articles (n=19987) met our inclusion criteria (Figure 1).

Figure 1. Summary of evidence search and selection.



Characteristics of 32 studies included in the meta-analysis

This systematic review and meta-analysis summarized data from 32 studies (n=19987), including 14 cross-sectional studies, 11 prospective studies, and 7 retrospective studies. They come from different countries and regions, including China, France, the United Kingdom, the United States, South Korea, Sweden, the Netherlands, etc. In our article, we mainly divide the regions of EPVS into BG, CS, and HP. According to anatomical characteristics, Swiss cheese striatum enlarged perivascular spaces (SCS EPVS) were classified into BG EPVS, and white matter enlarged perivascular spaces (WM EPVS) were classified into CS EPVS.

For cognitive impairment, 12 studies (n=9205) met our inclusion criteria [12, 21, 22, 26-34]. For movement disorders, 5 studies (n=1010) met our inclusion criteria [9, 12, 35-37]. For sleep disturbances, 8 studies (n=1846) met our inclusion criteria [11, 12, 20, 38-42]. For depressive symptoms, 5 studies (n=3465) met our inclusion criteria [10, 12, 18, 19, 39]. For stroke, 7 studies (n=6867) met our inclusion criteria [13, 31, 43-47]. The EPVS scoring scale used is mainly the Potter scale, and some studies have used other scales. The included studies mainly used 1.5 T/3.0 T MRI (nuclear magnetic sequence). Our articles included studies with a quality assessment of 7 scores and above. The basic characteristics and quality assessment reports of the included studies are shown in Table 2- 4.

Table 2. Characteristics of studies included in the meta-analysis.

Table 2. Characteristics of studies included in the meta-analysis

Study	Year	Total	Study Type	follow-up time	Clinical symptoms	OR (95% CI)	Brain region	Geographic region
Cognitive Disorder								
Zhu et al [26],	2010	1778	prospective	4 years	Dementia	5.8 (1.2- 28.4) 9.8 (1.7- 55.3)	BG WM	France
Melinda et al [12],	2014	79	retrospective	/	Dementia	1.57 (0.48-5.13)	SCS	Minnesota
Yao et al [27],	2014	1818	prospective	6.12 years	Dementia	0.95 (0.50-1.80)	HP	Dijon
Arba et al [28],	2016	234	retrospective	/	PSCI	2.66 (1.82- 3.87) 2.08 (1.42- 3.05)	BG CS	VISTA
Francesco et al [21],	2016	430	retrospective	/	Cognitive disorder	2.52 (1.90- 3.35) 1.67 (1.25- 2.18)	BG CS	VISTA
Riba et al [29],	2016	733	prospective	8 years	MCI	1.88(1.03- 3.41)	BG	Barcelona
Sara et al [30],	2017	1504	cross-sectional	/	Vascular dementia	11.1 (1.1- 112.2) 1.3 (0.6- 2.9)	BG CS	Sweden
Pinar et al [31],	2018	1651	prospective	7.2 years	Dementia	0.97 (0.35- 2.72)	BG	Netherlands
Li et al [32],	2018	158	cross-sectional	/	Dementia	1.283 (0.967-1.703)	CS	Massachusetts
Gargi et al [33],	2019	117	prospective	1 year	Cognitive impairment	2.60 (0.74- 9.19) 1.83 (1.06- 3.15)	BG CS	UK
Jae et al [22],	2020	109	cross-sectional	/	Memory function	2.142 (-0.515- 4.799)	HP	South Korea
Matthew et al [34],	2021	414	prospective	6 years	Dementia	3.25(1.14- 9.30) 1.77(0.58- 5.39)	BG CS	Sydney
Motor Disorder								
Wan et al [36],	2018	137	cross-sectional	/	PIGD	2.97 (0.98- 9.03)	CS	China

Vasileios et al [35],	2018	175	retrospective	/	Functional independence	1.4 (0.34- 5.77)	BG	USA
Oscar et al [37],	2019	288	cross-sectional	/	risk of falls	3.36 (1.85- 6.09)	BG	Atahualpa
Emerald et al [9],	2021	331	prospective	9 years	Walking speed limitation	2.13 (1.04- 4.36)	/	Sweden
Melinda et al [12],	2014	79	retrospective	/	Any movement disorder	1.47 (0.43-5.04)	SCS	Minnesota
Sleep Disorder								
Song et al [38],	2017	170	cross-sectional	/	Moderate-to-severe (AHI ≥ 15)	3.64 (1.02- 13.01)	/	South Korea
Wang et al [42],	2020	106	cross-sectional	/	ArI	2.108 (1.032- 4.017)	/	China
Joel et al [11],	2021	153	cross-sectional	/	Daytime Dysfunction	5.31 (1.38- 22.26)	BG	ONDRI
Oscar et al [39],	2019	338	cross-sectional	/	Sleep quality	1.68 (1.01- 2.79)	BG	Atahualpa
Oscar et al [40],	2020	146	cross-sectional	/	PLMS	1.36 (0.56- 3.33)	BG	Atahualpa
Melinda et al [12],	2014	79	retrospective	/	Any sleep disorder	1.37 (0.37- 4.97)	SCS	Minnesota
Benjamin et al [41],	2020	457	cross-sectional	/	Interrupted Sleep	1.84 (1.08- 3.15)	BG	Scotland
Yang et al [20],	2022	398	retrospective	/	Poor sleep quality	2.125 (1.113- 4.058) 1.882 (1.005- 3.527)	BG WM	China
Depressive Disorder								
Thomas et al [18],	2015	1949	prospective	5 years	Depression	3.44 (1.71- 6.91)	/	Reykjavik
Liang et al [10],	2018	725	cross-sectional	/	PSD	1.49 (1.04- 2.13)	CS	China
Zhang et al [19],	2016	374	cross-sectional	/	PSD	1.557 (0.958- 2.530)	/	China
Oscar et al [39],	2019	338	cross-sectional	/	Depression	1.359 (0.608- 3.039)	BG	Atahualpa
Melinda et al [12],	2014	79	retrospective	/	Depression	1.57 (0.48- 5.13)	SCS	Minnesota
Stroke								
Pinar et al [31],	2018	1651	prospective	7.2 years	Stroke	1.80 (0.71- 4.59)	BG	Netherlands
Andreas et al [13],	2013	121	retrospective	/	ICH	3.58 (1.70- 7.54) 0.74 (0.35- 1.57)	BG CS	UK and Belgium
Xu et al [46],	2021	167	cross-sectional	/	Large hematoma volume	0.395 (0.147- 1.064)	/	China
Zhang et al [45],	2020	1204	prospective	3 years	Stroke	3.34 (0.78- 14.37)	/	China
Gutierrez et al [43],	2017	1228	prospective	9 ±2 years	Stroke	0.9 (0.60- 1.61)	/	Manhattan
Lau et al [44],	2017	2002	prospective	42±23 months	Ischemic stroke Intracerebral hemorrhage Recurrent stroke Ischemic stroke Intracerebral hemorrhage	1.82 (1.18- 2.80) 2.58 (0.97- 6.89) 1.94 (1.31- 2.89) 0.83 (0.54- 1.28) 1.36 (0.51- 3.59)	BG BG BG CS CS	UK and China

					Recurrent stroke	0.89 (0.60- 1.33)	CS		
Song et al [47],	2021	494	retrospective	/	HT	0.638 (0.454- 0.897)	BG	China	
						0.690 (0.502- 0.949)	CS		

PSCI=post-stroke cognitive impairment; VISTA=Virtual International Stroke Trial Archive; MCI=mild cognitive impairment (MCI); PIGD=the postural instability and gait disability; AHI=apnea hyponea index; ArI=arousal index; PSD= poststroke depression; HT=hemorrhagic transformation; HR=hazard ratio; OR=odds ratios; BG=basal ganglia; CS=centrum semiovale; WM=white matter; SCS= swiss cheese striatum; HP= hippocampal; ICH= intracercbral hemorrhage; PLMS= periodic limb movements during sleep; ONDRI= Ontario Neurodegenerative Disease Research Initiative

Table 3. Eight questions of included study quality were evaluated according to Newcastle-Ottawa Scale (NOS) evaluation criteria

Table 3. Eight questions of included study quality were evaluated according to NOS evaluation criteria		
prospective		
1. Are EPVS major exposure factors?	YES (1)	NO (0)
2. Are the non-exposed group and the exposed group from the same population?	YES (1)	NO (0)
3. Whether the MRI sequence for EPVS contains T1, T2, Flair	YES (1)	NO (0)
4. Were the investigators ignorant of the patient's clinical symptoms when determining EPVS	YES (1)	NO (0)
5. The study controlled for the most important confounders (sex, age)	YES (2)	NO (0)
6. Is the assessment of clinical symptoms adequate?	YES (1)	NO (0)
7. Is the follow-up period long enough?	YES (1)	NO (0)
8. Is the follow-up adequate?	Complete follow-up or a small number of studies lost to follow-up without introducing bias (1)	Lost to follow-up but not described or follow-up not described (0)
retrospective or cross-sectional		
1. Evaluation of clinical symptoms by professionally trained personnel	YES (1)	NO (0)
2. Cases are representative	YES (1)	NO (0)
3. Whether it is a control of the same population as the case	YES (1)	NO (0)
4. No target clinical symptoms in the control group	YES (1)	NO (0)
5. The study controlled for the most important confounders (sex, age)	YES (2)	NO (0)
6. Whether the MRI sequence for EPVS contains T1, T2, Flair	YES (1)	NO (0)
7. Use the same evaluation criteria to assess the degree of EPVS in the case and control groups	YES (1)	NO (0)
8. The case group and the control group have the same non-response rate	YES (1)	NO (0)

NOS=Newcastle-Ottawa Scale; EPVS= Enlarged perivascular spaces; MRI= magnetic resonance imaging

Table 4. The quality of the included studies was assessed using eight criteria

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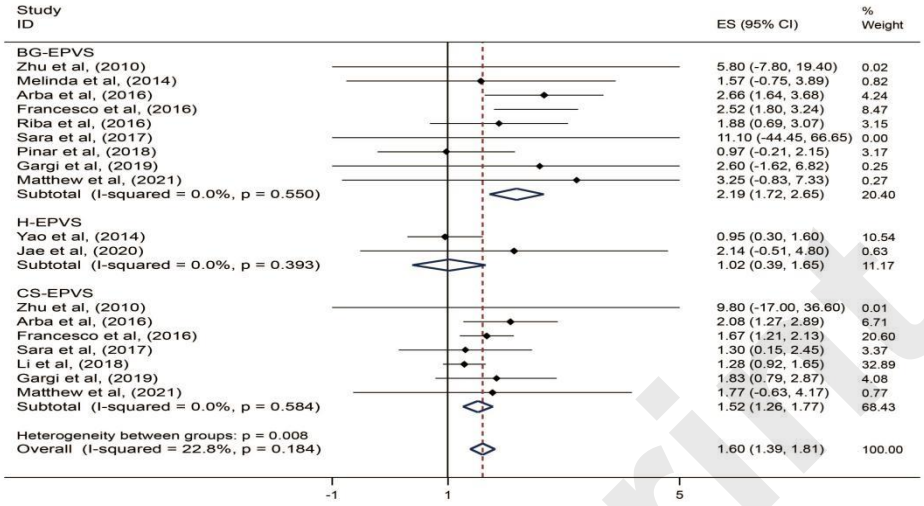
prospective										
Study	Year	1	2	3	4	5	6	7	8	Total
Zhu et al [26],	2010	Y	N	Y	Y	Y	Y	Y	Y	8

Yao et al [27],	2014	Y	N	Y	Y	Y	Y	Y	Y	8
Thomas et al [18],	2015	Y	Y	Y	Y	Y	N	Y	Y	8
Riba et al [29],	2016	Y	Y	Y	N	Y	N	Y	Y	7
Gutierrez et al [43],	2017	Y	N	Y	Y	Y	N	Y	Y	7
Lau et al [44],	2017	Y	N	Y	Y	Y	Y	Y	Y	8
Pinar et al [31],	2018	Y	Y	Y	N	Y	Y	Y	Y	8
Gargi et al [33],	2019	Y	Y	Y	Y	N	Y	Y	Y	7
Zhang et al [45],	2020	Y	N	Y	Y	Y	Y	Y	Y	8
Emerald et al [9],	2021	Y	Y	Y	N	Y	N	Y	Y	7
Matthew et al [34],	2021	Y	Y	Y	N	Y	Y	Y	Y	8
retrospective or cross-sectional										
Study	Year	1	2	3	4	5	6	7	8	Total
Andreas et al [13],	2013	Y	Y	Y	Y	N	Y	Y	Y	7
Melinda et al [12],	2014	Y	Y	Y	Y	N	Y	Y	Y	7
Arba et al [28],	2016	Y	Y	Y	Y	Y	N	Y	Y	8
Francesco et al [21],	2016	Y	N	Y	Y	Y	N	Y	Y	7
Song et al [38],	2016	Y	Y	Y	Y	Y	N	Y	Y	8
Zhang et al [19],	2016	Y	Y	Y	Y	N	Y	Y	Y	7
Sara et al [30],	2017	Y	Y	Y	Y	N	Y	Y	Y	7
Li et al [32],	2018	Y	Y	Y	Y	N	Y	Y	Y	7
Wan et al [36],	2018	Y	Y	Y	Y	Y	N	Y	Y	8
Vasileios et al [35],	2018	Y	Y	Y	Y	Y	N	Y	Y	8
Liang et al [10],	2018	Y	Y	Y	Y	N	Y	Y	Y	7
Oscar et al [37],	2019	Y	Y	Y	Y	N	Y	Y	Y	7
Oscar et al [39],	2019	Y	Y	Y	Y	N	Y	Y	Y	7
Oscar et al [40],	2019	Y	N	Y	Y	Y	Y	Y	Y	8
Benjamin et al [41],	2019	Y	Y	Y	Y	Y	N	Y	Y	8
Jae et al [22],	2020	Y	Y	Y	Y	Y	N	Y	Y	8
Wang et al [42],	2020	Y	N	Y	Y	Y	N	Y	Y	7
Joel et al [11],	2021	Y	Y	Y	Y	Y	N	Y	Y	8
Xu et al [46],	2021	Y	N	Y	Y	Y	Y	Y	Y	8
Song et al [47],	2021	Y	Y	Y	Y	N	Y	Y	Y	7
Yang et al [20],	2022	Y	Y	Y	Y	Y	N	Y	Y	8
Y= YES; N= NO										

Correlation between EPVS and Clinical symptoms

Cognitive Disorder. Twelve studies (n = 9205) reported on cognitive disorder and EPVS in BG, CS or Hippocampus. EPVS was significantly associated with cognitive disorder (OR: 1.60, 95 % CI: 1.39- 1.81, I^2=22.8 %, P = 0.184), most in the BG (OR: 2.19, 95% CI: 1.72- 2.65, I^2 = 0.0%, P = 0.550), then CS (OR: 1.52, 95 % CI: 1.26- 1.77, I^2 = 0.0%, P = 0.584). However, hippocampus was not significantly associated with cognitive disorder (OR: 1.02, 95%CI: 0.39- 1.65, I^2 = 0.0%, P = 0.393) (Table 2, Figure 2).

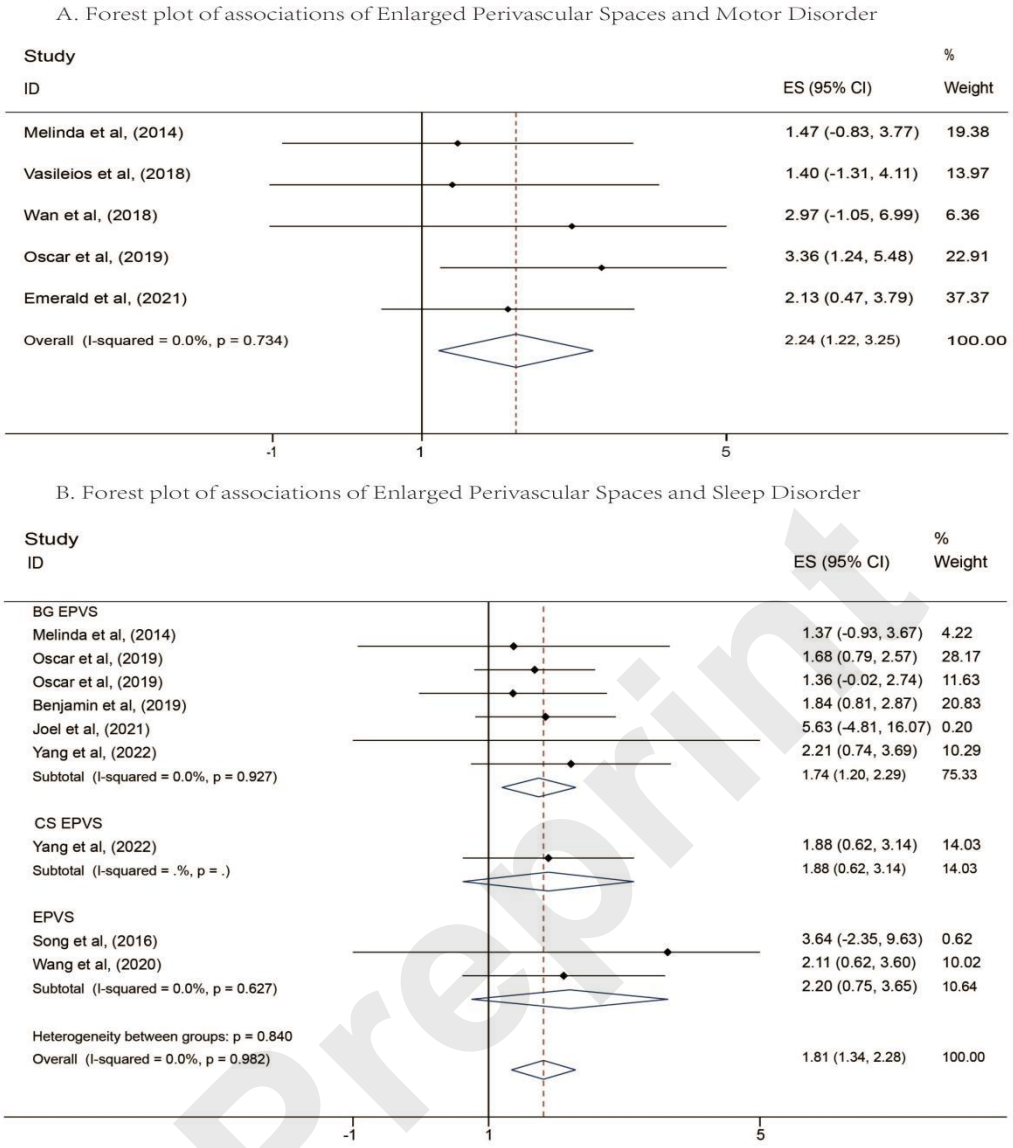
Figure 2. Forest plot of associations of Enlarged Perivascular Spaces and Cognitive Disorder



Motor Disorder. We found a significant association in 946 participants from five studies of EPVS with motor disorder (OR: 2.24, 95 % CI: 1.22- 3.25, I^2 = 0.0% , P = 0.734) (Table 2, Figure 3).

Sleep Symptoms. In 1846 participants from eight studies, EPVS was associated significantly with sleep disorders (OR: 1.81, 95 % CI: 1.34- 2.28, I^2=0.0% , P = 0.982), especially in BG EPVS (OR: 1.74, 95 % CI: 1.20- 2.29, I^2 = 0.0 % , P = 0.927). There were insufficient data to compare CS EPVS and sleep disorders (Table 2, Figure 3).

Figure 3. Forest plot of associations of Enlarged Perivascular Spaces and Motor Disorder and Sleep Disorder

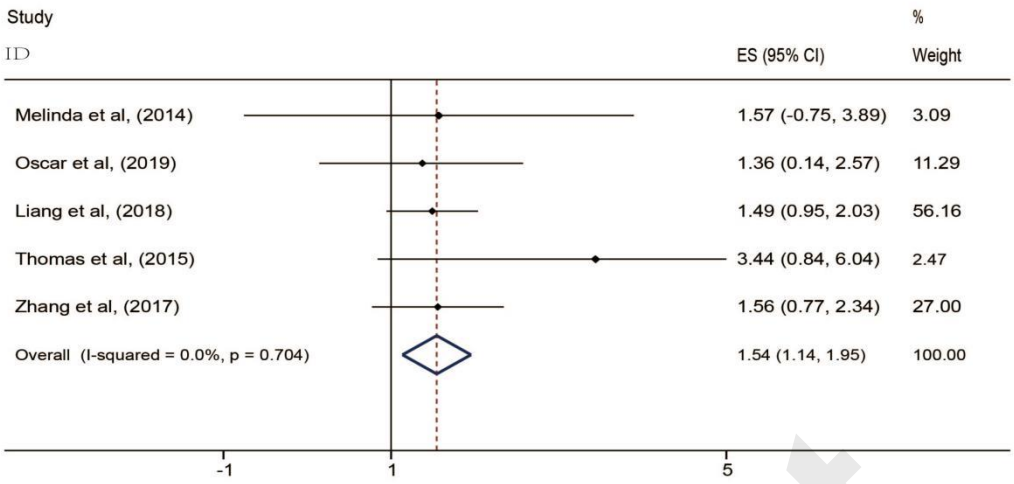


Depressive Disorder. Five studies (n = 3465) found that depressive disorder was associated with EPVS (OR: 1.54, 95 % CI: 1.14- 1.95, I^2=0.0% , P = 0.704) (Table 2, Figure 4).

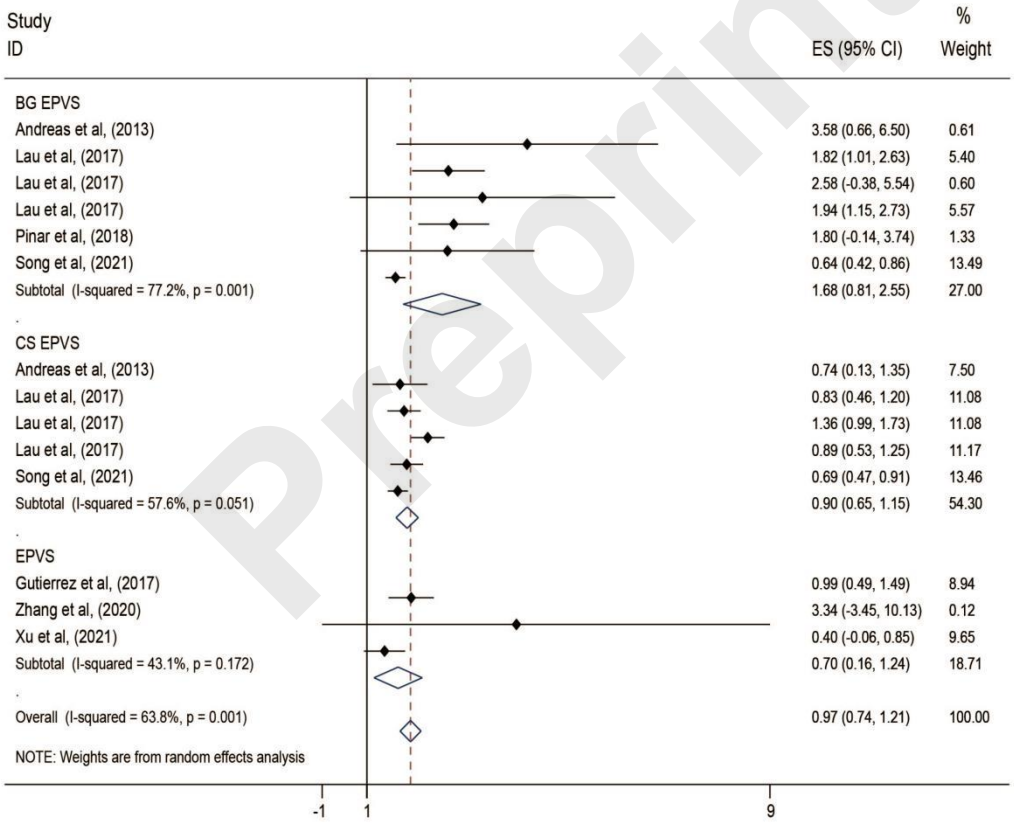
Stroke. Seven studies (n= 6867) found no association between stroke and EPVS (OR: 0.97, 95 % CI: 0.74- 1.21, I^2=63.8 % , P= 0.001)(Table 2, Figure 4). We also failed to find any correlations in further subgroup analyses based on the source of different brain regions.

Figure 4. Forest plot of associations of Enlarged Perivascular Spaces and Depressive Disorder and Stroke

A. Forest plot of associations of Enlarged Perivascular Spaces and Depressive Disorder



B. Forest plot of associations of Enlarged Perivascular Spaces and Stroke



Sensitivity analysis and Publication Bias

The purpose of the sensitivity analysis was to detect whether any of the included studies would affect the primary outcome of the meta-analysis. The OR values did not change significantly when either study was excluded (Supplementary Figure 5-9 shows the results of the sensitivity analysis). Begg's Test based on OR value and SE showed no publication bias (Table 5).

Table 5. Begg's Test

Table 5. Begg's Test	
Begg's Test	Value
Cognitive Disorder	Pr > |z| = 0.426
Motor Disorder	Pr > |z| = 1.000
Sleep Disorder	Pr > |z| = 0.061
Depressive Disorder	Pr > |z| = 0.327
Stroke	Pr > |z| = 0.079

Discussion

We investigated the correlation between EPVS and clinical symptoms using meta-analysis. Since BG EPVS and CS EPVS have different formation mechanisms, we performed a subgroup analysis to explore whether there are differences in their impact on clinical symptoms. Our findings showed that EPVS was associated with cognitive impairment, motor impairment, sleep disturbance, and depressive symptoms, but not with stroke.

In recent years, many studies have shown that EPVS is correlated with the occurrence of cognitive impairment [8]. Impaired cortical cholinergic pathways can lead to cognitive impairment, and a high load of EPVS may impair the cortical cholinergic pathways, leading to cognitive decline [48]. However, this result remains controversial. For example, a prospective study by Pinar Yilmaz et al. [31] showed that EPVS was not associated with the risk of dementia. The reason for this result may be that the number of people with EPVS imaging manifestations included in this study was too small. Our findings also show that BG EPVS is more associated with cognitive impairment than CS EPVS, which may be related to its different anatomical characteristics and formation mechanisms. Studies have shown that BG EPVS is more related to age and hypertension [17], and CS EPVS is more related to cerebral amyloid angiopathy (CAA) [30]. Combined with our results, we speculate that the influence of vascular risk factors such as age and hypertension on cognitive impairment may be higher than that of CAA, however, further clinical experiments are needed to confirm.

Several recent human studies have reported an association between sleep and EPVS. The perivascular space is a critical pathway for lymphatic flow and an important fluid waste removal system that may be associated with compensatory changes in human sleep physiology [49, 50]. Larger PVS volumes have been reported to be associated with periodic limb movements during sleep [51] and lower sleep quality [52]. These observations reflect the effect of sleep deprivation on the structure of the perivascular space. However, one study found that the association between sleep disturbance and EPVS disappeared after adjusting for relevant confounders [39]. After subgroup analysis, we found that BG EPVS was more significantly associated with sleep disturbance. There are few studies on CS EPVS and sleep disturbance, which may be related to the anatomical structure of cerebrospinal fluid drainage. BG EPVS can communicate directly with basal cisterns, while CS EPVS communicates with subarachnoid CSF at certain locations, which may lead to a stronger role of BG EPVS in CSF drainage than CS EPVS, thus making BG EPVS more correlated with sleep disorders [53, 54].

Our results show that EPVS is associated with dyskinesia, unfortunately, we did not perform a subgroup analysis due to the small number of eligible related studies. A prospective study with a 9-year follow-up showed that the highest tertile of EPVS increased the risk of dyskinesia by 2.13 times

(HR 2.13; CI 1.04 - 4.36), suggesting that dyskinesia may be related to the size and duration of EPVS [9]. However, the study by Daniela Pinter [55] showed that WMH was a significant predictor of gait and balance impairment, whereas EPVS was not significantly associated with movement impairment. This may be related to differences in its inclusion population, which was mainly non-disabled elderly subjects living in the community and with lower overall CSVD scores, which may reduce the magnitude of the association.

Our findings suggest that EPVS is a risk factor for developing depressive symptoms. Depression in later life is associated with cerebrovascular disease, and its treatment resistance may be associated with vascular lesions in the white matter and basal ganglia [56]. Common sites of EPVS overlap with emotion regulation pathways (such as frontal-subcortical loops, cingulate-cortical loops, and cortico-basal ganglia loops), disrupting neural circuits for emotion regulation and possibly contributing to the development of depression [57, 58]. A cross-sectional study by Tufail [56] also showed that EPVS was associated with an increased risk of developing depression and a low response to antidepressants, which was consistent with our total result. However, Zhang et al. [19] did not find a clear association between EPVS and poststroke depression (PSD). These differences may be related to differences in study populations and study designs, especially the assessment of PSD and EPVS. Future research should address these issues.

At present, the results of the association between EPVS and stroke are inconsistent, and our results show that the incidence of EPVS and stroke is not statistically significant. The study of Farah Francis et al. also found no correlation between the two [17]. While some studies have shown that CS EPVS is associated with lobar intracerebral hemorrhage (p=0.041), and BG EPVS is associated with non- CAA -induced intracerebral hemorrhage (OR 3.58, CI 1.70- 7.54) [13]. Since there are few studies on the correlation between EPVS and stroke, we did not compare ischemic stroke and hemorrhagic stroke separately, and there are contradictions in the treatment of these two diseases. Therefore, the relationship between EPVS and ischemic stroke and hemorrhagic stroke should be separately evaluated in the future.

Limitations

Our results have important implications for understanding the relationship of EPVS to clinical symptoms, but limitations remain. The source of heterogeneity may be related to the following reasons: (1) differences in included populations; (2) differences in study types; (3) differences in sample sizes; (4) differences in detection and evaluation methods for EPVS. Future studies should adopt more consistent, objective, and quicker methods to quantify EPVS. Currently, the potential of using automated methods to assess EPVS burden is being recognized. Boespflug et al. [59] developed a method for fully automatic identification and segmentation of EPVS based on multimodal MRI images. However, this technique needs to scan more sequences, which is obviously not advantageous in time. Dubost et al. [6] realized the automatic identification and quantitative measurement of high-quality EPVS using only the information of one sequence of T2WI. Second, while most studies used ORs, a few used HRs [9, 32, 43-45]. In meta-analyses, pooling the latter with ORs, although numerically similar to each other, may not fully validate the association of EPVS with clinical symptoms. Although the sensitivity analysis indicated that our results were reliable, it was considered a methodological limitation. In addition, due to limited literature, we have not been able to explore the relationship between EPVS in different regions and movement disorder and depressive symptoms, and high-quality

cohort studies need more time to complete. Although our results did not show publication bias, our findings require further validation in a large prospective meta-analysis using unified typing criteria and statistical models.

Conclusion

In conclusion, our results provide evidence for the correlation between EPVS and clinical symptoms, proving that EPVS is positively correlated with the risk of cognitive impairment, motor impairment, sleep disorders, and depressive symptoms, but not significantly correlated with the risk of stroke. After subgroup analysis, we found that BG EPVS was more associated with cognitive impairment and sleep disturbance, and CS EPVS was more associated with depressive symptoms. Therefore, we should conduct early prediction and assessment of the presence of relevant clinical symptoms and disease risk in people with EPVS, and conduct research on how to prevent and treat EPVS. Furthermore, future research should continuously optimize the automatic measurement method of EPVS images in terms of improving algorithms, acquisition sequences, and post-processing methods.

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Table 1. The search strategy of PubMed

Table 1	The search strategy of PubMed
Search	**Query**
#1	(((((((Enlarged Perivascular Space[MeSH Major Topic]) OR (Enlarged Virchow-Robin Spaces[Title/Abstract])) OR (Perivascular Spaces Enlargement[Title/Abstract])) OR (Virchow-Robin Spaces Enlargement[Title/Abstract])) OR (perivascular spaces[Title/Abstract])) OR (Virchow-robin spaces[Title/Abstract]))) OR (Enlarged Perivascular Spaces[Title/Abstract])
#2	((Clinical[Title/Abstract]) OR (Clinical Symptoms[Title/Abstract])) OR (Clinical Manifestation[Title/Abstract])
#3	((((Magnetic Resonance Imaging[Title/Abstract]) OR (Imaging[Title/Abstract])) OR (MR Tomography[Title/Abstract])) OR (MRI[Title/Abstract])) OR (fMRI[Title/Abstract])
#4	#2 OR #3
#5	#1 And #4

Table 2. Characteristics of studies included in the meta-analysis.

Table 2. Characteristics of studies included in the meta-analysis								
Study	**Year**	**Total**	**Study Type**	**follow-up time**	**Clinical symptoms**	**OR (95% CI)**	**Brain region**	**Geographic region**
Cognitive Disorder								
Zhu et al [26],	2010	1778	prospective	4 years	Dementia	5.8 (1.2- 28.4) 9.8 (1.7- 55.3)	BG WM	France
Melinda et al [12],	2014	79	retrospective	/	Dementia	1.57 (0.48-5.13)	SCS	Minnesota
Yao et al [27],	2014	1818	prospective	6.12 years	Dementia	0.95 (0.50-1.80)	HP	Dijon
Arba et al [28],	2016	234	retrospective	/	PSCI	2.66 (1.82- 3.87) 2.08 (1.42- 3.05)	BG CS	VISTA
Francesco et al [21],	2016	430	retrospective	/	Cognitive disorder	2.52 (1.90- 3.35) 1.67 (1.25- 2.18)	BG CS	VISTA
Riba et al [29],	2016	733	prospective	8 years	MCI	1.88(1.03- 3.41)	BG	Barcelona
Sara et al [30],	2017	1504	cross-sectional	/	Vascular dementia	11.1 (1.1- 112.2) 1.3 (0.6- 2.9)	BG CS	Sweden
Pinar et al [31],	2018	1651	prospective	7.2 years	Dementia	0.97 (0.35- 2.72)	BG	Netherlands
Li et al [32],	2018	158	cross-sectional	/	Dementia	1.283 (0.967-1.703)	CS	Massachusetts
Gargi et al [33],	2019	117	prospective	1 year	Cognitive impairment	2.60 (0.74- 9.19) 1.83 (1.06- 3.15)	BG CS	UK
Jae et al [22],	2020	109	cross-sectional	/	Memory function	2.142 (-0.515- 4.799)	HP	South Korea
Matthew et al [34],	2021	414	prospective	6 years	Dementia	3.25(1.14- 9.30) 1.77(0.58- 5.39)	BG CS	Sydney
Motor Disorder								
Wan et al [36],	2018	137	cross-sectional	/	PIGD	2.97 (0.98- 9.03)	CS	China
Vasileios et al [35],	2018	175	retrospective	/	Functional independence	1.4 (0.34- 5.77)	BG	USA
Oscar et al [37],	2019	288	cross-sectional	/	risk of falls	3.36 (1.85- 6.09)	BG	Atahualpa

Emerald et al [9],	2021	331	prospective	9 years	Walking speed limitation	2.13 (1.04- 4.36)	/	Sweden
Melinda et al [12],	2014	79	retrospective	/	Any movement disorder	1.47 (0.43-5.04)	SCS	Minnesota
Sleep Disorder								
Song et al [38],	2017	170	cross-sectional	/	Moderate-to-severe (AHI ⩾ 15)	3.64 (1.02- 13.01)	/	South Korea
Wang et al [42],	2020	106	cross-sectional	/	ArI	2.108 (1.032- 4.017)	/	China
Joel et al [11],	2021	153	cross-sectional	/	Daytime Dysfunction	5.31 (1.38- 22.26)	BG	ONDRI
Oscar et al [39],	2019	338	cross-sectional	/	Sleep quality	1.68 (1.01- 2.79)	BG	Atahualpa
Oscar et al [40],	2020	146	cross-sectional	/	PLMS	1.36 (0.56- 3.33)	BG	Atahualpa
Melinda et al [12],	2014	79	retrospective	/	Any sleep disorder	1.37 (0.37- 4.97)	SCS	Minnesota
Benjamin et al [41],	2020	457	cross-sectional	/	Interrupted Sleep	1.84 (1.08- 3.15)	BG	Scotland
Yang et al [20],	2022	398	retrospective	/	Poor sleep quality	2.125 (1.113- 4.058) 1.882 (1.005- 3.527)	BG WM	China
Depressive Disorder								
Thomas et al [18],	2015	1949	prospective	5 years	Depression	3.44 (1.71- 6.91)	/	Reykjavik
Liang et al [10],	2018	725	cross-sectional	/	PSD	1.49 (1.04- 2.13)	CS	China
Zhang et al [19],	2016	374	cross-sectional	/	PSD	1.557 (0.958- 2.530)	/	China
Oscar et al [39],	2019	338	cross-sectional	/	Depression	1.359 (0.608- 3.039)	BG	Atahualpa
Melinda et al [12],	2014	79	retrospective	/	Depression	1.57 (0.48- 5.13)	SCS	Minnesota
Stroke								
Pinar et al [31],	2018	1651	prospective	7.2 years	Stroke	1.80 (0.71- 4.59)	BG	Netherlands
Andreas et al [13],	2013	121	retrospective	/	ICH	3.58 (1.70- 7.54) 0.74 (0.35- 1.57)	BG CS	UK and Belgium
Xu et al [46],	2021	167	cross-sectional	/	Large hematoma volume	0.395 (0.147- 1.064)	/	China
Zhang et al [45],	2020	1204	prospective	3 years	Stroke	3.34 (0.78- 14.37)	/	China
Gutierrez et al [43],	2017	1228	prospective	9 ±2 years	Stroke	0.9 (0.60- 1.61)	/	Manhattan
Lau et al [44],	2017	2002	prospective	42±23 months	Ischemic stroke Intracerebral hemorrhage Recurrent stroke Ischemic stroke Intracerebral hemorrhage Recurrent stroke	1.82 (1.18- 2.80) 2.58 (0.97- 6.89) 1.94 (1.31- 2.89) 0.83 (0.54- 1.28) 1.36 (0.51- 3.59) 0.89 (0.60- 1.33)	BG BG BG CS CS CS	UK and China
Song et al [47],	2021	494	retrospective	/	HT	0.638 (0.454- 0.897) 0.690 (0.502- 0.949)	BG CS	China

PSCI=post-stroke cognitive impairment; VISTA=Virtual International Stroke Trial Archive; MCI=mild cognitive impairment (MCI); PIGD=the postural instability and gait disability; AHI=apnea hyponea index; ArI=arousal index; PSD= poststroke depression; HT=hemorrhagic transformation; HR=hazard ratio; OR=odds ratios; BG=basal ganglia;

CS=centrum semiovale; WM=white matter; SCS= swiss cheese striatum; HP= hippocampal; ICH= intracercbral hemorrhage; PLMS= periodic limb movements during sleep; ONDRI= Ontario Neurodegenerative Disease Research Initiative

Table 3. Eight questions of included study quality were evaluated according to NOS evaluation criteria

Table 3. Eight questions of included study quality were evaluated according to NOS evaluation criteria		
prospective		
1. Are EPVS major exposure factors?	YES (1)	NO (0)
2. Are the non-exposed group and the exposed group from the same population?	YES (1)	NO (0)
3. Whether the MRI sequence for EPVS contains T1, T2, Flair	YES (1)	NO (0)
4. Were the investigators ignorant of the patient's clinical symptoms when determining EPVS	YES (1)	NO (0)
5. The study controlled for the most important confounders (sex, age)	YES (2)	NO (0)
6. Is the assessment of clinical symptoms adequate?	YES (1)	NO (0)
7. Is the follow-up period long enough?	YES (1)	NO (0)
8. Is the follow-up adequate?	Complete follow-up or a small number of studies lost to follow-up without introducing bias (1)	Lost to follow-up but not described or follow-up not described (0)
retrospective or cross-sectional		
1. Evaluation of clinical symptoms by professionally trained personnel	YES (1)	NO (0)
2. Cases are representative	YES (1)	NO (0)
3. Whether it is a control of the same population as the case	YES (1)	NO (0)
4. No target clinical symptoms	YES (1)	NO (0)
5. The study controlled for the most important confounders (sex, age)	YES (2)	NO (0)
6. Whether the MRI sequence for EPVS contains T1, T2, Flair	YES (1)	NO (0)
7. Use the same evaluation criteria to assess the degree of EPVS in the case and control groups	YES (1)	NO (0)
8. The case group and the control group have the same non-response rate	YES (1)	NO (0)

Table 4. The quality of the included studies was assessed using eight criteria

Table 4. The quality of the included studies was assessed using eight criteria										
prospective										
Study	Year	1	2	3	4	5	6	7	8	Total
Zhu et al [26],	2010	Y	N	Y	Y	Y	Y	Y	Y	8
Yao et al [27],	2014	Y	N	Y	Y	Y	Y	Y	Y	8
Thomas et al [18],	2015	Y	Y	Y	Y	Y	N	Y	Y	8
Riba et al [29],	2016	Y	Y	Y	N	Y	N	Y	Y	7
Gutierrez et al [43],	2017	Y	N	Y	Y	Y	N	Y	Y	7
Lau et al [44],	2017	Y	N	Y	Y	Y	Y	Y	Y	8
Pinar et al [31],	2018	Y	Y	Y	N	Y	Y	Y	Y	8
Gargi et al [33],	2019	Y	Y	Y	Y	N	Y	Y	Y	7

Zhang et al [45],	2020	Y	N	Y	Y	Y	Y	Y	Y	8
Emerald et al [9],	2021	Y	Y	Y	N	Y	N	Y	Y	7
Matthew et al [34],	2021	Y	Y	Y	N	Y	Y	Y	Y	8
retrospective or cross-sectional										
Study	Year	1	2	3	4	5	6	7	8	Total
Andreas et al [13],	2013	Y	Y	Y	Y	N	Y	Y	Y	7
Melinda et al [12],	2014	Y	Y	Y	Y	N	Y	Y	Y	7
Arba et al [28],	2016	Y	Y	Y	Y	Y	N	Y	Y	8
Francesco et al [21],	2016	Y	N	Y	Y	Y	N	Y	Y	7
Song et al [38],	2016	Y	Y	Y	Y	Y	N	Y	Y	8
Zhang et al [19],	2016	Y	Y	Y	Y	N	Y	Y	Y	7
Sara et al [30],	2017	Y	Y	Y	Y	N	Y	Y	Y	7
Li et al [32],	2018	Y	Y	Y	Y	N	Y	Y	Y	7
Wan et al [36],	2018	Y	Y	Y	Y	Y	N	Y	Y	8
Vasileios et al [35],	2018	Y	Y	Y	Y	Y	N	Y	Y	8
Liang et al [10],	2018	Y	Y	Y	Y	N	Y	Y	Y	7
Oscar et al [37],	2019	Y	Y	Y	Y	N	Y	Y	Y	7
Oscar et al [39],	2019	Y	Y	Y	Y	N	Y	Y	Y	7
Oscar et al [40],	2019	Y	N	Y	Y	Y	Y	Y	Y	8
Benjamin et al [41],	2019	Y	Y	Y	Y	Y	N	Y	Y	8
Jae et al [22],	2020	Y	Y	Y	Y	Y	N	Y	Y	8
Wang et al [42],	2020	Y	N	Y	Y	Y	N	Y	Y	7
Joel et al [11],	2021	Y	Y	Y	Y	Y	N	Y	Y	8
Xu et al [46],	2021	Y	N	Y	Y	Y	Y	Y	Y	8
Song et al [47],	2021	Y	Y	Y	Y	N	Y	Y	Y	7
Yang et al [20],	2022	Y	Y	Y	Y	Y	N	Y	Y	8
Y= YES; N= NO										

Table 5. Begg's Test

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Begg's Test	Value
Cognitive Disorder	Pr > |z| = 0.426
Motor Disorder	Pr > |z| = 1.000
Sleep Disorder	Pr > |z| = 0.061
Depressive Disorder	Pr > |z| = 0.327
Stroke	Pr > |z| = 0.079

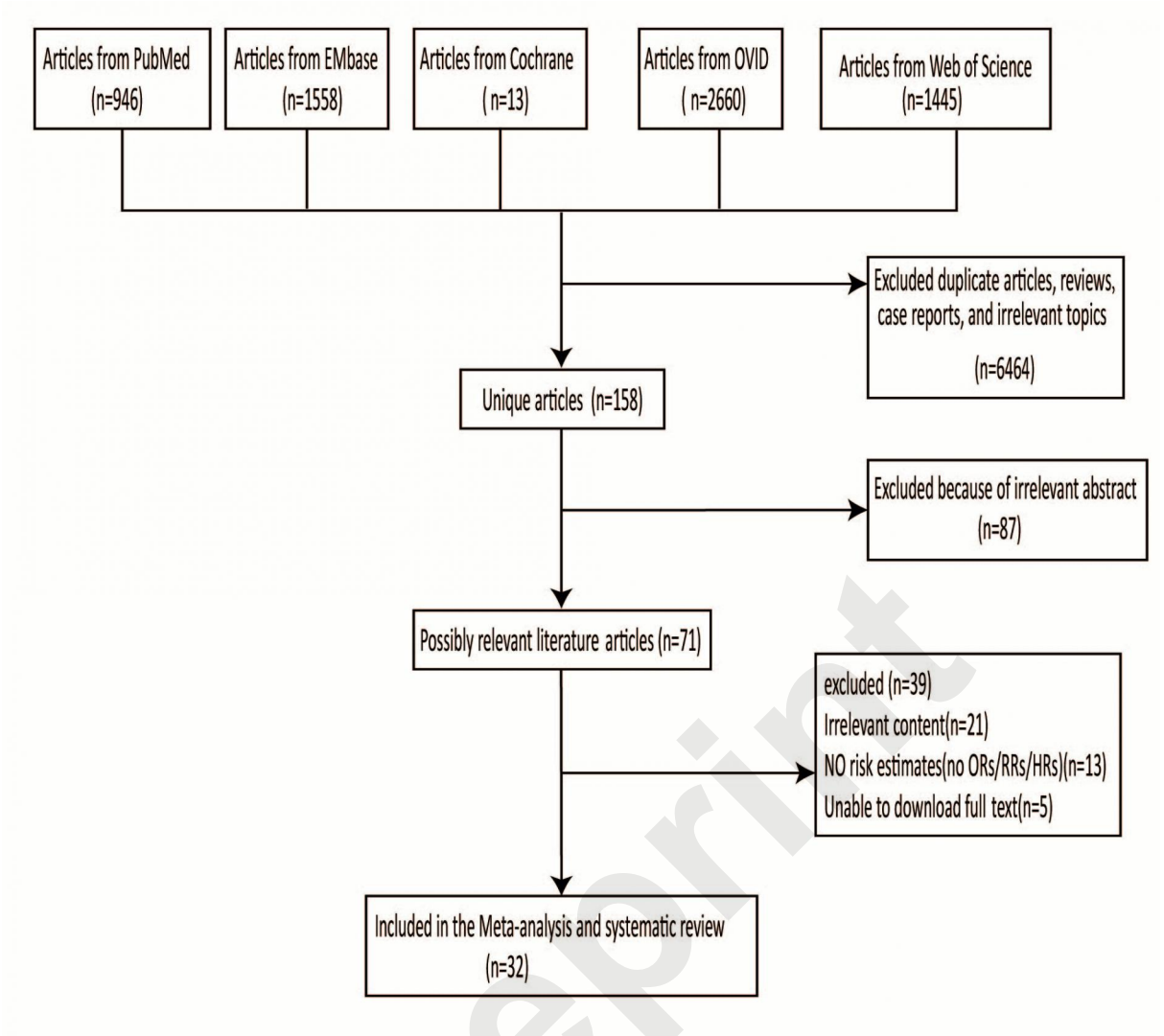

Figure 1.Summary of evidence search and selection

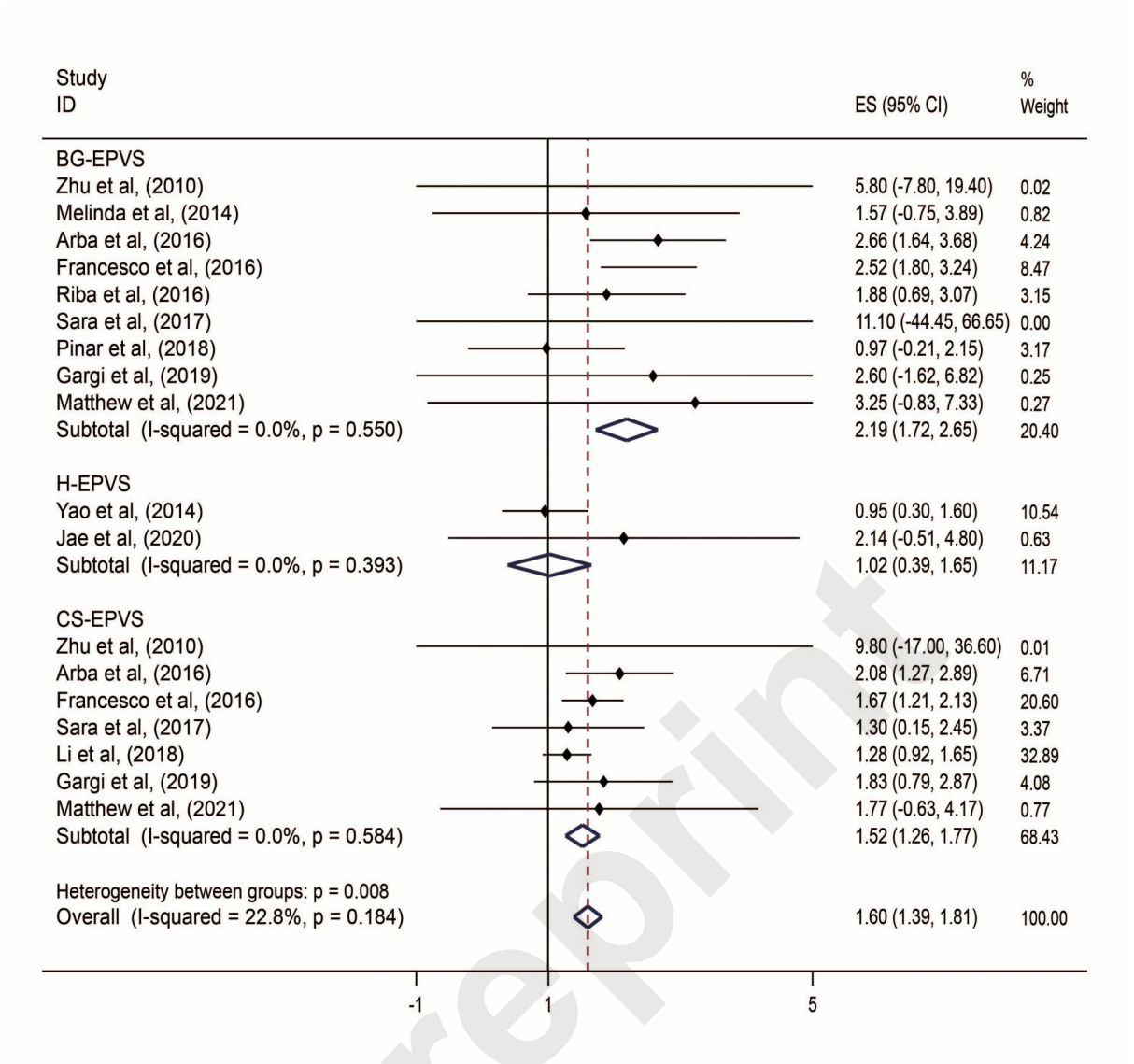

Figure 2. Forest plot of associations of Enlarged Perivascular Spaces and Cognitive Disorder

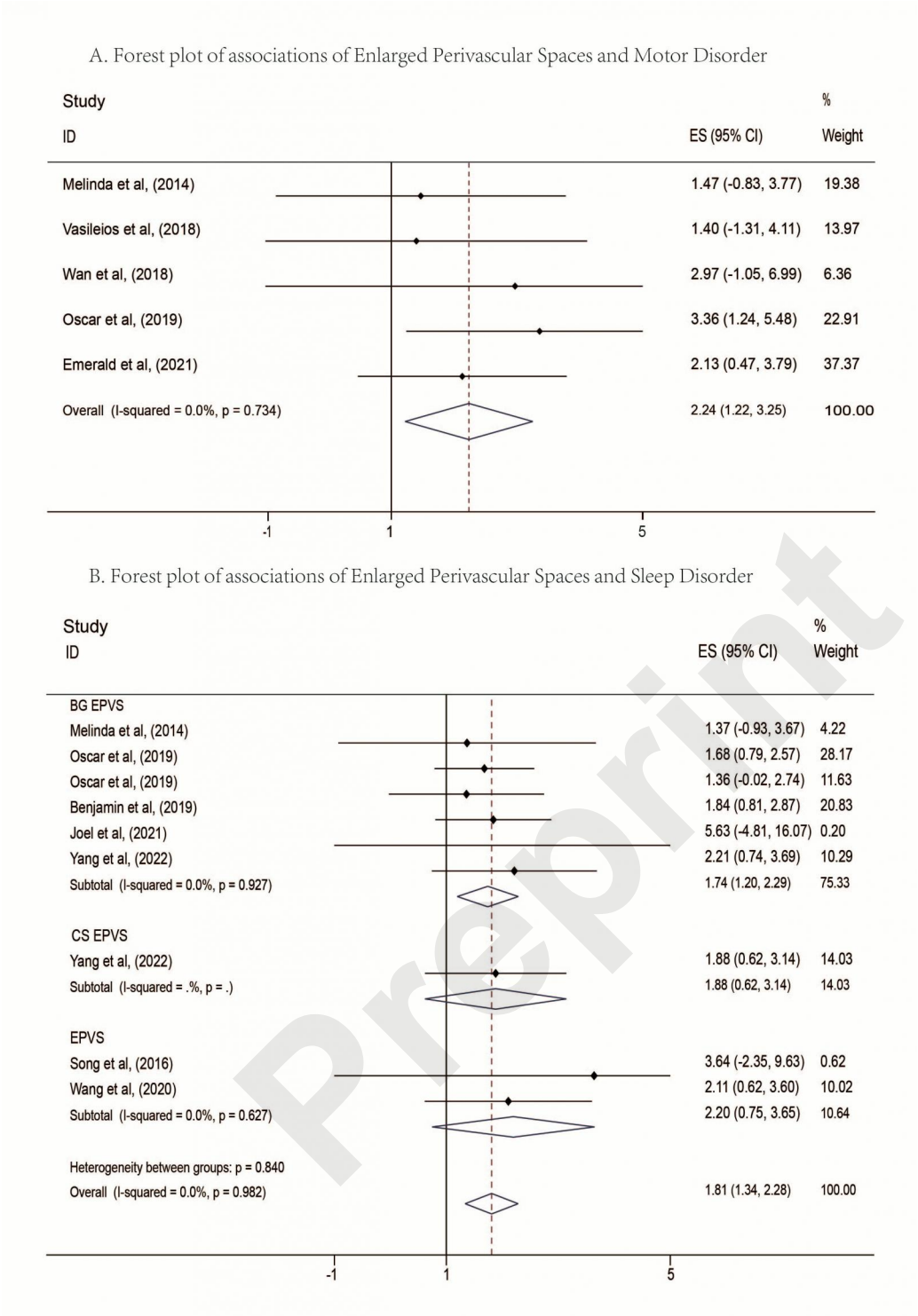

Figure 3. Forest plot of associations of Enlarged Perivascular Spaces and Motor Disorder and Sleep Disorder

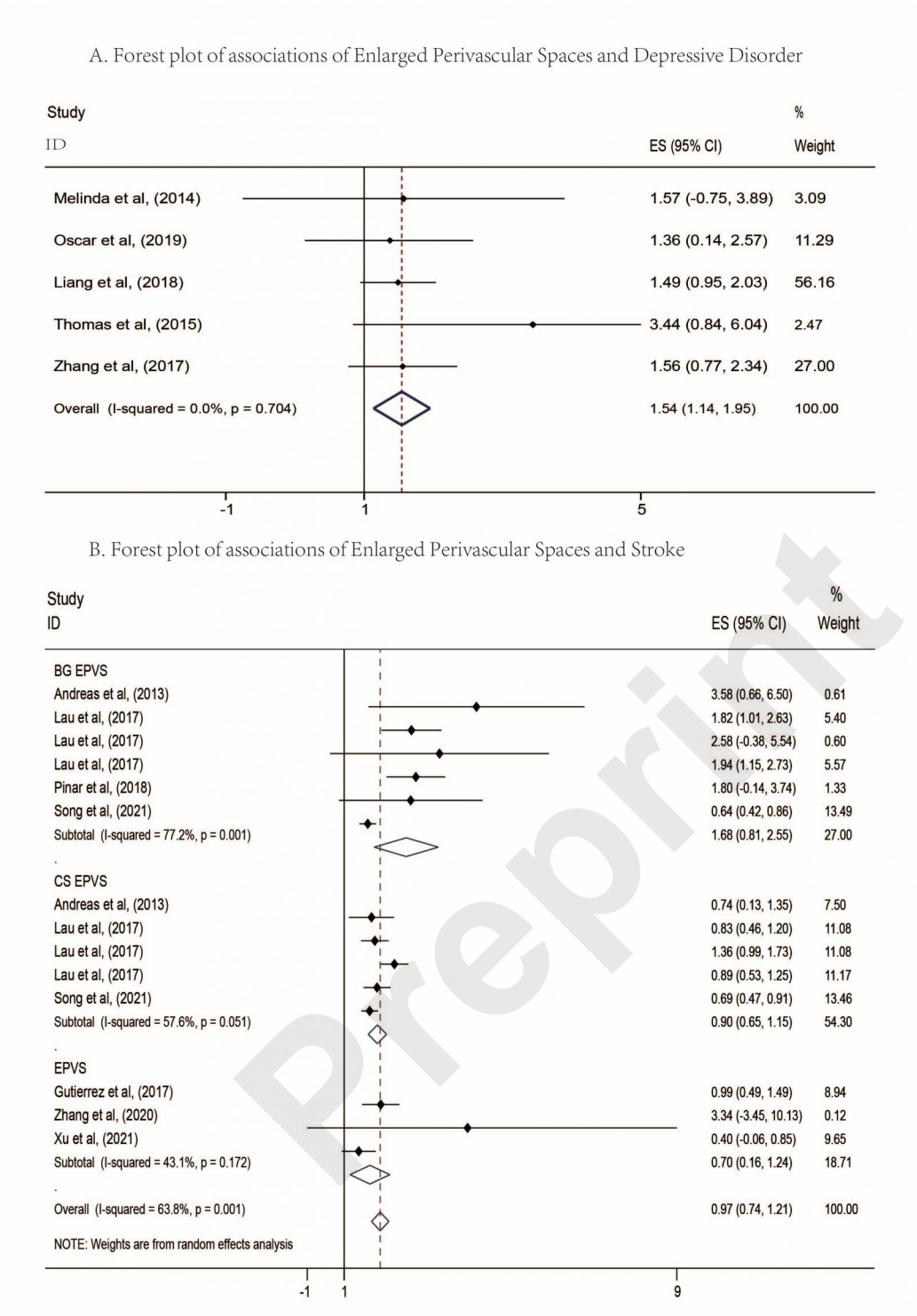

Figure 4. Forest plot of associations of Enlarged Perivascular Spaces and Depressive Disorder and Stroke

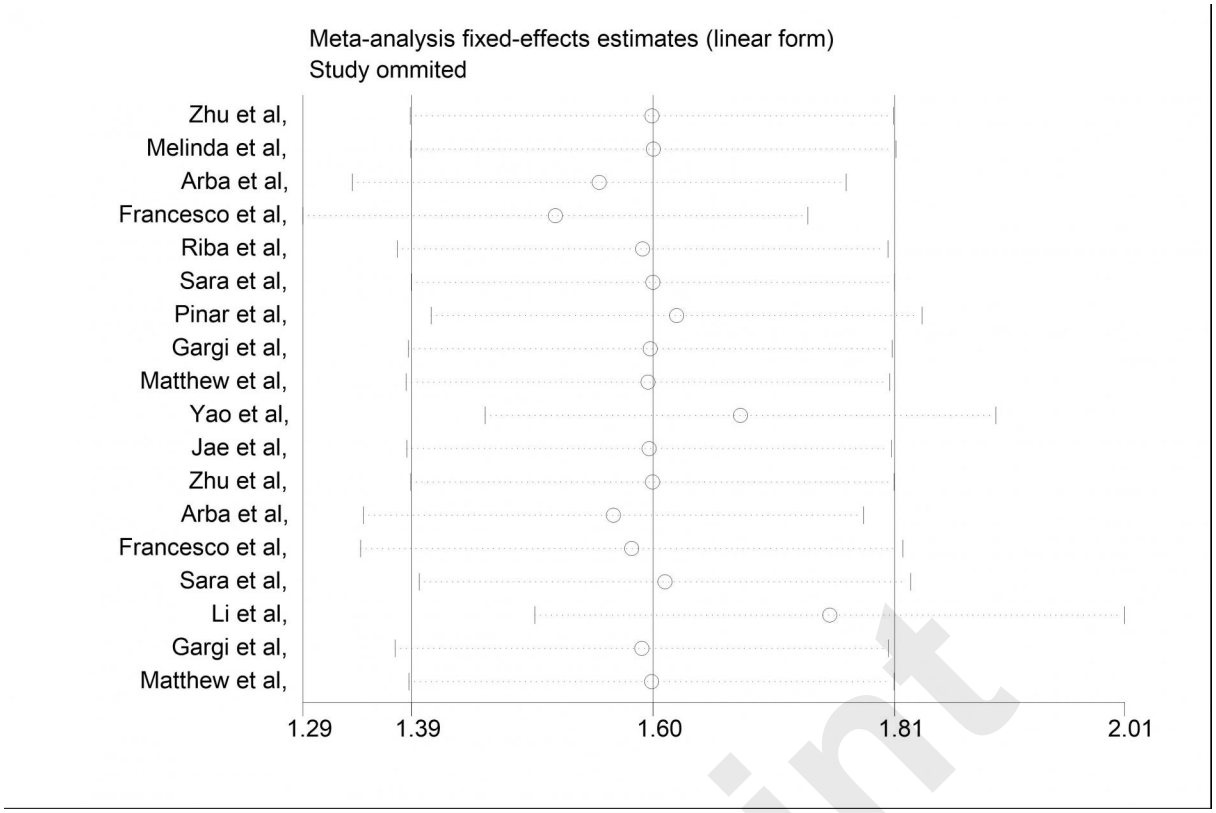

Figure 5. Sensitivity analysis used to assess the association between EPVS and Cognitive Disorder

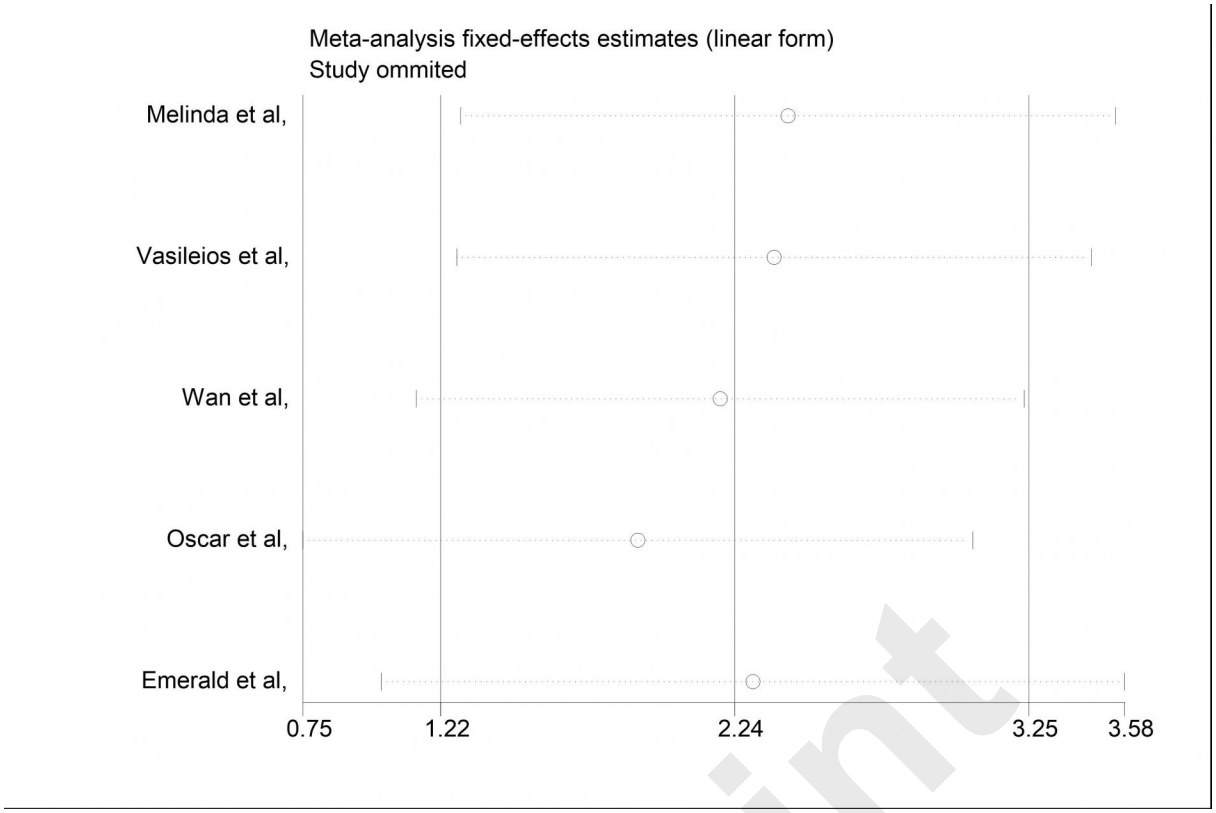

Figure 6. Sensitivity analysis used to assess the association between EPVS and Motor Disorder

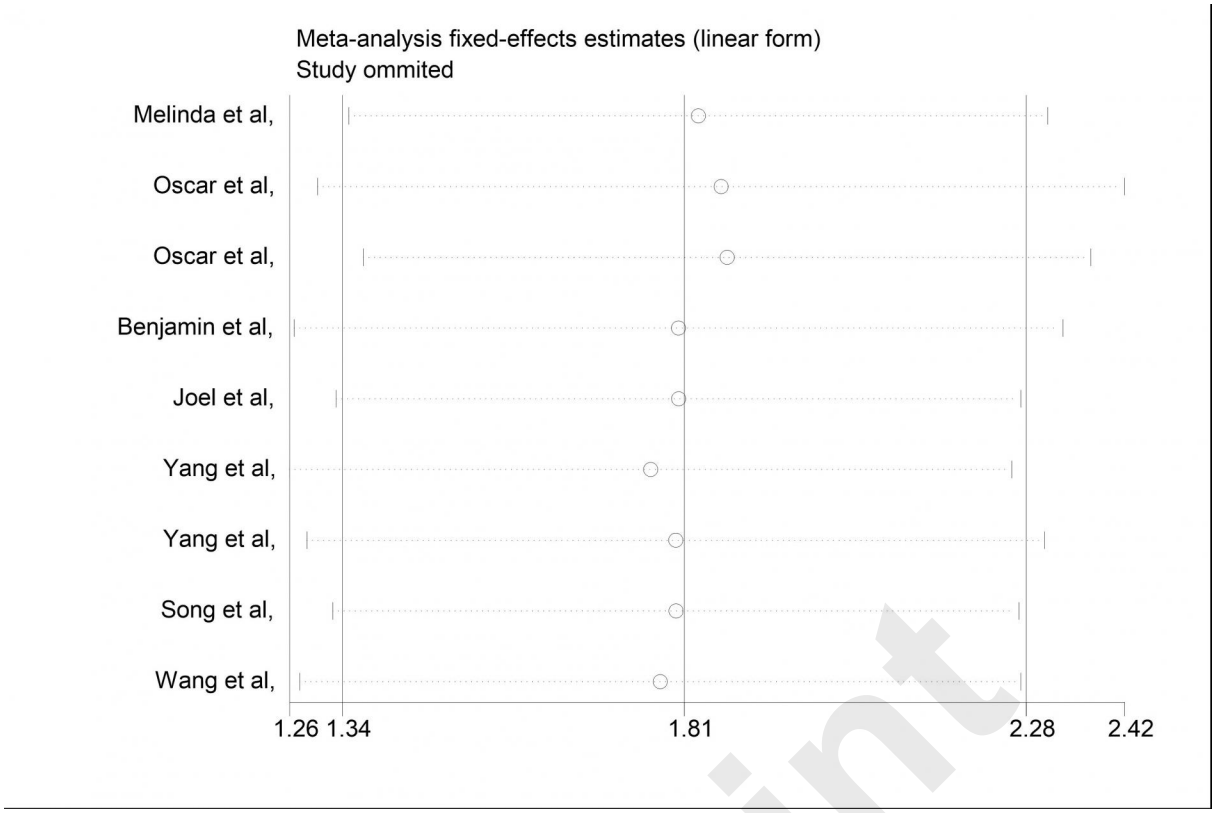

Figure 7. Sensitivity analysis used to assess the association between EPVS and Sleep Disorder

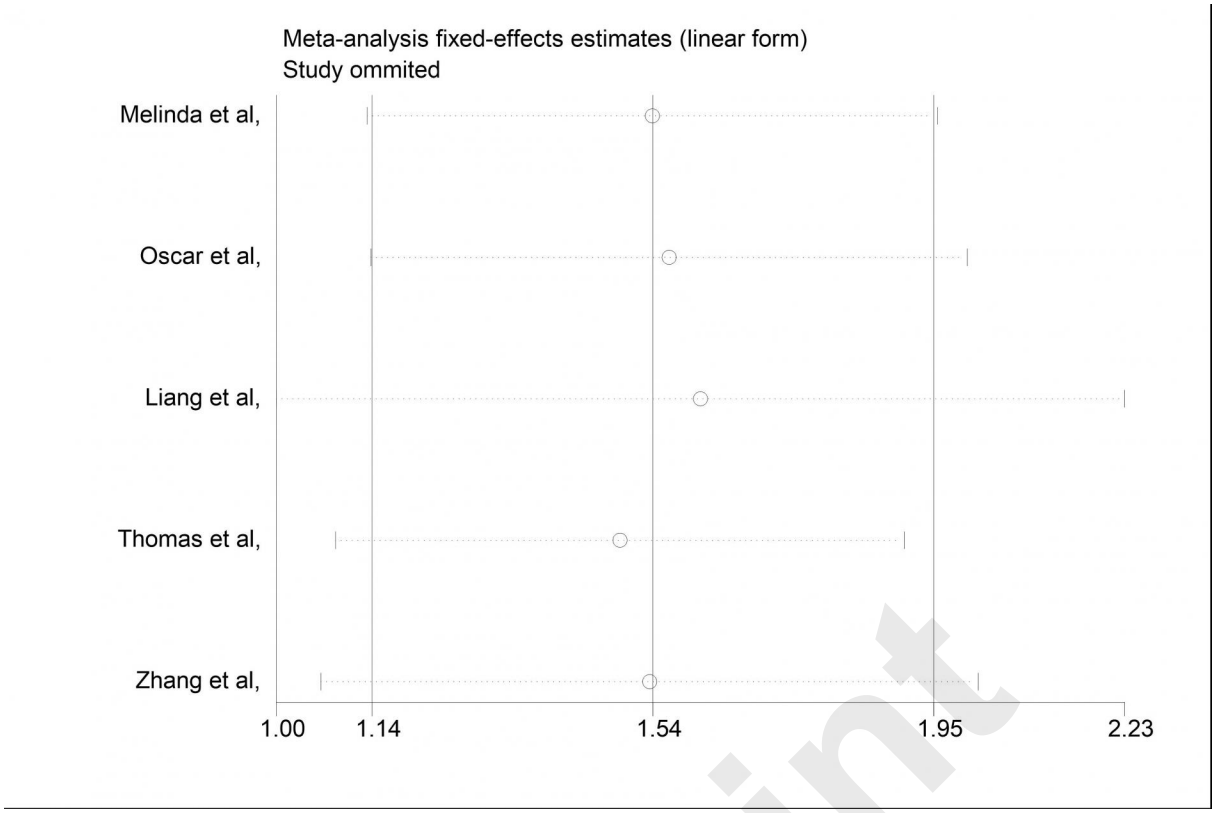

Figure 8. Sensitivity analysis used to assess the association between EPVS and Depression

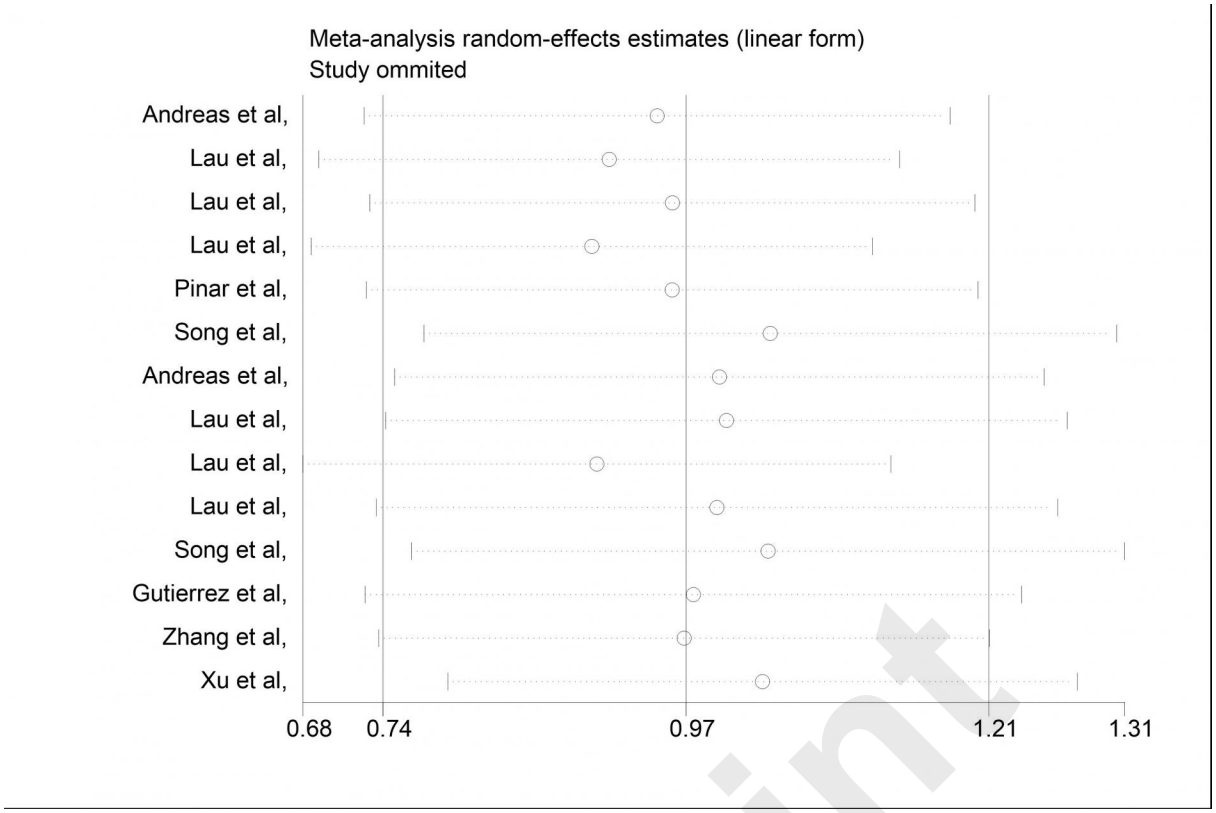

Figure 9. Sensitivity analysis used to assess the association between EPVS and Stroke