Perivascular spaces and their associations with risk factors, clinical disorders and neuroimaging features

Title: Perivascular spaces and their associations with risk factors, clinical disorders and neuroimaging features: A systematic review and meta-analysis

Short Title: Perivascular spaces associations

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Abstract

Background: Perivascular Spaces (PVS), visible on brain magnetic resonance imaging (MRI), are thought to be associated with small vessel disease (SVD), neuroinflammation, and to be important for cerebral haemodynamics and interstitial fluid drainage.

Aims: To benchmark current knowledge on PVS associations with risk factors, neurological disorders, and neuroimaging lesions, using systematic review and meta-analysis.

Summary of review: We searched three databases for PVS publications, calculated odds ratios with 95% confidence interval and performed meta-analyses to assess adjusted associations with PVS. We identified 116 relevant studies (n=36,108) but only 23 (n=12,725) were meta-analysable. PVS assessment, imaging and clinical definitions varied. PVS were associated (n; OR, 95%CI, p) with ageing (8395; 1.47, 1.28-1.69, p=0.00001), hypertension (7872; 1.67, 1.20-2.31, p=0.002), lacunes (4894; 3.56, 1.39-9.14, p=0.008), microbleeds (5015; 2.26, 1.04-4.90, p=0.04) but not WMH (4974; 1.54, 0.71-3.32, p=0.27), stroke or cognitive impairment. There was between-study heterogeneity. Lack of appropriate data on other brain disorders and demographic features such as ethnicity precluded analysis.

Conclusions: Despite many studies, more are required to determine potential pathophysiological PVS involvement in cerebrovascular, neurodegenerative and neuroinflammatory disorders.

Introduction

Perivascular spaces (PVS), also known as Virchow-Robin Spaces, are seen on magnetic resonance imaging (MRI) as thin linear or small punctate structures, of similar signal to CSF, in deep grey or white matter.[1] Increasing numbers of reports have detailed associations of visible PVS on MRI over the last two decades, notably with small vessel disease (SVD) lesions. PVS may provide an early biomarker for diagnosing developing disorders such as white matter hyperintensities (WMH)[2] which increase the risk of stroke and dementia,[3] or neurodegenerative diseases,[4] and are highly heritable.[5]

We aimed to benchmark current knowledge of associations between PVS and vascular risk factors, common neurological disorders and neuroimaging findings using systematic review with meta-analysis of all available published data.

Methods

We registered the study protocol (PROSPERO, CRD42017056052) and used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines[6].

Search Strategy

We searched comprehensively for studies published in full up to January 14, 2017, in PubMed, Web of Science and Ovid EMBASE. The search keywords included "perivascular spaces", "perivascular space", "Virchow-robin spaces", or "Virchow-robin space", combined with "MRI", "MR" or "magnetic resonance". We assessed articles with any combination of the above keywords and checked reference lists of review papers, our files, and hand searched the last five years of *Stroke*.

Inclusion and Exclusion Criteria

We aimed to include all papers that reported on PVS associations with vascular risk factors, common neurological disorders particularly cognitive impairment, dementia or stroke, or neuroimaging signs of vascular disease. We excluded case reports, animal studies and reviews without original data, studies with fewer than 10 subjects, on rare diseases, that were not published in English (we lacked resources for translation), lacked MRI, or did not provide quantitative data (or where quantitative data could not be extracted) on associations with PVS.

Data Extraction

We removed duplicates, screened the remaining titles and abstracts, removed irrelevant papers and assessed the remaining potentially eligible papers for inclusion.

Two reviewers (FFF, LB) extracted title, authors, publication year, number of subjects, mean age, sex, PVS location (basal ganglia, centrum semiovale, midbrain or hippocampus), rating method and scale used, and results of associations, including whether adjusted for major covariates. We used results that had been adjusted for major covariates wherever they were available.

We extracted criteria on study quality, four on risk of bias (patient selection, index test, reference standard, study timing) and three on applicability (patient selection, index test, reference standard), from the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) criteria (https://www.ncbi.nlm.nih.gov/pubmed/22007046).

We excluded duplicate data, including only the most recent or largest dataset from studies with multiple publications, but included all available outcomes. Disagreement was resolved by consensus or by a third reviewer (JW) who also double-checked the data extraction (JW).

Where associations were not provided as odds ratios (ORs) and 95% Confidence Intervals (CI) we calculated the ORs and 95%CI if possible. Where relevant information appeared to be available but was not in the publication, we sought additional information from authors. Where studies met all inclusion criteria except for providing data for meta-analysable ORs, we performed a qualitative narrative summary of the findings.

Statistical Analysis

We entered the ORs and 95% CI into Review Manager Software Version 5.3 (Cochrane, Oxford) for meta-analysis. We used generic inverse variance method and random effects model, plotted multivariate adjusted ORs and 95%CI and generated summary ORs. We assessed between-study heterogeneity using χ^2 test, with $p<0.05$ considered statistically significant, and used Higgin's I^2 test to calculate the percentage of variance across studies due to heterogeneity rather than chance.[7] I^2 of 25% or less was considered low, 26%-50% or

less moderate, 51-75% or less high and 76% and above as very high heterogeneity. We assessed publication bias using funnel plots.

Results

We identified 956 non-duplicate papers, and eliminated 301 studies based on title and abstract. Of the remaining 654 studies screened in full, 116 studies met the inclusion criteria. However, of these 116 studies, only 23/116 provided their results as ORs and were therefore suitable for meta-analysis. Supplementary Figure 1 summarises the search and selection.

Characteristics of 23 studies included in meta-analysis

The 23 studies with data suitable for meta-analysis included 12,725 patients (median N=268) from various demographic backgrounds (Table 1), performed in various geographical regions including the UK, Netherlands, Belgium, France, Sweden, China, Japan, USA and Canada.[8-14] The Northern Manhattan study included Hispanic, black,white and other populations,[15] but no studies presented data by ethnic group. The cohorts included men and women of age >50.. They included individuals with previous history of stroke and patients from memory clinics. Several studies reported multiple association, e.g., ageing and hypertension vs. PVS.[16]

On QUADAS-2 criteria, no studies were judged to have a high risk of bias, only 3/23 studies had unclear risk, with the rest being low risk; 3/23 studies were judged to have high risk of applicability concerns and the rest low risk (Supplementary Table 1).

Most papers used 1.5T MRI, 11/23 used T2 and the rest a mix of T1 and T2 sequences to identify PVS. Most studies reported on PVS in the basal ganglia (BG) and centrum semiovale (CS) although several papers reported PVS in the hippocampus.[12, 13]

Several PVS rating scales were used, one of the commonest being the scale of Potter[17] which classifies PVS by count into four categories from 0 (no PVS) to 4 (>40 PVS). Other papers used a categorical scale of Heier[18] which classifies PVS by their diameters into three categories: grade 1 (<2mm), grade 2 (2-3 mm) and grade 3 (>3mm). Others include the scale of Patankar,[19] which rates PVS according to brain regions, and the scale of Adams[20] which rates PVS ≥1mm separately from ≥3mm. Several studies used their own PVS method.[10, 21]

The included studies distinguished PVS from lacunes, according to size, shape and location as described in the STRIVE standards.[22]

Characteristics of 93 studies that could not be meta-analysed

The 93/116 non-meta-analysable studies (n=23,383) assessed 52 different risk factors, clinical or neuroimaging variables for their associations with PVS (Supplementary Table 2) as follows (numbers are number of studies):

Risk factors: ageing (4), hypertension (2), inflammation (2), hypercholesterolaemia (1) and 1 study each on adiponectin, blood brain barrier, peptide levels, PTEN mutation, and retinal microvascular calibre;

Clinical disorders: vascular disease unspecified (6), cognitive decline or Alzheimer's disease (6), unspecified dementia (4), stroke (4), large artery atheroma (2), Parkinsons disease (2), HIV (3), multiple sclerosis (4), depression (3), headache (3), head injury (2), myotonic dystrophy (2), systemic lupus erythematosus (SLE)/immunocompromised patients (2), autism (3), obsessive compulsive disorder (2), glaucoma (2), and 1 study each on tuberous sclerosis, unspecified neurological disorders, CADASIL, Tourette syndrome, adrenoleukodystrophy, asthma, hydrocephalus, infection, AGU, sickle cell anaemia, normal pressure hydrocephalus;

Neuroimaging: WMH (8), cerebral amyloid angiopathy (CAA) (5), microbleeds (1), microinfarcts (1), lacunes (1), and atrophy (1).

Meta-Analysis

The following meta-analyses of PVS associations are summarised in Table 2. There was no consistent evidence of publication bias in any of the following meta-analyses (see Supplement).

Risk factors

Ageing. Thirteen studies (n=8395) reported on ageing and PVS in BG, CS or Hippocampus (Table 2, Figure 1). PVS increased with age in all areas, most in the BG (OR 1.47, 95%CI 1.28, 1.69, P<0.00001), then CS (OR=1.26, 95% Cl, 1.07-1.49, P=0.005), then hippocampus (OR-1.14, 95% Cl, 1.01, 1.30, P=0.03), difference between the three areas $\chi^2 = 7.10$, P=0.03 and between-study heterogeneity (BG, χ^2=218.80, p=0.00001, I^2=96%; CS χ^2= 42.82, p=0.0001, I^2=86%).

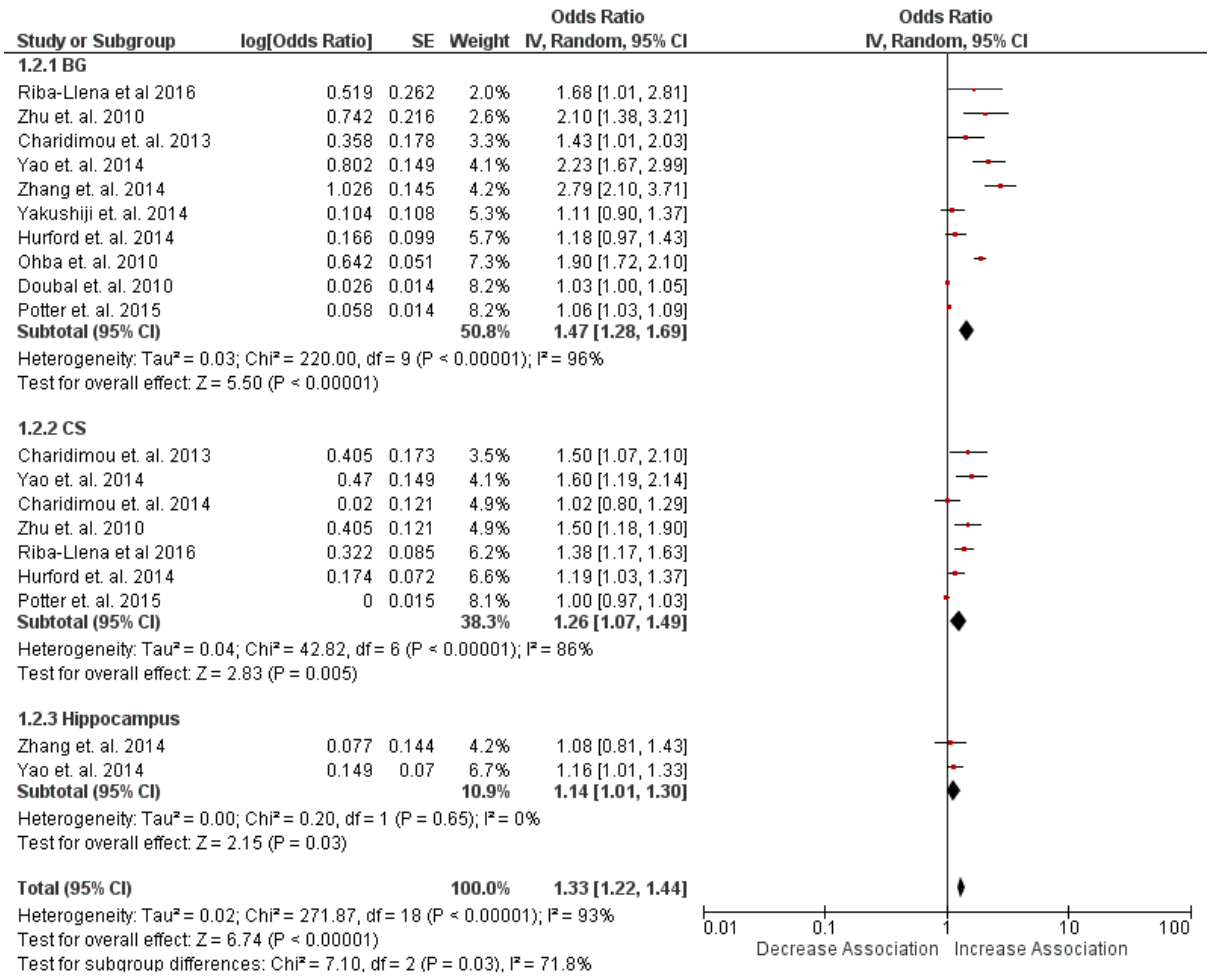


Figure 1 Forest plot of associations of PVS in BG, CS and Hippocampus with ageing

Diabetes. Five studies (n=3095) found no association between diabetes and PVS (Table 2, Supplementary figure 2).

Hypertension. Thirteen studies (n=7872) found BG PVS were associated with hypertension (OR=1.67, 95% Cl, 1.20-2.31, P=0.002), with significant between-study heterogeneity (χ^2= 63.72, p=0.00001, I^2=84%), Figure 2. The direction of effect was similar for CS PVS but did not reach significance.

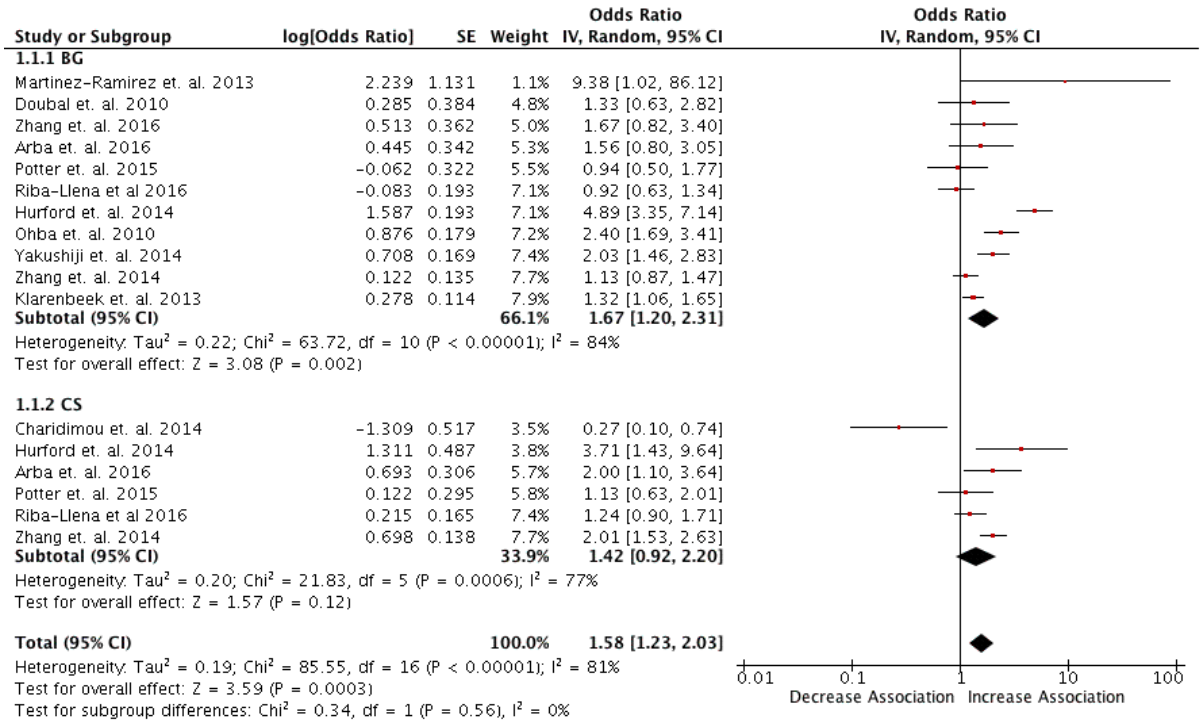


Figure 2 Forest plot of associations of PVS in BS and CS with hypertension

Neurological Diseases

Lacunar versus non-lacunar stroke. Five studies (n=1,173) showed no consistent association between BG or CS PVS in clinically-evident lacunar versus non-lacunar stroke subtypes,[9, 13, 21, 23, 24] (Table 2, Supplementary figure 3). However, stroke subtyping and imaging methods differed between studies.

Acute stroke. Two studies (n=682)[25, 26] found no association between acute stroke of any subtype and PVS, but only in CS (OR=3.99, 95% Cl, 0.47-34.17, P=0.21), (Table 2, Supplementary Figure 4).

Cognitive impairment. Three studies (n=1,272) did not find an association between cognitive impairment and PVS in BG region (OR=1.21, 95% Cl, 0.84-1.73, P=0.31), Table 2, Supplementary Figure 5). Only 1 study[27] assessed cognition and CS PVS finding a borderline significant association (OR=1.06, 95% Cl, 1.00-1.11). Amongst the 93 non-meta-analysable studies, only four assessed associations of PVS with dementia but all reported different statistics. Of these, three found that PVS were increased significantly in patients with dementia vs controls.[19, 28, 29] Three other studies examined associations of PVS and cognitive impairment, of which two found increased PVS with declining cognition.[30, 31]

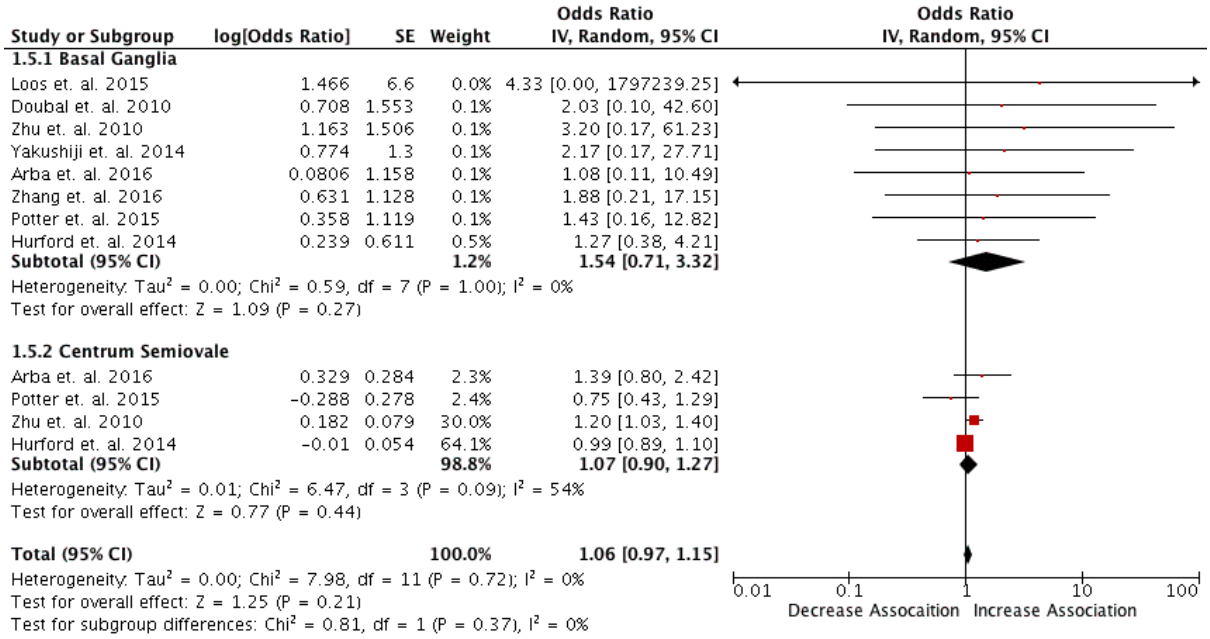
Neuroimaging Features:

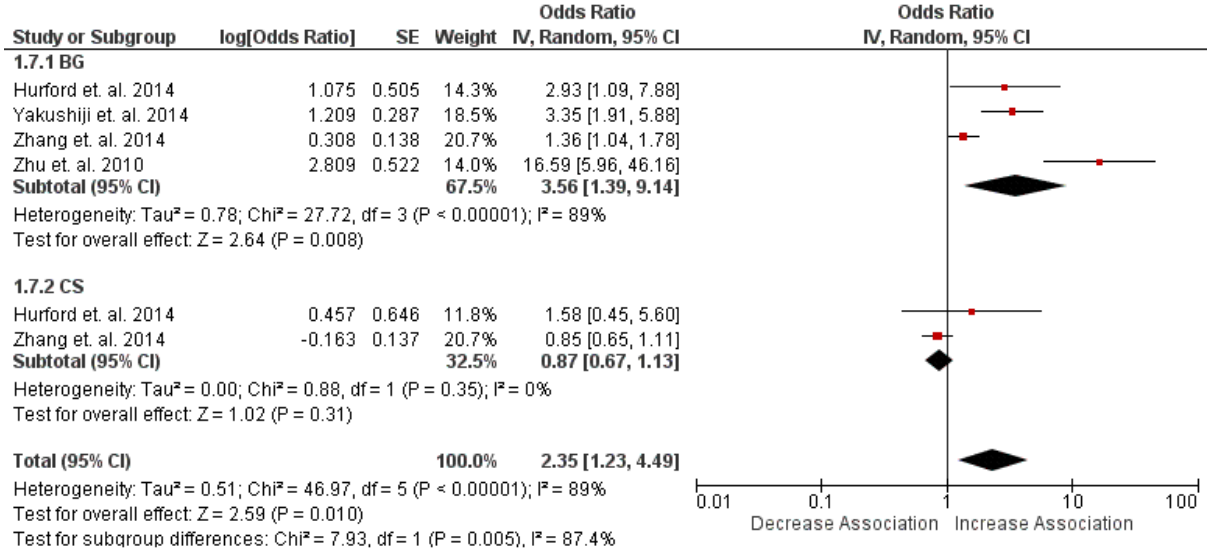
White matter hyperintensities. Eight studies (n=4974) examined WMH and PVS in BG and CS regions (Figure 3a). Although the direction of effect was for an association with WMH, it did not reach significance (OR 1.54, 95%CI 0.71, 3.32, P=0.27). Amongst the 93 non-meta-analysable studies, eight (n=3,333, range 32-1818) reported on associations of PVS and WMH. These used different statistics (adjusted beta, r, rho, chi squared) precluding direct comparison. However, most found positive associations between BG PVS and WMH with adjusted betas of 0.19 ($p<0.001$)[16] to 0.47 ($p<0.0001$),[2] and only one found a negative association.[32]

Lacunes. Four studies (n=4894) found an association between lacunes and PVS in the BG (OR= 3.56, 95% Cl, 1.39-9.14) but not CS region. There was high between-study heterogeneity (BG, χ^2=27.72, p=0.00001, I^2=89%), Figure 3b.

Microbleeds. Five studies (n=5015) found that cerebral microbleeds were associated with BG PVS (OR=2.26, 95% Cl, 1.25-4.00, P=0.04), but with between-study heterogeneity (χ^2= 27.35, p=0.00001, I^2=85%), Figure 3c. There were insufficient data to compare PVS and microbleeds by lobar or deep location.

Cortical Superficial Sclerosis (cSS). Two studies (n=1642) reporting on cSS and PVS found no association between combined BG and CS PVS and cSS (OR=2.28, 95% Cl, 0.75-9.13, Supplementary Figure 6).





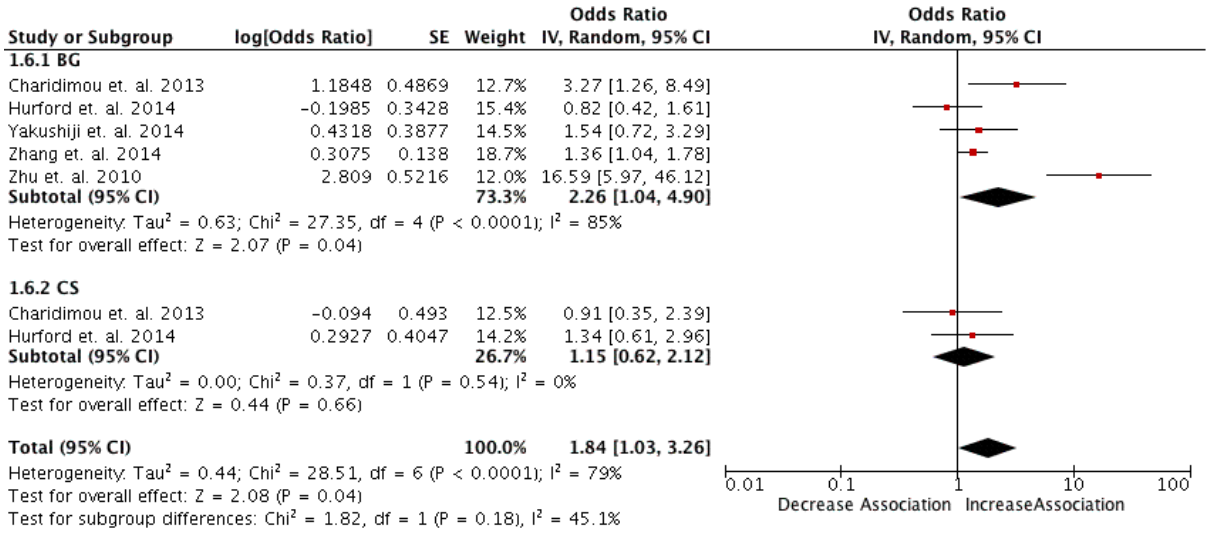


Figure 3 Forest plot of associations of PVS in BG and CS with WMH (a), lacunes (b), and cerebral microbleeds (c)

Discussion

We investigated vascular risk factor, clinical, and imaging lesion associates of PVS by meta-analysing risk factor-adjusted odds ratios. Although we found 116 potentially relevant papers, only 23 studies provided meta-analysable data, representing nearly 13,000 participants from various demographic groups, world regions and ethnicities. Surprisingly, we did not find conclusive evidence that PVS were associated with some expected clinical or neuroimaging features, although we did find most expected risk factor associations. There was no consistent association of PVS with lacunar vs non-lacunar stroke and a surprising lack of meta-analysable data on PVS and cognitive decline or dementia. Most surprisingly, although the direction of effect was positive, the association between PVS and WMH was not significant in meta-analysis.

We used risk-factor adjusted ORs, suggesting that some previously described PVS-WMH associations may reflect shared co-associations or differences in population characteristics. However, most of the eight non-meta-analysable papers on WMH (Supplementary Table 2) did account for key co-variates and did show WMH to be associated with PVS. Thus, the overall direction of effect suggests that PVS are associated with WMH. For microbleeds, there were fewer studies but a larger sample size (Table 2) than WMH for meta-analysis, perhaps reflecting the more recent description of microbleeds with more consistent methods thus facilitating meta-analysis. Although we confirmed a PVS association with microbleeds, the high heterogeneity indicates that more data are required.

Data were very limited for testing associations of PVS with stroke, cognitive impairment, dementia or sleep disorders. This was disappointing, since brain fluid drainage via PVS is thought to be important for maintaining brain health, and indicates the need for more research.

We meta-analysed the BG and CS PVS separately, since regional PVS associations may differ, there are known vessel wall anatomical differences between the BG and CS, hence meta-analysing the regions separately was biologically plausible.[19] Some variation in PVS associations between BG and CS may reflect a lack of data for one region indicating that +future studies should assess both regions. Alternatively, PVS may vary between brain regions, although the association of PVS and ageing, for which we had the most data, did not differ by brain region (Figure 2).

Overall, the studies had low risk of bias or applicability concerns (Supplementary Table 1), but there was high between-study heterogeneity for many associations, indicating the need for more data. Inconsistencies between studies included use of different PVS and lesion rating methods, disease diagnosis, scanner strength and sequences, although lack of data precluded further sensitivity testing. Alternatively, PVS differences may reflect unquantified demographic, genetic or environmental differences. The epidemiological origin of the cohorts may also influence results, however it was not possible to test effects of country or ethnic origin since the data were not provided. Although we did not find objective evidence of publication bias, it is likely to be present.[33] We were not able to include non-English language publications, but found many papers and the meta-analysed studies included nearly 13,000 subjects.

Computational methods to assess PVS are now emerging,[34-36] show promise for future large studies, may help reduce variability, and can provide PVS volume, orientation, location in the brain in addition to count or frequency which may increase sensitivity for detecting subtle associations. Future research should maximise sample size, report imaging methods in detail, adjust analyses to account for important co-variates especially vascular risk factors and age, and assess a much wider range of subject groups to investigate more fully the characteristics of PVS in different clinical situations.

Conclusion

Ageing, hypertension, cerebral microbleeds and lacunes were associated with PVS in risk-factor adjusted meta-analysis, with most data available for BG PVS. More studies are required to further validate the use of PVS as a risk marker for these diseases and to understand pathophysiological pathways for stroke, dementia and other common neurological disorders. Future studies should use consistent methods to determine PVS appearances, standard definitions and reporting of parameters for rating PVS.

Declaration of conflicting interests

The research was conducted without any commercial or financial relationships that could be construed as a potential conflicts of interest.

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Data Availability

All data used in this manuscript are publicly available in the original pubications; the extracted data are available from the authors on request.

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Table 1: Characteristics of studies included in the meta-analysis. WMH: white matter hyperintensities, MB: microbleeds, CMB: cerebral microbleeds, ICH: intracranial haemorrhage.

No.	Reference	Number of Subjects	Age (mean)	Subject Characteristics	Disorder Associated	Association test result, OR (95% Cl)	Brain Region	Geographic Region	Rating Scale	Type of scanner MRI sequence
1	Arba et al 2016[23]	430	64.7	Ischemic stroke and transient icshemic attack Ischemic Stroke and Transient Ischemic Attack	Lacunar stroke Lacunar stroke Hypertension Hypertension Cognitive impairment WMH WMH	0.91 (0.50-1.67 1.18 (0.67-2.08) 1.56 (0.08-3.04) 2 (1.10-3.63) 1.59 (1.07-2.39) 2.24 (1.29-3.89) 1.39 (0.80-2.42)	BG CS BG CS BG BG CS	Australia UK	5 point	NA, T1, T2 and FLAIR
2	Bae et al 2016[25]	481	68.2	Acute Stroke	Arterial stiffness	1.7 (1.0-2.7)	BG	China	4 points	NA T2
3	Charidimou et al 2013[9]	121	NA	ICH	Deep MB Lacunar Infarcts Lobar MB	3.27 (1.27-8.45) 1 (1-1.01) 0.43 (0.16-1.20)	BG BG BG	UK& Belgium	4 points	1.5T, T1, T2, FLAIR

						0.91 (0.35-2.38)				
					Deep MB	1 (0.99-1)	CS			
					Lacunar Infarcts	1.92 (0.74-4.96)	CS			
					Lobar MB	1.43 (1.01-2.02)	CS			
					Ageing	1.5 (1.08-2.10	BG			
					Ageing		CS			
4	Charidimou et al 2014[37]	138	71.8	Cerebral amyloid angiopathy	Cortical Superficial Siderosis	4.78 (1.64–13.87)	CS	UK and Belgium	4 points	1.5T, T2&FLAIR
					Ageing	1.02 (0.97–1.06)	CS			
					Hypertension	0.27 (0.10–0.74)	CS			
5	Doubal et al 2010[38]	235	NA	Acute ischemic lacunar or cortical stroke	Lacunar stroke	3.16 (1.49–6.70)	BG	UK	4 points	NA T2
					Ageing	1.03 (0.99–1.08)	BG			
					Diabetes	0.65 (0.24–1.74)	BG			
					WMH	2.03 (1.10–3.74)	BG			
					Hypertension	1.33 (0.63–2.81)	BG			

6	Gutierrez et al 2015[39]	1290	64	Stroke-free	Hypertension	1.14 (1.03-1.26)	Overall	US	NA	1.5T, T1& FLAIR
7	Hurford et al 2014[40]	246	62	Stroke	Lacunes Lobar CMB Deep CMB Lacunes Lobar CMB Ageing Ageing WMH WMH Hypertension Hypertension	2.93 (1.10-7.84) 0.82 (0.42-1.60) 1.77 (0.59-5.33) 1.58 (0.45-5.57) 1.34 (0.60-2.95) 1.18 (0.98-1.43 1.19 (1.04-1.37) 1.27 (1.14-1.43) 0.99 (0.89-1.10) 4.89 (1.39-17.21) 3.71 (1.42-9.59)	BG BG BG CS CS BG CS BG CS BG CS	UK	4 points	NA T2
8	Klarenbeek et al 2013[41]	122	64.6	First ever lacunar stroke	Hypertension	1.32 (1.05–1.65)	BG	Nether-lands	3 points	1.5T or 3T T2
9	Loos et al 2015[42]	118	63	First ever lacunar stroke	WMH	4.29 (1.28–14.32	BG	Nether-lands	None, mild to moder-ate and extens-ive	1.5T T2

10	Martinez-Ramirez et al 2013[43]	89	72.7	Massachusetts Alzheimer's Disease Research Centre	Higher lobar MB Strictly lobar MB Hypertension	1.53 (1.06–2.21) 1.78 (0.97–3.27) 9.38 (1.03–85.17)	WM WM BG	US	4 points	3T, T1 and T2
11	Ohba et al 2012[8]	1632	NA	The secondary Prevention of Small Subcortical Stroke trial	Multipe infarcts Aging Hypertension	1.7 (1.2-2.3) 1.9 (1.7-2.1) 2.4 (1.7-3.4)	BG BG BG	Canada	3 points	NA, T2
12	Potter et al 2015[13]	298	68	Stroke	Lacunar stroke Old infarcts Lacunar stroke Old Infarcts Ageing Ageing Diabetes Diabetes WMH WMH Hypertension Hypertension	2·08 (1·04–4·17) 0·76 (0·40–1·45 0·69 (0·37–1·29) 1·22 (0·66–2·23) 1.06 (1·02–1·09) 1.0 (0·98–1·03) 1·58 (0·56–4·46) 0·68 (0·24–1·98) 1·43 (0·81–2·54) 0·75 (0·44–1·29) 0·94 (0·50–1·76) 1·13 (0·63–2·01)	BG BG CS CS BG CS CS BG BG CS BG CS	UK	4 points	1.5T, T1, T2 and FLAIR

13	Riba-Llena et al 2016[44]	733	62.8	Hypertensive	Mild cognitive impairment Ageing Ageing Diabetes Diabetes Hypertension Hypertension	1.59 (0.84-3.01) 1.68 (1.37-2.06) 1.38 (1.18-1.63) 0.94 (0.75-1.17) 0.93 (0.78-1.13) 0.92 (0.64-1.34) 1.24 (0.90-1.71)	BG BG CS BG CS BG CS	Spain	4 points	1.5T, T1&T2
14	Rouhl et al 2008[16]	165	NA	Patients with first lacunar stroke	Silet ischemic lesion	10.58 (3.40–32.92)	BG	Nether-lands	3 points	1.5T T2
15	Shams et al 2016[14]	1504	63	Dementia patients with small vessel disease and cognition	Cortical Superficial Siderosis	1.73 (1.16-2.61) 1.16 (0.70-1.92)	BG CS	Sweden	4 points	1.5T, T1, T2&FLAIR
16	Uiterwijk et al 2014[27]	109	6.1	Hypertensive	Overal Cognition	0.99 (0.91–1.07 1.06 (1.00–1.11)	BG CS	Nether-lands	3 points	1.5T, T2 and FLAIR
17	Wu et al 2015[26]	201	Median: 70.97	ICH	spontaneous supratentorial ICH Acute brain infarct	12.56 (4.40-35.85) 2.77 (0.93-8.24) 12.56 (4.4-35.85)	CS BG CS	Israel China	4 points	1.5T T2

18	Yakushiji et al 2014[11]	1740	57.1	The Kashima Scan Study-age related brain changes	Deep of infratentorial CMB Lobar CMB Lacunes Ageing Diabetes WMH Hypertension	2.77 (1.62-4.74) 1.54 (0.73-3.28) 3.35 (1.92-5.86) 1.11 (0.90-1.37) 0.8 (0.48-1.33) 2.17 (1.42-3.31) 2.03 (1.46-2.82)	BG BG BG BG BG BG BG	Japan	4 points	1.5T T2
19	Yang et al 2016[33]	16	NA	Stroke	Lacunar infarct	1.204 (0.872-1.662)	BG	China	3 points	1.5, T1 and 3T, T2
20	Yao et al 2014[12]	344	50.8	Mutation in the Notch3 gene	Ageing Ageing	2.23 (1.67-2.98) 1.6 (1.2-2.14)	BG CS	France and Germany	4 points	1.5T, T1, T2 and FLAIR
21	Zhang et al 2014[21]	1090	NA	Ischemic stroke or transition ischemic attack	Lacunes Ageing Hypertension Hypertension	1.36 (1.05-1.78 2.79 (2.13-3.67) 1.13 (0.86-1.47) 2.01 (1.54-2.63)	BG BG BG CS	China	Their own	3.0T, T2, FLAIR&DWI
22	Zhang et al 2016[45]	89	72.93	Lacunar stroke	Deep WMH Brain Atrophy Diabetes WMH Hypertension	0.78 (0.4-1.50) 1.40 (1.13-1.73) 0.94 (0.45-1.97) 1.88 (1.24-2.83) 1.67 (0.83-3.38)	BG BG BG BG BG	China	4 points	3T, T1, T2 and FLAIR

					Hypertension					
23	Zhu et al 2010[28]	1818	NA	The Three-City cohort	Lacunar Stroke Ageing Ageing WMH WMH	16.6 (6.0–45.9) 2.1 (1.4-3.2) 1.5 (1.2-1.9) 3.2 (2.5–4.1) 1.2 (1.0–1.4)	BG BG CS BG CS	France	4 points	1.5T, T1 and T2

Table 2. Summary of Odds Ratios and 95%CI for PVS associations from meta-analysis.

Association of interest	Location of PVS	Number of studies	N of subjects[1]	OR	95% CI	P	I^2
Risk factors							
Age	BG	10	8395	1.47	1.28-1.69	0.00001	96%
	CS	7		1.26	1.07-1.49	0.005	86%
	hippocampus	2		1.14	1.01-1.30	0.03	0%
Hypertension	BG	11	7872	1.67	1.20-2.31	0.002	84%
	CS	6		1.42	0.92-2.20	0.12	77%
Diabetes	BG	5	3095	0.9	0.74-1.08	0.26	0%
	CS	2		0.95	0.78-1.15	0.58	0%
Neurological disorder							
Acute Stroke	CS	2	682	3.99	0.47-34.17	0.21	93%
Lacunar v non-lacunar stroke	BG	5	1173	1.26	0.83-1.93	0.28	69%
	CS	2		0.92	0.54-1.55	0.75	36%
Cognitive impairment	BG	3	1272	1.21	0.84-1.73	0.31	51%
Neuroimaging feature							
White matter hyperintensities	BG	8	4974	1.54	0.71-3.32	0.27	0%
	CS	4		1.07	0.90-1.27	0.21	0%
lacunes	BG	4	4894	3.56	1.39-9.14	0.008	89%
	CS	2		0.87	0.67-1.13	0.31	0%
microbleeds	BG	5	5015	2.26	1.04-4.90	0.04	85%
	CS	2		1.15	0.62-2.12	0.66	0%
Cortical superficial siderosis	BG/CS combined	2	1642	2.28	0.57-9.13	0.24	75%

[1] Indicates total sample for the association of interest.