The Relationship Between Enlarged Perivascular Spaces and Cognitive Function: A Meta-Analysis of Observational Studies

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Enlarged perivascular spaces (ePVS), visible on magnetic resonance imaging (MRI), are associated with aortic pulse wave changes produced by arterial stiffening. However, the relationship between ePVS and cognition is still unclear. We aimed to benchmark current knowledge of associations between ePVS and cognitive function using a meta-analysis of all available published data. We searched three databases for studies examining ePVS and cognition, identified seven studies involving 7,816 participants, plotted multivariate-adjusted odds ratio (OR) and 95% CI and generated summary OR with a fixed effects model. EPVS were related to the risk of impaired cognition (OR = 1.387, 95% CI = 1.198–1.606, z=4.38, P<0.001) with low heterogeneity. There was publication bias, which could be corrected by trimming and supplementation (OR=1.297, 95% CI= 1.130–1.490). EPVS were associated with impaired cognition and may be a sign of cognitive impairment rather than particular diseases. More studies are required to validate ePVS as a measurable risk marker for cognition using consistent methods to determine a characteristic appearance of ePVS.

Keywords: enlarged perivascular spaces (ePVS), impaired cognition, meta-analysis, cohort studies, odds ratio (OR)

INTRODUCTION

Perivascular spaces (PVS), also known as Virchow-Robin spaces, are a fluid-filled structure lined with tubes found at specific locations throughout the brain (Rudie et al., 2018). They can be seen on magnetic resonance imaging (MRI) in the centrum semiovale (CSO), basal ganglia (BG), the hippocampus (HP) and white matter (WM) (Schwartz et al., 2019). With increasing age, arteries become stiffer and reflected pressure waves return to the central aorta earlier in the cardiac cycle, producing augmentation of the systolic pulse wave and central arterial systolic pressure. It has been suggested that the development of cerebral small vessel disease (SVD) might represent a downstream effect of this haemodynamic change (Elías et al., 2009). In addition, recent findings have supported the hypothesis that changes in aortic pulse waves produced by arterial stiffening were associated with the presence of enlarged PVS (ePVS) (Thomas et al., 2019). An increasing
number of reports over the last two decades have detailed associations of ePVS on MRI, as a marker of SVD, with cognitive function (Francis, 2019). However, the relationship between ePVS and cognition is still unclear. Some articles have suggested that ePVS are related to cognition, while others have shown that they are not.

We aimed to benchmark current knowledge of the associations between ePVS and cognitive function, using meta-analysis of all available published data.

METHODS

We used the meta-analysis of observational studies in epidemiology (MOOSE) (Stroup et al., 2000) checklist.

Evaluation Procedure

Two independent investigators (WJ and GHL) selected all relevant studies based on title and abstract, retrieved selected full texts, performed eligibility assessments, extracted data, and assessed risk of bias. Disagreements between the reviewers were resolved by consensus. A third independent reviewer (ZL) resolved any persisting disagreements.

Information Sources and Search Strategy

We comprehensively searched for studies published in full up to 27 August 2019, in PubMed, MEDLINE, and Ovid EMBASE. The following search terms were used: ‘(((((((Virchow-Robin Spaces) OR Perivascular Spaces) OR Enlarged Virchow-Robin Spaces) OR Enlarged Perivascular Spaces) OR Virchow-Robin Spaces Enlargement) OR Perivascular Spaces Enlargement)) AND (((((Cognitive) OR Cognition) OR Cognitive Disorder) OR Cognitive Impairment) OR Cognitive Dysfunction) OR Cognitive Impaired) OR Dementia)’. We applied no language restrictions. A total of 2,828 articles were retrieved. We used the meta-analysis of observational studies in epidemiology (MOOSE) (Stroup et al., 2000) checklist. The scale uses a “star” rating system (maximum of nine stars) to assess the quality of case-control and cohort studies based on three aspects: selection of participants, comparability of study groups, and ascertainment of outcomes of interest (Stang, 2010). If the study scored nine stars, it was considered to be of high quality. Studies with a score of seven or eight stars were considered to be of medium quality. However, if a study scored less than seven stars, it was considered to be of low quality.

Statistical Analysis

We used a fixed effects model, plotted multivariate-adjusted ORs and 95% CI and generated summary ORs. Chi-square test was used to assess interstudy heterogeneity, and P <0.05 was considered statistically significant. Higgin’s I² test was used to calculate the percentage of variance between studies due to heterogeneity rather than random factors. I² of 25% or less was considered to be low, 26% to 50% or less moderate, 51%–75% or less high, and 76% or more was considered to be very high heterogeneity (Higgins and Thompson, 2002). The significance of the summary ORs was assessed using the Z-test, and a P-value < 0.05 was considered statistically significant. A sensitivity analysis was conducted to evaluate the stability of the results by systematically excluding a single study in each analysis. Funnel plots and Egger’s tests were used to investigate the potential publication bias. For the potential publication bias, we conducted a trim and fill analysis to yield an effect adjusted for funnel plot asymmetry. All statistical analyses were conducted using Stata software version 12.0 (StataCorp).

RESULTS

Retrieved Studies and Characteristics

We identified 746 articles. After screening titles and abstracts and deleting duplicate papers, we obtained 39 study reports for full-text review. After a full-text review, we finally included seven reports comprising 7,816 individuals for analysis (Figure 1) (Zhu et al., 2010; Yao et al., 2014; Riba-Llena et al., 2016; Ding et al., 2017; Liang and Chan, 2017; Banerjee et al., 2019; Park et al., 2019). Overall, they were cohort studies, with six reports published in a journal and only one was a conference abstract. Five of these studies were based in Europe, and two were based in Asia. Two reports were from the same study, but there was no conflict due to the different parts of ePVS studied (SC SG, 2003). Most papers used 1.5T MRI and T1 and T2 sequences to identify ePVS. Most studies reported on ePVS in the BG and CSO, although several papers reported ePVS in the HP and WM
(Zhu et al., 2010; Yao et al., 2014). The detailed characteristics of all included studies are shown in Table S1. The quality of studies based on the NOS scores is presented in Table 1. All studies were of medium to high quality (score ≥ 7).

**Associations Between ePVS and Cognitive Function**

Seven studies with 7,816 individuals evaluated the association between ePVS and cognitive function. Heterogeneity test results indicated low heterogeneity ($\chi^2 = 11.88, P=0.157, I^2 = 32.6$). The ePVS were significantly associated with cognitive function (OR = 1.387, 95% CI = 1.198–1.606, z=4.38, P<0.001) (Figure 2).

**Sensitivity Analysis and Publication Bias**

A sensitivity analysis was conducted by iteratively excluding individual studies from the analysis, and the results showed that no individual study influenced the overall OR (Figure 3), indicating that the results of this meta-analysis are relatively stable. Publication bias was observed in the results based on Egger’s test (P = 0.009) and a funnel plot (Figure 4). For the potential publication bias, we conducted a trim and fill analysis to yield an effect adjusted for funnel plot asymmetry. The result after trimming and supplementation (OR=1.297, 95% CI=1.130–1.490) was not significantly different from the previously determined OR (Figure 5).

**DISCUSSION**

This meta-analysis included seven studies involving a total of 7,816 participants. The combined analysis showed that ePVS counts were related to the risk of impaired cognition. To the best of our knowledge, this is the first meta-analysis in which the association between ePVS and risk of impaired cognition using longitudinal studies has been explored. Previous studies, including cross-sectional studies (n=7), case-control studies (n=3), and cohort studies (n=5), have investigated the association of ePVS and cognition, but the results were inconsistent. Most of the cross-sectional studies using adjusted OR have suggested that ePVS were related to cognition, (Riba et al., 2015; Muir et al., 2016; Banerjee et al., 2017; Shams et al., 2017; Arba et al., 2018; Shibata et al., 2019) which was consistent with our findings. However, a study by Hurford et al. reported that ePVS do not have an independent association with cognitive impairment (Hurford et al., 2014). Three case-control studies using Spearman’s rank correlation coefficients all reported that increased ePVS counts may contribute to cognitive decline (Chen et al., 2011; Yun, 2013; Favaretto et al., 2017). With further review of the cohort studies, most of them have suggested that ePVS were related to cognitive decline (Van Westen et al., 2017; Jimenez-Balado et al., 2018; van Westen et al., 2018; Passiak et al., 2019). However, one small-sample cohort study reported that it was lacunes but not ePVS that were a predictor of cognitive decline (Trippier et al., 2018). In addition, a conference abstract based on a cohort study showed that hippocampal ePVS did not show any relation with

![FIGURE 1](image1.png) | Flow chart of study selection.

![FIGURE 2](image2.png) | Flow chart of study selection.

![FIGURE 3](image3.png) | Flow chart of study selection.

![FIGURE 4](image4.png) | Flow chart of study selection.

![FIGURE 5](image5.png) | Flow chart of study selection.

**TABLE 1 | Quality assessment of included studies.**

| References                      | Year  | Selection | Comparability | Exposure | Total |
|---------------------------------|-------|-----------|---------------|----------|-------|
| (Park et al., 2019)             | 2019  | ★★★      | ★★            | ★★★      | 7     |
| (Banerjee et al., 2019)         | 2019  | ★★★      | ★★            | ★★★      | 7     |
| (Ong et al., 2017)              | 2017  | ★★★★★    | ★★            | ★★★      | 8     |
| (Riba-Ulana et al., 2016)       | 2016  | ★★★★★    | ★★            | ★★★      | 7     |
| (Yao et al., 2014)              | 2014  | ★★★★★    | ★★            | ★★★      | 8     |
| (Zhu et al., 2019)              | 2010  | ★★★★★    | ★★            | ★★★      | 8     |
| (Liang and Chan, 2017)          | 2017  | ★★★★     | ★★            | ★★★      | 7     |
**FIGURE 2** | Forest plot of associations of ePVS and cognitive function. ePVS, enlarged perivascular spaces.

**FIGURE 3** | Sensitivity analysis used to assess the association between ePVS and cognitive function.
our meta-analysis included a variety of clinical diseases, such as Parkinson’s disease, Alzheimer’s disease and cerebrovascular disease, which have different clinical pathogenesis. However, these results were consistent with our meta-analysis. This implies that ePVS, previously considered one of the markers of small vascular diseases and was most closely related to vascular cognitive impairment (Li et al., 2018), may be a sign of cognitive impairment rather than a sign of particular diseases. We look forward to more studies to test this idea.

However, the article has some limitations. Some studies have suggested that different ePVS locations have different outcomes, and the etiology of ePVS in different locations may be different (Banerjee et al., 2017; Shams et al., 2017). Unfortunately, we were unable to conduct regional subgroup analyses due to the lack of sufficient data. Based on the available data, we could only conduct subgroup analysis in the BG, and the result (OR=1.360, 95% CI 1.178–1.570) was consistent with our conclusions. More data are needed to further analyze the relationship between the other three regions (BG, WM, and HP) and cognition. In addition, the methods used to evaluate ePVS in the studies we included were not completely consistent. Some studies (Machulich et al., 2004; Trippier et al., 2018) have shown that ePVS and lacunes are sometimes indistinguishable, which may have influenced the results. In the future, studies should use consistent methods to determine a characteristic appearance of ePVS. In present, the potential of using automated methods to assess ePVS burden is being recognized. Boespflug et al (Boespflug et al., 2018) presented a fully automated method to extract enlarged PVS (ePVS) in clinical-field-strength MR imaging data. On this basis, Florian D et al (Dubost et al., 2019) improved the method and found that the PVS automated scoring method had good consistency and reproducibility which may replace visual scoring and facilitate large epidemiological and clinical studies of PVS.

CONCLUSIONS

EPVS counts were associated with impaired cognition in risk-factor–adjusted meta-analysis. EPVS may be a sign of cognitive impairment rather than a sign a particular diseases. More research is needed to further validate ePVS as a measurable risk marker for cognition using consistent methods to determine a characteristic appearance of ePVS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

HZ and ZL contributed to the conception and design of the meta-analysis. WJ, GLin, LL, and GLia were involved in the acquisition and analysis of the data. MO and ML interpreted
the results. WJ and GLin drafted the manuscript. All authors read and approved the final manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.00715/full#supplementary-material

**REFERENCES**

3C SG (2003). Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuropenepidemiology* 22, 26–35. doi: 10.1159/000072290

Arba, F., Quinn, T. J., Hankey, G. J., Wardlaw, J. M., Ali, M., Inzitari, D., et al. (2018). Enlarged perivascular spaces and cognitive impairment after stroke and transient ischemic attack. *Int. J. Stroke* 13, 47–56. doi: 10.11177/1747493016666091

Banerjee, G., Chan, E., Ambler, G., Wilson, D., Cipolotti, L., Shakeshaft, C., et al. (2019). Effect of small-vessel disease on cognitive trajectory after atrial fibrillation-related ischaemic stroke or TIA. *J. Neurology* 266, 1250–1259. doi: 10.1007/s00710-019-09256-6

Boesfphug, E. L., Schwartz, D. L., Lahna, D., Pollock, J., Iliff, J. J., Kaye, J. A., et al. (2018). MR imaging-based multimodal autoidentification of perivascular spaces (mMAPS): automated morphologic segmentation of enlarged perivascular spaces at clinical field strength. *Radiology* 286, 632–642. doi: 10.1148/radiol.2017170205

Chen, W., Song, X., and Zhang, Y. (2011). Assessment of the Virchow-Robin disease independently of amyloid burden. *Brain* 140, 1107–1116. doi: 10.1093/brain/awx003

Dubost, F., Yilmaz, P., Adams, H., Reis, C., Tao, T., Li, W., Li, X., et al. (2019). Enlarged perivascular spaces in basal ganglia predicted functional and cognitive outcome after first-ever stroke—a longitudinal study. *Cerebrovasc. Dis. 43, Supplement 1, 60.

Favaretto, A., Lazzarotto, A., Riccardi, A., Pravato, S., Margoni, M., Causin, F., et al. (2017). MRI-visible perivascular space location is associated with Alzheimer’s disease. *J. Neurol. Neurosurg. Psychiatry* 89, 651–656. doi: 10.1136/jnnp-2017-316724

Hurford, R., Charidimou, A., Fox, Z., Cipolotti, L., Jager, R., and Werring, D. J. (2019). Effect of small-vessel disease on cognitive trajectory after atrial fibrillation-related ischaemic stroke or TIA. *J. Neurology* 266, 1250–1259. doi: 10.1007/s00710-019-09256-6

Jimenez-Balado, J., Riba-Llena, I., Garde, E., Valor, M., Gutierrez, B., Pujadas, F., et al. (2018). Prevalence of hippocampal enlarged perivascular spaces in a sample of patients with hypertension and their relation with vascular risk factors and cognitive function. *J. Neurol. Neurosurg. Psychiatry* 89, 651–656. doi: 10.1136/jnnp-2017-316724

Li, Q., Yang, Y., Reis, C., Tao, T., Li, W., Li, X., et al. (2018). Cerebral Small Vessel Disease. *Cell Transplant.* 27, 1711–1722. doi: 10.1097/000078671895148

Li, Q., Yang, Y., Reis, C., Tao, T., Li, W., Li, X., et al. (2018). Cerebral Small Vessel Disease. *Cell Transplant.* 27, 1711–1722. doi: 10.1097/000078671895148

Macullich, A. M., Wardlaw, J. M., Ferguson, K. J., Starr, J. M., Seckl, J. R., and Deary, I. J. (2004). Enlarged perivascular spaces are associated with cognitive function in healthy elderly men. *J. Neurol. Neurosurg. Psychiatry* 75, 1519–1523. doi: 10.1136/jnnp.2003.03085

Mur, R., Edwards, J. D., Berezuk, C., Ramirez, C., Scott, C. J. M., Gao, F., et al. (2016). Regional relationships between enlarged perivascular spaces, white matter hyperintensities and cognitive impairment. *Alzheimers. Dement.* 12, P225–P225P226. doi: 10.1097/jalz.2016.06.405

Park, Y. W., Shin, N. Y., Chung, S. J., Kim, J., Lim, S. M., Lee, P. H., et al. (2019). Magnetic Resonance Imaging–Visible Perivascular Spaces in Basal Ganglia Predict Cognitive Decline in Parkinson’s Disease. *Mov. Disord.* 34, 1385–1374. doi: 10.1002/mds.27798

Qiang, Z., and Chan, Y. L. (2017). Autoidentification of perivascular spaces in white matter using clinical field strength. *AJNR Am. J. Neuroradiol.* 38, 280. doi: 10.1111/ajnr.12479

Riba, L. Y., Nafria, C., Mundet, X., Lopez-Rueda, A., Jimenez-Balado, J., Ioana, J. C., et al. (2015). Cerebral Small Vessel disease. *Radiology* 27, 1711–1722. doi: 10.1111/j.1524-158X.2012.12479

Shibata, K., Sugiura, M., Nishimura, Y., and Sakura, H. (2019). The effect of small vessel disease MRI markers in ischaemic stroke and TIA. *Eur. J. Neurol.* 26, 1250–1259. doi: 10.1111/ene.12979

Riba-Llena, I., Nafria, C., Mundet, X., Lopez-Rueda, A., Fernandez-Cortinas, I., Jarca, C. I., et al. (2016). Assessment of enlarged perivascular spaces and their relation to target organ damage and mild cognitive impairment in patients with hypertension. *Eur. J. Neurol.* 23, 1044–1050. doi: 10.1111/ene.12979

Riba-Llena, I., Nafria, C., Mundet, X., Lopez-Rueda, A., Fernandez-Cortinas, I., Jarca, C. I., et al. (2016). Assessment of enlarged perivascular spaces and their relation to target organ damage and mild cognitive impairment in patients with hypertension. *Eur. J. Neurol.* 23, 1044–1050. doi: 10.1111/ene.12979

Rawls, T. J., and Chan, Y. L. (2017). Autoidentification of perivascular spaces in white matter using clinical field strength T1 and FLAIR MR imaging. *Neuroimage* 202, 116126. doi: 10.1016/j.neuroimage.2019.116126

Shams, S., Martola, J., Charidimou, A., Larvie, M., Granberg, T., Shams, M., et al. (2017). Topography and Determinants of Magnetic Resonance Imaging (MRI)-Visible Perivascular Spaces in a Large Memory Clinic Cohort. *J. Am. Heart Assoc.* 6, e006279. doi: 10.1177/jaha.116666091

Shibata, K., Sugiura, M., Nishimura, Y., and Sakura, H. (2019). The effect of small vessel disease on motor and cognitive function in Parkinson’s disease. *Clin. Neurol. Neurosurg.* 182, 58. doi: 10.1016/j.clinneu.2018.04.029

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur. J. Epidemiol.* 25, 603–605. doi: 10.1007/s10654-010-9491-z

Stroup, D. F. B., Morton SCQ, J. A., and Williamson GD, I. (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-
analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 283 (15), 2008–2012, 2000. doi: 10.1001/jama.283.15.2008

Thomas, O., Cain, J., Nasralla, M., and Jackson, A. (2019). Aortic Pulsatility Propagates Intracranially and Correlates with Dilated Perivascular Spaces and Small Vessel Compliancy. J. Stroke Cerebrovasc. Dis. 28, 1252–1260. doi: 10.1016/j.jstrokecerebrovasdis.2019.01.020

Trippier, S., Benjamin, P., Zeestraten, E., Lambert, C., Lawrence, A. J., Williams, O. A., et al. (2018). Lacunar infarcts, but not perivascular spaces, are predictors of cognitive decline in cerebral small vessel disease. Stroke 49, 586–593. doi: 10.1161/STROKEAHA.117.017526

Van Westen, D., Clara, P., Lennart, M., and Oskar, H. (2017). Perivascular spaces in the hippocampus are associated with markers of vascular disease, and not of alzheimer’s disease. J. Neurodegener. Dis. 17, 513. doi: 10.1016/j.jalz.2018.06.431

van Westen, D., Gertje, E., and Hansson, O. (2018). Perivascular Spaces In the Hippocampus Are Associated with Cognitive Decline at Four-Year Follow-up In MCI Patients. Alzheimers. Dement. 14, P467. doi: 10.1016/j.jalz.2018.06.431

Yao, M., Zhu, Y. C., Soumare, A., Dufouil, C., Mazoyer, B., Tzourio, C., et al. (2014). Hippocampal perivascular spaces are related to aging and blood pressure but not to cognition. Neurobiol. Aging 35, 2118–2125. doi: 10.1016/j.neurobiolaging.2014.03.021

Yun, Y. H. (2013). The number of dilated perivascular spaces: Hallmarks of mild cognitive impairment. Alzheimer's Dementia J. Alzheimers Assoc. 9, P407–P407. doi: 10.1016/j.jalz.2013.05.806

Zhu, Y. C., Dufouil, C., Soumare, A., Mazoyer, B., Chabriat, H., and Tzourio, C. (2010). High degree of dilated Virchow-Robin spaces on MRI is associated with increased risk of dementia. J. Alzheimers Dis. 22, 663–672. doi: 10.3233/JAD-2010-100378

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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