The global burden of cerebral small vessel disease in low- and middle-income countries: A systematic review and meta-analysis

Bonnie Yin Ka Lam¹,²,³, Yuan Cai¹, Rufus Akinyemi⁴,⁵,⁶,⁷, Geert Jan Biessels⁸, Hilde van den Brink⁸, Christopher Chen⁹, Chin Wai Cheung¹, King Ngai Chow¹, Henry Kwun Hang Chung¹, Marco Duering¹,¹⁰,¹¹, Siu Ting Fu¹, Deborah Gustafson¹², Saima Hila⁹,¹³,¹⁴, Vincent Ming Ho Hui¹,², Rajesh Kalaria⁷, SangYun Kim¹⁵, Maggie Li Man Lam¹, Frank Erik de Leeuw¹⁶, Ami Sin Man Li¹,², Hugh Stephen Markus¹⁷, Anna Marseglia¹⁸, Huijing Zheng¹,², John O’Brien¹⁹, Leonardo Pantoni²⁰, Perminder Singh Sachdev²¹, Eric E Smith²², Joanna Wardlaw²³, and Vincent Chung Tong Mok¹,²

Abstract

Background: Cerebral small vessel disease (cSVD) is a major cause of stroke and dementia. Previous studies on the prevalence of cSVD are mostly based on single geographically defined cohorts in high-income countries. Studies investigating the prevalence of cSVD in low- and middle-income countries (LMICs) are expanding but have not been systematically assessed.

Aim: This study aims to systematically review the prevalence of cSVD in LMICs.

Results: Articles were searched from the Ovid MEDLINE and EMBASE databases from 1 January 2000 to 31 March 2022, without language restrictions. Title/abstract screening, full-text review, and data extraction were performed by two to seven independent reviewers. The prevalence of cSVD and study sample size were extracted by pre-defined world regions and health status. The Risk of Bias for Non-randomized Studies tool was used. The protocol was registered on PROSPERO (CRD42022311133). A meta-analysis of proportion was performed to assess the prevalence of different magnetic resonance imaging markers of cSVD, and a meta-regression was performed to investigate associations between cSVD prevalence and type of study, age, and male: female ratio. Of 2743 studies identified, 42 studies spanning 12 global regions were included in the systematic review. Most of the identified studies were from China (n = 23). The median prevalence of moderate-to-severe white matter hyperintensities (WMHs) was 20.5%, 40.5%, and 58.4% in the community, stroke, and dementia groups, respectively. The median prevalence of lacunes was 0.8% and 33.5% in the community and stroke groups. The median prevalence of cerebral microbleeds (CMBs) was 10.7% and 22.4% in the community and stroke groups. The median prevalence of moderate-to-severe perivascular spaces was 25.0% in the community. Meta-regression analyses showed that the weighted median age (51.4 ± 0.0 years old; range: 36.3–80.2) was a significant predictor of the prevalence of moderate-to-severe WMH and lacunes, while the type of study was a significant predictor of the prevalence of CMB. The heterogeneity of studies was high (>95%). Male participants were overrepresented.

Conclusions: This systematic review and meta-analysis provide data on cSVD prevalence in LMICs and demonstrated the high prevalence of the condition. cSVD research in LMICs is being published at an increasing rate, especially between 2010 and 2022. More data are particularly needed from Sub-Saharan Africa and Central Europe, Eastern Europe, and Central Asia.
Keywords
Cerebral small vessel disease, prevalence, low- and middle-income countries, systematic review, meta-analysis, white matter hyperintensities, lacunes, cerebral microbleed, perivascular space

Received: 17 August 2022; accepted: 18 October 2022

Introduction
Sporadic cerebral small vessel disease (cSVD) contributes crucially to a large variety of conditions including stroke and dementia. cSVD leads to one in four lacunar stroke cases and is the most common cause of vascular dementia. Other than stroke and dementia, cSVD also leads to non-stroke-related parkinsonism, gait disturbance, falls resulting in hip fractures, urinary incontinence, depression, and/or changes in behavior or personality. Furthermore, cSVD is common in the general population, affecting 5% of people aged 50 to almost 100% of people over 90 years old. The common manifestations of cSVD are white matter hyperintensities (of presumed vascular origin, WMHs), lacunes (of presumed vascular origin), cerebral microbleeds (CMBs), perivascular spaces (PVSs), cortical microinfarcts (CMIs), and cortical superficial siderosis (CSS).

Despite the immense impact of cSVD, its global prevalence is not known. Understanding the prevalence of cSVD in different global regions as well as their clinical manifestations can improve our understanding and management of cSVD. The prevalence of cSVD is challenging to estimate for the following reasons. First, the clinical expression of cSVD is highly variable, making the diagnosis not straightforward. Second, the prevalence of cSVD depends on the risk factor profile, which will be different in community, stroke, and dementia cohorts. This could create large differences in the reported prevalence of cSVD. Third, while standardized definitions for radiological presentations of cSVD have been published, these consensus criteria are not always applied. More importantly, cSVD is not limited to one single neuroimaging biomarker. Instead, there are at least three to four commonly used neuroimaging markers, together with other isolated imaging biomarkers for the...
disease, making the assessment of cSVD prevalence less straightforward. Fourth, the neuroimaging acquisition protocol and assessment method of cSVD imaging biomarkers (visual rating vs quantitative measure) vary depending on the type of study. Fifth, the prevalence of cSVD may differ depending on geography, race, culture, vascular risk factors, diet, lifestyle, socioeconomic status, healthcare, and public health policies of the region.

Only one semi-systematic review on the prevalence of cSVD in population-based studies has been published, to our knowledge. However, most of the population-based studies included in this review were from high-income countries. The prevalence of WMH ranged from 65% to 96%; of lacunes, 8% to 31%; and of CMB, 3.1% to 15.3%. It is important to investigate the prevalence of cSVD globally to estimate the full impact of the disease since the prevalence of cSVD in low- and middle-income countries (LMICs) is increasing but has not been systematically reviewed.

In this review, we aim to evaluate the existing evidence of the prevalence of cSVD in LMICs to address this gap in the literature. We hypothesize that the prevalence of cSVD in LMICs would be variable depending on the type of study, vascular risk factor profile, age, and ethnic background. While reviewing the prevalence of cSVD itself poses the aforementioned challenges, we may not be able to solve all issues. However, we attempted to use clear definitions so that relevant studies could be grouped and compared for a better overview of the prevalence of cSVD.

**Methods**

An international workgroup with a panel of experts in cSVD, including the International Society for Vascular and Cognitive Impairment members, was formed to initiate this review. This was further facilitated by the research group from the Division of Neurology, Department of Medicine and Therapeutics, Chinese University of Hong Kong, who developed the research question, search strategy, and inclusion and exclusion criteria, as well as performed the screening, data extraction, and synthesis, and discussed the analysis with the panel members.

**Search strategy and selection criteria**

We first searched PROSPERO to ensure there were no existing and ongoing reviews on a similar topic. To assess the prevalence of cSVD, we searched Ovid MEDLINE and EMBASE databases from 1 January 2000 until 31 March 2022, without language restrictions (see Supplementary material, pp. 1–3). A medical librarian (University of Oxford, UK) provided consultation on the search strategy. The Preferred Reporting in Systematic Review and Meta-Analysis (PRISMA) guidelines were used. For gray literature, we performed an additional search, such as government websites, to supplement the search. We also conducted an additional hand search on Google Scholar to include relevant articles. Searches were re-run before the final analyses and any further studies that were identified were retrieved for inclusion in the final analyses. We emailed the author for clarification regarding the publication if required.

The literature search consisted of three main concepts: “LMICs,” “prevalence,” and “cSVD.” For “LMICs,” we refer to the Global Burden of Disease (GBD), which has grouped the world into seven super-regions according to similar cause-of-death patterns. The seven super-regions are (1) High Income (including Southern Latin America, Western Europe, High-income North America, Australasia, and High-income Asia Pacific); (2) Latin America and Caribbean; (3) Sub-Saharan Africa; (4) North Africa and Middle East; (5) South East Asia, East Asia and Oceania; (6) South Asia; and (7) Central Europe, Eastern Europe and Central Asia. We defined LMIC regions as those included in GBD super-regions (2) to (7). For the exact search on LMIC names, we adopted the ScHARR LMIC filter. Please note that a publication was identified from Martinique, which is located in the Lesser Antilles of the West Indies in the eastern Caribbean Sea and is an overseas region of France. Considering the distinctive race and ethnicity that people from Martinique may have compared to people from France, as well as the scarcity of publications from the Caribbean, the international workgroup has decided to categorize this study in the GBD regions “Latin America and the Caribbean” based on its location for the data analyses. For “prevalence,” we used the terms “global burden of disease” or “prevalence” or “incidence” or “epidemiology,” including both MeSH or .mp. to increase search sensitivity. For cSVD, we referred to the STAndards for ReportIng Vascular changes on nEuroimaging (STRIVE) classifications of SVD, search strategies from relevant reviews, and updated cSVD terminologies from the research panel.

Inclusion criteria for the systematic review were published original research articles: (1) between 1 January 2000 to 31 March 2022; (2) without language restrictions; (3) assessed the prevalence of at least one kind of cSVD lesion on magnetic resonance imaging (MRI) with sample size ≥20 people; (4) including cSVD patients who were asymptomatic, or with stroke, mild cognitive impairment or dementia; or (5) longitudinal studies including the prevalence of cSVD at baseline. Exclusion criteria included (1) cSVD diagnosis without brain MRI (clinical only or with computed tomography (CT) only); (2) studies investigating genetic variants of cSVD (e.g., Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Cerebral autosomal recessive arteriopathy...
with subcortical infarcts and leukoencephalopathy (CARASIL); (3) studies that recruited based on a non-vascular or non-neurodegenerative disease etiology; (4) non-human studies; (5) case studies, letters, or studies not published in full; and (6) studies including participants who were not from LMICs.

Study selection

Title and abstract screening, full-text review, and data extraction were completed by two to seven reviewers using the COVIDENCE software. For details of reviewers and their involvement in the review, please see Supplementary material, p. 5.

Data extracted included authors’ last name, year of publication, journal name, study name, type of study, sample size, race, GBD region, age, male: female ratio (the number of males divided by the number of females), education, MRI manufacturer and model, MRI field strength, the prevalence of cSVD MRI markers (which included WMH, lacunes, CMB, PVS, CMI, CSS, total SVD score) and the criteria were used to assess cSVD marker. For WMH, mean and standard deviations were abstracted from volumetric assessments, while a cut-off of moderate-to-severe WMH was used for visual ratings. Disagreements were resolved by team discussion and senior researchers in the team (B.Y.K.L., Y.C., and V.C.T.M.).

Quality assessment

Study quality was assessed using the RoBANS tool (risk of bias assessment tool for non-randomized studies) to assess participant selection, adjust for confounders, assess adequate SVD features, blinding of cSVD raters to clinical profile, assess incomplete outcomes data, and assess selective outcomes reporting. Risk of bias was performed by four independent researchers. Disagreements were resolved by a senior researcher in the team (B.Y.K.L.).

The protocol of this systematic review was registered on PROSPERO on 24 April 2022 (CRD42022311133).

Data synthesis and analyses

Meta-analysis was performed according to the Meta-analyses Of Observational Studies in Epidemiology. The primary analyses were to assess the pooled prevalence of cSVD as estimated by each cSVD marker using the meta-analysis of proportions. We extracted the mean age, male: female ratio, the raw prevalence of the cSVD marker, and sample size for that specific marker for meta-analysis. Only means and standard deviations were used in the meta-analysis. The prevalence was based on the number of subjects with the specified cSVD marker divided by the total sample size from the study, without further adjustment. For the assessment of moderate-to-severe WMH via visual ratings, most studies applied the cut-off at $\geq 2$ using the Fazekas Score and Age-Related White Matter Changes scale, or as otherwise defined in the study. The assessment of moderate-to-severe PVS was defined as $> 10$ PVS on either hemisphere or otherwise defined in the study. Other markers of cSVD (lacunes, microbleeds, cerebral microinfarct, cerebral superficial siderosis, total SVD score) were defined by presence or absence.

For secondary analyses, random-effects meta-regression analyses were used to estimate the associations between the logit-transformed prevalence of cSVD and the type of study (community, stroke, or dementia), with mean age and male: female ratio as covariates. Meta-analysis was only performed if there were $\geq 8$ studies for a particular cSVD marker. This cut-off was set lower than the recommended 10 studies for each study-level variable due to the limited number of studies published in LMICs on cSVD prevalence and our intention to examine all available data. Heterogeneity was assessed using the $I^2$ statistic and cut-offs were applied for low (25%), moderate (50%), and substantial (75%) heterogeneity. Bubble plots were used to assess the correlation between mean age and cSVD prevalence. Funnel plots were included (x-axis: standard error; y-axis: residual value) to assess publication bias. Analyses were performed using the metafor package, and color illustrations of the forest plots were done using the meta package. Male: female ratio was calculated for each cohort and presented on a world map using the maps package (https://cran.r-project.org/web/packages/maps/maps.pdf). All analyses were performed using R v4.0.5.
Results

Our systematic literature search on the prevalence of cSVD resulted in 3398 studies, of which 655 were duplicates (Figure 1). Of the 2743 papers screened, 135 were eligible for full-text screening. We performed an additional hands-on search and identified 27 additional publications. One hundred twenty papers were excluded from the review as 85 were not from LMICs; 8 studies did not have a direct measure of cSVD; 6 were studies with cSVD but of non-vascular or non-degenerative etiology; and 21 were not original research articles. For an overview of all included studies, please see Supplementary material, pp. 6–8. An additional 14 studies were excluded from the meta-analyses as they were repeated publications from the same cohort (n=8); without complete data for meta-analysis (n=4); and with unclear results reporting (n=2). For multiple publications from the same cohort, we selected a representative study from each cohort based on the following: a greater number of cSVD markers reported, preference for more recent publications, and larger sample size. Forty-two studies were identified for inclusion and full-text screening, including a total of 511,140 subjects, with a median age of 51.4 ± 0.0 years old. For the PRISMA flow diagram, please refer to Figure 1.

Some studies assessed cSVD prevalence from multiple GBD regions, therefore, we separated each region as an individual entry and refer to it as a “cohort” in the systematic review (see Figure 1). This review included 42 studies, which represented data from 50 independent cohorts from six GBD super-regions. In Latin America and the Caribbean, there were 2 studies from Brazil, 1 from Martinique, and 4 from Ecuador. In Sub-Saharan Africa, there were 3 studies from West Africa. In North Africa and the Middle East, there were 3 studies from Egypt, and 2 from Qatar. In South East Asia, East Asia, and Oceania, there were 17 studies from China, 6 from Taiwan (Province of China), 1 from the Philippines, and 2 from Thailand. In South Asia, there were 6 studies from India and 2 studies from Pakistan. In Central Europe, Eastern Europe, and Central Asia, there was one study from Russia (see Figure 2 and Table 1). Overall, China contributed the highest number of publications (n=23).

All publications on cSVD prevalence from LMICs were published after 2010, and the number has expanded rapidly since then. The majority of the studies were community-based, followed by stroke and dementia studies. Among the cSVD markers reported, most reported visual ratings of WMH (n=32), and presence/absence or counts of lacune (n=29), CMB (n=26), or PVS (n=12). There were few data reported on WMH volume (n=7), CMI (n=0), CSS (n=2), and total SVD score (n=7); therefore, these outcomes were not included in the meta-analysis. For the assessment of cSVD MRI markers, 58% referred to STRIVE criteria and 46% of studies used 3.0 Tesla MRI while the remaining used an MRI with a lower field strength. The mean study quality score was 4.85 out of 6.0 using the RoBANS tool (see Table 1).

We identified 28 studies eligible for meta-analysis, representing 35 cohorts (weighted median age: 51.4 ± 0.0 years old; range: 36.3–80.2). For the meta-analysis of proportions, the median (± IQR) prevalence of moderate-to-severe WMH was 20.5 ± 12.6%, 40.5 ± 34.9%, and 58.4 ± 21.6% in the community, stroke, and dementia groups, respectively (total sample = 10,297; I² = 97%; 95% confidence interval (CI) = 0.23–0.48) (see Figure 3 and Figure 4(a)). The median prevalence of lacunes was 0.8 ± 0.0% and 33.5 ± 29.4% in the community
Table 1. Summary of studies included in the systematic review.

| Low- and middle-income regions | Latin America and Caribbean | Sub-Saharan Africa | North Africa and Middle East | South East Asia, East Asia, and Oceania | South Asia | Central Europe, Eastern Europe, and Central Asia |
|--------------------------------|-----------------------------|-------------------|------------------------------|------------------------------------------|-----------|-----------------------------------------------|
| Number of cohorts              | 7                           | 3                 | 5                            | 26                                       | 8         | 1                                             |
| Regions included               | Brazil (n = 2), Martinique (n = 1), Ecuador (n = 4) | West Africa (n = 3) | Egypt (n = 3), Qatar (n = 2) | China (n = 17), Taiwan (Province of China) (n = 6), Philippines (n = 1), Thailand (n = 2) | India (n = 6), Pakistan (n = 2) | Russia (n = 1) |
| Year of publication (n %)      | 2000–2009 (0) (0) (0) (0) (0) (0) (0) | 2010–2019 (4 (57.1)) (2 (66.7)) (4 (80)) (9 (34.6)) (4 (50)) (0 (0)) | >2019 (3 (42.9)) (1 (33.3)) (1 (20)) (17 (65.4)) (4 (50)) (1 (100)) | |
| Sample size (n %)              | < 100 (1 (14.3)) (2 (66.7)) (2 (40)) (0 (0)) (2 (25)) (1 (100)) | 100–1499 (6 (85.7)) (1 (33.3)) (3 (60)) (25 (96.2)) (6 (75)) (0 (0)) | 1500–2999 (0 (0)) (0 (0)) (0 (0)) (0 (0)) (0 (0)) (0 (0)) |
| cSVD lesions (n %)             | Presence of moderate-to-severe WMH (≥2) | Presence of lacune (≥2) | Presence of CMB (≥2) | Presence of moderate-to-severe PVS (≥10) | Presence of CMI | Presence of CSS |
| Presence of moderate-to-severe WMH (≥2) | 28.4% (Community), 46.8% (Stroke), 67.7% (Dementia) | 46.6% (Stroke) | 22.0% (Stroke) | 19.0% (Community), 36.0% (Stroke), 36.8% (Dementia) | 54.3% (Stroke) | 59.8% (Community) |
| Presence of lacune (≥2)        | 10.8% (Community), 33.5% (Stroke) | N/A | 16.2% (Community), 24.1% (Stroke) | 0.8% (Community), 25.5% (Stroke) | 49.6% (Community), 25.6% (Stroke) | 58.7% (Community) |
| Presence of CMB (≥2)           | 10.7% (Community), 21.4% (Stroke) | N/A | 16.2% (Community), 19.5% (Stroke) | 10.7% (Community), 19.5% (Stroke) | 9.4% (Community), 28.7% (Stroke) | 48.9% (Community) |
| Presence of moderate-to-severe PVS (≥10) | 30.5% (Community) | N/A | N/A | 19.4% (Community) | 9.4% (Community) | 58.7% (Community) |
| Total cSVD score (≥2)          | 24.9% (Community) | N/A | N/A | 34.9% (Community) | 59.1% (Stroke) | N/A |

(Continued)
| Low- and middle-income regions | Latin America and Caribbean | Sub-Saharan Africa | North Africa and Middle East | South East Asia, East Asia, and Oceania | South Asia | Central Europe, Eastern Europe, and Central Asia |
|--------------------------------|-----------------------------|-------------------|-----------------------------|----------------------------------------|-----------|---------------------------------------------|
| Mean age, years (n (%))        |                             |                   |                             |                                        |           |                                              |
| <60                            | 0 (0)                       | 2 (66.7)          | 3 (60)                      | 10 (38.5)                              | 4 (50)    | 1 (100)                                     |
| 60–69                          | 1 (14.3)                    | 1 (33.3)          | 2 (40)                      | 9 (34.6)                               | 2 (25)    | 0 (0)                                       |
| 70–79                          | 6 (85.7)                    | 0 (0)             | 0 (0)                       | 6 (23.1)                               | 2 (25)    | 0 (0)                                       |
| 80–89                          | 0 (0)                       | 0 (0)             | 0 (0)                       | 1 (3.8)                                | 0 (0)     | 0 (0)                                       |
| ≥90                            | 0 (0)                       | 0 (0)             | 0 (0)                       | 0 (0)                                  | 0 (0)     | 0 (0)                                       |
| Male (%)                       | 42.6                        | 59.8              | 66.0                        | 44.3                                   | 65.3      | 32.6                                        |
| Population-based studies (n (%)) | 5 (71.4)                   | 0 (0)             | 0 (0)                       | 6 (23.1)                               | 1 (12.5)  | 0 (0)                                       |
| Community elderly studies (n (%)) | 5 (71.4)                  | 0 (0)             | 1 (20)                      | 19 (73.1)                              | 3 (37.5)  | 1 (100)                                     |
| Stroke studies (n (%))         | 1 (14.3)                    | 3 (100)           | 4 (80)                      | 4 (15.4)                               | 5 (62.5)  | 0 (0)                                       |
| Dementia studies (n (%))       | 1 (14.3)                    | 0 (0)             | 0 (0)                       | 3 (11.5)                               | 0 (0)     | 0 (0)                                       |
| STRIVE criteria used (n (%))   | 3 (42.9)                    | 2 (66.6)          | 3 (60)                      | 19 (73.1)                              | 1 (12.5)  | 1 (100)                                     |
| MRI field strength ≥ 3T (n (%)) | 2 (28.6)                    | 0 (0)             | 2 (40)                      | 17 (65.4)                              | 1 (12.5)  | 1 (100)                                     |
| Risk of bias assessment (overall quality score) (Mean score out of 6) | 5.7                         | 4                 | 4                           | 5.92                                   | 4.5       | 5                                           |

WMH: white matter hyperintensities; NA: not applicable; CMB: cerebral microbleed; PVS: perivascular space; CMI: cortical microinfarct; CSS: cortical superficial siderosis; STRIVE: STandards for Reporting Vascular changes on nEuroimaging; MRI: magnetic resonance imaging.

This study did not report the mean age.

*This study focused on subjects with neuroimaging features of cSVD as the inclusion criteria and had a relatively small control group. The community group also included patients with prior stroke or dementia. Hence, the prevalence is relatively high for a community study. The finding was reported in Table 1 but not included in the meta-analysis due to the heterogeneity of data sampling.

In one of the included studies, scanning was done in both the 1.5 and 3T scanners.

One study did not specify scanner field strength.
and stroke groups, respectively (total sample = 499,920; I² = 100%; 95% CI = 0.13–0.30) (see Figure 3 and Figure 4(b)). The median prevalence of CMB was 10.7 ± 3.6% and 22.4 ± 7.3% in the community and stroke groups, respectively (total sample = 10,479; I² = 96%; 95% CI = 0.12–0.19) (see Figure 3 and Figure 4(c)). The median prevalence of moderate-to-severe PVS was 25.0 ± 14.5% in the community (total sample = 4634; I² = 96%; 95% CI = 0.13–0.27) (see Figure 3 and Figure 4(d)). As studies reporting WMH volume, CMI, CSS, and total SVD score were <8, the limited data prevented us from performing further analysis.

In the meta-regression, the association between the prevalence of moderate-to-severe WMH, and the type of studies (community, stroke, or dementia) were assessed, and adjusted with mean age and male: female ratio. The type of study did not predict the prevalence of cSVD. However, mean age was a significant predictor (β = 0.08, p = 0.002, 95% CI = 0.03–0.12).

The overall regression model predicting the prevalence of lacunes by the type of studies, mean age, and male: female ratio was significant (p = 0.0002). Mean age contributed to the prevalence of lacunes (β = 0.08, p = 0.008, 95% CI = 0.02–0.14).

The prevalence of CMB was significantly associated with the type of studies, adjusted with mean age and male: female ratio (p < 0.0001). Studies from the stroke group compared to the community group significantly predicted the prevalence of CMB (β = 1.09, p < 0.0001; CI = 0.59–1.59). There was no dementia group investigating CMB.

The prevalence of moderate-to-severe PVS was not significantly associated with the type of study, adjusted with mean age and male: female ratio (p = 0.89).

Bubble plots were used to demonstrate the association between mean age and cSVD prevalence. Mean age was positively correlated with moderate-to-severe WMH and lacune (see Supplementary Figure 1(a) and (b)) while the association between mean age and CMB or moderate-to-severe PVS was weak (see Supplementary Figure 1(c) and (d)). There were not enough studies to perform an analysis on cSVD prevalence by age group strata. Funnel plots showed that there were publication biases in studies reporting WMH, lacune, CMB, and PVS (see Supplementary Figure 2(a)–(d)). This may be due to the inclusion of a heterogeneous population sample (community, stroke, and dementia), large variability in age, and the inconsistent cSVD definitions used across studies.

In general, the male: female ratio ratios were high in the included studies (mean ± SD = 1.31 ± 1.0; min = 0.04; max = 6.0). A higher proportion of males was more apparent in the stroke or dementia group and in India (Supplementary Figure 3(a) and (b)). However, male: female ratio was not a significant contributor to the prevalence in all cSVD markers.

Discussion

This systematic review revealed a few key findings that have not been addressed in previous publications. First, this is the first systematic review of the prevalence of cSVD in LMICs, in which we found data from six GBD super-regions (12 sub-regions) including 42 studies (with 50 cohorts). All publications on cSVD prevalence from LMICs were published after 2010, with an increasing rate of publication generated over the past 12 years. The majority were community studies, followed by stroke, then dementia studies. The prevalence of moderate-to-severe WMH was doubled in the dementia group (58.4%) compared to the community.
Figure 4. (a) Forest plot showing the proportion of moderate-to-severe WMH, (b) lacune, (c) cerebral microbleed, and (d) moderate-to-severe perivascular space.
(20.5%), and the prevalence of the stroke group was in-between (40.5%). As expected, the prevalence of lacunes was high up to 33.5% in the stroke group but low in the community at 0.8%. The prevalence of CMB was also more than doubled in the stroke group (22.4%), compared to the community (10.7%). The prevalence of moderate-to-severe PVS was 25.0% in the community. Of the eight cSVD markers assessed, only four markers had \( \geq 8 \) studies for meta-analysis. In stroke studies addressing the co-presence of cSVD, the presence of lacunes was mainly assessed as acute lacunar infaracts while concurrent silent lacunes in different stroke subtypes, for example, intracranial large artery disease or extracranial large artery disease, were not assessed.

We might, thus, have underestimated the prevalence of lacunes within the context of stroke. However, other cSVD markers such as WMHs and microbleeds were assessed in all stroke subtypes, if available. For WMH, most studies used visual rating scales rather than volumetric analysis. A good proportion of studies (58.0%) referred to STRIVE criteria. The proportion of studies using 3.0 Tesla MRI for assessment of cSVD markers was 46% while the remaining studies used a lower magnetic field strength. The mean study quality score was 4.85 out of 6.0 using the RoBANS tool.

Second, the heterogeneity of the studies was substantial. Meta-regression analyses showed that this heterogeneity may be due to the mean age of the sample and the study population. The large variability in mean age across participants was a major contributor to heterogeneity. As fewer population-based studies were reporting on cSVD in LMICs, the prevalence of cSVD could only be gathered by including all cohorts that reported cSVD MRI markers, including community, stroke, and dementia. The inclusion of study cohorts of community and disease groups may also have increased heterogeneity. However, stratifying studies by healthy versus disease groups poses another challenge, since the small number of studies in each subgroup prevented us from running a subgroup meta-analysis. Other plausible explanations for the high heterogeneity could have been due to the variable acquisition protocols and different rating standards.

Third, 42 studies were identified, spanning 12 global regions from Latin America and the Caribbean, Sub-Saharan Africa, North Africa, the Middle East, South East Asia, East Asia and Oceania, South Asia, Central Europe, Eastern Europe, and Central Asia. China contributed the highest number of publications. There were two studies from Africa that did not report a direct prevalence of cSVD while one study measured WMH in a scale less comparable to other studies. Thus, data from Sub-Saharan Africa were not included in the meta-analysis. Therefore, this review most likely underestimated the prevalence of cSVD in Sub-Saharan Africa, given that the annual incidence of stroke in Africa is among the highest in the world. A semi-systematic review suggested that the prevalence of cSVD was higher than other contributors to strokes, and subsequently, vascular cognitive impairments in African populations; however, more prospective studies are warranted. Only one study from Central Europe, Eastern Europe, and Central Asia was identified. However, this study focused on subjects with neuroimaging features of cSVD as the inclusion criteria and had a relatively small control group. The cSVD group also included those with prior stroke and dementia. Hence, the prevalence is relatively high for a community study. Considering the scarcity of publications in this region, the findings were reported in the systematic review but not included in the meta-analysis due to the heterogeneity of data sampling. An additional hands-on search led to the retrieval of one published protocol paper from Russia but the results have not been published. More studies on cSVD prevalence are warranted to increase coverage and provide a better global perspective.

Fourth, we found that the male: female ratio was elevated, particularly in cohorts with stroke or dementia, and especially in India. This phenomenon was reported in a previous systematic review that reported a high male: female ratio in cohorts with higher SVD burden and among those with stroke. While this may reflect recruitment bias seen in many hospital-based stroke treatment trials that include neuroimaging for cSVD, it may also imply that males develop higher cSVD severity, especially in stroke presentations which may, in turn, reflect male: female ratio differences in metabolomic. Conversely, the male: female ratio did not predict cSVD prevalence in this meta-analysis, possibly due to the diluting effect of community-based studies in which cSVD prevalences are low.

Fifth, a direct comparison of mean cSVD prevalence in LMICs and high-income countries should be interpreted with caution since we did not have studies recruiting in both regions using similar protocols. Global aging, socioeconomic status, healthcare policies, control of vascular risk factors, and technological advances (new MRI machines with higher magnetic field strength) are factors affecting the prevalence of cSVD, and these factors need to be considered and adjusted when doing a direct comparison of prevalences. To add to the complexity, the year of assessing cSVD prevalence may be crucial since prevalence may decrease over time, in both high-income and LMICs with improvement in healthcare policies. Nonetheless, this review addressed brain MRI markers to assess cSVD prevalence, which is the gold standard for the assessment of cSVD. Although this may limit the number of studies included, using neuroimaging markers to capture cSVD prevalence provides a more reliable and comparable estimate across studies. Given the aforementioned factors, a direct comparison of cSVD prevalence in LMICs and high-income countries requires cautious interpretation. Studies that recruit participants in LMICs and high-income countries using the same methodologies are required for direct comparisons between socioeconomic income-based regions.
A major limitation of this study is that only 4 cSVD markers (visual rating of WMH, lacune, CMB, and PVS) were included in the final analyses. We were not able to assess the prevalence of other relevant cSVD markers such as WMH volume, CMI, CSS and the total SVD score due to the small number of studies available for each marker. This highlighted that much more emphasis should be focused on cSVD research on LMICs. Strengths of this review include having a broad search strategy that encompasses radiological SVD features according to standard criteria, independent screening, full-text review, and extraction by two to seven reviewers, moderate sample size across varied populations with good geographical spread, and inclusiveness of summary measures.

In summary, to our knowledge, this is the first systematic review and meta-analysis to investigate the published prevalence of cSVD in LMICs. The only other published review in 2019 on cSVD prevalence to our knowledge focused on population-based studies and was biased toward the inclusion of high-income countries. In this particular systematic review, there is also an imbalanced representation of LMICs in the published literature. Having representative samples from more diverse LMIC regions would add great value to the overall understanding of the prevalence of cSVD in LMICs as well as in terms of generalizability. As for future directions, there is a need for population-based studies to assess cSVD in LMICs, especially from Sub-Saharan Africa and Central Europe, Eastern Europe, and Central Asia. Future studies with at least 3.0T MRI, using harmonized methods for reporting cSVD neuroimaging markers (e.g. STRIVE criteria) and assessment of various cSVD markers (in addition to WMHs, lacunes, CMBs, and PVSs), will contribute to a better understanding of cSVD in LMICs. Understanding the prevalence of cSVD in different global regions as well as their clinical manifestations (in terms of cognitive deficits and neuroimaging features) can improve our understanding and management of cSVD.

Acknowledgement
We would like to acknowledge the participation of students, Mo Yin Joyce Ma, Charlotte Yi-sum Poon, Sing Yau Li, and Tin Jik Chris Zhou in the title/abstract screening. We would like to thank Kam Tat Leung for the support in statistical analyses. This is also acknowledged as a deliverable of the International Society for Vascular Behavioral and Cognitive Disorders (VasCog).

Author contributions
BYKL designed the research question; performed the searches, data extraction, and analysis; initiated discussion among the international workgroup; and wrote up the article. YC, CWC, ASML, KNC, STF, HKHC, and VMHH performed data extraction. VCTM designed the research question, initiated discussion among the international workgroup, provided advice on the systematic review, performed data interpretation, and commented on the draft of the manuscript. All other co-authors provided input on the design of the research question, provided advice on the systematic review, performed data interpretation, and commented on the draft of the manuscript.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Wellcome Centre for Integrative Neuroimaging is supported by core funding from the Wellcome Trust (203139/Z/16/Z). BYKL is supported by the Lee Hysan Postdoctoral Fellowship in Clinical Neurosciences. JW is supported by the UK Dementia Research Institute, which receives its funding from DRI Ltd (funded by the UK Medical Research Council, Alzheimer’s Society, and Alzheimer’s Research UK). RK is supported by a grant from the Royal Society and African Academy of Sciences. DG is supported by NIH/National Heart, Lung and Blood Institute (5U01HL146202-03); MACS/WIHS Combined Cohort Study (MWCCS): Brooklyn Clinical Research Site.

ORCID iDs
Bonnie Yin Ka Lam https://orcid.org/0000-0002-1656-2433
Rufus Akinyemi https://orcid.org/0000-0001-5286-428X
Geert Jan Biessels https://orcid.org/0000-0001-6862-2496
Chin Wai Cheung https://orcid.org/0000-0001-7514-2247
Marco Duering https://orcid.org/0000-0003-2302-3136
Ami Sin Man Li https://orcid.org/0000-0001-6723-5144
Hugh Stephen Markus https://orcid.org/0000-0002-9794-5996
Leonardo Pantoni https://orcid.org/0000-0001-7357-8530
Perninder Singh Sachdev https://orcid.org/0000-0002-9595-3220
Eric E Smith https://orcid.org/0000-0003-3956-1668
Joanna Wardlaw https://orcid.org/0000-0002-9812-6642

Availability of data and materials
The data used in this study and the analytic code are available upon request from the author.

Supplemental material
Supplemental material for this article is available online.

References
1. Pasi M and Cordonnier C. Clinical relevance of cerebral small vessel diseases. Stroke 2020; 51: 47–53.
2. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010; 9: 689–701.
3. De Silva TM and Faraci FM. Contributions of aging to cerebral small vessel disease. Annu Rev Physiol 2020; 82: 275.
4. Cannostraro RJ, Badi M, Eidelberg BH, Dickson DW, Middlebrooks EH and Meschia JF. CNS small vessel disease: a clinical review. Neurology 2019; 92: 1146–1156.
5. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013; 12: 822–838.
1. van Veluw SJ, Shih AY, Smith EE, et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol* 2017; 16: 730–740.

2. Charidimou A, Lim J, Vernooij MW, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain* 2015; 138: 2126–2139.

3. Das AS, Regenhardt RW, Vernooij MW, Blacker D, Charidimou A and Viswanathan A. Asymptomatic cerebral small vessel disease: insights from population-based studies. *J Stroke* 2019; 21: 121–138.

4. Sutton A and Campbell F. The ScHARR LMIC filter: adapting a low- and middle-income countries geographic search filter to identify studies on preterm birth prevention and management. *Res Synth Methods* 2022; 13: 447–456.

5. Clancy U, Gilmartin D, Jochems ACC, Knox L, Doublan FN and Wardlaw JM. Neuropsychiatric symptoms associated with cerebral small vessel disease: a systematic review and meta-analysis. *Lancet Psychiatry* 2021; 8: 225–236.

6. Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol* 2013; 66(4): 408–414.

7. Fazekas F, Chawluk JB, Alavi A, Hurtig HI and Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer’s dementia and normal aging. *AJR Am J Roentgenol* 1987; 149: 351–356.

8. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 2001; 32: 1318–1322.

9. Xiong Y, Yang J, Wong A, et al. Operational definitions improve reliability of the age-related white matter changes scale. *Eur J Neurol* 2011; 18: 744–749.

10. Vicchibauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36: 1–48.

11. Balduzzi S, Rücker G and Schwarzer G. How to perform a meta-analysis. *Res Synth Methods* 2022; 13: 447–456.

12. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36: 1–48.

13. Fazekas F, Chawluk JB, Alavi A, Hurtig HI and Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer’s dementia and normal aging. *AJR Am J Roentgenol* 1987; 149: 351–356.

14. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke* 2001; 32: 1318–1322.

15. Xiong Y, Yang J, Wong A, et al. Operational definitions improve reliability of the age-related white matter changes scale. *Eur J Neurol* 2011; 18: 744–749.

16. Vicchibauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36: 1–48.

17. Balduzzi S, Rücker G and Schwarzer G. How to perform a meta-analysis. *Res Synth Methods* 2022; 13: 447–456.

18. Van Veluw SJ, Shih AY, Smith EE, et al. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol* 2017; 16: 730–740.

19. Zhai FF, Ye YC, Chen SY, et al. Arterial stiffness and cerebral amyloid angiopathy and related conditions. *Brain* 2015; 138: 2126–2139.

20. Das AS, Regenhardt RW, Vernooij MW, Blacker D, Charidimou A and Viswanathan A. Asymptomatic cerebral small vessel disease: insights from population-based studies. *J Stroke* 2019; 21: 121–138.

21. Sutton A and Campbell F. The ScHARR LMIC filter: adapting a low- and middle-income countries geographic search filter to identify studies on preterm birth prevention and management. *Res Synth Methods* 2022; 13: 447–456.

22. Liu T, Liu Y, Wang S, et al. Brachial-ankle pulse wave velocity is related to the total cerebral small-vessel disease score in an apparently healthy asymptomatic population. *J Stroke Cerebrovasc Dis* 2020; 29: 105221.

23. Wang N, Allali G, Kesavadas C, et al. Cerebral small vessel disease and motoric cognitive risk syndrome: results from the Kerala-Einstein study. *J Alzheimers Dis* 2016; 50: 699–707.

24. Li P, Wang Y, Jiang Y, et al. Cerebral small vessel disease is associated with gait disturbance among community-dwelling elderly individuals: the Taizhou imaging study. *Aging* 2020; 12: 2814.

25. Del Brutto OH, Mera RM, Del Brutto VJ, Zambrano M, Wright CB and Rundek T. Clinical and neuroimaging risk factors for cognitive decline in community-dwelling older adults living in rural Ecuador. *Int J Geriatr Psychiatry* 2019; 34: 447–452.

26. Han F, Zhai FF, Wang Q, et al. Prevalence and risk factors of cerebral small vessel disease in a Chinese population-based sample. *J Stroke* 2018; 20: 239–246.

27. Chung CP, Chou KH, Chen WT, et al. Cerebral microbleeds are associated with physical frailty: a community-based study. *Neurobiol Aging* 2016; 44: 143–150.

28. Del Brutto OH, Mera RM, Del Brutto VJ, et al. Cerebral small vessel disease score and atherosclerosis burden—a population study in community-dwelling older adults. *Clin Neurol Neurosurg* 2020; 194: 105795.

29. Wang M, Li Y, Cong L, et al. High-density lipoprotein cholesterol and brain aging amongst rural-dwelling older adults: a population-based magnetic resonance imaging study. *Eur J Neurol* 2021; 28: 2882–2892.

30. Cui Y, Zhang H, Zhao Y, et al. Home-measured orthostatic hypotension associated with cerebral small vessel disease in a community-based older population. *Hypertens Res* 2020; 43: 798–807.

31. Zhang J, Han F, Liang X, et al. Lacune and large perivascular space: two kinds of cavities are of different risk factors and stroke risk. *Cerebrovasc Dis* 2020; 49: 522–530.

32. Chou KH, Wang PN, Peng LN, et al. Location-specific association between cerebral microbleeds and arterial pulsatility. *Front Neurol* 2019; 10: 1012.

33. Del Brutto OH, Del Brutto VJ, Mera RM, et al. Prevalence and correlates of intracranial atherosclerotic disease among community-dwelling older adults of Amerindian ancestry. *J Stroke Cerebrovasc Dis* 2020; 29: 105135.

34. Shih CY, Chen CY, Wen CJ, Liu HM and Kuo HK. Relationship between serum uric acid and cerebral white matter lesions in the elderly. *Nutr Metab Cardiovasc Dis* 2012; 22: 154–159.

35. Luo Q, Tang H, Xu X, et al. The prevalence and risk factors of cerebral microbleeds: a community-based study in China. *Ther Clin Risk Manag* 2021; 17: 165–171.

36. Del Brutto OH and Mera RM. Total cerebral small vessel disease score and anthropometric indices: a population-based study in older adults of Amerindian ancestry. *J Alzheimers Dis* 2020; 37: 2814.

37. Hilaal S, Mok V, Youn YC, Wong A, Ikram MK and Chen CL. Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries. *J Neurol Neurosurg Psychiatry* 2017; 88: 669–674.

38. Hao Z, Chen Y, Wright N, et al. Natural history of silent lacunar infarction: 10-year follow-up of a community-based prospective study of 0.5 million Chinese adults. *Lancet Reg Health West Pac* 2021; 17: 100309.
39. Ullah H and Ashfaq S. Age related white matter lesions on magnetic resonance imaging. *J Postgrad Med Inst* 2012; 26: 61–66.
40. Li J, Ogbole G, Aribisala B, et al. Association between white matter hyperintensities and stroke in a West African patient population: evidence from the Stroke Investigative Research and Educational Network study. *Neuroimage* 2020; 215: 116789.
41. Sudre CH, Smith L, David A, et al. Cardiovascular risk factors and white matter hyperintensities: difference in susceptibility in South Asians compared with Europeans. *J Am Heart Assoc* 2018; 7: e010533.
42. Sreedharan SE, Thomas B, Sylaja PN and Sarma SP. Cerebral amyloid angiopathy: a clinicoradiological study from South India. *Neuro India* 2020; 68: 378–382.
43. Kesav P, Menon D, Vysakha KV, et al. Differential distribution of cerebral microbleeds in subtypes of acute ischemic minor stroke and TIA as well as its association with vascular risk factors. *Neuro India* 2020; 68: 1139–1143.
44. Kamal AK, Majed F, Ilyas MS, et al. Distribution, severity and radiologic features of intracranial stenosis in asymptomatic Pakistanis. *Austin J Cerebrovasc Dis Stroke* 2014; 1: 1013.
45. Resende EPF, Costa-Silva L, Carmona KC, et al. Ischemic cerebrovascular burden evaluated by magnetic resonance imaging in an elderly Brazilian community: the Pietà study. *eNeurologicalSci* 2016; 5: 30–34.
46. El Senousy MY, Khalil MK, Bahnacy WS, El-Heneedy YA, Hassamien OA and El-Shafey R. Leukoaraiosis as a predictor of short term outcome of acute ischemic stroke. *Egypt J Neurol Psychiatry Neurosurg* 2013; 50: 339–345.
47. Mejdoubi M, Signate A, Colombani S, Arrigo A and Olindo S. Magnetic resonance imaging characteristics of ischemic stroke in an Afro-Caribbean population: a 1-year prospective MRI study on 534 consecutive patients. *J Neuroradiol* 2017; 44: 31–37.
48. Oyinloye O, Nzech D, Adesiyun O, Ibrahim M, Akande H and Sanya E. Neuroimaging of young adults with stroke in Ilorin Nigeria. *Ann Afr Med* 2015; 14: 82–88.
49. Akhtar N, Salam A, Kamran S, et al. Pre-existing small vessel disease in patients with acute stroke from the Middle East, Southeast Asia, and Philippines. *Transl Stroke Res* 2018; 9: 274–282.
50. Elkhatabi THM, Elsaid AF, Al-Molla RM, Khamis MEM and Fahmi RM. Prevalence and associated risk factors of cerebral microbleeds in Egyptian patients with acute ischemic stroke and atrial fibrillation. *J Stroke Cerebrovasc Dis* 2020; 29: 104703.
51. Potigumjon A, Watcharakorn A and Dhamasaroja PA. Prevalence of cerebral microbleeds in Thai patients with ischemic stroke. *J Neurosci Rural Pract* 2017; 8: 216–220.
52. Hiremath N, Kate M, Mohimen A, Kesavadas C and Sylaja PN. Risk factors of white matter hyperintensities in South Asian patients with transient ischemic attack and minor stroke. *Neuroradiology* 2020.
53. Aloush TK, Fahmy NA, Elaidy DA and Abdel-Baki RS. Site and degree of intracranial arterial stenosis in acute stroke patients with metabolic syndrome among a sample of Egyptian patients. *Egypt J Neurol Psychiatry Neurosurg* 2016; 53: 89.
54. Lam BYK, Yiu B, Ampil E, et al. High burden of cerebral white matter lesion in 9 Asian cities. *Sci Rep* 2021; 11: 1–12.
55. Mok V, Srikanth V, Xiong Y, et al. Race-ethnicity and cerebral small vessel disease—comparison between Chinese and White populations. *Int J Stroke* 2014; 9: 36–42.
56. Karjee H, Ghosh S and Dhibar T. Association of mid-life cerebral small vessel disease with diabetic retinopathy in type 2 diabetes in an Indian population. *J Diabetes Complications* 2022; 36: 108149.
57. Akinyemi RO, Firbank M, Ogbole GI, et al. Medial temporal lobe atrophy, white matter hyperintensities and cognitive impairment among Nigerian African stroke survivors. *BMC Neurol* 2015; 8: 1–10.
58. Dobrynina LA, Shabalina AA, Shamtieva KV, Gnedovskaya EV, Berdal AB and Krotenkova MV. The predictive value of salt sensitivity and osmotic fragility in the development of cerebral small vessel disease. *Int J Mol Sci* 2020; 21: 2036.
59. Akinyemi RO, Ovbiegele B, Adeniyi OA, et al. Stroke in Africa: profile, progress, prospects and priorities. *Nat Rev Neurol* 2021; 17: 634–656.
60. Akinyemi RO, Owalabi MO, Ihara M, et al. Stroke, cerebrovascular diseases and vascular cognitive impairment in Africa. *Brain Res Bull* 2019; 145: 97–108.
61. Spektor E, Fietze I and Poluektov MG. Periodic limb movements syndrome in patients with cerebral small vessel disease: protocol for a prospective observational study. *Front Neurol* 2021; 12: 700151.
62. Jiménez-Sánchez L, Hamilton OKL, Clancy U, et al. Sex differences in cerebral small vessel disease: a systematic review and meta-analysis. *Front Neurol* 2021; 12: 756887.
63. Sliz E, Shin J, Ahmad S, et al. Circulating metabolome and white matter hyperintensities in women and men. *Circulation* 2022; 145: 1040–1052.