Ackah *et al. Behavioral and Brain Functions* (2025) 21:12
https://doi.org/10.1186/s12993-025-00274-1

Behavioral and Brain Functions

REVIEW

Open Access

Imaging-validated correlates and implications of the pathophysiologic mechanisms of ageing-related cerebral large artery and small vessel diseases: a systematic review and meta-analysis

Joseph A. Ackah[1], Xuelong Li[2], Huixing Zeng[1] and Xiangyan Chen[3*]

Abstract

Background Cerebral large artery and small vessel diseases are considered substrates of neurological disorders. We explored how the mechanisms of neurovascular uncoupling, dysfunctional blood–brain-barrier (BBB), compromised glymphatic pathway, and impaired cerebrovascular reactivity (CVR) and autoregulation, identified through diverse neuroimaging techniques, impact cerebral large artery and small vessel diseases.

Methods Studies (1990–2024) that reported on neuroradiological findings on ageing-related cerebral large artery and small vessel diseases were reviewed. Fifty-two studies involving 23,693 participants explored the disease mechanisms, 9 studies (sample size = 3,729) of which compared metrics of cerebrovascular functions (CF) between participants with cerebral large artery and small vessel diseases (target group) and controls with no vascular disease. Measures of CF included CVR, cerebral blood flow (CBF), blood pressure and arterial stiffness.

Results The findings from 9 studies (sample size = 3,729, mean age = 60.2 ± 11.5 years), revealed negative effect sizes of CVR [SMD = − 1.86 (95% CI − 2.80, − 0.92)] and CBF [SMD = − 2.26 (95% CI − 4.16, − 0.35)], respectively indicating a reduction in cerebrovascular functions in the target group compared to their controls. Conversely, there were significant increases in the measures of blood pressure [SMD = 0.32 (95% CI 0.18, 0.46)] and arterial stiffness [SMD = 0.87 (95% CI 0.77, 0.98)], which signified poor cerebrovascular functions in the target group. In the combined model the overall average effect size was negative [SMD = − 0.81 (95% CI − 1.53 to − 0.08), p < 0.001]. Comparatively, this suggests that the negative impacts of CVR and CBF reductions significantly outweighed the effects of blood pressure and arterial stiffness, thereby predominantly shaping the overall model. Against their controls, trends of reduction in CF were observed exclusively among participants with cerebral large artery disease (SMD = − 2.09 [95% CI: − 3.57, − 0.62]), as well as those with small vessel diseases (SMD = − 0.85 [95% CI − 1.34, − 0.36]). We further delineated the underlying mechanisms and discussed their interconnectedness with cognitive impairments.

Conclusion In a vicious cycle, dysfunctional mechanisms in the glymphatic system, neurovascular unit, BBB, autoregulation, and reactivity play distinct roles that contribute to reduced CF and cognitive risk among individuals

*Correspondence:
Xiangyan Chen
fiona.chen@cpce-polyu.edu.hk
Full list of author information is available at the end of the article

with cerebral large artery and/or small vessel diseases. Reduction in CVR and CBF points to reductions in CF, which is associated with increased risk of cognitive impairment among ageing populations ≥ 60 years.

Keywords Ageing, Neuroimaging, Cerebral small vessel disease, Large artery disease, Pathophysiology, Cognitive

Introduction

The brain, a highly complex organ with nearly 100 billion neurones, is the most metabolically active organ in the body, consuming about 20% of the body's oxygen despite constituting only 2% of body weight [1, 2]. This high demand for essential oxygen and nutrients necessitates stable neurovascular coupling, ensuring an uninterrupted vascular system for adequate brain perfusion in addition to an effective glymphatic system for removing the metabolic waste [3, 4]. As the brain ages, cerebrovascular dysfunction becomes increasingly prominent with evidence of neurovascular uncoupling [5]. These ageing-related dysfunctional changes make the brain vasculature even more vulnerable to plaque accumulation, stenosis, stiffening, glymphatic disruption, and other endovascular issues, thereby compromising cerebral perfusion and waste removal [6–9]. Evidence suggests that exploring the mechanisms of neurovascular uncoupling, a dysfunctional blood–brain barrier (BBB), a compromised glymphatic pathway, and impaired cerebrovascular reactivity (CVR) and autoregulation in cerebrovascular dysfunctions may provide insights into ageing-related neurovascular alterations that contribute to cognitive decline [2, 10–13].

The clinical implications of these alterations are shown to range from silent to symptomatic manifestations, contingent on the severity, extent, size, morphology, and location of the underlying pathology [14]. The changes in the cerebral microvasculature present as cerebral small vessel diseases of presumed vascular origin, presenting typical phenotypes such as white matter hyperintensities (WMH), enlarged perivascular spaces (PVS), microbleeds, and lacune infarcts, as detected on neuroimaging [15–17]. Cerebral large artery diseases, on the other hand, present as intracranial atherosclerosis (ICAS) and intracranial arterial calcification (IAC) [18, 19]. Ageing-related cerebral large artery and small vessel diseases are considered strong predictors of neurological disorders, including stroke and cognitive impairment; however, their interconnectedness is complex [20–22]. Previous research has demonstrated a significant link between atherosclerotic diseases of the cerebral large arteries and the overall burden of cerebral small vessel diseases [23, 24]. However, contrasting evidence suggests that any coexisting association might be weak, arising primarily from shared risk factors common to both vascular conditions [25–27]. This dual perspective has spurred additional research, particularly in neuroimaging, to delve into the complex literature and offer a comprehensive understanding of these diverse interpretations. Notably, the advancements in neuroimaging hint that a deeper exploration of underlying mechanisms of cerebrovascular dysfunctions could uncover nuances beyond those explained by traditional risk factors [28–32].

Despite the progress, challenges remained in fully understanding how a dysfunction in one disease mechanism influences the others and whether such fluctuations impact the burdens of cerebral large artery diseases and small vessel diseases or their interconnectedness with cognitive impairment [28–31]. The varied applications of neuroimaging in various investigations with differences in interpretation and the complexity of integrating multimodal data have presented fragmented pieces of evidence [17, 33, 34]. Challenges stem from the limited generalisability of findings, as some studies focus exclusively on stroke patients, who may not represent the broader population affected by cerebral vascular diseases [35–37]. Furthermore, most studies often target specific aspects of cerebral vasculature or rely on particular imaging techniques, potentially overlooking the complex interplay of multiple disease mechanisms [24, 38–42]. Compounding these limitations has constrained our understanding of the comprehensive pathophysiology underlying both cerebral large artery and small vessel diseases [43, 44].

Therefore, this review aimed to explore how the mechanisms of neurovascular uncoupling, a dysfunctional BBB, a compromised glymphatic pathway, and impaired CVR and autoregulation, identified through diverse neuroimaging techniques, impact cerebral large artery and small vessel diseases. We further elucidated how these mechanisms facilitate the interconnectedness between the various cerebral large artery and small vessel diseases and cognitive impairment. The rationale for this endeavour was not merely to aggregate existing data but to apply critical synthesis techniques to explore patterns, relationships, and insights that are only visible through the lens of integrated analysis.

Methods

The review protocol was registered on PROSPERO with ID: CRD42024531238. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [45].

Eligibility criteria

Eligibility was set in accordance with the PICO framework, whose elements include the population, intervention, comparison, and outcomes considered in each study.

P (population): studies that analysed stroke-free participants of any gender or ethnicity, above 18 years of age, with either ageing-related cerebral large or small vessel diseases.

I (intervention): studies employed single or combined neuroimaging examinations such as magnetic resonance imaging (MRI) and MR angiography (MRA) for the evaluation of atherosclerotic large artery diseases and small vessel diseases as well as disease mechanisms; computed tomography (CT) and CT angiography (CTA) to assess vascular integrity and detect calcifications and haemorrhages; transcranial Doppler (TCD) and carotid duplex ultrasound to measure haemodynamic mechanism and lumenography. These modalities were selected for their complementary strengths in assessing cerebral vascular conditions, and this was necessary to capture the multifaceted nature of these conditions, as relying on a single modality may limit our understanding.

C (comparator): studies reported brain patterns, cerebrovascular functions, or haemodynamic mechanisms observed in healthy controls or subjects with no cerebral large artery and small vessel diseases.

O (outcome): neuroimaging correlates of the ageing-related neuroparenchyma changes, neurovascular changes, cerebrovascular haemodynamics, as well as cognitive assessments. Cerebral small vessel diseases encompassed key phenotypes such as WMH, enlarged PVS, microbleeds, and lacune infarcts, whereas cerebral large artery diseases referred to ICAS and IAC.

Inclusion

This study considered only peer-reviewed observational studies published within the period 1990–2024 with various designs and demographics. This year range was considered in recognition of the advancement in neuroimaging and the evolving understanding of ageing mechanisms in the past few decades. Thus, including articles from 1990 onwards ensures that the latest literature is captured. All articles that reported on neuroimaging or neuroradiological findings on ageing-related cerebral large artery and small vessel diseases were deemed eligible for inclusion. Our study evaluated a range of cognitive impairments associated with cerebral large artery and small vessel diseases, focusing on specific domains such as executive function, visuospatial abilities, verbal skills, memory, abstract thinking, attention, and processing speed. We chose not to impose a specific diagnostic framework of vascular dementia to ensure a comprehensive overview of cognitive deficits reported in the literature. This approach allows us to capture the full spectrum of cognitive challenges observed in these conditions. While vascular dementia is indeed a known implication, our intention was to highlight the individual cognitive domains affected without overlooking important articles that might not explicitly categorise findings under vascular dementia. To avoid potential issues such as misinterpretations, omissions, or errors from translating articles [46], only those published in English or with English translations were included in the study.

Exclusion

Primary research articles that did not address the pathophysiological mechanisms of ageing-related cerebral large artery or small vessel diseases, as well as those focusing on neuroimaging findings involved with stroke or those unrelated to ageing, were excluded. The study also excluded research on other neurodegenerative diseases such as Parkinson's syndrome, amyotrophic lateral sclerosis, and Alzheimer's disease. Additionally, studies involving non-human subjects, those reporting on genetic, environmental, and molecular mechanisms, and those with insufficient data integrity were not considered. Secondary studies, preprints, grey literature, conference reports, editorials, duplicate publications, and articles without an English full-text version or lacking peer review were also excluded.

Ethical approval

Although ethical approval is not a requirement for this type of study, we followed ethical reporting standards, as recommended by Kahrass and colleagues [47], to enhance integrity, credibility, or adherence to best practices.

Data sources

Electronic databases, including Web of Science, PubMed, Embase, Scopus, and EBSCOHost (including CNHIL and PsycINFO), were chosen for their extensive access to a wide range of journals, websites, organisational links, and other databases in biomedicine, health, sciences, and engineering. According to Bramer and colleagues [48], this combination ensures an optimal search outcome. Additionally, a manual search on Google Scholar was conducted to identify eligible papers that met the selection criteria, following the recommendation of Haddaway and colleagues [49].

Search strategy

Under the guidance of a certified librarian, researchers developed a robust search strategy incorporating critical features for an effective literature search in each database,

a step deemed essential for authentic research by Grewal et al. [50]. This strategy was adapted for each database, considering their unique sensitivities and search requirements.

The search strategy incorporated keywords such as [*(Ageing or aging); (Pathophysiology or mechanisms or "blood–brain barrier" or "cerebrovascular reactivity" or autoregulation or hypoperfusion or "oligodendrocyte precursor cells" or dysfunction or compromise or impairment or glymphatic or neurovascular coupling or "blood–brain barrier" or "BBB leakage" or "brain changes" or "vascular changes"); (Cerebrovascular or neurovascular or neurologic or cognitive or "brain vessels" or arteries or veins or microvasculature or vascular or haemodynamics or "haemodynamic mechanisms"); ("Cerebral artery diseases" or "large vessel diseases" or "small vessel diseases" or "large vessel diseases" or "white matter hyperintensities" or microbleeds or lacuna or "brain atrophy" or microangiopathy or "intracranial atherosclerosis" or ICAS or "intracranial arterial calcifications" or IAC); (Neuroimaging or magnetic resonance imaging or MRI or MRA or computed tomography or CT or CTA or ultrasound or transcranial ultrasound or TCD or TCCD or carotid doppler or Doppler)*] based on the research purpose.

These keywords were further refined using Boolean operators (AND, OR) and truncation (*) to combine related terms and synonyms, maximising sensitivity to capture relevant articles [51]. Two reviewers (JAA and HD) independently conducted an electronic literature search from April 1st to 15th, 2024, and it was updated on February 2, 2025.

Study selection and data extraction

After the initial data search, results from each source were combined, duplicates were removed, and a comprehensive dual screening was conducted using EndNote, which Stoll et al. suggest improves the precision of study selection [52]. Two reviewers independently screened the titles and abstracts of all retrieved articles according to a pre-established review protocol (PROSPERO with ID: CRD42024531238) validated by expert researchers. A full-text screening of the selected studies was then independently performed by two reviewers (JAA and HZ), with any discrepancies resolved by a third reviewer (XC) in consultation with the team.

Data extraction was carried out on the included papers. Two independent reviewers filled out tabular templates with relevant information, summarised in Tables 1 and 2 for neuroimaging and cognitive outcomes, respectively. Extracted characteristics included references and year of publication, sample size, age, gender, predicting or exposure variable, neuroimaging correlates of outcome variable, cognitive domains, and key findings. The lead investigator convened a consensus meeting to resolve any discrepancies. These methods were adopted to ensure a high level of methodological consistency, as recommended by Charrois [53].

Methodological quality assessment

Using the Newcastle–Ottawa Scale (NOS) for cohort studies, the included articles were rigorously evaluated against three domains (selection, comparability, and outcome) in order to assess their methodological quality.

Data synthesis and analysis

To integrate the results from the included studies, a narrative synthesis was employed to combine the findings from the qualitative and quantitative extracted data. This approach provides a comprehensive overview to bridge the research gap, as it allows for a robust synthesis and analysis of available data [54, 55]. A meta-analysis was performed using the Jamovi and R statistical software to integrate findings from nine studies. The 9/52 studies were selected because they were the only studies that compared the metrics of cerebrovascular functions measured between individuals with cerebral large artery and small vessel disease (target group) and those without any vascular disease (control group). CVR, cerebral blood flow, arterial stiffness, and blood pressure were the quantitative metrics of cerebrovascular functions measured between target and control groups. Since the metrics of cerebrovascular functions were quantified based on different scales and may change in opposing directions with disease progression, the standardised mean difference (SMD) was chosen to assess the outcome effect size in a random effects model. We defined the random-effects model based on the foundational method by DerSimonian and Laird, which accounts for the variability both within and between the studies included [56]. This model assumes that the true effects vary across studies due to differences in study populations, methodologies, and other factors. By using this approach, we could generalise our findings beyond the specific conditions of each study.

Using a two-step approach, we initially evaluated each metric separately then combined the four metrics—CVR, cerebral blood flow, arterial stiffness, and blood pressure—to obtain an overall effect size, as they co-occur in participants. This pooled SMD allows for a comparative evaluation of each metric's relative effect size against the direction and magnitude of the overall or combined effect size in the model. By examining the magnitude, direction, and statistical significance of each metric's SMD, we could identify the predominant metrics. From the statistical model, outcomes for random effects were reported, and the I^2 statistic was reliably reported for heterogeneity assessment, as it is less affected by the number

Table 1 Study Characteristics with neuroimaging outcomes

Ref	First author, year	Sample size & number of males	Age (years)	Predicting/Exposure variable	Imaging Correlate of Outcome variable	Association Type	Key Finding
1 [97]	Akoudad, 2016	50, 23 males	63.95 ± 4.9	CVR	Cerebral microbleed	Null	No significant association found.
2 [100]	Bokkers, 2010	43, 25 males	66.86 ± 6.3 target 69.36 ± 8.0 control	Cerebral territories ipsilateral to stenotic site	Cerebrovascular reactivity	Negative	Increased stenosis in the ipsilateral arterial territories is linked to reduced cerebrovascular reactivity
3 [101]	Conijn, 2012	49, 38 males	58.9	CVR	Microbleeds	Negative	Reduced CVR is linked to the presence of cerebral microbleeds.
4 [102]	Libecap, 2023	50, 19 males	70.0 ± 5.77	CVR	EPVS	Negative	Reduced cerebrovascular reactivity at baseline is linked to the development of ePVS in approximately 2.5 years later.
5 [103]	Sam, 2016	45, 25 males	74 ± 9.4	CVR	White matter diseases	Negative	Reduced CVR precede the progression from NAWM to WMH.
6 [57]	Staszewski, 2021	60, 30 males	72.6 ± 6.9	CVR	WMH/EPVS/Lacunes/microbleeds	Negative	Reduced CVR is linked with the development or progression clinical manifestations of CSVD over a period of 24 months.
7 [58]	Terborg, 2000	59	68.8 ± 9.6 target 66.8 ± 7.6 control	CVR/vasomotor reactivity	cerebral microangiopathy	Negative	Reduced vasomotor reactivity in basal arteries is linked to the presence of cerebral microangiopathy.
8 [59]	Alosco, 2013	52, 22 males	65.7 ± 8.9	Cerebral perfusion	Cortical thickness/atrophy	positive	Reduced total cerebral perfusion is linked to reduced cortical thickness.
9 [60]	Kaczmarz, 2021	59	70.25 ± 5.9	Intracranial endothelial function	Cerebral perfusion -blood flow / CVR	Negative	Increased arterial stenosis with poor cerebral perfusion is linked to decreased cerebrovascular function.
10 [61]	Bahrani, 2017	26, 3 males	77.8 ±6.8	Cerebral blood flow	WMH	Negative	Reduced cerebral blood flow is linked to regions of WMH
11 [62]	Marstrand, 2002	21	85	Cerebral blood flow and reactivity	WMH	Negative	Reduced cerebral blood flow and reactivity were linked to the brain regions with WMH.
12 [63]	Chuang, 2021	721, 320-males	62.6 ± 8.5	Blood flow velocity	WMH/Lacunes/microbleeds	Positive	Increased blood flow velocity is linked to increased overall CSVD burden.
13 [69]	López-Olóriz, 2014	95, 39 males	59.9 ± 3.3	Cerebral blood flow resistance/by Pulsatility index (PI)	White matter integrity	Negative	Increased resistance to cerebral blood flow, assessed by middle cerebral artery PI, is linked to increased disintegration of brain white matter (fornix, corticospinal and anterior thalamic).
14 [65]	Mok, 2012	205, 99 males	70 ± 10	Cerebral blood flow resistance/by Pulsatility index (PI)	White matter lesions	Positive	Increased resistance in middle cerebral artery, assessed by PI, is linked to increased white matter lesions severity.
15 [29]	Huang, 2021	86, 47 males	50-80	Cerebral blood flow-functional connectivity strength coupling (CBF-FCS coupling)	WMH	Negative	Decreased or disrupted CBF-FCS coupling is linked to higher loads of WMH.
16 [66]	Porcu, 2021	75, 58 males	N/S	Neurovascular coupling/by Neural activity	WMH	Negative	Reduced neural activity in several brain areas (in particular the prefrontal cortex, praecuneus and cerebellar crus I/II) is linked to higher WMH burden.
17 [67]	Purkayastha, 2014	48, 26 males	75.0 ± 7.0	Cerebral autoregulation	cerebral white matter structural integrity (WMH and DTI metrics)	Positive	Reduced levels of cerebral autoregulation are linked to reduced or impaired structural integrity of white matter.
18 [68]	Reinhard, 2019	29, 19 males	69.6 ± 10.5 target 68.3 ± 9.9 control	Cerebral autoregulation	microbleeds	Negative	Reduced phase shift in autoregulation is linked to increased total number of cerebral microbleeds.
19 [69]	Bjornfot, 2024	190, 119-males	66–85	Arterial stiffness	WMH/EPVS/Lacunes/microbleeds	Positive	Increased cerebral arterial stiffness, measured by gcPWV, is linked to global CSVD score, and volumes of WMH and PVS.
20 [70]	Ding, 2015	2512, 1042-males	74.6 (66–93)	arterial stiffness	Microbleed	Positive	Increased carotid arterial stiffness is linked to the development of cerebral microbleeds.
21 [7]	Jochemsen, 2015	526, 437M, with 308-follow-up	59 ± 10	Arterial stiffness	Brain atrophy/WMH/ nonlacunar infarcts	Positive	Increased stiffening of the carotid arteries was cross-sectionally linked to more brain atrophy, WMH volume, and nonlacunar infarcts.

Table 1 (continued)

22 [71]	Miyagi, 2023	1,894, 1,117-males	57±13	Arterial stiffness	WMH/EPVS/Lacunes/microbleeds	Positive	Increased arterial stiffness is linked to higher CSVD burden independent of blood pressure status.
23 [72]	Robert, 2022	272, 115-males	75.42 ± 6.77	Arterial stiffness	WMH/Lacunes/microbleeds	Positive	Increased carotid stiffness is linked to higher burdens of WMH and the presence of lacunes.
24 [73]	Salihović Hajdarević, 2016	60, 17 males	63.1±12.7 target 60.0±13.5 control	Arterial stiffness	white matter lesions/ lacunar infarcts	Positive	Increased arterial stiffness is linked to higher burdens of WMH and the presence of lacunes.
25 [74]	Zhai, 2018	953, 357-males	55.7 ± 9.4	Arterial stiffness	WMH/EPVS/Lacunes/microbleeds/atrophy	Positive	Increased arterial stiffness is linked to the imaging markers of CSVD, including PVS in white matter, larger WMH volume, strictly lobar CMBs, and brain atrophy.
26 [75]	Aine, 2014	55, 27 males	18-81	Systolic blood pressure	White matter integrity /Fractional anisotropy (FA)	Negative	Higher levels of systolic blood pressure were associated poor white matter integrity with lower fractional anisotropy (FA) values.
27 [76]	Badji, 2022	280	70.54 ±0.27	Hypertension/Systolic blood pressure	WMH/EPVS/Lacunes/microbleeds	Positive	Higher levels of blood pressure were linked to higher burden of CSVD phenotypes-WMH and EPVS.
28 [77]	Chen, 2009	477, 251-males	62.6 ± 1.45	Hypertension/ Systolic blood pressure	Lacunar infarcts	Positive	Increased systolic and mean arterial pressure are linked to the presence of lacunar infarcts.
29 [78]	Han, 2022	573	70.1 ± 8.4 for asymptomatic	Hypertension	Intracranial atherosclerotic disease	Positive	Increased levels hypertension is linked to higher burdens of intracranial atherosclerotic disease.
30 [79]	Elmståhl, 2019	344, 147-males	77 (70-87)	Hypertension (HT)/ Systolic, diastolic and peripheral pulse pressure (PPP)	Microbleeds	Positive	Increased systolic HT, diastolic HT, and increased PPP are linked with the presence of nonlobar microbleeds, but not with the lobar microbleeds.
31 [80]	Melgarejo, 2023	1458, 700-males	68 ± 5.7	Blood pressure	WMH/EPVS/Lacunes/microbleeds and intracranial arteriosclerosis	Positive	Increased blood pressure is linked to overall burden of CSVD, but this association is also mediated by intracranial arteriosclerosis.
32 [81]	Kerkhofs, 2021	43, 25 males	68 ± 12	Blood brain barrier (BBB) permeability	Perilesional zone of WMH	Positive	Increased parenchymal diffusivity in the perilesional zone of WMH in a 2-year follow-up is linked to increased BBB leakage at baseline.
33 [28]	Li, 2017	102, 48M	69.82± 9.06	Blood brain barrier (BBB) permeability	WMH	Positive	Increased BBB permeability is linked to higher WMH burden.
34 [82]	Li, 2018	99, 49M	70.3 ± 9.1	Blood brain barrier (BBB) permeability	WMH/EPVS/Lacunes/microbleeds	Positive	Increased in Increased BBB permeability, assessed by leakage rate and area under the leakage curve, in the NAWM, WMH, CGM, and DGM were linked to increase in total CSVD burden.
35 [83]	Zhang, 2017	116, 63-males	69.5 ± 11.5	Blood brain barrier (BBB) permeability	WMH	Positive	Increased permeability, assessed by leakage volume of the NAWM, WMH, and CGM is linked larger burden of CSVD.
36 [84]	Kennedy, 2009	77, 28M	56.49 ± 16.80	Parenchymal diffusivity	White matter integrity	Negative	Increased diffusivity is linked to decreased white matter integrity.
37 [85]	Cai, 2022	152, 75 males	63 ± 8	Glymphatic function/ALPS	WMH	Negative	Reduced glymphatic function, indicated by lower ALPS index, is linked to increased periventricular WMH.
38 [86]	Tang, 2022	133, 85 males	65.32	Glymphatic function/ALPS	WMH/EPVS/Lacunes/microbleeds	Negative	Reduced glymphatic function is linked to increased burden of cerebral small vessel diseases.
39 [87]	Brutto, 2020	333, 138-males	71.6 ± 8.4	Atherosclerosis	WMH/EPVS/Lacunes/microbleeds	Positive	Increased levels of atherosclerotic burden are linked to increased overall CSVD burden.
40 [88]	Pico, 2002	640	65.2 ± 2.9	Atherosclerosis	WMH	Positive	Increased levels of carotid atherosclerosis burden are linked to increased WMH 4 years later.
41 [24]	Wang, 2023	3061, 1424-males	61.20 ± 6.7	Intracranial atherosclerosis	WMH/EPVS/Lacunes/microbleeds	Positive	Increased intracranial atherosclerotic burden was linked to higher severity of the lacunes, modified WMH burden, presence of CMBs, and CMB burden.
42 [89]	Vinke, 2021	1489, 715-males	67.9 ± 5.7	Intracranial arteriosclerosis-calcification	WMH/EPVS/Lacunes/microbleeds	Positive	Increased burden of arterial calcifications (arteriosclerosis) in both the internal carotid and basilar arteries are linked to higher overall burden of CSVD over time.
43 [90]	Zhong, 2022	302, 139-males	69.7 ± 8.2	Intracranial arterial stenosis	WMH	Positive	Increased stenosis of the internal carotid artery is linked to higher WMHs progression after 3 years.

Table 1 (continued)

44 [91]	Schmitzer, 2024	58, 32 males	70.2 ± 5.7	Atherosclerotic arterial stenosis	Gray and White matter structural integrity	Negative	Increased stenosis-induced haemodynamic impairment in internal carotid artery is linked to reduced structural integrity of grey and white matter.
45 [92]	Della-Morte, 2018	1229, 492-males	71.0 ± 9.0	Intima-media thickness (IMT) of large arteries	WMH	Positive	Increased IMT is linked to increased volumes of cerebral white matter lesions.
46 [93]	Ekenze, 2023	3604, 1694-males	58 ± 13	Inflammation of large arteries	EPVS	Positive	Increased levels of vascular inflammation are linked to higher burdens of cerebral small vessel disease and perivascular drainage dysfunction, represented by PVS.
47 [94]	Feng, 2023	150, 100-males	63.1±10.5	Arterial stenosis/ Hypoperfusion of large arteries	WMH	Null	No significant association found.
48 [8]	Kalvach, 2007	199, 83-males	20-92	Arterial stenosis of large arteries	Intracranial and extracranial carotid Peak systolic velocity	Positive	Increased Stenotic of the internal carotid arteries are linked increased PSV in the range of 0.7–2.9 m/s.

of studies included in the meta-analysis. Subsequently, we performed subgroup analyses on participants who exclusively had cerebral small vessel diseases and those with cerebral large artery diseases. We focused on metrics with similar directional effects, specifically cerebrovascular reactivity (CVR) and cerebral blood flow in the subgroup analysis. Meta-regression with age, type of cerebral arterial disease, and risk of bias were performed to explore potential sources of heterogeneity. A two-sided P value < 0.05 was considered statistically significant.

Results

Study selection

We retrieved a total of 1165 articles after eliminating 447 duplicates from an initial pool of 1612 records: EBSCOhost (n = 449), Embase (n = 222), Scopus (n = 123), Web of Science (n = 437), and PubMed (n = 381). Subsequently, the screening process, based on titles and abstracts, excluded 1089 articles. After the initial screening, 76 articles remained for full-text assessment to determine their eligibility. Following the full-text screening against the predefined eligibility criteria, 44 articles remained for inclusion. Additionally, a manual search of relevant reference lists identified 8 articles that met the inclusion criteria. Finally, this review included a total of **52** primary studies, with **9** incorporated for meta-analysis, and the entire approach is outlined in accordance with the PRISMA flow chart Fig. 1.

Study characteristics

The included articles comprised 52 observational studies [7, 8, 24, 28, 31, 57–103] published from 2000 to 2024, including cohort-based, cross-sectional, longitudinal, and case–control studies. From a comprehensive dataset of 52 studies involving 23,693 adult participants (average age = 67.4 years), diverse features related to cerebral large artery and small vessel disease, normal cerebrovascular characteristics, as well as cognitive effects were reported. From the 52 included studies, 45 reported complete demographic data on gender, with 47.9% (10377 out of 21,643) participants being males. The distribution of the entire 52 studies by countries is shown in Fig. 2. The results were deduced from neuroimaging investigations that utilised MRI, CT, and ultrasound. Cognitive assessment tools, including the Mini Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and the Montreal Cognitive Assessment (MoCA), were utilised by various investigators to evaluate overall cognitive impairments. Cognitive effects were assessed by capturing the cumulative evaluation of various cognitive domains, including executive function, visuospatial abilities, verbal or language skills, memory, abstract thinking, attention, and processing speed. The Trail Making Test was also commonly used to assess specific aspects of executive function. The results were presented according to qualitative and quantitative outcomes.

Qualitative outcome

We qualitatively examined how various key disease mechanisms, as underlying predictors—neurovascular uncoupling, dysfunctional cerebrovascular reactivity and autoregulation, blood–brain barrier (BBB) leakage, and glymphatic dysfunction—influenced the burden of cerebral large artery diseases and small vessel pathology as well as their consequent cognitive implications. While many of these underlying mechanisms are typically considered as predictive or exposure variables, it is important to note that some investigations have identified impairments in these mechanisms as consequence or outcome variables. For instance, some neuroimaging features such as atherosclerotic stenosis and calcifications have significantly predicted impairment in cerebrovascular functions (Table 1). This bidirectional relationship is further elaborated in the following sections.

Table 2 Study characteristics with cognitive outcomes

Ref	First author, year	Sample size & number of males	Age (years)	Predicting variable	Cognitive function	Association Type	Key Finding
1 [31]	Li, 2017	102, 48M	69.82± 9.06	Blood brain barrier (BBB) permeability	Global cognitive function	Negative	Increased BBB permeability, assessed by leakage rate, is linked to overall decrease in cognitive function.
2 [28]	Huang, 2021	86, 47 males	50-80	Cerebral blood flow-functional connectivity strength coupling (CBF-FCS coupling)	Executive functions	Negative	Decreased or disruptive CBF-FCS coupling is linked to higher risk of cognitive impairment.
3 [64]	Alosco, 2013	52, 22 males	65.7 ± 8.9	Cerebral blood flow/perfusion	Memory/attention/executive functions	Positive	Reduced blood flow linked to poorer cognitive function, particularly on tests of memory and attention/executive function.
4 [69]	López-Olóriz, 2014	95, 39 males	59.9 ± 3.3	Cerebral blood flow resistance/by Pulsatility index (PI)	executive functioning, attention, verbal fluency, memory, visuospatial skills, and psychomotor speed.	Negative	Increased resistance to cerebral blood flow, assessed by middle cerebral artery PI, is linked to lower scores in all cognitive domains, except for visuospatial skills.
5 [71]	Porcu, 2021	75, 58 males	N/S	Neurovascular coupling/by Neural activity	Processing speed, cognitive sequencing, cognitive flexibility and visual-motor skills	Positive	Reduced neural activity is linked to reduced neurocognitive function.
6 [77]	Robert, 2022	272, 115- males	75.42 ± 6.77	Arterial stiffness	Executive functioning, language, memory, visuospatial function, and visuomotor speed.	Negative	Increased carotid stiffness is linked to decreased cognitive functions or leads to cognitive impairment and dementia.
7 [80]	Aine, 2014	55, 27 males	18-81	Systolic blood pressure	Spatial working memory	Negative	Increased systolic blood pressure linked to reduced spatial cognitive functions
8 [81]	Badji, 2022	280	70.54 ±0.27	Hypertension/Systolic blood pressure	Memory/attention/ processing speed/executive function/verbal fluency/and visuospatial abilities	Null	No significant association found
9 [91]	Tang, 2022	133, 85 males	65.32	Glymphatic function/ALPS	Executive function/ attention function/and memory	Positive	Increased ALPS index, which indicates good glymphatic function, is linked to higher measures of global cognitive function, executive function, and attention function.
10 [96]	Schmitzer, 2024	58, 32 males	70.2 ± 5.7	Cerebral small vessel pathology	Global cognitive function	Negative	Increased deterioration of white matter integrity is linked to decreased overall cognitive function.
11 [100]	Jolly, 2016	70, 35 males	66.90 ±9.57	White matter integrity - radial diffusivity (RaD)	Global cognitive function	Negative	Increased radial diffusivity, which depicts a decline in white matter integrity, is linked to reduced global cognitive performance.
12 [101]	Kerkhofs, 2021	51, 30 males	67 ± 12	BBB leakage volume/rate	Memory/executive/ Information processing speed functions	Negative	Increased baseline leakage volume and rate in the normal appearing white matter and cortical grey matter were linked with overall cognitive decline in a 2-year follow-up, but not at baseline.
13 [102]	Li, 2021	321 Target= 236 Control=85	73.5 ± 8.95 target 68.6± 8.62 control	Cerebral small vessel pathologies	Attention/processing speed/ executive function/memory aptitude/language facilities/ visuospatial abilities	Negative	Increased burden of cerebral small vessel diseases is linked to multiple categories of mild cognitive impairment presenting with decreased functions in attention/processing speed/ executive function/memory aptitude/language facilities/ and visuospatial abilities.
14 [103]	Mykola, 2020	97	65-90	Cerebral blood flow resistance/by resistive index (RI) and Pulsatility index (PI)	Global cognitive function	Negative	Increased resistance to cerebral blood flow, assessed by middle cerebral artery PI and RI, were linked to decreased scores in overall cognitive function.

Table 1 summarises the 48 studies [7, 8, 24, 28, 31, 57–99] that explored the intricate relationship between the ageing brain, underlying mechanisms, and their consequential neurovascular and neuro-parenchymal changes. Additionally, Table 2 summarises the 14 studies [28, 29, 59, 64, 66, 72, 75, 76, 86, 91, 95, 96, 98, 99] that meticulously documented the neurological and cognitive challenges accompanying the ageing-related cerebral large artery and small vessel diseases. The cognitive outcomes examined were exclusively associated with the ageing process, excluding other

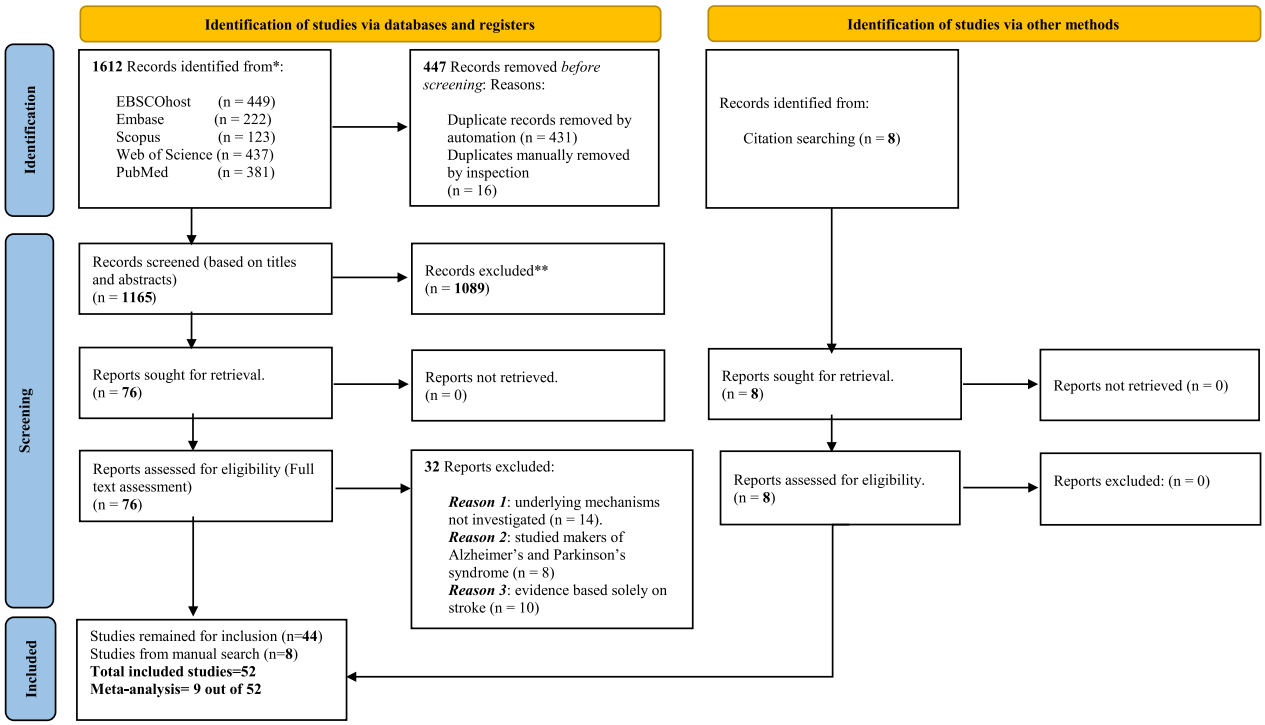

Fig. 1 PRISMA flow diagram for search and study selection

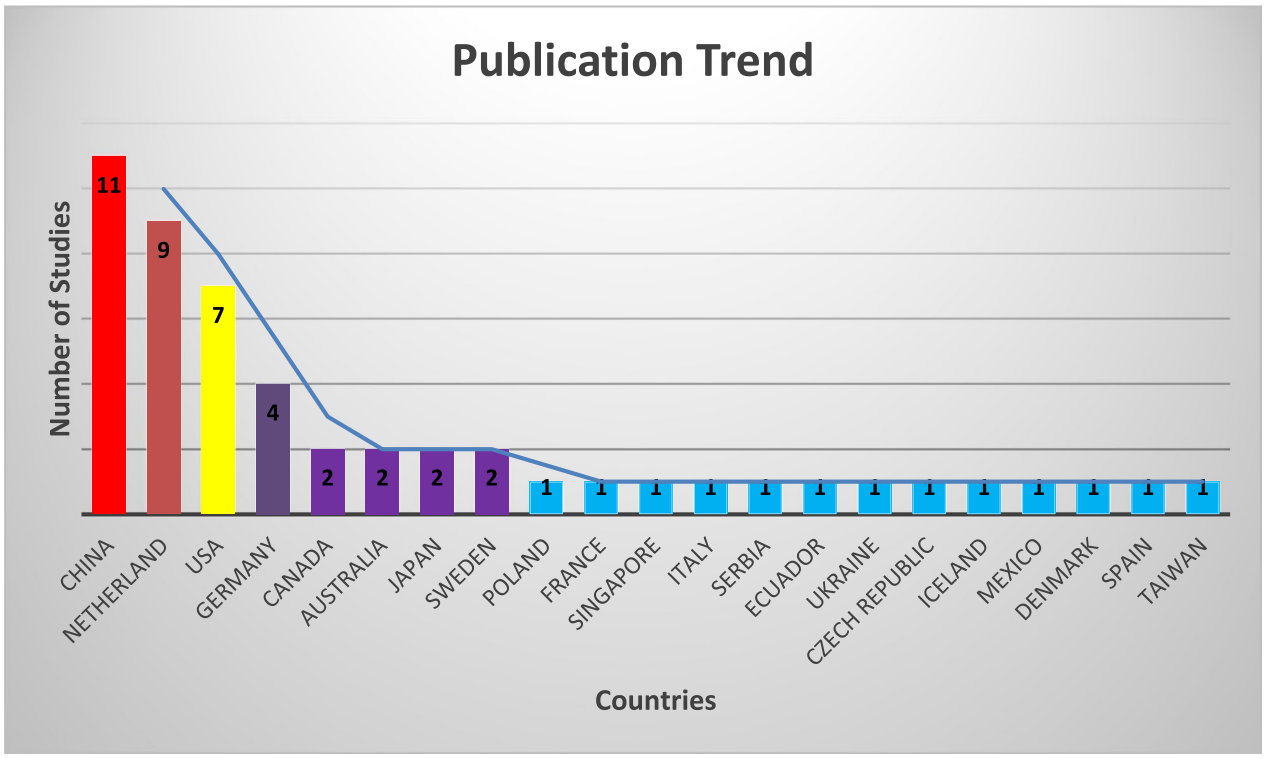

Fig. 2 Distribution of studies by countries. Overall, forest plot. A negative overall SMD indicates a reduction in effect size, while a positive SMD indicates an increase. This figure demonstrates an overall reduction in cerebrovascular function in participants with cerebral large artery and small vessel diseases compared to the control group without vascular disease

neurodegenerative conditions like Parkinson's disease, amyotrophic lateral sclerosis, or Alzheimer's disease.

The role of neurovascular coupling

The neurovascular unit, which is comprised of pericytes, astrocyte end-feet, and neurones surrounding the endothelial cells in the brain capillaries, maintains cerebrovascular health through neurovascular coupling [2, 104]. An effective neurovascular coupling regulates cerebral blood flow by coupling alterations of vascular dilation in response to the metabolic requirements for a given neuronal activity [105, 106]. Huang and colleagues combined resting-state functional magnetic resonance imaging and arterial spin labelling to investigate the dysfunctions in neurovascular coupling among 86 stroke-free individuals with cerebral small vessel diseases. The results showed that higher loads of cerebral small vessel diseases, specifically WMH, were attributed to neurovascular uncoupling with abnormal blood flow and poor functional connectivity strength noted in various regions of the prefrontal cortex, posterior cingulate cortex, thalamus, and parahippocampal gyrus [28]. The findings were corroborated by Porcu and colleagues, who observed similar trends and demonstrated that disruptions or reductions in neural activity within regions affected by white matter hyperintensities contributed to cognitive impairment in a study involving 75 healthy participants [71]. These outcomes could imply that reductions in cerebral neural activity and poor cerebral perfusion related with neurovascular uncoupling, may disrupt the cerebral microenvironment and facilitate neurotoxins due to impaired BBB [106]. The disturbances in cerebral microenvironment have been shown to affect the ability of the neurovascular unit to regulate blood flow responses to neuronal stimulations, which could disrupt the structural and functional integrity of the cerebral microvasculature with consequent cognitive impairment, depending on the region affected [107, 108]. While neurovascular uncoupling is recognised as a critical mechanism in cerebral small vessel disease at the microvascular level, further research is needed to explore its potential connections to cerebral large arterial disease, as current studies have yet to establish this link.

The role of cerebral BBB

Given that the BBB comprises specialised endothelial cells that facilitate the functions of the neurovascular unit in maintaining cerebral homeostasis [104], an impaired BBB may be implicated in cerebral artery and small vessel diseases. With ageing, there is a reduction in capillary density and length, which compromises the efficiency of the blood–brain barrier (BBB) with a dysfunctional haemodynamics and impediment to the transport of essential molecules [63, 86, 88]. Beyond the fact that several studies [32, 86, 87], have associated BBB leakage, as quantified by dynamic contrast-enhanced (DCE-MRI), to higher burdens of cerebral small vessel disease, our critical synthesis revealed that BBB leakage is diffusely distributed beyond the white matter regions [31]. In their study, Kerkhofs and colleagues did not establish a cross-sectional association between cerebral small vessel disease and compromised BBB or leakage; however, a 2-year follow-up showed a decline in cognitive functions [101]. This finding suggested that the detrimental effects of BBB leakage accumulate over time, and its association with poor cognitive function may be time-dependent. However, other perspectives proposed that the neurological implications of BBB leakage might not be solely time-bound but rather influenced by the severity of the leakage rate as well as the specific region of leakage [88, 104, 109]. This view is supported by studies from Porcu and colleagues, which indicate that small vessel lesions in the periventricular region, as opposed to the deep subcortical and juxtacortical areas, may significantly disrupt regional cerebral activity and have the greatest impact on cognitive impairments [71]. Although, cerebral large artery diseases such as intracranial atherosclerosis and arterial calcification have been associated with endothelial dysfunction [5], the pathway by which BBB leakage contributes has not been clearly elucidated and warrants further investigation.

The role of cerebrovascular autoregulation and reactivity

Cerebrovascular autoregulation and reactivity are both implicated in both cerebral large artery and small vessel diseases and not just in small vessel pathology [1, 110, 111]. While cerebrovascular autoregulation maintains constant cerebral blood to ensure cerebral perfusion irrespective of arterial pressure fluctuations [30], CVR ensures the proper adjustment to adequate blood flow in response to metabolic demand [112]. Evidence suggests that the two mechanisms complement each other, and an impairment in one disrupts the cerebral haemodynamic functions of brain perfusion and neuro-parenchymal nourishment. [11, 72, 111, 113]. In a regional assessment of normal-appearing white matter and areas of small vessel lesions in the brain, as studied by Marstrand et al. [67] and Sam et al. [114] it was revealed that a reduction in CVR led to decreased blood flow with decreased fractional anisotropy and increased diffusivity—both indicating impaired brain parenchymal integrity [89, 114]—and in regions with white matter diseases. Similar findings were observed in a longitudinal study by Sam and colleagues, who further revealed that normal-appearing brain regions that reduced CVR at baseline eventually progressed to small vessel disease in a 1-year follow-up

with poor structural integrity [61]. Such disease progression is partially explained by the insufficient haemodynamic function due to impaired autoregulation with poor cerebral perfusion disrupting the fibres of the brain matter with consequent cognitive impairment [64, 72, 73, 115, 116]. Reduced cerebrovascular autoregulation and CVR revealed in individuals with stenotic intracranial large artery diseases [65], is associated with arterial wall stiffness and poor blood flow [58, 117–119]. The study by Robert et al. found that arterial stiffening was linked to poorer cognitive functions, but these associations weakened after adjusting for cerebral small-vessel disease markers, highlighting the importance of addressing small-vessel disease in cognitive decline [77].

The role of the glymphatic system

The glymphatic pathway, which is responsible for cerebral fluid or waste clearance, is shown to be disrupted in ageing [4]. Through diverse pathways, different studies have associated impaired glymphatic system to cerebral large and small vessel diseases [33, 90, 98]. The evidence shows that different mechanisms may be implicated for glymphatic dysfunction depending on the underlying vascular disease. From the studies by Cai and colleagues [90], it can be inferred that small vessel lesions along the periventricular regions were predominantly attributed to venous impairment due to a dysfunctional glymphatic pathway. On the other hand, small vessel lesions along the deep subcortical regions are attributed to the cascades of ischaemia-hypoperfusion as well as glymphatic system impairment. A dysfunctional glymphatic pathway brings about the accumulation of waste cerebral metabolites and neurotoxins, which disrupts the cerebral microenvironment [4]. A dysfunctional cerebral waste drainage or clearance may promote neuroinflammation, endothelial dysfunction, and consequently atherosclerotic processes, affecting both the microvasculature as well as the basal cerebral arteries [3, 98]. Endothelial disruptions caused by glymphatic impairment, along with inflammatory changes, may initiate the atherosclerotic process in cerebral basal arteries, highlighting the role of glymphatic impairment in cerebral large artery diseases [120]. In a diffusion tensor imaging (DTI) analysis along the perivascular space, glymphatic dysfunction was shown to be associated with overall cognitive function, executive function, attention function, and memory, independent of the underlying phenotypes of small vessel diseases such as microbleeds, lacunes, WMH, enlarged PVS, and traditional vascular risk factors [91]. This has been partly explained by the neuro-axonal destruction in addition to the disruption of vascular integrity leading to stiffness and reduced vasomotor reactivity with consequent cognitive impairments [112, 121].

Quantitative outcome

A meta-analysis compared differences in effect size of cerebrovascular function metrics—CVR, blood flow, arterial stiffness, and blood pressure—between stroke-free individuals with cerebral large artery and small vessel disease and those without these conditions. Nine studies (3,729 participants, mean age = 60.2 ± 11.5 years) were included, revealing significant differences in these parameters, with estimates indicating poor cerebrovascular function in the target group compared to controls. From the individual random-effects model (Fig. 3), the analysis revealed negative effect sizes of CVR [SMD = − 1.86 (95% CI − 2.80, − 0.92)] and cerebral blood flow [SMD = − 2.26 (95% CI − 4.16, − 0.35)], respectively indicating a reduction in cerebrovascular functions in individuals with cerebral large artery and small vessel diseases compared to their control group with no vascular disease. Conversely, there were significant increases in the measures of blood pressure [SMD = 0.32 (95% CI 0.18, 0.46)] and arterial stiffness [SMD = 0.87 (95% CI 0.77, 0.98)], which signified poor cerebrovascular functions in the target group.

In the combined model (Fig. 4), the overall average effect size was negative [SMD − 0.81 (95% CI − 1.53 to − 0.08), $p < 0.001$]. Comparatively, this suggests that the negative impacts of CVR and cerebral blood flow reductions significantly outweighed the effects of blood pressure and arterial stiffness, thereby predominantly shaping the overall model.

(See figure on next page.)

Fig. 3 Forest plot assessing each metric of cerebrovascular function. From (**a**) and (**b**), the negative effect sizes of CVR [MSD = − 1.86 (95% CI − 2.80, − 0.92)] and cerebral blood flow [SMD = − 2.26 (95% CI − 4.16, − 0.35)], respectively, indicate a reduction in cerebrovascular functions in individuals with cerebral large artery and small vessel diseases compared to their control group with no vascular disease. Conversely, (**c**) and (**d**) respectively show positive effect sizes of blood pressure [MSD = 0.32 (95% CI 0.18, 0.46)] and arterial stiffness [MSD = 0.87 (95% CI 0.77, 0.98)] indicating an increase in these metrics, which signify poor cerebrovascular functions. Forest plot for subgroup analysis. CVR metrics significantly reduced in individuals with with cerebral large artery and small vessel diseases compared to the control group without vascular disease. Whiles, blood pressure and flow were elevated but this increase was insignificantly observed between the two groups. There were significant declines in cerebrovascular functions specifically noted in individuals with cerebral large artery disease (SMD= − 2.09 [95% CI − 3.57, − 0.62]

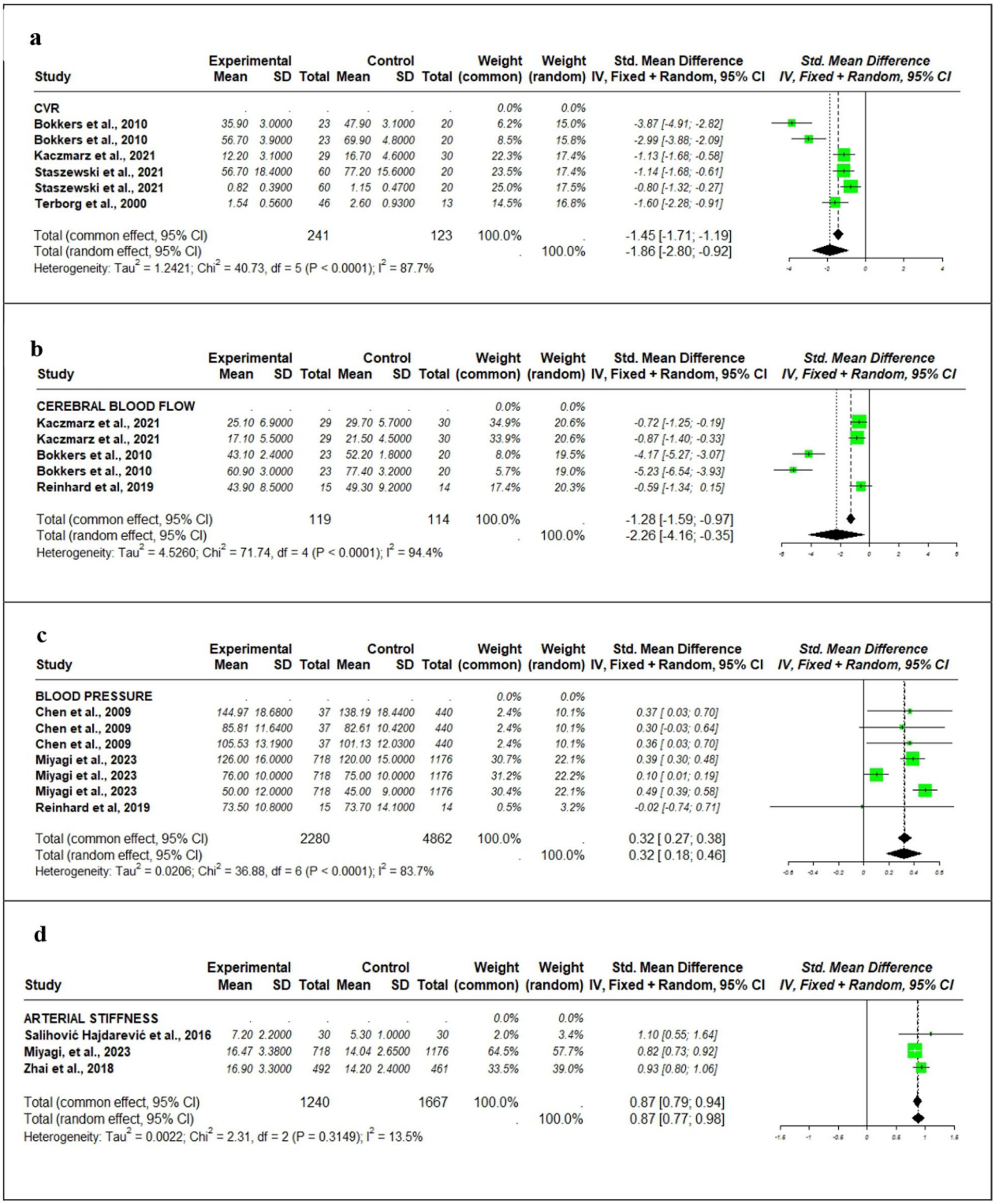

Fig. 3 (See legend on previous page.)

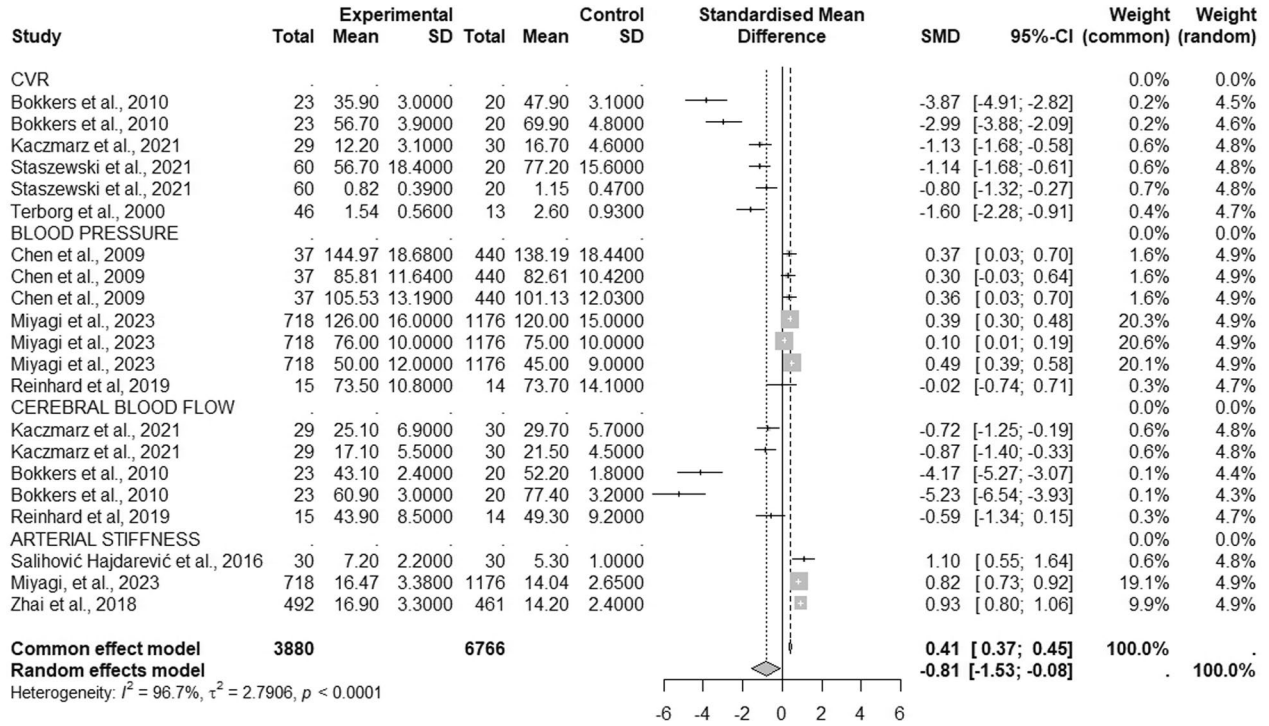

Fig. 4 Forest plot for combined metrics of cerebrovascular functions. The forest plot shows measures of CVR and cerebral blood flow were reduced in the target group compared to their control. Conversely, blood pressure and arterial stiffness were increased in the target group compared to their control group. There is indication that the negative effects of CVR and cerebral blood flow predominantly influenced the overall negative effect size of the random effects model in the combined measures of CVR, blood pressure, cerebral blood flow, and arterial stiffness

Heterogeneity assessment

The substantial heterogeneity among study outcomes may be largely associated with the impact of the different metrics of cerebrovascular function—such as CVR ($I^2 = 87.7\%$), cerebral blood flow ($I^2 = 94.4\%$), arterial stiffness ($I^2 = 13.5\%$), and blood pressure ($I^2 = 83.7\%$)—which capture distinct aspects of cerebrovascular functions, with varying impacts on disease burden. Meta-regression analysis revealed that age, sample size, and risk of bias scores do not account for the variability in findings. Meanwhile, the type of vascular disease (cerebral large artery disease or small vessel disease) significantly contributed to the variability (model coefficient, $F = 7.16$, $p = 0.017$). Figure 5 presents a subgroup analysis demonstrating that cerebrovascular functions, specifically CVR and cerebral blood flow, are significantly diminished in individuals who exclusively had cerebral large artery disease (SMD = − 2.09, 95% CI − 3.57 to − 0.62) and those with small vessel disease (SMD = − 0.85, 95% CI − 1.34 to − 0.36) compared to their respective controls. Due to the limited number of studies (n = 9), we did not further stratify the analysis by sample size.

Overall quality assessment outcome and risk of bias In strict compliance with the Newcastle–Ottawa Scale (NOS) guidelines for evaluating cohort studies, an excellent 100% risk-of-bias assessment outcome was attained among the analysed studies (supplementary table), demonstrating exceptional rigour and the high quality of the evidence presented in this study. These studies meticulously met all the criteria across the three critical domains of the NOS: selection, comparability, and outcome. Moreover, given the small number of studies included (n < 10), a publication bias assessment was not performed. This decision aligns with the Cochrane meta-analysis guidelines, which advise that publication bias outcomes from such a limited dataset are likely to be skewed and non-representative [122].

Discussions

From our qualitative synthesis, the impact of neurovascular uncoupling, impaired cerebrovascular reactivity and autoregulation, glymphatic impairment, and blood–brain barrier leakage is diverse and may not be specific to particular cerebral artery diseases; however, they collectively underscore the complex interplay of cerebrovascular dysfunction contributing to cognitive decline in ageing populations [9, 28, 71, 81, 102, 103, 116]. Cerebrovascular dysfunctions predominantly influence the severity or higher burdens of the cerebral

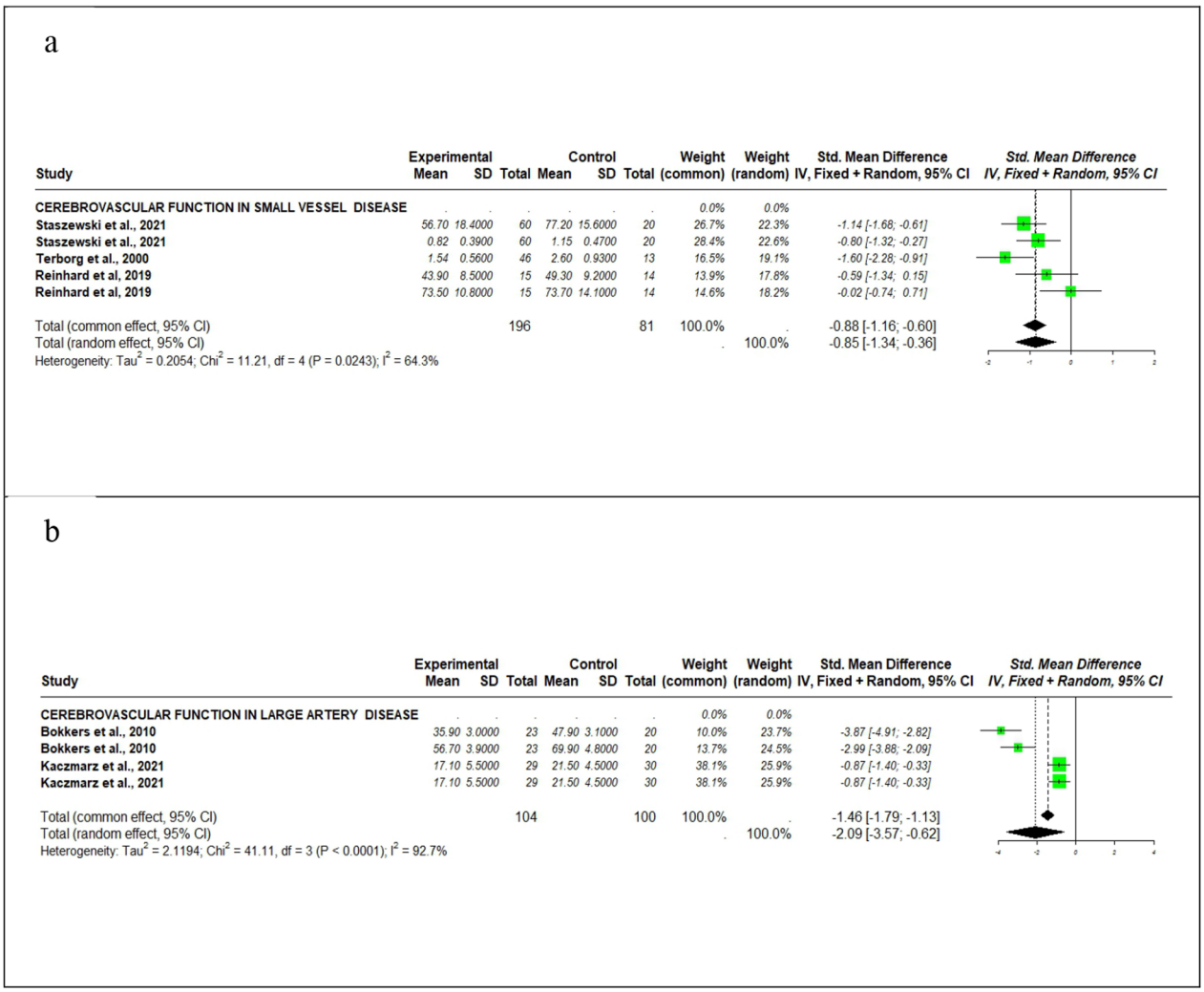

Fig. 5 Subgroup analysis according disease subtype. Using the measures of cerebral blood flow and CVR as the measures of cerebrovascular function in subgroup analyses: (**a**) Shows an overall negative effect size [SMD = – 0.85 (95% CI – 1.34, – 0.36)], which signifies a reduction in cerebrovascular functions in participants presenting exclusively with small vessel diseases. (**b**) Shows an overall negative effect size [SMD = – 2.09 (95% CI – 3.57, – 0.62)], which signifies a reduction in cerebrovascular functions in participants presenting exclusively with large arterial diseases. Schematic model for cerebral large artery and small vessel diseases. A simple diagram that could serve as a guide to explore the interconnectedness of underlying mechanisms implicated in cerebral large artery and small vessel diseases

large artery and small vessel diseases, although a bidirectional relationship may exist. In a meta-analysis, individuals with cerebral large artery and/or small vessel diseases were shown to exhibit significantly reduced or impaired cerebrovascular function compared to healthy controls. The meta-regression results suggest that for stroke-free individuals in their 60 s, the status of their cerebrovascular functions is significantly influenced by whether they have cerebral artery or small vessel diseases or they do not. The significant effects of CVR, cerebral blood flow, blood pressure, and arterial stiffness hint at the reliability that these parameters could serve as indicators of cerebrovascular health in a stroke-free population. Our model further suggested that the negative impact of cerebrovascular reactivity and cerebral blood flow reductions may outweigh other metrics such as arterial stiffness and blood pressure. This suggests that reductions in CVR and cerebral blood flow are more linked to decreased cerebrovascular functions. Given that reduction in cerebrovascular functions is previously associated with reduced cognitive functions [64, 112], our findings suggest that reductions in CVR and cerebral blood flow in individuals in their 60 s may indicate risks of cognitive impairment.

Neurovascular and neuroparenchyma changes

It is speculated that with advanced ageing, neurovascular uncoupling and BBB leakage compromise the cerebral microvascular circulation, but their association with the burdens of cerebral large artery diseases is not well-interrogated [28, 106]. Previous studies have speculated that ageing-related changes in arterial wall calibre, haemodynamic functions, and endothelial integrity may initiate the formation of new vasa vasorum in both the anterior and posterior intracranial arterial walls, increasing their vulnerability to plaque development and hypoxic-ischaemic events [6, 8, 123]. This association is still debatable, and elucidating the exact mechanism linking the presence of vasa vasorum to intracranial large arterial plaque formations may provide insights into the pathogenesis of cerebral large artery diseases and probably how the microvasculature impacts this process.

In actual cases of intracranial atherosclerotic stenosis or occlusion, the circle of Willis, through its communicating arteries, often serves as a compensatory network; however, its efficacy may be diminished by age-related increased vascular stiffness and loss of arterial compliance [39, 124]. Such ageing-related alterations—implicated in dysfunctional cerebrovascular reactivity and autoregulation—could aggravate cerebral hypoperfusion and subsequent ischaemic events [8, 9, 58, 67, 72]. The prominent regions showing parenchyma alterations include the prefrontal cortex and posterior cingulate cortex for lacune infarcts and microbleeds; periventricular and deep subcortical regions for white matter hyperintensities and lacune infarcts; basal ganglia and centrum semiovale for enlarged perivascular spaces; thalamus for lacune infarcts, as well as diffuse and focal alterations in the parahippocampal gyrus, brainstem, and brain matter tracts such as the corpus callosum [28, 31, 81, 86, 87, 89, 125].

From our synthesis, we could infer that the neuroparenchyma deterioration may be intricately linked to the vascular changes of both large and microvasculature, as they both impact blood flow and nutrient delivery, which, when disrupted, may exacerbate neuronal vulnerability and precipitate the pathogenesis of neurological disorders [126]. Over the years, a consensus, based on MRI investigations, has emerged among various researchers [61, 65, 80, 86, 96, 114], who have consistently reported similar findings of an age-related increase in neuroparenchyma diffusivity and a decline in anisotropy, indicating a reduction or loss of brain parenchymal integrity. What is also uncertain is whether ageing-related haemodynamic dysfunctions in non-occluded extracranial arteries (carotid or vertebral) could significantly influence those of the intracranial major vasculature as well as the microvasculature.

The interrelatedness of mechanisms

The interrelatedness of mechanisms describes how neurovascular uncoupling, BBB leakage, CVR, cerebral autoregulation, and glymphatic impairment are interconnected in contributing to the pathogenesis of both cerebral large artery diseases and cerebral small vessel diseases. Neurovascular uncoupling disrupts the coordinated response between neuronal activity and blood flow, leading to inadequate cerebral perfusion [2, 28, 127]. This, combined with impaired CVR and cerebral autoregulation, leaves this condition unresolved, which may exacerbate the ischaemic damage presenting as lacune infarcts and WMH [30, 59, 72, 73, 89, 103]. BBB leakage allows neurotoxic substances to enter the brain, and glymphatic impairment further hinders the clearance of these substances, contributing to neuroinflammation and vascular damage presenting as enlarged PVS and microbleeds [3, 31, 32, 86, 88]. Persistent inflammatory changes are potent factors for the endothelial alterations that may initiate atherosclerosis and calcification in various vascular beds, including the intracranial arteries [120, 128]. Together, these processes create a vicious cycle that accelerates the progression of both large and small vessel pathologies [9, 62]. Given this cycle, it can be inferred that a disruption in one of these key mechanisms directly or indirectly impacts the other, leading to cerebrovascular dysfunction. We also posit that the association between cerebral large artery disease and small vessel diseases may be bi-directional, such that changes in the microvasculature could disrupt the integrity of large arteries and vice versa. Notably, elevated blood pressure is a recognised moderator that contributes to the pathogenesis of cerebral large artery disease by promoting endothelial dysfunction, arterial stiffness, and atherosclerosis, while in small vessel disease, elevated blood pressure may facilitate arteriolosclerosis, microvascular damage, and impaired autoregulation, exacerbating ischaemic and haemorrhagic lesions [59, 93, 129–131]. Badji and colleagues contend that even with medication, uncontrolled high blood pressure significantly compromises cerebral perfusion and waste clearance [81], which in turn could accelerate cognitive decline as part of the advanced ageing process [66].

Figure 6 summarises the results, depicting the underlying mechanisms of cerebral small vessel disease or/and cerebral large artery diseases and their interrelatedness with cognitive impairment.

The imaging assessment of mechanisms

The neuroimaging assessments of the ageing-related pathophysiological mechanisms underlying cerebral large artery and small vessel diseases present varied and

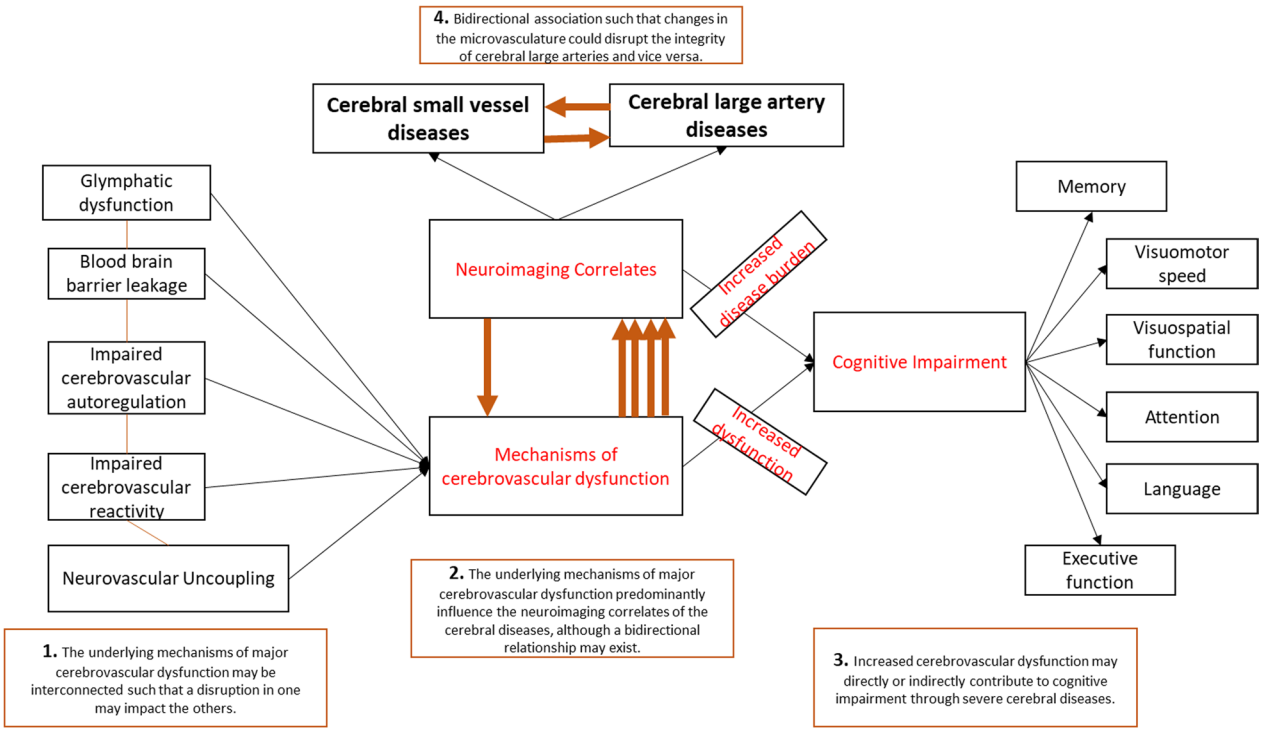

Fig. 6 Schematic diagram of study results

unique advantages in the neurological examinations (Table 3).

Clinical implications

Utilising multimodal imaging to non-invasively explore assessment metrics, as summarised in Table 3, can enhance the precision of diagnostics, preventative strategies, and disease-specific interventions. Blood oxygen level-dependent (BOLD) MRI signals are used to reflect functional connectivity in blood flow and oxygenation, where discrepancies between neuronal activity and BOLD signals can indicate neurovascular uncoupling. Arterial spin labelling (ASL) MRI can quantify changes in cerebral blood flow in response to metabolic demands, such as variations in arterial partial pressure of carbon dioxide, which is critical for assessing CVR. Transcranial ultrasound complements ASL-MRI by providing real-time data on cerebral blood flow velocity, aiding in the evaluation of autoregulation through continuous monitoring of blood pressure changes. Additionally, dynamic contrast-enhanced MRI is commonly used to evaluate BBB permeability by measuring leakage volume or rate. Diffusion tensor imaging (DTI) assesses diffusivity and the along perivascular space (ALPS) index, reflecting glymphatic function.

These metrics are essential for assessing the underlying mechanisms of cerebral large artery and small vessel diseases, enhancing our understanding of disease progression and the impact on cerebrovascular function, ultimately aiding in the maintenance of cognitive health in the elderly. We further recommend the clinical evaluation of CVR, which is an easily assessed cerebrovascular functional parameter, to be utilised to assess the vascular risk of cognitive impairment among the elderly. For this purpose, transcranial ultrasound, which is widely available, relatively cheaper, and non-ionising, has proven very effective and reliable in accessing the cerebral blood flow and global CVR of individuals [115, 132–134].

Limitations

This study acknowledges some limitations related to the study methodology and outcomes. The meta-analysis included only 9 studies with four different metrics measuring major mechanisms of cerebrovascular functions. This diversity in metrics introduced substantial heterogeneity, which may affect the generalisability of the findings. However, this approach enabled us to capture a comprehensive understanding of how different metrics influenced cerebrovascular function, revealing that the observed reductions in CVR and cerebral blood flow and increases in blood pressure and arterial stiffness are

Table 3 Imaging assessments of mechanisms

Mechanism	Structures under interrogation	Modality and assessment parameters
Cerebral blood flow	Cerebral artery: MCA	2 MHz TCD: flow dynamics Nasal canula: monitor the end-tidal pressure of carbon dioxide After 5 min. of stable phase the mean middle cerebral blood flow velocity (MCAVmean) is obtained Cerebrovascular conductance index (CVC) = MCAVmean divided by mean arterial blood pressure [6].
	Cerebral cortex	Cerebral perfusion is evaluated using Arterial Spin Labelling (ASL) MRI. This is followed by cortical segmentation to determine the boundaries of white and grey matter by thresholding tissue probability maps. The Desikan–Killiany is also used to calculate the mean ASL perfusion for each cerebral lobe, as well as the morphometrics of the T1 segmented volumes of grey, white, cerebrospinal fluid, and nonbrain tissues using the FreeSurfer software package [28, 64].
	Carotid arteries and MCA	Ultrasound for measuring blood flow velocity, Pulsatility index and Resistive index [103]
Arterial stiffness	Medium to small cerebral arteries	4D flow MRI is used for measuring global cerebral arterial pulse wave velocity which a novel MRI-based marker for cerebral stiffness [74].
	Peripheral arteries via extracranial carotid and femoral arteries concurrently	Tonometry sensors: Carotid-femoral pulse wave velocity for arterial stiffness calculated via semi-automated systems [6].
	Carotid arteries	Ultrasound with a Wall Track System with vessel wall moving detector Stiffness is assessed based on the distensibility of the carotid vessels. The distension of a vessel is defined as the change in diameter in systole divided by diastolic diameter during one cardiac cycle. Using semi- automated systems, the following measurement of stiffness could be obtained: distensibility coefficient (DC), stiffness index, compliance coefficient (CC), Peterson's modulus, B stiffness, and Young's elastic modulus [77].
Microvascular endothelial function	Peripheral arteries via the index finger	Finger plethysmography using pulse amplitude tonometry RHI = ratio of the average amplitude after and before occlusion in both the right and left fingers, as well as at the baseline level RHI is automatically calculated by software [6].
Cerebrovascular reactivity (CVR)	Occipital lobes of the brain	CVR to visual stimuli is assessed using BOLD-weighted echo-planar imaging with visual stimuli displayed on a screen inside the MRI scanner, which the participant views using a mirror mounted on the head coil [57]. The same metric of CVR could be acquired on BOLD-MRI following CO_2 inhalation [9, 61, 114].
	Brain-feeding arteries	CVR to vasodilatory stimulus using ASL-MRI is defined as the percentage of rise in blood flow following the intravenous administration of acetazolamide [58]. The same metric of CVR could be acquired on ASL following CO_2 inhalation [60, 118].
		CVR to vasodilatory stimulus via breath-holding on BOLD-fMRI [59, 65]
	Intracranial artery: MCA	Transcranial doppler ultrasound measures CVR to Breath-holding, [116] and CO_2 inhalation [62, 119, 135].
	Intracranial artery: MCA	Near-infrared spectroscopy (NIRS) could measure CO_2 -induced vasoreactivity changes [63].
Cerebral autoregulation	Brain tissues (grey matter supplied by internal carotid arteries (ICAs) and the basilar artery	Autoregulation is assessed using MRI with ASL quantified for pre-and-15 min-post administration of acetazolamide intravenously [58].

Table 3 (continued)

Mechanism	Structures under interrogation	Modality and assessment parameters
Diffusivity and glymphatic function	The periarterial spaces of the neuroparenchyma	Diffusion tensor imaging (DTI) is used to measure the along perivascular space index (ALPS index) to reflect glymphatic function [90, 91]. DTI also assesses the fractional anisotropy, apparent diffusion coefficient maps (for mean diffusivity and radial diffusivity) to evaluate the integrity of the neuroparenchyma [69, 72, 89, 96].
Blood brain barrier (BBB) leakage	The neurovasculature, and neuroparenchyma	Dynamic contrast-enhanced (DCE) MRI is used to quantify BBB permeability (leakage volume and rate) [31, 86, 88].
Neurovascular uncoupling	The nerves and neurovasculature	Resting state functional MR measures blood oxygen level-dependent (BOLD) signals, which reflect changes in blood flow and oxygenation. Arterial spin labelling MRI for examining brain functional connectivity, neural activity and blood flow dynamics [28, 71].
Cerebral autoregulation	Cerebral basal arteries including the middle cerebral artery (MCA) and posterior cerebral artery (PCA)	Cerebral blood flow velocity (CBFV) was recorded in MCA and PCA with 2 MHz transducers attached to a head band. Continuous arterial blood pressure (ABP) and heart rate recording are done with a finger plethysmograph. Dynamic cerebral autoregulation is determined using transfer function analysis of slow 0.1 Hz oscillations of ABP and CBFV induced by regular breathing at 6/minute over 180 s [73].

consistent across various assessment methods. Additionally, the limited number of studies constrained our ability to conduct more detailed subgroup analyses or assess publication bias reliably and hence more studies are needed in this domain. Nevertheless, the meta-analysis comprised exclusively high-quality studies, all free from significant risk of bias, with a cumulative sample size of 3,729 participants. This substantial sample size provides significant statistical power and enhances the reliability of the findings. Including studies of high methodological quality reflects the reliability of our findings. Again, the study excluded other neurodegenerative conditions like Parkinson's disease, amyotrophic lateral sclerosis, or Alzheimer's disease, reducing the generalisability of the results to a broader context of neurodegenerative diseases.

Conclusion

In a vicious cycle, the mechanisms of neurovascular uncoupling, BBB leakage, dysfunctional CVR and autoregulation, as well as glymphatic impairment, accelerate the progression of both large and small vessel pathologies. The association between cerebral large artery disease and small vessel diseases may be bi-directional, such that changes in the microvasculature could disrupt the large arteries and vice versa. Individuals with cerebral large artery and/or small vessel diseases exhibit significantly reduced cerebrovascular function compared to healthy controls. The negative impact of cerebrovascular reactivity and cerebral blood flow reductions may outweigh other metrics such as arterial stiffness and blood pressure. This suggests that reductions in CVR and cerebral blood flow are more linked to decreased cerebrovascular functions. Given that reduction in cerebrovascular functions is previously associated with reduced cognitive functions, our findings suggest that reductions in CVR and cerebral blood flow in individuals in their 60 s may indicate higher risks of cognitive impairment. This study confirms that the application of multimodal neuroimaging offers comprehensive insights that facilitate precise evaluation of cerebrovascular pathologies, enhancing our understanding of disease patterns and elucidating how various pathophysiological mechanisms influence cognitive impairment in stroke-free populations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12993-025-00274-1.

Additional file 1.

Acknowledgements
We extend our gratitude to the resource persons at the library unit of The Hong Kong Polytechnic University for their support in providing facilities and resources, which were instrumental in developing an effective search strategy and review protocol.

Author contributions
JA A and XC were responsible for conceptualizing the research idea and study design. JAA, XL, HZ and XC performed study selection, quality assessment, data extraction, analysis, and synthesis. JAA handled manuscript drafting and revision. XC resolved all methodological disparities and inconsistencies, and (JAA, XL and XC) further validated the scientific accuracy in literature. All authors approved this submission and take full responsibility of the content.

Funding
This work was funded by the start-up fund in Department of Health Technology and Informatics, and the seed fund from Research Institute for Smart Ageing (RISA), the Hong Kong Polytechnic University, Hong Kong.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Health Technology and Informatics, The Hong Kong Polytechnic University, Hong Kong SAR, China. [2]Department of Neurology, The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou, China. [3]Division of Science, Engineering, and Health Studies, College of Professional and Continuing Education, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China.

Received: 27 November 2024 Accepted: 21 March 2025
Published online: 22 April 2025

References

1. Li H, Cao W, Zhang X, et al. BOLD-fMRI reveals the association between renal oxygenation and functional connectivity in the aging brain. Neuroimage. 2018;2019(186):510–7. https://doi.org/10.1016/j.neuroimage.2018.11.030.
2. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron. 2017;96(1):17–42. https://doi.org/10.1016/j.neuron.2017.07.030.
3. Rodriguez Lara F, Toro AR, Pinheiro A, et al. Relation of MRI-visible perivascular spaces and other MRI markers of cerebral small vessel disease. Brain Sci. 2023;13(9):1–22. https://doi.org/10.3390/brainsci13091323.
4. Tian Y, Zhao M, Chen Y, Yang M, Wang Y. The underlying role of the glymphatic system and meningeal lymphatic vessels in cerebral small vessel disease. Biomol. 2022;12(6):748. https://doi.org/10.3390/BIOM12060748.
5. Xu X, Wang B, Ren C, et al. Age-related impairment of vascular structure and functions. Aging Dis. 2017;8(5):590–610. https://doi.org/10.14336/AD.2017.0430.
6. Akazawa N, Kumagai H, Yoshikawa T, Myoenzono K, Tanahashi K, Maeda S. Cerebral blood flow velocity is associated with endothelial function in men. J Mens health. 2021;17(3):41–6. https://doi.org/10.31083/jomh.2021.049.
7. Jochemsen HM, Muller M, Bots ML, et al. Arterial stiffness and progression of structural brain changes: the SMART-MR study. Neurology. 2015;84(5):448–55. https://doi.org/10.1212/WNL.0000000000001201.
8. Kalvach P, Gregová D, Škoda O, et al. Cerebral blood supply with aging: normal, stenotic and recanalized. J Neurol Sci. 2007;257(1–2):143–8. https://doi.org/10.1016/j.jns.2007.01.056.
9. Miller KB, Howery AJ, Rivera-Rivera LA, et al. Age-related reductions in cerebrovascular reactivity using 4D flow MRI. Front Aging Neurosci. 2019;11(October):1–11. https://doi.org/10.3389/fnagi.2019.00281.

10. Staszewski J, Skrobowska E, Piusińska-Macoch R, Brodacki B, Stępień A. Cerebral and extracerebral vasoreactivity in patients with different clinical manifestations of cerebral small-vessel disease: data from the significance of hemodynamic and hemostatic factors in the course of different manifestations of cerebral small-ves. J Ultrasound Med. 2019;38(4):975–87. https://doi.org/10.1002/jum.14782.
11. Rudziński W, Swiat M, Tomaszewski M, Krejza J. Cerebral hemodynamics and investigations of cerebral blood flow regulation. Nucl Med Rev. 2007;10(1):29–42.
12. Iulita MF, de la Colina Noriega A, Girouard H. Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? J Neurochem. 2018;144(5):527–48. https://doi.org/10.1111/jnc.14235.
13. Sleight E, Stringer MS, Clancy U, et al. Cerebrovascular reactivity in patients with small vessel disease: a cross-sectional study. Stroke. 2023;54(11):2776–84. https://doi.org/10.1161/STROKEAHA.123.042656.
14. Wu X, Ya J, Zhou D, Ding Y, Ji X, Meng R. Pathogeneses and imaging features of cerebral white matter lesions of vascular origins. Aging Dis. 2021;12(8):2031–51. https://doi.org/10.14336/AD.2021.0414.
15. Appleton JP, Woodhouse LJ, Adami A, et al. Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. Neurology. 2020;94(5):E439–52. https://doi.org/10.1212/WNL.0000000000008881.
16. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease—advances since 2013. Lancet Neurol. 2023;22(7):602–18. https://doi.org/10.1016/S1474-4422(23)00131-X.
17. 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(8):822–38. https://doi.org/10.1016/S1474-4422(13)70124-8.
18. Chen XY, Fisher M. Pathological characteristics. Front Neurol Neurosci. 2016;40(2):21–33. https://doi.org/10.1159/000448267.
19. Kockelkoren R, Vos A, Van Hecke W, et al. Computed tomographic distinction of intimal and medial calcification in the intracranial internal carotid artery. PLoS ONE. 2017. https://doi.org/10.1371/JOURNAL.PONE.0168360.
20. Al-Shahi Salman R, Minks DP, Mitra D, et al. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. Lancet Neurol. 2019;18(7):643–52. https://doi.org/10.1016/S1474-4422(19)30184-X.
21. Baradaran H, Culleton S, Stoddard G, et al. Association between high-risk extracranial carotid plaque and covert brain infarctions and cerebral microbleeds. Neuroradiology. 2023;65(2):287–95. https://doi.org/10.1007/s00234-022-03062-0.
22. Anufriev PL, Gulevskaya TS, Bolotova TA. Small focal cerebral ischemic changes caused by hypertension and tandem atherostenosis of the cerebral arteries. Arkh Patol. 2022;84(1):33–8. https://doi.org/10.17116/patol20228401133.
23. Zhu KL, Shang ZY, Liu B-J, et al. The association of intracranial atherosclerosis with cerebral small vessel disease imaging markers: a high-resolution magnetic resonance imaging study. Sci Rep. 2023;13(1):1–8. https://doi.org/10.1038/s41598-023-44240-1.
24. Wang Y, Cai X, Li H, et al. Association of intracranial atherosclerosis with cerebral small vessel disease in a community-based population. Eur J Neurol. 2023;30(9):2700–12. https://doi.org/10.1111/ene.15908.
25. Boulouis G, Charidimou A, Auriel E, et al. Intracranial atherosclerosis and cerebral small vessel disease in intracerebral hemorrhage patients. J Neurol Sci. 2016;369:324–9. https://doi.org/10.1016/j.jns.2016.08.049.
26. Jung KW, Shon YM, Yang DW, Kim BS, Cho AH. Coexisting carotid atherosclerosis in patients with intracranial small- or large-vessel disease. J Clin Neurol. 2012;8(2):104–8. https://doi.org/10.3988/JCN.2012.8.2.104.
27. Zhang W, Fu F, Zhan Z. Association between intracranial and extracranial atherosclerosis and white matter hyperintensities: a systematic review and meta-analysis. Front Aging Neurosci. 2023. https://doi.org/10.3389/fnagi.2023.1240509.
28. Huang H, Zhao K, Zhu W, Li H, Zhu W. Abnormal cerebral blood flow and functional connectivity strength in subjects with white matter hyperintensities. Front Neurol. 2021. https://doi.org/10.3389/fneur.2021.752762.
29. Wolf ME. Functional TCD: regulation of cerebral hemodynamics—cerebral autoregulation, vasomotor reactivity, and neurovascular coupling. Front Neurol Neurosci. 2014;36:40–56. https://doi.org/10.1159/000366236.
30. Panerai RB, Brassard P, Burma JS, et al. Transfer function analysis of dynamic cerebral autoregulation: a CARNet white paper 2022 update. J Cereb Blood Flow Metab. 2023;43(1):3–25. https://doi.org/10.1177/0271678X221119760.
31. Li Y, Li M, Zhang X, et al. Higher blood–brain barrier permeability is associated with higher white matter hyperintensities burden. J Neurol. 2017;264(7):1474–81. https://doi.org/10.1007/s00415-017-8550-8.
32. Rudilosso S, Stringer MS, Thrippleton M, et al. Blood-brain barrier leakage hotspots collocating with brain lesions due to sporadic and monogenic small vessel disease. J Cereb Blood Flow Metab. 2023;43(9):1490–502. https://doi.org/10.1177/0271678X231173444.
33. Puy L, Barbay M, Roussel M, et al. Neuroimaging determinants of poststroke cognitive performance: the GRECogVASC study. Stroke. 2018;49(11):2666–73. https://doi.org/10.1161/STROKEAHA.118.021981.
34. Yedavalli VS, Tong E, Martin D, Yeom KW, Forkert ND. Artificial intelligence in stroke imaging: current and future perspectives. Clin Imaging. 2021;69:246–54. https://doi.org/10.1016/J.CLINIMAG.2020.09.005.
35. Zhang XH, Liang HM. Systematic review with network meta-analysis: diagnostic values of ultrasonography, computed tomography, and magnetic resonance imaging in patients with ischemic stroke. Medicine. 2019. https://doi.org/10.1097/MD.0000000000016360.
36. Li X, Du H, Li J, Chen X. Intracranial artery calcification as an independent predictor of ischemic stroke: a systematic review and a meta-analysis. BMC Neurol. 2023;23(1):21–8. https://doi.org/10.1186/s12883-023-03069-x.
37. Du H, Li J, Yang W, et al. Intracranial arterial calcification and intracranial atherosclerosis: close but different. Front Neurol. 2022;13:799429. https://doi.org/10.3389/FNEUR.2022.799429/BIBTEX.
38. Blevins BL, Vinters HV, Love S, et al. Brain arteriolosclerosis. Acta Neuropathol. 2021;141(1):1–24. https://doi.org/10.1007/s00401-020-02235-6.
39. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9(7):689–701. https://doi.org/10.1016/S1474-4422(10)70104-6.
40. Wu S, Wu B, Liu M, et al. Stroke in China: advances and challenges in epidemiology, prevention, and management. Lancet Neurol. 2019;18(4):394–405. https://doi.org/10.1016/S1474-4422(18)30500-3.
41. Saxena A, Ng EYK, Lim ST. Imaging modalities to diagnose carotid artery stenosis: progress and prospect. Biomed Eng Online. 2019;18(1):1–23. https://doi.org/10.1186/s12938-019-0685-7.
42. Hosoki S, Sachdev PS. Molecular biomarkers for vascular cognitive impairment and dementia: the current status and directions for the future. Neural Regen Res. 2024;19(12):2579–80. https://doi.org/10.4103/NRR.NRR-D-23-01938.
43. Yilmaz A, Akpinar E, Topcuoglu MA, Arsava EM. Clinical and imaging features associated with intracranial internal carotid artery calcifications in patients with ischemic stroke. Neuroradiology. 2015;57(5):501–6. https://doi.org/10.1007/S00234-015-1494-8.
44. Wu LY, Chai YL, Cheah IK, et al. Blood-based biomarkers of cerebral small vessel disease. Ageing Res Rev. 2023;2024(95):102247. https://doi.org/10.1016/j.arr.2024.102247.
45. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021;88:105906. https://doi.org/10.1016/J.IJSU.2021.105906.
46. Ginting P. Translation challenges and strategies: a review of theories. SEALL J STKIP Al Maksum English Educ Linguist Lit J. 2022;3(1):76.
47. Kahrass H, Borry P, Gastmans C, et al. PRISMA-Ethics – Reporting Guideline for Systematic Reviews on Ethics Literature: development, explanations and examples. Published online January 29, 2024. https://doi.org/10.31219/OSF.IO/G5KFB
48. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev. 2017. https://doi.org/10.1186/S13643-017-0644-Y.
49. Haddaway NR, Collins AM, Coughlin D, Kirk S. The role of google scholar in evidence reviews and its applicability to grey literature searching. PLoS ONE. 2015;10(9):e0138237. https://doi.org/10.1371/JOURNAL.PONE.0138237.

50. Grewal A, Kataria H, Dhawan I. Literature search for research planning and identification of research problem. Indian J Anaesth. 2016;60(9):635. https://doi.org/10.4103/0019-5049.190618.
51. Lowe MS, Maxson BK, Stone SM, Miller W, Snajdr E, Hanna K. The Boolean is dead, long live the Boolean! natural language versus Boolean searching in introductory undergraduate instruction. Coll Res Libr. 2018;79(4):517. https://doi.org/10.5860/crl.79.4.517.
52. Stoll CRT, Izadi S, Fowler S, Green P, Suls J, Colditz GA. The value of a second reviewer for study selection in systematic reviews. Res Synth Methods. 2019;10(4):539. https://doi.org/10.1002/JRSM.1369.
53. Charrois TL. Systematic reviews: what do you need to know to get started? Can J Hosp Pharm. 2015;68(2):144. https://doi.org/10.4212/CJHP.V68I2.1440.
54. Norman C, Leeflang M, Névéol A. Data extraction and synthesis in systematic reviews of diagnostic test accuracy: a corpus for automating and evaluating the process. AMIA Annu Symp Proc. 2018;2018:817.
55. Kiyak C, Ijezie OA, Ackah JA, et al. Topographical distribution of neuroanatomical abnormalities following COVID-19 invasion. Clin Neuroradiol. 2023. https://doi.org/10.1007/s00062-023-01344-5.
56. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88. https://doi.org/10.1016/0197-2456(86)90046-2.
57. Akoudad S, Gurol ME, Fotiadis P, et al. Cerebral microbleeds and cerebrovascular reactivity in the general population: the EDAN study. J Alzheimer's Dis. 2016;53(2):497–503. https://doi.org/10.3233/JAD-151130.
58. Bokkers RPH, Van Osch MJP, Van Der Worp HB, De Borst GJ, Mali WPTM, Hendrikse J. Symptomatic carotid artery stenosis: Impairment of cerebral autoregulation measured at the brain tissue level with arterial spin-labeling MR imaging. Radiology. 2010;256(1):201–8. https://doi.org/10.1148/radiol.10091262.
59. Conijn MMA, Hoogduin JM, van der Graaf Y, Hendrikse J, Luijten PR, Geerlings MI. Microbleeds, lacunar infarcts, white matter lesions and cerebrovascular reactivity—a 7T study. Neuroimage. 2012;59(2):950–6. https://doi.org/10.1016/j.neuroimage.2011.08.059.
60. Libecap TJ, Bauer CE, Zachariou V, et al. Association of baseline cerebrovascular reactivity and longitudinal development of enlarged perivascular spaces in the basal ganglia. Stroke. 2023;54(11):2785–93. https://doi.org/10.1161/STROKEAHA.123.043882.
61. Sam K, Crawley AP, Conklin J, et al. Development of white matter hyperintensity is preceded by reduced cerebrovascular reactivity. Ann Neurol. 2016;80(2):277–85. https://doi.org/10.1002/ana.24712.
62. Staszewski J, Dębiec A, Skrobowska E, Stępień A. Cerebral vasoreactivity changes over time in patients with different clinical manifestations of cerebral small vessel disease. Front Aging Neurosci. 2021;13(October):1–12. https://doi.org/10.3389/fnagi.2021.727832.
63. Terborg C, Gora F, Weiller C, Röther J. Reduced vasomotor reactivity in cerebral microangiopathy: a study with near-infrared spectroscopy and transcranial Doppler sonography. Stroke. 2000;31(4):924–9. https://doi.org/10.1161/01.STR.31.4.924.
64. Alosco ML, Gunstad J, Jerskey BA, et al. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. Brain Behav. 2013;3(6):626–36. https://doi.org/10.1002/brb3.171.
65. Kaczmarz S, Göttler J, Petr J, et al. Hemodynamic impairments within individual watershed areas in asymptomatic carotid artery stenosis by multimodal MRI. J Cereb Blood Flow Metab. 2021;41(2):380–96. https://doi.org/10.1177/0271678X20912364.
66. Bahrani AA, Powell DK, Yu G, Johnson ES, Jicha GA, Smith CD. White matter hyperintensity associations with cerebral blood flow in elderly subjects stratified by cerebrovascular risk. J Stroke Cerebrovasc Dis. 2017;26(4):779–86. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.10.017.
67. Marstrand JR, Garde E, Rostrup E, et al. Cerebral perfusion and cerebrovascular reactivity are reduced in white matter hyperintensities. Stroke. 2002;33(4):972–6. https://doi.org/10.1161/01.STR.0000012808.81667.4B.
68. Chuang SY, Wang PN, Chen LK, et al. Associations of blood pressure and carotid flow velocity with brain volume and cerebral small vessel disease in a community-based population. Transl Stroke Res. 2021;12(2):248–58. https://doi.org/10.1007/s12975-020-00836-7.
69. López-Olóriz J, López-Cancio E, Arenillas JF, et al. Diffusion tensor imaging, intracranial vascular resistance and cognition in middle-aged asymptomatic subjects. Cerebrovasc Dis. 2014;38(1):24–30. https://doi.org/10.1159/000363620.
70. Mok V, Ding D, Fu J, et al. Transcranial Doppler ultrasound for screening cerebral small vessel disease: a community study. Stroke. 2012;43(10):2791–3. https://doi.org/10.1161/STROKEAHA.112.665711.
71. Porcu M, Cocco L, Cocozza S, et al. The association between white matter hyperintensities, cognition and regional neural activity in healthy subjects. Eur J Neurosci. 2021;54(4):5427–43. https://doi.org/10.1111/ejn.15403.
72. Purkayastha S, Fadar O, Mehregan A, et al. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. J Cereb Blood Flow Metab. 2014;34(2):228–34. https://doi.org/10.1038/jcbfm.2013.180.
73. Reinhard M, Lorenz L, Sommerlade L, et al. Impaired dynamic cerebral autoregulation in patients with cerebral amyloid angiopathy. Brain Res. 2019;1717(January):60–5. https://doi.org/10.1016/j.brainres.2019.04.014.
74. Björnfot C, Eklund A, Larsson J, et al. Cerebral arterial stiffness is linked to white matter hyperintensities and perivascular spaces in older adults—a 4D flow MRI study. J Cereb Blood Flow Metab. 2024. https://doi.org/10.1177/0271678X241230741.
75. Ding J, Mitchell GF, Bots ML, et al. Carotid arterial stiffness and risk of incident cerebral microbleeds in older people: the age, gene/environment susceptibility (AGES)-Reykjavik study. Arterioscler Thromb Vasc Biol. 2015;35(8):1889–95. https://doi.org/10.1161/ATVBAHA.115.305451.
76. Miyagi T, Ishida A, Shinzato T, Ohya Y. Arterial stiffness is associated with small vessel disease irrespective of blood pressure in stroke-free individuals. Stroke. 2023;54(11):2814–21. https://doi.org/10.1161/STROKEAHA.123.042512.
77. Robert C, Ling LH, Tan ESJ, et al. Effects of carotid artery stiffness on cerebral small-vessel disease and cognition. J Am Heart Assoc. 2022. https://doi.org/10.1161/JAHA.122.027295.
78. Salihović Hajdarević D, Pavlović AM, Smajlović D, et al. Carotid artery wall stiffness is increased in patients with small vessel disease: a case-control study. Srp Arh Celok Lek. 2016;144(1–2):6–9. https://doi.org/10.2298/SARH1602006S.
79. Zhai FF, Ye YC, Chen SY, et al. Arterial stiffness and cerebral small vessel disease. Front Neurol. 2018;9(AUG):1–7. https://doi.org/10.3389/fneur.2018.00723.
80. Aine CJ, Sanfratello L, Adair JC, et al. Characterization of a normal control group: are they healthy? Neuroimage. 2014;84:796–809. https://doi.org/10.1016/j.neuroimage.2013.09.025.
81. Badji A, Pereira JB, Shams S, et al. Cerebrospinal fluid biomarkers, brain structural and cognitive performances between normotensive and hypertensive controlled, uncontrolled and untreated 70-year-old adults. Front Aging Neurosci. 2022;13(January):1–14. https://doi.org/10.3389/fnagi.2021.777475.
82. Chen X, Wen W, Anstey KJ, Sachdev PS. Prevalence, incidence, and risk factors of lacunar infarcts in a community sample. Neurology. 2009;73(4):266–72. https://doi.org/10.1212/WNL.0b013e3181aa52ea.
83. Han Y, Zhang R, Yang D, et al. Risk factors for asymptomatic and symptomatic intracranial atherosclerosis determined by magnetic resonance vessel wall imaging in Chinese population: a case-control study. Ther Clin Risk Manag. 2022;18:61–70. https://doi.org/10.2147/TCRM.S335401.
84. Elmståhl S, Ellström K, Siennicki-Lantz A, Abul-Kasim K. Association between cerebral microbleeds and hypertension in the Swedish general population "good aging in Skåne" study. J Clin Hypertens. 2019;21(8):1099–107. https://doi.org/10.1111/jch.13606.
85. Melgarejo JD, Vernooij MW, Ikram MA, Zhang ZY, Bos D. Intracranial carotid arteriosclerosis mediates the association between blood pressure and cerebral small vessel disease. Hypertension. 2023;80(3):618–28. https://doi.org/10.1161/HYPERTENSIONAHA.122.20434.
86. Kerkhofs D, Wong SM, Zhang E, Staals J. Baseline blood-brain barrier leakage and longitudinal microstructural tissue damage in the periphery of white matter hyperintensities. Neurology. 2021. https://doi.org/10.1212/WNL.0000000000011783.
87. Li Y, Li M, Zuo L, et al. Compromised blood-brain barrier integrity is associated with total magnetic resonance imaging burden of cerebral small vessel disease. Front Neurol. 2018. https://doi.org/10.3389/fneur.2018.00221.

88. Zhang CE, Wong SM, Van De Haar HJ, et al. Blood-brain barrier leakage is more widespread in patients with cerebral small vessel disease. Neurology. 2017;88(5):426–32. https://doi.org/10.1212/WNL.0000000000003556.
89. Kennedy KM, Raz N. Pattern of normal age-related regional differences in white matter microstructure is modified by vascular risk. Brain Res. 2009;1297:41–56. https://doi.org/10.1016/j.brainres.2009.08.058.
90. Cai J, Sun J, Chen H, et al. Different mechanisms in periventricular and deep white matter hyperintensities in old subjects. Front Aging Neurosci. 2022. https://doi.org/10.3389/fnagi.2022.940538.
91. Tang J, Zhang M, Liu N, et al. The association between glymphatic system dysfunction and cognitive impairment in cerebral small vessel disease. Front Aging Neurosci. 2022;14(June):1–9. https://doi.org/10.3389/fnagi.2022.916633.
92. 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(February):105795. https://doi.org/10.1016/j.clineuro.2020.105795.
93. Pico F, Dufouil C, Lévy C, et al. Longitudinal study of carotid atherosclerosis and white matter hyperintensities: the EVA-MRI cohort. Cerebrovasc Dis. 2002;14(2):109–15. https://doi.org/10.1159/000064741.
94. Vinke EJ, Yilmaz P, van der Toorn JE, et al. Intracranial arteriosclerosis is related to cerebral small vessel disease: a prospective cohort study. Neurobiol Aging. 2021;105:16–24. https://doi.org/10.1016/j.neurobiolaging.2021.04.005.
95. Zhong T, Qi Y, Li R, et al. Contribution of intracranial artery stenosis to white matter hyperintensities progression in elderly Chinese patients: a 3-year retrospective longitudinal study. Front Neurol. 2022. https://doi.org/10.3389/fneur.2022.922320.
96. Schmitzer L, Kaczmarz S, Göttler J, et al. Macro- and microvascular contributions to cerebral structural alterations in patients with asymptomatic carotid artery stenosis. J Cereb Blood Flow Metab. 2024. https://doi.org/10.1177/0271678X241238935.
97. Della-Morte D, Dong C, Markert MS, et al. Carotid intima-media thickness is associated with white matter hyperintensities the Northern Manhattan Study. Stroke. 2018;49(2):304–11. https://doi.org/10.1161/STROKEAHA.117.018943.
98. Ekenze O, Pinheiro A, Demissie S, et al. Inflammatory biomarkers and MRI visible perivascular spaces: the Framingham heart study. Neurobiol Aging. 2023;127:12–22. https://doi.org/10.1016/j.neurobiolaging.2023.03.001.
99. Feng F, Kan W, Yang H, Ding H, Wang X, Dong R. White matter hyperintensities had a correlation with the cerebral perfusion level, but no correlation with the severity of large vessel stenosis in the anterior circulation. Brain Behav. 2023;13(4):1–10. https://doi.org/10.1002/brb3.2932.
100. Jolly TAD, Cooper PS, Wan Ahmadul Badwi SA, et al. Microstructural white matter changes mediate age-related cognitive decline on the montreal cognitive assessment (MoCA). Psychophysiology. 2016;53(2):258–67. https://doi.org/10.1111/psyp.12565.
101. Kerkhofs D, May S, Eleana W, Renske Z, Van Oostenbrugge J. Blood—brain barrier leakage at baseline and cognitive decline in cerebral small vessel disease : a 2—year follow—up study. GeroScience. 2021. https://doi.org/10.1007/s11357-021-00399-x.
102. Li X, Shen M, Jin Y, et al. The effect of cerebral small vessel disease on the subtypes of mild cognitive impairment. Front Psychiatry. 2021;12(July):1–11. https://doi.org/10.3389/fpsyt.2021.685965.
103. Mykola P, Svyrydova N, Trufanov Y. Susceptibility-weighted imaging and transcranial Doppler ultrasound in patients with cerebral small vessel disease. Neurol Sci. 2020;41(10):2853–8. https://doi.org/10.1007/s10072-020-04414-5.
104. Erickson MA, Banks WA. Blood-brain barrier dysfunction as a cause and consequence of Alzheimer's disease. J Cereb Blood Flow Metab. 2013;33(10):1500–13. https://doi.org/10.1038/JCBFM.2013.135.
105. Sorond FA, Kiely DK, Galica A, et al. Neurovascular coupling is impaired in slow walkers: the MOBILIZE boston study. Ann Neurol. 2011;70(2):213–20. https://doi.org/10.1002/ANA.22433.
106. Enager P, Piilgaard H, Offenhauser N, et al. Pathway-specific variations in neurovascular and neurometabolic coupling in rat primary somatosensory cortex. J Cereb Blood Flow Metab. 2009;29(5):976–86. https://doi.org/10.1038/JCBFM.2009.23.
107. Zhao Z, Nelson AR, Betsholtz C, Zlokovic BV. Establishment and dysfunction of the blood-brain barrier. Cell. 2015;163(5):1064–78. https://doi.org/10.1016/j.cell.2015.10.067.
108. Huang X, Tong Y, Qi CX, Xu YT, Dan HD, Shen Y. Disrupted topological organization of human brain connectome in diabetic retinopathy patients. Neuropsychiatr Dis Treat. 2019;15:2487–502. https://doi.org/10.2147/NDT.S214325.
109. Østergaard L, Engedal TS, Moreton F, et al. Cerebral small vessel disease: capillary pathways to stroke and cognitive decline. J Cereb Blood Flow Metab. 2016;36(2):302–25. https://doi.org/10.1177/0271678X15606723.
110. Sobczyk O, Battisti-Charbonney A, Fierstra J, et al. A conceptual model for CO2-induced redistribution of cerebral blood flow with experimental confirmation using BOLD MRI. Neuroimage. 2014;92:56–68. https://doi.org/10.1016/J.NEUROIMAGE.2014.01.051.
111. Kostoglou K, Bello-Robles F, Brassard P, et al. Time-domain methods for quantifying dynamic cerebral blood flow autoregulation: review and recommendations. A white paper from the cerebrovascular research network (CARNet). J Cereb Blood Flow Metab. 2024. https://doi.org/10.1177/0271678X241249276/FORMAT/EPUB.
112. Sforza M, Bianchini E, Alivernini D, Salvetti M, Pontieri FE, Sette G. The impact of cerebral vasomotor reactivity on cerebrovascular diseases and cognitive impairment. J Neural Transm. 2022;129(11):1321–30. https://doi.org/10.1007/S00702-022-02546-W/TABLES/1.
113. Lin W, Xiong L, Han J, et al. Hemodynamic effect of external counterpulsation is a different measure of impaired cerebral autoregulation from vasoreactivity to breath-holding. Eur J Neurol. 2014;21(2):326–31. https://doi.org/10.1111/ENE.12314.
114. Sam K, Crawley AP, Poublanc J, et al. Vascular dysfunction in leukoaraiosis. Am J Neuroradiol. 2016;37(12):2258–64. https://doi.org/10.3174/ajnr.A4888.
115. Bian Y, Wang JC, Sun F, et al. Assessment of cerebrovascular reserve impairment using the breath-holding index in patients with leukoaraiosis. Neural Regen Res. 2019;14(8):1412–8. https://doi.org/10.4103/1673-5374.251332.
116. Shim Y, Yoon B, Shim DS, Kim W, An JY, Yang DW. Cognitive correlates of cerebral vasoreactivity on transcranial Doppler in older adults. J Stroke Cerebrovasc Dis. 2015;24(6):1262–9. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.01.031.
117. Scheuermann BC, Parr SK, Schulze KM, et al. Associations of cerebrovascular regulation and arterial stiffness with cerebral small vessel disease: a systematic review and meta-analysis. J Am Heart Assoc. 2023;12(23):1–24. https://doi.org/10.1161/JAHA.123.032616.
118. Jefferson AL, Cambronero FE, Liu D, et al. Higher aortic stiffness is related to lower cerebral blood flow and preserved cerebrovascular reactivity in older adults. Circulation. 2018;138(18):1951–62. https://doi.org/10.1161/CIRCULATIONAHA.118.032410.
119. Lasek-Bal A, Kazibutowska Z, Gołba A, Motta E. Cerebral vasoreactivity in hypocapnia and hypercapnia in patients with diabetes mellitus type 2 with or without arterial hypertension. Neurol Neurochir Pol. 2012;46(6):529–35. https://doi.org/10.5114/ninp.2012.32175.
120. Csiszar A, Ungvari A, Patai R, et al. Atherosclerotic burden and cerebral small vessel disease: exploring the link through microvascular aging and cerebral microhemorrhages. GeroScience. 2024. https://doi.org/10.1007/s11357-024-01139-7.
121. Carotenuto A, Cacciaguerra L, Pagani E, Preziosa P, Filippi M, Rocca MA. Glymphatic system impairment in multiple sclerosis: relation with brain damage and disability. Brain. 2022;145(8):2785–95. https://doi.org/10.1093/BRAIN/AWAB454.
122. Chochrane. Cochrane Handbook for Systematic Reviews of Interventions - Google Books. Accessed February 16, 2023. https://books.google.co.uk/books?hl=en&lr=&id=cTqyDwAAQBAJ&oi=fnd&pg=PR3&ots=tvmLyexGng&sig=mQDaXr8vQHYFNOHE8WYkKXyslFw&redir_esc=y#v=onepage&q&f=false
123. Porcu M, Mannelli L, Melis M, et al. Carotid plaque imaging profiling in subjects with risk factors (diabetes and hypertension). Cardiovasc Diagn Ther. 2020;10(4):1005–18. https://doi.org/10.21037/cdt.2020.01.13.
124. Zwartbol MHT, Geerlings MI, Ghaznawi R, et al. Intracranial atherosclerotic burden on 7T MRI is associated with markers of extracranial atherosclerosis: the SMART-MR study. Am J Neuroradiol. 2019;40(12):2016–22. https://doi.org/10.3174/ajnr.A6308.

125. Joutel A, Chabriat H. Pathogenesis of white matter changes in cerebral small vessel diseases: beyond vessel-intrinsic mechanisms. Clin Sci. 2017;131(8):635–51. https://doi.org/10.1042/CS20160380.
126. Fang C, Magaki SD, Kim RC, Kalaria RN, Vinters HV, Fisher M. Arteriolar neuropathology in cerebral microvascular disease. Neuropathol Appl Neurobiol. 2023;49(1):1–18. https://doi.org/10.1111/nan.12875.
127. Stanimirovic DB, Friedman A. Pathophysiology of the neurovascular unit: disease cause or consequence. J Cereb Blood Flow Metab. 2012;32(7):1207–21. https://doi.org/10.1038/jcbfm.2012.25.
128. Gounis MJ, Van Der Marel K, Marosfoi M, et al. Imaging inflammation in cerebrovascular disease. Stroke. 2015;46(10):2991–7. https://doi.org/10.1161/STROKEAHA.115.008229.
129. Shima H, Mori T, Ooi M, et al. Silent cerebral microbleeds and longitudinal risk of renal and cardiovascular events in patients with CKD. Clin J Am Soc Nephrol. 2016;11(9):1557–65. https://doi.org/10.2215/CJN.13481215.
130. Zhang J, Li Y, Wang Y, et al. Arterial stiffness and asymptomatic intracranial large arterial stenosis and calcification in hypertensive Chinese. Am J Hypertens. 2011;24(3):304–9. https://doi.org/10.1038/ajh.2010.246.
131. Ackah JA, Zheng L, Tsz J, Chan L. Modulatory effects of hypertension on aging-related white matter hyperintensities: a comparative study among stroke patients and stroke-free community-based cohort. J Clin Hypertens. 2024. https://doi.org/10.1111/jch.70002.
132. Müller M, Voges M, Piepgras U, Schimrigk K. Assessment of cerebral vasomotor reactivity by transcranial Doppler ultrasound and breath-holding: a comparison with acetazolamide as vasodilatory stimulus. Stroke. 1995;26(1):96–100. https://doi.org/10.1161/01.STR.26.1.96.
133. Claassen JAHR, Zhang R, Fu Q, Witkowski S, Levine BD. Transcranial Doppler estimation of cerebral blood flow and cerebrovascular conductance during modified rebreathing. J Appl Physiol. 2007;102(3):870–7. https://doi.org/10.1152/JAPPLPHYSIOL.00906.2006.
134. Bakker SLM, De Leeuw FE, De Groot JC, Hofman A, Koudstaal PJ, Breteler MMB. Cerebral vasomotor reactivity and cerebral white matter lesions in the elderly. Neurology. 1999;52(3):578–83. https://doi.org/10.1212/wnl.52.3.578.
135. Kozera GM, Wolnik B, Kunicka KB, et al. Cerebrovascular reactivity, intima-media thickness, and nephropathy presence in patients with type 1 diabetes. Diabetes Care. 2009;32(5):878–82. https://doi.org/10.2337/dc08-1805.

Publisher's Note