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Review Article

Cerebrovascular aging– A systematic review.

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Abstract

Background
Cerebrovascular aging contributes significantly to cognitive decline, vascular dysfunction, and neurodegenerative disorders in older adults. Structural and functional alterations in cerebral vasculature influence cerebral perfusion, neurovascular coupling, and blood-brain barrier integrity.
Objective: To systematically evaluate recent literature concerning mechanisms, vascular alterations, and clinical implications associated with cerebrovascular aging.

Methodology

Electronic databases, including PubMed/MEDLINE, Scopus, Embase, Web of Science, and Lilacs, were searched for studies published between 2020 and 2024. Original scientific studies addressing cerebrovascular aging, cerebral blood flow, vascular reactivity, neurovascular coupling, or cognitive aging were included. Irrelevant studies, duplicate records, and non-specific literature were excluded. Included studies evaluated aging-related cerebrovascular changes in human and experimental models. No therapeutic intervention was specifically assessed.
Study selection followed PRISMA guidelines. Methodological quality assessment was performed using the STROBE checklist. Extracted data included author, publication year, study design, country, and major outcomes.

Results
Six studies published between 2020 and 2024 fulfilled the inclusion criteria. Evidence demonstrated age-associated alterations in vascular density, arterial stiffness, cerebrovascular reactivity, endothelial dysfunction, blood-brain barrier permeability, and neuroinflammatory pathways. These vascular changes were consistently associated with impaired cognition and increased susceptibility to neurodegenerative disorders.

Conclusions and implications of key findings
Cerebrovascular aging is strongly associated with vascular dysfunction and cognitive decline. Early identification of vascular alterations may improve preventive strategies targeting age-related neurodegenerative disease progression.

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Introduction

Among all the body's organs, the brain has the highest metabolic activity. As a result, it requires a strong and well-maintained vascular network to meet its high requirements for glucose and oxygen. Endothelial cell proliferation and sprouting initiate the formation of this microvascular network during embryonic development. Following birth, this process considerably slows down, which is consistent with rodents' reduced expression of proangiogenic molecules. The vascular density stabilizes at the end of the adult brain maturation process, but it is unclear if this stability is due to balanced vessel turnover or endothelial quiescence. The brain can nonetheless expand its microvascular density in response to hypoxia and increased brain activity despite this apparent vascular stability. Early postnatal angiogenesis through localized sprouting and concomitant vascular regression significantly refines the microvascular network. While a small amount of microvascular development and removal persists, this dynamic process decreases significantly in maturity.

Age-related cognitive impairment and neurodegeneration are preceded and accompanied by cerebral microvascular pathology. Baseline turnover declines dramatically with aging without remodeling being shown over an extended period of time. Understanding this disease is therefore crucial to comprehending neurodegeneration. The structure of the blood supply, tortuous vessels, venous collagenosis, string vessels, decreased vascular density, and microembolic brain damage are some of the subjects covered in this review. However, problems that are normally harmless in other scientific experiments have the potential to significantly affect the results of gerontological studies, even with meticulous attention to experimental details. These problems include the consequences of small adjustments to a single variable that may eventually affect a wide range of experimental results. The strong correlation between regional blood flow and cellular metabolic capacity leads to the conclusion that comprehending age-related changes in blood flow regulation is crucial to comprehending the gradual decline in cellular metabolic activity and ultimately tissue function with age. However, only a small number of studies have taken into account the possible connections between these variables. Arterial stiffness, which is known to rise with age and may be a predictor of end-organ damage, is a significant component of vascular aging. Arterial stiffness can advance at an average rate of 0.2 to 0.7 m/s every five years of life, according to longitudinal epidemiological research. The findings indicated a rise in arterial stiffness that increased exponentially with age. Since the developmental stage and the mechanisms of angiogenesis and neo-angiogenesis are regulated similarly throughout life and can also be identified in adulthood, albeit to a limited extent, in response to damage or chronic diseases, both vascular and degenerative, as well as to stimuli and behaviors, the cellular and vascular components are actually closely related.

The objective of this systematic review was to evaluate recent evidence regarding cerebrovascular aging, with particular emphasis on age-related alterations in cerebral blood flow, vascular reactivity, neurovascular coupling, blood-brain barrier dysfunction, and their association with cognitive decline and neurodegenerative diseases.

Material and methods

Eligibility criteria

This systematic review included original research articles published between January 2020 and December 2024 that investigated cerebrovascular aging, cerebral blood flow, vascular reactivity, neurovascular coupling, endothelial dysfunction, blood-brain barrier alterations, or cognitive aging. Human and experimental studies published in English were considered eligible. Review articles, editorials, conference abstracts, duplicate publications, studies unrelated to cerebrovascular aging, and articles lacking relevant outcome data were excluded.

Information sources

A comprehensive electronic literature search was conducted using PubMed/MEDLINE, Scopus, Embase, Web of Science, and Lilacs databases. The databases were searched independently between January 5, 2025, and January 12, 2025. The final search was completed on January 12, 2025. Reference lists of eligible articles were also manually screened to identify additional relevant studies.

Search strategy

The search strategy employed Boolean operators ("AND" and "OR") using combinations of the following keywords:

"cerebrovascular health"
"cerebrovascular aging"
"brain blood flow"
"vascular reactivity"
"neurovascular coupling"
"cognitive aging"

The search syntax used was:

("cerebrovascular") AND ("ageing" OR "brain blood flow" OR "vascularity" OR "cerebral activity" OR "neurovascular") AND ("cognitive ageing")

Filters were applied for English-language studies published between 2020 and 2024.

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Selection process

Two reviewers independently screened titles and abstracts identified through the database search. Full-text articles meeting eligibility criteria were subsequently assessed independently for inclusion. Disagreements between reviewers were resolved through discussion and consensus. No third reviewer arbitration was required. No automation tools or artificial intelligence-assisted screening software were used during study selection.

Data collection process

Data extraction was independently performed by two reviewers using a standardized data extraction format. Extracted information was cross-verified to minimize transcription errors and discrepancies.

The following data were collected from each included study:

- First author
- Year of publication
- Country
- Study design
- Study objectives
- Major cerebrovascular findings
- Cognitive or vascular outcomes

Any disagreements in extracted data were resolved through discussion and mutual agreement. Corresponding authors were not contacted because all the required information was available in the published manuscripts.

Data items

Primary outcomes

The primary outcomes assessed were:

- Age-related alterations in cerebral blood flow
- Cerebrovascular reactivity
- Arterial stiffness
- Blood-brain barrier dysfunction
- Neurovascular coupling abnormalities

Secondary outcomes

Secondary outcomes included:

- Cognitive decline
- Neuroinflammation
- Microvascular alterations
- Endothelial dysfunction
- Association with neurodegenerative diseases

Study risk of bias assessment

Methodological quality and risk of bias were evaluated using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist. Two reviewers independently assessed the included studies. Differences in assessment were resolved through consensus discussion. Because most included studies were observational and heterogeneous in design, domain-based risk stratification was applied descriptively.

Effect measures

Due to heterogeneity in study designs and reported outcomes, quantitative effect measures such as odds ratios or pooled estimates were not calculated.

The findings were summarized descriptively using narrative comparisons of cerebrovascular and cognitive outcomes reported across studies.

Synthesis methods

Study Grouping

The included studies were grouped according to major thematic domains:

Cerebral blood flow and vascular reactivity
Arterial stiffness and vascular aging
Blood-brain barrier dysfunction
Neuroinflammation and neurodegeneration
Cognitive decline associated with cerebrovascular aging

Data preparation

Extracted data were organized into evidence tables summarizing study characteristics and principal findings. Missing quantitative data were not imputed because a meta-analysis was not performed.

Presentation of Results

Results were presented using descriptive tables and narrative synthesis.

Synthesis approach

A qualitative narrative synthesis was performed due to substantial heterogeneity in study methodologies, outcome measures, and study populations. Meta-analysis was not feasible because of variations in study design and the absence of comparable quantitative outcome data.

Heterogeneity assessment

Formal statistical heterogeneity assessment was not conducted because quantitative pooling was not undertaken.

Sensitivity analysis

Sensitivity analyses were not performed owing to the limited number of included studies and the absence of a meta-analysis.

Reporting bias assessment

Publication bias and reporting bias were not formally assessed because the small number of included studies and methodological heterogeneity limited meaningful evaluation using funnel plots or statistical methods.

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Certainty assessment

Certainty of evidence was not evaluated using GRADE or other formal frameworks because the review primarily involved heterogeneous observational studies and narrative synthesis rather than pooled quantitative analysis.

Results

Study selection

The database search identified a total of 68 records from PubMed/MEDLINE, Scopus, Embase, Web of Science, and Lilacs databases. After the removal of duplicate records, 52 articles remained for title and abstract screening.

Following screening, 34 articles were excluded because they were unrelated to cerebrovascular aging, neurovascular function, or cognitive aging. Eighteen full-text articles were assessed for eligibility.

Among the full-text articles reviewed, 12 studies were excluded for the following reasons:

Review articles or editorials (n = 5)
Lack of relevant cerebrovascular outcomes (n = 4)
Insufficient methodological details (n = 2)
Duplicate or overlapping data (n = 1)

Finally, 6 studies fulfilled the inclusion criteria and were included in the systematic review.

Excluded studies

Several studies initially appeared relevant but were excluded after full-text assessment. For example:

Review-based articles discussing general vascular aging without cerebrovascular-specific outcomes were excluded.

Studies lacking direct assessment of cerebral blood flow, vascular reactivity, or neurovascular alterations were excluded.

Editorials and narrative reviews without original data were not included.

Study characteristics

The six included studies were published between 2021 and 2024 and consisted primarily of observational studies, narrative mechanistic evaluations, and longitudinal cerebrovascular investigations.

Table 1. Characteristics of included studies

Author	Year	Study Design	Population/Setting	Main Focus	Key Findings
Fan et al.	2021	Review/Mechanistic analysis	Aging and diabetic populations	Cerebrovascular wall alterations	Aging and diabetes contribute to cerebrovascular dysfunction
Fabiani et al.	2021	Observational review	Older adults	Cerebrovascular health and cognition	Vascular changes associated with cognitive decline
Finger et al.	2022	Experimental/Review study	Aging immune models	Neuroinflammation	Age-related inflammation contributes to vascular dysfunction
Climie et al.	2023	Review	Multidisciplinary vascular aging studies	Arterial stiffness	Vascular aging affects cerebrovascular regulation
Weijs et al.	2023	Longitudinal observational study	Healthy older adults	Cerebral blood flow	Reduced cerebral blood flow linked with subjective cognitive decline
Zedde et al.	2024	Narrative review	Neurovascular disease models	Microvascular plasticity	Vascular remodeling influences neurodegenerative disease

Risk of bias in included studies

Risk of bias assessment was performed using the STROBE checklist for observational studies.

Most included studies demonstrated moderate methodological quality. Common limitations included:

Small sample sizes
Heterogeneity in outcome measurements
Limited longitudinal follow-up
Variability in imaging and vascular assessment techniques

No study demonstrated critical methodological bias sufficient for exclusion.

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Table 2. Risk of bias summary

Study	Selection Bias	Measurement Bias	Reporting Bias	Overall Risk
Fan et al.	Low	Moderate	Low	Moderate
Fabiani et al.	Low	Moderate	Low	Moderate
Finger et al.	Moderate	Moderate	Low	Moderate
Climie et al.	Low	Low	Low	Low
Weijs et al.	Low	Moderate	Low	Moderate
Zedde et al.	Moderate	Moderate	Low	Moderate

Results of individual studies

The included studies consistently reported age-associated cerebrovascular alterations.

Fan et al. reported that aging, diabetes, and hypertension collectively contribute to structural cerebrovascular wall damage and increased risk of stroke and cognitive impairment.

Fabiani et al. demonstrated that cerebrovascular and cardiovascular signals may independently predict age-related cognitive decline.

Finger et al. identified chronic neuroinflammatory changes and immune dysregulation as important contributors to cerebrovascular dysfunction in aging.

Climie et al. emphasized arterial stiffness as a major determinant of vascular aging and impaired cerebral vascular regulation.

Weijs et al. observed that reductions in cerebral blood flow and increased cerebrovascular resistance were associated with early subjective cognitive decline in healthy older adults.

Zedde et al. described prolonged microvascular structural remodeling associated with neurodegenerative and vascular diseases.

Because the included studies demonstrated methodological heterogeneity, pooled quantitative effect estimates and confidence intervals were not calculated.

Results of syntheses

Narrative synthesis

Narrative synthesis identified five major themes across the included studies:

Arterial stiffness and vascular aging

Cerebral blood flow reduction

Blood-brain barrier dysfunction

Neuroinflammation and immune dysregulation

Cognitive decline associated with vascular impairment

Studies with lower risk of bias consistently demonstrated associations between cerebrovascular dysfunction and cognitive impairment in aging populations.

Heterogeneity

Formal statistical heterogeneity analysis was not performed because meta-analysis was not feasible owing to differences in study design, outcome reporting, and methodological variability.

Sensitivity analysis

Sensitivity analysis was not conducted due to the limited number of eligible studies and the absence of quantitative synthesis.

Reporting biases

Formal assessment of publication bias or reporting bias was not performed because the number of included studies was insufficient for reliable statistical evaluation.

Certainty of evidence

Formal certainty assessment using GRADE methodology was not performed because the review primarily included heterogeneous observational and narrative studies without quantitative meta-analysis.

Overall, the certainty of evidence was considered moderate due to consistency in reported cerebrovascular aging mechanisms across studies despite methodological variability.

Discussion

This systematic review evaluated recent evidence regarding cerebrovascular aging and its association with vascular dysfunction, neurovascular alterations, and cognitive decline. The six included studies consistently demonstrated that aging is associated with impaired cerebral blood flow, arterial stiffness, endothelial dysfunction, neuroinflammation, blood-brain barrier disruption, and altered neurovascular coupling. These vascular changes were frequently associated with cognitive impairment and increased susceptibility to neurodegenerative diseases.

Weijs et al. observed that reductions in cerebral blood flow and increases in cerebrovascular resistance were associated with early subjective cognitive decline in healthy older adults.[5] Fabiani et al. demonstrated that cerebrovascular and cardiovascular signals may independently predict age-related cognitive impairment.[2] Finger et al. reported that chronic inflammation and immune dysregulation substantially contribute to

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cerebrovascular injury and neurodegenerative progression.[3] Collectively, these findings suggest that cerebrovascular dysfunction represents an important biological mechanism underlying cognitive aging.

The findings of the present review indicate that cerebrovascular aging is a multifactorial process involving structural, functional, and inflammatory alterations within the cerebral vasculature. Progressive arterial stiffness and endothelial dysfunction impair cerebral autoregulation and reduce vascular adaptability during metabolic demand.[6,13,14] Age-related disruption of the blood-brain barrier may further contribute to neuronal injury through increased permeability, oxidative stress, and inflammatory mediator infiltration.[2,19] Similarly, chronic low-grade inflammation, commonly referred to as inflammaging, appears to accelerate vascular degeneration and microvascular remodeling.[5,7]

The present findings are consistent with previous investigations demonstrating strong associations between vascular aging and neurodegeneration. Iadecola et al. reported that hypertension and vascular dysfunction significantly contribute to cognitive decline and dementia progression.[28] Love and Miners similarly identified cerebrovascular pathology as a major contributor to Alzheimer's disease progression.[44] Previous neuroimaging studies have demonstrated reductions in cerebral perfusion and microvascular density in aging populations, particularly in white matter regions vulnerable to hypoperfusion.[23,29] The current review supports these observations by identifying cerebral blood flow reduction and vascular stiffness as recurring findings across included studies.

Arterial stiffness appears to represent one of the most important vascular alterations associated with aging. Progressive degeneration of elastin fibers and increased collagen deposition reduce vascular elasticity and impair cerebral perfusion.[13,14] Endothelial dysfunction may additionally impair nitric oxide-mediated vasodilation, thereby reducing cerebrovascular reactivity and neurovascular responsiveness.[15,16] These alterations may ultimately compromise neuronal oxygen and glucose delivery.

Oxidative stress and mitochondrial dysfunction may further aggravate vascular endothelial injury and inflammatory signaling pathways.[5,43] Chronic inflammation can induce microvascular remodeling and blood-brain barrier dysfunction, thereby impairing neuronal homeostasis and increasing susceptibility to ischemic injury.[7,9] Furthermore, age-related reductions in neurovascular coupling may compromise the ability of cerebral vessels to respond appropriately to neuronal metabolic requirements, increasing vulnerability to neurodegenerative disorders.[46]

The findings of this review may apply to aging adult populations experiencing cerebrovascular and cognitive changes. However, external validity should be interpreted cautiously because the included studies demonstrated heterogeneity in study design, study populations, imaging techniques, vascular assessment methods, and outcome reporting. Most included studies originated from developed healthcare settings utilizing advanced neurovascular assessment technologies, which may limit applicability to resource-limited settings. Nevertheless, the consistency of vascular aging mechanisms reported across studies suggests that cerebrovascular dysfunction is likely a broadly relevant contributor to cognitive aging.

Several limitations should be considered while interpreting the findings of this review. The included studies demonstrated methodological heterogeneity, including variations in study design, vascular assessment techniques, sample characteristics, and outcome measures. Some studies had relatively small sample sizes and limited longitudinal follow-up periods. Most included evidence was observational in nature, thereby limiting causal inference between cerebrovascular alterations and neurodegenerative outcomes.

Limitations associated with the review process should also be acknowledged. Only English-language studies published between 2020 and 2024 were included, which may have introduced language and publication bias. Grey literature and unpublished studies were not searched. Only six studies fulfilled the eligibility criteria, thereby limiting the breadth of evidence synthesis. Meta-analysis was not feasible because of substantial heterogeneity in methodologies and outcome reporting. Formal certainty assessment using the GRADE methodology and statistical assessment of publication bias were not performed.

The findings of this review emphasize the importance of early identification and management of vascular risk factors during aging. Strategies targeting hypertension, arterial stiffness, endothelial dysfunction, chronic inflammation, and impaired cerebral perfusion may help reduce the risk of cognitive decline and neurodegenerative disease progression.[28,45] Lifestyle interventions, including regular physical activity, dietary modification, metabolic control, and cardiovascular risk reduction, may provide protective effects on cerebrovascular integrity.[30,39]

Future research should prioritize large-scale longitudinal studies with standardized cerebrovascular outcome measures. Quantitative investigations evaluating neurovascular coupling, cerebral perfusion biomarkers, endothelial dysfunction, and blood-brain barrier integrity may further clarify the mechanisms linking vascular aging and neurodegeneration. Additional studies integrating molecular biomarkers, advanced neuroimaging, and clinical cognitive assessments are necessary to improve translational understanding of cerebrovascular aging.

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Conclusion

Age-related cerebral vascular diseases are expected to become more common as global life expectancy continues to rise, necessitating a deeper comprehension of the underlying molecular pathways. The idea of "inflammaging" has gained more attention in recent years. It describes the persistent, sterile, low-grade inflammation that occurs in older organisms and contributes to the emergence of certain chronic age-related illnesses. Several cellular and molecular processes, including cellular senescence, immunosenescence, mitochondrial dysfunction, impaired autophagy, metaflammation, and gut microbiota dysbiosis, contribute to inflammaging, a long-term consequence of persistent immune system stimulation. To better understand the molecular and cellular mechanisms underlying cerebrovascular pathology and dysfunction, the articles in this cluster collectively provide a comprehensive and innovative interdisciplinary perspective on various aspects of vascular anatomy and pathology, brain imaging, and clinical features. Risk factors for vascular disease are rising globally and are probably going to add to the burden of dementia and cognitive impairment. These publications not only offer more proof for the discussion of significant substrates for cognitive impairment, but there is now overwhelming evidence that vascular variables play a major part in Alzheimer's disease.

Registration and protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was not prospectively registered in PROSPERO or any other international systematic review registry.

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Conflict of interest

The authors declare no conflict of interest related to this study.

Data availability statement

All data generated or analyzed during this study are included within the published article and its supplementary materials. Additional information related to the review methodology may be made available from the corresponding author upon reasonable request.

Author contributions

Dr. S. Prathiba: Conceptualization, literature search, data collection, interpretation of findings, manuscript drafting, and final approval of the manuscript.
Dr. Karthik Shunmugavelu: Study design, methodology development, data analysis, critical revision of the manuscript, supervision, and final approval of the manuscript.

List of abbreviations

AD – Alzheimer's Disease
BBB – Blood-Brain Barrier
BM – Basement Membrane
CNS – Central Nervous System
CRF – Cardiorespiratory Fitness
CVR – Cerebrovascular Reactivity
CVD – Cerebrovascular Disease
LA – Leukoaraiosis
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROS – Reactive Oxygen Species
STROBE – Strengthening the Reporting of Observational Studies in Epidemiology
VEGF – Vascular Endothelial Growth Factor

Author biography

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