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Cerebral Small Vessel Disease as a Driver of Mixed Dementia: Mechanisms, Biomarkers, and Therapeutic Implications

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Abstract

"Mixed dementia" refers to dementia in which more than one neuropathological process contributes, most often Alzheimer's disease (AD) together with at least one other pathology. Far from being an exception, it is the most common substrate of dementia in older adults. Of the pathologies that accompany AD, cerebral small vessel disease (cSVD) is the most frequent and arguably the most consequential because it is the one with the strongest evidence for modifiability. In this narrative review, we argue that cSVD does not simply co-occur with AD but helps determine whether subclinical pathology becomes clinically overt dementia.

We searched PubMed from 1984 onward with a structured Boolean strategy, supplemented by citation searching, reported the search and selection using items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and included 83 sources spanning autopsy cohorts, consensus statements, randomized trials, meta-analyses, and mechanistic studies. We first examine why clinical, imaging, and neuropathological classifications of mixed dementia so often disagree.

We then review autopsy and population evidence on arteriolosclerosis, microinfarcts, and cerebral amyloid angiopathy (CAA); in pooled community-based autopsy data, 91% of decedents aged 80 years or older had more than one dementia-associated neuropathology, and vascular injury lowers the burden of Alzheimer pathology needed to produce dementia. We examine the leading mechanisms proposed to explain this relationship (endothelial and blood-brain barrier (BBB) failure, chronic hypoperfusion, impaired perivascular clearance, neuroinflammation, and oligodendrocyte injury) and consider how each might interact with amyloid-beta and tau. We then turn to the imaging and fluid biomarkers used to separate vascular from degenerative disease during life and argue that these tools are asymmetric: molecularly precise for AD, largely descriptive for cSVD.

Finally, we review the treatment evidence, including blood pressure lowering, endothelial-targeted therapy, and multidomain lifestyle intervention, and consider what cSVD means for eligibility, safety, and expected benefit from anti-amyloid monoclonal antibodies. We conclude that the field should move beyond an either/or model of dementia and instead measure and treat vascular disease in every patient with cognitive impairment.

Categories: Neurology, Medical Physics
Keywords: arteriolosclerosis, cerebral amyloid angiopathy, cerebral small vessel disease, cerebrovascular disease, mixed dementia, vascular cognitive impairment, white matter hyperintensities

Introduction And Background

For most of the 20th century, dementia was sorted into two boxes. One held Alzheimer's disease (AD), defined by plaques and tangles and understood as a primary neurodegenerative process; the other held vascular dementia, attributed to ischemic injury from a compromised blood supply. The diagnostic criteria written in the 1980s and 1990s were designed to tell the two apart [1,2], and clinicians were taught that stepwise decline (an abrupt drop in function followed by a plateau), focal neurologic signs, and sudden onset moved a case out of the Alzheimer box and into the vascular one.

Autopsy studies of older adults who were not selected for any particular diagnosis have shown that this two-box system does not match what is found in the brain. In the Rush Memory and Aging Project, mixed pathology accounted for most cases of dementia [3]; in the Medical Research Council Cognitive Function and Ageing Study (CFAS), dementia was rarely attributable to a single type of lesion, and vascular damage was about as common as Alzheimer pathology [4,5]; and in a harmonized analysis of six community-based autopsy cohorts, 91% of decedents aged 80 years or older had more than one dementia-associated neuropathology [6].

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Within this picture, cerebral small vessel disease (cSVD) stands out. It is the most common co-pathology, with arteriolosclerosis, microinfarcts, and cerebral amyloid angiopathy (CAA) together affecting most aged brains [7,8]; it is mechanistically heterogeneous; it is visible during life on routine MRI; and it has the strongest evidence for modifiability because blood pressure lowering is the only intervention shown in randomized trials both to slow progression of the imaging lesion and to reduce the incidence of mild cognitive impairment (MCI), although its effect on probable dementia alone has not reached statistical significance [9,10]. These features motivate our central argument: cSVD is best understood not as a second, independent cause of dementia that happens to coincide with AD but as a determinant of how mixed pathology is expressed clinically. If its contribution were simply additive, managing it would be arithmetic: treat the vascular component and subtract a fixed increment of risk. The evidence reviewed below suggests something less tidy. Vascular injury lowers the amount of Alzheimer pathology needed to produce dementia [11,12], may accelerate the accumulation of that pathology through impaired clearance and hypoxia-driven amyloid production, and damages the white matter networks on which cognitive reserve depends [13].

Throughout, we use cSVD to mean the group of disorders affecting the brain's small arteries, arterioles, capillaries, and venules, and mixed dementia to mean clinical dementia with two or more contributing pathologies, one of which is cSVD; both terms are contested, for reasons explained below. The objectives of this narrative review are to (i) synthesize neuropathological and epidemiological evidence that cSVD lowers the threshold for clinical dementia in the presence of Alzheimer pathology, (ii) evaluate the mechanisms proposed to link the two, (iii) appraise the imaging and fluid biomarkers used to separate their contributions during life, and (iv) summarize the treatment evidence, including the implications of cSVD for anti-amyloid immunotherapy.

This article is a narrative review. A narrative review was chosen rather than a systematic format because the question it addresses, how cSVD shapes the clinical expression of mixed dementia, spans neuropathology, epidemiology, mechanistic biology, neuroimaging, fluid biomarkers, genetics, and clinical trials, and no single search strategy or pooled outcome measure could capture it. Relevant literature was identified through searches of PubMed and Google Scholar using combinations of terms including "cerebral small vessel disease," "mixed dementia," "vascular cognitive impairment," "white matter hyperintensities," "cerebral amyloid angiopathy," "arteriolosclerosis," and "Alzheimer's disease," supplemented by hand-searching the reference lists of key reviews and consensus statements. We prioritized community-based autopsy cohorts, international consensus statements and diagnostic criteria, randomized controlled trials (RCTs), large population-based studies, and systematic reviews and meta-analyses, and we favored recent publications in areas that have changed rapidly, such as fluid biomarkers and anti-amyloid therapy. Because this is not a systematic review, no formal inclusion criteria or risk-of-bias assessment were applied, and the selection reflects the authors' judgment of the most informative and influential evidence.

Review

Methods

Review Design and Reporting Standards

This is a narrative review. A narrative rather than systematic format was chosen because the question it addresses, how cSVD shapes the clinical expression of mixed dementia, spans neuropathology, epidemiology, mechanistic biology, neuroimaging, fluid biomarkers, genetics, and clinical trials, and no single pooled outcome measure could capture it. To make the evidence base transparent and the search reproducible, we reported the search, eligibility criteria, and selection process using the applicable items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [14], and we structured the review against the Scale for the Assessment of Narrative Review Articles (SANRA) [15]. The protocol was not registered because registries of systematic review protocols, such as PROSPERO, do not accept narrative reviews.

Information Sources and Search Strategy

We searched PubMed (MEDLINE) from January 1, 1984, the year the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD were published [1], to (10/1/2026). The strategy combined three concept blocks with Boolean operators: cSVD and its markers (block 1), dementia and cognitive impairment (block 2), and the study designs prioritized for this review (block 3). Within each block, Medical Subject Headings (MeSH) terms and free-text terms searched in titles and abstracts were joined with OR, truncation (*) captured word variants, and the three blocks were joined with AND, with English language as the only additional limit (Table *1*). Because several mechanistic, genetic, and biomarker sources fall outside a search anchored on dementia outcomes, the database search was supplemented by backward citation searching of the reference lists of key consensus statements and reviews, forward citation searching in Google Scholar, targeted searches for consensus diagnostic criteria and imaging and neuropathology standards, and checks of trial registries (ClinicalTrials.gov and ISRCTN) for the status of ongoing trials. Records identified through these routes are reported separately as other methods.

Block	Concept	MeSH terms	Free-text terms (Title/Abstract field)
#1	Cerebral small vessel disease and its markers	Cerebral Small Vessel Diseases OR Cerebral Amyloid Angiopathy OR Leukoaraiosis OR Arteriolosclerosis	"small vessel disease*" OR arteriolosclerosis OR "cerebral amyloid angiopathy" OR "white matter hyperintensit*" OR leukoaraiosis OR "cerebral microbleed*" OR microinfarct* OR lacune* OR "lacunar infarct*" OR "perivascular space*"
#2	Dementia and cognitive impairment	Dementia (exploded, including Alzheimer Disease and Dementia, Vascular) OR Cognitive Dysfunction	dementia* OR alzheimer* OR "cognitive impairment" OR "cognitive decline" OR "vascular cognitive"
#3	Prioritized study designs	Autopsy OR Consensus OR Randomized Controlled Trial (publication type) OR Meta-Analysis (publication type) OR Systematic Review (publication type) OR Practice Guideline (publication type)	autops* OR neuropatholog* OR consensus OR criteria OR guideline* OR "population-based" OR "community-based" OR randomi*
Final	Combination and limits	None	#1 AND #2 AND #3; English language; publication date from 1984/01/01 to the search date

TABLE 1: PubMed search strategy

Within each block, MeSH terms (searched with automatic explosion of narrower terms) and free-text terms (searched in the Title/Abstract field) were combined with OR; the asterisk denotes truncation.

MeSH: Medical Subject Headings

Eligibility Criteria

We included English-language, peer-reviewed sources of the following types: community-based or clinicopathological autopsy studies relating vascular pathology to cognition or dementia; international consensus statements, diagnostic criteria, and neuroimaging or neuropathology standards; RCTs of interventions targeting vascular risk or cSVD with cognitive, functional, or imaging outcomes; population-based or clinical cohort studies relating cSVD imaging or fluid biomarkers to cognition; systematic reviews and meta-analyses; genetic studies of monogenic or sporadic cSVD; and experimental studies, including animal models, that directly tested a mechanism proposed to link vascular injury to white matter damage or Alzheimer pathology. Narrative reviews and expert syntheses were included to provide context and framing. We excluded case reports and small case series, conference abstracts, editorials and letters, studies of large-artery or cardioembolic stroke without a small vessel component, and analyses superseded by a larger or more recent report from the same cohort. Where evidence was abundant, we favored community-based over clinic-based samples and larger over smaller studies and, in rapidly changing areas such as fluid biomarkers and anti-amyloid therapy, recent over older publications.

Selection Process

Records retrieved by the database search were deduplicated and screened in two stages, first by title and abstract and then by full text, against the eligibility criteria. Screening was performed by CI, and uncertainties were resolved by discussion with CI. Because a narrative review aims to represent the most informative evidence rather than to capture every eligible study, sources that met the criteria were then selected on the basis of relevance to the review objectives, methodological strength, and non-redundancy with other included sources. This final step involved author judgment and is a recognized limitation of the narrative format. The flow of records through identification, screening, and inclusion is shown in a PRISMA 2020 flow diagram (Figure *1*).

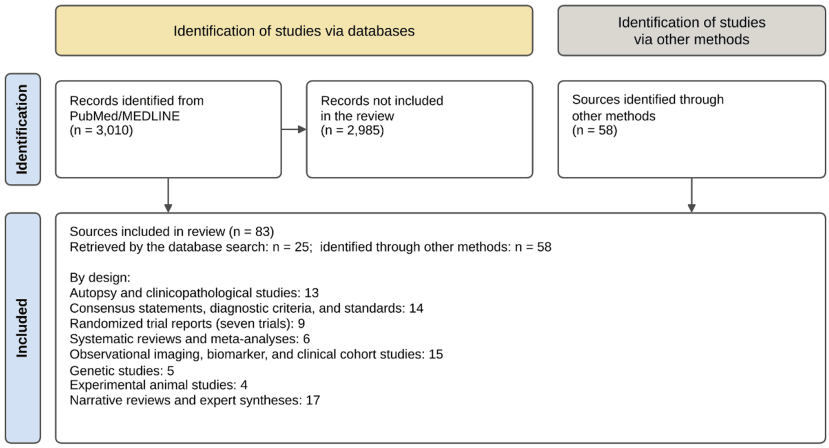


FIGURE 1: PRISMA 2020 flow diagram of the identification, screening, and inclusion of sources

Records were identified through the PubMed (MEDLINE) search and through other methods (citation searching, consensus documents, and trial registries). Included sources are classified by design; nine reports derive from seven randomized trials. Two references describing the reporting frameworks used for this review are not counted among the included sources. Adapted from the PRISMA 2020 flow diagram template [14].

cSVD: cerebral small vessel disease; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Data Items and Synthesis Methods

From each included source, we recorded the design, setting, population and sample size, exposure or intervention, outcomes, and principal effect estimates. Effect estimates are reported as published, as hazard ratios (HRs), odds ratios (ORs), or mean differences with 95% confidence intervals (CI) and p-values where the source provided them. Where a source reported counts but no interval for a proportion, we calculated an exact (Clopper-Pearson) binomial 95% CI and identified it as calculated. Because the included evidence spans incompatible designs, populations, exposures, and outcomes, no meta-analysis or meta-regression was performed, and the evidence was synthesized narratively and thematically under the headings that structure this review.

Risk of Bias and Certainty of Evidence

No formal risk-of-bias tool was applied to individual studies, and the certainty of the evidence was not graded, because the included sources span designs (autopsy cohorts, trials, consensus statements, and experimental studies) for which no single appraisal instrument is appropriate. Instead, each source was classified by design (Figure *1*), and design-specific limitations that bear on interpretation, such as early trial termination, open-label allocation, cross-sectional measurement, and selection by restrictive exclusion criteria, are discussed alongside the findings they qualify.

Characteristics of Included Sources

A total of 83 sources were included: 13 autopsy or clinicopathological studies; 14 consensus statements, diagnostic criteria, or standards; nine reports from seven RCTs; six systematic reviews or meta-analyses; 15 observational imaging, biomarker, or clinical cohort studies; five genetic studies; four experimental animal studies; and 17 narrative reviews or expert syntheses (Figure *1*). Two further references describe the reporting frameworks used for this review [14,15] and are not counted among the included sources.

Definitions, classification, and the problem of overlapping categories

What Counts as Small Vessel Disease

The term cSVD does not denote a single disease but a category of disorders affecting the brain's smallest blood vessels. The two dominant sporadic forms are arteriolosclerosis and CAA. Arteriolosclerosis, also called hypertensive arteriopathy, consists of concentric wall thickening, loss of smooth muscle, and luminal narrowing in the deep perforating arterioles, the small branches that pass directly from larger arteries into the deep brain [16,17]. CAA, by contrast, is the deposition of amyloid-beta in the walls of leptomeningeal and cortical vessels [16,17].

The two differ in distribution and in the pattern of bleeding they produce. Arteriolosclerosis affects the basal ganglia, thalamus, and deep white matter and gives rise to deep microbleeds. CAA favors cortical and lobar regions, particularly the occipital lobes, and produces lobar microbleeds and cortical superficial siderosis [18,19].

The distinction is clinically useful but biologically porous. The two often coexist and may interact: arteriolosclerosis may impair the perivascular drainage that normally clears amyloid, thereby promoting CAA, while CAA-related vessel damage may in turn impair autoregulation, the brain's capacity to hold blood flow steady across changes in blood pressure [18,20].

Beyond these two forms, cSVD also includes the inherited monogenic arteriopathies (discussed below with genetic insights), inflammatory and infectious vasculopathies, post-radiation microangiopathy, and venous collagenosis. These are easily overlooked but remain relevant to the differential diagnosis in younger or atypical patients.

How cSVD Is Defined on Imaging

Because neuropathology is unavailable during life, cSVD is in practice diagnosed by imaging, almost always MRI rather than CT, since CT misses most of the relevant findings. The 2013 STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) consensus standardized the terminology for six features: recent small subcortical infarcts, lacunes of presumed vascular origin, white matter hyperintensities (WMH) of presumed vascular origin, perivascular spaces, cerebral microbleeds, and brain atrophy [21]. STRIVE-2, published a decade later, retained these categories, added cortical cerebral microinfarcts, incidental diffusion-weighted imaging-positive lesions, and an expanded treatment of cortical superficial siderosis, and endorsed quantitative measures of tissue damage below the threshold of visual detection as legitimate research markers [22].

The qualifier "presumed vascular" is doing real work in that terminology. WMH are non-specific: they arise from ischemic demyelination, but also from inflammation, edema, and Wallerian degeneration secondary to cortical Alzheimer pathology. Neuropathological work has shown that parietal white matter lesions in AD track cortical neurodegenerative pathology rather than small vessel disease [23], and a later review makes the case explicitly that not all WMH are vascular in origin [24]. A radiology report describing "changes consistent with small vessel disease" is therefore an inference from lesion appearance, not an established diagnosis, and treating WMH volume as a pure index of vascular disease builds an assumption into the measurement.

Classifying Vascular Cognitive Impairment (VCI)

Several overlapping frameworks describe the cognitive consequences of vascular disease. The American Heart Association and American Stroke Association framed the field as "vascular contributions to cognitive impairment and dementia," a formulation deliberately broad enough to include mixed states [25]. The statement of the International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) offered operational diagnostic criteria for vascular cognitive disorders, that is, specific and checkable rules a clinician can apply at the bedside [26]. These have since been revised as the VasCog-2-WSO criteria, developed through a modified Delphi process [27]. The Vascular Impairment of Cognition Classification Consensus Study (VICCCS) proposed a hierarchy of mild and major VCI along with an explicit "mixed dementia" category that requires the co-occurring pathologies to be specified [28].

Each framework improved on the last, but all share the same weakness: they ask the clinician to attribute impairment to a cause. In a population where multiple pathologies are the norm, that attribution is often indeterminate. The VICCCS mixed-dementia category is an advance because it declines to force a single answer, but it still asks how much each pathology contributes, a question that cannot be answered with current biomarkers and may not be answerable at all if pathologies interact rather than simply add up [29].

A more useful framing, and one increasingly reflected in comprehensive reviews of VCI [30], treats cognitive status as the outcome of total brain injury and remaining reserve, with individual pathologies as partly independent contributors whose weights can be estimated at the population level but rarely for an individual [29].

The Neuropathology Criteria Problem

Neuropathology faces the same problem. For AD, the National Institute on Aging-Alzheimer's Association framework standardizes assessment through the ABC score, which combines Thal amyloid phase, Braak neurofibrillary tangle stage, and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque score [31]. Vascular pathology has no equivalent. The Vascular Cognitive Impairment Neuropathology Guidelines (VCING) study derived a short list of features that best predicted cognitive impairment attributable to vascular disease: moderate-to-severe occipital leptomeningeal CAA, moderate-to-severe arteriolosclerosis in the occipital white matter, and at least one large infarct [32]. The model

achieved an area under the receiver operating characteristic curve of 0.77. That so short a list captured most of the available predictive signal suggests that much of what pathologists routinely score adds little independent information.

Even so, vascular measures harmonize poorly across cohorts. In the six-cohort analysis cited above, the Alzheimer measures (Braak stage and CERAD score) fell into the high-confidence category for cross-study harmonization, macroinfarcts and microinfarcts into the moderate category, and arteriolosclerosis, atherosclerosis, CAA, and lacunes into the low-confidence category [6]. Any pooled estimate of the vascular contribution inherits this measurement noise, which biases it toward underestimating vascular effects.

What epidemiology and autopsy studies show

How Common Is cSVD in the Aging Brain

The base rates are high enough that the word "co-pathology" understates the situation. In autopsy series of people dying after age 80, some form of small vessel pathology, whether arteriolosclerosis, CAA, or microinfarcts, is present in most brains regardless of dementia status [7,8]. Moderate or worse arteriolosclerosis is reported in roughly a third to a half of aged brains, depending on the scoring system [6,7]. Microinfarcts, which are largely invisible on standard clinical MRI, occur at comparable frequencies [33]. Some degree of CAA is present in most AD brains and in a substantial minority of cognitively normal ones [8,18].

Because these prevalences are so high and rise with age, comparisons based on simple presence or absence are prone to confounding, which is one reason the clinical significance of cSVD was underestimated for decades. Where nearly everyone has some vascular pathology, only graded severity reveals the dose-response relationship. In population-based cohorts, it is the burden of MRI markers, rather than their mere presence, that predicts incident dementia; the risk rises with lesion burden, and the association persists after adjustment for conventional vascular risk factors [34-36]. This suggests that cSVD contributes to brain injury in its own right rather than serving merely as a marker of cardiovascular risk.

Multi-pathology Prevalence

Pure disease is uncommon. Schneider et al., in the Rush Memory and Aging Project, found that most people with dementia had mixed pathology, most often AD with macroscopic infarcts, and that those with multiple pathologies were nearly three times as likely to have dementia as those with a single pathologic diagnosis [3]. CFAS reached the same conclusion in England and Wales and added that population attributable risk was distributed across several pathologies rather than concentrated in one [4,5]. The largest estimate comes from the harmonized analysis of six community-based autopsy cohorts from the United States and United Kingdom: among decedents aged 80 years or older with complete data on six key dementia-associated neuropathologies, 2,443 of 2,695 (91%; 95% CI 89.5% to 91.7%) had more than one, and 1,106 of 2,695 (41%; 95% CI 39.2% to 42.9%) had three or more [6]. The original report gave counts, but not intervals for these proportions; the intervals shown are exact binomial estimates calculated from the reported counts and, because they do not account for clustering by cohort, should be read as descriptive.

Kapasi et al. synthesized this literature into a threshold model in which each additional pathology lowers the burden of any single pathology needed for overt dementia [7]. This is the core of the "driver" claim. A given Braak stage (the standard six-stage system for grading how far neurofibrillary tangles have spread through the brain) carries a markedly different probability of dementia depending on the accompanying vascular burden.

Boyle et al. went further and estimated how much each pathology contributed to cognitive decline in individual people. No single pathology explained most of the variance; combinations were the rule, and a substantial share of decline remained unexplained by everything that was measured [29,37]. That gap is worth dwelling on: we can count plaques, tangles, infarcts, and Lewy bodies and still not say why some people decline faster than others.

Evidence That Vascular Disease Lowers the Dementia Threshold

The observation is older than the recent literature might suggest. The Nun Study found that, among participants meeting neuropathological criteria for AD, those with lacunar infarcts in the basal ganglia, thalamus, or deep white matter had far higher odds of dementia and poorer cognitive function than those with comparable AD pathology and no infarcts, and that dementia appeared at lower levels of Alzheimer pathology when infarcts were present [11]. Schneider et al. examined the same question in 153 participants of the Religious Orders Study. Each unit of AD pathology increased the odds of dementia 4.4-fold (OR 4.40, 95% CI 2.33 to 8.32), the presence of one or more infarcts independently increased the odds 2.8-fold (OR 2.80, 95% CI 1.26 to 6.21), and there was no statistical interaction between infarcts and AD pathology ($p = 0.39$); the two contributions were additive on the odds scale [12].

That additive result is not at odds with a threshold model. Because the probability of dementia rises steeply through intermediate levels of AD pathology and flattens at either extreme, a fixed increase in the odds of dementia produces its largest change in absolute probability at intermediate AD burden, where the outcome is most uncertain, and its smallest change at the extremes (Figure 2). The practical implication is that the patients most likely to benefit from vascular risk management are those with intermediate, rather than maximal, AD burden.

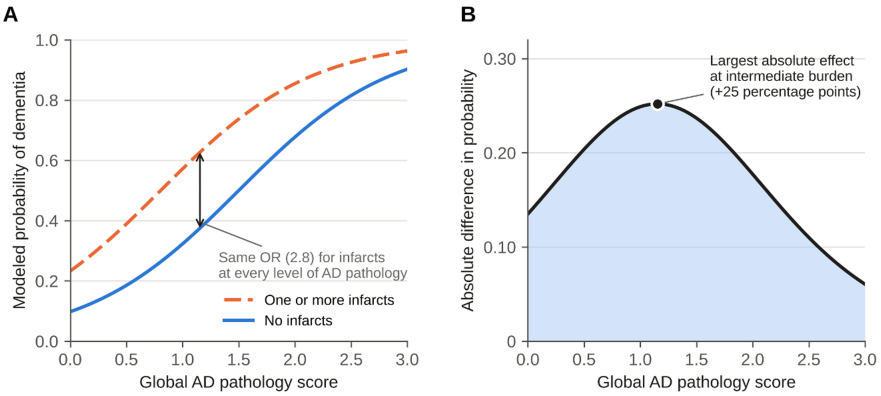


FIGURE 2: Additive effects on the odds scale produce the largest absolute effect at intermediate Alzheimer pathology burden

(A) Modeled probability of dementia across global AD pathology scores without infarcts (solid blue line) and with one or more infarcts (dashed orange line). (B) Absolute difference in probability attributable to infarcts. The curves use the published odds ratios of 4.40 per unit of AD pathology and 2.80 for one or more infarcts, with no interaction term, from the Religious Orders Study [12]. The intercept was chosen for display only; it shifts the location but not the height of the peak in panel B. The figure is an illustrative model, not a fit to individual-level data.

AD: Alzheimer's disease; OR: odds ratio

Direct Evidence for Small Vessel Pathology

Much of the early work used macroscopic infarcts as the vascular exposure because they are easy to identify. Arvanitakis et al. instead graded the vessel disease itself, and found that both atherosclerosis and arteriolosclerosis were associated with AD dementia and with lower cognitive function independently of infarcts and of AD pathology [38]. The vascular contribution is therefore not mediated solely through visible infarction.

Toledo et al., using the National Alzheimer's Coordinating Center database, likewise showed that cerebrovascular pathology was common in autopsy-confirmed neurodegenerative disease and modified its clinical presentation [39]. Attems and Jellinger, reviewing the overlap, argued that vascular and Alzheimer pathology co-occur more often than two independent age-related processes would predict, implying shared risk factors or causal interaction [8].

Beyond AD: The Wider Mixed Picture

AD is not the only pathology with which cSVD interacts. Limbic-predominant age-related TDP-43 encephalopathy (LATE), formally described in 2019, is a highly prevalent late-life pathology that produces an amnestic phenotype closely resembling AD and frequently co-occurs with both AD and vascular pathology [40]. Lewy body pathology, hippocampal sclerosis, and primary age-related tauopathy add further combinations. A clinician seeing an older patient with memory loss is, statistically, more likely to be looking at some combination of these processes than at any one of them alone. A review focused narrowly on the AD-cSVD pair therefore risks oversimplifying: cSVD is one of several interacting contributors, and the arithmetic in any individual patient is often opaque.

How cSVD damages the brain

The Neurovascular Unit

Current understanding centers on the neurovascular unit: endothelial cells, pericytes, vascular smooth muscle cells, astrocyte end-feet, neurons, and microglia, which together regulate perfusion, barrier

integrity, and interstitial homeostasis [41,42]. This concept has displaced an older, purely hemodynamic model of luminal narrowing and downstream ischemia, which could not explain why WMH progress despite well-controlled blood pressure, why lesion distribution does not follow simple watershed logic, or why endothelial dysfunction appears before structural lesions do [17,43].

Markus and Joutel's recent synthesis argues that sporadic cSVD is better understood as a diffuse, chronic failure of the neurovascular unit, with endothelial dysfunction upstream of ischemic injury rather than downstream of it [43]. Several lines of mechanistic evidence support this view.

Endothelial Dysfunction and Blood-Brain Barrier (BBB) Failure

The endothelium does more than line a conduit for blood. It maintains the BBB through tight junctions, the protein complexes that seal the gaps between endothelial cells and normally exclude large molecules from the brain. It also releases nitric oxide to regulate vessel tone, signals to oligodendrocytes and their precursors, and controls immune cell trafficking.

Contrast-enhanced MRI shows increased BBB permeability in lacunar stroke and WMH, in normal-appearing white matter as well as within lesions, and the degree of leakage predicts later lesion progression [44,45]. Nation et al. demonstrated hippocampal BBB breakdown, measured by contrast MRI and by a cerebrospinal fluid marker of pericyte injury (pericytes being the cells that wrap around small vessels and help maintain the barrier), in people with early cognitive dysfunction, independent of amyloid and tau status [46]. Montagne et al. had earlier shown that hippocampal BBB breakdown occurs with normal aging and worsens in MCI [47].

The downstream consequences are multiple and plausible. Extravasated fibrinogen is directly toxic to oligodendrocyte precursor cells and impairs remyelination; leaked albumin causes osmotic edema, and plasma-derived thrombin activates microglia [48]. Zlokovic's "two-hit" hypothesis casts BBB dysfunction and hypoperfusion as a first hit that damages neurons directly and promotes amyloid accumulation, with amyloid then acting as a self-amplifying second hit [49].

Animal work supports a causal role. Rajani et al., working in a rat strain that develops cSVD spontaneously, showed that endothelial dysfunction precedes and contributes to white matter damage, that it blocks oligodendrocyte precursor maturation through endothelial secretion of heat shock protein 90α, and that reversing the endothelial deficit pharmacologically reduced white matter injury [50]. Joutel et al. showed in a mouse model of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) that vascular dysfunction and microvascular rarefaction preceded the formation of white matter lesions [51].

Chronic Hypoperfusion and Impaired Blood Flow Regulation

Cerebral blood flow is reduced in cSVD, but the direction of causation is debated: reduced flow could reflect the lower metabolic demand of already-damaged tissue rather than cause the damage. A meta-analysis by Shi et al. found consistently lower blood flow in people with WMH than in controls, but most studies were cross-sectional, and the few longitudinal ones did not clearly show low flow preceding the lesions [52].

The more telling abnormality may be impaired reactivity rather than reduced resting flow: the vessels fail to dilate and constrict appropriately when local demand for oxygen and glucose changes. In cSVD, cerebrovascular reactivity to carbon dioxide is reduced, arterial pulsatility is increased, and neurovascular coupling is blunted [41,43]. Tissue is thereby left vulnerable to transient mismatches between supply and demand even when mean perfusion looks adequate, which fits the observation that cSVD progression does not simply track mean blood pressure.

The deep white matter is anatomically predisposed to this problem. It is supplied by long, thin, poorly collateralized perforating arterioles, so there is little backup supply if one vessel narrows, and its oligodendrocytes carry a high metabolic demand for myelin maintenance.

Failure of Perivascular Clearance

The description of a perivascular pathway that facilitates exchange between cerebrospinal fluid and interstitial fluid and clears solutes, including amyloid-beta, reframed the relationship between vascular and degenerative disease [53]. Whether the "glymphatic" model, with its emphasis on aquaporin-4-dependent bulk flow, is correct in every detail remains debated. The broader claim, that perivascular spaces are functional clearance conduits whose efficiency depends on arterial pulsation, is well supported. van Veluw et al. showed in awake mice that spontaneous vasomotion (rhythmic constriction and relaxation of the vessel wall) drives paravascular clearance, directly linking vessel function to solute removal [54]. In mice with CAA, vascular reactivity was impaired and clearance was correspondingly slower.

Related literature describes intramural periarterial drainage, in which fluid moves along the basement membranes of artery walls, driven by pulsation, in the direction opposite to blood flow [20]. Weller et al. proposed that vessel stiffening from aging and arteriolosclerosis degrades this drainage, causing amyloid-beta to accumulate within the vessel wall itself, which is to say causing CAA [20].

If correct, this describes a loop: arteriolosclerosis promotes amyloid deposition, the deposited amyloid stiffens the vessel further and degrades clearance further, and the cycle reinforces itself, connecting the two dominant forms of cSVD to each other and to AD.

Enlarged perivascular spaces, particularly in the centrum semiovale (the white matter above the lateral ventricles), have been proposed as an imaging proxy for clearance failure and are associated with CAA burden [55]. The marker is imperfect: its visibility depends on sequence, field strength, and rating scale, and enlarged spaces occur in healthy young people as well.

Neuroinflammation and Matrix Remodeling

Chronic neuroinflammation is a consistent feature of cSVD. It includes microglial activation around damaged vessels and white matter lesions, mislocalization of astrocytic aquaporin-4, and upregulation of matrix metalloproteinases (MMP-2 and MMP-9) that degrade tight junction and basal lamina proteins and so amplify barrier failure [43,48].

Whether inflammation is a primary driver or a downstream amplifier is unresolved, and the answer matters for treatment. Anti-inflammatory strategies are attractive if they interrupt a self-sustaining cycle, but only if inflammation is doing causal work rather than clearing debris.

White Matter and Oligodendrocyte Vulnerability

The characteristic lesion of sporadic cSVD is white matter damage: myelin loss with relatively preserved axons early on, progressing to axonal loss. Oligodendrocyte precursor cells are recruited to demyelinated regions but frequently fail to mature, partly because of the endothelial signaling deficits described above and partly because of the inhibitory environment created by extravasated plasma proteins [50].

This offers a treatment target distinct from vascular protection: promoting oligodendrocyte maturation might permit repair even where the vasculopathy is established. No such agent has yet reached late-phase testing in cSVD.

How cSVD and Alzheimer pathology might interact

The preceding sections establish that cSVD and AD co-occur and that cSVD damages the brain through identifiable mechanisms. The stronger claim, that cSVD drives the clinical expression of mixed disease, requires evidence that the two pathologies interact. Four candidate mechanisms merit examination.

Impaired Amyloid Clearance

The most direct argument concerns clearance. Amyloid-beta is removed by enzymatic degradation, by receptor-mediated transport across the BBB (mainly through LRP1, which shuttles amyloid out of the brain into the blood), and by perivascular drainage. Small vessel disease plausibly compromises at least two of these routes. BBB dysfunction alters transport in both directions: reduced LRP1-mediated efflux and increased influx through RAGE, a separate receptor that moves amyloid into the brain, have both been described with endothelial and pericyte injury [48,49]. Failure of perivascular drainage provides a second route by which vascular stiffening promotes amyloid retention [20].

The prediction that cSVD burden should track amyloid burden in living humans has been only partly confirmed. Studies relating WMH to amyloid positron emission tomography (PET) have produced mixed results, and several found no association after adjustment for age. Graff-Radford et al., in a population-based sample without dementia, found that higher amyloid PET burden was associated with greater WMH, but in a specific periventricular frontal and parietal pattern whose volume correlated strongly with lobar microbleeds [56]. That pattern points toward CAA as the mediating process rather than a generalized failure of parenchymal clearance, which is a narrower conclusion than the clearance hypothesis requires.

Hypoxia-Driven Amyloidogenesis

Chronic hypoperfusion upregulates hypoxia-inducible factor 1α, which in turn increases expression of BACE1, the rate-limiting enzyme in amyloidogenic processing of amyloid precursor protein. Cell and animal studies support this pathway, which offers a mechanism by which cSVD could increase amyloid production rather than merely reduce its clearance [49].

Human evidence remains indirect. The mechanism is biologically plausible and could explain the epidemiological link between midlife vascular risk and later amyloid burden, but it has not been demonstrated directly in humans, and the size of any effect is unknown.

Vascular Contributions to Tau Pathology

Tau has received less attention in this context, partly because the vascular hypothesis grew up around amyloid. In a large autopsy cohort, Kapasi et al. found that arteriolosclerosis in the posterior watershed region and WMH were both associated with greater neocortical tangle burden, without corresponding associations with amyloid [57]. Experimental work shows that hypoperfusion can promote tau phosphorylation through several kinase pathways. In vivo evidence is less consistent: the same imaging study that linked amyloid PET burden to a CAA-like WMH pattern found no relationship between tau PET burden and WMH [56].

If cSVD influences tau as well as amyloid, the interaction is more than a clearance phenomenon, and vascular risk management would bear not only on amyloid accumulation but on the pathology that correlates most closely with cognitive decline.

Network Disconnection as a Final Common Pathway

The fourth mechanism requires no molecular interaction at all. Cognition depends on distributed networks of brain regions working together; white matter tracts are the wiring that connects those regions, and cSVD damages white matter. On this view, cSVD and AD converge because they damage complementary components of the same system: AD degrades the cortical nodes, the gray matter regions that do the processing, while cSVD degrades the edges between them, the white matter connections that let those regions communicate.

Tuladhar et al. showed that structural network connectivity, derived from diffusion tractography (an MRI technique that maps white matter tracts by following the direction in which water diffuses along axons), mediated the relationship between cSVD lesion burden and cognition and explained variance that lesion volumes alone did not [13]. This finding has been widely replicated and supports network disruption as the proximate cause of impairment, with visible lesions serving as an imperfect upstream marker.

The disconnection model explains the threshold phenomenon without requiring any molecular interaction. If AD reduces node capacity and cSVD reduces connection efficiency, the two act multiplicatively on network performance even if neither influences the other's underlying pathology.

Interaction or Independence: What the Data Support

The evidence that vascular lesions lower the threshold for clinical dementia is stronger than the evidence for any specific mechanism. That effect is consistent across cohorts and methods [7,11,12], but because the key autopsy analysis found the contributions of infarcts and AD pathology to be additive on the odds scale [12], "interaction" in this literature refers to the joint effect on clinical expression rather than to a demonstrated statistical interaction term. The proposed molecular mechanisms are individually plausible but under-supported in humans, and the cleanest human test, the relationship between WMH and amyloid PET, points toward a CAA-mediated association rather than the generalized clearance failure the hypothesis predicts [56].

Meanwhile, the harmonized six-cohort analysis found that vascular and Alzheimer measures clustered separately in correlation analyses, which is what one would expect of independent processes converging on a shared clinical outcome [6]. Reconciling this with the threshold evidence points toward the network model: independent etiologies with interactive consequences. Figure *3* summarizes this model together with the candidate mechanisms and the strength of the human evidence for each link.

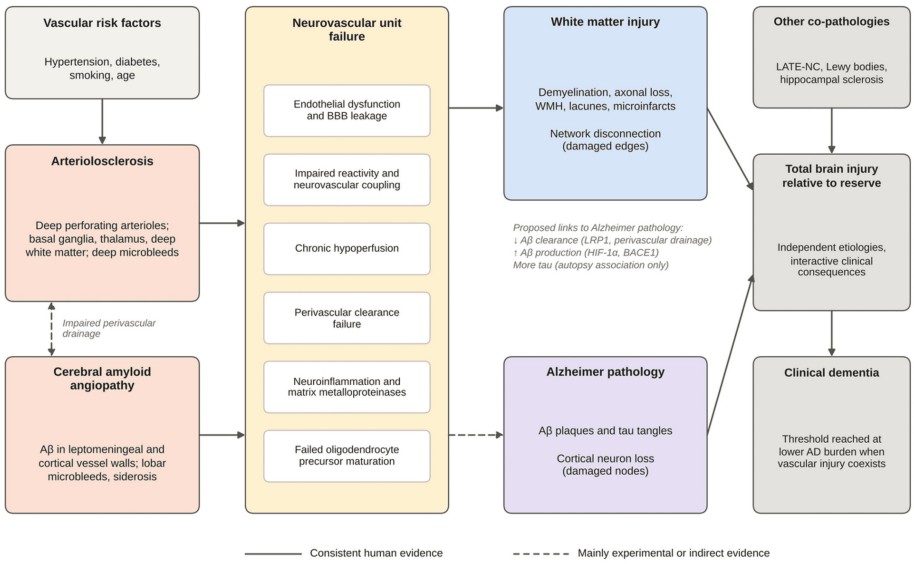


FIGURE 3: Conceptual model of how cerebral small vessel disease shapes the clinical expression of mixed dementia

Vascular risk factors drive arteriolosclerosis, which may promote cerebral amyloid angiopathy by impairing perivascular drainage. Both forms converge on failure of the neurovascular unit, which damages white matter and the network connections (edges) between cortical regions, whereas Alzheimer pathology damages the cortical regions themselves (nodes). Proposed molecular links from vascular injury to Alzheimer pathology are drawn with a dashed line because human evidence for them is limited. Together with other co-pathologies, these processes determine total brain injury relative to cognitive reserve, so that dementia appears at a lower burden of Alzheimer pathology when vascular injury coexists. Solid lines indicate links supported by consistent human evidence; dashed lines indicate links supported mainly by experimental or indirect evidence.

Aβ: amyloid-beta; AD: Alzheimer's disease; BACE1: beta-site amyloid precursor protein cleaving enzyme 1; BBB: blood-brain barrier; HIF-1α: hypoxia-inducible factor 1-alpha; LATE-NC: limbic-predominant age-related TDP-43 encephalopathy neuropathologic change; LRP1: low-density lipoprotein receptor-related protein 1; WMH: white matter hyperintensities

Neuroimaging markers and their interpretation

White Matter Hyperintensities (WMH)

WMH remain the most studied marker. Debette and Markus's meta-analysis established that WMH predict stroke (HR 3.3, 95% CI 2.6 to 4.4), dementia (HR 1.9, 95% CI 1.3 to 2.8), and death (HR 2.0, 95% CI 1.6 to 2.7) [35], and a later meta-analysis extended the finding to other MRI markers of vascular brain injury [36]. The LADIS study showed prospectively that baseline WMH severity predicted the transition to disability in older people who were initially independent [58].

Three limitations of WMH are worth bearing in mind in clinical practice. The first is non-specificity, discussed above: WMH on a scan report does not automatically indicate vascular damage. The second is a non-linear relationship with cognition, weak at modest lesion loads and steep beyond a threshold, so that small lesion volumes may carry little cognitive consequence while large ones carry a great deal. The third is location dependence: periventricular and deep WMH relate differently to cognition, and differently to CAA and arteriolosclerosis.

Quantitative segmentation, in which software measures lesion volume automatically, has largely replaced visual rating scales in research. The Fazekas scale, which grades periventricular and deep WMH separately from 0 to 3 and was derived from early 1.5T MRI work comparing patients with Alzheimer's dementia with normally aging controls [59], remains standard in clinical practice and retains prognostic value.

Lacunes, Microbleeds, and Perivascular Spaces

Lacunes, the small fluid-filled cavities left behind by old small subcortical infarcts, carry independent prognostic weight in population studies, where they predict incident stroke and death [36]. Their cognitive consequence depends on location more than on number: thalamic and basal ganglia lacunes matter more than those in less connected territories.

Microbleeds serve a dual role: as a general marker of severity and, by their location, as a way of distinguishing arteriolosclerosis from CAA. Strictly lobar microbleeds, especially with cortical superficial siderosis, point to CAA, whereas deep and infratentorial microbleeds point to hypertensive arteriopathy [18]. The Boston criteria version 2.0 formalized the MRI diagnosis of probable CAA and improved sensitivity by incorporating non-hemorrhagic markers, namely severe centrum semiovale perivascular spaces and a characteristic multispot WMH pattern [19].

Enlarged perivascular spaces are increasingly used in the same way, with basal ganglia predominance suggesting arteriolosclerosis and centrum semiovale predominance suggesting CAA [55]. Inter-rater reliability, meaning how consistently different raters score the same scan, remains limited.

Cortical Microinfarcts

Microinfarcts are among the most prevalent lesions at autopsy and the least visible during life. As van Veluw et al. noted, 7T MRI and increasingly optimized 3T sequences can detect a fraction of them, and that fraction correlates with the far larger number present pathologically [33]. Their functional consequences extend beyond the infarcted volume, with perilesional disruption out of proportion to lesion size.

Microinfarct burden is therefore a plausible candidate for the vascular contribution to cognitive decline that visible lesions fail to explain.

Composite Burden Scores

Because individual markers capture only part of the pathology, composite scores have been developed. Staals and colleagues proposed a simple total SVD score that awards one point each for lacunes, microbleeds, moderate-to-severe basal ganglia perivascular spaces, and confluent WMH [60]. It predicts outcomes better than individual markers and has been widely adopted for its simplicity. Its limitations are equally clear: equal weighting is arbitrary, and dichotomizing each marker discards information.

Subsequent work applying the score in community-dwelling older people found that greater total SVD burden was associated with lower general cognitive ability after adjustment for age, sex, childhood IQ, and vascular risk factors, and that the association was largely unchanged when WMH were removed from the composite, indicating that the score captures more than WMH alone [61].

Quantitative Diffusion Markers

The most important recent development is a shift toward quantitative measures of tissue microstructure rather than counting or measuring visible lesions. Peak width of skeletonized mean diffusivity (PSMD), introduced by Baykara et al., derives a single robust value from the distribution of mean diffusivity across the white matter skeleton [62]. It correlates strongly with processing speed, is fully automated and therefore free of inter-rater variability, shows larger effect sizes than WMH volume in several cohorts, and has better test-retest reliability. These are attractive properties for a trial endpoint.

Free water imaging, which separates the extracellular free water compartment from tissue-bound diffusion, tracks clinical status in cSVD at least as closely as conventional diffusion measures and accounts for much of the diffusion abnormality previously attributed to altered tissue microstructure [63]. It can be interpreted as interstitial fluid accumulation and plausibly links BBB leakage to its tissue-level consequences.

Diffusion tensor image analysis along the perivascular space (DTI-ALPS) was proposed as a non-invasive index of perivascular clearance function [64], but its interpretation is contested. The index is strongly influenced by white matter microstructure, including fiber orientation and crossing fibers, and its originators have since cautioned that it does not measure glymphatic function as directly as it was first taken to [65]. It should be regarded as exploratory rather than as a basis for clinical decisions.

STRIVE-2 explicitly endorsed these quantitative approaches as intermediary trial outcomes [22], which is likely to accelerate their adoption.

Molecular Imaging in Mixed Disease

Amyloid and tau PET have transformed the diagnosis of AD but complicate the mixed-dementia question. A patient with cognitive impairment, a high WMH burden, and a positive amyloid PET scan has demonstrable AD and vascular pathology, and PET cannot say what proportion of the impairment each explains. Nor can amyloid PET readily distinguish amyloid in the brain parenchyma from amyloid in vessel walls, although the occipital-predominant pattern characteristic of CAA offers a partial clue.

Tau PET tracks cognitive impairment more closely than amyloid PET does, so a patient whose impairment is out of proportion to tau burden and who carries a high vascular burden is, in principle, a candidate for

predominantly vascular attribution. This reasoning is used informally in specialist practice but has not been validated against neuropathology.

Fluid biomarkers

The Biomarker Asymmetry

The biomarker landscape is asymmetric. Blood-based AD markers, plasma p-tau217 above all, have advanced rapidly toward the accuracy of CSF and PET for determining amyloid status [66], raising the prospect that a blood test could replace PET or lumbar puncture in many patients. No comparable marker exists for cSVD.

Candidate Markers of Vascular Injury

Several candidates capture parts of the vascular process. Neurofilament light chain (NfL) reflects axonal injury of any cause. It is elevated in cSVD, correlates with WMH and lacunar infarcts, and predicts progression, but it is entirely non-specific, rising with almost any form of neuroaxonal damage, so an isolated elevation has limited diagnostic value. Glial fibrillary acidic protein (GFAP) reflects astrocytic activation and is associated with both AD and vascular pathology in the same cohorts. Markers of BBB integrity such as the CSF-to-serum albumin ratio and soluble PDGFRβ are mechanistically closer to the process but require CSF and are not standardized for clinical use [46].

What the field lacks is a fluid marker of small vessel pathology with anything like the specificity that p-tau217 offers for AD. Candidates under investigation include placental growth factor, MMP-9, endothelial microvesicles, and proteomic panels, none of which is close to clinical use.

Vascular Influence on Plasma Alzheimer Markers

Recent work sharpens the problem. In the Multi-Ethnic Study of Atherosclerosis, plasma GFAP, NfL, p-tau181, p-tau217, and p-tau231 were all associated with imaging markers of cSVD as well as with AD-related pathology [67]. NfL was positively associated with both WMH and white matter free water, GFAP with WMH, and the three p-tau species with white matter free water, all of which suggests vascular overlap.

This is awkward for the framing of these markers as AD-specific, because it shows that they are measurably influenced by vascular comorbidity. In a patient with mixed pathology, which describes most older patients, a plasma p-tau217 result carries less clean information than its performance in cohorts that excluded vascular disease would suggest. Studies reporting excellent discrimination between pure AD and pure cSVD typically achieve that purity through exclusion criteria that remove the population of interest: the patients with mixed pathology who make up most of a memory clinic's caseload.

Clinical phenotype and the limits of bedside discrimination

Classical Teaching and Its Limits

Classical teaching holds that VCI presents with prominent executive dysfunction, slowed processing speed, relatively preserved episodic memory, early gait disturbance, urinary symptoms, and apathy, in contrast to the amnestic, insidious presentation of AD.

The distinction is real at the group level and unreliable at the individual level. It describes average differences between large groups of patients with vascular dementia and AD, but it often fails when applied to a single patient. Deficits in processing speed are prominent in AD as well, especially late in the course. Episodic memory impairment occurs in cSVD, partly through disruption of frontal-subcortical circuits and partly through medial temporal involvement in mixed disease. Depression and apathy are common in both. And most patients, who have both pathologies, present with both phenotypes superimposed, which is what makes the classical teaching so hard to apply in practice.

Accuracy Against Autopsy

Studies that predict autopsy findings from clinical phenotype show modest accuracy. A meta-analysis of the Hachinski Ischemic Score against pathologically verified dementias found that it separated Alzheimer from multi-infarct dementia reasonably well but performed poorly for mixed cases [68], which are the cases of interest here. Clinical criteria for vascular dementia show high specificity but low sensitivity against autopsy, largely because they were designed around large-vessel infarction.

Gait as an Underused Sign

Gait and motor findings are underused. Slowed gait, shortened stride, and increased stride variability are associated with WMH burden and often precede cognitive decline. Assessment costs almost nothing and requires only serial comparison against the patient's own baseline.

The realistic conclusion is that phenotype narrows the differential but cannot settle attribution. A clinician assessing an older patient with cognitive impairment should start from mixed pathology as the prior and adjust on the basis of biomarkers rather than syndrome.

Genetic and monogenic insights

Monogenic Small Vessel Disease

The monogenic arteriopathies provide the closest thing available to a natural experiment that isolates cSVD from age-related co-pathology.

CADASIL, caused by cysteine-altering mutations in NOTCH3, is the most common of them [69,70]. Its pathology, which includes granular osmiophilic material, aggregation of the NOTCH3 ectodomain, and degeneration of vascular smooth muscle, produces migraine with aura, recurrent subcortical infarcts, mood disturbance, and progressive cognitive impairment, with dementia most often developing in the sixth or seventh decade [70]. The key point for this review is that patients with CADASIL develop the full subcortical cognitive syndrome without significant Alzheimer pathology, which demonstrates that cSVD alone is sufficient to cause dementia. That is a useful corrective whenever vascular dementia is treated as a lesser or secondary diagnosis.

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), caused by biallelic HTRA1 mutations, produces a similar arteriopathy accompanied by alopecia and spondylosis [71], and heterozygous HTRA1 variants have since been implicated in a substantial fraction of familial cSVD that appears sporadic. Mutations in COL4A1, and subsequently COL4A2, cause a basement membrane arteriopathy with a hemorrhage-predominant phenotype [72]. Fabry disease, TREX1-related retinal vasculopathy, and FOXC1-related disease complete the main list.

These conditions have contributed disproportionately to mechanistic understanding, the CADASIL mouse work being a clear example [51], and they define the phenotypic ceiling of what pure cSVD can do.

Common Variant Genetics

Genome-wide association studies of WMH volume, lacunar stroke, and composite cSVD phenotypes implicate extracellular matrix biology, blood pressure regulation, and vessel wall integrity. Traylor et al., in a pooled analysis of lacunar stroke, found evidence of a genetic architecture partly distinct from that of other ischemic stroke subtypes, supporting the view of lacunar stroke as a small vessel arteriopathy rather than a small embolic event caused by a clot from the heart or a large artery [73].

Common variants near COL4A2 and HTRA1, both genes that cause monogenic disease, are associated with sporadic cSVD, suggesting a continuum between rare severe and common mild variation in the same pathways. Mendelian randomization studies, which use genetic variants as a kind of natural randomized experiment to test causality, support a causal effect of elevated blood pressure on WMH volume, including in people without clinical hypertension, which strengthens the case for blood pressure as a treatment target [74].

Treatment, prevention, and the anti-amyloid era

Blood Pressure Lowering

Blood pressure is the best-established modifiable risk factor for cSVD, and the trial evidence for lowering it is the strongest available in this field, though it remains suggestive rather than definitive.

SPRINT MIND, the cognitive component of the Systolic Blood Pressure Intervention Trial (SPRINT), randomized 9,361 adults with hypertension and increased cardiovascular risk to intensive (systolic target below 120 mmHg) or standard (below 140 mmHg) blood pressure control. Over a median follow-up of 5.11 years, probable dementia, the primary cognitive outcome, occurred in 149 participants in the intensive arm and 176 in the standard arm (7.2 vs 8.6 cases per 1,000 person-years), a difference that fell short of significance (HR 0.83, 95% CI 0.67 to 1.04; p = 0.10). Intensive control significantly reduced MCI (14.6 vs 18.3 cases per 1,000 person-years; HR 0.81, 95% CI 0.69 to 0.95; p = 0.007) and the composite of MCI or probable dementia (20.2 vs 24.1 cases per 1,000 person-years; HR 0.85, 95% CI 0.74 to 0.97; p = 0.01) [9]. SPRINT was stopped early because intensive treatment reduced major cardiovascular events and death, which limited the median intervention period to 3.34 years and cut the statistical power for the cognitive endpoints, a consequence that has shaped every subsequent interpretation of the results. Extended follow-up over a median of about seven years, in which cognitive status was ascertained for 4,232 participants, found that the reduction in the composite outcome persisted after the intervention had ended (HR 0.89, 95% CI 0.79 to 0.99), the reduction in MCI was of borderline significance (HR 0.87, 95% CI 0.76 to 1.00), and probable dementia alone still fell short of significance (8.5 vs 10.2 cases per 1,000 person-years; HR 0.86, 95% CI 0.72 to 1.02) [75].

The neuroimaging substudy provided clearer mechanistic evidence. Among 449 participants with baseline and follow-up MRI, white matter lesion volume increased by 0.92 cm^3 with intensive control and by 1.45 cm^3 with standard control (between-group difference -0.54 cm^3, 95% CI -0.87 to -0.20), whereas total brain volume decreased slightly more with intensive control (between-group difference -3.7 cm^3, 95% CI -6.3 to -1.1) [10]. This is the most direct randomized evidence that treatment slows the progression of cSVD, even if the brain-volume finding is a reminder that aggressive treatment involves trade-offs.

Symptomatic lacunar disease is more complicated. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial randomized 3,020 patients with recent MRI-confirmed lacunar stroke to a systolic target below 130 mmHg or 130 to 149 mmHg. Over a mean follow-up of 3.7 years, the lower target produced a non-significant reduction in recurrent stroke (HR 0.81, 95% CI 0.64 to 1.03; p = 0.08) and a significant reduction in intracerebral hemorrhage (HR 0.37, 95% CI 0.15 to 0.95; p = 0.03) [76]. PRESERVE asked whether intensive lowering compromises cerebral perfusion in severe cSVD, a legitimate concern given that these patients often have impaired autoregulation. Among 62 patients with analyzable perfusion imaging, three months of intensive treatment did not reduce cerebral blood flow (mean change 0.7 vs -0.5 mL/100 g/min in the intensive and standard groups) [77], which is reassuring about the safety of aggressive treatment.

Endothelial-Targeted Therapy

The endothelial model predicts that improving endothelial function should slow progression. The Lacunar Intervention Trial (LACI) program has tested this prediction with two inexpensive licensed drugs: isosorbide mononitrate (ISMN), a nitric oxide donor that relaxes blood vessels, and cilostazol, a phosphodiesterase-3 inhibitor with endothelial and antiplatelet effects.

LACI-2, a phase 2 trial with a 2 × 2 factorial, open-label, blinded-endpoint design, randomized 363 patients with lacunar stroke across 26 UK stroke centers to ISMN, cilostazol, both, or neither, in addition to guideline stroke prevention. Its primary outcome was feasibility, which it met: 363 of the planned 400 participants (90.8%) were recruited, 358 (98.6%) were retained at 12 months, 257 of 272 (94.5%) took at least half of the allocated drug, and there were no safety concerns. On exploratory efficacy outcomes, in factorial comparisons of each drug against participants not allocated to it, neither ISMN (adjusted HR (aHR) 0.80, 95% CI 0.59 to 1.09; p = 0.16) nor cilostazol (aHR 0.77, 95% CI 0.57 to 1.05; p = 0.10) alone reduced the composite of vascular events, dependence, cognitive impairment, and death. ISMN was associated with less recurrent stroke (adjusted OR (aOR) 0.23, 95% CI 0.07 to 0.74; p = 0.01) and less cognitive impairment (aOR 0.55, 95% CI 0.36 to 0.86; p = 0.008), and cilostazol with less dependence (adjusted estimate 0.31, 95% CI 0.14 to 0.72; p = 0.006). Compared with no study drug, the combination was associated with a lower composite outcome (aHR 0.58, 95% CI 0.36 to 0.92; p = 0.02), less dependence (aOR 0.14, 95% CI 0.03 to 0.59; p = 0.008), and less cognitive impairment (aOR 0.44, 95% CI 0.23 to 0.85; p = 0.02) [78].

These results are encouraging but preliminary. The trial was not powered for efficacy; the single-drug comparisons were analyzed in 297 to 353 participants and the combination-versus-no-drug comparison in fewer, so the confidence intervals are wide; although outcome assessment was masked, treatment allocation was open, and the composite outcome included subjective components. Its value lies in supporting the endothelial hypothesis strongly enough to justify a definitive trial. LACI-3 (ISRCTN44436843), a phase 3 trial with cognitive impairment as its primary outcome and a target of 1,300 participants, began recruiting in 2025.

Antiplatelet and Antithrombotic Considerations

Antiplatelet therapy is standard after lacunar stroke, but the evidence base is weaker than for other stroke subtypes, and dual antiplatelet therapy carries a particular hemorrhagic risk when the microbleed burden is high. In covert cSVD without clinical stroke, there is no evidence to support antiplatelet therapy, and in the presence of CAA-pattern microbleeds the balance of risk and benefit is plausibly unfavorable. This argues against starting antiplatelet therapy reflexively in an older patient whose only finding is incidental white matter disease on an MRI obtained for some other reason.

Lifestyle and Multidomain Intervention

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) randomized 1,260 at-risk adults aged 60 to 77 years to a two-year multidomain intervention combining diet, exercise, cognitive training, and vascular risk monitoring, or to general health advice. The intervention produced a small but significant cognitive benefit: the between-group difference in the yearly change of the neuropsychological test battery (NTB) total score was 0.022 (95% CI 0.002 to 0.042; p = 0.030) [79]. Attempts at replication elsewhere have had mixed results, and whether the effect is vascular, neuroplastic, or an artifact of training transfer is unresolved. The principal quantitative results of the randomized trials discussed in this section are summarized in Table 2.

Trial	Population and follow-up	Comparison	Outcome	Effect estimate (95% CI)	p-

					value
SPRINT MIND [9]	9,361 adults with hypertension; median 5.11 years	SBP target below 120 vs below 140 mmHg	Probable dementia (primary)	HR 0.83 (0.67 to 1.04)	0.10
			MCI	HR 0.81 (0.69 to 0.95)	0.007
			MCI or probable dementia	HR 0.85 (0.74 to 0.97)	0.01
SPRINT MIND extended follow-up [75]	4,232 with cognitive status ascertained; median about 7 years	As above	Probable dementia	HR 0.86 (0.72 to 1.02)	NR
			MCI	HR 0.87 (0.76 to 1.00)	NR
			MCI or probable dementia	HR 0.89 (0.79 to 0.99)	NR
SPRINT MIND MRI substudy [10]	449 with baseline and follow-up MRI; median 3.97 years	As above	Change in WML volume	Difference -0.54 cm³ (-0.87 to -0.20)	NR
			Change in total brain volume	Difference -3.7 cm³ (-6.3 to -1.1)	NR
SPS3 [76]	3,020 with recent lacunar stroke; mean 3.7 years	SBP target below 130 vs 130 to 149 mmHg	All recurrent stroke	HR 0.81 (0.64 to 1.03)	0.08
			Intracerebral hemorrhage	HR 0.37 (0.15 to 0.95)	0.03
PRESERVE [77]	62 with severe cSVD and analyzable perfusion imaging; 3 months	SBP target below 125 vs 130 to 140 mmHg	Change in cerebral blood flow	0.7 vs -0.5 mL/100 g/min; no reduction with intensive treatment	NS
LACI-2 [78]	363 with lacunar stroke; 12 months	Feasibility (primary outcome)	Retention at 12 months	358 of 363 (98.6%)	NA
		ISMN vs no ISMN	Composite outcome	aHR 0.80 (0.59 to 1.09)	0.16
			Recurrent stroke	aOR 0.23 (0.07 to 0.74)	0.01
			Cognitive impairment	aOR 0.55 (0.36 to 0.86)	0.008
		Cilostazol vs no cilostazol	Composite outcome	aHR 0.77 (0.57 to 1.05)	0.10
			Dependence	Adjusted estimate 0.31 (0.14 to 0.72)	0.006
		ISMN plus cilostazol vs no study drug	Composite outcome	aHR 0.58 (0.36 to 0.92)	0.02
			Dependence	aOR 0.14 (0.03 to 0.59)	0.008
			Any cognitive impairment	aOR 0.44 (0.23 to 0.85)	0.02
FINGER [79]	1,260 at-risk adults aged 60 to 77 years; 2 years	Multidomain intervention vs general health advice	Yearly change in NTB total score	Difference 0.022 (0.002 to 0.042)	0.030

TABLE 2: Principal results of randomized trials relevant to cerebral small vessel disease and cognition

Effect estimates and p-values are as reported in the primary publications; NR indicates that a p-value was not reported, NA is not applicable, and NS is not statistically significant. LACI-2 was a phase 2 trial whose primary outcome was feasibility; its efficacy outcomes were exploratory, and single-drug

comparisons pooled participants across the other factorial arms. The cilostazol estimate for dependence is shown as an adjusted estimate because the trial report labels it inconsistently.

aHR: adjusted hazard ratio; aOR: adjusted odds ratio; CI: confidence interval; cSVD: cerebral small vessel disease; HR: hazard ratio; ISMN: isosorbide mononitrate; MCI: mild cognitive impairment; NTB: neuropsychological test battery; SBP: systolic blood pressure; WML: white matter lesion

The Lancet Commission on dementia has progressively expanded its list of modifiable risk factors, and its 2024 report attributes around 45% of dementia cases worldwide to 14 potentially modifiable exposures [80]. Several of the most heavily weighted factors, including hypertension, diabetes, obesity, smoking, and physical inactivity, act at least partly through cSVD. This provides a population-level argument for vascular risk management as dementia prevention, quite apart from what any single clinical trial has demonstrated directly.

The gap between this population-attributable reasoning and individual-level randomized evidence should be acknowledged. Attributable fractions assume causality and full reversibility, and neither assumption is secure. A risk factor can account for a large share of dementia cases in an epidemiological model without any trial having shown that correcting it in an individual patient prevents that patient's dementia.

cSVD in the Anti-amyloid Immunotherapy Era

The approval of lecanemab and donanemab has made the assessment of cSVD clinically consequential in three ways.

The first is eligibility. Both pivotal trials excluded patients with substantial cerebrovascular disease, including more than four microbleeds, any macrohemorrhage, cortical superficial siderosis, multiple lacunar infarcts or stroke in a major vascular territory, and severe white matter disease [81,82]. Applied in real-world memory clinics, these criteria exclude a very large share of patients. In a tertiary memory clinic cohort of 1,309 new patients, 8% met the approved label criteria, rising to 21% among those with a clinical diagnosis of MCI or AD, and falling to 6% and 15%, respectively, once APOE ε4 homozygotes and anticoagulant users were also excluded [83]. Because only 39% of that cohort had clinical MCI or AD to begin with, diagnosis and disease stage accounted for most of the ineligibility before imaging criteria were applied, although the relative weight of the cerebrovascular exclusions varies considerably between cohorts. Since cSVD burden rises with age, these criteria systematically exclude the oldest and most vascularly burdened patients, who are also among those most likely to present to a memory clinic.

The second is safety. Amyloid-related imaging abnormalities (ARIAs), the principal safety concern with these agents, are vascular in mechanism: the antibodies mobilize amyloid from vessel walls, and underlying CAA is the dominant risk substrate. ARIA takes two forms, ARIA-E (edema or effusion) and ARIA-H (hemorrhage, including microbleeds and superficial siderosis). Established risk factors include APOE ε4 homozygosity, pre-existing microbleeds, and antithrombotic use. Whether the background burden of white matter disease adds independently to ARIA risk beyond these factors has not been established.

The third is expected benefit, which is the least discussed of the three and possibly the most important. If impairment reflects both AD and cSVD, removing amyloid addresses only one contributor, and trial effect sizes derived from populations with minimal vascular disease may not transfer to patients with substantial mixed pathology. In a community-based autopsy series of older persons assessed against anti-amyloid eligibility criteria, 68% of those with Alzheimer neuropathologic change also carried at least one co-pathology, and tangle burden and LATE neuropathologic change (LATE-NC) independently predicted faster decline in episodic memory [84]. The vascular findings in that cohort are instructive: infarcts did not independently predict the rate of global cognitive decline, but arteriolosclerosis did, alongside tangles. That pattern is consistent with the autopsy evidence on direct small vessel pathology reviewed earlier, showing that the vascular contribution is not mediated solely through visible infarction, and it argues for graded small vessel measures rather than infarct counts alone when estimating how much of a given patient's impairment amyloid removal can be expected to address.

In practice, then, cSVD assessment now serves three purposes in the same patient: determining treatment eligibility, estimating hemorrhagic risk, and calibrating realistic expectations of benefit. That justifies systematic, structured reporting of cSVD markers, which remains inconsistent.

Gaps, controversies, and future directions

Measurement

The field's central problem is that cSVD is measured descriptively while AD is measured molecularly. A pathologist or radiologist describes what a vascular lesion looks like; an AD biomarker gives a specific molecular readout. Until a specific fluid or molecular marker of small vessel pathology exists, attribution in mixed disease will remain approximate. Priorities include validating proteomic panels against

neuropathology, developing markers that distinguish arteriolosclerosis from CAA during life, and standardizing quantitative MRI metrics such as PSMD and free water across sites.

Trial Design

Trials in cSVD face a structural problem. Clinical endpoints require long follow-up and large samples, while surrogate endpoints remain unvalidated. WMH progression, the most widely used surrogate, is slow, variable, and of uncertain meaning for the individual. The STRIVE-2 endorsement of diffusion metrics [22] may improve statistical efficiency, but no surrogate has been formally validated against clinical benefit.

Trials should also stop excluding mixed pathology. Both the AD and the vascular literature have selected for purity and have thereby produced evidence that does not apply to the patients clinicians actually see. Factorial designs testing vascular and anti-amyloid interventions together in unselected populations would be informative, and none is being conducted. That is a striking omission given that, as the discussion of anti-amyloid immunotherapy above shows, the two questions already converge in routine clinical practice.

Unresolved Mechanistic Questions

Does cSVD increase the accumulation of amyloid in humans, or only its clinical expression? The human imaging evidence is weaker than the mechanistic literature implies. Is the perivascular clearance framework correct in its details, and can clearance be measured reliably during life? Is neuroinflammation causal or reactive? Are the reported sex differences in cSVD burden real? A systematic review and meta-analysis found a higher male-to-female ratio among people with moderate-to-severe cSVD, but the ratio reversed between hospital-based and community-based cohorts, and the authors could not determine whether it reflected true differences in severity or differences in risk factor exposure, study participation, clinical recognition, or presentation [85]. None of these is a small question. Each, if answered, would change how aggressively clinicians should intervene on vascular risk factors in a given patient, and in what order.

Population Coverage

Most research on cSVD comes from high-income, predominantly white cohorts. The burden of vascular risk is higher in many low- and middle-income settings and in several minoritized populations within high-income countries, and the prevalence of cSVD is correspondingly higher. Whether the mechanisms, thresholds, and treatment responses described here generalize to these populations is largely untested. Because cSVD is the modifiable component of dementia risk, this gap has direct implications for equity and for practice in diverse populations.

Repair Rather Than Prevention

Almost all therapeutic effort is directed at preventing further vascular injury. The oligodendrocyte precursor literature raises the possibility of promoting remyelination within established lesions [50]. Given that patients present with lesions already accumulated, often years or decades after the underlying vasculopathy began, repair strategies deserve more attention than they receive. A prevention-only approach effectively writes off the damage already done in every patient who reaches clinical attention, which is to say nearly everyone currently being treated.

Limitations of this review

This review has limitations that follow from its design. The database search was limited to a single bibliographic database (PubMed/MEDLINE) and to English-language publications, so relevant evidence indexed only in other databases, such as Embase, or published in other languages may have been missed. The final selection of sources involved author judgment, which introduces a risk of selection bias that a systematic review with prespecified, exhaustive inclusion would reduce. No formal risk-of-bias or certainty-of-evidence assessment was performed, so the strength of individual findings is conveyed through description of study design rather than a graded rating. No quantitative synthesis was attempted, and effect estimates from different studies should not be compared directly. Finally, vascular measures harmonize poorly across autopsy cohorts [6], so the vascular contribution summarized here is more likely to be underestimated than overestimated.

Conclusions

cSVD is not a comorbidity of dementia; in a large proportion of patients, it is a constituent of it. Mixed pathology is the norm in late-life dementia; small vessel pathology is its most common vascular element, and vascular lesions lower the burden of Alzheimer pathology required for clinical impairment. Plausible routes of interaction, including barrier failure, hypoperfusion, impaired clearance, and inflammation, have been identified but not yet demonstrated decisively in humans, and current imaging markers predict outcomes without being able to apportion causation in the individual patient. The treatment evidence supports blood pressure control, tentatively supports endothelial-targeted therapy, and increasingly makes

cSVD assessment a prerequisite for decisions about anti-amyloid treatment.

Two conclusions follow for practice. First, “is this Alzheimer’s disease or vascular dementia?” is the wrong question for most older patients; the right question is which pathologies are present, in what proportion, and which of them can be modified, and trainees in particular should resist the instinct, instilled by older textbooks, to sort every patient into a single category. Second, because cSVD is the modifiable component, its assessment and treatment should be routine in every patient with cognitive impairment, not as an alternative to disease-specific therapy but alongside it. Until a biomarker of small vessel pathology exists with the specificity that plasma p-tau217 now provides for AD, managing mixed dementia will mean treating what is treatable while acknowledging what cannot yet be measured.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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