

Review

Vascular Aging Across the Cardiovascular–Alzheimer’s Continuum: Hemodynamics and Artificial Intelligence

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ABSTRACT: Predicting health trajectories and accurately measuring aging processes across the human lifespan remain profound scientific challenges. Assessing the effectiveness and impact of interventions targeting aging is even more elusive, largely due to the intricate, multidimensional nature of aging—a process that defies simple quantification. Traditional biomarkers offer only partial perspectives, capturing limited aspects of the aging landscape. Yet, over the past decade, groundbreaking advancements have emerged. Epigenetic clocks, derived from DNA methylation patterns, have established themselves as powerful aging biomarkers, capable of estimating biological age and assessing aging rates across diverse tissues with remarkable precision. These clocks provide predictive insights into mortality and age-related disease risks, effectively distinguishing biological age from chronological age and illuminating enduring questions in gerontology. Despite significant progress in epigenetic clock development, substantial challenges remain, underscoring the need for continued investigation to fully unlock their potential in the science of aging.

Keywords: Epigenesis, Genetic, DNA Methylation Aging, Biological Clocks, Biomarkers

1. Introduction

Alzheimer’s disease and related dementias (AD/ADRD) and cardiovascular disease (CVD) are major drivers of late-life disability, dependency, and loss of functional independence. Their frequent co-occurrence is not merely the result of age accumulation, but reflects shared upstream biology acting over long exposure windows. Across the life course, biological aging remodels vascular structure and function, perturbs immune and metabolic signaling, and diminishes organ reserve, thereby increasing susceptibility to both vascular cognitive impairment and dementia (VCID) and Alzheimer-type

neurodegeneration [1]. Because disease-modifying therapies for established Alzheimer’s disease currently have limited population-level reach, whereas the preclinical phase commonly extends over 15–25 years, prevention aimed at extending healthspan—delaying onset, slowing progression, and preserving function—has disproportionate clinical and public health value.

Recent prevention frameworks increasingly converge on modifiable determinants operating across the life course. The 2024 update of the *Lancet* Commission expanded the set of potentially actionable risk factors to include untreated vision loss and elevated low-density lipoprotein (LDL) cholesterol, and estimated that

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approximately 45% of dementia cases could, in principle, be delayed or prevented through risk reduction across the lifespan [2, 3]. In parallel, the American Heart Association (AHA) formalized the heart–brain connection in a 2024 scientific statement, emphasizing that common cardiac disorders—including heart failure, atrial fibrillation, and coronary artery disease (CAD) — contribute to cognitive impairment beyond clinically recognized stroke [4]. This position was reinforced by the 2025 AHA scientific statement on VCID, which argued that vascular contributions are pervasive and among the most preventable causes of clinically significant cognitive decline, estimating that elimination of cerebrovascular disease could avert roughly 27–33% of dementia cases [5].

Despite this convergence, cardiovascular prevention and dementia prevention are still often pursued in parallel rather than through a shared aging-informed framework [2, 4, 5]. In this review, we use the term cardiovascular–Alzheimer’s continuum as a translational organizing

framework, not as a new disease taxonomy. Alzheimer’s disease may refer to a biological process defined by amyloid and tau pathology, a clinical dementia syndrome, or a late-life mixed-pathology phenotype in which Alzheimer-related changes coexist with vascular brain injury. Our framework focuses mainly on this late-life mixed-vulnerability setting, while remaining compatible with AT(N)-based biological staging [6]. It complements, rather than replaces, established constructs such as the heart–brain axis, VCID, mixed dementia, CAA, and brain-heart syndrome. Its added value is to emphasize aging-related hemodynamic phenotypes that can be measured and potentially modified, including arterial pulsatility, blood pressure variability, orthostatic instability, atrial disease, rhythm burden, low forward flow, and peri-procedural stress. The intended clinical use is to support risk enrichment, treatment prioritization, biomarker-informed triage, and prevention trial design [4, 5]. The boundaries of this framework and its relationship to adjacent constructs are summarized in Box 1.

Box 1. Definition and boundaries of the cardiovascular–Alzheimer’s continuum

The cardiovascular–Alzheimer’s continuum is used in this review as a translational framework, not as a new disease category. It describes how vascular aging, hemodynamic dysregulation, cardiac disease, neurovascular injury, and Alzheimer-related biology interact over time to shape late-life cognitive vulnerability.

What does the framework add.

This framework emphasizes dynamic cardiovascular and hemodynamic phenotypes—pulsatility, blood pressure variability, orthostatic instability, rhythm burden, low forward flow, embolic propensity, and peri-procedural stress—as measurable pathways that may modify brain vulnerability before dementia becomes clinically established.

Relationship to existing constructs.

Existing construct	How it relates to this framework
Heart–brain axis	Broader bidirectional construct linking cardiac and brain health. The present framework focuses more specifically on aging, hemodynamics, neurovascular vulnerability, and dementia prevention.
VCID	A core component of the framework. The continuum includes VCID but also considers mixed vascular and Alzheimer-related pathology.
Mixed dementia	A common late-life clinical expression of the framework, especially when vascular brain injury coexists with amyloid, tau, or neurodegenerative injury.
AT(N)	A biological staging framework for Alzheimer-related pathology. The present framework uses AT(N)-related biomarkers for calibration, not as a replacement for vascular phenotyping.
CAA	An important vascular expression of amyloid pathology and a safety-relevant phenotype, but not the sole mechanism linking vascular aging with Alzheimer-related decline.
Brain-heart syndrome	Usually refers to acute brain-to-heart effects after neurological injury. The present framework mainly addresses chronic cardiovascular-to-brain and bidirectional aging-related vulnerability.

Clinical decisions the framework is intended to improve.

Intended uses include risk enrichment, individualized BP management, targeted rhythm monitoring, biomarker triage, peri-procedural risk assessment, and prevention-trial selection.

Within this framework, cardiovascular specialists routinely interpret risk through dynamic physiologic patterns—irregular rhythm, impaired forward flow, excessive pulsatility, blood pressure variability, microembolism, and peri-procedural perfusion instability—whereas population screening still relies heavily on coarse and largely static indicators [4, 5, 7–9].

A major translational challenge is to convert this specialist reasoning into scalable, longitudinally measurable phenotypes that can be deployed earlier in the prevention window.

Artificial intelligence is most relevant in this context not as a substitute for mechanism, but as a translation layer between biology and prevention. When rigorously

developed and appropriately governed, AI can transform high-dimensional physiologic signals and multimodal clinical data into computable phenotypes that reflect vascular aging, resilience, and brain vulnerability [10–12]. Examples include latent atrial fibrillation probability inferred from sinus-rhythm electrocardiograms [10, 11], longitudinal phenotypes of blood pressure variability and nocturnal dysregulation [8, 13], retinal microvascular aging signatures derived from fundus photography or OCT/OCTA [14, 15], and integrated profiles that combine these signals with frailty, sleep, and biomarker data [16–18].

Artificial intelligence is considered here only as an enabling layer for scalable phenotyping, not as a substitute for mechanism. It can help quantify clinically obtainable signals such as sinus-rhythm ECG features, blood pressure variability, nocturnal dysregulation, retinal microvascular aging, frailty, sleep, and biomarker profiles [8, 10–18].

Thus, this review focuses on how aging biology, hemodynamic stress, neurovascular vulnerability, and scalable phenotyping may be linked to healthspan-oriented prevention (Fig. 1).

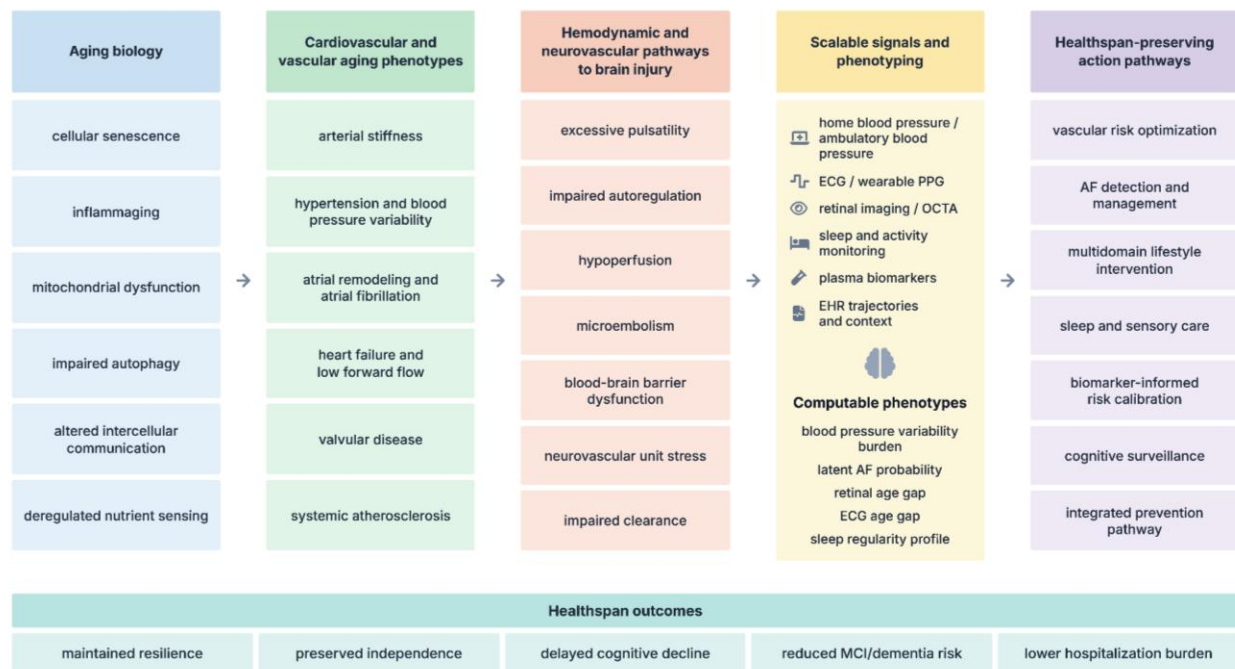


Figure 1. An aging-informed framework for the cardiovascular–Alzheimer’s continuum. Aging biology gives rise to vascular and cardiac phenotypes that shape hemodynamic exposure, neurovascular vulnerability, impaired clearance, and brain injury. Scalable signals from BP monitoring, ECG or wearable photoplethysmography, retinal imaging, sleep/activity monitoring, plasma biomarkers, and EHR trajectories can be translated into computable phenotypes that support prevention-oriented action. **Abbreviations:** AF, atrial fibrillation; BP, blood pressure; ECG, electrocardiography; EHR, electronic health record; MCI, mild cognitive impairment; OCTA, optical coherence tomography angiography; PPG, photoplethysmography.

2. Scope and approach

This article is a narrative review. Its aim is to integrate aging biology, cardiovascular pathophysiology, dementia prevention, scalable phenotyping, and translational implementation within a single aging-informed framework.

Literature selection was therefore guided by conceptual relevance, clinical importance, and translational value rather than by a prespecified systematic-review protocol. Priority was given to several categories of evidence: (1) major aging-biology frameworks and scientific statements relevant to aging, cardiovascular disease, and cognitive impairment [1, 4,

5]; (2) randomized trials and individual-participant or trial-level meta-analyses that anchor modifiable prevention strategies [19–21]; (3) systematic reviews, meta-analyses, and large cohort studies linking cardiovascular phenotypes to cognitive, neuroimaging, or functional outcomes [7, 8, 22, 23]; and (4) artificial-intelligence studies supported by external validation, clinically meaningful end points, or a plausible implementation pathway [10, 11, 14].

Emphasis was placed on recent literature while retaining selected landmark studies that remain foundational to the field. Because the review spans mechanistic biology and implementation science, the goal was not exhaustive coverage of every subfield, but a

selective synthesis of evidence most relevant to the proposition that biological aging and hemodynamic stress jointly shape vulnerability across the cardiovascular–Alzheimer’s continuum.

3. Aging biology as a shared substrate

3.1 Aging biology converts risk factors into vascular phenotypes

The expanded hallmarks of aging describe interdependent biological processes that accumulate across the life course and progressively reshape organ vulnerability [1]. In the cardiovascular system, these processes are not abstract descriptors of aging; they are expressed as recognizable vascular and cardiac phenotypes. Endothelial senescence, mitochondrial dysfunction, oxidative stress, impaired autophagy, chronic low-grade inflammation, and altered intercellular communication jointly reduce nitric oxide bioavailability, promote pro-thrombotic and pro-fibrotic signaling, accelerate extracellular matrix remodeling, and impair microvascular integrity [1, 24]. The clinical consequences include arterial stiffening, widened pulse pressure, increased blood pressure lability, atrial structural remodeling, conduction heterogeneity, reduced diastolic reserve, and greater susceptibility to episodic low-flow states [7, 9].

From an aging-biology perspective, these phenotypes are not merely coexisting cardiovascular disorders; they are downstream expressions of shared aging biology. This framing helps explain why vascular and neurodegenerative processes often cluster in late life and why single-disease silos may underestimate cardio-cognitive overlap [1, 4, 5].

3.2 Biological age, reserve, and resilience determine brain vulnerability

Chronological age alone does not adequately explain why similar hemodynamic exposures produce very different cognitive trajectories across older adults. An aging-informed framework instead emphasizes biological age, reserve, and resilience [1]. Reserve refers to the structural and functional capacity of organ systems to tolerate stress, whereas resilience refers to the ability to adapt and recover after perturbation. In late life, these properties are shaped by cumulative exposures, multimorbidity, frailty, inflammatory burden, sleep disruption, and sensory loss, among other factors [24, 25].

This helps reinterpret common cardiovascular exposures. An identical blood pressure profile, atrial rhythm disturbance, or peri-procedural hemodynamic insult may be buffered in one older adult yet contribute to covert brain injury in another, depending on vascular integrity,

autonomic adaptability, neurovascular reserve, and baseline brain pathology [4, 5]. Hemodynamic risk is therefore not simply a matter of exposure intensity; it is the interaction between exposure and a biologically aged host. This logic supports a healthspan-oriented view of prevention, whose goals are measurable rather than rhetorical: preserved independence in daily activities, mobility and gait stability, slower frailty progression, reduced hospitalization burden, maintained cognition, lower delirium burden or delirium-free survival after stressors, patient-reported quality of life, and quality-adjusted survival [2, 5, 21]. A prevention strategy that improves a biomarker or risk score but increases falls, treatment burden, or loss of independence would not be considered successful in older adults.

3.3 The neurovascular unit links systemic vascular aging to mixed brain pathology

The neurovascular unit (NVU) is a critical interface through which systemic vascular aging is translated into brain injury. Aging-associated endothelial dysfunction, perivascular structural change, astrocytic remodeling, and blood–brain barrier (BBB) leakiness reduce tolerance to pulsatile stress, impair vasomotor coupling, and increase vulnerability to inflammatory and metabolic injury [5, 26]. These changes also weaken the brain’s capacity to maintain stable perfusion during orthostatic shifts, arrhythmia, peri-procedural stress, or chronic low-flow states [9, 27, 28].

The same aging processes may also compromise clearance pathways, increasing susceptibility to mixed vascular and Alzheimer-related pathology. In this review, the neurovascular unit is therefore treated as a common interface through which systemic vascular aging is translated into brain vulnerability, while the specific roles of pericytes, aquaporin-4 polarity, perivascular spaces, and impaired perivascular clearance are discussed in greater detail in Section 4.8.

3.4 Hemodynamics as a measurable expression of aging biology

A practical advantage of this aging-biology framing is that many consequences of biological aging become measurable through hemodynamic phenotypes. Pulsatility, visit-to-visit and day-to-night blood pressure variability, orthostatic recovery, rhythm irregularity burden, forward-flow limitation, sleep–hemodynamic coupling, and peri-procedural instability each reflect how aging physiology absorbs stress, compensates, and fails over time [8, 9, 13, 27]. In this sense, hemodynamic traits can serve as intermediate phenotypes of resilience rather than as static exposure labels.

AI is useful here mainly for scalable quantification of dynamic physiologic dysregulation that conventional screening often misses [10–12, 29]. When anchored to interpretable biological constructs, computable hemodynamic phenotypes may help identify individuals on more adverse cardio-cognitive trajectories [14, 17, 30]. The overarching framework linking aging biology, hemodynamic stress, neurovascular vulnerability, and prevention-oriented action is summarized in Figure 1.

4. Mechanistic pathways across the cardiovascular–Alzheimer’s continuum

The cognitive phenotype expected from vascular aging and hemodynamic stress is not limited to global dementia diagnosis. Executive function, processing speed, attention, working memory, and complex task performance are especially sensitive to white matter injury, hypoperfusion, microvascular dysfunction, and impaired network efficiency [4, 5]. Episodic memory may also be affected, particularly when vascular injury coexists with medial temporal atrophy or Alzheimer-related pathology [4–6]. In acute stress states such as surgery, decompensated heart failure, infection, or hypotension, reduced reserve may present as delirium vulnerability or perioperative neurocognitive disorders (PND) [31, 32]. These domain-level outcomes should be considered alongside dementia incidence when evaluating cardio-cognitive prevention.

4.1 Arterial stiffness and pulsatility

Arterial stiffening is a cardinal feature of vascular aging. Loss of elastic compliance increases pulse pressure, alters wave reflections, and transmits greater pulsatile energy into the cerebral microcirculation. Downstream consequences include white matter hyperintensities (WMH), microbleeds, endothelial injury, and impaired autoregulation—processes central to VCID and likely to amplify vulnerability to Alzheimer-related pathology.

Current evidence supports arterial stiffness as a brain-relevant exposure. Higher pulse wave velocity (PWV) has been linked to both the presence and progression of WMH in older adults [7], and in hypertensive older populations it is also associated with cognitive decline and MRI markers of brain injury [33]. Analyses of estimated PWV (ePWV) in multiethnic cohorts further support arterial stiffness as an accessible phenotype for cognitive and neuroimaging risk stratification [34, 35]. These effects are unlikely to be anatomically uniform. Regions supplied by penetrating end-artery systems and tissues already vulnerable to perfusion instability—including periventricular white matter, deep perforator territories, and medial temporal structures—may be especially

sensitive to pulsatile injury and impaired damping. This regional susceptibility may help explain why arterial stiffness is linked both to white matter injury and to patterns of atrophy that overlap partly with early Alzheimer-related vulnerability.

Although PWV is not routinely measured in primary care, stiffness can be approximated using ePWV and waveform-derived indices from blood pressure and photoplethysmography. AI may help standardize waveform phenotyping and distill stiffness-related features into a longitudinal metric of pulsatility burden suitable for tracking vascular aging and brain vulnerability over time.

4.2 Hypertension, blood pressure variability, and cerebral small vessel disease

Hypertension promotes arteriolosclerosis, endothelial dysfunction, blood–brain barrier stress, and impaired autoregulation, thereby linking elevated blood pressure to VCID and to greater susceptibility to neurodegenerative pathology. In later life, however, mean blood pressure alone often provides an incomplete representation of risk; trajectories, variability, circadian patterning, and recovery after perturbation may better capture the underlying dysregulation.

The association between late-life systolic blood pressure and cognitive outcomes is not monotonic. In older adults, especially beyond age 75, dementia risk may follow a U-shaped or J-shaped pattern, such that both persistently elevated pressure and very low achieved pressure can be associated with worse outcomes [36]. This does not negate the harmful effects of long-standing hypertension. Rather, it suggests that, in advanced age, low blood pressure may sometimes reflect reverse causation, limited physiologic reserve, impaired cerebral autoregulation, or overtreatment in the setting of established small vessel disease. Sex may further modify this relationship. Women appear to experience accelerated vascular aging across the menopausal transition, with steeper worsening of arterial stiffness and endothelial dysfunction after estrogen loss [37]. This suggests that late-life blood pressure trajectories and pulsatile stress may not have identical biologic meaning across sexes and supports sex-aware interpretation of blood pressure variability and hypotension vulnerability in older adults.

Visit-to-visit blood pressure variability (BPV) provides additional information beyond mean systolic pressure. Higher late-life BPV, more than midlife BPV, has been associated with greater lifetime dementia risk, suggesting that BPV may function as a marker of late-life vulnerability and physiologic instability [13]. Meta-analytic evidence likewise links greater BPV with

dementia and cognitive impairment across heterogeneous cohorts and BPV definitions [8]. From a mechanistic standpoint, fluctuating pressure may amplify shear stress, endothelial injury, and failure of microvascular autoregulation, thereby accelerating covert cerebrovascular damage.

Ambulatory blood pressure monitoring adds another layer of biologic relevance by capturing nocturnal dipping status and other circadian phenotypes. Reduced nocturnal dipping has long been associated with silent cerebrovascular damage and cognitive vulnerability, whereas extreme dipping may represent a distinct high-risk phenotype in which excessive nocturnal pressure decline coexists with advanced ischemic small-vessel injury [38, 39]. More recent imaging work further suggests that nocturnal blood pressure abnormalities are linked to cognition partly through white matter hyperintensity burden [40]. These non-dipper and extreme-dipper patterns should therefore be viewed not as chronobiologic curiosities, but as clinically meaningful indicators of impaired vascular regulation and white matter vulnerability.

Randomized evidence supports blood pressure lowering as dementia-relevant prevention, but also argues against a one-size-fits-all interpretation. The original SPRINT trial established that intensive systolic blood pressure control improves major cardiovascular outcomes and survival [41]. In SPRINT MIND, intensive control reduced incident mild cognitive impairment and the composite outcome of mild cognitive impairment or probable dementia [19], and an individual patient data meta-analysis similarly supported a reduction in incident dementia with blood pressure lowering [20]. However, ACCORD-MIND, conducted in older adults with type 2 diabetes, did not show measurable cognitive benefit from intensive blood pressure lowering and found greater decline in total brain volume at 40 months [42]. Taken together, these trials suggest that benefit is context-dependent and likely modified by age, diabetes, baseline brain vulnerability, and treatment tolerability.

Mechanistic plausibility is reinforced by neuroimaging analyses from SPRINT MIND. Intensive blood pressure control was associated with increased whole-brain cerebral blood flow, alleviating concerns about universal cerebral hypoperfusion [43], and with more favorable trajectories of cerebral small vessel disease biomarkers [44]. These observations support the view that vascular-risk intervention can improve brain-relevant physiology, but they do not eliminate the need for caution in frail older adults or in those with orthostatic intolerance, extensive white matter disease, or limited reserve.

A practical implication is that intensive blood pressure control should be considered a phenotype- and

tolerance-guided strategy rather than a universal target for all older adults. Older adults most likely to benefit are those with persistent hypertension, elevated cardiovascular risk, reasonable functional reserve, low orthostatic symptom burden, and the ability to tolerate gradual medication intensification with monitoring [19, 20, 41, 43, 44]. Greater caution is needed in patients with frailty, recurrent falls, orthostatic hypotension, syncope, advanced renal dysfunction, polypharmacy, low achieved systolic pressure, extensive cerebral small vessel disease, or imaging markers suggestive of CAA [36, 42–45]. In these patients, standing blood pressure, home or ambulatory measurements, renal function, falls history, cognition, and medication burden should be reviewed before intensification. De-intensification may be appropriate when low pressure or orthostatic instability threatens perfusion, mobility, or independence [36, 42].

Home and ambulatory blood pressure monitoring now allow quantification of BPV, nocturnal dipping, morning surge, and orthostatic response outside the clinic. AI could classify blood pressure trajectories, quantify BPV burden, identify non-dipper or extreme-dipper phenotypes, and detect periods during which treatment intensification or de-intensification may better preserve vascular and brain health. In this context, blood pressure phenotypes function less as simple exposure summaries than as markers of resilience, autoregulatory capacity, and physiologic dysregulation.

4.3 Atrial fibrillation and atrial cardiomyopathy

Atrial fibrillation (AF) is a prototypical bridge condition across the cardiovascular–brain axis. Its links to cognitive impairment are mechanistically diverse, encompassing silent infarction and microembolism, cerebral hypoperfusion related to an irregular ventricular response, inflammation, endothelial dysfunction, and blood–brain barrier stress [9, 28]. This constellation helps explain why cognitive risk may remain elevated even in the absence of clinically recognized stroke.

However, AF should not be viewed as the entire substrate. The broader and more mechanistically informative concept is atrial cardiomyopathy, defined as structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations [46]. In an aging-informed context, this concept is especially useful because aging, hypertension, obesity, diabetes, heart failure, and sleep-disordered breathing can all promote atrial fibrosis, dilation, impaired reservoir and booster-pump function, conduction heterogeneity, and a thrombogenic atrial milieu before or beyond manifest AF [46, 47]. This means that the brain-relevant exposure may not be AF alone, but a broader atrial disease state capable

of generating embolic propensity, impaired atrial transport, rhythm instability, and systemic inflammatory signaling. Sex differences are also relevant in this pathway. Although AF is often diagnosed earlier and more frequently in men, women with AF have historically carried a higher risk of ischemic stroke and may present later, older, and with greater accumulated vascular vulnerability [48, 49]. In a cardio-cognitive framework, this implies that similar rhythm phenotypes may translate into different downstream brain risk across sexes, particularly when AF coexists with frailty, hypertension, or HFpEF.

This framing also helps explain why left atrial dysfunction may matter even when AF burden appears modest. Markers of left atrial myopathy have been associated with higher risks of stroke and cognitive impairment, suggesting that atrial remodeling may contribute to brain injury partly independent of clinically apparent AF episodes [50]. From this perspective, AF can be interpreted as one clinical expression of a broader atrial aging phenotype. Clinically, atrial cardiomyopathy can be approached through complementary structural, functional, electrical, biochemical, and rhythm-burden markers. Candidate markers include left atrial volume index, left atrial reservoir and booster-pump strain, P-wave indices such as P-wave terminal force in lead V1 and interatrial block, NT-proBNP or related natriuretic peptides, imaging evidence of atrial fibrosis, AF burden, premature atrial contraction burden, and left atrial appendage emptying or mechanical function [46, 47, 50]. These markers should not be interpreted as equivalent to clinically documented AF, but they may help identify an atrial substrate in which embolic propensity, impaired atrial transport, and rhythm instability contribute to brain vulnerability [46, 47, 50].

The association between AF and dementia remains well supported, although effect sizes vary by age, comorbidity burden, and outcome ascertainment [22]. Observational comparative-effectiveness analyses have further examined whether rhythm-control strategies might reduce dementia risk by lowering AF burden. Catheter ablation has been associated with lower risks of dementia and Alzheimer's disease than non-ablation management, although residual confounding remains unavoidable in observational data [51, 52]. Similar associations have also been reported when optimized anticoagulation accompanies ablation [53]. These findings do not establish causality, but they support AF burden as a dynamic and potentially brain-relevant exposure.

Randomized data strengthen the argument that AF burden is modifiable in clinically meaningful ways. In EAST-AFNET 4, an early rhythm-control strategy reduced the composite outcome of cardiovascular death, stroke, or hospitalization for heart failure or acute

coronary syndrome compared with usual care [54]. Subsequent analyses further suggested that attainment of sinus rhythm mediates much of this benefit, reinforcing the idea that rhythm burden is not merely descriptive but potentially actionable [55]. Importantly, EAST-AFNET 4 was not a dementia-prevention trial and should not be presented as direct proof of cognitive benefit. Its relevance here is conceptual and translational: it supports the proposition that earlier modification of the atrial-rhythm substrate may alter downstream brain-relevant exposure.

AF is also unusually actionable because detection can be scaled. Large-scale wearable irregular-pulse notification with confirmatory monitoring has proven feasible [56]. AI-enabled ECG models can detect an AF signature from a sinus-rhythm ECG, creating a strategy for targeted ambulatory monitoring rather than universal patching [10]. AI-guided targeted screening has also increased AF detection yield relative to usual care [11]. Together, these approaches provide a pathway through which latent AF probability, rhythm burden, and perhaps future markers of atrial cardiomyopathy can be translated into scalable public health metrics and linked to prevention-oriented care.

A final implication is that atrial disease may need to be monitored at more than one level: overt arrhythmia, underlying atrial substrate, and downstream embolic or hemodynamic consequences. This layered view fits naturally with the cardiovascular–Alzheimer's continuum, in which aging-related atrial remodeling may amplify mixed vascular and neurodegenerative vulnerability. Left atrial appendage occlusion may eventually become relevant to this discussion through its potential effects on thromboembolic and silent cerebral embolic burden, but current evidence remains emerging and is best reserved for future-direction or outlook sections rather than as a central pillar of the present review.

4.4 CAD and systemic atherosclerosis

CAD reflects systemic atherosclerotic burden, endothelial dysfunction, and inflammaging. Its association with cognitive outcomes likely operates through covert brain infarction, cerebral small vessel disease, shared cardiometabolic risk, and diminished physiologic reserve. Life-course epidemiology suggests that timing is critical. Earlier onsets of CAD is associated with higher risks of incident all-cause dementia, Alzheimer's disease, and vascular dementia, with particularly elevated risk among individuals diagnosed before midlife [57]. Earlier cardiovascular disease onset has likewise been linked to higher later-life dementia risk, whereas adherence to

recommended lifestyle factors after CVD diagnosis is associated with lower dementia risk [58].

Both onset age and cumulative exposure can be operationalized from the electronic health record, while longitudinal lipid and blood pressure trajectories may capture accelerated vascular aging. AI could integrate these features to identify individuals with early vascular aging who may benefit from more intensive, healthspan-oriented prevention.

4.5 Heart failure and low forward flow: perfusion reserve, frailty, and cognitive trajectories

The association between heart failure (HF) and adverse cognitive outcomes is well supported. HF has been linked to poorer cognitive performance and higher risks of dementia, and cognitive impairment and dementia are common in HF populations, particularly at older ages [23, 59]. These observations are consistent with the AHA scientific statement identifying HF, AF, and CHD as the three most prevalent cardiac contributors to cognitive impairment and dementia [4].

Two features are especially important in older adults. First, cognitive impairment in HF is not merely an accompanying condition; it directly affects adherence, self-care capacity, and participation in rehabilitation, thereby shaping healthspan trajectories. Second, hemodynamic instability in HF is often episodic—during decompensation, nocturnal congestion, or arrhythmic episodes—so brain risk is better represented by time-varying exposure than by a single ejection fraction value.

HF subtype also matters. In HFrEF, the dominant brain-relevant mechanism is often reduced forward flow with chronic or intermittent cerebral hypoperfusion, particularly when low cardiac output coexists with hypotension, arrhythmia, or impaired autoregulatory reserve [60]. In HFpEF, by contrast, the signal is often less about marked systolic flow failure and more about aging-related systemic disease: microvascular dysfunction, endothelial inflammation, metabolic comorbidity, myocardial stiffening, exercise intolerance, and impaired reserve [61]. This distinction is useful because it aligns HF subtypes with different cardio-cognitive vulnerability patterns rather than treating HF as a single homogeneous exposure.

HFpEF is especially relevant to the present aging-informed framework because it is common in older adults and increasingly conceptualized as a multisystem syndrome rather than an isolated filling-pressure disorder [61]. Its biology overlaps with vascular aging, frailty, obesity, diabetes, chronic kidney disease, and systemic inflammation, all of which may also heighten neurovascular vulnerability. In this setting, cognition may

be affected not only by perfusion instability but also by diffuse microvascular dysfunction and reduced resilience.

A further bridge is the close interaction between HFpEF and atrial fibrillation, a phenotype that is particularly frequent in older patients and may amplify brain risk through combined hemodynamic instability, atrial dysfunction, embolic propensity, and reduced exercise capacity [62]. This AF–HFpEF–cognition cluster is worth emphasizing because it fits the broader argument of the review: late-life cognitive vulnerability often emerges from overlapping cardiovascular aging phenotypes rather than from a single disease label.

Neurohormonal activation and systemic inflammation in HF may further interact with vascular aging to stress the neurovascular unit [60]. For prevention, the practical implication is that HF should be phenotyped dynamically: decompensation burden, nocturnal congestion, heart-rate recovery, activity decline, rhythm instability, and frailty may all be more informative than static left ventricular function alone. AI may be useful here not simply for prognosis, but for identifying trajectories of decompensation and reduced reserve that signal heightened brain vulnerability and the need for closer functional and cognitive follow-up.

4.6 Structural and valvular heart disease: hemodynamic correction as a brain-relevant intervention

Structural and valvular heart disease is common in later life and provides a distinctive setting in which a brain-relevant hemodynamic exposure can sometimes be directly corrected. Severe aortic stenosis, for example, imposes chronic outflow obstruction, low forward flow, altered pulsatility, and reduced cerebral perfusion reserve. In this sense, valvular intervention offers not only symptom relief, but also a natural experiment for testing whether correction of hemodynamic stress can improve brain-relevant physiology.

In severe symptomatic aortic stenosis treated with transcatheter aortic valve implantation (TAVI), improvements in cardiac output, cerebral blood flow, and cognitive function have been observed within months of intervention [27]. This is notable because it links a modifiable hemodynamic exposure to both an intermediate brain-relevant endpoint and cognitive performance. The CAPITA study rationale further reinforces the value of systematically capturing cardiac output, cerebral blood flow, and cognition around TAVI and related interventions [63].

At the same time, structural intervention should not be framed as purely restorative. TAVI is also a high-resolution model of procedure-related embolic and perfusion stress. Silent cerebral ischemic lesions on

diffusion-weighted MRI have been reported in a large proportion of patients after TAVI, and higher lesion burden may adversely affect early neurocognitive outcomes [64, 65]. Transcranial Doppler studies likewise support a substantial intraprocedural microembolic load, making TAVI a useful procedural model for understanding how embolic burden and impaired reserve interact in older brains [66].

This duality is important for interpretation. On one hand, relief of valvular obstruction may improve forward flow, cerebral perfusion, and cognition. On the other hand, the procedure itself may generate embolic injury that offsets some of that benefit in vulnerable patients. This is precisely why structural intervention is so informative within an aging-informed framework: it exposes both the reversibility of chronic hemodynamic stress and the limits imposed by embolic burden, frailty, and coexisting neurovascular pathology.

Cerebral embolic protection (CEP) devices have therefore attracted considerable interest. However, the most recent randomized evidence does not support an overly strong clinical claim. In BHF PROTECT-TAVI, routine CEP did not reduce periprocedural stroke within 72 hours [67], and a prespecified cognitive analysis found no improvement in short-term cognitive outcomes with routine CEP use [68]. However, cognitive outcomes were a prespecified secondary analysis, and the trial was not powered for this endpoint. The current implication is not that embolic protection is biologically irrelevant, but that the translation from captured debris and imaging surrogates to consistent clinical benefit remains unsettled.

The broader lesson extends beyond aortic stenosis. Mitral valve disease may influence the brain through somewhat different hemodynamic routes. In severe mitral regurgitation, the relevant exposure is often chronic volume overload, left atrial enlargement, venous and pulmonary congestion, reduced effective forward flow, and frequent coexistence with AF and HF rather than fixed valvular outflow obstruction. Small studies suggest that transcatheter mitral repair can be accompanied by improvement in cognitive performance and quality of life in selected high-risk patients [69], supporting the idea that relief of chronic hemodynamic and congestive stress may also be brain-relevant. In severe mitral regurgitation, impaired cerebral venous drainage has additionally been proposed as one contributor to cognitive vulnerability [70].

Structural interventions also provide a valuable platform for mechanistic discovery and validation. Protocol-driven peri-procedural monitoring makes it possible to align granular hemodynamic measures—including blood pressure variability during anesthesia, cerebral oximetry, and embolic signals—with short- and medium-term cognitive outcomes. More broadly, valvular

disease may function as a clinical stress test of neurovascular resilience: when cognitive or functional recovery remains incomplete after hemodynamic correction, limited reserve, mixed pathology, or underlying neurodegeneration should be considered, prompting integrated geriatric and cognitive follow-up.

4.7 Peri-procedural hemodynamic stress and PND

Perioperative care, particularly in cardiac surgery and structural interventions, offers a high-resolution view of brain vulnerability under hemodynamic stress. Using current terminology, these outcomes are best described within the framework of PND, an umbrella term that includes postoperative delirium as the acute syndrome, delayed neurocognitive recovery (dNCR) within the first 30 days after surgery, and postoperative neurocognitive disorder when cognitive decline persists over 30 days and up to 12 months [31]. This nomenclature is preferable to the older unspecific use of “POCD” because it aligns perioperative cognitive change with contemporary neurocognitive classification and more clearly distinguishes delirium from longer-lasting decline.

From the perspective of the present review, peri-procedural settings are valuable because they compress multiple brain-relevant insults into a short and observable time window. Hypotension burden, blood pressure lability, embolic load, impaired autoregulation, inflammatory activation, and anesthesia-related physiologic stress can converge on an older brain with limited reserve, unmasking vulnerability that may remain clinically silent in ordinary life [71–73]. In this sense, PND can be interpreted not only as complications, but also as stress-test phenotypes of neurovascular resilience.

Cardiac surgery with cardiopulmonary bypass (CPB) is especially informative as a mechanistic model. CPB concentrates several of the same exposures emphasized elsewhere in this review—microemboli, nonphysiologic flow, cerebral hypoperfusion risk, hemodilution, oxidative and inflammatory stress, and periods of impaired cerebral autoregulation—into an acute “extreme exposure” state [32, 74]. This does not mean that CPB should dominate the present review, but it does provide a useful validation model: if chronic vascular aging and hemodynamic dysregulation are central to late-life cognitive vulnerability, then CPB can be viewed as a procedural setting in which those mechanisms are amplified and made more directly observable.

This framing also clarifies the relationship between delirium and longer-term decline. Postoperative delirium is an acute neuropsychiatric syndrome and should not be conflated with dNCR or postoperative neurocognitive disorder, although the syndromes may coexist and often arise in the same high-risk patients [31, 32]. Their overlap

is clinically useful because it highlights a shared substrate of limited reserve, vascular fragility, inflammation, and impaired recovery capacity rather than a single unitary mechanism.

The translational implication is that peri-procedural monitoring may provide a practical window into modifiable vulnerability. Measures such as intraoperative blood pressure trajectories, near-infrared spectroscopy, transcranial Doppler embolic signals, cerebral autoregulation monitoring, and postoperative delirium surveillance can help identify patients who may benefit from closer longitudinal cognitive follow-up or intensified prevention after discharge [74, 75]. For this review, the key point is not to recast the article as a perioperative neuroprotection review, but to recognize peri-procedural neurocognitive injury as a clinically important and mechanistically revealing extension of the broader cardiovascular–Alzheimer’s continuum.

4.8 Neurovascular unit dysfunction, BBB failure, and impaired perivascular clearance

The neurovascular unit (NVU) provides the most biologically coherent interface between systemic vascular aging and late-life brain injury. Rather than acting as a passive barrier, the NVU coordinates endothelial function, pericyte support, astrocytic endfoot signaling, vascular tone, substrate delivery, and waste clearance. In aging, this integrated system becomes progressively less resilient: endothelial dysfunction, basement membrane remodeling, and impaired vasomotor coupling reduce tolerance to pulsatile and hypoperfusion stress, while blood–brain barrier (BBB) permeability increases vulnerability to inflammatory and blood-derived injury [5, 76].

Pericyte injury is especially relevant in this context because it links microvascular aging to both BBB failure and impaired protein clearance. Experimental and human studies from the Zlokovic group and others have shown that pericyte degeneration is associated with BBB breakdown, reduced capillary integrity, and impaired clearance of soluble amyloid- β from brain interstitial fluid [77]. This shifts the emphasis of the present review from hemodynamics alone toward hemodynamic stress acting on a biologically compromised clearance interface. In other words, excessive pulsatility, blood pressure variability, low-flow states, and inflammatory cardiac phenotypes are most likely to become brain-injurious when the aging NVU has already lost buffering capacity.

Astrocytic endfeet and aquaporin-4 (AQP4) polarity represent a second key component of this interface. The glymphatic and broader perivascular clearance systems

depend in part on preserved astrocyte–vascular organization, sleep physiology, and vascular pulsatility. Aging and vascular disease appear to disrupt this organization, with loss of AQP4 polarization and altered perivascular transport increasingly viewed as plausible contributors to impaired clearance of amyloid- β and tau [26, 78]. This makes sleep and nocturnal hemodynamics mechanistically relevant rather than merely associative: they may influence whether protein clearance remains efficient or progressively fails under conditions of vascular aging [79, 80].

Perivascular spaces (PVS), particularly when enlarged in the centrum semiovale, are also relevant because they provide an imaging-visible correlate of disturbed perivascular physiology. Recent diagnostic work in cerebral amyloid angiopathy has incorporated severe centrum semiovale PVS as one of the white-matter markers that improve in vivo recognition of vascular amyloid disease, reinforcing the idea that MRI-visible PVS burden can reflect impaired perivascular clearance rather than being dismissed as an incidental aging finding [45]. From a translational perspective, this strengthens the rationale for considering NVU dysfunction, BBB leakiness, sleep physiology, and PVS-related imaging features within a common framework of brain vulnerability.

This framework also helps reinterpret atrial fibrillation and related systemic inflammatory states. AF may compromise BBB integrity through hypoperfusion, endothelial injury, oxidative stress, and inflammatory signaling [28]. Yet the downstream consequence is unlikely to be limited to generic vascular damage. A more integrated view is that AF and other hemodynamic disorders may accelerate injury when they interact with an aging NVU already characterized by impaired neurovascular coupling, weakened barrier integrity, and reduced perivascular clearance capacity. This interaction is likely to be especially important in patients with mixed vascular and Alzheimer-related pathology.

These observations matter for prevention because they justify expanding the target beyond single risk-factor control. Preserving brain healthspan may require not only reducing hemodynamic stress but also protecting the biological systems that determine whether such stress is buffered or converted into covert brain injury. As summarized in Figure 2, cardiovascular aging converges on downstream pathways of perfusion dysregulation, BBB injury, neurovascular unit dysfunction, and impaired clearance.

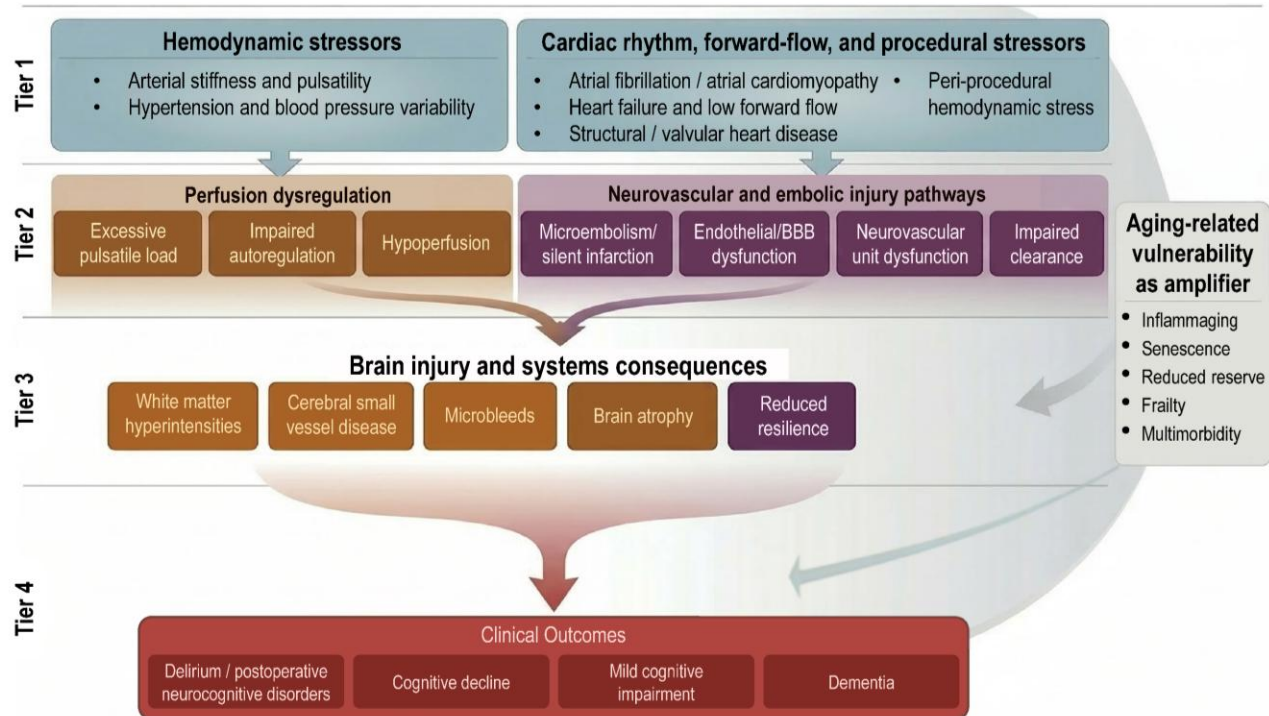


Figure 2. Mechanistic pathways linking cardiovascular aging to brain injury and cognitive decline. Cardiovascular aging contributes to brain injury through converging hemodynamic, embolic, and neurovascular mechanisms. Arterial stiffness, hypertension and blood pressure variability, atrial fibrillation, heart failure with low forward flow, structural heart disease, and peri-procedural stress promote perfusion dysregulation, endothelial and blood–brain barrier injury, neurovascular unit dysfunction, microembolism, and impaired clearance. These pathways converge on white matter injury, cerebral small vessel disease, microbleeds, brain atrophy, and reduced resilience, thereby contributing to delirium or postoperative neurocognitive disorders, cognitive decline, mild cognitive impairment, and dementia. Aging-related vulnerability acts throughout as an amplifier of susceptibility and clinical expression. **Abbreviations:** BBB, blood–brain barrier.

4.9 Cerebral amyloid angiopathy: a vascular expression of Alzheimer-related pathology

Cerebral amyloid angiopathy (CAA) is an important vascular expression of Alzheimer-related amyloid biology, but it should not be interpreted as the universal mechanism underlying vascular–Alzheimer overlap. Many older adults with cognitive decline have vascular brain injury, Alzheimer-related pathology, Lewy body disease, TDP-43 pathology, hippocampal sclerosis, or mixed combinations without CAA being the dominant process. In CAA, amyloid- β deposits within leptomeningeal and cortical vessel walls, linking impaired clearance to vascular fragility, microhemorrhage, impaired vasoreactivity, and tissue injury [81]. Its relevance to this review is therefore twofold: CAA provides a biologically specific example of vascular amyloid and impaired perivascular clearance, and it identifies a safety-relevant phenotype for anticoagulation decisions, hemorrhagic risk assessment, and anti-amyloid therapy surveillance [45, 81–83].

This makes CAA highly relevant to aging-informed framing. The same age-related processes discussed

above—arterial stiffening, impaired vasomotor function, basement membrane remodeling, BBB dysfunction, pericyte injury, and reduced perivascular clearance—create conditions in which vascular amyloid deposition can become self-reinforcing [81, 82]. Once vascular amyloid accumulates, vessel-wall integrity and perivascular drainage may deteriorate further, amplifying both hemorrhagic and non-hemorrhagic brain injury. CAA therefore should not be viewed as an isolated neuropathologic curiosity, but as a disease process that exemplifies how aging biology converts impaired clearance into clinically meaningful vascular brain injury.

The in vivo recognition of CAA has also advanced. The Boston criteria version 2.0 incorporate not only hemorrhagic markers such as lobar cerebral microbleeds and cortical superficial siderosis, but also white-matter features including severe centrum semiovale PVS and multispot white-matter hyperintensities, which together improve diagnostic sensitivity while preserving specificity [45]. This is directly relevant to the present review because it shows that MRI-visible manifestations of clearance failure and vascular fragility are already entering practical diagnostic frameworks.

CAA is also increasingly important in the era of anti-amyloid therapy. Reviews of amyloid-related imaging abnormalities (ARIA) emphasize that ARIA shares important radiological, biological, and pathophysiological overlap with CAA, and that baseline microhemorrhages and related vascular imaging abnormalities increase risk during anti-amyloid treatment [83]. In mechanistic terms, anti-amyloid mobilization may stress already compromised perivascular pathways and CAA-positive vessels, providing a contemporary clinical example of how clearance biology, vascular fragility, and Alzheimer pathology intersect [81, 83].

For cardiovascular and peri-procedural clinicians, the relevance of CAA extends beyond dementia taxonomy. CAA identifies a subgroup in whom microvascular fragility, hemorrhagic susceptibility, impaired clearance,

and mixed pathology are all more likely. This has implications for anticoagulation decisions, interpretation of MRI small-vessel markers, anti-amyloid safety surveillance, and the broader question of why some older adults show disproportionate cognitive consequences from apparently modest hemodynamic stress.

5. From specialist insight to scalable screening: computable hemodynamics and aging markers

Before individual signals are considered, it is important to clarify their evidentiary status. Because not all measurable phenotypes have the same clinical meaning, Box 2 distinguishes established modifiable risk factors from risk markers, mechanistic intermediates, and unvalidated surrogate endpoints [19, 20, 46, 47, 84, 85].

Box 2. Interpreting risk factors, risk markers, mechanistic intermediates, and surrogate endpoints

Category	Examples in this review	How to present them
Established modifiable risk factors	Hypertension, dyslipidemia, AF when present, heart failure optimization, smoking, diabetes, physical inactivity, sleep disorders when clinically diagnosed	Clinically actionable under existing guidelines; cognitive prevention may be an additional rationale.
Risk markers	Retinal age gap, ECG age gap, latent AF probability, elevated NfL/GFAP, retinal microvascular scores, activity decline slope	Useful for risk enrichment or triage; not direct treatment targets.
Mechanistic intermediates	Arterial stiffness, pulsatility burden, BP variability, orthostatic instability, AF burden, low forward flow, BBB dysfunction, impaired perivascular clearance	Biologically plausible links between exposure and brain injury; intervention responsiveness must be tested.
Unvalidated surrogate endpoints	BPV burden score, retinal age gap change, ECG age gap change, wearable sleep regularity score, multimodal AI risk score	Should not be assumed to predict clinical benefit unless linked to cognition, function, or healthspan outcomes in trials.

This box clarifies how phenotypes discussed in the review should be interpreted. The categories are not mutually exclusive in all settings, but they help distinguish clinically actionable risk factors from emerging markers and unvalidated surrogate endpoints.

Abbreviations: AF, atrial fibrillation; AI, artificial intelligence; BBB, blood–brain barrier; BP, blood pressure; BPV, blood pressure variability; ECG, electrocardiography; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain.

5.1 Retinal imaging as a microvascular aging biomarker

Retinal imaging provides a practical window into microvascular aging that fits naturally within an aging-informed framework: it is low burden, scalable, and rich in information on microvascular structure and biological aging. Deep-learning approaches can estimate retinal biological age, generating an “age gap” phenotype that may summarize cumulative vascular stress and microvascular rarefaction. A schematic overview of how clinically obtainable signals can be translated into intermediate computable phenotypes within an AI-enabled phenotyping layer is shown in Figure 3.

Retina-based prediction of cognitive decline and dementia has become increasingly plausible. Retinal aging biomarkers such as RetiPhenoAge have been associated with future cognitive decline and incident dementia, with replication for long-term incident

dementia in UK Biobank [14]. Their relevance extends beyond prediction alone, as retinal aging signals also track cerebral small vessel disease, brain atrophy, and aging-related plasma proteomic signatures, further supporting their value as microvascular and aging-relevant phenotypes [14].

Beyond fundus photography, optical coherence tomography angiography (OCTA) captures layered retinal microvasculature and choriocapillaris features that may align even more closely with cerebral microvascular biology. Deep-learning frameworks using OCTA have demonstrated the feasibility of detecting early Alzheimer’s disease and mild cognitive impairment from graph-based or layered vascular representations [15, 86]. Taken together, these developments suggest that retinal imaging is evolving from a descriptive ophthalmic modality into a scalable platform for quantifying microvascular aging in relation to brain health.

For implementation, retinal metrics offer two practical advantages. They can be communicated as interpretable aging markers, such as retinal age gaps, rather than opaque probabilities, and image acquisition can be integrated into existing optometry and primary-care networks, providing scalable infrastructure for risk enrichment. Retinal imaging may also intersect with amyloid biology more directly. Prior studies have reported retinal amyloid- β deposits in Alzheimer's

disease and correlations with cerebral amyloid burden, raising the possibility that retinal vascular and parenchymal signals may eventually help bridge microvascular aging phenotypes with amyloid-related pathology. Although this literature remains methodologically heterogeneous, it provides a potentially relevant parallel to the vascular amyloid biology discussed in Section 4.9.

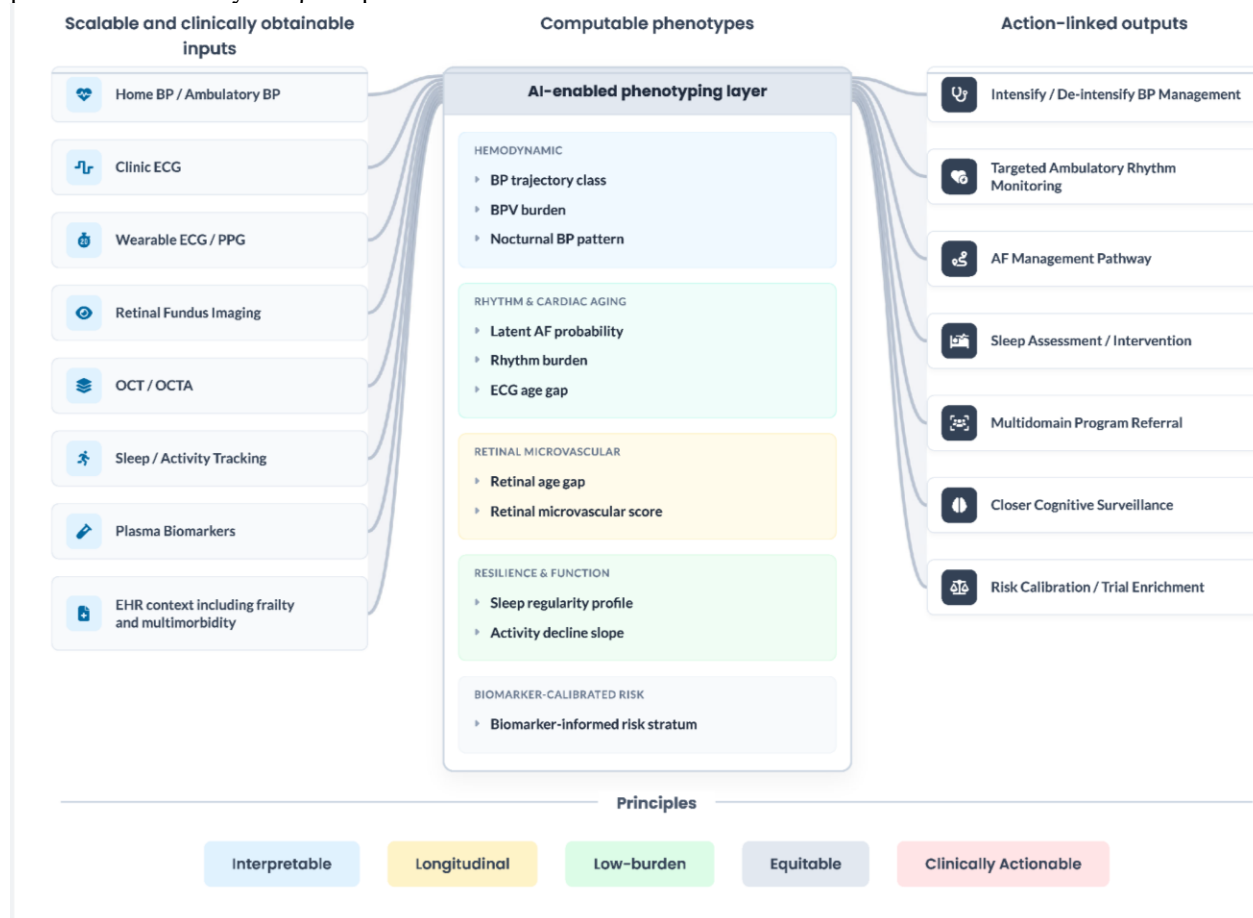


Figure 3. From scalable signals to computable phenotypes in cardio-cognitive prevention. Clinically obtainable inputs, including BP monitoring, ECG or wearable signals, retinal imaging, OCT/OCTA, sleep/activity tracking, plasma biomarkers, and EHR context, can be organized into hemodynamic, rhythm, cardiac aging, retinal microvascular, resilience/function, and biomarker-calibrated phenotypes. These phenotypes can support BP management, targeted rhythm monitoring, sleep intervention, multidomain referral, cognitive surveillance, risk calibration, and trial enrichment. **Abbreviations:** AF, atrial fibrillation; AI, artificial intelligence; BP, blood pressure; BPV, blood pressure variability; ECG, electrocardiography; EHR, electronic health record; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography.

5.2 ECG and PPG as scalable hemodynamic and aging signals

Electrocardiography provides a low-cost window into electrical aging, conduction heterogeneity, and rhythm disorders. AI-enabled ECG models can identify a latent AF signature from a sinus-rhythm ECG, enabling targeted monitoring of individuals at elevated AF risk [10, 11].

An extension of this logic is the concept of AI-derived “ECG age” as a marker of cardiac aging. AI-ECG age has been linked to cardiovascular events and mortality, supporting the interpretation that a positive heart age gap reflects accelerated cardiovascular aging [12]. This concept is also moving into wearable settings, where single-lead signals may support continuous estimation of cardiac aging and shift the emphasis from episodic event detection toward proactive risk management [29].

Photoplethysmography (PPG) from consumer wearables adds a population-scale signal for rhythm and pulsatility, although it remains more vulnerable to motion artifact and device heterogeneity. Large-scale wearable studies have established the feasibility of irregular-pulse notification followed by confirmatory monitoring [56]. In aging-informed applications, the value of PPG extends beyond AF detection to longitudinal quantification of physiologic dysregulation, including resting heart-rate trends, rhythm-irregularity burden, sleep–heart-rate coupling, and activity-related heart-rate recovery.

5.3 Blood pressure as real-world time series: trajectories, variability, and nocturnal patterns

Blood pressure is increasingly measured outside the clinic, enabling longitudinal assessment of exposure in everyday life. From an aging-informed perspective, the most informative features are likely to include cumulative exposure across decades, variability burden, nocturnal dipping and morning surge patterns, and recovery after orthostatic challenge.

Clinical data indicate that risk patterns are age-dependent and that variability adds information beyond mean blood pressure [13, 36]. These observations support AI approaches designed for time-series data, including trajectory clustering, variability decomposition, and individualized target recommendations. Clinical actionability and safety remain essential. In older adults, overly aggressive blood pressure lowering in the setting of frailty may increase falls and compromise perfusion; algorithms should therefore incorporate frailty and orthostatic tolerance and report calibrated risks with appropriate uncertainty estimates.

5.4 Sleep, activity, and circadian regularity as coupled hemodynamic exposures

Sleep and circadian regularity are aging-relevant determinants of resilience and are increasingly measurable with wearable devices. Disrupted sleep and irregular sleep–wake timing are associated with cardiometabolic risk, inflammation, and adverse cognitive outcomes. Considered together with nocturnal blood pressure patterns and heart-rate-variability features, they define a coupled phenotype of autonomic and vascular aging.

The expanding literature on sleep and glymphatic function further supports treating sleep features as more than behavioral correlates. Sleep physiology influences clearance pathways and interacts with vascular pulsatility and blood–brain barrier function [79, 80]. This provides a mechanistic basis for considering sleep regularity and

nocturnal hemodynamics as modifiable exposures within brain-healthspan programs.

5.5 Blood-based biomarkers as calibration tools within cardio-cognitive prevention

Blood-based biomarkers of Alzheimer-related pathology are rapidly maturing and are increasingly relevant to prevention-oriented risk calibration. Among currently available analytes, plasma p-tau217 remains the strongest single blood biomarker for identifying Alzheimer-related amyloid and tau pathology, with reproducible performance across cohorts and growing support for implementation-oriented workflows [16, 87, 88].

However, p-tau217 should not be viewed as a standalone solution. A more informative approach is to interpret blood biomarkers as a compact panel capturing partially distinct biological domains. Plasma A β 42/40 serves primarily as an amyloid-related marker and may be especially informative in earlier or preclinical stages and in multimarker combinations [89]. GFAP appears to reflect astrocytic reactivity that may rise early in response to amyloid-related injury and may help identify a biologically active interface between amyloid burden and downstream tau-related change [90]. By contrast, NfL is best understood as a marker of neuroaxonal injury rather than Alzheimer-specific pathology. This lack of specificity is not a weakness in the present framework; it is precisely what makes NfL useful in cardio-cognitive prevention, where mixed pathology, vascular brain injury, and hemodynamic stress commonly coexist [91].

The AT(N) framework provides a practical way to organize these signals [6]. In a prevention setting, plasma A β 42/40 can be viewed as an “A” marker, p-tau217 as the most clinically mature blood-based “T” marker, and NfL as an approximate “N” marker of injury burden. GFAP is better treated as a complementary glial or amyloid-responsive marker rather than as a core disease-defining marker, although it may provide important context when amyloid positivity is accompanied by active astroglial response [90]. This framing is particularly useful for individualized vascular prevention: a patient with high-risk hemodynamic phenotypes plus abnormal A/T signals may warrant intensified multidomain prevention and closer longitudinal follow-up, whereas elevated NfL or GFAP in the absence of a clear Alzheimer-specific signature may point toward mixed or vascular-predominant vulnerability rather than isolated Alzheimer biology [91].

Accordingly, blood-based biomarkers are likely to be most valuable within cardio-cognitive prevention as calibration and trial-enrichment tools rather than as universal screening tests. Their interpretation should account for pretest probability, assay platform, cut-point

variability, renal function, vascular brain injury, comorbid disease, and sex-specific prognostic behavior where supported by evidence [16, 87, 88, 92]. A positive p-tau217 or abnormal A β 42/40 result has different implications in a memory-clinic patient with progressive episodic memory impairment than in an asymptomatic older adult screened because of vascular risk [16, 87–89]. Likewise, elevated NfL or GFAP may reflect mixed injury, vascular brain disease, systemic illness, renal dysfunction, or neurodegeneration rather than Alzheimer-specific pathology [90, 91]. These issues are especially important when biomarkers are combined with AI-derived scores, because misclassification can lead to unnecessary anxiety, inappropriate referral, or inequitable access to follow-up testing [16, 84, 87, 88, 93].

6. AI as an enabling layer for aging-informed cardio-cognitive prevention

6.1 Multimodal learning: from single biomarkers to organism-level trajectories

Single-modality models are appealing because of their simplicity, but their transportability is often limited in older adults with multimorbidity, frailty, shifting baseline physiology, and heterogeneous data quality. Multimodal learning can provide a broader representation of risk by combining structured EHR data, imaging-derived microvascular and brain markers, physiologic time series, and aging-relevant context such as frailty, sleep regularity, and sensory impairment.

Routine health records have shown feasibility for population-level dementia prediction years before diagnosis [17, 30], but EHR-only approaches incompletely capture lifestyle exposures, sensor-derived physiology, and pre-clinical cognitive change. Recent work combining wearable accelerometry with MRI-derived brain parameters illustrates how real-world mobility signals can complement structural brain measures [94].

In cardio-cognitive prevention, multimodal outputs are most interpretable when each modality contributes a plausible biological signal, such as retinal age gap for microvascular aging, BP variability for vascular dysregulation, ECG age gap for cardiac aging, and sleep regularity for resilience and clearance coupling. These signals should support mechanism-aware intervention bundles rather than function as stand-alone black-box risk scores.

6.2 Data harmonization and interoperability

In multimodal prevention, the main practical barrier is often not model architecture, but data fragmentation.

Electronic health records vary across systems in coding practice, missingness, and temporality; wearable streams differ by manufacturer and firmware; and retinal imaging varies by camera type, field of view, and acquisition protocol. Without harmonization, models are likely to learn site- and device-specific artifacts rather than underlying biology.

Key operational requirements include time-aware feature construction, explicit handling of missingness, preservation of device and acquisition metadata, and clear endpoint definition. Models should specify whether they target mild cognitive impairment, all-cause dementia, AD dementia, VCID, or composite outcomes, and should avoid implying disease specificity where the outcome labels are mixed.

These considerations are central to whether a cardio-cognitive AI system is trustworthy, transportable, and clinically deployable.

6.3 Privacy-preserving collaboration across institutions

Cardio-cognitive prevention at scale will often require multi-institutional data, because no single site captures the full continuum from primary-care trajectories and hospital hemodynamics to specialty cognitive phenotyping and community outcomes. In this context, privacy-preserving collaborative learning approaches, including federated learning, may support model development without routine centralization of raw data [95, 96].

The focus here lies not in engineering design, but in its translational implication: collaborative learning may improve representation across populations and health systems and enable analysis of relatively rare but informative phenotypes, including peri-procedural hemodynamic stress linked to cognitive outcomes. However, such approaches do not eliminate the need for governance. Clear rules for participation, auditability, data-class eligibility, model updating, and harm monitoring remain essential [97, 98].

Accordingly, privacy-preserving learning should be viewed as an enabling option for transportable prevention research rather than as a central mechanistic component of the cardiovascular–Alzheimer’s continuum.

6.4 Low-burden monitoring and actionable inference

Continuous monitoring is becoming increasingly feasible through home blood pressure devices, wearable rhythm sensors, and passive tracking of mobility and sleep. For older adults, however, feasibility depends less on technical sophistication than on burden, usability, and clear clinical actionability.

Local or low-data-transfer inference may reduce unnecessary data transfer and support privacy-preserving monitoring. However, the central design principle should remain clinical simplicity: systems should prioritize robust summary metrics and actionable alerts for rhythm instability, BP variability, sleep irregularity, or activity decline over continuous notification streams [99, 100].

6.5 Transportability, fairness, and age-related bias in cardio-cognitive prevention

An equitable prevention framework requires that prevention should not widen disparities in healthspan. Algorithmic bias may arise from structural exclusion, including underrepresentation of older adults, rural communities, lower-income groups, and minoritized populations; from device-related measurement error; and from unequal access to diagnostic follow-up and treatment.

Recent syntheses have emphasized that fairness in healthcare AI cannot be reduced to a single metric, but instead requires context-sensitive evaluation across the data lifecycle, stakeholder responsibilities, and competing clinical values [84, 93]. Age-related bias is particularly salient in cardio-cognitive prevention, where older adults are often underrepresented in digital datasets and differ systematically in baseline physiology, multimorbidity, and treatment patterns. Strategies proposed to mitigate age-related bias include data balancing, augmentation, and algorithmic adjustment [101].

Equity-relevant model development is also beginning to emerge in population-specific settings. A 2025 study developed a two-year dementia risk model specifically for American Indian and Alaska Native individuals using Indian Health Service and Tribal health data, illustrating the value of aligning model development with population context rather than assuming universal transportability [102]. This is especially important in healthy-aging prevention research, where healthy-aging interventions must remain valid across diverse social and clinical settings.

Accordingly, fairness should be operationalized through subgroup performance, calibration, and false-positive/false-negative monitoring across age, sex, ancestry, and socioeconomic context.

6.6 Dataset shift, drift, and MLOps: sustaining performance over years

Long-horizon prevention is particularly vulnerable to dataset shift. Clinical practice changes, coding systems evolve, device firmware is updated, and population health patterns shift over time. Without explicit monitoring,

model performance may degrade silently and expose patients to harm through miscalibrated risk estimates.

Recent reviews of MLOps and dataset shift in healthcare have highlighted the importance of model monitoring, retraining strategies, workflow integration, and the detection of temporal and concept drift in real-world deployment [103, 104]. In cardio-cognitive prevention, drift monitoring should be treated as a clinical safety function rather than a technical afterthought.

Essential elements include periodic calibration checks, surveillance of key feature distributions—for example, blood pressure measurement frequency, wearable adoption, or retinal device type—targeted audits when performance changes are detected, and pre-specified rules for model updating. In older adults, drift may also arise from secular changes in frailty prevalence and treatment patterns, reinforcing the need for continuous evaluation.

6.7 Reporting standards and trial readiness

Because AI output may influence decisions such as intensifying blood pressure treatment, initiating rhythm monitoring, or referring for cognitive evaluation, transparent reporting is essential. The TRIPOD+AI statement provides updated guidance for reporting prediction-model studies that use regression or machine-learning methods, superseding the 2015 TRIPOD checklist [85]. For studies involving large language models, the TRIPOD-LLM extension identifies additional reporting elements, reflecting the continued evolution of reporting expectations [105].

Trial readiness also requires a clearly specified intervention pathway. Models should define their intended use—screening, monitoring, or risk stratification—the clinical action triggered at each decision threshold, and the anticipated balance of benefit and harm. This is particularly important when outcomes are long-horizon and multifactorial.

For clinical use, AI-derived phenotypes should meet a higher standard than statistical association. At minimum, models should show calibration in the target population, net benefit at clinically plausible thresholds, interpretability sufficient to support the proposed action, external validation across health systems and devices, subgroup performance across older and vulnerable populations, and monitoring for drift [84, 85, 93, 103–105]. For prevention, an additional requirement is intervention responsiveness: the phenotype should either identify a pathway that can be acted on, select patients for an evidence-based intervention, or serve as a monitoring measure whose change is linked to meaningful cognitive, functional, or safety outcomes [85, 106, 107]. Without this evidence, retinal age gap, ECG age gap, wearable

sleep metrics, and multimodal AI scores should be described as promising risk markers rather than clinical targets. Table 3 enumerates the minimum technical and governance requirements for AI-enabled cardio-cognitive

prevention systems, organized around dataset definition, outcome specification, performance evaluation, drift monitoring, equity assessment, and privacy governance.

Table 1. Translating hemodynamic and aging-related constructs into computable phenotypes and actionable prevention pathways.

Construct	Scalable signals	Computable phenotype	Analytic approach	Action pathway
Arterial stiffness and excessive pulsatility	Home BP, ambulatory BP monitoring, pulse pressure, PPG waveform features	Stiffness proxy, pulsatility burden	Time-series modeling, waveform phenotyping	BP optimization, management of stiffness-related drivers, closer follow-up
BP variability and dysregulated trajectories	Home BP, ambulatory BP monitoring, orthostatic BP	BP variability index, trajectory class, non-dipper/extreme-dipper profile, orthostatic instability profile	Trajectory clustering, variability decomposition, risk forecasting	Individualized BP targets, orthostatic/frailty-informed adjustment, monitoring intensification or de-intensification
Latent or paroxysmal atrial fibrillation	12-lead ECG, ambulatory ECG, wearable PPG/ECG	AF probability, rhythm-irregularity burden, episode density	AI-enabled ECG screening, rhythm classification, sequential monitoring strategies	Targeted ambulatory monitoring, anticoagulation assessment, rhythm-control evaluation
Cardiac aging and reduced reserve	ECG, activity data, heart-rate recovery, selected biomarkers	ECG age gap, decompensation risk, reduced physiologic reserve profile	AI-ECG aging models, multimodal risk modeling	Heart failure optimization, rehabilitation, exercise and sleep programs
Retinal microvascular aging	Fundus photography, OCT, OCTA	Retinal age gap, retinal microvascular feature score	Deep learning, graph-based retinal vascular modeling	Risk enrichment, lower threshold for cardio-cognitive surveillance
Sleep and circadian dysregulation	Wearable sleep/activity data, nocturnal heart rate, nocturnal BP	Sleep regularity index, circadian disruption profile, sleep-hemodynamic coupling phenotype	Longitudinal pattern analysis, multimodal time-series integration	Sleep evaluation, behavioral intervention, integration into multidomain prevention
Neurodegenerative pathology calibration	Plasma biomarkers	p-tau217 status, biomarker-informed risk stratum	Threshold-based clinical workflows, calibration models	Identification of higher-risk subgroups, trial enrichment, prioritization of intensified prevention

This table summarizes how specialist cardiovascular reasoning can be translated into scalable signals, computable phenotypes, and clinically actionable prevention pathways. The emphasis is on intermediate phenotypes that are measurable, biologically interpretable, and potentially modifiable.

Abbreviations: AF, atrial fibrillation; BP, blood pressure; ECG, electrocardiogram; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; PPG, photoplethysmography.

7. Implementation roadmap: from computable phenotypes to healthspan impact

7.1 From computable phenotypes to pragmatic action pathways

The central translational challenge is not risk prediction alone, but conversion of risk information into functional benefits. Table 1 summarizes how cardiovascular reasoning can be translated into scalable signals, computable phenotypes, and prevention pathways, while Figure 4 outlines an implementation roadmap. Table 5 provides clinical scenarios illustrating different levels of actionability and caution.

In practice, health systems should begin with low-burden, interoperable measurement and move to action-linked phenotyping rather than indiscriminate prediction. Home or ambulatory BP monitoring, clinic ECG, selected wearable rhythm or sleep/activity signals, retinal imaging, and longitudinal EHR context can be translated into phenotypes such as BP variability burden, latent AF probability, retinal microvascular aging, and resilience-related sleep or activity profiles [10, 11, 13, 14, 25]. These phenotypes should trigger guideline-concordant actions and be followed through physiologic, functional, and safety outcomes.

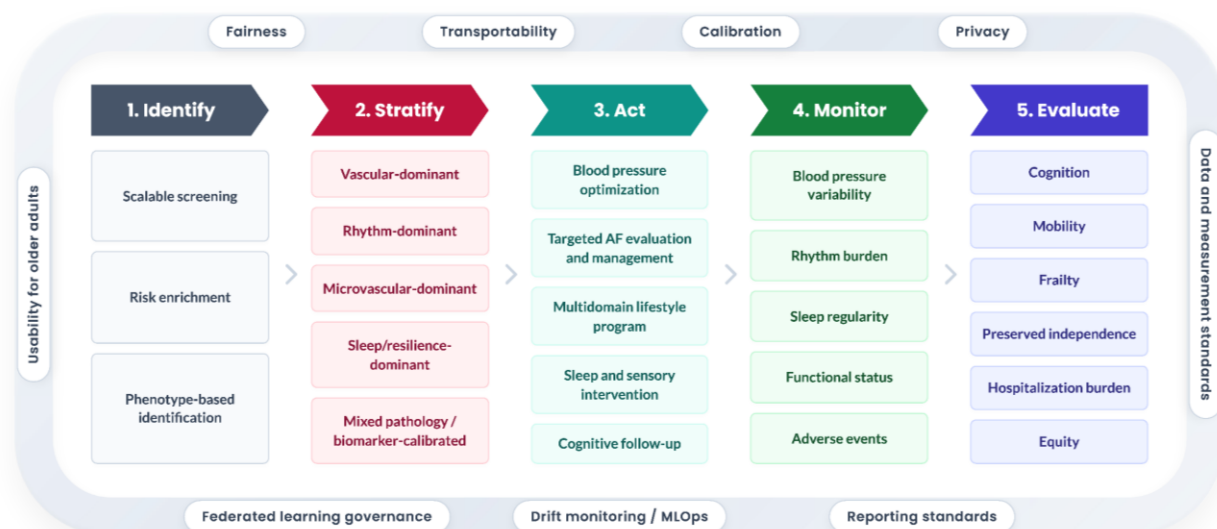


Figure 4. Implementation and evaluation roadmap for healthspan-oriented cardio-cognitive prevention. The roadmap proceeds from scalable screening and phenotype-based assessment to stratification into vascular-, rhythm-, microvascular-, sleep/resilience-, and mixed-pathology profiles. These profiles can be linked to BP optimization, AF evaluation, multidomain lifestyle programs, sleep and sensory intervention, cognitive follow-up, and longitudinal monitoring of intermediate and clinical outcomes. Cross-cutting requirements include fairness, transportability, calibration, privacy protection, usability for older adults, governance, drift monitoring, and reporting standards. **Abbreviations:** AF, atrial fibrillation; BP, blood pressure; MLOps, machine learning operations.

7.2 Stratified prevention bundles anchored in evidence

The value of computable phenotypes increases when they enrich for interventions with at least some evidence of benefit or strong mechanistic plausibility across the

cardio-cognitive pathway. The relative strength of mechanistic, observational, trial, biomarker, and clinical-actionability evidence across these pathways is summarized in Table 2.

Table 2. Evidence strength and clinical actionability across pathways

Pathway / phenotype	Mechanistic support	Observational evidence	Trial evidence	Biomarker/ imaging support	Clinical readiness/ actionability	Recommended framing
Hypertension / BP lowering	+++	+++	+++	++	+++	Established modifiable risk factor; targets require geriatric safety assessment.
BP variability, nocturnal BP, orthostatic instability	++	++	±	+	++	Risk marker and mechanistic intermediate; not yet a validated treatment target independent of BP care.
Arterial stiffness / pulsatility	+++	++	+/-	++	+	Mechanistic intermediate and risk marker; action through BP and vascular-risk control.
AF and AF burden	+++	+++	++ for CV outcomes; ± for dementia prevention	++	+++	Established clinical condition; brain relevance supports detection and guideline-based management.
Atrial cardiomyopathy without overt AF	++	++	-/±	++	+ / ++	Emerging substrate; useful for risk enrichment and targeted rhythm monitoring.

Heart failure / low forward flow	++	++	+ for HF outcomes; ± for cognition	+	++	Established CVD condition; cognitive follow-up and HF optimization are actionable.
CAD / systemic atherosclerosis / LDL burden	++	++/+++	++ for vascular prevention; ± for dementia-specific endpoints	+	+++	Established modifiable vascular risk domain; dementia prevention is indirect but clinically relevant.
Valvular disease / structural intervention	++	+	±	+	++	Hemodynamic correction is clinically indicated for valve disease; cognitive benefit remains context-dependent.
CAA / NVU dysfunction / BBB and clearance failure	+++	++	–	+++	+ / ++	Important safety and stratification phenotype, especially for anticoagulation and anti-amyloid therapy.
Retinal age gap / ECG age gap / wearable sleep metrics / multimodal AI scores	+ / ++	+ / ++	–	+ / ++	+	Promising risk markers and enrichment tools; not validated treatment targets or surrogate endpoints.

This table grades the relative strength of evidence and clinical actionability for major pathways discussed in this review. The grading is intended as a narrative synthesis rather than a formal GRADE assessment. +++ strong; ++ moderate; + limited or emerging; ± indirect, mixed, or context-dependent; – insufficient. Clinical readiness/actionability reflects whether a pathway can currently inform guideline-concordant care, targeted monitoring, risk enrichment, or trial design. **Abbreviations:** AF, atrial fibrillation; BBB, blood–brain barrier; BP, blood pressure; BPV, blood pressure variability; CAA, cerebral amyloid angiopathy; CAD, coronary artery disease; CV, cardiovascular; ECG, electrocardiography; HF, heart failure; LDL, low density lipoprotein; NVU, neurovascular unit.

Vascular risk control. Blood pressure lowering remains one of the best-supported interventions for dementia-relevant prevention. In SPRINT MIND, intensive control reduced incident mild cognitive impairment and the composite outcome of mild cognitive impairment or probable dementia [19]. An individual patient data meta-analysis similarly supported a reduction in incident dementia with blood pressure lowering [20], while neuroimaging analyses provide additional mechanistic support through improved cerebral blood flow and more favorable trajectories of small vessel disease markers [43, 44]. In practice, this supports phenotype-guided blood pressure management, while preserving frailty- and orthostasis-aware safeguards.

Multidomain lifestyle programs. Multidomain prevention remains important, but the evidence is mixed rather than uniformly positive. FINGER showed cognitive benefit in selected at-risk older adults [21], whereas MAPT and preDIVA yielded more variable or neutral overall results [108, 109]. These differences likely reflect variation in population selection, baseline risk, intervention intensity, adherence, and outcome choice [110]. The World-Wide FINGERS network has extended this field into adaptation and implementation science [110, 111], and MIND-ADmini suggests feasibility in more biomarker-enriched populations [112].

Cardiac rhythm management. Scalable AF detection is increasingly feasible through wearable irregular-pulse notification and AI-enabled ECG

strategies [10, 11, 56]. Observational comparative-effectiveness analyses suggest that lowering AF burden through catheter ablation may be associated with lower risks of dementia-related outcomes [51–53]. In practice, AF phenotypes should trigger confirmation of rhythm burden, optimization of anticoagulation and risk-factor control, and—where feasible—closer characterization of the underlying atrial substrate.

Sensory and sleep health. Vision loss and sleep are now established components of dementia prevention frameworks [2]. Mechanistic evidence linking sleep to clearance biology has also strengthened [78–80]. Accordingly, sleep regularity, nocturnal hemodynamics, and sensory access should be treated as actionable healthspan levers rather than peripheral correlates.

7.3 Biomarker-informed risk calibration and triage

As discussed in Section 5.5, blood-based biomarkers are most useful in this framework not as stand-alone screening tools, but as selective calibration instruments applied after scalable phenotyping has already identified potentially vulnerable individuals [16, 87]. In practice, abnormal A β 42/40 or p-tau217 profiles may justify escalation from general prevention advice to more intensive multidomain intervention, closer longitudinal monitoring, or trial enrichment [16, 88, 89], whereas NfL and GFAP are often more informative as markers of mixed or vascular-predominant vulnerability than as

isolated disease-specific signals [90, 91]. A staged pathway—scalable physiologic phenotyping first, biomarker refinement second—therefore fits health-system implementation better than indiscriminate testing.

Table 3. Minimum requirements for development, validation, and deployment of AI-enabled cardio-cognitive prevention systems.

Component	Minimum requirement	Why it matters	Reporting or governance alignment
Dataset definition	Explicit inclusion criteria, age distribution, frailty indicators, multimorbidity profile, device metadata	Older populations are heterogeneous, and hidden sampling bias can distort performance	TRIPOD+AI
Outcome definition	Clear distinction among mild cognitive impairment, all-cause dementia, Alzheimer's disease dementia, VCID, and composite outcomes	Prevents false claims of disease specificity and improves interpretability	TRIPOD+AI
Time structure	Time-stamped inputs, longitudinal feature construction, handling of missingness and censoring	Prevention depends on trajectories rather than isolated measurements	TRIPOD+AI
Performance evaluation	Discrimination, calibration, net benefit, subgroup performance	High AUC alone is insufficient for clinical prevention	TRIPOD+AI
External validation	Validation across independent health systems, devices, and population subgroups	Tests transportability and reduces the risk of site-specific overfitting	TRIPOD+AI
Safety evaluation	Monitoring of false positives, false negatives, overtreatment risk, and workflow burden	Prevention systems can cause harm if miscalibrated or poorly integrated	CONSORT-AI / SPIRIT-AI for interventional evaluation
Drift monitoring and updating	Prespecified recalibration checks, feature-distribution surveillance, and update rules	Long-horizon prevention is vulnerable to temporal shift and device drift	MLOps governance
Equity assessment	Stratified evaluation by age, sex, ancestry, socioeconomic context, and digital access	Prevents widening of healthspan disparities	Fairness and governance framework
Privacy and multi-site learning	Clear rules for node participation, permissible data classes, aggregation, auditability, and accountability	Federated or distributed learning still requires explicit governance	Federated learning governance framework

This table summarizes the minimum technical and governance requirements for systems intended to support real-world cardio-cognitive prevention. The focus is not only predictive performance, but also safety, transportability, equity, and long-term maintainability. Abbreviations: MLOps, machine learning operations; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis; VCID, vascular cognitive impairment and dementia.

7.4 Trial designs and evaluation metrics suitable for prevention

Because dementia outcomes evolve slowly, pragmatic evaluation requires designs that can capture intermediate, clinical, and implementation outcomes. Cluster-randomized trials, stepped-wedge rollouts, and registry-embedded pragmatic trials are well suited to interventions delivered at the clinic or health-system level. When AI influences clinical decisions, protocols and reports should follow AI-specific reporting standards [85, 106, 107].

As summarized in Table 4, healthspan-oriented evaluation should include cognitive trajectories, incident mild cognitive impairment or dementia, functional independence, mobility, falls, frailty progression, cardiovascular events, hospitalization burden, patient-reported quality of life, and equity.

Intermediate endpoints such as BPV burden, AF burden, sleep regularity, and retinal aging markers may support adaptive evaluation, but their validity as surrogates should be demonstrated rather than assumed. Prevention programs should also report calibration, net benefit, subgroup performance, reach, follow-up completion, and distribution of benefit across patient groups.

7.5 Governance, accountability, and sustainability

Long-horizon prevention is exposed to dataset shift, changing workflows, and evolving device ecosystems. Monitoring, recalibration, and updating should therefore be treated as safety requirements rather than engineering preferences [103, 104]. Federated or other privacy-preserving approaches may support multi-institutional learning, but they do not remove the need for governance

regarding accountability, auditability, and permissible data use [95–98]. Usability for older adults should remain central, with hybrid access routes such as clinic ECG,

pharmacy-based BP measurement, and optometry-delivered retinal imaging.

Table 4. Healthspan-oriented outcome framework for pragmatic evaluation of cardio-cognitive prevention programs.

Evaluation domain	Example outcomes	Why it matters	Typical evaluation horizon
Cognitive outcomes	Cognitive trajectory, incident mild cognitive impairment, probable dementia	Core brain-health outcomes remain essential, but change slowly	Medium to long term
Functional independence	Instrumental activities of daily living, medication management, self-care capacity, driving or community independence	Prevention should preserve independence, not only delay diagnosis	Medium term
Mobility and frailty	Gait decline, falls, frailty progression, activity decline	Mobility and frailty are central healthspan outcomes in older adults	Short to medium term
Cardiovascular outcomes	AF detection and burden, heart failure decompensation, stroke, hospitalization burden	Brain and cardiovascular outcomes should be evaluated together	Short to long term
Intermediate physiologic phenotypes	BP variability burden, nocturnal BP pattern, rhythm burden, sleep regularity, retinal aging markers	Provide shorter-cycle signals that the program is affecting relevant biology	Short term
Patient-reported outcomes	Quality of life, symptom burden, sleep quality, mental health	Captures patient-centered benefit and burden	Short to medium term
Equity and reach	Uptake, follow-up completion, subgroup calibration, false-positive and false-negative distributions	Determines whether benefit is fairly distributed	Continuous
Implementation outcomes	Feasibility, clinician adoption, alert burden, workflow integration, retention	Necessary for sustainable deployment in health systems	Continuous

This table summarizes outcome domains suitable for pragmatic evaluation of cardio-cognitive prevention programs. The framework emphasizes that success should be measured not only by dementia incidence, but also by function, mobility, frailty, cardiovascular events, patient-reported outcomes, equity, and implementation feasibility. **Abbreviations:** AF, atrial fibrillation; BP, blood pressure.

8. Methodological and translational challenges

8.1 Confounding, reverse causation, and competing risks

An aging-informed cardio-cognitive prevention framework must explicitly address causal ambiguity. In late life, relationships between cardiovascular phenotypes and cognitive outcomes are often shaped by reverse causation, frailty, selective survival, and competing mortality. Blood pressure is a clear example: low achieved pressure in older adults may reflect successful treatment in some cases, but limited reserve, underlying neurodegeneration, or incipient decline in others [36]. Likewise, late-life blood pressure variability may function less as a midlife-like causal exposure and more as a phenotype of physiologic instability [13]. AI models that ignore competing risks, informative censoring, and age-dependent heterogeneity are therefore at high risk of miscalibration and biologically misleading interpretation. Prediction should also be separated from causal targeting. A model that predicts dementia risk may be useful for prognostic enrichment or follow-up planning, but it does

not necessarily identify a modifiable mechanism [85, 105]. We therefore distinguish five uses of computable phenotypes: prognostic enrichment, in which high-risk individuals are selected for monitoring or trials; mechanistic phenotyping, in which the score reflects a biologically interpretable pathway; treatment selection, in which the phenotype identifies patients likely to benefit from a specific intervention; response monitoring, in which longitudinal change tracks the effect of management; and causal intervention targeting, which requires evidence that modifying the pathway improves clinical outcomes [85, 106, 107]. Most current AI phenotypes in this field remain in the first two categories.

8.2 Outcome heterogeneity and mixed pathology

Clinically meaningful endpoints such as all-cause dementia, mild cognitive impairment, functional decline, or institutionalization remain essential, but they are biologically heterogeneous. Vascular cognitive impairment and dementia and Alzheimer-related pathology frequently coexist, and many late-life cognitive trajectories reflect mixed disease rather than a single

dominant mechanism [5]. This matters because prediction models can easily overstate disease specificity when trained on broad clinical labels alone. Whenever possible, studies should clarify whether outcomes are biomarker-

informed, imaging-informed, or purely syndromic, and should avoid implying Alzheimer-specific prediction when the underlying labels remain mixed.

Table 5. Clinical interpretation scenarios across the cardiovascular–Alzheimer’s continuum.

Scenario	Interpretation	Practical action
Robust older adult with hypertension, high vascular risk, no orthostatic symptoms	May benefit from more intensive BP control if tolerated	Confirm home/ambulatory BP, assess orthostasis, titrate gradually, monitor renal function and falls.
Frail older adult with low achieved SBP, falls, orthostatic hypotension, extensive WMH or CAA markers	High risk of overtreatment and impaired perfusion reserve	Avoid automatic intensification; consider de-intensification, medication review, standing BP, shared decision-making.
Sinus rhythm ECG with high AI-predicted AF risk plus enlarged LA or elevated NT-proBNP	Possible atrial cardiomyopathy / latent AF substrate	Targeted ambulatory rhythm monitoring; evaluate AF burden, PAC burden, stroke risk, and anticoagulation only if clinically indicated.
Elevated retinal or ECG age gap without actionable clinical abnormality	Risk marker, not a treatment target	Use for risk discussion or trial enrichment; do not treat the score itself.
Abnormal p-tau217 or Aβ42/40 in a patient with vascular risk and WMH	Possible mixed vascular and Alzheimer-related vulnerability	Interpret using pretest probability, assay context, renal function, comorbidity, and consider specialist referral or trial eligibility.

This table illustrates how the proposed framework may guide interpretation of common clinical phenotypes. The examples are not prescriptive treatment algorithms and should be applied with clinical judgment and guideline-concordant care. Abbreviations: AF, atrial fibrillation; BP, blood pressure; CAA, cerebral amyloid angiopathy; ECG, electrocardiography; LA, left atrial; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; WMH, white matter hyperintensities.

8.3 Measurement bias, device heterogeneity, and aging-related artifact

Scalable prevention depends on real-world measurement, but real-world measurement is uneven. Wearables, home blood pressure devices, retinal cameras, and OCT/OCTA platforms differ across manufacturers, acquisition settings, firmware, and preprocessing pipelines. Without explicit metadata handling and calibration checks, models may learn site- or device-specific artifacts rather than transferable biology [98, 113].

This issue is amplified in older populations. Tremor, low perfusion, arrhythmia, hearing and visual impairment, and limited digital familiarity can all degrade signal quality. In retinal imaging specifically, cataract-related image degradation, glaucoma-related RNFL loss, and diabetic retinopathy may distort feature extraction and reduce transportability if not explicitly modeled or quality-controlled. Measurement bias should therefore be treated as a first-order scientific and deployment problem rather than a technical nuisance. In practice, this requires explicit image-quality filtering, predefined exclusion criteria, and sensitivity analyses across common aging-related ocular comorbidities rather than assuming that automated feature extraction will remain robust across all acquisition conditions.

8.4 Safety, overtreatment, and vulnerability in frailty

Prevention aimed at extending healthspan must avoid harm as well as delay decline. In older adults, aggressive blood pressure lowering without orthostatic assessment or frailty context can increase falls, syncope, and impaired recovery capacity. Similarly, large-scale AF screening without clear pathways for confirmatory testing, anticoagulation assessment, and shared decision-making may generate anxiety, low-value care, and unnecessary treatment. The broader lesson is that scalable phenotyping should not be equated with automatic intervention; action thresholds must remain conditional on reserve, frailty, competing goals, and treatment tolerance.

8.5 Fairness, digital exclusion, and transportability

Fairness in cardio-cognitive prevention cannot be reduced to a single performance metric. Bias may enter through structural underrepresentation, device-related measurement error, unequal access to follow-up care, or deployment into populations that differ from the development cohort [114, 115]. Older adults at highest dementia risk may be least represented because of frailty, tremor, sensory or cognitive impairment, rural residence, low digital literacy, limited broadband access, caregiver dependence, and socioeconomic barriers [84, 93, 101]. Equity-oriented deployment should include non-smartphone pathways, caregiver-supported measurement, clinic- or pharmacy-based BP and ECG acquisition, optometry-based retinal imaging, transportation-aware follow-up, and subgroup calibration across age, sex,

ancestry, frailty status, and socioeconomic context [84, 93, 101, 102, 114–116].

8.6 Sex-differential effects and inclusive model development

Sex-differential effects deserve explicit attention rather than simple adjustment. Vascular aging, AF-related stroke risk, and blood-based biomarker behavior may not be biologically equivalent across women and men, yet many current studies treat sex primarily as a covariate instead of a source of mechanistic heterogeneity [37, 92]. Future prevention studies should therefore test whether phenotype thresholds, treatment tolerance, and biomarker trajectories differ meaningfully by sex, and whether sex-aware calibration improves both validity and equity.

8.7 Limitations of this narrative review

This article is a narrative review rather than a systematic review or meta-analysis. The literature was selected for mechanistic relevance, clinical importance, and translational value, and the review does not provide exhaustive search results, formal risk-of-bias assessment, or quantitative effect estimates. Because the field spans cardiovascular disease, vascular brain injury, Alzheimer-related biomarkers, aging biology, and AI-enabled phenotyping, evidence strength varies substantially across pathways [4, 5, 16, 85]. Accordingly, mechanistic plausibility, observational association, trial evidence, biomarker support, and clinical readiness are distinguished throughout this review to avoid presenting emerging markers as validated treatment targets.

9. Conclusion and future directions

The evidence reviewed here supports a shift from parallel cardiovascular and dementia prevention toward an integrated, aging-informed cardio-cognitive strategy. Across the cardiovascular–Alzheimer’s continuum, arterial stiffness, blood pressure variability, atrial disease, heart failure, valvular pathology, CAA, and periprocedural stress should be interpreted as interacting contributors to late-life brain vulnerability rather than as isolated disease silos. The clinical goal is not only delayed dementia diagnosis, but preservation of function, independence, treatment safety, and resilience.

Future work should move beyond prediction alone. Biomarker- and imaging-informed studies should test whether CAA or mixed pathology modifies the intensity and tolerability of antihypertensive or anticoagulation strategies in older adults. Pragmatic trials should evaluate whether combined management of blood pressure variability, atrial-rhythm burden, sleep disruption, and

frailty can alter cognitive and functional trajectories more effectively than single-domain intervention. Finally, ECG age gap, retinal age gap, BPV burden, wearable sleep metrics, and multimodal AI scores should be tested as responsive mechanistic or enrichment measures rather than assumed to be valid surrogate endpoints.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Use of AI-assisted tools

During manuscript preparation and revision, the authors used ChatGPT (OpenAI; model/version: GPT-5.2) only for language editing, readability improvement, and organization of author-prepared text. Example prompts were limited to requests such as: “Please edit the following paragraph for clarity and concision without adding new scientific content.” The authors reviewed and edited all AI-assisted output, verified the scientific content and references, and took full responsibility for the final manuscript. The AI tool was not listed as an author, was not cited as a source, and was not used to generate data, analyses, scientific ideas, or conclusions.

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