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Review article

The Heart-Brain-Emotion Axis in aging: An integrated framework linking cardiovascular dysfunction, emotional dysregulation, and cognitive decline

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ABSTRACT

Population aging is accompanied by a parallel increase in cardiovascular disease (CVD), vascular cognitive impairment (VCI), and dementia, highlighting the urgent need to better understand the complex interactions linking cardiovascular, cognitive, and emotional health. Growing evidence suggests that cardiovascular dysfunction, emotional dysregulation, and cognitive decline are not isolated conditions but interconnected manifestations of shared vascular, inflammatory, neurohumoral, metabolic, and behavioral processes that progressively interact throughout aging. In this review, we examine current evidence supporting the Heart–Brain Axis and expand this concept into an integrated Heart–Brain–Emotion Axis, providing a comprehensive framework to explain the bidirectional relationships among cardiovascular dysfunction, emotional disturbances, and cognitive impairment. We discuss the major mechanisms underlying these interactions, including endothelial dysfunction, cerebral hypoperfusion, chronic low-grade inflammation, oxidative stress, autonomic imbalance, neuroendocrine dysregulation, and psychosocial factors such as depression, anxiety, chronic stress, and social isolation. Attention is given to the reciprocal amplification loops through which dysfunction in one domain may propagate across interconnected biological networks, increasing vulnerability to emotional and cognitive deterioration. Finally, we discuss the clinical implications of this integrated model, emphasizing the importance of early cardiovascular and cognitive screening, multidomain preventive approaches, personalized interventions, and the incorporation of cognitive and emotional assessment into cardiac rehabilitation programs. Recognizing the Heart–Brain–Emotion Axis may facilitate earlier identification of at-risk individuals and support more effective strategies to preserve both cardiovascular and brain health across the aging trajectory.

Summary: A growing body of evidence indicates that cardiovascular, emotional, and cognitive alterations should not be considered isolated phenomena but rather interconnected manifestations of a multisystem aging process. Age-related decline appears to arise from reciprocal interactions among cardiovascular, cerebrovascular, neural, and psychosocial mechanisms, whereby dysfunction in one domain propagates through interconnected biological networks, progressively amplifying vulnerability across the others. Shared pathophysiological pathways—including chronic low-grade inflammation, oxidative stress, autonomic dysfunction, neurohumoral imbalance, metabolic disturbances, and adverse lifestyle factors—simultaneously affect cardiovascular, brain, and emotional health, generating self-reinforcing feedback loops that accelerate functional decline. Within this framework, cardiovascular dysfunction contributes to cognitive impairment not only through vascular and neurovascular injury but also by influencing emotional well-being. Conversely, emotional dysregulation, including depression, anxiety, impaired stress adaptation, and reduced emotional resilience, can aggravate cardiovascular dysfunction through behavioral and physiological mechanisms, further compromising cognitive function. These reciprocal relationships support the concept of an integrated **Heart–Brain–Emotion Axis**, in which cardiovascular dysfunction, emotional dysregulation, and cognitive impairment interact dynamically throughout the aging trajectory. Viewing aging through this integrative framework provides a broader understanding of the mechanisms underlying functional decline and highlights the need for multidomain preventive strategies and personalized interventions. Cardiac rehabilitation may represent an ideal translational model by

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integrating cardiovascular risk management with cognitive and emotional interventions, thereby promoting healthy brain aging, preserving functional independence, and improving quality of life.

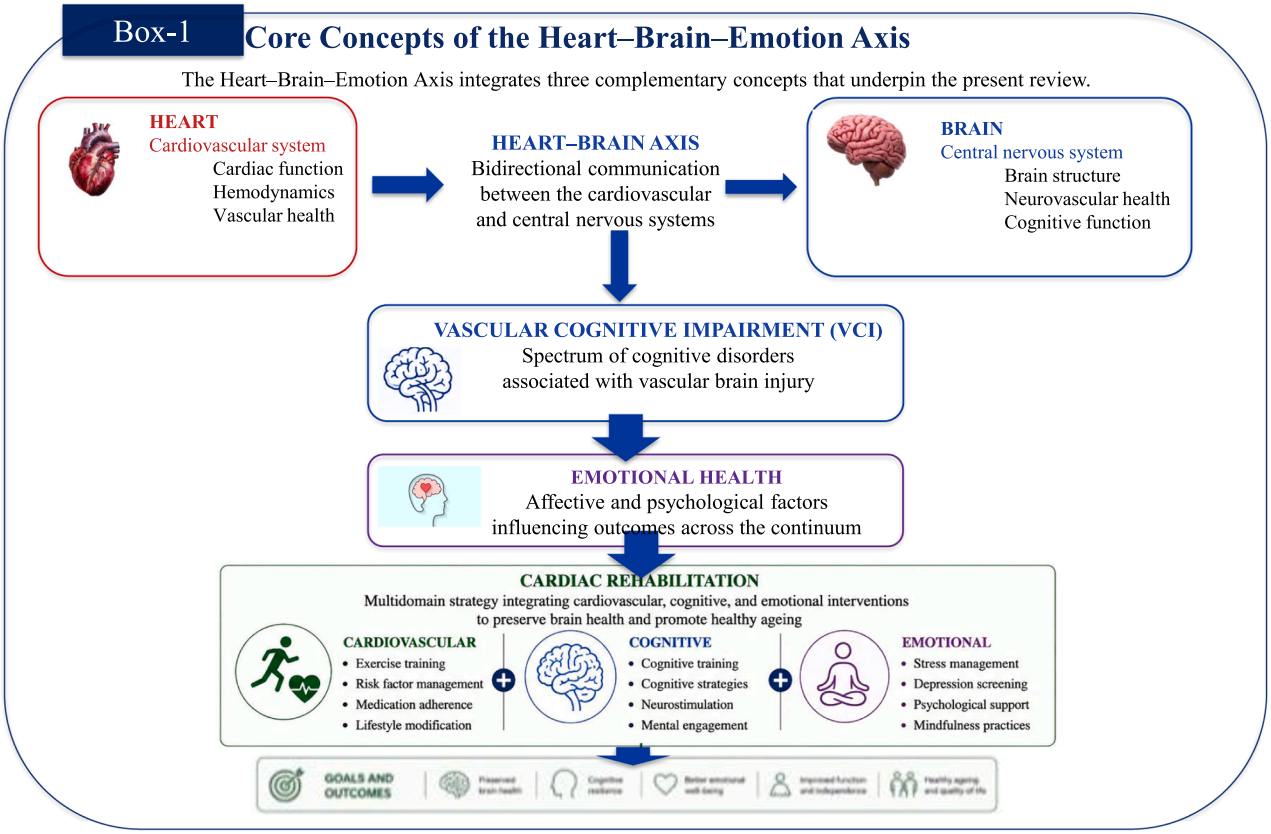
1. Introduction

Global population aging is driving a rapid increase in cardiovascular disease (CVD), vascular cognitive impairment (VCI), and dementia, posing one of the greatest healthcare challenges of the twenty-first century (Patnode et al., 2020; Pérez Palmer et al., 2022). As life expectancy continues to rise, preserving cardiovascular, cognitive, and emotional health has become a major public health priority (Balistreri and Monastero, 2023, 2025). Although CVD remains the leading cause of morbidity and mortality worldwide, accumulating evidence indicates that its consequences extend well beyond the cardiovascular system, substantially influencing brain function, emotional well-being, and healthy aging.

The relationship between cardiovascular dysfunction and cognitive decline has been interpreted within the framework of the *Heart–Brain Axis*, which describes the bidirectional communication between the cardiovascular and central nervous systems through interconnected vascular, neural, inflammatory, autonomic, and neurohumoral pathways (Ahmad et al., 2020; Schirò and Balistreri, 2022; Chen et al., 2024; Jost and Kujach, 2025). This paradigm has significantly advanced our understanding of how CVD contribute to cerebral dysfunction, vascular cognitive impairment, and dementia (Jin et al., 2025; Smith et al., 2025)). However, emerging evidence indicates that this framework does not fully capture the complexity of age-related multisystem interactions (Balistreri and Monastero, 2023, 2025). Emotional dysregulation, including depression, anxiety, chronic stress, impaired emotional resilience, and social isolation, has emerged not only as a frequent consequence of cardiovascular disease but also as an important determinant of cardiovascular outcomes and cognitive trajectories through shared biological and behavioral mechanisms (Liori et al., 2025; Manolis et al., 2025; Ozkan et al., 2025; Zhang, 2025).

Collectively, these findings support an expanded conceptual framework, the *Heart–Brain–Emotion Axis* (see Box1), in which cardiovascular dysfunction, emotional dysregulation, and cognitive decline represent interconnected manifestations of a common biological network rather than isolated clinical entities. Endothelial dysfunction, cerebral hypoperfusion, chronic low-grade inflammation, oxidative stress, autonomic imbalance, neurohumoral dysregulation, metabolic alterations, and psychosocial factors interact through reciprocal feedback mechanisms that progressively amplify dysfunction across cardiovascular,

Box 1
Core Concepts of the Heart–Brain–Emotion Axis.



emotional, and cognitive domains throughout the aging trajectory.

In this review, we synthesize current evidence supporting the Heart–Brain–Emotion Axis as an integrated aging network linking cardiovascular dysfunction, emotional dysregulation, and cognitive decline. We examine the principal biological and psychosocial mechanisms underlying these reciprocal interactions and discuss their implications for early risk stratification, multidomain prevention, personalized therapeutic strategies, and integrated cardiac rehabilitation aimed at preserving cardiovascular, emotional, and brain health during aging

1.1. *Epidemiological evidence supporting the Heart–Brain Axis*

The concept of the Heart–Brain Axis is supported by a substantial body of epidemiological evidence demonstrating that cognitive impairment is highly prevalent across the large spectrum of CVD. Approximately one-third of patients with CVD exhibits some degree of cognitive impairment, frequently involving deficits in memory, executive function, processing speed, attention, and treatment self-management (Jin et al., 2025; Smith et al., 2025). Despite its high prevalence and well-established prognostic significance, cognitive dysfunction remains substantially underrecognized in routine cardiovascular practice, often delaying diagnosis and limiting opportunities for timely multidisciplinary intervention (Balistreri and Monastero, 2023, 2025).

Among CVD, heart failure (HF) and congestive heart failure (CHF) exhibit some of the strongest associations with cognitive impairment, with reported prevalence ranging from 14% to 81%, depending on disease severity and assessment methods (Lovell et al., 2019; Oud et al., 2021; Wiersinga et al., 2021). A large meta-analysis involving approximately two million individuals demonstrated that HF is associated with an almost 60% increased risk of dementia during a 4–9-year follow-up (Wolters et al., 2018). Similarly, coronary artery disease (CAD) and coronary heart disease (CHD) are associated with a 26% increased risk of future dementia, while the prevalence of cognitive impairment ranges from 9% to 85%, particularly among older adults (Gu et al., 2019; Zhao et al., 2020). Degenerative valvular heart disease and atrial fibrillation (AF), both highly prevalent in aging populations, have likewise been consistently linked to cerebral hypoperfusion, silent cerebrovascular injury, VCI, and increased dementia risk (Vahanian et al., 2022; Weil et al., 2022). The epidemiological burden of cognitive impairment across major CVD is summarized in Table 1.

Across major CVD, advanced age consistently emerges as one of the strongest determinants of cognitive impairment, with the burden becoming particularly pronounced among individuals aged $\geq$ 65 years and increasing further in the oldest-old population ($\geq$80 years) (Abete et al., 2014; Wang et al., 2026). The relationship between CVD and cognitive decline is sustained by multiple interconnected pathophysiological processes, including chronic cerebral hypoperfusion, endothelial dysfunction, blood–brain barrier (BBB) and neurovascular unit impairment (NUV), systemic inflammation, microvascular damage, neurohumoral dysregulation, and silent cerebrovascular lesions such as microinfarcts and microhemorrhages (Allegra et al., 2021; Balistreri, 2021; Schirò and Balistreri, 2022; van Nieuwkerk et al., 2023; Wang et al., 2026). Consistent with these mechanisms, neuroimaging studies have demonstrated structural and functional alterations in brain connectivity networks, that correlate with impaired cognitive and executive performance in patients with CVD (Zhao et al., 2023; Humayra et al., 2024; Jaggi et al., 2024).

Beyond cognitive impairment, emotional dysregulation, including depression, anxiety, fatigue, mood disorders, and alexithymia, commonly coexist with CVD, contributing to greater symptom burden, reduced quality of life, and poorer clinical outcomes (Liori et al., 2025; Manolis et al., 2025; Ozkan et al., 2025; Zhang, 2025).

Together, these findings set the stage for the mechanistic framework discussed in the following sections, highlighting how cardiovascular dysfunction, emotional dysregulation, and cognitive decline interact within the Heart–Brain–Emotion Axis.

Table 1
Epidemiological burden of cognitive impairment across CVD and its association with aging.

Cardiovascular disease	Cognitive impairment epidemiology	Age-related association	Significant findings	References
Cardiovascular disease (CVD)	Approximately 1 in 3 patients with cardiovascular disease experience some degree of cognitive impairment	Cognitive decline increases markedly with aging; older adults ($\geq$60 years) with CVD demonstrated significantly lower cognitive performance than age-matched controls	Approximately 25% of dementia cases are attributable to cardiovascular risk factors and may potentially be preventable	Park et al., (2024); van Nieuwkerk et al., (2023); Smith et al., (2025)
Heart failure (HF)/ Congestive heart failure (CHF)	Cognitive impairment prevalence ranges from 14 to 81% depending on setting and assessment methods	Strong association with advanced age; patients aged $\geq$ 80 years showed an independent association between CHF and lower cognitive performance	Meta-analysis (~2 million patients): HF associated with 60% increased risk of dementia over 4–9 years; cognitive impairment identified in 22–36% of outpatient populations and missed in approximately half of cases	Wolters et al., (2018); Lovell et al., 2019; Oud et al., (2021); Wiersinga et al., (2021); Park et al., (2024)
Coronary artery disease (CAD)/coronary heart disease (CHD)	Cognitive impairment prevalence ranges from 9 to 85%, particularly among older adults	Mainly observed in patients aged $\geq$ 65 years; older age independently increases dementia risk	CAD/CHD associated with 26% increased risk of future dementia; among patients > 65 years with non-ST-segment elevation myocardial infarction (NSTEMI), 48% showed abnormal Montreal Cognitive Assessment (MoCA) scores	Zhao et al., (2020); Wolters et al., (2018); Gu et al., (2019); Bagai et al., (2019); Hajduk et al., (2021)
Degenerative valvular heart disease	Approximately one-third of elderly patients exhibit cognitive impairment	About 70% of newly diagnosed valvular diseases occur in patients > 65 years	Reduced cerebral perfusion and cerebral small-vessel disease contribute to cognitive decline	Vahanian et al., (2022)
Surgical aortic valve replacement (SAVR)	Early postoperative cognitive decline reported after surgery	Older age associated with increased susceptibility to postoperative cognitive deterioration	Meta-analysis reported cognitive decline at 2–6 months after surgery; stroke incidence ranged from 4 to 16%	Khan et al., (2018); De Carlo et al., (2020); Potluri et al., (2020)
Transcatheter aortic valve implantation (TAVI)	Cognitive decline prevalence 7–16% during the first postoperative week and 14–26% after 6 months	Mainly performed in patients aged $\geq$ 75 years or in those with elevated surgical risk and comorbidities	Silent cerebral infarctions occurred in 76% of patients; stroke incidence ranged from 2 to 3%	Vahanian et al., (2022); Oldham et al., (2018); Woldendorp et al., (2021); Kapadia et al., (2022)
Atrial fibrillation (AF)	Precise prevalence not reported, but AF is consistently associated with increased risk of cognitive decline and dementia	Prevalence increases substantially with age and predominantly affects elderly individuals	AF contributes to approximately one-third of ischemic strokes; up to one-third of affected individuals are asymptomatic	Weil et al., (2022)

1.2. The Heart–Brain–Emotion Axis: an integrated aging network

The epidemiological and mechanistic evidence discussed above suggests that cardiovascular dysfunction, emotional dysregulation, and cognitive decline should no longer be viewed as independent age-related conditions but rather as interconnected manifestations of a common biological network. Building upon the traditional Heart–Brain Axis, we propose the *Heart–Brain–Emotion Axis* as an expanded conceptual framework that integrates cardiovascular, cerebrovascular, neural, and psychosocial processes into a unified model of healthy and pathological aging.

Within this framework, dysfunction arising in one domain may propagate through reciprocal biological interactions, generating self-reinforcing feedback loops that progressively amplify vulnerability across cardiovascular, emotional, and cognitive systems. Shared mechanisms, including chronic low-grade inflammation, oxidative stress, endothelial dysfunction, autonomic dysregulation, neurohumoral imbalance, metabolic alterations, and lifestyle-related factors, simultaneously affect multiple physiological systems, accelerating functional decline throughout the aging trajectory (Franceschi et al., 2018; Ferrucci and Fabbri, 2018; Balistreri, 2021; Chen et al., 2024).

Cardiovascular dysfunction may therefore contribute not only to VCI and dementia through cerebrovascular and neurovascular alterations but also to emotional disturbances that adversely influence disease progression. Conversely, emotional dysregulation, including depression, anxiety, impaired stress adaptation, and reduced emotional resilience, may exacerbate cardiovascular dysfunction through behavioral and physiological mechanisms, thereby promoting further cognitive deterioration (Allegra et al., 2021; Schirò and Balistreri, 2022; Liori et al., 2025; Manolis et al., 2025). Rather than representing separate pathological processes, these reciprocal interactions form a dynamic biological network that underpins the Heart–Brain–Emotion Axis throughout aging (Humayra et al., 2024; Jaggi et al., 2024; van Nieuwkerk et al., 2023).

Accordingly, this review adopts the Heart–Brain–Emotion Axis as its guiding conceptual framework to integrate current evidence on the biological mechanisms, clinical manifestations, and multidomain preventive and therapeutic strategies linking cardiovascular dysfunction, emotional dysregulation, and cognitive decline (see Fig. 1).

2. Vascular and cerebrovascular determinants of cognitive decline within the Heart–Brain–Emotion Axis

Growing evidence indicates that vascular dysfunction is a major contributor to cognitive impairment and dementia during aging (Ahmad et al., 2020; Schirò and Balistreri, 2022; Smith et al., 2025). Rather than representing independent pathological entities, cardiovascular and cerebrovascular alterations interact through interconnected biological mechanisms that progressively compromise brain integrity. Within the Heart–Brain–Emotion Axis, vascular dysfunction constitutes a central pathway linking CVD to cognitive decline by impairing cerebral perfusion, endothelial function, neurovascular communication, and brain homeostasis.

Recent studies have identified advanced age as an independent risk factor for cognitive decline and dementia (Feng et al., 2025; Yang et al., 2025). In parallel, traditional cardiovascular risk factors, including hypertension, diabetes mellitus, systemic inflammation, and metabolic disturbances, interact with cerebrovascular abnormalities to increase brain vulnerability and accelerate cognitive decline (Aytenew et al., 2024; Feng et al., 2025; Yang et al., 2025; Ma et al., 2025).

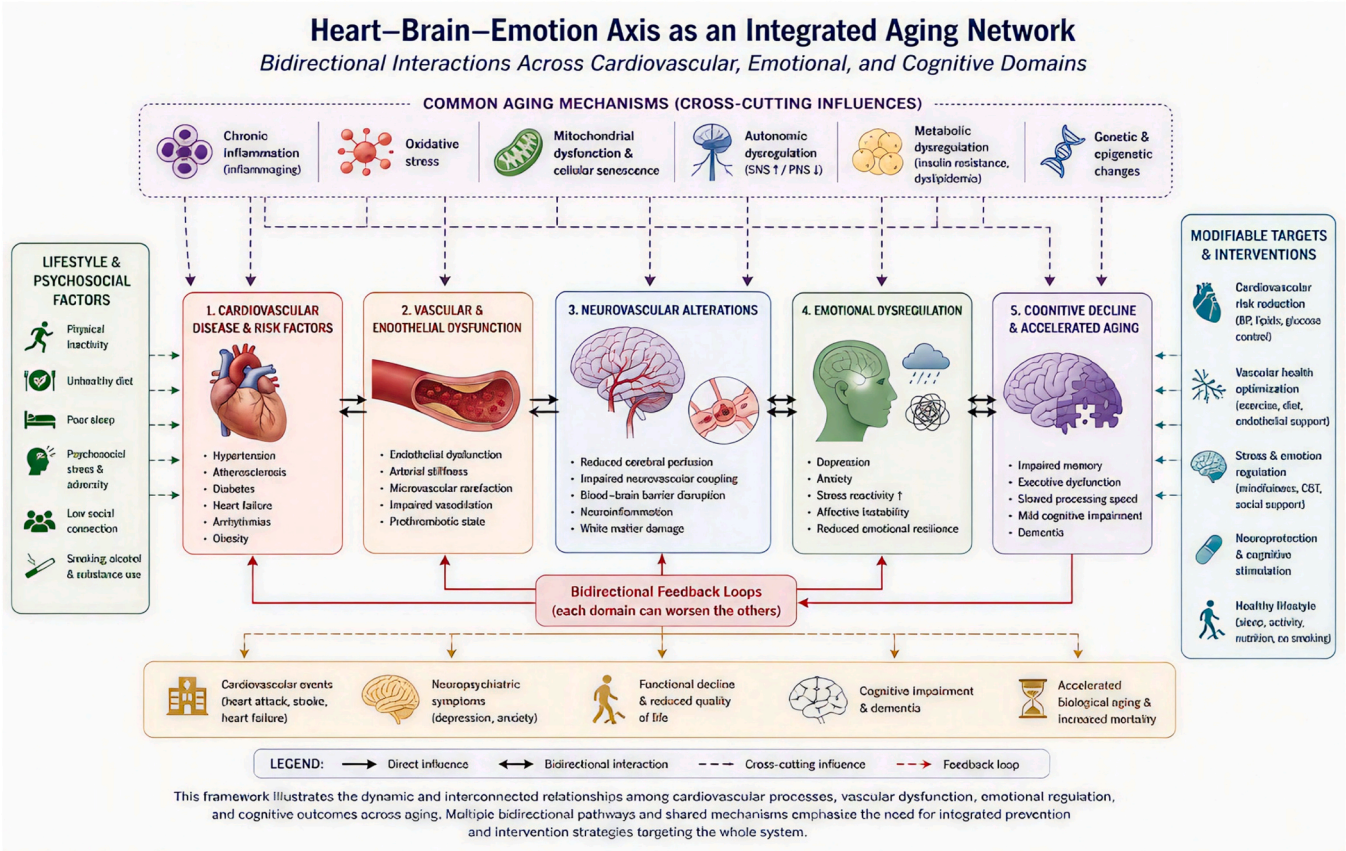


Fig. 1. Heart–Brain–Emotion Axis as an Integrated Aging Network. It summarizes the proposed Heart–Brain–Emotion Axis, illustrating how cardiovascular dysfunction, vascular and neurovascular alterations, emotional dysregulation, and cognitive decline interact through shared biological mechanisms and bidirectional feedback loops. The following sections examine each of these interconnected pathways in greater detail.

Macro-infarcts, microinfarcts, cerebral microhemorrhages, atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy have all been associated with cognitive impairment and dementia (Ahmad et al., 2020; Schirò and Balistreri, 2022; Smith et al., 2025). Likewise, alterations involving the BBB and the NVU contribute to impaired neurovascular homeostasis, reduced cerebral blood flow, and progressive neuronal dysfunction.

Collectively, these observations support the concept that cognitive decline frequently reflects the cumulative effects of vascular injury rather than isolated neurological processes. Consequently, preserving cardiovascular health may represent one of the most effective strategies for maintaining cognitive resilience during aging (see Table 2). These findings highlight that the assessment of vascular and cerebrovascular conditions should extend beyond the prediction of cardiovascular events and include the evaluation of cognitive vulnerability. In this context, predictive models integrating demographic, vascular, and biological variables may contribute to the identification of individuals at increased risk of cognitive decline. Such approaches are particularly relevant within the Heart–Brain–Emotion Axis framework, as they may facilitate earlier interventions aimed at preserving cardiovascular function, brain integrity, and emotional well-being during aging (see 2.1).

Table 2
Traditional vascular risk factors (age, diabetes, hypertension, hs-CRP, hcy) and cerebrovascular/pathophysiological conditions (infarctions, BBB, NVU, etc.).

Risk factors	Association with cognitive impairment/dementia	References
Advanced age	Strong predictor of cognitive decline and dementia; also identified as an independent risk factor	Aytenew et al., (2024); Feng et al., (2025); Yang et al., (2025)
Diabetes mellitus	Associated with increased risk of cognitive impairment and dementia	Aytenew et al., (2024)
Hypertension	Strong predictor contributing to cognitive decline and dementia risk	Aytenew et al., (2024)
Elevated hypersensitive C-reactive protein (hs-CRP) levels	Marker of systemic inflammation associated with increased risk of cognitive impairment	Aytenew et al., (2024)
Increased homocysteine (hcy) concentrations	Associated with increased risk of cognitive impairment and dementia	Aytenew et al., (2024)
Macro-infarcts	Significantly associated with onset of cognitive impairment	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)
Microinfarcts	Significantly associated with onset of cognitive impairment	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)
Cerebral microhemorrhages	Increased burden associated with cognitive impairment onset	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)
Atherosclerosis	Associated with cognitive impairment and vascular dysfunction	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)
Arteriolosclerosis	Associated with cognitive impairment development	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)
Cerebral amyloid angiopathy	Significantly associated with cognitive impairment onset	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)
Reduced cerebral blood flow	Contributes to neurodegenerative processes and cognitive decline	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)
Blood–brain barrier (BBB) dysfunction	Implicated in pathophysiological mechanisms underlying cognitive impairment	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)
Neurovascular unit (NVU) alterations	Contribute to neurodegenerative processes and cognitive decline	Ahmad et al., (2020); Schirò and Balistreri, (2022); Smith et al., (2025)

2.1. *Cardiovascular-based risk models for predicting cognitive decline*

The recognition that vascular dysfunction substantially contributes to cognitive decline and dementia, has stimulated the development of cardiovascular-based models aimed at identifying individuals at increased risk before the onset of clinical symptoms. These models integrate demographic, cardiovascular, and lifestyle-related variables to estimate long-term dementia risk and support preventive strategies (see Table 3).

Among the available approaches, the Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) score remains the most extensively validated prediction model. Developed in a middle-aged population, it incorporates age, sex, education, systolic blood pressure, body mass index, total cholesterol, physical activity, and apolipoprotein E ε4 (APOE4), demonstrating good performance for long-term prediction of dementia and associations with early structural brain changes (Kivipelto et al., 2006).

More recently, additional cardiovascular parameters have been incorporated to improve predictive performance. Resting heart rate (RHR), a simple marker of autonomic and cardiovascular regulation, has shown promise as a complementary predictor across more heterogeneous populations (Alaka et al., 2025a and b; Gu et al., 2026). Furthermore, machine-learning approaches (Guimarães et al., 2025; Lohner et al., 2025; Patai et al., 2025; Burlacu et al., 2026; Campanioni et al., 2026; Gou et al., 2026; Stern and Linial, 2026) are increasingly being explored to capture complex interactions among cardiovascular, clinical, and biological variables, potentially enabling more accurate and personalized risk prediction.

Despite these advances, implementation of cardiovascular-based risk models in routine clinical practice remains limited. Although current cardiovascular guidelines increasingly recognize cognitive impairment as an important comorbidity, systematic cognitive screening is still not routinely integrated into cardiology care. In this regard, the Heart–Brain Connection Consortium has proposed pragmatic screening pathways for identifying cognitive impairment in high-risk cardiovascular patients (van Nieuwkerk et al., 2023).

The clinical relevance of these strategies is underscored by the growing burden of VCI. According to recent epidemiological estimates from the American Heart Association, vascular dementia and mixed dementias with a vascular component affect millions of older adults, highlighting the urgent need for earlier identification of at-risk individuals (Smith et al., 2025). Future prediction models should therefore evolve toward multidimensional approaches integrating cardiovascular, cerebrovascular, and biological determinants within the Heart–Brain–Emotion Axis, thereby supporting precision prevention strategies aimed at preserving both cardiovascular and brain health.

3. Shared biological mechanisms underlying the Heart–Brain–Emotion Axis during aging

The progression of cardiovascular dysfunction, emotional dysregulation, and cognitive decline during aging is driven by a network of interconnected biological mechanisms that operate across multiple physiological systems. As introduced above, chronic low-grade inflammation, oxidative stress, endothelial dysfunction, autonomic dysregulation, neurohumoral imbalance, metabolic alterations, and lifestyle-related factors represent converging pathways through which cardiovascular, cerebral, and emotional domains become progressively interconnected (Franceschi et al., 2018; Ferrucci and Fabbri, 2018; Balistreri,

Table 3
Strengths and limitations of cardiovascular-based models for predicting dementia and cognitive decline risk.

Score / Model	Main variables/components	Advantages	Limitations	References
Cardiovascular Risk Factors, Aging and Incidence of Dementia (CAIDE) score	Age, sex, education, systolic blood pressure, body mass index (BMI), total cholesterol, physical activity, apolipoprotein E ε4 (APOE4)	Simple and clinically applicable tool; based on routinely collected variables; validated for long-term prediction of dementia risk (~20 years); associated with longitudinal brain atrophy even in midlife	Developed predominantly in White populations; moderate predictive accuracy; reduced or neutral predictive performance across some racial/ethnic groups, including Black African and Latino populations; limited generalizability	Kivipelto et al., (2006)
Modified CAIDE score including resting heart rate (RHR)	Traditional CAIDE variables + resting heart rate (RHR)	Improved predictive performance across more heterogeneous populations; incorporates a simple, inexpensive and non-invasive cardiovascular parameter; practical for routine clinical use	Requires additional external validation in different populations and clinical settings; long-term prognostic performance still requires further investigation	References cited in 2.1
Machine learning-based prediction models	Multivariable datasets including demographic, clinical, cardiovascular and potentially biological variables	Captures complex and non-linear relationships among variables; potentially greater predictive accuracy; may facilitate earlier identification of individuals at risk; enables personalized risk assessment	Reduced interpretability ("black-box" effect); dependence on large, high-quality datasets; potential overfitting; external validation and clinical implementation remain limited	References cited in 2.1

2021; Chen et al., 2024; **see** Fig. 2). Rather than acting independently, these mechanisms interact through reciprocal feedback loops that amplify biological vulnerability over time. Vascular injury, impaired cellular resilience, altered autonomic regulation, and metabolic dysfunction may simultaneously affect cardiovascular function, brain integrity, and emotional regulation, contributing to the progressive deterioration of the Heart–Brain–Emotion Axis during aging. Understanding these shared pathways provides the mechanistic foundation for interpreting how CVD may influence cognitive and emotional trajectories and how targeted multidomain interventions may preserve healthy aging.

3.1. Dysfunctional vascular endothelium as common pathogenic substrate of CVD and ND

Growing evidence supports the hypothesis that endothelial dysfunction, together with disruption of the endothelial glycocalyx (eGCX) and its associated molecular and cellular pathways, represents a common pathogenic substrate underlying not only CVD, but also several age-related disorders, including cognitive impairment and neurodegenerative diseases (Balistreri et al., 2024; Balistreri and Monastero, 2025; see Fig. 3).

The vascular endothelium is now recognized as a highly dynamic and metabolically active structure involved in the regulation of vascular homeostasis, inflammatory responses, thrombosis, and tissue signaling. Moreover, the endothelial glycocalyx has emerged as a critical regulator

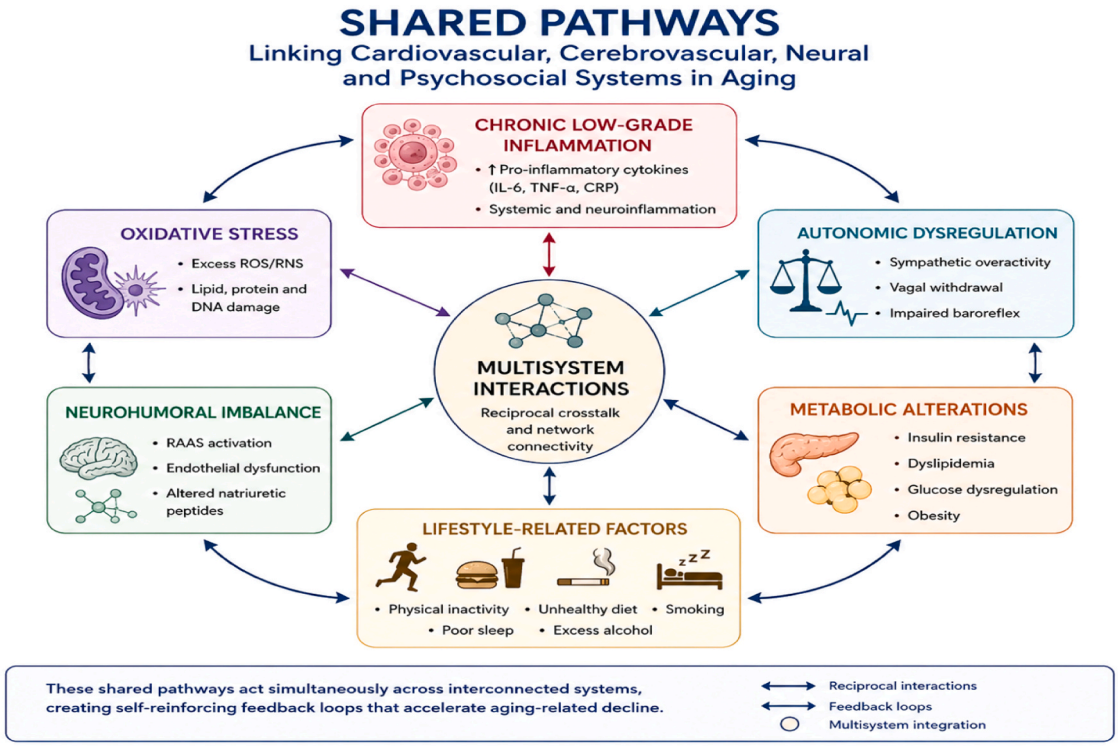


Fig. 2. Shared mechanisms underlying the Heart–Brain–Emotion Axis during aging. This figure illustrates the common biological pathways linking cardiovascular dysfunction, emotional dysregulation, and cognitive decline during aging. Chronic low-grade inflammation, oxidative stress, endothelial dysfunction, autonomic dysregulation, neurohumoral imbalance, metabolic alterations, and lifestyle-related factors act as interconnected mechanisms affecting multiple physiological systems. Through reciprocal interactions and feedback loops, these processes contribute to progressive cardiovascular, cerebral, and emotional vulnerability across the aging trajectory.

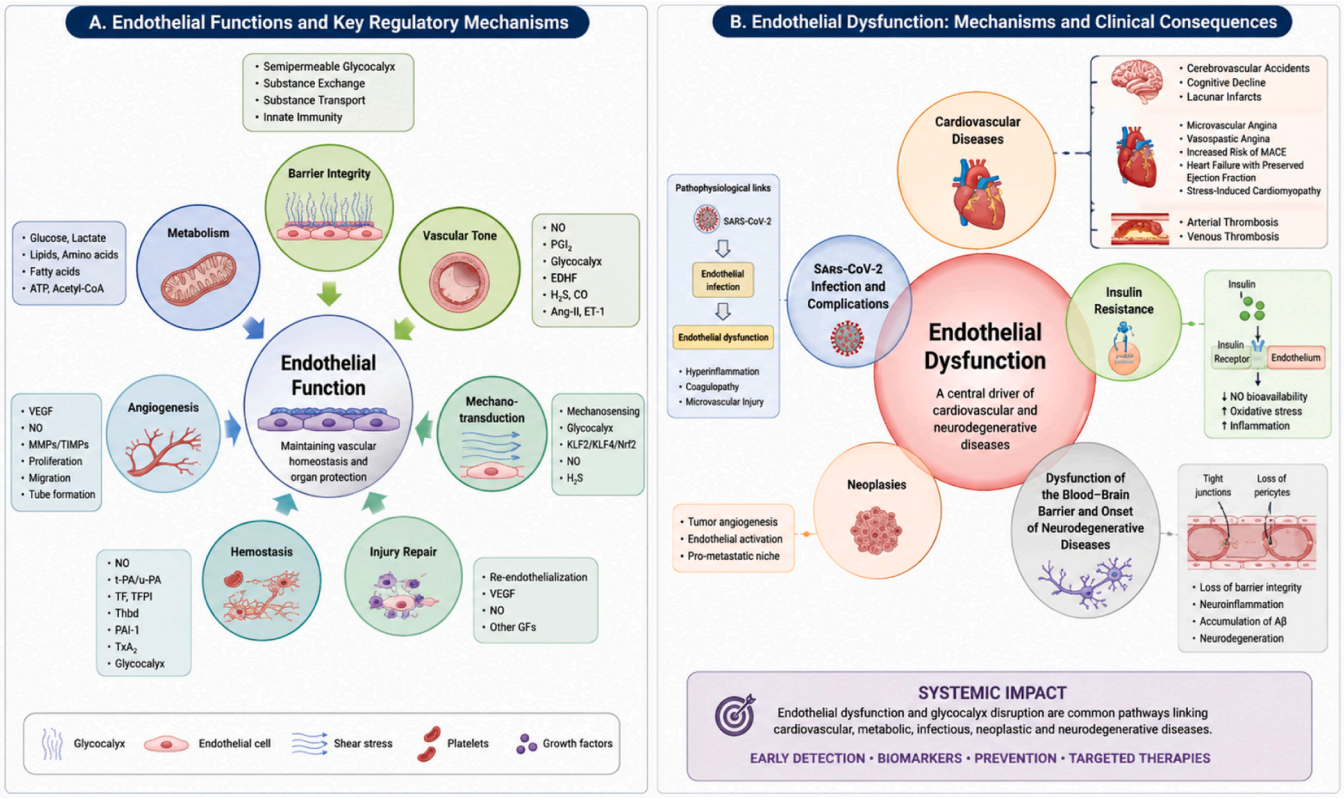


Fig. 3. The role of endothelium. The endothelium plays a crucial role in physiologically performing essential functions for the life of the individual in every tissue district, being the fundamental component of the stroma; when dysfunctional, it contributes to the onset of various pathologies in various tissues.

of vascular permeability and mechano-transduction, playing a fundamental role in maintaining endothelial integrity (Curry and Adamson, 2012; Reitsma et al., 2007; Weinbaum et al., 2007).

Importantly, endothelial cells are fundamental constituents of NVU and BBB, where they contribute to the maintenance of cerebral homeostasis (Balistreri and Monastero, 2023). Alterations affecting the NVU have increasingly been recognized as crucial mechanisms linking vascular dysfunction and neurodegeneration (Schaeffer and Iadecola, 2021). Endothelial and eGCX dysfunction within the central nervous system can induce BBB disruption, neurovascular uncoupling, oxidative stress, impaired cerebral perfusion, and chronic neuroinflammation, thereby promoting neuronal injury and cognitive decline. Several authors have proposed that vascular alterations may not simply accompany neurodegeneration but could actively contribute to its initiation and progression (Iadecola, 2004; Zlokovic, 2011; Sweeney et al., 2018). Accordingly, increasing evidence suggests that vascular dysfunction represents a central mechanism underlying cognitive impairment and dementia. The contribution of vascular alterations to cognitive deterioration has been comprehensively described in both experimental and clinical studies (Gorelick et al., 2011), while the role of modifiable vascular risk factors in dementia prevention has been further emphasized by the recent Lancet Commission report (Livingston et al., 2020). Given the multidimensional nature of endothelial dysfunction and its relationship with cognitive decline, future studies should adopt systems-level approaches capable of integrating molecular, clinical, and imaging information.

In this context, network medicine has emerged as a promising strategy for understanding complex disease interactions (Barabási et al., 2011), while multi-omics methodologies provide the opportunity to characterize biological systems through integrated high-dimensional datasets (Hasin et al., 2017). Combined with artificial intelligence (AI)-based analytical approaches, these strategies may facilitate more accurate prediction of cognitive impairment risk and support personalized disease management.

3.2. *Cellular and molecular mechanisms linking endothelial dysfunction to neuroinflammation and neurodegeneration*

Several cellular and molecular mechanisms have been implicated in the complex relationship between endothelial dysfunction, neuroinflammation, and neurodegeneration. These mechanisms involve alterations affecting vascular integrity, neurovascular communication, inflammatory signaling pathways, and tissue homeostasis, ultimately contributing to cognitive impairment and neurodegenerative disease progression. (Iadecola, 2004; Reitsma et al., 2007; Curry and Adamson, 2012; Weinbaum et al., 2007; Schaeffer and Iadecola, 2021).

One of the major consequences of endothelial dysfunction is the disruption of BBB integrity. Increased BBB permeability facilitates the infiltration of circulating toxins, inflammatory mediators, and neurotoxic molecules into the brain parenchyma, thereby triggering persistent neuroinflammatory responses that progressively contribute to neuronal injury and cognitive deterioration. BBB dysfunction has increasingly been recognized as an early pathological event in several neurodegenerative disorders and may precede clinically evident neuronal loss (Sweeney et al., 2018; Zlokovic, 2011). Furthermore, impaired clearance and consequent accumulation of amyloid-β (Aβ) peptide have been identified as major pathogenic mechanisms promoting NVU dysfunction and BBB damage, ultimately amplifying inflammatory signaling and neuronal toxicity (Zlokovic, 2011).

Additional pathogenic mechanisms include age-associated vascular alterations, pericyte injury, disruption of tight-junction proteins, endothelial morphological abnormalities, and dysregulated angiogenesis. Elevated levels of platelet-derived growth factor receptor-β (PDGFR-β) suggest a direct contribution of pericyte damage to BBB impairment. Simultaneously, alterations in vascular endothelial growth factor (VEGF) signaling pathways, including abnormal receptor expression and

defective receptor-mediated signaling, may contribute to altered angiogenic responses and abnormal vascular remodeling (Balistreri and Monastero, 2023).

Furthermore, increased matrix metalloproteinase (MMP)-2 and MMP-9 activity, oxidative stress resulting from vascular leakage and iron accumulation, together with alterations in neurovascular transport proteins such as glucose transporter-1 (Glut-1) and CD146, may further aggravate BBB and NVU dysfunction. Collectively, these mechanisms establish a self-perpetuating cycle linking endothelial dysfunction, vascular impairment, chronic neuroinflammation, and neuronal injury, ultimately contributing to cognitive decline and neurodegenerative disease progression. The relevance of these vascular mechanisms is further supported by growing evidence indicating that vascular risk reduction may represent an important strategy for delaying or preventing cognitive decline and dementia (Livingston et al., 2020).

3.3. Cellular, molecular, and systemic mechanisms linking CVD, neuroinflammation, and neurodegeneration

Several interconnected cellular, molecular, and systemic mechanisms have been implicated in the complex bidirectional relationship between CVDs, neuroinflammation, and neurodegeneration. Current evidence suggests that this association cannot be explained solely by vascular injury but rather by the interaction of multiple pathological pathways involving endothelial dysfunction, chronic inflammation, oxidative stress, immune dysregulation, metabolic alterations, neurovascular impairment, and systemic aging processes. These mechanisms collectively establish a network of biological events ultimately contributing to cognitive decline and NDD progression.

Among the earliest pathogenic events, endothelial dysfunction has emerged as a central mechanism, as extensively described in the previous paragraph (Reitsma et al., 2007; Curry and Adamson, 2012; Weinbaum et al., 2007). Endothelial dysfunction also directly affects NVU, and determines the disruption of BBB integrity, as above reported. BBB dysfunction increases vascular permeability and facilitates the infiltration of circulating inflammatory mediators, toxins, and neurotoxic molecules (e.g. nanoplastics; Balistreri and Monastero, 2025) into brain tissue, thereby initiating and perpetuating chronic neuroinflammatory responses (Sweeney et al., 2018; Zlokovic, 2011). Persistent systemic inflammation, frequently referred to as *inflammaging*, represents another critical mechanism linking CVDs and neurodegeneration. Aging is associated with chronic low-grade inflammation characterized by increased circulating levels of inflammatory mediators including interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and CRP. These inflammatory mediators contribute to endothelial activation, vascular remodeling, and atherosclerosis while simultaneously promoting microglial activation and neuronal injury (Franceschi and Campisi, 2014; Livingston et al., 2020).

Recent evidence also highlights the contribution of the NLRP3 inflammatory signaling, which amplifies inflammatory signaling and has been implicated in both cardiovascular pathology and neurodegenerative processes (Balistreri and Monastero, 2023).

In parallel, oxidative stress and mitochondrial dysfunction constitute important, shared mechanisms. Excessive production of reactive oxygen species (ROS) contributes to endothelial injury, reduced nitric oxide bioavailability, vascular remodeling, and myocardial damage. In the brain, oxidative stress induces synaptic dysfunction, neuronal injury, and activation of inflammatory pathways, thereby accelerating neurodegeneration (Sweeney et al., 2018; Zlokovic, 2011). Mitochondrial dysfunction further exacerbates these processes through impaired energy production and altered cellular metabolism (Balistreri and Monastero, 2023).

Several cerebrovascular alterations, including macro-infarcts, microinfarcts, microbleeds, atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy, have also been documented to directly impair NVU function and accelerate cognitive deterioration (Gorelick et al., 2011). Microvascular dysfunction may reduce cerebral blood flow and alter oxygen delivery to brain tissues, resulting in chronic hypoxia/ischemia, now recognized as a major trigger of persistent BBB disruption and neurovascular injury. Chronic cerebral hypoperfusion contributes to progressive neuronal damage and promotes neurodegenerative changes (Iadecola, 2013).

Recent studies have also emphasized the role of the gut–brain–heart axis in mediating interactions among cardiovascular, metabolic, and neurological disorders. Alterations in gut microbiota composition may increase the production of inflammatory metabolites such as lipopolysaccharides (LPS) and trimethylamine-N-oxide (TMAO), promoting endothelial dysfunction, systemic inflammation, and neuroinflammatory responses (Cryan et al., 2019; Tang et al., 2017). Such mechanisms may represent an additional pathway connecting peripheral and central pathological processes.

Furthermore, cellular senescence and the associated senescence-associated secretory phenotype (SASP) have emerged as important contributors to both vascular and neurodegenerative diseases. Senescent cells release inflammatory cytokines, chemokines, growth factors, and proteases capable of maintaining chronic inflammation and tissue dysfunction, thereby promoting both vascular aging and neuronal deterioration (Franceschi and Campisi, 2014).

Collectively, these mechanisms (see Table 4) establish a self-perpetuating pathological cycle in which systemic inflammation, endothelial dysfunction, oxidative stress, immune dysregulation, metabolic abnormalities, and neurovascular impairment interact continuously. The resulting chronic neuroinflammatory state promotes neuronal injury, synaptic dysfunction, amyloid accumulation, and ultimately neurodegenerative disease progression.

Understanding these complex interactions may provide opportunities for identifying novel biomarkers and developing integrated preventive and therapeutic strategies targeting both cardiovascular and brain health.

4. Emotional dysregulation as a bridge between CVD and neurodegeneration within the Heart–Brain–Emotion Axis

Emotional disturbances represent another important clinical feature commonly observed in patients with CVDs, significantly contributing to disease burden and clinical outcomes, and to onset of NDD (Liori et al., 2025; Manolis et al., 2025; Ozkan et al., 2025; Zhang, 2025; see Table 1). Among these, depression, delirium, sleep disorders, and alexithymia have emerged as particularly relevant conditions because of their close relationship with cognitive impairment and disease progression. These emotional and psychological disturbances may negatively affect treatment adherence, quality of life, functional status, and long-term prognosis (see Table 5).

Depression is among the most prevalent psychiatric comorbidities in patients with cardiovascular disease. For example, approximately 16% of patients with HF or CHF develop depression, with a higher prevalence observed among patients with preserved ejection fraction (22%) compared with those with reduced ejection fraction (11%) (Warraich et al., 2018). Importantly, depression frequently remains underdiagnosed; approximately 38% of HF patients presenting depressive symptoms were not recognized by their physicians. Female patients with HF also appear to be disproportionately affected, exhibiting a greater deterioration in quality of life and worse clinical outcomes (van Nieuwkerk et al., 2023).

Depression and cognitive impairment are closely interconnected and frequently share overlapping clinical manifestations, including fatigue, reduced motivation, apathy, and impaired concentration. Such similarities may complicate clinical recognition and contribute to delayed diagnosis and management. Accordingly, screening tools such as the Beck Depression Inventory-II (BDI-II) and the Cardiac Depression Scale (CDS) have been proposed to facilitate early identification of depressive symptoms in cardiac populations (González-Roz et al., 2019). The BDI-II

Table 4
Interconnected cellular, molecular, and systemic mechanisms have been implicated in the complex bidirectional relationship between CVDs, neuroinflammation, and neurodegeneration.

Systemic mechanism	Molecular/cellular pathways	Contribution to CVD	Contribution to neuroinflammation/ neurodegeneration
Chronic systemic inflammation ("inflammaging")	IL-1β, IL-6, TNF-α, CRP, NLRP3 inflammasome	Endothelial dysfunction, atherosclerosis, vascular remodeling	Microglial activation, neuronal injury, cognitive decline
Endothelial dysfunction and glycocalyx damage	eGCX shedding, reduced nitric oxide (NO), adhesion molecule activation	Impaired vascular homeostasis	BBB disruption, neurovascular dysfunction
Oxidative stress	Reactive oxygen species (ROS), mitochondrial dysfunction	Vascular injury and myocardial damage	Synaptic dysfunction, neuronal loss
Immune dysregulation	Monocyte/macrophage activation, T-cell imbalance	Chronic vascular inflammation	Sustained neuroinflammation
Blood–brain barrier (BBB) dysfunction	Tight-junction loss, altered permeability	Increased vascular damage	Entry of cytokines and neurotoxic molecules
Neurovascular unit (NVU) dysfunction	Endothelial–neuronal–glial uncoupling	Impaired cerebral circulation	Reduced neuronal survival
Impaired cerebral perfusion	Reduced cardiac output, microvascular dysfunction	Heart failure-associated cerebral hypoperfusion	Chronic ischemia and cognitive decline
Mitochondrial dysfunction	Reduced ATP synthesis, altered calcium homeostasis	Cardiomyocyte dysfunction	Neuronal energy failure
Gut–brain–heart axis dysregulation	Gut microbiota changes, lipopolysaccharides (LPS), trimethylamine-N-oxide (TMAO)	Atherosclerosis and inflammation	Microglial activation and neurodegeneration
Cellular senescence	Senescence-associated secretory phenotype (SASP)	Vascular aging	Chronic inflammatory state and neuronal dysfunction
Metabolic dysregulation	Insulin resistance, glucose metabolism abnormalities	Diabetes-associated vascular injury	Increased risk of dementia
Amyloid and protein aggregation pathways	Amyloid-β, tau, α-synuclein	Vascular amyloid deposition	AD and PD pathology
Hypoxia–ischemia	HIF-1α activation, angiogenic signaling alterations	Myocardial and vascular injury	Neuronal damage
Coagulation and thrombosis pathways	Platelet activation, fibrin deposition	Stroke and vascular disease	Microvascular brain injury

Table 5
Emotional/neuropsychiatric disturbance in CVD cases.

Emotional/ neuropsychiatric disturbance	Prevalence in CVD cases	CVD setting	Main characteristics and clinical implications	References
Depression	~16% in HF/CHF patients; 14–43% in CAD patients, particularly before CABG	Heart failure (HF), congestive heart failure (CHF), coronary artery disease (CAD)	Frequently underdiagnosed; associated with fatigue, apathy, reduced treatment adherence, lower quality of life, and increased mortality risk; more common in HF patients with preserved ejection fraction and in females	Warraich et al., (2018); Ravven et al., (2013); van Nieuwkerk et al., (2023)
Persistent/new-onset depression after cardiac procedures	11% persistent; 11% new-onset depression after SAVR/TAVI	Surgical aortic valve replacement (SAVR); transcatheter aortic valve implantation (TAVI)	Associated with increased prevalence of cognitive impairment and poorer postoperative outcomes	van Nieuwkerk et al., (2023)
Delirium	14–50% after cardiac surgery; 8–23% after TAVI	Cardiac surgery; TAVI	Acute neuropsychiatric complication; more frequent in non-transfemoral TAVI; preexisting cognitive impairment increases risk; associated with worsening cognitive function	van Nieuwkerk et al., (2023)
Perioperative sleep disturbances (PSD)	Up to 60% in cardiovascular surgical patients	Cardiac surgery	Includes insomnia, poor sleep quality, and sleep-disordered breathing; associated with increased postoperative delirium risk	Varpaei et al., (2025)
Postoperative delirium (POD)	Incidence range: 3.6–73%	Cardiac surgery	Strongly associated with poor sleep quality and reduced sleep duration; contributes to cognitive deterioration and prolonged recovery	Varpaei et al., (2025)
Alexithymia	~35% among stroke patients	Stroke and cerebrovascular disease	Deficit in emotional awareness and regulation; impaired recognition and communication of emotions; reduced insight into symptoms and motivation	Yuan et al., (2024); Sancassiani et al., (2023)
Cognitive impairment associated with emotional disorders	Higher prevalence among patients with depression	Multiple CVD settings	Bidirectional relationship with depression; worsens disease management, treatment adherence, and clinical outcomes	van Nieuwkerk et al., (2023)

consists of a 21-item self-report questionnaire validated across multiple populations and is currently considered one of the most extensively validated instruments within cardiac settings. Conversely, the CDS represents the only depression assessment specifically developed for cardiac patients and may provide greater sensitivity and responsiveness compared with conventional scales developed in non-cardiac populations (González-Roz et al., 2019).

Patients with CAD similarly demonstrate high rates of depressive symptoms, with prevalence estimates ranging from 14% to 43%, particularly among individuals undergoing coronary artery bypass grafting (CABG) procedures. Although depressive symptoms improve in approximately one-third of patients after surgery, persistence has been documented in nearly 20% of cases six months following intervention. Notably, postoperative cognitive decline has also been identified as a predictor of depressive symptoms during long-term follow-up, highlighting the close relationship between cognitive and emotional alterations (Ravven et al., 2013).

Delirium represents another common neuropsychiatric complication among cardiovascular patients, particularly following surgical procedures. It has been reported in approximately 14–50% of patients

undergoing cardiac surgery and in 8–23% of patients receiving transcatheter aortic valve implantation (TAVI), with higher incidence rates observed following non-transfemoral procedures (van Nieuwkerk et al., 2023). Preexisting cognitive impairment constitutes an important predisposing factor for delirium, while postoperative delirium itself may further accelerate cognitive deterioration. A prospective cohort study including 1035 patients undergoing surgical aortic valve replacement (SAVR) or TAVI demonstrated that 32% of patients met criteria for depression before intervention, although only 9% had documented diagnoses in medical records. Furthermore, persistent or newly developed depression after intervention was associated with a greater prevalence of cognitive impairment (van Nieuwkerk et al., 2023).

Sleep disturbances also represent frequent complications among patients undergoing cardiovascular surgery, affecting up to 60% of cases. A recent meta-analysis involving 33 studies reported a significant association between poor sleep quality and postoperative delirium (POD) (Varpaei et al., 2025). Specifically, higher scores on the Pittsburgh Sleep Quality Index (PSQI) and shorter total sleep duration were associated with an increased risk of POD. Poor sleep quality, insomnia, and sleep-disordered breathing therefore appear to constitute important risk factors contributing to postoperative neurocognitive complications.

Another emotional disturbance that is increasingly receiving attention is alexithymia, a multidimensional deficit characterized by impaired emotional awareness and difficulty identifying and expressing emotions. A recent meta-analysis involving stroke patients reported a pooled prevalence of approximately 35%, with significant geographical variability observed across populations (Yuan et al., 2024). Individuals with alexithymia often show limited awareness of emotional states and reduced insight into symptoms and motivation, potentially affecting psychological adaptation and disease management (Sancassiani et al., 2023).

Overall, patients with CVD exhibit substantially higher rates of emotional disturbances than the general population. The coexistence of cardiovascular disease and emotional disorders creates a complex clinical condition associated with impaired treatment adherence, reduced quality of life, poorer clinical outcomes, and increased mortality risk. These observations emphasize the importance of routine psychological and neurocognitive assessment as part of a multidimensional and personalized cardiovascular care approach.

4.1. *Alexithymia: as an appropriate biomarker of poorer cognitive functioning*

Among emotional disorders observed in patients with CVDs, alexithymia has emerged as a highly relevant and increasingly recognized condition, characterized by a multidimensional deficit in emotional awareness and regulation (Sancassiani et al., 2023). Specifically, alexithymia encompasses difficulties in identifying and verbalizing emotions, distinguishing emotional experiences from bodily sensations, an excessive focus on externally oriented thinking, and reduced imaginative capacity. Growing evidence suggests that these emotional processing deficits are also associated with cognitive dysfunction, as several studies have reported significant correlations between elevated alexithymia scores and poorer cognitive performance (Gawęda and Krężołek, 2019).

Within cardiovascular settings, alexithymia has been independently associated with increased long-term cardiovascular risk, showing a significant relationship with estimated 10-year cardiovascular risk (OR = 1.02; 95% CI = 1.01–1.04; $p = 0.009$), as well as maladaptive behavioral responses during acute cardiac events. Moreover, alexithymia has been proposed as a predictor of adverse cardiovascular outcomes and has been identified as a long-term risk factor for recurrent cardiac events and early mortality following myocardial infarction (Luminet et al., 2021; He et al., 2022). These observations suggest that emotional dysregulation may contribute not only to psychological burden but also to cardiovascular vulnerability through behavioral and biological mechanisms.

Recent evidence further indicates that alexithymia extends beyond cardiovascular disorders and frequently occurs in other chronic age-related diseases, including diabetes mellitus, asthma, multiple sclerosis, and cancer. For example, Okanli et al. (2018) demonstrated that alexithymia significantly influences illness perception among cancer patients, whereas Karpuz Seren et al. (2022) reported that alexithymia negatively affects both self-perception and social functioning in patients with multiple sclerosis. Such findings suggest that alexithymia may amplify negative interpretations of bodily symptoms and health-related experiences, thereby adversely affecting self-perceived aging (SPA) in older adults with multiple chronic conditions (Okanli et al., 2018; Karpuz Seren et al., 2022).

The prevalence of alexithymia appears particularly elevated in older populations. In Finland, its prevalence among older adults has been reported to reach approximately 29.3%, whereas studies conducted in China among community-dwelling older individuals with chronic diseases reported prevalence rates ranging from 44.3% to 49.4% (Novak et al., 2025). Therefore, the burden of alexithymia deserves increasing attention in aging populations, particularly among individuals affected by CVD and other chronic conditions (Monteiro et al., 2025).

Considering its close association with emotional regulation, cognitive functioning, and disease outcomes, assessment of alexithymia should potentially be incorporated into multidimensional screening strategies in cardiovascular care. The Toronto Alexithymia Scale-20 (TAS-20), one of the most widely validated tools for evaluating alexithymic traits (Bagby et al., 1994), could therefore be integrated into structured protocols for cognitive and psychological assessment in patients with CVD and chronic age-related diseases. Nevertheless, such protocols remain largely absent from routine clinical practice despite growing recommendations emphasizing the importance of psychological and cognitive evaluation in cardiovascular rehabilitation and geriatric care (Monteiro et al., 2025; Novak et al., 2025).

4.1.1. *Neurobiological basis and potential origins of alexithymia*

Several studies have investigated the neuroanatomical basis of alexithymia in later life to clarify its biological origins and clinical implications. Initial evidence was provided by Lane and colleagues (Lane et al., 1996), who proposed that dysfunction in brain regions involved in emotional processing may contribute to the development of alexithymia. Attention has been directed toward structures located predominantly within the right cerebral hemisphere, which, according to the *right hemisphere aging model*, may undergo earlier age-related deterioration than homologous regions of the left hemisphere. Given the predominant role of the right hemisphere in emotional processing and affective integration, accelerated age-related degeneration within these regions could partly explain the higher prevalence of alexithymia observed in older adults.

Subsequent research has focused on the anterior cingulate cortex (ACC), one of the major structures of the limbic system involved in emotional regulation and conscious emotional awareness (Paradiso et al., 2008). The ACC occupies a strategic anatomical position, connecting evolutionarily older brain structures with more recently developed cortical regions, thereby allowing emotional experiences to be integrated into conscious feelings. Damage involving the rostral ACC has been associated with impairment of subjective emotional experiences, while functional neuroimaging studies have consistently demonstrated reduced ACC activity in individuals with elevated alexithymia scores during exposure to emotional stimuli.

Importantly, aging-related alterations involving the ACC have also been described and include reduced regional cerebral blood flow, impaired glucose metabolism, neuronal dysfunction, and reductions in gray matter volume. Collectively, these findings suggest that alexithymia in older individuals may partly result from progressive structural and functional deterioration of the ACC, particularly within the right hemisphere. Recent investigations further indicate that the ACC

consists of distinct subregions showing differential susceptibility to age-related degeneration (Goerlich-Dobre et al., 2015; Hogeveen and Grafman, 2021). In particular, the rostral ACC appears especially vulnerable to environmental stressors and pathological processes. Proposed mechanisms include vascular dysfunction characterized by reduced regional cerebral blood flow, as well as neurodegenerative processes associated with altered glucose metabolism and progressive neuronal deterioration. Cross-sectional and longitudinal magnetic resonance imaging studies have consistently confirmed age-related structural changes affecting ACC morphology and function.

Overall, understanding the neural substrates underlying alexithymia in older adults, particularly those with chronic diseases, may provide important insights into the biological basis of emotional dysregulation and may contribute to explaining the under recognition of depressive symptoms and emotional distress frequently observed in vulnerable aging populations (Goerlich-Dobre et al., 2015; Hogeveen and Grafman, 2021).

5. Considerations of evidence described and suggestions: potential strategies

The close and well-established relationship between CVDs and cognitive impairment has important clinical implications, particularly for older adults, for whom preservation of cognitive function and maintenance of independence represent major priorities. Although the increased risk of cognitive impairment among older individuals with CVD is widely recognized, several clinically relevant questions remain unanswered, including *when*, *how*, *who*, and *how frequently* patients should undergo cognitive assessment and monitoring (Owens et al., 2020).

Early identification of cognitive impairment may provide substantial clinical benefits by facilitating timely implementation of pharmacological interventions, improving adherence to lifestyle modifications, and promoting a more comprehensive and personalized management approach for older adults affected by both CVD and cognitive dysfunction (see Table 6). Such an approach should encompass multidimensional and targeted interventions aimed at preserving cognitive and functional status. These interventions may include promotion of physical activity or, when not feasible, encouragement of regular movement and mobility programs; implementation of cognitive stimulation and rehabilitation strategies; early educational and support programs for both caregivers and patients; screening for emotional disorders, including depression and alexithymia, accompanied by appropriate preventive and therapeutic interventions; optimization of disease management; and individualized discharge planning adapted to patients' cognitive abilities and functional status.

The implementation of such strategies requires an accurate assessment of overall cardiovascular health (CVH), which can be achieved using validated metrics such as the Life's Essential 8 (LE8) framework (Lloyd-Jones et al., 2022; Sterling et al., 2024) (see Table 6). LE8 includes eight modifiable health behaviors and biological factors: diet quality, physical activity, nicotine exposure, sleep duration, body mass index (BMI), blood pressure, blood glucose levels, and blood lipid profiles. Each component is scored on a scale ranging from 0 to 100, with the overall CVH score calculated as the unweighted average of all domains (Lloyd-Jones et al., 2022; Sterling et al., 2024). Optimization of these cardiovascular metrics has been associated with reduced risk of dementia, slower rates of cognitive decline, and improved performance in several cognitive domains, including global cognition, Digit Symbol Substitution Test (DSST), Consortium to Establish a Registry for Alzheimer's Disease (CERAD) assessments, and verbal fluency tests.

Simultaneously, early assessment of cognitive performance in older individuals may facilitate the implementation of advanced care planning, improve shared decision-making regarding innovative therapeutic options, and support the development of personalized, patient-centered treatment strategies (Samieri et al., 2018; Cho et al., 2022). In this context, increasing attention has recently been directed toward the broader concept of brain health, which encompasses the preservation and optimization of cognitive, sensory, socio-emotional, behavioral, and motor functions throughout the lifespan (Pilatti et al., 2025) (see Table 6). This concept extends beyond the simple absence of neurological disease and emphasizes the maintenance of overall neurological well-being across aging trajectories.

Considering the urgent need to reduce both the onset and progression of cognitive impairment and related emotional disturbances in older adults with CVD, the implementation of Multidimensional Assessment (MDA) approaches has also been proposed. MDA may provide a more integrated framework for identifying biological, psychological, cognitive, functional, and social factors contributing to disease burden and clinical outcomes. A brief overview of this approach is

Table 6
Strategies for limiting the risk of CI in patients with CVD.

Intervention phase	Clinical evaluation and therapeutic interventions	Supportive care and assessment strategies	Target outcomes
Early assessment	Cardiovascular severity and cognitive/ emotional screening	Beck Depression Inventory (BDI-II) and Cardiac Depression Scale (CDS) to screen depression in patients with HF, to measure behavioural manifestations and severity of depression	Early detection of risk for depression, anxiety, and alexithymia
Multifactorial primary prevention	Life's Essential 8 (cardiovascular health metrics)	Promotion of physical activity, lifestyle modifications, and patient education and training	Facilitate early adherence to pharmacological therapy and improve adherence to lifestyle interventions
Management	Pharmacotherapy with ACE-inhibitors, empagliflozin monotherapy, or advanced interventions in patients with HF; CABG in patients with CAD; and surgical procedures including SAVR and TAVI, reducing postoperative adverse events in patients with valvular heart disease	Strategies for stopping/delaying the progression of depression/ alexithymia; disease management	Stabilize cardiovascular disease; reduce cognitive/ emotional decline
Rehabilitation and tertiary care	Cardiac rehabilitation, physical therapy and cognitive engagement (psychotherapy)	Immersive Virtual Reality (VR): enables us to create interactive, ecologically grounded and personalized training environments	Improve function, motivation and emotional well-being
Personalized care strategies	Discharge planning and long-term support	Multidimensional Assessment (MDA) for designing appropriate intervention strategies	Continuity of care, caregiver support and patient-reported outcomes

provided in the following section (see Table 6).

5.1. Multidimensional assessment (MDA): a potential strategy

MDA allows for the collection of clinical, biological, nutritional, functional, cognitive, and psychosocial information essential for assessing older adults (Zülke et al., 2019) (see Table 6). MDA is the gold standard reference method for designing appropriate intervention strategies, as also recognized by the World Health Organization (WHO), which published the document "Integrated care for older people (ICOPE): Guidelines on community-level interventions to manage declines in intrinsic capacity" (https://www.who.int/publications/i/item/WHO-FWC-ALC-19.1). This document indicates that maintaining the health of the older population is an investment in social and human capital, supporting the United Nations Sustainable Development Goals. The ICOPE document recognizes several functional domains to be integrated into the multidimensional assessment of older adults, such as cognition, motor function, psychological well-being, sensory skills, nutrition, socialization, pharmacological management, and falls prevention. However, this multidimensional approach remains underutilized due to fragmented healthcare management, limited resources, and poor information. To prevent cognitive and functional decline, numerous studies have demonstrated the superiority of multicomponent intervention protocols in terms of efficacy compared to single-component interventions targeting individual modifiable risk factors (Zülke et al., 2019). At the same time, the quality of evidence is poor overall, and the feasibility of such protocols in a community-dwelling older adult population remains a significant unknown. The World-Wide Fingers (WW-Fingers) study (Kivipelto et al., 2020) represents the most significant of the few international attempts to implement multidisciplinary interventions aimed at preventing and reducing the risk of dementia. Briefly, it is a randomized experimental study with a two-year follow-up that initially plans to screen the elderly population and subsequently evaluate the effectiveness of personalized, multicomponent interventions lasting several months among at-risk community-dwelling older adults, in accordance with recommendations already outlined by a panel of experts.

5.2. Immersive virtual reality (VR) as an emerging and promising strategy for cognitive remediation

Given the significant association between emotional disorders in patients with CVD, and the onset of cognitive impairment/dementia, some strategies for cognitive remediation have been proposed (Jahn et al., 2021; Ganigara et al., 2026; Kong et al., 2026; Islam et al., 2026) (see Table 6). They are based on cognitive rehabilitation and first include both compensatory strategy-based and more practice-based remediation interventions. However, they have been shown to be inconsistent because of poor evidence about the transfer effects of cognitive improvement on functional outcomes in patients' daily lives (Jahn et al., 2021; Ganigara et al., 2026; Kong et al., 2026; Islam et al., 2026). Another limitation for evidence of being an effective treatment is lack of motivation in the patients to participate in the assigned training, despite receiving encouragement and support. As a solution to these limitations, virtual reality (VR) training is proposed (Ganigara et al., 2026; Kong et al., 2026; Islam et al., 2026). VR enables interactive, ecologically grounded, and personalized training environments. Meta-analyses across neurological and psychiatric groups report gains in attention, executive functions, and motor skills after immersive VR interventions (Jahn et al., 2021; Ganigara et al., 2026; Kong et al., 2026; Islam et al., 2026). However, the scarcity of detailed VR program descriptions limits reproducibility and practical application. Initial data confirms the feasibility and efficacy of immersive VR-based remediation, particularly in bipolar disorder, for improving cognition, alexithymia, rhythm regulation, and quality of life. Early studies in cardiac rehabilitation also suggest that VR can benefit mood, attention, adherence, and self-care. Yet, trials targeting cognitive outcomes in CVDs remain rare (Ganigara et al., 2026; Kong et al., 2026; Islam et al., 2026). No validated VR protocol yet addresses the cognitive needs of this group. Creating such tools could enhance individualized care, boost cognitive resilience, and improve long-term outcomes via better engagement and adherence (Jahn et al., 2021; Ganigara et al., 2026; Kong et al., 2026; Islam et al., 2026).

A recent metanalysis including 190 trials involving a total of 7188 participants has been conducted to demonstrate the effectiveness of VR as a treatment in stroke rehabilitation (Laver et al., 2025). The results suggest that virtual reality may be beneficial in slightly improving upper limb function and activity (standardized mean difference (SMD) 0.20, 95% CI 0.12–0.28; 67 studies, 2830 participants; low-certainty evidence). Compared to alternative treatment approaches, virtual reality may have little or no effect on gait speed, but the evidence is highly uncertain (10 studies, 304 participants; very low-certainty evidence). Compared to alternative treatment approaches, virtual reality may be slightly beneficial for balance (SMD 0.26, 95% CI 0.12–0.40; 24 studies, 871 participants; low-certainty evidence) and possibly reduce activity limitation (SMD 0.21, 95% CI 0.11–0.32; 33 studies, 1495 participants; moderate-certainty evidence). However, it may have little or no effect on participation and quality of life (SMD 0.11, 95% CI −0.02–0.24; 16 studies, 963 participants; low-certainty evidence). Adding VR to traditional care or rehabilitation (resulting in increased therapy time for patients in the intervention group) likely increases upper limb function and activity compared to traditional care alone (SMD 0.42, 95% CI 0.26–0.58; 21 studies, 689 participants; moderate-certainty evidence). However, there may be no apparent benefit on gait speed, but the evidence is highly uncertain (3 studies, 57 participants; very low-certainty evidence). VR as an adjunct to usual care may be beneficial for balance (SMD 0.68, 95% CI 0.46–0.91; 12 studies, 321 participants; low-certainty evidence) and is probably helpful for activity limitation (SMD 0.22, 95% CI 0.04–0.41; 15 studies, 513 participants; moderate-certainty evidence). Evidence suggests that VR, as an adjunct to usual care, may not have a beneficial effect on participation and quality of life (2 studies, 76 participants; low-certainty evidence). Therefore, there is moderate to low-certainty evidence that the use of virtual reality and interactive video games is slightly more effective than alternative treatment approaches in improving upper limb function, balance, and activity limitations. Furthermore, greater benefits for upper limb function were observed when virtual reality was used in addition to usual care (to increase the overall duration of therapy). There was conflicting evidence regarding the effects on mobility outcomes, including gait speed, and insufficient evidence to draw conclusions about the effect of virtual reality and interactive video games on participation limitations and quality of life. Further studies are consequently needed.

5.3. Is it also important to treat alexithymia?

The literature suggests that a multifactorial approach can promote primary, secondary, and tertiary prevention of heart disease. It also appears necessary to reduce the co-occurrence of neurodegenerative diseases, starting with cognitive impairment. Consequently, this multifactorial approach should also consider not only the assessment of the possible presence of alexithymia, but also the identification of appropriate therapeutic approaches. The adherence to psychotherapy may be recommended, even if with limited success among people with alexithymia. On the other hand, they often experience psychological distress, manifesting somatic symptoms or emotional storms (Sancassiani et al., 2023).

Alternatively, supportive psychotherapy, including an initial phase of psychoeducation, different from the traditional interpretive psychodynamic approach, may be more beneficial for people with high levels of alexithymia. Other possibilities of treatment include biofeedback, relaxation techniques, autogenic training, and meditative practices. In

addition, it has been evidenced that a real relationship with patients affected by such emotional dysfunction might be another solution. Further studies are necessary to develop better treatments for alexithymia (Sancassiani et al., 2023).

6. Conclusions and proposed strategy for clinicians: algorithm for realistically implement cognitive and emotional screening in cardiology practice

Growing evidence indicates that CVD, cognitive impairment, and emotional dysregulation should no longer be considered independent clinical entities, but rather interconnected manifestations of a dynamic **Heart–Brain–Emotion Axis**. Aging amplifies reciprocal interactions among cardiovascular, cerebrovascular, neural, inflammatory, autonomic, metabolic, and psychosocial mechanisms, generating self-reinforcing pathways that progressively increase vulnerability to cognitive decline, dementia, and reduced emotional well-being. This integrative perspective provides a more comprehensive framework for understanding age-related functional decline and supports the development of multidomain preventive and therapeutic strategies.

The preventive and therapeutic approaches summarized in Fig. 4 highlight the potential benefits of combining optimal cardiovascular risk management with healthy lifestyle interventions, physical exercise, cognitive stimulation, psychosocial support, and emerging therapeutic strategies. Future perspectives may include regenerative medicine approaches, such as mesenchymal stem cell-based therapies, and senotherapeutics targeting fundamental mechanisms of biological aging (Balistreri et al., 2021; Balistreri, 2022). Furthermore, increasing evidence indicates that sex-specific mechanisms contribute to both CVD and ND, underscoring the importance of incorporating sexual dimorphism into future preventive and therapeutic models (Balistreri, 2023).

Another important challenge is the identification of reliable biomarkers capable of improving early risk stratification and predicting cognitive decline in individuals with cardiovascular disease. In this regard, circulating cardiac biomarkers, including NT-pro-BNP, BNP, and MR-pro-ANP, have shown promise as indicators of structural brain changes and cognitive impairment (Jensen et al., 2023; Asta et al., 2025), although their clinical utility requires validation in large prospective studies.

To facilitate the translation of current evidence into routine clinical practice, we propose a pragmatic framework for integrating cognitive and emotional assessment into cardiovascular care (Fig. 5). Rather than representing a prescriptive clinical algorithm, this model is intended to support the systematic identification of vulnerable individuals through multidimensional evaluation, promoting timely multidisciplinary referral and personalized interventions. Within this framework, cardiac rehabilitation may represent an ideal translational platform by integrating cardiovascular risk management with structured exercise, cognitive stimulation, psychosocial support, lifestyle modification, and patient education.

Ultimately, large prospective multicenter studies are needed to validate integrated care pathways targeting the **Heart–Brain–Emotion Axis** and to determine whether multidomain interventions can preserve cognitive function, enhance emotional well-being, reduce dementia risk, and promote healthy aging. Rather than representing parallel consequences of aging, cardiovascular dysfunction, emotional dysregulation, and cognitive impairment should be viewed as interacting manifestations of a shared biological continuum. Recognizing and targeting this interconnected axis may help shift clinical practice from disease-centered management toward integrated, person-centered strategies aimed at preserving cardiovascular, brain, and emotional health throughout aging.

CRediT authorship contribution statement

Professor Balistreri contributed initially to the conception, design, and drafting of all sections of the article, as well as reviewing, editing, and supervising. Drs. Di Salvo and Motis cured the preparation of figures

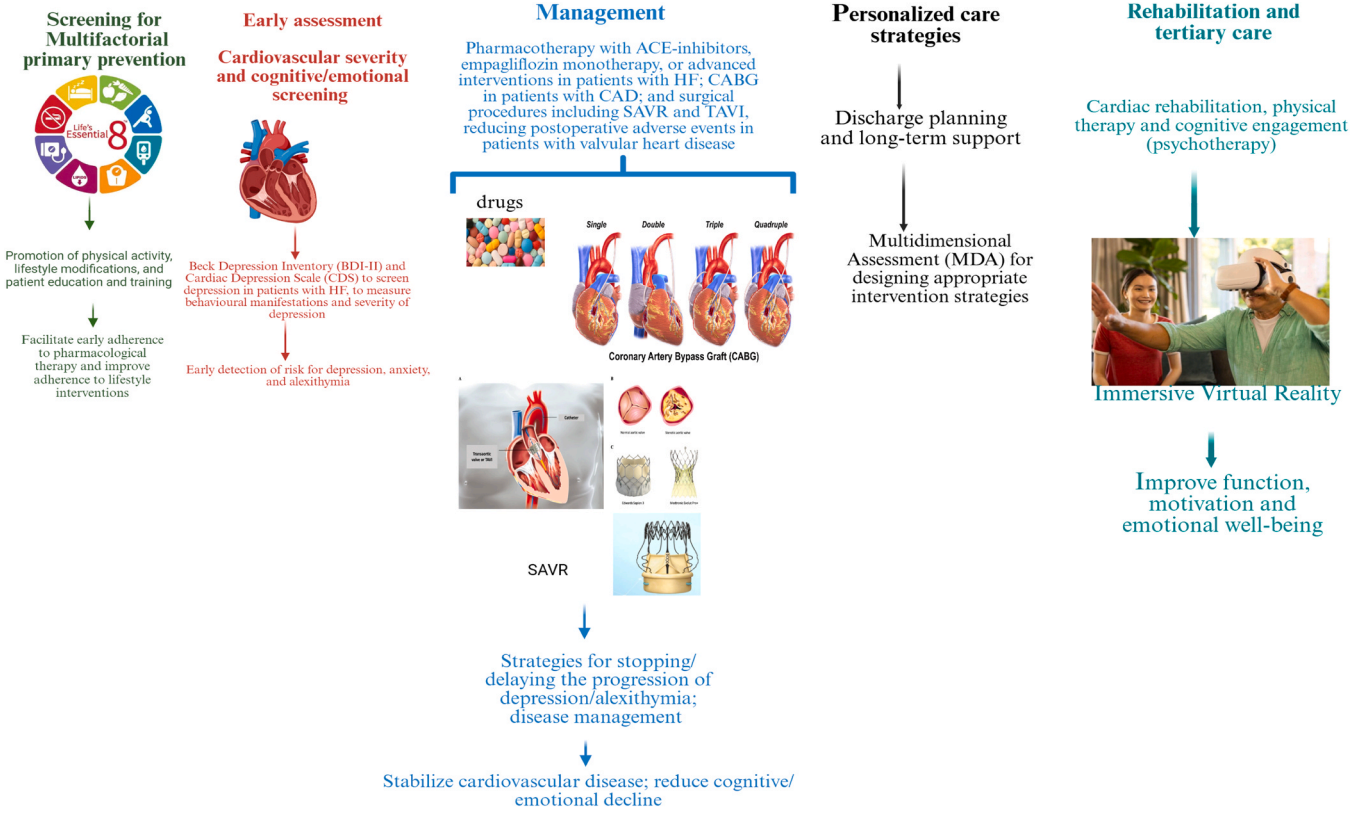


Fig. 4. Some strategies for limiting the elevated risks in older patients with CVD.

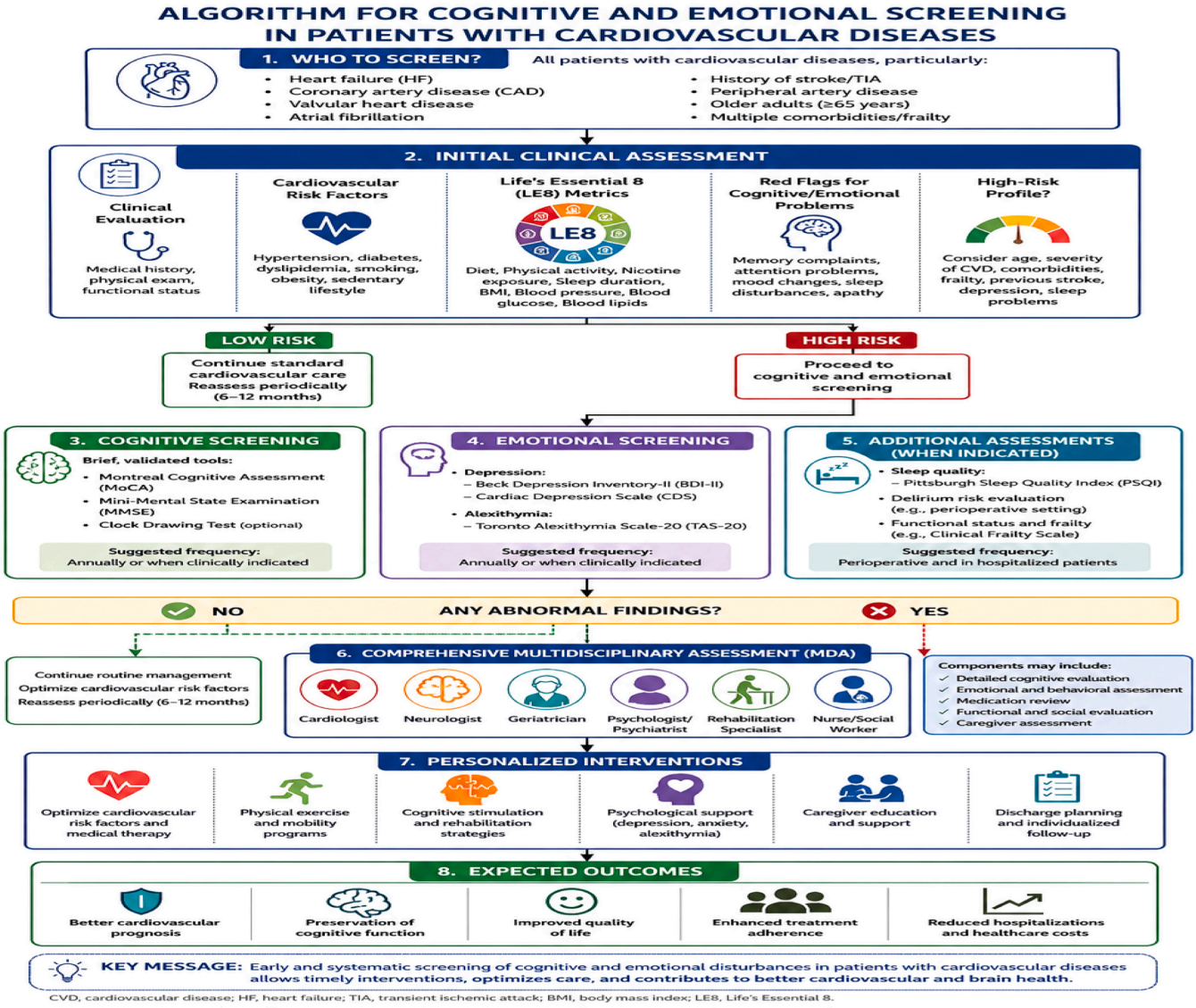


Fig. 5. Proposed practical algorithm for cognitive and emotional screening in patients with CVD.

and tables.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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