

REVIEW ARTICLE

Minds and hearts: Cardio-neural crosstalk in cardiovascular and neurodegenerative diseases

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Abstract

With increasing life expectancy, the prevalence of age-related cardiovascular diseases—including hypertension, atherosclerosis, atrial fibrillation, and heart failure—and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (PD) continues to rise. Emerging evidence indicates that the heart and brain are linked through complex, bidirectional pathways in which cardiovascular pathology can accelerate neurodegeneration, while neurodegenerative processes can precipitate or exacerbate cardiovascular dysfunction. This review critically appraises current knowledge on cardio-neural crosstalk, distinguishing well-established associations (e.g., hypertension and dementia) from more speculative mechanisms (e.g., receptor changes in ischemic PD). We integrate epidemiological findings with mechanistic insights, highlighting inflammation, hypoperfusion, blood–brain barrier disruption, autonomic dysfunction, and amyloid biology as convergent pathways. To enhance clarity, we summarize evidence strength in expanded tables and figures, including epidemiological hazard ratios, mechanistic pathways, and confidence grading. The main contribution of this review is to provide a structured synthesis of robust and emerging evidence on the bidirectional heart–brain axis, identifying gaps that limit causal inference. We emphasize future directions such as longitudinal biomarker studies, interventional trials repurposing cardiovascular therapies for neuroprotection, and systems biology approaches to integrate cardiovascular and neurodegenerative omics data. By consolidating current evidence and outlining actionable research priorities, this review aims to inform both clinical practice and translational research in cardio-neural disease.

Keywords: Cardio-neural crosstalk; Heart–brain axis; Cardiovascular diseases; Neurodegeneration; Alzheimer's disease; Parkinson's disease; Heart failure

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1. Introduction

With increasing life expectancy in the developed world, both the incidence and co-occurrence of neurodegenerative and cardiovascular diseases—both strongly age-related—have risen significantly.¹ This convergence has raised critical questions about

whether and how pathological processes in one system influence the other. A deeper understanding of inter-organ communication promises novel pharmacotherapeutic targets for both cardiovascular and neurodegenerative diseases. Understanding this crosstalk could provide clinicians and investigators with greater insight into prognosis, diagnosis, prevention, and therapeutic intervention to combat these diseases.² Early detection through imaging could prompt preemptive interventions to slow or avert cognitive decline.

Potential implications that would emerge with increased research into this cardio-neural crosstalk could include reductions in post-operative morbidities² and the development of novel pharmacotherapeutics that could blunt the onset and severity of cardiovascular and neurodegenerative outcomes.³ Due to the potential clinical utility of understanding this crosstalk, this review aims to summarize current evidence on how cardiovascular pathology may contribute to Alzheimer's disease (AD) and Parkinson's disease (PD) and to explore plausible reciprocal influences of AD and PD on cardiovascular morbidity. This review will help identify gaps in our understanding of the heart–brain axis to guide future research directions. By mapping these complex interactions, we seek to lay the groundwork for improved prognostic tools, preventative strategies, and therapeutics that address both neurodegenerative and cardiovascular disorders.

2. Methodological approach

This article is presented as a narrative review examining plausible mechanisms of cardio-neural crosstalk in the pathogenesis of cardiovascular and neurodegenerative diseases. To support this aim, an extensive literature search was conducted across PubMed, Embase, and Scopus between May 2023 and July 2023. In addition to these databases, relevant studies were also identified by reviewing the reference lists of articles retrieved through the primary search.

Both free-text keywords and medical subject headings (MeSH) terms were used. Free-text searches included various combinations of the following terms across all databases: “cardiomyopathy,” “heart failure,” “vascular disease,” “myocardial infarction,” “atherosclerosis,” “atrial fibrillation,” “A-fib,” “inflammation,” “blood–brain barrier,” “BBB,” “neuro-inflammation,” “Alzheimer,” “Alzheimer's disease,” “Parkinson,” “Parkinson's disease,” and “microglial.” The MeSH terms applied were: “heart failure,” “cardiomyopathy,” “ischemic cardiomyopathy,” “hypertension,” “atrial fibrillation,” “atherosclerosis,” “cerebral hypoperfusion,” “dementia,” “Alzheimer's disease,” and “Parkinson's disease.”

Articles were included if (i) they explicitly described a mechanism linking the cardiovascular system and the central nervous system (CNS), supported by experimental evidence or theoretical rationale; (ii) they provided relevant details on the pathogenesis of cardiovascular or CNS conditions that, even without directly addressing crosstalk, could inform its explanation; or (iii) they reported clinical or experimental studies or trials in which cardio-neural crosstalk was considered within the study hypotheses. Articles were excluded if (i) they were published before 2000, unless their findings were cited without refutation in post-2000 literature; (ii) they were purely speculative and lacked experimental, clinical, or theoretical support; or (iii) they were case reports.

3. Proposed mechanisms underlying the role of the cardiovascular system in neurodegenerative diseases

Emerging evidence highlights a compelling link between cardiovascular pathology and the progression of neurodegenerative diseases. Vascular dysfunction has been increasingly recognized as a contributing factor in conditions such as AD and PD, suggesting that vascular defects are not merely secondary effects but may play a direct role in disease onset and progression. In addition, thrombotic events and chronic inflammation associated with cardiovascular disease can exacerbate neuronal damage by promoting oxidative stress and neuroinflammation. These findings underscore the importance of cardiovascular health for maintaining brain function (Figure 1), a topic discussed in the following subsections.

3.1. Roles of vascular conditions in neurodegenerative diseases

Strong epidemiological evidence links vascular risk factors to neurodegenerative disease. Hypertension,⁴ diabetes mellitus, and dyslipidemia² are each associated with a higher incidence of cognitive decline and neurodegenerative pathology. This is illustrated in Table 1 below through the example of hypertension. However, the precise mechanism by which vascular dysfunction drives neuronal injury and degeneration is unclear.

3.1.1. Inflammation as a central mediator through inflammasomes

Inflammation has emerged as a key mediator of cardio-neural crosstalk in vascular contributions to AD and PD. Central to this process are inflammasomes⁵—multiprotein complexes expressed in microglia,^{5,6} neurons,^{5,7} astrocytes,^{5,8} endothelial cells,^{5,9,10} and circulating leukocytes.⁵

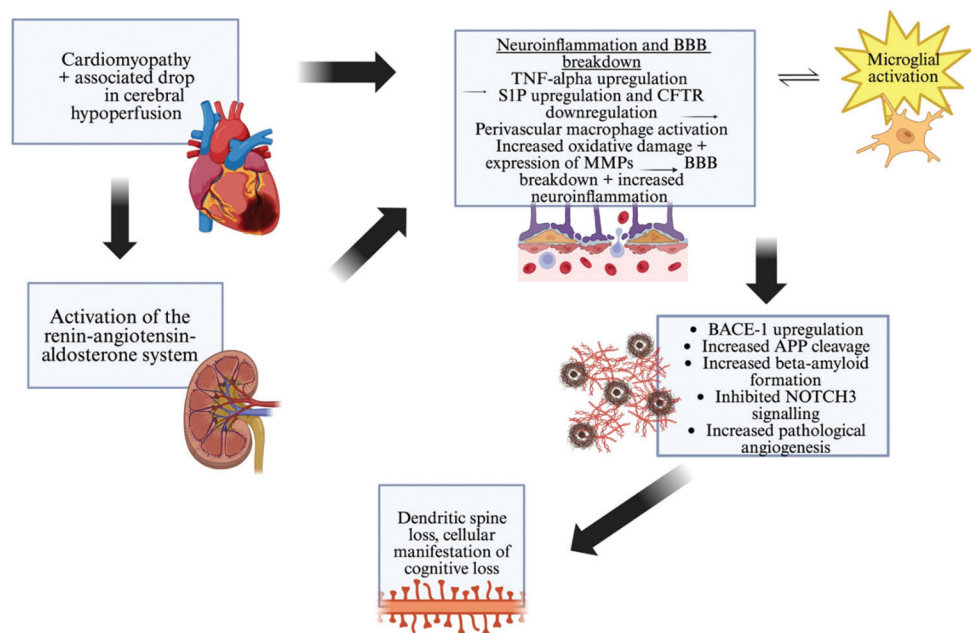


Figure 1. A pathogenesis model providing an explanatory template for the development of cognitive dysfunction in the setting of cardiomyopathy. It incorporates elements that underlie multiple cardiovascular morbidities (e.g., hypertension, atrial fibrillation, and heart failure). Created with BioRender. com. Amro, A. (2026) <https://BioRender.com/c1mc0v8>. Abbreviations: APP: Amyloid precursor protein; BACE-1: Beta-site APP-cleaving enzyme 1; BBB: Blood–brain barrier; CFTR: Cystic fibrosis transmembrane conductance regulator; MMP: Matrix metalloproteinase; NOTCH3: Neurogenic locus notch homolog protein 3; S1P: Sphingosine-1-phosphate; TNF-alpha: Tumor necrosis factor-alpha.

Table 1. Hypertension and dementia/Alzheimer’s disease risk

Hypertension exposure (life stage)	Alzheimer’s disease/dementia risk (effect estimate, 95% CI)
Midlife SBP≥160 versus 110–139 mmHg (untreated)	OR 4.8 (2.0–11.0)
Midlife DBP 90–94 versus 80–89 mmHg (untreated)	OR 3.8 (1.6–8.7)
Midlife DBP≥95 versus 80–89 mmHg (untreated)	OR 4.3 (1.7–10.8)
Midlife SBP≥160 versus<140 mmHg (untreated)	RR 2.6 (1.1–6.6)
Midlife history of hypertension versus normotension	RR 1.4 (0.75–2.62)
Late-life history of hypertension versus none	RR 0.95 (0.78–1.17)

Notes: Examining the OR and RR of developing Alzheimer’s disease/dementia across different populations with different blood pressure ranges. Data from Launer *et al.*⁴
Abbreviations: DBP: Diastolic blood pressure; OR: Odds ratio; RR: Relative risk; SBP: Systolic blood pressure.

The focus on inflammation and inflammasomes is supported by several studies suggesting that overactivity or even the presence of inflammasomes contributes to the disease process of both vascular and neurodegenerative conditions. For example, genetic deficiencies that result

in NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome overactivation have been linked to increased risk of hypertension¹¹ and coronary artery disease.^{5,11,12} Similarly, dyslipidemias and associated oxidative stress, such as hypercholesterolemia, can enhance NLRP3 activation and promote chronic inflammation.¹³ Inflammasome-induced caspase-1 hyperactivation has been implicated in AD,¹⁴ and NLRP3 activity is implicated in the progression of cognitive impairment.¹⁵ Moreover, overactivation of NLRP3 in the absence of uncoupling protein 2, which normally reduces NLRP3-induced oxidative damage, has also been associated with increased dopaminergic neuronal loss in mouse models, suggesting its involvement in PD.¹⁶

Second, inflammasomes have the potential to be discerned as a source of crosstalk between the peripheral vasculature and the CNS. This is suggested by the presence of shared inflammasome types across different tissues, or through cytokines released by inflammasomes in one region, triggering the activation of inflammasomes in another. For example, the NLRP3 inflammasome is implicated in all of hypertension, coronary heart disease,^{11,12} and cognitive impairment.¹⁵ Endothelial cells—whose pattern recognition receptors are subject to the inflammatory responses and attendant oxidative

stresses that come with inflammation-associated vascular diseases such as atherosclerosis, hypercholesterolemia, hypertension, and coronary artery disease—also possess NLRP1 and NLRP3 inflammasomes.⁹ Likewise, both NLRP1 and NLRP3 inflammasomes have been identified in microglia,^{5,17} astrocytes,^{5,18} and neurons.⁵ As a matter of fact, NLRP1 is overexpressed in neurons of mice with AD compared to control mice,^{4,7} and the NLRP-3-associated adaptor component, apoptosis-associated speck-like protein (ASC), is upregulated in astrocytes of patients with AD.¹⁹ Furthermore, NLRP3 activity in astrocytes has been tied to PD pathology.¹⁶

Beyond the shared expression and activation of inflammasomes in both vascular and neurodegenerative diseases, bidirectional crosstalk may also occur through cytokine trafficking. Cytokines released by inflammasomes—whether centrally or peripherally located—can induce tissue damage that, in turn, activates additional inflammasomes, perpetuating a self-reinforcing cycle of disease progression. Although the precise mechanisms of this crosstalk remain under investigation, several promising pathways have been proposed. For example, one hallmark of AD is the accumulation of amyloid-beta ($A\beta$) plaques, which contribute to neurotoxicity through mechanisms including neuroinflammation. These $A\beta$ plaques attract local microglia, whose inflammasomal pattern recognition receptors recognize $A\beta$ as an antigen^{5,20} and respond with the release of pro-inflammatory cytokines such as interleukin (IL)-1 β , IL-18, tumor necrosis factor (TNF), and nitric oxide (NO).^{5,20,21} These cytokines amplify neurotoxicity by promoting further inflammation, oxidative stress, and neuronal damage, while also recruiting additional microglia, thus reinforcing the cycle. The resulting oxidative stress and inflammatory damage produce damage-associated molecular patterns that can activate neighboring CNS inflammasomes.^{5,20} Given that NLRP3 inflammasomes are active in endothelial cells, upregulated in vascular conditions such as hypertension, atherosclerosis, and hyperlipidemia, and capable of releasing IL-1 β and IL-18,^{5,9,22} a potential mechanistic link between vascular pathology and neurodegeneration—such as AD—becomes plausible, either causally or as mutually exacerbating processes within a bidirectional relationship. $A\beta$ -induced cytokine release from microglial NLRP3 inflammasomes may act as one such bridge. A similar model has been proposed in PD, where inflammation is increasingly recognized as a key contributor to neurodegeneration, again pending further investigation.⁵ Supporting this, some studies have reported elevated IL-1 β levels in both serum²³ and cerebrospinal fluid,²⁴ though findings are mixed. Others have found no change in serum cytokines²⁴ or noted elevations in

anti-inflammatory cytokines.²³ In addition, α -synuclein, a hallmark protein in both AD and PD, has been shown to activate NLRP3 inflammasomes in monocytes, further promoting IL-1 β release.²⁵

Emerging research in aging further highlights inflammasomal crosstalk between the peripheral nervous system and CNS. One study proposed a link between low-grade peripheral inflammation mediated by NLRP3 and degenerative changes in both the brain and peripheral tissues.²⁶ Ablation of NLRP3 inflammasomes in aging mice resulted in improved cognitive and motor function, along with reduced structural degeneration. Thus, targeting inflammasomes could offer therapeutic potential in modulating cardio-neural communication without significantly compromising immune defense. Knockout models suggest that inflammasome inhibition merely delays, rather than abolishes, adaptive immune responses—a feature that may represent an evolutionary trade-off.²⁷

With respect to the literature exploring the role of inflammasomes in mediating cardio-neural crosstalk, it should be noted that the links explored above are plausible but, as of yet, have no clinical relevance. Animal models and *in vitro* studies underlie the bulk of the literature. Human data, in contrast, establish connections in a mostly speculative manner through surrogate values such as inflammatory biomarkers, postmortem analyses, or indirect imaging studies. There are no large-scale clinical studies to validate the proposed mechanisms. Moreover, there are also no inflammasome-targeted therapies that have been trialed to fortify these mechanisms either.

3.1.2. Chronic cerebral hypoperfusion as a mediator of cardio-neural crosstalk in neurodegeneration

Among the proposed mechanisms linking cardiovascular pathology to neurodegeneration, chronic cerebral hypoperfusion (i.e., ischemic hypoxia) has emerged as a compelling candidate. It is increasingly recognized for its role in the onset and progression of conditions characterized by cognitive decline, such as vascular cognitive impairment and dementia (VCID) and AD.²⁸ Chronic reductions in cerebral blood flow compromise the brain's metabolic equilibrium and can lead to cellular stress, inflammation, and structural damage—hallmarks of neurodegenerative processes. This link implicates several cardiovascular conditions, including coronary artery disease, hypertension, and hyperlipidemia,²⁸ which are known contributors to cerebrovascular dysfunction.

A growing body of literature supports the assertion that vascular disease is not merely a comorbidity but a primary driver in the pathogenesis of neurodegeneration.

Epidemiological studies have identified hypertension and atherosclerosis as independent risk factors for both cognitive and motor impairment, suggesting that vascular pathology and neurodegenerative disease may share overlapping mechanistic pathways.^{17,29} Importantly, these pathways may converge at the level of neurovascular coupling—a dynamic process by which cerebral blood flow is matched to neuronal activity. When this relationship is disrupted, neurons are deprived of the necessary oxygen and glucose required for normal function, potentially leading to cumulative damage over time (Figure 2).

Experimental models have provided significant insights into how chronic cerebral hypoperfusion may initiate and sustain neurodegeneration. In animal studies, rodent models subjected to prolonged reductions in cerebral blood flow exhibit key neuropathological features observed in human neurodegenerative diseases. One prominent example is white matter degeneration—a hallmark of both VCID and AD—which has been consistently reproduced across various experimental paradigms.²⁸ Specifically, the rat two-vessel occlusion (2VO) model³⁰ and the bilateral carotid artery stenosis (BCAS) model in mice³¹ have demonstrated significant white matter atrophy and gliosis following sustained hypoperfusion. Although the rat gradual stenosis model presents with less acute manifestations, it nonetheless replicates core structural impairments observed in more aggressive models.³² These studies collectively outline a sequence of pathophysiological events that may serve as a mechanistic bridge between cardiovascular dysfunction and CNS degeneration. Chronic hypoperfusion causes endothelial dysfunction and compromises the blood–brain barrier (BBB) integrity, contributing to neuroinflammation, oxidative stress, and glial activation. These processes, in turn, may accelerate the

formation of AD-related pathologies, such as A β plaques and tau hyperphosphorylation. Moreover, sustained hypoperfusion alters the composition of the neurovascular unit, impairing the regulatory capacity of astrocytes and pericytes—cells critical to maintaining vascular tone and BBB function. In short, many studies have established a set of events that have been observed in hypoperfused rodents that help outline a mechanistic pathway.

(a) Neurovascular uncoupling

In healthy brains, neuronal activity is tightly coupled with local blood flow. Vascular pathology can disrupt this coupling, leading to inadequate oxygen and nutrient delivery during periods of increased neuronal homeostatic metabolic demand.^{33,34} Neurovascular coupling is marked by the ability of the cerebrovasculature to regulate its blood flow to the CNS in response to other factors.³² This neurovascular coupling would be disrupted through alterations in hemodynamics and consequent endothelial cell dysfunction, which reinforce these alterations and so forth, eventually leading to cerebral hypoperfusion through a number of proposed mechanisms, including alteration of vascular reactivity and disruption of the BBB.^{28,30,34} The uncoupling also occurs through structural-functional disruptions of cells that make up the neurovascular unit, such as astrocytes—which function to maintain vascular integrity and mediate autoregulation through their foot processes attached to the endothelial vascular layer. This arrangement is disrupted in states of hypoperfusion and is strongly implicated in cognitive impairment due to altered hemodynamic regulation of the brain's microcirculations.²⁸ In addition, matrix metalloproteinase (MMP)-mediated breakdown of the extracellular matrix further disrupts tight junctions and endothelial cohesion, exacerbating neurovascular uncoupling.

(b) BBB dysfunction

Another event that occurs secondary to cerebral hypoperfusion in observed rodent models is the disruption of the BBB, increasing permeability between the periphery and the brain.²⁸ Vascular diseases can impair the integrity of the BBB, allowing neurotoxic substances, immune cells, and inflammatory mediators to enter the cerebral parenchyma. This disruption is implicated in the pathogenesis of AD and PD. Studies suggest that this increased permeability is due to MMP-9, released under pathologically stressful conditions by oligodendrocyte precursor cells (OPCs).³⁵ Increased BBB permeability can be highly neurotoxic and contribute to further neurodegeneration and cognitive/motor decline. As an example, increased BBB permeability facilitates the entry of systemic fibrinogen, which triggers inflammatory responses in microglia in the CNS.²⁸ This increased contribution to neuroinflammation is another

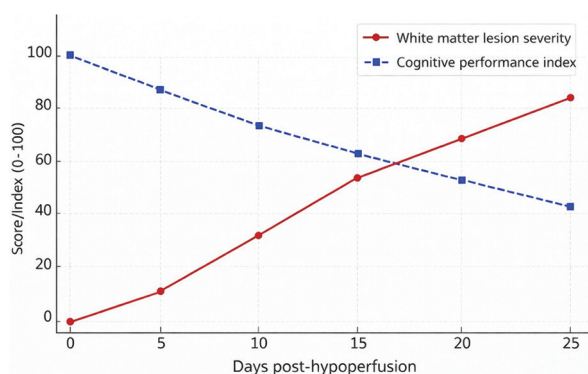


Figure 2. Temporal relationship between cardiac index and cerebral hypoperfusion in relation to white matter lesion severity and cognitive performance index. Graph generated by the authors through Microsoft Office, using data collated from Pantoni.²⁹

source of neurodegeneration in conditions of cerebral hypoperfusion and marks another event that occurs in these rodent models. In fact, along with oligodendrocyte degradation, the activation and proliferation of microglia are also observed to contribute to white matter lesions rapidly post-hypoperfusion. This is demonstrated by studies showing upregulation of genes involved in immune responses in white matter,³⁶ the presence of activated microglia in white matter lesions in human brains,³⁷ and a causal relationship between myelin degradation (which would be in the white matter) and microglial activation.²⁸ Like oligodendrocytes, microglia under these conditions also contribute to axonal–glial disruption.^{38,39}

Microglial activation also leads to the release of other neurotoxic substances, including reactive oxygen species (ROS), which destabilize endothelial cells through the disruption of NO signaling, thereby increasing tissue damage from oxidative stress and further disrupting neurovascular coupling and BBB integrity.^{28,40,41} Microglia also release MMPs, which promote neurotoxicity by degrading myelin—worsening white matter lesions⁴²—and breaking down extracellular matrix components that stabilize endothelial cells and tight junctions, further increasing BBB permeability and dysfunction.⁴³ In addition, activated microglia secrete pro-inflammatory cytokines that sustain a self-aggravating cycle of neuroinflammation.²⁸ This cascade is amplified by cerebrovascular endothelial activation, marked by the upregulation of adhesion molecules such as intracellular adhesion molecule 1 and vascular adhesion molecule 1, which facilitate leukocyte extravasation into the CNS and intensify the inflammatory response.^{44,45} Collectively, these microglia-derived factors have been shown to drive neurodegenerative processes across experimental models.

(c) Amyloid and tau pathology

There is an added element to consider: the relationship between A β and cerebral hypoperfusion. Vascular dysfunction may impair clearance of A β and tau proteins through the glymphatic system or through reduced perivascular drainage, contributing to their accumulation in AD.²⁸ A β has been demonstrated to increase in mouse models in response to cerebral hypoperfusion. In a study, transgenic mice (carrying mutations that allow endogenous production of human amyloid precursor protein [APP]) were compared to wild-type mice (which lack the capacity to produce A β). Both groups of mice were subjected to cerebral hypoperfusion, and the transgenic mice showed increased A β levels in the brain parenchyma as early as 1 month post-hypoperfusion. The A β load progressively increased over time, becoming less soluble. In turn, the parenchymal A β load inflicted its own form

of cerebrovascular disruption through promotion of oxidative stress through ROS production by nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2).⁴⁶ These ROS may further diminish cerebral blood flow through vasoconstriction and enhanced vascular reactivity in the cerebral artery.⁴⁷ In this way, the neurodegenerative effects of cerebral hypoperfusion—white matter lesions, microglia-induced neuroinflammation, increased BBB permeability, and so forth—are reproduced, thereby promoting greater A β formation and insolubility, which, in turn, increase cerebral hypoperfusion and contribute to the deleterious effects of A β in AD.⁴⁷

(d) Loss of oligodendrocytes

The rapid degradation of oligodendrocytes and OPCs was demonstrated as early as 3-day post-operation in the BCAS mouse models.^{28,36} The implications of this event are massive and should be investigated further. Oligodendrocytes have multiple functions in the CNS. They myelinate the axons of the CNS, forming the white matter of the brain and facilitating more efficient neuronal transmission. Oligodendrocytes also confer structural protection and help maintain axonal–glial integrity. They provide metabolic support to the white matter regions of the CNS.⁴⁸ Upon cerebral hypoxia secondary to hypoperfusion operations (e.g., BCAS surgery), white matter lesions and hyperintensities, pathological hallmarks of neurodegenerative diseases, are rapidly observed, partly attributed to the particular susceptibility of oligodendrocytes to hypoxia.²⁸ This relationship is substantiated by the fact that axonal–glial structural integrity is compromised, leading to mislocalization of axonal proteins, which is implicated in impaired neuronal signal conduction and cognitive decline,^{28,36} particularly in areas of white matter subjected to hypoperfusion.⁴⁹ This suggests that white matter lesions and the greater propensity for white matter injury relative to gray matter may be attributed to the heightened susceptibility of oligodendrocytes to hypoxia. This relationship between white matter damage, oligodendrocyte integrity, and cognitive decline is further reinforced by studies demonstrating the presence of hypoxic markers, such as hypoxia-inducible factors-1 and 2, which are primarily expressed in white matter lesions in hypoperfused models.⁵⁰

Degradation or damage to OPCs can occur due to various factors, including oxidative stress, inflammation, metabolic stress, excitotoxicity, and aging, leading to axonal demyelination, axonal damage and degeneration, motor and sensory impairment, cognitive deficits, and visual problems.

(e) Assessment of the role of chronic cerebral hypoperfusion in crosstalk pathology

Regarding the role of chronic cerebral hypoperfusion as a contributor to cognitive decline, the evidence suggesting a causal role is robust. Multiple human cohorts have consistently illustrated the predictive roles of microvascular disease and hypoperfusion in the subsequent development of white matter injury and general neurodegeneration.^{20,28} However, when examining the specific mechanisms that could explain this apparent causality, the evidentiary strength diminishes significantly. The bulk of the literature relies on animal models rather than studies on human samples. At present, the proposed mechanisms are almost entirely speculative and rely on theoretical plausibility rather than established clinical relevance. Further work is warranted in exploring these pathways in clinical populations.

3.1.3. Vascular dysfunction and PD

Many studies have tentatively established at least some sort of association between vascular conditions and PD.⁵¹ In this light, mechanisms that elucidate cardio-neural crosstalk can be proposed. Indeed, the pathogenesis of PD is still relatively murky.⁵² Hence, mechanisms underlying the connection between hypertension and PD are also necessarily speculative at this point. Nonetheless, multiple suggestions have been offered. One proposed mechanism is similar to a pathway discussed previously in this article (in the context of neurodegenerative diseases that impair cognition rather than motor function), the difference being that this pathway (according to the model) affects parts of the brain that are dopaminergic, such as the basal ganglia.⁵² Essentially, the proposal suggests that hypertension and other vasculopathies lead to cerebrovascular lesions that occlude and then diminish cerebral blood flow. In turn, lacunar infarcts, white matter lesions, and even some forms of hemorrhage emerge in response to this blood pressure-induced vasculopathy. The proposal is essentially an extrapolation of previous studies, which suggest a mild-to-moderate percentage of patients' PD etiology stemming from vasculopathy. However, further work is required to substantiate this claim, as many of these studies note that the nature of the lesions in patients with idiopathic Parkinsonism appears to be comorbid rather than causal. In short, there is more plausibility to the idea that vasculopathies can induce the symptoms of PD (namely, motor impairment) more easily than PD in patients without vasculopathies, as greater nigrostriatal dopaminergic neurodegeneration is observed in patients with greater white matter lesions, which have been illustrated to emerge in response to (among other factors) vasculopathies and diminished cerebral perfusion.⁵³

Another proposed model linking vascular conditions to PD development is the role of nicotine and nicotinic

receptors in PD pathogenesis.⁵² Nicotine has been suggested to mitigate PD symptoms by binding to nicotinic acetylcholine receptors (nAChRs) in the striatum of the basal ganglia, activating an ameliorative dopaminergic pathway. nAChRs, composed of alpha- and beta-subunits, degrade with age due to reduced subunit levels, which is thought to exacerbate the disease process and promote PD symptoms. However, while this degradation generally occurs in the $\beta 2$ subunit in aging patients, at least one study has demonstrated that PD patients with a history of cerebral micro-ischemia (status lacunaris) also exhibit degradation of the $\alpha 4$ nAChR subunit.⁵⁴ This finding could plausibly explain the more intense or rapid onset of PD symptoms. In this model, the activity of nicotine in brains affected by ischemia has been extrapolated to the role that cardiovascular conditions such as hypertension and atherosclerosis play in reducing cerebral perfusion.⁵² This conclusion—that the presence of vascular conditions exacerbates or promotes symptoms of PD—is somewhat supported by at least one study, with the caveat that hypertension, in particular, was more closely associated with symptoms of vascular Parkinsonism rather than PD.⁵⁵

Direct clinical extrapolation regarding causal links from the cardiovascular system to the CNS in PD is lacking. Compared to AD, the evidence supporting crosstalk in PD is significantly weaker and more reliant on speculative mechanistic proposals, albeit theoretically robust. While observational imaging studies suggest associations, they do not provide a basis for causal inference and thus have limited clinical relevance at present. Moreover, confounding factors pose significant challenges, as many studies fail to control for common comorbidities such as AD in PD patients (along with a whole host of cardiovascular comorbidities such as hypertension, heart failure (HF), and coronary artery disease). The strongest support for a causal relationship between endothelial dysfunction and nigrostriatal degeneration comes from animal studies, which limits their clinical utility in humans. In addition, the reported alterations of nicotinic receptors in ischemic milieus are largely speculative, supported by multiple studies with limited reproducibility. Thus, conclusions drawn from such studies should be considered educated hypotheses rather than established mechanisms to guide future studies.

3.2. Role of atrial fibrillation (A-fib) in neurodegenerative diseases

A-fib is a recognized risk factor for several conditions, including neurodegenerative diseases such as dementia and PD. Several studies have demonstrated an increased association between A-fib and the development of neurodegenerative diseases,^{56,57} with meta-analyses

reporting a 36% greater risk of developing dementia among patients with A-fib compared to those without.^{56,58} The relationship between A-fib and PD is less well established, partly due to the lower prevalence of both conditions. Nevertheless, research has suggested a potential association, with some studies proposing that A-fib may serve as a non-motor or even premotor indicator of PD.⁵⁹

Regarding the potential causal relations between A-fib and dementia, at least four plausible mechanisms have been proposed, each supported by varying degrees of empirical evidence⁶⁰: embolization, cerebral microbleeding, cerebral hypoperfusion, and neuroinflammation. This section exclusively focuses on the mechanisms of embolization and cerebral microbleeding, as the article has already discussed the literature on cerebral hypoperfusion and neuroinflammation above.

(i) Embolization

Among the proposed mechanisms linking A-fib to neurodegeneration, the most plausible involves the heightened risk of embolization. This stems from the frequent satisfaction of Virchow's triad for thrombogenesis by patients with A-fib, often secondary to the pathogenesis and abnormal electrophysiology of A-fib. This increased potential for thrombogenicity and embolization is why A-fib is such a significant risk factor for cerebral hypoperfusion, whether through overt, acute ischemic strokes or the gradual accumulation of silent infarcts over time.⁶⁰ Several studies have demonstrated a strong connection between A-fib and ischemic stroke. For example, one study attributed 14.7% of strokes to A-fib, with the proportion rising to 36.2% among individuals aged 80–89.⁶¹ Other reports noted that A-fib increases stroke risk by 4–5 times compared to individuals in normal sinus rhythm.⁶² Likewise, with regard to silent and covert cerebral infarcts, meta-analyses suggested a 2.6-fold increased risk in patients with A-fib relative to patients without it.^{60,62} In fact, these silent infarcts are more frequently found in A-fib patients compared to even overt ischemic cerebrovascular attacks.⁶³

Both overt and covert cerebrovascular ischemia are strongly associated with dementia. One study found that among stroke survivors, the prevalence of dementia reached nearly 30%, with incidence as high as 48% post-stroke; the risk of dementia doubles in individuals who experience and survive a stroke.⁶⁴ Silent infarcts also carry significant cognitive consequences. Studies have shown that the greater the incidence of brain infarcts, the greater the decline in cognitive performance.^{58,65} The decline in cognitive performance was positively associated with the magnitude of infarct load. Results from these studies with covert cerebral infarcts were even

extrapolated to assess cognitive performance in patients with A-fib compared to those with normal sinus rhythm, with magnetic resonance imaging (MRI)-based studies revealing a higher prevalence and broader distribution of silent cerebral ischemia (SCIs) in A-fib patients compared to controls.⁶⁶ These patients also performed worse on cognitive assessments, including the Repeatable Battery for the Assessment of Neuropsychological Status test for visuospatial ability. Further evidence suggests that A-fib independently increases the risk of dementia in elderly patients—even in those without acute stroke or baseline cognitive impairment.⁶⁶

This embolic mechanism is particularly compelling as a model of cardio-neural crosstalk because cerebral hypoperfusion is known to trigger a cascade of neurotoxic processes. These include white matter degeneration, BBB disruption, neurovascular uncoupling, oxidative stress, microglial activation, neuroinflammation, oligodendrocyte loss, and demyelination.⁶⁷ The key question becomes whether A-fib-associated cognitive decline is driven primarily by global cerebral ischemia or the cumulative burden of regionally distributed, multi-infarct injury.

(ii) Cerebral microbleeding

The second proposed mechanism implicating A-fib in the development of dementia is the role A-fib purportedly plays in the development of cerebral microbleeds in lobar regions of the brain.⁶⁸ Microbleeds would theoretically contribute to neurodegeneration by depriving cerebral tissue of necessary nutrients and oxygen while impairing waste clearance. However, this proposed mechanism is less viable because the association between A-fib and cerebral microbleeds is disputed. Meanwhile, many studies suggest that cerebral microbleeds emerge from the use of warfarin in patients with A-fib.⁶⁹ Furthermore, one study demonstrated no association between cerebral microbleeds and cognitive dysfunction. Therefore, further investigation is needed to explore the viability of this proposal.

3.2.1. A-fib and PD: An emerging but underexplored link

Although the literature exploring mechanisms connecting A-fib to PD remains limited, evidence of an association has emerged. As previously noted, studies have reported an 11.4% prevalence of A-fib among individuals later diagnosed with PD.^{70,71} Moreover, the hazard ratio—an index that gauges the association of a given risk factor with, in this case, a subsequent diagnosis of PD—for A-fib was measured at 1.16, comparable to other vascular diseases we discussed earlier, such as hypertension (1.30), hyperlipidemia (1.13), and coronary heart disease (1.26).⁷⁰ Despite the observed association, mechanistic explanations are lacking and

warrant further investigation. However, parallels with other vascular diseases suggest plausible hypotheses. For example, A-fib–induced cerebral ischemia—whether due to embolism, hypoperfusion, hemorrhage, or reduced cardiac output—could potentially impair nAChRs involved in PD symptom modulation.⁶⁶ It is also reasonable to speculate that ischemia from A-fib may lead to white matter lesions, cerebral atrophy, or hemorrhagic damage in regions such as the substantia nigra.⁶⁴ Of particular note is A-fib's elevated risk for stroke relative to other cardiovascular conditions.^{72,73} Stroke itself is considered a risk factor for PD, with a reported hazard ratio of 1.55 among stroke survivors.⁷⁰ However, the evidence supporting stroke as a precursor to PD remains inconclusive and highlights the need for deeper exploration.

3.2.2. Assessment of the role of A-fib in crosstalk pathology

Regarding the literature on A-fib's role in the development of neurodegenerative disease, the associations are particularly robust. However, in line with general studies on crosstalk between the CNS and cardiovascular system, the causative role of A-fib is still in the realm of hypothesis rather than clinically relevant substantiation that can be acted upon in pharmacologic trials. Interestingly, the evidentiary plausibility of the four listed mechanisms can be aggregated in a hierarchy, outlined in Table 2 below, along with cerebral small vessel disease. In summary, the relationship between embolization and cognitive decline (but not motor decline) is well established, supported by detailed MRI studies and clinical data. Further research exploring this particular mechanism is more likely to reach firmer conclusions on causation before studies on the other mechanisms (in descending order of evidentiary strength): hypoperfusion, microhemorrhaging, and neuroinflammation.

3.3. Role of HF in neurodegenerative diseases

HF is a cardiovascular condition in which the heart is unable to fully oxygenate and nourish body tissues to meet physiological needs, at least through physiologically normal mechanisms. The cardiovascular system often undergoes compensatory mechanisms to maintain physiologically standard cardiac output in response to HF. These mechanisms include hypertrophy (whether concentric or eccentric) during contractions of greater magnitude, tachycardia to boost heart rate and thus cardiac output, and vasoconstriction to raise blood pressure and ensure adequate perfusion, among others. However, if the underlying HF is not rectified, these compensatory mechanisms eventually cannot meet demand, leading to a host of symptoms secondary to the structural damage

they cause and to the poor cardiac output at the root of the entire problem.^{73,74} HF has several etiologies, including diabetes mellitus, valvular diseases, arrhythmias, various cardiomyopathies, myocardial infarctions, and many other antecedents, both acquired and genetic in nature.

3.3.1. HF and AD

To explore the connection between HF and neurodegenerative diseases, it is first helpful to assess observed associations—whether directly between HF and neurodegenerative diseases or between precursors to HF and such conditions. One study reported that cognitive dysfunction occurs in 35–50% of patients with congestive HF.⁶⁸ Another study identified a hazard ratio of 1.84 for the development of dementia following HF, and a hazard ratio of 1.80 for AD specifically—figures that surpass those of other cardiovascular risk factors for AD^{70,75}—thus strongly suggesting that HF is significantly associated with an increased risk of dementia and AD.⁷⁵ Moreover, hypertrophic cardiomyopathy (HCM) increases the risk of dementia, with affected patients experiencing 50% higher incidence rates than controls.⁷¹ Specifically, HCM patients demonstrate incidences of 23.0/1,000 for dementia and 18.0/1,000 for AD (Table 3). In addition, the Framingham Heart Study⁷² found that a reduced cardiac index—linked to MI, coronary heart disease, and angina—correlates with cognitive impairment and AD.

The pathophysiological mechanisms underlying cognitive impairment in HF remain speculative and warrant further study.⁷⁷ Nonetheless, several proposed mechanisms have been investigated to varying degrees. Broadly, these mechanisms align with the general pathways discussed earlier for other cardiovascular conditions, involving systemic inflammation,⁵ cerebral hypoperfusion,²⁸ and microthrombi formation.⁷² These processes can result in microglial activation and subsequent neuroinflammation, BBB disruption, increased BBB permeability, neurovascular uncoupling, and white matter lesions.⁷⁷ While many of these pathways have been elaborated upon, this section highlights specific findings and mechanisms by which HF may contribute uniquely to cognitive impairment and AD.

(a) Renin–angiotensin–aldosterone system activation and neurovascular compromise

HF activates compensatory mechanisms to sustain cardiac output, notably the renin–angiotensin–aldosterone system (RAAS).^{73,77} This response elevates serum levels of angiotensin II, which binds to perivascular macrophages, initiating a pro-inflammatory cascade.^{76,78} This includes NOX2 activity, generating ROS and NO (e.g., peroxynitrite [ONOO⁻]).⁷⁷ Concurrent activation of MMPs exacerbates oxidative stress and degrades structural components

Table 2. Proposed mechanisms for atrial fibrillation's causative role in neurodegeneration

Mechanism	Nature of evidence	Evidentiary strength	References
Microembolic injury/silent infarcts	MRI+cohort outcome studies	Most well-supported pathway; stroke-independent effects consistently shown	61–64
Cerebral hypoperfusion during A-fib rhythm	Perfusion MRI, TCD	Causal impact on long-term cognitive decline is still inferential	61
Systemic inflammation	Blood biomarkers	Potentially contributory but not A-fib-specific	61
Endothelial dysfunction+BBB leakage	Imaging and CSF markers	Hard to separate from aging+comorbid vascular disease	69,70
Cerebral small vessel disease	Clinical imaging	Association, but limited mechanistic studies	61

Abbreviations: A-fib: Atrial fibrillation; BBB: Blood–brain barrier; CSF: Cerebrospinal fluid; MRI: Magnetic resonance imaging; TCD: Theoretical conceptual development.

Table 3. Low cardiac index versus dementia risk⁷⁶

Cardiac index level	Relative dementia risk	Alzheimer's risk
Normal	Reference (HR=1.0)	Reference (HR=1.0)
Per 1 SD decrease	HR=1.66 (95% CI: 1.11–2.47)	HR=1.65 (95% CI: 1.07–2.54)
Clinically low	HR=2.07 (95% CI: 1.02–4.19)	Not reported (entire cohort)
Clinically low (No CVD/A-fib)	HR=2.92 (95% CI: 1.34–6.36)	HR=2.87 (95% CI: 1.21–6.80)

Abbreviations: A-fib: Atrial fibrillation; CVD: Cardiovascular disease; HR: Hazard ratio; SD: Standard deviation.

of the BBB, increasing its permeability.^{38,57,60,77} These changes facilitate the entry of circulating cytokines, fibrinogen, and leukocytes into the CNS, contributing to neuroinflammation and neurotoxicity—processes associated with dendritic spine loss and cognitive decline.⁷⁷

(b) Microglial activation and sustained neuroinflammation in HF

The role of microglial activation and neuroinflammation in neurodegeneration has already been discussed in some detail above. However, further discussion within the context of HF is warranted. Numerous studies have linked HF to elevated neuroinflammation through microglial activation.⁷⁷ Morphological changes in microglia, marked by increased expression of ionized calcium-binding adapter molecule 1 (Iba1) and CD11b and decreased Sholl interaction scores, are proxies for inflammation. In one mouse model, coronary artery ligation induced HF and triggered elevated levels of Ly6C, TNF- α , and CD68—markers that positively correlated with microglial activation.⁷⁸ A separate study observed progressive microglial “deramification” in the hypothalamic paraventricular nucleus—11.1% at 8 weeks, 17.1% at 14 weeks, and 30.8% at 16 weeks after HF onset⁷⁶ (Figure 3). This supports the view that longer HF duration, particularly with declining ejection fraction, is associated with increased neuroinflammation.^{76,77}

(c) Neuronal loss associated with HF

Animal studies have further revealed neuronal damage linked to HF. Rats with induced MI displayed greater Fluoro-Jade B staining in the basolateral amygdala—indicating increased cell death—compared to controls.⁷⁹ To corroborate, this study also measured levels of parvalbumin (PV)-, calbindin-, and calretinin-positive cells. PV, calbindin, and calretinin are calcium-binding proteins found in the GABA-mediated interneurons of the basolateral amygdala. Their presence suggests normal amygdala function. Diminished levels of these proteins demonstrate greater neurodegeneration in the amygdala. Upon immunohistochemical staining 14 days post-operation, there was a decline in the quantity and distribution of PV and calbindin staining, suggesting increased amygdala neurodegeneration in MI-induced rats. Decreased expression of PV and calbindin was also observed in another study, while calretinin remained unchanged.⁸⁰ In the hippocampus, caspases-3 and -6, key apoptotic enzymes, were upregulated in HF-induced rats, implicating cell death pathways.⁸¹

(d) Dendritic spine loss and functional decline

Besides pathological angiogenesis, the loss of dendritic spine density in the brain is another molecular manifestation of cognitive decline. Dendritic spine density, critical for neural plasticity and cognition, declines significantly in HF.⁸² In one study, HF-induced mice exhibited a 61% reduction in both basal and apical spines compared to controls.⁸³ This was associated with a concomitant decline in cognitive function. When TNF- α expression was genetically suppressed, spine loss was markedly reduced to approximately 17%, affirming the causal link between inflammation and structural brain degeneration.

(e) Assessment of the role of HF in crosstalk pathology (AD)

Epidemiologically, the association between HF and cognitive decline is robust. Multiple imaging studies

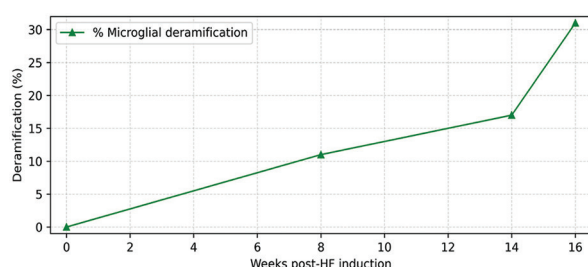


Figure 3. Temporal relationship of deramification, the index of microglial activation, post-heart failure induction. Graph generated by the authors through Microsoft Office, using data collated from Althammer *et al.*⁷⁶

and clinical trials support this association. Moreover, in terms of causal links, studies on dendritic spine loss are more robust than much of the literature examining causal links between the cardiovascular system and central neurodegeneration. However, the studies that have investigated HF's potential role in AD pathogenesis suffer from the same issue found in much of this crosstalk literature: theoretical plausibility with a scarcity of empiric manifestations and clinical relevance. Again, many of the studies are preclinical or *in vitro*. Nonetheless, future studies that seek to explore causal relationships between HF and AD have the greatest promise relative to other facets of crosstalk relationships covered in this review (e.g., HF–PD, A-fib–AD). This is primarily because multiple marketed therapeutic agents directly address facets implicated (theoretically) in HF's contribution to AD: the RAAS. This fact alone makes it easier for future studies to explore potential causality than other plausible mechanisms (such as BBB dysfunction).

Finally, many studies involving HF and AD also possess severe confounding issues, as many of the cited studies do not control for highly prevalent comorbidities, such as hypertension and coronary artery disease—two etiologies that are amongst the most common sources of HF in the first place.⁸¹

3.3.2. HF and PD

Regarding the relationship between HF and PD, it should be noted that the impetus behind studying this relationship is due, in part, to the increased prevalence of HF in elderly PD patients compared to elderly non-PD patients—roughly double.⁸⁴ Potential causative mechanisms of PD through HF are poorly developed or substantiated in the literature. Any proposed mechanism would be speculative. Therefore, although the literature tracing PD from HF is sparse, there is more research suggesting potential mechanisms of HF secondary to PD or as its sequelae, which will be explored later in this article, mainly in the context of dysautonomia.

3.4. Cardiovascular contributions to CNS dysfunction in neurodegenerative disease progression

In general, a recurring theme in the literature is the exploration of crosstalk between the cardiovascular system and neurodegenerative conditions such as AD and PD. This theme is explored due to assumed or established correlational relationships between cardiovascular morbidities and neurodegenerative diseases. These relationships are illustrated—with varying degrees of evidentiary substantiation—in Table 4 below. From there on, plausible mechanisms that could explain a causal relationship were explored, also with varying levels of certainty. Nonetheless, almost the entirety of the literature lacks clinical relevance for various reasons: the studies are *in vitro*, in preclinical trials, and/or are pure speculation with robust theoretical support but limited experimental/clinical data.

4. Proposed mechanisms that explore the role of neurodegenerative diseases in the pathogenesis of cardiovascular diseases

4.1. Role of AD in cardiovascular diseases

The co-occurrence of AD and cardiovascular diseases is well documented, particularly in geriatric populations. Several longitudinal studies have demonstrated that midlife vasculopathies—including hypertension, atherosclerosis, and dyslipidemia—are associated with both mild cognitive impairment and AD in later life; in contrast, fewer studies have suggested a less robust, though still notable, relationship between late-life hypertension and AD onset.⁸⁵ Similarly, HF, which disproportionately affects the elderly, is recognized as a risk factor due to its frequent co-presentation with dementia, including AD.⁸⁶ The central inquiry is whether this relationship is coincidental due to age-related decline, the result of shared pathological processes, or driven by direct causality. While the potential role of cardiovascular pathologies in the pathogenesis of neurodegeneration was discussed, the following sections address the potential role of AD in the development of cardiovascular diseases and the mechanisms underlying the pathogenesis.

Before delving into the different plausible mechanisms, it should be prefaced that causality, once again due to the scarcity of existing literature on the topic of crosstalk, has not been ascertained. Whereas the main question with the cardio-neural crosstalk was one of association versus causality, the main question with AD-to-cardiovascular crosstalk is that of causality versus increased susceptibility. The association is clear. While the mechanisms range

Table 4. Examples of established correlations between cardiovascular morbidities and neurodegenerative disorders

Cardiovascular condition	ND outcome	Key finding	Effect size	Source type
Hypertension (midlife)	Dementia/AD	Strong predictor of cognitive decline	HR: 1.30–1.50	Longitudinal cohorts ⁴
Hypertension (late-life)	AD	Weaker association	Mixed	Observational study ⁴
Atrial fibrillation	Dementia	Increased cognitive impairment independent of stroke	HR: 1.30–1.50	Large cohorts ⁶¹
Atrial fibrillation	PD	Emerging association	HR: 1.16	Limited data ⁶²
Heart failure	Dementia/AD	Cognitive impairment is common (35–50% prevalence)	HR: 1.80	Imaging+registry ^{69,72,73,78}
Heart failure	PD	Sparse, speculative	N/A	Retrospective only ^{69,72,73,78}
Diabetes mellitus	Dementia	Elevated risk	HR: 1.50+	Strong epidemiology ²⁹

Abbreviations: AD: Alzheimer's disease; HR: Hazard ratio; N/A: Not applicable; PD: Parkinson's disease.

from purely theoretical (the role of oxidative stress) to preclinical (amyloid deposition), there is also the added element of whether these factors merely accelerate clinical manifestations, hasten susceptibility, or are primary drivers. These are elements that are less prevalent in cardio-neural crosstalk. As a result, the evidentiary burden is greater in this section. The literature in this section is far sparser than in the earlier discussed mechanisms.

4.1.1. Oxidative stress-mediated peripheral and cardiac toxicity in AD

One proposed mechanism by which AD contributes to the pathogenesis of cardiovascular diseases is through heightened systemic and peripheral oxidative stress. At the cellular and molecular levels, AD leads to increased production of ROS in the CNS—including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO\bullet$)—as mitochondrial antioxidant function declines. This decline is driven by both AD-associated disruptions in neuro-metabolism and natural, age-related reductions in mitochondrial efficiency. These ROS facilitate lipid peroxidation and generate additional toxic byproducts that cause further cellular injury. More significantly, impaired mitochondrial function and oxidative stress also alter APP metabolism, contributing to $A\beta$ accumulation.⁸⁷ The presence of central ROS triggers the activation of reactive microglia and a broader neuroinflammatory response.⁸⁸ This inflammation includes cytokine-mediated recruitment of systemic immune cells into the CNS, potentially predisposing individuals to systemic inflammation.⁸⁹

Besides, the increased BBB permeability commonly observed in AD patients⁹⁰ enables the spillover of cytokines and ROS into peripheral circulation, reinforcing systemic oxidative stress.^{89,91} Supporting this, one study evaluating plasma oxidative stress biomarkers reported elevated peripheral levels of thiobarbituric acid-reactive substances (TBARS) and reduced total reactive antioxidant potential (TRAP) in AD patients compared with healthy controls.⁹¹ TBARS (a measure of lipid peroxidation) and TRAP (an

antioxidant capacity assay) are well-established markers of oxidative stress.

This systemic increase in ROS in AD is hypothesized to contribute to cardiovascular pathology through several pathways. First, elevated ROS—particularly O_2^- —accelerate the degradation of vascular NO, an endogenous vasodilator. NO depletion leads to endothelial dysfunction, predisposing individuals to vasculopathies, such as hypertension, atherosclerosis, and ischemic vascular diseases. NO deficiency also compromises endothelial structural integrity, promoting reactive inflammation, smooth muscle cell proliferation within the tunica media, fibrotic remodeling, and platelet aggregation. These processes collectively exacerbate vasoconstriction, downstream ischemia, and eventual end-organ damage, fueling atherogenesis and other vascular pathologies.⁹² Second, ROS-mediated mitochondrial stress in cardiomyocytes disrupts apoptotic regulation. Elevated oxidative stress promotes mitochondrial localization and upregulation of pro-apoptotic proteins such as p53, BAX, and BCL2-associated agonist of cell death (BAD). It also promotes cytochrome c release and heightened caspase activity—both key steps in the apoptotic pathway. This oxidative stress-induced cardiomyocyte apoptosis is implicated in numerous cardiac disorders, including ischemia-related injuries, vascular dysfunctions, and, importantly, the cardiac decompensation that precedes HF.⁹³ The loss of viable cardiomyocytes increases the workload on remaining cells, which, when combined with hypertrophy and hypoxia, can accelerate HF progression.^{93,94} Finally, increased cardiomyocyte apoptosis has also been linked to MI, a precursor to HF. One study reported Apoptotic Index scores ranging from 0.7 to 3.0 in hyperacute infarctions and 0.9 to 5.0 in acute infarctions, compared to 0.0 to 0.4 in healthy controls.⁹⁵

4.1.2. Amyloid- β deposition in vascular and cardiac tissue

Another proposed mechanism by which AD may contribute to cardiovascular disease involves $A\beta$ deposition in the

cerebral vasculature. In rat models, contact between these vascular A β deposits and endothelial cells triggered the production of superoxide radicals.^{60,80} These resulting ROS were suggested to propagate beyond the BBB, potentially affecting peripheral vasculature and contributing to the broader cardiovascular damage associated with systemic oxidative stress.⁶⁰

In addition, A β deposition within the myocardium itself has emerged as another potential link between AD and cardiac dysfunction. One study demonstrated increased levels of A β_{40} and A β_{42} peptides in the myocardial tissue of AD patients.⁹⁶ In this context, myocardial impairment secondary to A β accumulation has been proposed as a novel mechanism underlying certain heart conditions. This hypothesis was partially derived from previous research identifying similar myocardial A β deposits in patients with idiopathic dilated cardiomyopathy,^{96,97} which share biochemical characteristics with those found in AD.⁹⁶ While these findings offer a compelling hypothesis, the mechanisms by which central A β peptides cross into systemic circulation and accumulate in myocardial tissue remain unclear. Some have speculated that a pathologically permeable or compromised BBB may facilitate this process. Finally, these observations have not been consistently reproduced across all age cohorts or validated using uniform methodologies.⁹⁶

4.2. Role of PD in cardiovascular diseases

The co-occurrence of PD and cardiovascular comorbidities has been increasingly recognized, particularly in aging populations. For example, the incidence of HF among individuals with PD is approximately twice that of non-PD individuals.⁶⁸ In addition, vasculopathies, such as hypercholesterolemia, diabetes mellitus, and hypertension, are linked with an elevated risk of developing PD.⁵⁹ However, the nature of these associations remains unclear. Whether these links reflect causal relationships in one or both directions, or whether they arise from shared underlying risk factors—especially those related to aging—is still under investigation. This section focuses on potential mechanistic connections, particularly how PD may contribute to the development of cardiovascular disease. This section is unique insofar as it has the least evidentiary substantiation; almost everything in this section is purely theoretical and thus has almost no clinical yield as of the writing of this article.

PD is a progressive neurodegenerative disorder marked by motor dysfunction along with frequent cognitive and autonomic decline. It is widely considered a multifactorial disease, with both genetic and environmental risk factors playing key roles. More recently, monogenic or Mendelian forms of PD have been identified, providing opportunities

to examine gene-specific mechanisms of neuro-cardiac interaction. Genes encoding phosphatase and tensin homolog-induced kinase 1 and parkin, for example, have been implicated in these pathways. These proteins are critical for mitophagy—the selective autophagy of damaged mitochondria—a process vital in metabolically demanding tissues such as the brain and heart. Recessive mutations in these genes disrupt mitophagy and are associated with PD pathogenesis.⁹⁸ Notably, PINK1 also phosphorylates mitofusin 2, facilitating parkin-mediated ubiquitination of damaged mitochondria, a process essential for cardiac mitochondrial quality control.^{92,99}

Another key connection between PD and cardiovascular dysfunction lies in dysautonomia—a common non-motor symptom in PD. Under normal conditions, the CNS regulates cardiac and vascular function through autonomic innervation. Sympathetic nerves stimulate vascular smooth muscle contraction (vasoconstriction) and enhance cardiac chronotropy and inotropy. In contrast, parasympathetic activity promotes vasodilation and reduces heart rate and contractility.¹⁰⁰ In PD, this autonomic regulation is disrupted due to neurodegeneration of autonomic neurons. This degeneration involves the accumulation of Lewy bodies and α -synuclein aggregates, particularly within postganglionic sympathetic neurons and brainstem autonomic centers.¹⁰¹ These pathological changes result in reduced innervation of both vascular and cardiac tissues, evidenced by decreased neuronal fiber density and impaired myocardial uptake of biomarkers.⁹⁸

Clinically, dysautonomia manifests in PD patients as orthostatic hypotension—reported in 30–40% of cases¹⁰¹—and supine hypertension, which one study found in 34% of PD patients.¹⁰² These conditions are primarily due to impaired baroreflex responses, leading to insufficient vasomotor adjustments to postural and hemodynamic changes.¹⁰¹ Although dysautonomia is not strongly linked to increased rates of HF or MI, its complications can be significant. Supine hypertension is known to elevate the risk of MI, stroke, and left ventricular hypertrophy—consequences of chronic endothelial damage and vascular inflammation.^{101,102} Other dysautonomic cardiovascular effects in PD include nondrinking (a blunted nocturnal decrease in blood pressure) and postprandial hypotension (a significant drop in blood pressure following meals).¹⁰² These phenomena are associated with degeneration in brain regions such as the suprachiasmatic nucleus (involved in circadian regulation) and the nucleus coeruleus (a noradrenergic center).⁹⁸ Furthermore, emerging evidence suggests that α -synuclein pathology may ascend along the medullary vagal nucleus in a caudal-to-rostral pattern. This could account for dysautonomia appearing

before motor deficits and supports the idea that regions involved in autonomic control may be affected earlier than motor centers in the brainstem.⁸⁹ Pharmacologic treatment in PD may further compound dysautonomia. Levodopa, the mainstay of therapy, increases serum dopamine levels, which can promote peripheral vasodilation, natriuresis, and diuresis. These effects reduce vascular resistance and intravascular volume, exacerbating hypotensive episodes such as orthostatic hypotension.⁹⁸

An additional area of interest is the relationship between PD and A-fib.^{98,102} Several studies have shown that the early or premotor stages of PD are associated with a higher risk of A-fib, while later stages may be associated with a reduced risk.^{89,90} Although currently speculative, this temporal association aligns with observations that autonomic dysfunction often precedes classical motor and cognitive symptoms of PD. For example, early signs such as constipation, altered heart rate, and other autonomic irregularities may serve as prodromal markers. Smaller vagus nerves have been observed on ultrasonography, and abnormalities in the sympathetic ganglia and parasympathetic plexuses have also been noted in PD patients, supporting this progression.⁵⁹

4.3. Neuropeptides in neurodegeneration and the neuro-cardiac axis

Neurodegeneration can trigger abnormal release of neuropeptides from the brain, which in turn may significantly influence cardiac function. These peptides, such as neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), and substance P, are typically involved in regulating autonomic balance, vascular tone, myocardial contractility, electrophysiology, and inflammation. However, during neurodegenerative processes, dysregulated signaling can lead to maladaptive effects on the heart, including altered remodeling, arrhythmogenesis, and HF progression.^{103,104} Mechanistically, the degeneration of autonomic nuclei and compensatory hyperactivity of surviving neurons can shift the balance toward heightened sympathetic-like signaling (often amplified by NPY and substance P) or paradoxical parasympathetic dysfunction, altering sinoatrial and atrioventricular node behavior, coronary vasomotion, and myocardial calcium handling. Elevated sympathetic tone with reduced parasympathetic buffering—common in cognitive decline—can shift peptide release profiles, favoring NPY-augmented vasoconstriction and pro-arrhythmic conditions, while impaired VIP pathways may diminish adaptive vasodilation. Substance P's role in neuroinflammation and microvascular regulation may contribute to impaired coronary reserve and conduction instability. Although the precise peptide signatures vary by disease and stage, the shared theme is a stressed neuro-

cardiac axis in which brain pathology worsens cardiac outcomes.

When neurons degenerate, compensatory changes in neurotransmitter and neuropeptide release often occur. For example, NPY released in excess has been linked to the modulation of cardiac inflammation and fibrosis, sometimes protective but also potentially maladaptive depending on receptor subtype activation.^{103,105} Similarly, substance P and other peptides can amplify sympathetic drive, increasing cardiac workload and susceptibility to arrhythmias. The crosstalk between the degenerating nervous system and the cardiovascular system further highlights the bidirectional neuro-cardiac axis, where brain pathology may directly worsen cardiac outcomes. Understanding these mechanisms is crucial, as targeting neuropeptide signaling could provide therapeutic strategies to mitigate cardiac complications in patients with neurodegenerative diseases.^{104,106}

5. Conclusion

The current body of literature, though less extensive than in other clinical domains, consistently indicates a noteworthy bidirectional association between cardiovascular disease and neurodegeneration. Epidemiological studies consistently demonstrate correlations such as between hypertension and dementia, A-fib and cognitive decline, and HF and AD. Mechanistic investigations further implicate shared pathways, including chronic inflammation, cerebral hypoperfusion, BBB dysfunction, autonomic dysregulation, and amyloid biology. Together, these findings establish a strong correlational basis for cardio-neural crosstalk.

However, literature remains limited in its ability to establish causality. Most studies are observational, often confounded by comorbidities, and mechanistic insights are largely derived from preclinical models. This gap between correlation and causation represents the central challenge for the field. Addressing it will be critical for translating theoretical insights into clinical interventions that reduce morbidity and mortality across both cardiovascular and neurodegenerative domains.

To advance the field, several complementary strategies should be prioritized:

- (i) Longitudinal biomarker studies tracking plasma neurofilament light chain, cardiac troponins, and imaging markers, for example, are needed to document disease trajectories, clarify temporal relationships, and identify early predictors of disease progression.
- (ii) Interventional clinical trials repurposing cardiovascular therapies (such as RAAS inhibitors, anticoagulants, anti-inflammatory agents, and

lipid-lowering agents) are warranted to assess their neuroprotective potential. For example, examining whether adherence to RAAS-inhibiting therapies in HF patients reduces the risk of dementia could provide immediate translational insights.

- (iii) Integration of systems biology and omics (genomics, proteomics, metabolomics, and transcriptomic data) to uncover shared molecular networks and identify therapeutic targets across heart–brain pathways.
- (iv) Carefully designed population studies that control for comorbidities and stratify risk are needed to enable more precise causal inference.
- (v) Mechanistic exploration of reverse causality (e.g., neurodegenerative dysautonomia leading to cardiovascular dysfunction) remains underdeveloped. Neurodegenerative disorders, particularly PD, can drive cardiovascular dysfunction through dysautonomia and impaired neural regulation. Expanding investigation of these pathways would complement the current emphasis on cardiovascular disease-driven neurodegeneration.

By consolidating correlational evidence and outlining actionable strategies, this review underscores the need to move beyond descriptive associations toward a causal understanding. Such efforts will ultimately inform preventive strategies and therapeutic interventions, with the potential to reduce morbidity and mortality across both cardiovascular and neurodegenerative diseases.

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