

Review

Open Access



Impact of myocardial infarction on cerebral homeostasis: exploring the protective role of estrogen

Lana El-Samadi^{1,2}, Rana Zahreddine^{1,2} , Joanna A. Ziade^{1,2}, Alaa El Ghawi^{1,2}, Ghadir Amin^{1,2,3}, George W. Booz³, Fouad A. Zouein^{1,2,3}

¹Department of Pharmacology and Toxicology, Faculty of Medicine, American University of Beirut, Beirut 1107 2020, Lebanon.

²The Cardiovascular, Renal, and Metabolic Diseases Research Center of Excellence, American University of Beirut & Medical Center, Riad El-Solh, Beirut 1107 2020, Lebanon.

³Department of Pharmacology and Toxicology, School of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA.

Correspondence to: Dr. Fouad A. Zouein, Department of Pharmacology and Toxicology, Faculty of Medicine, American University of Beirut, Beirut, Lebanon; The Cardiovascular, Renal, and Metabolic Diseases Research Center of Excellence, American University of Beirut & Medical Center, Riad El-Solh, Beirut 1107 2020, Lebanon. E-mail: fz15@aub.edu.lb

How to cite this article: El-Samadi L, Zahreddine R, Ziade JA, El Ghawi A, Amin G, Booz GW, Zouein FA. Impact of myocardial infarction on cerebral homeostasis: exploring the protective role of estrogen. *J Cardiovasc Aging*. 2025;5:13. <https://dx.doi.org/10.20517/jca.2025.02>

Received: 3 Jan 2025 **First Decision:** 18 Apr 2025 **Revised:** 26 May 2025 **Accepted:** 16 Jun 2025 **Published:** 30 Jun 2025

Academic Editor: Moshi Song **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Myocardial infarction (MI), commonly known as a heart attack, results from the rupture of atherosclerotic plaques in coronary arteries, which triggers a series of pathological events including cardiomyocyte death, thrombus formation, and systemic inflammation. These pathological events lead to significant structural and functional changes in the heart, potentially precipitating heart failure. The ramifications of MI extend beyond cardiac dysfunction and impact cerebral health. Accordingly, this review examines the cerebral implications of MI, focusing on how systemic inflammation and reduced cardiac output post-MI affect cerebral blood flow and brain function. MI-induced changes in cardiac output can lead to cerebral hypoperfusion, while neuroinflammation and increased blood-brain barrier permeability contribute to cognitive decline and neuronal damage, with potential links to Alzheimer's disease (AD). Furthermore, the review explores the role of estrogen in modulating cardiovascular and cerebral health, particularly in postmenopausal women who exhibit distinct cardiovascular risk profiles. Estrogen protects the heart by regulating local renin-angiotensin-aldosterone system and has significant impacts on brain function. Declining estrogen levels during menopause exacerbate neuroinflammation and cognitive deficits,



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



highlighting the importance of estrogen in maintaining cerebrovascular function. Experimental studies on estrogen replacement therapies, including 17 β -estradiol and selective estrogen receptor modulators, show potential in mitigating these detrimental effects, enhancing neurogenesis, and improving cognitive outcomes. Estrogen therapy is crucial in preventing cognitive decline and reducing amyloid plaque formation in Alzheimer's models. This review underscores the potential benefits of estrogen therapy in promoting brain recovery post-MI and improving functional outcomes.

Keywords: MI, heart failure, inflammation, cerebral hypoperfusion, blood-brain barrier, cognitive decline, AD, 17 β -estradiol, menopause

INTRODUCTION

Cardiovascular diseases (CVDs) are considered the leading cause of global mortality and significantly reduce the quality of life^[1]. According to *The Lancet*, acute myocardial infarction (AMI) is the most severe form of coronary artery disease (CAD), responsible for over 2.4 million deaths in the USA, more than 4 million deaths in Europe and northern Asia, and over a third of annual deaths in developed countries^[2]. While the cardiac pathophysiology has been extensively studied, its impact on the brain remains an equally urgent yet underexplored area.

Neurological conditions, such as cognitive impairment, migraines, and epilepsy, have been linked to CAD, heart failure, and congenital heart abnormalities^[3]. Notably, MI is also frequently associated with brain injuries^[4] and behavioral disorders, such as anxiety, depression, and dementia^[5,6]. Evidence shows that microglia hyperactivation following MI leads to neuroinflammation *via* elevated brain cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α)^[7-9].

Furthermore, vascular injury, indicated by coronary artery calcium levels, correlates with an increased risk of dementia^[10]. Reduced cardiac output, cerebral blood flow (CBF), and blood-brain barrier (BBB) integrity, along with heightened sympathetic nerve and renin-angiotensin-aldosterone system (RAAS) activity, contribute to cognitive impairment in heart failure^[11-14]. In this context, estrogen emerges as a significant yet complex player. Estrogen acts as a neuroprotective agent and contributes to cognitive and neuronal development^[15]. Its decline during menopause is associated with an increased risk of neurovascular diseases and cognitive decline, due to the loss of its protective effects on cerebral blood vessels^[16,17].

Despite growing evidence on the cardiovascular effects of estrogen, the specific molecular mechanisms linking MI to long-term brain changes - particularly in a sex-specific content - remain poorly understood. This gap highlights the need to explore estrogen's role in modulating brain-heart interactions to inform sex-specific therapeutic strategies. This review aims to summarize and discuss the pathophysiology of MI and its impact on the brain and highlights the underexplored connection between MI-induced brain dysfunction on one hand, and estrogen's neuroprotective potential with a focus on sex-specific mechanisms that may inform future targeted therapies on the other hand.

MYOCARDIAL INFARCTION AND CEREBRAL COMPLICATIONS

Myocardial infarction pathophysiology

MI is characterized by cardiomyocyte death caused by an ischemic insult, typically due to thrombotic blockage of a coronary vessel following plaque rupture^[18]. This event arises from the destabilization or rupture of a susceptible atherosclerotic plaque, or endothelial erosion, which releases thrombogenic substances, activates platelets, and triggers the coagulation cascade, leading to thrombus formation. The

thrombus obstructs coronary blood flow, causing ischemia and tissue necrosis, which is detectable by elevated cardiac biomarkers^[2,19]. The severity of infarction depends on the degree of occlusion, the extent of necrosis, and collateral circulation^[19].

This cardiac hypertrophy progresses when the heart fails to compensate for increased ventricular volume. Hence, numerous mechanisms are altered post-MI; these mechanisms include alterations in hemodynamics, the autonomic nervous system, baroreflex sensitivity, the RAAS, sarcoplasmic reticulum calcium handling, the beta-adrenergic pathway, and oxidative stress, which are observed in both human subjects and experimental models^[19].

In parallel to understanding the pathophysiology of MI, identifying modifiable and non-modifiable risk factors is essential for prevention. Controllable factors include hypertension, diabetes, high cholesterol, and smoking, while age, sex, and genetic predisposition remain unmodifiable^[20]. The Framingham study was pivotal in identifying key risk factors such as hypertension, diabetes, obesity, hyperlipidemia, smoking, and sedentary behavior, leading to significant reductions in CVD rates in developed countries^[21]. However, developing nations experienced a rise in CVD rates due to rapid economic transitions^[22]. The INTERHEART study involving a multiethnic cohort from 52 countries, included 15,152 first-time MI patients and 14,820 age- and sex-matched controls, further highlighted the substantial association between common risk factors (such as smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, and psychosocial factors) and increased MI risk^[23].

At the cellular level, upon coronary occlusion, aerobic metabolism is halted, and metabolic byproducts accumulate. Ultrastructural changes in cardiomyocytes include depletion of glycogen, distortion of the transverse tubular system, and mitochondrial swelling. The heart survives the initial ischemic event, and a complex cascade of molecular, cellular, neurohumoral, hemodynamic, and morphological responses ensues^[24]. The heart's limited regenerative capacity leads to repair predominantly through inflammatory response and collagen scar formation, resulting in infarct expansion: thinning of the cardiac wall, and ventricular dilation^[25,26]. Functionally, the loss of cardiomyocyte leads to reduced ejection volume and increased ventricular wall stress, which triggers compensatory mechanisms such as hypertrophy^[27,28].

Systemic effects of MI and its impact on the brain

Beyond the heart, MI triggers a systemic inflammatory response that impacts distant organs, notably the brain. Systemic inflammation following MI exacerbates atherosclerotic inflammation and destabilizes plaques in arteries remote from the initial event^[29]. In parallel, MI heightens endoplasmic reticulum (ER) stress in the brain, characterized by increased levels of PERK, GRP78, and ATF4 proteins^[30]. This ER stress promotes protein aggregation in glial cells, reflecting the pathological features observed in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, and Amyotrophic Lateral Sclerosis^[30]. Notably, treatment with small-molecule ER stress relievers, attenuated these effects, underscoring the link between cardiovascular events and neurodegenerative changes^[30].

Homeostasis in the central nervous system (CNS) is maintained through a complex regulatory network, with astrocytes playing a key role in electrochemical processes such as ion regulation, neurotransmitter release, and signal transduction^[31].

The impact of MI on brain function is well-documented. A preclinical study by Kaplan *et al.* showed that acute MI is directly linked to brain function impairment. MI induces systemic inflammation and an elevated RAAS activation, which affect remote organs including the brain and have deteriorating

implications for brain perfusion^[11]. Human studies also reveal an association between MI and cerebral infarction. A cross-sectional study of patients who underwent both brain and cardiac MRI found that MI was specifically linked to cortical cerebral infarction, with no association to general infarction. The burden or size of MI was also unrelated to infarction risk, except in cases of apical MI, which showed a distinct correlation with cortical infarction^[32].

Impact of heart dysfunction on CBF regulation

Heart failure, a common sequela of MI, greatly increases brain vulnerability. Although the brain accounts for only 2% of body weight, it receives roughly 12% of cardiac output (CO)^[33]. HF-related reductions in CO impair cerebral blood flow (CBF) even when systemic blood pressure appears maintained^[33,34]. CBF is regulated by several robust mechanisms, including cerebral autoregulation, neurovascular coupling, and cerebrovascular reactivity to carbon dioxide and oxygen^[33]. Moreover, several other regulatory mechanisms ensure the tight control of CBF, including the mean arterial pressure, cerebral metabolism rate, and perivascular nerve activity. Any disruption in these regulatory mechanisms can lead to disturbances in CBF^[35]. While cerebral autoregulation usually keeps CBF constant within its blood pressure range, both acute and chronic changes in CO can still alter CBF even when blood pressure is unchanged^[33]. Reduced CO in heart failure impacts cerebral autoregulation, decreasing CBF. Although brain arterioles dilate to compensate for lower output, this adaptive response has limits, impairing cerebral autoregulation and cerebrovascular reactivity to CO₂.

Notably, the neurohumoral system, activated in congestive heart failure (CHF), further induces vasoconstriction in both peripheral and cerebral vessels. Over time, cerebral resistant vessels adapt chronically to low CO, which blunts autoregulation and further reduces CBF. Consequently, CHF patients face a higher risk of critically low CBF, even during routine activities^[34]. Research has connected older individuals with heart failure and global cognitive impairment to cerebral hypoperfusion, reduced blood flow velocity in the middle cerebral arteries (MCA-BFV), and elevated levels of inflammatory markers such as TNF- α , c-reactive protein (CRP), IL-6, IL-1, and toll-like receptor 4. Hypoperfusion also drives glial activation, mitochondrial dysfunction, loss of dendritic spines (leading to synaptic dysfunction), and neuronal apoptosis^[8,36]. Elevated CRP levels, in particular, correlate with impaired memory, slower information processing speed, and reduced executive function^[37].

Oxidative stress is another critical factor contributing to cognitive deficits. The brain's high metabolic rate, oxygen consumption, and lipid-rich content make it vulnerable to oxidative damage and lipid peroxidation^[38]. Elderly individuals with memory deficits exhibit elevated lipid peroxidation, while Alzheimer's patients show poor cognitive function linked to weakened antioxidant defenses. Similarly, heart failure is marked by high lipid peroxide levels, increased inflammation, and reduced antioxidant biomarkers like coenzyme Q10^[39].

MRI studies reveal structural brain changes in heart failure patients, including reduced gray matter density in cognitive regions (e.g., precuneus, cingulate cortex, hippocampus); correlating with lower ejection fractions and higher NT-pro-BNP levels^[40]. Kaplan *et al.* demonstrated that, despite an increased proportion of blood flow directed to the brain, total brain perfusion remains reduced for at least 30 days post-MI, illustrating the sustained cerebral impact^[11].

Impact of MI on neurons and cognition

Following acute MI, the inflammatory response significantly impacts neuronal function and recovery. Microglia, the central nervous system's immune cells, produce cytokines upon activation, leading to neuroinflammation, a process increasingly linked to the risk of neurodegenerative disorders. A study by

Thackeray *et al.* using coronary artery ligation on mice and PET imaging of the mitochondrial translocator protein (TSPO), a marker of activated microglia, revealed elevation of activated microglia at 1 week post-MI, which declined at 4 weeks but reappeared with progressive heart failure. Similar findings were observed in patients where elevated cardiac TSPO signals post-MI were accompanied by neuroinflammation^[41]. In addition to that, it was revealed that MI induces neuronal microtubule damage, increasing miR-1 levels and decreasing TPPP/p25 protein expression in the hippocampus of adult male C57BL/6 mice and Sprague Dawley (SD) rats^[42]. In rats, a significant increase of 40% to 50% in the proportion of activated microglia in the hypothalamic paraventricular nucleus (PVN) between 4 and 16 weeks post-MI was demonstrated. However, no significant increase in activated microglia was observed 24 h or 1 week after MI. It was suggested that microglial activation in the PVN does not occur immediately following MI but becomes evident over time and persists. Consequently, activated microglia play a role in the sustained elevation of cytokine levels observed after MI^[43].

Beyond inflammation, MI triggers oxidative and pathological changes in the brain. In MI model using wild-type and AD-prone APP/PS1 mice, MI-treated mice exhibited poorer performance in the social recognition test, Morris water maze, and plus-maze discriminative avoidance task. These behavioral changes were accompanied by elevated reactive oxygen species (ROS) levels and increased amyloid- β (A β) peptide aggregates and tau protein phosphorylation in the mouse brain, pathological features of AD. Additionally, microglia in MI-treated mice shifted to a more proinflammatory phenotype^[44]. Another rat study conducted 48 h post-MI, it showed a significant increase in activated and dystrophic microglia in the prefrontal cortex, hippocampus, thalamus, and PVN, alongside hypertrophic astrocytes. Dystrophic microglia, linked to tau pathology and early neurodegeneration, were suggested to contribute to neuronal dysfunction and cognitive decline^[45]. MI, followed by 72 h of reperfusion, revealed apoptosis in the amygdala, hippocampus, and vermis. MI rats showed significantly reduced PI3K activity, an increased Bax/Bcl-2 ratio, heightened caspase-3 activity, and a rise in TUNEL-positive cells in the amygdala, indicating localized apoptosis in the limbic system three days post-MI^[46].

Another study explored brain and heart protein changes after MI with a data-independent acquisition mode proteomics approach and found that microglial activation in the brain cortex was observed as early as 1 day post-MI in rats, remaining elevated at 3 and 7 days post-MI. This early activation suggests direct brain involvement following cardiac injury and helps explain the increased risk of stroke, depression, and cognitive impairment in MI and heart failure patients. Moreover, two brain-specific differentially expressed proteins were highlighted: ELOVL5, which supports myelin structure and nerve conduction, was altered, possibly contributing to neurological symptoms post-MI, and ABCG4, involved in lipid homeostasis and amyloid- β transport, was upregulated in the brain cortex, linking MI-induced neuroinflammation with Alzheimer's-like pathology^[47].

Although clinical data are more limited, emerging evidence reflects these preclinical observations. In a pilot study on 48 post-MI patients, 81.3% showed transient increases in serum S100B levels, a marker of glial alterations, with depressive symptoms^[48]. Knowing that heart failure manifests after MI, it was reported that heart failure mediates low CO and CBF reduction^[11]. For instance, worsening cognition in heart failure with reduced ejection fraction was primarily associated with a reduction in CBF, with a strong association seen in older adults^[49]. Building on that, in a study involving Stage C heart failure patients, lower hippocampal CBF was associated with higher depression scores and memory impairments^[50]. Moreover, midlife abnormalities in cardiac structure and diastolic function were associated with lower cognitive performance, consistent with findings from the Multi-Ethnic Study of Atherosclerosis and the Framingham Offspring Study. Interestingly, left ventricular hypertrophy and increased atrial volume, but not decreased ejection fraction,

were associated with impaired cognition, possibly through impaired brain perfusion or micro-embolisms^[51]. MRI studies further revealed significant right hippocampal atrophy and left frontal cortical atrophy in heart failure patients, particularly in regions regulating depression and executive function^[32,49,52].

Recent large-scale, longitudinal studies have confirmed the association between MI and cognitive outcomes. In a Danish National Registry study of over 300,000 MI survivors, MI was associated with an increased risk of vascular dementia (adjusted hazard ratio [aHR] 1.35), with a significantly higher risk observed in those who had a stroke after the MI (aHR 4.48). However, MI was not associated with an increased risk of AD, suggesting a vascular-specific cognitive pathway^[53]. Similarly, in a pooled analysis of six US cohorts ($n = 30,465$ adults), those who had suffered a MI ($n = 1,033$) did not experience acute cognitive decline, but did show accelerated deterioration in memory and executive function over time^[54]. In another study, 37% of patients hospitalized for MI had cognitive dysfunction, with 25% retaining deficits six months later. Notably, new cases of cognitive dysfunction also emerged during follow-up, often associated with depressive symptoms and sleep disturbances^[55].

Another study conducted on a biracial cohort of middle-aged adults found that premature CVD is significantly associated with worse cognitive performance, accelerated cognitive decline, and structural brain changes in midlife. These effects were observed across various cognitive domains and were not entirely explained by shared risk factors such as stroke, demographics, or cardiovascular risk factors. Importantly, the presence of white matter hyperintensities and altered white matter integrity in those with premature CVD parallels brain changes typically seen in the elderly^[56].

These findings reinforce the role of systemic inflammation, oxidative stress, and cerebrovascular dysregulation observed in animal models. Furthermore, elevated markers such as S100B and altered CBF in post-MI suggest early glial injury and neurovascular impairment^[48,50]. These data indicate that post-infarction follow-up should go beyond cardiac function to include cognitive screening, particularly in older adults or those with multiple cardiovascular risk factors [Table 1].

Impact of MI on the blood-brain barrier

Physiological processes regulating CBF include perivascular nerve constriction, arterial dilation, astrocyte end-foot modifications of arterial diameter, and endothelial release of hemodynamic and vasoactive elements. The BBB separates the brain from the peripheral circulation, and is composed of cerebral microvascular endothelial cells, astrocytes, pericytes, neurons, and extracellular matrix, which are particularly vulnerable to aging pathophysiology and neurological damage^[16]. The concept of “cardiogenic dementia”, initially proposed in *The Lancet*, highlights cognitive decline in patients following heart disease. Cognitive impairment is prevalent among individuals with heart failure, with up to 50% exhibiting varying degrees of cognitive decline^[57]. In healthy older adults, cognitive decline tends to occur at a very gradual pace, often becoming noticeable only over decades. However, older adults who develop heart failure are likely to experience a more rapid deterioration in cognitive function^[58]. Additionally, it is understood that coronary heart disease and atherosclerosis contribute to inflammation, impacting both large and small blood vessels in the brain. For instance, hypertension can compromise the cerebrovascular endothelium, raising BBB permeability. This increased permeability allows potentially damaging substances to infiltrate brain tissue, leading to neuroinflammation, particularly in white matter. Moreover, vascular risk factors can, through neuroimmune pathways and oxidative stress, stimulate the production of A β , which itself can cause vasoconstriction. Remarkably, reduced CBF and abnormal hemodynamic responses to neural activity are also observed in AD^[59].

Table 1. Impact of MI on neurons and cognition

Ref/Year	Model	Intervention	Result
29348018/2018	Permanent MI in mice	LAD ligation	↑ Myocardial inflammation at 7 days → Predicted adverse LV remodeling & ↑ neuroinflammation at 4 weeks ↑ Brain TSPO signal = activated microglia (especially in thalamus & hippocampus) Strong heart-brain inflammatory axis post-MI ↑ Cognitive dysfunction
29775643/2018	C57BL/6 male mice and Sprague Dawley rats with permanent MI	MI via LAD ligation	↑ Circulating miR-1 (cardiac-derived) → crosses BBB → ↓ TPPP/p25 in hippocampus ↓ Microtubule stability → Tau-like neurodegeneration in CA1 region
32065796/2020	Wild-type and AD-prone APP/PS1 mice	MI via LAD ligation	↓ Performance in social recognition, Morris water maze, & plus-maze tests ↑ ROS levels ↑ Aβ peptide aggregates ↑ Tau protein ↑ Proinflammatory phenotype of microglia
26266053/2015	Rat model of early MI	Prolonged moderate treadmill exercise vs. sedentary controls	Moderate exercise → ↓ astrocyte (GFAP ⁺) and microglial (Iba1 ⁺) activation in cortex and hippocampus ↓ IL-1β and TNF-α levels Exercise → ↓ MI-induced neuroinflammation
16202395/2006	Male Wistar rats	Permanent LAD ligation	↑ Neuronal apoptosis in the amygdala ↑ TUNEL ⁺ cells and caspase-3 activation
38514755/2024	Rat model of permanent LAD ligation	Permanent LAD ligation	↑ Expression of inflammatory proteins in both heart and brain ↓ ABCG4 and ↓ ELOVL5 in cortex Disrupts cortical lipid metabolism and neuroprotection → potential link to cognitive decline
37252710/2023	Prospective cohort study utilizing data from the ARIC, CARDIA, CHS, FOS, MESA, NOMAS studies	Incident MI	↓ Global cognitive function ↓ Executive function and processing speed
29025764/2017	Nationwide Danish cohort study	Compared MI survivors to matched controls for incidence of vascular dementia	MI survivors had ~35% higher risk of developing vascular dementia Risk especially elevated in < 60-year-old patients and during the first year post-MI
36697246/2023	CARDIA cohort study with midlife MRI and neurocognitive testing	-	Premature CVD → ↓ total brain and gray matter volumes ↓ Memory and executive performance compared to CVD-free peers
37568355/2023	Prospective Multicenter Clinical Study	Patients hospitalized for MI	Prevalence of Cognitive Impairment based on MMSE scores (during initial hospitalization) Low GFR and EF High BNP levels and SYNTAX score

LAD: Left anterior descending artery; TSPO: translocator protein; LV: left ventricle; BBB: blood-brain barrier; miR-1: microRNA-1; TPPP: tubulin polymerization-promoting protein; IL-1β: interleukin-1 beta; TNF-α: tumor necrosis factor alpha; HIF-1: hypoxia-inducible factor 1; ABCG4: ATP-binding cassette sub-family G member 4; ELOVL5: elongation of very long-chain fatty acids protein 5; MAPK: mitogen-activated protein kinase; CARDIA: coronary artery risk development in young adults; ARIC: atherosclerosis risk in communities study; CHS: cardiovascular health study; FOS: Framingham offspring study; MESA: multi-ethnic study of atherosclerosis; NOMAS: northern Manhattan study; MMSE: mini-mental state examination; GFR: glomerular filtration rate; EF: ejection fraction; BNP: B-type natriuretic peptide; SYNTAX: severity of coronary atherosclerosis; ↑: increase; ↓: decrease; ↔: unchanged.

As heart failure remains the leading cause of hospitalization in the U.S.^[60], its detrimental effects on the brain are a significant concern. Factors such as advanced age, multimorbidity (presence of multiple chronic conditions), and shared risk factors contribute to altered brain function and the potential development of cognitive impairment^[58]. Importantly, the early stages of heart failure induce vascular cognitive impairment due to impairment of BBB permeability. A study employing Tgaq*44 (model of progressing heart failure) and control FVB (wild-type control) mice, using the novel object recognition (NOR) test, demonstrated that Tgaq44 mice exhibit cognitive impairment. Additionally, these mice showed notable activation of astrocytes (GFAP) and glial cells (IBA-1), indicating neuroinflammatory processes^[61].

Recent findings highlight the role of inflammatory mediators in BBB disruption and neuroinflammation following MI. Elevated levels of IL-17A are observed in circulation and the brain during heart failure after MI. These increased levels contribute to both neuroinflammation and sympathetic activation. IL-17A disrupts BBB integrity, as demonstrated *in vitro* and *in vivo* models, by increasing transcytosis and degrading tight junction proteins. In a study involving male SD rats subjected to coronary artery ligation to induce heart failure, some heart failure rats received bilateral PVN microinjections of interleukin 17 receptor A small interfering RNA or a scrambled small interfering RNA adeno-associated virus. Expression analysis revealed augmented caveolin-1, a transcytosis marker, and reduced tight junction proteins in heart failure rats. Treatment with interleukin 17 receptor A small interfering RNA significantly attenuated BBB permeability in the PVN and reversed the expression of caveolin-1 and tight junction-associated proteins. These results suggest that enhanced IL-17A/IL-17 receptor A signaling promotes BBB permeability in heart failure by increasing caveolar transcytosis and degrading tight junctions^[62].

Additionally, MI triggers specific molecular and cellular mechanisms that intensify cognitive decline. Following MI, there is an accumulation of advanced glycation end products (AGEs), particularly Nε-(carboxymethyl)lysine (CML), in the vasculature of the heart^[63]. CML buildup is intensified by inflammation and oxidative stress, further contributing to inflammation and ROS production. Moreover, studies in atherosclerotic mice show CML accumulation in cerebral microvasculature, which is associated with cerebrovascular disease and cognitive decline. Post-MI, elevated levels of CML and NADPH oxidase 2 (NOX2) have been detected in the cerebral microvasculature, peaking between 6 h and 5 days after MI onset, likely driven by systemic inflammation. Reduced CBF and increased circulating CML levels post-MI further exacerbate cerebral inflammation and oxidative stress. The heightened presence of CML and NOX2 may indicate dysfunction in the brain, contributing to MI-associated depression and dementia^[64] [Figure 1].

MYOCARDIAL INFARCTION AND SEX DIFFERENCES

Types of MI and clinical perspectives

MI is classified into type 1 and type 2. Type 1 MI results from atherothrombotic CAD, typically triggered by plaque rupture or erosion. Diagnostic criteria include a rise and/or fall in cardiac troponin (cTn) levels, ischemic symptoms, ECG changes, and evidence of a new coronary thrombus^[65].

In contrast, Type 2 MI, on the other hand, occurs when there is a mismatch between myocardial oxygen supply and demand without acute atherothrombotic plaque disruption. It can be triggered by acute stressors such as gastrointestinal bleeding or sustained tachyarrhythmia, and its diagnosis also involves a rise in cTn levels with evidence of oxygen supply-demand imbalance^[66].

Sex difference in MI: diagnosis, risk factors and cardiovascular burden in women with a focus on MI and menopausal transition

Accurate diagnosis of MI necessitates an evaluation of all clinical information, with coronary angiography serving as a crucial tool in distinguishing between different MI subtypes, particularly type 1 MI^[67]. Studies

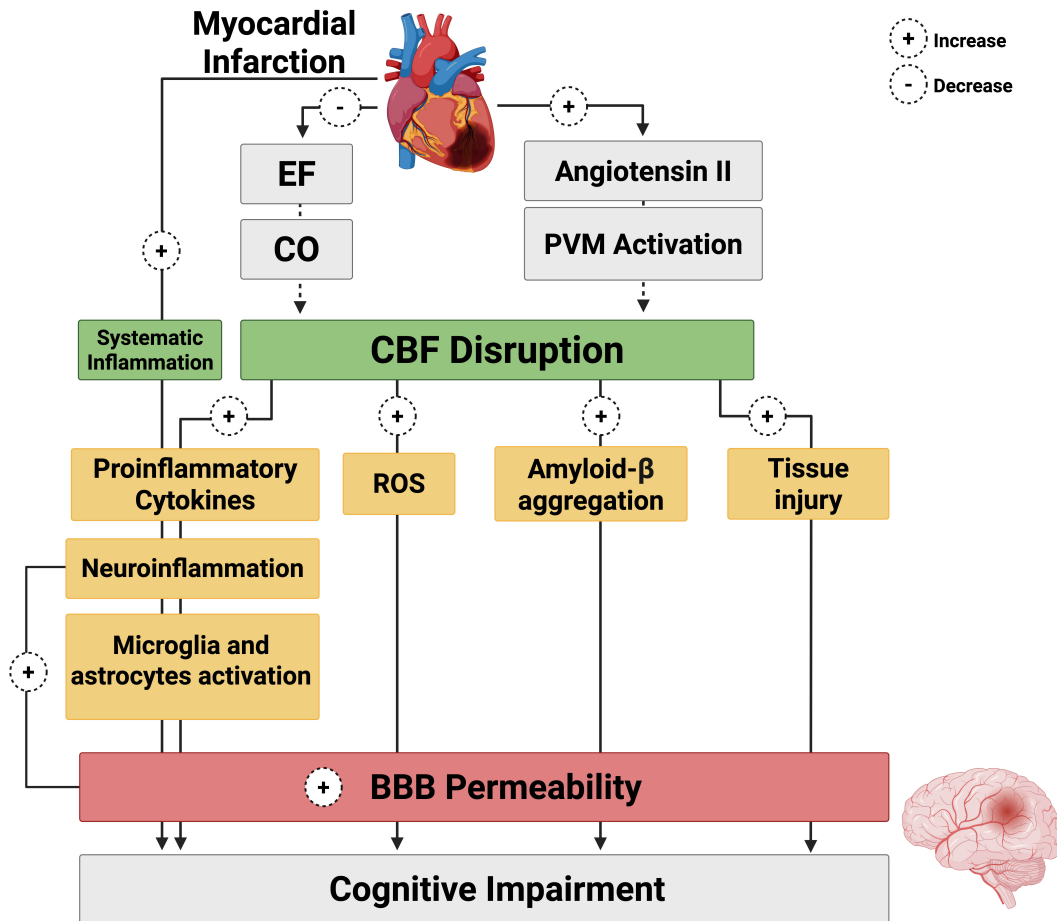


Figure 1. Pathophysiological pathways linking myocardial infarction to cognitive decline. This diagram illustrates the mechanisms by which cardiovascular dysfunction contributes to cognitive impairment. Reduced cardiac function, indicated by decreased EF and CO, triggers systemic inflammation, which causes the release of cytokines and the activation of perivascular macrophages through angiotensin II signaling. This cascade disrupts CBF, promoting the production of ROS, A β aggregation, and tissue injury, which exacerbates neuroinflammation. Neuroinflammation activates microglia and astrocytes, further leading to the release of proinflammatory cytokines. These processes compromise the integrity of the BBB, facilitating the progression of cognitive impairment. EF: Ejection fraction; CO: cardiac output; CBF: cerebral blood flow; ROS: reactive oxygen species; A β : amyloid beta; BBB: blood-brain barrier. Created in BioRender. Zouein, F. (2025), Available from: <https://BioRender.com/e58z159>.

show that Type 1 MI tends to occur in younger individuals, with higher cardiac troponin T and CK-MB levels compared to Type 2 MI, which is more common in older women with comorbidities such as heart failure, kidney disease, and atrial fibrillation^[68-70]. Women generally experience their first MI 6 to 10 years later than men, largely due to the protective cardiovascular effects of estrogen, which modulates lipid profiles and body fat distribution^[71]. Estrogen promotes a less atherogenic lipid profile partly by binding to ApoB-100, influencing LDL metabolism and contributing to lower LDL cholesterol levels^[72].

However, the risk factors for MI differ markedly between sexes. Hypertension, smoking, and diabetes confer a disproportionately higher excess risk of MI in women than in men^[73]. For instance, smoking substantially increases the risk of ST-segment elevation myocardial infarction (STEMI) in women, particularly younger women^[74]. Moreover, perimenopausal and postmenopausal women exhibit higher LDL cholesterol levels and greater systemic inflammation compared to men, exacerbating their susceptibility to MI^[75,76].

A study included a non-CHD cohort (individuals without prior coronary heart disease); younger women exhibited a markedly lower risk of developing CHD and MI compared to men of the same age, highlighting a strong female advantage in early adulthood. However, this protective effect diminished progressively with increasing age, as the sex-related hazard ratios for CHD and MI rose, indicating a narrowing gap between men and women in older age groups. In contrast, in the post-MI cohort, sex differences in outcomes were minimal, and age did not significantly modify the association between sex and the risk of CHD or MI. One notable exception was heart failure, where older women post-MI had slightly worse outcomes compared to their male counterparts^[77].

The menopausal transition represents a “critical window” for increased cardiovascular risk. Premature menopause (before age 40) significantly elevates the risk of cardiovascular diseases, including MI, compared to menopause at the typical age^[78]. This period is associated with unfavorable changes in body composition, lipid profiles, and vascular function^[79]. Post menopause, the decline in estrogen levels leads to further deterioration in lipid metabolism and vascular health, with studies showing that postmenopausal women exhibit elevated levels of proatherogenic factors such as proprotein convertase subtilisin/kexin type 9 (PCSK9), which is associated with increased risk of coronary artery disease (CAD) and major adverse cardiovascular events^[80,81].

ESTROGEN AND BRAIN HEALTH

Estrogen and estrogen receptors

Burgeoning evidence shows that E2, the most biologically active form of estrogen, has extensive effects on neurological, cognitive, neurodevelopmental, and neurodegenerative processes, as well as various behaviors and physiological functions in both males and females. 17 β -estradiol exerts wide-ranging effects on the brain via estrogen receptors (ERs), including ER α , ER β , and G-protein coupled estrogen receptor (GPER1), influencing cognitive function, neuroprotection, and aging. It was believed that circulating estrogens mediate their effects primarily through ER α and ER β , which, upon activation, function as homodimers or heterodimers to regulate gene transcription through the estrogen-response element. In addition to genomic actions, estrogens also activate rapid, non-genomic signaling pathways, particularly those involving cytosolic ERs.

ER α and ER β are ubiquitously distributed in the brain, where they coordinate neuroprotective signaling cascades and modulate CBF, energy metabolism, inflammation, and oxidative processes^[82-84]. The phosphoinositide 3-kinase (PI3K)/Akt pathway plays a key role in the rapid, membrane-initiated actions of ER α . A study examined E2 effects on PI3K/Akt signaling in the hypothalamic arcuate nucleus (ARC) and ventrolateral ventromedial nucleus (vVMN), both involved in energy homeostasis. In the ARC, E2 did not significantly activate the PI3K/Akt pathway, as phosphorylated Akt (pAkt) levels were unchanged across wild-type (ER $\alpha^{+/+}$), ER α knockout (ER $\alpha^{-/-}$), and nonclassical ER α signaling (ER α^{AA}) mice. Estrogen's influence on energy balance in the ARC is independent of the PI3K/Akt pathway. In contrast, E2 significantly activated the PI3K/Akt pathway in the vVMN, with marked pAkt induction in ER $\alpha^{+/+}$ mice. This effect was absent in ER $\alpha^{-/-}$ mice but restored in ER α^{AA} mice, indicating that nonclassical ER α signaling is sufficient for Akt activation in the vVMN. Thus, the vVMN mediates estrogen's regulation of energy homeostasis via PI3K/Akt, while the ARC relies on different mechanisms. Estrogen treatment, beyond PI3K/Akt signaling, also normalized energy expenditure, improved glucose and insulin sensitivity, and reduced serum leptin concentrations, highlighting its critical role in preventing obesity and metabolic syndrome through nonclassical ER α pathways^[85].

Estrogens play a crucial role in body-weight regulation, evidenced by the weight gain seen in postmenopausal women and ovariectomized (OVX) female rodents, which can be mitigated by estrogen supplementation. The anti-obesity effects of estrogens are primarily mediated by ER α in specific brain regions. Additionally, estrogens enhance hippocampal learning and memory through rapid activation of signaling cascades, including PI3K, protein kinase A, protein kinase C, phospholipase C, and mitogen-activated protein kinase. These pathways modulate synaptic transmission, protein phosphorylation, and dendritic spine density^[82]. More supporting data came from a study by Phan *et al.* that showed administering 17 β -estradiol or an estrogen receptor- α agonist (but not an ER- β agonist) into the dorsal hippocampus significantly improved discrimination learning in female mice. This was accompanied by increased dendritic spine density in CA1 neurons. Notably, the estrogen-induced spinogenesis reduced CA1 α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor activity, likely due to receptor internalization, creating silent or immature synapses^[86]. 17 β -estradiol and ER α agonists enhance social recognition, object recognition, and object placement performance, particularly following systemic administration or hippocampal infusion. ER β activation primarily improves spatial learning. Both 17 β -estradiol, ER α agonists, and GPER agonists increase dendritic spine density in the CA1 hippocampus. Evidence showed that systemic GPER activation also enhances social and object recognition, though its role in object placement learning remains unclear^[87].

Both the estrous cycle and sex influence the number and types of neuronal and glial profiles containing classical ERs, as well as synaptic levels in the rodent dorsal hippocampus. A recent study explored the role of the membrane estrogen receptor GPER1 in synaptic plasticity within the dorsal hippocampus of mice^[88]. GPER1 immunoreactivity (IR) was most prominent in the pyramidal cell layer and interneurons of the dentate gyrus, with the highest density in the stratum lucidum of CA3. GPER1-IR was also observed in unmyelinated axons and glial profiles, with estrogen increasing axonal labeling in females. The GPER agonist G1 replicated some estradiol-induced changes, such as increased postsynaptic density protein (PSD95)-IR in the strata oriens, lucidum, and radiatum of CA3, though only estradiol increased Akt phosphorylation. GPER1 modulates synaptic plasticity through distinct molecular pathways^[88]. In terms of ER distribution within the CNS, ER β proteins were found to be abundantly expressed in the granulosa cells of the ovary, epithelial cells of the prostate, and in cell populations within the anteroventral periventricular nucleus (AVPV) and paraventricular hypothalamic nucleus in rats^[89]. Interestingly, *in vivo* investigations indicated that combining immunoreactivity for ER β with that for ER α encompassed all regions in the mouse CNS, where binding was detected via autoradiography^[90]. ER α is broadly distributed at low levels in the rodent brain, with the highest expression in the hypothalamus, hippocampus, and cortex^[91], while high *Esr2* (which encodes ER β) expression was detected in the hippocampus^[92], anteroventral periventricular nucleus (AVPV), bed nucleus of stria terminalis, hypothalamic PVN, supraoptic nucleus, and medial amygdala and more than half of kisspeptin neurons in female AVPV expressed *Esr2*^[93].

Further evidence from normal midlife women participants at varying hormonal stages during menopause revealed neurological symptoms such as changes in thermoregulation, mood, sleep, and cognition. Despite the importance of ERs in neural function, knowledge about their activity in the human brain is limited. Using 18F-fluoroestradiol PET imaging, a study showed that ER density increases with the menopause stage, indicating higher ER density postmenopause. ER density was lowest in premenopausal women, with intermediate levels in perimenopause, particularly in brain regions such as the pituitary, amygdala, and hippocampus. E2 acts as a “master regulator” of neurological function through ERs such as ER α , ER β , and GPER1, influencing synaptic plasticity, neurogenesis, and gene expression. Higher ER density may be compensatory for declining estrogen levels and was associated with poorer memory and predicted mood and cognitive symptoms in postmenopausal women^[83] [Table 2].

Table 2. Action of 17 β -estradiol through estrogen receptors on neurological function

Ref/Year	Model	Intervention	Result
21245576/2011	Er α ^{-/-} mutant mice with ovariectomy on 45% HFD	Subcutaneous injection of estradiol-benzoate	↑ Obesity ↑ Serum leptin & glucose ↓ Energy expenditure ↔ pAkt activation
	Er α ^{-AA} mutant mice with ovariectomy on 45% HFD	Subcutaneous injection Estradiol-benzoate	Normalize body weight Normalize serum leptin and glucose Restore normal activity ↑ pAkt activation in VMN
26655342/2015	OVX Female CD1 mice	17 β -estradiol or an ER- α agonist administered to the dorsal hippocampus	↑ Object and social recognition ↑ CA1 dendritic spine density ↓ CA1 responses to AMPAR activation
28033587/2017	OVX Female CD1 mice	GPER agonist G-1 infusion in the dorsal hippocampus	↑ Social recognition ↑ Object recognition
25673833/2015	OVX C57BL6 female mice	Subcutaneous injections of GPER1 agonist G-1	↑ PSD95 in the strata oriens, lucidum, & radiatum of CA3 ↔ Akt phosphorylation
		Subcutaneous injections of estradiol benzoate	↑ Akt phosphorylation
38902275/2024	Postmenopausal women	-	↑ ER density levels ↓ Memory score (ER-associated) ↑ Cognitive symptoms (ER-associated)
	Premenopausal women	-	Low ER density levels

Er α ^{-/-}: Estrogen receptor α -null; Er α ^{-AA}: nonclassical Er α -knockin; pAkt: phosphorylated Akt; VMN: ventromedial nucleus; OVX: ovariectomized; ER- α : estrogen receptor- α ; CA: hippocampal cornu ammonis; AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GPER1: G protein-coupled estrogen receptor; ↑: increase; ↓: decrease; ↔: unchanged.

Influence of estrogen on the heart

ERs play roles beyond their endocrine functions, modulating the cardiovascular, renal, and immune systems through their anti-inflammatory and anti-apoptotic pathways. They help prevent necrosis of cardiomyocytes and endothelial cells and reduce cardiac hypertrophy^[94]. E2 protects against cardiac dysfunction, enhances nitric oxide synthesis, and limits vascular cell proliferation, providing protective benefits regardless of gender. These effects are mediated by ERs (ER α , ER β , or GPER), through genomic or non-genomic pathways, which help maintain cardiovascular function and prevent tissue remodeling^[94,95].

Involvement of E2 in cardio-protection was demonstrated in both male and female rodents. A study investigated cardiomyocyte-specific overexpression of ER α (ER α -OE) in transgenic mice following MI, revealed significant changes in left ventricle (LV) morphology 2 weeks post-MI: increased LV volume and decreased wall thickness were observed in wild-type mice and male ER α -OE mice, but not in female ER α -OE mice. ER α -OE enhanced the expression of

angiogenesis (VEGF) and lymphangiogenesis (Lyve-1) markers, promoting neovascularization in the peri-infarct area in both sexes. Notably, female ER α -OE mice exhibited reduced fibrosis, and greater JNK phosphorylation post-MI compared to males^[96].

Further mechanistic insights were gained from studies using ER α knockout (ERKO) mice, which showed reduced nitric oxide (NO) production and increased oxidative stress, suggesting that ER α helps maintain NO levels and prevents NOS-3 downregulation. During reperfusion, ERKO hearts show greater calcium accumulation, mainly in the mitochondria, leading to ATP depletion, mitochondrial dysfunction, oxidative stress, and myocardial structural damage, including contraction bands and mitochondrial destruction^[97].

The role of ER β has also been clarified in a heart failure model induced by pressure overload. A preclinical experimental study demonstrated that ER β activation using diarylpropionitrile (DPN) improved heart function in male mice with severe heart failure. DPN treatment increased EF, reduced fibrosis, and promoted angiogenesis, while normalizing collagen I and TGF- β 1 expression. In contrast, treatment with an ER α agonist had no significant effect on EF, fibrosis or angiogenesis. *In vitro*, DPN restored the expression of fibrotic markers to control levels^[98].

To examine the impact of long-term estrogen deprivation, ovariectomized (ACOV) models were used in heart failure induced by aortic constriction (AC) in female guinea pigs. ACOV animals showed worsened cardiac function, impaired Na⁺ extrusion, and reduced Na⁺/K⁺ ATPase current density, leading to calcium dysregulation and diastolic dysfunction. Supplementation with 17 β -estradiol (ACOV + E) restored global and cellular cardiac function to levels similar to those of intact controls. Estrogen improved the amplitude and decay rates of Ca²⁺ transients and shortened the duration of the action potential at 90% repolarization (APD₉₀), also reducing ventricular hypertrophy depending on the pathological insult^[99]. Complementary findings in Wistar rats further demonstrated the time-sensitive effects of E2 post-ischemia. Hearts subjected to 30 min of regional ischemia showed improved function when treated with pacing postconditioning (PPC) or short-term E2 administration during reperfusion. However, long-term E2 treatment for six weeks abolished the protective effects of PPC. PPC increased brain natriuretic peptide expression, reduced TNF- α levels in cardiomyocytes and coronary effluent, and decreased infarct size while enhancing contractility and coronary dynamics^[100] [Table 3].

Overall, these findings indicate that estrogen exerts robust cardioprotective effects in experimental models of heart failure, as ovariectomy exacerbates cardiac dysfunction, while estrogen supplementation reverses these effects by improving both cellular and global cardiac function. These protective actions appear to be mediated in a phase-specific manner, with ER α contributing to early benefits during acute MI and reperfusion *via* vascular support and mitochondrial preservation, and ER β playing a more prominent role in later stages by reducing fibrosis, modulating neuroinflammation, and enhancing cognitive recovery. Strategically targeting these receptor subtypes based on the pathological phase may enable more tailored and effective neuroprotective interventions.

Influence of estrogen deficiency on cerebral health and function

In the previously explored studies, estrogen's crucial role was elucidated in neurological regulation via ERs, such as synaptic plasticity, neurogenesis, and gene expression. Menopause, marked by the natural decline of ovarian function and circulating blood estrogen levels, significantly influences brain health. The menopausal transition typically unfolds gradually, beginning with alterations in the menstrual cycle, and is medically defined as "Perimenopause". Most women experience menopause between the ages of 45 and 55 years, marking a natural aspect of biological aging^[101]. The transition to menopause is concomitant with an

Table 3. Action of estrogen receptors in cardiovascular protection and heart failure

Ref/Year	Model	Intervention	Result
24977106/2014	ER α -OE transgenic female mice with MI	-	↑ Cardiac hypertrophy ↑ Angiogenesis ↑ Lymphangiogenesis ↓ Fibrosis ↑ Survival
	ER α -OE transgenic male mice with MI	-	↑ Cardiac hypertrophy ↑ Angiogenesis ↑ Lymphangiogenesis ↑ JNK Phosphorylation ↔ Fibrosis
10775144/2000	ER α knockout male mice with myocardial I/R	-	↓ NO ↑ Myocardial calcium ↑ Interstitial edema ↑ Mitochondrial & myocyte damage
30376877/2018	TAC in male CD-1 mice	DPN	↑ EF ↓ Fibrosis ↑ Angiogenesis
		PPT	↔ EF ↔ Fibrosis ↔ Angiogenesis
33015413/2020	TAC in OVX Female guinea pigs	-	↑ Heart weight ↑ Na ⁺ influx ↓ Na ⁺ /K ⁺ ATPase current density ↑ Intracellular Ca ²⁺ dysregulation Prolong ADP ₉₀
		17 β -estradiol implanted subcutaneously in the back region 90 days post-ovariectomy	↔ Heart weight ↔ Ca ²⁺ transient amplitude & decay rate Shortened APD ₉₀
24037795/2014	Female Wistar rats with regional ischemia (I/R)	PPC	↑ Coronary flow ↓ Vascular resistance ↑ LV contractility ↓ LVEDP ↑ BNP expression ↓ TNF- α expression
		PPC + Short E2	↑ Coronary flow ↓ Vascular resistance ↑ LV contractility ↓ LVEDP ↑ BNP expression ↓ TNF- α expression
		PPC + Long E2	Sustained flow impairment Sustained vascular resistance

Sustained contractility impairment
Sustained elevation in LVEDP
↔ BNP expression
↔ TNF- α expression

ER α -OE: Cardiomyocyte-specific overexpression of ER α ; JNK: Jun N-terminal kinase; LV: left ventricular; I/R: ischemia/reperfusion; NO: nitric oxide; TAC: transverse aortic constriction; EF: ejection fraction; DPN: diethylpropionitrile; PPC: pacing postconditioning; E2: estrogen; APD₉₀: action potential duration at 90% repolarization; LVEDP: left ventricular end-diastolic pressure; BNP: B-type natriuretic peptide; TNF- α : tumor necrosis factor α ; ↑: increase; ↓: decrease; ↔: unchanged.

increased risk of neurovascular diseases, worsened stroke outcomes, and cognitive decline primarily attributed to the loss of estrogen's neuroprotective, anti-inflammatory, vasodilatory, and metabolic effects on cerebral blood vessels^[16].

Experimental studies have provided mechanistic insights into these effects. Gannon *et al.* investigated vascular cognitive impairment and dementia (VCID) in C57BL/6J female mice utilizing unilateral carotid artery occlusion and chemically induced menopause with 4-vinylcyclohexene diepoxide^[102]. The study reported that menopausal mice exhibited increased weight gain, glucose intolerance, and visceral adiposity, alongside cognitive deficits, particularly when combined with VCID. Impairments in episodic-like memory (NOR) and activities of daily living (nest building) correlated with decreased myelin basic protein (MBP) expression in the corpus callosum, suggesting white matter alterations. Moreover, cognitive deficits were exacerbated, with increased GFAP expression in the cortex, highlighting menopause's detrimental impact on brain function in VCID. Despite these effects, no significant group differences were observed in estrogen receptor (ER α , ER β , and GPER1) expression in the hippocampus or cortex^[102].

Further research underscores the significant influence of menopause on neuroinflammation and estrogen receptor activity. Benedusi *et al.* provided critical insights demonstrating that ER activity declines with age in the hippocampus of OVX C57BL/6 repTOP-ERE-Luc mice^[103]. Ovariectomy triggered age-dependent increases in inflammatory mediators (TNF- α , IL1 β) and altered glial cell morphology, exacerbating neuroinflammation^[103]. Further emphasizing these findings, Tantipongpiradet *et al.* found that treatments targeting estrogen deficiency can mitigate menopause-induced alterations^[104]. Ovariectomy resulted in decreased hippocampal neurogenesis, as evidenced by a reduction in doublecortin (DCX)-immunopositive cells, correlating with depressive-like behaviors in OVX mice, which exhibited increased immobility in both the tail suspension test and forced swim test. Additionally, ovariectomy elevated serum corticosterone levels, indicating hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis. Treatment with 17 β -estradiol and puerarin effectively reversed these elevations and restored brain-derived neurotrophic factor (BDNF) expression, thus promoting neurogenesis in the hippocampus. These findings underscore the potential of estrogenic treatments to mitigate OVX-induced neurobiological alterations and depressive-like behaviors^[104].

The impact of estrogen deficiency on neuroimmune function has also been explored. Sanchez *et al.* also showed that OVX in female C57BL/6 mice increased anxiety-like behaviors, reduced social interaction, and decreased sucrose preference following LPS administration, and estradiol replacement was shown to mitigate these effects^[105]. The absence of estrogens led to the downregulation of the microglial receptor Cx3cr1, disinhibiting microglial responses to immune

stimuli. Furthermore, estradiol treatment reduced elevated proinflammatory markers Il1b and Il6 in OVX mice post-LPS challenge, which indicated heightened neuroinflammatory responses. Although OVX increased microglial density in the CA1 and dentate gyrus regions of the hippocampus, there were no significant changes in microglial morphology. These results indicated that estrogen loss primed microglia, resulting in heightened neuroimmune responses and increased susceptibility to negative affective behaviors^[105].

In addition to immune and cognitive effects, estrogen deficiency influences brain metabolism and oxidative stress. Gagnard *et al.* reported that young adult female C57BL/6J mice exhibit lower oxidative stress and higher NADH-linked respiration rates in the brain compared to males. This was associated with increased pyruvate dehydrogenase complex activity, which was significantly higher in females but decreased following OVX, suggesting that estrogen contributes significantly to mitochondrial efficiency and redox balance in the female brain^[106].

In parallel, recent clinical studies on postmenopausal women have shown significant findings of menopause on the hemodynamics of CBF. A cross-sectional study of 185 subjects, including premenopausal, and perimenopausal, postmenopausal women, and men, utilized arterial spin labeling MRI to assess CBF. The study found that premenopausal women had higher CBF across various brain regions compared to their perimenopausal and postmenopausal counterparts. The latter groups showed more white matter hyperintensities and exhibited declines in CBF with age, whereas premenopausal women experienced a slight increase in CBF with age^[107] [Table 4].

Influence of estrogen and age on cerebrovascular function and neuroprotection modulation

The mammalian brain regulates CBF through a mechanism called neurovascular coupling, or functional hyperemia, which adjusts regional CBF to meet the metabolic demands of activated brain regions. This response often exceeds metabolic needs, facilitating efficient oxygen diffusion to distant brain cells. Various cell types in the neurovascular unit, including astrocytes, vascular smooth muscle cells, pericytes, and endothelial cells, contribute to this process. Mural cells, in particular, control vessel diameter and blood flow through their contractile properties^[108].

Aging is closely associated with endothelial dysfunction and reduced cerebral blood flow, indicating a significant potential for interactions between age and estrogen in regulating cerebrovascular function. Recent studies in intact SD rats show that both age and sex significantly influence cerebrovascular reactivity, particularly in older female rats, which exhibit reduced production of prostacyclin (PGI₂) and thromboxane A₂ (TXA₂) in the middle cerebral artery (MCA). Research focused on perimenopausal and postmenopausal female rats indicates that estrogen plays a crucial role in regulating vasoconstrictor responses to vasopressin (VP) and exerts opposing effects on cerebrovascular function with advancing age. One of major finding is that estrogen treatment produced age-dependent divergent effects on VP-induced cerebrovascular vasoconstriction. Moreover, age determines the specific cyclooxygenase (COX) isoforms and resulting prostanoids produced under estrogen influence. The study revealed age-related shifts in the types of COX isoforms and prostanoids affected by estrogen. Younger rats have a higher role of COX-1-derived dilatory prostanoids (PGI₂), while older rats exhibit increased COX-2-derived constrictor prostanoids (TXA₂). Lastly, VP-stimulated PGI₂ and TXA₂ production increased in both multi-gravid adult (MA) and reproductively senescent (RS) rats. However, in older RS rats with estrogen replacement, VP-stimulated PGI₂ production decreases, and TXA₂ increases. In OVX MA rats with estrogen replacement, vasoconstriction decreases, and dilator prostanoid function increases. Conversely, in older OVX RS rats with estrogen replacement, vasoconstriction increases along with constrictor prostanoid function^[109].

Table 4. Effects of hormonal modulation on cerebral function in menopause models

Ref/Year	Model	Intervention	Result
37221553/2023	4-Vinyl cyclohexene diepoxide-induced ovarian failure in C57BL/6J mice	-	↑ Body weight ↑ Glucose intolerance ↓ MBP expression in corpus callosum
		UCCAO	↓ Daily activities ↓ Episodic-like memory
22492304/2012	OVX C57BL/6 repTOP-ERE-Luc mice	-	↓ Hippocampal ER activity ↑ TNF- α , IL1 β & MIP2 expression Modify microglia and astrocyte morphology
31847138/2019	OVX ICR mice	-	↑ Immobility in TST & FST ↑ Serum corticosterone levels ↓ ER- α & ER- β expression ↓ Hippocampal neurogenesis ↓ BDNF levels
		17 β -estradiol/ puerarin	↓ Immobility in TST & FST ↓ Serum corticosterone levels Restore hippocampal neurogenesis Restore BDNF levels Restore ER- α & ER- β levels
37256192/2023	OVX C57BL/6 mice	LPS	↑ Anxiety-like behaviors ↑ IL-1 β and IL-6 expression ↓ Sucrose preference ↓ Cx3cr1 expression ↑ Microglia in the CA1 & dentate gyrus regions
		Subcutaneous estradiol + LPS	↓ Anxiety-like behaviors ↓ Neuroinflammation ↑ Sucrose preference
26039154/2015	OVX C57BL6J mice	-	↓ PDHc activity ↓ NADH-linked respiration rate ↓ Mitochondrial GSH ↓ Aconitase to fumarase activity
37850361/2024	Premenopausal women	-	↑ CBF
	Perimenopausal & postmenopausal women	-	↓ CBF ↑ WMHs

UCCAO: Unilateral common carotid artery occlusion; MBP: myelin basic protein; OVX: ovariectomized; TNF- α : tumor necrosis factor α ; IL-1 β : interleukin-1 β ; IL-6: interleukin-6; MIP2: macrophage inflammatory protein-2; TST: tail suspension test; FST: forced swimming test; ER: estrogen receptor; BDNF: brain-derived neurotrophic factor; LPS: lipopolysaccharide; PDHc: Pyruvate Dehydrogenase Complex Activity; GSH: Glutathione; CBF: cerebral blood flow; WMH: white matter hyperintensity. ↑: increase; ↓: decrease.

In addition to understanding estrogen's role in cerebrovascular function across different ages, further investigation into dendritic spines and neuroplasticity in the prpTDP-43A315T mouse model of Amyotrophic Lateral Sclerosis (ALS) reveals that estrogen significantly influences synaptic plasticity. Two-photon live imaging showed that male TDP-43 mice exhibit diminished dendritic spine remodeling capacity compared to wild-type males. Conversely, female TDP-43 mice displayed increased remodeling capacity, with peak plasticity coinciding with elevated estrogen levels during the estrous cycle. Estrogen manipulation through ovariectomy and subsequent E2 replacement influenced spine density and alleviated disease severity. High circulating estrogen levels appear to protect female TDP-43 mice from dendritic spine deficits, increasing spine turnover in a dose-dependent manner and potentially mitigating ALS-like symptoms^[110].

In vitro studies by Ghisletti *et al.* identified a novel mechanism by which estrogen inhibits NF- κ B activation, a key player in inflammation^[111]. E2, in particular, prevents the nuclear transport of NF- κ B in macrophages by inhibiting its intracellular trafficking rather than suppressing I κ -Ba degradation, which is the target of most anti-inflammatory drugs. This effect is mediated through the estrogen receptor ER α via a nongenomic pathway involving PI3K activation. Notably, E2 rapidly induces PIP3 production, indicating that E2 modulates early inflammatory responses through lipid signaling at the plasma membrane. These findings indicate that E2 could serve as a unique anti-inflammatory agent, especially in contexts where chronic inflammation is prevalent, such as postmenopause. The study also highlights that common selective estrogen receptor modulators (SERMs), such as raloxifene and tamoxifen, may not replicate E2's anti-inflammatory benefits *in vivo*, pointing to the need for selective modulators that mimic these specific E2 activities without unwanted side effects^[111].

Findings also reveal the neuroprotective potential of SERMs in mitigating damage caused by cerebral ischemia. A study involving OVX adult Holtzman SD female rats indicated that raloxifene enhanced neurogenesis after middle cerebral artery occlusion (MCAO), while tamoxifen did not. Low-dose estrogen also significantly increased neurogenesis at day 5 post-MCAO. Neural progenitor cells migrated to injured areas (cortex and striatum) after MCAO, with E2 and raloxifene treatment increasing BrdU⁺ cells in these regions. Both raloxifene and tamoxifen, along with estrogen, significantly reversed ischemia-induced spine density loss in the cerebral cortex^[112] [Table 5].

Impact of estrogen therapy on maintaining cerebral homeostasis

Cognitive impairment is increasingly recognized as a common consequence of MI, affecting 30%-50% of patients in the long term^[113]. Data show that that approximately 50% of older MI patients experience some form of cognitive impairment within 1 month to 1 year after MI and about 25% develop moderate to severe cognitive impairment as early as 1 month post-discharge^[114]. This cognitive decline is not solely due to the infarct itself but often reflects broader vascular pathology, such as systemic atherosclerosis, cerebral small vessel disease, and chronic hypoperfusion^[115]. Comorbidities like diabetes and hypertension further exacerbate cognitive decline through mechanisms such as oxidative stress, endothelial dysfunction, and neuroinflammation^[116,117]. In this context, estrogen has been shown to exert neuroprotective effects by reducing neuroinflammation, preserving CBF, and promoting synaptic health^[118]. However, translating these potential benefits into clinical practice remains challenging.

A key concept of estrogen therapy is the “critical window” hypothesis, which suggests that estrogen replacement therapy (ERT) may only be beneficial if initiated early after menopause^[119,120]. However, systemic risks associated with ERT, such as thrombotic events and cancer, have limited its widespread adoption. Therefore, SERMs, such as raloxifene and bazedoxifene, have emerged as safer alternatives that

Table 5. Effects of estrogen and SERMs on cerebrovascular function in preclinical models

Ref/Year	Animal/Method	Drug/Application	Result
26993224/2016	Young OVX SD rats	ERT	↓ Cerebral vasoconstriction ↑ COX-1-derived dilatory prostanoids (TXA2) ↑ COX-2 derived dilatory prostanoids (PGI2)
	Old OVX SD rats	ERT	↑ Cerebral vasoconstriction ↑ COX-1-derived dilatory prostanoids (TXA2) ↓ COX-2 derived dilatory prostanoids (PGI2)
35249200/2022	OVX TDP-43 mice	E2 subcutaneous osmotic mini pump	↑ Dendritic spine turnover in the motor cortex ↑ Synaptic plasticity ↓ Severity of ALS & ALS-like symptoms
15798185/2005	RAW 264.7 macrophage cell line and primary cultures of microglia	E2 treatment	Inhibit NF-κB activation ↑ PIP3 production ↓ Inflammation
24815952/2015	MCAO in OVX Holtzman SD rats	Subcutaneous E2/Intramuscular raloxifene	↑ Neurogenesis ↓ Ischemia-induced spine density loss in the cerebral cortex
		Subcutaneous tamoxifen	↔ Neurogenesis ↓ Ischemia-induced spine density loss in the cerebral cortex

OVX: Ovariectomized; ERT; estrogen replacement therapy; E2: 17-β estradiol; COX: cyclooxygenase; PGI2: prostaglandin I2; TXA2: Thromboxane A2; ALS: amyotrophic lateral sclerosis; NF-κB: nuclear factor-kappa B; PIP3: Phosphatidylinositol 3,4,5-trisphosphate; MCAO: middle-cerebral artery occlusion. ↑: increase; ↓: decrease; ↔: unchanged.

may offer neuroprotective effects without the same systemic risks^[121-123]. These developments highlight the importance of refining hormonal treatments and tailoring them to the specific cardiovascular and neurocognitive risk profiles of post-MI women.

Recent studies have explored how estrogens and their receptor modulators influence brain homeostasis after cardiovascular events, with a particular focus on reducing Aβ accumulation, preventing tau hyperphosphorylation, and mitigating oxidative stress and inflammatory cytokine production^[118,124]. These neuroprotective effects are mediated by estrogen receptors ERα, ERβ, and GPER1, which activate signaling pathways such as PI3K/Akt and MAPK/ERK, promoting neuronal survival, synaptic plasticity, and mitochondrial stability^[111,124].

A promising approach in estrogen therapy is the development of brain-targeted estrogen treatments, including prodrugs such as 10β,17β-dihydroxyestra-1,4-dien-3-one (DHED), which is administered systemically but converted to 17β-estradiol in the brain. These therapies have shown promise in improving cognitive function without peripheral side effects, suggesting a viable route for clinical translation^[125]. As these findings indicate, personalized, phase-specific hormonal interventions may offer significant benefits in improving cognitive outcomes in women recovering from MI.

Despite these advantages, clinical observations reveal that some postmenopausal women on HRT still experience cognitive decline following MI. This inconsistency may be explained by the “timing hypothesis”, according to which initiation of HRT close to menopause confers neuroprotective benefits, while late initiation may be ineffective or even harmful. In support of this hypothesis, a neuroimaging study revealed that women who started HRT after the age of 60 had increased deposition of tau, a hallmark of AD, underlining the crucial importance of treatment timing^[126].

In men, the role of estrogen is more complex and less well understood. While low levels of endogenous estrogen can promote cognition and vascular function, excessive levels of estrogen or exogenous supplementation can upset the androgen-estrogen balance. Animal studies have shown that high estrogen levels impair reproductive behavior and spatial learning in males^[127,128]. Furthermore, sex-specific differences in estrogen receptor expression and downstream signaling pathways likely mediate divergent neurocognitive outcomes, emphasizing the need for sex-specific hormone therapies following MI.

Furthermore, the role of estrogen in cognitive health is well documented in AD. ERT is widely used to manage menopausal symptoms, and its potential to delay the onset of AD in postmenopausal women is a key area of research. Estrogen has been shown to act as a neuroprotective agent in AD by reducing A β and glutamate toxicity, enhancing synaptic plasticity, preserving neurotrophic factors, and decreasing tau hyperphosphorylation. For example, in female OVX mice, ERT prevents tau pathology, likely through its antioxidant properties^[129,130]. A β , a key molecular player in AD, forms neuritic plaques that promote disease progression^[131].

The “critical window” for ERT in postmenopausal women with AD reinforces the need for rapid intervention. Studies have shown that early estradiol treatment after OVX in a mouse model of AD (APP/PS1) prevents cognitive decline, inhibits A β accumulation, and restores telomerase activity, thereby improving cognitive performance^[132,133]. Conversely, late estradiol treatment offers limited benefits, highlighting the importance of timing for therapeutic efficacy^[133].

In addition, estrogen’s impact on neurogenesis has been studied after stroke. In studies with APP/Ar^{+/-} and APP/OVX mice, early treatment with estradiol significantly reduced A β production and plaque formation, while increasing neprilysin (NEP) activity, thereby facilitating A β clearance. Late treatments were less effective, highlighting the importance of early intervention for optimal outcomes^[134].

Estrogen’s neuroprotective effects extend beyond A β and tau pathology. In OVX mice subjected to global cerebral ischemia, estradiol treatment mitigated hippocampal CA1 neuronal damage and improved learning and memory function. These effects were absent in long-term estrogen-deprived mice, linking the loss of estrogen to diminished cognitive protection^[135]. Supporting this, 5-bromo-2'-deoxyuridine labeling studies (BrdU⁺ cells) demonstrated that early estrogen replacement significantly increased the proliferation and survival of newly generated neurons in the dentate gyrus and subventricular zone of the brain, after ischemia, correlating with improved spatial memory and behavioral recovery^[136].

Further investigating the timing of estrogen treatment, revealed that early estradiol administration significantly attenuated cognitive deficits in an AD mouse model (A β 1-42), by increasing hippocampal neurogenesis and reducing markers of oxidative stress^[137]. Importantly, early treatment also activated survival pathways and reduced gliosis, synaptic damage, and proinflammatory cytokines, whereas late treatment failed to deliver similar benefits^[137].

A more recent study highlights the importance of optimizing both the timing and delivery method of estrogen therapy to enhance its therapeutic efficacy while minimizing systemic side effects. Researchers investigated whether delivering estrogen exclusively to the brain could enhance cognitive performance in postmenopausal mice without peripheral adverse effects. Using a surgical menopause model, they treated young and middle-aged ovariectomized C57BL/6J female mice with the brain-selective prodrug DHED. DHED significantly improved spatial in young mice and enhanced both spatial and working memory in middle-aged mice. Importantly, unlike traditional estrogen therapies, DHED did not affect body weight, uterine weight, or visceral fat. These results highlight the potential of brain-targeted estrogen administration as a practical and safer alternative, and support the goal of refining the therapeutic window and route of administration for post-MI estrogen treatment^[119] [Table 6] [Figure 2].

CONCLUSION AND FUTURE DIRECTIONS

MI severely disrupts cerebral homeostasis through a cascade of cardiovascular and neuroinflammatory mechanisms. The acute systemic inflammatory response following MI induces elevated levels of cerebral proinflammatory cytokines, as observed in both non-transgenic and transgenic mouse models, including those predisposed to early-onset AD. Additionally, the reduction in CO and CBF flow post-MI leads to oxidative stress and increased BBB permeability. Elevated levels of circulating angiotensin II trigger perivascular macrophage activation and the overproduction of reactive oxygen species, further damaging the BBB and brain cells. This cascade contributes to cognitive impairments, such as declines in spatial memory and attention, and challenges the brain's ability to maintain homeostasis. Consequently, MI contributes to long-term cognitive deficits and increases susceptibility to neurodegenerative diseases.

On the other hand, estrogens, particularly E2, play a central role in preserving cerebral homeostasis and cognitive function through their neuroprotective and anti-inflammatory properties. E2 acts via ERs (ER α and ER β) distributed widely in brain regions crucial for memory, learning, and neuroprotection. These receptors mediate genomic and non-genomic actions, including PI3K/Akt and ERK/MAPK, that influence synaptic plasticity, neurogenesis, vascular tone, and inflammatory responses. Estrogen deficiency, occurring during menopause, disrupts these mechanisms and increases vulnerability to cognitive decline and neuroinflammation. Consequently, the dual impact of MI and estrogen loss presents an additive risk for cognitive dysfunction in postmenopausal women.

Although existing preclinical and clinical data strongly support this interaction, several limitations remain. Much of the mechanistic insights into estrogen's role in cerebral dysfunction post-MI derives from animal models, which may not fully represent human physiology, particularly in older populations and those with comorbidities^[102,103,105]. Clinical studies linking estrogen receptor subtype activity to cognitive outcomes are still limited, and results from hormone therapy trials are inconclusive due to variability in the timing, dosage and type of estrogen used^[132-134]. Although studies suggest an existence of a "critical window" for the neuroprotective efficacy of estrogen therapy, its application in clinical practice is complicated by established risks, such as thromboembolism and hormone-sensitive cancers^[135,138].

These limitations highlight the urgent need for more translation-relevant human models and data. Future studies should focus on receptor subtype-specific estrogen functions in the injured brain^[86-88], identification of optimal therapeutic time windows^[133-135], and validation of brain-selective estrogen delivery platforms, such as DHED, to minimize systemic side effects^[119]. Large-scale longitudinal human studies are also essential to assess cognitive trajectories after MI, stratified by sex, menopausal status, and hormone therapy use^[57,58,107]. Filling this knowledge gap will enable the development of more precise, sex-sensitive strategies to prevent cognitive decline and promote brain recovery in post-MI patients, particularly in postmenopausal women, a population particularly well placed at the intersection of cardiovascular and neurodegenerative risk.

Table 6. Impact of estrogen therapy on maintaining cerebral homeostasis

Ref/Year	Model	Intervention	Result
23779114/2013	47 older adults: 20 with normal cognition 27 with amnesic mild cognitive impairment	High in saturated fat and high glycemic index carbohydrates Low in saturated fat and low glycemic index carbohydrates	Participants with aMCI had higher baseline levels of LD A β 42 and A β 40 compared to cognitively normal participants APOE ϵ 4 carriers exhibited higher levels of LD apoE regardless of cognitive status $\uparrow$ LD A β 42 and A β 40 levels $\downarrow$ LD A β 42 and A β 40 levels
38917776/2024	OVX young C57BL/6 J mice OVX middle-aged female C57BL/6 J mice	Subcutaneous DHED capsule between the shoulder blades Subcutaneous DHED capsule between the shoulder blades	$\uparrow$ Spatial learning $\leftrightarrow$ Body weight, uterine weight, or visceral fat $\uparrow$ Spatial learning $\uparrow$ Working and recognition memory $\leftrightarrow$ Body weight, uterine weight, or visceral fat
15798185/2005	RAW 264.7 macrophages and primary microglia cultures	17 β -estradiol (E2) treatment	Inhibition of NF- κ B nuclear translocation $\downarrow$ Proinflammatory gene expression (e.g., IL-6, TNF- α)
2317288/1990	Neonatally gonadectomized male and female rats	Removal of gonadal hormones + spatial memory testing in adulthood	Males with intact hormones performed better than females Neonatal gonadectomy reduced male advantage
22138012/2012	<i>In vivo</i> : male & female rats <i>In vitro</i> : organotypic hippocampal cultures	17 β -estradiol (E2)	$\uparrow$ Synaptogenesis in female hippocampus only $\uparrow$ Synaptic density in both sexes Autonomous estradiol synthesis Synaptogenesis regulated by locally produced estradiol
11309635/2001	Multiple Outcomes of Raloxifene Evaluation trial including 7,478 postmenopausal women with osteoporosis	Raloxifene daily for three years	$\leftrightarrow$ Among the treatment groups on any cognitive test scores Trend toward lower risk of cognitive decline in raloxifene users $\downarrow$ Cognitive scores in older women compared to younger women
40139074/2025	Women aged 40–65 with a DSM-IV diagnosis of depressive disorder, confirmed menopause, and partial or no remission on stable antidepressant therapy	Intervention group: Received daily bazedoxifene + conjugated estrogen Placebo group	$\downarrow$ MADRS scores in both groups $\uparrow$ Improvement in Meno-D Scale $\downarrow$ MENQOL score in the treatment group
32804095/2020	Female hTau transgenic mice injected with A β ₁₋₄₂	17 β -estradiol (E2) pre-treatment	$\downarrow$ Tau hyperphosphorylation and PHF-like conformations $\uparrow$ miR-218 expression $\downarrow$ GSK3 β activation and oxidative stress Prevented A β -induced neurotoxicity
32903757/2020	APP/PS1 female mice • Early-OVX + immediate E2 • Late-OVX + delayed E2	Subcutaneous 17 β -estradiol pellet	$\uparrow$ Hippocampal NSC survival, $\uparrow$ Telomerase activity, $\downarrow$ A β deposition, $\uparrow$ Cognitive performance (MWM, NOR tests) $\leftrightarrow$ Cognitive improvement, $\leftrightarrow$ NSC protection
23180279/2013	APP/Ar ^{+/-} female APP/OVX	Subcutaneous E2 pellet Subcutaneous E2 pellet	$\downarrow$ BACE1 expression and activity $\downarrow$ A β 40 & A β 42 formation $\uparrow$ NEP expression and activity $\leftrightarrow$ BACE1 expression and activity $\downarrow$ A β 42 formation $\uparrow$ NEP expression and activity

32542593/2020	APP transfected HEK293 cells	E2 treatment	↓ BACE1 levels
	Short-term OVX C57BL/6 mice (1-week)	Subcutaneous E2 injections +GCI	↑ Learning & memory function ↓ Hippocampal CA1 neuronal damage
	Long-term OVX C57BL/6 mice (10-weeks)	Subcutaneous E2 injections+ GCI	↔ Impairment in learning & memory function Sustained hippocampal CA1 neuronal damage\ ↓ Hippocampal E2 levels ↓ Aromatase expression ↓ Estrogen receptor protein levels
32858306/2020	OVX female ERE-Luc transgenic mice	IP Bazedoxifene acetate	Bazedoxifene detected in serum, hippocampus & cortex in the treated group
	OVX C57BL/6J females	IP 17β-estradiol	Bazedoxifene not detected in the non-treated group Significant preference for the novel arm → enhanced memory ↑ Liver luciferase activity ↑ ER activation in brain regions compared to vehicle
20940729/2011	C57BL/6 Male & OVX female mice	E2 + MCAO	↑ Neurogenesis Rapid behavioral recovery
	Female Era ^{-/-} mice	E2 + MCAO	↓ Neurogenesis Slow behavioral recovery
27838872/2017	OVX C57BL/6 mice	Aβ ₁₋₄₂ insertion into the bilateral hippocampus + E2 (early stage of AD pathology)	↓ Cognitive deficits ↑ hippocampal neurogenesis ↓ NO & ROS production ↓ Cytochrome-c/Bax/Bcl-2/caspase-3 pathway ↑ BDNF/TrkB/STAT3/CREB/ERK pathway ↓ Gliosis levels ↓ Proinflammatory cytokines ↑ Anti-inflammatory cytokines ↑ Synaptic connections
		Aβ ₁₋₄₂ insertion into the bilateral hippocampus + E2 (late stage of AD pathology)	No improvement in cognitive function No improvement in hippocampal neurogenesis

aMCI: Amnesic mild cognitive impairment; LD: lipiddepleted; NSC: neural stem cells; MWM: morris water maze; NOR: novel object recognition; PS1: presenilin 1; ARIA: amyloid-related imaging abnormalities; OVX: ovariectomized; E2: 17-βestradiol; APP/Ar^{+/-}: APP23 mice with genetic deficiency of aromatase; MADRS: montgomery-asberg depression rating scale; Meno-D: menopausal depression; MENQOL: menopause-specific quality of life; BACE 1: β-secretase; Aβ: amyloid beta; NEP: neprilysin; GCI: global cerebral ischemia; MCAO: middle-cerebral artery occlusion; DHED: 10β,17β-dihydroxyestra-1,4-dien-3-one; ↑: increase; ↓: decrease; ↔: unchanged.

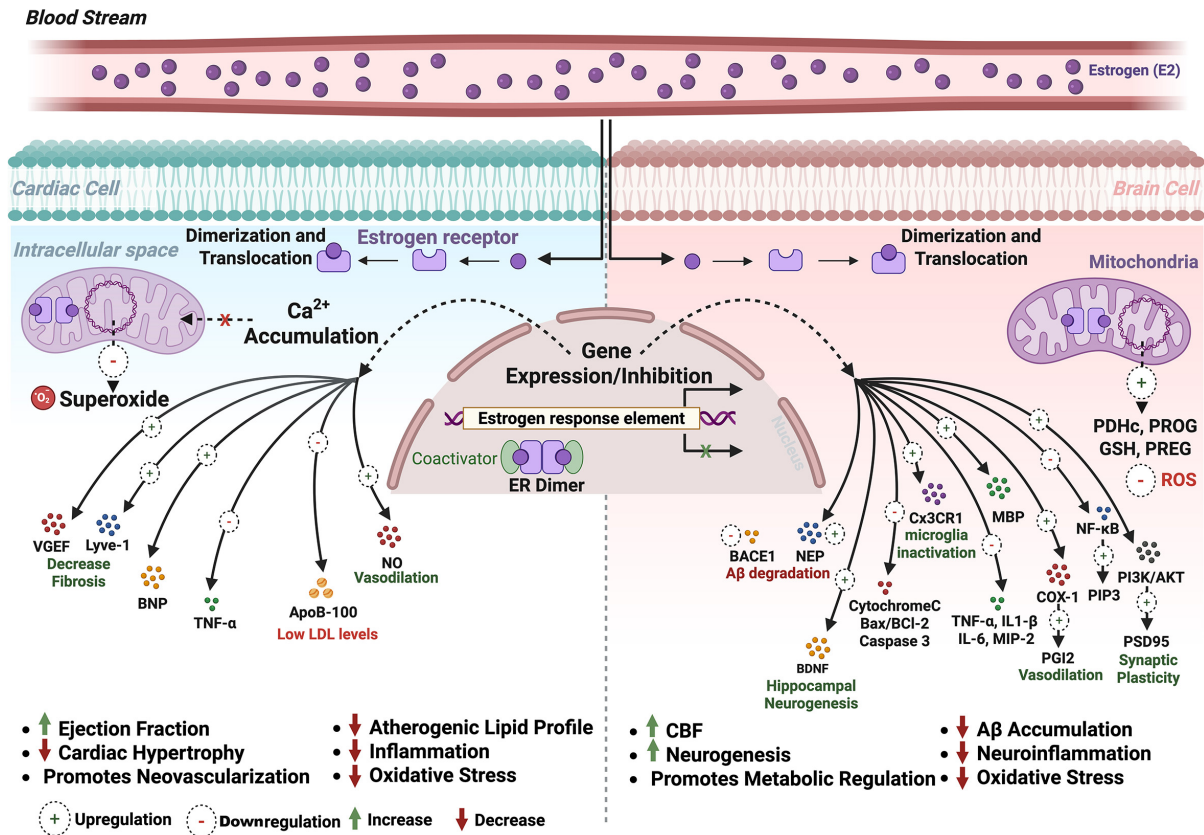


Figure 2. The Role of Estrogen in Cardiac and Brain Cellular Mechanisms: Impacts on Health and Disease. This illustration highlights the effects of E2 on cardiac and brain cells via ER-mediated pathways. In cardiac cells, estrogen enhances vasodilation through NO signaling, reduces fibrosis by upregulating VEGF and Lyve-1, and lowers LDL levels via ApoB-100 regulation. Conversely, it inhibits detrimental effects, such as superoxide and TNF- α production, while modulating Ca^{2+} accumulation in mitochondria. In brain cells, E2 promotes neuroprotection by increasing hippocampal neurogenesis (via BDNF) and synaptic plasticity (PSD95) while supporting vasodilation (PGI2). It mitigates neuroinflammatory responses by inactivating microglia (Cx3CR1), suppressing proinflammatory cytokines (TNF- α , IL-1 β , IL-6), and enhancing A β degradation through NEP regulation. Additionally, estrogen inhibits apoptotic pathways by decreasing cytochrome c release and caspase activation. These pathways demonstrate estrogen's role in reducing oxidative stress, balancing mitochondrial function, and influencing gene expression to protect against cardiovascular and neurodegenerative diseases. E2: Estrogen; ER: estrogen receptor; NO: nitric oxide; VEGF: vascular endothelial growth factor; Lyve-1: Lymphatic vessel endothelial hyaluronan receptor 1; LDL: low-density lipoprotein; ApoB: Apolipoprotein B; TNF- α : tumor necrosis factor alpha; BDNF: brain-derived neurotrophic factor; PSD95: postsynaptic density 95; PGI2: prostaglandin I2; Cx3CR1: CX3C chemokine receptor 1; IL-1 β : interleukin-1beta; IL-6: interleukin-6; A β : amyloid beta; NEP: neprilysin. Created in BioRender. Zouein, F. (2025), Available from: <https://BioRender.com/oicbvbg>.

DECLARATIONS

Acknowledgments

Booz GW acknowledges the support of the Pharmacology Clinical Research Core of the University of Mississippi Medical Center.

Authors' contributions

Conceptualized the review: Booz GW, Zouein FA

Wrote the manuscript and prepared the final version: El-Samadi L, Zahreddine R, Ziade JA, El Ghawi A, Amin G, Booz GW, Zouein FA

Made the figures: Ziade JA

Made the Tables: El Ghawi A, El-Samadi L

Wrote the Figure legends: El-Samadi L

Guided the writing and edited the manuscript: Booz GW, Zouein FA

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by grants from the American University of Beirut Faculty of Medicine [grant numbers: MPP - 320145; URB - 103949; URB - 104262; URB - 104115; URB - 104524] to FAZ.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2025.

REFERENCES

1. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *J Am Coll Cardiol*. 2019;74:2529-32. [DOI](#) [PubMed](#)
2. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *Lancet*. 2017;389:197-210. [DOI](#) [PubMed](#)
3. Sposato LA, Gupta AK, Wu KC. JAHA spotlight on neurocardiology: an emerging field gaining traction among neurologists and cardiologists. *J Am Heart Assoc*. 2024;13:e038026. [DOI](#) [PubMed](#) [PMC](#)
4. Gelosa P, Castiglioni L, Rzemieniec J, Muluhie M, Camera M, Sironi L. Cerebral derailment after myocardial infarct: mechanisms and effects of the signaling from the ischemic heart to brain. *J Mol Med*. 2022;100:23-41. [DOI](#) [PubMed](#) [PMC](#)
5. Feng HP, Chien WC, Cheng WT, Chung CH, Cheng SM, Tzeng WC. Risk of anxiety and depressive disorders in patients with myocardial infarction: a nationwide population-based cohort study. *Medicine*. 2016;95:e4464. [DOI](#) [PubMed](#) [PMC](#)
6. Wolters FJ, Segufa RA, Darweesh SKL, et al. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. *Alzheimers Dement*. 2018;14:1493-504. [DOI](#)
7. Li Q, Barres BA. Microglia and macrophages in brain homeostasis and disease. *Nat Rev Immunol*. 2018;18:225-42. [DOI](#) [PubMed](#)
8. Jinawong K, Apaijai N, Chattipakorn N, Chattipakorn SC. Cognitive impairment in myocardial infarction and heart failure. *Acta Physiol*. 2021;232:e13642. [DOI](#) [PubMed](#)
9. Althammer F, Ferreira-Neto HC, Rubaharan M, et al. Three-dimensional morphometric analysis reveals time-dependent structural changes in microglia and astrocytes in the central amygdala and hypothalamic paraventricular nucleus of heart failure rats. *J Neuroinflamm*. 2020;17:221. [DOI](#)
10. Fujiyoshi A, Jacobs DR Jr, Fitzpatrick AL, et al. Coronary artery calcium and risk of dementia in MESA (multi-ethnic study of atherosclerosis). *Circ Cardiovasc Imaging*. 2017;10:e005349. [DOI](#) [PubMed](#) [PMC](#)
11. Kaplan A, Yabluchanskiy A, Ghali R, Altara R, Booz GW, Zouein FA. Cerebral blood flow alteration following acute myocardial infarction in mice. *Biosci Rep*. 2018;38:BSR20180382. [DOI](#) [PubMed](#) [PMC](#)
12. Nouredine FY, Altara R, Fan F, Yabluchanskiy A, Booz GW, Zouein FA. Impact of the Renin-angiotensin system on the endothelium in vascular dementia: unresolved issues and future perspectives. *Int J Mol Sci*. 2020;21:4268. [DOI](#)
13. Testai FD, Gorelick PB, Chuang PY, et al. Cardiac contributions to Brain health: a scientific statement from the American Heart Association. *Stroke*. 2024;55:e425-38. [DOI](#)
14. Gruhn N, Larsen FS, Boesgaard S, et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke*. 2001;32:2530-3. [DOI](#)
15. Azcoitia I, Barreto GE, Garcia-Segura LM. Molecular mechanisms and cellular events involved in the neuroprotective actions of

- estradiol. Analysis of sex differences. *Front Neuroendocrinol*. 2019;55:100787. DOI PubMed
16. Raz L. Estrogen and cerebrovascular regulation in menopause. *Mol Cell Endocrinol*. 2014;389:22-30. DOI PubMed
17. Kim GW, Park K, Jeong GW. Effects of sex hormones and age on brain volume in post-menopausal women. *J Sex Med*. 2018;15:662-70. DOI
18. Frangogiannis NG. Pathophysiology of myocardial infarction. In: Terjung R, editor. *Comprehensive Physiology*. Wiley; 2011. pp. 1841-75. DOI
19. Moraes-Silva IC, Rodrigues B, Coelho-Junior HJ, Feriani DJ, Irigoyen M. Myocardial infarction and exercise training: evidence from basic science. In: Xiao J, editor. *Exercise for cardiovascular disease prevention and treatment*. Singapore: Springer; 2017. pp. 139-53. DOI
20. Kiani F, Hesabi N, Arbabisarjou A. Assessment of risk factors in patients with myocardial infarction. *Glob J Health Sci*. 2015;8:255-62. DOI PubMed PMC
21. Hajar R. Framingham contribution to cardiovascular disease. *Heart Views*. 2016;17:78-81. DOI PubMed PMC
22. Teo KK, Rafiq T. Cardiovascular risk factors and prevention: a perspective from developing countries. *Can J Cardiol*. 2021;37:733-43. DOI PubMed
23. Yusuf S, Hawken S, Ounpuu S. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-52. DOI PubMed
24. Christia P, Bujak M, Gonzalez-Quesada C, et al. Systematic characterization of myocardial inflammation, repair, and remodeling in a mouse model of reperfused myocardial infarction. *J Histochem Cytochem*. 2013;61:555-70. DOI PubMed PMC
25. Shinde AV, Frangogiannis NG. Fibroblasts in myocardial infarction: a role in inflammation and repair. *J Mol Cell Cardiol*. 2014;70:74-82. DOI PubMed PMC
26. Richardson WJ, Clarke SA, Quinn TA, Holmes JW. Physiological implications of myocardial scar structure. *Compr Physiol*. 2015;5:1877-909. DOI
27. Martin TP, MacDonald EA, Elbassioni AAM, et al. Preclinical models of myocardial infarction: from mechanism to translation. *Br J Pharmacol*. 2022;179:770-91. DOI
28. Zornoff LAM, Paiva SAR, Duarte DR, Spadaro J. Ventricular remodeling after myocardial infarction: concepts and clinical implications. *Arq Bras Cardiol*. 2009;92:150-64. DOI PubMed
29. Joshi NV, Toor I, Shah AS, et al. Systemic atherosclerotic inflammation following acute myocardial infarction: myocardial infarction begets myocardial infarction. *J Am Heart Assoc*. 2015;4:e001956. DOI PubMed PMC
30. Mainali N, Li X, Wang X, et al. Myocardial infarction elevates endoplasmic reticulum stress and protein aggregation in heart as well as brain. *Mol Cell Biochem*. 2024;479:2741-53. DOI PubMed PMC
31. Pereira A. Developing the concepts of homeostasis, homeorhesis, allostasis, elasticity, flexibility and plasticity of brain function. *NeuroSci*. 2021;2:372-82. DOI
32. Merkler AE, Alakbarli J, Barbar T, et al. Associations between the size and location of myocardial infarction and cerebral infarction. *J Neurol Sci*. 2020;419:117182. DOI
33. Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. *Anesthesiology*. 2015;123:1198-208. DOI PubMed
34. Doehner W, Ural D, Haeusler KG, et al. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. *Eur J Heart Fail*. 2018;20:199-215. DOI PubMed
35. Ovsenik A, Podbregar M, Fabjan A. Cerebral blood flow impairment and cognitive decline in heart failure. *Brain Behav*. 2021;11:e02176. DOI PubMed PMC
36. Athilingam P, Moynihan J, Chen L, D'Aoust R, Groer M, Kip K. Elevated levels of interleukin 6 and C-reactive protein associated with cognitive impairment in heart failure. *Congest Heart Fail*. 2013;19:92-8. DOI PubMed PMC
37. Kindermann I, Fischer D, Karbach J, et al. Cognitive function in patients with decompensated heart failure: the Cognitive Impairment in Heart Failure (CogImpair-HF) study. *Eur J Heart Fail*. 2012;4:404-13. DOI
38. Gironi M, Bianchi A, Russo A, et al. Oxidative imbalance in different neurodegenerative diseases with memory impairment. *Neurodegener Dis*. 2010;8:129-37. DOI PubMed
39. Kure CE, Rosenfeldt FL, Scholey AB, et al. Relationships among cognitive function and cerebral blood flow, oxidative stress, and inflammation in older heart failure patients. *J Card Fail*. 2016;22:548-59. DOI
40. Mueller K, Thiel F, Beutner F, et al. Brain damage with heart failure: cardiac biomarker alterations and gray matter decline. *Circ Res*. 2020;126:750-64. DOI PubMed PMC
41. Thackeray JT, Hupe HC, Wang Y, et al. Myocardial inflammation predicts remodeling and neuroinflammation after myocardial infarction. *J Am Coll Cardiol*. 2018;71:263-75.
42. Sun LL, Duan MJ, Ma JC, et al. Myocardial infarction-induced hippocampal microtubule damage by cardiac originating microRNA-1 in mice. *J Mol Cell Cardiol*. 2018;120:12-27. DOI PubMed
43. Dworak M, Stebbing M, Kompa AR, Rana I, Krum H, Badoer E. Sustained activation of microglia in the hypothalamic PVN following myocardial infarction. *Auton Neurosci*. 2012;169:70-6. DOI PubMed

44. Zhang W, Luo P. Myocardial infarction predisposes neurodegenerative diseases. *J Alzheimers Dis*. 2020;74:579-87. DOI PubMed
45. Rinaldi B, Guida F, Furiano A, et al. Effect of prolonged moderate exercise on the changes of nonneuronal cells in early myocardial infarction. *Neural Plast*. 2015;2015:265967. DOI PubMed PMC
46. Wann BP, Boucher M, Kaloustian S, Nim S, Godbout R, Rousseau G. Apoptosis detected in the amygdala following myocardial infarction in the rat. *Biol Psychiatry*. 2006;59:430-3. DOI PubMed
47. Chang M, Wang H, Lei Y, Yang H, Xu J, Tang S. Proteomic study of left ventricle and cortex in rats after myocardial infarction. *Sci Rep*. 2024;14:6866. DOI PubMed PMC
48. Tulner DM, Smith OR, de Jonge P, et al. Circulating cerebral S100B protein is associated with depressive symptoms following myocardial infarction. *Neuropsychobiology*. 2009;59:87-95. DOI PubMed
49. Ni RSS, Mohamed Raffi HQ, Dong Y. The pathophysiology of cognitive impairment in individuals with heart failure: a systematic review. *Front Cardiovasc Med*. 2023;10:1181979. DOI PubMed PMC
50. Suzuki H, Matsumoto Y, Ota H, et al. Hippocampal blood flow abnormality associated with depressive symptoms and cognitive impairment in patients with chronic heart failure. *Circ J*. 2016;80:1773-80. DOI
51. Rouch L, Hoang T, Xia F, Sidney S, Lima JAC, Yaffe K. Twenty-five-year change in cardiac structure and function and midlife cognition: the CARDIA study. *Neurology*. 2022;98:e1040-9. DOI PubMed PMC
52. Pan A, Kumar R, Macey PM, Fonarow GC, Harper RM, Woo MA. Visual assessment of brain magnetic resonance imaging detects injury to cognitive regulatory sites in patients with heart failure. *J Card Fail*. 2013;19:94-100. DOI PubMed PMC
53. Sundbøll J, Horváth-Puhó E, Adelborg K, et al. Higher risk of vascular dementia in myocardial infarction survivors. *Circulation*. 2018;137:567-77. DOI
54. Johansen MC, Ye W, Gross A, et al. Association between acute myocardial infarction and cognition. *JAMA Neurol*. 2023;80:723-31. DOI PubMed PMC
55. Kasprzak D, Kaczmarek-Majer K, Rzeźniczak J, et al. Cognitive impairment in cardiovascular patients after myocardial infarction: prospective clinical study. *J Clin Med*. 2023;12:4954. DOI
56. Jiang X, Lewis CE, Allen NB, Sidney S, Yaffe K. Premature cardiovascular disease and brain health in midlife: the CARDIA study. *Neurology*. 2023;100:e1454-63. DOI PubMed PMC
57. Huijts M, van Oostenbrugge RJ, Duits A, et al. Cognitive impairment in heart failure: results from the Trial of Intensified versus standard medical therapy in elderly patients with Congestive Heart Failure (TIME-CHF) randomized trial. *Eur J Heart Fail*. 2013;15:699-707. DOI PubMed
58. Goyal P, Didomenico RJ, Pressler SJ, et al. Cognitive impairment in heart failure: a heart failure society of America scientific statement. *J Card Fail*. 2024;30:488-504. DOI
59. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron*. 2017;96:17-42. DOI PubMed
60. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National burden of heart failure events in the United States, 2006 to 2014. *Circ Heart Fail*. 2018;11:e004873. DOI PubMed PMC
61. Adamski MG, Sternak M, Mohaissen T, et al. Vascular cognitive impairment linked to brain endothelium inflammation in early stages of heart failure in mice. *J Am Heart Assoc*. 2018;7:e007694. DOI PubMed PMC
62. Yu Y, Weiss RM, Wei SG. Interleukin 17A contributes to blood-brain barrier disruption of hypothalamic paraventricular nucleus in rats with myocardial infarction. *J Am Heart Assoc*. 2024;13:e032533. DOI PubMed PMC
63. Yang J, Zhang F, Shi H, et al. Neutrophil-derived advanced glycation end products-Nε-(carboxymethyl) lysine promotes RIP3-mediated myocardial necroptosis via RAGE and exacerbates myocardial ischemia/reperfusion injury. *FASEB J*. 2019;33:14410-22. DOI
64. Korn A, Baylan U, Simsek S, Schalkwijk CG, Niessen HWM, Krijnen PAJ. Myocardial infarction coincides with increased NOX2 and N^ε-(carboxymethyl) lysine expression in the cerebral microvasculature. *Open Heart*. 2021;8:e001842. DOI PubMed PMC
65. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114:1852-66. DOI PubMed
66. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634-53. DOI
67. Thygesen K, Alpert JS, Jaffe AS. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2018;40:237-69. DOI
68. Pandey AK, Duong T, Swiatkiewicz I, Daniels LB. A comparison of biomarker rise in type 1 and type 2 myocardial infarction. *Am J Med*. 2020;133:1203-8. DOI PubMed
69. McCarthy CP, Kolte D, Kennedy KF, Vaduganathan M, Wasfy JH, Januzzi JL Jr. Patient characteristics and clinical outcomes of type 1 versus type 2 myocardial infarction. *J Am Coll Cardiol*. 2021;77:848-57. DOI PubMed
70. Lambrecht S, Sarkisian L, Saaby L, et al. Different causes of death in patients with myocardial infarction type 1, type 2, and myocardial injury. *Am J Med*. 2018;131:548-54. DOI
71. Sagris M, Antonopoulos AS, Theofilis P, et al. Risk factors profile of young and older patients with myocardial infarction. *Cardiovasc Res*. 2022;118:2281-92. DOI
72. Papi M, Brunelli R, Ciasca G, et al. Estradiol protective role in atherogenesis through LDL structure modification. *J Phys D Appl Phys*. 2016;49:285402. DOI
73. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. *BMJ*. 2018;363:k4247. DOI PubMed PMC
74. Palmer J, Lloyd A, Steele L, et al. Differential risk of ST-segment elevation myocardial infarction in male and female smokers. *J Am*

- Coll Cardiol*. 2019;73:3259-66. DOI
75. Wei Y, Qi B, Xu J, et al. Age- and sex-related difference in lipid profiles of patients hospitalized with acute myocardial infarction in East China. *J Clin Lipidol*. 2014;8:562-7. DOI
 76. Zhang J, Wang H, Yang S, Wang X. Comparison of lipid profiles and inflammation in pre- and post-menopausal women with cerebral infarction and the role of atorvastatin in such populations. *Lipids Health Dis*. 2018;17:20. DOI PubMed PMC
 77. Peters SAE, Colantonio LD, Chen L, et al. Sex differences in incident and recurrent coronary events and all-cause mortality. *J Am Coll Cardiol*. 2020;76:1751-60. DOI
 78. Zhu D, Chung HF, Dobson AJ, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health*. 2019;4:e553-64. DOI PubMed PMC
 79. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American heart association. *Circulation*. 2020;142:e506-32. DOI
 80. Benjannet S, Rhainds D, Essalmani R, et al. NARC-1/PCSK9 and its natural mutants: zymogen cleavage and effects on the low density lipoprotein (LDL) receptor and LDL cholesterol. *J Biol Chem*. 2004;279:48865-75. DOI
 81. Zhang Z, Wei TF, Zhao B, et al. Sex differences associated with circulating PCSK9 in patients presenting with acute myocardial infarction. *Sci Rep*. 2019;9:3113. DOI PubMed PMC
 82. Saito K, Cui H. Emerging roles of estrogen-related receptors in the brain: potential interactions with estrogen signaling. *Int J Mol Sci*. 2018;19:1091. DOI PubMed PMC
 83. Mosconi L, Nerattini M, Matthews DC, et al. In vivo brain estrogen receptor density by neuroendocrine aging and relationships with cognition and symptomatology. *Sci Rep*. 2024;14:12680. DOI
 84. Żabińska M, Wiśniewska K, Węgrzyn G, Pierzynowska K. Exploring the physiological role of the G protein-coupled estrogen receptor (GPER) and its associations with human diseases. *Psychoneuroendocrinology*. 2024;166:107070. DOI
 85. Park CJ, Zhao Z, Glidewell-Kenney C, et al. Genetic rescue of nonclassical ER α signaling normalizes energy balance in obese Era-null mutant mice. *J Clin Invest*. 2011;121:604-12. DOI PubMed PMC
 86. Phan A, Suschkov S, Molinaro L, et al. Rapid increases in immature synapses parallel estrogen-induced hippocampal learning enhancements. *Proc Natl Acad Sci USA*. 2015;112:16018-23. DOI PubMed PMC
 87. Lymer J, Robinson A, Winters BD, Choleris E. Rapid effects of dorsal hippocampal G-protein coupled estrogen receptor on learning in female mice. *Psychoneuroendocrinology*. 2017;77:131-40. DOI PubMed
 88. Waters EM, Thompson LI, Patel P, et al. G-protein-coupled estrogen receptor 1 is anatomically positioned to modulate synaptic plasticity in the mouse hippocampus. *J Neurosci*. 2015;35:2384-97. DOI
 89. Ishii H, Otsuka M, Kanaya M, Higo S, Hattori Y, Ozawa H. Applicability of anti-human estrogen receptor β antibody PPZ0506 for the immunodetection of rodent estrogen receptor β proteins. *Int J Mol Sci*. 2019;20:6312. DOI PubMed PMC
 90. Merchenthaler I, Lane MV, Numan S, Dellovade TL. Distribution of estrogen receptor alpha and beta in the mouse central nervous system: in vivo autoradiographic and immunocytochemical analyses. *J Comp Neurol*. 2004;473:270-91. DOI PubMed
 91. Dietrich AK, Humphreys GI, Nardulli AM. Expression of estrogen receptor α in the mouse cerebral cortex. *Mol Cell Endocrinol*. 2015;406:19-26. DOI PubMed PMC
 92. Bean LA, Ianov L, Foster TC. Estrogen receptors, the hippocampus, and memory. *Neuroscientist*. 2014;20:534-45. DOI PubMed PMC
 93. Kanaya M, Higo S, Ozawa H. Neurochemical characterization of neurons expressing estrogen receptor β in the hypothalamic nuclei of rats using in situ hybridization and immunofluorescence. *Int J Mol Sci*. 2019;21:115. DOI PubMed PMC
 94. Silva JS, Montagnoli TL, Rocha BS, Tacco MLCA, Marinho SCP, Zapata-Sudo G. Estrogen receptors: therapeutic perspectives for the treatment of cardiac dysfunction after myocardial infarction. *Int J Mol Sci*. 2021;22:525. DOI PubMed PMC
 95. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biol Sex Differ*. 2017;8:33. DOI PubMed PMC
 96. Mahmoodzadeh S, Leber J, Zhang X, et al. Cardiomyocyte-specific estrogen receptor alpha increases angiogenesis, lymphangiogenesis and reduces fibrosis in the female mouse heart post-myocardial infarction. *J Cell Sci Ther*. 2014;5:153. DOI
 97. Zhai P, Eurell TE, Cooke PS, Lubahn DB, Gross DR. Myocardial ischemia-reperfusion injury in estrogen receptor-alpha knockout and wild-type mice. *Am J Physiol Heart Circ Physiol*. 2000;278:H1640-7. DOI PubMed
 98. Iorga A, Umar S, Ruffenach G, et al. Estrogen rescues heart failure through estrogen receptor Beta activation. *Biol Sex Differ*. 2018;9:48. DOI PubMed PMC
 99. Firth JM, Yang HY, Francis AJ, Islam N, MacLeod KT. The effect of estrogen on intracellular Ca²⁺ and Na⁺ regulation in heart failure. *JACC Basic Transl Sci*. 2020;5:901-12. DOI PubMed PMC
 100. Babiker FA, Joseph S, Juggi J. The protective effects of 17beta-estradiol against ischemia-reperfusion injury and its effect on pacing postconditioning protection to the heart. *J Physiol Biochem*. 2014;70:151-62. DOI
 101. WHO. Menopause; 2022. Available from: <https://www.who.int/news-room/fact-sheets/detail/menopause/> [Last accessed on 30 Jun 2025].
 102. Gannon OJ, Naik JS, Riccio D, et al. Menopause causes metabolic and cognitive impairments in a chronic cerebral hypoperfusion model of vascular contributions to cognitive impairment and dementia. *Biol Sex Differ*. 2023;14:34. DOI PubMed PMC
 103. Benedusi V, Meda C, Della Torre S, Monteleone G, Vegeto E, Maggi A. A lack of ovarian function increases neuroinflammation in aged mice. *Endocrinology*. 2012;153:2777-88. DOI PubMed PMC

104. Tantipongpiradet A, Monthakantirat O, Vipatpakpaiboon O, et al. Effects of Puerarin on the ovariectomy-induced depressive-like behavior in ICR mice and its possible mechanism of action. *Molecules*. 2019;24:4569. DOI PubMed PMC
105. Sanchez K, Wu SL, Kakkar R, Darling JS, Harper CS, Fonken LK. Ovariectomy in mice primes hippocampal microglia to exacerbate behavioral sickness responses. *Brain Behav Immun Health*. 2023;30:100638. DOI PubMed PMC
106. Gaignard P, Savouroux S, Liere P, et al. Effect of sex differences on brain mitochondrial function and its suppression by ovariectomy and in aged mice. *Endocrinology*. 2015;156:2893-904. DOI
107. Guo W, Wang X, Chen Y, Wang F, Qiu J, Lu W. Effect of menopause status on brain perfusion hemodynamics. *Stroke*. 2024;55:260-8. DOI
108. Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nat Rev Neurosci*. 2017;18:419-34. DOI PubMed PMC
109. Deer RR, Stallone JN. Effects of estrogen on cerebrovascular function: age-dependent shifts from beneficial to detrimental in small cerebral arteries of the rat. *Am J Physiol Heart Circ Physiol*. 2016;310:H1285-94. DOI PubMed PMC
110. Handley EE, Reale LA, Chuckowree JA, et al. Estrogen enhances dendrite spine function and recovers deficits in neuroplasticity in the prpTDP-43^{A315T} mouse model of amyotrophic lateral sclerosis. *Mol Neurobiol*. 2022;59:2962-76. DOI
111. Ghisletti S, Meda C, Maggi A, Vegeto E. 17beta-estradiol inhibits inflammatory gene expression by controlling NF-kappaB intracellular localization. *Mol Cell Biol*. 2005;25:2957-68. DOI PubMed PMC
112. Khan MM, Wakade C, de Sevilla L, Brann DW. Selective estrogen receptor modulators (SERMs) enhance neurogenesis and spine density following focal cerebral ischemia. *J Steroid Biochem Mol Biol*. 2015;146:38-47. DOI PubMed PMC
113. Hanson AJ, Bayer-Carter JL, Green PS, et al. Effect of apolipoprotein E genotype and diet on apolipoprotein E lipidation and amyloid peptides: randomized clinical trial. *JAMA Neurol*. 2013;70:972-80. DOI PubMed PMC
114. Thong EHE, Quek EJW, Loo JH, et al. Acute myocardial infarction and risk of cognitive impairment and dementia: a review. *Biology*. 2023;12:1154. DOI PubMed PMC
115. García PL, Rodríguez García D. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:e584. DOI PubMed
116. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol*. 2018;14:591-604. DOI PubMed PMC
117. Ungvari Z, Toth P, Tarantini S, et al. Hypertension-induced cognitive impairment: from pathophysiology to public health. *Nat Rev Nephrol*. 2021;17:639-54. DOI PubMed PMC
118. Gillies GE, Pienaar IS, Vohra S, Qamhawi Z. Sex differences in Parkinson's disease. *Front Endocrinol*. 2014;35:370-84. DOI PubMed
119. Salinero AE, Abi-Ghanem C, Venkataganesh H, et al. Treatment with brain specific estrogen prodrug ameliorates cognitive effects of surgical menopause in mice. *Horm Behav*. 2024;164:105594. DOI PubMed PMC
120. Maki PM, Henderson VW. Hormone therapy, dementia, and cognition: the Women's Health initiative 10 years on. *Climacteric*. 2012;15:256-62. DOI PubMed PMC
121. Yaffe K, Krueger K, Sarkar S, et al. Cognitive function in postmenopausal women treated with raloxifene. *N Engl J Med*. 2001;344:1207-13. DOI
122. Kulkarni J, Mu E, Li Q, et al. Bazedoxifene plus conjugated estrogen to treat menopausal depression-A pilot study. *J Pharmacol Exp Ther*. 2025;392:103527. DOI
123. Hill RA, Kouremenos K, Tull D, et al. Bazedoxifene - a promising brain active SERM that crosses the blood brain barrier and enhances spatial memory. *Psychoneuroendocrinology*. 2020;121:104830. DOI PubMed
124. Gaignard P, Fréchou M, Liere P, et al. Sex differences in brain mitochondrial metabolism: influence of endogenous steroids and stroke. *J Neuroendocrinol*. 2018;30. DOI
125. Prokai-Tatrai K, Prokai L. The impact of 17β-estradiol on the estrogen-deficient female brain: from mechanisms to therapy with hot flushes as target symptoms. *Front Endocrinol*. 2023;14:1310432. DOI PubMed PMC
126. Resnick SM, Espeland MA, Jaramillo SA, et al. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. *Neurology*. 2009;72:135-42. DOI PubMed
127. Williams CL, Barnett AM, Meck WH. Organizational effects of early gonadal secretions on sexual differentiation in spatial memory. *Behav Neurosci*. 1990;104:84-97. DOI PubMed
128. Fester L, Prange-Kiel J, Zhou L, et al. Estrogen-regulated synaptogenesis in the hippocampus: sexual dimorphism in vivo but not in vitro. *J Steroid Biochem Mol Biol*. 2012;131:24-9. DOI
129. Uddin MS, Rahman MM, Jakaria M, et al. Estrogen signaling in Alzheimer's disease: molecular insights and therapeutic targets for Alzheimer's dementia. *Mol Neurobiol*. 2020;57:2654-70. DOI
130. Guglielmotto M, Manassero G, Vasciaveo V, Venezia M, Tabaton M, Tamagno E. Estrogens inhibit amyloid-β-mediated paired helical filament-like conformation of Tau through antioxidant activity and miRNA 218 regulation in hTau mice. *J Alzheimers Dis*. 2020;77:1339-51. DOI PubMed
131. Zhang Y, Chen H, Li R, Sterling K, Song W. Amyloid β-based therapy for Alzheimer's disease: challenges, successes and future. *Signal Transduct Target Ther*. 2023;8:248. DOI
132. Ali N, Sohail R, Jaffer SR, et al. The role of estrogen therapy as a protective factor for Alzheimer's disease and dementia in postmenopausal women: a comprehensive review of the literature. *Cureus*. 2023;15:e43053. DOI PubMed PMC

133. Qin Y, An D, Xu W, et al. Estradiol replacement at the critical period protects hippocampal neural stem cells to improve cognition in APP/PS1 mice. *Front Aging Neurosci*. 2020;12:240. DOI PubMed PMC
134. Li R, He P, Cui J, Staufenbiel M, Harada N, Shen Y. Brain endogenous estrogen levels determine responses to estrogen replacement therapy via regulation of BACE1 and NEP in female Alzheimer's transgenic mice. *Mol Neurobiol*. 2013;47:857-67. DOI PubMed PMC
135. Qin P, Ma Y, Liu M, et al. Loss of estrogen efficacy against hippocampus damage in long-term OVX mice is related to the reduction of hippocampus local estrogen production and estrogen receptor degradation. *Mol Neurobiol*. 2020;57:3540-51. DOI
136. Li J, Siegel M, Yuan M, et al. Estrogen enhances neurogenesis and behavioral recovery after stroke. *J Cereb Blood Flow Metab*. 2011;31:413-25. DOI PubMed
137. Zheng JY, Liang KS, Wang XJ, Zhou XY, Sun J, Zhou SN. Chronic estradiol administration during the early stage of Alzheimer's disease pathology rescues adult hippocampal neurogenesis and ameliorates cognitive deficits in A β ₁₋₄₂ mice. *Mol Neurobiol*. 2017;54:7656-69. DOI PubMed
138. Song YJ, Li SR, Li XW, et al. The effect of estrogen replacement therapy on Alzheimer's disease and parkinson's disease in postmenopausal women: a meta-analysis. *Front Neurosci*. 2020;14:157. DOI