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REVIEW

Sex-specific mechanisms in vascular aging: exploring cellular and molecular pathways in the pathogenesis of age-related cardiovascular and cerebrovascular diseases

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Abstract Aging remains the foremost risk factor for cardiovascular and cerebrovascular diseases, surpassing traditional factors in epidemiological significance. This review elucidates the cellular and molecular mechanisms underlying vascular aging, with an emphasis on sex differences that influence disease progression and clinical outcomes in older adults. We discuss the convergence of aging processes at the macro- and microvascular levels and their contributions to the pathogenesis of vascular diseases. Critical analysis of both preclinical and clinical studies reveals significant sex-specific variations in these mechanisms, which could be pivotal in understanding the disparity in disease morbidity and mortality between sexes. The review highlights key molecular pathways, including oxidative stress, inflammation, and autophagy, and their differential roles in the vascular aging of males and females. We argue that recognizing these sex-specific differences is crucial for developing targeted therapeutic strategies aimed at preventing and managing age-related vascular pathologies. The implications for personalized medicine and potential areas for future research are also explored,

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emphasizing the need for a nuanced approach to the study and treatment of vascular aging.

Keywords Vascular aging · Cellular senescence · Menopause · Endocrine · Sex differences · Sexual dimorphism · Atherosclerosis · Vascular cognitive impairment · Ischemic heart disease

Introduction

The adage, "a man is as old as his arteries," attributed to the seventeenth-century physician Thomas Sydenham, succinctly encapsulates the pivotal role of vascular health in determining longevity and quality of life. Modern geroscience affirms this view, placing cardiovascular and cerebrovascular diseases at the forefront of morbidity and mortality in aging populations [1, 2]. While traditional risk factors such as hypertension, diabetes mellitus, obesity, and hypercholesterolemia are significant, advanced age emerges as the paramount predictor of vascular disease prevalence, underscoring the critical role of vascular aging in the pathogenesis of a wide range of cardiovascular and cerebrovascular diseases [1–3].

Vascular aging involves a multifaceted array of structural and functional alterations within both large vessels and the microcirculation, including pathological remodeling of the vascular wall, increased arterial stiffness and atherogenesis, endothelial dysfunction, pro-inflammatory phenotypic changes, barrier dysfunction, and microvascular rarefaction [1, 2]. These changes are not isolated phenomena but are driven by an intricate interplay of evolutionarily conserved molecular and cellular mechanisms of aging. Keys among these mechanisms are oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, cellular senescence, and impaired proteostasis. These aging processes not only undermine the structural and functional integrity of the vascular system but also exert widespread effects on other organ systems, influencing overall health span [1, 2]. The systemic impact of vascular aging highlights its role as both a driver and a consequence of the broader aging process, with far-reaching implications for the health and longevity of the entire organism [1, 2].

Emerging research, however, suggests that the impact and progression of vascular aging are not uniformly experienced across sexes [4–6]. Preclinical and clinical research reveals substantial sex differences in the molecular and cellular mechanisms of aging, which significantly influence the onset, progression, and therapeutic outcomes of age-related diseases in general [7], and cardiovascular and cerebrovascular disorders in particular [4–6, 8]. These distinctions, evident at the genetic,

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cellular, and systemic levels, underscore the need for a nuanced understanding of how aging impacts males and females differently, shaping disease manifestation and response to treatment in distinct ways. For instance, differences in hormone levels, gene expression, cellular stress resilience, immune function, endothelial reactivity, metabolic processing, and response to oxidative stress between males and females could explain variations in the prevalence and severity of vascular diseases [5, 6, 8, 9]. Additionally, sex-specific variations in autophagy, inflammatory response, and senescence-associated secretory phenotypes further influence how vascular aging manifests distinctly across sexe [5, 6, 8, 9]. These mechanisms collectively contribute to the differential risk and progression of cardiovascular and cerebrovascular conditions observed between males and females.

This review aims to dissect these sex differences in vascular aging, highlighting how they modulate the risk and progression of age-related vascular diseases. By integrating insights from recent preclinical and clinical studies, this overview explores how these distinctions can guide the development of targeted therapeutic interventions, paving the way for personalized medicine approaches that enhance cardiovascular and cerebrovascular health in older adults. Understanding these sex-specific pathways is not only crucial for advancing treatment but also for designing preventative strategies that accommodate the unique physiological profiles of males and females, ultimately improving health outcomes across the lifespan.

Sex differences in vascular aging

Vascular aging manifests differently between sexes, influencing the prevalence, progression, and outcomes of both age-related macrovascular and microvascular diseases [6, 8, 10, 11]. These sex differences are evident in various vascular conditions, including atherosclerotic diseases such as ischemic heart disease and acute myocardial infarction (AMI) [6, 12, 13], stroke [14–17], peripheral artery disease (PAD) [10], and aneurysms [18–22]. Sex differences are also apparent in vascular contributions to cognitive impairment and dementia (VCID) [23–28] and Alzheimer's disease (AD) [23, 29–33], as well as age-related macular degeneration (AMD) [34]. Understanding these differences is crucial for developing sex-specific prevention strategies and treatments.

Estrogen plays a pivotal role in modulating vascular health and vascular aging processes in women [8, 35]. Its protective effects include promoting a youthful endothelial phenotype by increasing nitric oxide bioavailability and reducing inflammation and oxidative stress [35–39]. Before menopause, these effects help delay the progression of atherosclerosis compared to men [35, 40, 41]. However, post-menopause, the decline in estrogen levels leads to an accelerated vascular aging process in women, often surpassing the risk levels seen in men [5, 8, 35, 39, 42–51]. Conversely, testosterone in men influences vascular tone and structure but tends to predispose them to earlier vascular stiffening and hypertension [52, 53].

Men typically develop atherosclerosis earlier than women, a disparity largely attributed to protective effects of estrogen in premenopausal women [41, 48, 50, 51]. However, the risk in women increases and may surpass that in men post-menopause, suggesting a role for sex hormones in modulating disease progression. Men have a higher incidence of AMI at a younger age compared to women [54]. However, women tend to have worse outcomes post-AMI, including higher mortality rates [54]. This discrepancy may be due to differences in the pathophysiology of AMI between sexes, with women more likely to experience microvascular dysfunction rather than large vessel obstruction [55, 56]. Stroke also exhibits sex-specific patterns, with men having a higher incidence at younger ages, but women catching up and even surpassing men in older age groups [54]. Women also tend to have poorer recovery and higher mortality rates after a stroke [54]. Differences in risk factors, such as the higher prevalence of atrial fibrillation in elderly women, contribute to these patterns [56–58]. PAD is common in both sexes but underdiagnosed in women, partly due to atypical presentation [59, 60]. Women with PAD often experience worse functional impairment and quality of life than men [61]. The reasons behind these differences are not fully understood but may involve sex-specific responses to ischemia [61]. Abdominal aortic aneurysms (AAAs) are more prevalent in men, while women with AAAs have a higher risk of rupture at smaller sizes [22, 62, 63], suggesting differences in the biology of the aneurysm wall or in the distribution of mechanical stress across it [64–66]. Differences in

body fat distribution, inflammatory responses, and plaque characteristics between sexes [67, 68] likely also influence the progression of PAD and the risk and rupture rates of aortic aneurysms.

Women are at a higher risk of developing AD [32, 33, 69] and VCID [26–28]. The link between vascular aging and neurodegenerative conditions such as AD is increasingly recognized as a critical factor in understanding sex differences in cognitive outcomes. Cerebrovascular health, particularly the integrity of the cerebral small vessels and the blood–brain barrier (BBB), plays a central role in maintaining brain homeostasis. Microvascular pathologies, including cerebral small vessel disease (CSVD), play a pivotal role in the development of VCID and AD [70–77]. Aging-related cerebrovascular changes, such as endothelial dysfunction, reduced capillary density, and impaired autoregulation of cerebral blood flow, exacerbate neuronal injury and cognitive decline. These microvascular changes can lead to a range of structural and functional abnormalities in the brain, including white matter lesions, microbleeds, and lacunar infarcts, which are closely associated with cognitive decline and dementia [78–84]. The disruption of the brain's microvascular network impairs cerebral blood flow regulation and BBB integrity, leading to chronic hypoperfusion, heightened neuroinflammation, and oxidative stress—conditions that exacerbate neuronal damage and neurodegeneration [71, 77, 85, 86]. In women, these risks may be further elevated due to life-course vascular risk factors such as hypertension and diabetes mellitus [87], which are known to predispose individuals to microvascular damage. Additionally, post-menopausal hormonal changes significantly affect vascular health, potentially increasing susceptibility to CSVD and its cognitive consequences [88–91]. Understanding the interplay between microvascular health and neurodegenerative processes is essential for developing targeted therapies that can mitigate the progression of VCID and AD, particularly in populations at increased risk due to sex-specific pathophysiological changes.

AMD is a complex eye condition that primarily affects the macula, the central part of the retina responsible for sharp, detailed vision [92–94]. AMD prevalence is slightly higher in women [34, 92, 95–97]. While the exact mechanisms underlying AMD are not fully understood, microvascular contributions play a significant role in the progression and severity of the disease [94, 98, 99]. One of the hallmarks of wet AMD (the more severe form of the disease) is the growth of abnormal blood vessels from the choroid into the macular region [99]. These vessels are often fragile and leaky, leading to hemorrhage, fluid accumulation, and rapid vision loss. The integrity of the retinal blood supply is crucial for maintaining photoreceptor health. In AMD, changes in the microvasculature, such as capillary drop-out and reduced perfusion, can lead to ischemic conditions within the retina [99]. This ischemia contributes to the degeneration of photoreceptors and the accumulation of waste products like lipofuscin and drusen, exacerbating the disease process. In AMD, inflammation around the retinal microvasculature can lead to structural changes in the blood-retina barrier, promoting further leakage and damage [99–101]. The inflammatory milieu can also accelerate the deposition of extracellular matrix components, contributing to drusen formation, a key feature in the early stages of AMD [99].

Age-related endothelial dysfunction: role of estrogen

Estrogen plays a crucial role in maintaining endothelial function, which is central to vascular health [39, 40]. One of its primary protective mechanisms involves the upregulation of endothelial nitric oxide synthase (eNOS), promoting the production of NO [37, 102, 103]. NO is a critical mediator of vascular tone, anti-inflammatory signaling, and vascular homeostasis. By increasing NO bioavailability, estrogen helps preserve endothelial function, delay arterial stiffening, and reduce oxidative stress and inflammation [104]. Before menopause, the presence of circulating estrogen confers significant vascular protection to women, delaying the onset of endothelial dysfunction and related cardiovascular diseases compared to men of the same age [4, 5, 8, 39, 105]. However, the decline in estrogen levels following menopause marks a pivotal shift in vascular aging for women [105]. Reduced estrogen levels lead to decreased NO production, increased oxidative stress, and an elevated inflammatory burden [5, 8, 105]. This decline accelerates endothelial dysfunction, contributing to a higher risk of developing age-related vascular diseases, including atherosclerosis, hypertension, and VCID [8]. Post-menopausal endothelial dysfunction is also linked to microvascular rarefaction and

impaired angiogenesis [106], exacerbating the risk of ischemic diseases and neurovascular complications [5, 8]. Estrogen's influence extends beyond direct vascular effects. It also modulates epigenetic and transcriptional pathways that regulate endothelial function [104]. For example, estrogen has been shown to influence DNA methylation patterns of vascular genes [107], histone acetylation [104], and the expression of non-coding RNAs such as miRNAs [106, 108] that regulate angiogenesis and inflammation. These molecular effects collectively shape the trajectory of endothelial aging in women. Understanding the role of estrogen in endothelial function underscores the need for targeted therapeutic strategies, such as hormone replacement therapy (HRT), to mitigate post-menopausal vascular aging [4, 5, 8, 35]. However, the risks and benefits of HRT remain an area of active research, necessitating individualized approaches based on cardiovascular risk profiles and other health considerations. Future studies should focus on identifying estrogen-mimetic therapies that preserve endothelial health without the adverse effects associated with traditional HRT, thereby providing a pathway to improve vascular aging outcomes in post-menopausal women.

Genetic predispositions and epigenetic modifications in vascular aging

Sex differences in vascular aging are influenced not only by hormonal factors but also by genetic predispositions and epigenetic modifications [6, 7,]. Genetic variations in genes related to vascular function, such as those encoding antioxidant enzymes and regulators of endothelial nitric oxide production, have been shown to differ between men and women. These genetic differences can predispose individuals to sex-specific patterns of vascular aging and associated disease risks [6}. Epigenetic modifications play a crucial role in mediating sex-specific differences in vascular function and aging [173]. This regulatory effect diminishes post-menopause, leading to an epigenetic shift that contributes to accelerated vascular aging in women. These genetic and epigenetic factors collectively contribute to the observed differences in clinical outcomes and disease progression between sexes. Understanding these mechanisms provides critical insights into the interplay between genetics, epigenetics, and sex hormones in vascular aging and highlights potential targets for personalized therapeutic interventions.

Mechanisms of vascular aging and sex differences

Vascular aging is governed by a complex interplay of evolutionarily conserved molecular and cellular mechanisms [1, 2] that exhibit significant sex differences [6, 8]. These differences influence how aging-related pathologies develop and respond to treatment in males and females [6, 8]. Vascular aging contributes to the pathogenesis and progression of a wide range of cardiovascular and cerebrovascular diseases [1, 2]. This process manifests across a continuum, where shared mechanisms promote age-related pathologies in both large vessels, such as atherosclerotic vascular diseases, and microvascular pathologies [1, 2, 86]. These microvascular issues range from contributions to cognitive decline and AD, to AMD, and microvascular pathologies in ischemic heart disease and intermittent claudication. This continuum underscores the interconnected nature of vascular aging, affecting various organ systems through similar pathological mechanisms [86]. Building on previous insights [1, 2, 71, 109–113], this section explores the critical mechanisms involved in vascular aging, highlighting how they differ between sexes.

Oxidative and nitrative stress

Oxidative stress, implicated in endothelial dysfunction associated with both macrovascular and microvascular aging, primarily arises from increased reactive oxygen species (ROS) production by NAD(P)H oxidases and mitochondria [1, 2, 109, 110]. This process results in endothelial dysfunction and arterial stiffening by inactivating nitric oxide (NO), a critical regulator of vascular tone and health [1, 2, 109]. Peroxynitrite, a potent oxidant formed from the interaction of NO with superoxide, exacerbates vascular aging through cytotoxic effects and the activation of inflammatory pathways, further contributing to large artery stiffening and the risk of microvascular pathologies such as cerebral microhemorrhages [114]. Additionally, ROS contributes to vascular aging by causing DNA damage, which promotes cellular senescence, and by activating NF-kB, a key factor in

the cascade leading to age-related sterile low-grade inflammation [1, 2, 115–118].

Cellular resilience to oxidative stress, critical for maintaining vascular health, is significantly compromised in aging by impaired function of nuclear factor erythroid 2-related factor 2 (Nrf2), a major transcriptional regulator of antioxidant response [117, 119–125]. Nrf2 dysfunction contributes to the pathophysiology of vascular aging by diminishing the cellular ability to counteract the damaging effects of ROS [117, 119–125]. Under normal conditions, Nrf2 activates the expression of various antioxidant enzymes that help detoxify ROS and protect cells from oxidative damage. However, with aging and in the presence of chronic oxidative stress, Nrf2 signaling is often disrupted, which not only reduces the cellular defenses against oxidative stress but also exacerbates endothelial dysfunction [117, 121, 125]. This impaired oxidative stress resilience due to Nrf2 dysfunction is further linked to several other aging-related vascular issues [117]. The decrease in protective antioxidant responses leads to enhanced oxidative damage to cellular components such as lipids, proteins, and DNA and thereby promotes cellular senescence. The resulting damage accelerates the aging process in vascular cells, promotes the development of atherosclerotic lesions, and increases the susceptibility of the vasculature to inflammatory injuries [117]. Therefore, restoring Nrf2 function and enhancing the cellular antioxidant capacity are promising therapeutic targets for mitigating vascular aging and its associated pathologies [124, 126, 127].

Sex differences in oxidative stress

Oxidative and nitrative stress play crucial roles in vascular aging, with significant differences observed between males and females in how these processes influence vascular health [128–131]. These differences are largely mediated by biological variations in hormone levels, antioxidant capacity, and cellular responses to oxidative damage.

Estrogen exerts a protective effect against oxidative stress [39, 132, 133]. It enhances the expression and activity of various antioxidant enzymes [132, 133] and can modulate the expression of NAD(P)H oxidases [134], which are primary sources of ROS in vascular cells. Estrogen's ability to upregulate eNOS also promotes higher nitric oxide availability [37, 103]. As a result, premenopausal women generally experience lower levels of oxidative and nitrative stress and better endothelial function compared to men of the same age, potentially delaying the onset of vascular aging [39, 135]. However, this protective effect diminishes with menopause, leading to an increase in oxidative stress that accelerates vascular aging in post-menopausal women [105, 136–139].

Men and women may also exhibit genetic differences that affect their cellular responses to oxidative stress. These can include variations in genes related to antioxidant defenses such as superoxide dismutase (SOD), catalase, and glutathione peroxidase [131]. Additionally, males may have a higher baseline oxidative status, partially due to the androgen testosterone, which has been linked to higher production of ROS [140]. This intrinsic difference could explain why men generally develop oxidative stress–related vascular diseases at a younger age compared to women.

Understanding these sex-specific pathways in oxidative and nitrative stress can guide more targeted interventions. Antioxidant therapies may have differing efficacies in men and women, particularly considering hormonal influences and genetic predispositions [141]. For instance, antioxidant supplementation that benefits post-menopausal women might not be as effective in men or premenopausal women, underscoring the need for personalized treatment strategies based on sex-specific research [141].

Mitochondrial dysfunction

Mitochondria are central to aging, with declines in respiratory chain efficiency leading to increased ROS production and decreased ATP generation [110, 142, 143]. Vascular aging is associated with impaired mitochondrial biogenesis and enhanced mitochondrial ROS output, which promotes oxidative stress and inflammation via mechanisms such as NF-κB activation [110, 144–151]. These changes negatively impact cellular energy metabolism and endothelial NO production, and are key drivers of vascular aging.

Sex differences in mitochondrial dysfunction

Mitochondrial dysfunction is a critical factor in vascular aging, with distinct manifestations observed between males and females [129, 152–156]. These differences are shaped by variations in mitochondrial

biogenesis, dynamics, and susceptibility to oxidative damage, which are influenced by genetic and hormonal factors. Estrogens play a significant role in modulating mitochondrial function [157–161]. They are known to enhance mitochondrial efficiency and promote the expression of genes involved in mitochondrial biogenesis through estrogen receptor–mediated mechanisms [162–167]. This results in better maintenance of mitochondrial DNA integrity and more efficient electron transport chain function in females, particularly before menopause [167]. Although one might anticipate premenopausal women to have lower levels of mitochondrial-derived reactive oxygen species (ROS) and a better cellular energy balance compared to men, the current evidence supporting this assumption is not robust. Further research is needed to clarify these potential sex-related differences in mitochondrial function and their implications for health [155]. Sex chromosomes themselves may influence mitochondrial function. The presence of two X chromosomes in females includes genes that impact mitochondrial activity and could provide a genetic buffer against mitochondrial decay that is not present in males [168, 169]. Additionally, epigenetic modifications regulated by sex hormones can alter the expression of mitochondrial and nuclear genes related to oxidative phosphorylation, affecting mitochondrial function differently in males and females [170–173]. The sex-specific differences in mitochondrial function may impact the development and progression of various vascular diseases [170]. Recognizing these sex differences in mitochondrial dysfunction is important for designing effective interventions. Therapies aimed at enhancing mitochondrial function, such as coenzyme Q10, resveratrol, and other mitochondria-targeted antioxidants, might be more effective if tailored to the specific mitochondrial health profiles of men and women. Additionally, hormone replacement therapy in post-menopausal women could be considered not only for its traditional benefits but also for its potential to maintain mitochondrial health [174].

Cellular senescence

Cellular senescence is a hallmark of aging that plays a critical role in the progression of various age-related diseases [117, 175–183]. Cells of the aging cardiovascular system also often enter a state of senescence, characterized by irreversible cell cycle arrest and adoption of a pro-inflammatory senescence-associated secretory phenotype (SASP) [1, 116, 117, 177, 184–189]. This state is particularly detrimental in vascular contexts, where senescent endothelial cells contribute significantly to endothelial dysfunction, impaired angiogenesis, and compromise the structural integrity of the microcirculatory network [187, 188, 190]. The removal of these senescent cells through experimental senolytic interventions has been shown to mitigate vascular aging effects and improve endothelial function, rescue blood–brain barrier, and prevent the genesis of cerebral microhemorrhages in preclinical models [188, 190–192].

Sex differences in cellular senescence

Estrogen is known to have a protective effect against the onset and progression of cellular senescence [104, 193, 194]. It enhances DNA repair mechanisms and modulates inflammatory responses, thereby delaying the senescence onset in vascular endothelial cells [195–199]. Estrogen also suppresses the activity of pathways commonly associated with senescence [200]. These preclinical studies suggest that as women approach menopause and experience declines in estrogen levels, there may be an acceleration in the rate of cellular senescence, which contributes to diminishing the observed differences in vascular aging between sexes noted in younger demographics [104]. The SASP includes the release of pro-inflammatory cytokines, chemokines, and proteases that can disrupt local tissue environments and promote paracrine senescence [184, 201–203]. Men and women may exhibit different SASP profiles due to hormonal influences [204, 205]. Additionally, sex differences in the production of certain inflammatory mediators could potentially exacerbate the local and systemic effects of SASP. Senescent cells likely contribute to a variety of vascular aging outcomes, including endothelial dysfunction [184, 186, 191, 201, 206, 207], barrier dysfunction [115, 207–210], atherogenesis [138, 181, 211–215], and impaired angiogenesis and capillarization [115, 207, 216–218], which are fundamental to the development of AMI, stroke, VCID, and other cardiovascular diseases. The acceleration of senescence in post-menopausal women [219] might lead to a more rapid decline in vascular health compared to men of the same age. Understanding sex differences in cellular senescence is critical

for designing effective senolytic therapies—treatments that selectively remove senescent cells. Current research in senolytic agents has shown promise in preclinical models, including the potential to restore endothelial function [184, 186, 190, 201, 207, 220], rescue the integrity of the blood–brain barrier [115, 207], and prevent cerebral microhemorrhages [188]. However, the efficacy and safety of these interventions may vary between sexes, necessitating sex-specific adjustments in therapeutic approaches.

Heightened state of inflammation

Chronic low-grade sterile inflammation is a hallmark of vascular aging and plays a pivotal role in the progression of various age-related vascular diseases [1, 2, 71, 86, 149, 209, 221]. This heightened state of inflammation is primarily driven by increased ROS, cellular senescence, and the activation of key inflammatory pathways such as NF-κB [113, 122, 216, 222–224]. These factors lead to endothelial activation and increased expression of pro-inflammatory cytokines, creating a vascular environment that is conducive to atherogenesis and other pathological changes. The process of atherogenesis is significantly influenced by inflammation [225–230]. Inflammatory cytokines along with chemokines and adhesion molecules, facilitate the recruitment and adhesion of monocytes to the endothelium. These monocytes then migrate into the intima, differentiate into macrophages, and ingest oxidized LDL, forming foam cells—a key event in the early stages of atherosclerotic plaque formation. Chronic inflammation also contributes to the progression and instability of these plaques [231, 232]. Cytokines and growth factors released in the inflamed vascular environment promote the proliferation of vascular smooth muscle cells, which migrate into the intima, contributing to plaque growth and the fibrous cap formation. Inflammation also impairs endothelial function and disrupts the barrier function of the endothelium, increasing its permeability. Inflammation also affects coagulation pathways, increasing the risk of thrombosis, and contributes to structural changes in the vasculature, which lead to increased arterial stiffness. This stiffening of arteries elevates systolic blood pressure and decreases diastolic pressure, which can impair coronary artery perfusion and contribute to myocardial ischemia. Additionally, the increased arterial stiffness is likely to play a significant role in the genesis of cerebrovascular injury and the pathogenesis of VCID [71, 84].

Sex differences in vascular inflammation

Notable sex differences in chronic low-grade sterile inflammation exist, significantly influencing its impact on vascular health [4, 9, 51, 205, 233]. These differences are crucial for understanding the disparities in the prevalence and progression of vascular diseases between males and females [6, 8, 9, 16, 20, 51, 233–235]. Estrogens have anti-inflammatory properties that play a significant role in modulating immune responses in women. These hormones generally suppress the activation of NF-κB and other pro-inflammatory pathways, reducing the production of inflammatory cytokines, chemokines, and adhesion molecules [6, 8, 51]. This mechanism helps premenopausal women maintain a lower inflammatory state within the vascular system, providing a protective buffer against atherogenesis and related vascular pathologies [9, 48, 51]. After menopause, the decline in estrogen levels leads to an increase in inflammatory activity, which can accelerate the progression of atherosclerosis and increase susceptibility to vascular diseases such as stroke and myocardial infarction [51]. Understanding these sex-specific inflammatory responses is vital for developing targeted interventions. Anti-inflammatory treatments may require customization to be effective and safe across different sex and age groups.

Autophagy impairment

Autophagy impairment is a significant factor in vascular aging, affecting the health and functionality of vascular cells [1, 2]. Autophagy is a critical cellular process for recycling damaged or dysfunctional cellular components, helping to maintain cell integrity and function [236–239]. As individuals age, the efficiency of the autophagy process diminishes, contributing to the accumulation of cellular debris and dysfunctional organelles. This decline has profound implications for vascular health, particularly in the endothelium and vascular smooth muscle cells.

In vascular endothelial and smooth muscle cells, autophagy regulates several key functions that impact overall vascular health [236, 239–241]. These include

the removal of oxidized and glycated proteins, which accumulate as a result of metabolic and oxidative stress, and the turnover of dysfunctional mitochondria (mitophagy), which is crucial to preventing the release of pro-inflammatory mitochondrial DNA and other DAMPs (damage-associated molecular patterns) into the cytoplasm [236, 239]. By maintaining the quality of mitochondria, autophagy directly influences the production of ROS and the overall oxidative stress burden within vascular cells [237, 242]. Impaired autophagy leads to the accumulation of oxidized proteins and damaged organelles, particularly mitochondria [236, 239]. This accumulation exacerbates oxidative stress within vascular cells, contributing to endothelial dysfunction and atherosclerotic changes. The build-up of cellular debris can activate innate immune responses, leading to chronic inflammation in the vascular wall [236, 239]. This inflammation can accelerate the progression of vascular diseases, including atherosclerosis and hypertension [236, 239–241]. The inability to clear dysfunctional components can accelerate the onset of cellular senescence in vascular cells. Enhancing autophagy represents a promising therapeutic strategy for mitigating the impacts of vascular aging [236, 237, 239, 242]. Interventions such as calorie restriction and other anti-aging dietary interventions, exercise, and pharmacological agents like rapamycin [243], which stimulates autophagy via inhibition of the mTOR pathway, have shown potential in restoring autophagic function and improving vascular health [239].

Sex differences in autophagy

Autophagy exhibits notable sex differences, particularly influenced by hormonal regulation [244–248]. Estrogen has been shown to enhance autophagic activity. However, post-menopause, as estrogen levels drastically decrease, there is a corresponding and significant decline in autophagic efficiency [161, 249]. Beyond hormonal effects, genetic and cellular differences between sexes also impact autophagy [250]. Research has identified sex-specific variations in the expression of genes integral to the autophagy pathway [246, 251]. These differences suggest that male and female sex hormones might regulate these genes in divergent ways, potentially influencing how cells from each sex initiate and process autophagic activity. Furthermore, the cellular response to metabolic and oxidative stress, which are critical triggers for autophagy, can differ markedly between males and females. Such differences may affect not only the baseline levels of autophagy but also the efficiency and outcomes of these processes under stress conditions.

Impaired proteostasis

Impaired proteostasis, characterized by disruptions in the balance and function of proteins within cells, is a critical factor in vascular aging [1, 2]. Proteostasis encompasses all aspects of protein synthesis, folding, trafficking, and degradation, ensuring that proteins maintain their correct structure and functional states [252]. As the vascular system ages, the mechanisms that support proteostasis become less effective, leading to the accumulation of misfolded proteins and the formation of protein aggregates [252]. This impairment can significantly affect the health and function of vascular cells, contributing to a variety of age-related vascular diseases [253].

With age, the efficiency of protein synthesis machinery declines, and the cellular environment becomes less conducive to correct protein folding [252]. This can be exacerbated by oxidative stress and inflammation, common in aging, which further disrupts protein structure and function [252]. Chaperone proteins, which assist in the folding and refolding of misfolded proteins, show reduced expression and functionality in aging vascular cells. Similarly, the ubiquitin–proteasome system, responsible for degrading unwanted proteins, becomes less efficient. This reduction in quality control contributes to the vascular pathologies associated with aging. As previously discussed, autophagy plays a significant role in removing damaged and dysfunctional proteins and organelles. A decline in autophagic activity with age leads to an accumulation of defective proteins and cellular components, further impairing vascular cell function and contributing to disease processes such as atherosclerosis.

Sex differences in proteostasis

Estrogens have been shown to influence several aspects of proteostasis, including enhancing the expression of molecular chaperones and components of the protein degradation machinery [253–256].

This hormonal support is vital in maintaining protein homeostasis, facilitating the proper folding and disposal of misfolded proteins, and preventing the accumulation of harmful protein aggregates that can lead to vascular cell damage. The protective effects of estrogens are particularly prominent in younger women but see a marked reduction as estrogen levels decline with age [257]. This reduction correlates with an increased proteostatic stress in post-menopausal women, potentially accelerating the process of vascular aging by allowing the build-up of damaged and dysfunctional proteins. Moreover, inherent sex differences exist in the baseline expression and activity of critical proteostatic components [256, 258, 259], including chaperones, elements of the ubiquitin–proteasome system, and autophagy-related proteins. These differences can lead to divergent responses to the challenges of maintaining protein homeostasis as both men and women age.

Epigenetic changes

Epigenetic modifications, which include DNA methylation, histone modifications, and the expression of non-coding RNAs, are crucial in regulating gene expression and play a pivotal role in the aging process, including the aging of the vascular system [1, 2, 177, 260, 261]. Changes in these epigenetic regulatory mechanisms can lead to altered cellular functions and are implicated in the development and progression of age-related vascular pathologies [1, 2]. Understanding and manipulating the epigenetic landscape in vascular cells provides a powerful approach to potentially reverse or mitigate the effects of aging on the vascular system, improving overall cardiovascular health and longevity [260, 262].

Methylation of DNA at cytosine bases adjacent to guanine (CpG sites) is a common epigenetic modification that generally represses gene expression [263–266]. In vascular aging, DNA methylation patterns change significantly [267]. These changes can lead to the repression of protective genes or the activation of harmful genes involved in processes such as inflammation, cell adhesion, and smooth muscle cell proliferation.

Histones can undergo various modifications, such as acetylation, methylation, and phosphorylation [261, 268, 269]. These modifications can influence chromatin structure and gene expression. In the context of vascular aging, changes in histone acetylation and methylation patterns can significantly affect genes involved in inflammatory pathways and oxidative stress responses [261, 267]. Importantly, pharmacological activation of histone deacetylases, such as SIRT-1, which leads to decreased histone acetylation levels, has been associated with downregulated expression of pro-inflammatory genes and improved mitochondrial function in endothelial cells [222, 270–274].

Non-coding RNAs, including miRNAs and long non-coding RNAs (lncRNAs), also play roles in regulating gene expression through epigenetic mechanisms. MiRNAs can degrade target mRNAs or inhibit their translation, affecting many aspects of vascular function, including cell proliferation, apoptosis, and capillary formation. Aging is associated with changes in the expression of specific miRNAs [122, 260, 275–277], which have been linked to impaired angiogenesis, atherosclerosis, and hypertension. LncRNAs are involved in the regulation of chromatin dynamics and transcription, influencing vascular aging by modifying the cellular environment to favor aging processes [278–281].

Sex differences in epigenetic regulation

Epigenetic modifications play a critical role in vascular aging, with distinct patterns observed between males and females [282–284]. In females, estrogens are known to influence the methylation of genes that are crucial for vascular protection [107, 285, 286]. This includes genes involved in anti-inflammatory responses and maintaining endothelial cell function. Sex hormones, including estrogen, are likely responsible for the multifaceted sex differences in DNA methylation [287–293]. As estrogen levels decline with menopause, changes in methylation patterns [294–297] can lead to the activation of genes that promote inflammation and vascular dysfunction, accelerating vascular aging in women. Histone modifications also show sex-specific variations [298, 299] that may affect vascular aging. For example, histone acetylation, which is generally associated with increased gene expression, can be differentially regulated by sex hormones. These modifications can affect the expression of genes involved in vascular smooth muscle cell proliferation, endothelial function, and inflammation, thereby modulating the progression of vascular aging

in a sex-dependent manner. The roles of miRNAs and lncRNAs in regulation of cellular aging processes also differ between sexes [300–302]. These small regulatory RNA molecules are crucial in fine-tuning the expression of genes associated with vascular aging, such as those regulating endothelial function, angiogenic processes, oxidative stress responses, and inflammation. Variations in the expression and activity of these miRNAs and lncRNAs between males and females can lead to differential susceptibility to vascular diseases as aging progresses. Understanding these sex-specific epigenetic modifications not only sheds light on the complex dynamics of vascular aging but also highlights potential therapeutic targets. By addressing these epigenetic factors, particularly in the context of the changes induced by menopause, targeted interventions can be developed to mitigate the heightened risk of vascular aging in women, aligning with precision medicine approaches.

Energy sensing pathways

Energy sensing pathways play a critical role in modulating cellular responses to environmental and metabolic cues and are intimately involved in the aging processes of the vascular system [1, 2]. Key pathways include those regulated by the mechanistic target of rapamycin (mTOR), adenosine monophosphate–activated protein kinase (AMPK), and sirtuins [1, 2, 238]. These pathways not only influence cellular metabolism and energy balance but also affect endothelial function and the structural integrity of the vascular system.

The mTOR pathway is a central regulator of cell growth and metabolism, responding to nutrients, growth factors, and cellular energy levels [303–306]. In vascular cells, mTOR activity influences endothelial cell proliferation, angiogenesis, and response to stress [238, 306–309]. However, overactivation of mTOR has been linked to accelerated aging, including increased endothelial cell senescence, enhanced inflammatory responses, and atherosclerosis [310, 311]. Inhibiting mTOR with compounds like rapamycin has been shown to extend lifespan in various organisms [312–316] and to ameliorate age-related vascular dysfunction [310, 311] by reducing oxidative stress, inflammation, and enhancing autophagy.

AMPK acts as a cellular energy sensor, activated under conditions of low energy (high AMP/ATP ratio) to restore energy balance by promoting catabolic processes and inhibiting anabolic ones [238, 317–320]. In the vascular system, AMPK activation improves endothelial function by enhancing the bioavailability of nitric oxide, reducing oxidative stress, and inhibiting inflammatory responses [238, 321, 322]. It also promotes vascular smooth muscle cell relaxation, thereby reducing arterial stiffness and hypertension. Drugs like metformin, which activate AMPK, have been used clinically to improve metabolic health and have shown promise in reducing age-related vascular diseases and extending lifespan [239, 323, 324].

Sirtuins are a family of NAD + -dependent deacetylases that play a major role in cellular stress resistance, metabolism, and aging [325, 326]. In vascular aging, sirtuins, particularly SIRT1, are critical for maintaining endothelial homeostasis [104, 273, 325, 327–331]. They regulate endothelial nitric oxide synthase (eNOS), protect cells from oxidative stress, and inhibit pro-inflammatory pathways [270, 272, 273, 328–334]. Sirtuins also influence the function of vascular smooth muscle cells and the extracellular matrix, affecting vascular elasticity and integrity [327, 335–342]. Enhancing sirtuin activity, through diet (such as calorie restriction), exercise, or pharmacological agents like resveratrol, has been shown to improve vascular function and reduce age-related arterial stiffening [124, 126, 127, 149, 223, 270, 273, 331, 332, 343–349].

Modulating these energy sensing pathways offers potential therapeutic strategies for combating vascular aging and its associated diseases. By targeting mTOR, AMPK, and sirtuins, it is possible to enhance endothelial function, reduce vascular inflammation and stiffness, and ultimately improve cardiovascular health in aging populations. Developing drugs that specifically and effectively modulate these pathways could provide a means to mitigate the effects of aging on the vascular system, potentially extending vascular health span and overall longevity.

Sex differences in energy sensing pathways

Energy sensing pathways may play differential roles in vascular aging across sexes due to intrinsic hormonal and metabolic differences [303, 350]. The mTOR pathway is influenced by sex due to hormonal interactions [350, 351]. Testosterone in males and estrogens

in females can modulate mTOR activity differently [303, 350, 352–354]. For example, estrogen is known to inhibit mTOR signaling, which may help delay the onset of mTOR-associated vascular aging phenomena. Additionally, lifespan extension by the mTOR inhibitor rapamycin has been observed to vary somewhat between males and females [312, 355]. Studies suggest that while both sexes benefit from rapamycin treatment, the extent and nature of these benefits can differ, potentially due to variations in baseline mTOR activity influenced by sex-specific hormonal environments [303, 350]. AMPK also exhibits sex-dependent activity variations, potentially due to differences in body composition and hormonal regulation [321, 356, 357]. Females typically have higher baseline levels of AMPK activity, possibly due to estrogen's effect on enhancing AMPK activation. This could confer a protective effect against the development of metabolic syndromes and their vascular consequences.

NAD^+ deficiency in vascular aging

NAD^+ is a vital coenzyme essential for redox reactions, playing a pivotal role in metabolizing nutrients to release energy within cells [358–360]. Beyond its critical role in metabolic processes, NAD^+ also serves as a substrate for several enzymes that are important in the regulation of cellular aging and stress responses, including sirtuins [361–363] and poly(ADP-ribose) polymerases (PARPs) [364]. As individuals age, NAD^+ levels in the body steadily decline, contributing significantly to the aging process, particularly in the vascular system [359, 360, 365].

The mechanisms of age-related NAD^+ decline include increased consumption, reduced biosynthesis, and inefficient recycling [360, 366–371]. Aging is associated with increased oxidative-notrative stress–mediated DNA damage, which activates PARPs [372–378]. PARPs use NAD^+ to repair damaged DNA, thus depleting cellular NAD^+ reserves [364, 372–378]. The rate of NAD^+ biosynthesis also decreases with age due to reduced expression of enzymes involved in the NAD^+ biosynthesis pathway, such as nicotinamide phosphoribosyltransferase (NAMPT) [360]. Additionally, NAD^+ is recycled in cells through the salvage pathway, which also declines with age, further contributing to reduced overall levels of NAD^+ [360, 371].

NAD^+ is essential for the function of sirtuins, particularly SIRT1, which plays a key role in maintaining endothelial health by deacetylating and activating eNOS, regulating mitochondrial function and oxidative stress resilience pathways [360, 371, 379, 380]. Reduced NAD + levels lead to diminished SIRT1 activity [371, 381, 382], impaired NO production, and endothelial dysfunction [360, 380], a precursor to VCID, atherosclerosis, and hypertension. The NAD + /sirtuin axis also regulate cellular antioxidant defenses [360]. With lower NAD^+ availability, these defenses weaken, increasing oxidative stress and vascular inflammation, which are critical drivers of vascular aging [360]. Caloric restriction and intermittent fasting have been shown to increase NAD^+ levels and activate sirtuins, enhancing vascular function and reducing oxidative stress [122, 331, 360, 383, 384]. Supplementing with NAD^+ precursors such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) has been shown to effectively restore cellular NAD^+ levels [385–387]. Inhibition of PARP-1 also increases cellular NAD^+ levels in aging [364, 373, 376–378]. In preclinical studies, supplementations with NAD^+ precursors and lifestyle interventions and pharmacological treatments [388–392] that increase NAD^+ levels have demonstrated potential in reversing age-related phenotypic and functional changes [388, 389], including enhancing endothelial function, diminishing oxidative stress, and promoting transcriptional rejuvenation in endothelial cells [147, 260, 271, 272, 364, 380].

Sex differences in NAD^+ metabolism

The decline in NAD^+ levels with age and its impact on aging processes exhibit significant sex differences [393–395]. Estrogen has been shown to enhance the expression of enzymes involved in the NAD^+ biosynthesis pathway, such as NAMPT [396, 397], and can improve the efficiency of NAD^+ recycling mechanisms. This hormonal support helps maintain higher NAD^+ levels in premenopausal women, providing them with a protective buffer against early vascular aging [393, 395]. As women enter menopause and estrogen levels decline, this metabolic advantage decreases, leading to a sharper drop in NAD^+ levels and accelerated vascular aging compared to men [393, 395]. Understanding these sex differences is key for optimizing NAD^+-boosting therapies, such as

supplementation with NR or NMN. These interventions can potentially restore NAD^+ levels and sirtuin activity more effectively if tailored to the specific metabolic needs and hormonal profiles of men and women. For example, post-menopausal women might benefit significantly from NAD^+ supplementation combined with strategies to modulate estrogen levels, thereby synergistically enhancing endothelial function and vascular health.

Systemic factors in vascular aging: insights from heterochronic parabiosis

Aging involves significant alterations in systemic factors that regulate vascular function, including various hormones, cytokines, and metabolites derived from different organs [1, 2, 398–404]. Vascular aging is notably influenced by circulating factors that can either accelerate aging (pro-geronic) or counteract it (anti-geronic) [399, 403, 404]. These factors are crucial in modulating cellular metabolism, inflammation, and the structural properties of blood vessels.

Heterochronic parabiosis is a research technique where two animals of different ages are surgically joined, creating a shared circulatory system [399, 403, 404]. This method has provided profound insights into the systemic regulation of aging. Studies using this approach have shown that older animals exhibit signs of rejuvenation when exposed to the blood of younger animals [403, 404]. Conversely, younger animals show signs of accelerated aging when their circulatory systems are combined with those of older animals [399]. These effects are thought to be mediated by various blood-borne factors that differ in concentration between young and old blood. Key findings from heterochronic parabiosis suggest that young blood contains factors that can rejuvenate aged tissue and improve vascular function, potentially reversing aspects of vascular aging such as endothelial dysfunction, oxidative stress, impaired barrier function, impaired angiogenesis, and dysregulation of the vascular mitochondrial transcriptome [398, 399, 403–406]. These factors include, but are not limited to, proteins and endocrine factors involved in enhancing blood flow, reducing inflammation, maintaining mitochondrial health, and promoting cellular repair and regeneration [398, 399, 403–406]. Circulating pro-geronic and anti-geronic factors, which modulate cellular aging processes throughout the body, are derived from the brain, endocrine system [400, 407–413], immune system, adipose tissue [179, 414], and other organs (including the gastrointestinal tract and the symbiotic microbiota). Sex differences in the function and secretory profile of these organs can significantly impact vascular aging, contributing to the observed differences in vascular aging phenotypes between males and females. For example, variations in the production of various endocrine and immune factors, and adipokines as well as microbiota-derived factors between men and women can influence the rate and nature of vascular aging in a sex-specific manner. Understanding these differences is crucial for developing targeted interventions aimed at mitigating the impact of aging on vascular health in both sexes.

Sex differences in endocrine regulation of aging

The endocrine system plays a crucial role in the regulation of aging and lifespan, with significant sex differences that influence how hormones such as estrogen and insulin-like growth factor 1 (IGF-1) impact age-related physiological changes [398, 415–419].

Estrogen is well-known for its role in modulating lifespan and the aging process, particularly evident in rodent studies [416–421]. In female mice, estrogen has been shown to enhance lifespan and delay the onset of age-related pathologies. This hormone exerts protective effects against oxidative stress, helps maintain mitochondrial function, and influences gene expression related to longevity. Estrogen's effects are partially mediated through its interaction with estrogen receptors, which can activate pathways that promote cellular health and prevent age-related decline. The decline in estrogen levels during menopause in humans correlates with an acceleration of aging symptoms and an increase in the risk of diseases such as osteoporosis and cardiovascular disorders, highlighting its critical role in aging trajectories.

IGF-1 is another key hormone implicated in the regulation of aging and lifespan [398]. It affects various age-related conditions including cardiovascular diseases, osteoporosis, and neurodegenerative disorders [398, 401, 422, 423]. IGF-1 levels naturally decrease with age, but the patterns of this decline and its physiological impacts vary significantly between the sexes [424, 425]. Research, including findings from the Mayo Clinic Study of Aging, indicates that men experience greater decreases in total IGF-1 levels

compared to women [424]. This differential trajectory can be attributed to factors such as baseline hormone levels, body mass index, comorbidities like hypertension and cardiovascular diseases, and lifestyle factors such as physical activity levels [424]. The variations in IGF-1 levels between sexes are also influenced by the use of hormone replacement therapy (HRT) in women [424]. HRT has been shown to modulate the natural decline of IGF-1, potentially mitigating some of the negative effects associated with lower hormone levels post-menopause. This suggests that exogenous hormones could play a beneficial role in managing age-related changes by supporting more stable IGF-1 levels. Recent findings have further highlighted the complex role of IGF-1 in aging, particularly its sex-specific effects on lifespan. Genetic IGF-1 deficiency has been shown to exert differing impacts on longevity in humans, with these effects varying significantly between males and females [426]. Preclinical studies have reinforced this observation, demonstrating that the influences of IGF-1 on lifespan regulation and aging processes are distinctly sex-dependent [422, 423].

In conclusion, the endocrine regulation of aging is profoundly influenced by sex, with estrogen and IGF-1 playing pivotal roles in determining aging trajectories and lifespan. Understanding these hormonal effects not only helps explain the differences in aging patterns between men and women but also offers potential avenues for therapeutic interventions. By targeting these hormonal pathways, possibly through approaches like HRT for post-menopausal women or interventions to stabilize IGF-1 levels, it may be possible to ameliorate age-related declines and improve the quality of life in older adults. Future research should continue to explore these sex differences and their implications for clinical strategies aimed at extending cardiovascular health span and managing age-associated cardiovascular and cerebrovascular diseases.

Impact of sex on therapeutic interventions

Sex differences significantly influence the efficacy and outcomes of therapeutic interventions aimed at mitigating aging processes, necessitating a tailored approach to treatment that considers these biological variations [205, 254, 312, 314, 355, 418, 427–432]. As research in this area advances, it is becoming increasingly clear that men and women respond differently to various therapies, including senolytics, antioxidants, and lifestyle modifications [7]. These differences underscore the importance of personalized medicine and the development of sex-specific treatment protocols.

Senolytics, a class of drugs designed to selectively eliminate senescent cells, have shown promise in preclinical studies in reducing vascular aging and improving cardiovascular health [115, 188, 190]. However, the response to senolytic therapies may vary between sexes [433–435]. For instance, estrogen may modulate the SASP, potentially altering the effectiveness of senolytic drugs in women, particularly those who are premenopausal or on hormone replacement therapy. Additionally, the expression of senescence markers and the accumulation of senescent cells can differ between men and women, influencing the therapeutic impact of senolytics. These factors highlight the need for sex-specific dosing and treatment strategies to optimize the benefits of senolytic therapies.

Antioxidants and mitochondria-targeted therapies, which aim to reduce oxidative stress and improve cellular energetics may also exhibit sex-dependent efficacy [436]. As women generally have more robust antioxidant defenses, the therapeutic benefits of antioxidant supplementation might differ between men and women, with men potentially deriving greater benefit from these interventions. However, post-menopausal women, who experience a decline in estrogen levels, may see a shift in this dynamic, making them more susceptible to oxidative damage and potentially more responsive to antioxidant therapy.

Lifestyle modifications, including dietary changes, exercise, and stress management, are foundational in managing vascular aging [1, 2, 4, 437]. However, the impact of these interventions can be influenced by sex-specific factors [4, 437–442]. For example, women may experience greater benefits from lifestyle interventions that promote estrogen activity, such as those that involve phytoestrogens or specific exercise regimens that modulate hormone levels. Men, on the other hand, may respond differently to calorie restriction or physical activity due to differences in metabolism and muscle mass. These differences necessitate a tailored approach to lifestyle interventions, ensuring

that recommendations are aligned with the unique physiological profiles of men and women.

Perspectives

As our understanding of vascular aging continues to evolve, it is clear that significant gaps remain in our knowledge of how sex differences influence this process. Addressing these gaps is crucial for developing more effective, personalized interventions to mitigate the impact of vascular aging on health. Despite advances in geroscience and vascular biology, the specific mechanisms by which sex differences affect vascular aging are not fully understood. Current research often overlooks the influence of sex hormones, genetic factors [443], and the interaction between sex-specific lifestyle factors and vascular aging. Additionally, many studies on vascular aging and its therapeutic interventions have predominantly used male models, leading to a lack of comprehensive data on female-specific pathways and responses. Preclinical research should also encourage the use of both male and female animal models from different species, including non-human primates and dogs [444, 445], to explore the underlying mechanisms of sex differences in vascular aging. These studies should examine how sex hormones, gene expression, and cellular stress responses contribute to the differential aging of the vasculature in males and females. There is also a pressing need for large-scale, longitudinal studies that track and compare vascular aging in both males and females over time. These studies should focus on identifying sex-specific risk factors, progression patterns, and outcomes related to vascular aging. By following individuals across different stages of life, we can better understand how sex influences the trajectory of vascular aging and how complex early interventions might alter these trajectories in a sex-specific manner.

The recognition of sex differences in the response to therapeutic interventions [446–448] has profound implications for personalized healthy longevity medicine [449]. It emphasizes the need for developing sex-specific treatment protocols that account for the unique biological and hormonal landscapes of men and women [450]. Personalized medicine approaches should consider these differences when designing clinical trials, interpreting outcomes, and implementing treatment plans. This tailored approach not only enhances the efficacy of interventions but also minimizes the risk of adverse effects, ultimately improving the quality of care for both sexes. Additionally, recruiting a balanced number of male and female participants in clinical trials is essential for generating data that accurately reflects sex differences in treatment outcomes. Further, research should explore the potential benefits of combining lifestyle interventions with pharmacological treatments to optimize outcomes for each sex.

Sex-specific biomarkers represent a crucial, yet underdeveloped, area in the assessment of vascular aging and disease risk. Current diagnostic approaches often fail to account for the distinct biological and hormonal factors that drive differences in vascular aging between men and women, resulting in sub-optimal predictive accuracy and therapeutic targeting. There is a need for more human research and research on non-human primates into the genomic and epigenomic factors that drive sex differences in vascular aging. Studies that explore how DNA methylation, histone modifications, and non-coding RNAs differ between men and women could provide new insights into the molecular underpinnings of vascular aging. Such research could also reveal potential biomarkers for early detection and targeted treatment of vascular aging. Emerging evidence points to the potential utility of sex-specific biomarkers, including inflammatory cytokines, epigenetic markers, and proteomic signatures, in refining diagnostic and prognostic models for vascular diseases. Furthermore, a critical area that requires more attention is the study of sex differences in microvascular aging. Microvascular health is crucial for the function of all organs, and its decline is implicated in a range of age-related conditions, including cognitive impairment [78, 86, 209, 451, 452] and ischemic heart disease. There is an urgent need to investigate how sex influences microvascular aging processes, including endothelial function, capillary density, and microcirculatory blood flow in humans. Additionally, the phenomenon of accelerated vascular aging, such as that observed in conditions like long COVID [453, 454], may manifest differently between sexes, potentially due to varying immune responses, hormonal influences, and underlying vascular health. Understanding these differences could provide vital insights

into how to tailor interventions for conditions characterized by accelerated vascular aging, ensuring that therapies are effective for both men and women.

Addressing the gaps in our understanding of sex differences in vascular aging is essential for advancing the field and improving health outcomes for both men and women. By focusing on these key areas for future research, we can develop more effective, personalized strategies to combat vascular aging, ultimately enhancing the quality of life and longevity across populations. The integration of sex-specific insights into clinical practice will mark a significant step forward in the pursuit of personalized healthy longevity medicine and prevention and optimal management of age-related vascular diseases [455].

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Declarations

Ethics approval The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The 4o version of ChatGPT, developed by OpenAI, was used as a language tool to refine our writing, enhancing the clarity of our work.

Competing interests Dr. Zoltan Papp, Dr. Andriy Yabluchanskiy, Dr. Andrea Maier, Dr. Stefano Tarantini, and Dr. Anna Csiszar serve as Associate Editors for GeroScience. Dr. Zoltan Ungvari serves as Editor-in-Chief for GeroScience and has personal relationships with individuals involved in the submission of this paper.

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