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The interplay between lifestyle and cardiovascular aging: mechanisms and therapeutic opportunities

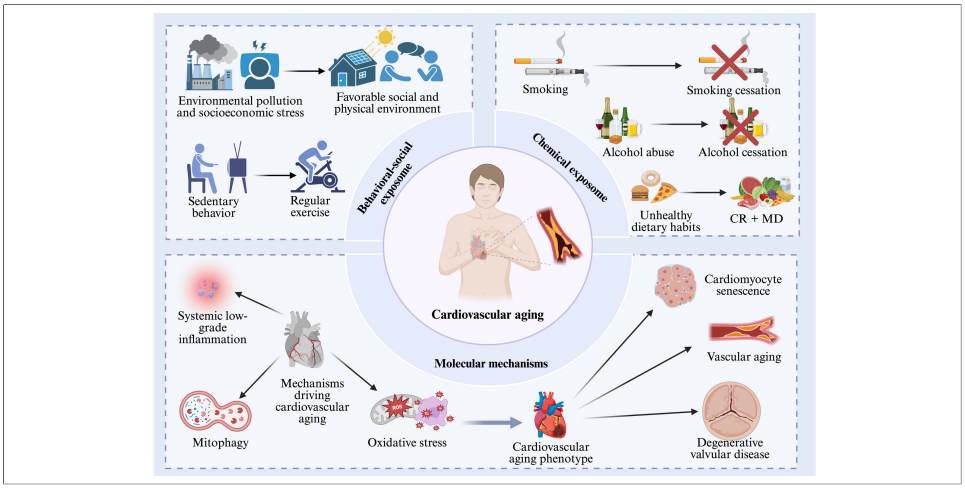
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Abstract

With the global trend of population aging, age-related diseases are increasing annually. The vascular system exhibits high sensitivity to aging, characterized by myocardial cell apoptosis, endothelial damage, oxidative stress, impaired autophagy, and chronic low-grade inflammatory responses. These factors significantly elevate the incidence of atherosclerosis, hypertension, myocardial infarction, and stroke, which are major cardiovascular diseases. Previous research has predominantly focused on the isolated impact of single lifestyle factors on cardiovascular aging, lacking a comprehensive framework that integrates multiple exposomes and their complex interactions. This review aims to reassess how the exposome factors, such as smoking, sedentary behavior, and the natural environment, interact and dysregulate core mechanisms such as oxidative stress and autophagy. These interactions collaboratively drive the aging of blood vessels, myocardium, and valves. We also propose targeted intervention strategies, providing insights for researchers investigating cardiovascular aging.

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INTRODUCTION

According to the global burden of disease data, cardiovascular diseases (CVDs) are significant causes of mortality and permanent disability among individuals aged 65 and above[1]. Aging induces degeneration in the cardiac and vascular systems, including changes in cardiac size and structure - such as left ventricular and left atrial dilation, reduced left ventricular diastolic function, and decreased left ventricular ejection fraction[2] - as well as increased arterial thickness and stiffness and impaired vascular endothelial function. These processes may involve complex pathophysiological mechanisms, including mitochondrial dysfunction, oxidative stress, myocardial cell death, and chronic inflammation. These mechanisms lead to remodeling and structural changes in the cardiovascular system, resulting in conditions such as atherosclerosis, atrial fibrillation, heart failure, and aortic valve stenosis[3].

In recent years, an increasing body of research has highlighted the impact of lifestyle on aging and CVDs. Sedentary behavior[4], smoking[5], obesity[6], insufficient sleep[7], and social and psychological stress are unhealthy lifestyle factors that may serve as risk factors for cardiovascular aging, promoting the occurrence of CVDs and accelerating the aging process[8] [Figure 1]. Conversely, a healthy lifestyle, such as aerobic exercise[9] and the consumption of fruits, vegetables, and legumes[10], plays a crucial role in enhancing cardiorespiratory function and maintaining cardiovascular health. However, current research predominantly focuses on the isolated impact of single lifestyle factors on cardiovascular aging, lacking a systematic framework that integrates multiple exposomes and their complex interactions. This paper aims to revisit the cumulative damage and accelerated biological aging of the cardiovascular system resulting from shared exposures to smoking, sedentary behavior, and the natural environment, using an exposome-based approach. Based on this, targeted intervention strategies are proposed, providing insights for researchers investigating cardiovascular aging.

COMPOSITION OF THE CARDIOVASCULAR EXPOSOME

Behavioral-social exposome

Sedentary behavior

Prolonged sedentary behavior is increasingly becoming one of the prevalent adverse lifestyles in modern society. In most adults, prolonged sitting occupies a large portion of daily time, and this behavior has become more prevalent due to the coronavirus disease 2019 (COVID-19) pandemic, emerging as a novel determinant of CVD risk[11]. Existing research has demonstrated a dose-response relationship between prolonged sitting time and increased CVD risk in elderly females, suggesting that extended periods of sedentary behavior may exacerbate the burden of CVDs[12], and elevate the incidence of heart failure and atrial fibrillation[13,14]. More alarmingly, a sedentary lifestyle can reduce testosterone levels, subsequently leading to depression, fatigue, decreased vitality, and weakened skeletal and muscular strength[15].

Fortunately, regular physical exercise, as a unique form of physiological stress, can trigger cardiovascular autophagy activity and exert a protective effect on the cardiovascular system. Studies have shown that exercise stimulates increased Parkin recruitment to mitochondria, thereby promoting mitochondrial autophagy. However, in Parkin knockout models, autophagy is absent, indicating that Parkin is essential for mitochondrial ubiquitination[16]. An early 10-year longitudinal cohort study confirmed that moderate physical activity can delay age-related decline in physical function[17]. It also promotes physiological left ventricular remodeling, enhances arterial function and aerobic capacity[18], improves blood pressure and maximal metabolic capacity[19], and reduces the risk of depression[20]. More recent research has provided a clearer elucidation of the benefits of exercise, with findings indicating that accumulating 9,000-10,500 steps of walking per day can significantly reduce the CVD risk associated with prolonged sitting[21], and this benefit is more pronounced in females[22]. Appropriate intensity of aerobic exercise aids in the production of reactive

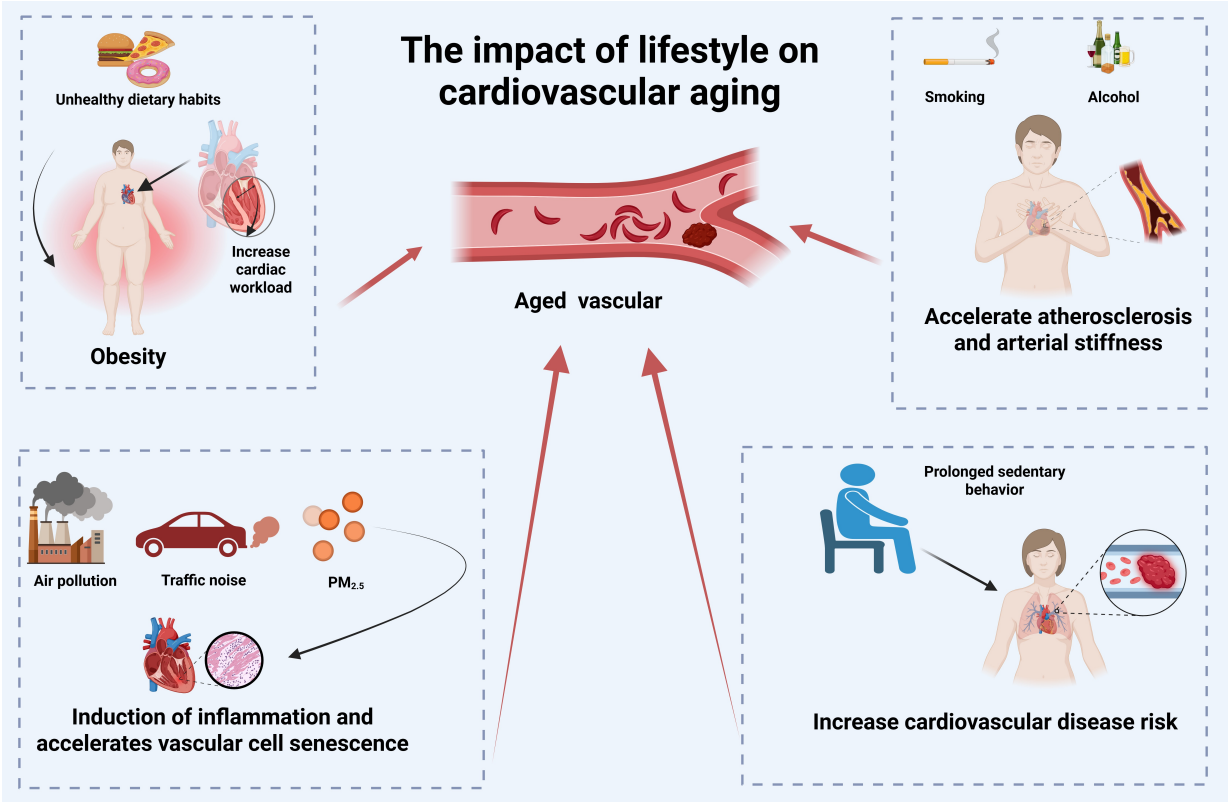


Figure 1. The impact of lifestyle on cardiovascular disease. Unhealthy lifestyle factors - such as sedentary behavior, smoking, alcohol consumption, obesity, and social or psychological stress - can contribute to cardiovascular aging, promote the development of cardiovascular disease, and accelerate aging. Created in BioRender Xu C (2025) https://BioRender.com/g1q8bpb.

oxygen species (ROS), activates interleukin (IL)-6 and its receptors, as well as glycoprotein 130 and other anti-inflammatory cytokines, promoting antioxidant processes in the vascular system[23,24]. With the development of artificial intelligence, its application in cardiovascular aging-related diseases has garnered increasing attention. Limited evidence suggests that interventions using wearable technology positively influence the daily activity patterns and blood pressure changes in the elderly, potentially improving CVD risk factors[25]. In the future, encouraging moderate physical activity should be a focal point in addressing the aging trend to alleviate the health burden associated with aging.

Environmental pollution and socio-economic pressures

Air pollution is a complex mixture of particulate matter (PM) and gaseous pollutants [e.g., ozone, nitrogen oxides (NO_x), and sulfur dioxide], and it is an important external factor contributing to cardiovascular aging. Major anthropogenic sources of air pollution include vehicular emissions and industrial discharges[26]. Currently, global health organizations such as the American Heart Association (AHA) and the European Society of Cardiology (ESC) have identified $PM_{2.5}$ as a significant risk factor for cardiovascular morbidity and mortality[27,28]. A study examining the relationship between urban traffic design and health risks demonstrated that cities with higher levels of public transportation show greater resilience to infectious diseases and cardiovascular threats. Lower private vehicle use was also associated with reduced all-cause mortality and a lower incidence of ischemic heart disease[29].

It is noteworthy that the living environment is closely associated with the incidence and mortality of CVDs. Higher traffic density is linked to an increased risk of coronary heart disease (CHD), whereas access to parks and green spaces is associated with a reduced incidence of CHD[30]. These associations are partly explained by

environmental exposures, as poorer living conditions are often characterized by higher levels of air pollution and noise, both of which are closely linked to the development of CVDs[31]. More direct evidence shows that living within 150 meters of major urban roads, compared with distances greater than 300 meters, is associated with a 6.67% increase in carotid intima-media thickness[32]. Epigenetic mechanisms, particularly DNA methylation, may further underlie these associations. DNA methylation patterns are influenced by traffic noise, air pollution, and green space exposure, and are enriched in pathways related to inflammation, cellular development, and immune responses[2,33].

External social stressors, including work stress[34] and low socioeconomic status[35], are significant risk factors for CVDs. These factors can trigger psychological stress and lead to physiological and behavioral responses, including anxiety[36], depression[37], and social inhibition[38]. Psychological stress promotes immune activation and inflammation, as well as endothelial dysfunction[39], thereby increasing the risk of adverse cardiovascular events such as CHD and heart failure. Together, these findings highlight the importance of both the living environment and the social context in shaping cardiovascular health.

Chemical exposome

Smoking

Smoking is one of the most significant risk factors for CVDs, with tobacco-derived smoke containing highly toxic compounds: nitrosamines and polycyclic aromatic hydrocarbons (PAHs). These compounds are known carcinogens and are associated with various complications, including CVDs[40,41]. Evidence indicates that smoking increases the incidence and mortality of CVDs, which is linked to smoking-induced endothelial dysfunction, reduced high-density lipoprotein (HDL) levels, and exacerbated inflammatory states[42]. Studies have shown that prolonged exposure to cigarette smoke in mice leads to macrophage infiltration, inducing vascular endothelial damage, increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase levels, and ROS production in the vasculature, thereby triggering a vicious cycle of oxidative stress and endothelial damage[43]. The harmful effects of secondhand smoke are also significant, and it has become an independent risk factor for CVDs. Research has found that exposure to secondhand smoke induces myocardial cell dysfunction, disrupts intracellular Ca^{2+} homeostasis, promotes cellular apoptosis, and impairs autophagy, with adiponectin deficiency exacerbating these effects[44].

There is a widespread misconception regarding the addictive potential and adverse health effects of waterpipe smoke, with many people believing that waterpipe smoking is less harmful and less addictive than cigarette smoking. However, the opposite is true; many harmful substances found in tobacco smoke are also present in waterpipe smoke, often at higher concentrations[45]. Notably, the AHA has stated that the acute cardiopulmonary toxicity of a single waterpipe smoking session is more severe than that of smoking a single cigarette, due to significantly higher levels of cardiopulmonary toxicants such as heavy metals and PM[46]. Research has shown that waterpipe smoking is associated with significantly lower levels of vascular endothelial growth factor (VEGF) in adolescents[47]. Additionally, long-term waterpipe smoking significantly increases the severity of coronary artery atherosclerosis, with similar cardiovascular changes being more pronounced in physically inactive individuals[48], indicating a critical role for physical activity in delaying cardiovascular aging.

This situation is similarly concerning for e-cigarettes. When e-cigarette liquids are heated, toxic aldehydes and ketones - notably formaldehyde and acrolein - are produced. These compounds can form toxic polymers with proteins and DNA, significantly elevating serum endothelin-1 (ET-1) and IL-8 levels, thereby exacerbating oxidative stress, mitochondrial dysfunction, and inflammation. This process intensifies with prolonged exposure to e-cigarettes[49]. Another study indicates that phagocytic NADPH oxidase (NOX-2) is one of the mechanisms by which e-cigarettes exert their effects. E-cigarette vapor exposure increases

oxidative stress in the vasculature, brain, and lungs through NOX-2-dependent mechanisms, significantly impairing endothelial function and increasing arterial stiffness[50]. Therefore, smoking cessation is crucial; it can lower circulating ET-1 and Tumour Necrosis Factor alpha (TNF-α) concentrations, reduce systemic inflammation, and decrease the risk of CVDs[51].

Alcohol consumption

Alcohol is another potential factor that endangers cardiovascular health. Genetic studies indicate that alcohol consumption may shorten lifespan[52]. Chronic heavy alcohol consumption can lead to alcoholic cardiomyopathy, characterized by left ventricular dilation, reduced myocardial contractility, and myocardial fibrosis, ultimately resulting in heart failure and arrhythmias[53]. Pulse wave velocity (PWV) is an independent indicator for assessing arterial stiffness and predicting CVD; studies have shown that light-to-moderate alcohol consumption is associated with higher PWV, thereby increasing arterial stiffness, while high alcohol intake accelerates arterial aging[54].

Ethanol is primarily enzymatically converted to acetaldehyde by alcohol dehydrogenase (ADH), which is then metabolized to acetate by aldehyde dehydrogenase. Acetaldehyde is subsequently transported to the mitochondria, where it is further converted to acetyl coenzyme A (acetyl-CoA). Excessive alcohol consumption can damage mitochondrial function, disrupt cholesterol and triglyceride metabolism, promote oxidative stress and inflammatory responses, and accelerate myocardial cell death and aging, leading to impaired cardiac diastolic function and reduced cardiovascular reserve capacity[55]. Peroxides can react with nitric oxide (NO) in a diffusion-limited manner to form peroxynitrite, a reactive nitrogen species (RNS). Both RNS and ROS can damage contractile proteins, enzymes, and mitochondria through oxidative and nitrosative processes, intensifying stress signaling, exacerbating cellular dysfunction, and ultimately leading to myocardial and endothelial cell (EC) death[56]. These findings suggest that alcohol intake is an independent risk factor for CVDs, and chronic heavy drinking impairs cardiovascular function, increasing the risk of CVDs. Reducing alcohol intake could help ameliorate the process of cardiovascular aging.

Dietary patterns

Caloric restriction is a dietary regimen that has been shown to benefit vascular health. Evidence indicates that animals subjected to caloric restriction exhibit signs of vascular rejuvenation, which may be associated with reduced extracellular matrix (ECM) and collagen deposition in the vascular wall, activation of endothelial nitric oxide synthase (eNOS), and increased NO levels, thereby mitigating oxidative stress and inflammation[57,58]. Nuclear factor erythroid-2-related factor 2 (Nrf2) confers protective effects against cellular oxidative stress; however, this effect diminishes with age. Further research has shown that caloric restriction reduces apoptosis in microvascular ECs of the brain in rats, significantly lowers the expression of miR-144, and upregulates NRF2, thereby restoring the physiological function of vascular ECs[59]. Similar phenomena occur at the cellular level, as the use of serum from calorically restricted monkeys to culture vascular ECs results in upregulated VEGF expression[60], suggesting that moderate caloric restriction may be a potential mechanism for improving cardiovascular function.

The Mediterranean diet (MD) is characterized by a high intake of vegetables, legumes, fruits, fish, nuts, and olive oil, with a reduced consumption of red meat and processed dairy products. It is currently considered one of the most healthful dietary patterns, with significant antioxidant and anti-inflammatory effects[61]. A strict adherence to the MD can significantly reduce the probability of vascular aging[62]. The Mediterranean-DASH (Dietary Approaches to Stop Hypertension) Intervention for Neurodegenerative Delay (MIND) diet is a novel dietary approach that combines elements of the Mediterranean and DASH diets, emphasizing the importance of berries and leafy greens[63]. These foods, rich in vitamins E, folate,

polyphenols, flavonoids, monounsaturated fatty acids (MUFAs), and omega-3 fatty acids, can inhibit the deposition of amyloid-beta (Aβ). Incorporating them into a healthy diet can serve as a lifestyle strategy to reduce the risk of CVDs and Alzheimer's disease (AD)[64]. Interestingly, a study has shown that moderate coffee consumption (1 to 5 cups per day) is associated with a reduced risk of heart failure, type 2 diabetes (T2D), and chronic kidney disease (CKD)[65]. However, further understanding of its underlying mechanisms is necessary to determine its benefits for cardiovascular health. Nevertheless, it is undoubtedly true that quality dietary habits confer significant benefits on the cardiovascular system.

MOLECULAR MECHANISMS OF CARDIOVASCULAR AGING INDUCED BY EXPOSOME

Oxidative stress

Oxidative stress-induced endothelial dysfunction is a critical mechanism for the increased risk of CVDs. With age, ROS gradually increase, while the capacity for endogenous antioxidant defense decreases, leading to reduced bioavailability of NO and impaired vascular dilation[66]. Under normal conditions, cells exert antioxidant functions through the production of glutathione peroxidase (GPX), glutathione reductase, catalase, NADPH-quinone oxidoreductase-1 (NQO1), heme oxygenase (HO-1), thioredoxin (Trx), and sulfiredoxin (Srx)[67]. In this process, cardiomyocytes maintain their function through high aerobic metabolism, with mitochondria accounting for 45% of cardiac cell volume; thus, mitochondrial oxidative phosphorylation is the primary source of adenosine triphosphate (ATP) in cardiomyocytes. Previous studies have highlighted that mitochondrial oxidative stress can lead to mutations in mitochondrial DNA (mtDNA) and increased permeability, thereby impairing mitochondrial and overall cardiomyocyte functions and playing a crucial role in the antioxidant process[68]. Additionally, it has been shown that transcription factor NRF2 is a key regulator of cellular redox homeostasis. Under conditions of oxidative damage, Kelch-like ECH-associated protein 1 (KEAP1) can dissociate from the NRF2-KEAP1 complex, thereby activating NRF2 to exert antioxidant functions[69] [Figure 2]. However, the detrimental effects of oxidative stress are not irreversible. Accumulating evidence suggests that a healthy lifestyle, characterized by moderate physical activity and balanced nutrition, can activate antioxidant mechanisms, thus achieving the goal of delaying aging[70].

Systemic low-grade inflammation

Inflammation is one of the key factors in vascular aging and plays a central role in age-related chronic diseases. Frasca *et al.* coined the term "inflammaging" to describe the chronic, low-grade, and systemic inflammation that occurs with age[71]. Studies have shown that chronic inflammation elevates the expression of biomarkers for heart failure, such as high-sensitivity cardiac troponin T (hs-cTnT), and exacerbates frailty in patients with CVDs[72]. Currently, pro-inflammatory molecules identified to be involved in the inflammatory process include IL-1, IL-6, IL-8, IL-13, IL-18, C-reactive protein (CRP), nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome, and TNF-α and its receptors[73,74], which are strongly associated with age-related diseases such as cancer[75], atherosclerosis[76], and AD[77]. Interestingly, some perspectives posit that certain inflammation may be beneficial; regular exposure to inflammatory stimuli can train the immune system to fine-tune its cellular processes, potentially leading to better outcomes in the face of life-threatening diseases[78].

Unhealthy lifestyle habits accelerate both vascular aging and cognitive decline. A study investigating the effects of a high-fat diet on systemic inflammation in aged mice demonstrated that a high-fat diet induces both systemic and localized neuroinflammation, alters exploratory behavior of both male and female mice, and impairs learning and memory abilities of male mice[79]. In contrast, a healthy lifestyle can help improve the inflammatory environment. For example, oats can reduce the expression of Eotaxin-1 protein, thereby alleviating systemic chronic inflammation[80], and increasing the intake of foods rich in omega-3, such as those found in the MD, is recommended[81]. Regular moderate exercise can also prevent premature vascular

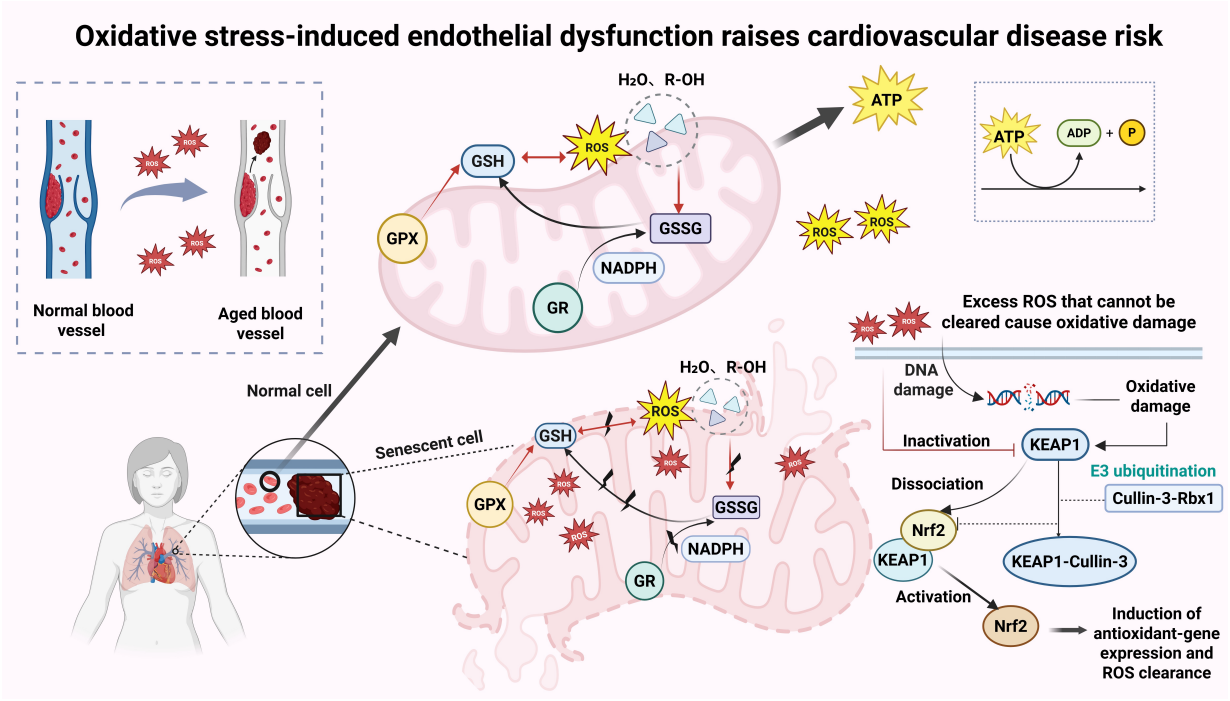


Figure 2. Oxidative stress-induced endothelial dysfunction increases cardiovascular disease risk. Oxidative stress elevates ROS levels, causes endothelial dysfunction, damages mitochondrial oxidative phosphorylation, gradually reduces endogenous antioxidant defenses, and impairs vasodilator function. Created in BioRender Xu C (2025) https://BioRender.com/pad4sgo. ROS: Reactive oxygen species; GPX: glutathione peroxidase; ATP: adenosine triphosphate; ADP: adenosine diphosphate; GR: glutathione reductase; NADPH: nicotinamide adenine dinucleotide phosphate; GSSG: glutathione disulfide; GSH: glutathione.

aging and reduce the risk of all-cause mortality[82]. Notably, the living environment is also a significant exacerbating factor in cardiovascular inflammation aging; for instance, long-term exposure to micro- and nanoplastics can promote oxidative stress, impair mitochondrial function, damage autophagy, and activate DNA damage responses, thereby increasing the production of pro-inflammatory factors[83]. Moreover, unhealthy social relationships, such as increased feelings of loneliness and social stress, can lead to glucocorticoid resistance, up-regulated expression of pro-inflammatory genes, and oxidative stress[84,85]. Considering these factors comprehensively is crucial for reducing inflammatory responses and promoting cardiovascular health.

Impaired autophagy

Cellular homeostasis is a prerequisite for optimal cardiovascular function. Autophagy, by removing accumulated proteins and damaged organelles, balances biosynthesis and catabolism of macromolecules, thereby maintaining cellular homeostasis and protecting organisms from CVDs such as myocardial infarction and atherosclerosis[86]. However, cardiac autophagy is impaired with age, leading to the accumulation of dysfunctional mitochondria and other metabolic waste in aging hearts. Activation of autophagy can help ameliorate cardiovascular damage caused by aging. Studies have confirmed that PTEN-induced putative kinase 1 (PINK)/Parkin[87], BCL2 Interacting Protein 3-Like/NIP3-like protein X (BNIP3L/NIX)[88], and FUN14 Domain Containing 1 (FUNDC1)[89] are critical pathways mediating mitophagy, which alleviates damage from myocardial infarction and heart failure. Consequently, autophagy has emerged as a potential therapeutic target for age-related cardiac dysfunction[90]. Current research suggests that mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), Autophagy-related gene (ATG) proteins, as well as insulin/Insulin-like Growth Factor 1 (IGF1), Target of Rapamycin (TOR), Protein Kinase A (PKA), and AKR mouse strain T/Protein Kinase B (AKT/PKB), show age-related changes

and may regulate or interact with autophagy. These molecules are therefore considered promising targets for autophagy regulation[91]. DBI/ACBP (dibenzylindole/acyl-CoA binding protein) is a phylogenetically conserved paracrine inhibitor that promotes aging by inhibiting macroautophagy/autophagy, while the knockdown of Acyl-CoA-binding protein (ACB1) induces autophagy and extends lifespan in an autophagy-dependent manner[92].

Previous studies have shown that trehalose, spermidine, and polyphenols are natural autophagy activators. They enhance myocardial relaxation function and reduce cardiac hypertrophy by activating transcription factor EB[93], improve myocardial diastolic function and reduce cardiac hypertrophy[94], thereby positively affecting redox and autophagy and promoting the repair of CVDs[95]. Spermidine, a natural polyamine present in durian, mushrooms, fresh green peppers, amaranth, broccoli, and soy products[96], delays the onset of cardiovascular and neurodegenerative diseases by stimulating protective autophagy, making it a candidate for aging research[97]. Recent studies have shown that lifestyle changes, such as caloric restriction and intermittent fasting, can induce enhanced autophagy, significantly reducing the incidence of CVDs and extending lifespan[98]. Additionally, physical exercise has emerged as an important intervention for regulating autophagy. Moderate-intensity physical activity upregulates proteins such as BECLIN1, microtubule-associated protein 1 light chain 3 (LC3), and autophagy-related protein 12 (ATG12), thereby enhancing autophagy, reducing ROS production, inhibiting NLRP3 inflammasome activation, and lowering IL-1β and IL-18 levels, ultimately restoring cellular homeostasis and reducing age-related inflammation[99]. This plays a positive role in mitigating the effects of aging and preventing age-related diseases.

AGING PHENOTYPES CAUSED BY DYSREGULATION OF MOLECULAR MECHANISMS

Cardiac remodeling

Cardiomyocytes are crucial for maintaining cardiac function. Given that the heart lacks endogenous cardiomyocyte regeneration capacity, the impact of cardiomyocyte death cannot be naturally reversed and is a primary cause of reduced cardiac function in CVDs[100,101]. The aging of cardiomyocytes is a result of various functional impairments. In aged cardiomyocytes, double-strand breaks (DSBs) activate cytoplasmic DNA sensing proteins (CDSPs), which, together with the DNA damage response pathway (DDR), induce the senescence-associated secretory phenotype (SASP)[102]. Furthermore, the accumulation of mitochondrial ROS[103]induces DNA damage characterized by telomere shortening[104], which subsequently triggers programmed cell death mechanisms such as apoptosis, autophagy, pyroptosis, and ferroptosis[105]. These processes lead to a reduction in the absolute number of cardiomyocytes, thereby promoting the development of CVDs, including myocardial infarction, ischemia-reperfusion injury, and heart failure.

In fact, another crucial component of cardiac tissue - non-myocytes, including ECs, fibroblasts, and immune cells[106] - is equally essential for the function of myocytes. Functional impairment of fibroblasts induced by aging and mechanical stress exacerbates the functional impairment and aging of myocytes[107]. ECs, through their high expression and release of Angiotensin II (AngII) and ET-1, can stimulate mitochondrial dysfunction, endoplasmic reticulum stress, contractile dysfunction, and hypertrophic growth in myocytes[108]. Macrophages are key immune cells in myocardial pathological remodeling and fibrosis, and inhibiting the CD206 macrophage IL-4Rα signaling pathway can reduce left ventricular remodeling in ischemic cardiomyopathy[109], thereby delaying the progression of heart disease [Figure 3]. However, encouragingly, research has already highlighted the benefits of the ECM on myocytes, which can promote myocyte proliferation, induce re-entry into the cell cycle, and protect against stress responses in senescent cells[110]. Further studies have revealed that the absence of Sirtuin 2 (SIRT2) in myocytes is a key feature of human cardiac aging, and the SIRT2-STAT3-Cyclin Dependent Kinase Inhibitor 2B (CDKN2B) regulatory axis is a potential therapeutic target for CVDs[111]. Emerging clinical evidence suggests that increasing cellular Nicotinamide adenine dinucleotide (NAD) content may be a promising therapeutic approach[112].

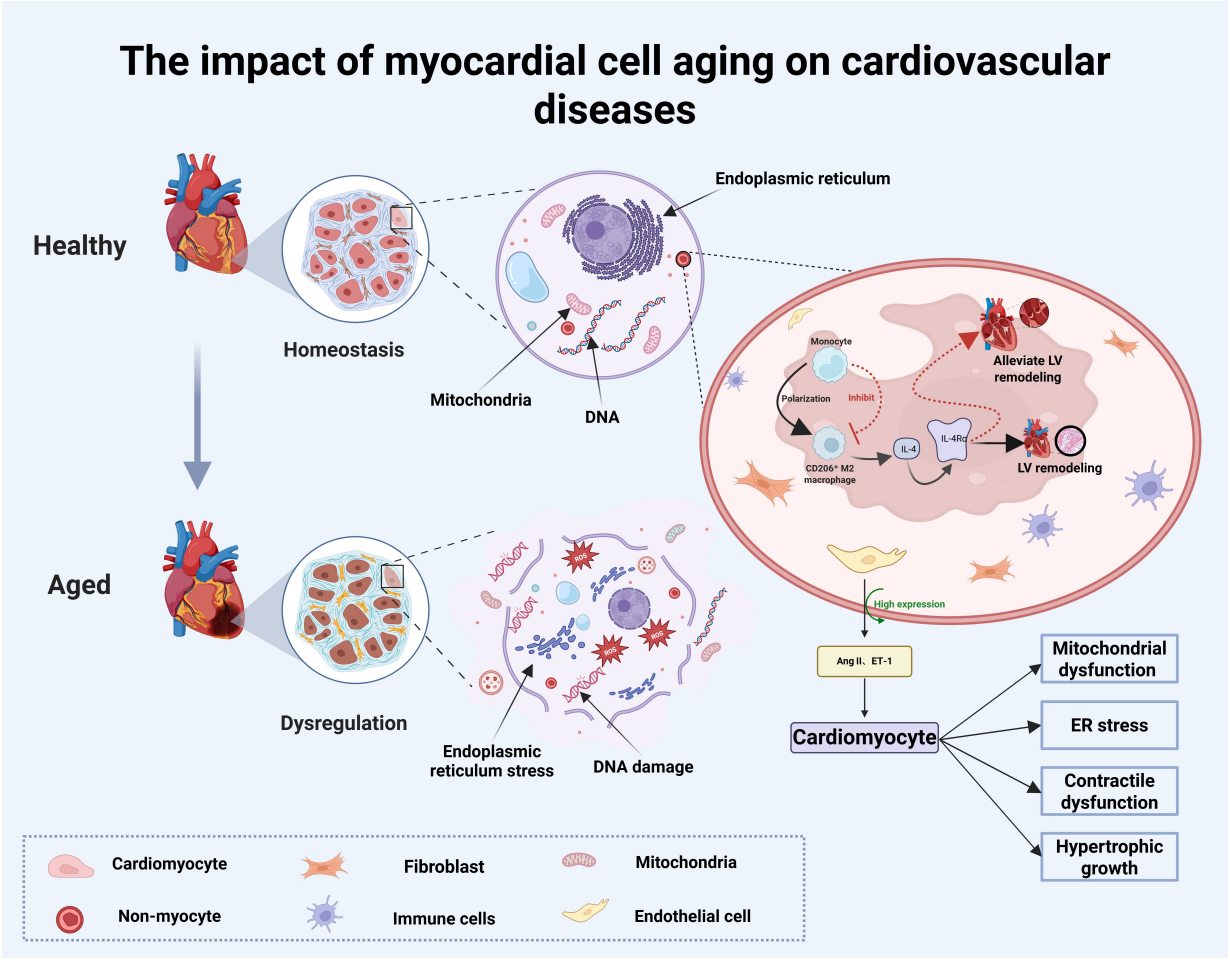


Figure 3. The impact of myocardial cell aging on cardiovascular diseases. Cardiovascular aging results from dysfunction in both cardiomyocytes and non-myocytes, including DNA damage responses, endoplasmic reticulum stress, mitochondrial dysfunction, SASP release, and other cellular changes. Created in BioRender Xu C (2025) https://BioRender.com/url7kgt. SASP: Senescence-associated secretory phenotype; ER: endoplasmic reticulum.

Nicotinamide riboside (NR) as a dietary supplement can be converted to NAD in cells to support mitochondrial energy metabolism. Mice treated with NR after ischemia/reperfusion (I/R) exhibited higher ejection fractions and smaller infarct areas[113]. Additionally, exercise is an important measure to delay myocyte aging, and moderate exercise training can improve myocyte function and delay age-related pathological changes in the heart[114]. This indicates that lifestyle changes can significantly enhance the vitality of myocytes.

Vascular aging

Vascular aging is a gradual process. Large longitudinal studies have shown that vascular endothelial dysfunction, a specific phenotype of vascular aging, is a core factor in the increased incidence and mortality of CVDs. Vascular ECs play an important physiological role in vascular homeostasis, maintaining blood flow, regulating vascular tone, pro-inflammatory responses and neovascularization. As aging progresses, ECs show aging-related phenotypes, leading to a decline in vascular endothelial function[115], an increase in arterial intima-media thickness, and a decrease in arterial distension[116]. These changes accelerate the occurrence of CVDs such as atherosclerosis, hypertension, and stroke[117], and have become potential risk factors for multi-organ diseases, including CKD[118] and pulmonary hypertension[119]. Many abnormal molecular pathways are involved in these pathophysiological changes, including the abnormal activation of

Sirtuin1, Klotho, fibroblast growth factor 21 (FGF21), the renin-angiotensin-aldosterone system (RAAS), Insulin-like Growth Factor Binding Protein (IGFBP), NRF2, and mTOR[120,121]. With age, another early change in vascular aging is vessel wall calcification, which is characterized by increased PWV and decreased Windkessel function[122]. It is currently believed that the main mechanism of vascular wall calcification is that as the body ages, the calcium and phosphorus content in the arterial wall increases specifically, leading to osteogenic transformation of vascular smooth muscle cells[123]. The process of vascular calcification involves the participation of multiple cytokines and growth factors, including pro-inflammatory cytokines (IL-6, TNF-α)[124], osteoprotegerin[125], sclerostin[126], and matrix gamma-carboxyglutamate (MGP). These changes result in increased systolic blood pressure, decreased diastolic blood pressure, and expanded pulse pressure, ultimately leading to damage to the heart, brain, and other end organs[127]. It is noteworthy that abnormal gene expression also serves as a critical intrinsic driver of vascular aging. Previous studies have shown that aberrant proteins induced by Lamin A/C (LMNA) mutations, known as progerin, accumulate in elderly coronary arteries, leading to nuclear defects and increased sensitivity to mechanical stress. This, in turn, triggers cell death and inflammatory responses, suggesting that progerin is a potential target for influencing vascular health[128].

Evidence has shown that vascular aging is positively correlated with sedentary time and negatively correlated with physical activity[129]. Regular and adequate aerobic exercise can significantly slow vascular aging, reduce age-related arterial stiffness, and lower the incidence of CVDs[130]. Excessive salt intake is another lifestyle that exacerbates vascular aging. Reducing salt intake helps restore aortic elasticity and reduces the risk of CVD by reducing the production of the pro-fibrotic factor Marinobufagenin (MBG)[131]. Surprisingly, vascular aging can occur in childhood[132] and progresses with increased psychosocial stress and unhealthy habits, such as exposure to air pollution and smoking[133]. It can be seen that early lifestyle changes and living environment adjustments have a profound impact on vascular aging.

Degenerative changes in valves

The mitral valve is a complex structure made up of anterior and posterior leaflets, chordae tendineae, and Papillary muscle. Its main function is to allow blood to flow from the left atrium to the left ventricle during diastole. It also prevents blood from flowing backward during systole, playing a crucial role in normal heart function[134]. With age, the compliance of cardiac valves to mechanical stress decreases, making them susceptible to degeneration, which is typically manifested as mitral valve calcification. The prevalence of this condition rises from 10% in people aged 60-69 to 30% in those aged 70-79, and reaches 60% in individuals over 80. It has become an independent risk factor for all-cause and cardiovascular mortality[135]. Mitral valve calcification can lead to mitral stenosis and mitral regurgitation[136,137]. Functional mitral regurgitation can result in left atrial dilation and reduced left atrial compliance, leading to adverse outcomes such as heart failure[138]. The aging process of the mitral valve is influenced by multiple molecular pathways. On the one hand, the renin-angiotensin system (RAS) induces inflammation by stimulating the release of inflammatory cytokines through angiotensin II, increasing the production of ROS[139]; On the other hand, the TGF-β signaling pathway enhances collagen accumulation, promoting the differentiation of fibroblasts into myofibroblasts, thus leading to valve fibrosis[140].

Recent evidence highlights the involvement of mitochondria in the development and progression of aortic valve stenosis. A key function of mitochondria is their involvement in the unfolded protein response (UPR). In this process, mitochondria reduce the accumulation of misfolded proteins, thereby lowering cell death and fibrosis, and decreasing plasma levels of cardiac injury biomarkers, such as high-sensitivity troponin T[141]. Additionally, Rogers *et al.* discovered that dynamin-related protein 1 (DRP1) is a critical regulator of mitochondrial fission in calcified human aortic valves. RNA-mediated interference in Human Aortic Valve Interstitial Cells (HAVICs) reduces calcium deposition by increasing SRY-box transcription factor 9 (SOX9) expression, thereby providing protective effects on cardiac tissue[142].

A 10-year absolute risk chart for aortic valve stenosis shows that factors such as high body mass index, poor adherence to dietary guidelines, smoking, and excessive alcohol use can raise the 10-year risk from less than 1% to 19%. This suggests that lifestyle changes can help reduce the risk of valvular heart disease[143]. Notably, long-term exposure to severe air pollution is a long-neglected factor contributing to valve calcification, with left-sided valvular calcification serving as a marker for CVD risk, directly related to atherosclerosis[144]. Therefore, a good living environment and a healthy lifestyle are beneficial factors in delaying valvular heart disease and maintaining cardiovascular health.

CONCLUSION

Aging of the cardiovascular system is a complex and inevitable physiological process, but it is strongly influenced by intrinsic biological factors, lifestyle choices, and the surrounding environment.

At the biological level, degeneration of cardiac and vascular structure and function serves as the pathological basis for cardiovascular aging. Vascular endothelial dysfunction, calcification of heart valves, and apoptosis of myocardial cells directly impair cardiac pumping efficiency. At the molecular level, chronic inflammation, impaired autophagy, mitochondrial dysfunction, and oxidative stress act as catalysts for aging, activating a series of age-related signaling pathways that accelerate cellular senescence and apoptosis.

However, these intrinsic aging processes are not independent; their rate and severity are significantly amplified by adverse lifestyle and environmental factors. Smoking and excessive alcohol consumption are well-recognized exogenous aging triggers. Harmful substances in tobacco directly induce oxidative stress and inflammation, damaging the vascular endothelium; alcohol may elevate blood pressure and exacerbate cardiac burden. Sedentary lifestyles contribute to energy metabolic imbalance, promoting obesity, insulin resistance, and dyslipidemia - each of which is an independent risk factor for CVD. Additionally, air pollution, an often-overlooked factor, has become a significant threat to cardiovascular health in modern society. These fine particulates can enter the bloodstream via the alveoli, inducing systemic oxidative stress and inflammation, and directly attacking the cardiovascular system.

In summary, cardiovascular aging is a result of the continuous interaction between intrinsic biological decline and extrinsic environmental factors such as lifestyle. Understanding this intertwined network not only elucidates the underlying mechanisms of aging but also points the way forward for interventions. By adopting positive lifestyle interventions, such as smoking cessation, moderate alcohol consumption, regular exercise, and improving the living environment, intrinsic biological aging can be delayed. On the other hand, through bioinformatics and artificial intelligence methods, integrating large global datasets with genomics, transcriptomics, and proteomics techniques, key biological targets in the process of cardiovascular aging can be identified. This will facilitate a comprehensive system from precise molecular targeted therapy to social care and lifestyle improvement, with the ultimate goal of achieving healthy cardiovascular aging.

DECLARATIONS

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Authors' contributions

Made contributions to this article equally: Zhang, S.; Xu, C.
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