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Exercise as medicine: Improving cardiovascular health through physical activity

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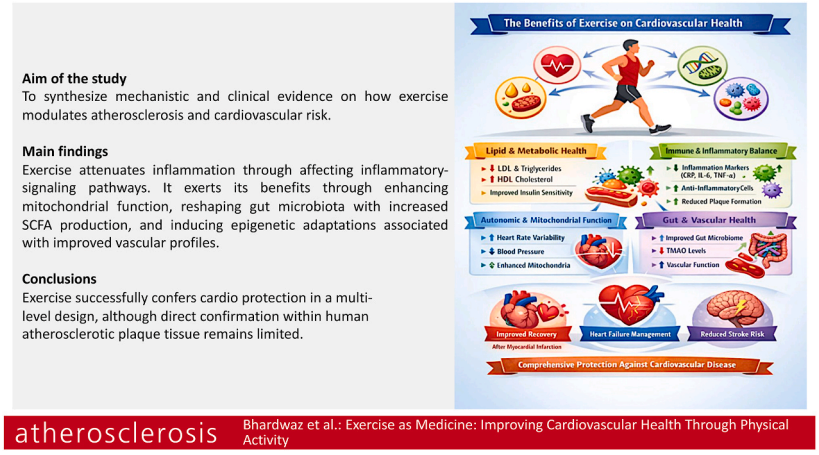
HIGHLIGHTS

- Exercise helps in lowering inflammation and slows plaque buildup in arteries.
- Exercise aids in improving heart recovery after a myocardial infarction and reduces stroke risk.
- Exercise reshapes heart failure management through refining gut health, mitochondrial function and metabolic health.
- Exercise maintains an immune and inflammatory balance, reducing CVD risk and plaque formation.

GRAPHICAL ABSTRACT



ABSTRACT

Cardiovascular diseases remain the leading cause of global mortality, and growing evidence shows that regular exercise is one of the most effective non-pharmacological strategies to prevent and modify their progression. Exercise exerts its benefits on the cardiovascular system in multiple ways. It improves lipid metabolism by lowering LDL-cholesterol, reducing triglycerides, and increasing HDL-cholesterol, which provides a protective function by slowing atherosclerotic plaque development. Exercise also reduces chronic inflammation by lowering circulating inflammatory markers and shifting immune cells toward anti-inflammatory profiles. In addition, regular physical activity enhances autonomic balance, increases heart rate variability, and supports healthier blood pressure regulation. Mitochondrial function and antioxidant capacity improve with exercise, helping to reduce oxidative stress and support overall cardiac health. Exercise further influences vascular and metabolic health through epigenetic mechanisms, myokine release, and favorable changes in the gut microbiome.

These molecular and systemic adaptations translate into meaningful clinical benefits, including improved recovery after myocardial infarction, better heart failure management, and a reduced risk of ischemic and hemorrhagic stroke. Overall, regular physical activity is a powerful and accessible tool for reducing cardiovascular disease risk and promoting long-term health.

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1. Introduction

Cardiovascular diseases refer to the pathologies surrounding the heart and its circulation system; the most prominent cardiovascular diseases include heart failure, myocardial infarction, stroke, and peripheral artery disease [1,2]. Despite the continuous growth in the field of cardiovascular therapeutics, the global increase in deaths due to cardiovascular disease is still on the rise. To battle this persistent increase, efforts need to shift towards prevention by aiming at the root causes. One promising strategy would be to focus on beneficial lifestyle interventions, particularly on physical activity and exercise. It not only reduces the occurrence of conventional risk factors but also promotes longevity of cardiovascular health by aiming at its molecular and systemic level [3–6]. The benefit of incorporating exercise in one's lifestyle not only aids in building a healthy cardiovascular system but also acts as a systemic regulator, efficiently regulating communication between different organs [7].

Exercise acts by orchestrating a series of metabolic, immune, and endocrine signals that work together to sustain healthy cardiovascular resilience. For example, certain muscle-derived signaling molecules like exerkines can influence immune cell behavior and vascular tone, while adaptations in both adipose tissue and intestine further modulate inflammation and lipid balance [7,8]. Most importantly, these effects extend beyond risk factor modification, providing a molecular basis for exercise as both preventive and reparative across different cardiovascular pathologies. This integrated viewpoint emphasizes why exercise frequently works where single-target therapies do not, and it shows how it can serve as a catalyst for therapeutic approaches [9,10].

Apart from its well-known role in fitness and weight management, exercise is also being recognized for its role in improving cardiovascular health. Unlike pharmacological interventions, which mostly focus on a single target, exercise tends to have a broad effect and could potentially reshape the entire physiological environment [11,12]. It influences sympathetic and parasympathetic activity and helps maintain metabolic adaptations in the body and cardiac remodeling, and thus exercise provides both preventive and reparative benefits [13–15]. These effects, upon accumulating over time, help in reinforcing resilience against the slow progression of atherosclerosis and the sudden onset of myocardial infarction or stroke. Through population studies, physically active individuals have demonstrated a lower rate of cardiovascular morbidity and mortality in comparison to those with a sedentary lifestyle [12,16,17].

In this narrative review, we summarize the latest evidence of how exercise promotes cardiovascular health. We focus on how incorporating small changes in lifestyle can lead to an overall change in the trajectory of developing cardiovascular disease and maintaining a healthy life.

2. Effects of exercise on the cardiovascular system and systemic adaptations

2.1. Impact of exercise on lipids and metabolomics

Lipid metabolism is one of the most crucial mechanisms that influences cardiovascular health. Dyslipidemia, increased levels of low-density lipoprotein cholesterol (LDL-C) along with reduced levels of high-density lipoprotein cholesterol (HDL-C) and increased triglycerides, plays a critical role in the development of CVDs and, crucially, atherosclerosis. LDL particles become modified upon entering the arterial wall, which further promotes the formation of foam cells, a well-established initial step towards the development of atherosclerosis. Low HDL-C is linked to reduced cholesterol removal from blood vessels, which further supports plaque growth. High triglycerides and their remnant particles also add to cardiovascular risk, as many population studies show they are associated with faster plaque progression [18,19]. One potential goal in the prevention of atherosclerosis or CVDs caused by dyslipidemia would be lifestyle changes, i.e., by incorporating regular exercise in one's life. This intervention leads to changes at both molecular and systemic levels that directly lead to reduced cardiovascular risk [19–21]. At molecular levels, exercise works by upregulating lipoprotein lipase (LPL) in muscles, which in turn accelerates the clearance process of triglyceride-rich lipoproteins from the circulation, which leads to increased production of cardioprotective HDL particles [22,23,24]. In parallel, exercise upregulates adiponectin, which is an adipokine that helps in improving insulin sensitivity. Insulin sensitivity describes how well the body's tissues respond to insulin to take up glucose and regulate metabolism. When insulin sensitivity improves, muscles take up more glucose, which reduces the liver's need to produce glucose and triglycerides. This leads to lower circulating triglycerides and fewer lipid residues entering the vascular wall. Better insulin sensitivity also decreases the release of free fatty acids from adipose tissue, further reducing hepatic triglyceride production. Together, these changes support a healthier metabolic profile and lower cardiovascular risk [25]. This exerts anti-inflammatory and anti-atherogenic actions on the vascular endothelium. Lipid catabolism and systemic energy balance are also enhanced by increased endurance activity, which causes secretion of fibroblast growth factor 21 (FGF21), this in turn leads to reduced deposition of atherogenic lipids within the vascular wall [26,23,27,28]. A key signaling pathway that regulates this process is AMP-activated protein kinase (AMPK). Exercise activates AMPK in skeletal muscle and other tissues, and this shifts the metabolism towards fatty acid oxidation [29,30]. This activation in turn enhances muscle lipid utilization and reduces hepatic triglyceride production, thereby improving insulin sensitivity [31].

Exercise also plays a role in modifying adipose tissue, as fat distribution is a key determinant for CVD. Beyond acute signaling, exercise modifies white and brown adipose tissues by altering their mitochondrial activity [32,33]. This is exerted by upregulation of uncoupling protein-1 (UCP-1) and mitochondrial biogenesis; this in turn lowers low-grade inflammation, improves lipid clearance, and promotes a healthy metabolic profile that protects against atherogenesis. These molecular changes underline the clinical benefits of exercise [34,35].

Physically active individuals demonstrate higher HDL-C and lower LDL-C, reduced triglycerides, and improvements in lipoprotein quality [36,37]. Importantly, these changes lead to plaque stabilization through the formation of a thick fibrous cap, smaller lipid cores, and reduced inflammation in the atherosclerotic lesion. These changes are important as they lead to reduced risk of plaque rupture, which can lead to myocardial infarction and ischemic stroke. Altogether, these data show how exercise modulates the lipid-metabolic axis by coordinating with several mediators like LPL, adiponectin, and AMPK and reduces atherogenic burden and strengthens overall cardiovascular health [37–39]. The improvements in lipid metabolism described above help explain how exercise exerts its beneficial effects in slowing atherosclerosis progression. By lowering LDL-C, raising HDL-C, reducing triglycerides, and decreasing vascular inflammation, exercise directly reduces several major risk factors that drive plaque formation. These molecular and metabolic changes translate into slower progression of atherosclerosis and more stable plaques. Because exercise improves lipid handling and reduces inflammatory activity in the arterial wall, its effects are consistently associated with lower rates of coronary events. The clinical manifestation of atherosclerosis primarily begins with the coronary and carotid arteries and is one of the leading causes of mortality with coronary heart disease (CHD) [40]. Numerous factors have been identified as the cause of atherosclerosis; lifestyle and genetic factors influence the disease's progression and clinical symptoms. Defects in lipid and lipoprotein metabolism play a significant role in this development. The results of cholesterol-lowering medication intervention trials highlight the link between elevated plasma cholesterol levels, especially low-density lipoprotein (LDL) cholesterol, and CHD [41–43]. HDL cholesterol levels are inversely correlated with the occurrence of atherosclerotic CHD, according to numerous epidemiological studies. In

addition to its well-known cardioprotective function in reverse cholesterol transport, high-density lipoprotein (HDL) possesses anti-inflammatory and anti-oxidative properties. HDL is indeed a significant CHD risk indicator [44–46]. Exercise's positive effects include increased HDL cholesterol and decreased adiposity, triglyceride levels, the ratio of total cholesterol to HDL cholesterol, and an estimated 10-year risk of coronary heart disease [47,48] (Fig. 1).

2.2. Impact of exercise on immunity

A sedentary lifestyle promotes low-grade chronic inflammation. Low-grade chronic inflammation is persistent low-level activation of the immune system, which is accompanied by continuous release of inflammatory molecules in low levels [49]. It sustains endothelial dysfunction, which further leads to an enhanced process of atherogenesis and worsened post-infarct remodeling. This chronic inflammatory state also increases the expression of adhesion molecules on the vessel wall, making it easier for immune cells to enter the artery and promote plaque formation [50,51]. As a result, inflammation not only accelerates atherogenesis but also impairs the heart's ability to heal after an infarction, leading to worse remodeling outcomes. Exercise in this case helps by reprogramming the immune network. Certain circulating biomarkers of cardiovascular risk, like tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and C-reactive protein (CRP), show reduced levels upon persistent exercise, especially aerobic training [39,52,53]. Exercise reduces interleukin (IL-1β/IL-18) signaling, which drives plaque instability, by attenuating activation of NF-κB and the NLRP3 inflammasome. Mechanistic research in murine models indicates that exercise suppresses NLRP3 inflammasome activation in metabolic and cardiovascular contexts by reducing the production of IL-1β and IL-18 (e.g., aerobic exercise downregulates NLRP3 signaling in adipose tissue and macrophages in experimental models), further stabilizing atherosclerotic plaques. Moreover, human studies from peripheral blood mononuclear cells show that chronic moderate-intensity exercise significantly attenuates NLRP3 inflammasome activation in healthy adults, suggesting translational relevance of its inhibition. Nonetheless, direct demonstration of exercise-induced NLRP3 suppression within human atherosclerotic plaque tissue remains limited [54–56].

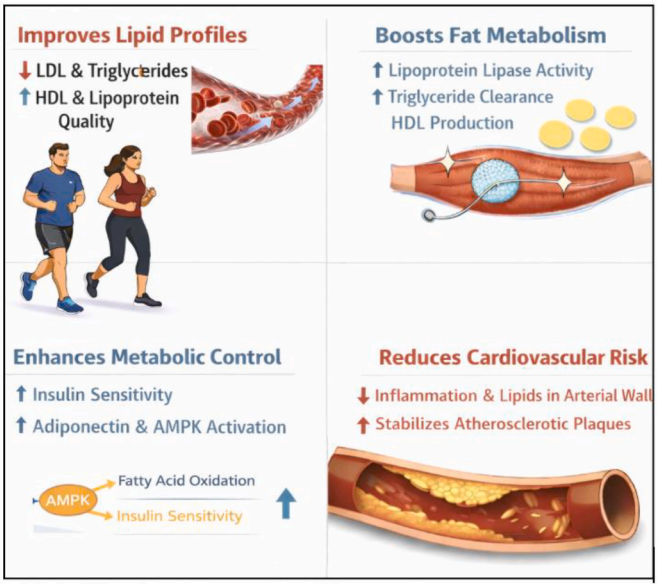

Fig. 1. Exercise improves circulating lipid profiles by reducing LDL cholesterol and triglycerides while increasing HDL levels. Through activation of AMPK, it enhances fatty acid oxidation and insulin sensitivity, reduces vascular inflammation, slows atherosclerosis progression, and promotes stabilization of atherosclerotic plaques, thereby lowering overall cardiovascular risk.

Changes in signaling processes are mirrored by changes at cellular levels. Exercise promotes anti-inflammatory changes in lymphocytes and monocytes, and it aids macrophages in transforming into the anti-inflammatory phenotype. The anti-inflammatory/reparative phenotype of macrophages is associated with an improved efferocytosis and reduced necrotic-core expansion in atherosclerosis; thereby, exercise helps in creating an intricate balance between cell repair and inflammation by acting on the immune levels [57–59]. Moreover, exercise also tends to exert its influence on the adaptive immune system: systematic reviews show expansion and/or functional activation of regulatory T cells (Tregs) after exercise, a change linked to lower endothelial activation and better vascular homeostasis [60]. Exercise has also been shown to affect the immune system by modulating cell adhesion molecules (CAMs). CAMs play an important role in leukocyte recruitment and migration. Several studies have shown that different types of exercises can regulate their activity and behavior [61–63]. Another distinctive contributor to the immune effects of exercise is the regulation of the exocrine environment and exercise-induced signals from muscle and other tissues. These signals propagate anti-inflammatory effects system-wide, improving endothelial nitric-oxide bioavailability, dampening monocyte adhesion, and tuning immune-cell metabolism. Several contemporary reviews and human omics studies have shown that single bouts and training blocks trigger coordinated proteomic, metabolomic, and immune shifts that are consistent with reduced inflammation and vascular protection [7,64–66].

Another potent target, nitric oxide (NO), is a strong mediator of vascular modulations induced by exercise. In active muscle, vasodilatation creates a pressure gradient, which in turn raises blood flow and causes upstream arteries to produce more NO. Therefore, greater microvascular flow can be made possible without lowering muscle perfusion pressure through NO-mediated dilatation of feed arteries. Regular exercise seems to alter this system, which may contribute to the lower cardiovascular risk associated with a trained state [67–69]. These molecular and cellular adaptations after exercise can translate into slower atherosclerotic progression with less proteolytic activity in plaques, leading to stable plaques, as well as better post-MI healing with improved cardiac remodeling [70,71]. Additionally, exercise has been shown to modulate the gut microbiota [72] by increasing short-chain fatty acid (SCFA) production (butyrate, propionate) via microbiome remodeling [73,74]. This immune-inflammatory reframing helps explain why exercise leads to better outcomes (Fig. 2).

2.3. Impact of exercise on the neuro-immune axis

The autonomic nervous system is important for regulating heart rate, cardiac output, vascular tone, and blood pressure. In healthy individuals, balanced sympathetic and parasympathetic activity ensures efficient cardiac function, appropriate vasodilation, and stable blood pressure control. This balance also supports normal baroreflex sensitivity and maintains healthy heart-rate variability, which are strong indicators of cardiovascular resilience. Regular shifts in autonomic tone during daily activity help preserve flexible vascular responses and protect against blood pressure instability [75,76]. In cardiovascular disease, autonomic balance becomes disrupted: sympathetic activity is persistently elevated while vagal tone is reduced, contributing to hypertension, endothelial dysfunction, and increased arrhythmic risk. Reduced baroreflex sensitivity and higher catecholamine release further worsen ventricular remodeling and promote disease progression. These autonomic abnormalities are consistently seen in heart failure, coronary artery disease, and myocardial infarction, where they predict poorer outcomes [77–79].

One of the major triggers leading to the onset of cardiovascular diseases is dysregulation between the immune system and the autonomic nervous system. Overstimulation of the sympathetic nervous system, combined with the suppression of vagal function, can lead to chronic inflammation with cardiac remodeling [80,81–83]. Exercise

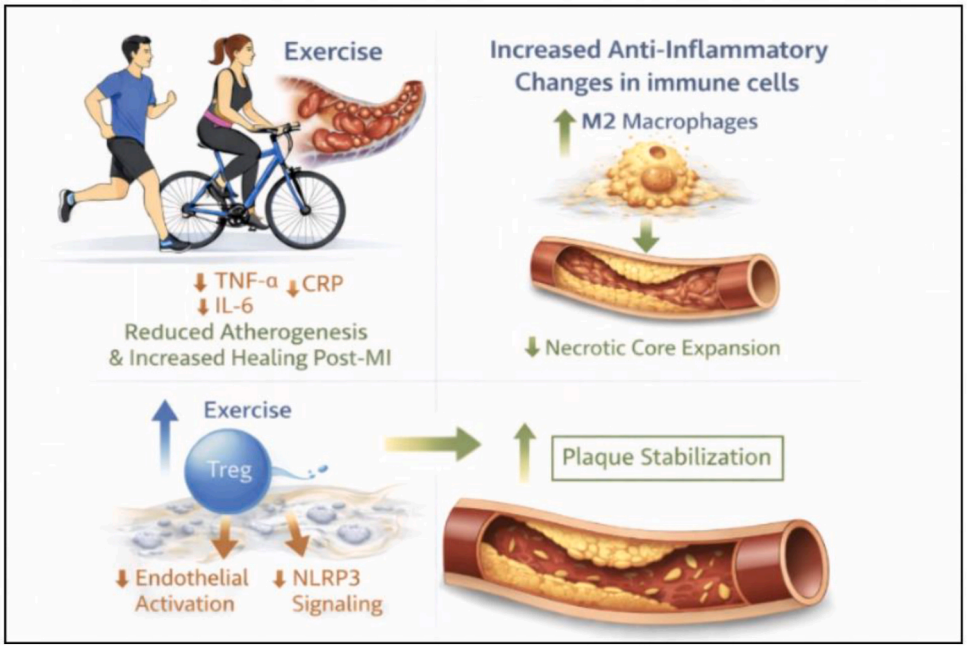

Fig. 2. Exercise reduces circulating pro-inflammatory mediators in circulation, thereby attenuating atherogenesis and promoting enhanced healing post-MI. It induces anti-inflammatory reprogramming of immune cells by polarization toward M2 macrophages, leading to a reduced necrotic core expansion within atherosclerotic plaques. In parallel, it increases regulatory T cell (Treg) abundance, leading to decreased endothelial activation and suppression of NLRP3 inflammasome signaling, collectively promoting plaque stabilization and reduced cardiovascular risk.

here has the capability to optimize the relation between the neuro-immune system and cardiovascular diseases by affecting the autonomic nervous system (ANS) and the immune system [84,85]. However, excessive physical activity may upset the balance between the formation of reactive oxygen species (ROS) and antioxidant defenses, potentially leading to cellular damage and maladaptive immunological responses, even if moderate exercise has been shown to have cardioprotective effects [86–88].

By encouraging angiogenesis and cardiac development, the brain-derived neurotropic factor (BDNF) is an essential signaling molecule that keeps the heart's vascular wall intact. Exercise helps in regulating this factor by increasing the amount of circulating BDNFs, which further support neural plasticity and vascular nitric oxide signaling [89,90]. Synthesis of this protein in humans during disease progression (e.g., multiple sclerosis, type-2 diabetes) shows a short-term increase in BDNF circulation with exercise training [91–93].

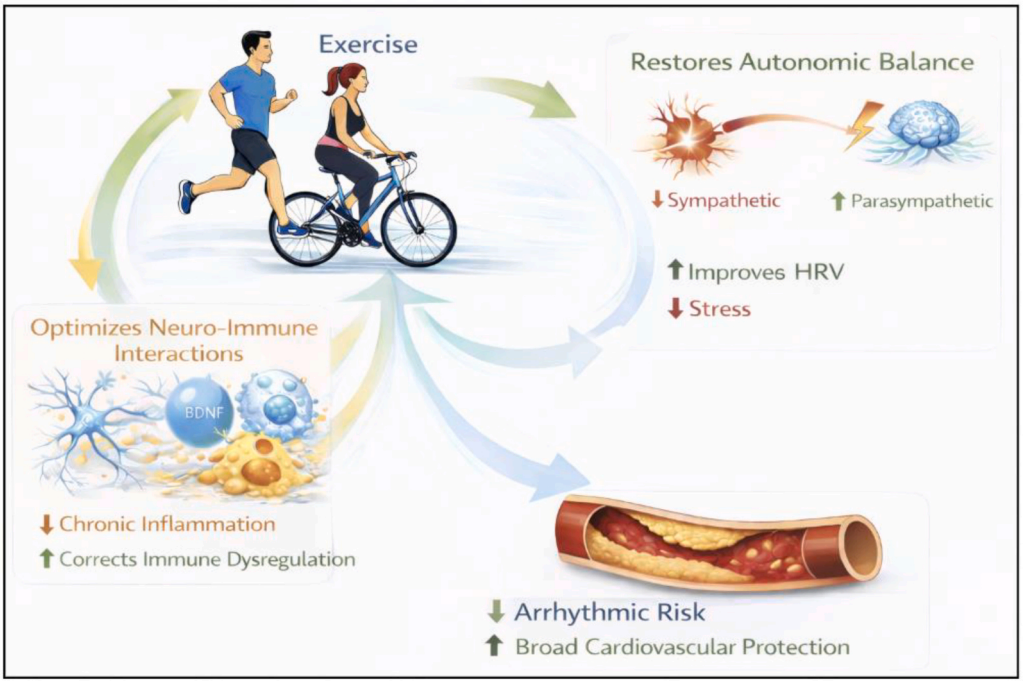

Fig. 3. Exercise shifts autonomic regulation toward reduced sympathetic and enhanced parasympathetic activity, resulting in improved heart rate variability (HRV) and reduced stress. In parallel, exercise regulates neuro-immune interactions by lowering chronic inflammation and correcting immune dysregulation.

Muscles upon exercise release certain signaling molecules called myokines, like BDNF and interleukin 6 (IL-6). This plays a vital role in muscle recovery after exercising and modulates brain function [81]. Exercise, therefore, promotes interorgan communication, which leads to lowered systemic inflammation and enhances neuroprotection [7,94,95]. Repeated training sessions direct the autonomic tone more toward greater parasympathetic and lower sympathetic drive, manifesting in a higher heart rate variability (HRV) and a lower resting heart rate, adaptations linked to better prognosis in both healthy and diseased populations [96,97]. Exercise also exerts its influence on the most important mechanoreceptors, the baroreceptors, which play a crucial role in transmitting information from changes in blood pressure within the autonomic system. This leads to a lowered risk of arrhythmogenic incidents and an optimized ventricular filling phase during stress [94,98,99].

In sum, the neuro-immune-muscle axis is a systems-level substrate through which exercise delivers cardiovascular protection (Fig. 3).

2.4. Impact of exercise on the intestine and microbiome

The gut microbiome refers to the bacteria that live in the gastrointestinal tract and help regulate digestion, metabolism, and immune function. Many studies have shown that these microbes influence inflammation and lipid metabolism, both of which are important for cardiovascular health. The gut microbiota is a key factor in maintaining metabolic and cardiovascular homeostasis [100,101]. Frequent resistance or endurance training has been shown to make significant enhancements of microbial diversity and specifically enriches taxa that produce short-chain fatty acids (SCFAs) [102,103]. These changes in the gut microbiome through exercise play an important role in the pathogenesis of CVDs [73]. By activating G protein-coupled receptors, SCFAs like acetate, propionate, and butyrate promote fatty acid oxidation, inhibit de novo lipogenesis, and reduce endothelial and macrophage inflammation in general. This, in turn, strengthens the endothelial barrier, limits lipopolysaccharide (LPS) translocation and subsequent Toll-like-receptor-4 signaling in the vascular walls [104–107]. In experimental models, SCFAs have shown to strengthen intestinal barrier function and attenuate innate inflammatory signaling, including NLRP3-related pathways (e.g., by enhancing tight junctions and reducing inflammasome activation in epithelial cells). However, in human studies, exercise has shown to modify gut microbiota composition by enhancing SCFA production, which correlates with improved systemic inflammatory profiles, although direct causal links to vascular or plaque-level NLRP3 modulation need further exploration [108,109].

Additionally, exercise also acts on trimethylamine-N-oxide (TMAO) metabolism. This is a small nitrogen-containing organic compound that is produced by the gut microbiota. Physically active individuals often exhibit reduced values of trimethylamine-N-oxide (TMAO) and its microbial precursors, which are linked to reduced atherogenesis and improved endothelial function [110–112]. Through modulation of bile acid profiles and SCFA signaling, these microbial shifts contribute to favorable hepatic lipid handling, characterized by decreased triglycerides and increased HDL. The gut–brain interface further mediates neuroprotective and autonomic benefits, as SCFAs and microbial metabolites regulate vagal activity and hypothalamic inflammation [113]. These findings indicate that exercise-induced microbiome remodeling and increased SCFA availability can lessen systemic and vascular inflammation during atherosclerotic progression. Although SCFAs are thought to enhance gut barrier function and reduce endotoxemia, direct evidence linking exercise-derived SCFAs to endothelial tight-junction regulation or leukocyte adhesion in humans remains limited [114]. Overall, exercise successfully helps in maintaining cardiovascular health by transforming the gut ecosystem into an anti-inflammatory, metabolically adaptive network [115,116]. Cross-sectional analyses show that a higher cardiorespiratory fitness is associated with greater microbial functional profiles as well as α-diversity (the mean species diversity in a site at a local scale), after considering diet and body composition adjustments. Furthermore, interventional studies show that short-term aerobic training increases microbial richness and alters community composition. Comparisons between endurance athletes and sedentary controls show a higher variance in microbial diversity and enrichment of metabolic pathways and fecal concentrations of SCFAs in athletes [117–119]. Ex-vivo and animal studies show that oral butyrate administration in *ApoE*$^{-/-}$ mice is able to reduce fatty streaks in aortas and change the plaque composition, whereas in the ex-vivo model of endothelial cells and macrophages, it results in a lower production of ROS and NO, leading to anti-inflammatory effects. However, there is limited clinical evidence to relate the effects of SCFAs and altered composition of atherosclerotic plaque in humans [107,120] (Fig. 4).

3. Systemic signaling networks: exercise modifies immunity, metabolism, and vascular health

3.1. Exerkines and myokines

During exercise, the skeletal muscles act as an endocrine organ by releasing exerkines into the circulation. Some of the key exerkines released are irisin, IL-15, FGF21, myonectin, and BDNF. These molecules, in turn, influence distant tissues such as the endothelium, adipose tissue, liver, and central nervous system [121,122]. Irisin, a molecule secreted by muscles, helps in browning white adipose tissue, which further improves mitochondrial oxidative capacity and systemic lipid metabolism. FGF21, on the other hand, modulates glucose and lipid turnover, enhances endothelial nitric-oxide synthase (eNOS) activation, and protects cardiomyocytes against oxidative stress, and IL-15 facilitates lipid oxidation and supports anti-inflammatory immune phenotypes. BNDF helps in shaping a stable neuro-heart communication that strengthens the autonomic nervous system [123–127]. Myonectin helps to reduce inflammation and apoptosis in the heart, especially in acute myocardial injury [128].

Through these modulations, exercise leads to systemic homeostasis of metabolic, vascular, and neuronal circuits, underscoring its dual preventive and reparative cardiovascular role.

3.2. Energy-sensing pathways and oxidative stress mitigation

Mitochondria play a central role in supplying energy to the cardiomyocytes, and in healthy individuals they maintain efficient ATP production and low levels of oxidative stress. Regular exercise enhances mitochondrial biogenesis, improves respiratory capacity, and increases antioxidant defences, all of which support optimal cardiac function. In cardiovascular disease, however, mitochondria become less efficient, produce more reactive oxygen species, and show impaired ATP generation, contributing to contractile dysfunction and disease progression. Mitochondrial damage is also linked to maladaptive remodeling after myocardial infarction and heart failure. Exercise helps counter these defects by improving mitochondrial quality control and restoring more balanced energy metabolism. These adaptations are key contributors to the cardioprotective effects of long-term physical activity [129–131]. Exercise helps in maintaining cellular energy homeostasis and mitochondrial stability, primarily by regulating the AMPK-mTORC1 axis. During exercise, the high levels of AMP/ATP released stimulate the AMPK axis, which in turn improves post-infarct cardiac function. This stimulation of AMP/ATP also promotes fatty acid oxidation and inhibits HMG-CoA reductase, thereby reducing cholesterol production. Similarly, mTORC1 is suppressed by AMPK, thereby reducing inflammatory cell production and excessive protein synthesis [132–134,135]. Mitochondrial dysfunction, an essential source of excess reactive oxygen species (ROS), contributes to oxidative stress in cardiovascular disease. Therefore, the mitochondrial improvements induced by exercise not only enhance energy production but also reduce ROS generation, creating a foundation for oxidative-stress mitigation.

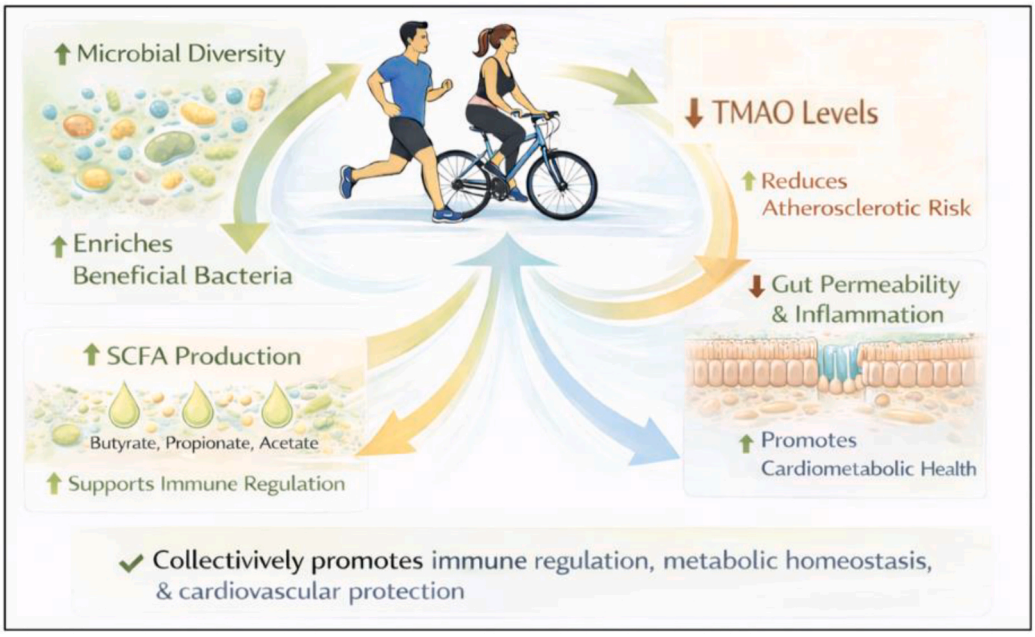

Fig. 4. Exercise increases microbial diversity, enhances production of short-chain fatty acids (SCFAs), and lowers trimethylamine-N-oxide (TMAO) levels. These exercise-induced microbial changes strengthen the gut barrier, reduce systemic inflammation, and support cardiovascular health.

Oxidative-stress mitigation plays an important role in exercise-mediated cardioprotection. Chronic inflammatory responses and oxidative stress are common characteristics of endothelial dysfunction and cardiovascular diseases [136,137]. Oxidative stress is a strong stimulus driving the pathogenesis and development of several CVDs. It makes individuals susceptible to cardiovascular risks like hypertension, atherosclerosis, ischemic heart disease, and cardiomyopathy [137].

In clinical research and animal models, elevated ROS levels have been linked to vascular dysfunction [138–140]. Several reports have shown that ROS-mediated activation of retrograde signaling pathways, such as NF-κB, results in chronic low-grade systemic inflammation that promotes the development of vascular disease in the elderly [141–143]. Also, Machi et al. [137] reported that elevated tissue oxidative stress may be linked to heart function impairment. While endothelial function, vascular tone, and heart function are thought to benefit from low levels of ROS, excessive ROS production can interfere with cellular signaling and cause cellular damage, thereby promoting atherosclerotic progression [137,144]. During myocardial infarction, excess mitochondrial ROS damage heart cells and worsen long-term healing by disrupting mitochondria, triggering inflammation, and promoting cell death [145, 146]. Increased antioxidant capacity and reduced oxidative stress levels are exercise-induced benefits that maintain cellular homeostasis. According to a recent study, eight weeks of cardiovascular exercise (CVE) training improved total antioxidant capacity (TAC) and lessened oxidative stress-induced heart damage in rats [147]. In Wistar rats with chronic heart failure, eight weeks of CVE training (swimming) improved left ventricular end-diastolic pressure, raised levels of the anti-inflammatory cytokine IL-10, lowered TBARS in skeletal muscle, and decreased lipid peroxidation [148,149]. Similarly, in post-myocardial infarction HF mice, CVE training over an 8-week period reduced cardiac endoplasmic reticulum stress by restoring cardiac proteasome activity, which is linked to better left ventricular (LV) function and exercise capacity [150]. In rats with aortic stenosis-induced heart failure, Gomes et al. [151] have demonstrated that low-intensity exercise training for 8 weeks enhanced cardiac structure and function, decreased oxidative stress, maintained antioxidant enzyme activity, and increased the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2, without any changes in NADPH oxidase activity or NF-κB pathway protein expression [152].

3.3. *Epigenetic reprogramming and post-transcriptional modulation*

Epigenetic mechanisms, such as DNA methylation and histone modification, regulate this process by controlling whether specific genes are turned on or off. In atherosclerosis, harmful epigenetic changes can promote inflammation, impair endothelial function, and increase lipid accumulation in the arterial wall. Exercise has been shown to reverse many of these adverse patterns by enhancing beneficial histone acetylation and reducing DNA methylation at genes involved in anti-inflammatory and antioxidant pathways. Through these well-established effects, exercise-driven epigenetic remodeling contributes to slowing plaque progression and improving vascular health [153,154].

Beyond altering acute signaling, exercise also induces epigenetic modifications that confer cardiovascular protection. Exercise leads to an increased activation of AMPK, which in turn leads to an increased phosphorylation of histone deacetylase 4 (HDAC4), which is an epigenetic repressor responsive to stress and protects against heart failure. This leads to an improved cardiac function in conditions of pressure overload or heart failure [155,156].

Exercise can also alter miRNA expression levels in cardiac tissues, leading to advantageous changes in heart function. One of the most researched miRNAs, miR-1, is elevated after aerobic exercise in both humans and rats, improving cardiac contractility and promoting the heart's structural and functional remodeling [157–159]. By modulating the pro-apoptotic and anti-apoptotic balance, exercise training can decrease the risk of coronary artery disease, heart failure, and cardiomyopathy. Similarly, miR133a levels rise in response to endurance exercises like marathons [160–162]. These results point to the preventive function of miR-133 against pathological cardiac remodeling. Another important miRNA that is elevated by different types of exercise, such as high-intensity interval training and aerobic exercise, is miR-21 [163, 164]. Several positive outcomes have been linked to the upregulation of miR-21, including the improvement of lipid metabolism, which can be especially helpful in conditions like hyperlipidemia and heart failure, and the downregulation of programmed cell death protein 4 (PDCD4), which can reduce apoptosis [165,166].

Acute training has been shown to induce DNA methylation changes that are not immediately restored to pre-exercise baseline levels [167]. Pilotto et al. (2024) successfully proved that the cells from the human

skeletal muscle have the capability to retain an epigenetic memory based on high intensity interval training and CpG methylation signatures have the capability to retain their alterations after a period of detraining, despite decline in physiological adaptations [168]. Circulating miRNAs have been linked to plaque composition in coronary artery disease patients, and exercise induced changes in specific miRNAs have been linked to a decrease in plaque burden. However, there has not been any direct confirmation within the plaque tissue itself. Furthermore, there is currently a limitation in evidence showing sustained molecular reprogramming in relation with long-lasting plaque stabilization [169,170].

4. Clinical effects of exercise on cardiovascular health

4.1. Myocardial infarction and post-infarct remodeling

Exercise training has a beneficial effect on several aspects of cardiac structure and function, especially after myocardial infarction (MI). In recent MI patients, it has been proven that early exercise training improves left-ventricular perfusion and contractility and is often associated with less adverse remodeling on follow-up imaging [171–173]. Exercise-based cardiac rehabilitation consistently reports better reduced all-cause mortality and reinfarction [174,175].

In experimental MI models, endurance training reduces inflammatory remodeling and scar thinning. Treadmill exercise or voluntary running in mice after MI attenuates expression of pro-inflammatory mediators in the infarct border zone, limits wall thinning, and reduces LV remodeling by attenuating inflammation [176,177]. Similar studies in rats show that aerobic or swimming training reduces myocardial fibrosis and improves diastolic and systolic function post-MI [178,179].

A central mechanism through which exercise confers protection after acute myocardial infarction is mitochondrial regulation. Mitochondrial dysfunction plays a key role in heart failure after an acute MI [180]. Long-term exercise training enhances replication of mitochondrial DNA, thereby upregulating PGC-1α, a master regulator of mitochondrial metabolism that is known to be inducible following exercise and is reduced in later stages of MI. In experimental myocardial infarction models, exercise augments PGC-1α signaling and mitochondrial biogenesis. There is strong evidence for skeletal muscle PGC-1α elevation, most of the evidence for exercise induced cardiac mitochondrial adaptations in humans comes from enhanced heart metabolic performance [181,182,183]. Significantly, long-term exercise may be helpful to improve the early adaptive response of mitochondrial biogenesis in the acute phase of MI, which may be linked to an upregulation of PGC-1α. Overall, chronic exercise reduced infarct size, limited cardiomyocyte apoptosis and autophagy, and improved myocardial metabolic profile in the acute MI setting [182,184–186].

4.2. Contractile dysfunction and heart failure

Exercise training through several autonomic and myocardial adaptations in the heart can lead to the prevention of heart failure. These autonomic adaptations help to enhance autonomic balance and reduce arrhythmic burden, both of which are often disrupted in HF [187,188]. Physiologic cardiac remodeling appears as concentric remodeling with resistance training and eccentric remodeling with endurance training, depending on the hemodynamic load applied [189]. Nonetheless, there is a great deal of flexibility in these remodeling patterns. Studies of two weeks of forced bed rest, which produced LV mass decreases compatible with cardiac atrophy and were avoided by supine exercise training, best demonstrate this [190].

In fact, exercise has been shown to reduce apoptotic signaling in cardiomyocytes in animal models. In a rat model, moderate exercise raised the expression of heat shock protein 70, which is known to decrease cardiomyocyte death, and attenuated age-associated increases in the Bax/Bcl-2 ratio (Bax and Bcl-2 are cytosolic proteins, with a higher ratio encouraging apoptosis) [191,192].

4.3. Stroke and cerebrovascular health

Regular exercise has been shown to reduce hypertension and obesity, improve glucose and lipid metabolic abnormalities, and lessen abnormal blood rheological characteristics. Overall, it leads to a decrease in ischemic and haemorrhagic stroke [193–196]. These benefits occur because exercise improves vascular function, helps maintain healthier blood pressure over time, and reduces the buildup of atherosclerotic plaque in major cerebral arteries. Regular physical activity also supports better endothelial health, which contributes to more stable cerebral blood flow. Together, these well-documented effects explain why physically active individuals consistently show lower stroke risk in large epidemiological studies. Exercise increases cerebrovascular resilience to ischemic injury through several experimentally confirmed changes [197]. One of the most regularly documented methods includes an increase in neurotrophic factors, particularly BDNF. Voluntary running boosts BDNF expression in the hippocampus, increasing neuroprotection, synaptic plasticity, and neurogenesis [198,199–202].

The second key mechanism through which exercise modulates ischemic cerebrovascular diseases is through regulating the production of VEGF and matrix metalloproteinase 2 (MMP2) after cerebral ischemia. This results in vascular remodeling and angiogenesis. Treadmill training increases the production of VEGF and MMP-2 following cerebral ischemia, which further promotes cerebral blood flow and improves neurobehavioral scores; these effects are attenuated when VEGF is neutralized, implicating a VEGF–MMP-2–dependent pathway [203–205]. Furthermore, exercise preconditioning may also protect against ischemia/reperfusion injury by enhancing brain microvascular integrity via TNF-alpha, which increases integrin production [206].

5. Clinical translation: prescription exercise and responses by population

Endurance exercise is recommended at a minimum of 150 min per week of moderate-intensity activity (e.g., brisk walking, cycling) or 75 min per week of vigorous-intensity activity (e.g., running, swimming). This can also be distributed throughout the week to cover the recommended hours, with additional strength training for muscles on an average of 2 days [207,208]. Exercise modality further influences outcomes. For example, aerobic training mostly focuses on improving cardiorespiratory fitness, whereas resistance sport helps in maintaining glucose metabolism, and muscular strength [209,210].

In a study with post-infarction heart failure patients, it has been shown that moderate intensity training improves lipid profiles, blood pressure, endothelial function, as well as inflammatory markers, whereas high intensity training has shown to produce increases in peak VO_2 [211]. By adding weekly exercise routine leads to progressive decreases in cardiovascular risk, although advantages level off at exceedingly high activity levels. Responses to exercise differ in various demographic and clinical settings. In middle-aged and older adults leading a sedentary life, a brief, moderate intensity aerobic exercise intervention (e.g., brisk daily walking for 12 weeks) can improve carotid artery compliance and restore vascular endothelial function [212]. In postmenopausal women, endurance exercise training enhances endothelial function, which is affected in the presence of estrogen, suggesting that vascular adaptations to exercise in women are significantly affected by hormonal status and may be diminished in estrogen deficient conditions [213].

Responses to exercise vary depending on the cardiovascular status at baseline. Training supports primary prevention by improving endothelial function, cardiometabolic risk profiles, and cardiorespiratory fitness in healthy individuals [214]. Supervised aerobic exercise improves peak VO_2, functional capacity, and health-related quality of life in patients with chronic HFrEF while also modestly lowering the risk of

cardiovascular hospitalization. Exercise training enhances exercise tolerance and quality of life in HFpEF, but its effects on hard clinical outcomes are still unclear [215].

6. Conclusion

Exercise supports cardiovascular health in several way, the most common being improvements in cholesterol level, lowering inflammation, enhancing insulin sensitivity, and strengthening blood vessels. Exercise also helps the heart to recover after injury, improves heart function in heart failure, and reduces the risk of stroke by supporting healthy blood pressure and brain blood flow. These benefits arise from changes in metabolism, immune activity, the nervous system, and even the gut microbiome. Because exercise influences many pathways at once, it provides beneficial effects that single medications cannot. Overall, regular physical activity, even in small amounts, can significantly lower the risk of cardiovascular disease and improve long-term health.

7. Future direction

Although exercise is well known to protect the heart and vessels, several questions remain for future research. More studies are needed to understand exactly how much and what type of exercise gives the best benefits for different individuals, especially those with existing heart disease. Although exercise clearly improves lipid metabolism, lowers inflammation, balances autonomic activity, strengthens mitochondrial function, and remodels the gut microbiome, it is still not fully understood how these mechanisms interact to slow atherosclerosis or prevent CVDs. More human studies using integrated multi-omics, microbiome profiling, and autonomic monitoring are needed to map these connections. It will also be important to determine which types and intensities of exercise most effectively target specific mechanisms, such as NLRP3 suppression, SCFA production, or epigenetic remodeling. Finally, to develop individualized, multi-system approaches for the prevention and treatment of cardiovascular disease, future research should examine how exercise might be integrated with newly developed treatments.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used ChatGPT (ChatGPT based on GPT-5.2) language editing. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of competing interest

The authors declare no conflicts of interest.

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