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A Comprehensive Review of Physical Activity and Exercise in Cardiovascular Disease Prevention: Mechanisms, Benefits, and Clinical Recommendations

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for approximately 18.6 million deaths annually. Physical inactivity has emerged as one of the most significant modifiable risk factors for CVD development and progression. This comprehensive review synthesizes evidence from major studies and clinical guidelines to examine the role of physical activity (PA) and exercise in cardiovascular disease prevention. The paper explores the epidemiological evidence linking physical inactivity to CVD risk, the physiological mechanisms underlying exercise-induced cardioprotection, including improvements in plasma lipid profiles, insulin sensitivity, blood pressure regulation, and vascular function. Additionally, this review examines emerging evidence on epigenetic modifications induced by exercise, including DNA methylation, histone modifications, and non-coding RNA expression that contribute to cardiovascular health. Current WHO guidelines recommend 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic PA weekly for adults, with additional muscle-strengthening activities. The review also addresses exercise considerations for specific CVD populations, risk stratification approaches, and practical strategies for healthcare professionals to counsel patients on physical activity adoption. Despite robust evidence supporting exercise benefits, global physical inactivity rates remain high at 31% among adults and 81% among adolescents, necessitating urgent public health interventions and policy implementations.

Keywords: - Physical activity, Cardiovascular disease prevention, Exercise physiology, Epigenetic modifications, Clinical recommendations

1. INTRODUCTION

Cardiovascular disease (CVD) encompasses a range of conditions affecting the heart and blood vessels, including coronary artery disease, heart failure, congenital heart defects, cerebrovascular disease, and peripheral artery disease (Sun et al., 2025). With nearly 18.6 million deaths annually, CVD remains the leading cause of death globally, imposing a substantial burden on morbidity, quality of life, and healthcare systems worldwide (Roth et al., 2020).

Among the many risk factors that predispose individuals to CVD development and progression, physical inactivity has been recognized as a leading contributor to poor cardiovascular health. The World Health Organization (WHO) defines physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure, encompassing all movement during leisure time, transport, work, or domestic activities (WHO, 2024). Exercise, a subset of physical activity, is characterized as planned, structured, repetitive activity undertaken with the objective of improving or maintaining physical fitness (Nystoriak & Bhatnagar, 2018).

Extensive epidemiological evidence demonstrates that regular physical activity is robustly associated with decreased cardiovascular mortality and reduced risk of developing CVD. Physically active individuals exhibit lower blood pressure, enhanced insulin sensitivity, more favorable plasma lipoprotein profiles, and improved cardiorespiratory fitness (Nystoriak & Bhatnagar, 2018). Despite this compelling evidence, global physical inactivity rates remain alarmingly high, with approximately 31% of adults and 81% of adolescents failing to meet recommended physical activity levels (WHO, 2024).

This comprehensive review aims to synthesize current knowledge on the relationship between physical activity and cardiovascular disease prevention, examining epidemiological evidence, physiological mechanisms, emerging epigenetic insights, and practical clinical recommendations for healthcare professionals.

2. EPIDEMIOLOGICAL EVIDENCE: PHYSICAL INACTIVITY AS A CARDIOVASCULAR RISK FACTOR

2.1 Global Burden of Physical Inactivity

Physical inactivity has been identified as one of the leading risk factors for non-communicable disease mortality. A pooled analysis of 507 population-based surveys with 5.7 million participants revealed that nearly one-third (31%) of the world's adult population approximately 1.8 billion adults are physically inactive, failing to meet the global recommendation of at least 150 minutes of moderate-intensity physical activity per week (Strain et al., 2024). This represents a 5 percentage point increase between 2010 and 2022, with projections indicating that if current trends continue, 35% of adults will be insufficiently active by 2030.

The public health impact of physical inactivity is substantial. A study analyzing population-attributable risk across 168 countries estimated that global all-cause mortality and CVD mortality rates attributable to physical inactivity are 7.2% and 7.6%, respectively (Katzmarzyk et al., 2022). The healthcare costs associated with physical inactivity-related non-communicable diseases are estimated at approximately US$ 53.8 billion annually, with the total economic burden projected to reach US$ 300 billion between 2020 and 2030 if inactivity levels are not reduced (WHO, 2024).

2.2 Dose-Response Relationship

A clear inverse linear dose-response relationship exists between physical activity volume and all-cause mortality rates in both men and women, across younger and older populations. Minimal adherence to current physical activity guidelines, yielding an energy expenditure of approximately 1000 kcal per week, is associated with a significant 20-30% reduction in all-cause mortality risk (Fundakar, 2023). Further risk reductions are observed at higher volumes of energy expenditure, although the optimal dose-response curve and potential upper limits remain subjects of ongoing investigation. Studies examining the effects of exercise intensity and duration have revealed that even small amounts of physical activity confer cardiovascular benefits. Moving from a completely sedentary lifestyle to an activity level of approximately 72 minutes per week—just over 10 minutes daily—significantly improves cardiorespiratory fitness and reduces CVD risk (Carnehton, 2009).

2.3 Demographic Variations

Notable demographic disparities exist in physical activity levels globally. Women are consistently less active than men by an average of 5 percentage points, a gap that has persisted since 2000. After age 60, physical inactivity levels increase in both sexes. Among adolescents aged 11-17 years, 81% are physically inactive, with adolescent girls (85%) being less active than adolescent boys (78%) (Guthold et al., 2019). Geographically, physical inactivity rates are significantly higher in high-income countries (36.8%) compared to low-income countries (16.2%), reflecting differences in occupational physical activity, transportation patterns, and leisure-time activity opportunities (Katzmarzyk et al., 2022).

3. PHYSIOLOGICAL MECHANISMS OF EXERCISE-INDUCED CARDIOPROTECTION

3.1 Effects on Plasma Lipids and Atherogenesis

Regular endurance training is associated with favorable modifications in circulating lipoprotein profiles. Studies have demonstrated that exercise training elevates high-density lipoprotein (HDL) levels and, to a lesser extent, reduces triglyceride concentrations—both changes that reduce coronary heart disease risk (Nystoriak & Bhatnagar, 2018). A dose-dependent effect of exercise on plasma lipids has been established, with higher intensity and duration producing greater improvements in LDL, triglycerides, and very low-density lipoprotein (VLDL) particle size.

Beyond quantitative changes in lipoprotein concentrations, exercise induces qualitative improvements in lipoprotein function. HDL particle size, a key determinant of ATP-binding cassette transporter A1 (ABCA1)-mediated cholesterol efflux capacity, increases with exercise training. Studies investigating dose-dependent effects of exercise on cholesterol efflux have reported significant increases in HDL cholesterol and efflux capacity, particularly in high-amount/high-intensity intervention groups (Sarzynski et al., 2018).

Exercise also directly impacts arterial wall homeostasis, antagonizing atherosclerotic disease progression. In animal models, exercised ApoE-deficient mice exhibit elevated endothelial nitric oxide synthase (eNOS) expression and suppressed neointimal formation after injury compared to sedentary controls (Pynn et al., 2004). Regular physical activity in high-cholesterol diet-fed LDL receptor-null mice preserves aortic valve endothelial integrity, reduces inflammatory cell recruitment, and prevents aortic valve calcification (Matsumoto et al., 2010).

3.2 Insulin Sensitivity Enhancement

Physical activity profoundly influences systemic insulin sensitivity, a critical factor in cardiovascular health. Insulin resistance promotes heart disease development, in part by altering blood lipid profiles, increasing free fatty acid release, and promoting triglyceride and VLDL production (Ginsberg, 2000). Multiple studies have demonstrated that individuals with insulin-dependent and non-insulin-dependent diabetes mellitus exhibit improved insulin sensitivity and glycemic control following exercise training. Even a single low-intensity exercise session (50% VO_2max, 350 kcal expended) results in significantly improved insulin sensitivity and fatty acid uptake when measured the following day (Newsom et al., 2013). The cellular mechanisms underlying exercise-enhanced insulin sensitivity involve adaptive remodeling of insulin signaling pathways. During exercise, insulin levels are slightly reduced, while contracting muscle exhibits greater glucose uptake via enhanced insulin-independent sarcolemmal translocation of GLUT4 glucose transporters (Richter et al., 1989). Exercise conditioning is associated with adaptive changes in the expression and regulation of components within the insulin receptor/insulin receptor substrate (IRS)/PI3K/Akt signaling cascade (Kirwan et al., 2000).

3.3 Blood Pressure Regulation

While acute exercise transiently increases cardiac output and mean arterial blood pressure, long-term exercise promotes net reduction in resting blood pressure. A meta-analysis of randomized controlled interventional studies found that regular moderate to intense exercise performed 3-5 times weekly lowers blood pressure by an average of 3.4/2.4 mmHg (Fagard, 2001). Although this change may appear modest, even a 1 mmHg reduction in systolic BP is associated with 13-20 fewer heart failure events per 100,000 person-years (Hardy et al., 2015).

The blood pressure-lowering effects of chronic aerobic and resistance exercise are driven largely by reduced systemic vascular resistance. Shear forces and metabolites released from active skeletal muscle during exercise stimulate endothelial production and release of nitric oxide (NO) and prostacyclin, promoting enhanced vasodilation via vascular smooth muscle relaxation (Niebauer & Cooke, 1996). Long-term exercise training increases eNOS expression and NO production in hypertensive individuals, consistent with blood pressure-lowering effects (Zago et al., 2010). Additional contributors to exercise-induced blood pressure reduction include adaptive reductions in sympathetic nerve activity, prevention or reversal of arterial stiffening, and suppression of inflammation (Wilund, 2007; Fleenor et al., 2010).

3.4 Cardiac Adaptations

The heart undergoes morphological adaptation to recurrent exercise by increasing mass through ventricular chamber wall thickening. Unlike pathological remodeling associated with chronic pressure overload, exercise-induced cardiac hypertrophy occurs with preservation or enhancement of contractile function (Borlaug et al., 2009).

Experimental animal models have identified several cellular and molecular alterations involved in physiological cardiac growth. Mitochondrial biogenesis and fatty acid oxidation capacity are enhanced following exercise, contrasting with pathological remodeling characterized by reduced oxidative energy production (Burelle et al., 2004). Insulin-like growth factor-1 (IGF-1) and insulin receptor signaling via the PI3K/Akt1 pathway play dominant roles in activating transcriptional pathways associated with protein synthesis and hypertrophy (McMullen et al., 2004). Exercise training improves systolic and diastolic function, enhances cardiomyocyte contraction-relaxation velocities, and increases force generation. These functional adaptations may relate to alterations in intracellular calcium transient dynamics, including enhanced coupling efficiency between L-type calcium channels and ryanodine receptors, and increased expression of sarcoendoplasmic reticulum calcium ATPase (SERCA2a) and sodium-calcium exchanger (NCX) (Wisloff et al., 2002; Kemi et al., 2008).

3.5 Vascular Adaptations

The resistance arterial network undergoes functional and structural adaptation to exercise. Repeated exercise leads to increased vascular density coupled with greater vasodilatory capacity in skeletal muscle arterioles, enabling enhanced perfusion following conditioning (Sun et al., 1994; Laughlin et al., 2017). Endothelial synthesis of NO is substantially increased at rest and during exercise in conditioned individuals and animals (Taddei et al., 2000).

Similar adaptive responses occur in coronary vasculature, including expansion of intramyocardial arteriole and capillary density, enhanced microvascular collateral formation, and improved responsiveness to vasoactive stimuli (White et al., 1998; Mobius-Winkler et al., 2016). Some studies implicate hydrogen peroxide (H_2O_2)-mediated vasodilation in opposing exertion-induced arterial dysfunction following exercise training, suggesting enhanced contribution of NO-independent mechanisms to improved microvascular endothelial function (Durand et al., 2015).

4.EPIGENETIC MODIFICATIONS: THE MOLECULAR INTERFACE BETWEEN EXERCISE AND CARDIOVASCULAR HEALTH

4.1 Exercise as an Epigenetic Modulator

Emerging evidence indicates that exercise serves as a potent epigenetic modulator, triggering immediate and lasting genetic changes that activate biological signals associated with cardiovascular health (Sun et al., 2025). Exercise induces various epigenetic modifications, including DNA methylation changes, post-translational histone modifications, and non-coding RNA expression alterations, which can directly modify cardiac epigenetic status, improve vascular function, reduce inflammatory responses, alter myocardial metabolism, and protect the heart from pathological insults (Wu et al., 2021).

4.2 DNA Methylation Changes

DNA methylation, primarily involving cytosine methylation at CpG sites to form 5-methylcytosine (5mC), is commonly associated with gene silencing. Exercise induces significant demethylation across the genome, particularly in CpG islands and gene promoter regions, promoting transcriptional activity of genes related to cardiovascular function (Denham et al., 2015). A four-week sprint interval training intervention in young men revealed elevated cardiorespiratory fitness, decreased LDL cholesterol levels, and significant genome-wide demethylation. Altered methylation status of epidermal growth factor and associated miRNAs (miR-21 and miR-210) affected expression of genes related to cardiovascular function (Denham et al., 2015). Exercise also modulates hypertension through DNA methylation-mediated regulation of ion channels. Studies demonstrate that exercise increases methylation of genes encoding the α1c subunit of L-type calcium channels and the β1 subunit of large-conductance calcium-activated potassium channels, reducing their expression and function and contributing to arterial blood pressure reduction in hypertensive states (Zhang et al., 2020).

4.3 Histone Modifications

Although studies of exercise-induced histone modifications in cardiovascular health remain limited, evidence indicates that strenuous exercise alters histone conformation in human skeletal muscle. Exercise increases acetylation of histone H3K36, a modification associated with enhanced gene expression during transcriptional elongation (McGee et al., 2009). Exercise also leads to nuclear export of specific histone deacetylases (HDAC4 and HDAC5), relieving their inhibitory effects on transcription. Activation of signaling pathways such as AMPK and CaMKII during exercise promotes extranuclear export of HDAC4 and HDAC5, regulating histone acetylation status.

4.4 Non-Coding RNAs in Cardiovascular Disease

Non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), play central roles in biological processes and contribute to CVD development (Gevaert et al., 2022). Exercise modulates the expression of numerous ncRNAs involved in cardiovascular health.

Aerobic exercise slows atherosclerotic plaque development by downregulating the lncRNA NEAT1 through reduced N6-methyladenosine (m6A) modification and decreased activity of the m6A-modifying enzyme METTL14 (Yang et al., 2023). NEAT1 drives endothelial cell pyroptosis by binding to the KLF4 transcription factor and activating NLRP3 transcription. By reducing NEAT1 expression, exercise inhibits endothelial cell death, ameliorating atherosclerosis. In chronic heart failure models, eight weeks of aerobic exercise significantly enhanced cardiac function, reduced reactive oxygen species and inflammatory factors, and promoted cardiomyocyte autophagy. These benefits appear mediated through lncRNA MALAT1 regulation of miR-150-5p and downstream PI3K/Akt signaling (Hu et al., 2021). Following myocardial infarction, moderate-intensity aerobic exercise improves cardiac function, reduces myocardial fibrosis and apoptosis, and regulates expression of specific lncRNAs—decreasing MIAT and increasing H19 and GAS5 expression (Farsangi et al., 2021).

5. PHYSICAL ACTIVITY GUIDELINES AND RECOMMENDATIONS

5.1 WHO Guidelines

The World Health Organization 2020 Guidelines on Physical Activity and Sedentary Behavior provide evidence-based recommendations for all age groups (Bull et al., 2020). For adults, the guidelines recommend:

- **150-300 minutes** of moderate-intensity aerobic physical activity per week, **or**
- **75-150 minutes** of vigorous-intensity aerobic physical activity per week, **or**

An equivalent combination of moderate- and vigorous-intensity activity. For additional health benefits, adults should perform muscle-strengthening activities involving all major muscle groups at moderate intensity on two or more days per week. For adults aged 65 years and older, additional participation in varied multicomponent

physical activity focusing on functional balance and strength training at moderate or greater intensity on three or more days per week is recommended to enhance functional capacity and prevent falls.

5.2 Intensity Classification

Physical activity intensity can be categorized based on the individual's maximum aerobic capacity (VO_2max). Moderate-intensity activities (40-60% VO_2max) include brisk walking (2.4 to 4 mph), biking (5 to 9 mph), active yoga, and recreational swimming. Vigorous-intensity activities (>60% VO_2max) include jogging/running, biking (>10 mph), tennis, and competitive swimming (Regmi & Siccardi, 2019). The Rating of Perceived Exertion (RPE) provides an alternative method for monitoring exercise intensity, particularly useful for patients taking medications that affect heart rate response, such as beta-blockers.

5.3 Exercise Prescription for CVD Patients

The American College of Sports Medicine (ACSM) has published guidelines adapted for patients with cardiovascular disease (ACSM, 1994). Key recommendations include:

Frequency: Minimum of three non-consecutive days per week

Duration: 10-minute warm-up and cool-down phases including stretching and flexibility exercises; 20-40 minutes of continuous or interval cardiovascular exercise

Intensity: 40-85% VO_2max, 40-85% maximal heart rate reserve, or 55-90% of maximal heart rate; moderate intensity in supervised programs

Mode: Continuous exercise using large muscle groups (walking, swimming, group aerobics) for cardiovascular endurance; upper extremity exercises for individuals with lower extremity limitations; resistance exercises using circuit training approach (10-12 exercises, 10-12 repetitions)

Progression: Slow progression of exercise duration and intensity with careful patient observation

6. PHYSICAL ACTIVITY IN SPECIFIC CARDIOVASCULAR CONDITIONS

6.1 Coronary Artery Disease

Exercise is indicated in both primary and secondary prevention of coronary artery disease (CAD). Studies demonstrate that regular exercise intervention outperforms percutaneous coronary intervention (PCI) on multiple measures over two years: event-free survival rates of 78% in exercise groups versus 62% in PCI cohorts; VO_2max increases of 10% versus 7%; and significant reductions in inflammatory markers (high-sensitive C-reactive protein and interleukin-6) in exercise groups with no relevant changes in PCI groups (Walther et al., 2008).

6.2 Heart Failure

Exercise programs for patients with heart failure improve exercise tolerance and quality of life, with modest impacts on all-cause mortality, heart failure-specific mortality, and hospitalization rates (Rees et al., 2004). Exercise training without restrictions is recommended for stable heart failure patients on optimal medical therapy with low NT-proBNP and low New York Heart Association scores. High-risk patients require individually tailored sports advice.

6.3 Hypertension

Inactive individuals have 30-50% greater risk of developing hypertension compared to active individuals (Whelton et al., 2013). Aerobic fitness training provides the greatest blood pressure-lowering benefits, followed by dynamic resistance and isometric resistance training at moderate intensity (Cornelissen & Smart, 2013).

6.4 Valvular Heart Disease, Aortic Disease, and Arrhythmias

Asymptomatic individuals with mild to moderate valvular heart disease can engage in all types of physical activity, but careful assessment of exercise-induced cardiac event risk based on symptoms and valve dysfunction severity is essential before initiating exercise (Pelliccia et al., 2021). Physical activity is advised for all patients with aortic pathology, even with aortic dilation. However, due to blood pressure increases and wall stress during intense exercise, some activities may promote further aortic enlargement, increasing acute aortic dissection risk. As aneurysm-related hazard increases (larger diameter, hereditary pathology, rapid growth, or hypertension), more intensive sports become contraindicated (Thijssen et al., 2019). For arrhythmogenic conditions, sports participation management is based on three principles: prevention of life-threatening arrhythmias during exercise, symptom management enabling sports participation, and evaluation of arrhythmogenic condition progression due to sports involvement (Pelliccia et al., 2021).

7. RISK STRATIFICATION AND SAFETY CONSIDERATIONS

7.1 Contraindications to Exercise

- Absolute contraindications to exercise include (Revalidation Support Unit, 2019):

Uncontrolled or poorly controlled asthma

- Cancer or blood disorders with leukocytes below 0.5 × 10⁹/L, hemoglobin below 60 g/L, or platelets below 20 × 10⁹/L
- Unstable COPD with oxygen saturation below 88-90%
- Diabetes with blood glucose >13 mmol/L or <5.5 mmol/L
- Acute myocardial infarction or unstable angina (until stable for at least 5 days)
- Dyspnea at rest, pericarditis, myocarditis, endocarditis
- Symptomatic aortic stenosis, cardiomyopathy
- Unstable or acute heart failure, uncontrolled tachycardia
- Resting blood pressure >180 mmHg systolic or >100 mmHg diastolic
- Acute pulmonary embolus or pulmonary infarction
- Any acute severe illness

7.2 Exercise Risks

For patients with coronary heart disease, exercise-associated risks include acute myocardial infarction, cardiac arrest, and sudden death. Incidence in supervised cardiac rehabilitation programs is approximately: 1 myocardial infarction per 294,000 patient hours, 1 cardiac arrest per 112,000 patient hours, and 1 death per 784,000 patient hours. Over 80% of individuals reporting cardiac arrest symptoms during exercise are successfully resuscitated with prompt defibrillation (Thompson et al., 2007).

7.3 Risk Stratification Approach

Following 2020 ESC Guidelines on sports cardiology, risk assessment should include thorough physical examination, electrocardiography, and complete clinical history (Pelliccia et al., 2021). Low-risk patients with CVD (low-risk CAD, stable heart failure, asymptomatic/mild valvular heart disease, low-risk aortic disease, well-tolerated atrial fibrillation, simple congenital heart disease) require no exercise restrictions. High-risk patients require additional assessment including echocardiography, exercise stress testing, and advanced imaging when indicated, with individualized exercise plans and more frequent counseling.

8. PRACTICAL STRATEGIES FOR PHYSICAL ACTIVITY COUNSELING

8.1 The Counseling Approach

Effective lifestyle counseling should address six domains: exercise, diet, substance use, sleep, social interactions, and relaxation (Eimers, 2023). When counseling patients on physical activity, it is essential to:

1. Assess the patient's understanding of physical activity benefits
2. Classify current lifestyle status
3. Identify preferred types of physical activity
4. Address fears or concerns about physical activity participation
5. Identify personal obstacles to regular activity
6. Determine needed support from healthcare systems

Starting with small improvements in domains where patients demonstrate highest intrinsic motivation increases likelihood of maintaining healthy habits long-term and facilitates improvements in other domains.

8.2 Overcoming Common Obstacles

Common obstacles to physical activity engagement include financial limitations, time constraints, transportation challenges, insufficient social support, concerns about potential harm, limited access to exercise facilities, physical limitations, and cultural or social norms. Healthcare professionals should work collaboratively with patients to develop individualized strategies addressing these barriers.

8.3 Cardiac Rehabilitation and Prehabilitation

International guidelines advise cardiac rehabilitation following acute coronary syndrome, focusing on physical and mental recovery and prevention of recurrent cardiac events through cardiovascular risk factor modification and healthy lifestyle adoption (den Uijl et al., 2021). Prehabilitation—physical activity proposed prior to surgery to enhance cardiorespiratory fitness—potentially improves postoperative outcomes and complications. Although limited evidence exists regarding exercise prehabilitation before cardiac surgery, multidisciplinary team involvement ensures safety, and further research in this area is warranted (Barberan-Garcia et al., 2018).

9. CONCLUSIONS AND FUTURE DIRECTIONS

Regular physical activity confers substantial cardiovascular benefits through multiple mechanisms, including improvements in plasma lipid profiles, insulin sensitivity, blood pressure regulation, cardiac and vascular function, and emerging epigenetic modifications. Current evidence supports a dose-response relationship between physical activity volume and cardiovascular risk reduction, with even small amounts of activity

providing meaningful benefits. Despite robust evidence supporting exercise benefits, global physical inactivity rates remain alarmingly high at 31% among adults and 81% among adolescents, necessitating urgent public health interventions. Healthcare professionals should implement physical activity as a general treatment strategy, recognizing that any type of physical activity yields positive effects on cardiovascular health, contributing to a 27% reduction in relative risk of cardiovascular mortality. Future research should address several key questions: the optimal dose-response relationship and potential upper limits of exercise benefit; mechanisms underlying sex differences in exercise response; the role of epigenetic modifications in exercise-induced cardioprotection; effective strategies for long-term physical activity adherence; and personalized exercise prescription based on genetic and epigenetic profiles.

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