

Exercise benefits in cardiovascular diseases: from mechanisms to clinical implementation

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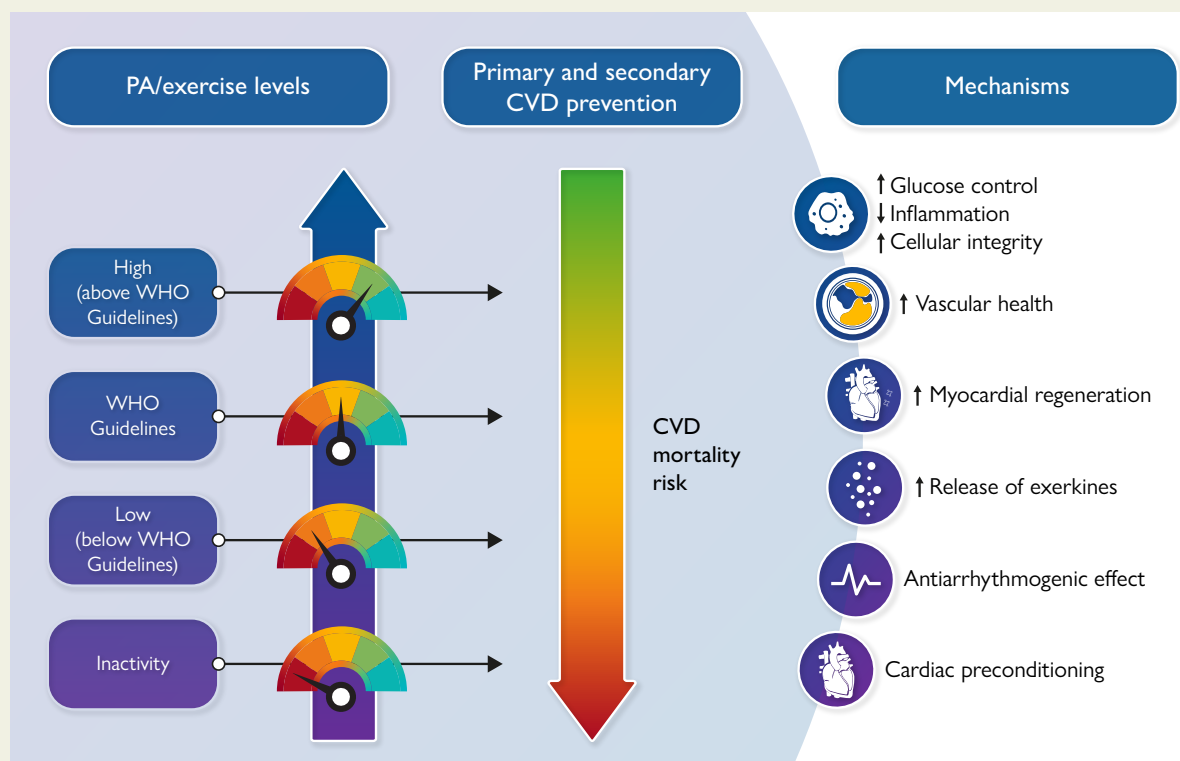
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Graphical Abstract



Summary of the main effects of regular physical activity (PA) and exercise on cardiovascular disease (CVD). WHO, World Health Organization.

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Abstract

There is a pandemic of physical inactivity that appears to parallel the widespread prevalence of cardiovascular disease (CVD). Yet, regular physical activity (PA) and exercise can play an important role not only in primary cardiovascular prevention but also in secondary prevention. This review discusses some of the main cardiovascular effects of PA/exercise and the mechanisms involved, including a healthier metabolic milieu with attenuation of systemic chronic inflammation, as well as adaptations at the vascular (antiatherogenic effects) and heart tissue (myocardial regeneration and cardioprotection) levels. The current evidence for safe implementation of PA and exercise in patients with CVD is also summarized.

Keywords

Exercise and cardiovascular disease • Primary cardiovascular prevention • Secondary cardiovascular prevention • Cardiovascular mortality • Exercise implementation

Cardiovascular disease prevention: epidemiological evidence

Primary prevention

More than one in four adults fail to meet World Health Organization (WHO) recommendations regarding aerobic physical activity (PA)—that is, 150–300 or 75–150 min/week of moderate (MPA, e.g. walking) or vigorous (VPA, e.g. brisk/very brisk walking) PA, respectively, or a combination thereof [MVPA, equalling ~750 metabolic equivalents of task (MET)-min/week].¹ Of note, PA is defined as ‘any bodily movement produced by skeletal muscles that requires energy expenditure and includes the domains of occupational, domestic, transportation, and leisure time’ (e.g. walking to work or walking the dog),¹ whereas physical exercise (or ‘exercise training’) is a form of more structured leisure-time PA with the purpose of improving or maintaining health (e.g. enrolling in supervised cardiac rehabilitation programmes or training for a 10 km running race). Although both terms are frequently used interchangeably, the bulk of observational epidemiological evidence is based on PA data—whether objectively determined (e.g. with accelerometers) or, more commonly, self-reported—whereas exercise is frequently used in intervention trials and preclinical studies assessing biological outcomes (e.g. molecular adaptations). Physical inactivity has major effects on global health and is an important risk factor for incident cardiovascular disease (CVD) and overall mortality, whereas regular MVPA has the opposite (and largely dose-responsive) effects.² In a large ($n = 116\,221$) 30-year follow-up, both self-reported leisure-time MPA and VPA were independently and inversely associated with CVD and all-cause mortality risk (19%–25% and 15%–31% lower risk if meeting aforementioned WHO recommendations of MPA or VPA, respectively).³ However, no positive—or negative—association was observed beyond this level. A follow-up report (median ~5 years) found an inverse dose-response association between objectively determined (with accelerometers) PA levels—whether measured as MPA, VPA, or total MVPA—and incident CVD, with no upper limit for this association.⁴ Individuals in the highest quarter of total MVPA had a 53% lower risk of incident CVD than those in the lowest quarter.⁴ In addition, a higher number of daily step counts, particularly if performed at high intensity (30/min) seems associated with a lower CVD incidence (–10% for each 2000 steps), at least up to ~10 000 steps/day.⁵ On the other hand, low PA doses might also be beneficial, with recent evidence that, although VPA around 50–60 min/week was associated with the largest reduction in incident CVD and CVD-specific mortality (i.e. nadir of the dose-response association curve), a ~40% decrease in CVD mortality risk was nevertheless found at only 15–20 min/week.⁶

Current international guidelines¹ also recommend performing regular strengthening activities (e.g. lifting weights) for their health effects that include not only improvements in bone and muscle mass but also in cardiovascular health (e.g. 17% lower risk of CVD mortality with 40–60 min/week of this type of activity).⁷ Of note, although both MVPA and strengthening activities are associated with improvements in cardiometabolic health and mortality risk, it is the combination of the two that provides the greatest effects.^{7–9} It is important, on the other hand, to limit the amount of time spent in sedentary pursuits (any waking behaviour characterized by an energy expenditure <1.5 MET while in a sitting, lying, or reclining posture, e.g. recreational screen time, sitting for long hours at work) for enduring cardiovascular health, as per recent WHO recommendations.¹ Although there is some controversy, prolonged daily sedentary time is associated with a higher risk of incident CVD or of all-cause or CVD mortality, regardless of PA level.^{10–16} For instance, meta-analytical evidence showed a positive association between excessive sedentary time (>10 h/day) and incident CVD¹² and a threshold of 6–8 and 3–4 h/day has been identified for total sitting and TV viewing, respectively, above which the risk of all-cause and CVD mortality is increased.¹⁴ There is also meta-analytical evidence (using accelerometer measures of PA) that meeting minimum WHO-recommended levels of MVPA (150 min/week, the equivalent of ~20 min/day) does not seem enough to offset the association of prolonged sedentary time with higher all-cause mortality risk, with higher levels (30–40 min/day) needed.¹⁶

Cardiorespiratory fitness (CRF)—a variable that, despite having an important heritability component, is likely to improve with regular MVPA/exercise¹⁷—also shows an inverse association with CVD. In a classic study, CRF was shown to be a more powerful predictor of mortality among men than other established CVD risk factors (hypertension, smoking, diabetes, hypercholesterolaemia, or obesity),¹⁸ a finding that has since been corroborated in other cohorts. In a study with 122 007 participants, CRF was inversely associated with mortality risk during a median 8.4-year follow-up; the magnitude of this association was similar to—or even greater than—the influence of traditional CVD risk factors and with no apparent upper limit for the observed benefits.¹⁹ More recently, a study in 750 302 adults supported an inverse association between CRF and mortality risk irrespective of age (including very old people), sex, or race.²⁰ Additionally, there is strong meta-analytical evidence supporting an inverse dose-response association between CRF and CVD mortality risk (13% risk reduction for each MET increase), with a 51% lower risk for the highest CRF levels compared with those individuals with the lowest values.²¹

Can one do ‘too much’ exercise?

Controversy exists as to whether there might be an upper limit of exposure—especially in the long term—to strenuous endurance exercise

(e.g. marathon/ultramarathon running), above which the risk of CVD and related conditions might actually increase, notably atrial fibrillation (AF), coronary artery calcification (CAC), or myocardial fibrosis.²² There is, however, no evidence for an increased risk of CVD mortality in former elite athletes, and in fact, there are consistent findings for the opposite trend^{23–25} (e.g. 27% lower standard mortality rate in a meta-analysis including 35 920 athletes²³). Likewise, exposure to very high levels of *leisure-time* MVPA does not seem to increase the risk of CVD or related events, at least in previously healthy adults.²⁶ Notably, MVPA levels exceeding 5–7 times international recommendations (5000 MET-min/week) were associated with a lower (–27%) CVD mortality risk than adherence to current recommendations (750 MET-min/week), with no apparent upper MVPA-threshold for this association.²⁶ Moreover, although acute and unaccustomed heavy physical exertion can trigger the onset of acute CVD events such as myocardial infarction (MI) and cardiac sudden death, this is particularly true for the habitually least active individuals, with higher habitual PA levels associated with a reduced risk.^{27,28}

Concerns exist on the association between ‘excessive’ exercise/PA and CAC. Evidence overall suggests that athletes—particularly those exposed to lifelong endurance exercise—show higher CAC scores than the general population²⁹ and CAC scores might be associated with the incidence of coronary events in this population.^{30,31} Notwithstanding, there is also evidence suggesting that, although very high MVPA levels can be associated with higher CAC scores in the general population, the latter do not seem to be associated with an increased incidence of CVD events or mortality in ‘exposed’ individuals.^{32,33} In addition, atherosclerotic plaques might not necessarily have the same clinical relevance in athletes and nonathletes, as they are often (but not always³⁴) more calcific—which are considered more stable and less prone to rupture—in the former.^{35,36} There is also pre-clinical evidence for a stabilizing effect of aerobic exercise on atherosclerotic plaque composition, as discussed below (‘vascular health’). (In this Review, the terms ‘aerobic exercise’ and ‘endurance exercise’ are used interchangeably.)

Although sports participation seems associated with incident AF,³⁷ there is more debate for PA. A recent umbrella review of meta-analyses reported that sports participation was indeed associated with a higher AF risk (+64%), but no robust evidence was found for total or intense PA.³⁸ The association between ‘excess’ MVPA and higher AF incidence observed in some studies might be biased by potential methodological limitations—mainly, non-objective AF/PA determination. Indeed, a meta-analysis of prospective studies with low risk of bias reported that, as opposed to sports participation—which was associated with a markedly (7–8-fold) higher risk—self-reported (using validated questionnaires) MVPA was inversely associated with the risk of medically ascertained AF.³⁹ Recent evidence also suggests no detrimental effects (and actually an inverse association) of objectively measured MVPA,^{40,41} even at >395 min/week.⁴² The link between sports participation and AF deserves further research given the deleterious consequences of this condition. Yet, preliminary evidence suggests that the risk of AF-associated events (e.g. stroke, mortality) might be lower in athletes than in the general population.^{43,44}

Despite the positive effects of *leisure-time* PA (e.g. sports, recreation, transportation) on cardiovascular health, higher levels of *occupational* PA (i.e. related to the job) could actually be associated with a higher incidence of CVD events—the so-called ‘physical activity paradox’.^{45,46} In a recent study, very high levels of self-reported leisure-time PA were associated with a reduced risk (–15%) of major CVD events during a 10-year follow-up, but high levels of occupational PA showed the

opposite trend (+35%).⁴⁶ The underlying mechanisms for this apparent paradox remain unknown but some have been proposed, such as the high intensity or long-duration PA (>8 h) coupled with insufficient recovery that characterizes some jobs (e.g. construction), which can be linked to increased blood pressure (BP), overuse injuries, and elevated heart rate for several hours, as well as a proinflammatory milieu.⁴⁷ In addition, the low socioeconomic status usually associated with high levels of occupational PA might also have a confounding effect.⁴⁷

Secondary prevention

There is evidence supporting PA/exercise intervention in patients with established CVD.^{2,48–53} Current guidelines recommend in fact an active lifestyle as a cornerstone for secondary CVD prevention, with advice for patients not essentially different from healthy people (Table 1), although some caution is needed particularly for the former (see Pelliccia et al.⁴⁸ for specific exercise recommendations in CVD).

A recent 6-year follow-up study in 131 558 patients with different types of CVD [e.g. stroke, ischaemic cardiomyopathy, heart failure (HF)] found an inverse association between PA and mortality risk that was actually stronger than in CVD-free referents (14% and 7% risk reduction in patients and nonpatients, respectively, with every 500 MET-min/week).⁴⁹ Indeed, although the slope of the association tended to flatten in healthy individuals above 500 MET-min/week, an inverse dose–response association was still observed beyond this point in patients, and performing very high PA levels (≥1000 MET-min/week) resulted in a mortality risk similar to nonpatients. Of note, these observations were consistent irrespective of the specific type of CVD. A study in 7058 outpatients with CVD also reported that those with highest leisure-time—but not occupational—PA levels had a lower risk of recurrent CVD events and all-cause mortality risk (–28% and –7%, respectively) during a 9-year follow-up than their less active peers.⁵¹ In a cohort of 15 486 patients with stable coronary heart disease (CHD), those in the highest PA tertile showed a lower risk of a major CVD event (–19%), as well as of CVD-specific (–29%) and all-cause mortality (–30%), than those in the least active tertile.⁵² A recent pooled analysis of nine prospective studies in patients with CHD found that maintaining PA levels or becoming physically active if previously inactive was associated with a meaningful reduction (–50% and –45%, respectively) in CVD and all-cause mortality.⁵³ Physical activity has also proven to play a major role in other CVD conditions such as AF, with self-reported PA levels inversely associated with the risk of AF-related adverse events (e.g. thromboembolic event, bleeding) and CVD-specific mortality in affected people.⁵⁵ Like with primary prevention, avoiding sedentarism should also be recommended in individuals with CVD,⁵⁶ which is of particular relevance if considering that these patients have been reported to spend more time in sedentary activities than their healthy peers.⁵⁷

Participation in exercise programmes—ideally in the frame of comprehensive cardiac rehabilitation programmes including other lifestyle changes (smoking cessation, dietary advice)—is recommended for secondary CVD prevention.^{58,59} A ~5-year follow-up study reported a substantially lower (–32%) mortality risk in patients with CVD (e.g. with previous MI or cardiothoracic surgery, or with unstable angina pectoris, stable angina pectoris, or HF) participating in cardiac rehabilitation programmes as compared with nonparticipants.⁶⁰ A recent Cochrane review ($n = 23\,430$ patients with CHD) concluded that exercise-based cardiac rehabilitation results in a reduced mortality risk and an improved quality of life (QoL).⁵⁰ A meta-epidemiological study including 16 meta-analyses and 305 randomized controlled trials

Table 1 Exercise prescription for adults, including those with cardiovascular disease

Component	Recommendation (per week)	Examples of prescription
'Aerobic' (endurance)	150–300 min of moderate-intensity PA, 75–150 min of vigorous-intensity PA, or a combination thereof	F: 5 times/week: 40%–69% of $\text{VO}_{2\text{peak}}$ or HRR, or RPE scale 12–13 T: 30–60 min/session T: continuous jogging/brisk walking/cycling or F: 3 times/week I: 70%–85% of $\text{VO}_{2\text{peak}}$ or HRR, or RPE scale 14–16 T: 25–50 min/session T: continuous running/fast cycling, intervals of higher intensities
Muscle strengthening ('resistance training')	Muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days	F: 2–3 times/week I: 50%–80% of 1-RM or 8–15 repetitions to failure T: 1–3 sets per muscle group T: 8–10 dynamic or static resistance exercises including all major muscle groups
Sedentarism	Limiting the amount of time spent being sedentary	- Replacing sedentary time with PA of any intensity (including light intensity) - Doing more than the recommended weekly levels of moderate-to-vigorous PA

Examples are provided following the FITT principle (i.e. frequency, intensity, time, and type), except for sedentarism.

1-RM, one-repetition maximum; HRR, heart rate reserve; PA, physical activity; RPE, rate of perceived exertion; $\text{VO}_{2\text{peak}}$, peak oxygen uptake.

Sources: 2020 World Health Organization guidelines on physical activity and sedentary behaviour,¹ 2020 European Society of Cardiology guidelines on sports cardiology and exercise in patients with cardiovascular disease,⁴⁸ and the 2022 position statement from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology.⁵⁴

found not only no consistent differences between drug and exercise intervention for secondary prevention of some conditions such as CHD or prediabetes, but also greater effects provided by exercise intervention in some conditions such as stroke—albeit with a greater mortality risk reduction induced by diuretics compared with exercise in individuals with HF.⁶¹ Meta-analytical evidence supports that exercise training improves exercise capacity and QoL in patients with HF, as well as some cardiac function indicators [e.g. left ventricular ejection fraction (LVEF)].⁶² In patients with AF, physical exercise does not only improve physical capacity but also symptoms' burden and cardiac function.^{63,64} Exercise intervention also appears as a promising strategy for improving physical capacity after surgery for aortic stenosis⁶⁵ or heart transplantation.^{66,67}

Although moderate-intensity continuous aerobic training (MICT) is the most commonly prescribed intervention, high-intensity interval training (HIIT)—i.e. repeated bouts of high-intensity exercise [$>85\%$ of peak oxygen uptake ($\text{VO}_{2\text{peak}}$) or heart rate reserve, or $>90\%$ of age-predicted maximum heart rate] interspersed with active/passive recovery periods—has gained popularity in recent years. HIIT has proven safe in the cardiac rehabilitation setting^{68,69} and, although there is some debate, meta-analytical evidence suggests that this modality is more effective—or at least more time-efficient—than MICT to improve CRF and QoL in patients with CVD.^{70–72} The role of muscle strength or 'resistance' training (RT) should not be disregarded, as this modality has proven feasible and effective for most CVD⁴⁸ (e.g. recent MI,⁷³ end-stage HF,⁷⁴ chronic HF,⁷⁵ or CHD⁷⁶). For instance, this modality has proven to improve not only muscle strength but also CRF, mobility, and body composition in patients with CVD,^{77–79} although the combination of aerobic exercises and RT appears as the most effective

option—compared with aerobic or RT exercise alone—for improving CRF, body composition, and muscle strength.^{80,81}

Exercise training intervention should be individualized and progressively adapted attending to participants' characteristics and preferences. A maximum exercise test with $\text{VO}_{2\text{peak}}$ assessment should be ideally recommended for proper risk stratification and determination of exercise training zones before exercise prescription.⁵⁴ Exercise training—particularly of vigorous intensity—is contraindicated in some situations such as the first two days after an acute coronary syndrome or in conditions like uncontrolled arrhythmia, active endo-, myo-, or pericarditis, symptomatic severe aortic stenosis, decompensated HF, acute pulmonary embolism, deep vein thrombosis, or acute aortic dissection.^{48,54,82} In individuals with uncontrolled hypertension (resting systolic BP >160 mmHg) high-intensity exercise is not recommended until BP is controlled.⁴⁸

Mechanisms

Metabolism, inflammation, and cellular integrity

Chronically elevated plasma levels of low-density lipoprotein (LDL)-cholesterol and triglyceride-rich lipoproteins (e.g. very low-density lipoproteins) are both strongly associated with CVD.^{83,84} Thus, lowering plasma LDL-cholesterol—by reducing intestinal cholesterol resorption, hepatic cholesterol synthesis or, more recently, enhancing hepatic LDL-cholesterol uptake—has led to population-wide reductions in the prevalence of CVD events and is associated with differences in atherosclerotic plaque morphology.⁸⁵ In this effect, recent

meta-analytical evidence indicates that not only 'polypills' but also exercise interventions are effective in improving blood lipid profile [total/LDL-cholesterol, and especially triglycerides and high-density lipoprotein (HDL)-cholesterol, particularly the latter].⁸⁶ Furthermore, despite overall superior effects of polypills without antiplatelet treatment on total/LDL-cholesterol, aerobic interval exercise (followed by RT) seems the most effective intervention to improve HDL-cholesterol.⁸⁶ In addition, exercise training was also reported to increase HDL-cholesterol mediated vascular effects [i.e. nitric oxide (NO $\cdot$) production and flow-mediated dilatation (FMD)] in patients with chronic HF.⁸⁷ Similar to plasma LDL-cholesterol, higher fasting blood glucose levels (>100 mg/dL) are associated with progressively higher risks of atherosclerotic CVD (CHD, MI, and thrombotic stroke), with meta-analytical evidence supporting the efficacy of exercise to reduce glycaemia.^{88–90}

Acute intense exercise triggers the release of energy substrates [glucose, free fatty acids (FFA), triglycerides] into the bloodstream *via* sympathetic activation, which is followed by their uptake and oxidation by muscle. Regular exposure to these acute bouts (i.e. exercise training) boosts the uptake and oxidation of FFA and glucose in skeletal myocytes, mediated to varying degrees by β -adrenergic signalling, AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor- γ coactivator1 α signalling, which enhances mitochondrial biogenesis.^{91–93} Accordingly, insulin sensitivity, as well as insulin-independent glucose uptake (mediated in part by AMPK) can be improved by exercise training interventions^{94,95} (Figure 1). Mechanistically, the integrity of a well-formed mitochondrial network, involving fusion, fission, and autophagy ('mitophagy') within the skeletal muscle, is crucial for ensuring effective substrate oxidation and a low release of reactive oxygen species (ROS), and is linked to improved insulin sensitivity.^{96,97} Exercise enhances skeletal muscle mitochondrial biogenesis and remodelling through several signalling pathways—involving NO $\cdot$ synthase (NOS), sirtuins, mitofusin proteins, and PGC1 α .^{98–102} Exercise training also promotes both endothelial NOS-dependent mitochondrial biogenesis and glucose uptake in the heart.⁹⁷

A state of low-grade, non-infective ('sterile') systemic chronic inflammation (SCI) is characterized by the long-lasting (months-to-years) activation of immune components that are often distinct from those engaged during acute immune responses.¹⁰³ This condition, which is reflected by high circulating levels of C-reactive protein (CRP) and tumour necrosis factor- α , together with the overproduction of immune cells and enhanced leucocyte recruitment to target tissues, is a common hallmark of many major chronic diseases, and there is strong evidence for its involvement in the onset and progression of CVD.¹⁰³ In this regard, although acute exercise, particularly at high intensities, can increase inflammatory markers [e.g. white blood cells, interleukin (IL)6, IL10, CRP],¹⁰⁴ regular exercise—even at high intensities—induces the opposite response¹⁰⁵ (see also section on 'exerkines'), as confirmed by recent meta-analytical evidence.^{106,107} A major systemic benefit of regular exercise is indeed its ability to attenuate SCI. Notably, there is preclinical evidence that exercise modulates haematopoietic stem and progenitor cell proliferation and leucocyte production *via* diminished leptin signalling to bone marrow niche cells, thereby reducing the haematopoietic output of inflammatory leucocytes.¹⁰⁸ This preclinical finding is consistent with the reduced leucocyte blood counts reported in patients with cardiometabolic conditions after an exercise training programme.¹⁰⁹ Endurance exercise, particularly when intense, has also been reported to restrain the progressive increase of modified (i.e. oxidized) lipoproteins and advanced glycated end-products (AGEs, which are formed when protein or fat combine with glucose in the

bloodstream, and can impair insulin sensitivity) in the plasma of not only healthy young people¹¹⁰ but also of patients with CVD such as CHD¹¹¹ or in animal models of HF with preserved ejection fraction.¹¹² This is potentially important because oxidized lipoproteins and AGEs can activate pattern recognition receptors to trigger the release of inflammatory components, which enhance the influx of inflammatory leucocytes and promote tissue damage and further oxidation.^{113,114}

Several cellular maintenance processes including responses to DNA damage and endoplasmic reticulum stress, as well as mitochondrial fusion and fission, decline not only with senescence but also in the presence of CVD.¹¹⁵ Regular exercise, particularly—but not only—endurance modalities, provides numerous benefits that help to promote cellular maintenance and repair processes. These include attenuation of endoplasmic reticulum stress in atherosclerotic coronary arterioles,¹¹⁶ promotion of endogenous antioxidant defence capacity¹¹⁷ (e.g. with antioxidative effects in the skeletal muscle of patients with chronic HF) due to a higher activity of radical scavenger enzymes,¹¹⁸ together with protection against exogenously induced DNA damage,¹¹⁹ reduction of vascular ROS generation in patients with CHD,¹²⁰ and attenuation of telomere length attrition in the heart tissue through upregulation of cardiac telomere-protective genes.^{121,122}

Vascular health

Endothelial cell integrity

Important functions of the endothelium (selective barrier function, low adhesion to leucocytes, anti-thrombogenicity, and regulation of vascular tone) are impaired in people with—or at risk of—CVD, including their angiogenic response to ischaemia.¹²³ In contrast, regular endurance exercise helps to maintain endothelial cell integrity through several mechanisms (Figure 2). These include an improved release of circulating angiogenic cells occurring, in part, *via* an NO-dependent antiapoptotic effect, and inhibition of neointima formation, in addition to enhanced angiogenesis.¹²⁴ Moreover, regular endurance exercise activates antioxidant scavenger mechanisms *via* mitohormesis¹¹⁷—a process wherein low levels of mitochondrial-derived ROS act as signalling molecules to initiate a cascade of cellular events that ultimately protect the endothelial cells from harmful effects—thereby reducing oxidative damage and NOS uncoupling.¹²⁵ Exercise training-mediated endothelial 'normality' or quiescence also includes a decline in endothelium-derived adhesion molecules such as vascular cell adhesion molecule 1 or intercellular adhesion molecule 1, as shown in a preclinical model of vascular endothelial dysfunction (VED) induced by high cholesterol feeding¹²⁶ and in patients with peripheral arterial disease.¹²⁷ In people with symptomatic CHD, endurance exercise training reduces vascular expression of nicotinamide adenine dinucleotide phosphate oxidase and the angiotensin II (AngII) type 2 receptor, resulting in diminished local ROS generation and, ultimately, reduced AngII-mediated vasoconstriction.¹²⁰ Of note, attenuation of AngII-induced vasoconstriction through aerobic training has also been corroborated in preclinical research.¹²⁸

Endothelial function

VED is characterized by a shift in the actions of the endothelium towards reduced vasodilation, a proinflammatory state and prothrombotic properties, and is therefore associated with atherosclerotic development and most forms of CVD.¹²⁹ VED is characterized by impaired NO bioavailability, particularly in hypertension.¹³⁰ In this effect, both aerobic training and RT, or a combination thereof, seem to induce similar effects against VED in patients with prehypertension/

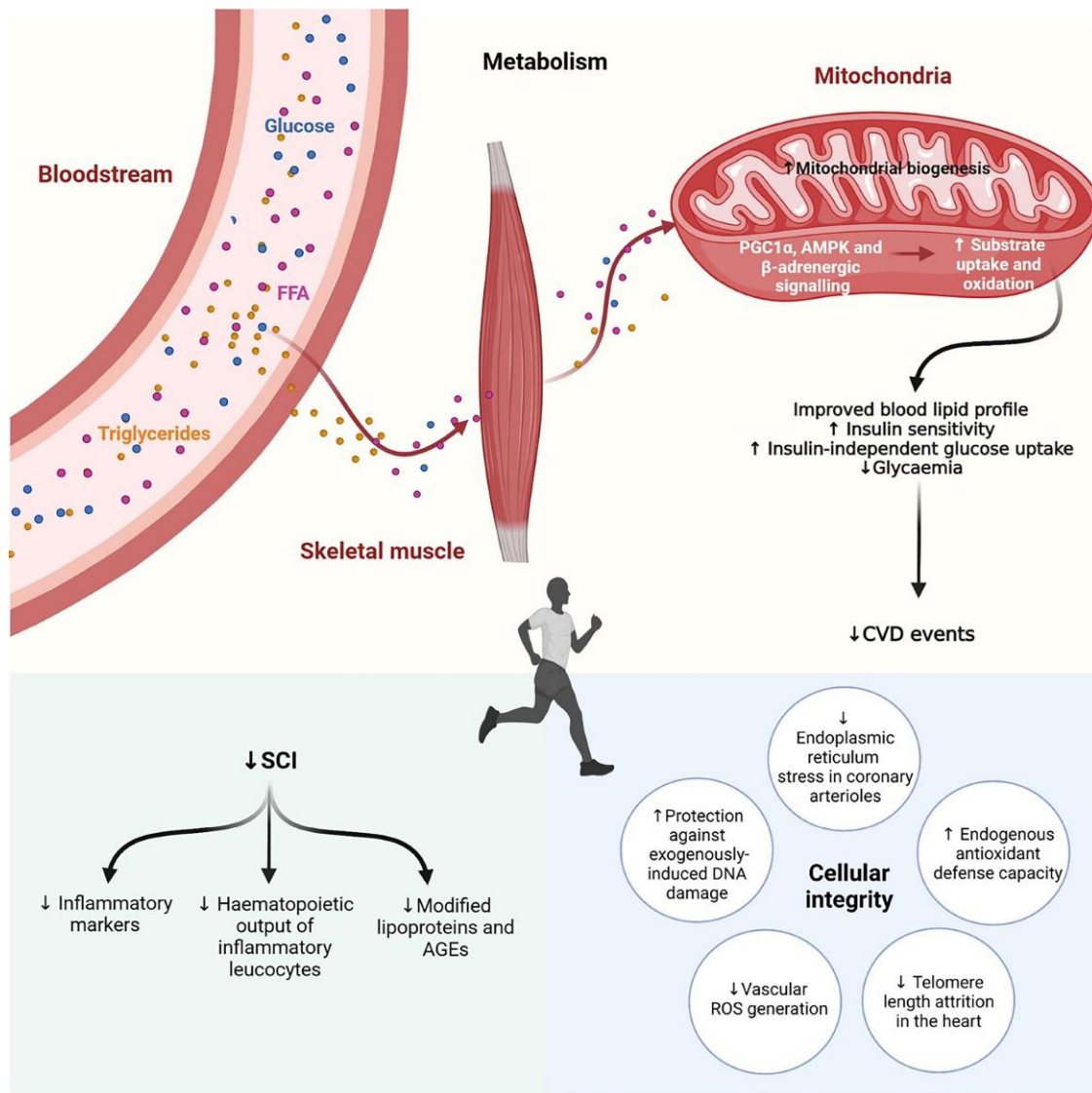


Figure 1 Main mechanisms explaining improvements in metabolism, inflammation, and cellular integrity induced by regular physical activity/exercise. AGEs, advanced glycated end-products; AMPK, AMP-activated protein kinase; CVD, cardiovascular diseases; FFA, free fatty acids; PGC1 α , proliferator-activated receptor-gamma coactivator 1 α ; ROS, reactive oxygen species; SCI, systemic chronic inflammation.

hypertension.¹³¹ Indeed, not only aerobic exercise,¹³² but also RT^{132,133} improves endothelial function—as typically assessed by FMD of the brachial artery—in people with/without CVD, with a dose–response relationship between exercise intensity (for aerobic exercise) or frequency (for RT) and the effects obtained.¹³² On the one hand, each bout of aerobic exercise raises shear stress, with subsequent increases in NO $\cdot$ synthesis.¹³⁴ Accordingly, in patients with CVD, repetitive increases in shear stress induced by a 4-week bicycle exercise training improved endothelium-dependent vasodilatation in coronary vessels¹³⁵ and also NO $\cdot$ bioavailability by upregulating endothelial NOS.¹³⁶ On the other hand, it seems less clear what mechanism could explain RT-induced effects on endothelial function. However, mechanical compression of resistance vessels induced by muscle contractions during this exercise modality produces transient ischaemia and, upon muscle relaxation, the release of blood flow results in hyperaemia, with a subsequent increase in shear stress.¹³⁷ In addition, endurance

training can also improve endothelial function by reducing SCI^{138,139}—see also section on ‘exerkines’. Of note, improvement in endothelial integrity and function contributes to attenuate atherosclerotic plaque development, as discussed below.

Antiatherogenic adaptations

Maintenance of endothelial barrier function counteracts lipid accumulation in the subendothelial vascular wall, the initial step of atherosclerotic plaque formation. A recent preclinical study found that early commencement of regular exercise improves elastin and collagen content (a marker of cap stability) and results in lower lipid accumulation and stenosis, but has no effects on macrophage content.¹⁴⁰

Repeated exposure to haemodynamic stimuli during exertion can induce antiatherogenic vascular adaptations independent of traditional CVD risk factors.¹⁴¹ Besides the aforementioned benefits of VED, a

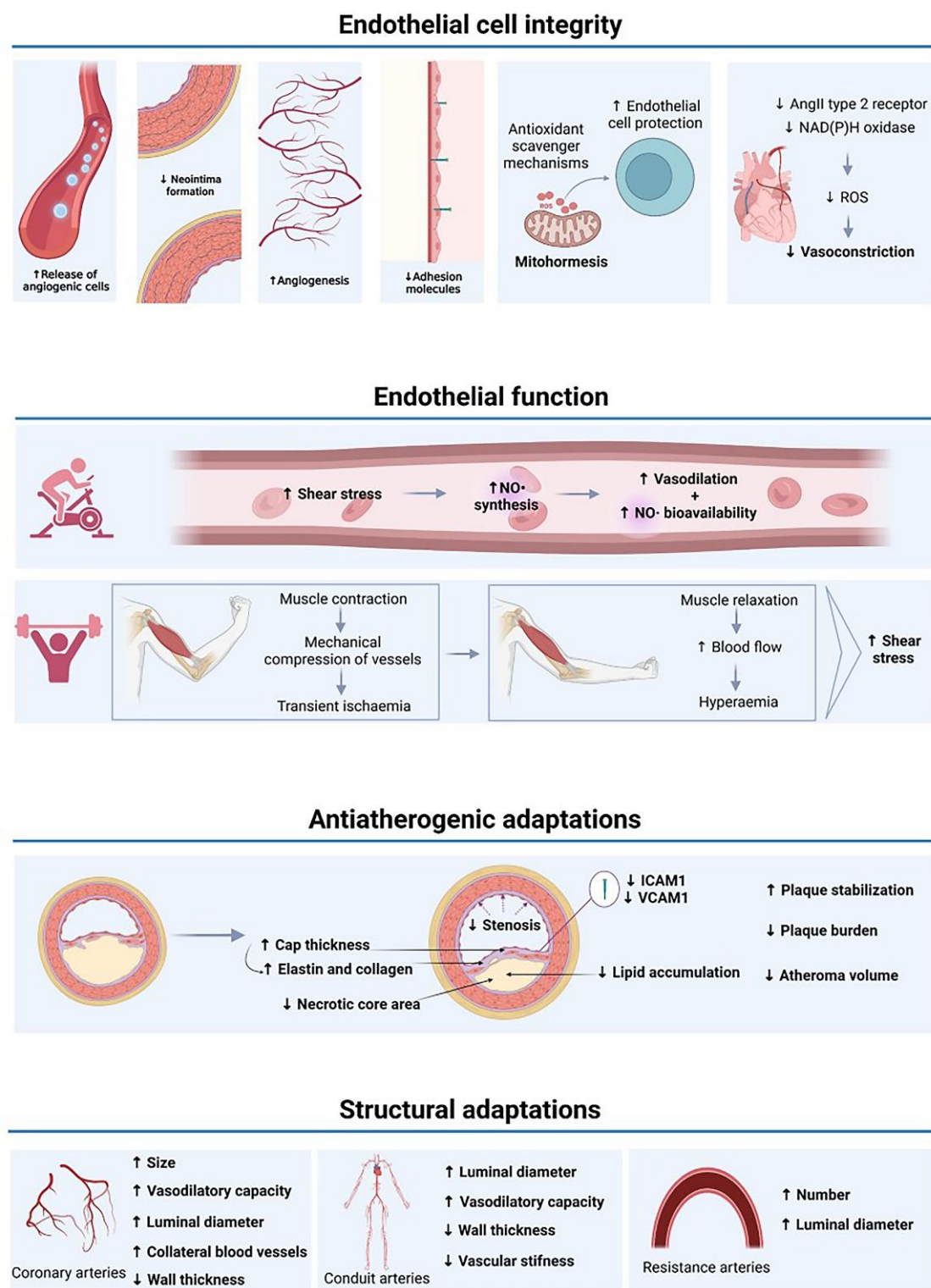


Figure 2 Main mechanisms explaining improvements in vascular health induced by regular physical activity/exercise. Of note, there is controversy regarding the actual occurrence of antiatherogenic adaptations associated with strenuous endurance exercise, with some negative effects reported (in older athletes, as explained in the text). AngII, angiotensin II; NAD(P)H, nicotinamide adenine dinucleotide phosphate; ICAM1, intercellular adhesion molecule 1; NO $\cdot$, nitric oxide; ROS, reactive oxygen species; VCAM1, vascular cell adhesion molecule 1.

key player in the development of atherosclerosis, exercise training stabilizes experimental atherosclerotic plaques (through increases in collagen content and decreases in intercellular adhesion molecule 1)

irrespective of changes to serum lipid profiles.¹⁴² In patients with CVD, high CRF is associated with a low lipid volume and a high fibrous volume and cap thickness of coronary plaques,¹⁴³ and regular exercise

reduces both the necrotic core area and plaque burden.¹⁴⁴ A recent study found that, in patients with established CHD, a 6-month supervised HIIT intervention decreased atheroma volume in residual coronary atheromatous plaques.¹⁴⁵

Regarding lifetime strenuous endurance exercise, evidence overall suggests that endurance athletes—particularly those who are middle-aged and older—show higher CAC scores and a greater prevalence of atherosclerotic plaques than their age-matched nonathletic referents,²⁷ which has been associated with a greater incidence of coronary events,^{28,29} yet, not all data support these findings.³⁴ In turn, exercise intensity, but not volume, seems to be associated with coronary atherosclerosis progression in middle-aged and older male athletes.¹⁴⁶ Nonetheless, the plaque composition of these athletes might show a more benign composition—with fewer mixed plaques and more often only calcified plaques³⁵ and in fact high MVPA levels seem to offset the detrimental association between CAC scores and CVD events.^{32,33}

Structural adaptations

Regular exercise induces healthy structural adaptations at the vascular level, notably in conduit arteries. Exercise training improves the size and dilatation capacity of coronary arteries,^{147,148} while also increasing the luminal diameter¹⁴¹ and reducing the wall thickness¹⁴⁹ of conduit arteries in general. As such, in the event of atherosclerotic disease, exercise-induced remodelling in the conduit arterial wall—characterized by a markedly increased luminal reserve—attenuates plaque development.¹⁵⁰ Exercise training can also reduce the carotid intima-media thickness in patients with hypertension¹⁵¹ and increase not only the luminal diameter of conduit arteries but also the number—and luminal diameter—of resistance vessels, thereby tempering increases in BP.¹⁵²

Aerobic exercise training induces the development of coronary collateral blood vessels, which increases perfusion of the collateralized myocardium. This, in turn, limits the extension of the infarcted lesion if a coronary artery is blocked, further supporting implementation of exercise intervention in the management of CVD.¹⁵⁰ Exercise, especially of high intensity, also attenuates age-related increases in vascular stiffness—as shown by a reduction in carotid-femoral pulse wave velocity.¹⁵³ Postulated mechanisms include: attenuation of metabolic conditions (impaired glucose tolerance, hypertension, dyslipidaemia, or abdominal obesity) associated with changes in the arterial system (e.g. elastin fibre fragmentation, increased pressure on the collagen fibres of the arterial wall, vascular damage) and ultimately leading to increased arterial stiffness;¹⁵⁴ reduction of oxidative stress;¹⁵⁵ and increased expression of genes associated with local vasodilatory signalling (prostaglandin EP2 receptor, C-type natriuretic peptide, and particularly endothelial NOS).¹⁵⁵

Myocardial regeneration

Novel therapeutic approaches are needed to mitigate left ventricular (LV) adverse remodelling associated with MI.¹⁵⁶ There is preclinical evidence that, compared with control group, regular exercise *prior* to MI reduces infarct size and improves cardiac function (LVEF) as well as the molecular responses (e.g. stress response proteins) involved in heart repair, while downregulating those associated with adverse remodelling (proinflammatory, profibrotic, or proapoptotic pathways).¹⁵⁷ In turn, although some authors have reported no exercise-induced changes in the cardiac function of patients¹⁵⁸ or mice,¹⁵⁹ exercise intervention *after* MI can enhance myocardial angiogenesis and perfusion, reduce cardiac diameters, and improve LV

contractility in post-ischaemic failing rat hearts¹⁶⁰ or induce a favourable LV remodelling (decreased LV end-diastolic volume) while remarkably reducing N-terminal pro-brain natriuretic peptide (NT-proBNP)—a hormone released from ventricles in response to myocyte stretch—after MI in patients with moderate LV dysfunction.¹⁶¹ A previous meta-analysis¹⁶² found that exercise training following MI can improve LV remodelling, notably by reducing LV end-systolic volume (LVESV)—a strong predictor of mortality after MI—with these benefits maximized if exercise implementation starts early (~1 week) after the event. More recently, meta-analytical evidence¹⁶³ also supports a decrease with exercise-based rehabilitation not only of LVESV but also of LV end-diastolic diameter, together with an increase in LVEF, in patients with MI subjected to percutaneous coronary intervention.

There are several mechanisms behind exercise-mediated improvement in myocardial regenerative capacity, particularly after MI: reductions in wall stress together with increases in early LV diastolic filling in the context of an improved LV remodelling (as reflected by lower NT-proBNP levels);¹⁶⁴ improvements in autonomic balance [towards a persistent increase in parasympathetic nervous system (PNS) tone to the heart, known to be associated with a better prognosis; see also section on 'protection against malignant arrhythmias'];¹⁶⁵ VED¹⁶⁶ (see also previous section on 'endothelial function') and myocardial contractility (through an ameliorated beta-adrenergic receptor signalling and function),¹⁶⁰ or activation of telomerase in damaged cardiac tissues¹⁵⁶ (with telomerase playing an important role for normal cardiovascular development and function and telomerase dysfunction correlated with impaired tissue repair or regeneration in several disease states including HF).¹⁶⁷ Indeed, physical exercise can upregulate myocardial telomere-regulating proteins, thereby decreasing the risk of HF, as suggested by research in aging mice¹²² or of an important signalling pathway involved in cardiomyocyte proliferation/regeneration such as the growth factor neuregulin-1 and its tyrosine kinase receptors ErbB2 and ErbB4¹⁶⁸ (Figure 3).

Exercise—particularly if intense enough to induce transient myocardial ischaemia^{169,170}—can also stimulate circulating angiogenic progenitor cells (whose levels are inversely associated with CVD risk¹⁷¹), thereby increasing the number and/or function of these cells in people with cardiometabolic conditions such as metabolic syndrome or obesity.¹⁶⁹ Postulated mechanisms for an exercise-induced increase of circulating angiogenic cells include the release into the exercise milieu of several *exerkines* with proangiogenic functions—see below for more details—such as hypoxia-inducible factor 1 α , vascular endothelial growth factor (VEGF), IL6, or NO $\cdot$ (derived not only from the endothelium but also from the bone marrow or angiogenic cells *per se*).¹⁶⁹

Exerkines

The benefits of exercise on cardiovascular health go beyond 'traditional' CVD risk factors, partly owing to the release of exercise-derived factors or *exerkines* (Figure 4). These are a broad variety of signalling molecules—hormones, metabolites (e.g. lactate), proteins/peptides (mainly, but not only, cytokines, such as IL6), nucleic acids, or free radicals (e.g. NO $\cdot$)—released from several different tissues (including skeletal muscle, i.e. the so-called *myokines*) in response to acute and/or chronic exercise; that can travel as free molecules or inside extracellular vesicles; and exert their effects on multiple organ systems (including the cardiovascular system) through endocrine, paracrine, and/or autocrine pathways.^{172,173} Notably, the interplay between the endothelium and the exerkines NO $\cdot$ ¹⁷⁴ and VEGF¹⁷⁵ can modulate vascular tone, inflammation, regeneration, and thrombosis, with an important role in

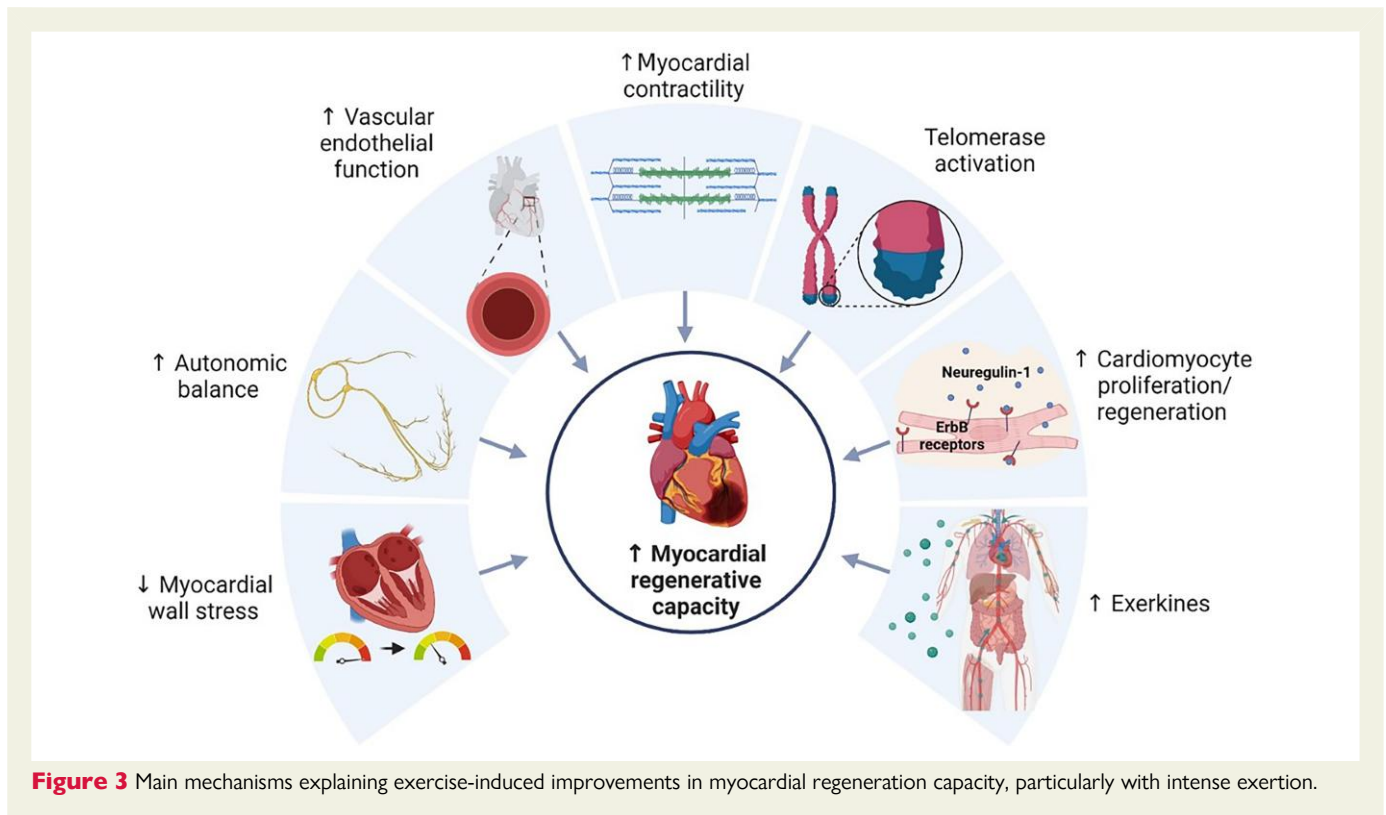


Figure 3 Main mechanisms explaining exercise-induced improvements in myocardial regeneration capacity, particularly with intense exertion.

cardiovascular resilience—that is, absence of actual CVD despite existing risk factors.¹⁷⁶

Contracting skeletal muscle produces many molecules that can enhance the cardiovascular system, such as angiopoietin 1, fractalkine, fibroblast growth factor, IL8, musclin, myonectin, or the abovementioned IL6 and VEGF, among others, most of which are generally increased mainly with acute exercise.^{169,172} The cardiovascular effects induced by exerkines include enhancement of vascularization and angiogenesis, decreases in BP, and improvements in endothelial function, resulting in cardioprotection. Particularly, while the precise role of the myokine follistatin-like 1 in exercise-induced myocardial repair remains to be elucidated, it appears to have myocardium-regenerating effects, at least when released from the epicardium.¹⁷⁷ Other exerkine-induced effects include improved lipolysis, thermogenesis, and glucose metabolism.^{169,172} IL6 is principally known to be a proinflammatory cytokine—with elevated levels linked to several chronic conditions, including increased intima-media thickness in individuals with (or at risk of) CVD, as well as in apparently healthy individuals,¹⁷⁸ and also linked to an increased risk of death from CVD and all-cause death in the general elderly population.¹⁷⁹ But, its release by contracting muscles leads to direct and indirect anti-inflammatory effects and improvement of skeletal muscle insulin resistance.^{180,181} As a pleiotropic factor, the effect of IL6 on metabolism and inflammation remains context-dependent.¹⁷² In addition, there is evidence for an important role of IL6 receptor signalling on the reduction of cardiac—especially epicardial—fat depots and increases in LV mass with aerobic training.¹⁸²

Protection against malignant arrhythmias

Protection against life-threatening arrhythmias is yet another beneficial effect of regular exercise. This is important when considering that

ventricular fibrillation in the context of CHD remains a leading cause of sudden cardiac death and of all-cause and CVD mortality worldwide.¹⁸³ The antiarrhythmogenic effect of exercise is mediated by the improvement in autonomic balance, specifically a higher PNS tone without changes in intrinsic sinoatrial node function together with a reduction of β_2 -adrenergic receptor sensitivity and expression^{184,185} (Figure 5). Regular PA/exercise increases heart rate variability (HRV)—a measure of efferent PNS (vagal nerve) activity to the heart, with low HRV being a marker of autonomic dysfunction associated with poor cardiovascular outcomes—in both healthy individuals and in patients with CVD.^{186,187} Additionally, with regular exercise training blood vessels in barosensitive areas of the carotid arteries become more compliant and are thus able to distend better in response to a rise in BP, with this adaptation increasing afferent signalling to the brainstem and evoking reflex increases in PNS activity to the heart while at the same time decreasing sympathetic nervous system (SNS) activity.^{188–191} Endurance training can also induce neuroplasticity adaptations in the cardiovascular centres of the brainstem (rostral ventrolateral medulla) involved in SNS regulation, leading to lower SNS activity.¹⁹² This is also an important cardioprotective effect given the strong evidence showing that inactivity-related diseases such as hypertension, obesity, and diabetes are associated with SNS overactivity.¹⁹²

Cardiac preconditioning

Regular exercise can prevent fatal arrhythmias by inducing *cardiac preconditioning*—a phenomenon whereby brief periods of myocardial ischaemia before prolonged coronary occlusion are cardioprotective against subsequent ischaemia/reperfusion injury—which reduces the size of the MI lesion and the risk of ventricular fibrillation.¹⁹³ The

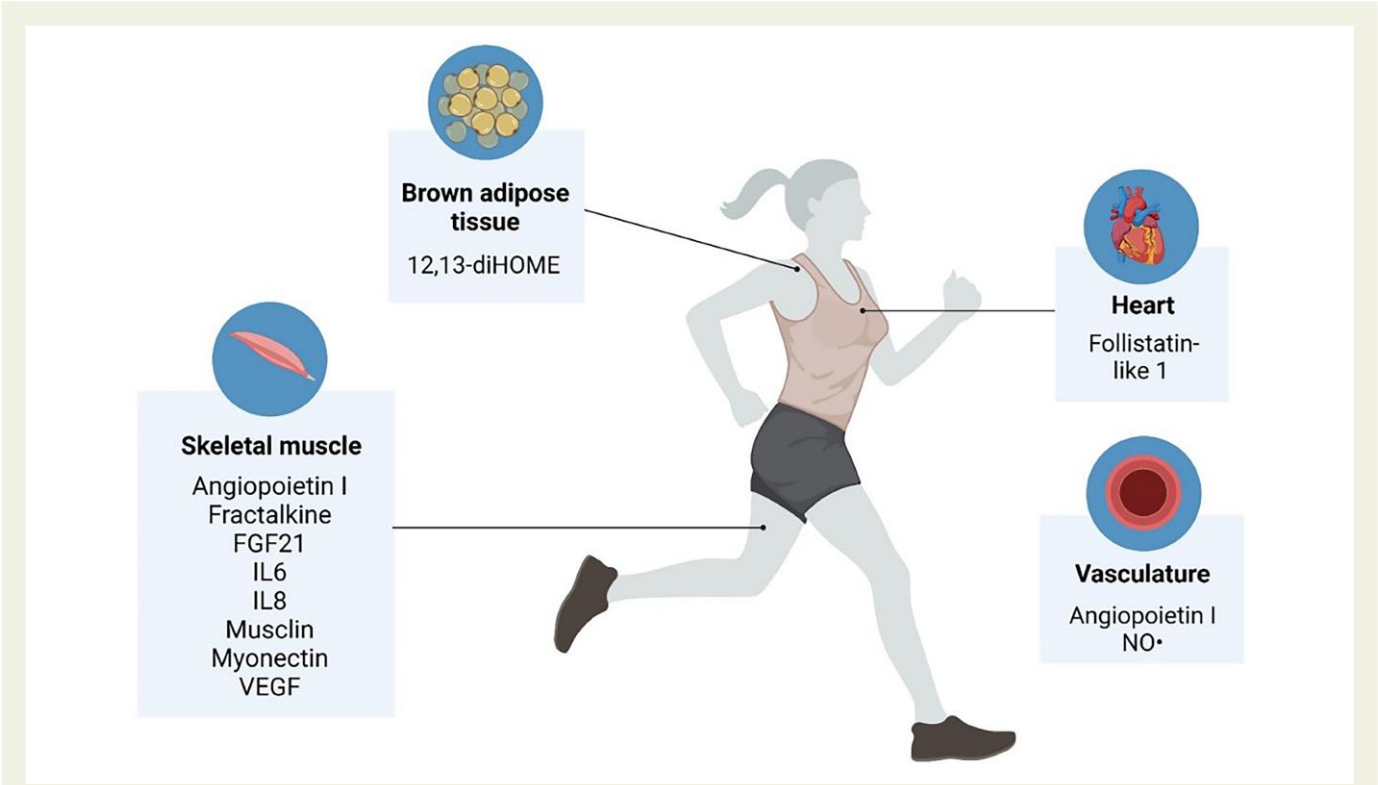


Figure 4 Main exerkines that are candidates to exert a beneficial effect on the cardiovascular system. Of note, some other cytokines might also impact the cardiovascular system more indirectly (e.g. through a decrease in systemic inflammation or an increase in muscle mass). The main tissue of origin is indicated for the relevant myokine (although these molecules could also be released from other tissues, at least outside the exercise milieu). 12,13-diHOME, 12,13-dihydroxy-9Z-octadecenoic acid; FGF-21, fibroblast growth factors-21; IL6, interleukin 6; IL8, interleukin 8; NO•, nitric oxide; VEGF, vascular endothelial growth factor.

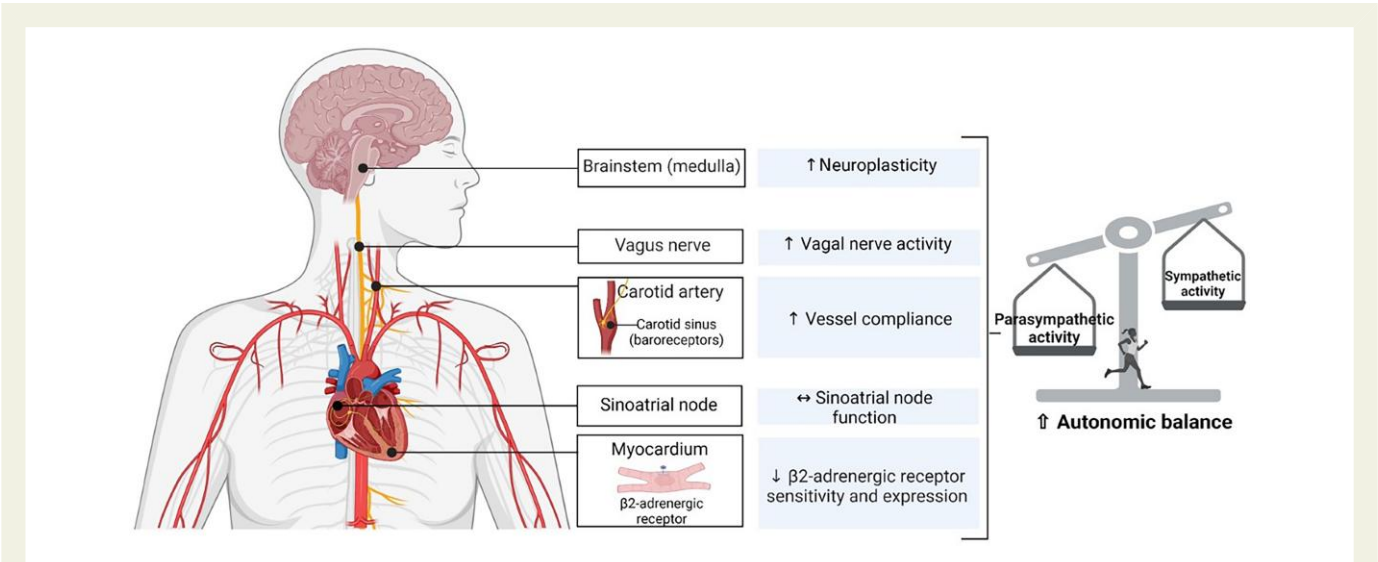


Figure 5 Antiarrhythmic effects of exercise mediated by an improved autonomic balance.

mechanisms through which exercise induces cardiac preconditioning include heightened defence against oxidative stress, upregulated expression of sarcolemmal ATP-sensitive potassium channel subunits,

mitochondrial adaptations (i.e. improved capacity to withstand apoptotic stimuli or a higher capacity for scavenging endogenous ROS),¹⁹⁴ β_3 -adrenergic receptor stimulation, and increased cardiac storage of

NO[•] metabolites.¹⁹⁵ In obese mice, exercise training reduced MI lesions (−67%), which was mediated by the activation of pro-survival kinases of the reperfusion injury salvage kinase pathway, a decrease in the levels of phosphatases, and an improved capacity of mitochondria to retain calcium.¹⁹⁶ Exercise is also cardioprotective against necrosis, an effect mediated—at least partly—by activation of δ -opioid receptors or other factors released in a dose-dependent manner with exertion such as adenosine and bradykinin.¹⁹⁷

Preclinical research indicates that cardioprotection is apparent after only five days of acute exercise.^{198,199} Even moderate-intensity exercise can be cardioprotective,^{200,201} thereby suggesting that the presence of exertional ischaemia is not a critical factor for achieving cardioprotection. There is also meta-analytical evidence for an immediate, exercise-induced attenuation of cardiac ischaemia in patients with angina who showed a remarkable delay in the onset of ST-segment depression and a decrease in the magnitude of this phenomenon on a second exercise test when compared with the first test.²⁰²

Conclusions

Regular PA and exercise can induce major beneficial effects in the context of both primary and secondary CVD prevention (*Graphical Abstract*). Furthermore, the benefits of an active lifestyle are fundamentally dose-dependent (with some evidence for PA benefits even above current WHO recommendations). Notably, there are numerous biological mechanisms supporting PA/exercise-induced cardiovascular benefits involving not only the heart tissue but also the metabolic and inflammatory milieu. Indeed, the recognition of the multisystem benefits of exercise can help to create a more holistic perspective in cardiovascular research as well as in patient care.

Data availability

No data were generated or analysed for this manuscript.

Conflict of interest

All authors declare no conflict of interest for this contribution.

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Erratum

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Erratum to: Iron deficiency in heart failure across the spectrum of left ventricular ejection fraction: dotting the i's

This is an erratum to: Faro R Verelst, Emeline M Van Craenenbroeck, Andreas B Gevaert, Iron deficiency in heart failure across the spectrum of left ventricular ejection fraction: dotting the i's, *European Heart Journal*, 2023, ehad131, <https://doi.org/10.1093/eurheartj/ehad131>

In the originally published version of this manuscript, the gradients in Figure 1 were incorrect.

This error has now been corrected.