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INVITED REVIEW

Exercise effects on cardiovascular disease: from basic aspects to clinical evidence

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Abstract

Cardiovascular (CV) disease (CVD) remains the leading cause of major morbidity and CVD- and all-cause mortality in most of the world. It is now clear that regular physical activity (PA) and exercise training (ET) induces a wide range of direct and indirect physiologic adaptations and pleiotropic benefits for human general and CV health. Generally, higher levels of PA, ET, and cardiorespiratory fitness (CRF) are correlated with reduced risk of CVD, including myocardial infarction, CVD-related death, and all-cause mortality. Although exact details regarding the ideal doses of ET, including resistance and, especially, aerobic ET, as well as the potential adverse effects of extreme levels of ET, continue to be investigated, there is no question that most of the world's population have insufficient levels of PA/ET, and many also have lower than ideal levels of CRF. Therefore, assessment and promotion of PA, ET, and efforts to improve levels of CRF should be integrated into all health professionals' practices worldwide. In this state-of-the-art review, we discuss the exercise effects on many areas related to CVD, from basic aspects to clinical practice.

Keywords Endurance exercise • Molecular mechanisms • Physiological adaptations • Mortality • Cardiovascular disease • Prevention

1. Introduction

Cardiovascular (CV) disease (CVD) appears, at least in part, to be due to inappropriate or poor dietary and other lifestyle habits, which can be summarized as maladaptive diet and lifestyle factors. A critical constituent element of lifestyle is physical activity (PA) and exercise training (ET). Discreet modifications in common CVD risk factors, mainly those related to inflammation, haemostasis, and blood pressure (BP), include countless significant benefits of PA on CVD, with important consequences on primary prevention of CVD.[1] In effect, regular ET and a high level of physical fitness are correlated with decreased risks of myocardial infarction (MI) and stroke, CVD–related death, and all-cause mortality.[2,3] Exercise is likely protective against coronary heart disease (CHD) events by reducing several physiological risk factors (i.e. elevated BP, obesity, hyperlipidaemia, and insulin resistance) and providing positive remodelling effects directly to the myocardium.[2] Since it is recognized and well-known for centuries that being active is beneficial for the CV system in all populations, and in order to not reiterate the evident, we do not discuss here the history of ET in CV medicine, but provide a comprehensive review of the potential benefits of PA and/or ET by encompassing both basic molecular and clinical aspects. Isometric ET, i.e. muscle contractions with no change in the muscle length and no joint movement, scarcely affects volume load, stroke volume, or cardiac output, and minimally improve aerobic capacity or CV efficiency; therefore, the CV adaptations to isometric ET are different from those observed with dynamic ET (i.e. concentric and eccentric contractions in which the muscle shortens, generates force and the joints move). Although we are aware that practicing resistance training and maintaining an acceptable

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level of muscular strength is important to maintain a high cardiorespiratory fitness (CRF) and prevent CVD, we particularly focus on one type of ET or PA, aerobic exercise, which is often referred to as cardio training. Although there is a clear difference between the terms PA (any movement requiring energy) and physical exercise or ET (movement intended to maintain or increase physical health and/or performance), in this manuscript, we will use interchangeably the terms PA, physical exercise, aerobic ET, or simply ET since numerous studies use these terms synonymously.

1.1 Conceptual framework of ET

In brief, a load of physical exercise or ET is essentially classified by its type, frequency, duration, and intensity. ET can be performed consistently (endurance), dynamically (e.g. cycling or running), or statically.[4,5] It can also be considered as exhaustive (aerobic or anaerobic)[6] or non-exhaustive.[4,5] Depending on the athlete's fitness, ET intensity and physiological demands will provoke certain physiological stress levels and responses.

1.2 PA and ET: a treatment polypill and a multisystemic-prevention CVD vaccine

The beneficial effects of regular PA/ET in promoting health and preventing CVD have been extensively documented.[7] Physical exercise confers salutary systemic effects in humans. Indeed, ET reduces the prevalence of the most critical CVD-related risk factors, such as type 2 diabetes mellitus (T2DM), hyperlipidaemia, obesity, and hypertension (HTN).[8,9] In effect, low levels of PA are associated with higher prevalence of all the aforementioned CVD risk factors.[10] A constellation of data supports the routine prescription of exercise for all patients, and particularly for patients with CVD, such as CHD and heart failure (HF).[10] According to up-to-date data, and from our point of view, physical exercise may represent a useful and practical prescription 'drug,' or even a 'polypill,' within the armamentarium to treat CVD as well as a highly recommended 'vaccine' in CVD prevention, due to its cardioprotective effects (*Figure 1*).[4,11] Finally, it should also be underlined that, while there is overwhelming data on the association between exercise and lower CVD risk, there is no large-scale randomized data to support actively prescribing high-intensity endurance exercise (i.e. exercising at 70–85% of VO_{2max}). Finally, we must also keep in mind that high-intensity endurance exercise can be counterproductive to certain individuals.

2. Physiological CV adaptations in response to physical exercise

2.1 Cardiac function and structure: the athlete's heart

The athlete's heart, induced by the practice of long-term physical exercise, is characterized by physiological adaptations, such as enlarged left ventricle (LV) and increased LV muscle mass [LV hypertrophy (LVH)], with normal or supra-normal LV systolic/diastolic function.[12–15] Greater ventricular diastolic chamber compliance and distensibility is also commonly observed.[16] This adaptations tend to disappear with ET interruption. However, in pathological LVH, the septal wall thickness decreases after only 3 months of detraining.[17] The LV cavity dimension returns to pre-training values after 1–13 years of ET cessation.[18] Although LV end-diastolic diameter can be persistently elevated for up to 5 years of detraining, it is not accompanied by impaired LV function, nor does it lead to adverse CVD events.[19] Likewise, LV mass augmentation is usually associated with normal resting ejection fraction (EF), whereas systolic volume is normal or augmented.[13,20–23] In some individuals, extreme endurance training and chronic participation in events, such as marathons, ultra-marathons, long-distance bicycle races, and full distance triathlons, has been associated with myocardial fibrosis, particularly in the right ventricle and interventricular septum.[24]

2.2 CRF and CVD

CRF is closely linked to ET levels, and its relationship with CVD warrants particular attention. CRF is a very useful prognostic tool,[25] and indeed, poor CRF is one of the most important CVD risk factors (*Figure 2*).[26] High CRF itself is a robust indicator of low morbidity, low risk of death, and good metabolic health.[25] Cabanas-Sánchez *et al.*[27] have recently demonstrated that changes in the estimated CRF may predict the incidence of biological CVD risk factors, particularly in patients with HTN and T2DM. ET practiced regularly is the most effective strategy to improve CRF, by increasing the mitochondrial content and desaturation of myoglobin in skeletal muscle tissue, which ultimately improves skeletal muscle oxidative capacity.[28,29] An increase in CRF of only one metabolic equivalent (MET) decreases the risk of CVD by 15%.[30] CRF declines with age, physical inactivity (PI), and sedentarism,[30] while sitting time is associated with CVD mortality.[31] However, reaching moderate-to-high CRF levels is associated with a reduced risk of CVD events.[30]

2.3 Modulation of autonomic function: electrophysiological effects

Resting bradycardia is one of the most recognized adaptations to ET,[32] resulting from a combination of (i) increased parasympathetic tone, (ii) decreased response to adrenergic stimulation, and (iii) decreased intrinsic heart rate (HR).[33] An increased parasympathetic tone also provokes increased HR variability (HRV), then potentially lowering CVD morbidity and mortality.[32] HRV is a marker for the degree of activation of the efferent vagal nerve to the heart.[34] Regular ET augments cardiac parasympathetic tone and improves HRV, including in patients with HF or T2DM, restores normal β-adrenergic receptor equilibrium and protects against ventricular fibrillation.[35,36] ET also shortens cardiac action potentials by activating adenosine triphosphate (ATP)-sensitive potassium channels, which ultimately preserves myocardial energy.[37] Low HRV has been associated with impaired CV health and poor outcomes, such as increased mortality in patients with MI or HF,[38] or first CVD events in individuals without apparent CVD.[39] ET improves vagal tone by augmenting the compliance of the blood vessels in barosensitive areas of the carotid arteries, which makes them more distensible in response to BP increments,[40] as well as increasing afferent signalling to the brainstem, activating the vagal nerve and inhibiting sympathetic activity to the heart.[41] Finally, the autonomic nervous system, particularly increased vagal tone induced by regular ET, is involved in protecting against life-threatening arrhythmias, which will be further discussed below.

3. Molecular mechanisms involved in CVD-ET benefits

As it has been shown above, a wide array of effects on CVD and its risk factors can be attributed to different manifestations of long-term aerobic physical exercise. The exact mechanisms through which these changes take place at the molecular level are yet to be fully elucidated.[42]

Figure 1 Endurance exercise-related pivotal mechanisms, physiological adaptations, and clinical improvements.

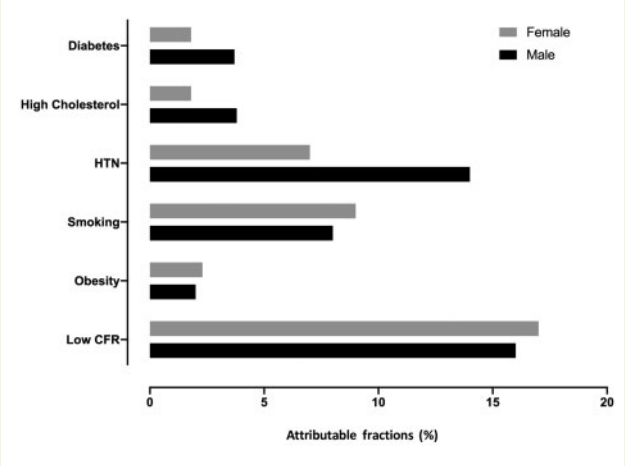

Figure 2 Attributable percentage for all-cause deaths in the Aerobics Center Longitudinal Study. The percentage is adjusted for age and each other item in the figure. CRF was determined by a maximal exercise test on a treadmill. CRF, cardiorespiratory fitness; HTN, hypertension. Extracted from Blair (2009)[239] with permission.

However, an extensive body of research on this topic in recent years has led to the identification of different proteins, signalling molecules, and transcription factors involved in the exercise-induced CV function improvements.

3.1 Cardiac remodelling

Exercise has been found to stimulate the cardiac secretion of insulin-like growth factor 1 (IGF-1), which is closely related to ventricular hypertrophy.[43,44] Rodents with elevated levels of IGF-1 presented with heavier hearts, with an increase in both the size and number of cardiomyocytes,[45,46] whereas mice with a genetically induced deficiency of the IGF-1 receptor were unable to obtain these benefits following aerobic training.[47]

IGF-1, along with neuregulin 1, which is also up-regulated by exercise,[48] activates the phosphoinositide-3 kinase (PI3K)/serine-threonine kinase (AKT1) pathway. PI3K is a particularly interesting marker, since it plays a role in physiological cardiac hypertrophy, but is absent from pathological remodelling, thus differentiating both phenomena.[49] Downstream of this metabolic cascade is AKT1, which is also critical for cardiomyocyte growth.[48] More specifically, AKT1 knockout mice did not experience adaptations when physically trained or treated with IGF-1.[50]

Additionally, AKT1 down-regulates the expression in the nucleus of the transcriptional factor CCAAT-enhancer-binding protein β, which in turn stimulates cardiac myocyte hypertrophy and proliferation.[51] This relation seems to be mediated by CBP/p300-interacting transactivator with ED-rich carboxy-terminal domain 4, a transcription factor that has recently been linked with inhibition of adverse cardiac remodelling.[52]

3.2 Metabolic optimization

It has been extensively demonstrated in experimental models that ET has the potential to improve cardiac metabolic disturbances induced by T2DM and obesity.[53,54]

As exercise demands an increase in the ATP requirements not only in the skeletal muscle but also in the myocardium, it becomes necessary to enhance the energy generation capability of the cardiomyocytes. The main mechanism to achieve this is mediated by the peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), a transcription factor that is also present in homeostatic thermoregulation.[55,56] Its imbalance has been linked with different disorders, such as obesity, diabetes, and cardiomyopathy.[57] Exercise increases the concentration of PGC-1α in the heart,[58] where it promotes mitochondrial biogenesis and the expression of genes related to fatty acid oxidation, oxidative phosphorylation, and ATP synthesis,[59] which is key in exercise-mediated cardioprotective effects. In addition, the transcriptional activity of PGC-1α can be directly increased by AMP-activated protein kinase (AMPK), a protein that is key for the equilibrium between anabolic and catabolic pathways regulating the energy availability in the cardiac tissue.[60] Sirtuin (Sirt) 1 and Sirt3, proteins linked to oxidative stress response and fibrosis resistance, also activate both AMPK PGC-1α.[61]

At the mitochondrial level, proline dehydrogenase (PRODH) has recently been identified as an important regulator of normal mitochondrial function in hypoxic environments.[62] In murine models, the deficiency of PRODH is present in HF and was linked to increased levels of CVD markers.[62] Importantly, ET re-establishes its levels in an animal model of HF, representing a target of exercise in failing hearts.

3.3 Angiogenesis

The catecholamines epinephrine and norepinephrine that are released into the blood flow and into the heart directly after aerobic exercise, couple with the β3-adrenergic receptors of the cardiac tissue, resulting in the phosphorylation of the endothelial nitric oxide (NO) synthase (eNOS).[63] The phosphorylated eNOS is active, and it liberates NO locally and back into the bloodstream, stimulating angiogenesis and reducing myocardial fibrosis.[63] Likewise, vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1 α (HIF-1α), both angiogenic factors induced by ET, play a central role in inducing endothelial cell mitosis and stimulating capillarization.

3.4 Protection against ischaemia-reperfusion injuries

Exercise-induced adaptations of the cardiac tissue have also been shown to act as a protective agent following acute ischaemic events, with a reduction in the infarcted area, cardiomyocyte apoptosis, and fibrosis. Exercise may mitigate cardiomyocyte death due to myocardial ischaemia-reperfusion (IR) and simulate the positive, cardioprotective effects of ischaemic preconditioning by reducing myocardial damage.[2]

Some of the mechanisms previously described also play a part in the protection of the heart. In addition, the oxidative stress induced by exercise promotes the expression of heat shock protein 72, which shields the cardiac tissue from contractile dysfunction and infarction.[64] Moreover, the HIF-1α is a transcription factor that is strongly activated after acute or chronic exercise that exerts an ischaemic/hypoxic preconditioning in the heart, by means of a complex mechanism involving the regulation of mitochondrial function, of reactive oxygen species (ROS) and vascular remodelling.[65]

In mice after suffering a large MI, exercise attenuates global LV remodelling and dysfunction by normalizing MI-induced increase in myofilament Ca^{2+}-sensitivity and thus improving myofilament function. These effects were PKA-mediated and related to improvements in β1-adrenergic signalling. Exercise reduced diastolic $Ca2^{2+}$-concentrations had no effect on $Ca2^{2+}$-transient amplitude, which indicates that the improved LV and cardiomyocyte shortening were mainly due to myofilament function improvements.[66] Moreover, these exercise-related effects on LV remodelling and dysfunction depend critically on endogenous eNOS expression.[67] de Waard and Duncker[68] also observed in an acute MI mice model that ET before MI decreases post-MI mortality. Likewise, the infarct area was thicker, whereas interstitial fibrosis and apoptosis in LV myocardium were blunted.

It is important to highlight that the processes described thus far do not take place independently, since these metabolic pathways are intertwined, resulting in an integrated response to exercise. For instance, PI3K coordinates hypertrophic and metabolic adaptations,[69] and both AMPK and AKT-1 are able to perform eNOS phosphorylation[70,71] and the latter also presents cardioprotective functions, inhibiting cardiomyocyte apoptosis and preserving cardiac function.[72,73] Additionally, the balance of NO plasma levels is crucial to ensure that the exercise-induced protective mechanisms against IR damage are operative.[63] Likewise, the cardiac response to exercise in the context of IR injury is also affected by circulating levels of myokines (e.g. irisin and myonectin).[42] This issue will be further discussed in a separate section.

3.5 Oxidative stress, antioxidant defence, and inflammation

The capacity of physical exercise to reduce ROS and inflammatory cytokines might be of particular relevance, given that different conditions associated with an increase in CVD risk, such as dyslipidaemia or insulin resistance, have a concomitant increase in oxidative stress and inflammation status.[74]

It is well-known that mitochondrial dysfunction provokes increases in oxidative stress levels, which in turn cause systemic damage.[25] As such, the increase in ROS that causes oxidative stress is associated with different manifestations of CVD[75] and plays an important role in endothelial dysfunction.[76,77] Although exercise acutely raises the mitochondrial ROS production, the exercise-related increase in the efficiency of antioxidant systems buffers this initial rise, resulting in a net loss of oxidative load.[78] However, after about 50–60 min of continuous strenuous exercise, the ongoing generation of ROS outstrips the buffering capacity, resulting in systemic oxidative stress. Yet, when facing an episode of IR, which is characterized by an increase in the oxidative stress and inflammatory levels resulting from the absence of oxygen in the heart,[79] the cardiomyocyte of a trained subject is more resistant to injury due to the improved mitochondrial antioxidant capability.[80]

Inflammation is a controversial topic in cardioprotection. It is supposed that inflammation increases during IR and provokes cardiomyocyte damage, while PA decreases inflammation and protects the heart.[81] For instance, both interleukin (IL)-6 and IL-10 increase with exercise and might be implicated in cardioprotection. Exercise-induced up-regulation of IL-6 and circulating levels of IL-6 receptors and the phosphorylated forms of p44/42 MAPK (Thr202/Tyr204) and p38 MAPK (Thr180/Tyr182) have been associated with an attenuation of IR-induced necrosis and arrhythmias, which suggest that these may also be mechanisms for cardioprotection.[82] Administering IL-10 exogenously reduced myocardial infarct size and reduce neutrophil adhesion to vascular endothelium,[83] while incrementing its circulating levels may prevent LV remodelling.[84,85]

3.6 Calcium handling and cardiomyocyte contractility and relaxation

In animal models ET re-establishes both the abundance and activity of sarcoplasmic reticulum Ca^{2+} ATPase2a (SERCA2a) and its regulatory proteins (i.e. Ca^{2+}/calmodulin-dependent protein kinase II)[86] that control excitation–contraction coupling. Restoring SERCA2a levels improves myocardium contractility in older rats.[87] In aged rodents, ET also restores the levels and activity of SERCA2a, calcium handling, and cardiomyocyte contractility and relaxation.[88,89]

3.7 Emerging concepts and active areas of research in exercise science

3.7.1microRNA

All the previous adaptations are based on a series of changes in the genetic regulation and transcriptomics that initiate a cascade of genetic regulatory mechanisms. Additionally, small, non-coding fragments of RNA, denoted as microRNA (miR), have the potential to modulate the expression levels of up to 60% of all human genes.[90] miR can circulate in urine, blood, or plasma and, therefore, they are capable of fulfilling an endocrine function.[91]

The exact relationship between miR and different manifestations of exercise in humans is still unknown, but initial trials seem to point towards a potential dose–response relationship between these factors.[92] Additionally, the efforts to catalogue the existence and function of all human miR are still ongoing. Stimulation of miR-17-3p by means of PA results in increments of hypertrophy in the cardiomyocytes and improves ischaemic protection, indirectly acting upon the PI3K-AKT1 cascade.[93] On the other hand, exercise decreases the levels of miR-233, which has been shown to inhibit cardiac hypertrophy, although, unlike PI3K or AKT, it does not allow the discrimination between physiological or pathological hypertrophy.[94]

3.7.2Myokines

Muscle was traditionally regarded as a merely mechanical organ. However, more than 600 signalling molecules secreted by myocytes during muscular contraction have been unveiled throughout the present century. These cytokines, known as myokines, are associated with muscular contraction and serve autocrine, paracrine, and endocrine purposes.[95] Three myokines have recently been associated with a cardiac response: irisin, myonectin, and follistatin-like 1 protein (Fstl1). Irisin acts as a protective agent of cardiac tissue against IR injuries by means of a scavenging mechanism of the ROS,[96] although its excess can trigger an increase in oxidative stress and apoptosis.[97] Mice with an intact expression of myonectin showed a reduction in the infarcted area following an ischaemic procedure compared to their knockout counterparts.[98] Importantly, myonectin is up-regulated by ET, protecting the heart from IR injury.[98] Fstl1 has been proposed as a potential mediator of exercise-induced cardioprotection.[99] This molecule is secreted by both the skeletal and cardiac muscle cells, so it can also be considered as a cardiomyokine.[100]

Other myokines have also been suggested to be involved in exercise-induced cardioprotection, such as meteorin-like protein, an exercise-related myokine that improves glucose tolerance and stimulates thermogenesis,[101] fibroblast growth factor 21, a factor induced by the PI3K–AKT pathway that acts protecting muscle tissue against insulin resistance and increases brown fat thermogenesis,[102] and musclin or osteocrin, a myokine that may improve CRF by activating mitochondrial biogenesis.[103]

Exercise-induced benefits through sestrins (SESN) pathway are also relevant at the cardiac level,[104] especially in the elderly.[105] Loss of SESNs activity has been related to fat accumulation, mitochondrial dysfunction, and cardiac arrhythmias, which is why inactivity provokes accumulation of visceral fat, inflammation, insulin resistance, atherosclerosis, neurodegeneration, and tumour growth.[106] SESNs are involved in p53 and peroxiredoxins (PRX) signalling pathways.[107] In effect, the stress-inducible SESNs protein family is crucial in PRX regeneration. Exercise reduces age-related changes in p53 activity and raises its circulating levels, which ultimately induces protective effects in cardiac muscle. Likewise, exercise up-regulates PRX isoforms in cardiac muscle cells. Since the use of certain types of exercise is not a viable option for many patients with cardiac diseases, further research of molecules targeting cardiac SESNs is highly encouraged to reverse certain cardiac conditions.

3.7.3 Atrial and B-type/ventricular natriuretic peptides: exercise 'Sacubitril-Like effect'

Important cardiokines involved in CV health are both the atrial and B-type/ventricular natriuretic peptides (ANP and BNP, respectively). Both cardiokines are released under atrial and ventricle stress, which activate downstream receptors leading to vasodilation, natriuresis, and diuresis. ANP and BNP are cleaved and inactivated by a ubiquitous membrane-bound endopeptidase, neprilysin. Inhibition of neprilysin leads to reduced breakdown and increased concentration of ANP and BNP. Interestingly, the drug sacubitril is a prodrug neprilysin inhibitor used in combination with valsartan to reduce the risk of CVD events in patients with chronic HF (NYHA Class II-IV) and reduced EF. Acute exercise increases cardiac output and ANP secretion.[108] It has been reported that ANP and BNP secretion increases during exercise.[109,110] Hamasaki *et al.*[111] also reported that circulating BNP levels were positively associated with PA levels. As a holistic view of the potential effects of exercise on the CV system further than the classic ones, these cardiokines should not be overlooked since they represent an important contributor in improving CV health. In effect, we can here suggest an exercise-induced 'sacubitril-like effect', which ultimately leads to reduced clearance of biologically active natriuretic peptides.

3.7.4 Cardiac regeneration capacity

Exercise can play an adjuvant role as regenerative medicine therapy by stimulating certain stem cells named circulating angiogenic cells (CAnCs), which are inversely associated with the risk of CVD.[112] Likewise, endurance ET increases telomerase activity and telomere length, which are directly involved in cellular senescence and regenerative capacity.[113] From 17 to 90 years of age, we progressively lose ~30% of cardiomyocytes.[114] The rate of cardiomyocyte turnover is very low (between 0.3% and 1% per year).[115] Cardiomyocyte regeneration can be stimulated through different techniques.[116] Exercise increased the formation of new cardiomyocytes in adult mice, which indicates that ET can activate the adult mammalian heart's endogenous regeneration capacity.[117] Although it remains controversial, ET stimulates the proliferation of CAnCs in subjects with CVD, with high-intensity ET being the most potent stimulus.[118] From a mechanistic point of view, HIF-1α, VEGF, IL-6, and NO are among the factors mainly involved in CAnCs overstimulation.[119]

Finally, regular PA may overexpress 'cardioregenerative' myokines, such as Fstl1, and that is why patients with CVD should be highly encouraged to stay fit and active.[120] Telomerase activation or NRG1-dependent activation of receptor tyrosine-protein kinase ERBB2 and

ERBB4 signalling are among other mechanisms implicated in exercise-induced myocardial repair after MI.[121,122] Although this is still an evolving concept, it may represent a promising approach to prevent cardiac damage by means of ET-activated mechanisms.

4. Exercise effects on CVD risk factors

Aside from the effects on the molecular mechanisms directly involving CV structure and function, PA also attenuates different CVD risk factors, thus playing a crucial role in both primary and secondary prevention of CVD.

4.1 Plasma lipids and atherosclerosis

Higher plasma concentrations of atherogenic lipids expressed as total cholesterol, low-density lipoproteins (LDL), or the ratio of total cholesterol to high-density lipoproteins (HDL), are associated with increases in adverse CVD events.[123] Moreover, a decrease in LDL levels results in a reduction of CVD risk, independently of the baseline level.[124]

The effects of PA on the lipid profile are not consistent since they appear to depend on the type, intensity, and duration of the ET, with diet as a potential confounding factor.[125] Recent meta-analyses focused on different activity modalities have found disparate results, with benefits arising from aerobic training,[126] particularly when performed at a high intensity,[127] whereas no differences or minor improvement were noted in the lipid profile of either overweight or normal weight population following high-intensity resistance interval training.[128] These effects, however, can be small even with high training volumes.[126,129] Additionally, the inclusion of an exercise routine in dyslipidaemic subjects does not confer further LDL benefits than those achieved with statin administration.[130]

The degree to which the changes in the lipid profile contribute the ET-related reduction in CVD remains unclear.[7] However, recent research suggests that the relationship between PA and atherogenic risk may not be merely limited to the modulation of plasma concentrations. HDL particle size affects cholesterol efflux capacity.[131] *In vitro* cholesterol efflux capacity correlates with CVD prevalence, independently of HDL concentration.[131] Therefore, the increase in HDL size observed after training can play a role in CVD prevention.[132] Additionally, PA could also reduce atherosclerotic progression by altering the homeostasis of the arterial wall.[7]

The exact mechanism through which exercise affects the plasma lipids and the atherogenic risk is yet to be fully elucidated.[133] Some proposed pathways involve the stimulation of lipoprotein lipase activity or an increase in the expression of ATP-binding cassette transporter A1 and liver X receptor-alpha.[134,135]

4.2 Insulin sensitivity

Insulin resistance is a strong mediator in the previously mentioned association between the lipid profile and CVD risk. An inadequate sensitivity to insulin of fat tissue causes it to release free fatty acids that trigger an increase of triglyceride and very-LDL production in the liver, resulting in a lipid imbalance which, in turn, provokes an increase in CVD risk.[136] A reduction in HDL levels is an inherent component of insulin resistance and contributes to the formation and progression of atherosclerotic plaques.[137] The compensatory hyperinsulinaemia, together with the increased sympathetic activity present in T2DM patients, can also elicit vascular smooth muscle proliferation and vasoconstriction of arterioles, contributing to the development of HTN and peripheral artery disease.[138,139]

Previous meta-analyses have shown that PA is able to improve glycaemic control and insulin sensitivity.[140,141] Aerobic exercise has shown to be more efficient than resistance exercise or a combined training for improving glycaemic control.[142]

4.3 BP and vessels

Elevated BP or HTN is a highly-prevalent condition (with nearly a third of the population affected)[143,144] that poses a significant risk for various CVD events, such as HF, MI, and stroke.[133] ET reduces arterial stiffness, measured as pulse wave velocity, in adults with HTN.[145] Higher intensity levels of ET provoke greater diminutions in resting BP than does lower intensity exercise.[8]

Acutely, PA elicits an increase in both HR and cardiac stroke volume, resulting in an augmented cardiac output which, in combination with the elevated peripheral vascular resistance produced by muscular contractions, causes an increase in mean BP.[146] In contrast, the chronic adaptations to aerobic training include a decrease in resting and ambulatory BP of ~3 mmHg, as shown in previous meta-analyses.[147,148] Even though this effect might seem clinically irrelevant, a recent multicentric study with over 15 000 participants showed that reductions in this parameter as small as 1 mmHg are associated with a significant decrease in the incidence of HF.[149] In fact, this exercise-mediated reduction in BP has been proposed to be potentially higher than that of single antihypertensive drugs and similar to those of their most common treatment combinations.[133]

Different mechanisms contribute to the reduction of BP observed after long-term exercise, such as variations in artery diameter,[150] prevention of arterial stiffness,[151] inhibition of inflammatory status,[152] reductions in sympathetic nervous activity,[153] and restoration of the baroreflex sensitivity.[154] However, the main factor associated with the anti-HTN properties of exercise seems to be a chronic reduction in peripheral resistance,[155] resulting from an improved expression and activation of eNOS.[156] The subsequent increase in NO generates a reduction in the tone of the vascular smooth muscle.[157]

5. Clinical evidence of ET-associated positive effects on CVD

5.1 Coronary artery disease (CAD)/CHD

Currently, it seems obvious that ET represents a key element of primary and secondary prevention in CHD. The connection between PI and CHD is well documented.[158] The current burden of PI-related deaths caused by ischaemic heart disease is ~10% (5.46 out of 55.14 million deaths).[159] ET increases coronary blood flow and myocardial oxygen delivery, reducing angina and MI. Coronary artery disease (CAD) patients who participated in exercise-based cardiac rehabilitation programmes have a 27% reduction in total mortality compared to those who received usual care.[160] Moreover, ET improves the patient's ability to conduct daily living activities and their quality of life (QoL).[160] A meta-analysis from 48 studies with a total of 8940 patients who had MI, angina, CAD documented by angiography, or undergone percutaneous coronary intervention (PCI), showed a decrease of 20% in total mortality and of 26% in CVD mortality as a result of ET intervention.[161] Similarly, Hambrecht *et al.*[162] demonstrated that regular ET significantly increases

both peak oxygen uptake and event-free survival rate at 12 months follow-up in CAD patients who underwent PCI in comparison with those receiving medical therapy. In patients who enrolled in a PA programme after a PCI vs. those who remained inactive, the Exercise Training Intervention After Coronary Angioplasty trial reported increases in peak oxygen uptake of 26%, improvements in QoL of 27%, and reductions in CVD events of 20%, i.e. reductions in MI and hospital admissions.[163]

5.2 Stroke

Since ET has beneficial effects on many risk factors for stroke, such as HTN, dyslipidaemia, T2DM, obesity, excessive alcohol consumption, and tobacco use, physically active individuals have lower stroke risk than those with a low level of PA.[164] A greater CRF is inversely associated with stroke mortality. Lee and Blair[165] showed a 68% lower risk of stroke and death among individuals with higher CRF than those with lower CRF, remaining after adjusting for confounding variables, such as smoking, alcohol consumption, BMI, HTN, T2DM, and CAD history, while it was also demonstrated that the risk of stroke immediately after practicing moderate-to-vigorous exercise is significantly lower among physically active individuals than those physically inactive.[166]

5.3 Heart failure

The benefits of aerobic ET in HF have been extensively demonstrated, implicating both central and peripheral modifications. These benefits are clinically translated to increased exercise capacity, anti-remodelling effects, and reduced morbidity and mortality.[167,168] ET has been proven to be safe and with no adverse effects on LV remodelling in HF patients. Although a Cochrane meta-analysis did not find significant differences in total mortality at 1-year follow-up in patients who underwent ET vs. those who did not,[169] the authors found a reduction in both overall and HF-related hospitalizations. The ExTraMATCH II meta-analysis also reported important benefits regarding CRF and QoL.[170,171] The HF-ACTION trial concluded that ET was associated with an 11% lower adjusted risk for all-cause mortality or all-cause hospitalization and a 15% lower adjusted risk for CVD mortality or HF hospitalization in 2331 patients with HF with reduced EF.[172]

ET should be recommended to patients with HF regardless of their NYHA class.[173] The beneficial effects of ET are also present in patients with impaired LV EF and are directly associated with patient compliance and ET intensity.[173] Since the beneficial effects of ET are lost within few weeks after stopping ET, adherence is crucial.[173] Finally, it is now well-known that certain HF patients do not respond to exercise. Accordingly, ET programmes should be specifically tailored to those individuals, possibly with higher intensity ET.[174]

5.4 Hypertension

HTN is the most prevalent, modifiable, and costly CVD risk factor. ET reduces both resting and ambulatory BP.[175–177] For this reason, PA/ET is a cornerstone lifestyle and non-pharmacologic therapy for HTN.[178] One bout of aerobic exercise consistently lowers both office and ambulatory BP of hypertensive adults for up to 2 h during the post-exercise period.[179] However, this effect is variable in magnitude and duration, suggesting that individual and exercise characteristics might contribute to the variability of the aerobic post-exercise hypotension response.[179] This wide range in the BP reduction magnitude associated with ET may in part be due to a paucity of studies on the effects of ET on HTN.[180] Also, many studies performed on anti-HTN effects of ET are conducted in small samples and in individuals without HTN.

Regarding regular aerobic ET practice, it has been found to significantly reduce both the office and ambulatory BP of hypertensive individuals.[175,181] Thus, the final consensus is to practice 30 min/d or more of moderate-intensity aerobic exercise (i.e. exercising at 60–70% of VO_{2max}) to a total of 150 min/wk or more for adults with pre- to established HTN.[180]

5.5 Cardiac arrhythmias

The risk of atrial fibrillation (AF) and ventricular arrhythmias is lower among physically active individuals.[182–184] Exercising according to the guideline's recommendations, i.e. >500 MET-min/wk, is associated with a reduced risk of AF probably due to increased risk factor control, preserved cardiac function, and lower exposure to the potential arrhythmogenic effects of inflammation and oxidative stress.[185]

The repeated exposure to extreme endurance exercise has potential arrhythmogenic effects, thereby increasing the risk of AF.[186–188] Several studies indicated that long-term practice of very high doses of endurance exercise (i.e. those athletes who exercised a large part of their lives) is associated with a higher risk of AF.[189,190] The association might be particularly strong in competitive athletes. Although more mechanistic studies are needed, potential factors by virtue of which long-term endurance exercise might trigger AF in previously 'normal' hearts include left-atrial enlargement, LVH or dilatation, and an increase in parasympathetic tone.[191] The association of AF with strenuous exercise remains a topic of concern that should be clarified in future studies.

An 11–22% risk reduction of ventricular arrhythmias among physically active individuals (range: 500–2500 MET-min/wk) has been reported, most likely as a consequence of the stabilization and regression of atherosclerosis and a more favourable autonomic balance.[185] Interestingly, in an experimental model of dogs that were susceptible to ischaemia-induced ventricular fibrillation after suffering a MI, the animals showed a restoration of ryanodine receptor (RyR) channel activity mediated by the exercise-induced reduction in calcium/calmodulin-dependent protein kinase type II-mediated hyperphosphorylation of RyR at Ser2814, which limited the spread of unstable cardiac electrical signals and thus preventing malignant arrhythmias.[192] The association between PA and the incidence of bradyarrhythmias was also evaluated, concluding that bradyarrhythmias were not more common with higher volumes of total PA.[185] They found that vigorous PA (500–2500 MET-min/wk) was associated with a 9–18% lower risk of bradyarrhythmias in women. Thus, higher PA may be associated with a preservation of sinus node function and AV nodal conduction.

5.6 Gut microbiota-related CVD

Gut microbiota plays an important role in CVD, since it has been previously associated with certain microbial metabolites and gut microbiomes.[193] Recent studies implicate the gut microbiota in BP regulation, atherosclerosis and thrombosis development, HF, and cardiomyopathy.[194] In effect, it has been recently demonstrated that gut microbiota changes are associated with the development of HF, which supports restoring gut microbiota to prevent HF.[195] Increased production of the microbial metabolite trimethylamine N-oxide, endotoxaemia, and/or bacterial translocation may increase the risk of CVD.[196–198] Habitual PA, aerobic ET, and high CRF can increase microbiota diversity and/or modulate the gut microbiota;[193,199–201] in effect, its composition may also influence ET adaptation and athletic performance.[202] The alterations in the

composition and functional capacity of the gut microbiota induced by exercise are independent of diet.[203] Future studies are needed to elucidate which metabolites produced by the gut microbiota are more affected by physical exercise and how exercise-induced modifications in the gut microbiota are connected to CVD risk.

5.7 PA and mortality

Exercise-based cardiac rehabilitation reduces exercise-associated total mortality. For instance, moderate-intensity PA frequently practiced (~60–75 min per day) counteract the augmented risk of death associated with long periods of sitting time.[204] Likewise, higher PA levels at whichever intensity plus less sedentary time reduce the risk for premature mortality.[205] A recent meta-analysis concluded that achieving the recommended PA levels reduces the CVD events by 17%, CVD mortality by 23%, and the incidence of suffering T2DM by 26%.[206] These results were also confirmed by Kivimäki *et al.*,[207] concluding that PI was associated with 24% higher risk of CHD, 16% enhanced risk of stroke, and 42% higher risk of T2DM.

6. Long-term potential deleterious effects of high-intensity ET

Sports-related sudden cardiac death (SCD) is a rare but alarming event.[188] While some genetic disorders (cardiomyopathies/channelopathies) are the underlying disorder responsible for the fatal event in some young subjects (<35 years), unnoticed and asymptomatic coronary atherosclerosis—also referred to as subclinical CAD—is one of the most frequent causes of sudden cardiac arrest (SCA)/SCD in apparently healthy subjects aged ≥35 years.[208,209] In effect, several SCA/SCD cases associated with subclinical CAD have been reported in competitive and recreational athletes.[210]

Although PI is a large concern for the majority of the general population,[211] little attention has been paid to the coronary atherosclerosis origination/progression in response to high-intensity ET over prolonged time periods and accompanied strenuous exercise events, such as endurance and/or ultra-endurance races (i.e. marathons, ultra-marathons, triathlons, or iron man). This fact is particularly relevant given the growing number of people taking part in these competitions; it is estimated that there are 50 million runners across Europe.[212] In this regard, ET-induced inflammation has been connected with atherothrombotic disease.[213,214] In effect, the most active amateur endurance athletes (i.e. individuals who engage in ET on a regular basis and take part in competitions) have an increased risk for myocardial fibrosis[215,216] and coronary calcification.[217–219] Laddu *et al.*[220] evaluated whether 25 years of practicing PA was associated with coronary artery calcification, concluding that the most active individuals has an increased probability of developing subclinical coronary atherosclerosis in older ages. Two other studies have reported that between 42% and 53% of veteran endurance athletes had calcific CAD.[218,221] To be emphasized, the plaques in athletes were calcified rather than mixed, i.e. more benign and stable, less likely to rupture and cause an acute CHD event. Nevertheless, concerns about the safety of ET at the highest level for certain populations have emerged.[210,222,223]

Notably, the European Association of Preventive Cardiology recommends that individuals with CAD must be discouraged from sports competitions only when there is a considerable risk of adverse CVD events or disease progression exists (i.e. asymptomatic patients with CAD and inducible ischaemia or arrhythmia on functional tests, among others).[224] Patients at low risk of CVD events may be individually advised to participate in sports competitions.[224] However, to the best of our knowledge, the effect of an increase in the intensity of exercise (e.g. preparation for an endurance competition) on subclinical atherosclerosis (generation, progression, extent, and/or vulnerability) has not been longitudinally studied. Similarly, the impact of endurance training on myocardial phenotype, eventually predisposing to adverse CVD events (i.e. LV trabeculation) in this population, has been barely evaluated. Thus, the effects of high-intensity endurance ET might represent a stress for the CV system (vessel wall and myocardium) that may result in an adverse event where the subclinical atherosclerotic disease is involved. Importantly, vigorous physical exercise has been recently associated with a higher prevalence of CV magnetic resonance imaging-detected LV non-compaction phenotype in a recent community-based study, independently of LV volumes. Thus, vigorous exercise should be considered as a possible cause of LV hypertrabeculation in asymptomatic subjects.[225]

7. ET, CV system, and viral infections, such as coronavirus disease 2019 (COVID-19): the importance of being fit to be protected against environmental threats

A higher COVID-19 severity is, at least in part, due to the presence of CVD risk factors, such as HTN, T2DM, obesity, or CAD, among others, which is associated with a less favourable prognosis and worse outcomes in COVID-19 patients.[226] In effect, there is increased mortality in COVID-19 patients with CVD,[227] which indicates that there is a connection between myocardial injury and COVID-19 severity, with a higher frequency of myocardial injury in critically ill patients and non-survivors.[228] In addition, it has been recently reported that COVID-19 patients with ST-segment elevation MI (STEMI) show more HF on hospital arrival than non-COVID-19 patients (31.9% vs. 18.4%, $P = 0.002$).[229] These authors also observed a substantial increase in in-hospital stent thrombosis and cardiogenic shock development after PCI in COVID-19 patients with STEMI.[229] Importantly, it has been reported that maximal exercise capacity is independently and inversely correlated with the probability of hospitalization of COVID-19 patients, which supports the crucial connection between CRF and health outcomes.[230]

Detrimental effects have also been described after acute PA interruption, which may occur in sudden quarantine. It has been associated with insulin resistance, muscle atrophy, decreases in venous return, and reductions in coronary perfusion.[231,232] Positive metabolic and CV adaptations in response to ET can be lost in <2weeks of PI, impairing CRF and/or increasing BP. The production of atherogenic lipoproteins may rise, which promotes the accumulation of circulating lipids and obesity, accelerating atherosclerosis.[231] The resting HR also increases after the acute cessation of ET/PA, rapidly amplifying the risk of CVD events and mortality. During quarantines, staying physically active and regularly performing ET is essential to preserve CV health.[233,234] Overall, it is important to be aware that exercise and increased CRF may protect against a wide range of environmental threats,[235] including but not limited to viral (e.g. COVID-19) and bacterial infections.

8. Recommendations, future perspectives, and concluding remarks

It is now clear that regular ET/PA induces a wide range of direct and indirect physiological adaptations and pleiotropic benefits for human CV health. PA, exercise, and CRF evaluations and interventions should be incorporated into all health professionals' practice.[236] ET/PA is a mainstay to prevent and control the global problem of CVD. To this end, health care professionals must interact with individuals in our long-term efforts to reduce sedentarism and PI and increase ET/PA to reduce CVD. Although hypothetically, there is no universal exercise prescription,[237] general guidelines can be developed for all levels of CRF. An individualized approach in terms of a patient's CRF and health/disease status, on one side, and exercise type and dosage, on the other side, needs to be considered.[238]

Despite the extensive history of research into exercise and cardioprotection, many questions remain unanswered. The duration and intensity of ET needed to optimize cardioprotection remain uncertain, and the underlying mechanisms are still unclear. Elucidating exercise-associated positive mechanisms may generate promising therapeutic targets for cardioprotection.

In addition to improving traditional CVD risk factors (i.e. blood lipid and glucose levels, obesity, and HTN), exercise confers benefits through other mechanisms, such as myokines. Importantly, exercise is safe and with no adverse effects, and its benefits are, in some measure, dose–dependent. It is time to view exercise as medicine for the management of CVD.

Additionally, the molecular intermediaries involved in exercise effects may open new possibilities to enhance exercise's effects using more effective or targeted strategies. The exercise-based concept for cardiac drug target discovery has great potential to positively affect society and public-health systems by alleviating CVD's burden. Although this aim may appear futuristic, its positive benefits should be a robust motivation for further research in the field. Meanwhile, the evidence of benefits that are already obvious should be applied and adopted as critical priorities.[238]

In the COVID-19 era, in which we are relying on an effective vaccine to protects the community against severe acute respiratory syndrome coronavirus 2, ET/PA represents a potential co-adjuvant 'vaccine' or a non-pharmacological treatment that should be recommended and spread to prevent and/or treat one of the deadliest diseases in the world, CVD.

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References

1. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* 2007;**116**:2110–2118.
2. Chowdhury MA, Sholl HK, Sharrett MS, Haller ST, Cooper CC, Gupta R, Liu LC. Exercise and cardioprotection: a natural defense against lethal myocardial ischemia-reperfusion injury and potential guide to cardiovascular prophylaxis. *J Cardiovasc Pharmacol Ther* 2019;**24**:18–30.
3. Gielen S, Laughlin MH, O'Conner C, Duncker DJ. Exercise training in patients with heart disease: review of beneficial effects and clinical recommendations. *Prog Cardiovasc Dis* 2015;**57**:347–355.
4. Vina J, Sanchis-Gomar F, Martinez-Bello V, Gomez-Cabrera MC. Exercise acts as a drug; the pharmacological benefits of exercise. *Br J Pharmacol* 2012;**167**:1–12.
5. Sanchis-Gomar F, Lippi G. Physical activity - an important preanalytical variable. *Biochem Med (Zagreb)* 2014;**24**:68–79.
6. Finsterer J. Biomarkers of peripheral muscle fatigue during exercise. *BMC Musculoskelet Disord* 2012;**13**:218.
7. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. *Front Cardiovasc Med* 2018;**5**:135.
8. Perez-Quilis C, Kingsley JD, Malkani K, Cervellin G, Lippi G, Sanchis-Gomar F. Modulation of heart rate by acute or chronic aerobic exercise. Potential effects on blood pressure control. *Curr Pharm Des* 2017;**23**:4650–4657.
9. Platt C, Houstis N, Rosenzweig A. Using exercise to measure and modify cardiac function. *Cell Metab* 2015;**21**:227–236.
10. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee DC, Earnest CP, Church TS, O'Keefe JH, Milani RV, Blair SN. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. *Circ Res* 2015;**117**:207–219.
11. Quindry JC, Franklin BA. Cardioprotective exercise and pharmacologic interventions as complementary antidotes to cardiovascular disease. *Exerc Sport Sci Rev* 2018;**46**:5–17.
12. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991;**324**:295–301.
13. Fagard R, Van den Broeke C, Amery A. Left ventricular dynamics during exercise in elite marathon runners. *J Am Coll Cardiol* 1989;**14**:112–118.
14. Fagard RH. Impact of different sports and training on cardiac structure and function. *Cardiol Clin* 1997;**15**:397–412.
15. Levine BD. Can intensive exercise harm the heart? The benefits of competitive endurance training for cardiovascular structure and function. *Circulation* 2014;**130**:987–991.
16. Levine BD, Lane LD, Buckey JC, Friedman DB, Blomqvist CG. Left ventricular pressure-volume and Frank-Starling relations in endurance athletes. Implications for orthostatic tolerance and exercise performance. *Circulation* 1991;**84**:1016–1023.
17. Maron BJ, Pelliccia A, Spataro A, Granata M. Reduction in left ventricular wall thickness after deconditioning in highly trained Olympic athletes. *Br Heart J* 1993;**69**:125–128.
18. Pelliccia A, Maron BJ, De Luca R, Di Paolo FM, Spataro A, Culasso F. Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. *Circulation* 2002;**105**:944–949.
19. Urhausen A, Albers T, Kindermann W. Are the cardiac effects of anabolic steroid abuse in strength athletes reversible? *Heart* 2004;**90**:496–501.
20. Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med* 1999;**130**:23–31.
21. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. *Ann Intern Med* 1975;**82**:521–524.
22. D'Andrea A, Limongelli G, Caso P, Sarubbi B, Della Pietra A, Brancaccio P, Cice G, Scherillo M, Limongelli F, Calabrò R. Association between left ventricular structure and cardiac performance during effort in two morphological forms of athlete's heart. *Int J Cardiol* 2002;**86**:177–184.
23. George KP, Warburton DE, Oxborough D, Scott JM, Esch BT, Williams K, Charlesworth S, Foulds H, Oxborough A, Hoffman MD, Shave R. Upper limits of physiological cardiac adaptation in ultramarathon runners. *J Am Coll Cardiol* 2011;**57**:754–755.
24. O'Keefe JH, Patil HR, Lavie CJ, Magalski A, Vogel RA, McCullough PA. Potential adverse cardiovascular effects from excessive endurance exercise. *Mayo Clin Proc* 2012;**87**:587–595.
25. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary behavior, exercise, and cardiovascular health. *Circ Res* 2019;**124**:799–815.
26. Lavie CJ, Ozemek C, Kachur S. Promoting physical activity in primary and secondary prevention. *Eur Heart J* 2019;**40**:3556–3558.
27. Cabanas-Sánchez V, Artero EG, Lavie CJ, Higueras-Fresnillo S, García-Esquinas E, Sadarangani KP, Ortolá R, Rodríguez-Artalejo F, Martínez-Gómez D. Prediction of cardiovascular health by non-exercise estimated cardiorespiratory fitness. *Heart* 2020;**106**:1832–1838.
28. Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. *Front Cardiovasc Med* 2019;**6**:69.
29. Harber MP, Kaminsky LA, Arena R, Blair SN, Franklin BA, Myers J, Ross R. Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009. *Prog Cardiovasc Dis* 2017;**60**:11–20.
30. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009;**301**:2024–2035.

31. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. *Diabetes* 2007;**56**:2655–2667.
32. Iwasaki K, Zhang R, Zuckerman JH, Levine BD. Dose-response relationship of the cardiovascular adaptation to endurance training in healthy adults: how much training for what benefit? *J Appl Physiol (1985)* 2003;**95**:1575–1583.
33. Sidhu S, Marine JE. Evaluating and managing bradycardia. *Trends Cardiovasc Med* 2020;**30**:265–272.
34. Billman GE, Cagnoli KL, Csepe T, Li N, Wright P, Mohler PJ, Fedorov VV. Exercise training-induced bradycardia: evidence for enhanced parasympathetic regulation without changes in intrinsic sinoatrial node function. *J Appl Physiol (1985)* 2015;**118**:1344–1355.
35. Pearson MJ, Smart NA. Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart Fail Rev* 2018;**23**:91–108.
36. Villafaina S, Collado-Mateo D, Fuentes JP, Merellano-Navarro E, Gusi N. Physical exercise improves heart rate variability in patients with type 2 diabetes: a systematic review. *Curr Diab Rep* 2017;**17**:110.
37. Zingman LV, Zhu Z, Sierra A, Stepniak E, Burnett CM, Maksymov G, Anderson ME, Coetzee WA, Hodgson-Zingman DM. Exercise-induced expression of cardiac ATP-sensitive potassium channels promotes action potential shortening and energy conservation. *J Mol Cell Cardiol* 2011;**51**:72–81.
38. Sessa F, Anna V, Messina G, Cibelli G, Monda V, Marsala G, Ruberto M, Biondi A, Cascio O, Bertozzi G, Pisanelli D, Maglietta F, Messina A, Mollica MP, Salerno M. Heart rate variability as predictive factor for sudden cardiac death. *Aging (Albany NY)* 2018;**10**:166–177.
39. Hillebrand S, Gast KB, de Mutsert R, Swenne CA, Jukema JW, Middeldorp S, Rosendaal FR, Dekkers OM. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. *Europace* 2013;**15**:742–749.
40. Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. *J Physiol* 2009;**587**:5551–5558.
41. Deley G, Picard G, Taylor JA. Arterial baroreflex control of cardiac vagal outflow in older individuals can be enhanced by aerobic exercise training. *Hypertension* 2009;**53**:826–832.
42. Moreira JBN, Wohlwend M, Wisloff U. Exercise and cardiac health: physiological and molecular insights. *Nat Metab* 2020;**2**:829–839.
43. Frystyk J. Exercise and the growth hormone-insulin-like growth factor axis. *Med Sci Sports Exerc* 2010;**42**:58–66.
44. Neri Serneri GG, Boddi M, Modesti PA, Cecioni I, Coppo M, Padeletti L, Michelucci A, Colella A, Galanti G. Increased cardiac sympathetic activity and insulin-like growth factor-I formation are associated with physiological hypertrophy in athletes. *Circ Res* 2001;**89**:977–982.
45. McMullen JR, Shioi T, Huang WY, Zhang L, Tarnavski O, Bisping E, Schinke M, Kong S, Sherwood MC, Brown J, Riggi L, Kang PM, Izumo S. The insulin-like growth factor 1 receptor induces physiological heart growth via the phosphoinositide 3-kinase(-p110alpha) pathway. *J Biol Chem* 2004;**279**:4782–4793.
46. Reiss K, Cheng W, Ferber A, Kajstura J, Li P, Li B, Olivetti G, Homcy CJ, Baserga R, Anversa P. Overexpression of insulin-like growth factor-1 in the heart is coupled with myocyte proliferation in transgenic mice. *Proc Natl Acad Sci USA* 1996;**93**:8630–8635.
47. Kim J, Wende AR, Sena S, Theobald HA, Soto J, Sloan C, Wayment BE, Litwin SE, Holzenberger M, LeRoith D, Abel ED. Insulin-like growth factor I receptor signaling is required for exercise-induced cardiac hypertrophy. *Mol Endocrinol* 2008;**22**:2531–2543.
48. Wei X, Liu X, Rosenzweig A. What do we know about the cardiac benefits of exercise? *Trends Cardiovasc Med* 2015;**25**:529–536.
49. McMullen JR, Shioi T, Zhang L, Tarnavski O, Sherwood MC, Kang PM, Izumo S. Phosphoinositide 3-kinase(p110alpha) plays a critical role for the induction of physiological, but not pathological, cardiac hypertrophy. *Proc Natl Acad Sci USA* 2003;**100**:12355–12360.
50. DeBosch B, Treskov I, Lupu TS, Weinheimer C, Kovacs A, Courtois M, Muslin AJ. Akt1 is required for physiological cardiac growth. *Circulation* 2006;**113**:2097–2104.
51. Bostrom P, Mann N, Wu J, Quintero PA, Plovie ER, Panakova D, Gupta RK, Xiao C, MacRae CA, Rosenzweig A, Spiegelman BM. C/EBPbeta controls exercise-induced cardiac growth and protects against pathological cardiac remodeling. *Cell* 2010;**143**:1072–1083.
52. Lerchenmuller C, Rabolli CP, Yeri A, Kitchen R, Salvador AM, Liu LX, Ziegler O, Danielson K, Platt C, Shah R, Damilano F, Kundu P, Riechert E, Katus HA, Saffitz JE, Keshishian H, Carr SA, Bezzerides VJ, Das S, Rosenzweig A. CITED4 protects against adverse remodeling in response to physiological and pathological stress. *Circ Res* 2020;**127**:631–646.
53. Hafstad AD, Boardman N, Aasum E. How exercise may amend metabolic disturbances in diabetic cardiomyopathy. *Antioxid Redox Signal* 2015;**22**:1587–1605.
54. Kolwicz SC Jr. An "Exercise" in cardiac metabolism. *Front Cardiovasc Med* 2018;**5**:66.
55. Puigserver P, Spiegelman BM. Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha): transcriptional coactivator and metabolic regulator. *Endocr Rev* 2003;**24**:78–90.
56. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* 1998;**92**:829–839.
57. Liang H, Ward WF. PGC-1alpha: a key regulator of energy metabolism. *Adv Physiol Educ* 2006;**30**:145–151.
58. Botta A, Laher I, Beam J, Decoffe D, Brown K, Halder S, Devlin A, Gibson DL, Ghosh S. Short term exercise induces PGC-1alpha, ameliorates inflammation and increases mitochondrial membrane proteins but fails to increase respiratory enzymes in aging diabetic hearts. *PLoS One* 2013;**8**:e70248.
59. Arany Z, He H, Lin J, Hoyer K, Handschin C, Toka O, Ahmad F, Matsui T, Chin S, Wu PH, Rybkin II, Shelton JM, Manieri M, Cinti S, Schoen FJ, Bassel-Duby R, Rosenzweig A, Ingwall JS, Spiegelman BM. Transcriptional coactivator PGC-1 alpha controls the energy state and contractile function of cardiac muscle. *Cell Metab* 2005;**1**:259–271.
60. Jager S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. *Proc Natl Acad Sci USA* 2007;**104**:12017–12022.
61. Pillai VB, Sundaresan NR, Jeevanandam V, Gupta MP. Mitochondrial SIRT3 and heart disease. *Cardiovasc Res* 2010;**88**:250–256.
62. Moreira JBN, Wohlwend M, Fenk S, Amellem I, Flatberg A, Kraljevic J, Marinovic J, Ljubkovic M, Bjorkoy G, Wisloff U. Exercise reveals proline dehydrogenase as a potential target in heart failure. *Prog Cardiovasc Dis* 2019;**62**:193–202.
63. Calvert JW, Condit ME, Aragon JP, Nicholson CK, Moody BF, Hood RL, Sindler AL, Gundewar S, Seals DR, Barouch LA, Lefer DJ. Exercise protects against myocardial ischemia-reperfusion injury via stimulation of beta(3)-adrenergic receptors and increased nitric oxide signaling: role of nitrite and nitrosothiols. *Circ Res* 2011;**108**:1448–1458.
64. Hamilton KL, Staib JL, Phillips T, Hess A, Lennon SL, Powers SK. Exercise, antioxidants, and HSP72: protection against myocardial ischemia/reperfusion. *Free Radic Biol Med* 2003;**34**:800–809.
65. Tekin D, Dursun AD, Xi L. Hypoxia inducible factor 1 (HIF-1) and cardioprotection. *Acta Pharmacol Sin* 2010;**31**:1085–1094.
66. de Waard MC, van der Velden J, Bito V, Ozdemir S, Biesmans L, Boontje NM, Dekkers DH, Schoonderwoerd K, Schuurbiers HC, de Crom R, Stienen GJ, Sipido KR, Lamers JM, Duncker DJ. Early exercise training normalizes myofilament function and attenuates left ventricular pump dysfunction in mice with a large myocardial infarction. *Circ Res* 2007;**100**:1079–1088.
67. de Waard MC, van Haperen R, Soullie T, Tempel D, de Crom R, Duncker DJ. Beneficial effects of exercise training after myocardial infarction require full eNOS expression. *J Mol Cell Cardiol* 2010;**48**:1041–1049.
68. de Waard MC, Duncker DJ. Prior exercise improves survival, infarct healing, and left ventricular function after myocardial infarction. *J Appl Physiol (1985)* 2009;**107**:928–936.
69. O'Neill BT, Kim J, Wende AR, Theobald HA, Tuinei J, Buchanan J, Guo A, Zaha VG, Davis DK, Schell JC, Boudina S, Wayment B, Litwin SE, Shioi T, Izumo S, Birnbaum MJ, Abel ED. A conserved role for phosphatidylinositol 3-kinase but not Akt signaling in mitochondrial adaptations that accompany physiological cardiac hypertrophy. *Cell Metab* 2007;**6**:294–306.
70. Zhang QJ, McMillin SL, Tanner JM, Palionyte M, Abel ED, Symons JD. Endothelial nitric oxide synthase phosphorylation in treadmill-running mice: role of vascular signalling kinases. *J Physiol* 2009;**587**:3911–3920.
71. Dimmeler S, Fleming I, Fisslthaler B, Hermann C, Busse R, Zeiher AM. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature* 1999;**399**:601–605.
72. Matsui T, Li L, del Monte F, Fukui Y, Franke TF, Hajjar RJ, Rosenzweig A. Adenoviral gene transfer of activated phosphatidylinositol 3'-kinase and Akt inhibits apoptosis of hypoxic cardiomyocytes in vitro. *Circulation* 1999;**100**:2373–2379.
73. Matsui T, Tao J, del Monte F, Lee KH, Li L, Picard M, Force TL, Franke TF, Hajjar RJ, Rosenzweig A. Akt activation preserves cardiac function and prevents injury after transient cardiac ischemia in vivo. *Circulation* 2001;**104**:330–335.
74. You T, Arsenis NC, Disanzo BL, Lamonte MJ. Effects of exercise training on chronic inflammation in obesity: current evidence and potential mechanisms. *Sports Med* 2013;**43**:243–256.
75. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. *Vascul Pharmacol* 2018;**100**:1–19.
76. de Picciotto NE, Gano LB, Johnson LC, Martens CR, Sindler AL, Mills KF, Imai S, Seals DR. Nicotinamide mononucleotide supplementation reverses vascular dysfunction and oxidative stress with aging in mice. *Aging Cell* 2016;**15**:522–530.
77. Durrant JR, Seals DR, Connell ML, Russell MJ, Lawson BR, Folian BJ, Donato AJ, Lesniewski LA. Voluntary wheel running restores endothelial function in conduit arteries of old mice: direct evidence for reduced oxidative stress, increased superoxide dismutase activity and down-regulation of NADPH oxidase. *J Physiol* 2009;**587**:3271–3285.
78. Bloomer RJ, Goldfarb AH, Wideman L, McKenzie MJ, Consitt LA. Effects of acute aerobic and anaerobic exercise on blood markers of oxidative stress. *J Strength Cond Res* 2005;**19**:276–285.
79. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. *Int Rev Cell Mol Biol* 2012;**298**:229–317.

80. Camara AK, Bienengraeber M, Stowe DF. Mitochondrial approaches to protect against cardiac ischemia and reperfusion injury. *Front Physiol* 2011;**2**:13.
81. Lakka TA, Lakka HM, Rankinen T, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Effect of exercise training on plasma levels of C-reactive protein in healthy adults: the HERITAGE Family Study. *Eur Heart J* 2005;**26**:2018–2025.
82. McGinnis GR, Ballmann C, Peters B, Nanayakkara G, Roberts M, Amin R, Quindry JC. Interleukin-6 mediates exercise preconditioning against myocardial ischemia reperfusion injury. *Am J Physiol Heart Circ Physiol* 2015;**308**:H1423–H1433.
83. Hayward R, Nossuli TO, Scalia R, Lefer AM. Cardioprotective effect of interleukin-10 in murine myocardial ischemia-reperfusion. *Eur J Pharmacol* 1997;**334**:157–163.
84. Serra AJ, Santos MH, Bocalini DS, Antonio EL, Levy RF, Santos AA, Higuchi ML, Silva JA, Magalhaes FC, Barauna VG, Krieger JE, Tucci PJ. Exercise training inhibits inflammatory cytokines and more than prevents myocardial dysfunction in rats with sustained beta-adrenergic hyperactivity. *J Physiol* 2010;**588**:2431–2442.
85. Kesherwani V, Chavali V, Hackfort BT, Tyagi SC, Mishra PK. Exercise ameliorates high fat diet induced cardiac dysfunction by increasing interleukin 10. *Front Physiol* 2015;**6**:124.
86. Hamilton S, Terentyev D. Altered Intracellular Calcium Homeostasis and Arrhythmogenesis in the Aged Heart. *Int J Mol Sci* 2019;**20**:2386.
87. Schmidt U, del Monte F, Miyamoto MI, Matsui T, Gwathmey JK, Rosenzweig A, Hajjar RJ. Restoration of diastolic function in senescent rat hearts through adenoviral gene transfer of sarcoplasmic reticulum Ca(2+)-ATPase. *Circulation* 2000;**101**:790–796.
88. Tate CA, Helgason T, Hyek MF, McBride RP, Chen M, Richardson MA, Taffet GE. SERCA2a and mitochondrial cytochrome oxidase expression are increased in hearts of exercise-trained old rats. *Am J Physiol* 1996;**271**:H68–H72.
89. Iemitsu M, Miyauchi T, Maeda S, Tanabe T, Takanashi M, Matsuda M, Yamaguchi I. Exercise training improves cardiac function-related gene levels through thyroid hormone receptor signaling in aged rats. *Am J Physiol Heart Circ Physiol* 2004;**286**:H1696–H1705.
90. Catalanotto C, Cogoni C, Zardo G. MicroRNA in control of gene expression: an overview of nuclear functions. *Int J Mol Sci* 2016;**17**:1712.
91. Zampetaki A, Willeit P, Drozdov I, Kiechl S, Mayr M. Profiling of circulating microRNAs: from single biomarkers to re-wired networks. *Cardiovasc Res* 2012;**93**:555–562.
92. Ramos AE, Lo C, Estephan LE, Tai YY, Tang Y, Zhao J, Sugahara M, Gorcsan J III, Brown MG, Lieberman DE, Chan SY, Baggish AL. Specific circulating microRNAs display dose-dependent responses to variable intensity and duration of endurance exercise. *Am J Physiol Heart Circ Physiol* 2018;**315**:H273–H283.
93. Shi J, Bei Y, Kong X, Liu X, Lei Z, Xu T, Wang H, Xuan Q, Chen P, Xu J, Che L, Liu H, Zhong J, Sluijter JP, Li X, Rosenzweig A, Xiao J. miR-17-3p contributes to exercise-induced cardiac growth and protects against myocardial ischemia-reperfusion injury. *Theranostics* 2017;**7**:664–676.
94. Care A, Catalucci D, Felicetti F, Bonci D, Addario A, Gallo P, Bang ML, Segnalini P, Gu Y, Dalton ND, Elia L, Latronico MV, Hoydal M, Autore C, Russo MA, Dorn GW III, Ellingsen O, Ruiz-Lozano P, Peterson KL, Croce CM, Peschle C, Condorelli G. MicroRNA-133 controls cardiac hypertrophy. *Nat Med* 2007;**13**:613–618.
95. Lee JH, Jun HS. Role of myokines in regulating skeletal muscle mass and function. *Front Physiol* 2019;**10**:42.
96. Wang Z, Chen K, Han Y, Zhu H, Zhou X, Tan T, Zeng J, Zhang J, Liu Y, Li Y, Yao Y, Yi J, He D, Zhou J, Ma J, Zeng C. Irisin protects heart against ischemia-reperfusion injury through a SOD2-dependent mitochondria mechanism. *J Cardiovasc Pharmacol* 2018;**72**:259–269.
97. Ho MY, Wen MS, Yeh JK, Hsieh IC, Chen CC, Hsieh MJ, Tsai ML, Yang CH, Wu VC, Hung KC, Wang CC, Wang CY. Excessive irisin increases oxidative stress and apoptosis in murine heart. *Biochem Biophys Res Commun* 2018;**503**:2493–2498.
98. Otaka N, Shibata R, Ohashi K, Uemura Y, Kambara T, Enomoto T, Ogawa H, Ito M, Kawanishi H, Maruyama S, Joki Y, Fujikawa Y, Narita S, Unno K, Kawamoto Y, Murate T, Murohara T, Ouchi N. Myonectin is an exercise-induced myokine that protects the heart from ischemia-reperfusion injury. *Circ Res* 2018;**123**:1326–1338.
99. Xi Y, Gong DW, Tian Z. FSTL1 as a potential mediator of exercise-induced cardioprotection in post-myocardial infarction rats. *Sci Rep* 2016;**6**:32424.
100. Oshima Y, Ouchi N, Sato K, Izumiya Y, Pimentel DR, Walsh K. Follistatin-like 1 is an Akt-regulated cardioprotective factor that is secreted by the heart. *Circulation* 2008;**117**:3099–3108.
101. Rao RR, Long JZ, White JP, Svensson KJ, Lou J, Lokurkar I, Jedrychowski MP, Ruas JL, Wrann CD, Lo JC, Camera DM, Lachey J, Gygi S, Seehra J, Hawley JA, Spiegelman BM. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell* 2014;**157**:1279–1291.
102. Tezze C, Romanello V, Sandri M. FGF21 as modulator of metabolism in health and disease. *Front Physiol* 2019;**10**:419.
103. Subbotina E, Sierra A, Zhu Z, Gao Z, Koganti SR, Reyes S, Stepniak E, Walsh SA, Acevedo MR, Perez-Terzic CM, Hodgson-Zingman DM, Zingman LV. Musclin is an activity-stimulated myokine that enhances physical endurance. *Proc Natl Acad Sci USA* 2015;**112**:16042–16047.
104. Sun Y, Wu Y, Tang S, Liu H, Jiang Y. Sestrin proteins in cardiovascular disease. *Clin Chim Acta* 2020;**508**:43–46.
105. Carbone S, Billingsley HE, Rodriguez-Miguelez P, Kirkman DL, Garten R, Franco RL, Lee DC, Lavie CJ. Lean mass abnormalities in heart failure: the role of sarcopenia, sarcopenic obesity, and cachexia. *Curr Probl Cardiol* 2020;**45**:100417.
106. Haidurov A, Budanov AV. Sestrin family - the stem controlling healthy ageing. *Mech Ageing Dev* 2020;**192**:111379.
107. Sanchis-Gomar F. Sestrins: novel antioxidant and AMPK-modulating functions regulated by exercise? *J Cell Physiol* 2013;**228**:1647–1650.
108. Barletta G, Stefani L, Del Bene R, Fronzaroli C, Vecchiarino S, Lazzeri C, Fantini F, La Villa G. Effects of exercise on natriuretic peptides and cardiac function in man. *Int J Cardiol* 1998;**65**:217–225.
109. Mandroukas A, Metaxas TI, Heller J, Vamvakoudis E, Christoulas K, Riganas CS, Sendelides T, Stefanidis P, Kotoglou K, Karamouzis I, Mandroukas K. The effect of different exercise-testing protocols on atrial natriuretic peptide. *Clin Physiol Funct Imaging* 2011;**31**:5–10.
110. Eijsvogels TM, Fernandez AB, Thompson PD. Are there deleterious cardiac effects of acute and chronic endurance exercise? *Physiol Rev* 2016;**96**:99–125.
111. Hamasaki H, Yanai H, Kakei M, Noda M, Ezaki O. The association between daily physical activity and plasma B-type natriuretic peptide in patients with glucose intolerance: a cross-sectional study. *BMJ Open* 2015;**5**:e006276.
112. Bakogiannis C, Tousoulis D, Androulakis E, Briasoulis A, Papageorgiou N, Vogiatzi G, Kampoli AM, Charakida M, Siasos G, Latsios G, Antoniades C, Stefanadis C. Circulating endothelial progenitor cells as biomarkers for prediction of cardiovascular outcomes. *Curr Med Chem* 2012;**19**:2597–2604.
113. Werner CM, Hecksteden A, Morsch A, Zundler J, Wegmann M, Kratzsch J, Thiery J, Hohl M, Bittenbring JT, Neumann F, Bohm M, Meyer T, Laufs U. Differential effects of endurance, interval, and resistance training on telomerase activity and telomere length in a randomized, controlled study. *Eur Heart J* 2019;**40**:34–46.
114. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. *Circ Res* 1991;**68**:1560–1568.
115. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabé-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S, Frisén J. Evidence for cardiomyocyte renewal in humans. *Science* 2009;**324**:98–102.
116. Lazar E, Sadek HA, Bergmann O. Cardiomyocyte renewal in the human heart: insights from the fall-out. *Eur Heart J* 2017;**38**:2333–2342.
117. Vujic A, Lerchenmuller C, Wu TD, Guillermier C, Rabolli CP, Gonzalez E, Senyo SE, Liu X, Guerquin-Kern JL, Steinhauser ML, Lee RT, Rosenzweig A. Exercise induces new cardiomyocyte generation in the adult mammalian heart. *Nat Commun* 2018;**9**:1659.
118. Adams V, Lenk K, Linke A, Lenz D, Erbs S, Sandri M, Tarnok A, Gielen S, Emmrich F, Schuler G, Hambrecht R. Increase of circulating endothelial progenitor cells in patients with coronary artery disease after exercise-induced ischemia. *Arterioscler Thromb Vasc Biol* 2004;**24**:684–690.
119. Bernardo BC, Ooi JYY, Weeks KL, Patterson NL, McMullen JR. Understanding key mechanisms of exercise-induced cardiac protection to mitigate disease: current knowledge and emerging concepts. *Physiol Rev* 2018;**98**:419–475.
120. Sanchis-Gomar F, Perez-Quilis C, Lucia A. Overexpressing FSTL1 for heart repair. *Trends Mol Med* 2016;**22**:353–354.
121. Sanchis-Gomar F, Lucia A. Acute myocardial infarction: 'telomerasing' for cardioprotection. *Trends Mol Med* 2015;**21**:203–205.
122. Cai MX, Shi XC, Chen T, Tan ZN, Lin QQ, Du SJ, Tian ZJ. Exercise training activates neuregulin 1/ErbB signaling and promotes cardiac repair in a rat myocardial infarction model. *Life Sci* 2016;**149**:1–9.
123. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, Mente A, Yusuf S. Reducing the global burden of cardiovascular disease, part 1: the epidemiology and risk factors. *Circ Res* 2017;**121**:677–694.
124. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;**388**:2532–2561.
125. Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc* 2001;**33**:S502–S515.
126. Nordengen S, Andersen LB, Solbraa AK, Riiser A. Cycling and cardiovascular disease risk factors including body composition, blood lipids and cardiorespiratory fitness analysed as continuous variables: part 2-systematic review with meta-analysis. *Br J Sports Med* 2019;**53**:879–885.
127. Tesema G, George M, Hadgu A, Haregot E, Mondal S, Mathivana D. Does chronic high-intensity endurance training have an effect on cardiovascular markers of active populations and athletes? Systematic review and meta-analysis. *BMJ Open* 2019;**9**:e032832.
128. Batacan RB Jr, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med* 2017;**51**:494–503.
129. Sarzynski MA, Ruiz-Ramie JJ, Barber JL, Slentz CA, Apolzan JW, McGarrah RW, Harris MN, Church TS, Borja MS, He Y, Oda MN, Martin CK, Kraus WE, Rohatgi A. Effects of increasing exercise intensity and dose on multiple measures of HDL (high-density lipoprotein) function. *Arterioscler Thromb Vasc Biol* 2018;**38**:943–952.
130. Gui YJ, Liao CX, Liu Q, Guo Y, Yang T, Chen JY, Wang YT, Hu JH, Xu DY. Efficacy and safety of statins and exercise combination therapy compared to statin

monotherapy in patients with dyslipidaemia: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2017;**24**:907–916.
131. Anastasius M, Kockx M, Jessup W, Sullivan D, Rye KA, Kritharides L. Cholesterol efflux capacity: an introduction for clinicians. *Am Heart J* 2016;**180**:54–63.
132. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med* 2002;**347**:1483–1492.
133. Gronek P, Wielinski D, Cyganski P, Rynkiewicz A, Zając A, Maszczyk A, Gronek J, Podstawski R, Czarny W, Balko S, Ct Clark C, Celka R. A review of exercise as medicine in cardiovascular disease: pathology and mechanism. *Aging Dis* 2020;**11**:327–340.
134. Zhang JQ, Smith B, Langdon MM, Messimer HL, Sun GY, Cox RH, James-Kracke M, Thomas TR. Changes in LPLa and reverse cholesterol transport variables during 24-h postexercise period. *Am J Physiol Endocrinol Metab* 2002;**283**:E267–E274.
135. Butcher LR, Thomas A, Backx K, Roberts A, Webb R, Morris K. Low-intensity exercise exerts beneficial effects on plasma lipids via PPARgamma. *Med Sci Sports Exerc* 2008;**40**:1263–1270.
136. Ginsberg HN. Insulin resistance and cardiovascular disease. *J Clin Invest* 2000;**106**:453–458.
137. Borggreve SE, De Vries R, Dullaart RP. Alterations in high-density lipoprotein metabolism and reverse cholesterol transport in insulin resistance and type 2 diabetes mellitus: role of lipolytic enzymes, lecithin:cholesterol acyltransferase and lipid transfer proteins. *Eur J Clin Invest* 2003;**33**:1051–1069.
138. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;**287**:2570–2581.
139. Wang CC, Gurevich I, Draznin B. Insulin affects vascular smooth muscle cell phenotype and migration via distinct signaling pathways. *Diabetes* 2003;**52**:2562–2569.
140. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001;**286**:1218–1227.
141. Sampath Kumar A, Maiya AG, Shastry BA, Vaishali K, Ravishankar N, Hazari A, Gundmi S, Jadhav R. Exercise and insulin resistance in type 2 diabetes mellitus: a systematic review and meta-analysis. *Ann Phys Rehabil Med* 2019;**62**:98–103.
142. Umpierre D, Ribeiro PA, Kramer CK, Leitao CB, Zucatti AT, Azevedo MJ, Gross JL, Ribeiro JP, Schaan BD. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2011;**305**:1790–1799.
143. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, RW, Sorlie, PD, Stein, J, Towfighi, A, Turan, TN, Virani, SS, Woo, D, Yeh, RW, Turner, MB; American Heart Association Statistics Committee, Stroke Statistics Subcommittee. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;**133**:e38–e360.
144. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, Group E; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
145. Lopes S, Afreixo V, Teixeira M, Garcia C, Leitao C, Gouveia M, Figueiredo D, Alves AJ, Polonia J, Oliveira J, Mesquita-Bastos J, Ribeiro F. Exercise training reduces arterial stiffness in adults with hypertension: a systematic review and meta-analysis. *J Hypertens* 2021;**39**:214–222.
146. Shepherd JT. Circulatory response to exercise in health. *Circulation* 1987;**76**:VI3–VI10.
147. Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. *Med Sci Sports Exerc* 2001;**33**:S484–S492.
148. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension* 2005;**46**:667–675.
149. Hardy ST, Loehr LR, Butler KR, Chakladar S, Chang PP, Folsom AR, Heiss G, MacLehose RF, Matsushita K, Avery CL. Reducing the blood pressure-related burden of cardiovascular disease: impact of achievable improvements in blood pressure prevention and control. *J Am Heart Assoc* 2015;**4**:e002276.
150. Spence AL, Carter HH, Naylor LH, Green DJ. A prospective randomized longitudinal study involving 6 months of endurance or resistance exercise. Conduit artery adaptation in humans. *J Physiol* 2013;**591**:1265–1275.
151. Fleenor BS, Marshall KD, Durrant JR, Lesniewski LA, Seals DR. Arterial stiffening with ageing is associated with transforming growth factor-beta1-related changes in adventitial collagen: reversal by aerobic exercise. *J Physiol* 2010;**588**:3971–3982.
152. Wilund KR. Is the anti-inflammatory effect of regular exercise responsible for reduced cardiovascular disease? *Clin Sci (Lond)* 2007;**112**:543–555.
153. Carter JR, Ray CA. Sympathetic neural adaptations to exercise training in humans. *Auton Neurosci* 2015;**188**:36–43.
154. Laterza MC, de Matos LDNJ, Trombetta IC, Braga AMW, Roveda F, Alves MJNN, Krieger EM, Negrao CE, Rondon MUPB. Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. *Hypertension* 2007;**49**:1298–1306.
155. Laughlin MH, Davis MJ, Secher NH, van Lieshout JJ, Arce-Esquivel AA, Simmons GH, Bender SB, Padilla J, Bache RJ, Merkus D, Duncker DJ. Peripheral circulation. *Compr Physiol* 2012;**2**:321–447.
156. Hambrecht R, Adams V, Erbs S, Linke A, KräNkel N, Shu Y, Baither Y, Gielen S, Thiele H, Gummert JF, Mohr FW, Schuler G. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation* 2003;**107**:3152–3158.
157. Bohlen HG. Nitric oxide and the cardiovascular system. *Compr Physiol* 2015;**5**:808–823.
158. Winzer EB, Woitek F, Linke A. Physical activity in the prevention and treatment of coronary artery disease. *J Am Heart Assoc* 2018;**7**:e007725.
159. Lippi G, Sanchis-Gomar F. An estimation of the worldwide epidemiologic burden of physical inactivity-related ischemic heart disease. *Cardiovasc Drugs Ther* 2020;**34**:133–137.
160. Bruning RS, Sturek M. Benefits of exercise training on coronary blood flow in coronary artery disease patients. *Prog Cardiovasc Dis* 2015;**57**:443–453.
161. Taylor RS, Brown A, Ebrahim S, Jolliffe J, Noorani H, Rees K, Skidmore B, Stone JA, Thompson DR, Oldridge N. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004;**116**:682–692.
162. Hambrecht R, Walther C, MöBius-Winkler S, Gielen S, Linke A, Conradi K, Erbs S, Kluge R, Kendziorra K, Sabri O, Sick P, Schuler G. Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease: a randomized trial. *Circulation* 2004;**109**:1371–1378.
163. Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D, Purcaro A. Exercise training intervention after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol* 2001;**37**:1891–1900.
164. Prior PL, Suskin N. Exercise for stroke prevention. *Stroke Vasc Neurol* 2018;**3**:59–68.
165. Lee CD, Blair SN. Cardiorespiratory fitness and stroke mortality in men. *Med Sci Sports Exerc* 2002;**34**:592–595.
166. Mittleman MA, Mostofsky E. Physical, psychological and chemical triggers of acute cardiovascular events: preventive strategies. *Circulation* 2011;**124**:346–354.
167. Fleg JL, Cooper LS, Borlaug BA, Haykowsky MJ, Kraus WE, Levine BD, Pfeffer MA, Pina IL, Poole DC, Reeves GR, Whellan DJ, Kitzman DW, National HL; National Heart, Lung, and Blood Institute Working Group. Exercise training as therapy for heart failure: current status and future directions. *Circ Heart Fail* 2015;**8**:209–220.
168. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, Abdelhamed A, Haykowsky MJ. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol* 2013;**62**:584–592.
169. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019;**1**:CD003331.
170. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, Whellan D, O'Connor C, Keteyian SJ, Coats A, Davos CH, Dalal HM, Dracup K, Evangelista LS, Jolly K, Myers J, Nilsson BB, Passino C, Witham MD, Yeh GY, ExTra MIIC; ExTraMATCH II Collaboration. Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis. *J Am Coll Cardiol* 2019;**73**:1430–1443.
171. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, O'Connor C, Whellan D, Keteyian SJ, Coats A, Davos CH, Dalal HM, Dracup K, Evangelista L, Jolly K, Myers J, McKelvie RS, Nilsson BB, Passino C, Witham MD, Yeh GY, Zwisler AO; ExTraMATCH II Collaboration. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail* 2018;**20**:1735–1743.
172. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
173. Zores F, Iliou MC, Gellen B, Kubas S, Berthelot E, Guillo P, Bauer F, Lamblin N, Bosser G, Damy T, Cohen-Solal A, Beauvais F. Physical activity for patients with heart failure: position paper from the heart failure (GICC) and cardiac rehabilitation (GERS-P) Working Groups of the French Society of Cardiology. *Arch Cardiovasc Dis* 2019;**112**:723–731.
174. Bakker EA, Snoek JA, Meindersma EP, Hopman MTE, Bellersen L, Verbeek ALM, Thijssen DHJ, Eijsvogels TMH. Absence of fitness improvement is associated with outcomes in heart failure patients. *Med Sci Sports Exerc* 2018;**50**:196–203.
175. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;**2**:e004473.
176. Sosner P, Guiraud T, Gremeaux V, Arvisais D, Herpin D, Bosquet L. The ambulatory hypotensive effect of aerobic training: a reappraisal through a meta-analysis of selected moderators. *Scand J Med Sci Sports* 2017;**27**:327–341.

177. Costa EC, Hay JL, Kehler DS, Boreskie KF, Arora RC, Umpierre D, Szwajcer A, Duhamel TA. Effects of high-intensity interval training versus moderate-intensity continuous training on blood pressure in adults with pre- to established hypertension: a systematic review and meta-analysis of randomized trials. *Sports Med* 2018; **48**:2127–2142.
178. Pescatello LS, MacDonald HV, Lamberti L, Johnson BT. Exercise for hypertension: a prescription update integrating existing recommendations with emerging research. *Curr Hypertens Rep* 2015;**17**:87.
179. Boutcher YN, Boutcher SH. Exercise intensity and hypertension: what's new? *J Hum Hypertens* 2017;**31**:157–164.
180. Pescatello LS, MacDonald HV, Ash GI, Lamberti LM, Farquhar WB, Arena R, Johnson BT. Assessing the existing professional exercise recommendations for hypertension: a review and recommendations for future research priorities. *Mayo Clin Proc* 2015;**90**:801–812.
181. Cornelissen VA, Buys R, Smart NA. Endurance exercise beneficially affects ambulatory blood pressure: a systematic review and meta-analysis. *J Hypertens* 2013;**31**: 639–648.
182. Chung MK, Eckhardt LL, Chen LY, Ahmed HM, Gopinathannair R, Joglar JA, Noseworthy PA, Pack QR, Sanders P, Trulock KM, American Heart Association E, Arrhythmias C, Exercise CR, Secondary Prevention Committee Of The Council On Clinical C, Council On AT, Vascular B, Council On C, Stroke N, Council On L, Cardiometabolic H; American Heart Association Electrocardiography and Arrhythmias Committee and Exercise, Cardiac Rehabilitation, and Secondary Prevention Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Lifestyle and Cardiometabolic Health. Lifestyle and risk factor modification for reduction of atrial fibrillation: a scientific statement from the American Heart Association. *Circulation* 2020;**141**:e750–e772.
183. Qin R, Murakoshi N, Xu D, Tajiri K, Feng D, Stujanna EN, Yonebayashi S, Nakagawa Y, Shimano H, Nogami A, Koike A, Aonuma K, Ieda M. Exercise training reduces ventricular arrhythmias through restoring calcium handling and sympathetic tone in myocardial infarction mice. *Physiol Rep* 2019;**7**:e13972.
184. Azarbal F, Stefanick ML, Assimes TL, Manson JE, Bea JW, Li W, Hlatky MA, Larson JC, LeBlanc ES, Albert CM, Nassir R, Martin LW, Perez MV. Lean body mass and risk of incident atrial fibrillation in post-menopausal women. *Eur Heart J* 2016;**37**: 1606–1613.
185. Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, Verdicchio CV, Hendriks JML, Lau DH, La Gerche A, Sanders P. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J* 2020;**41**:1479–1486.
186. Kwok CS, Anderson SG, Myint PK, Mamas MA, Loke YK. Physical activity and incidence of atrial fibrillation: A systematic review and meta-analysis. *Int J Cardiol* 2014; **177**:467–476.
187. Sanchis-Gomar F, Perez-Quilis C, Lippi G, Cervellin G, Leischik R, Löllgen H, Serrano-Ostáriz E, Lucia A. Atrial fibrillation in highly trained endurance athletes - Description of a syndrome. *Int J Cardiol* 2017;**226**:11–20.
188. Franklin BA, Thompson PD, Al-Zaiti SS, Albert CM, Hivert MF, Levine BD, Lobelo F, Madan K, Sharrief AZ, Eijsvogels TMH; American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Stroke Council. Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risks into perspective-an update: a scientific statement from the American Heart Association. *Circulation* 2020;**141**:e705–e736.
189. Drca N, Wolk A, Jensen-Urstad M, Larsson SC. Atrial fibrillation is associated with different levels of physical activity levels at different ages in men. *Heart* 2014;**100**: 1037–1042.
190. Aizer A, Gaziano JM, Cook NR, Manson JE, Buring JE, Albert CM. Relation of vigorous exercise to risk of atrial fibrillation. *Am J Cardiol* 2009;**103**:1572–1577.
191. Ruiz JR, Joyner M, Lucia A. CrossTalk opposing view: prolonged intense exercise does not lead to cardiac damage. *J Physiol* 2013;**591**:4943–4945.
192. Bonilla IM, Belevych AE, Sridhar A, Nishijima Y, Ho HT, He Q, Kukielka M, Terentyev D, Terentyeva R, Liu B, Long VP, Gyorke S, Carnes CA, Billman GE. Endurance exercise training normalizes repolarization and calcium-handling abnormalities, preventing ventricular fibrillation in a model of sudden cardiac death. *J Appl Physiol (1985)* 2012;**113**:1772–1783.
193. Jie Z, Xia H, Zhong SL, Feng Q, Li S, Liang S, Zhong H, Liu Z, Gao Y, Zhao H, Zhang D, Su Z, Fang Z, Lan Z, Li J, Xiao L, Li J, Li R, Li X, Li F, Ren H, Huang Y, Peng Y, Li G, Wen B, Dong B, Chen JY, Geng QS, Zhang ZW, Yang H, Wang J, Wang J, Zhang X, Madsen L, Brix S, Ning G, Xu X, Liu X, Hou Y, Jia H, He K, Kristiansen K. The gut microbiome in atherosclerotic cardiovascular disease. *Nat Commun* 2017;**8**:845.
194. Xu H, Wang X, Feng W, Liu Q, Zhou S, Liu Q, Cai L. The gut microbiota and its interactions with cardiovascular disease. *Microb Biotechnol* 2020;**13**:637–656.
195. Gutiérrez-Calabrés E, Ortega-Hernández A, Modrego J, Gómez-Gordo R, Caro-Vadillo A, Rodríguez-Bobada C, González P, Gómez-Garre D. Gut microbiota profile identifies transition from compensated cardiac hypertrophy to heart failure in hypertensive rats. *Hypertension* 2020;**76**:1545–1554.
196. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WH, Bushman FD, Lusis AJ, Hazen SL. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med* 2013;**19**:576–585.
197. Patel PN, Shah RY, Ferguson JF, Reilly MP. Human experimental endotoxemia in modeling the pathophysiology, genomics, and therapeutics of innate immunity in complex cardiometabolic diseases. *Arterioscler Thromb Vasc Biol* 2015;**35**:525–534.
198. Lanter BB, Sauer K, Davies DG. Bacteria present in carotid arterial plaques are found as biofilm deposits which may contribute to enhanced risk of plaque rupture. *mBio* 2014;**5**:e01206–e01214.
199. Zeppa SD Agostini D, Gervasi M, Annibalini G, Amatori S, Ferrini F, Sisti D, Piccoli G, Barbieri E, Sestili P, Stocchi V. Mutual interactions among exercise, sport supplements and microbiota. *Nutrients* 2019;**12**:17.
200. Yang Y, Shi Y, Wiklund P, Tan X, Wu N, Zhang X, Tikkanen O, Zhang C, Munukka E, Cheng S. The association between cardiorespiratory fitness and gut microbiota composition in premenopausal women. *Nutrients* 2017;**9**:792.
201. Allen JM, Mailing LJ, Niemiro GM, Moore R, Cook MD, White BA, Holscher HD, Woods JA. Exercise alters gut microbiota composition and function in lean and obese humans. *Med Sci Sports Exerc* 2018;**50**:747–757.
202. Mohr AE, Jager R, Carpenter KC, Kerksick CM, Purpura M, Townsend JR, West NP, Black K, Gleeson M, Pyne DB, Wells SD, Arent SM, Kreider RB, Campbell BI, Bannock L, Scheiman J, Wissent CJ, Pane M, Kalman DS, Pugh JN, Ortega-Santos CP, Ter Haar JA, Arciero PJ, Antonio J. The athletic gut microbiota. *J Int Soc Sports Nutr* 2020;**17**:24.
203. Mailing LJ, Allen JM, Buford TW, Fields CJ, Woods JA. Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health. *Exerc Sport Sci Rev* 2019;**47**:75–85.
204. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, Bauman A, Lee IM; Lancet Physical Activity Series 2 Executive Committee; Lancet Sedentary Behaviour Working Group. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. *Lancet* 2016;**388**: 1302–1310.
205. Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, Whincup P, Diaz KM, Hooker SP, Chernofsky A, Larson MG, Spartano N, Vasan RS, Dohrn IM, Hagstromer M, Edwardson C, Yates T, Shiroma E, Anderssen SA, Lee IM. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ* 2019;**366**:l4570.
206. Wahid A, Manek N, Nichols M, Kelly P, Foster C, Webster P, Kaur A, Smith FC, Wilkins E, Rayner M, Roberts N, Scarborough P. Quantifying the association between physical activity and cardiovascular disease and diabetes: A systematic review and meta-analysis. *J Am Heart Assoc* 2016;**5**:e002495.
207. Kivimaki M, Singh-Manoux A, Pentti J, Sabia S, Nyberg ST, Alfredsson L, Goldberg M, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Nordin M, Oksanen T, Strandberg T, Suominen SB, Theorell T, Vahtera J, Vaananen A, Virtanen M, Westerholm P, Westerlund H, Zins M, Seshadri S, Batty GD, Sipila PN, Shipley MJ, Lindbohm JV, Ferrie JE, Jokela M; IPD-Work consortium. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. *BMJ* 2019;**365**:l1495.
208. Dores H, de Araujo Goncalves P, Monge J, Costa R, Tata L, Malhotra A, Sharma S, Cardim N, Neuparth N. Subclinical coronary artery disease in veteran athletes: is a new preparticipation methodology required? *Br J Sports Med* 2018;**54**:349–353.
209. DeFina LF, Radford NB, Barlow CE, Willis BL, Leonard D, Haskell WL, Farrell SW, Pavlovic A, Abel K, Berry JD, Khera A, Levine BD. Association of all-cause and cardiovascular mortality with high levels of physical activity and concurrent coronary artery calcification. *JAMA Cardiol* 2019;**4**:174–181.
210. Sanchis-Gomar F, Perez-Quilis C, Pareja-Galeano H, Lippi G. Undetected coronary artery disease in apparently healthy athletes. *Eur J Prev Cardiol* 2019;**26**:2009–2011.
211. Ding D, Lawson KD, Kolbe-Alexander TL, Finkelstein EA, Katzmarzyk PT, van Mechelen W, Pratt M; Lancet Physical Activity Series 2 Executive Committee. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *Lancet* 2016;**388**:1311–1324.
212. Scheerder J, Breedveld K, Borgers J. *Running Across Europe: The Rise and Size of One of the Largest Sport Markets*. Basingstoke: Palgrave Macmillan; 2015.
213. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol* 2007;**49**:2129–2138.
214. Ibanez B, Fuster V. CANTOS: a gigantic proof-of-concept trial. *Circ Res* 2017;**121**: 1320–1322.
215. Breuckmann F, Mohlenkamp S, Nassenstein K, Lehmann N, Ladd S, Schmermund A, Sievers B, Schlosser T, Jockel KH, Heusch G, Erbel R, Barkhausen J. Myocardial late gadolinium enhancement: prevalence, pattern, and prognostic relevance in marathon runners. *Radiology* 2009;**251**:50–57.
216. van de Schoor FR, Aengevaeren VL, Hopman MT, Oxborough DL, George KP, Thompson PD, Eijsvogels TM. Myocardial fibrosis in athletes. *Mayo Clin Proc* 2016; **91**:1617–1631.

217. Mohlenkamp S, Lehmann N, Breuckmann F, Brocker-Preuss M, Nassenstein K, Halle M, Budde T, Mann K, Barkhausen J, Heusch G, Jockel KH, Erbel R; on behalf of the Marathon Study Investigators and the Heinz Nixdorf Recall Study Investigators. Running: the risk of coronary events: prevalence and prognostic relevance of coronary atherosclerosis in marathon runners. *Eur Heart J* 2008;**29**:1903–1910.
218. Aengevaeren VL, Mosterd A, Braber TL, Prakken NHJ, Doevendans PA, Grobbee DE, Thompson PD, Eijsvogels TMH, Velthuis BK. Relationship between lifelong exercise volume and coronary atherosclerosis in athletes. *Circulation* 2017;**136**: 138–148.
219. Aengevaeren VL, Mosterd A, Sharma S, Prakken NHJ, Mohlenkamp S, Thompson PD, Velthuis BK, Eijsvogels TMH. Exercise and coronary atherosclerosis: observations, explanations, relevance, and clinical management. *Circulation* 2020;**141**: 1338–1350.
220. Laddu DR, Rana JS, Murillo R, Sorel ME, Quesenberry CP Jr, Allen NB, Gabriel KP, Carnethon MR, Liu K, Reis JP, Lloyd-Jones D, Carr JJ, Sidney S. 25-year physical activity trajectories and development of subclinical coronary artery disease as measured by coronary artery calcium: the coronary artery risk development in young adults (CARDIA) study. *Mayo Clin Proc* 2017;**92**:1660–1670.
221. Merghani A, Maestrini V, Rosmini S, Cox AT, Dhutia H, Bastiaenan R, David S, Yeo TJ, Narain R, Malhotra A, Papadakis M, Wilson MG, Tome M, AlFakih K, Moon JC, Sharma S. Prevalence of subclinical coronary artery disease in masters endurance athletes with a low atherosclerotic risk profile. *Circulation* 2017;**136**:126–137.
222. Lavie CJ, Wisloff U, Blumenthal RS. Extreme physical activity and coronary artery calcification-running heavily and safely with "Hearts of Stone". *JAMA Cardiol* 2019;**4**: 182–183.
223. Lavie CJ, Hecht HF, Wisloff U. Extreme physical activity may increase coronary calcification, but fitness still prevails. *Mayo Clin Proc Innov Qual Outcomes* 2019;**3**: 103–105.
224. Borjesson M, Dellborg M, Niebauer J, LaGerche A, Schmied C, Solberg EE, Halle M, Adami E, Biffi A, Carre F, Caselli S, Papadakis M, Pressler A, Rasmusen H, Serratosa L, Sharma S, van Buuren F, Pelliccia A. Recommendations for participation in leisure time or competitive sports in athletes-patients with coronary artery disease: a position statement from the Sports Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J* 2019;**40**:13–18.
225. de la Chica JA, Gómez-Talavera S, García-Ruiz JM, García-Lunar I, Oliva B, Fernández-Alvira JM, López-Melgar B, Sánchez-González J, de la Pompa JL, Mendiguren JM, Martínez de Vega V, Fernández-Ortiz A, Sanz J, Fernández-Friera L, Ibáñez B, Fuster V. Association between left ventricular noncompaction and vigorous physical activity. *J Am Coll Cardiol* 2020;**76**:1723–1733.
226. Aggarwal G, Cheruiyot I, Aggarwal S, Wong J, Lippi G, Lavie CJ, Henry BM, Sanchis-Gomar F. Association of cardiovascular disease with coronavirus disease 2019 (COVID-19) severity: a meta-analysis. *Curr Probl Cardiol* 2020;**45**:100617.
227. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**: 1054–1062.
228. Sandoval Y, Januzzi JL Jr, Jaffe AS. Cardiac troponin for assessment of myocardial injury in COVID-19: JACC review topic of the week. *J Am Coll Cardiol* 2020;**76**: 1244–1258.
229. Rodriguez-Leor O, Alvarez C, de Prado AB, Rossello AP, Ojeda X, Serrador S, Lopez-Palop A, Martin-Moreiras R, Rumoroso J, Cequier JR, Ibanez A, Cruz-Gonzalez B, Romaguera I, Moreno R. In-hospital outcomes of patients with ST-segment elevation myocardial infarction and COVID-19. *EuroIntervention* 2021; **16**:1426–1433.
230. Brawner CA, Ehrman JK, Bole S, Kerrigan DJ, Parikh SS, Lewis BK, Gindi RM, Keteyian C, Abdul-Nour K, Keteyian SJ. Maximal exercise capacity is inversely related to hospitalization secondary to coronavirus disease 2019. *Mayo Clin Proc* 2021; **96**:32–39.
231. Charansonney OL. Physical activity and aging: a life-long story. *Discov Med* 2011;**12**: 177–185.
232. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA III, Fulton JE, Gordon NF, Haskell WL, Link MS, Maron BJ, Mittleman MA, Pelliccia A, Wenger NK, Willich SN, Costa F; American College of Sports Medicine. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation* 2007;**115**: 2358–2368.
233. Lippi G, Henry BM, Sanchis-Gomar F. Physical inactivity and cardiovascular disease at the time of coronavirus disease 2019 (COVID-19). *Eur J Prev Cardiol* 2020;**27**: 906–908.
234. Sallis R, Young DR, Tartof SY, Sallis JF, Sall J, Li Q, Smith GN, Cohen DA. Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48 440 adult patients. *Br J Sports Med* 2021;bjsports-2021-104080.
235. Lavie CJ, Sanchis-Gomar F, Arena R. Fit is it in COVID-19, future pandemics, and overall healthy living. *Mayo Clin Proc* 2021;**96**:7–9.
236. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting physical activity and exercise: JACC health promotion series. *J Am Coll Cardiol* 2018; **72**:1622–1639.
237. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behaviour*. Geneva: World Health Organization; 2020.
238. Zubin Maslov P, Schulman A, Lavie CJ, Narula J. Personalized exercise dose prescription. *Eur Heart J* 2018;**39**:2346–2355.
239. Blair SN. Physical inactivity: the biggest public health problem of the 21st century. *Br J Sports Med* 2009;**43**:1–2.