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Review

Exercise pills for cardiometabolic health cannot mimic the exercise milieu

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Physical exercise can play an important role both in primary and secondary cardiovascular disease prevention by virtue of its multisystem effects. These beneficial adaptations at the whole-body level include improvements in mitochondrial health, vascular function, and autonomic balance, together with attenuation of inflammation and the release of 'exerkines' with pleiotropic effects. Thus, several research groups have attempted to develop so-called 'exercise pills' or 'exercise mimetics': that is, substances that are theoretically capable of reproducing some of the cardiometabolic benefits associated with regular exercise. In this review we summarize pharmacological and phytochemical agents which, when used alone or in combination with exercise, may improve cardiometabolic health. We also discuss the current gaps and future steps needed to translate these findings into therapeutic applications.

Highlights

Physical exercise plays an important role in primary and secondary cardiovascular disease prevention through its multisystemic effects.

Some pharmacological and phytochemical agents are potential 'exercise mimetics', capable of improving cardiometabolic health whether used alone or in combination with exercise.

'Multi-omic' approaches can help to identify potential exercise mimetics that mediate the cardiometabolic benefits of exercise.

The bulk of the evidence comes from preclinical research. More data are needed in humans, particularly with respect to safety and dosage.

The multisystemic benefits effects of exercise and the unique exercise milieu itself are difficult to mimic in a pill.

No pill is expected to fully replace exercise in the foreseeable future.

Understanding the cardiometabolic benefits of physical exercise

Physical exercise (see Glossary) can promote primary and secondary cardiovascular disease prevention through several mechanisms [1], including improvements in 'traditional' risk factors (hypertension, overweight/obesity, diabetes, and dyslipidemia) as well as other beneficial adaptations [2]. Over the past two decades advances in our understanding of the molecular mechanisms behind the cardiometabolic benefits of exercise have paved the way for research on synthetic drugs or compounds, so-called exercise pills (or exercise mimetics), designed to replicate some of the effects of exercise on endurance performance and/or cardiometabolic health. One such compound, 5-aminomidazole-4-carboxamide-1-β-D-ribofuranoside (**AICAR**), was developed by PeriCor Therapeutics and licensed to Schering-Plough in 2007 for phase III studies. Along with **GW501516 (GW1516, GSK-516, cardarine, or endurubol)**, AICAR was postulated as a potential 'orally active drug to enhance training adaptation or even to increase endurance without exercise' [3]. In 2009, the Anti-Doping Agency included both substances in the Prohibited List (www.wada-ama.org/en/prohibited-list) and several athletes were suspended for testing positive for them [4].

The potential use of exercise pills in the general population, especially in people with chronic cardiometabolic conditions such as diabetes (who are often too inactive) is a topic of interest [5]. Furthermore, this is an expanding field with a growing number of pill candidates (as identified with recent multi-omics approaches) emerging each year. Importantly, exercise pills could be particularly beneficial for individuals who are essentially unable to do physical exercise, such as in cases of paralysis. In this review we summarize pharmaceutical as well as plant-derived agents with potential exercise-mimetic effects, capable of improving cardiometabolic health, alone or in combination with exercise. We also discuss the implications of the current state of the field on the potential development of exercise pills and shed light on the methodological gaps that will need to be bridged to translate the promise of exercise pills to clinical use.

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Physical exercise exerts whole-body effects

Physical exercise impacts multiple types of cells simultaneously (largely through the release of a myriad **exerkines** with pleiotropic effects), well beyond muscle-tissue signaling [6]. The metabolic stress induced by each exercise session provides the basis for long-term adaptations to occur with regular exercise (i.e., through repeated acute episodes) across various tissues and systems [7–9]. The latter includes not only the skeletal muscle and the cardiovascular system but also other connected tissues (notably adipose tissue, liver, pancreas, and brain) [7–9]. Exercise pills aim to mimic some of the exercise-induced effects described as follows.

Mitochondrial health

Each exercise bout increases the uptake and subsequent oxidation of free fatty acids and glucose in skeletal myotubes through β-adrenergic, AMP-activated protein kinase (AMPK), and peroxisome proliferator activated receptor γ (PPAR)-γ coactivator (PPARGC1A, a.k.a. PGC1-α) signaling [10]. Thus, the frequent repetition of acute bouts (i.e., regular exercise) improves mitochondrial function, insulin sensitivity, and insulin-independent glucose uptake (Figure 1A) [10,11].

Regular exercise increases mitochondrial network quality in skeletal muscle through fusion, fission, and mitophagy (a form of **autophagy**) of these organelles [12,13], which is crucial for ensuring effective substrate oxidation and handling of reactive oxygen species (ROS), and is linked to improved insulin sensitivity [11].

Chronic inflammation

A major substrate for cardiometabolic diseases is low-grade systemic chronic inflammation, characterized by increased circulating levels of C-reactive protein (CRP) and proinflammatory cytokines, notably tumor necrosis factor (TNF)-α [14]. Although acute exercise – particularly if intense – can transiently increase inflammatory markers (e.g., CRP), regular exercise (even if intense) attenuates chronic inflammation through different mechanisms (Figure 1B) [6,15,16]. One such mechanism involves decreases in the hematopoietic output of inflammatory leukocytes through modulation of progenitor cell proliferation and leukocyte production via diminished leptin signaling to bone marrow niche cells [16]. Attenuation of two activators of **pattern recognition receptors (PRRs)**, lipoprotein oxidation and **advanced glycated end products**, is also involved. An additional mechanism is the release of anti-inflammatory exerkines [6], as explained further as follows.

Vascular health

Regular exercise improves vascular endothelial function through several mechanisms: a higher release of circulating angiogenic cells, partly via a nitric oxide (NO·)-dependent anti-apoptotic effect; inhibition of neointima formation and enhanced angiogenesis; and **mitohormesis** (Figure 1C). Besides, regular exercise induces a decline in endothelium-derived adhesion molecules – for example, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1) – and in the vascular expression of the angiotensin II type 2 receptor (resulting in diminished local ROS generation and, ultimately, in attenuation of angiotensin II-mediated vasoconstriction) [11]. However, shear stress increases during each exercise bout, with subsequent increases in NO· synthesis in coronary vessels and thus in endothelium-dependent vasodilatation and NO· bioavailability.

Exercise training can stabilize atherosclerotic plaques through increases in collagen content and decreases in ICAM-1, besides increasing the luminal diameter and dilation capacity

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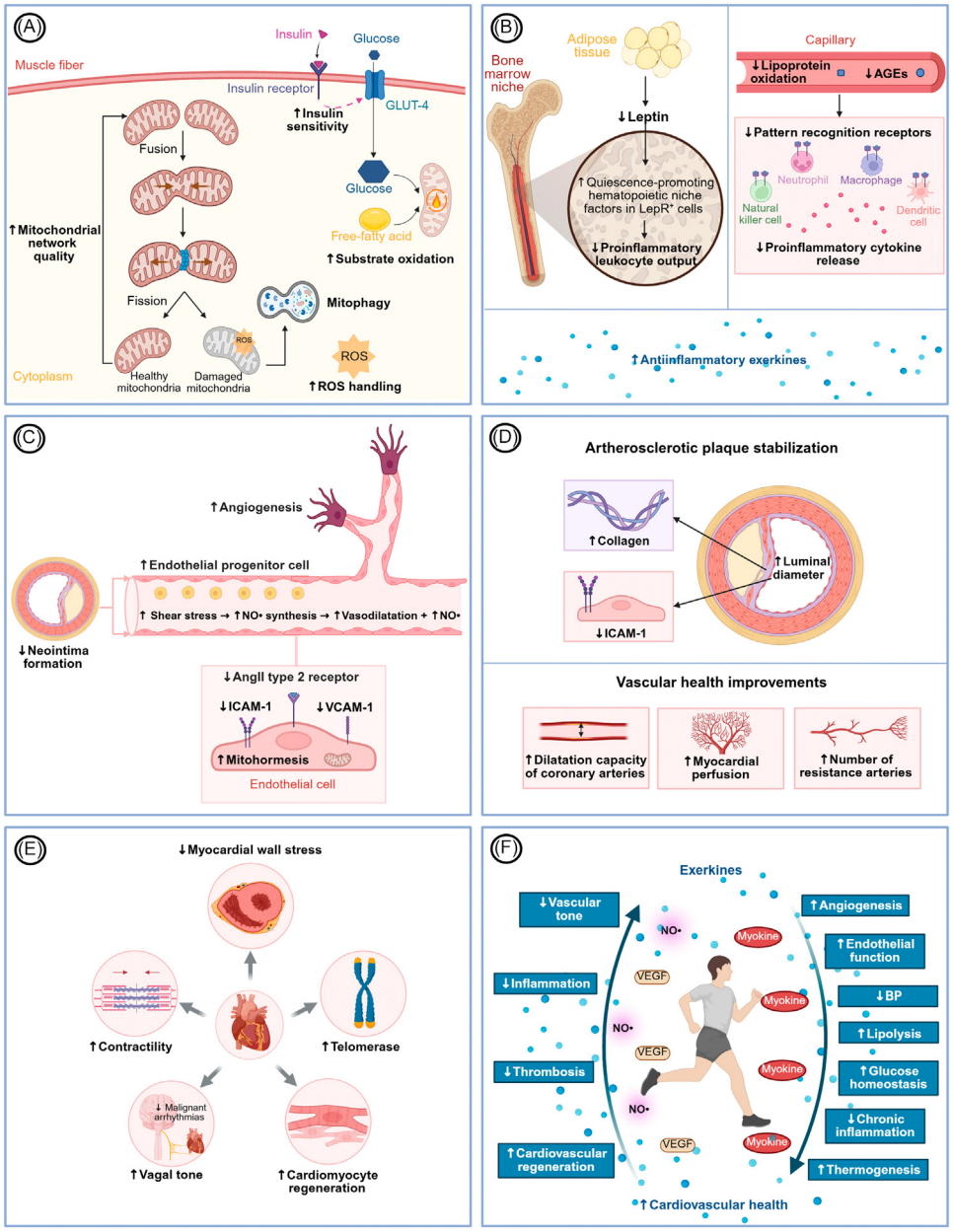

Figure 1. Cardiometabolic effects of exercise: key biological mechanisms. Improved mitochondrial health (A); modulation of chronic inflammation (B); attenuation of vascular endothelial dysfunction (C) and atherosclerosis (D); cardioprotection (included an improved autonomic balance) (E); and exerkine release (F). Abbreviations: AGEs, advanced glycated end-products; AngII, angiotensin II; BP, blood pressure; GLUT-4, glucose transporter 4; ICAM-1, intercellular adhesion molecule; NO·, nitric oxide; ROS, reactive oxygen species; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor. Figure created with BioRender.

of coronary arteries as well as the number of collateral coronaries, thereby improving myocardial perfusion (Figure 1D) [11]. Aerobic regular exercise also increases the number of **resistance arteries** and thus reduces blood pressure (BP) [17] and – especially if performed

Glossary

Advanced glycated end products: proteins or lipids that become glycated due to exposure to sugars.
AICAR: a synthetic AMP analog that activates AMPK in muscle.
Autophagy: the natural, lysosome-dependent removal of unnecessary/dysfunctional cellular components.
Becker muscular dystrophy: a genetic disorder characterized by progressive muscle degeneration and weakness.
C2C12 muscle cells: a myoblast cell line.
Cardiovascular resilience: absence of actual cardiovascular disease in the presence of risk factors.
CRISPR-Cas9: clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9): a gene-editing technology that allows genome modifications.
Exerkines: a broad variety of signaling moieties – metabolites, hormones, proteins, peptides (notably cytokines such as interleukin-6), nucleic acids, or reactive oxygen species (e.g., NO·) – released by different tissues – for example, skeletal (myokines), cardiac (cardiokines), or adipose (adipokines) tissues – in response to acute and/or chronic exercise.
GW501516 (GW1516, GSK-516, cardarine, or endurubol): a peroxisome proliferator activated receptor-δ agonist.
Mitohormesis: a process wherein low levels of mitochondria-derived reactive oxygen species induced by each exercise bout act as signaling molecules that initiate a cascade of cellular events that ultimately protect the endothelial cells from harmful effects.
Myotonic dystrophy type 1: a muscular dystrophy caused by an expansion of CTG repeats in the 3′-untranslated region of the *DMPK* gene, resulting in mutant RNAs which accumulate in affected tissues as foci that sequester RNA-binding proteins (leading to their dysfunction and downstream molecular defects).
Pattern recognition receptors (PRRs): germline-encoded host sensors that detect molecules typical of pathogens and play a crucial role in the proper function of the innate immune system.
Phosphodiesterases: enzymes that degrade the phosphodiester bond of the secondary messengers (e.g., AMP) and then terminate its action, leading to elevated cAMP levels.

at high intensities – attenuates increases in arterial stiffness through a lowered oxidative stress and an increased expression of genes associated with local vasodilatory signaling: prostaglandin EP2 receptor, C-type natriuretic peptide, and endothelial NO· synthase (eNOS) [11].

Autonomic balance

Regular aerobic exercise confers protection against malignant ventricular arrhythmias. This is mediated by an improved vagal tone to the heart together with an attenuation of sympathetic stimulation to this organ (Figure 1E), as typically manifested by an increase in resting heart rate variability [18,19]. Improved autonomic balance is particularly important in the context of aging [20] and some cardiovascular conditions: indeed, excess sympathetic activation (such as in older individuals or in patients with hypertension) induces deleterious collateral effects (e.g., impaired baroreflex function, or higher risk for insulin sensitivity or metabolic syndrome) [21].

Myocardial tissue

Regular exercise reduces myocardial wall stress while increasing contractility (owing to an ameliorated β-adrenergic receptor signaling and function), activates telomerase, and upregulates telomere-regulating protein (Figure 1E) [22]. Exercise also activates an important signaling pathway for cardiomyocyte regeneration, the growth factor neuregulin-1 and its tyrosine kinase receptors ErbB2 and ErbB4 [1,11]. Exercise, at least if intense enough to induce transient myocardial ischemia, stimulates circulating angiogenic progenitor cells through the release of proangiogenic exerkines: for example, vascular endothelial growth factor (VEGF), interleukin (IL)-6, and NO· (see next section) [6,8].

Exerkines

Two exerkines, NO· and VEGF, can promote **cardiovascular resilience** by attenuating vascular tone, inflammation, and thrombosis while promoting cardiovascular regeneration [6,8] (Figure 1F). Several myokines (angiopoietin 1, fractalkine, fibroblast growth factor, IL-6, IL-8, musclin, myonectin, VEGF) released from the skeletal muscle, mainly during acute exercise, can exert direct (improved angiogenesis and endothelial function, and decreased BP) or indirect (improved lipolysis, thermogenesis, and glucose homeostasis, and decreased chronic inflammation) cardiovascular benefits [6,8,11].

Pharmacological agonists can simulate some of the effects of physical exercise

AMPK agonists

AMPK is a main cellular energy sensor that is activated by muscle activity, ultimately resulting in improvements in insulin sensitivity and glucose uptake, together with a decrease in hepatic glucose production. A seminal study in mice showed that AICAR treatment with no concomitant exercise intervention improved endurance running capacity while also activating AMPK and increasing the gene expression signature related to oxidative metabolism in muscle tissue (Figure 2A) [3]. AICAR induced similar effects to metformin (the main first-line medication for diabetes treatment) on cardiomyocytes: that is, an increased Akt phosphorylation via AMPK signaling induction to promote glucose transporter type 4 expression, leading to improved glucose uptake and insulin sensitivity [23]. Recently, AICAR treatment mimicked the effects of moderate-intensity aerobic training on skeletal muscle regeneration – by attenuating muscle loss, increasing satellite cell activity, and reducing fibrosis – in aged mice [24]. AICAR combined with exercise training induced more fiber hypertrophy in the skeletal muscle of adult male, and especially female, mice with **myotonic dystrophy type 1** compared with pharmacological treatment alone without exercise [25].

Treatment with another synthetic AMPK activator, the mitochondrial complex I inhibitor R419, improved exercise capacity and insulin sensitivity in the skeletal muscle tissue of high fat diet (HFD)-fed mice [26].

Physical exercise: a subset of physical activity that is planned and structured to improve fitness/health (e.g., jogging).
Replication fork: a region where the DNA double helix has been unwound and separated.
Resistance arteries: small-diameter vessels in the microcirculation.
REV-ERBα: nuclear receptor subfamily 1, group D, member 1, molecules that induce the expression of mitochondrial genes through the AMPK–sirtuin-1–peroxisome proliferator activated receptor-γ coactivator 1-α pathway.

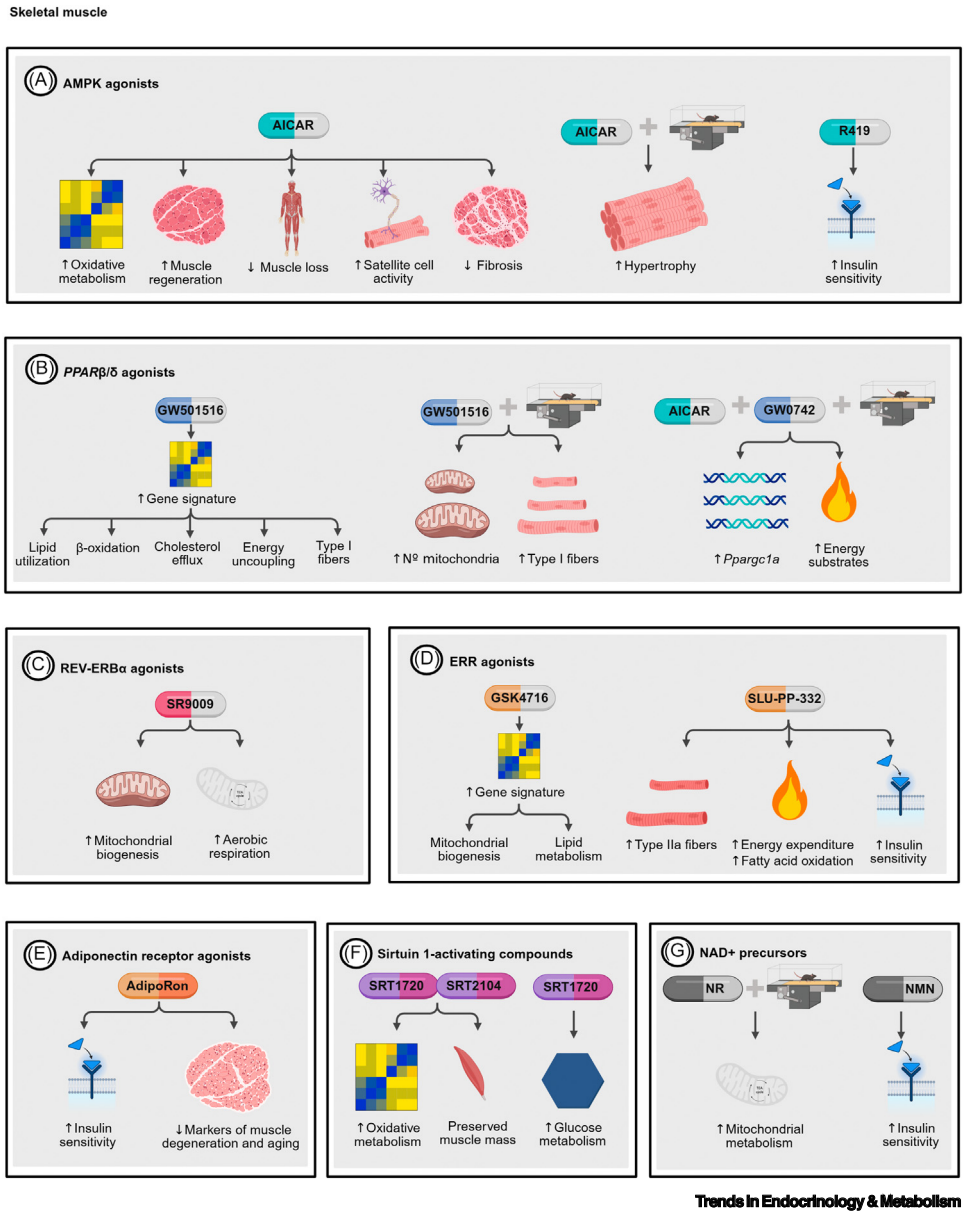

Figure 2. Pharmacological agonists: effects at the skeletal muscle tissue level. Main pharmacological agonists improving exercise performance: that is, AMP-activated protein kinase (AMPK) (A), peroxisome proliferator activated receptor β/δ (PPARβ/δ) (B), REV-ERBα (C), orphan nuclear estrogen receptor-related receptor (ERR) agonists (D), adiponectin receptor agonists (E), sirtuin 1-activating compounds (F) and NAD^+ precursors (G). Other abbreviations: AICAR, 5-aminomidazole-4-carboxamide-1-β-D-ribofuranoside; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; Ppargc1a, peroxisome proliferator activated receptor-γ coactivator1α. Figure created with BioRender.

PPAR β/δ agonists

PPARs are nuclear receptors that regulate the expression of genes involved in energy metabolism, inflammatory processes, and cell differentiation. In **C2C12 muscle cells**, the PPARβ/δ agonist GW501516 induced expression of genes involved in preferential lipid utilization, β-oxidation, cholesterol efflux, and energy uncoupling [27] (Figure 2B). In HFD-fed mice, GW501516

treatment increased the expression of genes related to oxidative (type I) muscle fibers and attenuated weight gain, while the activation of PPARδ improved exercise performance [28]. Although shorter treatment *per se* did not alter mouse fiber-type composition and exercise capacity [3], when combined with aerobic (treadmill) training, GW501516 increased the number of mitochondria in skeletal muscle and the proportion of oxidative fibers, while also improving endurance performance [3].

Combined with AICAR, treatment with the PPARδ agonist GW0742 potentiated endurance training effects by inducing transcriptional changes (e.g., upregulation of *Ppargc1a* gene expression) in muscle and liver, thereby increasing available energy substrates [29,30].

REV-ERBα agonists

REV-ERBα is a circadian regulator of metabolic pathways across tissues such as the liver, brown adipose tissue, and skeletal muscle. Upregulation of REV-ERBα expression in skeletal muscle, or alternatively its pharmacological activation with the synthetic agonist SR9009, improved endurance performance in mice [31] (Figure 2C). Additionally, REV-ERBα overexpression increased mitochondrial biogenesis and aerobic respiration in C2C12 muscle cells [31]. In another study, the REV-ERB-α/β agonist SR9011 increased energy expenditure and reduced fat mass in mice [32]. In this context, several synthetic agonists of REV-ERB-α/β (SR9009, SR9011, SR10067, GSK4112) have been postulated as potential exercise pills [33]. Recently, synthetic SR9009 analogs (5m and 5p) improved exercise tolerance and reduced blood lipids in mice [34].

Estrogen-related receptors agonists

The orphan nuclear estrogen-related receptors (ERRs, including ERRα, ERRβ, and ERRγ) are molecules that can regulate oxidative phosphorylation (OXPHOS), mitochondrial biogenesis, and fat oxidation in muscle tissue [4]. ERRγ is highly expressed in type I muscle and, when transgenically expressed in type II muscles (i.e., in ERRGO mice), induced metabolic and vascular transformation in the absence of exercise; ERRGO mice showed increased expression of genes promoting fat metabolism, mitochondrial respiration, and type I fiber specification [35].

A selective synthetic ERRγ agonist, GSK4716, upregulated genes involved in mitochondrial biogenesis and lipid metabolism in fibroblast-like (COS-1) cell lines [36] (Figure 2D). ERRα and ERRγ are induced in human skeletal muscle in response to an endurance exercise bout, and mice lacking both ERRs show a broad and dramatic disruption of muscle gene expression, especially with respect to OXPHOS and tricarboxylic acid (TCA) cycle genes [37]. There is recent preclinical evidence that treatment – without concomitant exercise intervention – with SLU-PP-332, a synthetic agonist for ERRα (and to a lesser degree for ERRβ and ERRγ), increases endurance capacity [38], the proportion of type IIa oxidative fibers [38], energy expenditure, and insulin sensitivity (while decreasing fat mass accumulation) [39] in mouse models of metabolic syndrome. It also confers protection against pressure overload-induced heart failure *in vivo* [40].

Adiponectin receptor agonists

Adiponectin is an adipokine with antioxidant and anti-inflammatory properties, which can also regulate lipid and glucose metabolism. AdipoRon, an orally active agonist of adiponectin receptor 1 (AdipoR1) and AdipoR2, showed very similar effects to adiponectin in muscle and liver (activation of AMPK and PPARα pathways, improved insulin resistance) in HFD-fed *db/db* mice, together with increased longevity [41] (Figure 2E). This compound was thus postulated as a promising antidiabetic agent [41]. In muscle-specific human AdipoR1-transgenic

HFD-fed mice, AdipoRon attenuated insulin resistance and improved endurance exercise capacity [42]. Additionally, AdipoRon attenuated markers of muscle aging (fat infiltration) and degeneration (tubular aggregates and cylindrical spirals) while improving endurance exercise capacity in HFD-fed mice [43].

Diacylglycerol kinase agonists

Muscle levels of diacylglycerol kinase (DGK)δ, the most abundant isoform of DGKs (enzymes that catalyze the conversion of diacylglycerol into phosphatidic acid, a modulator of various signaling and cellular processes via its versatile effects) are reduced in patients with type 2 diabetes [44]. A recent study showed improvements in metabolic-related outcomes – enhanced glucose homeostasis and lipolysis, with concomitant loss of body mass and epididymal fat – induced by DGKδ2 overexpression in transgenic HFD-fed mice compared with wild-type littermates [45]. Furthermore, DGKδ overexpression recapitulated the beneficial effects of endurance exercise training on metabolic outcomes and gene expression at the muscle level, with DGKδ overexpression and exercise exerting a synergistic effect on body weight reduction [45].

Sirtuin 1-activating compounds and NAD^+ precursors

Sirtuin 1 (SIRT-1) is an NAD^+-dependent deacetylase that controls metabolic processes when nutrient availability is low. In young [46] and adult [47] mice, the SIRT-1 synthetic activators SRT1720 [46] and SRT2104 [47] improved oxidative metabolism in muscle, liver, and brown adipose tissue – thereby conferring protection against diet-induced obesity and insulin resistance – as well as exercise capacity [46], and preserved muscle/bone mass while also improving survival [47] (Figure 2F). Improvements in glucose metabolism were also found with a similar compound, SRT1720, in mice [48]. A randomized controlled trial (RCT) in older (60–80-year-old) participants showed that oral SRT2104 was safe and effective to improve blood lipids: total/low density lipoprotein (LDL)-cholesterol and triglycerides [49].

NAD^+ precursors such as nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN) can improve exercise adaptations. In mice, endurance exercise training combined with NR supplementation induced greater improvements in aerobic capacity and skeletal muscle mitochondrial metabolism than the exercise intervention alone [50] (Figure 2G). Yet an RCT in old men showed that, despite inducing a certain anti-inflammatory effect (i.e., decrease in some circulating proinflammatory cytokines), oral NR treatment did not affect skeletal muscle mitochondrial bioenergetics, handgrip strength, or cardiovascular risk markers (body weight, BP, lipid profile, and fasting glucose/insulin) [51]. Another RCT found an increase in fat-free mass but no changes in the muscle mitochondrial function or insulin sensitivity of individuals with overweight/obesity after oral NR treatment [52]. However, NR can improve mitochondrial function [53] and reduce adipocyte cell size [54] in the brown adipose tissue of HFD-fed mice. In postmenopausal women who had insulin resistance, NMN supplementation (without exercise) improved insulin sensitivity in the muscle tissue [55].

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1-RA) are drugs used in obesity management that inhibit appetite while also stimulating insulin release and decreasing glucagon secretion in response to hyperglycemia. One-year treatment with a GLP-1-RA, liraglutide, combined with exercise intervention improved healthy weight loss maintenance more than exercise or medication alone in adults with obesity [56]. Additionally, liraglutide induced a similar amount of weight loss compared with exercise alone, but decreased bone mineral density at clinically relevant sites [57]. Yet the combination of liraglutide with exercise did not affect bone mineral density [57]. Nevertheless, although exercise alone or in combination with another GLP-1-RA, tirzepatide, was effective in improving cardiometabolic health in patients with obesity, higher fitness improvements

were observed with exercise alone [58], suggesting that this compound could interfere with exercise adaptations. The combination of another GLP-1-RA, semaglutide, with anti-myostatin antibodies induced loss of fat mass while preserving lean mass in HFD-fed mice and non-human primates [59]. However, two thirds of patients under treatment with GLP-1-RAs stop taking the relevant drug in the first year and regain one-half to two-thirds of the weight lost within this period [60].

Phytochemicals are potential exercise mimetics with pleiotropic effects

Phytochemicals are chemical compounds (e.g., polyphenols) produced by plants, generally to help them resist infections or consumption by animals (e.g., insects). Their main effects as potential exercise mimetics are summarized in Figure 3.

Resveratrol

Resveratrol, a plant-derived polyphenol abundant in blueberries, grapes, and peanuts, improved aerobic capacity, mitochondrial function, and insulin sensitivity in mouse muscle and brown adipose tissue, these effects being mediated largely by a decrease/increase in PGC-1α acetylation/activity [61]. Six-month resveratrol treatment shifted the overall health status of HFD-fed mice towards those fed a standard diet, with increases in insulin sensitivity, mitochondrial biogenesis, and survival [62]. Additionally, this treatment reduced insulin-like growth factor-1 levels while increasing AMPK and PGC-1α activity [62].

The metabolic effects of resveratrol can also result from competitive inhibition of cAMP-degrading **phosphodiesterases**. Treatment with a selective phosphodiesterase-4 inhibitor, rolipram, recapitulated the metabolic benefits of resveratrol in mice: including prevention of HFD-induced obesity and improvements in mitochondrial function, physical stamina, and glucose tolerance [63]. Resveratrol mitigated vascular endothelial dysfunction in HFD-fed mice through increases in PPARδ transcriptional activity in endothelial cells [64]. The salutary vascular changes induced by resveratrol also include an improved angiogenesis in the rat myocardium following infarction, an effect mediated by an upregulated expression of VEGF and its tyrosine kinase receptor Flk-1, together with increases in eNOS and in the inducible isoform of NOS [65].

There is meta-analytical evidence that large resveratrol doses reduce blood glycemia as well as systolic and diastolic BP in patients with type 2 diabetes [66]. Another meta-analysis failed to report changes in the BP of people with cardiometabolic conditions, but also found that doses >300 mg/day could be effective in reducing BP in those with diabetes [67].

(–)-Epicatechin

(–)-Epicatechin is a flavonoid found in green tea, cacao, and many fruits. In mice, (–)-epicatechin improved exercise performance, as well as mitochondrial volume/density and capillarity in muscle tissue (Figure 3) [68]. Additionally, this treatment increased the expression of components of the OXPHOS complexes and of the inner (mitofilin) and outer (porin) mitochondrial membrane, neuronal and phosphorylated NOS, and mitochondrial transcription factor A (TFAM, a key activator of mitochondrial transcription) in both skeletal and cardiac muscle tissue [68]. Of note, (–)-epicatechin alone or in combination with exercise induced larger improvements than exercise alone [68]. The combination of (–)-epicatechin and aerobic exercise (treadmill) training induced a greater improvement in the running performance of mice than either treatment alone [69]. In this effect, the muscle expression levels of angiogenic and mitochondrial biogenesis factors (e.g., VEGF-receptor 2, PGC-1β, TFAM) were also highest when (–)-epicatechin was combined with exercise [69].

In middle-aged patients with **Becker muscular dystrophy**, (–)-epicatechin improved 'aerobic efficiency' (as reflected by decreases in heart rate, oxygen uptake, and blood lactate during

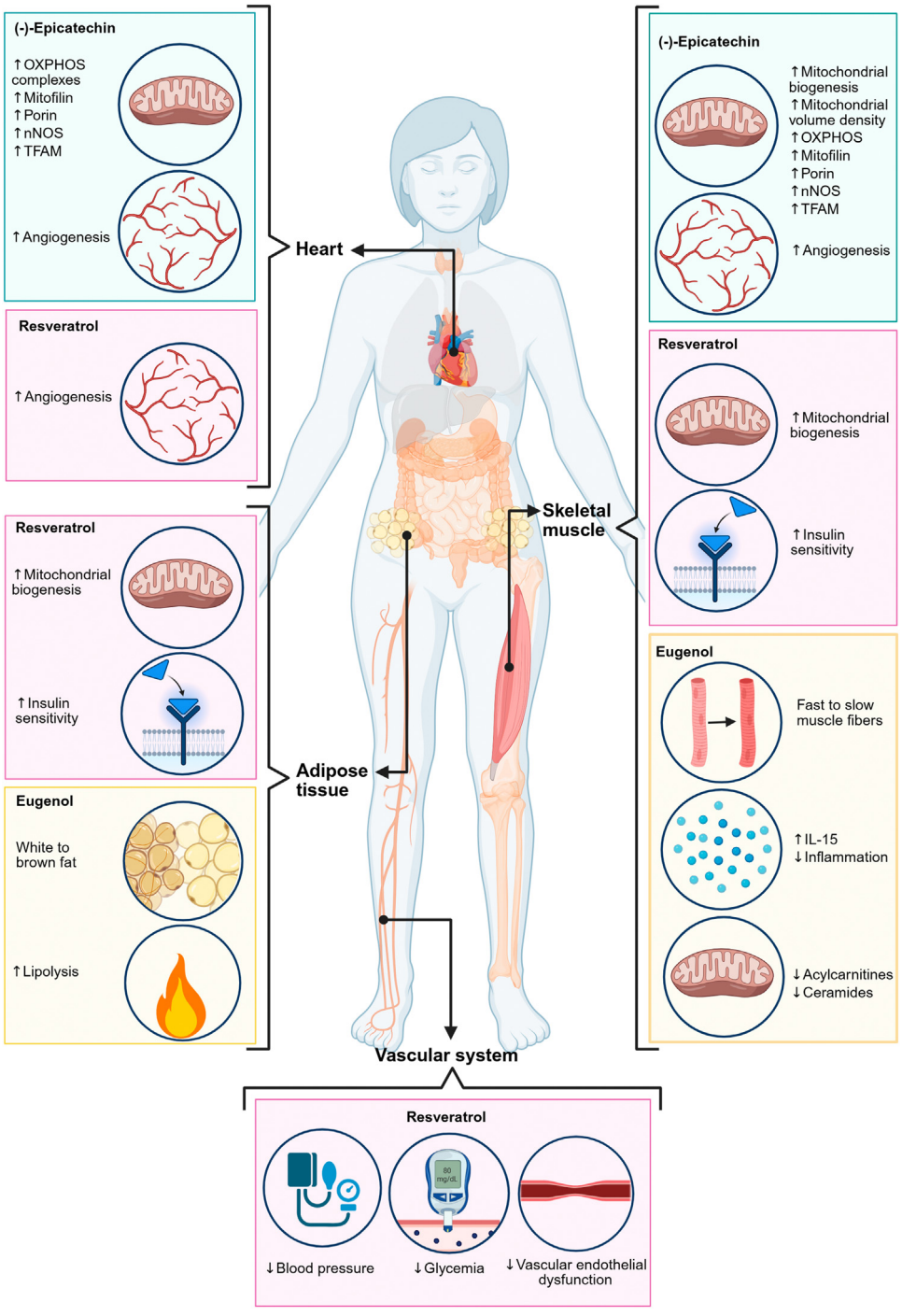

Figure 3. Phytochemicals: main effects on cardiometabolic health, muscle tissue, and (endurance) exercise performance. Abbreviations: IL-15, interleukin-15; nNOS, neuronal nitric oxide synthase; OXPHOS, oxidative phosphorylation; TFAM, mitochondrial transcription factor A. Figure created with BioRender.

submaximal exercise) [70]. At the skeletal muscle tissue level, (–)-epicatechin induced upregulation of growth/regeneration markers [70]; it also stimulated mitochondrial biogenesis, as well as abundance of mitochondrial cristae and associated mitofilin, while decreasing the levels of a muscle growth inhibitor, myostatin [70]. However, in healthy adults, acute [71] or 4-week (combined with endurance training) [72] (–)-epicatechin supplementation failed to improve vasodilation or performance during a resistance exercise session [71] or myostatin gene expression and mitochondrial proteins in muscle tissue [72] compared with a placebo. In fact, a deleterious effect was reported on some markers of aerobic training adaptation: peak oxygen uptake (VO_{2peak}) and skeletal muscle succinate dehydrogenase protein content [72].

Eugenol and urolithin A

Eugenol (a phenolic molecule found in various spices such as cinnamon, basil, cloves, and bay leaves) improved endurance swimming performance in mice, while also inducing the conversion of fast to slow muscle fibers and promoting white fat browning and lipolysis [73] (Figure 3). At the mechanistic level, eugenol can bind to transient receptor potential cation channel subfamily V member (TRPV1), thereby activating the nuclear factor of activated T cells, cytoplasmic 1 (NFATc1) pathway in the skeletal muscle [73]. NGATC1 signaling promotes the muscle expression of the myokine IL-15 [6] (which is involved in fat loss) as well as improvements in glucose metabolism via stimulation of the AMPK pathway [6,73]. Interestingly, higher treatment doses (200 mg/kg) failed to induce TRPV1 desensitization in skeletal muscle [73].

Urolithin A, a microflora-derived metabolite and a known autophagy activator, is well tolerated and improves cardiorespiratory fitness (VO_{2peak} and performance in the 6-min walk test) [74] and muscle endurance (number of muscle contractions until fatigue) [75] while reducing mitochondrial (acylcarnitines [74,75] and/or ceramides [75]) and inflammatory (CRP) biomarkers [74,75] in middle-aged [74] and older adults [75].

Exercise omics is expanding the landscape of exercise physiology

Advances in multi-omics, with a growing availability of high-throughput platforms (together with single-cell approaches), are allowing researchers to study the molecular signatures of exercise at the multisystem and multicellular level [8,76]. Novel findings in this emerging field can provide insights into the molecular networks altered by exercise and how they impact cardiometabolic health. Furthermore, a growing number of studies are identifying molecules that are candidates to become ‘new’ exerkines and, eventually, potential components of future ‘exercise pills’.

A study showed dramatic elevations after acute intense exercise of Lac-Phe: a blood-borne signaling metabolite produced in the immune, epithelial, and mesenchymal stem cells (MSCs) of diverse organs [77]. Lac-Phe administration improved glucose homeostasis and body composition in mice, whereas genetic ablation of Lac-Phe biosynthesis increased food intake and obesity following exercise training [77]. Another study in mice validated 2-hydroxybutyrate (a biomarker of glucose homeostasis) as a liver- and muscle-derived exerkine [78].

Muscle-secreted fibronectin 1 increased in circulation after acute exercise in mice and mediated exercise-induced hepatic autophagy and systemic insulin sensitization, via the hepatic receptor α5β1 integrin and the downstream inhibitor of nuclear factor κB (NF-κB) (IκB) and IκB kinase (IKK)α/β–JNK1–beclin-1 pathway [79]. In a comprehensive cell type-specific map of the endurance exercise training-regulated secretome in mice, two of the most robust exercise-inducible molecules belonged to the same family of carboxylesterase (CES) enzymes released by the liver, CES2A and CES2C [80]. When delivered to HFD-fed mice, these enzymes showed anti-

obesity, anti-diabetes, and endurance-enhancing effects and were thus postulated as hepatic exerkines able to improve cardiometabolic health [80].

A recent article reported the multi-omics and multisystemic signature of endurance exercise in rats [9]. The majority (~60%) of the thousands of molecular alterations induced by exercise were sex-specific, and there was a high overlap between 'exercise-responsive' genes in rats and humans, which in turn are related to major cardiometabolic conditions [9]. Another related study showed that exercise training upregulated protein networks in rats that were in turn downregulated in patients with diabetes and cirrhosis [81]. Notably, the training-induced increase in HSD17B10 (a mitochondrial multifunctional enzyme) was postulated to coordinate adaptations to exercise in response to the perturbations in cellular metabolic stress [81]. Finally, a recent integrated multi-omics analysis identified betaine, a metabolite that binds to and inhibits TANK-binding kinase 1 (a regulator of cell proliferation, apoptosis, autophagy, and antitumor immunity), as an exercise mimetic for healthy aging [82].

It has been suggested that administration of exerkines might mimic some of the cardiometabolic benefits conferred by exercise in individuals with disabilities who cannot perform muscle work [6], but the evidence is still essentially confined to preclinical models. Notably, plasma transferred from adult mice that performed voluntary wheel-running to sedentary controls decreased neuroinflammatory gene expression in the latter, as well as in mice with experimentally induced brain inflammation [83]. These effects were linked to complement and coagulation pathways, including clusterin: an extracellular molecular chaperone that can target brain endothelial cells and broadly reduce interferon signaling [83].

Adverse effects of potential exercise mimetics

Physical exercise is essentially safe, at least in the absence of severe cardiac conditions [11]. However, exercise pills, especially pharmacological agonists, are not devoid of potential toxicities. There is preclinical evidence for potential tumorigenic effects of GW501516 – through VEGF upregulation in colon carcinoma cells, with VEGF directly promoting colon tumor epithelial cell survival through activation of the PI3K–Akt pathway [84] – together with impairments in bone formation in ovariectomized rats, leading to reductions in bone density [85]. Furthermore, treatment of tumor cells with a direct AMPK activator (A769662) promoted their proliferation under hypoxic conditions [86]. However, a higher level of evidence is needed to corroborate this type of toxicity at the clinical level. Indeed, the possible adverse consequences of long-term treatments with pharmacological agents, such as AMPK activators, remain to be identified. In healthy volunteers, oral AICAR showed poor bioavailability [87] and was associated with increases in BP and circulating lactic/uric acid, making this compound unsuitable for long-term use [87,88]. However, GLP1-RAs (e.g., liraglutide) are generally associated with mild adverse events such as nausea and vomiting [89]. Similarly, the adverse effects of rapamycin (sirolimus), a US Food and Drug Administration (FDA)-approved drug with immune-modulating properties that is prescribed off-label as a preventative therapy to maintain healthspan, appear to be mild (i.e., transient mouth ulcers, when occurring) [90]. More clinical trials assessing the safety of these drugs are needed before their eventual prescription as exercise pills.

Phytochemicals like resveratrol, (–)-epicatechin [70], and urolithin A [74,75] are typically well tolerated, with no serious adverse events reported in most human trials [67]. However, some might have potential negative effects, at least at the preclinical level. Notably, although resveratrol can increase survival in preclinical models, a genome-wide **CRISPR-Cas9** – clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) –

approach in human cells showed that it might deplete nucleotide pools, inhibit **replication fork** progression, and induce low-level replicative stress, which can lead to genomic instability, a hallmark of tumorigenesis [91].

Could we ever take pills instead of exercise?

Research on exercise pills has primarily focused on muscle-specific pathways, such as fast to slow fiber distribution, mitochondrial biogenesis, or OXPHOS. However, not only different organs besides the muscle itself, but also different molecular pathways within a given organ or tissue are involved in exercise adaptations [9]. For instance, although PGC-1α is traditionally considered the master regulator of mitochondrial biogenesis in the skeletal muscle, evidence for the occurrence of exercise-induced mitochondrial biogenesis in PGC-1α-deficient mice suggests that PGC-1α is dispensable for mitochondrial adaptations to occur in this tissue [92].

The transient perturbation of homeostasis elicited by each exercise session provides the basis for long-term adaptations to occur with regular exercise (i.e., through repeated acute episodes) across various tissues and systems, not only the skeletal muscle or the cardiovascular system, but also the adipose tissue, liver, pancreas, and brain, or even the gut microbiota [7]. In this regard, there is currently no exercise pill capable of mimicking the concomitant, positive impact of exercise on multiple cardiometabolic health traits, such as for instance cardiorespiratory fitness, myocardial repair, endothelial function, glucose control, fat metabolism, or muscle mass preservation. Furthermore, individual adaptations to exercise differ depending on several factors such as baseline fitness and health conditions and the characteristics of the exercise stimulus (i.e., mode, frequency, intensity, and duration of each session) [93]. These factors are difficult to control when attempting to replace exercise with a drug. Additionally, several extrinsic factors (circadian rhythms, sleep habits, dietary interactions, medication use) and intrinsic factors (sex, age, hormonal status, race/ethnicity, genetics) influence exercise responses and health outcomes [94], and must be considered when attempting to recapitulate exercise benefits. Furthermore, there are not only time (of the day)- but also tissue-dependent patterns in exerkine (metabolite) responses to exertion [78].

Many exercise-induced adaptations are inherently linked to acute biological stimuli triggered by exertion (e.g., increased arterial shear stress, adrenaline secretion, transient tissue damage in the form of oxidative stress, or acute inflammation). Such stimuli are virtually impossible to reproduce by taking a pill [93]. Finally, exercise induces the release of myriad exerkines with pleiotropic, whole-body effects at different concentrations over different time windows; how could this be reproduced with a pill?

Concluding remarks and future perspectives

The complex, whole-body effects of exercise cannot be mimicked pharmacologically, making the concept of exercise mimetics largely speculative (see Figure 4 for a summary). As such, although tantalizing, the concept of 'exercise in a pill' appears unrealistic at present. Besides, several questions need to be addressed before actual prescription of exercise pills (see Outstanding questions). That said, research in the field can have relevant applications, notably identification of novel molecular therapeutic targets for cardiometabolic health.

Physical inactivity is becoming a real pandemic that aggravates the widespread burden of cardiometabolic disease. Thus, policies directed at healthy individuals should prioritize promotion of regular exercise to ensure that the full spectrum of benefits is achieved. However, in the future, exercise pills could offer some cardiometabolic benefits for individuals who are unable to perform muscle work due to severe physical limitations, such as in cases of paralysis.

Outstanding questions

Are all the exerkines induced by exercise equally important (i.e., which of them should be preferentially incorporated into an eventual exercise pill)?

Should there be different exercise pills based on age or sex?

How can we mimic some specific unique features of the exercise milieu (e.g., adrenergic stimulation) that can be harmful under resting conditions?

Given the pandemic of inactivity, instead of thinking of replacing exercise with a pill, why not identify the best possible exercise dose to improve individual cardiometabolic health?

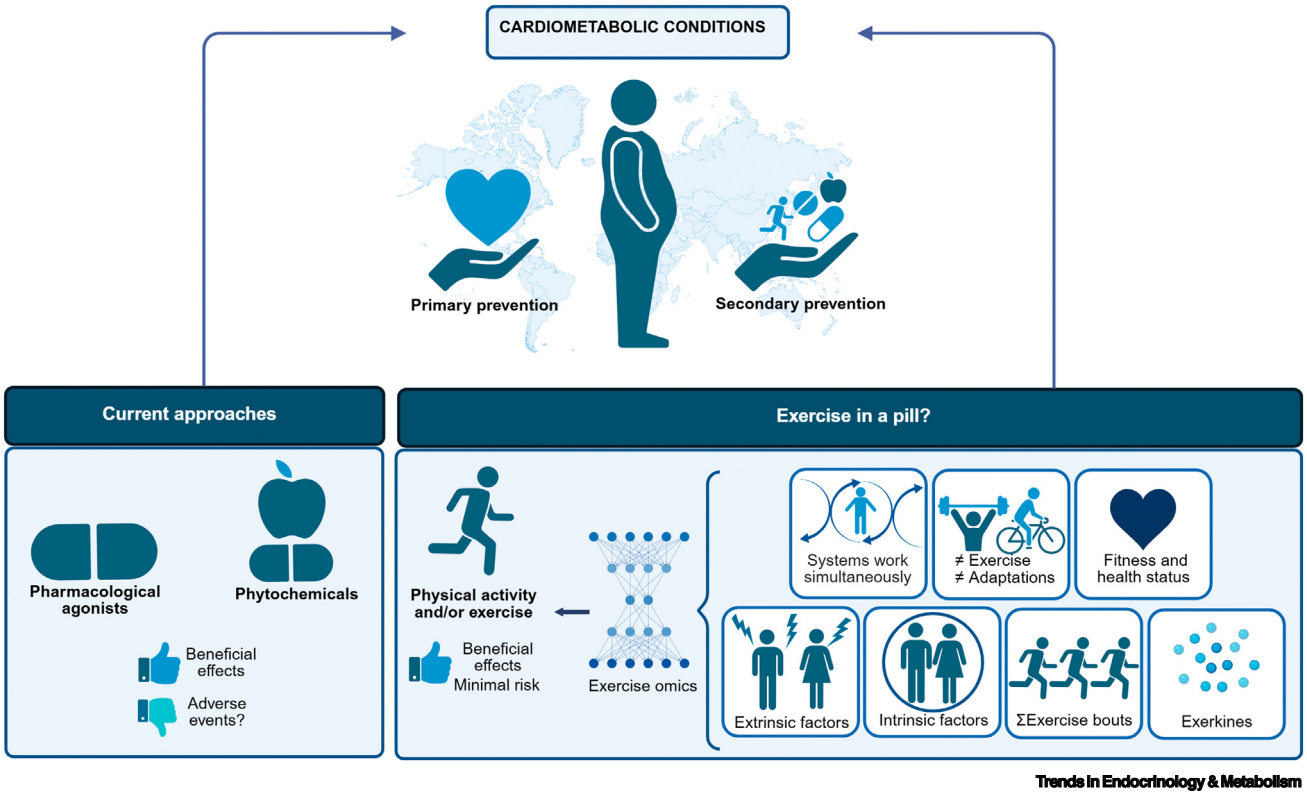

Figure 4. Can we replace exercise with pills? Main reasons that explain why, at present, the multisystem benefits of exercise cannot be mimicked by a pill developed *ad hoc*. Figure created with BioRender.

Author contributions

A.P.F. and A.L. wrote the first draft of the article. C.F.L. created the figures. All authors read, critically revised, and edited the different drafts. All authors have read and approved the final version of the manuscript and agree with the authors' order of presentation.

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Declaration of interests

The authors declare no competing interests.

References

1. Khetarpal, S.A. *et al.* (2025) Molecular mediators of the cardiac benefits of exercise. *Circ. Res.* 137, 163–183
2. Jin, L. *et al.* (2024) Exerkines and cardiometabolic benefits of exercise: from bench to clinic. *EMBO Mol. Med.* 16, 432–444
3. Narkar, V.A. *et al.* (2008) AMPK and PPARδ agonists are exercise mimetics. *Cell* 134, 405–415
4. Fan, W. and Evans, R.M. (2017) Exercise mimetics: impact on health and performance. *Cell Metab.* 25, 242–247
5. Xu, L. *et al.* (2023) Prevalence of sufficient physical activity among general adult population and sub-populations with chronic conditions or disability in the USA. *Eur. J. Pub. Health* 33, 891–896
6. Chow, L.S. *et al.* (2022) Exerkines in health, resilience and disease. *Nat. Rev. Endocrinol.* 18, 273–289
7. Ashcroft, S.P. *et al.* (2024) Exercise induces tissue-specific adaptations to enhance cardiometabolic health. *Cell Metab.* 36, 278–300

8. Katz, D.H. *et al.* (2025) Charting the molecular terrain of exercise: energetics, exerkines, and the future of multiomic mapping. *Physiology* 40, 185–202
9. MoTrPAC Study Group, Lead Analysts, & MoTrPAC Study Group (2024) Temporal dynamics of the multi-omic response to endurance exercise training. *Nature* 629, 174–183
10. Smith, J.A.B. *et al.* (2023) Exercise metabolism and adaptation in skeletal muscle. *Nat. Rev. Mol. Cell Biol.* 24, 607–632
11. Valenzuela, P.L. *et al.* (2023) Exercise benefits in cardiovascular diseases: from mechanisms to clinical implementation. *Eur. Heart J.* 44, 1874–1889
12. Khemraj, P. *et al.* (2025) Adaptations in mitochondrial quality control and interactions with innate immune signaling within skeletal muscle: a narrative review. *J. Sport Health Sci.*, Published online May 1, 2025. https://doi.org/10.1016/j.jshs.2025.101049
13. Wang, Y. *et al.* (2023) Exercise improves the coordination of the mitochondrial unfolded protein response and mitophagy in aging skeletal muscle. *Life* 13, 1–23
14. Furman, D. *et al.* (2019) Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* 25, 1822–1832
15. Luo, B. *et al.* (2024) The anti-inflammatory effects of exercise on autoimmune diseases: a 20-year systematic review. *J. Sport Health Sci.* 13, 353–367
16. Frodermann, V. *et al.* (2019) Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nat. Med.* 25, 1761–1771
17. Yang, Y. *et al.* (2025) Effects of different exercise modalities on blood pressure and endothelial function in prehypertension individuals: a systematic review and network meta-analysis. *Front. Cardiovasc. Med.* 12, 1550435
18. Amekran, Y. and El hangouche, A.J. (2024) Effects of exercise training on heart rate variability in healthy adults: a systematic review and meta-analysis of randomized controlled trials. *Cureus* 16, 1–26
19. Deng, Y. *et al.* (2024) The effect of exercise training on heart rate variability in patients with hypertension: a systematic review and meta-analysis. *J. Sports Sci.* 42, 1272–1287
20. Baker, S.E. *et al.* (2018) Aging alters the relative contributions of the sympathetic and parasympathetic nervous system to blood pressure control in women. *Hypertension* 72, 1236–1242
21. Grassi, G. and Drager, L.F. (2024) Sympathetic overactivity, hypertension and cardiovascular disease: state of the art. *Curr. Med. Res. Opin.* 40, 5–13
22. Kim, J.J. *et al.* (2023) Exercise as a therapy to maintain telomere function and prevent cellular senescence. *Exerc. Sport Sci. Rev.* 51, 150–160
23. Jiao, Z. *et al.* (2021) Metformin protects against insulin resistance induced by high uric acid in cardiomyocytes via AMPK signalling pathways in vitro and in vivo. *J. Cell. Mol. Med.* 25, 6733–6745
24. Li, F. *et al.* (2024) Aerobic exercise suppresses CCN2 secretion from senescent muscle stem cells and boosts muscle regeneration in aged mice. *J. Cachexia. Sarcopenia Muscle* 15, 1733–1749
25. Misquitta, N.S. *et al.* (2023) Combinatorial treatment with exercise and AICAR potentiates the rescue of myotonic dystrophy type 1 mouse muscles in a sex-specific manner. *Hum. Mol. Genet.* 32, 551–566
26. Marcinko, K. *et al.* (2015) The AMPK activator R419 improves exercise capacity and skeletal muscle insulin sensitivity in obese mice. *Mol. Metab.* 4, 643–651
27. Dressel, U. *et al.* (2003) The peroxisome proliferator-activated receptor β/δ agonist, GW501516, regulates the expression of genes involved in lipid catabolism and energy uncoupling in skeletal muscle cells. *Mol. Endocrinol.* 17, 2477–2493
28. Wang, Y.X. *et al.* (2004) Regulation of muscle fiber type and running endurance by PPARδ. *PLoS Biol.* 2, 1532–1539
29. Lendoye, E. *et al.* (2011) PPARβ activation induces rapid changes of both AMPK subunit expression and ampk activation in mouse skeletal muscle. *Mol. Endocrinol.* 25, 1487–1498
30. Manio, M.C.C. *et al.* (2016) Combined pharmacological activation of AMPK and PPARδ potentiates the effects of exercise in trained mice. *Phys. Rep.* 4, 1–18
31. Woldt, E. *et al.* (2013) Rev-erb-α modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. *Nat. Med.* 19, 1039–1046
32. Solt, L.A. *et al.* (2012) Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. *Nature* 485, 62–68
33. Thevis, M. and Schänzer, W. (2016) Emerging drugs affecting skeletal muscle function and mitochondrial biogenesis – potential implications for sports drug testing programs. *Rapid Commun. Mass Spectrom.* 30, 635–651
34. Li, L. *et al.* (2024) Regulation of exercise ability and glycolipid metabolism by synthetic SR9009 analogues as new REV-ERB-α agonists. *Bioorg. Med. Chem.* 111, 117845
35. Narkar, V.A. *et al.* (2011) Exercise and PGC-1α-independent synchronization of type i muscle metabolism and vasculature by ERRγ. *Cell Metab.* 13, 283–293
36. Kim, Y. *et al.* (2009) Efficient discovery of selective small molecule agonists of estrogen-related receptor γ using combinatorial approach. *J. Comb. Chem.* 11, 928–937
37. Wattez, J.S. *et al.* (2023) Loss of skeletal muscle estrogen-related receptors leads to severe exercise intolerance. *Mol. Metab.* 68, 101670
38. Billon, C. *et al.* (2023) Synthetic ERRα/β/γ agonist induces an ERRα-dependent acute aerobic exercise response and enhances exercise capacity. *ACS Chem. Biol.* 18, 756–771
39. Billon, C. *et al.* (2024) A synthetic ERR agonist alleviates metabolic syndrome. *J. Pharmacol. Exp. Ther.* 388, 232–240
40. Xu, W. *et al.* (2024) Novel pan-ERR agonists ameliorate heart failure through enhancing cardiac fatty acid metabolism and mitochondrial function. *Circulation* 149, 227–250
41. Okada-Iwabu, M. *et al.* (2013) A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. *Nature* 503, 493–499
42. Iwabu, M. *et al.* (2021) AdipoR agonist increases insulin sensitivity and exercise endurance in AdipoR-humanized mice. *Commun. Biol.* 4, 45
43. Selvais, C.M. *et al.* (2023) AdipoRon enhances healthspan in middle-aged obese mice: striking alleviation of myosteatosis and muscle degenerative markers. *J. Cachexia. Sarcopenia Muscle* 14, 464–478
44. Chibalin, A.V. *et al.* (2008) Downregulation of diacylglycerol kinase delta contributes to hyperglycemia-induced insulin resistance. *Cell* 132, 375–386
45. Jollet, M. *et al.* (2024) Diacylglycerol kinase delta overexpression improves glucose clearance and protects against the development of obesity. *Metabolism* 158, 155939
46. Feige, J.N. *et al.* (2008) Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. *Cell Metab.* 8, 347–358
47. Mercken, E.M. *et al.* (2014) SRT2104 extends survival of male mice on a standard diet and preserves bone and muscle mass. *Aging Cell* 13, 787–796
48. Park, S.J. *et al.* (2017) Specific Sirt1 activator-mediated improvement in glucose homeostasis requires Sirt1-independent activation of AMPK. *EBioMedicine* 18, 128–138
49. Libri, V. *et al.* (2012) A pilot randomized, placebo controlled, double blind phase I Trial of the novel SIRT1 activator SRT2104 in elderly volunteers. *PLoS One* 7, e51395
50. Crisol, B.M. *et al.* (2020) NAD^+ precursor increases aerobic performance in mice. *Eur. J. Nutr.* 59, 2427–2437
51. Elhassan, Y.S. *et al.* (2019) Nicotinamide riboside augments the aged human skeletal muscle NAD^+ metabolome and induces transcriptomic and anti-inflammatory signatures. *Cell Rep.* 28, 1717–1728.e6
52. Remie, C.M.E. *et al.* (2020) Nicotinamide riboside supplementation alters body composition and skeletal muscle acetylcarnitine concentrations in healthy obese humans. *Am. J. Clin. Nutr.* 112, 413–426
53. Braga, R.R. *et al.* (2025) NAD replenishment restores mitochondrial function and thermogenesis in the brown adipose tissue of mice with obesity. *J. Physiol.*, Published online May 5, 2025. https://doi.org/10.1113/JP288453
54. Nascimento, E.B.M. *et al.* (2021) Nicotinamide riboside enhances *in vitro* beta-adrenergic brown adipose tissue activity in humans. *J. Clin. Endocrinol. Metab.* 106, 1437–1447
55. Yoshino, M. *et al.* (2021) Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. *Science* 372, 1224–1229
56. Lundgren, J.R. *et al.* (2021) Healthy weight loss maintenance with exercise, liraglutide, or both combined. *N. Engl. J. Med.* 384, 1719–1730
57. Jensen, S.B.K. *et al.* (2024) Bone health after exercise alone, GLP-1 receptor agonist treatment, or combination treatment: a

secondary analysis of a randomized clinical trial. *JAMA Netw. Open* 7, e2416775
58. Bagherzadeh-Rahmani, B. *et al.* (2024) Tirzepatide and exercise training in obesity. *Clin. Hemorheol. Microcirc.* 87, 465–480
59. Mastaitis, J.W. *et al.* (2025) GDF8 and activin A blockade protects against GLP-1–induced muscle loss while enhancing fat loss in obese male mice and non-human primates. *Nat. Commun.* 16, 4377
60. Conte, C. *et al.* (2024) Is weight loss-induced muscle mass loss clinically relevant? *JAMA* 332, 9–10
61. Lagouge, M. *et al.* (2006) Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. *Cell* 127, 1109–1122
62. Baur, J.A. *et al.* (2006) Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 444, 337–342
63. Park, S.J. *et al.* (2012) Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. *Cell* 148, 421–433
64. Cheang, W.S. *et al.* (2019) Resveratrol ameliorates endothelial dysfunction in diabetic and obese mice through sirtuin 1 and peroxisome proliferator-activated receptor δ. *Pharmacol. Res.* 139, 384–394
65. Fukuda, S. *et al.* (2006) Resveratrol ameliorates myocardial damage by inducing vascular endothelial growth factor-angiogenesis and tyrosine kinase receptor Flk-1. *Cell Biochem. Biophys.* 44, 43–49
66. Gu, W. *et al.* (2022) Effects of resveratrol on metabolic indicators in patients with type 2 diabetes: a systematic review and meta-analysis. *Int. J. Clin. Pract.* 2022, 9734738
67. Fogacci, F. *et al.* (2019) Effect of resveratrol on blood pressure: a systematic review and meta-analysis of randomized, controlled, clinical trials. *Crit. Rev. Food Sci. Nutr.* 59, 1605–1618
68. Nogueira, L. *et al.* (2011) (–)-Epicatechin enhances fatigue resistance and oxidative capacity in mouse muscle. *J. Physiol.* 589, 4615–4631
69. Lee, I. *et al.* (2015) (–)-Epicatechin combined with 8 weeks of treadmill exercise is associated with increased angiogenic and mitochondrial signaling in mice. *Front. Pharmacol.* 6, 43
70. McDonald, C.M. *et al.* (2021) (–)-Epicatechin induces mitochondrial biogenesis and markers of muscle regeneration in adults with Becker muscular dystrophy. *Muscle Nerve* 63, 239–249
71. Schwarz, N.A. *et al.* (2020) Acute (–)-epicatechin consumption: effects on local vasodilation following resistance exercise and high-intensity exercise performance. *Sports* 8, 22
72. Schwarz, N.A. *et al.* (2018) (–)-Epicatechin supplementation inhibits aerobic adaptations to cycling exercise in humans. *Front. Nutr.* 5, 132
73. Huang, T. *et al.* (2023) Eugenol mimics exercise to promote skeletal muscle fiber remodeling and myokine IL-15 expression by activating TRPV1 channel. *Elife* 12, RP90724
74. Singh, A. *et al.* (2022) Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. *Cell Rep. Med.* 3, 100633
75. Liu, S. *et al.* (2022) Effect of urolithin A supplementation on muscle endurance and mitochondrial health in older adults: a randomized clinical trial. *JAMA Netw. Open* 5, e2144279
76. Sanford, J.A. *et al.* (2020) Molecular Transducers of Physical Activity Consortium (MoTrPAC): mapping the dynamic responses to exercise. *Cell* 181, 1464–1474
77. Li, V.L. *et al.* (2022) An exercise-inducible metabolite that suppresses feeding and obesity. *Nature* 606, 785–790
78. Sato, S. *et al.* (2022) Atlas of exercise metabolism reveals time-dependent signatures of metabolic homeostasis. *Cell Metab.* 34, 329–345.e8
79. Kuramoto, K. *et al.* (2023) Exercise-activated hepatic autophagy via the FN1-α5β1 integrin pathway drives metabolic benefits of exercise. *Cell Metab.* 35, 620–632.e5
80. Wei, W. *et al.* (2023) Organism-wide, cell-type-specific secretome mapping of exercise training in mice. *Cell Metab.* 35, 1261–1279.e11
81. Amar, D. *et al.* (2024) The mitochondrial multi-omic response to exercise training across rat tissues. *Cell Metab.* 36, 1411–1429.e10
82. Geng, L. *et al.* (2025) Systematic profiling reveals betaine as an exercise mimetic for geroprotection. *Cell*, Published online June 25, 2025. https://doi.org/10.1016/j.cell.2025.06.001
83. De Miguel, Z. *et al.* (2021) Exercise plasma boosts memory and dampens brain inflammation via clusterin. *Nature* 600, 494–499
84. Wang, D. *et al.* (2006) Crosstalk between peroxisome proliferator-activated receptor and VEGF stimulates cancer progression. *Proc. Natl. Acad. Sci. U. S. A.* 103, 19069–19074
85. Mosti, M.P. *et al.* (2014) Effects of the peroxisome proliferator-activated receptor (PPAR)-δ agonist GW501516 on bone and muscle in ovariectomized rats. *Endocrinology* 155, 2178–2189
86. Vincent, E.E. *et al.* (2015) Differential effects of AMPK agonists on cell growth and metabolism. *Oncogene* 34, 3627–3639
87. Dixon, R. *et al.* (1991) AICA-riboside: safety, tolerance, and pharmacokinetics of a novel adenosine-regulating agent. *J. Clin. Pharmacol.* 31, 342–347
88. Goodyear, L.J. (2008) The exercise pill – too good to be true? *N. Engl. J. Med.* 359, 1842–1843
89. Vosoughi, K. *et al.* (2021) Association of glucagon-like peptide 1 analogs and agonists administered for obesity with weight loss and adverse events: a systematic review and network meta-analysis. *EClinicalMedicine* 42, 101213
90. Hudson, J. *et al.* (2024) Evaluation of off-label rapamycin use on oral health. *Geroscience* 46, 4135–4146
91. Benslimane, Y. *et al.* (2020) Genome-wide screens reveal that resveratrol induces replicative stress in human cells. *Mol. Cell* 79, 846–856.e8
92. Rowe, G.C. *et al.* (2012) PGC-1α is dispensable for exercise-induced mitochondrial biogenesis in skeletal muscle. *PLoS One* 7, e41817
93. Hawley, J.A. *et al.* (2021) Mimicking exercise: what matters most and where to next? *J. Physiol.* 599, 791–802
94. Noone, J. *et al.* (2024) Understanding the variation in exercise responses to guide personalized physical activity prescriptions. *Cell Metab.* 36, 702–724