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Review

# Exercise induces tissue-specific adaptations to enhance cardiometabolic health

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## SUMMARY

The risk associated with multiple cancers, cardiovascular disease, diabetes, and all-cause mortality is decreased in individuals who meet the current recommendations for physical activity. Therefore, regular exercise remains a cornerstone in the prevention and treatment of non-communicable diseases. An acute bout of exercise results in the coordinated interaction between multiple tissues to meet the increased energy demand of exercise. Over time, the associated metabolic stress of each individual exercise bout provides the basis for long-term adaptations across tissues, including the cardiovascular system, skeletal muscle, adipose tissue, liver, pancreas, gut, and brain. Therefore, regular exercise is associated with a plethora of benefits throughout the whole body, including improved cardiorespiratory fitness, physical function, and glycemic control. Overall, we summarize the exercise-induced adaptations that occur within multiple tissues and how they converge to ultimately improve cardiometabolic health.

## MODALITIES OF EXERCISE

Individuals who meet the current recommendations for physical activity see a reduction in the risk associated with multiple cancers, cardiovascular disease, diabetes, and all-cause mortality.[1,2] The current recommendations state that adults should perform 150–300 min of moderate-intensity exercise (e.g., walking) or 75–150 min of vigorous-intensity exercise (e.g., running) per week.[3] This should incorporate multiple components, including endurance, muscle strengthening, and balance-related activities. When prescribing an exercise program, there are many variables to consider, including intensity, duration, frequency, recovery between sessions, time of day, genetic variants, and sex, all of which will influence the adaptive outcome.[4,5] Endurance exercise is often defined by the intensity at which it is performed and is prescribed relative to an individual's maximum heart rate, maximal oxygen uptake ($\dot{V}O_{2max}$), or maximal power output ($\dot{W}_{max}$).[6] For example, endurance exercise can be broken down into moderate-intensity continuous training (MICT: 50%–75% $\dot{W}_{max}$), high-intensity interval training (HIIT: intervals at <100% $\dot{W}_{max}$), sprint interval training (SIT: intervals of >10 s at >100% $\dot{W}_{max}$), or repeated sprints (sprints of <10 s at maximum effort) (Figure 1).[6] Similarly, when performing resistance exercise, the intensity is prescribed by the load, which is often a percentage of the individual's one-repetition maximum. The number of sets, repetitions, and rest intervals can be manipulated depending upon the overall training goals, such as increased strength or hypertrophy.[7] Regardless of modality, exercise interventions generally adhere to the principle of progressive overload, whereby the training load is progressively increased over time to maximize the adaptive response.

Overall, the aim of this review is to describe the physiological responses to acute exercise and the adaptive responses to chronic exercise from a multi-tissue perspective. We will focus primarily on endurance and resistance exercise, and where possible, human intervention studies will be prioritized. For some tissues, such data may be limited; therefore, key studies utilizing preclinical models will be discussed.

## ACUTE EXERCISE METABOLISM INVOLVES COORDINATION BETWEEN MULTIPLE TISSUES

Exercise profoundly increases energy demand and alters systemic metabolic homeostasis (Figure 2). At the onset of exercise, there is up to a 100-fold increase in the demand for ATP, which is met via the simultaneous activation of anaerobic and aerobic ATP production.[8] During short (<30 s) and intense (>100% $\dot{W}_{max}$) bouts of endurance exercise, as well as resistance exercise, the increased demand for ATP is predominantly supplied by the anaerobic processes such as phosphocreatine (PCr) hydrolysis and anaerobic glycolysis.[9,10] Such processes can produce ATP in milliseconds via an increase in the concentration of allosteric regulators such as ADP, AMP, Pi, and the release of calcium ($Ca^{2+}$) from the sarcoplasmic reticulum.[8] The result is a rapid utilization of skeletal muscle PCr and glycogen stores and an increase in lactate production.[11,12] Should the duration of the exercise bout continue (15–30 s), there is an increase in the contribution of oxidative phosphorylation to the total ATP turnover rate,[8] and as exercise continues further (>2 min),

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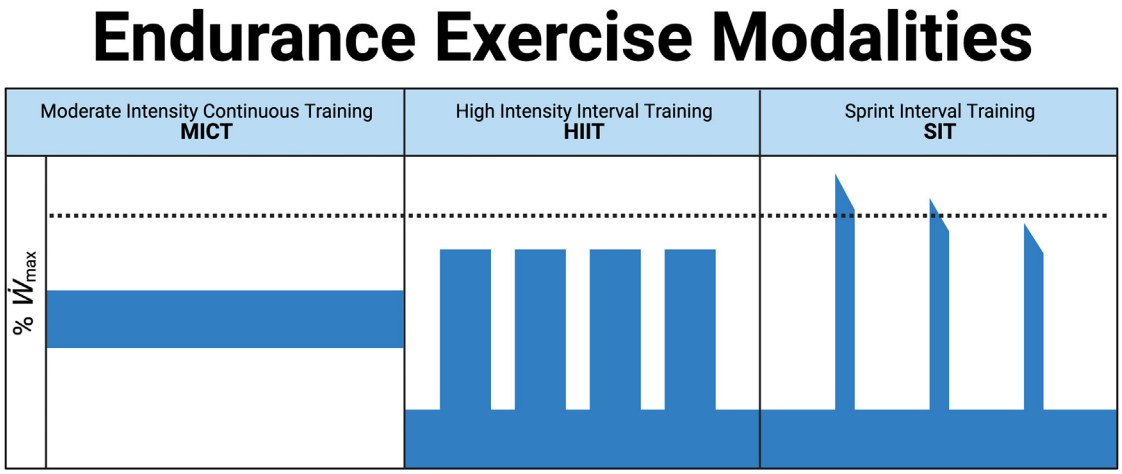


**Figure 1. Endurance exercise modalities**

When using an individual's maximal power output ($\dot{W}_{max}$) to define the intensity, endurance exercise can be broken down into moderate-intensity continuous training (MICT: 50%–75% $\dot{W}_{max}$), high-intensity interval training (HIIT: intervals at <100% $\dot{W}_{max}$), and sprint interval training (SIT: intervals of >10 s at >100% $\dot{W}_{max}$).[6] Dashed line represents 100% $\dot{W}_{max}$.

aerobic metabolism becomes the predominate source of ATP production.[13] This is facilitated by a large increase in $O_2$ consumption, cardiac output, and a redistribution of blood flow from the renal and splanchnic tissues to the working musculature.[14,15]

During continuous-endurance exercise performed at submaximal intensities (<100% $\dot{W}_{max}$), energy provision is maintained through alterations in whole body substrate metabolism, which involves the metabolic coordination of multiple tissues.[17,18] The metabolic effects that ensue within the working musculature and peripheral tissues are dependent upon exercise intensity, duration, training status, nutritional status, and sex.[17–19] During low- to moderate-intensity exercise (40%–55% $\dot{W}_{max}$), the increased energy demand from rest is met by an increase in carbohydrate and fat oxidation rates.[18] The increased rates of fat oxidation are achieved via the β-adrenergic stimulation of adipose tissue lipolysis, the release of free fatty acids (FFAs) into circulation, and the oxidation of intramuscular triglyceride (IMTG) stores.[18,20] Exercise also increases skeletal muscle glucose uptake, and euglycemia is maintained primarily via hepatic glycogenolysis and glucose delivery from the gastrointestinal tract, subject to prior ingestion.[21] During exercise, insulin release is diminished via the α-adrenergic inhibition of pancreatic β cells, thereby altering the ratio of insulin to glucagon.[22] This alteration, together with changes in glucose availability, results in the stimulation of hepatic glucose output.[23–25] Intramuscular glycogen stores can be utilized via glycogenolysis, and with increasing exercise intensity (75% $\dot{W}_{max}$), skeletal muscle glycogen becomes the predominant fuel source.[18] At such higher exercise intensities, the rate of fat oxidation markedly decreases through reduced oxidation of plasma FFA and IMTG.[18] A reduction in the rate of fat oxidation occurs as a result of reduced adipose tissue blood flow and an impaired transport of long-chain fatty acids into the mitochondria.[17,26]

During prolonged (120–240 min) moderate-intensity exercise, a decrease in carbohydrate oxidation and a shift toward fat oxidation occurs.[16] This is due to a reduction in the availability of skeletal muscle glycogen stores and the inactivation of pyruvate dehydrogenase (PDH).[16,27] Despite this, the relative contribution of plasma glucose to total energy expenditure remains relatively stable, and euglycemia is maintained[16] via hepatic glycogenolysis and an increased contribution from gluconeogenesis.[28] Furthermore, plasma glucagon levels continue to rise, which stimulates the hepatic uptake of gluconeogenic precursors such as lactate, pyruvate, glycerol, and alanine and, therefore, the maintenance of hepatic glucose output.[28,29] The increase in fat oxidation during this period is predominantly driven by an increase in the delivery of plasma FFAs as opposed to an increased oxidation of IMTG stores.[16] During the latter stage of the exercise bout, arterial glucose concentrations begin to fall as hepatic glucose output fails to meet the energy demand, and fatigue would eventually ensue.[21]

Overall, during short and intense (>100% $\dot{W}_{max}$) exercise, energy provision is skeletal muscle-centric; however, should exercise continue at submaximal intensities (<100% $\dot{W}_{max}$), energy provision is maintained via the coordinated interaction of multiple tissues.

## EXERCISE-INDUCED SIGNAL TRANSDUCTION AND TRANSCRIPTION

Acute exercise activates a comprehensive network of signal transduction pathways and transcriptional programs that are responsive to contraction within the working musculature, cellular energy availability, the hormonal milieu, ion flux, $O_2$ availability, and redox state.[30] For example, acute exercise alters a core of ~400 phosphosites on ~200 proteins, inclusive of canonical exercise signaling pathways such as AMP-activated protein kinase (AMPK), $Ca^{2+}$/calmodulin-dependent protein kinases (CaMKs), mitogen-activated protein kinases (MAPKs), the mammalian target of rapamycin (mTOR), and protein kinase A (PKA).[31] Similarly, acute exercise activates transcriptional programs in a temporal manner, which are driven by multiple

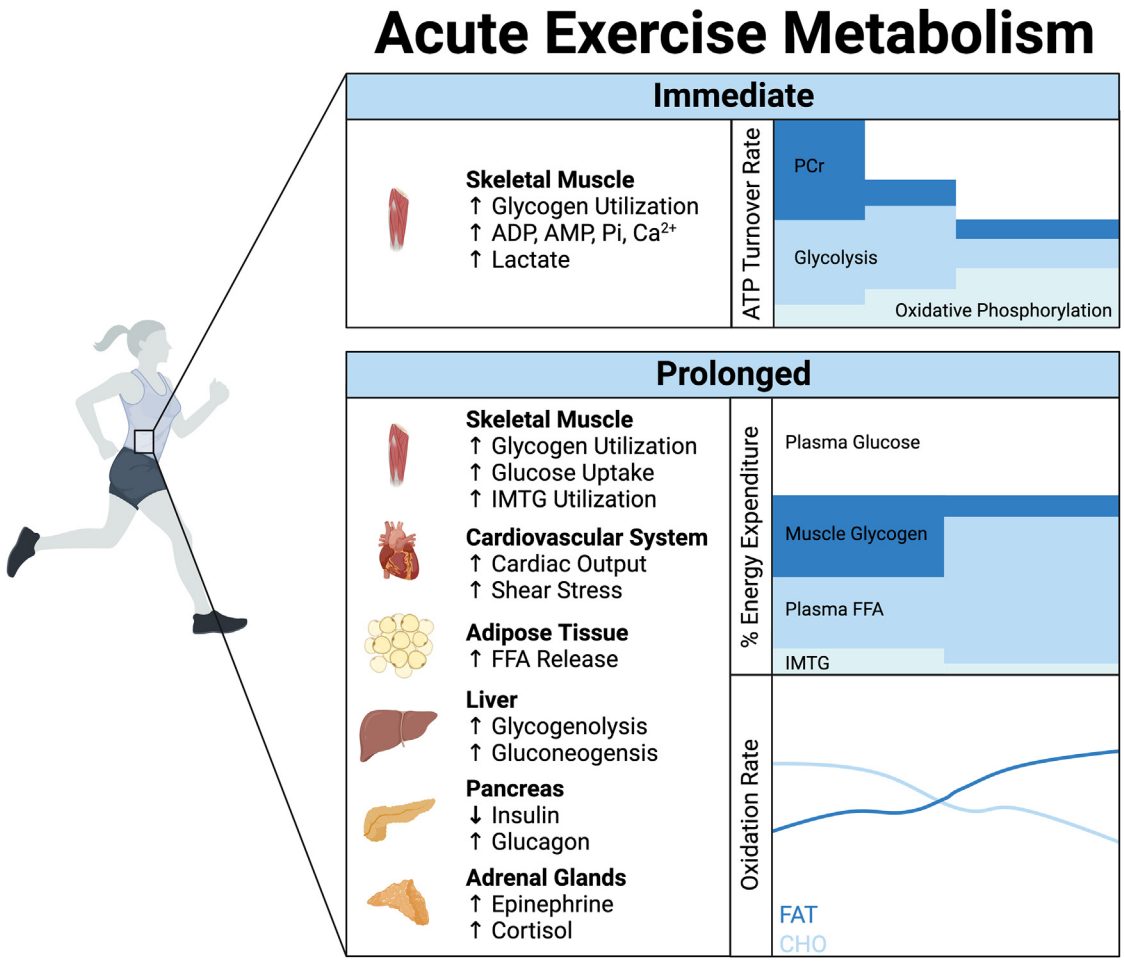


**Figure 2. Multi-tissue coordination of acute exercise metabolism**

During the immediate onset of exercise (0–30 s at >100% $\dot{W}_{max}$), energy provision is muscle-centric and involves the rapid utilization of skeletal muscle glycogen stores, the production of allosteric regulators such as ADP, AMP, Pi, and $Ca^{2+}$ as well as an increased production of lactate. As such, the ATP production is predominantly supplied by PCr hydrolysis and glycolysis at the onset (0–6 s); however, as exercise duration continues (15–30 s), the contribution of oxidative phosphorylation begins to increase. During prolonged exercise (0–240 min) at submaximal intensities (<100% $\dot{W}_{max}$), energy provision involves the coordination of multiple tissues. During the first half of the exercise bout (0–120 min), energy provision is maintained via the utilization of plasma glucose, plasma free fatty acids (FFAs), and intramuscular glycogen and intramuscular triglyceride (IMTG) stores. However, as the exercise bout continues (120–240 min), a shift in substrate oxidation from carbohydrate to fat oxidation is observed, which is a result of an increased utilization of plasma FFA. Representation of ATP turnover rate adapted with permission from the American Physiological Society.[8] Representation of energy expenditure and oxidation rate adapted with permission from the Physiological Society.[16]

transcription factors, as well as transcriptional coactivators and corepressors.[32–35] A particular emphasis has been placed on the role of the peroxisome proliferator-activated receptor-γ coactivator 1-alpha (PGC-1α) as transcriptional coactivator and the consequent recruitment and co-regulation of transcription factors.[36–42] Indeed, PGC-1α forms a central node for exercise-stimulated signaling to converge upon, whereby signals from AMPK, CaMKs, and MAPKs can be integrated to coordinate transcriptional regulation in various tissues.[43–46] Although a core of canonical signal transducers is activated in response to exercise (AMPK, mTOR, and PGC-1α), many features of adaptation remain even in their absence.[47,48] Furthermore, the post-translational and transcriptional responses to acute exercise are modality and tissue specific.[31,33,49] Therefore, how these signals mediate chronic adaptations across multiple tissues warrants further exploration.

## THE ROLE OF EXERKINES IN INTER-ORGAN SIGNALING

The idea that skeletal muscle-derived humoral factors are released during exercise was first postulated by Goldstein,[50] and more recently, the term exerkine has been widely utilized to cover a broad range of exercise-induced signaling molecules.[51] An exerkine may be defined as a signaling moiety that is released in response to an acute exercise bout or chronic exercise training, which exert effects on target tissues via endocrine, paracrine, and autocrine pathways.[51] The term exerkine covers a range of signaling moieties including lipids and metabolites, proteins (cytokines), and peptides, as well as, nucleic acids (microRNA, mRNA, and mitochondrial DNA [mtDNA]), which are often packaged and released in the form of extracellular vesicles (EVs).[51] Although initial investigations focused upon skeletal muscle-derived factors (myokines), the release

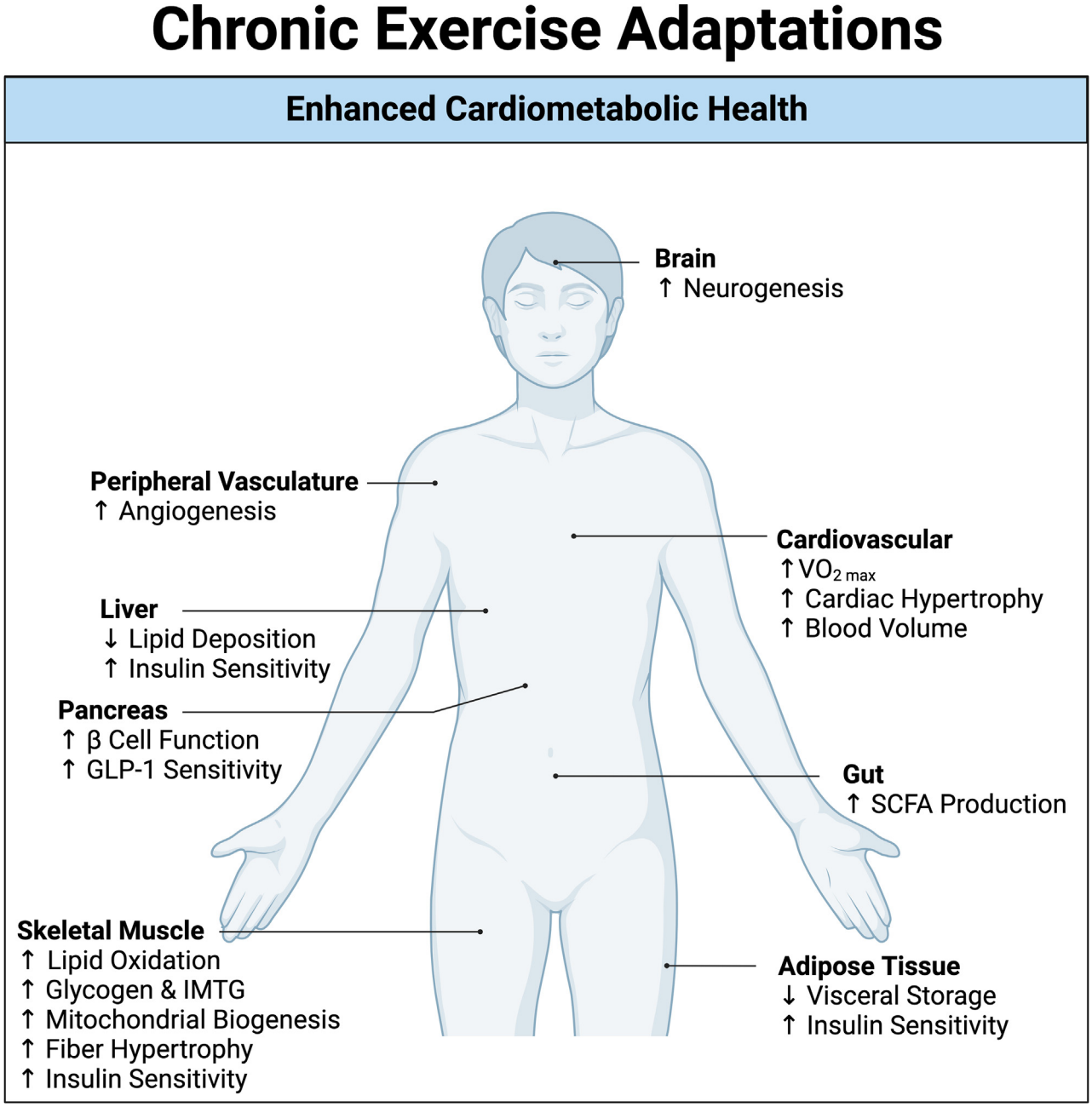


**Figure 3. Chronic exercise adaptations**

Chronic exercise is associated with a plethora of benefits throughout the whole body. Within the cardiovascular system, chronic exercise results in an increase in maximal oxygen uptake ($\dot{V}O_{2max}$), cardiac hypertrophy, and an increase in blood volume. This is associated with the enhancement of angiogenesis within the peripheral vasculature. Adaptations within skeletal muscle include an increased capacity to oxidize lipids and storage of substrates such as glycogen and intramuscular triglycerides (IMTGs), as well as mitochondrial biogenesis and muscle fiber hypertrophy. There is also a reduction in the storage of adipose tissue in visceral regions and reduction in lipid deposition within the liver. Such adaptations are associated with enhanced insulin sensitivity in multiple tissues including skeletal muscle, adipose tissue, and the liver. Furthermore, exercise is associated with an enhanced pancreatic β cell function and sensitivity to glucagon-like peptide 1 (GLP-1). Finally, chronic exercise is also associated with an enhanced production of short-chain fatty acids (SCFAs) from the gut and an enhanced neurogenesis within the brain. Ultimately, these adaptations converge to enhance cardiometabolic health.

and uptake of exerkines are now appreciated to entail multiple organs including the liver, brain, heart, pancreas, gut, and adipose tissue.[51]

Of the bona fide exerkines, the cytokine interleukin-6 (IL-6) has been the most extensively characterized. IL-6 is released from immune cells and skeletal muscle myofibers, and circulating concentrations have been observed to increase in response to endurance and resistance exercise.[52,53] IL-6 also exerts metabolic effects on peripheral tissues, including increasing adipose tissue lipolysis[54] and skeletal muscle glucose uptake[55] at rest,

while also influencing glucose metabolism during exercise.[56] In addition, IL-6-dependent reductions in visceral adipose tissue have been observed following HIIT in individuals with obesity, suggesting IL-6 influences exercise adaptation.[57,58] However, the exercise-induced improvements in $\dot{V}O_{2peak}$ were unaffected by IL-6 blockade via the IL-6 receptor antagonist, tocilizumab.[57]

Recent efforts to characterize the metabolic effects of acute exercise in both rodents[59,60] and humans[61–65] have focused upon the utilization of "omics" technologies to capture a wider range of exercise-responsive factors. For example, a multi-omics investigation utilized lipidomics, metabolomics, proteomics, transcriptomics, and epigenomics to profile the exercise-induced alterations in blood-derived plasma and peripheral blood mononuclear cells.[61] Acute exercise-induced alterations in 57% (>9,000) of the total analytes measured inclusive of inflammatory cytokines, FFAs, acylcarnitines, amino acids, and ketone bodies.[61] Therefore, it is tempting to propose that such alterations provide the basis for the signals that mediate the long-term positive benefits of exercise. However, although such data highlight the pronounced metabolic changes that are associated with an acute bout of exercise, further investigations are warranted to validate the role of individual exerkines in mediating exercise adaptations. For example, further validation, including confirming an increase in circulating concentrations during or following exercise, identifying the tissue and cell type of origin and respective target tissue, and interrogating the mechanism of action, remains a future challenge for the field. A more detailed overview of individual exerkines is beyond the scope of this review and can be found elsewhere.[51,66,67]

## CHRONIC EXERCISE ADAPTATIONS

Regular exercise training affects nearly all cells and organs in the body (Figure 3). The cumulative effects of each exercise bout increase health and performance outcomes in a tissue-specific manner. Thus, the mechanisms by which exercise training affects the cardiovascular system, skeletal muscle, adipose tissue, liver, pancreas, gut, and brain will be individually discussed in the following sections. Special consideration is also given to the role of exercise training as a countermeasure against several non-communicable diseases, including cardiovascular, metabolic, and cognitive diseases.

## CARDIORESPIRATORY FITNESS AND FUNCTION

A key adaptive endpoint associated with regular endurance exercise training is an increase in $\dot{V}O_{2max}$.[68] Increases are observed following resistance exercise; however, this is predominantly observed in individuals with low baseline fitness levels.[69] The exercise-induced adaptations that facilitate an increase in $\dot{V}O_{2max}$ are found primarily within the cardiovascular system, including increased cardiac output, red blood cell volume, and hemoglobin mass.[70] However, adaptations with the working musculature including an increase in capillary density and mitochondrial function also contribute to enhance $O_2$ extraction.[71] Therefore, increases in $\dot{V}O_{2max}$ are mediated by the enhancement in the capacity for $O_2$ delivery and extraction. The exercise-induced increases in $\dot{V}O_{2max}$ are, however, heterogeneous,[72,73] and both the baseline and trainability of $\dot{V}O_{2max}$ are ~50% dependent upon genetic traits.[74,75] In elite athletes such as cross-country skiers, values of ~90 $mL \cdot min^{-1} \cdot kg^{-1}$ are often reported and are facilitated by a high baseline $\dot{V}O_{2max}$ and a high degree of trainability.[76] Therefore, the factors that limit $\dot{V}O_{2max}$ are likely to vary between individuals.

Following long-term exercise training, the heart undergoes substantial remodeling and enlargement, an adaptation often referred to as the "athlete's heart."[77] Cross-sectional data indicate that elite athletes display cardiac hypertrophy, as well as greater measures of right ventricular systolic function and left and right ventricular diastolic function.[78–80] Extreme cases of enlargement consistent with those observed in hypertrophic cardiac myopathy have been observed in endurance athletes such as rowers, cyclists, and cross-country skiers.[81,82] Yet in previously untrained individuals, the exercise-induced increases in left ventricular mass often fall within normal ranges.[83,84] Cardiac remodeling following exercise training is supported by longitudinal assessments (2–12 months), whereby increases in left ventricular mass have been observed in previously sedentary,[83,85] obese,[86] and athletic populations.[87] For example, endurance training (6 months) led to eccentric cardiac hypertrophy, resulting from a simultaneous increase in left ventricular mass and end diastolic volume.[83] Conversely, resistance exercise was associated with a pattern of concentric hypertrophy resulting from an increase in ventricular mass but not volume.[87] However, upon direct comparison to endurance exercise, no such pattern was observed following resistance training.[83] Consequently, both endurance and resistance exercise result in a similar pattern of cardiac hypertrophy, although the effects are more pronounced following endurance exercise.[88] Alongside structural changes, functional alterations are also apparent. For example, endurance-trained individuals display a continuous rise in stroke volume during incremental exercise, likely a result of the enhanced diastolic function that is observed in athletic populations.[80,89] Moreover, in endurance-trained athletes, a 3-month intervention resulted in an increase in left and right ventricular diastolic function.[87] Nevertheless, minimal functional adaptations have been reported in previously sedentary individuals following 6- to 12-month exercise interventions.[83,85] Therefore, although cardiac hypertrophy is apparent regardless of prior training status, functional adaptations may require longer interventions and may also be influenced by genetic factors.[4] The mechanisms associated with cardiac remodeling have been elucidated utilizing preclinical models. As such, the exercise-induced remodeling of the heart involves alterations to the cardiac transcriptome[49,90] and proteome.[91] Physiological cardiac hypertrophy is associated with the activation of the phosphoinositide 3-kinase (PI3K)-Akt pathway, which is activated by hypertrophic factors such as insulin-like growth factor 1 (IGF1).[92,93] Cardiac remodeling is also associated with metabolic adaptations, and across multiple preclinical models, exercise training results in the stimulation of cardiac mitochondrial biogenesis.[91,94,95]

Chronic exercise training also results in a remodeling of the peripheral vasculature and improvements in vascular endothelial function.[96] During acute exercise, there is a substantial increase in blood flow to the working musculature and, as a result, alterations in hemodynamic forces such as shear stress and transmural pressure, which collectively provide the stimuli for vascular remodeling.[97] For example, exercise interventions

increase the size of conduit and resistance arteries.[98,99] Furthermore, such effects are localized to working musculature, as evidenced by an increase in femoral artery diameter only in the exercised leg during one-legged exercise,[99] and are dependent upon the increase in shear stress.[97] Exercise is also a potent stimulator of angiogenesis, with increased capillary growth observed in skeletal muscle[100–105] and adipose tissue[103,106,107] following training. Skeletal muscle angiogenesis occurs following endurance[101,102,104,105,108] or resistance exercise,[109,110] with increases observed following training at moderate[101,102,104,105] or high intensities.[100,109,111–113] Furthermore, such effects are apparent in both type I and II skeletal muscle fibers[111,112] and mediated in part via the secretion of vasodilators such as nitric oxide (NO) and pro-angiogenic factors, such as vascular endothelial growth factor (VEGF). During exercise, the increased blood flow and shear stress result in an increase in several vasodilators, including NO, which regulates the expression of VEGF.[114] Following acute exercise, VEGF accumulates within the muscle interstitium[115] and exerts paracrine effects on local endothelial cells to increase capillarization.[100] Overall, an increase in capillary density allows for a greater perfusion of skeletal muscle during exercise and a more homogeneous distribution of the training-induced increase in cardiac output.[116,117] This results in a greater surface area for diffusion and a greater arteriovenous $O_2$ difference across the working musculature.[118,119]

Chronic exercise training is also associated with substantial hematological adaptations, including an increase in plasma and red blood volume.[70,120] Observational studies have reported blood volume is 20%–25% higher in trained individuals and 40% higher in elite athletes as compared with untrained individuals.[121] During the initial phase of training (<14 days), the observed hypovolemia is a result of an increase in plasma volume, which can be observed as early as 24–72 h following an acute exercise bout.[122–124] As training progresses, there is an increase in red blood cell volume until a plateau is reached and both the plasma and red blood cell volume are 10% above the pretraining values.[125] The expansion of red blood cell volume results in an increase in hemoglobin mass, which in turn facilitates a greater $O_2$ carrying capacity and, therefore, $O_2$ delivery.[70] Following the expansion in blood volume, hematocrit levels return to pretraining levels.[125] The mechanisms that facilitate the erythropoietic effects of exercise are incompletely resolved and likely involve multiple processes including hematological, hemodynamic, and hormonal factors.[126] The relative importance of hematological changes to overall training adaptations has been demonstrated across numerous studies.[127–129] For example, following an acute blood volume expansion in untrained individuals, diastolic filling rate, cardiac output, and stroke volume were all increased, resulting in an increase in $\dot{V}O_{2max}$.[128] Correspondingly, both $\dot{V}O_{2max}$ and maximal cardiac output were restored to pretraining values when the training-induced increases in blood volume were reduced to that of pretraining values via the use of phlebotomy.[70,129]

## SKELETAL MUSCLE FORM AND FUNCTION

Skeletal muscle adaptations to exercise training involve a coordinated set of changes in form and function, which contribute to improved fatigue resistance during subsequent exercise sessions.[130] For example, endurance exercise training results in an enhanced capacity for aerobic energy provision in skeletal muscle and a shift toward increased lipid oxidation—and decreased carbohydrate oxidation—at the same absolute exercise intensity as the pretraining state.[131–133] However, exercise training also increases the maximal capacity for carbohydrate oxidation,[134] which primarily facilitates a higher power output during intense endurance exercise, whereas the increased capacity for lipid oxidation facilitates the ability to sustain power output during prolonged submaximal exercise. These enhancements are underpinned at a cellular level by increased abundance of proteins involved in $O_2$ delivery to and extraction from skeletal muscle,[135] antioxidant capacity,[136] glucose transport and glycogen synthesis,[137] glycolytic metabolism,[138] lactate transport and pH regulation,[139] mobilization, transport and oxidation of fatty acids,[140,141] the TCA cycle,[142] and mitochondrial ATP production.[143] The increased skeletal muscle content of proteins that facilitate the sarcolemmal transport of glucose[144] and fatty acids[140] facilitates a higher maximal capacity to utilize glucose[145] and FFA[146] from the circulation during exercise. Such changes also contribute to an enhanced capacity to store higher amounts of intramuscular glycogen[147] and triglyceride[148] in the trained state.

The exercise-training-induced increase in skeletal muscle oxidative capacity is largely due to an increase in mitochondrial biogenesis. As such, mitochondrial biogenesis is a well-established response to endurance exercise in the form of MICT,[149] HIIT/SIT,[150–152] and in some cases, resistance exercise.[153] This is reflected by an increased volume density, respiratory capacity,[133,154,155] and a remodeling of the mitochondrial proteome, acetylome, and lipidome,[156–159] as well as a higher maximal activity of the enzyme complexes PDH[160] and carnitine palmitoyltransferase I (CPTI),[161] which are regarded as rate-determining for carbohydrate and lipid oxidation respectively. As opposed to being considered individual organelles, mitochondria are now described as a dynamic reticulum.[162,163] Mitochondrial fission-fusion dynamics,[164] the mitochondrial unfolded protein response, and mitochondrial quality control through mitophagy (the specific degradation and recycling of dysfunctional mitochondria through the autophagosome-lysosomal system)[165] are increasingly studied. For example, exercise training increases the ratio of fusion-to-fission proteins, promoting the fusion of mitochondria to form a reticular network.[165] Autophagic processes and lysosome plasticity are also evident[166–168] and may be required for the adaptation to endurance exercise training.[169–171] In addition, several anabolic roles for the lysosome have been described in skeletal muscle, including as a site of mTOR complex 1 (mTORC1) activation and, therefore, the activation of protein synthesis.[167] Lastly, under resting conditions, the capacity for autophagy and mitophagy regulation is increased in human skeletal muscle by exercise training.[172–174] Therefore, the current model suggests that acute exercise induces turnover of the mitochondrial pool within skeletal muscle in a coordinated process of removal of dysfunctional mitochondria, in collaboration with the activation of biogenesis.[164] Although mitochondrial protein synthesis is increased during chronic exercise training,[159,175] the precise role of mitophagy in mediating mitochondrial turnover following training remains

unclear and is likely time course dependent.[172,173,176–179] Recent advancements in the assessment of post-translational modifications such as phosphorylation[31] and ubiquitination[180] will provide useful tools for the further examination of skeletal muscle proteostasis following acute and chronic exercise.

Resistance exercise training induces morphological and neurological adaptations within skeletal muscle including an enhanced force-generating capacity, a greater capacity for non-oxidative energy provision, and an increase in skeletal muscle size resulting from an increase in muscle fiber cross-sectional area.[181] Myofibrillar protein accretion is proposed as the primary mechanism by which the cross-sectional area of individual muscle fibers increase in size.[182,183] Consequently, the regulation of muscle protein synthesis,[184] and breakdown,[185] is a central focus for understanding the mechanistic basis of adaptation to resistance exercise training.[186,187] Rates of cellular protein synthesis depend on translational *efficiency* (protein synthesis per unit amount of mRNA) and on translational *capacity* (i.e., ribosomal content per unit of tissue).[188] Much of the focus on translational capacity has been on ribosomal biogenesis, which in this context refers to the *de novo* synthesis of ribosomes, a process that involves the transcription and processing of ribosomal RNA (rRNA) and the assembly of ribosomal proteins, as reviewed elsewhere.[188,189] Several lines of evidence point to increased translational capacity as a result of exercise-training-induced ribosomal biogenesis.[159,188,190] Neural adaptations, including improvements in motor unit activation, firing frequency, and synchrony of high threshold motor units are also important for the enhanced force-generating capacity of skeletal muscle.[191,192] Neural adaptations occur rapidly and tend to precede hypertrophic adaptations,[193] which occur at a slower rate since the rate of muscle protein synthesis must exceed breakdown for a period of time before a measurable accretion of contractile protein occurs.[194]

Although adaptations tend to be specific to a given exercise modality, as the volume of exercise training is increased, the contribution of various adaptations can overlap between different types of exercise. For example, endurance exercise training can produce modest hypertrophy of muscle fibers,[195] and neural adaptations in terms of muscle recruitment are evident in endurance athletes,[196,197] whereas resistance exercise training can increase mitochondrial protein content and function[198–201] and $\dot{V}O_{2max}$,[69] such that an improvement in fatigue resistance is often observed.[181] Similarly, short sprint training can produce a broad range of adaptive responses, including some that resemble the traditional endurance or strength/power phenotypes.[202] Sprint training is mainly associated with an enhanced capacity for non-oxidative energy provision, but adaptive changes are highly dependent on the duration of sprint bouts, recovery between bouts, and total volume within sessions,[202] such that sprint training and SIT are also a potent stimulus to increase the skeletal muscle content of membrane proteins involved in lactate and ion regulation.[203–205] Although increased muscle fiber cross-sectional area is sometimes observed after sprint training,[202] marked skeletal muscle hypertrophy is not generally observed.[206] In fact, SIT has a remarkable capacity to produce an endurance phenotype in skeletal muscle,[207–212] and improve endurance performance.[151]

Acute and chronic exercise improves metabolic health via the enhancement of peripheral insulin sensitivity across multiple populations, including sedentary,[213–215] obese,[216–219] and type 2 diabetes.[220–224] Acute exercise stimulates an increase in insulin-independent skeletal muscle glucose uptake[225] while also sensitizing skeletal muscle to insulin for up to 48 h following the exercise bout.[214] The mechanisms underlying the promotion of post-exercise insulin sensitivity involve the coordinated enhancement of glycogen synthase activity, signaling via TBC1 domain family member 4 (TBC1D4), insulin-responsive microvascular perfusion, as well as the intracellular redistribution of glucose transporter type 4 (GLUT4).[215,226] The increased microvascular perfusion in response to insulin was observed in an NO-dependent manner and serves to increase skeletal muscle glucose delivery, whereas the enhanced molecular signaling and redistribution of GLUT4 primes the muscle for increased glucose uptake.[215,226] Conversely, chronic alterations in insulin sensitivity are associated with a remodeling of the skeletal muscle proteome and microvasculature, alongside the alterations in substrate metabolism described above. Notably, chronic exercise increases the abundance of key proteins involved in glucose handling such as GLUT4 and hexokinase II (HKII).[227,228] Although the acute enhancement in molecular signaling is not fiber-type specific,[229] chronic adaptations are particularly evident in oxidative type I fibers.[230] Although this enhances the capacity for glucose uptake, substrate delivery is improved via the exercise-associated stimulation of skeletal muscle angiogenesis.[104] The improvements in peripheral insulin sensitivity are rapid and have been observed following short-term (<2 weeks) interventions in individuals with type 2 diabetes,[221,231] although they are equally rapidly reversed following detraining.[232]

## ADIPOSE TISSUE METABOLISM

A key adaptation often associated with regular physical activity is weight loss. Overall, physical activity interventions result in small but clinically relevant reductions in body mass[233] which is associated with a loss of fat mass from multiple depots including visceral adipose tissue.[234–236] Such reductions are associated with the energy deficit created via increasing physical activity and represent no greater changes than creating an energy deficit via reducing energy intake.[237,238] Although the ability of exercise to induce weight loss in the absence of dietary manipulation is minimal, exercise may confer additional metabolic benefits aside from weight loss such as a protection in the loss of fat-free mass when compared with caloric restriction alone.[236,239] In addition, regular exercise training reduces the amount of lipids in circulation,[235] as well as the ectopic deposition of lipids in liver,[234,235] heart,[240,241] and pancreas,[242] even in cases where no overall reductions in fat mass are observed.[235] Exercise training also reduces intramuscular lipid deposition in metabolically impaired individuals[243]; however, in highly trained individuals, exercise increases intramuscular lipid stores, a phenomenon referred to as the athlete's paradox.[244] This is associated with increased lipid droplets in the intermyofibrillar region of oxidative type I fibers,[245] which provide a fuel source during exercise,[246] as well as, an increase in the levels of adipose triglyceride lipase (ATGL) and perilipin-5 (PLIN5), which enhance the capacity for lipid droplet turnover in trained skeletal muscle.[245]

Following exercise training, alterations in adipocyte morphology have been reported, which may be related to either

a reduction in adipocyte size or number. A greater proportion of smaller adipocytes is considered to result in improved adipose tissue metabolic health as these adipocytes exhibit a lower pro-inflammatory macrophage infiltration[247] and enhanced insulin sensitivity.[248] Generally, studies employing short-term exercise interventions (2–12 weeks) have failed to identify alterations in adipocyte morphology.[106,249] However, studies employing longer interventions (12–24 weeks) consisting of MICT and HIIT have identified a shift toward a greater proportion of smaller adipocytes.[107,250–252] In addition, reductions in adipocyte size have been observed when participants were required to maintain weight throughout the intervention, highlighting the ability of exercise to improve metabolic health in the absence of weight loss.[107] Although the adipocyte number is reduced in rodents following exercise training,[253,254] the data in humans do not corroborate this finding.[106,250,255] Such measurements in humans, however, are limited by the fact that they are generally taken from one site (abdominal subcutaneous), and depot-specific effects may be apparent. For example, white adipose tissue is a heterogeneous tissue comprising of multiple cell types, including subpopulations of adipocytes that display distinct sensitivities to insulin.[256,257] In rodents, exercise training results in an increase in insulin-sensitive populations of adipocytes.[258] Therefore, single-nucleus RNA sequencing (snRNA-seq)[259] may provide a powerful tool in future efforts to understand both the acute and chronic responses to exercise in human adipose tissue.

Following chronic endurance training, an increase in fat oxidation during submaximal exercise is consistently observed across multiple populations.[146,260–262] However, this likely reflects alterations in skeletal muscle fuel utilization as opposed to alterations in adipose tissue lipolysis. Basal adipocyte lipolysis assessed *ex vivo* is generally unchanged following exercise interventions,[250,263–266] whereas β-adrenergic-stimulated lipolysis is increased[250,251,264,267] or unchanged.[263,265] However, the assessment of maximal lipolytic rate in response to supraphysiological doses of catecholamines may not reflect physiological adaptations. Following exercise training, adipose tissue-derived fatty acid availability is not increased during exercise[262,268] or following catecholamine stimulation.[269,270] Furthermore, exercise training results in a reduced catecholamine response during exercise at the same relative intensity, which may influence lipolytic rate.[261] Therefore, the increase in fat oxidation following training is a result of an increased utilization of IMTG stores and not adipose tissue lipolysis.[261,262] Adipose tissue lipolysis is in part regulated by insulin, and adipose tissue insulin sensitivity is improved following exercise training when assessed via the insulin-mediated suppression of lipolysis[271–273] or via indirect measures such as the adipose tissue insulin resistance index (ADIPO-IR).[274] Furthermore, insulin-stimulated glucose uptake in adipocytes is increased following exercise training.[106,275] This effect is dependent upon exercise intensity with SIT stimulating an improvement in visceral adipose tissue glucose uptake compared with MICT.[106] Improvements in adipose tissue insulin sensitivity may in part be mediated by increases in GLUT4 protein levels. In individuals with type 2 diabetes, 4 weeks MICT resulted in an increase in adipose tissue GLUT4 protein abundance[276]; however, in healthy individuals, GLUT4 protein content was unchanged following 10 days of exercise.[277] Therefore, either longer-term exercise is needed to increase adipose tissue GLUT4 protein abundance or exercise only facilitates an increase when basal levels are reduced. The metabolic benefits of exercise on adipose tissue, such as improved insulin sensitivity are often greater when a degree of weight loss is apparent.[274] In many of the studies highlighted above, the post-training metabolic assessment was performed 24–96 h following the final training bout. Therefore, some of the adaptations described above may be residual effects from the final training bout as both lipid oxidation and insulin sensitivity remain elevated following acute exercise.[214,278]

In rodents, exercise training increases the oxidative capacity of adipose tissue[279]; however, the data in humans are less clear. For example, 10 days of MICT and HIIT in previously untrained males did not increase adipose tissue palmitate oxidation.[280] Furthermore, adipose tissue mitochondrial function as assessed by high-resolution respirometry is unaltered following exercise interventions in previously sedentary individuals,[281] individuals with obesity[282–285] or at risk of type 2 diabetes.[255] When normalized to a marker of mitochondrial content such as mtDNA or citrate synthase (CS) activity, intrinsic mitochondrial function is increased following exercise training in endurance trained or individuals with obesity in some,[283,285] but not all studies.[282,284] Alterations in oxidative capacity may be underpinned by changes in mitochondrial volume. However, when assessed via electron microscopy, mitochondrial volume remained unchanged following 10 days of MICT/HIIT in previously sedentary males.[280] Similarly, multiple markers of mitochondrial content (mtDNA or oxidative phosphorylation protein content) are unaltered in individuals with obesity following an exercise intervention,[249,283–285] although one study did report an increase in the expression succinate dehydrogenase complex subunit A (SDHA) following 10 weeks of MICT/HIIT in the subcutaneous adipose tissue of healthy individuals.[286] The conflicting evidence likely stems from multitude of factors including training modality, intensity, populations studied, and methodological differences, making the influence of exercise on adipose tissue difficult to discern. However, a notable similarity between the studies described above is that they are relatively short term (<12 weeks).[249,255,282–285] Following a long-term (6 months) endurance exercise intervention, genes related to oxidative phosphorylation are increased,[287] and cross-sectional data indicate that lifelong training increases adipose tissue mitochondrial function as a result of increased mitochondrial content.[288] Therefore, long-term interventions may be required to confer adaptations within adipose tissue mitochondria.

Exercise training increases the number of white adipocytes that phenocopy brown adipocytes in rodents.[279] This process has been referred to as "beiging," and these adipocytes display a multilocular phenotype and an increased expression of browning genes such as uncoupling protein 1 (*UCP1*). Despite the observations in rodents, evidence for the beiging of white adipose tissue in humans is limited. Although one study observed that *UCP1* gene expression trended to increase following 12 weeks of combined endurance and resistance exercise,[289] the majority of studies have not corroborated this finding.[249,280,281,286,287,290] In some cases, UCP1 was undetectable at both the gene and protein level in human white adipose tissue,[249,290] and there was no evidence of multilocular adipocytes following training.[290]

Brown adipose tissue predominantly resides within the supraclavicular region, and a detectable level of this thermogenic fat depot is associated with a reduced prevalence of cardiometabolic disease.[291] However, in endurance-trained athletes, brown adipose tissue activity is lower when compared with respective sedentary counterparts.[292] Furthermore, following a 24-week intervention consisting of combined endurance and resistance training, no change in brown adipose tissue volume or activity was observed.[293] Finally, many of the exerkines associated with adipose tissue browning or brown adipose tissue metabolism remain unchanged following exercise training.[294] Therefore, exercise training seems to have minimal effects on brown adipose tissue, although the current literature is limited in breadth.

## HEPATIC METABOLISM

The liver represents a key site of dysregulation in the development of insulin resistance and type 2 diabetes[295]; therefore, investigations examining the effects of exercise within the liver have focused upon the regulation of glycemia and insulin sensitivity. Following endurance exercise training, the rate of appearance of glucose during exercise is reduced at the same relative intensity, suggesting a reduced rate of hepatic glycogenolysis.[261] Furthermore, basal endogenous glucose production remains unchanged in individuals with obesity[272,296] or impaired glucose tolerance.[297,298] Conversely, in individuals with type 2 diabetes or impaired fasting glucose, basal endogenous glucose production is generally reduced,[216,221,222,299] albeit not in every case.[300] Therefore, for exercise to exert beneficial effects, a degree of impairment in basal endogenous glucose production may need to be present prior to the initiation of training. Endogenous glucose production can also be suppressed by insulin, and following exercise interventions consisting predominantly of endurance exercise, hepatic insulin sensitivity was enhanced in healthy,[222] individuals with obesity,[216,272,296,298] and type 2 diabetes.[221,222,300] However, exercise failed to improve hepatic insulin sensitivity in individuals with both impaired fasting glucose and glucose intolerance,[216] as well as during acute FFA-induced insulin resistance.[298] Therefore, the degree of insulin resistance present prior to the onset of training may be an important determinant in the ability of exercise to improve hepatic insulin sensitivity.[216] Furthermore, following interventions that do not result in weight loss, improvements in hepatic insulin sensitivity were not apparent.[297,299]

Under conditions of excess energy consumption, an increase in the ectopic deposition of lipids within the liver may occur, leading to metabolic dysfunction-associated steatotic liver disease (MASLD).[301] The gold standard in the assessment of hepatic steatosis involves an invasive liver biopsy, and therefore, the deposition of intrahepatic lipids (IHLs) is commonly assessed non-invasively utilizing proton magnetic resonance spectroscopy ($^1$H-MRS). When exercise is administered in the absence of dietary manipulation, exercise consistently reduces IHL across multiple populations including healthy[302] and obese,[234,235,303–305] as well as type 2 diabetes[306] and MASLD.[307–315] Reductions in IHL have predominantly been observed following interventions consisting of MICT[234,235,302–305,307,308,310,312,314] but are also apparent following HIIT,[306,310] SIT,[313] resistance training,[303,307,309] and combined training.[311,315] However, multiple short-term interventions (7 days) have failed to decrease IHL.[316,317] Although exercise results in a reduction in IHL in the absence of weight loss, the effects are more potent when weight loss occurs.[318] Therefore, although exercise represents a useful therapeutic in the reduction of IHL and the prevention of MASLD, a combination of exercise and dietary manipulation would yield greater benefits.

## PANCREATIC β CELL FUNCTION

Research into the effects of exercise on the pancreas has mainly focused upon adaptations within the insulin producing β cells. Exercise training alters the function of the β cell; however, these adaptations are context dependent. For example, in healthy individuals, endurance training reduces insulin secretion in response to glucose or secretagogues such as arginine,[319–322] whereas in individuals with type 2 diabetes, glucose-stimulated insulin secretion is increased.[323,324] In healthy individuals, the reduction in insulin secretion is likely a result of increased insulin sensitivity,[324] whereas in individuals with type 2 diabetes, the resulting increase in insulin secretion is possibly related to a reduction in circulating glucose and lipids, which contribute to β cell overload[324] and diminish β cell function. Importantly, the degree of residual β cell function may determine the effectiveness of an exercise intervention,[323,325] with a pretraining impairment in insulin secretion predicting an impaired response to endurance exercise training.[325] When assessing β cell function, glucose-stimulated insulin secretion is commonly measured; however, changes in insulin sensitivity alongside this axis are important to consider. Such an assessment is often referred to as the disposition index (DI),[326] which has been utilized to assess the effects of exercise on β cell function.

β cell function is improved in individuals with overweight/obesity,[327–330] and pre- or type 2 diabetes following an exercise intervention.[217,324,325,331–333] Such improvements are apparent regardless of whether the intervention consists of endurance[217,324,325,329–333] or resistance exercise.[328] Improvements in β cell function are greater when endurance and resistance training are combined; however, this is likely related to the increased training volume.[327] Short duration interventions (<4 weeks) are not as effective in improving β cell function,[334] further supporting the notion that training volume is an important determinant in improving β cell function.

Alongside the observed reduction in β cell function in individuals with type 2 diabetes, β cell mass is also reduced.[335,336] Therefore, interventions to increase the mass and improve the morphology of the islet may provide clinical benefits. Due to the difficulty in sampling from the pancreas, research efforts have mainly been conducted within preclinical models. In Zucker diabetic fatty (ZDF) rats and pancreatectomized rats, exercise interventions resulted in higher β cell proliferation and reduced β cell apoptosis when compared with respective controls.[337,338] Such effects are possibly mediated via the induction of the insulin/IGF1 signaling cascade.[337] Under high-fat diet conditions, chronic exercise attenuates the loss of β cell mass and maintains islet morphology via a reduction in fibrosis,[339] possibly via reductions in pro-inflammatory markers such as IL-1β and tumor necrosis factor alpha (TNF-α).[339] Such effects on β cell function may be driven via indirect effects, as exercise results

in the removal of glucose and FFA from circulation, which may drive β cell dysfunction under conditions of excess.

Pancreatic β cells secrete insulin in response to incretins like glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). However, during the development of type 2 diabetes, this response becomes blunted.[340] In individuals with obesity, an intervention consisting of MICT improved β cell sensitivity to GLP-1, although whether such effects are independent of weight loss remains unknown.[341] GLP-1 receptor agonists have been utilized as pharmacological approaches in the treatment of obesity and type 2 diabetes. Therefore, an exercise-induced enhancement of β cell GLP-1 sensitivity may improve the efficacy of such therapeutics. For example, a combination of exercise and treatment with the GLP-1 receptor agonist, liraglutide, enhanced β cell function, whereas exercise or liraglutide treatment alone did not.[342] Therefore, the addition of exercise may be complementary to pharmacological treatments of obesity and type 2 diabetes. In addition, although the current pharmacological treatments have been successful to promote weight loss, this often comprises lean mass.[343] The addition of exercise interventions may offer some protection against the loss of lean mass, although this has yet to be studied.

## GUT MICROBIOTA

The intestinal lumen of the gastrointestinal tract plays host to a large number ($10^{13}$) of microbes, collectively referred to as the microbiome. Remarkable diversity is observed within these microbes dependent upon diet, ethnicity, age, sex, and body mass index.[344] An imbalance of the gut microbiota has been linked to intestinal diseases,[345] as well as metabolic diseases such as obesity, type 2 diabetes, and chronic liver diseases.[346,347] Therefore, interventions that increase the diversity of gut microbiome have been postulated to possess a therapeutic benefit.

Athletes display an increase in gut microbial diversity when compared with healthy individuals,[348,349] although this is likely influenced by a multitude of factors including substantial differences in dietary intake and energy expenditure.[348] In rodents, exercise alters the composition of the gut microbiome independent of diet.[350–352] In human intervention studies, the α-diversity, representing a measure of within-sample diversity, was unchanged following short-term (6–8 week) MICT and resistance exercise in athletic, sedentary, and obese individuals.[353–359] Conversely, long-term (6 months) MICT interventions induce modest increases in the α-diversity of the gut microbiota in overweight individuals,[360] whereas in patients with MASLD, a loss of α-diversity from that observed in untrained individuals was prevented.[361]

Exercise may also influence the production of microbial-derived gut metabolites such as short-chain fatty acids (SCFAs). For example, longitudinal studies provide evidence for increased levels of fecal SCFAs acetate, propionate, and butyrate following exercise training.[353] SCFAs are produced due to the intestinal fermentation of carbohydrates and protein[362] and may influence gut and peripheral metabolism in part via G protein-coupled receptors (GPRs).[363] SCFAs increase the secretion of gut-derived satiety hormones GLP-1 and peptide YY (PYY) in a GPR41 and GPR43 dependent manner.[364,365] Furthermore, GPR41 is expressed predominantly in white adipose tissue and to a lesser degree in skeletal muscle and liver, suggesting multiple avenues by which SCFAs could influence peripheral metabolism.[363,366] However, much of data associating exercise and SCFAs are derived from rodent models, and the human data are inconsistent.[367] Furthermore, whether the increases in fecal SCFAs translates to meaningful changes in circulating concentrations post-exercise is currently unclear.

## BRAIN METABOLISM

Engaging in physical activity has been associated with the maintenance of cognitive health including, improved cognition, mood, and memory,[368] whereas physical inactivity is considered a modifiable risk factor for the incidence of neurological diseases such as dementia.[369] Therefore, much of the exercise-associated research has focused upon preventing cognitive decline during aging.

Evidence from rodent models suggests that voluntary wheel running results in the stimulation of hippocampal neurogenesis in both young and aged animals.[370,371] In humans, MICT resulted in an increase in hippocampal volume and offset the age-associated decline observed in those with dementia.[372] More specifically, exercise increased the volume of the anterior hippocampus, a brain region associated with learning and memory.[373] Although many trials display positive effects of exercise on cognitive function across multiple populations,[374] the current data from randomized control trials are inconsistent.[375] Participants with high adherence and achieving an exercise intensity of at least 70% maximum heart rate did, however, improve on the primary outcome assessment of cognition.[376] Therefore, a dose-response relationship has been hypothesized to exist between exercise and cognition, but further trials are warranted to confirm this. Improvements in cognition may be partly mediated by changes in cerebral blood flow. Increases in cerebral blood may be mediated by an increase in angiogenesis, which has been observed across multiple brain regions following an exercise intervention in rodents.[377] In humans, high cardiorespiratory fitness is associated with improved cerebrovascular function; however, intervention studies have reported heterogeneous results and are limited in quantity and quality.[378]

Obesity and type 2 diabetes result in an increased risk of developing neurological diseases such as Alzheimer's disease.[379] Although the central nervous system does not depend on insulin for glucose utilization, insulin receptors are expressed within the brain.[380] Furthermore, insulin resistance has been observed in the human brain[381] and central insulin action has been linked to peripheral insulin sensitivity.[382] The central actions of insulin have been examined via the intranasal administration of insulin and the utilization of functional MRI (fMRI) in concert with measures of cerebral blood flow.[383] For example, 8 weeks of MICT improved brain insulin action in overweight individuals,[384] although the intervention was limited by a lack of an appropriate control group.[384] The neurometabolic effects of exercise have been further studied in preclinical models and suggest that exercise stimulates mitochondrial biogenesis across multiple brain regions.[385,386] Furthermore, exercise ameliorated increases in cerebral reactive oxygen species production and decreased proteostasis, which led to an accumulation of oxidized mitochondrial proteins in diet-induced obese mice.[386]

However, the exercise intervention improved body composition, which may also contribute to the improvements in peripheral metabolism.[386] Further studies are warranted to ascertain the molecular mechanisms accounting for neurometabolic effects of exercise.

## ADAPTATIONS CONVERGE TO IMPROVE CARDIOMETABOLIC HEALTH

Exercise interventions induce metabolic adaptations across multiple tissues, which, when viewed at the whole-body level, converge to improve cardiometabolic health. Although adaptations are often studied at the individual tissue level, adaptations within specific tissues often overlap and interact with other tissues, thereby improving whole-body metabolism. For example, chronic exercise facilitates an increase in whole-body lipid turnover. This is associated with adaptations within skeletal muscle including an increase in the capacity for fat oxidation, the expression of proteins regulating lipolysis,[245,261] and a reduction in insulin desensitizing lipid species such as diacylglycerols and ceramides.[387,388] Furthermore, a greater degree of lipid turnover results in the reduction in the amount of lipids in circulation,[235] as well as the ectopic deposition of lipids within the liver,[234,235] heart,[240,241] and pancreas.[242] Therefore, exercise provides an avenue to reduce the lipotoxicity that is associated with poor metabolic health and insulin resistance.[389–391] As such, exercise interventions often result in improvements in insulin sensitivity within skeletal muscle,[213–224] adipose tissue,[271–273] liver,[221,222,300] and brain.[384] Improvements in insulin sensitivity are mediated in part by adaptations at the individual tissue level including an increase in the abundance of key proteins involved in glucose handling such as GLUT4 within skeletal muscle[227,228] and adipose tissue.[276] However, adaptations within one tissue may provide complementary metabolic adaptations to another tissue. For example, the removal of lipids from circulation may be facilitated by an increased oxidation within skeletal muscle or an enhancement in the insulin-mediated suppression of lipolysis. This may in turn provide a mechanism by which hepatic insulin sensitivity is improved[272] or β cell overload is prevented.[324] Metabolic adaptations are often associated with improvements in oxidative metabolism within individual tissues. As such, mitochondrial biogenesis following exercise training has been reported within skeletal muscle,[149–151,153] the heart,[91,94,95] and multiple brain regions,[385,386] although not as consistently within adipose tissue.[282–285] Tissue oxygenation may also be improved by a broad upregulation of angiogenesis, and as such, increased capillary growth has been observed in skeletal muscle[100–105] adipose tissue,[103,106,107] and brain[385,386] following training. This may in turn provide an alleviation of chronic inflammation, which has been associated with poor cardiometabolic health.[392] The resulting adaptations at the individual tissue level converge to positively effect multiple cardiometabolic risk factors such as blood pressure, cardiorespiratory fitness, insulin resistance, blood lipid profiles, and lipid deposition.[393,394]

## CONCLUDING REMARKS

Overall, both acute and chronic exercise interventions provide beneficial effects on whole-body metabolism; however, the effects are often heterogeneous[4,325] and are dependent upon genetic and environmental factors.[4,395] Thus, exercise prescription and training modalities may vary depending on individual needs, including desired performance outcomes, or alternatively, a particular disease prevention or treatment strategy. Given the widespread benefits of regular exercise training on the cardiometabolic health, further interrogation of this biology and how it can be used to achieve optimal health and performance across diverse populations, as well as in the prevention and treatment of non-communicable diseases, is warranted.

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## DECLARATION OF INTERESTS

J.R.Z. is an Advisory Board member for *Cell* and *Cell Metabolism*.

## INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

## REFERENCES

1. Kyu, H.H., Bachman, V.F., Alexander, L.T., Mumford, J.E., Afshin, A., Estep, K., Veerman, J.L., Delwiche, K., Iannarone, M.L., Moyer, M.L., et al. (2016). Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ *354*, i3857.

2. Zhao, M., Veeranki, S.P., Magnussen, C.G., and Xi, B. (2020). Recommended physical activity and all cause and cause specific mortality in US adults: prospective cohort study. BMJ *370*, m2031.

3. Piercy, K.L., Troiano, R.P., Ballard, R.M., Carlson, S.A., Fulton, J.E., Galuska, D.A., George, S.M., and Olson, R.D. (2018). The physical activity guidelines for Americans. JAMA *320*, 2020–2028.

4. Bouchard, C., An, P., Rice, T., Skinner, J.S., Wilmore, J.H., Gagnon, J., Pérusse, L., Leon, A.S., and Rao, D.C. (1999). Familial aggregation of VO(2max) response to exercise training: results from the Heritage Family Study. J. Appl. Physiol. *87*, 1003–1008.

5. Gabriel, B.M., and Zierath, J.R. (2019). Circadian rhythms and exercise - re-setting the clock in metabolic disease. Nat. Rev. Endocrinol. *15*, 197–206.

6. Granata, C., Jamnick, N.A., and Bishop, D.J. (2018). Principles of exercise prescription, and how they influence exercise-induced changes of transcription factors and other regulators of mitochondrial biogenesis. Sports Med. *48*, 1541–1559.

7. Schoenfeld, B.J., Grgic, J., Ogborn, D., and Krieger, J.W. (2017). Strength and hypertrophy adaptations between low- vs. high-load resistance training: a systematic review and meta-analysis. J. Strength Cond. Res. *31*, 3508–3523.

8. Parolin, M.L., Chesley, A., Matsos, M.P., Spriet, L.L., Jones, N.L., and Heigenhauser, G.J. (1999). Regulation of skeletal muscle glycogen phosphorylase and PDH during maximal intermittent exercise. Am. J. Physiol. *277*, E890–E900.

9. Gaitanos, G.C., Williams, C., Boobis, L.H., and Brooks, S. (1993). Human muscle metabolism during intermittent maximal exercise. J. Appl. Physiol. (1985) *75*, 712–719.

10. MacDougall, J.D., Ray, S., Sale, D.G., McCartney, N., Lee, P., and Garner, S. (1999). Muscle substrate utilization and lactate production. Can. J. Appl. Physiol. *24*, 209–215.

11. Cheetham, M.E., Boobis, L.H., Brooks, S., and Williams, C. (1986). Human muscle metabolism during sprint running. J. Appl. Physiol. (1985) *61*, 54–60.

12. Hokken, R., Laugesen, S., Aagaard, P., Suetta, C., Frandsen, U., Ørtenblad, N., and Nielsen, J. (2021). Subcellular localization- and fibre type-dependent utilization of muscle glycogen during heavy resistance exercise in elite power and olympic weightlifters. Acta Physiol. Oxf. *231*, e13561.

13. Medbø, J.I., and Tabata, I. (1989). Relative importance of aerobic and anaerobic energy release during short-lasting exhausting bicycle exercise. J. Appl. Physiol. (1985) *67*, 1881–1886.

14. De Cort, S.C., Innes, J.A., Barstow, T.J., and Guz, A. (1991). Cardiac output, oxygen consumption and arteriovenous oxygen difference following a sudden rise in exercise level in humans. J. Physiol. *441*, 501–512.

15. McAllister, R.M. (1998). Adaptations in control of blood flow with training: splanchnic and renal blood flows. Med. Sci. Sports Exerc. *30*, 375–381.

16. Watt, M.J., Heigenhauser, G.J., Dyck, D.J., and Spriet, L.L. (2002). Intramuscular triacylglycerol, glycogen and acetyl group metabolism during 4 h of moderate exercise in man. J. Physiol. *541*, 969–978.

17. Romijn, J.A., Coyle, E.F., Sidossis, L.S., Gastaldelli, A., Horowitz, J.F., Endert, E., and Wolfe, R.R. (1993). Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. Am. J. Physiol. *265*, E380–E391.

18. van Loon, L.J., Greenhaff, P.L., Constantin-Teodosiu, D., Saris, W.H., and Wagenmakers, A.J. (2001). The effects of increasing exercise intensity on muscle fuel utilisation in humans. J. Physiol. *536*, 295–304.

19. Venables, M.C., Achten, J., and Jeukendrup, A.E. (2005). Determinants of fat oxidation during exercise in healthy men and women: a cross-sectional study. J. Appl. Physiol. (1985) *98*, 160–167.

20. Arner, P., Kriegholm, E., Engfeldt, P., and Bolinder, J. (1990). Adrenergic regulation of lipolysis in situ at rest and during exercise. J. Clin. Invest. *85*, 893–898.

21. Wahren, J., Felig, P., Ahlborg, G., and Jorfeldt, L. (1971). Glucose metabolism during leg exercise in man. J. Clin. Invest. *50*, 2715–2725.

22. Järhult, J., and Holst, J. (1979). The role of the adrenergic innervation to the pancreatic islets in the control of insulin release during exercise in man. Pflugers Arch. *383*, 41–45.

23. Wolfe, R.R., Nadel, E.R., Shaw, J.H., Stephenson, L.A., and Wolfe, M.H. (1986). Role of changes in insulin and glucagon in glucose homeostasis in exercise. J. Clin. Invest. *77*, 900–907.

24. Jenkins, A.B., Chisholm, D.J., James, D.E., Ho, K.Y., and Kraegen, E.W. (1985). Exercise-induced hepatic glucose output is precisely sensitive to the rate of systemic glucose supply. Metabolism *34*, 431–436.

25. Jenkins, A.B., Furler, S.M., Chisholm, D.J., and Kraegen, E.W. (1986). Regulation of hepatic glucose output during exercise by circulating glucose and insulin in humans. Am. J. Physiol. *250*, R411–R417.

26. Sidossis, L.S., Gastaldelli, A., Klein, S., and Wolfe, R.R. (1997). Regulation of plasma fatty acid oxidation during low- and high-intensity exercise. Am. J. Physiol. *272*, E1065–E1070.

27. Watt, M.J., Heigenhauser, G.J., LeBlanc, P.J., Inglis, J.G., Spriet, L.L., and Peters, S.J. (2004). Rapid upregulation of pyruvate dehydrogenase kinase activity in human skeletal muscle during prolonged exercise. J. Appl. Physiol. (1985) *97*, 1261–1267.

28. Ahlborg, G., Felig, P., Hagenfeldt, L., Hendler, R., and Wahren, J. (1974). Substrate turnover during prolonged exercise in man. Splanchnic and leg metabolism of glucose, free fatty acids, and amino acids. J. Clin. Invest. *53*, 1080–1090.

29. Lavoie, C., Ducros, F., Bourque, J., Langelier, H., and Chiasson, J.L. (1997). Glucose metabolism during exercise in man: the role of insulin and glucagon in the regulation of hepatic glucose production and gluconeogenesis. Can. J. Physiol. Pharmacol. *75*, 26–35.

30. Egan, B., and Zierath, J.R. (2013). Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab. *17*, 162–184.

31. Blazev, R., Carl, C.S., Ng, Y.K., Molendijk, J., Voldstedlund, C.T., Zhao, Y., Xiao, D., Kueh, A.J., Miotto, P.M., Haynes, V.R., et al. (2022). Phosphoproteomics of three exercise modalities identifies canonical signaling and C18ORF25 as an AMPK substrate regulating skeletal muscle function. Cell Metab. *34*, 1561–1577.e9.

32. McGee, S.L., and Hargreaves, M. (2020). Exercise adaptations: molecular mechanisms and potential targets for therapeutic benefit. Nat. Rev. Endocrinol. *16*, 495–505.

33. Pillon, N.J., Gabriel, B.M., Dollet, L., Smith, J.A.B., Sardón Puig, L., Botella, J., Bishop, D.J., Krook, A., and Zierath, J.R. (2020). Transcriptomic profiling of skeletal muscle adaptations to exercise and inactivity. Nat. Commun. *11*, 470.

34. Pillon, N.J., Smith, J.A.B., Alm, P.S., Chibalin, A.V., Alhusen, J., Arner, E., Carninci, P., Fritz, T., Otten, J., Olsson, T., et al. (2022). Distinctive exercise-induced inflammatory response and exerkine induction in skeletal muscle of people with type 2 diabetes. Sci. Adv. *8*, eabo3192.

35. Amar, D., Lindholm, M.E., Norrbom, J., Wheeler, M.T., Rivas, M.A., and Ashley, E.A. (2021). Time trajectories in the transcriptomic response to exercise - a meta-analysis. Nat. Commun. *12*, 3471.

36. Wu, Z., Puigserver, P., Andersson, U., Zhang, C., Adelmant, G., Mootha, V., Troy, A., Cinti, S., Lowell, B., Scarpulla, R.C., and Spiegelman, B.M. (1999). Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell *98*, 115–124.

37. Handschin, C., Rhee, J., Lin, J., Tarr, P.T., and Spiegelman, B.M. (2003). An autoregulatory loop controls peroxisome proliferator-activated receptor gamma coactivator 1alpha expression in muscle. Proc. Natl. Acad. Sci. USA *100*, 7111–7116.

38. Czubryt, M.P., McAnally, J., Fishman, G.I., and Olson, E.N. (2003). Regulation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1 alpha) and mitochondrial function by MEF2 and HDAC5. Proc. Natl. Acad. Sci. USA *100*, 1711–1716.

39. Schreiber, S.N., Knutti, D., Brogli, K., Uhlmann, T., and Kralli, A. (2003). The transcriptional coactivator PGC-1 regulates the expression and activity of the orphan nuclear receptor estrogen-related receptor alpha (ERRalpha). J. Biol. Chem. *278*, 9013–9018.

40. Schreiber, S.N., Emter, R., Hock, M.B., Knutti, D., Cardenas, J., Podvinec, M., Oakeley, E.J., and Kralli, A. (2004). The estrogen-related receptor alpha (ERRalpha) functions in PPARgamma coactivator 1alpha (PGC-1alpha)-induced mitochondrial biogenesis. Proc. Natl. Acad. Sci. USA *101*, 6472–6477.

41. Huss, J.M., Torra, I.P., Staels, B., Giguère, V., and Kelly, D.P. (2004). Estrogen-related receptor alpha directs peroxisome proliferator-activated receptor alpha signaling in the transcriptional control of energy metabolism in cardiac and skeletal muscle. Mol. Cell. Biol. *24*, 9079–9091.

42. Mootha, V.K., Handschin, C., Arlow, D., Xie, X., St Pierre, J., Sihag, S., Yang, W., Altshuler, D., Puigserver, P., Patterson, N., et al. (2004). Erralpha and Gabpa/b specify PGC-1alpha-dependent oxidative phosphorylation gene expression that is altered in diabetic muscle. Proc. Natl. Acad. Sci. USA *101*, 6570–6575.

43. Gerhart-Hines, Z., Rodgers, J.T., Bare, O., Lerin, C., Kim, S.H., Mostoslavsky, R., Alt, F.W., Wu, Z., and Puigserver, P. (2007). Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha. EMBO J. *26*, 1913–1923.

44. Jäger, S., Handschin, C., St-Pierre, J., and Spiegelman, B.M. (2007). AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. Proc. Natl. Acad. Sci. USA *104*, 12017–12022.

45. Wright, D.C., Geiger, P.C., Han, D.H., Jones, T.E., and Holloszy, J.O. (2007). Calcium induces increases in peroxisome proliferator-activated receptor gamma coactivator-1alpha and mitochondrial biogenesis by a

pathway leading to p38 mitogen-activated protein kinase activation. J. Biol. Chem. *282*, 18793–18799.

46. Puigserver, P., Rhee, J., Lin, J., Wu, Z., Yoon, J.C., Zhang, C.Y., Krauss, S., Mootha, V.K., Lowell, B.B., and Spiegelman, B.M. (2001). Cytokine stimulation of energy expenditure through p38 MAP kinase activation of PPARgamma coactivator-1. Mol. Cell *8*, 971–982.

47. Fentz, J., Kjøbsted, R., Kristensen, C.M., Hingst, J.R., Birk, J.B., Gudiksen, A., Foretz, M., Schjerling, P., Viollet, B., Pilegaard, H., and Wojtaszewski, J.F. (2015). AMPKα is essential for acute exercise-induced gene responses but not for exercise training-induced adaptations in mouse skeletal muscle. Am. J. Physiol. Endocrinol. Metab. *309*, E900–E914.

48. Ballmann, C., Tang, Y., Bush, Z., and Rowe, G.C. (2016). Adult expression of PGC-1α and -1β in skeletal muscle is not required for endurance exercise-induced enhancement of exercise capacity. Am. J. Physiol. Endocrinol. Metab. *311*, E928–E938.

49. Moore, T.M., Lee, S., Olsen, T., Morselli, M., Strumwasser, A.R., Lin, A.J., Zhou, Z., Abrishami, A., Garcia, S.M., Bribiesca, J., et al. (2023). Conserved multi-tissue transcriptomic adaptations to exercise training in humans and mice. Cell Rep. *42*, 112499.

50. Goldstein, M.S. (1961). Humoral nature of hypoglycemia in muscular exercise. Am. J. Physiol. *200*, 67–70.

51. Chow, L.S., Gerszten, R.E., Taylor, J.M., Pedersen, B.K., van Praag, H., Trappe, S., Febbraio, M.A., Galis, Z.S., Gao, Y., Haus, J.M., et al. (2022). Exerkines in health, resilience and disease. Nat. Rev. Endocrinol. *18*, 273–289.

52. Steensberg, A., van Hall, G., Osada, T., Sacchetti, M., Saltin, B., and Klarlund Pedersen, B. (2000). Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. J. Physiol. *529*, 237–242.

53. Phillips, M.D., Mitchell, J.B., Currie-Elolf, L.M., Yellott, R.C., and Hubing, K.A. (2010). Influence of commonly employed resistance exercise protocols on circulating IL-6 and indices of insulin sensitivity. J. Strength Cond. Res. *24*, 1091–1101.

54. van Hall, G., Steensberg, A., Sacchetti, M., Fischer, C., Keller, C., Schjerling, P., Hiscock, N., Møller, K., Saltin, B., Febbraio, M.A., and Pedersen, B.K. (2003). Interleukin-6 stimulates lipolysis and fat oxidation in humans. J. Clin. Endocrinol. Metab. *88*, 3005–3010.

55. Glund, S., Deshmukh, A., Long, Y.C., Moller, T., Koistinen, H.A., Caidahl, K., Zierath, J.R., and Krook, A. (2007). Interleukin-6 directly increases glucose metabolism in resting human skeletal muscle. Diabetes *56*, 1630–1637.

56. Febbraio, M.A., Hiscock, N., Sacchetti, M., Fischer, C.P., and Pedersen, B.K. (2004). Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. Diabetes *53*, 1643–1648.

57. Wedell-Neergaard, A.S., Lang Lehrskov, L., Christensen, R.H., Legaard, G.E., Dorph, E., Larsen, M.K., Launbo, N., Fagerlind, S.R., Seide, S.K., Nymand, S., et al. (2019). Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling: a randomized controlled trial. Cell Metab. *29*, 844–855.e3.

58. Christensen, R.H., Lehrskov, L.L., Wedell-Neergaard, A.S., Legaard, G.E., Ried-Larsen, M., Karstoft, K., Krogh-Madsen, R., Pedersen, B.K., Ellingsgaard, H., and Rosenmeier, J.B. (2019). Aerobic exercise induces cardiac fat loss and alters cardiac muscle mass through an interleukin-6 receptor-dependent mechanism: cardiac analysis of a double-blind randomized controlled clinical trial in abdominally obese humans. Circulation *140*, 1684–1686.

59. Sato, S., Dyar, K.A., Treebak, J.T., Jepsen, S.L., Ehrlich, A.M., Ashcroft, S.P., Trost, K., Kunzke, T., Prade, V.M., Small, L., et al. (2022). Atlas of exercise metabolism reveals time-dependent signatures of metabolic homeostasis. Cell Metab. *34*, 329–345.e8.

60. Mittenbuhler, M.J., Jedrychowski, M.P., Van Vranken, J.G., Sprenger, H.G., Wilensky, S., Dumesic, P.A., Sun, Y., Tartaglia, A., Bogoslavski, D., A., et al. (2023). Isolation of extracellular fluids reveals novel secreted bioactive proteins from muscle and fat tissues. Cell Metab. *35*, 535–549.e7.

61. Contrepois, K., Wu, S., Moneghetti, K.J., Hornburg, D., Ahadi, S., Tsai, M.S., Metwally, A.A., Wei, E., Lee-McMullen, B., Quijada, J.V., et al. (2020). Molecular choreography of acute exercise. Cell *181*, 1112–1130.e16.

62. Whitham, M., Parker, B.L., Friedrichsen, M., Hingst, J.R., Hjorth, M., Hughes, W.E., Egan, C.L., Cron, L., Watt, K.I., Kuchel, R.P., et al. (2018). Extracellular vesicles provide a means for tissue crosstalk during exercise. Cell Metab. *27*, 237–251.e4.

63. Guseh, J.S., Churchill, T.W., Yeri, A., Lo, C., Brown, M., Houstis, N.E., Aragam, K.G., Lieberman, D.E., Rosenzweig, A., and Baggish, A.L. (2020). An expanded repertoire of intensity-dependent exercise-responsive plasma proteins tied to loci of human disease risk. Sci. Rep. *10*, 10831.

64. Morville, T., Sahl, R.E., Moritz, T., Helge, J.W., and Clemmensen, C. (2020). Plasma metabolome profiling of resistance exercise and endurance exercise in humans. Cell Rep. *33*, 108554.

65. Robbins, J.M., Rao, P., Deng, S., Keyes, M.J., Tahir, U.A., Katz, D.H., Beltran, P.M.J., Marchildon, F., Barber, J.L., Peterson, B., et al. (2023). Plasma proteomic changes in response to exercise training are associated with cardiorespiratory fitness adaptations. JCI Insight *8*, e165867.

66. Murphy, R.M., Watt, M.J., and Febbraio, M.A. (2020). Metabolic communication during exercise. Nat. Metab. *2*, 805–816.

67. Leuchtmann, A.B., Adak, V., Dilbaz, S., and Handschin, C. (2021). The role of the skeletal muscle secretome in mediating endurance and resistance training adaptations. Front. Physiol. *12*, 709807.

68. Saltin, B., and Astrand, P.O. (1967). Maximal oxygen uptake in athletes. J. Appl. Physiol. *23*, 353–358.

69. Ozaki, H., Loenneke, J.P., Thiebaud, R.S., and Abe, T. (2013). Resistance training induced increase in VO2max in young and older subjects. Eur. Rev. Aging Phys. Act. *10*, 107–116.

70. Montero, D., Cathomen, A., Jacobs, R.A., Flück, D., de Leur, J., Keiser, S., Bonne, T., Kirk, N., Lundby, A.K., and Lundby, C. (2015). Haematological rather than skeletal muscle adaptations contribute to the increase in peak oxygen uptake induced by moderate endurance training. J. Physiol. *593*, 4677–4688.

71. Costill, D.L., Fink, W.J., and Pollock, M.L. (1976). Muscle fiber composition and enzyme activities of elite distance runners. Med. Sci. Sports *8*, 96–100.

72. Bouchard, C., Sarzynski, M.A., Rice, T.K., Kraus, W.E., Church, T.S., Sung, Y.J., Rao, D.C., and Rankinen, T. (2011). Genomic predictors of the maximal O(2) uptake response to standardized exercise training programs. J. Appl. Physiol. (1985) *110*, 1160–1170.

73. Montero, D., and Lundby, C. (2017). Refuting the myth of non-response to exercise training: 'non-responders' do respond to higher dose of training. J. Physiol. *595*, 3377–3387.

74. Bouchard, C., Daw, E.W., Rice, T., Pérusse, L., Gagnon, J., Province, M.A., Leon, A.S., Rao, D.C., Skinner, J.S., and Wilmore, J.H. (1998). Familial resemblance for VO2max in the sedentary state: the Heritage Family Study. Med. Sci. Sports Exerc. *30*, 252–258.

75. Bouchard, C., Rankinen, T., Chagnon, Y.C., Rice, T., Pérusse, L., Gagnon, J., Borecki, I., An, P., Leon, A.S., Skinner, J.S., et al. (2000). Genomic scan for maximal oxygen uptake and its response to training in the Heritage Family Study. J. Appl. Physiol. (1985) *88*, 551–559.

76. Sandbakk, Ø., and Holmberg, H.C. (2014). A reappraisal of success factors for Olympic cross-country skiing. Int. J. Sports Physiol. Perform. *9*, 117–121.

77. Fagard, R. (2003). Athlete's heart. Heart *89*, 1455–1461.

78. Scharhag, J., Schneider, G., Urhausen, A., Rochette, V., Kramann, B., and Kindermann, W. (2002). Athlete's heart: right and left ventricular mass and function in male endurance athletes and untrained individuals determined by magnetic resonance imaging. J. Am. Coll. Cardiol. *40*, 1856–1863.

79. D'Andrea, A., Riegler, L., Cocchia, R., Scarafile, R., Salerno, G., Gravino, R., Golia, E., Vriz, O., Citro, R., Limongelli, G., et al. (2010). Left atrial volume index in highly trained athletes. Am. Heart J. *159*, 1155–1161.

80. Baggish, A.L., Yared, K., Weiner, R.B., Wang, F., Demes, R., Picard, M.H., Hagerman, F., and Wood, M.J. (2010). Differences in cardiac parameters among elite rowers and subelite rowers. Med. Sci. Sports Exerc. *42*, 1215–1220.

81. Pelliccia, A., Maron, B.J., Spataro, A., Proschan, M.A., and Spirito, P. (1991). The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. N. Engl. J. Med. *324*, 295–301.

82. Pelliccia, A., Culasso, F., Di Paolo, F.M., and Maron, B.J. (1999). Physiologic left ventricular cavity dilatation in elite athletes. Ann. Intern. Med. *130*, 23–31.

83. Spence, A.L., Naylor, L.H., Carter, H.H., Buck, C.L., Dembo, L., Murray, C.P., Watson, P., Oxborough, D., George, K.P., and Green, D.J. (2011). A prospective randomised longitudinal MRI study of left ventricular adaptation to endurance and resistance exercise training in humans. J. Physiol. *589*, 5443–5452.

84. Shapiro, L.M., and Smith, R.G. (1983). Effect of training on left ventricular structure and function. An echocardiographic study. Br. Heart J. *50*, 534–539.

85. Arbab-Zadeh, A., Perhonen, M., Howden, E., Peshock, R.M., Zhang, R., Adams-Huet, B., Haykowsky, M.J., and Levine, B.D. (2014). Cardiac remodeling in response to 1 year of intensive endurance training. Circulation *130*, 2152–2161.

86. Vogelsang, T.W., Hanel, B., Kristoffersen, U.S., Petersen, C.L., Mehlsen, J., Holmquist, N., Larsson, B., and Kjaer, A. (2008). Effect of eight weeks of endurance exercise training on right and left ventricular volume and mass in untrained obese subjects: a longitudinal MRI study. Scand. J. Med. Sci. Sports *18*, 354–359.

87. Baggish, A.L., Wang, F., Weiner, R.B., Elinoff, J.M., Tournoux, F., Boland, A., Picard, M.H., Hutter, A.M., Jr., and Wood, M.J. (2008). Training-specific changes in cardiac structure and function: a prospective and longitudinal assessment of competitive athletes. J. Appl. Physiol. (1985) *104*, 1121–1128.

88. Utomi, V., Oxborough, D., Whyte, G.P., Somauroo, J., Sharma, S., Shave, R., Atkinson, G., and George, K. (2013). Systematic review and meta-analysis of training mode, imaging modality and body size influences on the morphology and function of the male athlete's heart. Heart *99*, 1727–1733.

89. Gledhill, N., Cox, D., and Jamnik, R. (1994). Endurance athletes' stroke volume does not plateau: major advantage is diastolic function. Med. Sci. Sports Exerc. *26*, 1116–1121.

90. Strøm, C.C., Aplin, M., Ploug, T., Christoffersen, T.E., Langfort, J., Viese, M., Galbo, H., Haunsø, S., and Sheikh, S.P. (2005). Expression profiling reveals differences in metabolic gene expression between exercise-induced cardiac effects and maladaptive cardiac hypertrophy. FEBS Journal *272*, 2684–2695.

91. Al-Menhali, A.S., Anderson, C., Gourine, A.V., Abramov, A.Y., D'Souza, A., and Jaganjac, M. (2021). Proteomic analysis of cardiac adaptation to exercise by high resolution mass spectrometry. Front. Mol. Biosci. *8*, 723858.

92. McMullen, J.R., Shioi, T., Zhang, L., Tarnavski, O., Sherwood, M.C., Kang, P.M., and Izumo, S. (2003). Phosphoinositide 3-kinase(p110alpha) plays a critical role for the induction of physiological, but not pathological, cardiac hypertrophy. Proc. Natl. Acad. Sci. USA *100*, 12355–12360.

93. McMullen, J.R., Shioi, T., Huang, W.Y., Zhang, L., Tarnavski, O., Bisping, E., Schinke, M., Kong, S., Sherwood, M.C., Brown, J., et al. (2004). The insulin-like growth factor 1 receptor induces physiological heart growth via the phosphoinositide 3-kinase(p110alpha) pathway. J. Biol. Chem. *279*, 4782–4793.

94. Vettor, R., Valerio, A., Ragni, M., Trevellin, E., Granzotto, M., Olivieri, M., Tedesco, L., Ruocco, C., Fossati, A., Fabris, R., et al. (2014). Exercise training boosts eNOS-dependent mitochondrial biogenesis in mouse heart: role in adaptation of glucose metabolism. Am. J. Physiol. Endocrinol. Metab. *306*, E519–E528.

95. Campos, J.C., Queliconi, B.B., Bozi, L.H.M., Bechara, L.R.G., Dourado, P.M.M., Andres, A.M., Jannig, P.R., Gomes, K.M.S., Zambelli, V.O., Rocha-Resende, C., et al. (2017). Exercise reestablishes autophagic flux and mitochondrial quality control in heart failure. Autophagy *13*, 1304–1317.

96. Ashor, A.W., Lara, J., Siervo, M., Celis-Morales, C., Oggioni, C., Jakovljevic, D.G., and Mathers, J.C. (2015). Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials. Sports Med. *45*, 279–296.

97. Tinken, T.M., Thijssen, D.H., Hopkins, N., Dawson, E.A., Cable, N.T., and Green, D.J. (2010). Shear stress mediates endothelial adaptations to exercise training in humans. Hypertension *55*, 312–318.

98. Dinenno, F.A., Tanaka, H., Monahan, K.D., Clevenger, C.M., Eskurza, I., DeSouza, C.A., and Seals, D.R. (2001). Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. J. Physiol. *534*, 287–295.

99. Miyachi, M., Tanaka, H., Yamamoto, K., Yoshioka, A., Takahashi, K., and Onodera, S. (2001). Effects of one-legged endurance training on femoral arterial and venous size in healthy humans. J. Appl. Physiol. (1985) *90*, 2439–2444.

100. Jensen, L., Bangsbo, J., and Hellsten, Y. (2004). Effect of high intensity training on capillarization and presence of angiogenic factors in human skeletal muscle. J. Physiol. *557*, 571–582.

101. Ingjer, F. (1979). Effects of endurance training on muscle fibre ATP-ase activity, capillary supply and mitochondrial content in man. J. Physiol. *294*, 419–432.

102. Mortensen, S.P., Winding, K.M., Iepsen, U.W., Munch, G.W., Marcussen, N., Hellsten, Y., Pedersen, B.K., and Baum, O. (2019). The effect of two exercise modalities on skeletal muscle capillary ultrastructure in individuals with type 2 diabetes. Scand. J. Med. Sci. Sports *29*, 360–368.

103. Walton, R.G., Finlin, B.S., Mula, J., Long, D.E., Zhu, B., Fry, C.S., Westgate, P.M., Lee, J.D., Bennett, T., Kern, P.A., and Peterson, C.A. (2015). Insulin-resistant subjects have normal angiogenic response to aerobic exercise training in skeletal muscle, but not in adipose tissue. Physiol. Rep. *3*, e12415.

104. Andersen, P., and Henriksson, J. (1977). Capillary supply of the quadriceps femoris muscle of man: adaptive response to exercise. J. Physiol. *270*, 677–690.

105. Murias, J.M., Kowalchuk, J.M., Ritchie, D., Hepple, R.T., Doherty, T.J., and Paterson, D.H. (2011). Adaptations in capillarization and citrate synthase activity in response to endurance training in older and young men. J. Gerontol. A Biol. Sci. Med. Sci. *66*, 957–964.

106. Honkala, S.M., Motiani, P., Kivelä, R., Hemanthakumar, K.A., Tolvanen, E., Motiani, K.K., Eskelinen, J.J., Virtanen, K.A., Kemppainen, J., Heiskanen, M.A., et al. (2020). Exercise training improves adipose tissue metabolism and vasculature regardless of baseline glucose tolerance and sex. BMJ Open Diabetes Res. Care *8*, e000830.

107. Ahn, C., Ryan, B.J., Schleh, M.W., Varshney, P., Ludzki, A.C., Gillen, J.B., Van Pelt, D.W., Pitchford, L.M., Howton, S.M., Rode, T., et al. (2022). Exercise training remodels subcutaneous adipose tissue in adults with obesity even without weight loss. J. Physiol. *600*, 2127–2146.

108. Klausen, K., Andersen, L.B., and Pelle, I. (1981). Adaptive changes in work capacity, skeletal muscle capillarization and enzyme levels during training and detraining. Acta Physiol. Scand. *113*, 9–16.

109. Leuchtmann, A.B., Mueller, S.M., Aguayo, D., Petersen, J.A., Ligon-Auer, M., Flück, M., Jung, H.H., and Toigo, M. (2020). Resistance training preserves high-intensity interval training induced improvements in skeletal muscle capillarization of healthy old men: a randomized controlled trial. Sci. Rep. *10*, 6578.

110. Hepple, R.T., Mackinnon, S.L., Goodman, J.M., Thomas, S.G., and Plyley, M.J. (1997). Resistance and aerobic training in older men: effects on VO2peak and the capillary supply to skeletal muscle. J. Appl. Physiol. (1985) *82*, 1305–1310.

111. Tan, R., Nederveen, J.P., Gillen, J.B., Joanisse, S., Parise, G., Tarnopolsky, M.A., and Gibala, M.J. (2018). Skeletal muscle fiber-type-specific changes in markers of capillary and mitochondrial content after low-volume interval training in overweight women. Physiol. Rep. *6*, 6.

112. Cocks, M., Shaw, C.S., Shepherd, S.O., Fisher, J.P., Ranasinghe, A., Barker, T.A., and Wagenmakers, A.J. (2016). Sprint interval and

moderate-intensity continuous training have equal benefits on aerobic capacity, insulin sensitivity, muscle capillarisation and endothelial eNOS/NAD(P)Hoxidase protein ratio in obese men. J. Physiol. *594*, 2307–2321.

113. Cocks, M., Shaw, C.S., Shepherd, S.O., Fisher, J.P., Ranasinghe, A.M., Barker, T.A., Tipton, K.D., and Wagenmakers, A.J. (2013). Sprint interval and endurance training are equally effective in increasing muscle microvascular density and eNOS content in sedentary males. J. Physiol. *591*, 641–656.

114. Gavin, T.P., Spector, D.A., Wagner, H., Breen, E.C., and Wagner, P.D. (2000). Nitric oxide synthase inhibition attenuates the skeletal muscle VEGF mRNA response to exercise. J. Appl. Physiol. (1985) *88*, 1192–1198.

115. Höffner, L., Nielsen, J.J., Langberg, H., and Hellsten, Y. (2003). Exercise but not prostanoids enhance levels of vascular endothelial growth factor and other proliferative agents in human skeletal muscle interstitium. J. Physiol. *550*, 217–225.

116. Snell, P.G., Martin, W.H., Buckey, J.C., and Blomqvist, C.G. (1987). Maximal vascular leg conductance in trained and untrained men. J. Appl. Physiol. (1985) *62*, 606–610.

117. Kalliokoski, K.K., Oikonen, V., Takala, T.O., Sipilä, H., Knuuti, J., and Nuutila, P. (2001). Enhanced oxygen extraction and reduced flow heterogeneity in exercising muscle in endurance-trained men. Am. J. Physiol. Endocrinol. Metab. *280*, E1015–E1021.

118. Beere, P.A., Russell, S.D., Morey, M.C., Kitzman, D.W., and Higginbotham, M.B. (1999). Aerobic exercise training can reverse age-related peripheral circulatory changes in healthy older men. Circulation *100*, 1085–1094.

119. Murias, J.M., Kowalchuk, J.M., and Paterson, D.H. (2010). Time course and mechanisms of adaptations in cardiorespiratory fitness with endurance training in older and young men. J. Appl. Physiol. (1985) *108*, 621–627.

120. Kjellberg, S.R., Rudhe, U., and Sjöstrand, T. (1949). Increase of the amount of hemoglobin and blood volume in connection with physical training. Acta Physiol. Scand. *19*, 146–151.

121. Heinicke, K., Wolfarth, B., Winchenbach, P., Biermann, B., Schmid, A., Huber, G., Friedmann, B., and Schmidt, W. (2001). Blood volume and hemoglobin mass in elite athletes of different disciplines. Int. J. Sports Med. *22*, 504–512.

122. Convertino, V.A., Brock, P.J., Keil, L.C., Bernauer, E.M., and Greenleaf, J.E. (1980). Exercise training-induced hypervolemia: role of plasma albumin, renin, and vasopressin. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. *48*, 665–669.

123. Gillen, C.M., Lee, R., Mack, G.W., Tomaselli, C.M., Nishiyasu, T., and Nadel, E.R. (1991). Plasma volume expansion in humans after a single intense exercise protocol. J. Appl. Physiol. (1985) *71*, 1914–1920.

124. Green, H.J., Thomson, J.A., Ball, M.E., Hughson, R.L., Houston, M.E., and Sharratt, M.T. (1984). Alterations in blood volume following short-term supramaximal exercise. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. *56*, 145–149.

125. Sawka, M.N., Convertino, V.A., Eichner, E.R., Schnieder, S.M., and Young, A.J. (2000). Blood volume: importance and adaptations to exercise training, environmental stresses, and trauma/sickness. Med. Sci. Sports Exerc. *32*, 332–348.

126. Montero, D., and Lundby, C. (2018). Regulation of red blood cell volume with exercise training. Compr. Physiol. *9*, 149–164.

127. Hopper, M.K., Coggan, A.R., and Coyle, E.F. (1988). Exercise stroke volume relative to plasma-volume expansion. J. Appl. Physiol. (1985) *64*, 404–408.

128. Krip, B., Gledhill, N., Jamnik, V., and Warburton, D. (1997). Effect of alterations in blood volume on cardiac function during maximal exercise. Med. Sci. Sports Exerc. *29*, 1469–1476.

129. Bonne, T.C., Doucende, G., Flück, D., Jacobs, R.A., Nordsborg, N.B., Robach, P., Walther, G., and Lundby, C. (2014). Phlebotomy eliminates the maximal cardiac output response to six weeks of exercise training. Am. J. Physiol. Regul. Integr. Comp. Physiol. *306*, R752–R760.

130. Booth, F.W., and Thomason, D.B. (1991). Molecular and cellular adaptation of muscle in response to exercise: perspectives of various models. Physiol. Rev. *71*, 541–585.

131. Saltin, B., and Gollnick, P.D. (1983). Skeletal Muscle Adaptability: Significance for Metabolism and Performance. In Handbook of Physiology, Section 10: Skeletal Muscle, L.D. Peachy, R.H. Adrian, and S.R. Geiger, eds. (American Physiological Society), pp. 555–631.

132. Brooks, G.A. (2012). Bioenergetics of exercising humans. Compr. Physiol. *2*, 537–562.

133. Holloszy, J.O., and Coyle, E.F. (1984). Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. *56*, 831–838.

134. Westgarth-Taylor, C., Hawley, J.A., Rickard, S., Myburgh, K.H., Noakes, T.D., and Dennis, S.C. (1997). Metabolic and performance adaptations to interval training in endurance-trained cyclists. Eur. J. Appl. Physiol. Occup. Physiol. *75*, 298–304.

135. Gavin, T.P., Ruster, R.S., Carrithers, J.A., Zwetsloot, K.A., Kraus, R.M., Evans, C.A., Knapp, D.J., Drew, J.L., McCartney, J.S., Garry, J.P., and Hickner, R.C. (2007). No difference in the skeletal muscle angiogenic response to aerobic exercise training between young and aged men. J. Physiol. *585*, 231–239.

136. Powers, S.K., Criswell, D., Lawler, J., Ji, L.L., Martin, D., Herb, R.A., and Dudley, G. (1994). Influence of exercise and fiber type on antioxidant enzyme activity in rat skeletal muscle. Am. J. Physiol. *266*, R375–R380.

137. Perseghin, G., Price, T.B., Petersen, K.F., Roden, M., Cline, G.W., Gerow, K., Rothman, D.L., and Shulman, G.I. (1996). Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. N. Engl. J. Med. *335*, 1357–1362.

138. Tremblay, A., Simoneau, J.A., and Bouchard, C. (1994). Impact of exercise intensity on body fatness and skeletal muscle metabolism. Metabolism *43*, 814–818.

139. Dubouchaud, H., Butterfield, G.E., Wolfel, E.E., Bergman, B.C., and Brooks, G.A. (2000). Endurance training, expression, and physiology of LDH, MCT1, and MCT4 in human skeletal muscle. Am. J. Physiol. Endocrinol. Metab. *278*, E571–E579.

140. Kiens, B., Kristiansen, S., Jensen, P., Richter, E.A., and Turcotte, L.P. (1997). Membrane associated fatty acid binding protein (FABPpm) in human skeletal muscle is increased by endurance training. Biochem. Biophys. Res. Commun. *231*, 463–465.

141. Alsted, T.J., Nybo, L., Schweiger, M., Fledelius, C., Jacobsen, P., Zimmermann, R., Zechner, R., and Kiens, B. (2009). Adipose triglyceride lipase in human skeletal muscle is upregulated by exercise training. Am. J. Physiol. Endocrinol. Metab. *296*, E445–E453.

142. Egan, B., Dowling, P., O'Connor, P.L., Henry, M., Meleady, P., Zierath, J.R., and O'Gorman, D.J. (2011). 2-D DIGE analysis of the mitochondrial proteome from human skeletal muscle reveals time course-dependent remodelling in response to 14 consecutive days of endurance exercise training. Proteomics *11*, 1413–1428.

143. Holloszy, J.O. (1967). Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. J. Biol. Chem. *242*, 2278–2282.

144. Houmard, J.A., Shinebarger, M.H., Dolan, P.L., Leggett-Frazier, N., Bruner, R.K., McCammon, M.R., Israel, R.G., and Dohm, G.L. (1993). Exercise training increases GLUT-4 protein concentration in previously sedentary middle-aged men. Am. J. Physiol. *264*, E896–E901.

145. Kristiansen, S., Gade, J., Wojtaszewski, J.F., Kiens, B., and Richter, E.A. (2000). Glucose uptake is increased in trained vs. untrained muscle during heavy exercise. J. Appl. Physiol. (1985) *89*, 1151–1158.

146. Kiens, B., Essen-Gustavsson, B., Christensen, N.J., and Saltin, B. (1993). Skeletal muscle substrate utilization during submaximal exercise in man: effect of endurance training. J. Physiol. *469*, 459–478.

147. Greiwe, J.S., Hickner, R.C., Hansen, P.A., Racette, S.B., Chen, M.M., and Holloszy, J.O. (1999). Effects of endurance exercise training on muscle glycogen accumulation in humans. J. Appl. Physiol. (1985) *87*, 222–226.

148. van Loon, L.J., and Goodpaster, B.H. (2006). Increased intramuscular lipid storage in the insulin-resistant and endurance-trained state. Pflugers Arch. *451*, 606–616.

149. Hoppeler, H., Howald, H., Conley, K., Lindstedt, S.L., Claassen, H., Vock, P., and Weibel, E.R. (1985). Endurance training in humans: aerobic capacity and structure of skeletal muscle. J. Appl. Physiol. (1985) *59*, 320–327.

150. Jacobs, R.A., Flück, D., Bonne, T.C., Bürgi, S., Christensen, P.M., Toigo, M., and Lundby, C. (2013). Improvements in exercise performance with high-intensity interval training coincide with an increase in skeletal muscle mitochondrial content and function. J. Appl. Physiol. (1985) *115*, 785–793.

151. MacInnis, M.J., and Gibala, M.J. (2017). Physiological adaptations to interval training and the role of exercise intensity. J. Physiol. *595*, 2915–2930.

152. Ruegsegger, G.N., Pataky, M.W., Simha, S., Robinson, M.M., Klaus, K.A., and Nair, K.S. (2023). High-intensity aerobic, but not resistance or combined, exercise training improves both cardiometabolic health and skeletal muscle mitochondrial dynamics. J. Appl. Physiol. (1985) *135*, 763–774.

153. Groennebaek, T., and Vissing, K. (2017). Impact of resistance training on skeletal muscle mitochondrial biogenesis, content, and function. Front. Physiol. *8*, 713.

154. Lundby, C., and Jacobs, R.A. (2016). Adaptations of skeletal muscle mitochondria to exercise training. Exp. Physiol. *101*, 17–22.

155. Hoppeler, H., Baum, O., Lurman, G., and Mueller, M. (2011). Molecular mechanisms of muscle plasticity with exercise. Compr. Physiol. *1*, 1383–1412.

156. Granata, C., Caruana, N.J., Botella, J., Jamnick, N.A., Huynh, K., Kuang, J., Janssen, H.A., Reljic, B., Mellett, N.A., Laskowski, A., et al. (2021). High-intensity training induces non-stoichiometric changes in the mitochondrial proteome of human skeletal muscle without reorganisation of respiratory chain content. Nat. Commun. *12*, 7056.

157. Deshmukh, A.S., Steenberg, D.E., Hostrup, M., Birk, J.B., Larsen, J.K., Santos, A., Kjøbsted, R., Hingst, J.R., Schéele, C.C., Murgia, M., et al. (2021). Deep muscle-proteomic analysis of freeze-dried human muscle biopsies reveals fiber type-specific adaptations to exercise training. Nat. Commun. *12*, 304.

158. Hostrup, M., Lemminger, A.K., Stocks, B., Gonzalez-Franquesa, A., Larsen, J.K., Quesada, J.P., Thomassen, M., Weinert, B.T., Bangsbo, J., and Deshmukh, A.S. (2022). High-intensity interval training remodels the proteome and acetylome of human skeletal muscle. eLife *11*, e69802.

159. Robinson, M.M., Dasari, S., Konopka, A.R., Johnson, M.L., Manjunatha, S., Esponda, R.R., Carter, R.E., Lanza, I.R., and Nair, K.S. (2017). Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. Cell Metab. *25*, 581–592.

160. Leblanc, P.J., Howarth, K.R., Gibala, M.J., and Heigenhauser, G.J. (2004). Effects of 7 wk of endurance training on human skeletal muscle metabolism during submaximal exercise. J. Appl. Physiol. (1985) *97*, 2148–2153.

161. Starritt, E.C., Howlett, R.A., Heigenhauser, G.J., and Spriet, L.L. (2000). Sensitivity of CPT I to malonyl-CoA in trained and untrained human skeletal muscle. Am. J. Physiol. Endocrinol. Metab. *278*, E462–E468.

162. Picard, M., White, K., and Turnbull, D.M. (2013). Mitochondrial morphology, topology, and membrane interactions in skeletal muscle: a quantitative three-dimensional electron microscopy study. J. Appl. Physiol. (1985) *114*, 161–171.

163. Glancy, B., Hartnell, L.M., Malide, D., Yu, Z.X., Combs, C.A., Connelly, P.S., Subramaniam, S., and Balaban, R.S. (2015). Mitochondrial reticulum for cellular energy distribution in muscle. Nature *523*, 617–620.

164. Hood, D.A., Tryon, L.D., Carter, H.N., Kim, Y., and Chen, C.C. (2016). Unravelling the mechanisms regulating muscle mitochondrial biogenesis. Biochem. J. *473*, 2295–2314.

165. Halling, J.F., and Pilegaard, H. (2017). Autophagy-dependent beneficial effects of exercise. Cold Spring Harb. Perspect. Med. *7*, a029777.

166. Martin-Rincon, M., Morales-Alamo, D., and Calbet, J.A.L. (2018). Exercise-mediated modulation of autophagy in skeletal muscle. Scand. J. Med. Sci. Sports *28*, 772–781.

167. Abou Sawan, S., Mazzulla, M., Moore, D.R., and Hodson, N. (2020). More than just a garbage can: emerging roles of the lysosome as an anabolic organelle in skeletal muscle. Am. J. Physiol. Cell Physiol. *319*, C561–C568.

168. Markby, G.R., and Sakamoto, K. (2020). Transcription factor EB and TFE3: new metabolic coordinators mediating adaptive responses to exercise in skeletal muscle? Am. J. Physiol. Endocrinol. Metab. *319*, E763–E768.

169. Lira, V.A., Okutsu, M., Zhang, M., Greene, N.P., Laker, R.C., Breen, D.S., Hoehn, K.L., and Yan, Z. (2013). Autophagy is required for exercise training-induced skeletal muscle adaptation and improvement of physical performance. FASEB J. *27*, 4184–4193.

170. Lo Verso, F., Carnio, S., Vainshtein, A., and Sandri, M. (2014). Autophagy is not required to sustain exercise and PRKAA1/AMPK activity but is important to prevent mitochondrial damage during physical activity. Autophagy *10*, 1883–1894.

171. Ju, J.S., Jeon, S.I., Park, J.Y., Lee, J.Y., Lee, S.C., Cho, K.J., and Jeong, J.M. (2016). Autophagy plays a role in skeletal muscle mitochondrial biogenesis in an endurance exercise-trained condition. J. Physiol. Sci. *66*, 417–430.

172. Fritzen, A.M., Madsen, A.B., Kleinert, M., Treebak, J.T., Lundsgaard, A.M., Jensen, T.E., Richter, E.A., Wojtaszewski, J., Kiens, B., and Frøsig, C. (2016). Regulation of autophagy in human skeletal muscle: effects of exercise, exercise training and insulin stimulation. J. Physiol. *594*, 745–761.

173. Brandt, N., Gunnarsson, T.P., Bangsbo, J., and Pilegaard, H. (2018). Exercise and exercise training-induced increase in autophagy markers in human skeletal muscle. Physiol. Rep. *6*, e13651.

174. Balan, E., Schwalm, C., Naslain, D., Nielens, H., Francaux, M., and Deldicque, L. (2019). Regular endurance exercise promotes fission, mitophagy, and oxidative phosphorylation in human skeletal muscle independently of age. Front. Physiol. *10*, 1088.

175. Scalzo, R.L., Peltonen, G.L., Binns, S.E., Shankaran, M., Giordano, G.R., Hartley, D.A., Klochak, A.L., Lonac, M.C., Paris, H.L., Szallar, S.E., et al. (2014). Greater muscle protein synthesis and mitochondrial biogenesis in males compared with females during sprint interval training. FASEB J. *28*, 2705–2714.

176. Masschelein, E., Van Thienen, R., D'Hulst, G., Hespel, P., Thomis, M., and Deldicque, L. (2014). Acute environmental hypoxia induces LC3 lipidation in a genotype-dependent manner. FASEB J. *28*, 1022–1034.

177. Schwalm, C., Jamart, C., Benoit, N., Naslain, D., Prémont, C., Prévet, J., Van Thienen, R., Deldicque, L., and Francaux, M. (2015). Activation of autophagy in human skeletal muscle is dependent on exercise intensity and AMPK activation. FASEB J. *29*, 3515–3526.

178. Dickinson, J.M., Reidy, P.T., Gundermann, D.M., Borack, M.S., Walker, D.K., D'Lugos, A.C., Volpi, E., and Rasmussen, B.B. (2017). The impact of postexercise essential amino acid ingestion on the ubiquitin proteasome and autophagosomal-lysosomal systems in skeletal muscle of older men. J. Appl. Physiol. (1985) *122*, 620–630.

179. Mazo, C.E., D'Lugos, A.C., Sweeney, K.R., Haus, J.M., Angadi, S.S., Carroll, C.C., and Dickinson, J.M. (2021). The effects of acute aerobic and resistance exercise on mTOR signaling and autophagy markers in untrained human skeletal muscle. Eur. J. Appl. Physiol. *121*, 2913–2924.

180. Parker, B.L., Kiens, B., Wojtaszewski, J.F.P., Richter, E.A., and James, D.E. (2020). Quantification of exercise-regulated ubiquitin signaling in human skeletal muscle identifies protein modification cross talk via neddylation. FASEB J. *34*, 5906–5916.

181. Abernethy, P.J., Jürimäe, J., Logan, P.A., Taylor, A.W., and Thayer, R.E. (1994). Acute and chronic response of skeletal muscle to resistance exercise. Sports Med. *17*, 22–38.

182. Haun, C.T., Vann, C.G., Roberts, B.M., Vigotsky, A.D., Schoenfeld, B.J., and Roberts, M.D. (2019). A critical evaluation of the biological construct

skeletal muscle hypertrophy: size matters but so does the measurement. Front. Physiol. *10*, 247.

183. Jorgenson, K.W., Phillips, S.M., and Hornberger, T.A. (2020). Identifying the structural adaptations that drive the mechanical load-induced growth of skeletal muscle: a scoping review. Cells *9*, 1658.

184. Hodson, N., West, D.W.D., Philp, A., Burd, N.A., and Moore, D.R. (2019). Molecular regulation of human skeletal muscle protein synthesis in response to exercise and nutrients: a compass for overcoming age-related anabolic resistance. Am. J. Physiol. Cell Physiol. *317*, C1061–C1078.

185. Nishimura, Y., Musa, I., Holm, L., and Lai, Y.C. (2021). Recent advances in measuring and understanding the regulation of exercise-mediated protein degradation in skeletal muscle. Am. J. Physiol. Cell Physiol. *321*, C276–C287.

186. McGlory, C., van Vliet, S., Stokes, T., Mittendorfer, B., and Phillips, S.M. (2019). The impact of exercise and nutrition on the regulation of skeletal muscle mass. J. Physiol. *597*, 1251–1258.

187. Wackerhage, H., Schoenfeld, B.J., Hamilton, D.L., Lehti, M., and Hulmi, J.J. (2019). Stimuli and sensors that initiate skeletal muscle hypertrophy following resistance exercise. J. Appl. Physiol. (1985) *126*, 30–43.

188. Figueiredo, V.C., and McCarthy, J.J. (2019). Regulation of ribosome biogenesis in skeletal muscle hypertrophy. Physiology (Bethesda) *34*, 30–42.

189. Kressler, D., Hurt, E., and Baßler, J. (2017). A puzzle of life: crafting ribosomal subunits. Trends Biochem. Sci. *42*, 640–654.

190. Brook, M.S., Wilkinson, D.J., Smith, K., and Atherton, P.J. (2019). It's not just about protein turnover: the role of ribosomal biogenesis and satellite cells in the regulation of skeletal muscle hypertrophy. Eur. J. Sport Sci. *19*, 952–963.

191. Ross, A., Leveritt, M., and Riek, S. (2001). Neural influences on sprint running: training adaptations and acute responses. Sports Med. *31*, 409–425.

192. Sale, D.G. (1988). Neural adaptation to resistance training. Med. Sci. Sports Exerc. *20*, S135–S145.

193. Moritani, T., and deVries, H.A. (1979). Neural factors versus hypertrophy in the time course of muscle strength gain. Am. J. Phys. Med. *58*, 115–130.

194. Wong, T.S., and Booth, F.W. (1990). Protein metabolism in rat gastrocnemius muscle after stimulated chronic concentric exercise. J. Appl. Physiol. (1985) *69*, 1709–1717.

195. Konopka, A.R., and Harber, M.P. (2014). Skeletal muscle hypertrophy after aerobic exercise training. Exerc. Sport Sci. Rev. *42*, 53–61.

196. Paavolainen, L., Nummela, A., Rusko, H., and Häkkinen, K. (1999). Neuromuscular characteristics and fatigue during 10 km running. Int. J. Sports Med. *20*, 516–521.

197. Chapman, A.R., Vicenzino, B., Blanch, P., and Hodges, P.W. (2008). Patterns of leg muscle recruitment vary between novice and highly trained cyclists. J. Electromyogr. Kinesiol. *18*, 359–371.

198. Tang, J.E., Hartman, J.W., and Phillips, S.M. (2006). Increased muscle oxidative potential following resistance training induced fibre hypertrophy in young men. Appl. Physiol. Nutr. Metab. *31*, 495–501.

199. Salvadego, D., Domenis, R., Lazzer, S., Porcelli, S., Rittweger, J., Rizzo, G., Mavelli, I., Simunic, B., Pisot, R., and Grassi, B. (2013). Skeletal muscle oxidative function in vivo and ex vivo in athletes with marked hypertrophy from resistance training. J. Appl. Physiol. (1985) *114*, 1527–1535.

200. Porter, C., Reidy, P.T., Bhattarai, N., Sidossis, L.S., and Rasmussen, B.B. (2015). Resistance exercise training alters mitochondrial function in human skeletal muscle. Med. Sci. Sports Exerc. *47*, 1922–1931.

201. Lim, C., Kim, H.J., Morton, R.W., Harris, R., Phillips, S.M., Jeong, T.S., and Kim, C.K. (2019). Resistance exercise-induced changes in muscle phenotype are load dependent. Med. Sci. Sports Exerc. *51*, 2578–2585.

202. Ross, A., and Leveritt, M. (2001). Long-term metabolic and skeletal muscle adaptations to short-sprint training: implications for sprint training and tapering. Sports Med. *31*, 1063–1082.

203. Juel, C. (2006). Training-induced changes in membrane transport proteins of human skeletal muscle. Eur. J. Appl. Physiol. *96*, 627–635.

204. McKenna, M.J., Schmidt, T.A., Hargreaves, M., Cameron, L., Skinner, S.L., and Kjeldsen, K. (1993). Sprint training increases human skeletal muscle Na(+)-K(+)-ATPase concentration and improves K+ regulation. J. Appl. Physiol. (1985) *75*, 173–180.

205. Hostrup, M., and Bangsbo, J. (2017). Limitations in intense exercise performance of athletes - effect of speed endurance training on ion handling and fatigue development. J. Physiol. *595*, 2897–2913.

206. McGlory, C., Devries, M.C., and Phillips, S.M. (2017). Skeletal muscle and resistance exercise training; the role of protein synthesis in recovery and remodeling. J. Appl. Physiol. (1985) *122*, 541–548.

207. Saltin, B., Nazar, K., Costill, D.L., Stein, E., Jansson, E., Essén, B., and Gollnick, D. (1976). The nature of the training response; peripheral and central adaptations of one-legged exercise. Acta Physiol. Scand. *96*, 289–305.

208. Jacobs, I., Esbjörnsson, M., Sylvén, C., Holm, I., and Jansson, E. (1987). Sprint training effects on muscle myoglobin, enzymes, fiber types, and blood lactate. Med. Sci. Sports Exerc. *19*, 368–374.

209. MacDougall, J.D., Hicks, A.L., MacDonald, J.R., McKelvie, R.S., Green, H.J., and Smith, K.M. (1998). Muscle performance and enzymatic adaptations to sprint interval training. J. Appl. Physiol. (1985) *84*, 2138–2142.

210. Burgomaster, K.A., Hughes, S.C., Heigenhauser, G.J., Bradwell, S.N., and Gibala, M.J. (2005). Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. J. Appl. Physiol. (1985) *98*, 1985–1990.

211. Gibala, M.J., Little, J.P., van Essen, M., Wilkin, G.P., Burgomaster, K.A., Safdar, A., Raha, S., and Tarnopolsky, M.A. (2006). Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. J. Physiol. *575*, 901–911.

212. Burgomaster, K.A., Howarth, K.R., Phillips, S.M., Rakobowchuk, M., Macdonald, M.J., McGee, S.L., and Gibala, M.J. (2008). Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. J. Physiol. *586*, 151–160.

213. Lanza, I.R., Short, D.K., Short, K.R., Raghavakaimal, S., Basu, R., Joyner, M.J., McConnell, J.P., and Nair, K.S. (2008). Endurance exercise as a countermeasure for aging. Diabetes *57*, 2933–2942.

214. Mikines, K.J., Sonne, B., Farrell, P.A., Tronier, B., and Galbo, H. (1988). Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am. J. Physiol. *254*, E248–E259.

215. Sjøberg, K.A., Frøsig, C., Kjøbsted, R., Sylow, L., Kleinert, M., Betik, A.C., Shaw, C.S., Kiens, B., Wojtaszewski, J.F.P., Rattigan, S., et al. (2017). Exercise increases human skeletal muscle insulin sensitivity via coordinated increases in microvascular perfusion and molecular signaling. Diabetes *66*, 1501–1510.

216. Malin, S.K., Haus, J.M., Solomon, T.P., Blaszczak, A., Kashyap, S.R., and Kirwan, J.P. (2013). Insulin sensitivity and metabolic flexibility following exercise training among different obese insulin-resistant phenotypes. Am. J. Physiol. Endocrinol. Metab. *305*, E1292–E1298.

217. Malin, S.K., Solomon, T.P., Blaszczak, A., Finnegan, S., Filion, J., and Kirwan, J.P. (2013). Pancreatic beta-cell function increases in a linear dose-response manner following exercise training in adults with prediabetes. Am. J. Physiol. Endocrinol. Metab. *305*, E1248–E1254.

218. Prior, S.J., Blumenthal, J.B., Katzel, L.I., Goldberg, A.P., and Ryan, A.S. (2014). Increased skeletal muscle capillarization after aerobic exercise training and weight loss improves insulin sensitivity in adults with IGT. Diabetes Care *37*, 1469–1475.

219. Newsom, S.A., Everett, A.C., Hinko, A., and Horowitz, J.F. (2013). A single session of low-intensity exercise is sufficient to enhance insulin sensitivity into the next day in obese adults. Diabetes Care *36*, 2516–2522.

220. Dela, F., Larsen, J.J., Mikines, K.J., Ploug, T., Petersen, L.N., and Galbo, H. (1995). Insulin-stimulated muscle glucose clearance in patients with NIDDM. Effects of one-legged physical training. Diabetes *44*, 1010–1020.

221. Kirwan, J.P., Solomon, T.P., Wojta, D.M., Staten, M.A., and Holloszy, J.O. (2009). Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus. Am. J. Physiol. Endocrinol. Metab. *297*, E151–E156.

222. Meex, R.C., Schrauwen-Hinderling, V.B., Moonen-Kornips, E., Schaart, G., Mensink, M., Phielix, E., van de Weijer, T., Sels, J.P., Schrauwen, P., and Hesselink, M.K. (2010). Restoration of muscle mitochondrial function and metabolic flexibility in type 2 diabetes by exercise training is paralleled by increased myocellular fat storage and improved insulin sensitivity. Diabetes *59*, 572–579.

223. Bruce, C.R., Kriketos, A.D., Cooney, G.J., and Hawley, J.A. (2004). Disassociation of muscle triglyceride content and insulin sensitivity after exercise training in patients with type 2 diabetes. Diabetologia *47*, 23–30.

224. Holten, M.K., Zacho, M., Gaster, M., Juel, C., Wojtaszewski, J.F., and Dela, F. (2004). Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. Diabetes *53*, 294–305.

225. Lund, S., Holman, G.D., Schmitz, O., and Pedersen, O. (1995). Contraction stimulates translocation of glucose transporter GLUT4 in skeletal muscle through a mechanism distinct from that of insulin. Proc. Natl. Acad. Sci. USA *92*, 5817–5821.

226. Knudsen, J.R., Steenberg, D.E., Hingst, J.R., Hodgson, L.R., Henriquez-Olguin, C., Li, Z., Kiens, B., Richter, E.A., Wojtaszewski, J.F.P., Verkade, P., and Jensen, T.E. (2020). Prior exercise in humans redistributes intramuscular GLUT4 and enhances insulin-stimulated sarcolemmal and endosomal GLUT4 translocation. Mol. Metab. *39*, 100998.

227. O'Gorman, D.J., Karlsson, H.K., McQuaid, S., Yousif, O., Rahman, Y., Gasparro, D., Glund, S., Chibalin, A.V., Zierath, J.R., and Nolan, J.J. (2006). Exercise training increases insulin-stimulated glucose disposal and GLUT4 (SLC2A4) protein content in patients with type 2 diabetes. Diabetologia *49*, 2983–2992.

228. Frøsig, C., Rose, A.J., Treebak, J.T., Kiens, B., Richter, E.A., and Wojtaszewski, J.F. (2007). Effects of endurance exercise training on insulin signaling in human skeletal muscle: interactions at the level of phosphatidylinositol 3-kinase, Akt, and AS160. Diabetes *56*, 2093–2102.

229. Larsen, M.R., Steenberg, D.E., Birk, J.B., Sjøberg, K.A., Kiens, B., Richter, E.A., and Wojtaszewski, J.F.P. (2020). The insulin-sensitizing effect of a single exercise bout is similar in type I and type II human muscle fibres. J. Physiol. *598*, 5687–5699.

230. Albers, P.H., Pedersen, A.J., Birk, J.B., Kristensen, D.E., Vind, B.F., Baba, O., Nøhr, J., Højlund, K., and Wojtaszewski, J.F. (2015). Human muscle fiber type-specific insulin signaling: impact of obesity and type 2 diabetes. Diabetes *64*, 485–497.

231. Dela, F., Ingersen, A., Andersen, N.B., Nielsen, M.B., Petersen, H.H.H., Hansen, C.N., Larsen, S., Wojtaszewski, J., and Helge, J.W. (2019). Effects of one-legged high-intensity interval training on insulin-mediated skeletal muscle glucose homeostasis in patients with type 2 diabetes. Acta Physiol. Oxf. *226*, e13245.

232. Vukovich, M.D., Arciero, P.J., Kohrt, W.M., Racette, S.B., Hansen, P.A., and Holloszy, J.O. (1996). Changes in insulin action and GLUT-4 with 6 days of inactivity in endurance runners. J. Appl. Physiol. (1985) *80*, 240–244.

233. Shaw, K., Gennat, H., O'Rourke, P., and Del Mar, C. (2006). Exercise for overweight or obesity. Cochrane Database Syst. Rev. *2006*, CD003817.

234. Keating, S.E., Hackett, D.A., Parker, H.M., O'Connor, H.T., Gerofi, J.A., Sainsbury, A., Baker, M.K., Chuter, V.H., Caterson, I.D., George, J., and Johnson, N.A. (2015). Effect of aerobic exercise training dose on liver fat and visceral adiposity. J. Hepatol. *63*, 174–182.

235. Johnson, N.A., Sachinwalla, T., Walton, D.W., Smith, K., Armstrong, A., Thompson, M.W., and George, J. (2009). Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. Hepatology *50*, 1105–1112.

236. Wilmore, J.H., Després, J.P., Stanforth, P.R., Mandel, S., Rice, T., Gagnon, J., Leon, A.S., Rao, D., Skinner, J.S., and Bouchard, C. (1999). Alterations in body weight and composition consequent to 20 wk of endurance training: the Heritage Family Study. Am. J. Clin. Nutr. *70*, 346–352.

237. Christiansen, T., Paulsen, S.K., Bruun, J.M., Overgaard, K., Ringgaard, S., Pedersen, S.B., Positano, V., and Richelsen, B. (2009). Comparable reduction of the visceral adipose tissue depot after a diet-induced weight loss with or without aerobic exercise in obese subjects: a 12-week randomized intervention study. Eur. J. Endocrinol. *160*, 759–767.

238. Larson-Meyer, D.E., Redman, L., Heilbronn, L.K., Martin, C.K., and Ravussin, E. (2010). Caloric restriction with or without exercise: the fitness versus fatness debate. Med. Sci. Sports Exerc. *42*, 152–159.

239. Giannopoulou, I., Ploutz-Snyder, L.L., Carhart, R., Weinstock, R.S., Fernhall, B., Goulopoulou, S., and Kanaley, J.A. (2005). Exercise is required for visceral fat loss in postmenopausal women with type 2 diabetes. J. Clin. Endocrinol. Metab. *90*, 1511–1518.

240. Kim, M.K., Tomita, T., Kim, M.J., Sasai, H., Maeda, S., and Tanaka, K. (2009). Aerobic exercise training reduces epicardial fat in obese men. J. Appl. Physiol. (1985) *106*, 5–11.

241. Jonker, J.T., de Mol, P., de Vries, S.T., Widya, R.L., Hammer, S., van Schinkel, L.D., van der Meer, R.W., Gans, R.O., Webb, A.G., Kan, H.E., et al. (2013). Exercise and type 2 diabetes mellitus: changes in tissue-specific fat distribution and cardiac function. Radiology *269*, 434–442.

242. Heiskanen, M.A., Motiani, K.K., Mari, A., Saunavaara, V., Eskelinen, J.J., Virtanen, K.A., Koivumäki, M., Löyttyniemi, E., Nuutila, P., Kalliokoski, K.K., and Hannukainen, J.C. (2018). Exercise training decreases pancreatic fat content and improves beta cell function regardless of baseline glucose tolerance: a randomised controlled trial. Diabetologia *61*, 1817–1828.

243. Murphy, J.C., McDaniel, J.L., Mora, K., Villareal, D.T., Fontana, L., and Weiss, E.P. (2012). Preferential reductions in intermuscular and visceral adipose tissue with exercise-induced weight loss compared with calorie restriction. J. Appl. Physiol. (1985) *112*, 79–85.

244. Goodpaster, B.H., He, J., Watkins, S., and Kelley, D.E. (2001). Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. J. Clin. Endocrinol. Metab. *86*, 5755–5761.

245. Daemen, S., Gemmink, A., Brouwers, B., Meex, R.C.R., Huntjens, P.R., Schaart, G., Moonen-Kornips, E., Jörgensen, J., Hoeks, J., Schrauwen, P., and Hesselink, M.K.C. (2018). Distinct lipid droplet characteristics and distribution unmask the apparent contradiction of the athlete's paradox. Mol. Metab. *17*, 71–81.

246. Koh, H.E., Nielsen, J., Saltin, B., Holmberg, H.C., and Ørtenblad, N. (2017). Pronounced limb and fibre type differences in subcellular lipid droplet content and distribution in elite skiers before and after exhaustive exercise. J. Physiol. *595*, 5781–5795.

247. Weisberg, S.P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R.L., and Ferrante, A.W., Jr. (2003). Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Invest. *112*, 1796–1808.

248. Olefsky, J.M. (1977). Insensitivity of large rat adipocytes to the antilipolytic effects of insulin. J. Lipid Res. *18*, 459–464.

249. Stinkens, R., Brouwers, B., Jocken, J.W., Blaak, E.E., Teunissen-Beekman, K.F., Hesselink, M.K., van Baak, M.A., Schrauwen, P., and Goossens, G.H. (2018). Exercise training-induced effects on the abdominal subcutaneous adipose tissue phenotype in humans with obesity. J. Appl. Physiol. (1985) *125*, 1585–1593.

250. Després, J.P., Bouchard, C., Savard, R., Tremblay, A., Marcotte, M., and Thériault, G. (1984). The effect of a 20-week endurance training program on adipose-tissue morphology and lipolysis in men and women. Metabolism *33*, 235–239.

251. Després, J.P., Bouchard, C., Savard, R., Tremblay, A., and Allard, C. (1985). Lack of relationship between changes in adiposity and plasma lipids following endurance training. Atherosclerosis *54*, 135–143.

252. You, T., Murphy, K.M., Lyles, M.F., Demons, J.L., Lenchik, L., and Nicklas, B.J. (2006). Addition of aerobic exercise to dietary weight loss preferentially reduces abdominal adipocyte size. Int. J. Obes. (Lond) *30*, 1211–1216.

253. Gollisch, K.S., Brandauer, J., Jessen, N., Toyoda, T., Nayer, A., Hirshman, M.F., and Goodyear, L.J. (2009). Effects of exercise training on subcutaneous and visceral adipose tissue in normal- and high-fat diet-fed rats. Am. J. Physiol. Endocrinol. Metab. *297*, E495–E504.

254. Craig, B.W., Hammons, G.T., Garthwaite, S.M., Jarett, L., and Holloszy, J.O. (1981). Adaptation of fat cells to exercise: response of glucose uptake and oxidation to insulin. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. *51*, 1500–1506.

255. Hoffmann, C., Schneeweiss, P., Randrianarisoa, E., Schnauder, G., Kappler, L., Machann, J., Schick, F., Fritsche, A., Heni, M., Birkenfeld, A., et al. (2020). Response of mitochondrial respiration in adipose tissue and muscle to 8 weeks of endurance exercise in obese subjects. J. Clin. Endocrinol. Metab. *105*, e4023–e4037.

256. Emont, M.P., Jacobs, C., Essene, A.L., Pant, D., Tenen, D., Colleluori, G., Di Vincenzo, A., Jørgensen, A.M., Dashti, H., Stefek, A., et al. (2022). A single-cell atlas of human and mouse white adipose tissue. Nature *603*, 926–933.

257. Bäckdahl, J., Franzén, L., Massier, L., Li, Q., Jalkanen, J., Gao, H., Andersson, A., Bhalla, N., Thorell, A., Rydén, M., et al. (2021). Spatial mapping reveals human adipocyte subpopulations with distinct sensitivities to insulin. Cell Metab. *33*, 1869–1882.e6.

258. Nigro, P., Vamvini, M., Yang, J., Caputo, T., Ho, L.L., Carbone, N.P., Papadopoulos, D., Conlin, R., He, J., Hirshman, M.F., et al. (2023). Exercise training remodels inguinal white adipose tissue through adaptations in innervation, vascularization, and the extracellular matrix. Cell Rep. *42*, 112392.

259. Maniyadath, B., Zhang, Q., Gupta, R.K., and Mandrup, S. (2023). Adipose tissue at single-cell resolution. Cell Metab. *35*, 386–413.

260. Sial, S., Coggan, A.R., Hickner, R.C., and Klein, S. (1998). Training-induced alterations in fat and carbohydrate metabolism during exercise in elderly subjects. Am. J. Physiol. *274*, E785–E790.

261. Phillips, S.M., Green, H.J., Tarnopolsky, M.A., Heigenhauser, G.F., Hill, R.E., and Grant, S.M. (1996). Effects of training duration on substrate turnover and oxidation during exercise. J. Appl. Physiol. (1985) *81*, 2182–2191.

262. Horowitz, J.F., Leone, T.C., Feng, W., Kelly, D.P., and Klein, S. (2000). Effect of endurance training on lipid metabolism in women: a potential role for PPARalpha in the metabolic response to training. Am. J. Physiol. Endocrinol. Metab. *279*, E348–E355.

263. Poehlman, E.T., Tremblay, A., Marcotte, M., Pérusse, L., Thériault, G., and Bouchard, C. (1987). Heredity and changes in body composition and adipose tissue metabolism after short-term exercise-training. Eur. J. Appl. Physiol. Occup. Physiol. *56*, 398–402.

264. Després, J.P., Bouchard, C., Savard, R., Tremblay, A., Marcotte, M., and Thériault, G. (1984). Effects of exercise-training and detraining on fat cell lipolysis in men and women. Eur. J. Appl. Physiol. Occup. Physiol. *53*, 25–30.

265. Krotkiewski, M., Lönnroth, P., Mandroukas, K., Wroblewski, Z., Rebuffé--Scrive, M., Holm, G., Smith, U., and Björntorp, P. (1985). The effects of physical training on insulin secretion and effectiveness and on glucose metabolism in obesity and type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia *28*, 881–890.

266. Wirth, A., Diehm, C., Hanel, W., Welte, J., and Vogel, I. (1985). Training-induced changes in serum lipids, fat tolerance, and adipose tissue metabolism in patients with hypertriglyceridemia. Atherosclerosis *54*, 263–271.

267. De Glisezinski, I., Crampes, F., Harant, I., Berlan, M., Hejnova, J., Langin, D., Rivière, D., and Stich, V. (1998). Endurance training changes in lipolytic responsiveness of obese adipose tissue. Am. J. Physiol. *275*, E951–E956.

268. van Aggel-Leijssen, D.P., Saris, W.H., Wagenmakers, A.J., Hul, G.B., and van Baak, M.A. (2001). The effect of low-intensity exercise training on fat metabolism of obese women. Obes. Res. *9*, 86–96.

269. Horowitz, J.F., Braudy, R.J., Martin, W.H., 3rd, and Klein, S. (1999). Endurance exercise training does not alter lipolytic or adipose tissue blood flow sensitivity to epinephrine. Am. J. Physiol. *277*, E325–E331.

270. van Aggel-Leijssen, D.P., Saris, W.H., Homan, M., and van Baak, M.A. (2001). The effect of exercise training on beta-adrenergic stimulation of fat metabolism in obese men. Int. J. Obes. Relat. Metab. Disord. *25*, 16–23.

271. DiPietro, L., Dziura, J., Yeckel, C.W., and Neufer, P.D. (2006). Exercise and improved insulin sensitivity in older women: evidence of the enduring benefits of higher intensity training. J. Appl. Physiol. (1985) *100*, 142–149.

272. Shojaee-Moradie, F., Baynes, K.C., Pentecost, C., Bell, J.D., Thomas, E.L., Jackson, N.C., Stolinski, M., Whyte, M., Lovell, D., Bowes, S.B., et al. (2007). Exercise training reduces fatty acid availability and improves the insulin sensitivity of glucose metabolism. Diabetologia *50*, 404–413.

273. Hickner, R.C., Racette, S.B., Binder, E.F., Fisher, J.S., and Kohrt, W.M. (2000). Effects of 10 days of endurance exercise training on the suppression of whole body and regional lipolysis by insulin. J. Clin. Endocrinol. Metab. *85*, 1498–1504.

274. Engin, B., Willis, S.A., Malaikah, S., Sargeant, J.A., Yates, T., Gray, L.J., Aithal, G.P., Stensel, D.J., and King, J.A. (2022). The effect of exercise training on adipose tissue insulin sensitivity: a systematic review and meta-analysis. Obes. Rev. *23*, e13445.

275. Stallknecht, B., Larsen, J.J., Mikines, K.J., Simonsen, L., Bülow, J., and Galbo, H. (2000). Effect of training on insulin sensitivity of glucose uptake and lipolysis in human adipose tissue. Am. J. Physiol. Endocrinol. Metab. *279*, E376–E385.

276. Hussey, S.E., McGee, S.L., Garnham, A., Wentworth, J.M., Jeukendrup, A.E., and Hargreaves, M. (2011). Exercise training increases adipose tissue GLUT4 expression in patients with type 2 diabetes. Diabetes Obes. Metab. *13*, 959–962.

277. Flores-Opazo, M., Boland, E., Garnham, A., Murphy, R.M., McGee, S.L., and Hargreaves, M. (2018). Exercise and GLUT4 in human subcutaneous adipose tissue. Physiol. Rep. *6*, e13918.

278. Henderson, G.C., Fattor, J.A., Horning, M.A., Faghihnia, N., Johnson, M.L., Mau, T.L., Luke-Zeitoun, M., and Brooks, G.A. (2007). Lipolysis and fatty acid metabolism in men and women during the postexercise recovery period. J. Physiol. *584*, 963–981.

279. Stanford, K.I., Middelbeek, R.J., Townsend, K.L., Lee, M.Y., Takahashi, H., So, K., Hitchcox, K.M., Markan, K.R., Hellbach, K., Hirshman, M.F., et al. (2015). A novel role for subcutaneous adipose tissue in exercise-induced improvements in glucose homeostasis. Diabetes *64*, 2002–2014.

280. Camera, D.M., Anderson, M.J., Hawley, J.A., and Carey, A.L. (2010). Short-term endurance training does not alter the oxidative capacity of human subcutaneous adipose tissue. Eur. J. Appl. Physiol. *109*, 307–316.

281. Dreher, S.I., Irmler, M., Pivovarova-Ramich, O., Kessler, K., Jürchott, K., Sticht, C., Fritsche, L., Schneeweiss, P., Machann, J., Pfeiffer, A.F.H., et al. (2023). Acute and long-term exercise adaptation of adipose tissue and skeletal muscle in humans: a matched transcriptomics approach after 8-week training-intervention. Int. J. Obes. (Lond) *47*, 313–324.

282. Brandao, C.F.C., de Carvalho, F.G., Souza, A.O., Junqueira-Franco, M.V.M., Batitucci, G., Couto-Lima, C.A., Fett, C.A., Papoti, M., Freitas, E.C., Alberici, L.C., and Marchini, J.S. (2019). Physical training, UCP1 expression, mitochondrial density, and coupling in adipose tissue from women with obesity. Scand. J. Med. Sci. Sports *29*, 1699–1706.

283. Dohlmann, T.L., Hindsø, M., Dela, F., Helge, J.W., and Larsen, S. (2018). High-intensity interval training changes mitochondrial respiratory capacity differently in adipose tissue and skeletal muscle. Physiol. Rep. *6*, e13857.

284. Larsen, S., Danielsen, J.H., Søndergård, S.D., Søgaard, D., Vigelsoe, A., Dybboe, R., Skaaby, S., Dela, F., and Helge, J.W. (2015). The effect of high-intensity training on mitochondrial fat oxidation in skeletal muscle and subcutaneous adipose tissue. Scand. J. Med. Sci. Sports *25*, e59–e69.

285. Mendham, A.E., Larsen, S., George, C., Adams, K., Hauksson, J., Olsson, T., Fortuin-de Smidt, M.C., Nono Nankam, P.A., Hakim, O., Goff, L.M., et al. (2020). Exercise training results in depot-specific adaptations to adipose tissue mitochondrial function. Sci. Rep. *10*, 3785.

286. Riis, S., Christensen, B., Nellemann, B., Møller, A.B., Husted, A.S., Pedersen, S.B., Schwartz, T.W., Jørgensen, J.O.L., and Jessen, N. (2019). Molecular adaptations in human subcutaneous adipose tissue after ten weeks of endurance exercise training in healthy males. J. Appl. Physiol. (1985) *126*, 569–577.

287. Rönn, T., Volkov, P., Tornberg, A., Elgzyri, T., Hansson, O., Eriksson, K.F., Groop, L., and Ling, C. (2014). Extensive changes in the transcriptional profile of human adipose tissue including genes involved in oxidative phosphorylation after a 6-month exercise intervention. Acta Physiol. Oxf. *211*, 188–200.

288. Gudiksen, A., Qoqaj, A., Ringholm, S., Wojtaszewski, J., Plomgaard, P., and Pilegaard, H. (2022). Ameliorating effects of lifelong physical activity on healthy aging and mitochondrial function in human white adipose tissue. J. Gerontol. A Biol. Sci. Med. Sci. *77*, 1101–1111.

289. Norheim, F., Langleite, T.M., Hjorth, M., Holen, T., Kielland, A., Stadheim, H.K., Gulseth, H.L., Birkeland, K.I., Jensen, J., and Drevon, C.A. (2014). The effects of acute and chronic exercise on PGC-1alpha, irisin and browning of subcutaneous adipose tissue in humans. FEBS J. *281*, 739–749.

290. Tsiloulis, T., Carey, A.L., Bayliss, J., Canny, B., Meex, R.C.R., and Watt, M.J. (2018). No evidence of white adipocyte browning after endurance exercise training in obese men. Int. J. Obes. (Lond) *42*, 721–727.

291. Becher, T., Palanisamy, S., Kramer, D.J., Eljalby, M., Marx, S.J., Wibmer, A.G., Butler, S.D., Jiang, C.S., Vaughan, R., Schöder, H., et al. (2021). Brown adipose tissue is associated with cardiometabolic health. Nat. Med. *27*, 58–65.

292. Vosselman, M.J., Hoeks, J., Brans, B., Pallubinsky, H., Nascimento, E.B., van der Lans, A.A., Broeders, E.P., Mottaghy, F.M., Schrauwen, P., and van Marken Lichtenbelt, W.D. (2015). Low brown adipose tissue activity in endurance-trained compared with lean sedentary men. Int. J. Obes. (Lond) *39*, 1696–1702.

293. Martinez-Tellez, B., Sanchez-Delgado, G., Acosta, F.M., Alcantara, J.M.A., Amaro-Gahete, F.J., Martinez-Avila, W.D., Merchan-Ramirez, E., Muñoz-Hernandez, V., Osuna-Prieto, F.J., Jurado-Fasoli, L., et al. (2022). No evidence of brown adipose tissue activation after 24 weeks of supervised exercise training in young sedentary adults in the ACTIBATE randomized controlled trial. Nat. Commun. *13*, 5259.

294. Mendez-Gutierrez, A., Aguilera, C.M., Osuna-Prieto, F.J., Martinez-Tellez, B., Rico Prados, M.C., Acosta, F.M., Llamas-Elvira, J.M., Ruiz, J.R., and Sanchez-Delgado, G. (2023). Exercise-induced changes on exerkines that might influence brown adipose tissue metabolism in young sedentary adults. Eur. J. Sport Sci. *23*, 625–636.

295. DeFronzo, R.A., Simonson, D., and Ferrannini, E. (1982). Hepatic and peripheral insulin resistance: a common feature of type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetes mellitus. Diabetologia *23*, 313–319.

296. DeFronzo, R.A., Sherwin, R.S., and Kraemer, N. (1987). Effect of physical training on insulin action in obesity. Diabetes *36*, 1379–1385.

297. Winnick, J.J., Sherman, W.M., Habash, D.L., Stout, M.B., Failla, M.L., Belury, M.A., and Schuster, D.P. (2008). Short-term aerobic exercise training in obese humans with type 2 diabetes mellitus improves whole-body insulin sensitivity through gains in peripheral, not hepatic insulin sensitivity. J. Clin. Endocrinol. Metab. *93*, 771–778.

298. Haus, J.M., Solomon, T.P., Marchetti, C.M., Edmison, J.M., González, F., and Kirwan, J.P. (2010). Free fatty acid-induced hepatic insulin resistance is attenuated following lifestyle intervention in obese individuals with impaired glucose tolerance. J. Clin. Endocrinol. Metab. *95*, 323–327.

299. Segal, K.R., Edano, A., Abalos, A., Albu, J., Blando, L., Tomas, M.B., and Pi-Sunyer, F.X. (1991). Effect of exercise training on insulin sensitivity and glucose metabolism in lean, obese, and diabetic men. J. Appl. Physiol. (1985) *71*, 2402–2411.

300. Gregory, J.M., Muldowney, J.A., Engelhardt, B.G., Tyree, R., Marks-Shulman, P., Silver, H.J., Donahue, E.P., Edgerton, D.S., and Winnick, J.J. (2019). Aerobic exercise training improves hepatic and muscle insulin sensitivity, but reduces splanchnic glucose uptake in obese humans with type 2 diabetes. Nutr. Diabetes *9*, 25.

301. Byrne, C.D., and Targher, G. (2015). NAFLD: a multisystem disease. J. Hepatol. *62*, S47–S64.

302. Finucane, F.M., Sharp, S.J., Purslow, L.R., Horton, K., Horton, J., Savage, D.B., Brage, S., Besson, H., De Lucia Rolfe, E., Sleigh, A., et al. (2010). The effects of aerobic exercise on metabolic risk, insulin sensitivity and intrahepatic lipid in healthy older people from the Hertfordshire Cohort Study: a randomised controlled trial. Diabetologia *53*, 624–631.

303. Lee, S., Bacha, F., Hannon, T., Kuk, J.L., Boesch, C., and Arslanian, S. (2012). Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat, intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. Diabetes *61*, 2787–2795.

304. van der Heijden, G.J., Wang, Z.J., Chu, Z.D., Sauer, P.J., Haymond, M.W., Rodriguez, L.M., and Sunehag, A.L. (2010). A 12-week aerobic exercise program reduces hepatic fat accumulation and insulin resistance in obese, Hispanic adolescents. Obesity (Silver Spring) *18*, 384–390.

305. Lee, S., Deldin, A.R., White, D., Kim, Y., Libman, I., Rivera-Vega, M., Kuk, J.L., Sandoval, S., Boesch, C., and Arslanian, S. (2013). Aerobic exercise but not resistance exercise reduces intrahepatic lipid content and visceral fat and improves insulin sensitivity in obese adolescent girls: a randomized controlled trial. Am. J. Physiol. Endocrinol. Metab. *305*, E1222–E1229.

306. Cassidy, S., Thoma, C., Hallsworth, K., Parikh, J., Hollingsworth, K.G., Taylor, R., Jakovljevic, D.G., and Trenell, M.I. (2016). High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial. Diabetologia *59*, 56–66.

307. Bacchi, E., Negri, C., Targher, G., Faccioli, N., Lanza, M., Zoppini, G., Zanolin, E., Schena, F., Bonora, E., and Moghetti, P. (2013). Both resistance training and aerobic training reduce hepatic fat content in type 2 diabetic subjects with nonalcoholic fatty liver disease (the RAED2 randomized trial). Hepatology *58*, 1287–1295.

308. Pugh, C.J., Spring, V.S., Kemp, G.J., Richardson, P., Shojaee-Moradie, F., Umpleby, A.M., Green, D.J., Cable, N.T., Jones, H., and Cuthbertson, D.J. (2014). Exercise training reverses endothelial dysfunction in nonalcoholic fatty liver disease. Am. J. Physiol. Heart Circ. Physiol. *307*, H1298–H1306.

309. Hallsworth, K., Fattakhova, G., Hollingsworth, K.G., Thoma, C., Moore, S., Taylor, R., Day, C.P., and Trenell, M.I. (2011). Resistance exercise reduces liver fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. Gut *60*, 1278–1283.

310. Winn, N.C., Liu, Y., Rector, R.S., Parks, E.J., Ibdah, J.A., and Kanaley, J.A. (2018). Energy-matched moderate and high intensity exercise training improves nonalcoholic fatty liver disease risk independent of changes in body mass or abdominal adiposity - a randomized trial. Metabolism *78*, 128–140.

311. Brouwers, B., Schrauwen-Hinderling, V.B., Jelenik, T., Gemmink, A., Sparks, L.M., Havekes, B., Bruls, Y., Dahlmans, D., Roden, M., Hesselink, M.K.C., and Schrauwen, P. (2018). Exercise training reduces intrahepatic lipid content in people with and people without nonalcoholic fatty liver. Am. J. Physiol. Endocrinol. Metab. *314*, E165–E173.

312. Sullivan, S., Kirk, E.P., Mittendorfer, B., Patterson, B.W., and Klein, S. (2012). Randomized trial of exercise effect on intrahepatic triglyceride content and lipid kinetics in nonalcoholic fatty liver disease. Hepatology *55*, 1738–1745.

313. Sargeant, J.A., Bawden, S., Aithal, G.P., Simpson, E.J., Macdonald, I.A., Turner, M.C., Cegielski, J., Smith, K., Dorling, J.L., Gowland, P.A., et al. (2018). Effects of sprint interval training on ectopic lipids and tissue-specific insulin sensitivity in men with non-alcoholic fatty liver disease. Eur. J. Appl. Physiol. *118*, 817–828.

314. Cuthbertson, D.J., Shojaee-Moradie, F., Sprung, V.S., Jones, H., Pugh, C.J., Richardson, P., Kemp, G.J., Barrett, M., Jackson, N.C., Thomas, E.L., et al. (2016). Dissociation between exercise-induced reduction in liver fat and changes in hepatic and peripheral glucose homoeostasis in obese patients with non-alcoholic fatty liver disease. Clin. Sci. (Lond.) *130*, 93–104.

315. Houghton, D., Thoma, C., Hallsworth, K., Cassidy, S., Hardy, T., Burt, A.D., Tiniakos, D., Hollingsworth, K.G., Taylor, R., Day, C.P., et al. (2017). Exercise reduces liver lipids and visceral adiposity in patients with nonalcoholic steatohepatitis in a randomized controlled trial. Clin. Gastroenterol. Hepatol. *15*, 96–102.e3.

316. Malin, S.K., Mulya, A., Fealy, C.E., Haus, J.M., Pagadala, M.R., Scelsi, A.R., Huang, H., Flask, C.A., McCullough, A.J., and Kirwan, J.P. (2013).

Fetuin-A is linked to improved glucose tolerance after short-term exercise training in nonalcoholic fatty liver disease. J. Appl. Physiol. (1985) *115*, 988–994.

317. Haus, J.M., Solomon, T.P., Kelly, K.R., Fealy, C.E., Kullman, E.L., Scelsi, A.R., Lu, L., Pagadala, M.R., McCullough, A.J., Flask, C.A., and Kirwan, J.P. (2013). Improved hepatic lipid composition following short-term exercise in nonalcoholic fatty liver disease. J. Clin. Endocrinol. Metab. *98*, E1181–E1188.

318. Sargeant, J.A., Gray, L.J., Bodicoat, D.H., Willis, S.A., Stensel, D.J., Nimmo, M.A., Aithal, G.P., and King, J.A. (2018). The effect of exercise training on intrahepatic triglyceride and hepatic insulin sensitivity: a systematic review and meta-analysis. Obes. Rev. *19*, 1446–1459.

319. King, D.S., Dalsky, G.P., Staten, M.A., Clutter, W.E., Van Houten, D.R., and Holloszy, J.O. (1987). Insulin action and secretion in endurance-trained and untrained humans. J. Appl. Physiol. (1985) *63*, 2247–2252.

320. Dela, F., Mikines, K.J., Tronier, B., and Galbo, H. (1990). Diminished arginine-stimulated insulin secretion in trained men. J. Appl. Physiol. (1985) *69*, 261–267.

321. King, D.S., Staten, M.A., Kohrt, W.M., Dalsky, G.P., Elahi, D., and Holloszy, J.O. (1990). Insulin secretory capacity in endurance-trained and untrained young men. Am. J. Physiol. *259*, E155–E161.

322. Kirwan, J.P., Kohrt, W.M., Wojta, D.M., Bourey, R.E., and Holloszy, J.O. (1993). Endurance exercise training reduces glucose-stimulated insulin levels in 60- to 70-year-old men and women. J. Gerontol. *48*, M84–M90.

323. Dela, F., von Linstow, M.E., Mikines, K.J., and Galbo, H. (2004). Physical training may enhance beta-cell function in type 2 diabetes. Am. J. Physiol. Endocrinol. Metab. *287*, E1024–E1031.

324. Solomon, T.P., Haus, J.M., Kelly, K.R., Rocco, M., Kashyap, S.R., and Kirwan, J.P. (2010). Improved pancreatic beta-cell function in type 2 diabetic patients after lifestyle-induced weight loss is related to glucose-dependent insulinotropic polypeptide. Diabetes Care *33*, 1561–1566.

325. Solomon, T.P., Malin, S.K., Karstoft, K., Kashyap, S.R., Haus, J.M., and Kirwan, J.P. (2013). Pancreatic beta-cell function is a stronger predictor of changes in glycemic control after an aerobic exercise intervention than insulin sensitivity. J. Clin. Endocrinol. Metab. *98*, 4176–4186.

326. Bergman, R.N., Ader, M., Huecking, K., and Van Citters, G. (2002). Accurate assessment of beta-cell function: the hyperbolic correction. Diabetes *51*, S212–S220.

327. AbouAssi, H., Slentz, C.A., Mikus, C.R., Tanner, C.J., Bateman, L.A., Willis, L.H., Shields, A.T., Piner, L.W., Penry, L.E., Kraus, E.A., et al. (2015). The effects of aerobic, resistance, and combination training on insulin sensitivity and secretion in overweight adults from STRRIDE AT/RT: a randomized trial. J. Appl. Physiol. (1985) *118*, 1474–1482.

328. Croymans, D.M., Paparisto, E., Lee, M.M., Brandt, N., Le, B.K., Lohan, D., Lee, C.C., and Roberts, C.K. (2013). Resistance training improves indices of muscle insulin sensitivity and beta-cell function in overweight/obese, sedentary young men. J. Appl. Physiol. (1985) *115*, 1245–1253.

329. Shih, K.C., and Kwok, C.F. (2018). Exercise reduces body fat and improves insulin sensitivity and pancreatic beta-cell function in overweight and obese male Taiwanese adolescents. BMC Pediatr. *18*, 80.

330. Slentz, C.A., Tanner, C.J., Bateman, L.A., Durheim, M.T., Huffman, K.M., Houmard, J.A., and Kraus, W.E. (2009). Effects of exercise training intensity on pancreatic beta-cell function. Diabetes Care *32*, 1807–1811.

331. Backx, K., McCann, A., Wasley, D., Dunseath, G., Luzio, S., and Owens, D. (2011). The effect of a supported exercise programme in patients with newly diagnosed type 2 diabetes: a pilot study. J. Sports Sci. *29*, 579–586.

332. Madsen, S.M., Thorup, A.C., Overgaard, K., and Jeppesen, P.B. (2015). High intensity interval training improves glycaemic control and pancreatic beta cell function of type 2 diabetes patients. PloS One *10*, e0133286.

333. Dela, F., and Stallknecht, B. (2010). Effect of physical training on insulin secretion and action in skeletal muscle and adipose tissue of first-degree relatives of type 2 diabetic patients. Am. J. Physiol. Endocrinol. Metab. *299*, E80–E91.

334. Hordern, M.D., Cooney, L.M., Beller, E.M., Prins, J.B., Marwick, T.H., and Coombes, J.S. (2008). Determinants of changes in blood glucose response to short-term exercise training in patients with type 2 diabetes. Clin. Sci. (Lond.) *115*, 273–281.

335. Rahier, J., Guiot, Y., Goebbels, R.M., Sempoux, C., and Henquin, J.C. (2008). Pancreatic beta-cell mass in European subjects with type 2 diabetes. Diabetes Obes. Metab. *10*, 32–42.

336. Marselli, L., Suleiman, M., Masini, M., Campani, D., Bugliani, M., Syed, F., Martino, L., Focosi, D., Scatena, F., Olimpico, F., et al. (2014). Are we overestimating the loss of beta cells in type 2 diabetes? Diabetologia *57*, 362–365.

337. Choi, S.B., Jang, J.S., Hong, S.M., Jun, D.W., and Park, S. (2006). Exercise and dexamethasone oppositely modulate beta-cell function and survival via independent pathways in 90% pancreatectomized rats. J. Endocrinol. *190*, 471–482.

338. Király, M.A., Bates, H.E., Yue, J.T., Goche-Montes, D., Fediuc, S., Park, E., Matthews, S.G., Vranic, M., and Riddell, M.C. (2007). Attenuation of type 2 diabetes mellitus in the male Zucker diabetic fatty rat: the effects of stress and non-volitional exercise. Metabolism *56*, 732–744.

339. Carvalho, V.H.C., Wang, Q., Xu, X., Liu, L., Jiang, W., Wang, X., Wang, J., Li, W., Chen, J., Li, T., et al. (2023). Long-term exercise preserves pancreatic islet structure and beta-cell mass through attenuation of islet inflammation and fibrosis. FASEB J. *37*, e22822.

340. Holst, J.J., Knop, F.K., Vilsbøll, T., Krarup, T., and Madsbad, S. (2011). Loss of incretin effect is a specific, important, and early characteristic of type 2 diabetes. Diabetes Care *34*, S251–S257.

341. Åkerström, T., Stolpe, M.N., Widmer, R., Dejgaard, T.F., Højberg, J.M., Møller, K., Hansen, J.S., Trinh, B., Holst, J.J., Thomsen, C., et al. (2022). Endurance training improves GLP-1 sensitivity and glucose tolerance in overweight women. J. Endocr. Soc. *6*, bvac111.

342. Jensen, S.B.K., Juhl, C.R., Janus, C., Lundgren, J.R., Martinussen, C., Wiingaard, C., Knudsen, C., Frikke-Schmidt, R., Stallknecht, B.M., Holst, J.J., et al. (2023). Weight loss maintenance with exercise and liraglutide improves glucose tolerance, glucagon response, and beta cell function. Obesity (Silver Spring) *31*, 977–989.

343. Sargeant, J.A., Henson, J., King, J.A., Yates, T., Khunti, K., and Davies, M.J. (2019). A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans. Endocrinol. Metab. (Seoul) *34*, 247–262.

344. Brooks, A.W., Priya, S., Blekhman, R., and Bordenstein, S.R. (2018). Gut microbiota diversity across ethnicities in the United States. PLoS Biol. *16*, e2006842.

345. de Vos, W.M., Tilg, H., Van Hul, M., and Cani, P.D. (2022). Gut microbiome and health: mechanistic insights. Gut *71*, 1020–1032.

346. Fan, Y., and Pedersen, O. (2021). Gut microbiota in human metabolic health and disease. Nat. Rev. Microbiol. *19*, 55–71.

347. Tilg, H., Cani, P.D., and Mayer, E.A. (2016). Gut microbiome and liver diseases. Gut *65*, 2035–2044.

348. Clarke, S.F., Murphy, E.F., O'Sullivan, O., Lucey, A.J., Humphreys, M., Hogan, A., Hayes, P., O'Reilly, M., Jeffery, I.B., Wood-Martin, R., et al. (2014). Exercise and associated dietary extremes impact on gut microbial diversity. Gut *63*, 1913–1920.

349. Barton, W., Penney, N.C., Cronin, O., Garcia-Perez, I., Molloy, M.G., Holmes, E., Shanahan, F., Cotter, P.D., and O'Sullivan, O. (2018). The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level. Gut *67*, 625–633.

350. Kang, S.S., Jeraldo, P.R., Kurti, A., Miller, M.E., Cook, M.D., Whitlock, K., Goldenfeld, N., Woods, J.A., White, B.A., Chia, N., and Fryer, J.D. (2014). Diet and exercise orthogonally alter the gut microbiome and reveal independent associations with anxiety and cognition. Mol. Neurodegener. *9*, 36.

351. Allen, J.M., Berg Miller, M.E., Pence, B.D., Whitlock, K., Nehra, V., Gaskins, H.R., White, B.A., Fryer, J.D., and Woods, J.A. (2015). Voluntary and forced exercise differentially alters the gut microbiome in C57BL/6J mice. J. Appl. Physiol. (1985) *118*, 1059–1066.

352. Matsumoto, M., Inoue, R., Tsukahara, T., Ushida, K., Chiji, H., Matsubara, N., and Hara, H. (2008). Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum. Biosci. Biotechnol. Biochem. *72*, 572–576.

353. Allen, J.M., Mailing, L.J., Niemiro, G.M., Moore, R., Cook, M.D., White, B.A., Holscher, H.D., and Woods, J.A. (2018). Exercise alters gut microbiota composition and function in lean and obese humans. Med. Sci. Sports Exerc. *50*, 747–757.

354. Cronin, O., Barton, W., Skuse, P., Penney, N.C., Garcia-Perez, I., Murphy, E.F., Woods, T., Nugent, H., Fanning, A., Melgar, S., et al. (2018). A prospective metagenomic and metabolomic analysis of the impact of exercise and/or whey protein supplementation on the gut microbiome of sedentary adults. mSystems *3*. e00044–e00018.

355. Munukka, E., Ahtiainen, J.P., Puigbó, P., Jalkanen, S., Pahkala, K., Keskitalo, A., Kujala, U.M., Pietilä, S., Hollmén, M., Elo, L., et al. (2018). Six-week endurance exercise alters gut metagenome that is not reflected in systemic metabolism in over-weight women. Front. Microbiol. *9*, 2323.

356. Craven, J., Cox, A.J., Bellinger, P., Desbrow, B., Irwin, C., Buchan, J., McCartney, D., and Sabapathy, S. (2022). The influence of exercise training volume alterations on the gut microbiome in highly-trained middle-distance runners. Eur. J. Sport Sci. *22*, 1222–1230.

357. Zhong, F., Wen, X., Yang, M., Lai, H.Y., Momma, H., Cheng, L., Sun, X., Nagatomi, R., and Huang, C. (2021). Effect of an 8-week exercise training on gut microbiota in physically inactive older women. Int. J. Sports Med. *42*, 610–623.

358. Taniguchi, H., Tanisawa, K., Sun, X., Kubo, T., Hoshino, Y., Hosokawa, M., Takeyama, H., and Higuchi, M. (2018). Effects of short-term endurance exercise on gut microbiota in elderly men. Physiol. Rep. *6*, e13935.

359. Torquati, L., Gajanand, T., Cox, E.R., Willis, C.R.G., Zaugg, J., Keating, S.E., and Coombes, J.S. (2023). Effects of exercise intensity on gut microbiome composition and function in people with type 2 diabetes. Eur. J. Sport Sci. *23*, 530–541.

360. Kern, T., Blond, M.B., Hansen, T.H., Rosenkilde, M., Quist, J.S., Gram, A.S., Ekstrøm, C.T., Hansen, T., and Stallknecht, B. (2020). Structured exercise alters the gut microbiota in humans with overweight and obesity-a randomized controlled trial. Int. J. Obes. (Lond) *44*, 125–135.

361. Cheng, R., Wang, L., Le, S., Yang, Y., Zhao, C., Zhang, X., Yang, X., Xu, T., Xu, L., Wiklund, P., et al. (2022). A randomized controlled trial for response of microbiome network to exercise and diet intervention in patients with nonalcoholic fatty liver disease. Nat. Commun. *13*, 2555.

362. Macfarlane, G.T., and Macfarlane, S. (2012). Bacteria, colonic fermentation, and gastrointestinal health. J. AOAC Int. *95*, 50–60.

363. Brown, A.J., Goldsworthy, S.M., Barnes, A.A., Eilert, M.M., Tcheang, L., Daniels, D., Muir, A.I., Wigglesworth, M.J., Kinghorn, I., Fraser, N.J., et al. (2003). The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J. Biol. Chem. *278*, 11312–11319.

364. Tolhurst, G., Heffron, H., Lam, Y.S., Parker, H.E., Habib, A.M., Diakogiannaki, E., Cameron, J., Grosse, J., Reimann, F., and Gribble, F.M. (2012). Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes *61*, 364–371.

365. Psichas, A., Sleeth, M.L., Murphy, K.G., Brooks, L., Bewick, G.A., Hanyaloglu, A.C., Ghatei, M.A., Bloom, S.R., and Frost, G. (2015). The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. Int. J. Obes. (Lond) *39*, 424–429.

366. Al-Lahham, S.H., Roelofsen, H., Priebe, M., Weening, D., Dijkstra, M., Hoek, A., Rezaee, F., Venema, K., and Vonk, R.J. (2010). Regulation of adipokine production in human adipose tissue by propionic acid. Eur. J. Clin. Investig. *40*, 401–407.

367. Canfora, E.E., Jocken, J.W., and Blaak, E.E. (2015). Short-chain fatty acids in control of body weight and insulin sensitivity. Nat. Rev. Endocrinol. *11*, 577–591.

368. Erickson, K.I., Hillman, C.H., and Kramer, A.F. (2015). Physical activity, brain, and cognition. Curr. Opin. Behav. Sci. *4*, 27–32.

369. Norton, S., Matthews, F.E., Barnes, D.E., Yaffe, K., and Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. *13*, 788–794.

370. van Praag, H., Kempermann, G., and Gage, F.H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat. Neurosci. *2*, 266–270.

371. van Praag, H., Shubert, T., Zhao, C., and Gage, F.H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. J. Neurosci. *25*, 8680–8685.

372. Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., et al. (2011). Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. USA *108*, 3017–3022.

373. Zeidman, P., and Maguire, E.A. (2016). Anterior hippocampus: the anatomy of perception, imagination and episodic memory. Nat. Rev. Neurosci. *17*, 173–182.

374. Northey, J.M., Cherbuin, N., Pumpa, K.L., Smee, D.J., and Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. Br. J. Sports Med. *52*, 154–160.

375. Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S.G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., et al. (2017). Dementia prevention, intervention, and care. Lancet *390*, 2673–2734.

376. Hoffmann, K., Sobol, N.A., Frederiksen, K.S., Beyer, N., Vogel, A., Vestergaard, K., Brændgaard, H., Gottrup, H., Lolk, A., Wermuth, L., et al. (2016). Moderate-to-high intensity physical exercise in patients with Alzheimer's disease: a randomized controlled trial. J. Alzheimers Dis. *50*, 443–453.

377. Morland, C., Andersson, K.A., Haugen, Ø.P., Hadzic, A., Kleppa, L., Gille, A., Rinholm, J.E., Palibrk, V., Diget, E.H., Kennedy, L.H., et al. (2017). Exercise induces cerebral VEGF and angiogenesis via the lactate receptor HCAR1. Nat. Commun. *8*, 15557.

378. Smith, E.C., Pizzey, F.K., Askew, C.D., Mielke, G.I., Ainslie, P.N., Coombes, J.S., and Bailey, T.G. (2021). Effects of cardiorespiratory fitness and exercise training on cerebrovascular blood flow and reactivity: a systematic review with meta-analyses. Am. J. Physiol. Heart Circ. Physiol. *321*, H59–H76.

379. Xue, M., Xu, W., Ou, Y.N., Cao, X.P., Tan, M.S., Tan, L., and Yu, J.T. (2019). Diabetes mellitus and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 144 prospective studies. Ageing Res. Rev. *55*, 100944.

380. Potau, N., Escofet, M.A., and Martinez, M.C. (1991). Ontogenesis of insulin receptors in human cerebral cortex. J. Endocrinol. Invest. *14*, 53–58.

381. Tschritter, O., Preissl, H., Hennige, A.M., Stumvoll, M., Porubska, K., Frost, R., Marx, H., Klösel, B., Lutzenberger, W., Birbaumer, N., et al. (2006). The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. Proc. Natl. Acad. Sci. USA *103*, 12103–12108.

382. Heni, M., Wagner, R., Kullmann, S., Veit, R., Mat Husin, H., Linder, K., Benkendorff, C., Peter, A., Stefan, N., Häring, H.U., et al. (2014). Central insulin administration improves whole-body insulin sensitivity via hypothalamus and parasympathetic outputs in men. Diabetes *63*, 4083–4088.

383. Kullmann, S., Kleinridders, A., Small, D.M., Fritsche, A., Häring, H.U., Preissl, H., and Heni, M. (2020). Central nervous pathways of insulin action in the control of metabolism and food intake. Lancet Diabetes Endocrinol. *8*, 524–534.

384. Kullmann, S., Goj, T., Veit, R., Fritsche, L., Wagner, L., Schneeweiss, P., Hoene, M., Hoffmann, C., Machann, J., Niess, A., et al. (2022). Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese. JCI Insight *7*, e161498.

385. Steiner, J.L., Murphy, E.A., McClellan, J.L., Carmichael, M.D., and Davis, J.M. (2011). Exercise training increases mitochondrial biogenesis in the brain. J. Appl. Physiol. (1985) *111*, 1066–1071.

386. Ruegsegger, G.N., Vanderboom, P.M., Dasari, S., Klaus, K.A., Kabiraj, P., McCarthy, C.B., Lucchinetti, C.F., and Nair, K.S. (2019). Exercise

and metformin counteract altered mitochondrial function in the insulin-resistant brain. JCI Insight *4*, e130681.

387. Shepherd, S.O., Cocks, M., Meikle, P.J., Mellett, N.A., Ranasinghe, A.M., Barker, T.A., Wagenmakers, A.J.M., and Shaw, C.S. (2017). Lipid droplet remodelling and reduced muscle ceramides following sprint interval and moderate-intensity continuous exercise training in obese males. Int. J. Obes. (Lond) *41*, 1745–1754.

388. Dubé, J.J., Amati, F., Stefanovic-Racic, M., Toledo, F.G., Sauers, S.E., and Goodpaster, B.H. (2008). Exercise-induced alterations in intramyocellular lipids and insulin resistance: the athlete's paradox revisited. Am. J. Physiol. Endocrinol. Metab. *294*, E882–E888.

389. Dresner, A., Laurent, D., Marcucci, M., Griffin, M.E., Dufour, S., Cline, G.W., Slezak, L.A., Andersen, D.K., Hundal, R.S., Rothman, D.L., et al. (1999). Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. J. Clin. Invest. *103*, 253–259.

390. Boden, G., Chen, X., Ruiz, J., White, J.V., and Rossetti, L. (1994). Mechanisms of fatty acid-induced inhibition of glucose uptake. J. Clin. Invest. *93*, 2438–2446.

391. Ferrannini, E., Barrett, E.J., Bevilacqua, S., and DeFronzo, R.A. (1983). Effect of fatty acids on glucose production and utilization in man. J. Clin. Invest. *72*, 1737–1747.

392. You, T., Arsenis, N.C., Disanzo, B.L., and LaMonte, M.J. (2013). Effects of exercise training on chronic inflammation in obesity. Sports Med. *43*, 243–256.

393. Lin, X., Zhang, X., Guo, J., Roberts, C.K., McKenzie, S., Wu, W.C., Liu, S., and Song, Y. (2015). Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. J. Am. Heart Assoc. *4*, e002014.

394. Ashton, R.E., Tew, G.A., Aning, J.J., Gilbert, S.E., Lewis, L., and Saxton, J.M. (2020). Effects of short-term, medium-term and long-term resistance exercise training on cardiometabolic health outcomes in adults: systematic review with meta-analysis. Br. J. Sports Med. *54*, 341–348.

395. Hawley, J.A., Lundby, C., Cotter, J.D., and Burke, L.M. (2018). Maximizing cellular adaptation to endurance exercise in skeletal muscle. Cell Metab. *27*, 962–976.