


Molecular Mechanisms of Exercise and Healthspan

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Abstract: Healthspan is the period of our life without major debilitating diseases. In the modern world where unhealthy lifestyle choices and chronic diseases taper the healthspan, which lead to an enormous economic burden, finding ways to promote healthspan becomes a pressing goal of the scientific community. Exercise, one of humanity's most ancient and effective lifestyle interventions, appears to be at the center of the solution since it can both treat and prevent the occurrence of many chronic diseases. Here, we will review the current evidence and opinions about regular exercise promoting healthspan through enhancing the functionality of our organ systems and preventing diseases.

Keywords: healthspan; exercise; chronic diseases; adaptations



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1. Introduction

Two thousand and two hundred years have passed since the first Chinese emperor, Qin Shi Huang, ordered a nationwide hunt for the elixir for eternal life. Proven to be futile, his effort gave rise to the creation of a glorious terracotta army of 8000 that was buried alongside with him to embargo the pursuit for longevity [1]. Throughout the history of modern medicine, much like the emperor's dream, scientists have never halted the search for ways to extend our lifespan. In the past 50 years, extensive research and development with tremendous amount of investment have led to an increase of lifespan in the U.S. by 10 years [2]. In 2019, there were over 703 million of the world population aged 65 or more; this number is projected to be over 1.5 billion by 2050 [3]. However, healthspan, the period of our life without major debilitating diseases, has not been prolonged [2]. Because aging remains the most important risk factor for nearly all chronic diseases [4,5], this creates a conundrum that the extended lifespan without improvement of healthspan leads to significant aging of the society and unsustainable economy.

Evidence and theories from research in the recent decades have shown that human life expectancy may have reached or come close to a limit set primarily by natural causes (chronic diseases) and genetics [6,7]. The concept of "healthy aging", that is, to maximally expand the expectancy of healthy living before a person suffers from permanent aging-associated disabilities and chronic diseases, has emerged in the past two decades and gained significant popularity [8–10]. In the 21st century, there is a dire need of research on extending our healthspan [11–13]. Up to date, over 2100 active clinical trials in the United States are focusing on therapies that improve the quality of life (QOL) under the conditions of chronic diseases. Much like lifespan, healthspan can be influenced by numerous factors, namely genetics, environmental factors, social-economic status, lifestyle choices including dietary intake, physical activities, etc.

2. Exercise as Medicine to Promote Healthspan

The most ancient and potent “medicine” known to mankind that promotes healthspan is the engagement in organized, repeated and purposeful physical activities, or exercise training. The first documented exercise prescriptions by surgeons can be traced back to thousands of years ago in various ancient civilizations like the Ancient Greece and the Yellow River Civilization in China [14]. Over the recent decades, public health studies have shown indisputable evidence that high physical fitness is the most crucial factor for delaying all-cause mortality and the onset of chronic diseases, especially cardiovascular diseases, metabolic disorders and cancer [15–17]. Immense amount of research evidence has also demonstrated that long-term exercise training reshapes the molecular basis of multiple organ systems, including cardiorespiratory, musculoskeletal, neurological, endocrine and immune system [18–20]. For example, in a 12-year study in over 400,000 individuals, Wen et al. found the evidence that led to the conclusion that even 15 min a day or 90 min a week of moderate intensity exercise can reduce all-cause mortality [21].

Overall, exercise can be divided into two types: endurance and resistance exercise. Endurance exercise, often called aerobic exercise, is defined as exercise regimens that heavily rely on oxygen-utilizing energy metabolism, i.e., mitochondrial respiration, such as distance running, swimming and cycling. The main effects of endurance exercise include increase in mitochondrial content, capillary density, mass of slow-twitch oxidative myofibers and proportion of fast-twitch, oxidative myofibers in skeletal muscles along with enhanced cardiorespiratory function [22–24]. Resistance exercise, sometimes referred to as anaerobic exercise, relies primarily on anaerobic energy metabolism, namely creatine phosphate (CP) and anaerobic glycolysis for force production in a short period of time with less reliance on oxygen consumption. Typical resistance exercise regimens are heavy, low-rep weight training like bicep curls, leg extensions, sprinting and powerlifting. Adaptation of resistance exercise mainly include hypertrophy of the fast-twitch, glycolytic muscles, and usually does not or only moderately increase mitochondrial content [25,26]. Recent evidence suggests that although quantity of mitochondria might be unaltered, resistance exercise may still improve functionality of existing mitochondria, suggesting resistance exercise may also contribute to the regulation of mitochondrial quality [27].

Although the most direct executers of exercise are skeletal muscle and heart, regular exercise also leads to systemic changes in virtually all organ systems with superb, multi-faceted benefits to health (Figure 1). In this review, we will summarize current opinions and evidence on how exercise training is important in promoting healthspan through enhancing the functionality of the cardiovascular system, skeletal muscle, nervous system and preventing the occurrence of cancer.

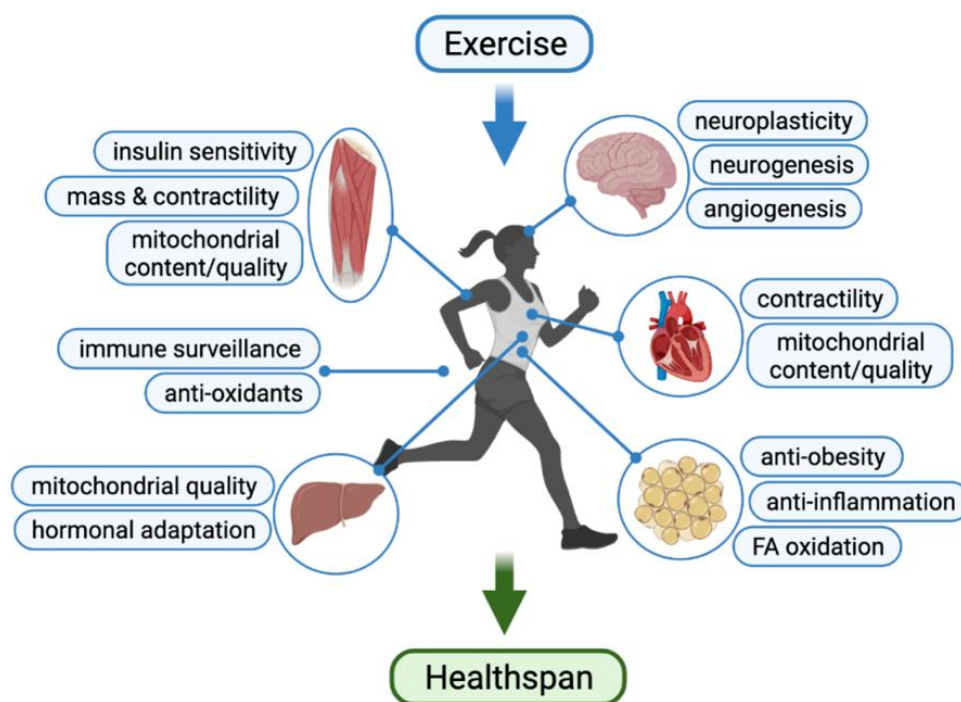


Figure 1. Illustration of exercise benefits in prolonging healthspan.

3. Cardiovascular System

3.1. Exercise Benefits in Promoting Cardiovascular Function

Cardiovascular diseases are the leading cause of all mortalities around the world, with sedentary lifestyle being one of the biggest risk factors [28,29]. The most direct clinical indicators of cardiorespiratory fitness are cardiac output and $VO_2\max$, both are major parameters that decline with aging, potentially a determining factor for healthspan [30]. Cardiac output is defined as the amount of oxygenated blood pumped by the left ventricle per minute and calculated as the product of stroke volume and heart rate. In a healthy individual, rigorous exercise may increase cardiac output by 4-fold; in trained elite athletes, this increase may be up to 6–8 fold [17]. $VO_2\max$ is the maximal amount of oxygen that is utilized by the all the organ systems during exercise. Since the 1980s, it has been well categorized that $VO_2\max$ increases with endurance exercise training regardless of age, sex or exercise mode, and is a critical measurement of risk factors of aging-related diseases [31]. A thorough analysis by Gries et al. showed that enhanced $VO_2\max$ by exercise training during adulthood can even be kept up to the eighth decades in athletes [32].

One of the mechanisms proposed for exercise-mediated promotion of cardiovascular fitness is via physiological hypertrophy, i.e., an increase in heart muscle mass along with enhanced contractile function, as opposed to pathological hypertrophy along with pathological changes such as fibrosis that may lead to heart failure. Physiological hypertrophy occurs in response to increased wall stress and other signaling events during exercise training. A series of studies discovered that the insulin and insulin-like growth factor 1 (IGF1) pathways including insulin receptor substrate 1/2 (Akt1/2), IGF receptor and phosphoinositide 3-kinase (PI3K) are important in exercise-mediated physiological hypertrophy in mice [33–37]. In addition to hypertrophy, many other adaptations including contractile apparatus remodeling, mitochondrial remodeling, change in metabolism and angiogenesis along with altered gene expression also occur during exercise training [33,38,39]. Other pathways that are pertinent to physiological heart growth in response to exercise training remain to be fully explored. Therefore, future studies that focus on a more thorough investigation of the mechanisms behind exercise-induced physiological hypertrophy and enhanced cardiac function will provide new insights into healthspan benefits of exercise.

3.2. Exercise Benefits in Ameliorating Cardiovascular Diseases (CVD)

Endurance exercise has also been demonstrated to have both preventative and therapeutic effects on myocardial infarction [40–44], atherosclerosis [45,46], and hypertension [47–49], which are among the biggest risk factors that shorten our healthspan. Substantial amount of evidence have shown that long-term endurance exercise can delay aging-associated decline of both cardiac output and VO_2max , contributing to disease prevention and promotion of quality of life [50–54]. In the past decade, the notion of “exercise as medicine” has gained tremendous popularity, which has prompted a number of clinical studies focusing on exercise regimens and methodologies to tackle cardiovascular challenges in patients [55–58]. Overall, it is recommended to prescribe moderate to low intensity (<60% maximal HR) endurance exercise at a frequency of 3–5 times per week to patients with cardiovascular diseases [55]. Significant effort has been committed in the past 50 years to unravel the molecular mechanisms behind exercise-mediated protection against CVD and promotion of recovery from cardiac injuries like ischemia-reperfusion (I/R); however, our understanding is still incomplete.

Heart failure is one of the top leading causes of death worldwide. Exercise is the best intervention for prevention and even treatment of heart failure without causing further cardiac injuries [59–63]. An early study in exercise intervention in human chronic heart failure patients in 1999 showed that one year of moderate intensity cycling (60% VO_2max) led to better cardiac outcomes and quality of life improvements [64]. The mechanisms of exercise benefits on heart failure are multifaceted, without clear understanding of the exact molecular targets. Potential aspects that exercise may positively impact on preventing heart failure include enhanced energy metabolism [39,65], mitigated oxidative stress [66], improved mitochondrial function [64,67]; a clear understanding of the molecular mechanisms is yet to be investigated.

Atherosclerosis is a prevalent, chronic vascular disease that affects millions of people worldwide. The pathology of atherosclerosis is complicated and multifaceted, with inflammatory factors and endothelial activation being early contributors; eventually, arterial wall lesions form, and cholesterol-rich lipids form blockades in the vessels, causing detrimental damage. Exercise has been discovered to (1) enhance endothelial function, and (2) exhibit anti-inflammatory and antioxidant effects as ways to help prevent the onset of atherosclerosis [68–76].

Overall, molecular mechanisms underlying exercise benefits in CVD is multi-faceted and incompletely understood. First and foremost, physiological stress signaling induced by exercise may be key. The most studied stress signaling kinase in exercise is 5' AMP-activated kinase (AMPK) since it is activated during energetic stress, i.e., increased AMP/ADP concentration [77]. Studies over the years have found it to be a critical signaling molecule in CVD like ischemia/reperfusion (I/R), fibrosis and vascular dysfunction [78–82]. AMPK is a heterotrimeric complex with a catalytic α domain, a non-catalytic β domain and a regulatory, AMP/APD-binding γ domain. Each subunit has different isoforms that are encoded by separate genes, which determines AMPK expression of different tissues ($\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$, $\gamma 1$, $\gamma 2$, and $\gamma 3$). In heart, $\alpha 2$ -, $\beta 2$ - and $\gamma 1$ -subunit are most commonly expressed [83]. Acute exercise causes energetic stress and signaling events that are sensed by AMPK and activates AMPK, leading to a series of phosphorylation cascades to regulate downstream signaling. Recent evidence also suggested that subcellular localization of AMPK may also be of importance, e.g., exercise may specifically activate mitochondria-associated AMPK [84]. Future studies on subcellular AMPK pools will improve the understanding in how AMPK regulates exercise benefits.

Mitochondria may also be a key player in exercise-mediated protection from CVD due to its central role in CVD progression [85,86]. Exercise training can potentially both improve mitochondrial content (biogenesis) and dynamics (fission, fusion and mitophagy). It has been well-established that increases in transcription and abundance of peroxisome proliferator-activated receptor co-activator (PGC-1 α), a master transcriptional co-activator for mitochondrial and oxidative metabolism, is responsible for increased mitochondrial

biogenesis after exercise [87–89]. In addition, recent evidence suggests that the improved quality of mitochondria, alongside with increase in quantity, may also be a key factor in protecting the heart from CVD [67,90–92]. Mitochondrial quality is usually measured with O₂ consumption, membrane integrity and morphology, which can all be enhanced by regular exercise [93–98]. A 2019 study found that mitophagy, more than macroautophagy, is critical in maintaining cardiac function in diabetic cardiomyopathy [99]. Although the necessity of exercise-induced mitophagy is not explored in this model, it has been suspected that, in other cardiac injury models, exercise may help maintain cardiac function through upregulating mitophagy [100–102].

Last but not least, skeletal muscle-derived humoral factors by endurance exercise may provide protection against pathological development of heart failure under disease conditions. For example, extracellular superoxide dismutase (EcSOD) is a superoxide scavenger that is upregulated in skeletal muscle upon exercise and travels to the peripheral tissues/organs, including the heart through the circulation, which has been shown to prevent diabetic cardiomyopathy [103,104].

4. Skeletal Muscle

4.1. Exercise Benefits in Skeletal Muscle Mass & Strength

Skeletal muscle quality, comprised of muscle mass (the number and size of muscle fibers) and strength (force production and contractility of muscle fibers), is one of the most important factors for quality of life as it is crucial for mobility, balance, motor coordination. Importantly, loss of muscle mass and strength both contribute to decreased healthspan [105,106]. Aging-associated loss of skeletal muscle mass (sarcopenia) and frailty are among the most prevalent causes of morbidity in aged population, affecting over 10% of the population over 60 years of age [107–109]. However, loss of muscle mass can be significantly delayed or even prevented by regular exercise, lengthening healthspan [110,111]. Clinical studies have found that aging may account for ~20–25% loss of muscle cross-sectional area compared to that of young individuals [112,113]. Importantly, anaerobic exercise is able to significantly delay the aging-associated sarcopenia as measured by muscle cross-sectional area or muscle mass [113–115]. Some evidence also suggests that endurance exercise can also improve sarcopenic conditions [116,117].

The mechanisms underlying exercise-mediated promotion and conservation of muscle mass is poorly understood. Several targets have been identified as important players in regulating muscle mass. Myostatin is a transforming growth factor- β (TGF- β) superfamily member that inversely regulates muscle growth and is upregulated in patients with sarcopenia [118]. Both endurance exercise and resistance exercise decrease muscle and plasma levels of myostatin, which may contribute to the mitigation of muscle wasting [119–122]. A combination of siRNA-mediated knockdown of myostatin and endurance exercise training has been shown to promote skeletal muscle hypertrophy with activation of resident stem cells [123]. Studies have also shown that protein synthesis via anabolic signaling, such as the Akt-mTOR pathway, is also associated with improvement in muscle mass by exercise training [124,125]. Interestingly, both rapamycin-sensitive and -insensitive mTOR seem to be important for resistance exercise-induced muscle protein synthesis [126,127]. In addition, proteolytic ubiquitin ligases, like MuRF-1 and Atrogin-1, which contribute to muscle wasting, can be reduced by exercise training [128]. Altogether, the mechanisms exercise benefits are clearly multifaceted. Therefore, future studies with genetic animal models are needed to improve our understanding.

Muscle strength, the ability of maximal force production per unit of muscle mass, is also important for quality of life. This is measured by the amplitude and velocity of muscle contraction, which are usually impaired as we age [129]. Resistance exercise improves muscle function also through improving muscle strength. Healthy young men can have 30–42% increase of fiber peak power after a 12-week resistance exercise intervention [130]. Endurance exercise has also been shown to improve the contractile profile of muscle fiber [131–133]. Interestingly, women in their seventies with lifelong aerobic exercise

training had increased strength in type I fibers and increased contractile velocity in type IIa fibers without increase in fiber size or mass compared to sedentary counterparts [134]. A possible mechanism is the enhanced Ca^{2+} sensitivity, defined as the force produced when the fiber is exposed to a given submaximal Ca^{2+} concentration. Although no change was observed after sprint training for type I, IIa, or IIa/IIx fibers [135], and no difference was observed between master runners and sedentary individuals for type I and IIa fibers [136], the effects of resistance training on Ca^{2+} sensitivity has been observed in type I fibers in old women [137].

The clinically relevant assessment of skeletal muscle function is exercise capacity, often measured by treadmill running, ergometer bike or 6-min walk. Importantly, exercise capacity is inversely correlated with all-cause mortality [138], and numerous randomized clinical trials showed that exercise interventions improve exercise capacity in various health and disease populations [139–141]. Underlying the improved exercise capacity upon exercise training, particularly endurance exercise training, are a variety of physiological and biochemical adaptations in skeletal muscle, including mitochondrial biogenesis, angiogenesis, and fiber type transformation. These adaptive changes are the basis for the improvement of physical performance and other health benefits. Specifically, fiber type transformation induced by endurance exercise training in the direction of type IIb/IIc/x to IIa fibers appear to be caused by activation of the calcineurin-nuclear factor of activated T-cells (NFAT) pathway [142–144]. Exercise training also induces adaptations closely related to regulation of energetic homeostasis. Exercise training, particularly endurance exercise, induced mitochondrial biogenesis in skeletal muscle, which is caused by induced expression/activity of transcriptional co-activator, peroxisome proliferator-activated receptor γ co-activator 1 α (PGC-1 α), coordinating the transcription of the mitochondrial and nuclear genomes for new mitochondrial biogenesis [88,145–147]. Finally, improved exercise capacity by endurance exercise training is also associated with angiogenesis, an expansion of the capillary network from preexisting capillaries in recruited skeletal muscles to improve gas and nutrient delivery. PGC-1 α has emerged as a key regulator of angiogenesis in skeletal muscle in a hypoxia-inducible factor (HIF)-independent manner where PGC-1 α coactivates the orphan nuclear receptor estrogen-related receptor- α (ERR α) [148]. Whole body *Pgc-1 α* gene deletion led to reduced VEGF protein expression and blunted response to acute and chronic exercise training [149]. Importantly, muscle-specific deletion of the *Pgc-1 α* gene led to significant attenuation of contractile activity-induced VEGF expression and exercise-induced angiogenesis but not fiber type transformation [147,150]. Muscle-specific deletion of the *Vegfa* gene led to significantly reduced capillary density and exercise training-induced angiogenesis in skeletal muscle [151,152].

In summary, a sophisticated signaling-transcription network mediates exercise-induced skeletal muscle adaptations, leading to improved mass, strength and endurance capacity. These improved contractile functions profoundly promote healthspan. Continued research efforts will elucidate the highly coordinated remodeling processes in skeletal muscle and unveil further the importance of skeletal muscle health in healthspan.

4.2. Exercise Benefits in Skeletal Muscle Metabolism

Metabolic diseases like insulin resistance and obesity are one of the major roadblocks to healthspan. Skeletal muscle, an organ that accounts for ~40% of body weight, is responsible for the majority of postprandial glucose uptake [153]. Fortunately, skeletal muscle is also one of the biggest beneficiaries of exercise intervention, making many metabolic diseases, such as type II diabetes, avoidable or delayable by lifestyle intervention [154]. For long, it has been shown that muscle contraction stimulates increased insulin sensitivity in muscle [155–157]. Long-term studies also found exercise training in a prolonged period result in improved insulin sensitivity [158–162]. Molecularly, it was established that muscle contractions during exercise lead to stimulation of translocation of glucose transporter 4 (GLUT4) vesicles to plasma membrane, significantly elevating glucose uptake [163,164], which is controlled via exercise-induced AMPK phosphorylation of TBC1D1 [165–167]. In

addition, mitochondrial content and quality is also upregulated in response to exercise, contributing to more efficient energy production during prolonged exercise [87,168–171]. More recently, mitochondrial dynamics that control mitochondrial quality, i.e., fission, fusion and mitophagy, has been brought up as another important aspect of exercise benefits in skeletal muscle metabolism [172–174]. Interestingly, nearly all of the mitochondria-related mechanisms of exercise seem to require the signaling of AMPK, the energetic sensor activated by exercise [175]. Recent evidence by our lab have discovered that a unique pool of AMPK is localized to mitochondria; others have also suggested that AMPK may be localized to other organelles in regulating key pathways [84,176]. Future studies in organelle-specific AMPK may greatly contribute to the understanding of how exercise induces metabolic improvements in skeletal muscle.

4.3. Exercise-Induced Muscle-Derived Antioxidant

Clinical and animal studies in the past decade have found that oxidative stress caused by uncontrolled overproduction of reactive oxygen species (ROS) is a major problem underlying many conditions like aging, diabetes and cardiometabolic diseases, making it one of the biggest impediments in increasing healthspan [177,178]. Exercise-induced antioxidant actions have then been proposed to promote health in this regard, however its mechanisms still remain incompletely understood [179–181].

The idea of exercise-mediated promotion of antioxidant system is different from the one of pharmacological supplementation. Exercise causes a “physiological” increase in oxidative stress in skeletal muscle, which then turns on physiological pathways that increase enzymatic responses to counteract oxidative damage, thus benefiting other tissue/organs as well [182,183]. Recently, studies on superoxide dismutases (SODs), a family of enzymes that neutralize superoxide anions (O_2^-) as the first line of defense against oxidative stress, have proposed that these enzymes might be important in exercise-mediated benefits through enhancing antioxidant system [184]. In particular, extracellular superoxide dismutase (EcsOD) is the only known antioxidant that has a capacity of scavenging ROS on cell surface and extracellular matrix, gaining much attention [185,186]. A study from our lab in 2015 showed that EcsOD is primarily expressed in skeletal muscle and can be upregulated by exercise training, which then travels through circulation and accumulates in primarily heart and lung, exerting antioxidant effects in the condition of diabetic cardiomyopathy [187]. A follow-up study in 2017 further demonstrated that skeletal muscle derived EcsOD, through genetic overexpression and serum transfusion, generates protective effects through inhibition of endothelial activation to protect mice in a model of multi-organ dysfunction [187]. Altogether, this evidence showed that cross talks between muscle and other organs in terms of strengthening whole-body antioxidant capacity may partly explain exercise benefits in prolonging healthspan. Future studies are also warranted to expand current knowledge in the detailed mechanisms of how EcsOD and other myokines may achieve this protection.

5. Adipose Tissue

Obesity, measured by body mass index in the general public, is a complex disease involving an excessive amount of body fat. Obesity has risen to a pandemic proportion in the U.S. and has become a major global health problem [188]. It is one of the most serious metabolic syndromes that correlate with many other diseases, like cardiovascular diseases and diabetes, becoming a huge burden on healthspan. To date, the most efficient countermeasure of obesity is lifestyle managements, including healthy diet and physical exercise [189–191]. Mechanistically, excessive adiposity leads to decreased insulin sensitivity in skeletal muscle, potentially through lipotoxicity to mitochondria [192–194]. Excessive adiposity is also detrimental due to the production and secretion of pro-inflammatory and pro-oxidant factors [195–198]. The exact mechanisms underlying these pathways are still not fully understood. On the other hand, exercise is known to induce fatty acid oxidation in order to meet the energy demand [199,200], and long-term exercise training appears to enhance the capacity of muscle to uptake fatty acids as well as fatty acid oxidation [201–204].

Future studies should investigate the molecular targets of exercise benefit in adipose tissue in these regards.

Adipose tissue is also a metabolic organ in mammals, consisting of primarily white adipose tissue (WAT) and brown adipose tissue (BAT). WAT stores energy in the form of triglycerides, whereas BAT is responsible for shivering thermogenesis, a process that generates heat through uncoupling mitochondria when activated [205]. It was later discovered that adipose tissue browning, a conversion of WAT to BAT, may positively contribute to metabolism and negatively correlated with aging, making it a potential important aspect of prolonging healthspan [206,207]. Exercise-induced browning of white adipose tissue is well documented [208,209]. However, its mechanism still remains elusive. A study in 2019 showed that deletion of the fibronectin type III domain containing 5 (Fndc5) gene in mice which produces irisin, a peptide that has been shown to induce WAT browning, leads to significantly less exercise-induced metabolic benefits [210]. Another study reported that interleukin 6 (IL-6) is required for both baseline expression and exercise-induced upregulation of uncoupling protein 1 (UCP1), the main molecular mediator of thermogenesis in BAT [211]. Therefore, future studies that elucidates the mechanisms behind exercise-induced browning of WAT is still warranted to generate a clear understanding of how exercise-mediated muscle-adipose tissue crosstalk may prolong healthspan.

6. Liver

Non-alcoholic fatty liver disease (NAFLD) is defined as liver disease caused by accumulation of fatty acids and not by alcohol use. NAFLD is a globally prevalent disease that includes a range of conditions ranging from hepatic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis; it may eventually progress into liver failure, becoming a major impediment that reduces healthspan [212,213]. NAFLD is largely considered a hepatic manifestation of metabolic syndrome. Therefore, one would reasonably argue that metabolic exercise benefits would lead to improved or delayed onset of NAFLD. Indeed, two independent randomized controlled clinical trials have confirmed that exercise training, either aerobic or resistance training, could reduce hepatic fat in NAFLD patients [214,215].

Since exercise effects are extremely multifaceted and NAFLD may benefit from “secondary” effects such as weight loss or improved insulin sensitivity, it is difficult to narrow down to specific pathways regarding the molecular mechanisms of exercise benefits in NAFLD. On top of that, some inconsistencies between animal phenotypes of NAFLD models and human patients also create difficulties in hepatic factors that may mediate exercise benefits [216]. Nevertheless, several studies in rodent models suggest that improved insulin resistance, reduced hyperlipidemia and reduced hepatic inflammation are potential mechanisms of exercise benefits [217–219]. One study in 2014 suggested that exercise was able to restore impaired hepatic mitochondrial respiration in a mouse NASH model, raising a possibility that exercise benefits may be mediated by mitochondrial regulation [220]. Altogether, future mechanistic studies are needed in order to formulate a more complete understanding of the molecular actions in exercise benefits in NAFLD.

Fibroblast growth factor 21 (FGF21) is a hormone that is primarily released in liver and muscle, and can be significantly upregulated during stress conditions, like exercise, which then can localize to different tissue/organ through circulation [221–224]. A study in 2016 showed that FGF21 is required in improving glucose tolerance and hepatic triglyceride in rats after voluntary wheel running, demonstrating the potentials of FGF21 to be an important mediator of exercise benefits [225]. Another study showed that FGF21 is required in hepatic mitochondrial function. However, the functional role of FGF21 appears to be paradoxical; its regulators and exact mechanisms of action are not clearly understood. For example, a study in 2019 showed that FGF21^{-/-} mice are protected from fasting-induced muscle atrophy potentially through regulating Bnip3-mediated mitophagy [226]. Therefore, it is critical for future studies to focus on the up-/downstream regulators of FGF21 to fully understand how FGF21 mediates exercise benefits in healthspan.

7. Central Nervous System

7.1. Exercise-Mediated Benefits on Neurological Health

Neurological disorders have become a tremendous burden in the United States and the world, being projected to cost over \$16 trillion USD by 2030 [227–229]. Common neurological disorders that contribute to loss of quality of life and are worsened by aging include Alzheimer's disease, dementia, Parkinson's disease, multiple sclerosis, epilepsy, etc. In the past decades, substantial evidence suggest that regular exercise is clearly the most potent method in both mitigating and preventing cognitive decline [230–238], Parkinson's disease [238–240], multiple sclerosis [241–249], and depression [250–252]. In all age groups, regular exercise has been shown to enhance central nervous system functions including but not limited to cognitive function, coordination, visuospatial memory, and learning abilities [253–257]. A recent study by Hatch et al. found that even a 30-min high intensity intermittent exercise is sufficient to enhance cognitive function in young adults [255]. Another recent clinical trial by Carta et al. demonstrated that a 12-week moderate intensity exercise with a combination of endurance, resistance exercise and balancing activities significantly improved cognitive function in healthy elderly people [256]. Of note, clinical studies and meta-analyses did not find that vigorous exercise regime is superior in enhancing brain function compared to moderate exercise, suggesting that an “ideal dose” of exercise may exist, and other factors need to be considered in determining the best exercise program for different populations [258–260]. This notion encouraged numerous studies that evaluated different modes of exercise in enhancing brain function [261,262], such as high intensity interval training (HIIT) [257], coordinative exercise [263,264], mind-body exercise like Tai Chi [265,266], etc. Overall, regular exercise remains to be the most prominent life-style intervention in improving healthspan with regard to the mental/neurological function.

7.2. Mechanisms of Exercise Benefits on Central Nervous System

7.2.1. Neuroplasticity

Neuroplasticity describes the process and capacity for neuronal network to undergo structural and functional changes as it adapts to behavioral stimulations, like exercise. In both rodent and human exercise models, studies have shown that endurance exercise training increases brain volume of different regions such as the hippocampus [267,268]. Exercise training also enhances dendrite length and complexity in many areas of the brain, including but not limited to the hippocampus, basolateral amygdala area, medial prefrontal cortex, and nitrenergic neurons in the cerebral cortex [269–272]. All these morphological changes in brain volume and dendrites are thought to contribute to the exercise-induced improvements in motor skill, memory and cognitive functions, as well as protection from neurodegenerative diseases [273–275].

Exercise-mediated neuroplasticity enhancement is often associated neuronal functional changes, which are multi-faceted [276]. Exercise may improve long-term potentiation, a process that describes the long-term strengthening of neuronal communication/signal transmission due to persistent, patterned stimulation, in the hippocampal area in both young and aged rodents, and this adaptation appears to be intensity- and duration-dependent [277–282]. A study in 2015 showed that 12 days of voluntary wheel running also increased hippocampal astrocytic markers and altered astrocyte morphology, suggesting glial function may also play a role in enhanced hippocampal plasticity by exercise [283]. Altogether, this evidence clearly demonstrated that neuroplasticity is an important aspect of exercise benefits in healthspan. Future investigations on molecular mediators in these pathways are essential.

Brain-derived neurotrophic factor (BDNF) was among the first molecules discovered to be important in exercise-mediated enhancement in neuroplasticity [284,285]. In an early study in rats, expression of BDNF and its receptor tropomyosin receptor kinase B (TrkB) both increased dramatically after voluntary wheel running exercise [286], which is confirmed by later studies with different exercise modes and in different ages [287,288]. Conversely, pharmacological inhibition of TrkB blocked the exercise-induced increase in neuroplasticity markers [286]. Indeed, human studies also reported strong correlation

between exercise-induced BDNF and improved cognitive function, involving the hippocampal area [289,290]. However, the mechanisms on the regulation of BDNF and its downstream targets by exercise are elusive. An early study showed that blocking hippocampal insulin-like growth factor (IGF-1) receptor reversed the induction of exercise-stimulated BDNF expression, suggesting the importance of IGF-1 [291,292]. Blocking of IGF-1 receptor also blunted exercise-induced synapsin I expression, calcium/calmodulin protein kinase II (CaMKII) and mitogen-activated protein kinase II (MAPKII) phosphorylation in the hippocampus [291]. Interestingly, recent evidence suggests that aerobic exercise and resistance exercise, although both improves cognitive function may act through different downstream molecular pathways [293,294]. In conclusion, future studies in molecular pathways involving BDNF, IGF-1 and their downstream cascades are crucial in understanding how neuroplasticity plays a pivotal role in exercise benefits in brain health.

7.2.2. Angiogenesis

On the cellular level, endurance exercise has been shown to reshape cellular pathways that promotes neurogenesis, angiogenesis, neuronal plasticity, and vasculature function in the brain [295–297]. It is now established that VO_2 max is a predictor of vascular function in the brain, which is closely associated with maintenance of cognitive abilities during aging [298]. Ainslie et al. found that blood flow velocity in the middle cerebral artery (MCAv) in the endurance exercise trained individuals is ~17% greater than the sedentary counterparts in almost all age groups (18–79), even though both groups still suffer from the aging-induced loss of MCAv [295]. Akazawa et al. showed that a 12-week cycling intervention was able to significantly enhance the cerebral microvascular tone in older adults compare with the sedentary control group [299].

7.2.3. Neurogenesis

Long-term endurance exercise can significantly delay the loss of neuronal volume in the hippocampus area, which underlies some cognitive disorders associated with aging, such as dementia and Alzheimer's disease [267]. Several molecules with neurogenesis-stimulating potentials have been shown to be important in exercise-induced neurogenesis in the hippocampus area, including BDNF, insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) [285,300–302]. Importantly, studies have suggested that exercise-induced BDNF is significant in promoting neurogenesis in the elderly population, emphasizing the importance of this mechanism in neuronal healthspan [303]. Cathepsin B (CTSB) is a newly identified myokine from skeletal muscle that is upregulated by aerobic exercise and crosses blood-brain barrier to potentially regulate brain biochemistry, although its function and whether it directly acts on promoting neurogenesis are not completely understood [304].

Resistance exercise is also effective in preserving cognitive function although the evidence is relatively limited, and its mechanism(s) is yet to be investigated [305]. One study showed that a 24-week of either moderate- or high-intensity resistance exercise was able to improve cognitive function in older adults [306]; a similar study showed that resistance exercise at the rate of once or twice a week is effective in enhancing cognitive function among older women [307]. In conclusion, the molecular and cellular mechanism(s) behind exercise adaptations that result in enhanced neurological function is still elusive. Interestingly, a recent meta-analysis of clinical studies showed that an increase in BDNF is more significant when training regimes incorporate more resistance training than moderate-intensity endurance exercise in older adults [308]. More mechanistic studies in the future are needed to improve our understanding of how regular exercise enhances neurological health hence our healthspan.

8. Cancer Prevention

Cancer claims more than 600,000 lives each year in the US alone [309]. For long, it has been known that regular exercise is very effective in preventing many if not all kinds

of cancers [310]. Cancer cachexia, weight loss, and cognitive decline are among the most detrimental comorbidities associated with cancer that greatly compromise healthspan. Cancer begins with mutations of tumor suppression genes that control normal cell growth, which then causes uncontrollably growing, transforming regular cells into tumor cells. If enabled by matured tumor microenvironment, tumor cells may eventually develop into full-blown cancer [311]. Extensive clinical trials and meta-analyses reveal that the level of physical activity or regular exercise positively correlates with lower risks of many types of cancer, including at least colon, breast, kidney, endometrial, bladder, esophagus, stomach and lung cancers [312–316]. Research on how exercise training can be used as a primary or secondary treatment and prevention of cancers has been proposed and will have huge societal impact [317,318].

The prominent hypotheses about the molecular mechanism(s) underlying the anti-cancer effects of regular exercise are proposed around exercise-mediated tuning of the immune system, which can be circumvented by tumor cells via microenvironment [319]. Given its known beneficial effects to the immune system, regular exercise may help to inhibit the development of tumor microenvironment by improving the innate and adaptive immune system [317]. A recent study by Pedersen et al. showed that voluntary wheel running induces infiltration of natural killer (NK) cells in tumor tissues in a mouse model of subcutaneous melanoma, which may contribute to the inhibition of tumor growth [320]. Another potential mechanism is that exercise training reduces overall cellular oxidative stress, which has been linked to oncogenesis [321,322]. We have previously shown that endurance exercise results in upregulation of extracellular superoxide dismutase (EcSOD) in skeletal muscle, which circulates to the heart, lung and other peripheral organs and protects them from oxidative damage [104,187]. In conclusion, there is a strong need to unravel the mechanism(s) underlying exercise-mediated anti-cancer effects in order to understand the broader impacts of exercise on prolonging our healthspan.

9. Conclusions

In summary, exercise training remains the most potent “medicine” that preserves quality of life and expands healthspan. The molecular understanding of exercise impacts in different organ systems reinstates that exercise is the most powerful lifestyle intervention against chronic diseases. While human lifespan seems to approach its limit, great potentials lie in promoting physical activities among any given communities to improve the healthspan and possibly lifespan as well.

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References

1. Katz, B. 2000-Year-Old Texts Reveal the First Emperor of China’s Quest for Eternal Life. Available online: <https://www.smithsonianmag.com/smart-news/2000-year-old-texts-reveal-first-emperor-chinas-quest-eternal-life-180967671/> (accessed on 24 December 2021).
2. Medina, L.; Sabo, S.; Vespa, J. *Living Longer: Historical and Projected Life Expectancy in the United States, 1960 to 2060*; U.S. Department of Commerce, U.S. Census Bureau: Suitland, MD, USA, 2020.
3. United Nations Department of Economic and Social Affairs Population Division. *World Population Ageing 2020 Highlights: Living Arrangements of Older Persons (ST/ESA/SER.A/451)*; United Nations Department of Economic and Social Affairs: New York, NY, USA, 2020.
4. Zhang, Z.D.; Milman, S.; Lin, J.R.; Wierbowski, S.; Yu, H.; Barzilai, N.; Gorbunova, V.; Ladiges, W.C.; Niedernhofer, L.J.; Suh, Y.; et al. Genetics of extreme human longevity to guide drug discovery for healthy ageing. *Nat. Metab.* **2020**, *2*, 663–672. [CrossRef] [PubMed]

5. Pifferi, F.; Aujard, F. Caloric restriction, longevity and aging: Recent contributions from human and non-human primate studies. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2019**, *95*, 109702. [CrossRef] [PubMed]
6. Dong, X.; Milholland, B.; Vijg, J. Evidence for a limit to human lifespan. *Nature* **2016**, *538*, 257–259. [CrossRef] [PubMed]
7. Olshansky, S.J.; Carnes, B.A.; Cassel, C. In search of Methuselah: Estimating the upper limits to human longevity. *Science* **1990**, *250*, 634–640. [CrossRef]
8. Pijnenburg, M.A.; Leget, C. Who wants to live forever? Three arguments against extending the human lifespan. *J. Med. Ethics* **2007**, *33*, 585–587. [CrossRef]
9. Goldman, D.P.; Cutler, D.; Rowe, J.W.; Michaud, P.C.; Sullivan, J.; Peneva, D.; Olshansky, S.J. Substantial health and economic returns from delayed aging may warrant a new focus for medical research. *Health Aff.* **2013**, *32*, 1698–1705. [CrossRef] [PubMed]
10. Nikolic-Žugich, J.; Goldman, D.P.; Cohen, P.R.; Cortese, D.; Fontana, L.; Kennedy, B.K.; Mohler, M.J.; Olshansky, S.J.; Perls, T.; Perry, D.; et al. Preparing for an Aging World: Engaging Biogerontologists, Geriatricians, and the Society. *J. Gerontol. A Biol. Sci. Med. Sci.* **2016**, *71*, 435–444. [CrossRef]
11. Olshansky, S.J. From Lifespan to Healthspan. *JAMA* **2018**, *320*, 1323–1324. [CrossRef]
12. Olshansky, S.J.; Martin, G.M.; Kirkland, J.L. *Aging: The Longevity Dividend*; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, USA, 2016.
13. Sierra, F. The Emergence of Geroscience as an Interdisciplinary Approach to the Enhancement of Health Span and Life Span. *Cold Spring Harb. Perspect. Med.* **2016**, *6*, a025163. [CrossRef]
14. Tipton, C.M. The history of “Exercise Is Medicine” in ancient civilizations. *Adv. Physiol. Educ.* **2014**, *38*, 109–117. [CrossRef]
15. Katzmarzyk, P.T.; Church, T.S.; Craig, C.L.; Bouchard, C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med. Sci. Sports Exerc.* **2009**, *41*, 998–1005. [CrossRef] [PubMed]
16. Blair, S.N.; Kohl, H.W.; Paffenbarger, R.S.; Clark, D.G.; Cooper, K.H.; Gibbons, L.W. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* **1989**, *262*, 2395–2401. [CrossRef] [PubMed]
17. Myers, J.; Prakash, M.; Froelicher, V.; Do, D.; Partington, S.; Atwood, J.E. Exercise capacity and mortality among men referred for exercise testing. *N. Engl. J. Med.* **2002**, *346*, 793–801. [CrossRef]
18. Timmons, J.A.; Knudsen, S.; Rankinen, T.; Koch, L.G.; Sarzynski, M.; Jensen, T.; Keller, P.; Scheele, C.; Volvaard, N.B.; Nielsen, S.; et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J. Appl. Physiol.* **2010**, *108*, 1487–1496. [CrossRef] [PubMed]
19. Ross, R.; de Lannoy, L.; Stotz, P.J. Separate Effects of Intensity and Amount of Exercise on Interindividual Cardiorespiratory Fitness Response. *Mayo Clin. Proc.* **2015**, *90*, 1506–1514. [CrossRef] [PubMed]
20. Keller, P.; Volvaard, N.B.; Gustafsson, T.; Gallagher, I.J.; Sundberg, C.J.; Rankinen, T.; Britton, S.L.; Bouchard, C.; Koch, L.G.; Timmons, J.A. A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. *J. Appl. Physiol.* **2011**, *110*, 46–59. [CrossRef] [PubMed]
21. Wen, C.P.; Wai, J.P.; Tsai, M.K.; Yang, Y.C.; Cheng, T.Y.; Lee, M.C.; Chan, H.T.; Tsao, C.K.; Tsai, S.P.; Wu, X. Minimum amount of physical activity for reduced mortality and extended life expectancy: A prospective cohort study. *Lancet* **2011**, *378*, 1244–1253. [CrossRef]
22. Fletcher, G.F.; Balady, G.; Blair, S.N.; Blumenthal, J.; Caspersen, C.; Chaitman, B.; Epstein, S.; Sivarajan Froelicher, E.S.; Froelicher, V.F.; Pina, I.L.; et al. Statement on exercise: Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation* **1996**, *94*, 857–862. [CrossRef]
23. Harber, M.P.; Konopka, A.R.; Udem, M.K.; Hinkley, J.M.; Minchev, K.; Kaminsky, L.A.; Trappe, T.A.; Trappe, S. Aerobic exercise training induces skeletal muscle hypertrophy and age-dependent adaptations in myofiber function in young and older men. *J. Appl. Physiol.* **2012**, *113*, 1495–1504. [CrossRef]
24. Akimoto, T.; Ribar, T.J.; Williams, R.S.; Yan, Z. Skeletal muscle adaptation in response to voluntary running in Ca²⁺/calmodulin-dependent protein kinase IV-deficient mice. *Am. J. Physiol. Cell Physiol.* **2004**, *287*, C1311–C1319. [CrossRef]
25. Seynnes, O.R.; de Boer, M.; Narici, M.V. Early skeletal muscle hypertrophy and architectural changes in response to high-intensity resistance training. *J. Appl. Physiol.* **2007**, *102*, 368–373. [CrossRef] [PubMed]
26. Schoenfeld, B.J. *Science and Development of Muscle Hypertrophy*; Human Kinetics: Champaign, IL, USA, 2016.
27. Porter, C.; Reidy, P.T.; Bhattarai, N.; Sidossis, L.S.; Rasmussen, B.B. Resistance Exercise Training Alters Mitochondrial Function in Human Skeletal Muscle. *Med. Sci. Sports Exerc.* **2015**, *47*, 1922–1931. [CrossRef] [PubMed]
28. Centers for Disease Control and Prevention. Leading Causes of Death. Available online: <https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm> (accessed on 24 December 2021).
29. United Nations. Mortality. Available online: <https://unstats.un.org/unsd/demographic/sconcerns/mortality/mort2.htm#DYB> (accessed on 24 December 2021).
30. Hagberg, J.M. Effect of training on the decline of VO₂max with aging. *Fed. Proc.* **1987**, *46*, 1830–1833. [PubMed]
31. Ross, R.; Blair, S.N.; Arena, R.; Church, T.S.; Després, J.P.; Franklin, B.A.; Haskell, W.L.; Kaminsky, L.A.; Levine, B.D.; Lavie, C.J.; et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement from the American Heart Association. *Circulation* **2016**, *134*, e653–e699. [CrossRef] [PubMed]

32. Gries, K.J.; Raue, U.; Perkins, R.K.; Lavin, K.M.; Overstreet, B.S.; D'Acquisto, L.J.; Graham, B.; Finch, W.H.; Kaminsky, L.A.; Trappe, T.A.; et al. Cardiovascular and skeletal muscle health with lifelong exercise. *J. Appl. Physiol.* **2018**, *125*, 1636–1645. [[CrossRef](#)]
33. Perrino, C.; Naga Prasad, S.V.; Mao, L.; Noma, T.; Yan, Z.; Kim, H.S.; Smithies, O.; Rockman, H.A. Intermittent pressure overload triggers hypertrophy-independent cardiac dysfunction and vascular rarefaction. *J. Clin. Investig.* **2006**, *116*, 1547–1560. [[CrossRef](#)]
34. Riehle, C.; Wende, A.R.; Zhu, Y.; Oliveira, K.J.; Pereira, R.O.; Jaishy, B.P.; Bevins, J.; Valdez, S.; Noh, J.; Kim, B.J.; et al. Insulin receptor substrates are essential for the bioenergetic and hypertrophic response of the heart to exercise training. *Mol. Cell Biol.* **2014**, *34*, 3450–3460. [[CrossRef](#)]
35. Kim, J.; Wende, A.R.; Sena, S.; Theobald, H.A.; Soto, J.; Sloan, C.; Wayment, B.E.; Litwin, S.E.; Holzenberger, M.; LeRoith, D.; et al. Insulin-like growth factor I receptor signaling is required for exercise-induced cardiac hypertrophy. *Mol. Endocrinol.* **2008**, *22*, 2531–2543. [[CrossRef](#)]
36. 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. The insulin-like growth factor 1 receptor induces physiological heart growth via the phosphoinositide 3-kinase(p110alpha) pathway. *J. Biol. Chem.* **2004**, *279*, 4782–4793. [[CrossRef](#)]
37. DeBosch, B.; Treskov, I.; Lupu, T.S.; Weinheimer, C.; Kovacs, A.; Courtois, M.; Muslin, A.J. Akt1 is required for physiological cardiac growth. *Circulation* **2006**, *113*, 2097–2104. [[CrossRef](#)]
38. Chen, Z.; Zhou, Z.; Peng, X.; Sun, C.; Yang, D.; Li, C.; Zhu, R.; Zhang, P.; Zheng, L.; Tang, C. Cardioprotective responses to aerobic exercise-induced physiological hypertrophy in zebrafish heart. *J. Physiol. Sci.* **2021**, *71*, 33. [[CrossRef](#)] [[PubMed](#)]
39. Gibb, A.A.; Epstein, P.N.; Uchida, S.; Zheng, Y.; McNally, L.A.; Obal, D.; Katragadda, K.; Trainor, P.; Conklin, D.J.; Brittan, K.R.; et al. Exercise-Induced Changes in Glucose Metabolism Promote Physiological Cardiac Growth. *Circulation* **2017**, *136*, 2144–2157. [[CrossRef](#)] [[PubMed](#)]
40. O'Connor, G.T.; Buring, J.E.; Yusuf, S.; Goldhaber, S.Z.; Olmstead, E.M.; Paffenbarger, R.S.; Hennekens, C.H. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* **1989**, *80*, 234–244. [[CrossRef](#)] [[PubMed](#)]
41. Blond, K.; Brinkløv, C.F.; Ried-Larsen, M.; Crippa, A.; Grøntved, A. Association of high amounts of physical activity with mortality risk: A systematic review and meta-analysis. *Br. J. Sports Med.* **2020**, *54*, 1195–1201. [[CrossRef](#)] [[PubMed](#)]
42. Maessen, M.F.; Eijsvogels, T.M.; Stevens, G.; van Dijk, A.P.; Hopman, M.T. Benefits of lifelong exercise training on left ventricular function after myocardial infarction. *Eur. J. Prev. Cardiol.* **2017**, *24*, 1856–1866. [[CrossRef](#)]
43. Peytz, N.C.; Jabbari, R.; Bojesen, S.E.; Nordestgaard, B.; Schnohr, P.; Prescott, E. Physical activity and risk of instant and 28-day case-fatality in myocardial infarction. *PLoS ONE* **2019**, *14*, e0217398. [[CrossRef](#)]
44. de Waard, M.C.; Duncker, D.J. Prior exercise improves survival, infarct healing, and left ventricular function after myocardial infarction. *J. Appl. Physiol.* **2009**, *107*, 928–936. [[CrossRef](#)]
45. Pedersen, B.K. The disease of physical inactivity-and the role of myokines in muscle-fat cross talk. *J. Physiol.* **2009**, *587*, 5559–5568. [[CrossRef](#)]
46. Szostak, J.; Laurant, P. The forgotten face of regular physical exercise: A 'natural' anti-atherogenic activity. *Clin. Sci.* **2011**, *121*, 91–106. [[CrossRef](#)]
47. Laterza, M.C.; de Matos, L.D.; Trombetta, I.C.; Braga, A.M.; Roveda, F.; Alves, M.J.; Krieger, E.M.; Negrão, C.E.; Rondon, M.U. Exercise training restores baroreflex sensitivity in never-treated hypertensive patients. *Hypertension* **2007**, *49*, 1298–1306. [[CrossRef](#)]
48. Pagani, M.; Somers, V.; Furlan, R.; Dell'Orto, S.; Conway, J.; Baselli, G.; Cerutti, S.; Sleight, P.; Malliani, A. Changes in autonomic regulation induced by physical training in mild hypertension. *Hypertension* **1988**, *12*, 600–610. [[CrossRef](#)] [[PubMed](#)]
49. Somers, V.K.; Conway, J.; Johnston, J.; Sleight, P. Effects of endurance training on baroreflex sensitivity and blood pressure in borderline hypertension. *Lancet* **1991**, *337*, 1363–1368. [[CrossRef](#)]
50. Garber, C.E.; Blissmer, B.; Deschenes, M.R.; Franklin, B.A.; Lamonte, M.J.; Lee, I.M.; Nieman, D.C.; Swain, D.P.; Medicine, A.C.o.S. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. *Med. Sci. Sports Exerc.* **2011**, *43*, 1334–1359. [[CrossRef](#)]
51. Cordina, R.L.; O'Meagher, S.; Karmali, A.; Rae, C.L.; Liess, C.; Kemp, G.J.; Puranik, R.; Singh, N.; Celermajer, D.S. Resistance training improves cardiac output, exercise capacity and tolerance to positive airway pressure in Fontan physiology. *Int. J. Cardiol.* **2013**, *168*, 780–788. [[CrossRef](#)]
52. Helgerud, J.; Høydal, K.; Wang, E.; Karlsen, T.; Berg, P.; Bjerkaas, M.; Simonsen, T.; Helgesen, C.; Hjorth, N.; Bach, R.; et al. Aerobic high-intensity intervals improve VO₂max more than moderate training. *Med. Sci. Sports Exerc.* **2007**, *39*, 665–671. [[CrossRef](#)]
53. Bacon, A.P.; Carter, R.E.; Ogle, E.A.; Joyner, M.J. VO₂max trainability and high intensity interval training in humans: A meta-analysis. *PLoS ONE* **2013**, *8*, e73182. [[CrossRef](#)] [[PubMed](#)]
54. Park, H.Y.; Park, W.; Lim, K. Living High-Training Low for 21 Days Enhances Exercise Economy, Hemodynamic Function, and Exercise Performance of Competitive Runners. *J. Sports Sci. Med.* **2019**, *18*, 427–437. [[PubMed](#)]
55. Hansen, D.; Niebauer, J.; Cornelissen, V.; Barna, O.; Neunhäuserer, D.; Stettler, C.; Tonoli, C.; Greco, E.; Fagard, R.; Coninx, K.; et al. Exercise Prescription in Patients with Different Combinations of Cardiovascular Disease Risk Factors: A Consensus Statement from the EXPERT Working Group. *Sports Med.* **2018**, *48*, 1781–1797. [[CrossRef](#)]

56. Garvey, C.; Bayles, M.P.; Hamm, L.F.; Hill, K.; Holland, A.; Limberg, T.M.; Spruit, M.A. Pulmonary Rehabilitation Exercise Prescription in Chronic Obstructive Pulmonary Disease: Review of Selected Guidelines: An Official Statement from The American Association Of Cardiovascular And Pulmonary Rehabilitation. *J. Cardiopulm. Rehabil. Prev.* **2016**, *36*, 75–83. [[CrossRef](#)]
57. Pedersen, B.K.; Saltin, B. Exercise as medicine—Evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand. J. Med. Sci. Sports* **2015**, *25*, 1–72. [[CrossRef](#)]
58. Bray, N.W.; Smart, R.R.; Jakobi, J.M.; Jones, G.R. Exercise prescription to reverse frailty. *Appl. Physiol. Nutr. Metab.* **2016**, *41*, 1112–1116. [[CrossRef](#)] [[PubMed](#)]
59. Piepoli, M.F.; Davos, C.; Francis, D.P.; Coats, A.J.; Collaborative, E. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* **2004**, *328*, 189. [[CrossRef](#)] [[PubMed](#)]
60. Davies, E.J.; Moxham, T.; Rees, K.; Singh, S.; Coats, A.J.; Ebrahim, S.; Lough, F.; Taylor, R.S. Exercise training for systolic heart failure: Cochrane systematic review and meta-analysis. *Eur. J. Heart Fail.* **2010**, *12*, 706–715. [[CrossRef](#)]
61. Sagar, V.A.; Davies, E.J.; Briscoe, S.; Coats, A.J.; Dalal, H.M.; Lough, F.; Rees, K.; Singh, S.; Taylor, R.S. Exercise-based rehabilitation for heart failure: Systematic review and meta-analysis. *Open Heart* **2015**, *2*, e000163. [[CrossRef](#)] [[PubMed](#)]
62. Smart, N.; Marwick, T.H. Exercise training for patients with heart failure: A systematic review of factors that improve mortality and morbidity. *Am. J. Med.* **2004**, *116*, 693–706. [[CrossRef](#)]
63. Harwood, A.E.; Russell, S.; Okwose, N.C.; McGuire, S.; Jakovljevic, D.G.; McGregor, G. A systematic review of rehabilitation in chronic heart failure: Evaluating the reporting of exercise interventions. *ESC Heart Fail* **2021**, *8*, 3458–3471. [[CrossRef](#)] [[PubMed](#)]
64. Belardinelli, R.; Georgiou, D.; Cianci, G.; Purcaro, A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: Effects on functional capacity, quality of life, and clinical outcome. *Circulation* **1999**, *99*, 1173–1182. [[CrossRef](#)]
65. Lopaschuk, G.D.; Karwi, Q.G.; Tian, R.; Wende, A.R.; Abel, E.D. Cardiac Energy Metabolism in Heart Failure. *Circ. Res.* **2021**, *128*, 1487–1513. [[CrossRef](#)]
66. Tsutsui, H.; Kinugawa, S.; Matsushima, S. Oxidative stress and heart failure. *Am. J. Physiol. Heart Circ. Physiol.* **2011**, *301*, H2181–H2190. [[CrossRef](#)]
67. Kwak, H.B.; Song, W.; Lawler, J.M. Exercise training attenuates age-induced elevation in Bax/Bcl-2 ratio, apoptosis, and remodeling in the rat heart. *FASEB J.* **2006**, *20*, 791–793. [[CrossRef](#)]
68. Keller, C.; Steensberg, A.; Pilegaard, H.; Osada, T.; Saltin, B.; Pedersen, B.K.; Neufer, P.D. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: Influence of muscle glycogen content. *FASEB J.* **2001**, *15*, 2748–2750. [[CrossRef](#)] [[PubMed](#)]
69. Steensberg, A.; van Hall, G.; Osada, T.; Sacchetti, M.; Saltin, B.; Klarlund Pedersen, B. Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *J. Physiol.* **2000**, *529*, 237–242. [[CrossRef](#)] [[PubMed](#)]
70. Green, D.J.; Maiorana, A.; O'Driscoll, G.; Taylor, R. Effect of exercise training on endothelium-derived nitric oxide function in humans. *J. Physiol.* **2004**, *561*, 1–25. [[CrossRef](#)]
71. Maiorana, A.; O'Driscoll, G.; Taylor, R.; Green, D. Exercise and the nitric oxide vasodilator system. *Sports Med.* **2003**, *33*, 1013–1035. [[CrossRef](#)]
72. Hong, J.; Park, E.; Lee, J.; Lee, Y.; Rooney, B.V.; Park, Y. Exercise training mitigates ER stress and UCP2 deficiency-associated coronary vascular dysfunction in atherosclerosis. *Sci. Rep.* **2021**, *11*, 15449. [[CrossRef](#)] [[PubMed](#)]
73. Krams, D.M.; Aspen, A.J.; Abramowitz, B.M.; Kreimendahl, T.; Hood, W.B. Reduction of coronary atherosclerosis by moderate conditioning exercise in monkeys on an atherogenic diet. *N. Engl. J. Med.* **1981**, *305*, 1483–1489. [[CrossRef](#)] [[PubMed](#)]
74. Napoli, C.; Williams-Ignarro, S.; de Nigris, F.; Lerman, L.O.; D'Armiento, F.P.; Crimi, E.; Byrns, R.E.; Casamassimi, A.; Lanza, A.; Gombos, F.; et al. Physical training and metabolic supplementation reduce spontaneous atherosclerotic plaque rupture and prolong survival in hypercholesterolemic mice. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 10479–10484. [[CrossRef](#)] [[PubMed](#)]
75. Kim, Y.J.; Shin, Y.O.; Bae, J.S.; Lee, J.B.; Ham, J.H.; Son, Y.J.; Kim, J.K.; Kim, C.; Lee, B.K.; Oh, J.K.; et al. Beneficial effects of cardiac rehabilitation and exercise after percutaneous coronary intervention on hsCRP and inflammatory cytokines in CAD patients. *Pflug. Arch.* **2008**, *455*, 1081–1088. [[CrossRef](#)]
76. Trøseid, M.; Lappégård, K.T.; Claudi, T.; Damás, J.K.; Mørkrid, L.; Brendberg, R.; Mollnes, T.E. Exercise reduces plasma levels of the chemokines MCP-1 and IL-8 in subjects with the metabolic syndrome. *Eur. Heart J.* **2004**, *25*, 349–355. [[CrossRef](#)]
77. Coven, D.L.; Hu, X.; Cong, L.; Bergeron, R.; Shulman, G.I.; Hardie, D.G.; Young, L.H. Physiological role of AMP-activated protein kinase in the heart: Graded activation during exercise. *Am. J. Physiol. Endocrinol. Metab.* **2003**, *285*, E629–E636. [[CrossRef](#)]
78. Russell, R.R.; Li, J.; Coven, D.L.; Pypaert, M.; Zechner, C.; Palmeri, M.; Giordano, F.J.; Mu, J.; Birnbaum, M.J.; Young, L.H. AMP-activated protein kinase mediates ischemic glucose uptake and prevents postischemic cardiac dysfunction, apoptosis, and injury. *J. Clin. Invest* **2004**, *114*, 495–503. [[CrossRef](#)] [[PubMed](#)]
79. Morrison, A.; Yan, X.; Tong, C.; Li, J. Acute rosiglitazone treatment is cardioprotective against ischemia-reperfusion injury by modulating AMPK, Akt, and JNK signaling in nondiabetic mice. *Am. J. Physiol. Heart Circ. Physiol.* **2011**, *301*, H895–H902. [[CrossRef](#)] [[PubMed](#)]
80. Ma, X.; Fu, Y.; Xiao, H.; Song, Y.; Chen, R.; Shen, J.; An, X.; Shen, Q.; Li, Z.; Zhang, Y. Cardiac Fibrosis Alleviated by Exercise Training Is AMPK-Dependent. *PLoS ONE* **2015**, *10*, e0129971. [[CrossRef](#)] [[PubMed](#)]

81. Li, F.Y.; Lam, K.S.; Tse, H.F.; Chen, C.; Wang, Y.; Vanhoutte, P.M.; Xu, A. Endothelium-selective activation of AMP-activated protein kinase prevents diabetes mellitus-induced impairment in vascular function and reendothelialization via induction of heme oxygenase-1 in mice. *Circulation* **2012**, *126*, 1267–1277. [[CrossRef](#)] [[PubMed](#)]
82. Miller, E.J.; Li, J.; Leng, L.; McDonald, C.; Atsumi, T.; Bucala, R.; Young, L.H. Macrophage migration inhibitory factor stimulates AMP-activated protein kinase in the ischaemic heart. *Nature* **2008**, *451*, 578–582. [[CrossRef](#)]
83. Thornton, C.; Snowden, M.A.; Carling, D. Identification of a novel AMP-activated protein kinase beta subunit isoform that is highly expressed in skeletal muscle. *J. Biol. Chem.* **1998**, *273*, 12443–12450. [[CrossRef](#)]
84. Drake, J.C.; Wilson, R.J.; Laker, R.C.; Guan, Y.; Spaulding, H.R.; Nichenko, A.S.; Shen, W.; Shang, H.; Dorn, M.V.; Huang, K.; et al. Mitochondria-localized AMPK responds to local energetics and contributes to exercise and energetic stress-induced mitophagy. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2025932118. [[CrossRef](#)]
85. Vásquez-Trincado, C.; García-Carvajal, I.; Pennanen, C.; Parra, V.; Hill, J.A.; Rothermel, B.A.; Lavandero, S. Mitochondrial dynamics, mitophagy and cardiovascular disease. *J. Physiol.* **2016**, *594*, 509–525. [[CrossRef](#)]
86. Bonora, M.; Wieckowski, M.R.; Sinclair, D.A.; Kroemer, G.; Pinton, P.; Galluzzi, L. Targeting mitochondria for cardiovascular disorders: Therapeutic potential and obstacles. *Nat. Rev. Cardiol.* **2019**, *16*, 33–55. [[CrossRef](#)]
87. Wu, Z.; Puigserver, P.; Andersson, U.; Zhang, C.; Adelmant, G.; Mootha, V.; Troy, A.; Cinti, S.; Lowell, B.; Scarpulla, R.C.; et al. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* **1999**, *98*, 115–124. [[CrossRef](#)]
88. Lin, J.; Wu, H.; Tarr, P.T.; Zhang, C.Y.; Wu, Z.; Boss, O.; Michael, L.F.; Puigserver, P.; Isotani, E.; Olson, E.N.; et al. Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature* **2002**, *418*, 797–801. [[CrossRef](#)] [[PubMed](#)]
89. Akimoto, T.; Pohnert, S.C.; Li, P.; Zhang, M.; Gumbs, C.; Rosenberg, P.B.; Williams, R.S.; Yan, Z. Exercise stimulates Pgc-1alpha transcription in skeletal muscle through activation of the p38 MAPK pathway. *J. Biol. Chem.* **2005**, *280*, 19587–19593. [[CrossRef](#)] [[PubMed](#)]
90. 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. Exercise reestablishes autophagic flux and mitochondrial quality control in heart failure. *Autophagy* **2017**, *13*, 1304–1317. [[CrossRef](#)] [[PubMed](#)]
91. Kavazis, A.N.; McClung, J.M.; Hood, D.A.; Powers, S.K. Exercise induces a cardiac mitochondrial phenotype that resists apoptotic stimuli. *Am. J. Physiol. Heart Circ. Physiol.* **2008**, *294*, H928–H935. [[CrossRef](#)]
92. Chen, L.; Knowlton, A.A. Mitochondria and heart failure: New insights into an energetic problem. *Minerva Cardioangiol.* **2010**, *58*, 213–229.
93. Rivera-Alvarez, I.; Pérez-Treviño, P.; Chapoy-Villanueva, H.; Vela-Guajardo, J.E.; Nieblas, B.; Garza-González, S.; García-Rivas, G.; García, N. A single session of physical activity restores the mitochondrial organization disrupted by obesity in skeletal muscle fibers. *Life Sci.* **2020**, *256*, 117965. [[CrossRef](#)]
94. Rosa-Caldwell, M.E.; Brown, J.L.; Perry, R.A.; Shimkus, K.L.; Shirazi-Fard, Y.; Brown, L.A.; Hogan, H.A.; Fluckey, J.D.; Washington, T.A.; Wiggs, M.P.; et al. Regulation of mitochondrial quality following repeated bouts of hindlimb unloading. *Appl. Physiol. Nutr. Metab.* **2020**, *45*, 264–274. [[CrossRef](#)]
95. Baumbach, P.; Neu, C.; Derlien, S.; Bauer, M.; Nisser, M.; Buder, A.; Coldewey, S.M. A pilot study of exercise-induced changes in mitochondrial oxygen metabolism measured by a cellular oxygen metabolism monitor (PICOMET). *Biochim. Biophys. Acta. Mol. Basis Dis.* **2019**, *1865*, 749–758. [[CrossRef](#)]
96. Wilson, R.J.; Drake, J.C.; Cui, D.; Ritger, M.L.; Guan, Y.; Call, J.A.; Zhang, M.; Leitner, L.M.; Gödecke, A.; Yan, Z. Voluntary running protects against neuromuscular dysfunction following hindlimb ischemia-reperfusion in mice. *J. Appl. Physiol.* **2019**, *126*, 193–201. [[CrossRef](#)]
97. Arribat, Y.; Broskey, N.T.; Greggio, C.; Boutant, M.; Conde Alonso, S.; Kulkarni, S.S.; Lagarrigue, S.; Carnero, E.A.; Besson, C.; Cantó, C.; et al. Distinct patterns of skeletal muscle mitochondria fusion, fission and mitophagy upon duration of exercise training. *Acta. Physiol.* **2019**, *225*, e13179. [[CrossRef](#)]
98. Zhao, D.; Sun, Y.; Tan, Y.; Zhang, Z.; Hou, Z.; Gao, C.; Feng, P.; Zhang, X.; Yi, W.; Gao, F. Short-Duration Swimming Exercise after Myocardial Infarction Attenuates Cardiac Dysfunction and Regulates Mitochondrial Quality Control in Aged Mice. *Oxid. Med. Cell Longev.* **2018**, *2018*, 4079041. [[CrossRef](#)] [[PubMed](#)]
99. Tong, M.; Saito, T.; Zhai, P.; Oka, S.I.; Mizushima, W.; Nakamura, M.; Ikeda, S.; Shirakabe, A.; Sadoshima, J. Mitophagy Is Essential for Maintaining Cardiac Function During High Fat Diet-Induced Diabetic Cardiomyopathy. *Circ. Res.* **2019**, *124*, 1360–1371. [[CrossRef](#)] [[PubMed](#)]
100. He, W.; Tang, Y.; Li, C.; Zhang, X.; Huang, S.; Tan, B.; Yang, Z. Exercise Enhanced Cardiac Function in Mice with Radiation-Induced Heart Disease. *Front. Physiol.* **2021**, *12*, 739485. [[CrossRef](#)] [[PubMed](#)]
101. Opichka, M.; Shute, R.; Marshall, K.; Slivka, D. Effects of exercise in a cold environment on gene expression for mitochondrial biogenesis and mitophagy. *Cryobiology* **2019**, *90*, 47–53. [[CrossRef](#)]
102. Yuan, Y.; Pan, S.S. Parkin Mediates Mitophagy to Participate in Cardioprotection Induced by Late Exercise Preconditioning but Bnip3 Does Not. *J. Cardiovasc. Pharmacol.* **2018**, *71*, 303–316. [[CrossRef](#)]
103. Hitomi, Y.; Watanabe, S.; Kizaki, T.; Sakurai, T.; Takemasa, T.; Haga, S.; Ookawara, T.; Suzuki, K.; Ohno, H. Acute exercise increases expression of extracellular superoxide dismutase in skeletal muscle and the aorta. *Redox Rep.* **2008**, *13*, 213–216. [[CrossRef](#)]

104. Call, J.A.; Chain, K.H.; Martin, K.S.; Lira, V.A.; Okutsu, M.; Zhang, M.; Yan, Z. Enhanced skeletal muscle expression of extracellular superoxide dismutase mitigates streptozotocin-induced diabetic cardiomyopathy by reducing oxidative stress and aberrant cell signaling. *Circ. Heart Fail.* **2015**, *8*, 188–197. [[CrossRef](#)]
105. Yu, F.; Hedström, M.; Cristea, A.; Dalén, N.; Larsson, L. Effects of ageing and gender on contractile properties in human skeletal muscle and single fibres. *Acta. Physiol.* **2007**, *190*, 229–241. [[CrossRef](#)]
106. Larsson, L.; Grimby, G.; Karlsson, J. Muscle strength and speed of movement in relation to age and muscle morphology. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* **1979**, *46*, 451–456. [[CrossRef](#)]
107. Chang, S.F.; Lin, P.L. Frail phenotype and mortality prediction: A systematic review and meta-analysis of prospective cohort studies. *Int. J. Nurs. Stud.* **2015**, *52*, 1362–1374. [[CrossRef](#)]
108. Cruz-Jentoft, A.J.; Baeyens, J.P.; Bauer, J.M.; Boirie, Y.; Cederholm, T.; Landi, F.; Martin, F.C.; Michel, J.P.; Rolland, Y.; Schneider, S.M.; et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* **2010**, *39*, 412–423. [[CrossRef](#)] [[PubMed](#)]
109. Moore, A.Z.; Caturegli, G.; Metter, E.J.; Makrogiannis, S.; Resnick, S.M.; Harris, T.B.; Ferrucci, L. Difference in muscle quality over the adult life span and biological correlates in the Baltimore Longitudinal Study of Aging. *J. Am. Geriatr. Soc.* **2014**, *62*, 230–236. [[CrossRef](#)] [[PubMed](#)]
110. Paterson, D.H.; Jones, G.R.; Rice, C.L. Ageing and physical activity: Evidence to develop exercise recommendations for older adults. *Can. J. Public Health* **2007**, *98*, S69–S108. [[PubMed](#)]
111. Vina, J.; Borras, C.; Sanchis-Gomar, F.; Martinez-Bello, V.E.; Olaso-Gonzalez, G.; Gambini, J.; Ingles, M.; Gomez-Cabrera, M.C. Pharmacological properties of physical exercise in the elderly. *Curr. Pharm. Des.* **2014**, *20*, 3019–3029. [[CrossRef](#)]
112. Narici, M.V.; Maganaris, C.N.; Reeves, N.D.; Capodaglio, P. Effect of aging on human muscle architecture. *J. Appl. Physiol.* **2003**, *95*, 2229–2234. [[CrossRef](#)]
113. Zampieri, S.; Pietrangelo, L.; Loeffler, S.; Fruhmans, H.; Vogelaer, M.; Burggraf, S.; Pond, A.; Grim-Stieger, M.; Cvecka, J.; Sedliak, M.; et al. Lifelong physical exercise delays age-associated skeletal muscle decline. *J. Gerontol. A Biol. Sci. Med. Sci.* **2015**, *70*, 163–173. [[CrossRef](#)]
114. Suetta, C.; Andersen, J.L.; Dalgas, U.; Berget, J.; Koskinen, S.; Aagaard, P.; Magnusson, S.P.; Kjaer, M. Resistance training induces qualitative changes in muscle morphology, muscle architecture, and muscle function in elderly postoperative patients. *J. Appl. Physiol.* **2008**, *105*, 180–186. [[CrossRef](#)]
115. Liu, C.J.; Latham, N.K. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst. Rev.* **2009**, CD002759. [[CrossRef](#)]
116. Tromm, C.B.; Pozzi, B.G.; Paganini, C.S.; Marques, S.O.; Pedroso, G.S.; Souza, P.S.; Silveira, P.C.; Silva, L.A.; De Souza, C.T.; Pinho, R.A. The role of continuous versus fractionated physical training on muscle oxidative stress parameters and calcium-handling proteins in aged rats. *Ageing Clin. Exp. Res.* **2016**, *28*, 833–841. [[CrossRef](#)]
117. Capelli, C.; Rittveger, J.; Brusellini, P.; Calabria, E.; Tam, E. Maximal aerobic power and anaerobic capacity in cycling across the age spectrum in male master athletes. *Eur. J. Appl. Physiol.* **2016**, *116*, 1395–1410. [[CrossRef](#)]
118. Siriett, V.; Platt, L.; Salerno, M.S.; Ling, N.; Kambadur, R.; Sharma, M. Prolonged absence of myostatin reduces sarcopenia. *J. Cell Physiol.* **2006**, *209*, 866–873. [[CrossRef](#)] [[PubMed](#)]
119. Lenk, K.; Erbs, S.; Höllriegel, R.; Beck, E.; Linke, A.; Gielen, S.; Winkler, S.M.; Sandri, M.; Hambrecht, R.; Schuler, G.; et al. Exercise training leads to a reduction of elevated myostatin levels in patients with chronic heart failure. *Eur. J. Prev. Cardiol.* **2012**, *19*, 404–411. [[CrossRef](#)] [[PubMed](#)]
120. Hittell, D.S.; Axelson, M.; Sarna, N.; Shearer, J.; Huffman, K.M.; Kraus, W.E. Myostatin decreases with aerobic exercise and associates with insulin resistance. *Med. Sci. Sports Exerc.* **2010**, *42*, 2023–2029. [[CrossRef](#)] [[PubMed](#)]
121. Gielen, S.; Sandri, M.; Kozarez, I.; Kratzsch, J.; Teupser, D.; Thiery, J.; Erbs, S.; Mangner, N.; Lenk, K.; Hambrecht, R.; et al. Exercise training attenuates MuRF-1 expression in the skeletal muscle of patients with chronic heart failure independent of age: The randomized Leipzig Exercise Intervention in Chronic Heart Failure and Aging catabolism study. *Circulation* **2012**, *125*, 2716–2727. [[CrossRef](#)]
122. Lenk, K.; Schur, R.; Linke, A.; Erbs, S.; Matsumoto, Y.; Adams, V.; Schuler, G. Impact of exercise training on myostatin expression in the myocardium and skeletal muscle in a chronic heart failure model. *Eur. J. Heart Fail.* **2009**, *11*, 342–348. [[CrossRef](#)]
123. Mosler, S.; Relizani, K.; Mouisel, E.; Amthor, H.; Diel, P. Combinatory effects of siRNA-induced myostatin inhibition and exercise on skeletal muscle homeostasis and body composition. *Physiol. Rep.* **2014**, *2*, e00262. [[CrossRef](#)]
124. You, J.S.; McNally, R.M.; Jacobs, B.L.; Privett, R.E.; Gundermann, D.M.; Lin, K.H.; Steinert, N.D.; Goodman, C.A.; Hornberger, T.A. The role of raptor in the mechanical load-induced regulation of mTOR signaling, protein synthesis, and skeletal muscle hypertrophy. *FASEB J.* **2019**, *33*, 4021–4034. [[CrossRef](#)]
125. Goodman, C.A.; Frey, J.W.; Mabrey, D.M.; Jacobs, B.L.; Lincoln, H.C.; You, J.S.; Hornberger, T.A. The role of skeletal muscle mTOR in the regulation of mechanical load-induced growth. *J. Physiol.* **2011**, *589*, 5485–5501. [[CrossRef](#)]
126. Ogasawara, R.; Sugihara, T. Rapamycin-insensitive mechanistic target of rapamycin regulates basal and resistance exercise-induced muscle protein synthesis. *FASEB J.* **2018**, fj201701422R. [[CrossRef](#)]
127. Ogasawara, R.; Fujita, S.; Hornberger, T.A.; Kitaoka, Y.; Makanae, Y.; Nakazato, K.; Naokata, I. The role of mTOR signalling in the regulation of skeletal muscle mass in a rodent model of resistance exercise. *Sci. Rep.* **2016**, *6*, 31142. [[CrossRef](#)]

128. Zanchi, N.E.; de Siqueira Filho, M.A.; Lira, F.S.; Rosa, J.C.; Yamashita, A.S.; de Oliveira Carvalho, C.R.; Seelaender, M.; Lancha, A.H. Chronic resistance training decreases MuRF-1 and Atrogin-1 gene expression but does not modify Akt, GSK-3beta and p70S6K levels in rats. *Eur. J. Appl. Physiol.* **2009**, *106*, 415–423. [[CrossRef](#)] [[PubMed](#)]
129. Skelton, D.A.; Greig, C.A.; Davies, J.M.; Young, A. Strength, power and related functional ability of healthy people aged 65–89 years. *Age Ageing* **1994**, *23*, 371–377. [[CrossRef](#)] [[PubMed](#)]
130. Widrick, J.J.; Stelzer, J.E.; Shoepe, T.C.; Garner, D.P. Functional properties of human muscle fibers after short-term resistance exercise training. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2002**, *283*, R408–R416. [[CrossRef](#)] [[PubMed](#)]
131. Bullimore, S.R.; Saunders, T.J.; Herzog, W.; MacIntosh, B.R. Calculation of muscle maximal shortening velocity by extrapolation of the force-velocity relationship: Afterloaded versus isotonic release contractions. *Can. J. Physiol. Pharmacol.* **2010**, *88*, 937–948. [[CrossRef](#)] [[PubMed](#)]
132. Schluter, J.M.; Fitts, R.H. Shortening velocity and ATPase activity of rat skeletal muscle fibers: Effects of endurance exercise training. *Am. J. Physiol.* **1994**, *266*, C1699–C1713. [[CrossRef](#)]
133. Widrick, J.J.; Trappe, S.W.; Blaser, C.A.; Costill, D.L.; Fitts, R.H. Isometric force and maximal shortening velocity of single muscle fibers from elite master runners. *Am. J. Physiol.* **1996**, *271*, C666–C675. [[CrossRef](#)]
134. Gries, K.J.; Minchev, K.; Raue, U.; Grosicki, G.J.; Begue, G.; Finch, W.H.; Graham, B.; Trappe, T.A.; Trappe, S. Single-muscle fiber contractile properties in lifelong aerobic exercising women. *J. Appl. Physiol.* **2019**, *127*, 1710–1719. [[CrossRef](#)]
135. Lynch, G.S.; McKenna, M.J.; Williams, D.A. Sprint-training effects on some contractile properties of single skinned human muscle fibres. *Acta Physiol. Scand.* **1994**, *152*, 295–306. [[CrossRef](#)]
136. Korhonen, M.T.; Cristea, A.; Alén, M.; Häkkinen, K.; Sipilä, S.; Mero, A.; Viitasalo, J.T.; Larsson, L.; Suominen, H. Aging, muscle fiber type, and contractile function in sprint-trained athletes. *J. Appl. Physiol.* **2006**, *101*, 906–917. [[CrossRef](#)]
137. Godard, M.P.; Gallagher, P.M.; Raue, U.; Trappe, S.W. Alterations in single muscle fiber calcium sensitivity with resistance training in older women. *Pflug. Arch.* **2002**, *444*, 419–425. [[CrossRef](#)]
138. Kodama, S.; Saito, K.; Tanaka, S.; Maki, M.; Yachi, Y.; Asumi, M.; Sugawara, A.; Totsuka, K.; Shimano, H.; Ohashi, Y.; et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *JAMA* **2009**, *301*, 2024–2035. [[CrossRef](#)] [[PubMed](#)]
139. Martínez-Velilla, N.; Casas-Herrero, A.; Zambom-Ferraresi, F.; Sáez de Asteasu, M.L.; Lucia, A.; Galbete, A.; García-Baztán, A.; Alonso-Renedo, J.; González-Glaría, B.; Gonzalo-Lázaro, M.; et al. Effect of Exercise Intervention on Functional Decline in Very Elderly Patients During Acute Hospitalization: A Randomized Clinical Trial. *JAMA Intern. Med.* **2019**, *179*, 28–36. [[CrossRef](#)]
140. Casas-Herrero, A.; Anton-Rodrigo, I.; Zambom-Ferraresi, F.; Sáez de Asteasu, M.L.; Martínez-Velilla, N.; Elempuru-Estomba, J.; Marin-Epelde, I.; Ramon-Espinoza, F.; Petidier-Torregrosa, R.; Sanchez-Sanchez, J.L.; et al. Effect of a multicomponent exercise programme (VIVIFRAIL) on functional capacity in frail community elders with cognitive decline: Study protocol for a randomized multicentre control trial. *Trials* **2019**, *20*, 362. [[CrossRef](#)] [[PubMed](#)]
141. Hojan, K.; Kwiatkowska-Borowczyk, E.; Leporowska, E.; Górecki, M.; Ozga-Majchrzak, O.; Milecki, T.; Milecki, P. Physical exercise for functional capacity, blood immune function, fatigue, and quality of life in high-risk prostate cancer patients during radiotherapy: A prospective, randomized clinical study. *Eur. J. Phys. Rehabil. Med.* **2016**, *52*, 489–501. [[PubMed](#)]
142. Oh, M.; Rybkin, I.I.; Copeland, V.; Czubyrt, M.P.; Shelton, J.M.; van Rooij, E.; Richardson, J.A.; Hill, J.A.; De Windt, L.J.; Bassel-Duby, R.; et al. Calcineurin is necessary for the maintenance but not embryonic development of slow muscle fibers. *Mol. Cell Biol.* **2005**, *25*, 6629–6638. [[CrossRef](#)] [[PubMed](#)]
143. Parsons, S.A.; Wilkins, B.J.; Bueno, O.F.; Molkentin, J.D. Altered skeletal muscle phenotypes in calcineurin Aalpha and Abeta gene-targeted mice. *Mol. Cell Biol.* **2003**, *23*, 4331–4343. [[CrossRef](#)]
144. Naya, F.J.; Mercer, B.; Shelton, J.; Richardson, J.A.; Williams, R.S.; Olson, E.N. Stimulation of slow skeletal muscle fiber gene expression by calcineurin in vivo. *J. Biol. Chem.* **2000**, *275*, 4545–4548. [[CrossRef](#)]
145. Handschin, C.; Chin, S.; Li, P.; Liu, F.; Maratos-Flier, E.; Lebrasseur, N.K.; Yan, Z.; Spiegelman, B.M. Skeletal muscle fiber-type switching, exercise intolerance, and myopathy in PGC-1alpha muscle-specific knock-out animals. *J. Biol. Chem.* **2007**, *282*, 30014–30021. [[CrossRef](#)]
146. Handschin, C.; Choi, C.S.; Chin, S.; Kim, S.; Kawamori, D.; Kurpad, A.J.; Neubauer, N.; Hu, J.; Mootha, V.K.; Kim, Y.B.; et al. Abnormal glucose homeostasis in skeletal muscle-specific PGC-1alpha knockout mice reveals skeletal muscle-pancreatic beta cell crosstalk. *J. Clin. Invest.* **2007**, *117*, 3463–3474. [[CrossRef](#)]
147. Geng, T.; Li, P.; Okutsu, M.; Yin, X.; Kwek, J.; Zhang, M.; Yan, Z. PGC-1alpha plays a functional role in exercise-induced mitochondrial biogenesis and angiogenesis but not fiber-type transformation in mouse skeletal muscle. *Am. J. Physiol. Cell Physiol.* **2010**, *298*, C572–C579. [[CrossRef](#)]
148. Arany, Z.; Foo, S.Y.; Ma, Y.; Ruas, J.L.; Bommi-Reddy, A.; Girnun, G.; Cooper, M.; Laznik, D.; Chinsomboon, J.; Rangwala, S.M.; et al. HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1alpha. *Nature* **2008**, *451*, 1008–1012. [[CrossRef](#)] [[PubMed](#)]
149. Leick, L.; Hellsten, Y.; Fentz, J.; Lyngby, S.S.; Wojtaszewski, J.F.; Hidalgo, J.; Pilegaard, H. PGC-1alpha mediates exercise-induced skeletal muscle VEGF expression in mice. *Am. J. Physiol. Endocrinol. Metab.* **2009**, *297*, E92–E103. [[CrossRef](#)]
150. Chinsomboon, J.; Ruas, J.; Gupta, R.K.; Thom, R.; Shoag, J.; Rowe, G.C.; Sawada, N.; Raghuram, S.; Arany, Z. The transcriptional coactivator PGC-1alpha mediates exercise-induced angiogenesis in skeletal muscle. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 21401–21406. [[CrossRef](#)] [[PubMed](#)]

151. Olfert, I.M.; Howlett, R.A.; Tang, K.; Dalton, N.D.; Gu, Y.; Peterson, K.L.; Wagner, P.D.; Breen, E.C. Muscle-specific VEGF deficiency greatly reduces exercise endurance in mice. *J. Physiol.* **2009**, *587*, 1755–1767. [[CrossRef](#)] [[PubMed](#)]
152. Olfert, I.M.; Howlett, R.A.; Wagner, P.D.; Breen, E.C. Myocyte vascular endothelial growth factor is required for exercise-induced skeletal muscle angiogenesis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2010**, *299*, R1059–R1067. [[CrossRef](#)] [[PubMed](#)]
153. Ferrannini, E.; Simonson, D.C.; Katz, L.D.; Reichard, G.; Bevilacqua, S.; Barrett, E.J.; Olsson, M.; DeFronzo, R.A. The disposal of an oral glucose load in patients with non-insulin-dependent diabetes. *Metabolism* **1988**, *37*, 79–85. [[CrossRef](#)]
154. Wahren, J.; Felig, P.; Ahlborg, G.; Jorfeldt, L. Glucose metabolism during leg exercise in man. *J. Clin. Invest* **1971**, *50*, 2715–2725. [[CrossRef](#)]
155. Battaglia, G.M.; Zheng, D.; Hickner, R.C.; Houmard, J.A. Effect of exercise training on metabolic flexibility in response to a high-fat diet in obese individuals. *Am. J. Physiol. Endocrinol. Metab.* **2012**, *303*, E1440–E1445. [[CrossRef](#)]
156. Richter, E.A.; Garetto, L.P.; Goodman, M.N.; Ruderman, N.B. Muscle glucose metabolism following exercise in the rat: Increased sensitivity to insulin. *J. Clin. Invest.* **1982**, *69*, 785–793. [[CrossRef](#)]
157. Borghouts, L.B.; Keizer, H.A. Exercise and insulin sensitivity: A review. *Int. J. Sports Med.* **2000**, *21*. [[CrossRef](#)]
158. Ryan, B.J.; Schleh, M.W.; Ahn, C.; Ludzki, A.C.; Gillen, J.B.; Varshney, P.; Van Pelt, D.W.; Pitchford, L.M.; Chenevert, T.L.; Gioscia-Ryan, R.A.; et al. Moderate-Intensity Exercise and High-Intensity Interval Training Affect Insulin Sensitivity Similarly in Obese Adults. *J. Clin. Endocrinol. Metab.* **2020**, *105*, e2941–e2959. [[CrossRef](#)] [[PubMed](#)]
159. Houmard, J.A.; Tanner, C.J.; Slentz, C.A.; Duscha, B.D.; McCartney, J.S.; Kraus, W.E. Effect of the volume and intensity of exercise training on insulin sensitivity. *J. Appl. Physiol.* **2004**, *96*, 101–106. [[CrossRef](#)] [[PubMed](#)]
160. Lin, X.; Zhang, X.; Guo, J.; Roberts, C.K.; McKenzie, S.; Wu, W.C.; Liu, S.; Song, Y. 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.* **2015**, *4*, e002014. [[CrossRef](#)] [[PubMed](#)]
161. Kim, J.; Solis, R.S.; Arias, E.B.; Cartee, G.D. Postcontraction insulin sensitivity: Relationship with contraction protocol, glycogen concentration, and 5' AMP-activated protein kinase phosphorylation. *J. Appl. Physiol.* **2004**, *96*, 575–583. [[CrossRef](#)]
162. Hamada, T.; Arias, E.B.; Cartee, G.D. Increased submaximal insulin-stimulated glucose uptake in mouse skeletal muscle after treadmill exercise. *J. Appl. Physiol.* **2006**, *101*, 1368–1376. [[CrossRef](#)]
163. Fazakerley, D.J.; Holman, G.D.; Marley, A.; James, D.E.; Stöckli, J.; Coster, A.C. Kinetic evidence for unique regulation of GLUT4 trafficking by insulin and AMP-activated protein kinase activators in L6 myotubes. *J. Biol. Chem.* **2010**, *285*, 1653–1660. [[CrossRef](#)]
164. Hansen, P.A.; Nolte, L.A.; Chen, M.M.; Holloszy, J.O. Increased GLUT-4 translocation mediates enhanced insulin sensitivity of muscle glucose transport after exercise. *J. Appl. Physiol.* **1998**, *85*, 1218–1222. [[CrossRef](#)]
165. Kjøbsted, R.; Munk-Hansen, N.; Birk, J.B.; Foretz, M.; Viollet, B.; Bjørnholm, M.; Zierath, J.R.; Treebak, J.T.; Wojtaszewski, J.F. Enhanced Muscle Insulin Sensitivity After Contraction/Exercise Is Mediated by AMPK. *Diabetes* **2017**, *66*, 598–612. [[CrossRef](#)]
166. O'Neill, H.M.; Maarbjerg, S.J.; Crane, J.D.; Jeppesen, J.; Jørgensen, S.B.; Schertzer, J.D.; Shyroka, O.; Kiens, B.; van Denderen, B.J.; Tarnopolsky, M.A.; et al. AMP-activated protein kinase (AMPK) beta1beta2 muscle null mice reveal an essential role for AMPK in maintaining mitochondrial content and glucose uptake during exercise. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 16092–16097. [[CrossRef](#)]
167. Frøsig, C.; Pehmøller, C.; Birk, J.B.; Richter, E.A.; Wojtaszewski, J.F. Exercise-induced TBC1D1 Ser237 phosphorylation and 14-3-3 protein binding capacity in human skeletal muscle. *J. Physiol.* **2010**, *588*, 4539–4548. [[CrossRef](#)]
168. Baar, K.; Wende, A.R.; Jones, T.E.; Marison, M.; Nolte, L.A.; Chen, M.; Kelly, D.P.; Holloszy, J.O. Adaptations of skeletal muscle to exercise: Rapid increase in the transcriptional coactivator PGC-1. *FASEB J.* **2002**, *16*, 1879–1886. [[CrossRef](#)]
169. Holloszy, J.O. Biochemical adaptations in muscle. Effects of exercise on mitochondrial oxygen uptake and respiratory enzyme activity in skeletal muscle. *J. Biol. Chem.* **1967**, *242*, 2278–2282. [[CrossRef](#)]
170. Reichmann, H.; Hoppeler, H.; Mathieu-Costello, O.; von Bergen, F.; Pette, D. Biochemical and ultrastructural changes of skeletal muscle mitochondria after chronic electrical stimulation in rabbits. *Pflug. Arch.* **1985**, *404*, 1–9. [[CrossRef](#)] [[PubMed](#)]
171. Larsen, S.; Nielsen, J.; Hansen, C.N.; Nielsen, L.B.; Wibrand, F.; Stride, N.; Schroder, H.D.; Boushel, R.; Helge, J.W.; Dela, F.; et al. Biomarkers of mitochondrial content in skeletal muscle of healthy young human subjects. *J. Physiol.* **2012**, *590*, 3349–3360. [[CrossRef](#)] [[PubMed](#)]
172. Toyama, E.Q.; Herzig, S.; Courchet, J.; Lewis, T.L.; Losón, O.C.; Hellberg, K.; Young, N.P.; Chen, H.; Polleux, F.; Chan, D.C.; et al. Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. *Science* **2016**, *351*, 275–281. [[CrossRef](#)] [[PubMed](#)]
173. Moore, T.M.; Zhou, Z.; Cohn, W.; Norheim, F.; Lin, A.J.; Kalajian, N.; Strumwasser, A.R.; Cory, K.; Whitney, K.; Ho, T.; et al. The impact of exercise on mitochondrial dynamics and the role of Drp1 in exercise performance and training adaptations in skeletal muscle. *Mol. Metab.* **2019**, *21*, 51–67. [[CrossRef](#)]
174. Laker, R.C.; Drake, J.C.; Wilson, R.J.; Lira, V.A.; Lewellen, B.M.; Ryall, K.A.; Fisher, C.C.; Zhang, M.; Saucerman, J.J.; Goodyear, L.J.; et al. Ampk phosphorylation of Ulk1 is required for targeting of mitochondria to lysosomes in exercise-induced mitophagy. *Nat. Commun.* **2017**, *8*, 548. [[CrossRef](#)]
175. Winder, W.W.; Holmes, B.F.; Rubink, D.S.; Jensen, E.B.; Chen, M.; Holloszy, J.O. Activation of AMP-activated protein kinase increases mitochondrial enzymes in skeletal muscle. *J. Appl. Physiol.* **2000**, *88*, 2219–2226. [[CrossRef](#)]

176. Miyamoto, T.; Rho, E.; Sample, V.; Akano, H.; Magari, M.; Ueno, T.; Gorshkov, K.; Chen, M.; Tokumitsu, H.; Zhang, J.; et al. Compartmentalized AMPK signaling illuminated by genetically encoded molecular sensors and actuators. *Cell Rep.* **2015**, *11*, 657–670. [[CrossRef](#)]
177. Vatner, S.F.; Zhang, J.; Oydanich, M.; Berkman, T.; Naftalovich, R.; Vatner, D.E. Healthful aging mediated by inhibition of oxidative stress. *Ageing Res. Rev.* **2020**, *64*, 101194. [[CrossRef](#)]
178. Egea, J.; Fabregat, I.; Frapart, Y.M.; Ghezzi, P.; Görlach, A.; Kietzmann, T.; Kubaichuk, K.; Knaus, U.G.; Lopez, M.G.; Olasso-Gonzalez, G.; et al. European contribution to the study of ROS: A summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS). *Redox Biol.* **2017**, *13*, 94–162. [[CrossRef](#)] [[PubMed](#)]
179. Tofas, T.; Draganidis, D.; Deli, C.K.; Georgakouli, K.; Fatouros, I.G.; Jamurtas, A.Z. Exercise-Induced Regulation of Redox Status in Cardiovascular Diseases: The Role of Exercise Training and Detraining. *Antioxidants* **2019**, *9*, 13. [[CrossRef](#)] [[PubMed](#)]
180. Lu, Y.; Wiltshire, H.D.; Baker, J.S.; Wang, Q. Effects of High Intensity Exercise on Oxidative Stress and Antioxidant Status in Untrained Humans: A Systematic Review. *Biology* **2021**, *10*, 1272. [[CrossRef](#)]
181. Kawamura, T.; Muraoka, I. Exercise-Induced Oxidative Stress and the Effects of Antioxidant Intake from a Physiological Viewpoint. *Antioxidants* **2018**, *7*, 119. [[CrossRef](#)]
182. McArdle, A.; Pattwell, D.; Vasilaki, A.; Griffiths, R.D.; Jackson, M.J. Contractile activity-induced oxidative stress: Cellular origin and adaptive responses. *Am. J. Physiol. Cell Physiol.* **2001**, *280*, C621–C627. [[CrossRef](#)] [[PubMed](#)]
183. Ji, L.L. Exercise-induced modulation of antioxidant defense. *Ann. N. Y. Acad. Sci.* **2002**, *959*, 82–92. [[CrossRef](#)] [[PubMed](#)]
184. Zelko, I.N.; Mariani, T.J.; Folz, R.J. Superoxide dismutase multigene family: A comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. *Free Radic. Biol. Med.* **2002**, *33*, 337–349. [[CrossRef](#)]
185. Yan, Z.; Spaulding, H.R. Extracellular superoxide dismutase, a molecular transducer of health benefits of exercise. *Redox Biol.* **2020**, *32*, 101508. [[CrossRef](#)]
186. Okutsu, M.; Call, J.A.; Lira, V.A.; Zhang, M.; Donet, J.A.; French, B.A.; Martin, K.S.; Peirce-Cottler, S.M.; Rembold, C.M.; Annex, B.H.; et al. Extracellular superoxide dismutase ameliorates skeletal muscle abnormalities, cachexia, and exercise intolerance in mice with congestive heart failure. *Circ. Heart Fail.* **2014**, *7*, 519–530. [[CrossRef](#)]
187. Call, J.A.; Donet, J.; Martin, K.S.; Sharma, A.K.; Chen, X.; Zhang, J.; Cai, J.; Galarreta, C.A.; Okutsu, M.; Du, Z.; et al. Muscle-derived extracellular superoxide dismutase inhibits endothelial activation and protects against multiple organ dysfunction syndrome in mice. *Free Radic. Biol. Med.* **2017**, *113*, 212–223. [[CrossRef](#)]
188. Bray, G.A.; Heisel, W.E.; Afshin, A.; Jensen, M.D.; Dietz, W.H.; Long, M.; Kushner, R.F.; Daniels, S.R.; Wadden, T.A.; Tsai, A.G.; et al. The Science of Obesity Management: An Endocrine Society Scientific Statement. *Endocr. Rev.* **2018**, *39*, 79–132. [[CrossRef](#)] [[PubMed](#)]
189. Johns, D.J.; Hartmann-Boyce, J.; Jebb, S.A.; Aveyard, P.; Group, B.W.; Management, R. Diet or exercise interventions vs combined behavioral weight management programs: A systematic review and meta-analysis of direct comparisons. *J. Acad. Nutr. Diet* **2014**, *114*, 1557–1568. [[CrossRef](#)] [[PubMed](#)]
190. Petridou, A.; Siopi, A.; Mougios, V. Exercise in the management of obesity. *Metabolism* **2019**, *92*, 163–169. [[CrossRef](#)] [[PubMed](#)]
191. Beaulieu, K.; Blundell, J.E.; van Baak, M.A.; Battista, F.; Busetto, L.; Carraça, E.V.; Dicker, D.; Encantado, J.; Ermolao, A.; Farpour-Lambert, N.; et al. Effect of exercise training interventions on energy intake and appetite control in adults with overweight or obesity: A systematic review and meta-analysis. *Obes. Rev.* **2021**, *22*, e13251. [[CrossRef](#)]
192. Holland, W.L.; Knotts, T.A.; Chavez, J.A.; Wang, L.P.; Hoehn, K.L.; Summers, S.A. Lipid mediators of insulin resistance. *Nutr. Rev.* **2007**, *65*, S39–S46. [[CrossRef](#)]
193. Kraegen, E.W.; Cooney, G.J. Free fatty acids and skeletal muscle insulin resistance. *Curr. Opin. Lipidol.* **2008**, *19*, 235–241. [[CrossRef](#)]
194. Krssak, M.; Falk Petersen, K.; Dresner, A.; DiPietro, L.; Vogel, S.M.; Rothman, D.L.; Roden, M.; Shulman, G.I. Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: A ¹H NMR spectroscopy study. *Diabetologia* **1999**, *42*, 113–116. [[CrossRef](#)]
195. Van Gaal, L.F.; Mertens, I.L.; De Block, C.E. Mechanisms linking obesity with cardiovascular disease. *Nature* **2006**, *444*, 875–880. [[CrossRef](#)]
196. Bastard, J.P.; Maachi, M.; Lagathu, C.; Kim, M.J.; Caron, M.; Vidal, H.; Capeau, J.; Feve, B. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur. Cytokine Netw.* **2006**, *17*, 4–12.
197. Hauck, A.K.; Huang, Y.; Hertz, A.V.; Bernlohr, D.A. Adipose oxidative stress and protein carbonylation. *J. Biol. Chem.* **2019**, *294*, 1083–1088. [[CrossRef](#)]
198. Fernández-Sánchez, A.; Madrigal-Santillán, E.; Bautista, M.; Esquivel-Soto, J.; Morales-González, A.; Esquivel-Chirino, C.; Durante-Montiel, I.; Sánchez-Rivera, G.; Valadez-Vega, C.; Morales-González, J.A. Inflammation, oxidative stress, and obesity. *Int. J. Mol. Sci.* **2011**, *12*, 3117–3132. [[CrossRef](#)] [[PubMed](#)]
199. Holloway, G.P.; Bezaire, V.; Heigenhauser, G.J.; Tandon, N.N.; Glatz, J.F.; Luiken, J.J.; Bonen, A.; Spriet, L.L. Mitochondrial long chain fatty acid oxidation, fatty acid translocase/CD36 content and carnitine palmitoyltransferase I activity in human skeletal muscle during aerobic exercise. *J. Physiol.* **2006**, *571*, 201–210. [[CrossRef](#)] [[PubMed](#)]
200. Schenk, S.; Horowitz, J.F. Acute exercise increases triglyceride synthesis in skeletal muscle and prevents fatty acid-induced insulin resistance. *J. Clin. Investig.* **2007**, *117*, 1690–1698. [[CrossRef](#)] [[PubMed](#)]

201. Turcotte, L.P.; Richter, E.A.; Kiens, B. Increased plasma FFA uptake and oxidation during prolonged exercise in trained vs. untrained humans. *Am. J. Physiol.* **1992**, *262*, E791–E799. [[CrossRef](#)]
202. Bergman, B.C.; Butterfield, G.E.; Wolfel, E.E.; Casazza, G.A.; Lopaschuk, G.D.; Brooks, G.A. Evaluation of exercise and training on muscle lipid metabolism. *Am. J. Physiol.* **1999**, *276*, E106–E117. [[CrossRef](#)]
203. Coggan, A.R.; Raguso, C.A.; Gastaldelli, A.; Sidossis, L.S.; Yeckel, C.W. Fat metabolism during high-intensity exercise in endurance-trained and untrained men. *Metabolism* **2000**, *49*, 122–128. [[CrossRef](#)]
204. Horowitz, J.F.; Leone, T.C.; Feng, W.; Kelly, D.P.; Klein, S. Effect of endurance training on lipid metabolism in women: A potential role for PPAR α in the metabolic response to training. *Am. J. Physiol. Endocrinol. Metab.* **2000**, *279*, E348–E355. [[CrossRef](#)]
205. Fedorenko, A.; Lishko, P.V.; Kirichok, Y. Mechanism of fatty-acid-dependent UCP1 uncoupling in brown fat mitochondria. *Cell* **2012**, *151*, 400–413. [[CrossRef](#)]
206. Matsushita, M.; Yoneshiro, T.; Aita, S.; Kameya, T.; Sugie, H.; Saito, M. Impact of brown adipose tissue on body fatness and glucose metabolism in healthy humans. *Int. J. Obes.* **2014**, *38*, 812–817. [[CrossRef](#)]
207. Yoneshiro, T.; Aita, S.; Matsushita, M.; Okamatsu-Ogura, Y.; Kameya, T.; Kawai, Y.; Miyagawa, M.; Tsujisaki, M.; Saito, M. Age-related decrease in cold-activated brown adipose tissue and accumulation of body fat in healthy humans. *Obesity* **2011**, *19*, 1755–1760. [[CrossRef](#)]
208. Stanford, K.I.; Goodyear, L.J. Muscle-Adipose Tissue Cross Talk. *Cold Spring Harb. Perspect. Med.* **2018**, *8*, a029801. [[CrossRef](#)] [[PubMed](#)]
209. Aldiss, P.; Betts, J.; Sale, C.; Pope, M.; Budge, H.; Symonds, M.E. Exercise-induced ‘browning’ of adipose tissues. *Metabolism* **2018**, *81*, 63–70. [[CrossRef](#)] [[PubMed](#)]
210. Xiong, Y.; Wu, Z.; Zhang, B.; Wang, C.; Mao, F.; Liu, X.; Hu, K.; Sun, X.; Jin, W.; Kuang, S. Fndc5 loss-of-function attenuates exercise-induced browning of white adipose tissue in mice. *FASEB J.* **2019**, *33*, 5876–5886. [[CrossRef](#)] [[PubMed](#)]
211. Knudsen, J.G.; Murholm, M.; Carey, A.L.; Biensø, R.S.; Basse, A.L.; Allen, T.L.; Hidalgo, J.; Kingwell, B.A.; Febbraio, M.A.; Hansen, J.B.; et al. Role of IL-6 in exercise training- and cold-induced UCP1 expression in subcutaneous white adipose tissue. *PLoS ONE* **2014**, *9*, e84910. [[CrossRef](#)] [[PubMed](#)]
212. Targher, G.; Bertolini, L.; Padovani, R.; Poli, F.; Scala, L.; Tessari, R.; Zenari, L.; Falezza, G. Increased prevalence of cardiovascular disease in Type 2 diabetic patients with non-alcoholic fatty liver disease. *Diabet Med.* **2006**, *23*, 403–409. [[CrossRef](#)]
213. Adams, L.A.; Angulo, P.; Lindor, K.D. Nonalcoholic fatty liver disease. *CMAJ* **2005**, *172*, 899–905. [[CrossRef](#)]
214. 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. Exercise Reduces Liver Lipids and Visceral Adiposity in Patients with Nonalcoholic Steatohepatitis in a Randomized Controlled Trial. *Clin. Gastroenterol. Hepatol.* **2017**, *15*, 96–102.e103. [[CrossRef](#)]
215. Bacchi, E.; Negri, C.; Targher, G.; Faccioli, N.; Lanza, M.; Zoppini, G.; Zanolin, E.; Schena, F.; Bonora, E.; Moghetti, P. 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* **2013**, *58*, 1287–1295. [[CrossRef](#)]
216. Yasari, S.; Dufresne, E.; Prud’homme, D.; Lavoie, J.M. Effect of the detraining status on high-fat diet induced fat accumulation in the adipose tissue and liver in female rats. *Physiol. Behav.* **2007**, *91*, 281–289. [[CrossRef](#)]
217. Baek, K.W.; Gim, J.A.; Park, J.J. Regular moderate aerobic exercise improves high-fat diet-induced nonalcoholic fatty liver disease via monoacylglycerol O-acyltransferase 1 pathway suppression. *J. Sport Health Sci.* **2020**, *9*, 472–478. [[CrossRef](#)]
218. Marcinko, K.; Sikkema, S.R.; Samaan, M.C.; Kemp, B.E.; Fullerton, M.D.; Steinberg, G.R. High intensity interval training improves liver and adipose tissue insulin sensitivity. *Mol. Metab.* **2015**, *4*, 903–915. [[CrossRef](#)] [[PubMed](#)]
219. Kawanishi, N.; Yano, H.; Mizokami, T.; Takahashi, M.; Oyanagi, E.; Suzuki, K. Exercise training attenuates hepatic inflammation, fibrosis and macrophage infiltration during diet induced-obesity in mice. *Brain Behav. Immun.* **2012**, *26*, 931–941. [[CrossRef](#)] [[PubMed](#)]
220. Gonçalves, I.O.; Maciel, E.; Passos, E.; Torrella, J.R.; Rizo, D.; Viscor, G.; Rocha-Rodrigues, S.; Santos-Alves, E.; Domingues, M.R.; Oliveira, P.J.; et al. Exercise alters liver mitochondria phospholipidomic profile and mitochondrial activity in non-alcoholic steatohepatitis. *Int. J. Biochem. Cell Biol.* **2014**, *54*, 163–173. [[CrossRef](#)] [[PubMed](#)]
221. Kruse, R.; Vienberg, S.G.; Vind, B.F.; Andersen, B.; Højlund, K. Effects of insulin and exercise training on FGF21, its receptors and target genes in obesity and type 2 diabetes. *Diabetologia* **2017**, *60*, 2042–2051. [[CrossRef](#)] [[PubMed](#)]
222. Izumiya, Y.; Bina, H.A.; Ouchi, N.; Akasaki, Y.; Kharitonov, A.; Walsh, K. FGF21 is an Akt-regulated myokine. *FEBS Lett.* **2008**, *582*, 3805–3810. [[CrossRef](#)]
223. Coskun, T.; Bina, H.A.; Schneider, M.A.; Dunbar, J.D.; Hu, C.C.; Chen, Y.; Moller, D.E.; Kharitonov, A. Fibroblast growth factor 21 corrects obesity in mice. *Endocrinology* **2008**, *149*, 6018–6027. [[CrossRef](#)]
224. Kharitonov, A.; Wroblewski, V.J.; Koester, A.; Chen, Y.F.; Clutinger, C.K.; Tigno, X.T.; Hansen, B.C.; Shanafelt, A.B.; Etgen, G.J. The metabolic state of diabetic monkeys is regulated by fibroblast growth factor-21. *Endocrinology* **2007**, *148*, 774–781. [[CrossRef](#)]
225. Loyd, C.; Magrisso, I.J.; Haas, M.; Balusu, S.; Krishna, R.; Itoh, N.; Sandoval, D.A.; Perez-Tilve, D.; Obici, S.; Habegger, K.M. Fibroblast growth factor 21 is required for beneficial effects of exercise during chronic high-fat feeding. *J. Appl. Physiol.* **2016**, *121*, 687–698. [[CrossRef](#)]
226. Oost, L.J.; Kustermann, M.; Armani, A.; Blaauw, B.; Romanello, V. Fibroblast growth factor 21 controls mitophagy and muscle mass. *J. Cachexia Sarcopenia Muscle* **2019**, *10*, 630–642. [[CrossRef](#)]

227. Collaborators, G.N. Global, regional, and national burden of neurological disorders, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **2019**, *18*, 459–480. [[CrossRef](#)]
228. Feigin, V.L.; Vos, T.; Nichols, E.; Owolabi, M.O.; Carroll, W.M.; Dichgans, M.; Deuschl, G.; Parmar, P.; Brainin, M.; Murray, C. The global burden of neurological disorders: Translating evidence into policy. *Lancet Neurol.* **2020**, *19*, 255–265. [[CrossRef](#)]
229. Patel, V.; Saxena, S.; Lund, C.; Thornicroft, G.; Baingana, F.; Bolton, P.; Chisholm, D.; Collins, P.Y.; Cooper, J.L.; Eaton, J.; et al. The Lancet Commission on global mental health and sustainable development. *Lancet* **2018**, *392*, 1553–1598. [[CrossRef](#)]
230. Firth, J.; Stubbs, B.; Vancampfort, D.; Schuch, F.; Lagopoulos, J.; Rosenbaum, S.; Ward, P.B. Effect of aerobic exercise on hippocampal volume in humans: A systematic review and meta-analysis. *Neuroimage* **2018**, *166*, 230–238. [[CrossRef](#)]
231. Sofi, F.; Valecchi, D.; Bacci, D.; Abbate, R.; Gensini, G.F.; Casini, A.; Macchi, C. Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *J. Intern. Med.* **2011**, *269*, 107–117. [[CrossRef](#)] [[PubMed](#)]
232. Santos-Lozano, A.; Pareja-Galeano, H.; Sanchis-Gomar, F.; Quindós-Rubial, M.; Fiuza-Luces, C.; Cristi-Montero, C.; Emanuele, E.; Garatachea, N.; Lucia, A. Physical Activity and Alzheimer Disease: A Protective Association. *Mayo Clin. Proc.* **2016**, *91*, 999–1020. [[CrossRef](#)]
233. Heyn, P.; Abreu, B.C.; Ottenbacher, K.J. The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. *Arch. Phys. Med. Rehabil.* **2004**, *85*, 1694–1704. [[CrossRef](#)]
234. Pitkälä, K.H.; Pöysti, M.M.; Laakkonen, M.L.; Tilvis, R.S.; Savikko, N.; Kautiainen, H.; Strandberg, T.E. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): A randomized controlled trial. *JAMA Intern. Med.* **2013**, *173*, 894–901. [[CrossRef](#)]
235. Bossers, W.J.; van der Woude, L.H.; Boersma, F.; Hortobágyi, T.; Scherder, E.J.; van Heuvelen, M.J. A 9-Week Aerobic and Strength Training Program Improves Cognitive and Motor Function in Patients with Dementia: A Randomized, Controlled Trial. *Am. J. Geriatr. Psychiatry* **2015**, *23*, 1106–1116. [[CrossRef](#)]
236. Chapman, S.B.; Aslan, S.; Spence, J.S.; Defina, L.F.; Keebler, M.W.; Didehbani, N.; Lu, H. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. *Front. Aging Neurosci.* **2013**, *5*, 75. [[CrossRef](#)]
237. Zhao, L.; Liu, G.; Zhang, L.; Du, Y.; Lei, L.; Zhang, X.; Zhao, Y.; Shen, D. Long-term Physical Exercise Improves Finger Tapping of Patients with Alzheimer’s Disease. *Curr. Alzheimer Res.* **2021**, *18*, 1077–1086. [[CrossRef](#)]
238. Otobe, Y.; Yamada, M.; Hiraki, K.; Onari, S.; Taki, Y.; Sumi, H.; Hachisuka, R.; Han, W.; Takahashi, M.; Suzuki, M.; et al. Physical Exercise Improves Cognitive Function in Older Adults with Stage 3–4 Chronic Kidney Disease: A Randomized Controlled Trial. *Am. J. Nephrol.* **2021**, *52*, 929–939. [[CrossRef](#)]
239. Lau, Y.S.; Patki, G.; Das-Panja, K.; Le, W.D.; Ahmad, S.O. Neuroprotective effects and mechanisms of exercise in a chronic mouse model of Parkinson’s disease with moderate neurodegeneration. *Eur. J. Neurosci.* **2011**, *33*, 1264–1274. [[CrossRef](#)] [[PubMed](#)]
240. Goodwin, V.A.; Richards, S.H.; Taylor, R.S.; Taylor, A.H.; Campbell, J.L. The effectiveness of exercise interventions for people with Parkinson’s disease: A systematic review and meta-analysis. *Mov. Disord.* **2008**, *23*, 631–640. [[CrossRef](#)] [[PubMed](#)]
241. Grazioli, E.; Tranchita, E.; Borriello, G.; Cerulli, C.; Minganti, C.; Parisi, A. The Effects of Concurrent Resistance and Aerobic Exercise Training on Functional Status in Patients with Multiple Sclerosis. *Curr. Sports Med. Rep.* **2019**, *18*, 452–457. [[CrossRef](#)] [[PubMed](#)]
242. Patten, S.B.; Williams, J.V.; Lavorato, D.H.; Terriff, D.; Metz, L.M.; Berzins, S.; Bulloch, A.G. Perceived met and unmet health-care needs in a community population with multiple sclerosis. *Int. J. MS Care* **2012**, *14*, 2–8. [[CrossRef](#)]
243. Dalgas, U.; Stenager, E.; Ingemann-Hansen, T. Multiple sclerosis and physical exercise: Recommendations for the application of resistance-, endurance- and combined training. *Mult. Scler.* **2008**, *14*, 35–53. [[CrossRef](#)]
244. Mostert, S.; Kesselring, J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. *Mult. Scler.* **2002**, *8*, 161–168. [[CrossRef](#)]
245. Kileff, J.; Ashburn, A. A pilot study of the effect of aerobic exercise on people with moderate disability multiple sclerosis. *Clin. Rehabil.* **2005**, *19*, 165–169. [[CrossRef](#)]
246. Oken, B.S.; Kishiyama, S.; Zajdel, D.; Bourdette, D.; Carlsen, J.; Haas, M.; Hugos, C.; Kraemer, D.F.; Lawrence, J.; Mass, M. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology* **2004**, *62*, 2058–2064. [[CrossRef](#)]
247. Petajan, J.H.; Gappmaier, E.; White, A.T.; Spencer, M.K.; Mino, L.; Hicks, R.W. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann. Neurol.* **1996**, *39*, 432–441. [[CrossRef](#)]
248. Schulz, K.H.; Gold, S.M.; Witte, J.; Bartsch, K.; Lang, U.E.; Hellweg, R.; Reer, R.; Braumann, K.M.; Heesen, C. Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. *J. Neurol. Sci.* **2004**, *225*, 11–18. [[CrossRef](#)] [[PubMed](#)]
249. van den Berg, M.; Dawes, H.; Wade, D.T.; Newman, M.; Burridge, J.; Izadi, H.; Sackley, C.M. Treadmill training for individuals with multiple sclerosis: A pilot randomised trial. *J. Neurol. Neurosurg. Psychiatry* **2006**, *77*, 531–533. [[CrossRef](#)] [[PubMed](#)]
250. Gerber, M.; Minghetti, A.; Beck, J.; Zahner, L.; Donath, L. Sprint Interval Training and Continuous Aerobic Exercise Training Have Similar Effects on Exercise Motivation and Affective Responses to Exercise in Patients with Major Depressive Disorders: A Randomized Controlled Trial. *Front. Psychiatry* **2018**, *9*, 694. [[CrossRef](#)] [[PubMed](#)]
251. Rethorst, C.D.; Wipfli, B.M.; Landers, D.M. The antidepressive effects of exercise: A meta-analysis of randomized trials. *Sports Med.* **2009**, *39*, 491–511. [[CrossRef](#)]
252. Nebiker, L.; Lichtenstein, E.; Minghetti, A.; Zahner, L.; Gerber, M.; Faude, O.; Donath, L. Moderating Effects of Exercise Duration and Intensity in Neuromuscular vs. Endurance Exercise Interventions for the Treatment of Depression: A Meta-Analytical Review. *Front. Psychiatry* **2018**, *9*, 305. [[CrossRef](#)]

253. Serra, L.; Raimondi, S.; di Domenico, C.; Maffei, S.; Lardone, A.; Liparoti, M.; Sorrentino, P.; Caltagirone, C.; Petrosini, L.; Mandolesi, L. The beneficial effects of physical exercise on visuospatial working memory in preadolescent children. *AIMS Neurosci.* **2021**, *8*, 496–509. [[CrossRef](#)]
254. Aleksić Veljković, A.; Katanić, B.; Masanovic, B. Effects of a 12-Weeks Yoga Intervention on Motor and Cognitive Abilities of Preschool Children. *Front. Pediatr.* **2021**, *9*, 799226. [[CrossRef](#)]
255. Hatch, L.M.; Dring, K.J.; Williams, R.A.; Sunderland, C.; Nevill, M.E.; Cooper, S.B. Effect of Differing Durations of High-Intensity Intermittent Activity on Cognitive Function in Adolescents. *Int. J. Env. Res. Public Health* **2021**, *18*, 11594. [[CrossRef](#)]
256. Carta, M.G.; Cossu, G.; Pintus, E.; Zaccheddu, R.; Callia, O.; Conti, G.; Pintus, M.; Aviles Gonzalez, C.I.; Massidda, M.V.; Mura, G.; et al. Moderate Exercise Improves Cognitive Function in Healthy Elderly People: Results of a Randomized Controlled Trial. *Clin. Pract. Epidemiol. Ment. Health* **2021**, *17*, 75–80. [[CrossRef](#)]
257. Lo, L.L.H.; Lee, E.H.M.; Hui, C.L.M.; Chong, C.S.Y.; Chang, W.C.; Chan, S.K.W.; Lin, J.J.; Lo, W.T.L.; Chen, E.Y.H. Effect of high-endurance exercise intervention on sleep-dependent procedural memory consolidation in individuals with schizophrenia: A randomized controlled trial. *Psychol. Med.* **2021**, 1–13. [[CrossRef](#)]
258. Wu, Z.; Zhang, H.; Miao, X.; Li, H.; Pan, H.; Zhou, D.; Liu, Y.; Li, Z.; Wang, J.; Liu, X.; et al. High-intensity physical activity is not associated with better cognition in the elder: Evidence from the China Health and Retirement Longitudinal Study. *Alzheimers Res.* **2021**, *13*, 182. [[CrossRef](#)] [[PubMed](#)]
259. Chekroud, S.R.; Gueorguieva, R.; Zheutlin, A.B.; Paulus, M.; Krumholz, H.M.; Krystal, J.H.; Chekroud, A.M. Association between physical exercise and mental health in 1.2 million individuals in the USA between 2011 and 2015: A cross-sectional study. *Lancet Psychiatry* **2018**, *5*, 739–746. [[CrossRef](#)]
260. Erickson, K.I.; Hillman, C.; Stillman, C.M.; Ballard, R.M.; Bloodgood, B.; Conroy, D.E.; Macko, R.; Marquez, D.X.; Petruzzello, S.J.; Powell, K.E.; et al. Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines. *Med. Sci. Sports Exerc.* **2019**, *51*, 1242–1251. [[CrossRef](#)]
261. Di Lorito, C.; Long, A.; Byrne, A.; Harwood, R.H.; Gladman, J.R.F.; Schneider, S.; Logan, P.; Bosco, A.; van der Wardt, V. Exercise interventions for older adults: A systematic review of meta-analyses. *J. Sport Health Sci.* **2021**, *10*, 29–47. [[CrossRef](#)] [[PubMed](#)]
262. de Souto Barreto, P.; Demougeot, L.; Vellas, B.; Rolland, Y. Exercise Training for Preventing Dementia, Mild Cognitive Impairment, and Clinically Meaningful Cognitive Decline: A Systematic Review and Meta-analysis. *J. Gerontol. A Biol. Sci. Med. Sci.* **2018**, *73*, 1504–1511. [[CrossRef](#)] [[PubMed](#)]
263. Burton, E.; Cavalheri, V.; Adams, R.; Browne, C.O.; Boverly-Spencer, P.; Fenton, A.M.; Campbell, B.W.; Hill, K.D. Effectiveness of exercise programs to reduce falls in older people with dementia living in the community: A systematic review and meta-analysis. *Clin. Interv. Aging* **2015**, *10*, 421–434. [[CrossRef](#)] [[PubMed](#)]
264. Farlie, M.K.; Robins, L.; Haas, R.; Keating, J.L.; Molloy, E.; Haines, T.P. Programme frequency, type, time and duration do not explain the effects of balance exercise in older adults: A systematic review with a meta-regression analysis. *Br. J. Sports Med.* **2019**, *53*, 996–1002. [[CrossRef](#)]
265. Lam, L.C.; Chau, R.C.; Wong, B.M.; Fung, A.W.; Tam, C.W.; Leung, G.T.; Kwok, T.C.; Leung, T.Y.; Ng, S.P.; Chan, W.M. A 1-year randomized controlled trial comparing mind body exercise (Tai Chi) with stretching and toning exercise on cognitive function in older Chinese adults at risk of cognitive decline. *J. Am. Med. Dir. Assoc.* **2012**, *13*, 568–e15. [[CrossRef](#)]
266. Huang, Z.G.; Feng, Y.H.; Li, Y.H.; Lv, C.S. Systematic review and meta-analysis: Tai Chi for preventing falls in older adults. *BMJ Open* **2017**, *7*, e013661. [[CrossRef](#)]
267. 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. Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 3017–3022. [[CrossRef](#)]
268. Colcombe, S.J.; Erickson, K.I.; Scalf, P.E.; Kim, J.S.; Prakash, R.; McAuley, E.; Elavsky, S.; Marquez, D.X.; Hu, L.; Kramer, A.F. Aerobic exercise training increases brain volume in aging humans. *J. Gerontol. A Biol. Sci. Med. Sci.* **2006**, *61*, 1166–1170. [[CrossRef](#)] [[PubMed](#)]
269. Redila, V.A.; Christie, B.R. Exercise-induced changes in dendritic structure and complexity in the adult hippocampal dentate gyrus. *Neuroscience* **2006**, *137*, 1299–1307. [[CrossRef](#)] [[PubMed](#)]
270. Lin, T.W.; Chen, S.J.; Huang, T.Y.; Chang, C.Y.; Chuang, J.I.; Wu, F.S.; Kuo, Y.M.; Jen, C.J. Different types of exercise induce differential effects on neuronal adaptations and memory performance. *Neurobiol. Learn. Mem.* **2012**, *97*, 140–147. [[CrossRef](#)] [[PubMed](#)]
271. Pietrelli, A.; López-Costa, J.J.; Goñi, R.; López, E.M.; Brusco, A.; Basso, N. Effects of moderate and chronic exercise on the nitrenergic system and behavioral parameters in rats. *Brain Res.* **2011**, *1389*, 71–82. [[CrossRef](#)]
272. Eddy, M.C.; Green, J.T. Running wheel exercise reduces renewal of extinguished instrumental behavior and alters medial prefrontal cortex neurons in adolescent, but not adult, rats. *Behav. Neurosci.* **2017**, *131*, 460–469. [[CrossRef](#)]
273. Levy, M.J.F.; Bouille, F.; Steinbusch, H.W.; van den Hove, D.L.A.; Kenis, G.; Lanfumey, L. Neurotrophic factors and neuroplasticity pathways in the pathophysiology and treatment of depression. *Psychopharmacology* **2018**, *235*, 2195–2220. [[CrossRef](#)]
274. Phillips, C. Physical Activity Modulates Common Neuroplasticity Substrates in Major Depressive and Bipolar Disorder. *Neural Plast.* **2017**, *2017*, 7014146. [[CrossRef](#)]
275. Duzel, E.; van Praag, H.; Sendtner, M. Can physical exercise in old age improve memory and hippocampal function? *Brain* **2016**, *139*, 662–673. [[CrossRef](#)]

276. Lin, T.W.; Tsai, S.F.; Kuo, Y.M. Physical Exercise Enhances Neuroplasticity and Delays Alzheimer's Disease. *Brain Plast.* **2018**, *4*, 95–110. [[CrossRef](#)]
277. O'Callaghan, R.M.; Ohle, R.; Kelly, A.M. The effects of forced exercise on hippocampal plasticity in the rat: A comparison of LTP, spatial- and non-spatial learning. *Behav. Brain Res.* **2007**, *176*, 362–366. [[CrossRef](#)]
278. O'Callaghan, R.M.; Griffin, E.W.; Kelly, A.M. Long-term treadmill exposure protects against age-related neurodegenerative change in the rat hippocampus. *Hippocampus* **2009**, *19*, 1019–1029. [[CrossRef](#)] [[PubMed](#)]
279. Farmer, J.; Zhao, X.; van Praag, H.; Wodtke, K.; Gage, F.H.; Christie, B.R. Effects of voluntary exercise on synaptic plasticity and gene expression in the dentate gyrus of adult male Sprague-Dawley rats in vivo. *Neuroscience* **2004**, *124*, 71–79. [[CrossRef](#)] [[PubMed](#)]
280. Radahmadi, M.; Hosseini, N.; Alaei, H. Effect of exercise, exercise withdrawal, and continued regular exercise on excitability and long-term potentiation in the dentate gyrus of hippocampus. *Brain Res.* **2016**, *1653*, 8–13. [[CrossRef](#)] [[PubMed](#)]
281. Patten, A.R.; Sickmann, H.; Hryciw, B.N.; Kucharsky, T.; Parton, R.; Kernick, A.; Christie, B.R. Long-term exercise is needed to enhance synaptic plasticity in the hippocampus. *Learn Mem.* **2013**, *20*, 642–647. [[CrossRef](#)] [[PubMed](#)]
282. Liu, H.L.; Zhao, G.; Cai, K.; Zhao, H.H.; Shi, L.D. Treadmill exercise prevents decline in spatial learning and memory in APP/PS1 transgenic mice through improvement of hippocampal long-term potentiation. *Behav. Brain Res.* **2011**, *218*, 308–314. [[CrossRef](#)] [[PubMed](#)]
283. Brockett, A.T.; LaMarca, E.A.; Gould, E. Physical exercise enhances cognitive flexibility as well as astrocytic and synaptic markers in the medial prefrontal cortex. *PLoS ONE* **2015**, *10*, e0124859. [[CrossRef](#)]
284. von Bohlen und Halbach, O. Involvement of BDNF in age-dependent alterations in the hippocampus. *Front. Aging Neurosci.* **2010**, *2*, 36. [[CrossRef](#)]
285. Griffin, É.; Mullally, S.; Foley, C.; Warmington, S.A.; O'Mara, S.M.; Kelly, A.M. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol. Behav.* **2011**, *104*, 934–941. [[CrossRef](#)]
286. Vaynman, S.; Ying, Z.; Gomez-Pinilla, F. Interplay between brain-derived neurotrophic factor and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. *Neuroscience* **2003**, *122*, 647–657. [[CrossRef](#)]
287. Soya, H.; Nakamura, T.; Deocaris, C.C.; Kimpara, A.; Iimura, M.; Fujikawa, T.; Chang, H.; McEwen, B.S.; Nishijima, T. BDNF induction with mild exercise in the rat hippocampus. *Biochem. Biophys. Res. Commun.* **2007**, *358*, 961–967. [[CrossRef](#)]
288. Aguiar, A.S.; Castro, A.A.; Moreira, E.L.; Glaser, V.; Santos, A.R.; Tasca, C.I.; Latini, A.; Prediger, R.D. Short bouts of mild-intensity physical exercise improve spatial learning and memory in aging rats: Involvement of hippocampal plasticity via AKT, CREB and BDNF signaling. *Mech. Ageing Dev.* **2011**, *132*, 560–567. [[CrossRef](#)] [[PubMed](#)]
289. Nilsson, J.; Ekblom, Ö.; Ekblom, M.; Lebedev, A.; Tarassova, O.; Moberg, M.; Lövdén, M. Acute increases in brain-derived neurotrophic factor in plasma following physical exercise relates to subsequent learning in older adults. *Sci. Rep.* **2020**, *10*, 4395. [[CrossRef](#)] [[PubMed](#)]
290. Whiteman, A.S.; Young, D.E.; He, X.; Chen, T.C.; Wagenaar, R.C.; Stern, C.E.; Schon, K. Interaction between serum BDNF and aerobic fitness predicts recognition memory in healthy young adults. *Behav. Brain Res.* **2014**, *259*, 302–312. [[CrossRef](#)]
291. Ding, Q.; Vaynman, S.; Akhavan, M.; Ying, Z.; Gomez-Pinilla, F. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience* **2006**, *140*, 823–833. [[CrossRef](#)] [[PubMed](#)]
292. Trejo, J.L.; Llorens-Martín, M.V.; Torres-Alemán, I. The effects of exercise on spatial learning and anxiety-like behavior are mediated by an IGF-I-dependent mechanism related to hippocampal neurogenesis. *Mol. Cell. Neurosci.* **2008**, *37*, 402–411. [[CrossRef](#)] [[PubMed](#)]
293. Vilela, T.C.; Muller, A.P.; Damiani, A.P.; Macan, T.P.; da Silva, S.; Canteiro, P.B.; de Sena Casagrande, A.; Pedroso, G.D.S.; Nesi, R.T.; de Andrade, V.M.; et al. Strength and Aerobic Exercises Improve Spatial Memory in Aging Rats Through Stimulating Distinct Neuroplasticity Mechanisms. *Mol. Neurobiol.* **2017**, *54*, 7928–7937. [[CrossRef](#)] [[PubMed](#)]
294. Lloyd, B.A.; Hake, H.S.; Ishiwata, T.; Farmer, C.E.; Loetz, E.C.; Fleshner, M.; Bland, S.T.; Greenwood, B.N. Exercise increases mTOR signaling in brain regions involved in cognition and emotional behavior. *Behav. Brain Res.* **2017**, *323*, 56–67. [[CrossRef](#)]
295. Ainslie, P.N.; Cotter, J.D.; George, K.P.; Lucas, S.; Murrell, C.; Shave, R.; Thomas, K.N.; Williams, M.J.; Atkinson, G. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *J. Physiol.* **2008**, *586*, 4005–4010. [[CrossRef](#)]
296. Maass, A.; Düzel, S.; Goerke, M.; Becke, A.; Sobieray, U.; Neumann, K.; Lövdén, M.; Lindenberger, U.; Bäckman, L.; Braun-Dullaeus, R.; et al. Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol. Psychiatry* **2015**, *20*, 585–593. [[CrossRef](#)]
297. Sujkowski, A.; Hong, L.; Wessells, R.J.; Todi, S.V. The protective role of exercise against age-related neurodegeneration. *Ageing Res. Rev.* **2021**, *74*, 101543. [[CrossRef](#)]
298. Brown, A.D.; McMorris, C.A.; Longman, R.S.; Leigh, R.; Hill, M.D.; Friedenreich, C.M.; Poulin, M.J. Effects of cardiorespiratory fitness and cerebral blood flow on cognitive outcomes in older women. *Neurobiol. Aging* **2010**, *31*, 2047–2057. [[CrossRef](#)] [[PubMed](#)]
299. Akazawa, N.; Tanahashi, K.; Kosaki, K.; Ra, S.G.; Matsubara, T.; Choi, Y.; Zempo-Miyaki, A.; Maeda, S. Aerobic exercise training enhances cerebrovascular pulsatility response to acute aerobic exercise in older adults. *Physiol. Rep.* **2018**, *6*, e13681. [[CrossRef](#)] [[PubMed](#)]
300. Mattson, M.P.; Maudsley, S.; Martin, B. BDNF and 5-HT: A dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends Neurosci.* **2004**, *27*, 589–594. [[CrossRef](#)] [[PubMed](#)]

301. Fernández-Rodríguez, R.; Álvarez-Bueno, C.; Martínez-Ortega, I.A.; Martínez-Vizcaíno, V.; Mesas, A.E.; Notario-Pacheco, B. Immediate effect of high-intensity exercise on brain-derived neurotrophic factor in healthy young adults: A systematic review and meta-analysis. *J. Sport Health Sci.* 2021; *in press*. [CrossRef]
302. Fabel, K.; Tam, B.; Kaufer, D.; Baiker, A.; Simmons, N.; Kuo, C.J.; Palmer, T.D. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur. J. Neurosci.* 2003, 18, 2803–2812. [CrossRef]
303. Coelho, F.G.; Gobbi, S.; Andreatto, C.A.; Corazza, D.I.; Pedroso, R.V.; Santos-Galduróz, R.F. Physical exercise modulates peripheral levels of brain-derived neurotrophic factor (BDNF): A systematic review of experimental studies in the elderly. *Arch. Gerontol. Geriatr.* 2013, 56, 10–15. [CrossRef]
304. Moon, H.Y.; Becke, A.; Berron, D.; Becker, B.; Sah, N.; Benoni, G.; Janke, E.; Lubejko, S.T.; Greig, N.H.; Mattison, J.A.; et al. Running-Induced Systemic Cathepsin B Secretion Is Associated with Memory Function. *Cell Metab.* 2016, 24, 332–340. [CrossRef]
305. Nagamatsu, L.S.; Handy, T.C.; Hsu, C.L.; Voss, M.; Liu-Ambrose, T. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment. *Arch. Intern. Med.* 2012, 172, 666–668. [CrossRef]
306. Cassilhas, R.C.; Viana, V.A.; Grassmann, V.; Santos, R.T.; Santos, R.F.; Tufik, S.; Mello, M.T. The impact of resistance exercise on the cognitive function of the elderly. *Med. Sci. Sports Exerc.* 2007, 39, 1401–1407. [CrossRef]
307. Liu-Ambrose, T.; Nagamatsu, L.S.; Graf, P.; Beattie, B.L.; Ashe, M.C.; Handy, T.C. Resistance training and executive functions: A 12-month randomized controlled trial. *Arch. Intern. Med.* 2010, 170, 170–178. [CrossRef]
308. Marinus, N.; Hansen, D.; Feys, P.; Meesen, R.; Timmermans, A.; Spildooren, J. The Impact of Different Types of Exercise Training on Peripheral Blood Brain-Derived Neurotrophic Factor Concentrations in Older Adults: A Meta-Analysis. *Sports Med.* 2019, 49, 1529–1546. [CrossRef]
309. National Cancer Institute. Cancer Statistics. Available online: <https://www.cancer.gov/about-cancer/understanding/statistics> (accessed on 24 December 2021).
310. Booth, F.W.; Gordon, S.E.; Carlson, C.J.; Hamilton, M.T. Waging war on modern chronic diseases: Primary prevention through exercise biology. *J. Appl. Physiol.* 2000, 88, 774–787. [CrossRef] [PubMed]
311. Hinshaw, D.C.; Shevde, L.A. The Tumor Microenvironment Innately Modulates Cancer Progression. *Cancer Res.* 2019, 79, 4557–4566. [CrossRef] [PubMed]
312. Ashcraft, K.A.; Peace, R.M.; Betof, A.S.; Dewhurst, M.W.; Jones, L.W. Efficacy and Mechanisms of Aerobic Exercise on Cancer Initiation, Progression, and Metastasis: A Critical Systematic Review of In Vivo Preclinical Data. *Cancer Res.* 2016, 76, 4032–4050. [CrossRef] [PubMed]
313. Friedenreich, C.M.; Woolcott, C.G.; McTiernan, A.; Ballard-Barbash, R.; Brant, R.F.; Stanczyk, F.Z.; Terry, T.; Boyd, N.F.; Yaffe, M.J.; Irwin, M.L.; et al. Alberta physical activity and breast cancer prevention trial: Sex hormone changes in a year-long exercise intervention among postmenopausal women. *J. Clin. Oncol.* 2010, 28, 1458–1466. [CrossRef]
314. Bernstein, L.; Henderson, B.E.; Hanisch, R.; Sullivan-Halley, J.; Ross, R.K. Physical exercise and reduced risk of breast cancer in young women. *J. Natl. Cancer Inst.* 1994, 86, 1403–1408. [CrossRef]
315. Friedenreich, C.M.; Neilson, H.K.; O'Reilly, R.; Duha, A.; Yasui, Y.; Morielli, A.R.; Adams, S.C.; Courneya, K.S. Effects of a High vs Moderate Volume of Aerobic Exercise on Adiposity Outcomes in Postmenopausal Women: A Randomized Clinical Trial. *JAMA Oncol.* 2015, 1, 766–776. [CrossRef]
316. Moore, S.C.; Lee, I.M.; Weiderpass, E.; Campbell, P.T.; Sampson, J.N.; Kitahara, C.M.; Keadle, S.K.; Arem, H.; Berrington de Gonzalez, A.; Hartge, P.; et al. Association of Leisure-Time Physical Activity with Risk of 26 Types of Cancer in 1.44 Million Adults. *JAMA Intern Med.* 2016, 176, 816–825. [CrossRef]
317. Koelwyn, G.J.; Quail, D.F.; Zhang, X.; White, R.M.; Jones, L.W. Exercise-dependent regulation of the tumour microenvironment. *Nat. Rev. Cancer* 2017, 17, 620–632. [CrossRef]
318. Iyengar, N.M.; Jones, L.W. Development of Exercise as Interception Therapy for Cancer: A Review. *JAMA Oncol.* 2019, 5, 1620–1627. [CrossRef]
319. Joyce, J.A.; Fearon, D.T. T cell exclusion, immune privilege, and the tumor microenvironment. *Science* 2015, 348, 74–80. [CrossRef]
320. Pedersen, L.; Idorn, M.; Olofsson, G.H.; Lauenborg, B.; Nookaew, I.; Hansen, R.H.; Johannesen, H.H.; Becker, J.C.; Pedersen, K.S.; Dethlefsen, C.; et al. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metab.* 2016, 23, 554–562. [CrossRef] [PubMed]
321. Acharya, A.; Das, I.; Chandhok, D.; Saha, T. Redox regulation in cancer: A double-edged sword with therapeutic potential. *Oxid. Med. Cell Longev.* 2010, 3, 23–34. [CrossRef] [PubMed]
322. Prasad, S.; Gupta, S.C.; Tyagi, A.K. Reactive oxygen species (ROS) and cancer: Role of antioxidative nutraceuticals. *Cancer Lett.* 2017, 387, 95–105. [CrossRef] [PubMed]