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Review

Exercise Physiology: A Review of Established Concepts and Current Questions

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Abstract: Exercise physiology is the science that studies the processes of physical activity and their impact on the body. It usually requires a multidisciplinary approach with a team of experts because of the multiple physiological systems involved. At the cellular level, exercise can trigger a cascade of events that involve metabolic pathways, muscle recruitment and conditioning, neuromuscular adaptations, and optimization of energy production. On a systematic level, this has involved the cardiovascular system, the respiratory system, the musculoskeletal system, the peripheral and central nervous systems, and even the endocrine system to improve adaptation to meet the demands of exercise, improving strength and endurance with the goal of maximizing performance. This field, which began largely with a focus on the kinetics of oxygen consumption and the relationship between aerobic and anaerobic metabolism, has expanded with technological advancements such as wearable devices, advanced imaging techniques, and genomics, which has allowed for a greater appreciation of the physiologic responses of exercise at the level of molecular and cellular interactions. Recently, this science has evolved into the study of overall health promotion and disease prevention to meet individual fitness needs and goals. This philosophy, which is captured by the motto "Exercise is Medicine", has been adopted as a Global Health Initiative by the World Health Organization (WHO). Despite the advancements in technology and impactful, large-scale studies, a variety of questions, such as how physical activity interacts with aging to affect physical and cognitive function, how inactivity influences acute and chronic disease states, and how we maximize human performance in extreme conditions like microgravity environments, remain. The purpose of this review is to present and discuss established concepts, controversial topics, and unanswered questions within exercise physiology that have allowed this field to become a science that embraces the overall well-being of individuals.

Keywords: exercise; exercise physiology; benefits of exercise; physical activity; metabolic syndrome; preventive medicine

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1. Introduction

Physical activity is defined as the bodily movement created from skeletal muscle activity, and when this is structured, organized, and intentional, physical activity becomes 'exercise'. With one of the first exercise prescriptions recommended by Hippocrates in Greece circa 600 B.C., exercise and its connection with wellbeing has been asserted for thousands of years [1]. This assertion that physical activity and exercise may have health benefits has been reinforced by a massive volume of medical literature and adopted as a recommendation by a plethora of governing bodies, such as the CDC, the World Health Organization (WHO), the American College of Cardiology/American Heart Association (ACC/AHA), the American Diabetes Association (ADA), the National Council on Aging,

the American College of Sports Medicine, and the American Cancer Society. However, recommendations of specific exercises in clinical care can be made with increasing knowledge about different exercises and their duration and interval potential to create varying effects on the body. The revelation that different exercise plans can produce a variety of different effects on the body has fostered the development of exercise physiology, a field that aims to understand and explain how physical activity can impact genetics, cell signaling pathways, tissue health and maintenance, organ system function, and the body as a whole.

Exercise physiology has seen an expansion of its body of knowledge over the past several decades in accordance with new technology, which has permitted advancements in exercise study protocols, data tracking, and analysis. Previously, the roots of exercise physiology began with a focus on energy production during exercise. This work led to the establishment of aerobic and anaerobic descriptions of physical activity based on the oxygen dependence of metabolic pathways used to generate ATP/energy [2]. Aerobic exercises such as jogging, rowing, walking, swimming, and dancing require oxygen to create energy, while anaerobic exercises, such as weightlifting, sprinting, plyometrics, and high intensity interval training (HIIT), are predominantly independent of oxygen. While this fundamental understanding of human physiology has guided exercise studies since the 1980s, this categorization does not adequately capture and describe all the vast benefits that exercise has on organ systems within the body [2–4]. More recent research and literature has focused on changes outside of the cardiopulmonary system and benefitted from advancements in studying gene expression and molecular biology [5]. Connections between physical activity and the central nervous, endocrine, musculoskeletal, gastrointestinal, and immune systems are now better understood, but some questions and controversies persist. This review aims to discuss impactful studies establishing the physiologic changes influenced by exercise and raise questions that remain unanswered within the field of exercise physiology.

2. Effects of Exercise per Organ System

2.1. Cardiopulmonary and Vascular

The relationship between the heart, lungs, and central and peripheral vascular systems has been appropriately answered by some exercise physiology research [2,6,7]. Initially, studies focused on acute responses to physical activity and how the body manages the metabolic and, more specifically, oxygen demands required by exercise. As skeletal muscle workload increases with physical activity, cardiac functions such as stroke volume, preload, and heart rate all increase to meet the metabolic demands of the activated skeletal muscle and lead to an increase in cardiac output during physical activity [8,9].

Cardiac output, which is defined by Heart Rate $\times$ Stroke Volume (CO = HR $\times$ SV), is increased by both acute and chronic exercise. An increase in heart rate is not the only way that acute exercise improves cardiac output. During acute exercise, there are increased filling pressures and an increase in cardiac contractility, which cause a several-fold increase in stroke volume and play a large role in the increase in cardiac output during acute exercise. Beneficial histological changes to the heart occur through remodeling in response to chronic exercise. This remodeling allows for increased ventricular dilation and preload, while ventricular hypertrophy improves the contractility of the heart. Hypertrophy has been demonstrated to respond differently to strength training (anaerobic) and endurance training (aerobic) [10]. Comparisons of echocardiographic data from strength-trained (wrestlers) and endurance-trained (swimmers) athletes with controls revealed concentric hypertrophy that occurred in regular strength training compared to eccentric hypertrophy in endurance-trained athletes [11]. However, this hypertrophy may alter baseline cardiac function. Cyclists who were participants in three separate years of the Tour de France were evaluated by echocardiogram and compared to healthy, body-surface-matched sedentary male controls. The cyclists were found to have a decrease in left ventricular ejection fraction of 11.6% that accompanied left ventricular dilation (>60 mm), and the authors offer several possible explanations, including illicit substance use [12]. Ultimately, pathologic dilation

may be a consequence of excessive exercise, but the parameters to define excessive exercise have yet to be defined.

Some types of exercise are more dependent on the cardiopulmonary system, which include aerobic exercise such as cycling, jogging, swimming, rowing, and many others. With combined insight from molecular and clinical markers, a robust understanding of aerobic exercise can benefit the cardiac, pulmonary, and vascular systems. Firstly, oxygen uptake and CO_2 output offer critical value in the assessment of aerobic exercise and have become an essential means to concretely measure VO_{2max}. Oxygen uptake, which is universally interpreted by VO_{2max} has been a key determinant of exercise capacity since 1923, when Hill and Lupton first discussed the concept [2,13]. VO_{2max} is derived from cardiac output and the arteriovenous oxygen pressure difference (Fick equation). During its conceptualization, VO_{2max} was defined as an individual's maximum capacity for the cardiopulmonary system and has become a surrogate marker for cardiorespiratory fitness (CRF) within many exercise physiology observations investigating the connection between aerobic exercise and health benefits [13].

Robust data have validated VO_{2max} and have connected improvements in physical activity with all-cause and cardiovascular mortality risk [14]. The effect of chronic aerobic exercise has cumulative, beneficial effects on the cardiovascular and respiratory systems, both as a preventative health tool and as a countermeasure to common cardiovascular conditions like coronary artery disease, heart failure, high blood pressure, and even peripheral vascular disease. One notable prospective study comparing age adjusted all-cause mortality and physical fitness in 9777 men found a 7.9% decrease in mortality for each minute increase in maximum treadmill time performed by the subject [15]. Additional research with a greater focus on markers of cardiovascular risk has shown that lower physical activity levels amongst men and women contribute to cardiovascular risk factors such as cholesterol, obesity, glucose metabolism, and blood pressure [16–18]. A host of risk factors for cardiovascular disease are positively influenced, confirming not only the ability of aerobic exercise and physical activity to reduce the risk of mortality and prevent cardiac disease, but also that exercise is a useful treatment for existing cardiovascular disease.

While VO_{2max} is a validated assessment for the maximum workload of the cardiopulmonary system, it is limited in that it can only be used to study maximum load. Maximum workload is not necessary for many common forms of aerobic exercise. Additionally, the early experimentation of authors like Hill and Lupton still has relevance, and key questions regarding CRF and how it contributes to maximal exercise capacity remain incompletely understood.

An additional century of observation and experimentation has continued to seek answers to elusive questions such as 'what limits maximal exercise capacity' and 'what is the value in VO_{2max} when it comes to clinical medicine and wellbeing' and 'what influences VO_{2max}'. Some theories assert that cardiopulmonary function is limited by cardiac output, i.e., as the heart rate increases, there is increased oxygen demand by the myocardium and a decrease in supply as myocardial contraction reduces myocardial perfusion [8,19]. This concept is commonly referred to as the 'plateau phenomenon'. If this is assumed to be true, then CRF (VO_{2max}) is not equivalent to maximal exercise capacity because exercise capacity has anaerobic components that do not fully rely on oxygen uptake for its demands. Thus, despite the substantial measurements and analysis performed to understand CRF and its influence on cardiovascular disease and mortality, maximal exercise capacity remains a challenging, controversial topic, but more may be revealed as the field of exercise physiology continues to expand its boundaries.

2.2. Cognitive/Psychological

In the early 20th century, CRF was established as an objective measurement of physical fitness. Researchers can now draw new conclusions on the benefits of exercise on other organ systems like the central nervous system (CNS), with vast implications for human health. To study the effect of exercise on CNS structure and function, clinical tests such as

cognitive assessments (e.g., memory, concentration, social cognition, attention, etc.) and technologically advanced diagnostic assessments that have progressed with technological advancements such as magnetic resonance imaging (MRI) and functional MRI (fMRI) imaging, demonstrated both structural and clinical changes in the CNS [20].

Sleep is a required restoration period for the CNS, and it plays a critical role in overall wellbeing by maintaining cognitive function, solidifying memory, and regulating emotions. Studies have connected higher sleep quality in healthy men and women with decreased symptoms of disorders such as insomnia. A 2023 systematic review of physical activity's effect on sleep quality showed that improvement in sleep quality was most strongly associated with moderate intensity activity that followed the exercise guidelines of the World Health Organization (WHO) and the Center for Disease Control and Prevention (CDC) (Table 1) [21]. The effects of physical activity on sleep quality may be explained by physiologic changes that occur with exercise, such as an increase in melatonin release, improvement in anxiety, increased relaxation by serotonin, and norepinephrine release [22,23].

Table 1. Physical activity and exercise recommendations of health organizations. A variety of regional, national, and international organizations recommend regular exercise for primary and secondary prevention of health problems. A summary of some of the more noteworthy organizations and their respective recommendations is listed.

Health Organization	Population	Physical Activity/Exercise Recommendation
U.S. Department of Health and Human Services	Preschool Children Children–Adolescents Adult Older Adult	Encouragement of physical activity and play of all types 1 h of moderate-to-vigorous activity per day 2.5–5 h of moderate–vigorous or 1.25 h of vigorous activity; 2 sessions of muscle strengthening per week As tolerated per individual, but up to 2.5 h of moderate aerobic activity
World Health Organization	Children (3–17 years) Adults Elderly	60 min moderate–vigorous aerobic activity per day 2.5–5 h of moderate–vigorous aerobic activity per week 2.5 h of moderate–vigorous activity per week; focus on strength and balance training
American College of Cardiology/American Heart Association	Children Adults	60 min of moderate–vigorous activity per day 2.5 h of moderate-to-vigorous activity per week
American Diabetic Association American College of Sports Medicine	Adults Adults	150 min of moderate exercise per week 30 min of moderate–vigorous activity per day, 5 days per week; strength training, 2 days per week

Approximately 10% of individuals aged 70 or older and 20% of individuals aged 80 or older will experience mild cognitive impairment, which can progress to dementia [23]. While a variety of pathological processes, such as amyloid deposits, vascular insults, and frontotemporal degeneration, can contribute to dementia, physical activity can reduce all causes of dementia risk [24,25]. Additionally, improvements in cognitive domains have also been demonstrated in healthy adults in a meta-analysis of 29 randomized controlled trials that found modest improvement in memory, attention and processing speed, and executive function, in healthy subjects exposed to aerobic exercise [26]. Currently, the dosage of aerobic exercise that induces cognition improvement is poorly defined. The physiologic pathways through which these improvements occur also remain under investigation but could be related to reduced cerebrovascular disease burden or an attenuation of the degenerative processes that accompany Alzheimer's disease and frontotemporal dementia.

Exercise has been previously tied to anxiolysis, a reduction in stress, and a reduction in pain symptoms [27–29]. More recently, the cellular signaling responsible for the euphoria known as a "runner's high" was explored through PET detection of a radioligand that opioidergic effects occur acutely after 30 min of running in the limbic/paralimbic and prefrontal regions [30]. When exercise has been applied to challenging chronic pain syndromes such as fibromyalgia, clinical benefits are seen. A systematic review and meta-analysis of thirty-five randomized control trials saw a reduction in the severity of symptoms such as

pain, depressed mood, and fatigue, which are hallmarks of fibromyalgia, after only two to three exercise sessions per week [31].

2.3. Musculoskeletal

It is intuitive that the musculoskeletal system benefits from regular physical activity and exercise, as it is critical for the completion of moving the body and mechanical loads. To meet the energy demands of regular physical activity or aerobic exercise, cellular mitochondrial concentration is increased to utilize glycogen and fat as energy sources. Meanwhile, anaerobic activity such as strength training can increase muscle size and strength—a process known as hypertrophy [32]. Both acute responses to exercise by the musculoskeletal system lend insight into the physiologic adaptations of chronic exercise, which include improvements in bone density, lean body mass, and flexibility [33].

As humans age, musculoskeletal function declines due to inherent cellular and molecular mechanisms and secondary factors such as environment and demand [34]. These declines can present as hip fractures that can occur with osteoporosis. Studies have identified that peak bone mass, defined as the greatest level of bone mass throughout an individual's lifetime, may be encountered at different ages between men and women, but both occur prior to the age of 30 [35]. After this age, bone strength deteriorates because of aging and occurs at a variable rate that is dependent upon factors such as genetics, hormones like PTH, estrogen, and testosterone, and the mechanical loads placed on the human skeleton [7]. Decreasing estrogen production in perimenopausal women leads to increased bone resorption and loss, making them vulnerable to decreased bone strength and fractures [36].

2.4. Endocrine/Metabolic

The pathways like anaerobic and aerobic metabolism that are utilized in exercise have been studied for nearly a century, but more recent studies with a molecular focus demonstrate the far-reaching benefits of exercise on human health. Acutely, physical activity requires fuel sources for energy production and largely comes from glucose-consuming metabolic pathways, with amino acids also playing a limited role. For this reason, exercise can lead to the prevention and improvement in metabolic diseases like type II diabetes and its complications through improved blood sugar control and lowered low-density lipoprotein (LDL). Certain modalities of exercise have also been shown to have a positive impact on symptom control for chronic pain conditions like fibromyalgia via the release of endogenous neurotransmitters for moderating pain.

Blood glucose regulation during exercise occurs through increased glucose utilization by skeletal muscle, followed by the metabolism of free fatty acids and hepatic glycogenolysis [37]. Though insulin insensitivity is present in type II diabetes, skeletal muscle can utilize glucose through pathways independent of insulin and thus does not encourage additional insulin release for glucose uptake. Randomized control trials demonstrated clinical improvements in diabetic men undergoing regular aerobic or anaerobic exercise, regardless of aerobic or anaerobic, with decreases in hemoglobin A1c, blood glucose levels, and visceral fat content [38].

The foundational dysregulation of glucose metabolism found in type II diabetics accompanies a change in lipid and fatty acid metabolism and accounts for some of the increased risk of cardiovascular events experienced by diabetics compared to non-diabetics [39]. As the duration of physical activity increases, the utilization of lipid stores as fuel for skeletal muscle increases. However, the metabolic consequences of diabetes may impair lipid oxidation by skeletal muscle during exercise in obese patients with type II diabetes [40]. This process may be countered by exercise. Pruchnic et al. demonstrated increased intramyocellular fat oxidation in men and women undergoing an aerobic exercise intervention for 12 weeks [41]. There has been conflicting evidence regarding whether this makes a significant impact on the lipid profiles of diabetics, but a recent meta-analysis

completed in 2007 compared seven studies and found a ~5% decrease in LDL cholesterol is experienced by men and women after exercise intervention for eight weeks or greater [42].

While some data in diabetic mortality outcomes have improved since the 1970s, type II diabetes continues to double all-cause mortality and nearly triple the risk of cardiovascular mortality in men and women with diabetes compared to those without diabetes [39]. As the number of diabetics continues to increase, it will continue to contribute to premature death amongst men and women. Exercise presents an affordable intervention that can prevent and counteract metabolic dysfunction through glucose and lipid metabolism regulation. While some data show some stronger benefits to improved lipid profiles with weight training, both aerobic and anaerobic exercise provide vast benefits to prediabetic and diabetic patients and is recommended by the ADA, WHO, and CDC for diabetic patients. Furthermore, the implementation of an exercise program can be difficult for a diabetic, who may experience consequences such as iatrogenic hypoglycemia, peripheral neuropathy, foot ulcers, etc. Additional work is necessary to further refine which specific exercise modalities provide the most clinical and mortality benefits and what recommendations and accommodations can be provided for diabetics experiencing challenges with implementing an exercise regimen.

2.5. Gastrointestinal

Advancements in molecular and genetic studies such as The Human Microbiome Project, The Flemish Gut Flora, and the American Gut Project have brought new focus to the important balance that exists between the gut microbiome and an individual's gastrointestinal system. The interplay between gastrointestinal function, gut microbiome, and exercise has also been explored [43,44]. Overall, there are several loosely established benefits to exercise, which include improved gut motility, microbiome diversity, and a decreased risk of inflammatory bowel conditions.

Perhaps one of the most important benefits that has been shown is the reduction of the risk of gastrointestinal cancers such as esophageal adenocarcinoma and colorectal cancer [45]. A meta-analysis published in 2009 examined 52 studies, and although the mechanisms are not well understood, there is an estimated 24% risk reduction for colon cancer in men and women who walk approximately 5 to 6 h per week [46,47]. This data supports the American Cancer Society's guidelines regarding the benefits of exercise (Table 1). Similar benefits are seen with exercise, and the prevention of esophageal cancer was seen in a meta-analysis of nine studies, which found a reduction in the risk of esophageal cancer by 29% in physically active men and women [45]. Unfortunately, the dose–response relationship and mechanism of how exercise protects against gastrointestinal neoplasms remain poorly understood.

2.6. Genetics and Exercise

Exercise programs completed by cohort populations have produced varied responses amongst study subjects, and it has been theorized that genetic variability may explain these differences. Numerous studies have sought to tease out which gene alleles and/or downstream products, i.e., mRNA transcripts, proteins, etc., are responsible for the varied increases in strength, power, and cardiorespiratory response to a specific training program. Cumulatively, these studies have found that up to 80% of strength, power, and cardiorespiratory adaptations can be explained by genetic variance [48–51], which has transitioned the focus onto identifying specifically which genes contribute to the physiologic responses of exercise. These 'candidate genes' frequently play a role in energy storage, hormones, protein synthesis, or other key molecular and cellular interactions that influence exercise and physical activity.

Despite the high heritability of responses to exercise being supported by research, a comprehensive understanding of genetic influences on exercise physiology and response to exercise training regimens has been elusive for several reasons. Firstly, several studies have failed to identify single genes or polymorphisms that fully explain the varied responses to

exercise interventions and the trainability of power, cardiorespiratory fitness, and muscular strength within different individuals [52,53]. Furthermore, it is unknown if the candidate genes that explain the responses to exercise programs lead to clinically relevant benefits for the individual. As with many genetic studies, what is done with the information becomes an important question. When <5% of the population in the United States completes greater than 30 min of moderate physical activity daily, does genetic information serve a clinical purpose, i.e., do recommendations about exercise change based on an individual's genetic profile? Are there safe interventions or modifications to these genetic variants that can enhance responses in individuals with less favorable genetic profiles? While knowledge about the relationship between an individual's genetic makeup and their response to exercise has expanded, several questions regarding the impact of this knowledge remain unanswered, and those questions about what specific gene alleles contribute to varied exercise responses have not led to meaningful clinical impact.

3. Discussion

There is a multitude of evidence from nearly a century of exercise physiology research to support the benefits of exercise. More specifically, improved knowledge on the human body's acute responses to exercise and advancements in assessment of gene expression, molecular signaling cascades, and even wearable technology have contributed to the massive body of work describing the benefits of exercise. Of the numerous improvements made to the gastrointestinal, endocrine, nervous, cardiovascular, pulmonary, and musculoskeletal systems, the most striking may be that regular physical activity can have a far-reaching impact, especially on disease processes that cause significant morbidity and mortality worldwide, e.g., cardiovascular disease and diabetes. Despite the support for exercise and the growing body of evidence, several unanswered questions remain.

3.1. What Are the Optimal Recommendations for Exercise?

Standardized exercise prescriptions exist within the recommendations and guidelines of many governing health organizations (Table 1), based on extensive cardiovascular research demonstrating the protective effects of exercise on the cardiovascular and endocrine systems. However, recommendations for more novel uses of exercise, such as control of fibromyalgia and prevention of cognitive declines, exist. As many of the disease processes affected by exercise are also related to aging, e.g., dementia, osteoporosis, diabetes, etc., there may be significant challenges to the elderly completing a typical exercise activity such as jogging or swimming. Furthermore, suggestions about the detriments of excessive exercise have been postulated, and with evidence to support that exercise somewhere beyond three to four times the physical activity recommendations proposed by several medical and health organizations (Table 1) can lead to accelerated coronary artery calcification and plaque formation, increased cardiac fibrosis, and a possible increased risk of atrial fibrillation [54]. Outside of the cardiovascular consequences of excessive exercise, what constitutes excessive exercise and how it may harm other organ systems is poorly understood.

Stress injuries and stress fractures are well-studied consequences of exercise caused by excessive mechanical loading, and subsequent stress injuries and fractures from certain forms of exercise have been more frequently identified in track and field athletes and military populations. These activities can increase osteoclastic activity. Eventually, continued exposure to the loading event or activity can overcome the rate at which osteoblasts can rebuild bone, which can result in stress fractures [55]. Several anatomic and physiologic factors have been identified that are associated with increased risk for stress injury, such as muscle fatigue, calf girth, tibial width, and the degree of external rotation of the hip joint [56–58]. There remain several unanswered questions about musculoskeletal responses to exercise, including what activities place an individual at risk, what duration and/or frequency of each activity, and what modifications can be made for the known anatomical and physiologic characteristics (e.g., calf girth, muscle fatigue, tibial width, etc.) that increase

risk for stress injuries. Therefore, more work on the dose–response relationship between exercise and the expected benefit should be further investigated.

3.2. What Modalities of Exercise Are Best?

While population-based studies and cohort studies have supported exercise recommendations for nearly all individuals across the globe, exercise prescriptions likely need to be tailored to an individual's needs. Unfortunately, a limited understanding of exercise prescriptions and how to blend various forms of exercise to maximize the benefits based on an individual's risk factors remains. In fact, some forms of exercise may cause a worsening of organ system function. Exercise that tends to offload mechanical forces on the skeleton, such as swimming or horse riding, when compared to physical activities known to mechanically load the skeleton, such as basketball, gymnastics, and volleyball, has been found to decrease bone mineral density in swimmers and horse jockeys [59]. Additionally, exercise intensity seems to be an important component to capture cognitive health benefits such as improved sleep metrics, as Alkhaldi et al. found that vigorous exercise for greater than 90 min has been associated with poor sleep quality, while Dubinina et al. described increased frequency (6 days per week) of vigorous exercise to be associated with poor sleep initiation [60,61]. Physical activity has been recommended as a protective behavior for thousands of years and looks different across the globe, which is why more investigation into the benefits of specific modalities of exercise, the frequency, and intensity (by METs or % max HR) may lend more insight into which forms are best recommended.

Undoubtedly, future questions and research in the field of exercise physiology will continue. With wearable technology like smart watches, monitoring heart rate, respiratory rate, skin temperature, sleep duration, and blood pressure may provide data that are easy to measure and track within larger cohort studies and allow individuals to track exercise with various physiologic parameters such as sleep, blood pressure, and heart rate [62]. Additionally, newer frontiers are studying the benefits of exercise in alternate environments such as spaceflight, where muscle atrophy and decreases in bone strength are known consequences [63]. Equipment modifications such as those used for the advanced resistive exercise device (aRED) have been developed for exercise in microgravity, which is crucial to mitigating bone loss from space flight. Ultimately, these engineering breakthroughs may continue to reveal crucial insights into how to best apply exercise to the entire human population (Figure 1).

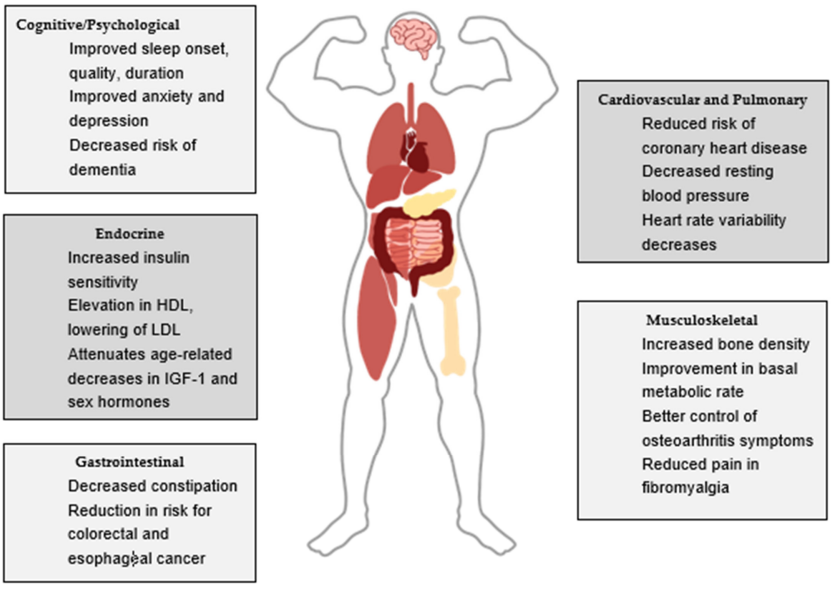

Figure 1. Exercise's impact on the body. When considering a variety of exercise modalities, the possible physiologic impact of exercise is far-reaching. Several beneficial impacts of exercise are summarized and organized per organ system affected.

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