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Review

Health benefits of physical activity: What role does skeletal muscle-organ crosstalk play?

Scott K. Powers[a,*], Erica Goldstein[b], Ronette Lategan-Potgieter[b], Matthew Schrager[b], Michele Skelton[b], Haydar Demirel[c]

[a] Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL, USA
[b] Department of Health Sciences, Stetson University, Deland, FL, USA
[c] Near East University, Nicosia, Cyprus

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ABSTRACT

The observation that physical activity (PA) reduces the risk of coronary heart disease dates back more than 70 years ago and it is now established that regular PA reduces all-cause mortality, in part, by reducing the risk of numerous chronic diseases including coronary heart disease, stroke, cancer, type 2 diabetes, and Alzheimer's disease. During the past decade the increased use of activity tracking devices has significantly improved our understanding of the dose-response relationships between PA and all-cause mortality. Further, our appreciation of the impact that prolonged sitting has on all-cause mortality has increased. Moreover, new research provides key insight into the signaling mechanisms that connect PA to the reduced risk of disease in multiple organ systems. Therefore, given the recent advances in the study of PA and all-cause mortality, it is an appropriate time to review the latest evidence on this topic as well as the mechanisms responsible for the PA-induced protection against all-cause mortality. Therefore, this review will summarize recent data on the dose-response association between PA on all-cause mortality and the negative impact that sedentary behavior has on all-cause mortality. Further, we also highlight potential mechanisms linking PA with the reduced risk of developing several chronic diseases. Finally, we conclude with a brief discussion of the emerging evidence that the health benefits associated with PA are derived, in part, from skeletal muscle-organ crosstalk involving muscle produced hormones (myokines) that exert their effects in either an autocrine, paracrine, or endocrine manner.

1. Introduction

Physical activity (PA) refers to bodily movement produced by contracting skeletal muscles (e.g. gardening, walking, running, etc.).[1] The importance that PA plays in promoting good health was first reported over 70 years ago in a study revealing that sedentary workers have a higher risk of death from coronary heart disease compared to workers performing jobs that require PA throughout the workday.[2] Following this inaugural study, many investigations have confirmed that regular PA reduces the incidence of premature mortality by lowering the risk of developing chronic diseases.[3–11] Although studies consistently report the benefit of PA on health, many investigations are observational studies that link self-reported PA to health outcomes. Unfortunately, self-report questionnaires that track both PA and sedentary behavior are subject to biases due to impaired cognitive recall and/or inaccurate reporting of PA and sedentary behavior by participants. To remove the limitations of self-report methods, more recent studies have used sensors (e.g., accelerometers) capable of detecting the time spent in both sedentary behaviors and during PA.[12,13] Importantly, a new picture of the dose-response effect that PA and sedentary behavior have on all-cause mortality is now emerging.

While the health benefits of PA are undeniable, the molecular mechanisms linking PA to a reduced risk of all-cause mortality remain a topic of debate. Although numerous mechanisms can contribute to the adaptative responses to PA, skeletal muscle-organ crosstalk has emerged as a key contributor to connect PA with positive health outcomes.

Given the recent advances in the study of PA and all-cause mortality, it is an appropriate time to review the new evidence on the impact of PA on all-cause mortality and the biological mechanisms responsible for the PA-induced protection against all-cause mortality. The goals of this narrative review are two-fold. Part 1 of this report will discuss the latest

* Corresponding author. Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL, USA.
E-mail address: spowers@ufl.edu (S.K. Powers).

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Abbreviations

PA	Physical activity
MET	Metabolic equivalent
MVPA	Moderate-to-vigorous PA
WHO	World Health Organization
SB	Sedentary behavior
CHD	Coronary heart disease
LDL	Low density lipoprotein
HDL	High density lipoprotein
NK	Natural killer cells
IL-6	Interleukin-6
TAZ	PDZ-binding motif
YAP	Yes-associated protein
GLUT4	Glucose transporter 4
AD	Alzheimer's disease
LIF	Leukemia inhibitory factor
IL-7	Interleukin-7
IL-15	Interleukin-15
AMPK	activation adenosine 5′-monophosphate-activated protein kinase
BDNF	brain-derived neurotropic factor
I-R	Ischemia-reperfusion injury
SOD2	Superoxide dismutase 2
Nrf2	Nuclear factor erythroid 2-related factor
CTSB	Cathepsin-B
cAMP	cyclic AMP
PKA	Protein kinase A
CREB	cAMP response element-binding protein

research on the dose-response association between PA and all-cause mortality, as well as the detrimental effects of sedentary behavior on all-cause mortality. Moreover, this first segment also summarizes the potential biological mechanisms linking PA with a reduced risk of developing several chronic diseases. Part 2 of this review examines the emerging evidence that the health benefits associated with PA are derived, in part, from skeletal muscle-organ crosstalk involving muscle produced hormones (myokines) that exert their effects in either an autocrine, paracrine, or endocrine manner.

2. Impact of inactivity and PA on health

Prior to discussing the health benefits of PA and the negative health consequences of prolonged sedentary behavior, several exercise epidemiological terms should be defined and the current recommendations for PA will be summarized. PA was briefly defined earlier and refers to any bodily movement produced by contracting skeletal muscles.[1] The term "exercise" is a form of PA that is performed intentionally to improve physical fitness (e.g., endurance or resistance exercise). In the context of this report, we will use the terms PA and exercise interchangeably. Epidemiologists classify the intensity of PA into three categories based on the level of energy expenditure required to perform the activity. Precisely, PA is classified using multiples of a metabolic equivalent (MET); 1 MET is equal to the resting metabolic rate. Light PA refers to activities requiring 1.6 METs −2.9 METs of energy expenditure. Activities that require 3.0 METs-5.9 METs are labeled as moderate PA whereas vigorous PA is defined as activities requiring an energy expenditure of 6 METs or more. Because individuals often engage in PA that incorporates both moderate and vigorous PA, the term moderate-to-vigorous PA (MVPA) is used to describe sessions of PA that include both moderate and vigorous PA.

Using these categories of PA, global health organizations have formulated guidelines for both the intensity and duration of PA associated with a decreased risk of premature death. Currently, the World Health Organization (WHO) recommends that individuals perform both aerobic and resistance exercise training weekly.[14] The recommendation for aerobic activity is that adults should accumulate at least 150 minutes (min) of moderate PA or 75 min of vigorous PA per week.[14] It follows that these guidelines can also be met by combining varying durations of both moderate and vigorous PA (i.e., MVPA). Current evidence suggests that the mortality risk reduction associated with PA is primarily driven by the volume of PA (i.e., total energy expended) and not the intensity.[15] However, when comparing equal volumes of PA, MVPA appears to provide greater health benefits compared to light PA.[15,16] Further, recent evidence confirms that even short bouts of sporadic exercise (i.e., 5 min–10 min of MVPA) can provide protection against pre-mature death.[17] Finally, the PA guidelines also advise adults to perform resistance exercise, targeting all major muscle groups, on at least two days a week. Resistance training is included in the recommendations for PA because a recent study reveals that resistance training alone reduces all-cause mortality in older adults.[18]

Two terms used to classify low levels of energy expenditure are sedentary behavior (SB) and physical inactivity (PI). SB refers to waking behaviors requiring less than 1.5 METs to complete (e.g., sitting or lying down). Notably, PI is distinct from SB; an individual is classified as physically inactive when they do not meet the recommended PA guidelines. A short summary of the impact that SB and PI have on all-cause mortality follows.

2.1. SB increases the risk of all-cause mortality

The observation that prolonged SB (e.g., sitting) is associated with an increased risk of coronary heart disease was first reported in 1953.[2] Following this seminal report, many studies have examined the dose-response relationship between the time spent in SB and the risk of all-cause mortality.[19–21] Fig. 1 illustrates the non-linear dose-response relationship between sedentary time and all-cause mortality derived from two methodologically diverse meta-analysis studies. The solid line in Fig. 1 represents a meta-analysis using self-report data from studies involving > 595 000 male and female adults.[22] The dashed line in Fig. 1

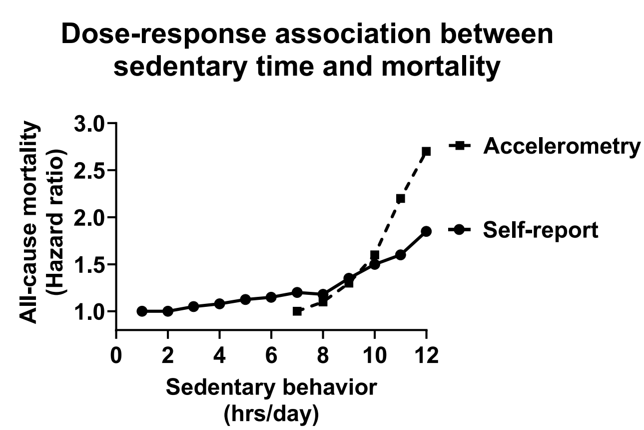

Fig. 1. A comparison of the dose-response association between total sedentary behavior and all-cause mortality measured by self-report questionnaire and accelerometry. The dashed line represents total daily sedentary behavior time measured using accelerometry; data are from Ref. 16 The solid line represents total sedentary behavior derived from a self-report questionnaire; data are from Ref. 22 See text for details.

illustrates the dose-response association between sedentary time measured by accelerometry and all-cause mortality from studies involving > 36 000 adult men and women.[16] Regardless of the method of data collection (e.g., self-report vs. accelerometry), the relationship between the daily duration of SB and risk of mortality is curvilinear with longer durations of SB resulting in the greatest risk of all-cause mortality (Fig. 1). In the self-report meta-analysis, all-cause mortality risk gradually rose from 4 hours (h) to 8 h of sedentary time and rapidly increased from 8 h to 12 h of SB. Similarly, in accelerometry assessed sedentary time investigations, all-cause mortality gradually increased after 7 h–8 h of sedentary time and rose sharply after 8 h–12 h of SB. The primary difference in the hazard ratios between these two approaches to study the impact of SB on mortality exists at the longer durations of SB. Specifically, the self-report data suggest that 12 continuous hours of SB results in an all-cause mortality hazard ratio of ~1.9 whereas the accelerometry data indicates that 12 h of SB results in a significantly greater risk of death (hazard ratio ~2.9); these divergent results may be due to cognitive recall bias associated with self-report of SB.[5] Therefore, due to the potential measurement error associated with self-report studies, the negative health outcomes of prolonged SB behavior may be underestimated using this method.[5]

Note that the self-report meta-analysis study examined the impact of SB on mortality over a wide duration of sedentary time (1 h–12 h) whereas the accelerometry assessed the health impact of 7 h–12 h of total sedentary time (Fig. 1). Nonetheless, numerous studies have examined the shape of the dose-response relationship between SB and all-cause mortality over a wide range of durations. In general, in individuals classified as physically inactive, > 4 h per day of SB is associated with an increased risk of developing chronic diseases and all-cause mortality.[20,22]

Finally, a large self-report meta-analysis study concludes that differences in mortality risk exist when comparing total daily sitting time (e.g., sitting during work, transportation, and watching TV) with TV-viewing alone.[8] Specifically, this study concluded that the effect of TV-viewing on the risk of all-cause mortality is significantly greater than total sitting time; similar results have been reported by others.[23] This finding is surprising because if sitting time at work and TV-viewing time involves the same level of SB, it is expected that the mortality risk would be similar between these two forms of SB. The explanation for the differences in risk of mortality between TV-viewing time and sitting time at work/-transportation remains unclear. However, several possible explanations exist. First, it is feasible that differences exist in the reporting accuracy between these behaviors.[8] Second, for the populations studied in these investigations, TV sitting time occurred in the evening following a meal.[8] This is significant because prolonged sitting after eating is detrimental for lipid metabolism.[24–26] Specifically, elevated plasma triglycerides are an independent risk factor for atherosclerosis and prolonged sitting impairs triglyceride clearance from the blood following a meal.[25] Third, it is also plausible that people break-up sitting time more frequently during work when compared to TV watching; this is potentially important because breaking up sedentary time reduces cardiometabolic risk factors.[27] For example, interrupting sitting with short bouts of light-or moderate intensity PA lowers postprandial glucose and insulin levels in both overweight and obese adults.[28] A final possible explanation for the differences in all-cause mortality risk between total sitting time and TV-viewing time is the possibility that TV viewing is often associated with snacking; thus, dietary behavior may also contribute to the differences in all-cause mortality observed in these studies.[8] Clearly, additional research is warranted to better understand the impact of total sitting time versus TV viewing alone on all-cause mortality.

2.2. PA decreases all-cause mortality

The fact that regular PA reduces the risk of premature mortality is now irrefutable. Indeed, research spanning the past 70 years has consistently confirmed that PA reduces the risk of all-cause mortality (reviewed in Refs. 3,8,10,11,20,29–31). One of the first studies to suggest a dose-response association between PA and health outcomes was the Harvard Alumni Study published in 1978.[32] This landmark investigation revealed that compared to an inactive reference group, active individuals (e.g., stairs climbed, distance walked, etc.) were at a lower risk of death from coronary heart disease. Subsequently, hundreds of studies have examined the dose-response relationship between PA and the risk of all-cause mortality.

Fig. 2 illustrates a comparison of the relationship between self-reported MVPA (solid line) and accelerometer-assessed MVPA (dashed line) and all-cause mortality. The data depicting the association between self-report PA and mortality is derived from an influential report that pools data from six independent studies involving a total of 661 137 men and women.[29] The data describing the dose-response associations between accelerometry measured PA comes from another widely cited study involving a harmonized meta-analysis of eight studies that included 36 383 men and women.[16]

Note that the shape of the dose-response curve is similar between the two methods of assessing PA. However, a major difference between the two methods of evaluating the impact of PA on all-cause mortality is that the risk reduction is much greater in magnitude when comparing accelerometry with self-report.[16,29] Indeed, the risk reduction of all-cause mortality for the same amount of MVPA is significantly greater in magnitude when PA is measured using accelerometry. Ekelund et al. argues that this difference is likely explained by the fact that, compared to a self-report questionnaire, accelerometry provides a more precise measurement of PA.[16] Hence, it is possible that due to report bias, self-report studies overestimate the amount of PA performed by participants.

2.3. Can PA attenuate the detrimental effects of prolonged SB?

Sedentary behavior is prevalent in adults from high income countries.[33,34] For example, studies from both the United States and Norway indicate that adults and older people spend 55%–62% of their daily waking time in sedentary behaviors; this translates to 7.7 h–9.9 h of SB each day.[33,34] As discussed earlier, long durations of SB are associated with increased risk of all-cause mortality. Given that sufficient levels of PA can lower the risk of mortality, this raises the question, "can PA attenuate the detrimental effects of daily sitting time on all-cause mortality?"

Evidence from both self-report studies and accelerometer-measured PA and sedentary time reveal that PA decreases the all-cause mortality risk associated with prolonged sitting in a dose-dependent manner.[8,35,36] Fig. 3 illustrates the positive impact that moderate intensity PA has on

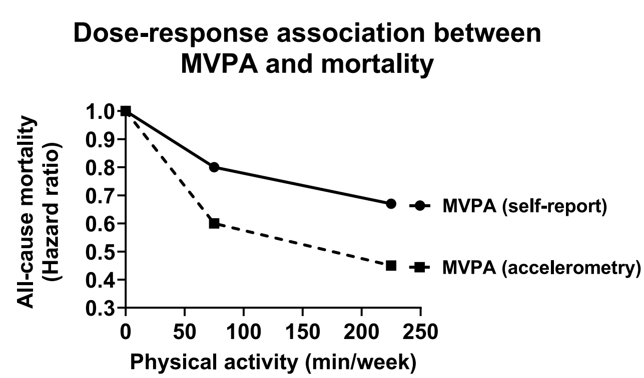

Fig. 2. A comparison of the dose-response association between moderate/vigorous physical activity (MVPA) and all-cause mortality measured by self-report questionnaire and accelerometry. The dashed line represents MVPA measured using accelerometry; data are from Ref. 16 The solid line represents MVPA determined from a self-report questionnaire; data are from Ref. 29 See text for details.

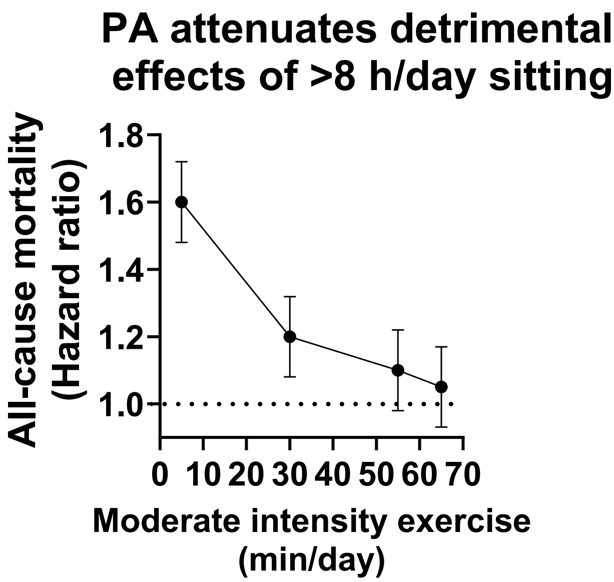

Fig. 3. Meta-analyses of the joint association of > 8 h/day sitting time and moderate intensity PA with all-cause mortality. All data are referenced to individuals that sit < 4 h/day and exercise > 35 MET/h/week. Data are from Ekelund et al.[8] and are presented as means with 95% confidence interval. See text for details.

reducing the risk of all-cause mortality associated with prolonged SB. Note that for individuals that perform < 5 min/day of MVPA, sitting > 8 h/day results in a 60% increase in the risk of all-cause mortality (i.e., hazard ratio = 1.6). In contrast, 30 min/day-75 min/day of moderate intensity PA reduces this risk in a dose-response fashion. Note that while 30 min/day of moderate intensity PA does lower the risk of all-cause mortality, 60 min/day-75 min/day or more of moderate intensity PA is required to entirely eliminate the risk associated with prolonged sitting (i.e., 8 h/day).[8]

2.4. PA reduces the risk of noncommunicable diseases

A recent report from the WHO indicates that seven noncommunicable diseases are currently included in the top 10 causes of death worldwide.[37] Specifically, coronary heart disease, stroke, chronic obstructive lung disease, cancer, diabetes, Alzheimer's disease, and kidney diseases were all among the top 10 causes of death globally. Similarly, in the United States, heart disease, cancer, stroke, diabetes, and Alzheimer's disease are also among the top 10 causes of death.[38] Importantly, abundant evidence reveals that regular PA is associated with a reduced risk of developing cardiovascular diseases, several types of cancer, type 2 diabetes, and Alzheimer's disease. The next segments discuss the evidence that regular PA reduces all-cause mortality, in part, by lowering the risk of cardiovascular diseases (i.e., heart disease and stroke), type 2 diabetes, and Alzheimer's disease.

PA reduces the risk of death from cardiovascular disease. Coronary heart disease (CHD) and stroke are two major causes of mortality around the world. Indeed, CHD can lead to a fatal myocardial infarction and remains the number one cause of death worldwide whereas stroke is the third leading cause of mortality.[37] Fortunately, regular PA can reduce the risk of both CHD and stroke.[39] In this regard, CHD and stroke share many of the same risk factors that are modifiable by regular PA.[39–41] A synopsis of how regular PA modifies key risk factors for both CHD and stroke follows.

High blood pressure is an established risk factor for both CHD and stroke. Notably, PA is one of the most potent nonpharmacological interventions to lower blood pressure. For example, a recent review concludes that regular PA lowers both resting systolic and diastolic blood pressure.[42] Specifically, evidence reveals that a linear dose-response relationship exists between aerobic PA and the risk of developing hypertension.[43] Regular PA can lower blood pressure via several mechanisms including increased synthesis of nitric oxide in blood vessels, reduced rate of plaque formation in blood vessels, and increased angiogenesis.[44]

Dyslipidemia refers to an unhealthy blood lipid profile; importantly, dyslipidemia is a major risk factor for both CHD and stroke.[41] The effects of exercise on the blood lipid profile have been studied extensively and it is widely agreed that regular bouts of PA can reduce the risk of CHD and stroke by improving the blood cholesterol profile.[45] Specifically, cholesterol is transported in the blood as particles comprised of both lipids and proteins (lipoproteins). These lipoproteins are traditionally classified into two major categories known as low-density lipoproteins (LDL) and high-density lipoproteins (HDL). LDL is a cholesterol rich particle that is associated with the formation of plaque buildup in arteries.[46] Conversely, HDL can protect against atherosclerosis by removing cholesterol from blood vessels.[47] Evidence indicates that increased HDL cholesterol is the component of the lipid profile that is most responsive to increased PA.[46,48,49] Although some studies report that PA results in small decreases of LDL levels in the blood, this finding is more common in studies involving vigorous exercise.[46] Therefore, regardless of whether PA lowers total LDL levels in the blood, PA promotes a healthy lipid profile by increasing circulating levels of HDL.

Obesity is a key risk for both heart disease and stroke and directly contributes to other risk factors including hypertension, type 2 diabetes, sleep disorders, and dyslipidemia.[50] Although regular bouts of PA can contribute to loss of body fat, studies suggest that large amounts of weight loss primarily occur when the volume of PA exceeds 200 min per week.[51] Nonetheless, in combination with reduced calorie intake, regular PA can be beneficial in promoting both weight loss and weight maintenance, and importantly, regular PA promote the preservation of lean mass during calorie-restricted weight loss.[52,53] Moreover, regular PA has been shown to reduce both abdominal adiposity and systemic inflammation.[54,55] The PA-induced reduction in abdominal fat has been linked to exercise-induced release of hormones (e.g., interleukin-15 [IL-15]) from the working skeletal muscles.[56–58] A reduction in abdominal fat is significant because abdominal obesity is associated with low-grade inflammation independent of body mass index.[55] Reducing chronic systemic inflammation is important because inflammation is a risk factor for several chronic diseases including type 2 diabetes, atherosclerosis, and Alzheimer's disease.[55]

Finally, regular aerobic exercise can also reduce the risk of death from CHD by protecting the heart against damage during an ischemia-reperfusion (I-R) insult (i.e., myocardial infarction).[59–63] Indeed, as few as 3 days–5 days of aerobic exercise provides cardioprotection against I-R-induced injury.[59–63] This exercise-induced cardioprotection is due, at least in part, to training-induced changes in mitochondrial phenotype and increases in myocardial antioxidants; together, these adaptations protect cardiac myocytes against I-R-induced oxidative damage to myocardial lipids and proteins.[64–67] The potential mechanisms responsible for these exercise-induced adaptations will be discussed later in this report.

PA reduces the risk of cancer. Cancer remains a leading cause of death around the world. Fortunately, epidemiological studies involving millions of patients from the United States and Europe reveal that regular PA lowers the risk of 13 types of cancer including esophageal adenocarcinoma, liver, lung, kidney, gastric cardia, endometrial, myeloid leukemia, myeloma, colon, head and neck, rectal, bladder, and breast.[68,69] Further, research also reveals that regular PA reduces the risk of tumor recurrence for breast, prostate, and colon cancer.[70–72]

The association between PA and the reduced risk of cancer follows a dose-response relationship with the greatest protection provided by PA that exceeds > 30 MET/h/week; this amount of PA is equivalent to approximately four times the PA guidelines recommended by the

WHO.[73] A meta-analysis suggests that, compared to moderate intensity PA, vigorous PA may provide more protection against some types of cancer.[74]

Consistent with results from investigations on humans, numerous animal studies also demonstrate that regular PA protects against several types of cancer. In particular, using a variety of PA/exercise interventions (e.g., wheel running, swimming, treadmill running), research indicates that exercise training in rodents reduces tumor incidence, tumor growth, and metastasis across a range of tumor models.[75,76] Nonetheless, evidence also indicates that cancers of different genetic backgrounds can display a differential sensitivity to exercise training.[77,78] Regardless of this variance, abundant evidence supports the notion that regular PA reduces the risk of many types of cancers in humans and other animals.[79]

The mechanism(s) responsible for the exercise-induced protection against the risk of developing cancer remains a hot topic for research. A detailed discussion of the biological links between PA and a reduced risk of cancer exceeds the scope of this review and therefore, only a brief synopsis will be provided. For more details on this topic, the reader is referred to several comprehensive reviews.[55,75,79–82]

Tumor formation and growth occur due to multiple interactions between the systemic environment, the tumor cell, and the tumor microenvironment.[79,83] Many preclinical studies investigating the effect of PA/exercise on cancer outcomes have focused on the impact of exercise on the rate of tumor growth.[79] Notably, although preclinical studies indicate that exercise cannot reduce the size of existing tumors, voluntary wheel running in mice decreases tumor growth rates by > 60%.[79,84] Moreover, in mice injected with carcinogens, voluntary exercise reduced the incidence of tumor development by ~60%.[84]

Potential mechanisms linking exercise to prevention of cancer and tumor growth include the exercise-induced mobilization of natural killer (NK) cells into the circulation, increased circulating interleukin-6 (IL-6) levels, and activation of the Hippo signaling pathway.[79,84] Together, these exercise-induced responses form a basis for the protective effect of PA on cancer risk and tumor growth.[79,83] An overview of each of these mechanisms follows.

NK cells are the immune cells that are the most responsive to exercise training and a single acute bout of exercise significantly increases circulating NK cells.[85] This exercise-induced increase in plasma NK cells results from increases in blood levels of IL-6 and epinephrine-dependent factors as both mechanisms play a role in mobilization and activation of NK cells.[85,86] Increased levels of circulating NK are significant in the prevention of cancer because NK cells are lymphoid cells that recognize and destroy cancer cells.[85,86] Specifically, NK cells can kill cancer cells in several ways including cell lysis, receptor-mediated apoptosis, and antibody-dependent cell-mediated cytosis.[85]

Interestingly, the role of IL-6 in cancer is paradoxical in that IL-6 can both prevent or promote cancer development depending upon the context.[87] Specifically, chronically high levels of IL-6 in the tumor microenvironment promote both low-grade inflammation and activation of tumor-promoting signaling pathways.[87] In contrast to chronically elevated levels of IL-6 that results in inflammation and negative health outcomes, the acute, intermittent exercise-induced increase in circulating IL-6 (i.e., IL-6 released from contracting skeletal muscle) follows a different signaling pathway.[88] Specifically, muscle-derived IL-6 acts with soluble IL-6 receptor (sIL-6R) and soluble glycoprotein 130 (sgp 130) receptors locally and systemically, enabling muscle-organ cross-talk.[88] This exercise-induced intermittent pattern of IL-6 increase has anti-inflammatory effects, mobilizes NK cells, and reduces DNA damage in cancer cells[87]; hence, in this context, IL-6 provides protection against cancer.

Finally, acute bouts of exercise can inhibit tumor formation by activating the Hippo signaling pathway. The Hippo pathway is an evolutionarily conserved regulator of tissue growth; dysregulation of this pathway is implicated in many cancers.[89] The Hippo pathway consists of a core kinase cascade that is regulated by both intracellular and extracellular signals.[90] Hippo signaling serves as a tumor suppressor pathway by phosphorylating two key transcriptional co-factors (i.e., Yes-associated protein [YAP] and transcriptional co-activator with PDZ-binding motif [TAZ]). Phosphorylation of YAP and TAZ by Hippo signaling results in retention of both YAP and TAZ in the cytoplasm and subsequent degradation by the ubiquitin proteasome system, thus preventing nuclear translocation and activation of target genes that express proteins required for growth and proliferation of cancer cells.[90]

PA reduces the risk of type 2 diabetes. A recent WHO global report on diabetes reveals that diabetes remains the 8th leading cause of death globally and unfortunately, the number of adults living with diabetes has quadrupled since 1980.[91] This rapid increase is largely due to the increased incidence of type 2 diabetes which accounts for ~90% of diabetics worldwide.[91] Risk factors for diabetes include excess body fat and low levels of physical activity. Fortunately, it is established that regular PA/exercise can reduce the risk of developing type 2 diabetes.[92] Indeed, PA has potent effects on glucose homeostasis because of exercise-induced metabolic adaptations in skeletal muscle and several other tissues including the pancreas and white adipocytes.[93] A synopsis of the effects that regular PA/exercise has on these organs follows.

Skeletal muscle is the largest sink for glucose uptake in the body and accounts for ~75% of glucose disposal following a meal.[93–95] Glucose uptake in skeletal muscle during exercise occurs by facilitated diffusion resulting from the translocation of glucose transporter 4 (GLUT4) from intracellular locations to the sarcolemma and t-tubules.[96] Indeed, glucose uptake in skeletal muscle during exercise occurs almost exclusively from GLUT4 actions as deletion of GLUT4 in muscle results in marked attenuation of glucose uptake in contracting muscle fibers.[97–99] A single bout of exercise results in increased expression of GLUT4 and regular exercise training increases the abundance of GLUT4 in trained muscles (reviewed in Refs. 96,100). This increase in GLUT4 abundance in muscle fibers improves glucose uptake in contracting muscle and also results in increased postprandial insulin-mediated glucose uptake in skeletal muscles.[101–103]

In addition to the increase in GLUT4 in the trained skeletal muscles, regular exercise increases both mitochondrial volume and the number of capillaries surrounding the trained muscle fibers. The exercise-induced increase in mitochondrial volume augments the muscle's ability to metabolize both glucose and fats.[104] The exercise training-induced increase in capillaries surrounding the trained muscle fibers is beneficial because increased capillarization amplifies the delivery of glucose to muscles at rest and during exercise.[105] This is important because both preclinical and human experiments report that insulin resistance in type 2 diabetics is associated with a reduced capillary density surrounding skeletal muscle fibers.[106,107]

Growing evidence suggests that exercise training promotes adaptations in white adipose tissue that positively impacts metabolic health. For example, in humans, an acute bout of exercise promotes transcriptomic changes in 37 transcripts including a significant decrease in the expression of enzymes involved in lipogenesis and lipid storage in subcutaneous white adipocytes.[108] Moreover, human studies suggest that exercise can lower adipose tissue inflammation particularly when exercise training is associated with weight loss.[108,109]

Adipose tissue also expresses GLUT4 and deletion of GLUT4 in adipocytes results in impaired insulin-mediated uptake of glucose.[110] Notably, compared to healthy individuals, type 2 diabetics possess a lower abundance of GLUT4 in adipocytes.[111] Although exercise training increases GLUT4 expression in adipocytes of rodents,[112–114] few studies have investigated the direct impact of regular exercise on GLUT4 abundance in human adipocytes. Nonetheless, exercise training is associated with increased insulin action in adipose tissue in humans[115] and indirect evidence suggests that this increase is due to increased GLUT4 abundance in adipocytes.[116] Additional research is required to fully explore the impact that regular PA has on GLUT4 expression in human adipocytes.

The release of glucagon and insulin from the pancreas plays an important role in blood glucose homeostasis by promoting insulin-mediated glucose uptake into tissues and hepatic gluconeogenesis.[93] A recent review concludes that exercise training provides health benefits to pancreatic β-cells including proliferation of β-cells and reduced β-cell apoptosis; together, these changes promote improved β-cell function.[117] Because of the invasive methods required to obtain β-cells from the pancreas, most investigations into the effect that exercise has on the pancreas are preclinical studies. In this regard, animal studies consistently show that exercise increases β-cell mass by three primary mechanisms: 1) β-cell proliferation; 2) reduced β-cell death due to apoptosis; and 3) increased β-cell viability.[117] Collectively, these changes result in improved glucose sensing, augmented insulin storage, and increased insulin secretion.[117] For details on the benefits of regular PA/exercise on the health of the pancreatic β-cell see Curran et al.[117]

PA reduces the risk of Alzheimer's disease. Alzheimer's disease (AD) is a progressive neurodegenerative disease that accounts for 60%–80% of all dementia cases.[118] Increasing age, poor cardiovascular health, and physical inactivity are all risk factors for developing AD and unfortunately, the number of Alzheimer's patients worldwide is expected to triple during the next 25 years.[119]

The pathology that distinguishes AD from other forms of dementia is the accumulation of amyloid-β into extracellular plaques and increased intracellular levels of phosphorylated tau protein into intracellular neurofibrillary tangles within neurons in the brain.[120] As the pathology associated with Alzheimer's progresses, there is a loss of both astrocyte function and neuronal atrophy/death.[121,122] Currently, there is no cure for AD and the development of drugs for treatment of Alzheimer's disease has been challenging with a high failure rate.[120]

Because physical inactivity is a risk factor for the development of AD, increased PA and/or exercise has been proposed as an intervention to reduce the risk of developing AD and for treatment of existing AD in patients (reviewed in Refs. 120,123). In this regard, numerous transgenic animal models of AD have been created and used to investigate the impact of treatments to prevent and delay the progression of the AD. A recent review on the effect of exercise on cognitive function and synaptic plasticity in animal models of AD concludes that regular aerobic exercise has a positive effect on improving memory and enhancing synaptic plasticity in animal models of AD; this exercise-induced neuroprotective role is often more effective when exercise training was introduced prior to developing significant AD pathology.[123] In reference to exercise-induced reduction in AD pathology, evidence indicates that aerobic exercise reduces the levels of soluble amyloid-β in rodent models of AD.[120] Similarly, aerobic exercise also lowers the levels of hyperphosphorylated tau protein in the brains of transgenic AD mice; this is significant because phosphorylation of tau proteins precedes the formation of neurofibrillary tangles.[124] Further, regular aerobic exercise increases the number of synapses and dendritic spines in the hippocampus of transgenic AD animals.[123] Together, these preclinical studies support the conclusion that regular aerobic exercise provides beneficial effects on AD pathology.

Like the aforementioned animal studies, numerous human studies also suggest that regular aerobic exercise has the potential to reduce the risk of developing AD (reviewed in Refs. 120,125,126). Indeed, many epidemiological studies reveal that regular exercise can lower the risk of developing AD by reducing cardiovascular risk factors, promoting neurogenesis via exercise-released hormones/metabolites, reducing oxidative stress in the brain, and providing anti-inflammatory effects on the brain.[125,127,128] Although exercise interventions in humans appear to provide the most benefits in patients prior to significant clinical manifestations of AD, several studies also conclude that regular PA/exercise can decrease the rate of cognitive decline in AD patients.[129–131] For a summary of the literature on this topic see reference 120,132,133.

To summarize, part 1 of this review highlighted the evidence that regular exercise reduces the risk of all-cause mortality and counteracts the negative health consequences of prolonged sitting. This first segment also discussed the evidence that exercise lowers the risk of developing several chronic diseases that rank among the top 10 causes of death worldwide. Part 2 of this review will discuss the growing evidence that the health benefits associated with PA are derived, in part, from skeletal muscle-organ crosstalk involving muscle produced hormones that exert their effects in either an autocrine, paracrine, or endocrine manner.

3. Skeletal muscle-organ crosstalk

While the health benefits of exercise are well-established, our understanding of the molecular mechanisms responsible for these PA-related health benefits remains incomplete. The search for the "exercise factor" that promotes exercise training-induced changes in multiple organ systems has been a subject of investigation for several decades. Notably, a break-through in this search occurred in 2000 with the discovery that contracting skeletal muscles release the cytokine interleukin-6 (IL-6) into the blood; this finding provided the first evidence that skeletal muscle is an endocrine organ and that muscle-derived hormones are possible contributors to exercise-induced health benefits in multiple organs.[134] Following this discovery, Pedersen et al. proposed the term "myokines" to describe the proteins and peptides released from skeletal muscles.[134] Subsequent studies reveal that contracting skeletal muscles produce and secrete hundreds of molecules that exert crosstalk effects on numerous organs and tissues.[135] Moreover, it is now clear that in addition to skeletal muscles, many other tissues also release signaling molecules into the blood in response to muscular exercise; collectively, the total of all signaling moieties released into the blood during a bout of exercise are labeled as "exerkines".[136] Exerkines include a wide range of molecules (e.g., proteins, peptides, metabolites, and nucleic acids) that exert their effects on various organs and tissues via autocrine, paracrine, and endocrine signaling.[136,137] While exerkines produced in several tissues can contribute to the health benefits of exercise, myokines released from skeletal muscles have received significant attention. The next segments highlight the potential role that myokines play in mediating exercise-induced adaptations in several organs.

3.1. Muscle-organ crosstalk: role of myokines

Since the discovery that contracting muscles release IL-6 into the blood, studies have revealed that contracting muscles produce numerous myokines that exert their crosstalk effects on many organs and tissues via autocrine, paracrine, or endocrine signaling.[138] A detailed discussion of the impact that myokines have on all tissues is outside the scope of this review. Nonetheless, the following sections discuss muscle-organ crosstalk between select myokines and skeletal muscle, the heart, and the brain. We begin with a discussion of muscle-muscle crosstalk.

3.1.1. Muscle-muscle crosstalk

Numerous myokines exert their signaling effect directly on skeletal muscle fibers via autocrine signaling. The next sections highlight the role that specific myokines play in both the regulation of muscle mass and control of glucose uptake and fat oxidation.

Myokines and regulation of muscle mass. Several myokines exert their signaling effect directly on skeletal muscle fibers via autocrine and paracrine signaling. For example, at least six different myokines regulate muscle mass by either promoting hypertrophy or inhibiting muscle growth (Fig. 4A). In reference to myokines that inhibit muscle growth, myostatin was the first myokine discovered that impairs hypertrophy.[139] Myostatin is a member of the transforming growth factor beta superfamily that negatively regulates muscle growth by binding to the activin receptor type IIB to down-regulate myogenesis genes and up-regulate atrogenes (i.e., proteases).[140] Indeed, deletion of the myostatin gene results in significant muscle hypertrophy in myostatin knockout mice, dogs, and cattle.[139,141,142] Exercise has been shown to decrease the negative impact that myostatin has on muscle mass in at least two ways. First, exercise increases the circulating levels of decorin, a myokine that binds to myostatin and decreases its activity.[143,144] Second, regular exercise decreases the levels of myostatin both in muscle and blood.[145,146]

In regard to myokines that promote muscle growth, the myokines IL-

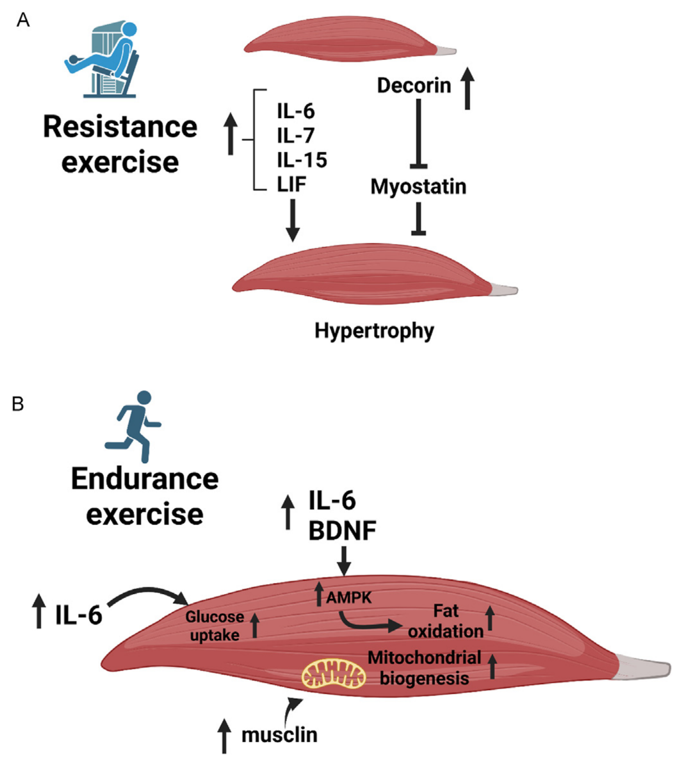

Fig. 4. Muscle-muscle crosstalk A) Resistance exercise training results in the increase in several myokines that promote muscle hypertrophy by stimulating protein synthesis and blocking the activity of myostatin. B) Endurance exercise results in increased production of myokines that promote mitochondrial biogenesis, increased fat oxidation, and glucose uptake into the muscle. See text for details. Figure modified from Ref. 135 and created by Biorender.

6, Interleukin-7 (IL-7), IL-15, and leukemia inhibitory factor (LIF) have all been shown to promote muscle hypertrophy.[135] Specifically, both IL-6 and LIF are released from human muscle fibers in response to exercise or electrical stimulation.[147] Although IL-6 and LIF exert multiple metabolic actions, both molecules activate myotube mammalian target of rapamycin (mTORC1) signaling to increase protein synthesis in a dose-dependent fashion.[148] Further, evidence exists that both IL-6 and LIF are important regulators of satellite cell-mediated muscle hypertrophy.[149,150]

Further, the myokines IL-7 and IL-15 both have anabolic properties in skeletal muscle fibers.[151–155] For example, IL-15 was first reported to be a growth factor in skeletal muscle in 1994.[153] Studies of isolated rat muscle suggest that the primary mechanism responsible for anabolic effects of IL-15 is a decrease in the rate of proteolysis as IL-15 does not appear to increase protein synthesis.[154] IL-7 is produced and secreted by human muscle cells during exercise.[152] IL-7 is hypothesized to contribute to muscle hypertrophy by promotion of myoblast migration and differentiation.[155]

Impact of myokines on skeletal muscle metabolism. Several myokines promote exercise-induced metabolic alterations in skeletal muscle. In particular, IL-6, brain-derived neurotropic factor (BDNF), and musclin are all increased in response to an acute bout of exercise and each of these myokines impacts both glucose and lipid metabolism in skeletal muscle.[135] A synopsis of how these myokines impact muscle metabolism follows.

IL-6 exerts influence as both a paracrine and endocrine signaling molecule. Interestingly, both obesity and physical inactivity in humans are associated with high circulating levels of IL-6.[156] In contrast, an acute bout of exercise results in a transient increase in circulating IL-6 with blood levels rapidly declining to baseline during recovery from exercise.[156] At the conclusion of an intense exercise bout, blood levels of IL-6 can increase up to 100 fold.[156] In general, the intensity and duration of exercise are the primary determinants of the peak blood levels of IL-6 during exercise.[156,157] Regular bouts of endurance exercise training increases the abundance of IL-6 receptors in the trained muscle; this key finding suggests that muscle sensitivity to IL-6 signaling is elevated by training.[158] Notably, evidence indicates that IL-6 signaling in the muscle increases GLUT4 translocation and amplifies glucose uptake into the muscle.[159] Moreover, increased circulating IL-6 promotes insulin-stimulated glucose uptake in humans; the mechanism responsible for this increase in glucose uptake is mediated via activation adenosine 5′-monophosphate-activated protein kinase (AMPK) which promotes GLUT4 translocation resulting in glucose uptake into the cell.[158] Together, these IL-6 mediated changes in glucose uptake provide a potential mechanism to explain why regular exercise reduces the risk of developing type 2 diabetes. Finally, elevated IL-6 can also increase whole body fatty acid oxidation via AMPK activation.[159,160]

Exercise also promotes the expression of brain-derived neurotrophic factor (BDNF) in active muscle fibers; however, this myokine is not released into the circulation.[135] Instead, BDNF remains in the fiber and acts in an autocrine manner in muscle to activate AMPK and enhance lipid oxidation.[161]

Finally, musclin is another exercise-inducible myokine that has been reported to increase endurance in rodents, in part, by increasing mitochondria biogenesis in skeletal muscle.[162] Therefore, by increasing mitochondrial biogenesis, musclin also enhances the ability for the trained muscle fiber to metabolize lipids.[162] The influences of IL-6, BDNF, and musclin on muscle metabolism are illustrated in Fig. 4B.

3.1.2. *Muscle-heart crosstalk*

As discussed previously, regular bouts of aerobic exercise alter the phenotype of cardiac myocytes to provide cardioprotection against ischemia-reperfusion (I-R) injury.[63,163] Emerging evidence suggests that exercise-induced increases in circulating levels of two myokines, musclin and irisin, contribute to this exercise-induced cardioprotection. For example, recent experiments reveal that genetic deletion of the musclin gene in the rat heart blunts exercise-induced cardioprotection.[164] Specifically, the disruption of musclin signaling is linked with suppression of peroxisome proliferator-activated receptor γ coactivator 1-α and a reduction in exercise-induced mitochondrial biogenesis.[164] This is significant because exercise-induced adaptations in mitochondria in cardiac myocytes contributes to cardioprotection against I-R injury.[59,66]

Evidence also exists that the myokine irisin, a muscle-origin peptide that is derived from cleavage of the fibronectin type III domain-containing protein 5, participates in exercise-induced cardioprotection.[165] For example, administration of exogenous irisin to rats provides a dose-dependent protection against myocardial ischemia-reperfusion injury. The proposed mechanism linking irisin to cardioprotection is that irisin increases the activity of superoxide dismutase 2 (SOD2) in cardiac myocytes.[165] This is significant because increased SOD2 activity in cardiac myocytes protects myocytes from I-R-induced oxidative damage.[59] Nonetheless, although it is established that irisin is produced and released from skeletal muscles during exercise in rodents, controversy exists about whether exercise increases irisin levels in the blood of humans.[166] This controversy emerged from a study revealing that several commercial ELISA assays used to detect irisin were inaccurate because of cross reactivity with several serum proteins.[167] More recently, evidence that human exercise increases circulating irisin by 20% has been provided by the application of sensitive mass spectrometry to detect irisin levels.[168] Additional studies to confirm these findings are warranted.

Finally, emerging evidence suggests that exercise-induced cardioprotection is due, in part, to the cargo contained in extracellular vesicles released into the circulation following a bout of aerobic exercise.[169–173] Indeed, several studies and recent reviews conclude that plasma derived extracellular vesicles released during a bout of endurance exercise promote cardioprotection against I-R-induced injury.[169,170,172,174–176] However, to date, it is unclear whether skeletal muscles are the primary source for the release of extracellular vesicles containing cardioprotective cargo. In this

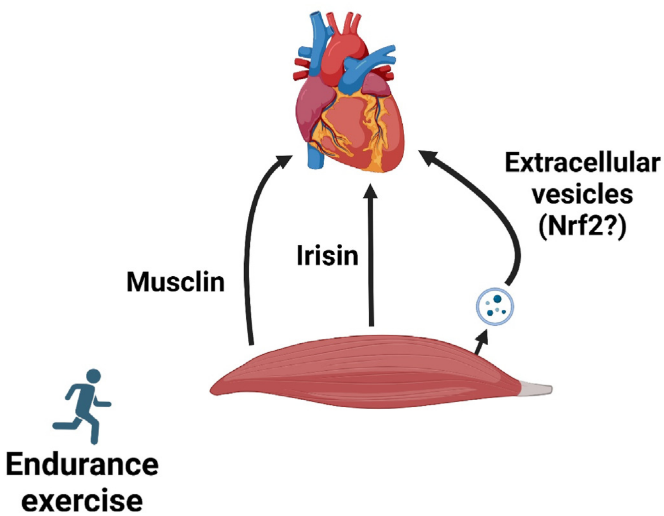

Fig. 5. Muscle-heart crosstalk. Endurance exercise training results in cardioprotection against ischemia-reperfusion injury. Growing evidence indicates that the exercise-induced release of myokines in the blood contributes to this protection. See text for details. Figure created by Biorender.

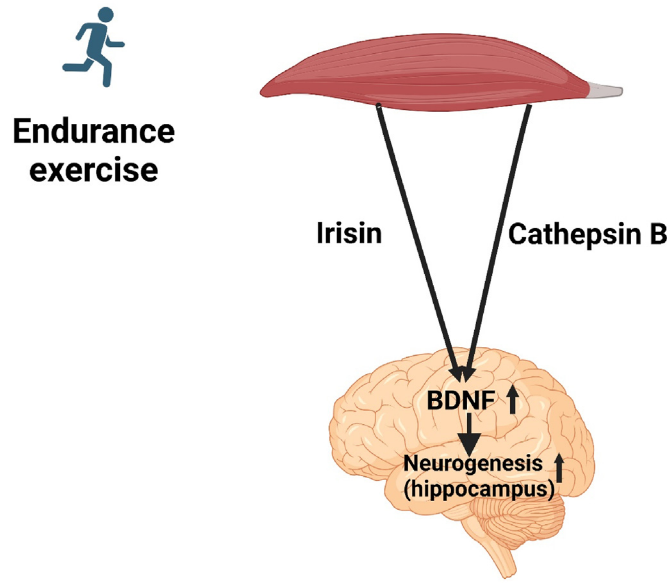

Fig. 6. Muscle-brain crosstalk. Growing evidence indicates that the connection between exercise and brain health is facilitated, at least in part, by a brain-endocrine loop mediated by myokine signaling. Emerging research suggests that this exercise-induced muscle-brain cross-talk is the result of the myokines cathepsin-B and irisin that are released into the blood during exercise to promote BDNF synthesis in the hippocampus. Figure modified from Ref. 135 and created by Biorender.

regard, Gao and colleagues recently proposed that exercise-induced cardioprotection is achieved, at least in part, by the release of extracellular vesicles containing nuclear factor erythroid 2-related factor (Nrf2). Following release into the blood, extracellular vesicles are delivered to cardiomyocytes to promote cardioprotection.[170] Specifically, Nrf2 is a key transcription factor that plays a key role in the exercise-induced expression of key antioxidant proteins.[177] Therefore, in theory, the extracellular vesicle delivery of Nrf2 to cardiac myocytes could promote cardioprotection by increasing the antioxidant capacity in cardiac myocytes.[67] This postulate has been experimentally supported in recent work revealing that plasma-derived extracellular vesicles released during exercise provide cardioprotection against I-R injury, in part, due to increases in antioxidant activity in the heart.[172] Nonetheless, additional research is needed to better understand the specific role that extracellular vesicles and/or specific myokines play in cardioprotection against I-R-induced cardiac injury (Fig. 5).

3.1.3. *Muscle-brain crosstalk*

As discussed earlier, regular exercise reduces the risk of developing AD and preclinical studies consistently reveal that exercise delays the advancement of AD.[128] Recent evidence suggests that the connection between exercise and brain health is facilitated, at least in part, by a brain-endocrine loop mediated by myokine signaling. A brief discussion of two myokines that influence brain health follows.

The hippocampus is a complex brain structure that plays a key role in learning and memory; unfortunately, the hippocampus is one of the first regions of the brain to suffer damage during the onset of AD.[128] Exercise benefits the hippocampus by increasing blood flow, promoting neurogenesis in the dentate gyrus, and increasing synaptic plasticity.[128,178] In this regard, BDNF plays an important role in mediating the benefits of exercise on the hippocampus.[128,178] Specifically, preclinical studies show that BDNF protein levels increase in the hippocampus in response to endurance exercise and that BDNF is mechanistically linked to exercise-induced improvement in memory and cognitive functions in the brain.[128]

As discussed earlier, although contracting skeletal muscles produce BDNF, muscle does not release BDNF into the blood.[135] Nonetheless, emerging evidence suggests that two myokines (cathepsin-B [CTSB] and irisin) are released into the blood during exercise and both can promote BDNF synthesis in the hippocampus (Fig. 6).[179,180] Specifically, four months of running exercise results in elevated blood levels of CTSB in mice, rhesus monkeys, and humans; notably, CTSB has been reported to cross the blood-brain barrier in mice.[179,181] A recent study reveals that CTSB plays a required role in exercise-induced hippocampal growth and improved cognition in mice; cause and effect was confirmed by the finding that CTSB knockout mice are resistant to exercise-induced hippocampal growth, suggesting that the increase in circulating CTSB plays a key role in exercise-induced improvements in hippocampal neurogenesis and cognition.[179]

As discussed earlier, exercise training increases circulating levels of irisin and irisin is mechanistically linked to the increased expression of BDNF in the brain.[182] Importantly, elevated blood levels of irisin increases synaptic plasticity and memory in mouse models of AD.[183] At present, our understanding of the regulation of BDNF gene expression in the brain is incomplete.[184] Nonetheless, it appears that the molecular connection between irisin and increased expression of BDNF occurs via a cyclic AMP (cAMP), protein kinase A (PKA), and cAMP response element-binding protein (CREB) signaling pathway.[183] Specifically, aerobic exercise results in elevated blood levels of irisin. This circulating irisin crosses the blood-brain barrier and acts upon neurons by binding to unidentified receptors on the cell membrane to promote the accumulation of cAMP which activates PKA; active PKA phosphorates the transcription factor CREB to trigger expression of BDNF which improves cognition and synaptic plasticity.[183]

Together, these preclinical studies suggest that at least two myokines (CTSB and irisin) can contribute to the exercise-induced improvement of cognition and a reduced risk of developing AD. Nonetheless, future work is required to confirm that these myokines contribute to exercise-induced improved cognition in humans suffering from AD.

4. Summary and future directions

The first evidence that prolonged periods of SB is associated with an increased risk of all-cause mortality appeared in the literature over 70 years ago. More recent research using accelerometry to measure inactivity in subjects reveals that the negative impact that SB has on health and longevity has been grossly underestimated by previous self-report studies.

During the past several decades, hundreds of studies confirm that regular PA provides numerous health benefits and reduces the risk of all-cause mortality. More specifically, a non-linear dose-response association exists between PA and all-cause mortality with the greatest benefits being achieved with approximately 225 min/week of MVPA. Moreover, recent studies using accelerometry to measure PA demonstrate that regular PA provides significantly greater health benefits compared to self-report studies. This PA/exercise-induced increase in longevity occurs because regular PA reduces the risk of developing numerous chronic diseases including coronary heart disease, stroke, cancer, type 2 diabetes, and Alzheimer's disease.

Although the health benefits of exercise are clearly established, the mechanism(s) responsible for PA-related health benefits remains a hot topic for research. The search for the "exercise factors" responsible for PA-induced benefits to multiple organs has led to the discovery that during exercise, contacting skeletal muscles and other tissues release signaling molecules into the blood; collectively, these molecules are called "exerkines". Exerkines include a wide range of molecules (e.g., proteins, peptides, and nucleic acids) that exert their effects on numerous tissues via autocrine, paracrine, and endocrine signaling. Exerkines produced in skeletal muscles are labeled myokines and emerging evidence identifies several myokines as key players responsible for exercise-induced adaptations in multiple organs. Specifically, muscle-organ crosstalk exists between several organs including skeletal muscle itself, the brain, and the heart.

While research during the past several decades has provided abundant information about the benefits of PA on health, many unanswered questions remain. For example, the explanation for why TV-viewing poses greater health risks than total sitting time remains an enigma. Further, there is much more to be learned about the mechanisms responsible for exercise-induced benefits to multiple organ systems. Indeed, mechanistic studies identifying the role that specific exerkines play in PA-induced health benefits are needed. Precisely, the identification of exerkines and their specific roles could lead to the development of novel therapeutics. Furthermore, identifying key exerkines that lead to health benefits can be used as biomarkers for determining the modes, intensities, and amount of exercise required to optimize health benefits for healthy people as well as individuals suffering from cancer, heart disease, diabetes, and Alzheimer's disease. Finally, another exciting area of future research is the investigation of the sources and contents of extracellular vesicles produced during exercise. Improving our knowledge of health benefits from the contents of extracellular vesicles can also lead to the development of therapeutics for the prevention of numerous non-communicable diseases. Clearly, there is much more to be learned about the important topic of the health benefits of exercise.

CRediT authorship contribution statement

Scott K. Powers: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Erica Goldstein:** Writing – review & editing, Investigation. **Ronette Lategan-Potgieter:** Writing – review & editing. **Matthew Schrager:** Writing – review & editing. **Michele Skelton:** Writing – review & editing. **Haydar Demirel:** Writing – review & editing.

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