



## Report of a Meeting

# Muscle movement and metabolism: exercise and skeletal muscle as mediators of health—a report from the 26th Annual Harvard Nutrition Obesity Symposium, 2025



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## ABSTRACT

Skeletal muscle is a crucial facilitator of many of the effects of exercise on metabolic health. Intrinsic myocellular mechanisms, exercise-induced myokine secretion, and crosstalk between multiple organ systems contribute to the maintenance of energy homeostasis, cardiovascular health, strength, cognition, and quality of life. Investigating the molecular underpinnings of the skeletal muscle response to exercise from multiple perspectives, including the genetic, physiological, and environmental factors leading to metabolic dysfunction, has advanced our understanding of disease risk and helped identify avenues for the prevention and treatment of metabolic disorders and chronic diseases. The National Institutes of Health-funded Boston Area Nutrition Obesity Research Center, in partnership with the Harvard Medical School Division of Nutrition, hosted its 26th Annual Symposium, “Muscle Movement and Metabolism: Exercise and Skeletal Muscle as Mediators of Health,” in June of 2025. Speakers presented novel research and unique perspectives on exercise and skeletal muscle as key determinants of health. This manuscript synthesizes the symposium’s major themes: 1) physiological and molecular mechanisms of exercise, 2) clinical implications of physical inactivity and reduced muscle function, and 3) individual variability and personalized medicine. By bridging mechanistic and clinical insights with principles of personalized medicine, the symposium provided key insights into the current landscape of treatments for metabolic diseases and evidence-based strategies for disease prevention.

**Abbreviations:** ActRII, activin type II receptor; BHB, β-hydroxybutyrate; BHB-Phe, N-β-hydroxybutyryl phenylalanine; BMAL 1, basic helix-loop-helix ARNT-like 1; CCG, clock-controlled gene; CGM, continuous glucose monitoring; CLOCK, clock circadian regulator; CNDP2, cytosolic nonspecific dipeptidase 2; Cry, Cryptochrome; CS, citrate synthase; CT, computerized tomography; DAG, diacylglycerol; D<sub>3</sub>-Cr, D<sub>3</sub>-creatine; DXA, dual-energy X-ray absorptiometry; EV, extracellular vesicles; HFD, high-fat diet; GLP-1RA, glucagon-like peptide receptor agonist; IMCL, intramyocellular lipid; iPOP, integrative personal omics profiling; KO, knock-out; Lac-Phe, N-lactoyl phenylalanine; MitovD, mitochondrial volume density; miRNA, microRNA; MoTrPAC, Molecular Transducers of Physical Activity Consortium; MRI, magnetic resonance imaging; Per, period; RCT, randomized controlled trial; SOD3, superoxide dismutase 3; T2D, type 2 diabetes; WAT, white adipose tissue; WL, weight loss; WLEX, weight loss with exercise; WT, wild type.

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**Keywords:** skeletal muscle, metabolism, obesity, diabetes, exercise, sarcopenia

## Introduction

The interplay between physical activity, skeletal muscle, and metabolism has profound effects on health and longevity [1–5]. The Centers for Disease Control and Prevention defined physical activity as any bodily movement that produces energy expenditure, whereas exercise is a subtype of activity that is planned, structured, and repetitive [3,6]. Indeed, engaging in regular physical activity and exercise is known to protect against a broad range of health concerns across the lifespan, including cardiovascular disease, stroke, cancers, diabetes, and age-related cognitive decline [7–11]. Physical activity in childhood is associated with improved cognitive functioning, academic performance, and mental health [12–15], early childhood exercise is also linked with improvements in cardiovascular risk factors, bone development, and body fat and mass measures [16–19]. In older adults, physical activity reduces the risk of chronic age-related conditions and improves quality of life, mental and physical health, and cognition [20–24]. The WHO consistently recommends limiting sedentary behavior and maintaining physical activity based on robust evidence that exercise reduces the risk of adverse health outcomes while controlling for other risk factors [3,25,26].

With the increasing life expectancy of humans, scientific investigations have focused on identifying strategies to optimize healthful years, termed the “healthspan” [27,28]. Physical activity typically declines with age due to environmental factors and chronic disease onset [29,30], which highlights the clinical relevance of determining how exercise-induced enhancements in skeletal muscle and metabolism can protect against the decline of health. Physical activity and exercise play a key role in improving the healthspan through their multisystem effects on skeletal muscle mass, glucose metabolism, and cardiovascular health [31]. The function of skeletal muscle has been compared with that of an endocrine organ [32,33]. As such, in-depth characterizations of the cytokines and other immunomodulating peptides produced and released by muscle fibers demonstrate the far-reaching effects of muscle-contracting exercise on other organ systems [33–37]. These endocrine-like processes via muscle-derived myokines are thought to induce metabolic adaptations with impacts across multiple organ systems, ultimately leading to lifelong benefits in health [8].

Novel technologies have allowed for in-depth longitudinal monitoring of health and lifestyle data in large cohorts of participants [38–40]. The ability to integrate longitudinal data incorporating lifestyle factors and physiological outcomes provides exciting possibilities for this field, results of which have elucidated how exercise, nutrition, environmental exposures, and pathogens influence health over time [38, 39]. This approach applies the principles of personalized care and precision medicine to the study of exercise science [41–43]. The 2025 Harvard Nutrition and Obesity Research Center Symposium featured experts who presented topics broad in scope, but united under this framework. Presenters reviewed the physiological [44,45] and molecular [46] mechanisms of physical activity and exercise, particularly in their regulation of glucose metabolism and the central role of skeletal muscle in metabolic adaptation [47,48]. After reviewing foundational literature and emerging studies, presenters discussed clinical applications, potential benefits, and practical considerations of exercise intervention in distinct populations and future directions for the field.

## Physiological and Molecular Mechanisms of Exercise

### Mechanisms of exercise and the role of skeletal muscle

Healthy skeletal muscle plays an important role in maintaining energy homeostasis and protecting against insulin-regulated disorders such as type 2 diabetes (T2D). Insulin resistance is a hallmark of cardiometabolic dysregulation and T2D, where insulin-stimulated glucose uptake is impaired [49,50]. Evidence from studies in human muscle biopsies and rodent models suggests that elevated concentrations of skeletal muscle lipids contribute to the pathogenesis of insulin resistance typical of obesity and T2D [45,51–53]. Goodpaster et al. [54] support this hypothesis, showing that the lipid content in muscle fibers is increased in T2D, but not in obesity without T2D, corroborating initial findings in animal models. Additionally, intramyocellular lipids (IMCLs) are associated with BMI and insulin resistance, independent of total fat mass and age [45,54,55]. These findings led to more in-depth investigation of IMCLs and their relationship to insulin resistance in T2D, in response to weight loss (WL), and in endurance-trained athletes.

IMCL comprises mostly of relatively inert intramuscular triglyceride but also includes diacylglycerols (DAG), ceramides, and other sphingolipids and phospholipids. The pathways by which IMCL contribute to insulin resistance likely involve disruptions in oxidation with excess lipid content. Typically, intramuscular triglycerides are an important fuel source for skeletal muscle during exercise [55,56]. The energy supply depends on the availability of fatty acids in circulation and stored in myofibers, relative to exercise duration and intensity, and the mitochondrial capacity for fatty acid oxidation [49]. With elevated IMCL concentration in the context of obesity and T2D, oxidative capacity is reduced, which lowers fatty acid oxidation [56]. In obesity, elevated lipid concentrations and incomplete fatty acid oxidation facilitate the production of DAG, ceramide, and reactive oxygen species [56]. These processes produce intermediaries associated with the development of insulin resistance [56]. In individuals with obesity or T2D, WL interventions reduce skeletal muscle lipid concentration, demonstrating how lipid accumulation can be altered with lifestyle changes and corresponding WL [48,54].

Muscle’s oxidative capacity also regulates glucose uptake, dependent on insulin-stimulated microvasculature blood flow and intramuscular triglyceride accumulation [57]. Reduced mitochondrial oxidation, inadequate fatty acid oxidation, and accumulation of sphingolipids and DAG are interdependent mechanisms linking elevated IMCLs to insulin resistance [56,58,59]. Through insulin-dependent signaling, acute bouts of exercise induce an insulin-sensitizing reaction in the myofiber in individuals with T2D [60–62], but these effects are attenuated in exercise-trained individuals [63]. Long-duration, consistent exercise training in T2D promotes insulin sensitivity by increasing mitochondrial capacity for fatty acid oxidation and facilitating insulin-stimulated glucose uptake [64,65]. More detailed descriptions of the mechanisms of glucose uptake in myofibers and alterations in insulin resistance are reviewed in Whytock and Goodpaster [49].

Although exercise training improves insulin sensitivity by increasing lipid and fatty acid oxidation [66–68], disparate studies

have found both increases and decreases in intramuscular triglycerides after exercise training [69–71]. These studies have led to more complex hypotheses describing skeletal muscle triglycerides and the link to insulin resistance. Specifically, endurance-trained athletes appear to have surprisingly higher muscle fiber lipid content than their insulin sensitivity would otherwise suggest, given that insulin sensitivity is typically correlated with lower IMCL accumulation in sedentary individuals [45]. This contradictory finding, referred to as “the athlete’s paradox,” is explained, in part, by differences in oxidative metabolism (Figure 1). Skeletal muscle of endurance-trained athletes has higher oxidative capacity, despite their high lipid content. Therefore, oxidative metabolism has been identified as an intermediate regulatory mechanism in the processes that can ultimately lead to insulin resistance [45]. A follow-up study found that progressive, moderate-intensity aerobic training in previously sedentary individuals increased intramuscular triglycerides, decreased DAG and ceramide content, and improved insulin sensitivity [72]. These changes occurred with favorable changes in skeletal muscle glycogen storage, oxidative capacity, and capillary density [72]. Interestingly, DAGs and ceramides have also been identified as mediators of the athlete’s paradox, with studies showing higher DAG content in highly insulin-sensitive skeletal muscle compared with skeletal muscle of participants with obesity [73], despite their seemingly beneficial reduction with the introduction of exercise training [72,74].

With the hypothesis that oxidative capacity may be central to the athlete’s paradox and evidence that physical activity increases mitochondrial content, fat oxidation, and insulin sensitivity, Dubé et al. [75] tested whether endurance-trained athletes are protected from lipid-induced insulin resistance. In endurance-trained athletes and sedentary individuals, acute lipid oversupply led to comparable decreases in total glucose disposal, but nonoxidative glucose disposal was maintained in endurance-trained athletes. This demonstrates better metabolic flexibility in trained individuals, as oxidation preferentially switches from glucose to lipid to preserve glycogen stores [75].

Overall, the research to date shows complex relationships between exercise, skeletal muscle lipid content, and insulin sensitivity, converging to support the beneficial impacts of exercise and WL on insulin sensitivity and mitochondrial capacity.

### Small extracellular vesicles as facilitators of exercise-induced tissue crosstalk

The secretion of extracellular vesicles (EVs) is an evolutionarily conserved process by which cells release proteins, lipids, metabolites, and genetic material contained in a lipid bilayer into their

environment, allowing intercellular communication [76]. This transfer of information affects the regulation of recipient cells [76,77]. For example, microRNA (miRNA) released in small EVs from adipose cells can travel to and regulate gene expression in the liver and other tissues [78]. Exercise causes a transient increase in the number of small EVs in circulation, making them important carriers of exercise-induced secreted factors [79,80]. Methods of assessing circulating EVs enable the investigation of their effects in differently exercised model organisms [80]. Acute exercise not only boosts the quantity of small EVs released but also affects the makeup of their cargo [80,81]. Differential enrichment of proteins and miRNAs after physical activity can affect systemic metabolism, muscle growth, and glucose homeostasis [82]. Some circulating miRNAs are responsive specifically to chronic exercise, demonstrating another mechanism of long-term adaptation [83]. As key coordinators of the molecular response to exercise, exercise EVs have the potential to be leveraged for developing treatments for cardiovascular disease, T2D, obesity, and cognitive decline [80,82,84,85].

### Multimic responses to exercise

The effects of exercise are broad and integrative of multiple interconnected organ systems [86]. Exercise affects cells, tissues, and organ systems, creating widespread homeostatic adaptations dependent on cellular and molecular mechanisms [46,86]. In response to a noted lack of funding for research programs investigating the biology of physical activity outside of the scope of disease prevention, the Molecular Transducers of Physical Activity Consortium (MoTrPAC) was established with the goal of building a molecular map of the response to exercise in diverse populations across the lifespan [46]. Since its establishment, MoTrPAC has brought together researchers across scientific disciplines, from preclinical studies in animal models to clinical studies in humans, with centralized resources to manage sample collection and distribution, study logistics, and bioinformatics (Figure 2). Advanced, multimic network analyses in rodents and humans capture the dynamic response to exercise by investigating changes in biological pathways, including structural, immune, and mitochondrial changes occurring with exercise.

Typically, transcriptome, epigenome, proteome, and metabolome platforms are studied separately, rather than in tandem, due to limited sample volume and expense-related concerns. Many experiments are limited by studying only 1 sex, thus lacking the ability to investigate potential sex differences. MoTrPAC’s Preclinical Animal Study Sites utilized male and female rats to obtain large enough tissue quantity for multimics, thereby enabling multiple assays to be carried out in the same tissue and with enough power to detect sex differences [87].

|                                  | Intramuscular lipid content | Insulin sensitivity | Muscle oxidative capacity <sup>1</sup> |
|----------------------------------|-----------------------------|---------------------|----------------------------------------|
| <b>Obese</b>                     | = Trained                   | < Trained           | < Trained                              |
| <b>T2D</b>                       | = Trained                   | < Trained           | < Trained                              |
| <b>Lean</b>                      | < Trained                   | = Trained           | = Trained                              |
| <b>Post-exercise<sup>2</sup></b> | ↑                           | ↑                   | ↑                                      |

**FIGURE 1.** Summary of results describing the athlete’s paradox. Comparisons between endurance-trained athletes ( $n = 9$ ), lean subjects ( $n = 9$ ), and subjects with obesity ( $n = 11$ ) or T2D ( $n = 8$ ) in intramuscular lipid content (trained vs. lean,  $P < 0.05$ ), insulin sensitivity (trained vs. obese and T2D,  $P < 0.05$ ), and muscle oxidative capacity (trained vs. obese and T2D,  $P < 0.05$ ) evaluated by one-way ANOVA with Bonferroni correction for group comparisons. Adapted from Goodpaster et al. [45] and Dubé et al. [72]. <sup>1</sup>Quantified by succinate dehydrogenase (SDH) staining. <sup>2</sup>In sedentary subjects. ANOVA, analysis of variance; T2D, type 2 diabetes.

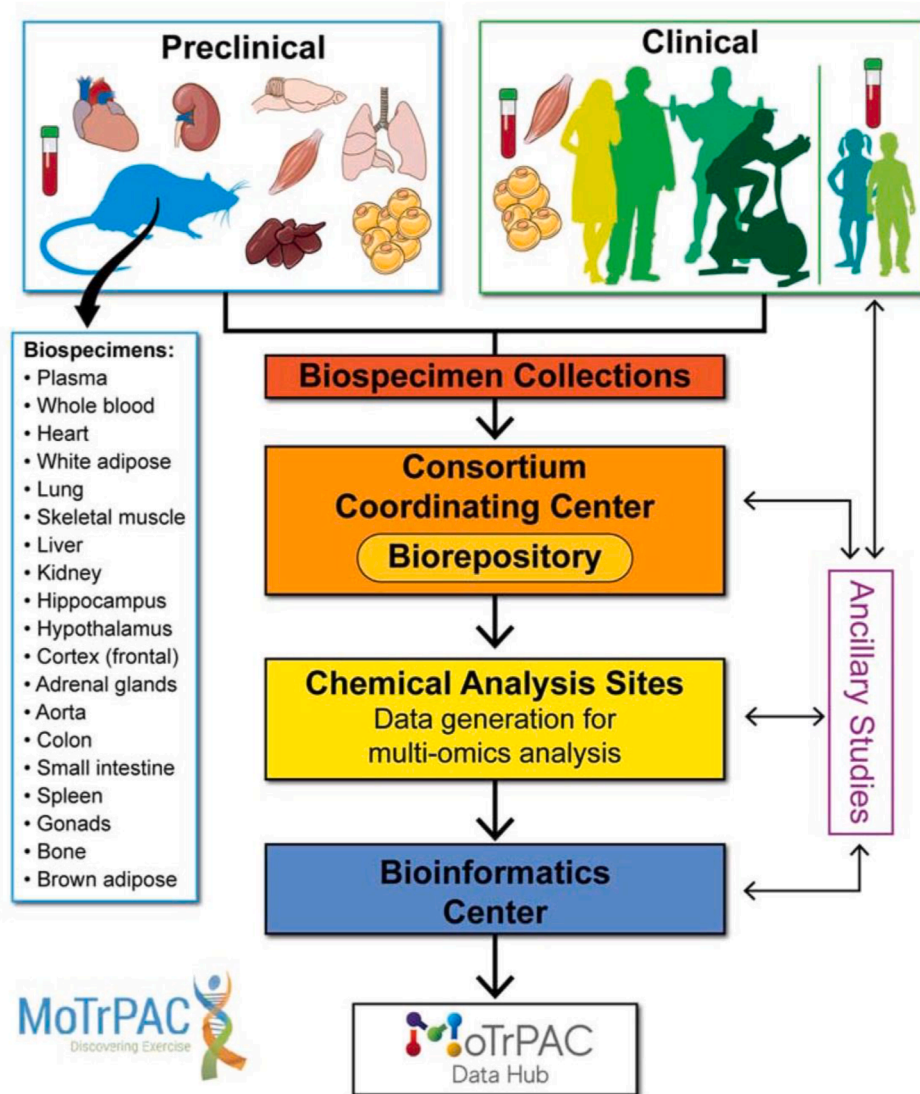


**FIGURE 2.** Organization of MoTrPAC. Reprinted with permission from Sanford et al. [46]. MoTrPAC, Molecular Transducers of Physical Activity Consortium.

MoTrPAC performed a comprehensive analysis of molecular networks driving the temporal and phenotypic responses to exercise. Samples from 18 solid tissues and blood of male and female Fischer 344 inbred rats that underwent progressive endurance exercise training at 6 mo of age were compared with sedentary controls. Body composition and VO<sub>2</sub>max were measured before the 8-wk progressive treadmill training regimen, which consisted of treadmill running for 5 consecutive days per week for 1, 2, 4, or 8 wk with periodically increasing treadmill grade, speed, and duration. Although all animals in the exercise group showed improved VO<sub>2</sub>max compared with sedentary controls, only male exercise-trained rats had decreased whole-body fat at the end of 8 wk [88].

A key finding was that all organs responded to exercise training from a multiomic perspective, and almost 60% of the 8-wk differential features showed sex-specific regulation. Gene expression was most robustly regulated by exercise training in the adrenal gland, with distinct tissue-specific gene responses in the skeletal muscle (gastrocnemius), subcutaneous white adipose tissue (WAT), heart, liver, lung, and kidney [88]. In the proteomic analysis, all organs assayed, including the gastrocnemius, heart, liver, WAT, lung, kidney,

and cortex, had differential regulation in protein abundance and post-translational modifications. In skeletal muscle, exercise training was associated with enrichment of proteins related to peroxisome proliferator-activated receptor signaling and lipid synthesis and degradation, and enrichment of metabolites related to either lipid or glycerophospholipid metabolism. These exercise-driven, multiomic changes in skeletal muscle highlight its profound role in regulating muscle lipid composition, storage, synthesis, and metabolism. Despite differing effects between males and females in various tissues throughout the study, there was a consistent response by week 8 in the striated muscle cluster, including the gastrocnemius, vastus lateralis, and heart, primarily associated with metabolic adaptation [88].

A follow-up MoTrPAC study investigated the molecular underpinnings of sexual dimorphism in subcutaneous WAT in these rats [87]. WAT distribution is highly dimorphic in humans and animals, a phenomenon typically attributed to hormonal differences, but molecular mechanisms related to subcutaneous WAT biology had not previously been characterized. Sex differences were found across an abundance of molecules from all 'omes and multiple tissues. Of note, transcripts related to lipid metabolic processes and unsaturated fatty

acid synthesis were elevated in sedentary male WAT, whereas molecules involved in growth factor signaling, adipogenesis, and glucose uptake were elevated in sedentary female WAT. In males, these markers were further increased with training, as were markers of fat oxidation in females, although to a lesser extent compared with males. This study provides insight into the cellular regulators of the female-specific cardioprotective role of subcutaneous WAT, which may be explained by molecular markers of increased adipogenesis, lipid buffering and recycling, and insulin signaling [87].

In terms of mitochondrial metabolism, the MoTrPAC study showed that rats had sex-consistent trajectories across timepoints, with an overall upregulation of metabolic proteins in skeletal muscle over 8 wk of endurance training [89]. In the mitochondrial pathways, there was an increase in protein oxidation in male rats, whereas females showed an increase in glycolytic protein oxidation (MoTrPAC, unpublished results). The first results from the MoTrPAC clinical trial in adults (NCT03960827) elucidated the effects of 1 acute bout of endurance- or resistance-based exercise [90]. Samples were collected before exercise and at 3 time points within the 24 h after exercise. In skeletal muscle, cluster analyses reveal distinct clusters of analytes from all omes, with different trajectories of metabolic adaptations at each time point (MoTrPAC, unpublished results).

MoTrPAC prioritizes the dissemination of data and resources for future research and encourages open access to databases in the biomedical research community. All MoTrPAC data from human intervention studies, typically encompassing 12-wk protocols including screening, phenotyping, and biospecimen collection, which do not compromise Personal Health Information are available through the MoTrPAC Data Hub (<https://motrpac-data.org>). The comprehensive results generated from these data and the opportunity for further analysis will promote discovery of the molecular mechanisms of health for targeted interventions relevant to individualized exercise recommendations.

### Chemical control of energy metabolism

Combining large-scale studies with focused experimentation of candidate molecules, Li et al. introduced *N*-lactoyl phenylalanine (Lac-Phe), a blood-borne signaling metabolite of lactate, and its dependent pathways regulating the feeding response to exercise [91–93]. A targeted metabolomics analysis in mice and racehorses showed increases in lactate, fumarate, and succinate after acute exercise, whereas untargeted metabolomics revealed a surprising and significant increase in Lac-Phe. Lac-Phe was previously shown to be synthesized by the intracellular enzyme cytosolic nonspecific dipeptidase 2 (CNDP2) in response to exercise [94]. However, its physiological role in relation to feeding and weight regulation was not clear.

After confirming a substantial increase in Lac-Phe after an acute bout of running in mice, a CNDP2-dependent pathway was further defined in a macrophage cell line, where the addition of lactate to the medium facilitated Lac-Phe synthesis. In *Cndp2* knock-out (KO) cell lines, Lac-Phe was reduced by 75%. This shows that Lac-Phe synthesis by CNDP2 is regulated by extracellular lactate and aligns with the documented increases in lactate and Lac-Phe after exercise [91].

These findings led to the hypothesis that Lac-Phe regulates energy balance, which can be measured by food intake after Lac-Phe treatment in mice with diet-induced obesity. Acute Lac-Phe treatment suppressed food intake without affecting overall activity, oxygen consumption, carbon dioxide production, respiratory exchange ratios,

or levels of the appetite-regulating hormones leptin and ghrelin. Lac-Phe did not have this effect in lean mice, even at 3-fold higher doses, demonstrating a unique regulation of food intake by Lac-Phe in obesity [91].

In a *Cndp2*-KO mouse model, exercise-induced Lac-Phe was reduced compared with WT mice, and food intake was increased. When WT and *Cndp2*-KO mice were fed a high-fat diet (HFD), food intake and body weight did not differ unless they were also exposed to treadmill running. Treadmill running led to significant WL in WT mice, an effect that was blunted in the *Cndp2*-KOs, showing that exercise is required to stimulate CNDP2/Lac-Phe energy regulation [91]. These findings translate to experiments in humans, where plasma Lac-Phe levels were significantly increased after 3 different modalities of exercise: endurance, resistance, and sprint training [91]. In participants with overweight or obesity, Lac-Phe levels after acute exercise were correlated with adipose tissue loss after an 8-wk exercise intervention [95].

The Lac-Phe pathway is also implicated as a mediator of the anti-diabetic medication, metformin [96]. Metformin is a first-line treatment for T2D due to its antihyperglycemic effects, with patients often experiencing WL and appetite reduction [97,98]. In a mouse model, metformin increased plasma Lac-Phe, mediated by gut-specific CNDP2 [96]. Leveraging human data from the Multi-Ethnic Study of Atherosclerosis, a large longitudinal study with a mean follow-up of 9.5 y, metformin was found to be associated with higher levels of circulating Lac-Phe and more WL. Reduction in BMI associated with metformin was mediated by Lac-Phe, such that the direct effect of metformin on BMI reduction was weakened when Lac-Phe was added to the model; no mediating effect was found for lactate, demonstrating the specific effect of Lac-Phe as a metabolite. The Lac-Phe production pathways are visualized in Figure 3 [96].

Another nutrient-responsive metabolite of relevance to the CNDP2/Lac-Phe pathway is  $\beta$ -hydroxybutyrate (BHB), a ketone body that rises dramatically during ketosis [99,100]. BHB is structurally similar to lactate and is likewise conjugated to amino acids in CNDP2-activated enzymatic reactions. The BHB amino acid *N*- $\beta$ -hydroxybutyryl phenylalanine (BHB-Phe) is considered a feeding suppressive shunt pathway induced by ketosis. BHB-Phe and Lac-Phe are important regulators of energy homeostasis relevant to weight management in overweight and obesity [101].

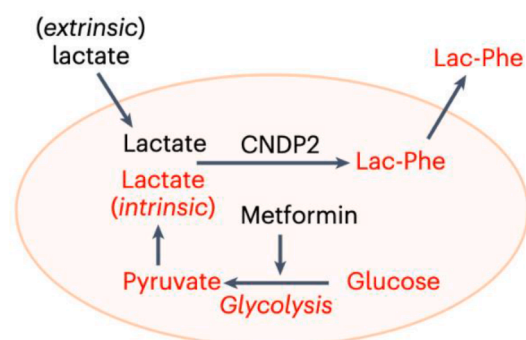


**FIGURE 3.** Illustration of Lac-Phe production pathway. CNDP2 facilitates the production of Lac-Phe from extrinsic lactate and glycolysis-derived lactate in response to metformin treatments. Reprinted with permission from Xiao et al. [96]. CNDP2, cytosolic nonspecific dipeptidase 2; Lac-Phe, *N*-lactoyl phenylalanine.

## Clinical Implications of Physical Inactivity and Reduced Muscle Function

### Correcting metabolic inflexibility

It is well established that physical inactivity contributes to obesity and insulin resistance, and this may be related to differing patterns of skeletal muscle utilization of fatty acids [48,102]. Weight gain and regain after WL are associated with reduced reliance on lipid oxidation, suggesting an inherent impairment in lipid oxidation as a function of obesity [103,104]. As described in the "Mechanisms of exercise and the role of skeletal muscle" section, lean, endurance-trained athletes have a higher mitochondrial respiratory capacity than individuals with obesity, allowing for a shift to whole-body fat oxidation at the expense of carbohydrate oxidation during acute lipid oversupply [75]. These findings support a hypothesis centering on metabolic flexibility as a key driver of the insulin response [48]. Investigators at the symposium presented evidence of changes in the metabolic flexibility of skeletal muscle after WL achieved through diet, exercise, or both.

Lean individuals have a greater baseline degree of lipid oxidation in skeletal muscle compared with individuals with obesity; whereas insulin stimulation increased the muscle's energy expenditure and glucose oxidation in lean individuals, individuals with obesity maintained the same energy expenditure and proportion of lipid-to-glucose oxidation in fasting and insulin-stimulated conditions. This evidence supports the concept that decreased fasted fatty acid metabolism correlates with skeletal muscle insulin resistance [48]. In individuals with obesity, a diet-based WL intervention consisting of a very low-calorie diet, starting at 800 kcal/d without altering physical activity, improved glucose oxidation in insulin-stimulated conditions, but did not affect fasting lipid oxidation [48]. Thus, the WL intervention led to an insulin response resembling more flexible oxidative patterns, despite having a modest effect on fasting fatty acid metabolism [48].

Although WL through caloric restriction improves insulin resistance, it is prudent to distinguish the effects of WL from caloric restriction alone from those of physical activity in addition to diet-induced WL. In a randomized controlled trial (RCT) in older adults with obesity, the effects of diet-induced WL and weight loss with exercise (WLEX) were compared with a control group that received health education with no WL intervention. Controlling for circulating insulin concentrations, only the WLEX group improved insulin sensitivity compared with the control group. However, controlling for WL, neither group significantly changed insulin sensitivity. Given that the WLEX group lost more weight than the WL group, the benefit of exercise on insulin sensitivity cannot be attributed to exercise alone. The exercise intervention, consisting of moderate aerobic and resistance training, preserved muscle strength and lean mass and improved cardiorespiratory fitness, whereas diet-induced WL decreased muscle strength and lean mass (Figure 4). Therefore, WL without exercise offers some benefit to insulin sensitivity, but may impede the recovery of metabolic flexibility and increase the risk of muscle loss [105].

Similar results have been shown in participants assigned an exercise intervention after bariatric surgery. Although bariatric surgery is an effective treatment for obesity and can help patients achieve remission of T2D, many patients regain weight after surgery. A 6-mo moderate aerobic exercise program after bypass surgery improved insulin sensitivity and glucose effectiveness (i.e., the ability of glucose itself to stimulate glucose uptake), compared with a health education control group [106]. Another RCT found dose-dependent effects of

exercise on insulin sensitivity, with improvements correlating with time spent exercising [107]. Participants assigned to low, middle, and high exercise groups all lost weight, but body composition changes were only apparent in the high exercise group. In the same study, exercise was also associated with skeletal muscle mitochondrial performance. Although WL can lead to improvements in insulin sensitivity, only WL coupled with regular exercise could improve mitochondrial capacity and fatty acid oxidation, which may be vital to repair metabolic inflexibility [106,107]. Important considerations of glucagon-like peptide receptor agonists (GLP-1RAs) in WL intervention are discussed in maintaining muscle mass vulnerable to sarcopenia in aging and WL section.

### Assessing sarcopenia and physical function

Given the mechanical, structural, and metabolic functions of skeletal muscle in supporting daily living, maintaining muscle mass is a concern for older adults at risk of sarcopenia, the age-associated loss of muscle mass and function [108,109]. Loss of skeletal muscle mass and functional capacity is expected as early as the fourth decade of life [110], but it can be exacerbated by risk factors such as obesity, WL, physical disability, muscle disuse, malnutrition, and dysfunction of endocrine, immune, and metabolic systems [109–113]. Health complications associated with loss of strength, balance, and movement can reduce quality of life and cause poor health outcomes, including death [114]. Although males have a higher muscle mass relative to body mass than females, it is not clear whether this protects them from sarcopenia [110]. Higher rates of sarcopenia have been reported in females compared with males, but depending on the population sampled and diagnostic criteria, the opposite has also been shown [109,115].

Measuring skeletal muscle mass and functional strength are both integral for identifying sarcopenia. Skeletal muscle mass can be measured using computerized tomography (CT), MRI, or dual-energy X-ray absorptiometry (DXA) [108]. However, the high cost of CT and MRI limits their practicality for large-scale research and routine examinations, and DXA can only estimate soft lean mass by subtracting fat and bone mineral mass from total mass [116]. Therefore, more pragmatic methods of estimating muscle mass, such as ingestion of a D3-creatine tracer and performing a subsequent fasted urine analysis of D3-creatine enrichment, are being developed [116].

Loss of strength and physical performance are also core components defining sarcopenia and are essential for determining susceptibilities to physical function in later life. Common assessments may include handgrip strength, knee flexion and extension, and maximum isotonic and isokinetic arm and leg force. Coordination, aerobic fitness, lung function, and balance may also be included in performance tests [108]. The short physical performance battery is a composite measure of gait, balance, and sit-to-stand ability often used as an outcome in clinical trials due to its robust association with disability and all-cause mortality in older adults [117]. These measures of strength and functionality are also associated with plasma biomarkers of cellular senescence, which accumulate in response to cellular, metabolic, and inflammatory stress throughout life [118].

### Maintaining muscle mass vulnerable to sarcopenia in aging and WL

The severity of age- and weight-loss-associated declines in physical strength can be reduced, prevented, and reversed with targeted interventions. Strength training with a standard 12-wk resistance

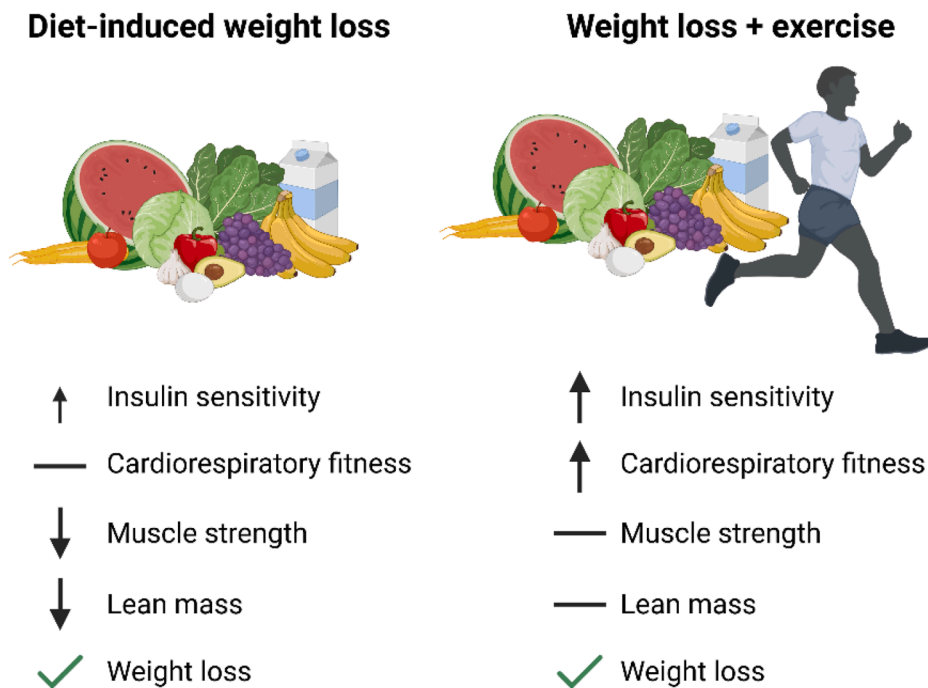


**FIGURE 4.** The effects of weight loss and exercise ( $n = 28$ ) compared with diet-induced weight loss ( $n = 31$ ) compared with healthy controls ( $n = 25$ ) in a study of older adults with obesity [105]. Arrows indicate significant increases and decreases from healthy controls at  $P < 0.05$  as evaluated by analysis of covariance, with baseline value, sex, and age as covariates, followed by pairwise comparisons. Dashes indicate no difference between intervention and healthy control. Both groups achieved similar weight loss.

routine led to increases in thigh and quadricep area, muscle hypertrophy, type I and II muscle fibers, and myofibrillar protein turnover in older males [119]. A larger study including both males and females showed that 12 wk of progressive resistance training improved lower body torque capacity and strength [119,120]. Females susceptible to osteoporosis also show benefits in strength and bone mineral density with high-intensity strength training [121].

WL can exacerbate age-related muscle loss [112]. During dietary WL, 20%–40% of total mass lost is typically fat-free mass [122,123]. Different modalities of exercise have been studied for their potential to improve body composition and functionality in WL. An RCT compared the effects of aerobic, resistance, and combined training programs in dieting older adults with obesity [112]. Six months of aerobic training had the greatest benefit on cardiovascular function, whereas resistance training increased strength. Interestingly, combined training resulted in cardiovascular and strength improvements comparable to the aerobic-only and resistance-only interventions, respectively. Although all interventions led to similar WL, the resistance-only and combined training groups preserved more lean mass than the aerobic-only training group [112].

In further support of the added benefit of exercise training in preserving lean mass during WL, a meta-analysis examined 14 clinical trials comparing body composition outcomes in groups assigned to caloric restriction or caloric restriction plus exercise [124]. The meta-analysis included studies that employed caloric restriction with aerobic, resistance, and/or combined exercise programs. Overall, WL without regular exercise training provides little to no benefit on muscle strength. Aerobic or resistance training both mitigated loss of lean mass and increased loss of fat mass compared with caloric restriction

alone [124]. Another meta-analysis of 6 RCTs tested the effects of caloric restriction with and without resistance training on lean mass loss [125]. Resistance training prevented 93% of the lean mass loss resulting from caloric restriction without affecting total body and fat mass loss [125]. Together, these show that caloric restriction with exercise can preserve muscle mass while promoting WL, a target that diet alone cannot achieve.

There is evidence that high-protein diets ( $>1.2$  g/kg/d) can improve WL and body composition when paired with resistance training [126, 127], but the effects of protein are modest in the absence of exercise and may be age dependent [128,129]. Other evidence shows that loss of lean mass in caloric restriction is correlated with overall energy reduction, and not specifically protein intake [122]. For people taking GLP-1RAs, which facilitate WL by reducing energy consumption, it is particularly important to maintain diet quality with a balanced macronutrient profile to ensure adequate intake [130]. Guidelines emphasize protein and micronutrients as key areas to monitor to promote preservation of lean mass and prevent vitamin deficiencies [130].

Pharmacological interventions for muscle preservation are being developed. Bimagrumab is a monoclonal antibody that blocks the signaling of activin type II receptor (ActRII), preventing the processes that typically inhibit skeletal muscle growth [131,132]. Mechanistically, ActRII inhibition acts on the PI3K/Akt/mTOR signaling axis, a regulator of anabolic processing, to support protein synthesis and muscle growth [133,134]. In a human trial, bimagrumab increased lean mass by 2.7% [90% confidence interval (CI): 0.45%, 5.01%] and reduced total body fat mass by 7.9% (90% CI: –12.5%, –3%) over a 10-wk period in nondieting healthy participants [131]. Bimagrumab

also improved insulin sensitivity by ~20% according to a 2-step hyperinsulinemia-euglycemic clamp protocol [21.8% (90% CI: -8.9%, 62.7%)] in step 1 and 18.2% (90% CI: -7.4%, 50.9%) in step 2], whereas an intravenous glucose tolerance test detected a ~40% reduction in insulin responses to glucose load [AUC0-20 min: -38% (90% CI: -52.6%, -19%)] [131]. A 48-wk phase 2 placebo-controlled study of bimagrumab compared with placebo in patients with T2D similarly found greater increases in lean mass {3.6% [1.70 kg (80% CI: 1.1 kg, 2.3 kg)] compared with -0.8% [-0.4 kg (80% CI: -1.0 kg, 0.1 kg)]} and greater reductions in fat mass {-20.5% [-7.5 kg (80% CI: -8.3 kg, -6.6 kg)] compared with -0.5% [-0.18 kg (80% CI: -0.99 kg, 0.63 kg)]}, waist circumference [-9.0 cm (80% CI: -10.3 cm, -7.7 cm) compared with 0.5 cm (80% CI: -0.8 cm, 1.7 cm)], HbA1c level [-0.76 percentage points (80% CI: -1.05, -0.48 percentage points) compared with 0.04 percentage points (80% CI: -0.23, 0.31 percentage points)], and body weight {-6.5% [-5.9 kg (80% CI: -7.1, -4.7 kg)] compared with -0.8% [-0.8 kg (80% CI: -1.9 to 0.3 kg)]} with bimagrumab [135]. The phase 2 study confirmed earlier reports that bimagrumab causes fat mass loss, increases lean mass, and decreases HbA1c levels, showing that bimagrumab could be a safe and effective method of preserving muscle and improving glycemic control during WL [135].

The ability of ActRII blockade to adjust body composition during GLP-1RA-induced WL was tested in a rodent model of obesity. Mice were maintained on an HFD and treated with either semaglutide (a GLP-1RA), bimagrumab (or IgG1 control), or a combination of semaglutide and bimagrumab for 14 d. Combination treatment resulted in the greatest percent of fat mass loss (~70% with combination treatment compared with ~30% with bimagrumab and ~50% with semaglutide alone) and preservation of lean mass (indistinguishable from the control group) compared with either bimagrumab or semaglutide alone. With semaglutide, lean mass decreased by ~10%, whereas bimagrumab increased lean mass by ~8% and reduced fat mass (Figure 5) [136].

A phase 2b clinical trial (BELIEVE, NCT05616013) of bimagrumab and semaglutide combination therapy has been completed [137]. The randomized, double-blind, placebo-controlled, multicenter trial investigated the effects of bimagrumab alone or with semaglutide in adults with overweight or obesity for 40 wk. The results aligned with the preclinical study, showing that combination treatment yields the greatest benefits in terms of body weight, fat mass, visceral fat, and

inflammation [138]. Combination treatment yielded a 22.1% decrease in bodyweight, 92.8% of which was fat mass. This was more than bimagrumab alone (-10.8% bodyweight) and semaglutide alone (-15.7% bodyweight) [138]. Interestingly, 100% of the weight lost with bimagrumab alone was attributable to fat mass, and there was a 2.5% increase in lean mass. Weight lost with semaglutide alone was 71.8% attributable to fat mass [138]. A clinical trial of bimagrumab in combination with the GLP-1RA tirzepatide was planned (NCT06901349), but has since been discontinued for reasons related to business strategy [139]. Still, with the rise of GLP-1RAs for WL, treatment options are being considered to meet the emerging goal of preserving muscle mass, which may lead to added metabolic and functional benefits [136]. Other options being explored include a monoclonal antibody tevogrumab [140], a corticotropin-releasing factor receptor antagonist COR-1167 [141], and a selective androgen receptor modulator enobosarm [142].

### Effects of exercise on cognitive function and mitigating T2D-related risk of cognitive impairment

The aging population is also faced with cognitive decline and dementia, major causes of disability and death among the elderly globally [143]. Among the modifiable risk factors, physical activity can reduce dementia risk and slow cognitive decline [144–148]. The physiological effects of exercise stimulate neuroprotective pathways that can both prevent and modify the course of cognitive impairment [149]. Blood circulation, neurogenesis, mitochondrial function, and neurotrophic factors are major contributors to cognitive protection [150].

Physical activity has acute and long-term benefits on the circulatory system [151], including blood flow to the brain [152]. Increasing regional cerebral blood flow allows efficient passage of nutrients across the blood–brain barrier [152,153]. Specifically, animal studies suggest that exercise increases blood flow to the hippocampus, a major brain region involved in learning and memory [154]. Cardiovascular fitness and physical activity are associated with greater white matter structure, functional grey matter health, and cognitive performance in older adults with mild cognitive impairment [150,155–157].

Exercise training promotes mitochondrial biogenesis, antioxidant capacities, energy production, and mitochondrial affinity for oxygen in the skeletal muscle [158,159], animal studies suggest that this

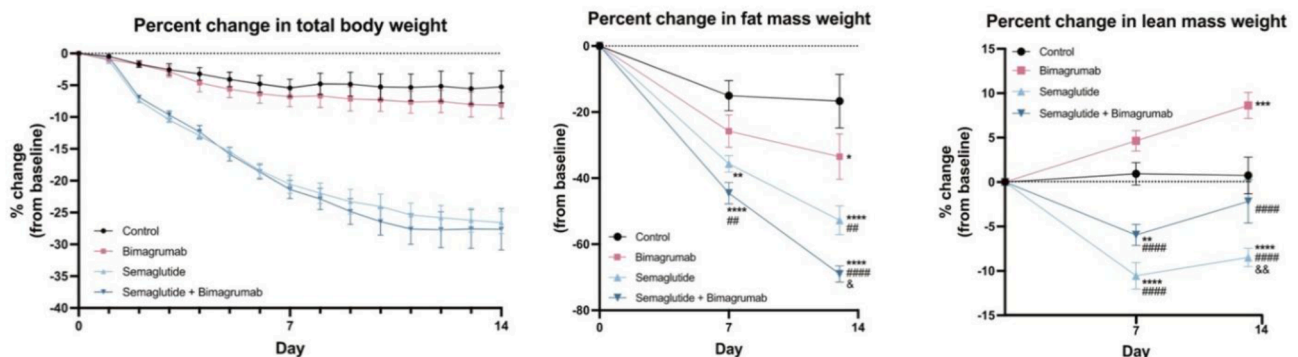


**FIGURE 5.** Changes in total body weight, fat mass, and lean mass with bimagrumab, semaglutide, or combination therapy. Combination bimagrumab + semaglutide led to the greatest reductions in fat mass while preserving lean mass. Data were analyzed using 2-way ANOVA followed by Tukey's multiple comparisons.  $n = 3$  mice per group for days 1–4;  $n = 2$  for control group;  $n = 3$  for semaglutide, bimagrumab, and semaglutide plus bimagrumab groups for days 5–12. \* $P < 0.05$ , \*\* $P < 0.001$ , \*\*\* $P < 0.0005$ , \*\*\*\* $P < 0.0001$  for control vs. bimagrumab, semaglutide, and semaglutide + bimagrumab; # $P < 0.05$ , ## $P < 0.001$ , ### $P < 0.0005$ , #### $P < 0.0001$  for bimagrumab vs. semaglutide and semaglutide + bimagrumab; and  $P < 0.05$ , and  $P < 0.001$  for semaglutide vs. semaglutide + bimagrumab. Adapted and reprinted with permission from Nunn et al. [136]. ANOVA, analysis of variance.

evidence may extend to mitochondria in the brain [160]. Further small animal studies suggest that improved mitochondrial function may contribute to downregulation of amyloid- $\beta$  in the hippocampus, which has implications for mitochondrial dysfunction contributing to Alzheimer's disease [161]. In human and animal studies, exercise-induced myokines upregulate circulating neurotrophic factors, including morphology and synaptic plasticity [154,162–164]. Similar associations between brain-derived neurotrophic factor and insulin-like growth factor and exercise have been shown in the brain and blood in animal models [154]. The passage of neurotrophic factors across the blood–brain barrier depends on efficient blood flow, demonstrating the interconnected nature of these molecular determinants of cognitive decline [154,165].

Aerobic training has the most robust evidence in support of its reduction of dementia risk [149,166–168]. Different exercise types may have a greater effect depending on the cause of dementia, time spent training, adherence, and intensity [169–172]. Meta-analyses of RCTs suggest that aerobic exercise is more beneficial than nonaerobic interventions in elderly patients with dementia, including Alzheimer's disease, and for those with genetic risk for Alzheimer's disease [169, 173]. In contrast, a meta-analysis of RCTs of resistance, aerobic, or multicomponent training in patients with all-cause dementia did not find a mediating effect of the type, duration, or intensity of exercise on improved cognitive function, but greater adherence was a significant predictor of improved cognitive function [171].

T2D is an additional risk factor for cognitive impairment and dementia/Alzheimer's disease [174]. Glycemic control and weight management reduce the risk of complications with T2D [175–177], but whether these interventions can reverse the risk of cognitive impairment incurred by T2D is not known. To address this gap, the Look AHEAD study (NCT00017953) measured cognitive function in participants with T2D assigned an intensive lifestyle intervention or diabetes support and education [178]. Across both interventions, improved glycemic control was correlated with improved cognition. Importantly, the participants' history of cardiovascular disease and obesity at baseline determined whether WL and physical activity were associated with cognitive improvements. Individuals with baseline cardiovascular disease and lower baseline weight (overweight without obesity) were most likely to benefit from WL, improved glycemic control, and physical activity. With these results and the mixed literature on the effects of specific types and intensities of exercise, individual characteristics must be considered to optimize the benefits of lifestyle changes [178].

### Multigenerational effects of exercise

The prenatal and perinatal environment is associated with metabolic function, T2D, and obesity in future generations [179]. Exercise during pregnancy is beneficial for the mother, preventing hypertension and excessive weight gain while supporting healthy birth weight [180]. Studies in humans and rodents show metabolic consequences of maternal overnutrition and undernutrition that can manifest in offspring during childhood or adulthood [179,180]. In mice, HFD during pregnancy impaired glucose tolerance, increased insulin concentrations, and increased body fat in offspring as they age, but these were prevented with maternal exercise [181]. Maternal exercise during pregnancy also mitigates the effects of HFD on offspring liver function [182]. Whereas offspring of sedentary HFD dams had increased basal hepatic glucose production, offspring of exercise-trained HFD dams were protected from liver dysfunction, and these improvements were observable before other metabolic improvements and glucose

tolerance [182]. In mice, maternal exercise in the parent generation (F0) improves liver metabolic functioning, insulin concentrations, glucose tolerance, and fat mass in both the first (F1) and second (F2) generation offspring [183]. These effects are maintained regardless of HFD exposure and without any intervention in F1 (Figure 6) [183].

The placenta is a crucial interface between mother and fetus, transmitter of signals, and regulator of placental endocrine factors [184,185]. Some of the metabolic and physiologic benefits of exercise are transmitted from pregnant mothers to offspring through placental superoxide dismutase 3 (SOD3) signaling. SOD3 is an antioxidant protein found at higher levels in the placenta and serum of active pregnant females and the placenta and serum of trained pregnant mice [185,186]. Exercise-induced SOD3 production regulates liver functioning by activating the AMPK-Tet pathway in the offspring liver, an effect that can be mimicked with SOD3 treatment in hepatoblasts. The upregulation of placental superoxide dismutase 3 (*Sod3*) gene expression by exercise is promoted by vitamin D through vitamin D receptor signaling. A series of experiments described in Kusuyama et al. [185] demonstrate the effects of exercise-induced placental SOD3, its regulation by vitamin D, and its contribution to improved glucose homeostasis in offspring.

## Individual Variability and Personalized Medicine

### Examining T2D risk and exercise effects with high-frequency monitoring data

Within clinical populations of interest, molecular patterns in individuals and cohort-wide changes over time can identify correlates of early stages of disease and relative risk [38]. High-throughput multiomics profiling provides comprehensive metrics that can be correlated with individual characteristics and health outcomes, including age and disease status. Multiomics profiling has also been applied to the study of T2D and prediabetes using high-volume and high-frequency sampling via blood panels, microsampling, and wearable devices [38,187,188]. This approach provides a roadmap for understanding individual risk factors for metabolic disorders and how exercise can augment risk.

These analyses can also help distinguish typical patterns of healthy aging by characterizing immune response profiles, composition of the gut microbiome, muscle mass, lipid metabolism, and hormones across the lifespan [40,189]. Together, genomic, proteomic, and metabolomic studies in healthy and clinical populations reveal biological patterns associated with specific characteristics. The emergence of wearable devices provides detailed, real-world data relevant to smaller-scale variations in individual characteristics.

The ubiquity of wearable devices allows for in-depth tracking of individuals over time. Wearable devices have been used in a range of clinical contexts, including detecting infection [190], identifying early glucose dysregulation [188], and monitoring cardiovascular health [191]. Analyses can be large-scale or granular. For example, deep molecular changes were measured in a single participant using integrative personal omics profiling (iPOP) as they transitioned to diabetes [192]. In a more expansive study in 106 healthy or prediabetic participants over 4 y, iPOP found distinct personal baseline characteristics and multiomic differences between insulin-resistant and insulin-sensitive individuals [38]. Larger-scale studies have further revealed risk factors associated with age-related chronic illness based on whole genome sequences, clinical tests, metabolomes, proteomes, microbiomes, and daily activity tracking [38,193,194].

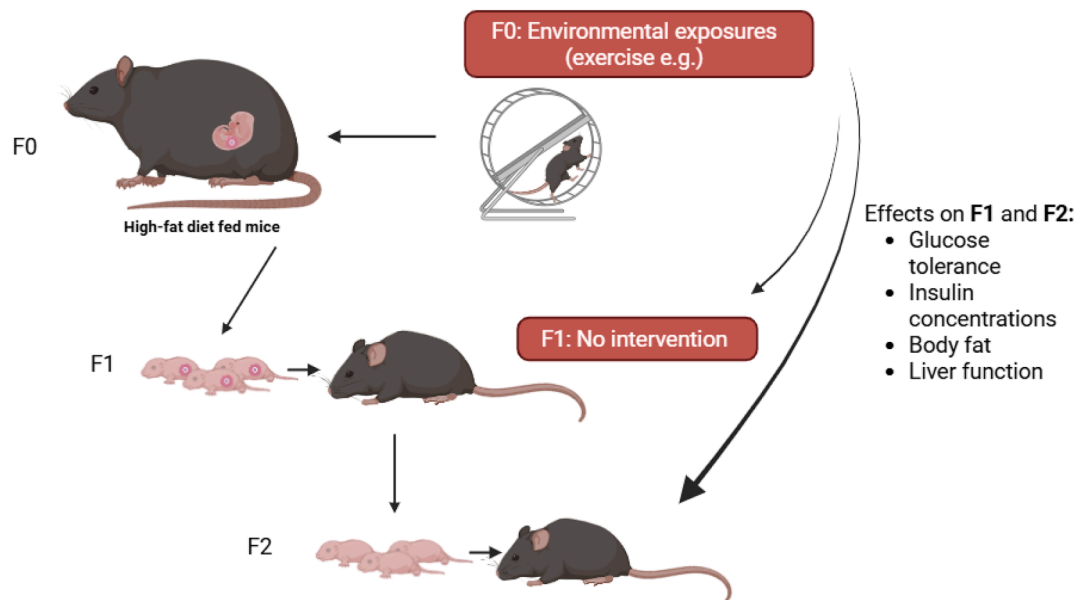


**FIGURE 6.** Illustration of intergenerational effects of F0 environment on subsequent generations. Treadmill running in pregnant F0 dams prevents the negative effects of high-fat diet on glucose tolerance, fasting insulin concentrations, body fat, and liver function in F1 and F2 offspring. F0, parent generation; F1, first generation; F2, second generation.

In a longitudinal study, 109 participants who were at risk for T2D were profiled through quarterly clinical laboratory tests and multiomics assessments [39]. Participants' T2D status and cardiovascular risk factors were recorded and monitored, and multiomics analyses were generated with samples taken every 3 mo. Continuous physiology and activity data were tracked with an activity-monitoring watch and a continuous glucose monitoring (CGM) system. Combining the rich iPOP dataset from the longitudinal glucose metabolism data with the multiomics profiles, trajectories of T2D were associated with multiomics measures. Metabolomics clustering revealed associations between glucose disposition index and glycerolphospholipids, phingolipids, free fatty acids, and androgenic steroids. Underlying relationships between glucose and inflammation were analyzed, revealing expected relationships between HbA1c, fasting plasma glucose, and glucose homeostasis markers, as well as high-sensitivity C-reactive protein associations with other inflammatory proteins. A dynamic analysis found changes in glucose measures and inflammation related to complement activation, innate immune system activation, and oxidative damage. The study revealed 67 health discoveries related to metabolic, cardiovascular, and oncologic pathophysiology based on multiomics molecular pathways [39].

Hall et al. [188] report a novel approach to identifying prediabetes and risk of progression to T2D using personalized data from CGM. This approach may improve the diagnosis of T2D with HbA1c or single blood glucose concentration measurements alone, which fail to capture the nuances of glycemic patterns. Developing a comprehensive measure of glycemic variability, a critical aspect of diabetes identification and management, lends the ability to classify patients and determine optimal treatments based on individualized characteristics. With spectral clustering of glycemic signatures from CGM data, distinct glycemic profiles, or "glucotypes," were defined by their degree of glucose variability. Glucotypes correlated with metabolic measures of glucose homeostasis, including HbA1c, oral glucose tolerance test, steady-state plasma glucose, BMI, and age. Glucotypes could also predict the response to standardized meals of differing nutritional qualities, diabetic/prediabetic diagnosis, and measures of

insulin metabolism and glucose response. Defining 3 distinct glucotypes (low, moderate, or severe glucose variability) using continuous at-home monitoring data provides a realistic estimate of daily glucose fluctuations, which may be more informative than traditional tests. This has the potential to be a powerful diagnostic aid in identifying early T2D and prediabetes [188]. Similarly, biological omics data can be linked with age to find specific molecular aging differences. Another study incorporated insulin status to make molecular aging comparisons between insulin-resistant and insulin-sensitive participants. Between individuals, omics data revealed personal age-dependent markers, demonstrating individual differences despite common age-wide changes [40].

Distinct metabolic profiles may be associated with specific food group sensitivities and responses to exercise, meals at different times of day, and nutritional makeup (Park, Metwally, et al. unpublished data) [187]. Given that responses to food vary based on the epigenome, metabolome, and other regulators, Shen et al. [187] characterized metabolite, lipid, cytokines, and hormone responses to a nutrition shake using self-drawn blood microsamples of participants at several time points after consumption. Metabolic scores were derived from the carbohydrate, lipid, free fatty acid, protein, insulin secretion and cytokine responses to the nutrition shake. Hierarchical clustering of metabolic scores resulted in 5 distinct groups based on their similarities in these domains. For example, 1 group was characterized by higher average fat and amino acid responses compared with other groups. Despite each group internally correlating on metabolic measures, there was immense heterogeneity in individual responses, even within groups. For example, 1 participant had a considerably lower fat and amino acid response compared with the group average. This information is applicable to individualizing diet modifications. Lifestyle data were collected from the same cohort using wearable devices to track heart rate, sleep, and activity. Many correlations were revealed between lifestyle factors, physiological status, and molecular changes. Clusters in the metabolic panel were related to circadian patterns, and 447 molecules, primarily lipids, were associated with lifestyle metrics. These multiomics relationships reflecting internal processes and

behavioral patterns demonstrate the utility of continuous monitoring to provide insight into one's health status [187].

### Leveraging circadian clocks to optimize training

In humans, respiration, energy expenditure, muscle force output, and skeletal muscle mitochondrial oxidative capacity follow a diurnal rhythm [195,196]. Behavioral and environmental cues can disrupt body-wide circadian rhythms and lead to metabolic dysfunction [197]. The circadian clock is a 24-h transcriptional feedback loop, with clock circadian regulator (CLOCK) and basic helix-loop-helix ARNT-like 1 (BMAL1) proteins transcriptionally activating *Cryptochrome* (*Cry1–2*) and *Period* (*Per1–3*) genes, which in turn encode proteins that repress CLOCK and BMAL1 [197]. The clock mechanism is conserved between humans and mice, with daily fluctuations in gene expression corresponding to rest and active periods. The core clock transcription factors are consistent across tissues, but unique clock-controlled genes (CCGs) expressed in specific tissues regulate their distinct processes. In skeletal muscle, rhythmic transcription of CCGs contributes to daily muscle maintenance and myokine secretion [197].

Exercise has been proposed to be an environmental time cue, or zeitgeber, which can shift circadian clock rhythms. Flexibly shifting the circadian clock with exercise has the potential to promote metabolic health, as demonstrated by clinical outcomes of different time-of-day exercise routines [198–201]. For example, afternoon and evening exercise was shown to be favorable for reducing HbA1c and insulin resistance in T2D compared with morning exercise, and morning or afternoon exercise was more effective than unscheduled exercise [198–201]. Therefore, understanding the mechanisms of beneficial time-of-day training may inform clinical applications.

In mice, repeated, scheduled exercise training during zeitgeber time 4–6 (4–6 h after lights turn on, or midday) over 4 wk induced a phase advance of muscle clock gene expression in skeletal muscle and lung tissue [202]. Exercise-trained mice also showed a substantial increase in rhythmically expressed genes compared with sedentary mice [203]. In skeletal muscle, many of these genes are involved in carbohydrate and lipid metabolism, some through regulation of the central clock gene BMAL1 [203]. In addition to chronic exercise, a single 60-min bout of treadmill running was able to shift the muscle clock phase in mice, dependent on the time of exercise [204].

These studies provide evidence that scheduled exercise can impact the muscle clock and its molecular outputs. This supports the application of scheduled exercise, particularly in the afternoon, as an intervention to support circadian clock alignment across the body capitalizing on daily muscle rhythms as an emerging recommendation for metabolic disorders [195,201,205].

### The complexities of prescribing exercise as medicine

Exercise, with multiple health benefits clearly established, may be considered a form of medicine to treat and prevent disease. As with other therapies, it is important to understand how different specifications of the treatment influence outcomes. For exercise, the “prescription” often includes frequency (number of sessions), duration (time), type (cardiorespiratory or resistance), volume (intensity/load  $\times$  time/repetitions), progression (gradual increase in exercise stress), and intensity [206]. Intensity is difficult to describe objectively, but can be defined by metabolic thresholds marking detectable changes in metabolism. Metabolic thresholds usually correspond with changes in blood lactate, ventilatory parameters, oxygen consumption, and carbon dioxide output. Although exercise intensities are also often

defined by a percentage of a fixed maximum value [e.g., maximum heart rate (HR<sub>max</sub>), rate of oxygen consumption (VO<sub>2max</sub>)], people experience different cardiorespiratory and metabolic stress when exercising at a specific percentage of their HR<sub>max</sub> or VO<sub>2max</sub>. This caveat must be considered when evaluating responses to prescribed exercise intensities.

Measuring mitochondrial adaptations in response to exercise variables may reveal the characteristics important for prescribing exercise in specific clinical contexts. For example, mitochondrial volume density (MitoVD) and citrate synthase (CS) activity, an indirect biomarker of mitochondrial content, are correlated with training volume [207–209]. When training volume is low-to-moderate, MitoVD increases with volume, but there is a plateau in MitoVD at higher training volumes, suggesting an upper limit to the advantages gained from high-volume training (Figure 7A and B) [207].

Conversely, the relationship between exercise intensity and changes in MitoVD and CS activity is not linear. High-intensity exercise, defined by relative workload related to VO<sub>2max</sub>, induces greater changes in MitoVD and CS activity, but only when the statistical comparison group is very low-intensity exercise. Therefore, MitoVD and CS activity may only be sensitive to the extremes of exercise intensity [206–209]. The greatest adaptations in mass-specific mitochondrial respiration typically occur with high-volume, high-intensity cardiorespiratory training compared with low-, moderate-, and very high-intensity exercise [206,210,211]. Very high-intensity exercise can benefit mitochondria-specific respiration only if performed for very short periods (i.e., sprint interval training) [208,212,213]. Therefore, the greatest benefit in mass-specific mitochondrial respiration may be achieved with a balance of intensity and volume (Figure 7C) [208].

Ongoing research is investigating the pathways controlling the differential effects of exercise intensity and volume on mitochondrial adaptations [214]. However, from the available data, it appears that different volumes and intensities of exercise produce unique homeostatic disturbances that drive unique signaling pathways [86]. More research is required to discover the unique stress signals responsible for the divergent mitochondrial adaptations to different exercise prescriptions.

### Exercise mimetics: pros and cons of pharmacologic intervention

The application of molecular techniques to exercise biology has provided greater understanding of the mechanistic bases of skeletal muscle bioenergetics and metabolism and has stimulated scientific and commercial interest in the identification of bioactive oral compounds that mimic or potentiate the effects of exercise, so-called “exercise pills” or “exercise mimetics” [215]. Despite WHO guidelines for physical activity and warnings about sedentary behavior, the ability to adhere to consensus-based recommendations is not universal, and exercise mimetics may help in this regard [3,216]. The idea of taking a pill (or pills) to acquire the benefits of exercise in the absence of physical movement and energy expenditure has mass appeal for many sedentary individuals who, for a variety of reasons, do not obtain sufficient physical activity to improve their general health. Although there is a great degree of variability in how individuals respond to exercise, there are relatively few people who fail to benefit entirely [217]. However, for people who cannot attain adequate physical activity, either due to physical disability or perceived barriers such as lack of time, pharmacologic interventions may be a useful alternative [218,219].

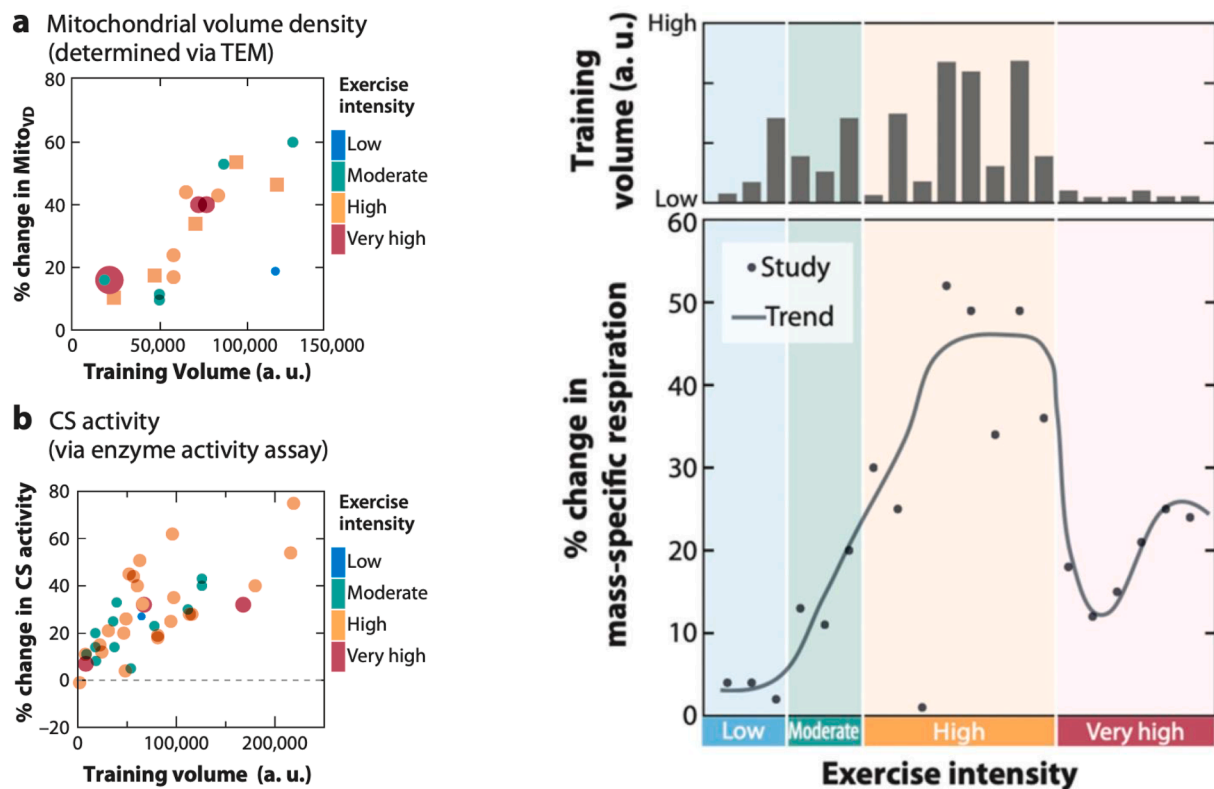


**FIGURE 7.** Effects of training volume and exercise intensity on mitochondrial volume density (Mitov<sub>D</sub>) and changes in citrate synthase (CS) activity. The relationship between training volume, intensity, and (A) change in mitov<sub>D</sub>, (B) change in CS activity, and (C) change in mass-specific respiration. For (A) and (B), colors correspond to intensity zones and the area of the shapes is proportional to the training intensity. For (C), each point represents an individual study, and the solid line represents the trend of the relationship between exercise intensity and change in respiration. Adapted and reprinted from Bishop et al. [209] as permitted under the Creative Commons Attribution 4.0 International License. au, arbitrary units; Mitov<sub>D</sub>, mitochondrial volume density; TEM, transmission electron microscopy.

To date, the majority of compounds have typically targeted skeletal muscle in an attempt to stimulate some of the adaptations to exercise induced by endurance-based training. As such, they fail to impart many of the broad health-protecting effects of exercise that are seen in tissues and organs other than skeletal muscle. Indeed, 2 of the most notable exercise mimetics in clinical development, PPAR $\delta$  and AMPK agonists, are known for their effects on enhancing endurance capacity. PPAR $\delta$  is abundant in skeletal muscle and regulates fiber-type determination, mitochondrial function, lipid metabolism, and fatigue resistance [220,221]. In transgenic mice, overexpression of PPAR $\delta$  in skeletal muscles increased oxidative muscle fibers and enhanced running endurance [222]. Combined with exercise training, mice treated with the PPAR $\delta$  agonist GW1516 were able to run longer and further than untreated mice [223]. AMPK is a mediator of cellular metabolism and, in skeletal muscle, regulates muscle fiber-type shift and adaptations in response to training [224,225]. 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) is an AMPK activator with exercise-mimicking effects found in sedentary mice, including mitochondrial biogenesis and fatty acid oxidation, along with improved running endurance [223,226]. Recreating the effects of exercise- and fasting-induced lactate and ketone body production has also been a target of drug development. A low molecular weight ester, LaKe, converts to its constituents (S')-lactate and (R')-BHB and thus mimics postexercise conditions, including an increase in Lac-Phe, which suppresses appetite and feeding in rats [227].

On the basis of the multiplicity of human systems impacted by exercise and the influence of genetic and environmental factors, some

experts advocate for a tempered expectation that a single treatment could reproduce the complex effects of exercise [228]. A major limitation of exercise mimetics is their evasion of the principles of skeletal muscle hypertrophy and progressive overload [229]. Endurance and resistance training both promote adaptive improvements and growth with progressive training—endurance training for cardiac volume hypertrophy, and resistance training for muscle fiber size and strength. Muscle tension is required to achieve increases in the rate of protein synthesis, and the adaptations to increasing training loads cannot currently be reproduced with pharmacologic intervention [230]. There is also a question as to whether a comprehensive mimetic would be feasible or desirable. The reductionist approach to exercise mimetics that attempt to target a single molecule or pathway ignores the complexity of the body's homeostatic response to exercise in a real-world context. The idea of a "Polypill" with multiple compounds has been proposed to reduce cardiovascular risk from several mechanistic angles simultaneously. If such a treatment regimen were developed to, at best, partially mimic the effects of exercise, issues with tolerability, adherence, and financial burden would likely arise.

In conclusion, the complex dynamics between physical activity and skeletal muscle metabolism have broad implications for the prevention of metabolic disorders, prolonging healthful years, preserving cognition, and optimizing everyday habits to maximize benefits. The 2025 Harvard Nutrition and Obesity Research Center Symposium highlighted critical advances in this field of research. Speakers examined the mechanisms regulating exercise-induced changes in skeletal muscle and across 'omes; clinical applications related to disease,

aging, and cognition in individuals and across generations; and considerations for precision medicine and pharmacological development. For example, research supports the crucial role of exercise in maintaining healthy insulin responses, mitochondrial capacity, metabolic flexibility, and cognition, whereas resistance training is specifically important for maintaining muscle mass in aging and WL. In terms of future treatments, exercise-induced EVs and the nutrient-responsive metabolite Lac-Phe were presented as important regulators of metabolism and energy homeostasis that may be promising targets for future study. Overall, the breadth of topics presented demonstrated the nuance of exercise's role in health. Initiatives like MoTrPAC, which built an evolving platform to collaboratively investigate large-scale translational and clinical data, will help further our understanding of the molecular response to exercise and inform individualized treatment targets. The topics presented here are foundational for future research investigating behavioral and pharmacological approaches contributing to improved health and disease prevention.

### Author contributions

The authors' responsibilities were as follows – LC: wrote the initial draft and edited the manuscript; EAL, TLS, JW, SKG: edited the manuscript and authorized final approval; RB, LTF, JSG, MSH: moderated the symposium; DJB, OC, KAE, MAF, RAF, BHG, LJG, JAH, SBH, MEL, JZL, MPS, MW: presented at the symposium; and all authors: read, edited, and approved the final manuscript.

### Declaration of Generative AI and AI-assisted technologies in the writing process

No generative AI tools were used in the preparation of this manuscript.

### Conflicts of interest

LC reports no relevant disclosures. EAL receives grant support and research study drug from Tonix Pharmaceuticals and receives royalties from UpToDate. EAL and/or immediate family member holds/recently held stock in Thermo Fisher Scientific, Zoetis, Danaher Corporation, Intuitive Surgical, Merck, West Pharmaceutical Services, Gilead Sciences, and Illumina. EAL is an inventor on PCTUS2025/030536 entitled, "Oxytocin-based therapeutics to improve cognitive control in individuals with attention deficit hyperactive disorder" filed on 22 May, 2025. TLC reports no relevant disclosures. JW reports no relevant disclosures. RB reports advisory fees from Novartis, BetterLife Inc, and Parameter Health unrelated to the current work. RB was funded by the Harvard Catalyst K12 Award (K12TR004381-01) and the Sarnoff Cardiovascular Research Foundation Scholar Award. DJB reports no relevant disclosures. OC received research funding from Eli Lilly Corp and the NIH. KAE reports no relevant disclosures. MAF is a coinventor of IC7Fc and hold patents for this molecule (US 60/920,822; WO/2008/119110 A1). MAF is a Founder and shareholder of Celesta Therapeutics. MAF is Founder and Shareholder of Calmodulus Therapeutics. MAF is on the Scientific Advisory Board of Gallant Bio. RAF serves on the scientific advisory board for Biohytis, Epirium Bio, Entelo Bio, Inside Tracker, Rejuvenate Biomed, Cytookinetics, and Amazentis. RAF has consulting roles with Merck, and Novo Nordisk. LTF serves as a consultant to Theratechnologies, Chiesi Farmaceutici, and Rhythm Pharmaceuticals; receives grant funding to her institution from Chiesi Farmaceutici and Rhythm Pharmaceuticals outside of this work; and receives in-kind support (study drug) for a research study from Theratechnologies. BHG

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