

## Review

# Understanding the variation in exercise responses to guide personalized physical activity prescriptions

John Noone,<sup>1,2</sup> Justine M. Mucinski,<sup>1,2</sup> James P. DeLany,<sup>1</sup> Lauren M. Sparks,<sup>1</sup> and Bret H. Goodpaster<sup>1,\*</sup>

<sup>1</sup>Translational Research Institute, AdventHealth, Orlando, FL 32804, USA

<sup>2</sup>These authors contributed equally

\*Correspondence: [bret.goodpaster@adventhealth.com](mailto:bret.goodpaster@adventhealth.com)

<https://doi.org/10.1016/j.cmet.2023.12.025>

## SUMMARY

Understanding the factors that contribute to exercise response variation is the first step in achieving the goal of developing personalized exercise prescriptions. This review discusses the key molecular and other mechanistic factors, both extrinsic and intrinsic, that influence exercise responses and health outcomes. Extrinsic characteristics include the timing and dose of exercise, circadian rhythms, sleep habits, dietary interactions, and medication use, whereas intrinsic factors such as sex, age, hormonal status, race/ethnicity, and genetics are also integral. The molecular transducers of exercise (i.e., genomic/epigenomic, proteomic/post-translational, transcriptomic, metabolic/metabolomic, and lipidomic elements) are considered with respect to variability in physiological and health outcomes. Finally, this review highlights the current challenges that impede our ability to develop effective personalized exercise prescriptions. The Molecular Transducers of Physical Activity Consortium (MoTrPAC) aims to fill significant gaps in the understanding of exercise response variability, yet further investigations are needed to address additional health outcomes across all populations.

## INTRODUCTION

Exercise, which is structured, intentional, repetitive activity aimed at improving physical fitness, provides a potent stimulus for physiological adaptations to multiple systems throughout the body, irrespective of age, sex, socioeconomic, or disease status.<sup>1–4</sup> These positive, integrative effects of exercise significantly impact overall disease risk, pathobiology, health status, and outcomes. Further, they can be modified by exercise modality, frequency, intensity, length of each exercise session, and duration of training—factors that have been discussed in detail previously.<sup>5</sup>

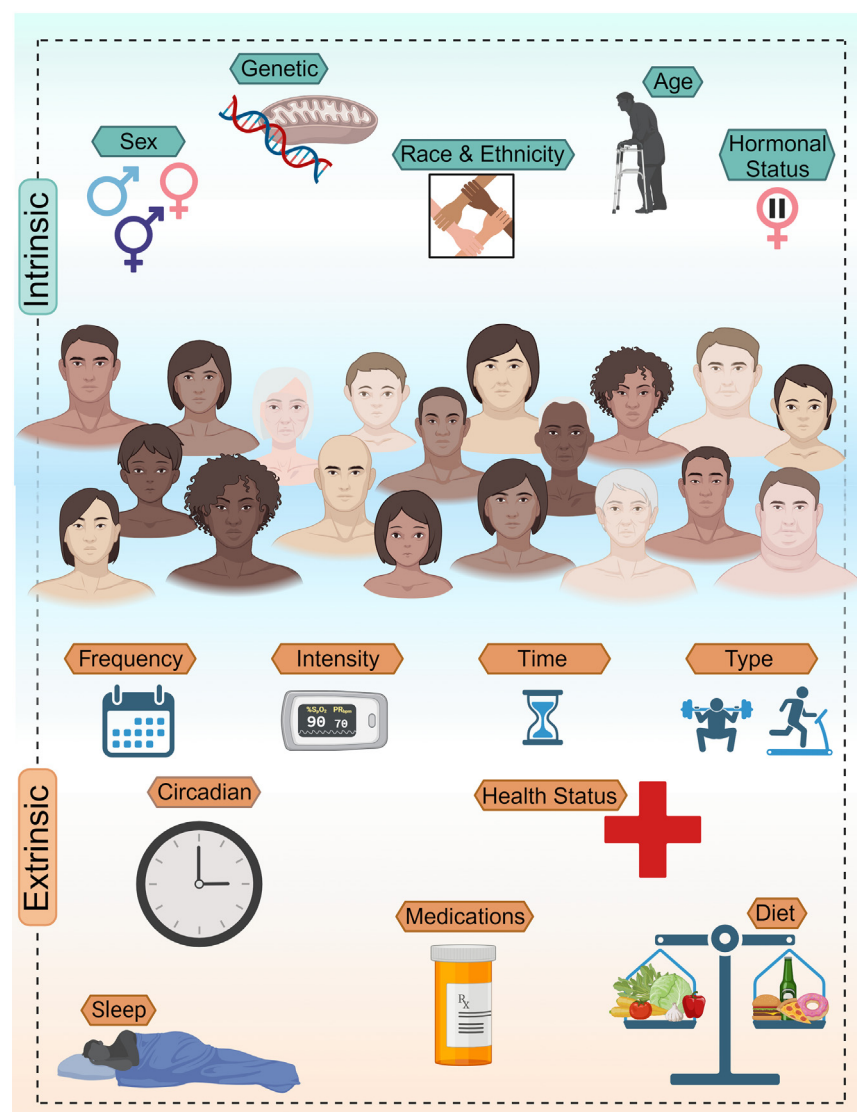
Our knowledge of the effects—and benefits—of exercise is largely based on typical, average responses, usually inferred from small sample sizes, with narrowly defined or prescribed exercise stimuli with limited outcomes. Although most of the literature focuses on aerobic exercise, which is reflected in this review, both aerobic (dynamic activities, involving large muscle groups, resulting in substantial increases in heart rate and energy expenditure) and resistance (activities to increase muscular strength, power, and endurance) exercise are discussed throughout. Studies in previously sedentary (prolonged sitting/reclining in the absence of bodily movement) or inactive (not meeting physical activity [PA] guidelines) individuals are also included. Responses to exercise are dependent on a myriad of factors, including extrinsic (e.g., environment) and intrinsic (e.g., sex, age, and race) influences, as well as the general components of exercise training (Figure 1). Yet, no single study can comprehensively assess all parameters determining exercise response variability. An essential goal is to identify

and implement effective personalized exercise programs suited to the individual according to their practical circumstances, conditions, and personal goals. To accomplish this, we first need to understand the causes of exercise response variation, specific to the desired health outcomes. The purpose of this review is to present evidence of key molecular and mechanistic factors that influence response to exercise and associated health outcomes so that we can eventually and successfully implement personalized exercise as medicine to improve health.

The documented health benefits of exercise include improvements in cardiorespiratory fitness (CRF), strength, physical function, energy expenditure, metabolism, body composition, and mitigation of disease risk.<sup>6–8</sup> However, it is well recognized that these physiological and phenotypic responses to exercise are highly variable and significantly depend on the outcome of interest. Variations in the physiological responses to exercise can occur for specific outcomes, such that one outcome may significantly improve within an individual, whereas another may not change or even worsen in the same individual (Figure 2). Before we consider the intrinsic and extrinsic factors that drive exercise response variability, we present various exercise-associated outcomes relevant to health and disease, each of which possesses a specific response variation, and examine the molecular changes that play a role in the exercise response variation.

## CRF

Given the importance CRF has in public health,<sup>10</sup> understanding its response variation is vital. CRF is perhaps the most-studied



**Figure 1. Intrinsic and extrinsic factors contributing to individual response variability**

Responses to exercise are dependent on a myriad of factors, including intrinsic and extrinsic influences as well as the general components of exercise training. Intrinsic or endogenous factors include sex, genetics, race and ethnicity, age, and hormonal status. Extrinsic or exogenous factors can include the exercise frequency, intensity, time (duration), and type along with environmental factors like circadian rhythms, sleep, health status (and history), medication use, and diet. Each of these factors will play distinct and additive roles in an individual's response to exercise, thereby complicating the understanding of interindividual variation. These factors further complicate the development of personalized exercise prescriptions and ultimately should be considered when designing sophisticated studies to understand individual exercise response variation.

ability).<sup>9</sup> Identification of non-responding individuals remains ambiguous due to a lack of consensus on quantification of individual response variability to exercise. However, some evidence suggests that increasing exercise dose may abolish individual CRF non-response to exercise training.<sup>23</sup>

### Body composition and energy expenditure

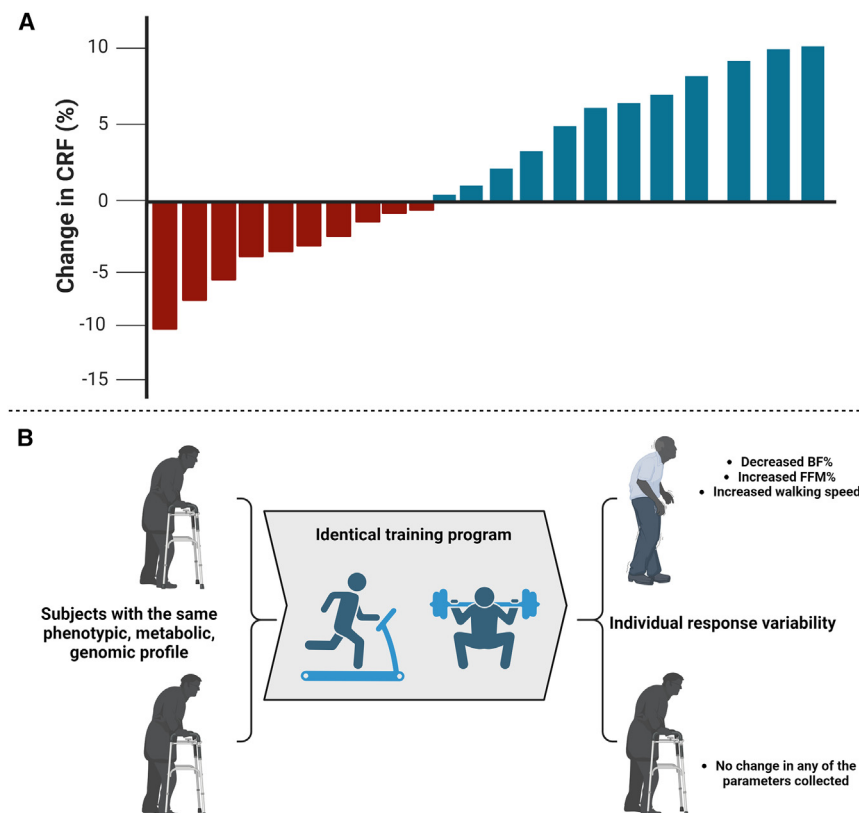
Exercise can alter body composition,<sup>24,25</sup> and like CRF, these changes are highly variable. Exercise can reduce body weight in men and women with obesity, perhaps related to different effects on energy expenditure, energy intake, and subjective hunger.<sup>26,27</sup> Indeed, these effects on weight and body fat remain after adjustments for net exercise energy

phenotype and clinically relevant outcome with regards to response variation, primarily due to its strong associations with all-cause mortality.<sup>11</sup> To date, studies specifically designed to explore response variability in CRF (i.e.,  $\text{VO}_2\text{max}$ ) report significant heterogeneity across various cohorts, supporting the heritability of CRF.<sup>12</sup> Assessing the biological variability in CRF, like any other outcome, depends on the compliance and adherence to exercise, the duration of the exercise program, exercise intensity, volume, and other factors including baseline CRF.<sup>13–18</sup> Investigating the exercise response variability in CRF has highlighted a key controversy as to whether some individuals truly do not respond, or rather, whether this is merely part of the response variation. This phenomenon, termed “non-response,” was defined by Sisson et al. and Chmelo et al. as a change by  $\leq 0$  L/min,<sup>19,20</sup> whereas Pandey and colleagues define it as a change of  $<5\%$ ,<sup>21</sup> whereas others attribute non-response to day-to-day variability.<sup>22</sup> Ross and colleagues defined non-response as a change in  $\text{VO}_2\text{max}$  by less than one technical error (TE, a combination of measurement error and day-to-day vari-

expenditure and changes in energy intake.<sup>28</sup> Murine studies point to a genetic contribution for such response variation,<sup>29,30</sup> and body composition and sex only account for a small portion of exercise-induced weight loss, reduction in adiposity, and energy consumption.<sup>31</sup> The variation in body weight, food intake, and energy balance produced by exercise in humans, however, remains to be determined.

### Cardiovascular and metabolic disease risk

Exercise significantly improves cardiometabolic disease risk and health status across adult lifespan. Either alone or in combination with weight loss, exercise improves insulin sensitivity and cardiometabolic disease risk in adults with obesity.<sup>32–34</sup> The HERITAGE family study reported significant improvements in outcomes relating to insulin sensitivity without weight loss following 20 weeks of endurance exercise in healthy, sedentary subjects.<sup>35</sup> The variation in cardiometabolic disease risk factors in response to exercise, however, is common. For example, improvements in glucose homeostasis and insulin



**Figure 2. Interindividual variability in exercise training response**

(A) Graphical representation of hypothetical data within a waterfall plot illustrating interindividual variability with respect for change in cardiorespiratory fitness (CRF) following exercise training. Adapted from Ross et al.,<sup>9</sup> red columns represent a negative response in CRF to exercise training compared with baseline. Blue columns represent an increase in CRF to exercise training compared with baseline.

(B) Representation of interindividual response to identical exercise programs. Comparable subjects in respect to age, sex, race, phenotypic, metabolic, and genotypic profile complete identical exercise programs. With interindividual variation in exercise response, some subjects will respond with significant change, as represented here by a decrease in body fat percent (BF%), an increase in fat-free mass percentage (FFM%), and improvements in walking speed. Other subjects may not respond to exercise, also known as “non-responders,” signifying variability in response to exercise training but also the need for personalized exercise programs.

ence rates,<sup>19,20,45–47</sup> raises the key question of which outcome(s) is(are) more important or clinically relevant when designing an individual’s exercise prescription. Ultimately, the current health status and goals of each individual are paramount.

sensitivity can be blunted in individuals with impaired glucose tolerance and type 2 diabetes (T2D).<sup>36–38</sup> These data support an interaction between baseline glycemic levels and the level of exercise-associated improvement in glucose control with some reports demonstrating non-response in individuals with ambient hyperglycemia.<sup>39</sup> Moreover, the duration of T2D also appears to impact response to exercise.<sup>6,40</sup> Church et al.<sup>6</sup> reported individual variability in HbA1c in individuals with T2D in response to resistance or endurance training. Similarly, a recent study reported that 35% of participants with T2D who underwent 10 weeks of supervised endurance training showed no improvement in HbA1c or skeletal muscle mitochondrial capacity despite ubiquitous improvements in CRF.<sup>41</sup> By contrast, 43% of individuals with T2D were deemed “fitness non-responders” after showing no improvement in  $\text{VO}_2\text{max}$  following 9 months of supervised exercise training.<sup>6,42</sup> However, CRF improvements may not be necessary to improve glycemic control as evidenced by significant improvements in HbA1c, waist circumference, and percentage body fat across all subjects.<sup>21</sup> Finally, in a meta-analysis of >1,500 individuals who underwent a supervised clinical exercise intervention, adverse responses in cardiometabolic outcomes were reported in 7% of participants.<sup>43</sup> This ambiguity surrounding HbA1c and exercise response is also consistent with data from Solomon<sup>44</sup> who identified a specific threshold of HbA1c as a marker of lower response of exercise to improve glycemia in patients with T2D.

The well-documented variability in exercise response, even in studies with rigorously controlled interventions and high adher-

## EXTRINSIC FACTORS SHOWN TO INFLUENCE EXERCISE RESPONSE VARIATION

### Timing of exercise and circadian rhythm

Numerous extrinsic factors can influence the exercise response considering the specified outcome. From a biological or physiological perspective, extrinsic means “relating to or developing from external factors.” In the context of exercise, one extrinsic factor that has garnered much attention in the past 20+ years is exercise timing. In other words, the time of day at which one engages in exercise can influence their response to the exercise. Furthermore, optimizing the timing of exercise bouts could enhance exercise performance and aid existing therapeutic interventions for the management of cardiometabolic disease. Exercise timing is intertwined with one’s circadian rhythm. The human circadian system comprises a network of cellular clocks that autonomously maintain a circadian rhythm,<sup>48–50</sup> and the alignment of these clocks to cellular clocks in other tissues and external cues is critical,<sup>48,51</sup> especially with regard to the control of metabolic processes (e.g., blood glucose and insulin levels). An extensive network of clock-controlled genes in skeletal muscle facilitates the circadian and metabolic program, which, when disrupted or misaligned, can lead to deleterious metabolic consequences and has been extensively reviewed recently<sup>52</sup> and identified elsewhere.<sup>53</sup> In general, there is a significant rise in transcriptional activity of genes related with muscle contraction, substrate metabolism, and mitochondrial biogenesis within a few hours following an acute exercise bout that are all under control of the CLOCK.

Poor sleep patterns or erratic shift work can have similar detrimental effects on human metabolism via indirect disruption of the core clock machinery.<sup>52,54,55</sup> Exercise and PA, i.e., any bodily movement requiring energy, have been shown to positively influence the rhythm of the clock machinery in skeletal muscle through impacting both the amplitude and phase of circadian rhythms<sup>56–59</sup>; however, the optimal exercise timing for cardiometabolic health and the potential for exercise training to reduce the impact of misaligned circadian rhythms are far from resolved. Identifying an individual's optimal time of day for exercise to maximize their physiological response, inclusive of all tissues beyond just skeletal muscle, may be important for implementing personalized exercise prescriptions.

In terms of maximal exercise performance, endurance, skeletal muscle strength, and size all peak in the late afternoon and evening. Even when controlling scheduling bias and environmental factors, athletes competing in the early evening break more world records.<sup>60,61</sup> It may therefore be beneficial to align time of exercise with the time of maximal performance. There have, however, been conflicting results. For example, when measured in the evening, skeletal muscle strength was similar in subjects who trained in the morning vs. the evening.<sup>62</sup> A recent systematic review concluded that (1) at baseline, strength is greater in the evening than in the morning; (2) exercise training in the morning brings the level of strength in the morning to that observed in the evening; and (3) training in the evening maintains the strength differences between morning and evening.<sup>63</sup> Thus, training in the morning or evening hours may elicit similar responses in strength regardless of the time of day at which the testing is performed. One major limitation of this systematic review is the wide age range in participants across the studies as younger and older individuals are unlikely to exhibit similar responses to resistance training.<sup>64,65</sup> This area of research is ripe for investigations into exercise response variation employing rigorously controlled exercise interventions.

Although extensive evidence supports the role of PA at any intensity and modality in reducing mortality risk,<sup>66–68</sup> the association between exercise at different times of day and health risk is less clear. In terms of metabolic health, blood glucose and insulin levels fluctuate throughout the day, and results from exercise timing studies are somewhat inconclusive and even contradictory.<sup>69–71</sup> In healthy humans, glucose tolerance demonstrates a diurnal rhythm<sup>72</sup> with improved glucose tolerance in the morning compared with the afternoon and evening,<sup>73</sup> whereas in individuals with T2D and their first-degree relatives, this rhythm is blunted.<sup>74,75</sup> Recent work has reported that blood glucose excursions and glycemic control are more responsive to endurance training when performed in the late afternoon and evening.<sup>71</sup> A handful of clinical exercise trials have reported either a greater reduction in glucose with afternoon or evening exercise<sup>69–71</sup> or no differences in glucose among the groups training at different times of the day.<sup>50,76</sup> By contrast, one study reported a more robust metabolic effect of morning exercise compared with night exercise,<sup>77</sup> whereas a similar clinical exercise trial found that both morning and post-meal walking tended to be more effective in improving 24 h glycemic control than afternoon walking, with post-meal walking being the most effective.<sup>69</sup> It is worth noting that many of the conclusions around time-of-day effectiveness on metabolism and glycemic control have been largely based on indirect

comparisons among several studies,<sup>78</sup> thus highlighting the need for more prospective randomized controlled exercise trials (RCTs) in large cohorts of humans to decipher the optimal efficacy of exercise timing for maximal benefits in metabolic health.

### Sleep

Regular adequate sleep contributes to many health benefits ranging from consolidation of memory to removal of free radicals and neurotoxic waste,<sup>79–81</sup> which are potentially related to improved exercise adaptation<sup>82</sup> and performance.<sup>83</sup> By contrast, poor sleep of insufficient quantity is associated with an increased risk of T2D and obesity.<sup>79,84–87</sup> In coordination with other factors, sleep may also impact exercise response with respect to CRF, skeletal muscle strength, metabolic homeostasis, and cognitive processing.<sup>78,88</sup> Few studies, however, have identified direct relationships between sleep deprivation and exercise performance. For example, no differences were detected for maximal neuromuscular or aerobic performance (i.e., strength, force development, and CRF) following 60 h of sleep deprivation in young males (26 ± 2 years),<sup>89</sup> which corroborates with previous literature.<sup>90</sup> Yet in similarly aged men (18–28 years), sleep deprivation reduced submaximal aerobic performance by ~7%, maximal heart rate by ~6%, and maximal isometric strength by ~17%.<sup>89,91,92</sup> These findings point to the potential role of vagal hyperactivity in lowering heart rate at rest and during submaximal workloads following sleep deprivation, akin to functional overreaching in athletes.<sup>93</sup> Further, a depletion of skeletal muscle glycogen stores following sleep deprivation translated to performance impairments, potentially due to reduced substrate availability.<sup>94</sup> Although the evidence in relation to sleep and physical performance is lacking, compelling data suggest sleep deprivation can adversely impact cognitive function, which is integral to overall exercise performance, decision-making, and central motivation.<sup>95</sup> The timing of sleep restriction (i.e., early wake or late sleep) may also impact PA, energy intake, and certain metabolic factors, whereby recovery sleep was able to rescue the adverse effects on glucose metabolism, although a bout of aerobic exercise did not.<sup>96,97</sup> Although less data are available on sleep extension, increased sleep duration reduced energy intake resulting in a negative energy balance in adults with overweight.<sup>98</sup> Future investigations should examine the relationships between sleep restriction or extension on exercise response and health outcomes.

### Diet interactions

There is currently considerable interest in time-restricted eating or intermittent fasting as alternatives to conventional energy restriction strategies for weight loss and improving metabolic health. The timing of nutrient intake can also be impacted by ethnicity or religious practices, such as Ramadan fasting. One consequence of fasting is a shift in substrate utilization from glucose to fatty acid oxidation in peripheral tissues corroborated by gene expression patterns, ultimately impacting metabolism and exercise performance. A recent review including 46 studies addressing exercise performance and metabolism in the fasted vs. fed state indicated that pre-exercise feeding enhanced prolonged, but not shorter, duration aerobic exercise performance.<sup>99</sup> When compared with the fed state, metabolic effects of acute exercise following an overnight fast included reduced

energy intake, circulating lipid (triacylglycerol [TAG] and free fatty acids [FFAs]), and liver fat with improved glycemic control.<sup>99,100</sup> Within skeletal muscle, exercise while fasting elicits a decrease in glycogen and increased intramyocellular lipid (IMCL) utilization, together with increases in *GLUT4* (glucose transport), *FAT/CD36* (fatty acid transport), *CPT1* (fatty acid transport), *PDK4* (glucose metabolism), and *AMPK* (energy sensing) expression.<sup>101,102</sup> In adipose tissue, all but *CPT1* and *AMPK* were increased, along with FFA utilization and *IRS2* (insulin signaling) gene expression and protein content.<sup>103</sup> It is less clear whether these same effects are observed with chronic adaptation. Some studies have reported increased glycogen content, confirming the acute effect of decreased glycogen use and increased *GLUT4*, *FAT/CD36*, and *FABP* (fatty acid transport) protein levels.<sup>104,105</sup> Further research is needed to investigate the chronic metabolic effects of exercise in the fed state before we know whether it is more advantageous to exercise while fasted.

The timing of nutrient intake may be an important strategy for optimizing exercise responses,<sup>106</sup> particularly carbohydrate intake to ensure adequate glycogen storage, and protein intake for muscle protein synthesis.<sup>107</sup> It is well established that glycogen preloading protects against glycogen-associated exhaustion during endurance exercise, and consumption of carbohydrates post-exercise optimizes glycogen repletion.<sup>107–109</sup> This is particularly important when limited time elapses between subsequent bouts of endurance exercise. Indeed, skeletal muscle glycogen availability appears to play a role in subsequent endurance capacity and in situations when carbohydrate ingestion is sub-optimal. Further, adding protein during post-exercise recovery may be beneficial for restoration of skeletal muscle glycogen and thereby exercise performance.<sup>108</sup> Post-exercise consumption of carbohydrate and protein together has been shown to improve exercise performance, protein synthesis, and intracellular signaling for protein synthesis.<sup>110,111</sup> Protein intake is important for resistance training, exhaustive endurance exercise, and eccentric activities.<sup>107</sup> Finally, some evidence suggests that ingestion of whole foods containing protein, vitamins, minerals, and other macronutrients may better stimulate post-exercise skeletal muscle protein remodeling compared with protein alone.<sup>112</sup>

In addition to protein and carbohydrate recommendations, the macronutrient composition of the diet and specific nutrients likely influence exercise outcomes. For example, low-carbohydrate, high-fat diets have been thoroughly studied for treating obesity and reducing cardiometabolic disease risk. The propensity of this diet to induce loss of skeletal muscle mass, along with reducing carbohydrate availability, however, may raise concerns. Indeed, several studies have examined the effect of low-carbohydrate diets on exercise performance and lean mass.<sup>113–115</sup> A 10-week RCT examining a low-carbohydrate diet and exercise revealed no significant effect on body composition, CRF, or cardiovascular risk factors compared with a normal diet.<sup>113</sup> A similar 8-week intervention resulted in small improvements in  $\text{VO}_2\text{max}$  but greater losses of lean mass with a low-carbohydrate diet.<sup>114</sup> A short 4-week study examining the effects of a very low-carbohydrate diet on high-intensity interval training (HIIT) responses revealed minimal effects on  $\text{VO}_2\text{max}$  and heart rate and no effect on time to exhaustion.<sup>115</sup> Overall,

the evidence from these short-term studies demonstrated that the effects of a low-carbohydrate compared with a normal diet are relatively small, yet further studies in larger cohorts with extensive dietary control and greater phenotyping of cardiometabolic and health outcomes may produce larger effect sizes. Many studies have examined the effects of various supplementation on improving exercise performance and recovery, including (but not limited to) creatine, ketones, branched-chain amino acids (BCAAs), and antioxidants like vitamin C or E. These nutrient-exercise interactions have been reviewed elsewhere<sup>109,116,117</sup> and remain a key avenue of research that may uncover dietary, macronutrient, or micronutrient interactions driving variability in exercise response.

### Pharmacological treatments/medications

Multiple pharmacological therapies and medications ranging in their target application can impact exercise capacity and response. Over the counter, nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used and may impact individual response to exercise.<sup>118</sup> Specifically, chronic,<sup>118–121</sup> but not acute,<sup>122</sup> use of NSAIDs promoted greater skeletal muscle mass and strength gains than placebo in older men and women (60–78 years) following resistance training. However, it is unclear if the same effects would be observed in individuals with less chronic inflammatory stress, which often characterizes inactive older individuals.<sup>123</sup> Aspirin also inhibited the same prostaglandin/cyclooxygenase pathway in young, healthy men and women ( $25 \pm 2$  years) completing resistance and aerobic exercise, although this occurred in a sex-dependent manner.<sup>124</sup>

Other widely used medications, including metformin and statins, have also been reported to impact exercise response.<sup>125</sup> Metformin reduces blood glucose predominantly through reductions in hepatic glucose output but also impacts skeletal muscle through inhibition of mitochondrial enzymes,<sup>125,126</sup> activation of 5' adenosine monophosphate-activated protein kinase (AMPK),<sup>127</sup> and blunting of pro-inflammatory cytokines in macrophages.<sup>128</sup> Although metformin has been studied for over 70 years,<sup>129</sup> the literature describing the effects of metformin on exercise response are inconsistent. Some reports indicate that resistance and aerobic exercise combined with metformin work antagonistically with respect to exercise effects on insulin sensitivity, CRF, and skeletal muscle mitochondrial respiration.<sup>130–134</sup> The MASTERS trial demonstrated blunted skeletal muscle hypertrophy in older participants (64–91 years) taking metformin during a 14-week progressive resistance training program, although this did not translate to reduced strength gains.<sup>135</sup> In healthy, young adults ( $28 \pm 3$  years), 1 week of metformin treatment significantly reduced CRF, and other factors associated with maximal exercise capacity compared with a placebo.<sup>136</sup> This finding was extended into medication-naïve individuals with prediabetes.<sup>131</sup> Alternatively, minimal effects of metformin on exercise response have also been reported.<sup>136–140</sup> These inconsistencies may be due to differences in glycemic/diabetes status, duration of disease, or medication use,<sup>141,142</sup> heterogeneous impacts on skeletal muscle mitochondria,<sup>130</sup> IMCL,<sup>143</sup> or the age of the participants.<sup>144</sup> Interestingly, combined metformin and statin use in subjects who participated in the Metformin to Augment Strength Training Effective Response

in Seniors (MASTERS) trial resulted in the rescue of metformin-related impairments in growth response to progressive resistance training but did not impact strength.<sup>145</sup> Statin use alone is also associated with impairments in aerobic and resistance exercise training adaptations in some,<sup>125,146,147</sup> but not all,<sup>148–151</sup> studies. Despite improvements in metabolic syndrome and fat oxidation, blunted aerobic exercise effects on CRF have been reported in both chronic<sup>152</sup> and naive<sup>125</sup> statin users when compared with exercise without statins.<sup>152</sup> Alternatively, older individuals (72 ± 5 years) on a statin improved their skeletal muscle fatigue resistance<sup>149</sup> and increased lean muscle mass<sup>151</sup> more than non-statin users following 6 or 12 weeks of resistance training, respectively. Finally, myalgia is a common occurrence in statin users,<sup>153</sup> and managing side effects is key to promoting and supporting both structured exercise and leisure PA.

Glucose-lowering medications including sodium-glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 (GLP1) agonists, and combination therapies are also commonly prescribed, yet little is known about their impact on exercise response in humans. A recent report in rats with T2D suggested a synergistic effect of SGLT2i and exercise on improving indices of glycemic control and submaximal exercise capacity.<sup>154</sup> SGLT2i alone improved parameters associated with exercise capacity in patients with heart failure.<sup>155</sup> However, combined with exercise training, SGLT2i was ineffective in improving CRF more than placebo with improvements in insulin sensitivity attenuated.<sup>156</sup> With regards to GLP1 agonists, improvements in CRF were reported in sedentary patients with T2D taking liraglutide or placebo, combined with 16 weeks of aerobic and resistance exercise.<sup>157</sup> Medications targeting cardiovascular health may also impact response to exercise training and have been reviewed elsewhere.<sup>158,159</sup>

Finally, anabolic androgenic steroids, a commonly used drug among recreational athletes and bodybuilders,<sup>160,161</sup> are reported to increase protein synthesis<sup>162</sup> leading to enhanced skeletal muscle size and strength.<sup>163,164</sup> A placebo-controlled RCT demonstrated that supraphysiologic doses of testosterone administered for 10 weeks in healthy eugonadal men resulted in increased lean mass and strength, particularly when combined with resistance training.<sup>164</sup> These effects are reported to be similar in healthy older males,<sup>165–167</sup> and correlate linearly with dosage, without evidence of plateau.<sup>168,169</sup> An observational study in men who chronically used anabolic steroids supported these findings.<sup>170</sup> Although women do report using anabolic androgenic steroids,<sup>160</sup> little research is available describing the effects on exercise performance in women. Despite the potential for negative long-term consequences on health, the combination of testosterone replacement and exercise may be a promising intervention in clinical populations.<sup>171–173</sup>

### Summary of extrinsic factors

Extrinsic factors influencing variations in exercise response include exercise timing, circadian rhythms, sleep, diet, and pharmacological interactions. With regard for exercise timing, late afternoon and evening exercise may optimize endurance, skeletal muscle strength, and size. Yet, timing effects on glucose metabolism remain ambiguous, and conflicting findings highlight the need for further investigations, especially considering age-related variations and the potential for diet in-

teractions, which renders dissection of these effects difficult. Sleep patterns, which are crucial for optimal health, also impact exercise response, although research on sleep and exercise performance is limited. Regarding nutrient timing and macronutrient composition, the literature emphasizes the importance of adequate carbohydrate and protein intake for optimal exercise performance and recovery. Eating strategies like intermittent fasting and time-restricted feeding are gaining interest, but their chronic effects on exercise remain underexplored. Depending on the selected outcome, drug interactions exert both positive (NSAIDs, statins, GLP1, anaerobic steroids) and negative (metformin, statins, anaerobic steroids) effects on exercise response. Inconsistencies in the literature emphasize the need for further research on medication-exercise interactions. Overall, understanding these extrinsic factors is crucial for tailoring exercise recommendations and optimizing health outcomes.

### INTRINSIC FACTORS SHOWN TO INFLUENCE EXERCISE RESPONSE VARIATION

#### Sex

Intrinsic factors can drive response variation to exercise. From a disease perspective, intrinsic means “not attributable to any external or environmental factor.” Clear sex differences in response to exercise have been documented.<sup>5</sup> However, given historical bias toward the study of males in clinical and physiological research, understanding and comparing the physiological adaptations to exercise in both sexes is a critical knowledge gap that must be addressed. Here, we refer to sex as its socially constructed, binary definition of male and female but recognize gender-diverse individuals and the complexities this contributes to understanding exercise response variation. How sex influences exercise response will depend on the specific outcomes; some may show sex differences while others will not. Selected adaptive responses to exercise are similar between sexes, with endurance exercise eliciting improvements in CRF, resistance exercise eliciting improvements in physical function, and both exerting an overall benefit to metabolic state. However, the mechanisms to elicit these responses may be different among sexes.<sup>174,175</sup> Skeletal muscle, for example, has been shown to adapt to exercise quite differently between males and females.<sup>176,177</sup> Females, in general, have lower CRF in comparison with males<sup>178,179</sup> and may have different exercise adaptations in cardiorespiratory factors, including increased heart rate and arteriovenous blood supply.<sup>180,181</sup> Females may also oxidize proportionally more lipid during exercise when compared with males.<sup>182,183</sup> Sex differences are particularly important when we consider the interaction between sex and age in the response variability to exercise in the goal to prescribe individualized exercise programs.

#### Age

PA levels and CRF generally decline with age<sup>184</sup> with an estimated rate of 1% reduction in  $\dot{V}O_{2\max}$  per year after age 40.<sup>185</sup> Skeletal muscle mass and strength decrease<sup>186–189</sup> while the risks of chronic disease and metabolic dysfunction increase.<sup>188</sup> Exercise can prevent or delay some age-related chronic diseases,<sup>190</sup> thereby increasing healthspan<sup>191</sup> as reported in exercise-trained older subjects.<sup>189,192</sup> Chronic PA

may mitigate many age- and physical inactivity-related declines in physical function, exercise efficiency, and skeletal muscle mitochondrial energetics,<sup>192–194</sup> although these effects may be intensity-dependent.<sup>195</sup> Conversely, the effects of aging can impact the ability to perform and adapt to exercise; in older individuals, these responses may be preserved,<sup>196–202</sup> exaggerated,<sup>197,203</sup> or blunted,<sup>189,192,193,197,204</sup> specific to the physiological systems in question (i.e., cardiovascular, skeletal muscle, endocrine systems).

With regard to trainability of the cardiorespiratory system, healthy older men and women (60–71 years) improved CRF ~20% following 9–12 months of aerobic exercise, which was similar to responses observed in young people.<sup>196</sup> Yet the literature is inconsistent; while others have described similar findings,<sup>200,205</sup> both lesser improvements in  $\text{VO}_2\text{max}$ <sup>193,195</sup> and greater relative increases in exercise efficiency and  $\text{VO}_2$  kinetics than younger counterparts<sup>193,206,207</sup> have been reported. These results may be related to changes in skeletal muscle mitochondrial function and content, which are reduced with age,<sup>208–210</sup> but only partially rescued in endurance-trained older adults,<sup>192,210,211</sup> and can increase with exercise in inactive older individuals<sup>189,192,195</sup> similar to young adults.<sup>195,205</sup> Altogether, the effects of age on exercise response are highly heterogeneous and likely depend on multiple factors. For example, baseline values not only play a role in the ability to adapt to exercise training but also the rate at which an individual declines naturally with age.<sup>191,212,213</sup> Highly trained older adults experience a higher rate of decline in CRF when compared with healthy, sedentary adults of the same age (+50 years),<sup>214,215</sup> although not all studies support these observations.<sup>216</sup>

Skeletal muscle mass and function deteriorate with age both through disuse (age-independent)<sup>194</sup> and anabolic resistance (age-dependent).<sup>197,217</sup> Anabolic resistance consists of a blunted muscle protein synthesis response following resistance exercise in older men (70 ± 5 years) compared with BMI-matched younger men (24 ± 6 years).<sup>197</sup> Despite these and other findings,<sup>204,218,219</sup> aerobic,<sup>195,220</sup> resistance,<sup>195,221–224</sup> or combined training<sup>195</sup> in older individuals likely elicits beneficial skeletal muscle adaptations, including increased muscle cell size, strength, and power.

Older individuals generally have favorable exercise-induced adaptations in insulin sensitivity and other cardiometabolic risk factors,<sup>195</sup> but they often fail to reach levels observed in younger subjects,<sup>225–227</sup> potentially due to body composition factors, namely adiposity.<sup>211</sup> With regard to aging and cognition, an fMRI image task analysis demonstrated that greater strenuous PA and CRF in older individuals were protective against some age-associated declines in cognitive and brain function, yet this effect was not global.<sup>228</sup> Although reduced plasticity with age might constrain the response when compared with younger participants,<sup>204,217,219</sup> older adults still demonstrate improved CRF and skeletal muscle mitochondrial function, strength and lean mass, metabolic, and cognitive outcomes with exercise training.

The Health, Risk Factors, Exercise Training and Genetics (HERITAGE) study, which included sedentary subjects (17–65 years), reported that age accounted for almost 4% of the variation in CRF following 20 weeks of aerobic exercise.<sup>229</sup> Although the age-related factors that impact exercise response

in adolescent, young adults, and middle-aged individuals are unclear, reduced CRF in early life can increase risk for cardiovascular disease later in life.<sup>230</sup> Exercise also benefits brain development and cognition throughout life,<sup>231</sup> although larger effect sizes have been reported in the exercise effects on cognition and age in younger individuals as compared with older individuals.<sup>232,233</sup> Unfortunately, in addition to older adults, children, adolescents, and young adults are not meeting PA guidelines<sup>234</sup> and rates of obesity and chronic disease are on the rise.<sup>235</sup> Other factors that may impact exercise response in young people include puberty and endocrine factors, daily PA levels and body composition, and metabolic exercise capacity, especially in young children. Further investigation is needed to understand how exercise response varies in younger aged groups, which ultimately will be fundamental to our understanding of risk reduction for disease and physical dysfunction throughout life.

### Hormonal status

Although exercise elicits changes in hormone production, natural fluctuations in basal hormone levels and metabolism are intrinsic factors that can significantly impact exercise performance and the exercise response, especially as it pertains to cardiometabolic health outcomes. For example, in male recreational cyclists, performance was superior in the evening versus the morning hours, yet the noradrenaline response was higher in the morning time trial,<sup>236</sup> indicating that the time of the day impacts hormonal response to exercise. In a separate study in healthy, untrained men, plasma testosterone and cortisol displayed diurnal variations before and following a maximal aerobic effort throughout the day, although the magnitude of the response was similar between the evening and the morning exercise bouts.<sup>237</sup> The testosterone:cortisol ratio, however, was higher in the evening rather than in the morning. From these findings, one could speculate that acute diurnal variations in response to resistance exercise may be influenced by fluctuations in circulating testosterone and/or cortisol. By contrast, studies in previously resistance-trained and -naïve men found that rises in anabolic hormones (e.g., testosterone) post-acute exercise were not related to or indicative of exercise-mediated gains in skeletal muscle mass or strength.<sup>238–243</sup> Thus, the physiological relevance of these diurnal rhythms and fluctuations in hormones and their potential impact on exercise outcomes remains debatable.

The exercise-associated vascular endothelial adaptations can also be modulated by sex hormones. Clinical exercise studies in older men have demonstrated that macro- (brachial artery flow-mediated dilation) and microvascular (forearm blood flow response to acetylcholine) endothelial function were enhanced by regular endurance exercise.<sup>244</sup> Similar exercise benefits were diminished or completely absent in post-menopausal women,<sup>244</sup> which may be connected to the drastic decrease in circulating estrogen. In previously sedentary, post-menopausal women, moderate-intensity exercise improved endothelial function, but only in participants treated with estrogen.<sup>244</sup> Thus, the exercise signal may be “recoupled” or reconnected via estrogen to elicit favorable adaptations in endothelial function. A related study found that endurance exercise had no effect on vascular oxidative stress and its tonic suppression of endothelial function

in post-menopausal women without high circulating estrogen, whereas oxidative-stress-related suppression of endothelial function was ameliorated with endurance exercise in women with high circulating estrogen.<sup>245</sup> In summary, endurance exercise in older men enhanced antioxidant defenses and increased resistance to oxidative stress with subsequent improvements in endothelial function, whereas in post-menopausal women, vascular adaptations to endurance exercise were diminished following menopause-related declines in estrogen. These maladaptations within the vascular system in post-menopausal women may be due to a failure of endurance exercise-associated adaptations in antioxidant defenses, which help to mitigate vascular oxidative stress.

A relatively new theory in this field of research is the “exercise timing hypothesis”<sup>246</sup> which proposes that greater vascular function improvements in women may be attained if exercise training is initiated in middle age, soon after menopause, rather than several years (5–10 years) after the onset of menopause. This rationale originates from observations in studies of women at or beyond middle age, showing no improvement in cardiovascular function after a period of exercise,<sup>180,245,247</sup> however, other studies show a substantial improvement.<sup>248–250</sup> One difference in the design between these studies was the age of the women, where vascular benefits were achieved in “early”<sup>248,249</sup> but not “late”<sup>245,251</sup> post-menopausal women. Moreover, skeletal muscle estrogen-related receptor- $\alpha$  (ERR $\alpha$ ) may be involved in adaptations in the early but potentially not in the late post-menopausal period.<sup>246,249</sup> Another prospective reason for a timing effect could be garnered from studies on hormone replacement therapy<sup>252</sup>; preventing the decline in cardiovascular health may be easier to achieve than reversing established dysfunction in the vascular system. These striking data support exercise-related benefits to the vascular system as critical to overall health benefits of exercise and suggest that future investigations examining exercise adaptations and variation, particularly as they relate to vascular outcomes, should consider changes in sex hormones, oxidative stress, and onset of exercise training.

There is a long line of evidence that pre- vs. post-menopause levels of estrogen influence energy expenditure and substrate metabolism, specifically fat oxidation.<sup>253</sup> Experimentally reducing estrogen levels in women decreases lean mass and energy expenditure and increases central fat mass.<sup>253</sup> Preliminary evidence suggests that maintaining regular exercise during the menopausal transition may be an effective strategy for minimizing some of the changes in body composition associated with estrogen loss. Exercise does not, however, appear to preclude the decrease in resting energy expenditure that occurs with loss of estrogen. Some evidence suggests that estrogen therapy may increase moderate-to-vigorous PA (MVPA), which may ultimately work in combination to restore energy expenditure during menopause.<sup>254</sup> Pre- vs. post-menopausal status also likely influences transcriptional responses to exercise in women, but this is yet to be determined. It is evident that more work is needed in this area of research to determine the role of hormones in the molecular and physiological adaptive responses to exercise in men, women, and in gender-diverse populations.

### Race/ethnicity

Regardless of ethnic origin, aerobic capacity is inversely related to disease risk and is a strong predictor of all-cause mortality.<sup>255,256</sup> Non-Hispanic Black (NHB) individuals have been shown to have lower CRF when compared with non-Hispanic White (NHW) individuals.<sup>257–261</sup> PA plays a major role in aerobic capacity, but a limitation of most studies in NHB is that an objective assessment of free-living PA is not obtained. The cardiorespiratory system and skeletal muscle/metabolic properties are also major determinants of aerobic capacity. With regard to oxygen delivery, differences in hemoglobin levels have been shown to be associated with lower CRF in NHB, but they do not fully explain the racial difference.<sup>259</sup> In addition, myofiber type also differs by race with NHB possessing greater type II fibers than NHW.<sup>262,263</sup> Despite these differences, our group and others have found that lower relative VO<sub>2</sub>max in young, healthy NHB women compared with NHW women was associated with lower skeletal muscle mitochondrial respiration.<sup>262,264</sup> Despite lower baseline CRF in NHB, the HERITAGE study reported similar responses following 20 weeks of endurance training in NHB and NHW.<sup>257</sup> The HERITAGE and dose-response to exercise in women (DREW) studies reported that in NHW and NHB women, race only explained 1.0%–5.1% of the total variability in absolute CRF response to exercise, depending on the dosage.<sup>265</sup> Socio-economic status, which is correlated with physical function and health outcomes in older adults,<sup>266–268</sup> is also strongly related to race,<sup>269</sup> and understanding the independent effects of race on health-related outcomes is challenging. Less is known about differences in exercise response in other ethnic groups,<sup>270–272</sup> yet it is clear that race and ethnicity play a role in baseline and acute exercise differences and likely contribute to exercise response variability.

### Genetics

A meta-analysis of twin-sibling studies from childhood to adulthood found that genetic factors accounted for over half of the variability in CRF.<sup>264</sup> Although genetics have been shown to play a large role in this variability, research utilizing candidate gene and genome-wide association studies (GWASs) approaches have failed to determine the genetic predictors of CRF changes in response to exercise training.<sup>273</sup> HERITAGE subsequently reported a maximum heritability estimate for VO<sub>2</sub>max response to an exercise program was 47%, and maternal transmission was as high as 28%.<sup>45</sup> The authors suggested that this high maternal influence raises the possibility that mitochondrial DNA (mtDNA) is involved in the exercise response heterogeneity. This group later reported that mtDNA sequence variations may contribute to individual differences in both the baseline levels and the trainability of VO<sub>2</sub>max.<sup>274</sup> A recent HERTIAGE analysis in NHW subjects examined whether mtDNA haplogroup or sequence variation differed between individuals characterized as low (LR) or high responders (HR) in VO<sub>2</sub>max.<sup>275</sup> Individuals in the LR and HR groups were found to have different mtDNA haplogroup subtypes; haplogroup J was not present in HR but had the highest prevalence in the LR group. In addition, 10 single nucleotide polymorphisms (SNPs) not associated with mtDNA haplogroup showed significantly different variant frequencies between the LR and HR. In a more recent study, mtDNA haplogroups

were found to differentiate response to exercise in 1,036 Finnish military conscripts, with haplogroups J and K shown to be markers of LR in exercise training.<sup>276</sup> Lower  $\text{VO}_2\text{max}$  has been reported in NHW individuals with haplogroup J compared with non-J, and a higher  $\text{VO}_2\text{max}$  has been observed in individuals with haplogroup H.<sup>277,278</sup> Furthermore, skeletal muscle mitochondrial respiration has been shown to be lower in cybrids with haplogroup J compared with H.<sup>279,280</sup> Thus, haplogroup J is associated with lower skeletal muscle mitochondrial respiration, lower cross-sectional  $\text{VO}_2\text{max}$ , and a lower response to exercise training. These findings support the concept that mtDNA haplogroup explains variation in cross-sectional and longitudinal changes in  $\text{VO}_2\text{max}$  that may impact physical function. However, investigations examining the impact of genetics and mtDNA haplogroups on other exercise outcomes are lacking, a knowledge gap providing opportunity for future research.

### Summary of intrinsic factors

Intrinsic factors influencing variations in exercise response include sex, age, hormonal status, race/ethnicity, and genetics. Until recently, the exercise literature has been heavily biased toward the inclusion of men, yet evidence supports dimorphic mechanisms in exercise responses in males and females, with variations in cardiovascular and metabolic outcomes. The literature clearly demonstrates age-related declines in physical function, muscle mass, and metabolic efficiency, and a wide heterogeneity in exercise response exists among older adults. Some of these effects may be in part due to hormonal changes. For example, estrogen levels in menopausal females blunt vascular adaptations to exercise and influence substrate use. In men, testosterone and cortisol appear to influence exercise performance in a diurnal fashion. Race and ethnicity contribute to baseline differences in aerobic capacity, with NHB having a lower CRF, but studies show similar exercise responses among different racial groups. Finally, genetic factors, including mtDNA variations, play a significant role in exercise response heterogeneity. Despite efforts to identify genetic predictors of exercise response, the complexity of genetic influence remains a challenge. In summary, the interplay of sex, age, hormones, race, and genetics contributes to the diversity in exercise responses. Our understanding of these factors is crucial for prescribing individualized exercise programs and optimizing health outcomes across different populations.

## HOW DO THE MOLECULAR TRANSDUCERS OF EXERCISE EXPLAIN THE VARIABILITY IN PHYSIOLOGICAL AND HEALTH OUTCOMES?

### Genomic and epigenomic

Variation in physiological responses to exercise are in part shaped by genetic code (i.e., genetics) and the mechanisms by which it is transcribed, translated, and post-translationally modified (i.e., epigenetics).<sup>9,281,282</sup> Epigenomic programming or “memory” in tissues can be influenced by stimuli, throughout the lifespan, that modulates the intra- and intercellular metabolic environment.<sup>283</sup> Epigenetic changes are reversible, and can impact how your body reads (i.e., transcribes) a DNA sequence through numerous actions including DNA methylation, histone

modifications, changes in chromatin structure, and the transcription of DNA into RNA.

The promoter regions of key genes involved in substrate metabolism can be hypomethylated following a single voluntary skeletal muscle contraction, which results in increased transcription and subsequent protein translation and action.<sup>53</sup> This established response lends itself to speculation that key substrate metabolism genes with hypermethylated promoter regions may blunt a contraction response (such as during exercise), thereby contributing to the lack of exercise-induced metabolic improvements. Baseline differences in skeletal muscle transcriptional profiles have been linked to exercise response variation, whereby HR exhibited 70% greater upregulation of mitochondrial-related gene expression compared with LR.<sup>42</sup> Maintenance of the donor’s metabolic phenotype in myogenic progenitor cells enables *in vitro* investigations of cell-autonomous contributions to exercise response variation. Using this human cell model, pre-exercise differences in DNA methylation and transcriptomic profiles were related to exercise response variation in clinical risk factors in individuals with T2D.<sup>41</sup> Ultimately, it is important to consider the complicated relationship between epigenomic programming of skeletal muscle (and other tissues) and metabolic milieu across the lifespan, which may impact the degree of exercise-associated adaptations to standardized interventions. Prior to an exercise intervention, the identification of response variation predictors, whether genetic or epigenetic, may aid in the implementation of targeted exercise interventions and prescriptions.

### Proteomic and post-translational modifications

Exercise-induced skeletal muscle contractions can change the cellular proteome with a gradual alteration in protein content and enzymatic activity.<sup>211</sup> Such adaptations drive the intercellular responses and ultimately, the systemic effects of acute and chronic exercise training.<sup>284</sup> Chronic endurance training upregulates skeletal muscle mitochondrial capacity for ATP generation,<sup>285</sup> vascularization,<sup>286,287</sup> intracellular signaling,<sup>288</sup> oxygen delivery, antioxidant capacity, remodeling of contractile proteins,<sup>289,290</sup> and the regulation of mitochondrial protein synthesis.<sup>291</sup>

Several proteins and signaling pathways within skeletal muscle may play an integral role in exercise response variability. For example, the mammalian target of rapamycin (mTOR)-p70S6K axis is activated by resistance exercise and skeletal muscle contraction<sup>292,293</sup> to increase muscle mass and the rate of muscle protein synthesis.<sup>294</sup> By contrast, the ubiquitin-proteasome pathway, via the action of E3 ubiquitin ligases, atrophy F box (atrogin-1/MAFbx), and muscle RING finger 1 (MuRF1), plays an integral role in the regulation of skeletal muscle degradation. The translocation and activation of FOXO proteins have proven to be fundamental in the upregulation of these atrogin-1/MAFbx and MuRF1 proteins resulting in skeletal muscle atrophy.<sup>295</sup> These proteins are known to transiently fluctuate in transcriptional expression during recovery from acute exercise, demonstrating the importance of timing in sample collection.<sup>296,297</sup>

Exercise impacts the translational expression of fundamental proteins to coordinate myogenesis and mitochondrial biogenesis<sup>298,299</sup> to alter carbohydrate and lipid metabolism<sup>300</sup> and

enhance ATP generation.<sup>301</sup> Post-translational modifications are key mechanisms governing these exercise responses. Acute exercise has been shown to significantly phosphorylate proteins relating to cellular energetics. For example, Hoffman et al.<sup>302</sup> employed global phosphoproteomics to identify 1,004 unique phosphoproteins on 562 proteins implicated in exercise signaling. Needman et al.,<sup>303</sup> subsequently generated a comprehensive phosphoproteomic dataset of exercise and insulin signaling in human skeletal muscle to show individual variation in responses. Though few studies have explored the exercise effects on the proteome in subjects with metabolic dysfunction, key proteomic differences between patients with and without T2D, predominantly relating to energy metabolism via glycolysis,  $\beta$ -oxidation, electron transport chain, and reduced nicotinamide adenine dinucleotide (NADH) shuttling have been reported.<sup>304</sup> Similarly, Vanderboom and colleagues<sup>305</sup> demonstrated that obesity affects the exercise-responsive phosphoproteome. Although Savikj et al.<sup>71</sup> demonstrated that timing of exercise training impacts proteomics responses. Additional studies are needed to understand how these important protein phosphorylation and other post-translational modifications responses can be translated to personalized exercise prescription.

### Transcriptomic

Repeated transient increases in mRNA transcripts are likely a foundation of cellular and systemic exercise-induced adaptations.<sup>3</sup> In humans, the transcriptomic response to exercise has been studied in blood,<sup>306</sup> skeletal muscle,<sup>307–310</sup> and occasionally other tissues such as adipose tissue.<sup>311,312</sup> The ability to assess the role of transcriptomic responses to acute and chronic exercise has been limited by small sample sizes and relatively homogeneous target populations. Recent meta-analyses have described modality-specific and time-dependent transcriptomic effects of exercise.<sup>313,314</sup> These results are corroborated by recent data from exercise-trained rats from the Molecular Transducers of Physical Activity in Humans (MoTrPAC) study.<sup>315</sup> A recent single-nucleus, multi-omic analysis of human skeletal muscle before and after a bout of aerobic exercise (70%  $\text{VO}_2\text{max}$ ) identified specific gene and transcriptional responses including a distinct role of peroxisome proliferator-activated receptor delta (PPAR $\delta$ ) in fast-twitch fibers.<sup>316</sup> Although variability exists in the timing of gene induction, the peak usually occurs 4–8 h post-exercise, with return to baseline after 24 h,<sup>317</sup> although this varies across tissues.<sup>315</sup> Transcriptomic responses to exercise are also unique across metabolic states, ages, and sexes, and each of these variables can impact an individual's response to exercise.<sup>313,314</sup>

The response of CRF to exercise training has been associated with baseline skeletal muscle gene expression.<sup>318</sup> These predictor genes may regulate transcriptional networks required for exercise adaptations and thus partially explain individual variability in responses. Indeed, these predictor genes were related to the top-ranked high-responding transcriptional networks in a follow-up study from the same group.<sup>308</sup> Transcriptional profiles appear to differ between aerobic and resistance exercise.<sup>310,314</sup> The attenuated adaptation to resistance training in older individuals<sup>218,219</sup> could be explained by differences in both basal and exercise-induced transcriptional changes. Indeed, older adults

displayed altered basal transcriptome signatures in skeletal muscle pre-training<sup>309</sup> in combination with a transcriptional inflammatory response to exercise that differed from young individuals.<sup>313,319</sup> Sex-specific differentially regulated transcripts are also reported,<sup>313</sup> yet they require additional investigation to understand how they impact exercise response variation.<sup>229</sup> Finally, exercise training-mediated effects on transcription may help explain variability in insulin sensitivity. Subjects with lower insulin sensitivity show a reduced mRNA response to exercise.<sup>320–324</sup> The impact of insulin sensitivity on the transcriptional response to exercise could in turn lead to blunted exercise adaptations, further exacerbating the defects in insulin action. These results and others support the importance of the acute and chronic exercise transcriptomic responses in impacting training-related physiologic adaptations with the individual variability in exercise response potentially driven by these interactions.<sup>313,325</sup>

### Metabolic/metabolomic

The biologically active molecules that make up the metabolome perform many functions, which include supplying energy for skeletal muscle contraction as well as protein and glycogen synthesis. The impact of exercise extends far beyond skeletal muscle to include the adipose tissue, liver, brain, pancreas, and other organs. In concert with skeletal muscle, these tissues release factors during and after exercise, termed “exerkines,” which contribute to complex inter-organ networks facilitating exercise adaptation.<sup>326–328</sup> One example is skeletal muscle-derived interleukin 6 (IL-6), which is upregulated and secreted during contractile activity, interacting with other tissues to influence glucose metabolism.<sup>327</sup> During exercise, IL-6 enhances hepatic fat oxidation and glucose production to meet the needs of working skeletal muscle while also stimulating adipose tissue lipolysis and FFA mobilization, thereby supporting reductions in visceral adipose tissue.<sup>329</sup> Recently, fibronectin has been identified in mice as an exercise-induced, muscle-secreted circulating factor that induced hepatic autophagy and insulin sensitization through  $\alpha 5\beta 1$  (also known as the fibronectin receptor) integrin signaling.<sup>330</sup> Secretome mapping in animals identified a hepatic exerkine (carboxylesterase 2A/C [CES2A/C]), which was important in improved glucose tolerance, fat loss, and exercise performance.<sup>331</sup> In humans, hepatic exerkines, such as fibroblast growth factor 21 (FGF21) and angiopoietin-like 4 (ANGPTL4), also regulate adaptations to exercise as they relate to circulating lipids, skeletal muscle mass and strength, and glucose metabolism.<sup>332,333</sup> Leptin and adiponectin, two highly studied adipokines, are indirectly reduced following exercise-related reductions in fat mass,<sup>334</sup> although exercise-specific effects on these circulating factors and their impact on response variation are not well defined. Recently, reanalysis of blood from two human exercise cohorts identified lactoylphenylalanine (Lac-Phe) as an exercise-sensitive circulating metabolite in humans, and in animals, Lac-Phe inhibited feeding and obesity.<sup>335</sup>

Finally, the exercise training effects on the gut microbiome deserve mention given that the metabolic byproducts have been implicated in response variation<sup>336</sup> and microbial diversity correlates with CRF.<sup>337</sup> In men with prediabetes, the gut

microbiome was impacted by exercise training as evidenced by increased capacity to form BCAAs and short-chain fatty acids (SCFAs).<sup>336</sup> The biosynthesis of these metabolites was enhanced only in subjects who improved glucose homeostasis and insulin sensitivity. These effects were recapitulated in mice receiving fecal transplants from the responding and non-responding human participants.<sup>336</sup> Gut-derived BCAAs have been highlighted as a key factor in exercise response,<sup>338</sup> and SCFAs are also related to exercise-induced improvements in insulin sensitivity.<sup>336</sup> Indeed, SCFA content distinguished subjects with normal weight from those with obesity who underwent 6 weeks of aerobic training.<sup>339</sup> Taken together, the heterogeneity in exercise effects on physiological outcomes is greatly impacted by circulating metabolites, many of which are derived from metabolic tissues responsive to exercise. More research in humans is needed to identify specific metabolites involved in the exercise response.

### Lipidomic

Fatty acids serve as an essential fuel source for exercising skeletal muscle,<sup>340</sup> along with other peripheral organs including the liver, with lipids important for cholesterol synthesis and other cellular functions. Advancements within the field of mass spectrometry have enhanced our understanding of the cellular lipidome and its adaptation to exercise in healthy and diseased states.<sup>341</sup> Such progress has given rise to the discovery of novel lipid signaling mechanisms potentially driving the development of metabolic diseases including insulin resistance and T2D.<sup>342–347</sup> Lipids within muscle, or IMCLs, including TAG, diacylglycerols (DAGs), sphingolipids, long-chain acyl-coenzyme A (LCA-CoA), phospholipids, and acylcarnitines, along with their respective isoforms and species, accumulate within skeletal muscle of humans with obesity and insulin resistance.<sup>348</sup> These observations have shed light on the complexities of the “athletes paradox,” whereby endurance-trained athletes have IMCL content similar to those with T2D, yet they exhibit greater insulin sensitivity.<sup>349</sup> This is further complicated by evidence supporting increases in total DAG content in endurance-trained athletes following exercise,<sup>225,347,350,351</sup> opposing observations in individuals with overweight and obesity where content remains unchanged or decreased.<sup>225,347,350–352</sup> These opposing observations emphasize the importance of skeletal muscle lipid compositional profiling through lipidomics in the understanding of variation in exercise adaptations in both healthy and unhealthy states.

Goto-Inoue et al.<sup>353</sup> reported significant fatty acid remodeling of phospholipids in 3-week-old male Wistar rats following 12 weeks of high-fat diet and 6 weeks of chronic exercise training. In humans, Peake et al.<sup>354</sup> reported that plasma lipidomic profiles were altered after acute exercise. Significant alterations in tricarboxylic acid intermediates and monounsaturated fatty acids in this study by Peake and colleagues provided detailed insight into the metabolic and lipidomic demands of different exercise types. In addition, these results exemplify that specific lipid species released from active tissue (e.g., “lipokines”) may explain acute exercise response variability.

Lipokines released from the adipose tissue<sup>355,356</sup> and liver<sup>357,358</sup> have also been shown to have an intriguing role in the metabolic response of skeletal muscle to acute exercise.

Of these, 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) has been reported to be a particularly sensitive exercise-induced lipokine in mice and humans, correlating to greater skeletal muscle mitochondrial respiration and increased fatty acid uptake in response to acute exercise.<sup>359</sup> Such adaptations with chronic aerobic exercise were not apparent in previously inactive women with obesity and insulin resistance,<sup>360</sup> suggesting that such responses may depend on disease state or exercise duration.

Lipidomic analysis permits the identification of changes in lipid isomers, species, and localization after acute and chronic exercise. However, further work is needed to garner a greater understanding of the lipidomic response to exercise aiding in our comprehension of the interindividual response to exercise.

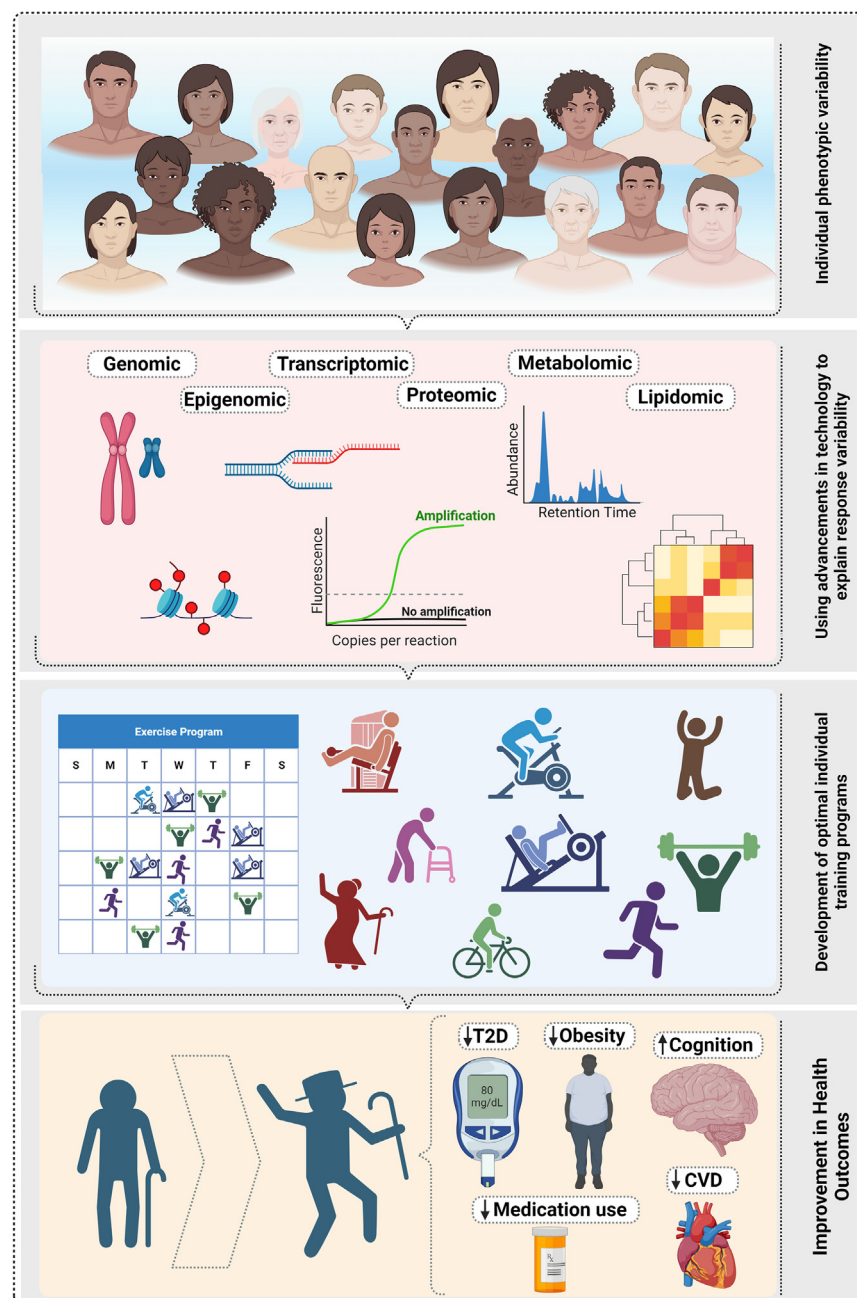
### Summary of how the molecular transducers of exercise explain the variability in physiological and health outcomes

Different “omic” approaches will aid in the identification of molecular transducers of exercise and how these in-depth techniques have been used to date to uncover significant interindividual variability in response to exercise in healthy and unhealthy populations. In particular, the use of genomics and epigenomics, proteomics and post-translational analysis, transcriptomics, metabolomics, and lipidomics will uncover the molecular transducers underpinning exercise response variability from multiple intrinsic (endogenous) and extrinsic (exogenous) perspectives. These known regulators of exercise response variability are so often considered in isolation. Gathering a clearer understanding of these in unison, i.e., multi-omic analyses, will uncover mechanisms relating to response variability and, as such, are crucial in the development of specifically tailored exercise programs.

### SYNTHESIS AND CONCLUDING REMARKS

#### The challenge

Integrating our understanding of the molecular transducers of exercise with clinical outcomes to guide personalized exercise prescriptions is a significant challenge facing exercise medicine. As “omics” technologies continue to evolve and become more accessible, our understanding of the interplay between metabolites and physiological and health outcomes of exercise will become clearer, allowing for more effective personalized exercise training prescriptions focused on patients’ needs. Consistencies in study design, greater sample sizing, marked preciseness in post-exercise sample collection (i.e., acute versus chronic exercise), and a more integrative approach of investigating intrinsic and extrinsic factors that interact with the molecular transducers of exercise are needed. Incorporating clinical and molecular data from trials to guide personalized exercise prescriptions for targeted outcome measures will require multidisciplinary research collaborations. Additionally, standardized procedures and protocols, state-of-the-art methodologies, and quality control, including objective measures of adherence, combined with tracking and robust analytical approaches, are crucial. We have highlighted how exercise type, frequency, intensity, duration, and many other variables influence the adaptations to training, hence the variability in exercise interventions. These variables,



**Figure 3. Molecular and health outcomes predicting exercise response variability**

Molecular and health outcomes predicting exercise response variability are dependent on multiple interlinked primary and secondary intrinsic and extrinsic factors as evidenced by differences in subject weight, age, race, sex, or disease state. Primarily, these factors account for interindividual variation in response to exercise training. However, advancements in technology in the measurement of genomic, epigenomic, transcriptomic, proteomic, metabolomic, and lipidomic responses are rapidly developing to help explain these differences in response. These technologies possess significant potential in the field of molecular and health diagnosis. Yet their capability in the development of optimal individual exercise training programs is still in its infancy. The use of these tools, in line with expert interpretation within the field of exercise science and medicine, has the capability to significantly improve individual health outcomes to exercise programs. Such personalized exercise training programs will not only act to improve health from multiple perspectives, be this through a reduction in medication use, a decrease in non-communicable disease development (obesity, type 2 diabetes [a progressive loss of adequate  $\beta$  cell insulin secretion frequently on the background of insulin resistance<sup>361</sup>], cardiovascular disease [a group of disorders of the heart and blood vessels mainly caused by blockage preventing blood flow<sup>362</sup>], etc.), or an improvement in cognitive function and survival, but also act to improve the overall exercise performance.

accounts for sex, race/ethnicity, age, hormonal status, and previous PA (Figure 3). This approach will also require sophisticated bioinformatics to better understand the mechanisms underlying exercise response variation.

The National Institutes of Health Common Fund launched a large-scale innovative project, the MoTrPAC<sup>363</sup> to examine the physiological and molecular (i.e., genetic, epigenetic, lipidomic, metabolomic, proteomic, etc.) responses to exercise training. An important goal in the MoTrPAC is to link the molecular changes in blood, skeletal muscle, and adipose tissue (human studies) in addition to other tissues in exercised rat

in tandem with response variations in health outcomes (i.e., CRF, physical function, body composition, energy expenditure, and cardiovascular and cardiometabolic risk status), make this even more challenging.

In recent years, there has been a significant push from publishers to present individual response data. This approach will help to reveal individual variability to clinical interventions, which, in turn, aids in identifying exercise response variations in context with individual adherence. An attractive approach to this complicated challenge is to use a combination of molecular and physiological response variability to predict individual exercise response—a personalized exercise approach<sup>3</sup> that

models to the variability in key phenotypic and health outcomes. Data will be integrated across the omics platforms to disentangle the complex relationships between intrinsic and extrinsic factors that drive the variation in exercise responses across individuals. The combined power of omics platforms and clinical phenotyping will allow exercise interventions to be targeted to specific types and amounts, thereby shifting the paradigm of exercise metabolism and biology and maximizing exercise-related benefits at the individual level. Although MoTrPAC will fill significant gaps in our understanding of exercise response variation in healthy humans, more prospective clinical exercise interventions are needed to address

cardiometabolic outcomes, populations with disease or other comorbidities such as T2D, and with longer follow-up. Identifying the underlying mechanisms that link exercise and improved health is key for the discovery of novel therapeutic targets, non-exercise therapies, and development and implementation of precision exercise medicine.

#### AUTHOR CONTRIBUTIONS

Conceptualization, J.N., L.M.S., and B.H.G. conceptualized the review and original outline; writing – original draft, J.N., J.M.M., J.P.D., L.M.S., and B.H.G.; writing – review & editing, J.N., J.M.M., J.P.D., L.M.S., and B.H.G.; visualization, J.N., J.M.M., and B.H.G.; supervision, B.H.G.

#### DECLARATION OF INTERESTS

The authors declare no competing interests.

#### REFERENCES

- Bull, F.C., Al-Ansari, S.S., Biddle, S., Borodulin, K., Buman, M.P., Cardon, G., Carty, C., Chaput, J.P., Chastin, S., Chou, R., et al. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br. J. Sports Med.* 54, 1451–1462.
- Cohen, N.D., Dunstan, D.W., Robinson, C., Vulkikh, E., Zimmet, P.Z., and Shaw, J.E. (2008). Improved endothelial function following a 14-month resistance exercise training program in adults with type 2 diabetes. *Diabetes Res. Clin. Pract.* 79, 405–411.
- Egan, B., and Zierath, J.R. (2013). Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab.* 17, 162–184.
- Neufer, P.D., Bamman, M.M., Muoio, D.M., Bouchard, C., Cooper, D.M., Goodpaster, B.H., Booth, F.W., Kohrt, W.M., Gerszten, R.E., Mattson, M.P., et al. (2015). Understanding the cellular and molecular mechanisms of physical activity-induced health benefits. *Cell Metab.* 22, 4–11.
- Lavin, K.M., Coen, P.M., Baptista, L.C., Bell, M.B., Drummer, D., Harper, S.A., Lixandrão, M.E., McAdam, J.S., O'Bryan, S.M., Ramos, S., et al. (2022). State of knowledge on molecular adaptations to exercise in humans: historical perspectives and future directions. *Compr. Physiol.* 12, 3193–3279.
- Church, T.S., Blair, S.N., Cocroham, S., Johannsen, N., Johnson, W., Kramer, K., Mikus, C.R., Myers, V., Nauta, M., Rodarte, R.Q., et al. (2010). Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 304, 2253–2262.
- Balducci, S., Zanuso, S., Nicolucci, A., De Feo, P., Cavallo, S., Cardelli, P., Fallucca, S., Alessi, E., Fallucca, F., Pugliese, G., et al. (2010). Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). *Arch. Intern. Med.* 170, 1794–1803.
- Snowling, N.J., and Hopkins, W.G. (2006). Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care* 29, 2518–2527.
- Ross, R., Goodpaster, B.H., Koch, L.G., Sarzynski, M.A., Kohrt, W.M., Johannsen, N.M., Skinner, J.S., Castro, A., Irving, B.A., Noland, R.C., et al. (2019). Precision exercise medicine: understanding exercise response variability. *Br. J. Sports Med.* 53, 1141–1153.
- Bonafiglia, J.T., Preobrazenski, N., Islam, H., Walsh, J.J., Ross, R., Johannsen, N.M., Martin, C.K., Church, T.S., Slentz, C.A., Ross, L.M., et al. (2021). Exploring differences in cardiorespiratory fitness response rates across varying doses of exercise training: a retrospective analysis of eight randomized controlled trials. *Sports Med.* 51, 1785–1797.
- Blair, S.N., Wei, M., and Lee, C.D. (1998). Cardiorespiratory fitness determined by exercise heart rate as a predictor of mortality in the Aerobics Center Longitudinal Study. *J. Sports Sci.* 16 (Suppl), S47–S55.
- Pérusse, L., Gagnon, J., Province, M.A., Rao, D.C., Wilmore, J.H., Leon, A.S., Bouchard, C., and Skinner, J.S. (2001). Familial aggregation of sub-maximal aerobic performance in the HERITAGE Family study. *Med. Sci. Sports Exerc.* 33, 597–604.
- Ahtainen, J.P., Sallinen, J., Häkkinen, K., and Sillanpää, E. (2020). Inter-individual variation in response to resistance training in cardiometabolic health indicators. *Scand. J. Med. Sci. Sports* 30, 1040–1053.
- Ahtainen, J.P., Walker, S., Peltonen, H., Holviala, J., Sillanpää, E., Karavirta, L., Sallinen, J., Mikkola, J., Valkeinen, H., Mero, A., et al. (2016). Heterogeneity in resistance training-induced muscle strength and mass responses in men and women of different ages. *Age (Dordr)* 38, 10.
- Damas, F., Angleri, V., Phillips, S.M., Witard, O.C., Ugrinowitsch, C., Santanello, N., Soligon, S.D., Costa, L.A.R., Lixandrão, M.E., Conceição, M.S., et al. (2019). Myofibrillar protein synthesis and muscle hypertrophy individualized responses to systematically changing resistance training variables in trained young men. *J. Appl. Physiol.* (1985) 127, 806–815.
- Pesta, D.H., Goncalves, R.L.S., Madiraju, A.K., Strasser, B., and Sparks, L.M. (2017). Resistance training to improve type 2 diabetes: working toward a prescription for the future. *Nutr. Metab. (Lond.)* 14, 24.
- Meyler, S., Bottoms, L., and Muniz-Pumares, D. (2021). Biological and methodological factors affecting VO2max response variability to endurance training and the influence of exercise intensity prescription. *Exp. Physiol.* 106, 1410–1424.
- Davidson, P.K., Gallagher, I.J., Hartman, J.W., Tarnopolsky, M.A., Dela, F., Helge, J.W., Timmons, J.A., and Phillips, S.M. (2011). High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J. Appl. Physiol.* (1985) 110, 309–317.
- Chmelo, E.A., Crotts, C.I., Newman, J.C., Brinkley, T.E., Lyles, M.F., Leng, X., Marsh, A.P., and Nicklas, B.J. (2015). Heterogeneity of physical function responses to exercise training in older adults. *J. Am. Geriatr. Soc.* 63, 462–469.
- Sisson, S.B., Katzmarzyk, P.T., Earnest, C.P., Bouchard, C., Blair, S.N., and Church, T.S. (2009). Volume of exercise and fitness nonresponse in sedentary, postmenopausal women. *Med. Sci. Sports Exerc.* 41, 539–545.
- Pandey, A., Swift, D.L., McGuire, D.K., Ayers, C.R., Neeland, I.J., Blair, S.N., Johannsen, N., Earnest, C.P., Berry, J.D., and Church, T.S. (2015). Metabolic effects of exercise training among fitness-nonresponsive patients with type 2 diabetes: the HART-D Study. *Diabetes Care* 38, 1494–1501.
- Dalleck, L.C., Haney, D.E., Buchanan, C.A., and Weatherwax, R.M. (2016). Does a personalised exercise prescription enhance training efficacy and limit training unresponsiveness? A randomised controlled trial. *J. Fit. Res.* 5, 15–27.
- Montero, D., and Lundby, C. (2017). Refuting the myth of non-response to exercise training: 'non-responders' do respond to higher dose of training. *J. Physiol.* 595, 3377–3387.
- Fogarasi, A., Gonzalez, K., Dalamaga, M., and Magkos, F. (2022). The impact of the rate of weight loss on body composition and metabolism. *Curr. Obes. Rep.* 11, 33–44.
- Kerksick, C.M., Wismann-Bunn, J., Fogt, D., Thomas, A.R., Taylor, L., Campbell, B.I., Wilborn, C.D., Harvey, T., Roberts, M.D., La Bounty, P., et al. (2010). Changes in weight loss, body composition and cardiovascular disease risk after altering macronutrient distributions during a regular exercise program in obese women. *Nutr. J.* 9, 59.
- King, N.A., Hopkins, M., Caudwell, P., Stubbs, R.J., and Blundell, J.E. (2008). Individual variability following 12 weeks of supervised exercise: identification and characterization of compensation for exercise-induced weight loss. *Int. J. Obes. (Lond)* 32, 177–184.
- Barwell, N.D., Malkova, D., Leggate, M., and Gill, J.M. (2009). Individual responsiveness to exercise-induced fat loss is associated with change in resting substrate utilization. *Metabolism* 58, 1320–1328.
- Broskey, N.T., Martin, C.K., Burton, J.H., Church, T.S., Ravussin, E., and Redman, L.M. (2021). Effect of aerobic exercise-induced weight loss on

- the components of daily energy expenditure. *Med. Sci. Sports Exerc.* 53, 2164–2172.
29. Lightfoot, J.T., Turner, M.J., Pomp, D., Kleeberger, S.R., and Leamy, L.J. (2008). Quantitative trait loci for physical activity traits in mice. *Physiol. Genomics* 32, 401–408.
30. Nehrenberg, D.L., Wang, S., Hannon, R.M., Garland, T., Jr., and Pomp, D. (2010). QTL underlying voluntary exercise in mice: interactions with the “mini muscle” locus and sex. *J. Hered.* 101, 42–53.
31. Kelly, S.A., Nehrenberg, D.L., Hua, K., Garland, T., Jr., and Pomp, D. (2011). Exercise, weight loss, and changes in body composition in mice: phenotypic relationships and genetic architecture. *Physiol. Genomics* 43, 199–212.
32. Brennan, A.M., Standley, R.A., Yi, F., Carnero, E.A., Sparks, L.M., and Goodpaster, B.H. (2020). Individual response variation in the effects of weight loss and exercise on insulin sensitivity and cardiometabolic risk in older adults. *Front. Endocrinol. (Lausanne)* 11, 632.
33. Prior, S.J., Blumenthal, J.B., Katzel, L.I., Goldberg, A.P., and Ryan, A.S. (2014). Increased skeletal muscle capillarization after aerobic exercise training and weight loss improves insulin sensitivity in adults with IGT. *Diabetes Care* 37, 1469–1475.
34. Ryan, A.S., Katzel, L.I., Prior, S.J., McLenithan, J.C., Goldberg, A.P., and Ortmeier, H.K. (2014). Aerobic exercise plus weight loss improves insulin sensitivity and increases skeletal muscle glycogen synthase activity in older men. *J. Gerontol. A Biol. Sci. Med. Sci.* 69, 790–798.
35. Boulé, N.G., Weisnagel, S.J., Lakka, T.A., Tremblay, A., Bergman, R.N., Rankinen, T., Leon, A.S., Skinner, J.S., Wilmore, J.H., Rao, D.C., et al. (2005). Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. *Diabetes Care* 28, 108–114.
36. Malin, S.K., and Kirwan, J.P. (2012). Fasting hyperglycaemia blunts the reversal of impaired glucose tolerance after exercise training in obese older adults. *Diabetes Obes. Metab.* 14, 835–841.
37. Osler, M.E., Fritz, T., Caidahl, K., Krook, A., Zierath, J.R., and Wallberg-Henriksson, H. (2015). Changes in gene expression in responders and nonresponders to a low-intensity walking intervention. *Diabetes Care* 38, 1154–1160.
38. Stefan, N., Staiger, H., Wagner, R., Machann, J., Schick, F., Häring, H.U., and Fritsche, A. (2015). A high-risk phenotype associates with reduced improvement in glycaemia during a lifestyle intervention in prediabetes. *Diabetologia* 58, 2877–2884.
39. Solomon, T.P., Malin, S.K., Karstoft, K., Haus, J.M., and Kirwan, J.P. (2013). The influence of hyperglycemia on the therapeutic effect of exercise on glycemic control in patients with type 2 diabetes mellitus. *JAMA Intern. Med.* 173, 1834–1836.
40. Johannsen, N.M., Sparks, L.M., Zhang, Z., Earnest, C.P., Smith, S.R., Church, T.S., and Ravussin, E. (2013). Determinants of the changes in glycemic control with exercise training in type 2 diabetes: a randomized trial. *PLoS One* 8, e62973.
41. Stephens, N.A., Brouwers, B., Eroshkin, A.M., Yi, F., Cornell, H.H., Meyer, C., Goodpaster, B.H., Pratley, R.E., Smith, S.R., and Sparks, L.M. (2018). Exercise response variations in skeletal muscle PCr recovery rate and insulin sensitivity relate to muscle epigenomic profiles in individuals with type 2 diabetes. *Diabetes Care* 41, 2245–2254.
42. Stephens, N.A., Xie, H., Johannsen, N.M., Church, T.S., Smith, S.R., and Sparks, L.M. (2015). A transcriptional signature of “exercise resistance” in skeletal muscle of individuals with type 2 diabetes mellitus. *Metabolism* 64, 999–1004.
43. Bouchard, C., Blair, S.N., Church, T.S., Earnest, C.P., Hagberg, J.M., Häkkinen, K., Jenkins, N.T., Karavirta, L., Kraus, W.E., Leon, A.S., et al. (2012). Adverse metabolic response to regular exercise: is it a rare or common occurrence? *PLoS One* 7, e37887.
44. Solomon, T.P.J. (2018). Sources of inter-individual variability in the therapeutic response of blood glucose control to exercise in type 2 diabetes: going beyond exercise dose. *Front. Physiol.* 9, 896.
45. Bouchard, C., An, P., Rice, T., Skinner, J.S., Wilmore, J.H., Gagnon, J., Pérusse, L., Leon, A.S., and Rao, D.C. (1999). Familial aggregation of VO<sub>2</sub>(max) response to exercise training: results from the HERITAGE Family Study. *J. Appl. Physiol.* (1985) 87, 1003–1008.
46. Karavirta, L., Häkkinen, K., Kauhanen, A., Arijia-Blázquez, A., Sillanpää, E., Rinkinen, N., and Häkkinen, A. (2011). Individual responses to combined endurance and strength training in older adults. *Med. Sci. Sports Exerc.* 43, 484–490.
47. Ross, R., de Lannoy, L., and Stotz, P.J. (2015). Separate effects of intensity and amount of exercise on interindividual cardiorespiratory fitness response. *Mayo Clin. Proc.* 90, 1506–1514.
48. Roenneberg, T., and Merrow, M. (2016). The circadian clock and human health. *Curr. Biol.* 26, R432–R443.
49. Schroder, E.A., and Esser, K.A. (2013). Circadian rhythms, skeletal muscle molecular clocks, and exercise. *Exerc. Sport Sci. Rev.* 41, 224–229.
50. Teo, S.Y.M., Kanaley, J.A., Guelfi, K.J., Marston, K.J., and Fairchild, T.J. (2020). The effect of exercise timing on glycemic control: a randomized clinical trial. *Med. Sci. Sports Exerc.* 52, 323–334.
51. Dyar, K.A., Lutter, D., Artati, A., Ceglia, N.J., Liu, Y., Armenta, D., Jastroch, M., Schneider, S., de Mateo, S., Cervantes, M., et al. (2018). Atlas of circadian metabolism reveals system-wide coordination and communication between clocks. *Cell* 174, 1571–1585.e11.
52. Martin, R.A., Viggars, M.R., and Esser, K.A. (2023). Metabolism and exercise: the skeletal muscle clock takes centre stage. *Nat. Rev. Endocrinol.* 19, 272–284.
53. Barrès, R., Yan, J., Egan, B., Treebak, J.T., Rasmussen, M., Fritz, T., Caidahl, K., Krook, A., O’Gorman, D.J., and Zierath, J.R. (2012). Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab.* 15, 405–411.
54. Gekakis, N., Staknis, D., Nguyen, H.B., Davis, F.C., Wilsbacher, L.D., King, D.P., Takahashi, J.S., and Weitz, C.J. (1998). Role of the CLOCK protein in the mammalian circadian mechanism. *Science* 280, 1564–1569.
55. King, D.P., Zhao, Y., Sangoram, A.M., Wilsbacher, L.D., Tanaka, M., Antoch, M.P., Steeves, T.D., Vitaterna, M.H., Kornhauser, J.M., Lowrey, P.L., et al. (1997). Positional cloning of the mouse circadian clock gene. *Cell* 89, 641–653.
56. Akashi, M., Tsuchiya, Y., Yoshino, T., and Nishida, E. (2002). Control of intracellular dynamics of mammalian period proteins by casein kinase I epsilon (CKIepsilon) and CKIdelta in cultured cells. *Mol. Cell. Biol.* 22, 1693–1703.
57. Eide, E.J., Vielhaber, E.L., Hinz, W.A., and Virshup, D.M. (2002). The circadian regulatory proteins BMAL1 and cryptochromes are substrates of casein kinase Iepsilon. *J. Biol. Chem.* 277, 17248–17254.
58. Koike, N., Yoo, S.H., Huang, H.C., Kumar, V., Lee, C., Kim, T.K., and Takahashi, J.S. (2012). Transcriptional architecture and chromatin landscape of the core circadian clock in mammals. *Science* 338, 349–354.
59. Soliman, L., El Safouri, S., Megahed, G.M., and El Maola, G. (1975). Copper and zinc levels in the blood serum and urine of bilharzial hepatic fibrosis. *Experientia* 31, 280–281.
60. Atkinson, G., and Reilly, T. (1996). Circadian variation in sports performance. *Sports Med.* 21, 292–312.
61. Gabriel, B.M., and Zierath, J.R. (2019). Circadian rhythms and exercise - re-setting the clock in metabolic disease. *Nat. Rev. Endocrinol.* 15, 197–206.
62. Chtourou, H., Driss, T., Souissi, S., Gam, A., Chaouachi, A., and Souissi, N. (2012). The effect of strength training at the same time of the day on the diurnal fluctuations of muscular anaerobic performances. *J. Strength Cond. Res.* 26, 217–225.
63. Grgic, J., Lazinic, B., Garofolini, A., Schoenfeld, B.J., Saner, N.J., and Mikulic, P. (2019). The effects of time of day-specific resistance training on adaptations in skeletal muscle hypertrophy and muscle strength: a systematic review and meta-analysis. *Chronobiol. Int.* 36, 449–460.
64. Roth, S.M., Martel, G.F., Ivey, F.M., Lemmer, J.T., Metter, E.J., Hurley, B.F., and Rogers, M.A. (2000). High-volume, heavy-resistance strength

training and muscle damage in young and older women. *J. Appl. Physiol.* (1985) 88, 1112–1118.

65. Peterson, M.D., Rhea, M.R., Sen, A., and Gordon, P.M. (2010). Resistance exercise for muscular strength in older adults: a meta-analysis. *Ageing Res. Rev.* 9, 226–237.
66. Grønberg, M., and Flatmark, T. (1988). Inhibition of the H<sup>+</sup>-ATPase in bovine adrenal chromaffin granule ghosts by diethylstilbestrol. Evidence for a tight coupling between ATP hydrolysis and proton translocation. *FEBS Lett.* 229, 40–44.
67. Strain, T., Wijndaele, K., Dempsey, P.C., Sharp, S.J., Pearce, M., Jeon, J., Lindsay, T., Wareham, N., and Brage, S. (2020). Wearable-device-measured physical activity and future health risk. *Nat. Med.* 26, 1385–1391.
68. Millard, L.A.C., Tilling, K., Gaunt, T.R., Carslake, D., and Lawlor, D.A. (2021). Association of physical activity intensity and bout length with mortality: an observational study of 79,503 UK Biobank participants. *PLoS Med.* 18, e1003757.
69. DiPietro, L., Gribok, A., Stevens, M.S., Hamm, L.F., and Rumpel, W. (2013). Three 15-min bouts of moderate postmeal walking significantly improves 24-h glycemic control in older people at risk for impaired glucose tolerance. *Diabetes Care* 36, 3262–3268.
70. Moholdt, T., Parr, E.B., Devlin, B.L., Debik, J., Giskeødegård, G., and Hawley, J.A. (2021). The effect of morning vs evening exercise training on glycaemic control and serum metabolites in overweight/obese men: a randomised trial. *Diabetologia* 64, 2061–2076.
71. Savikj, M., Gabriel, B.M., Alm, P.S., Smith, J., Caidahl, K., Björnholm, M., Fritz, T., Krook, A., Zierath, J.R., and Wallberg-Henriksson, H. (2019). Afternoon exercise is more efficacious than morning exercise at improving blood glucose levels in individuals with type 2 diabetes: a randomised crossover trial. *Diabetologia* 62, 233–237.
72. Stenvers, D.J., Scheer, F.A.J.L., Schrauwen, P., la Fleur, S.E., and Kalsbeek, A. (2019). Circadian clocks and insulin resistance. *Nat. Rev. Endocrinol.* 15, 75–89.
73. Van Cauter, E., Polonsky, K.S., and Scheen, A.J. (1997). Roles of circadian rhythmicity and sleep in human glucose regulation. *Endocr. Rev.* 18, 716–738.
74. O'rahilly, S., Turner, R.C., and Matthews, D.R. (1988). Impaired pulsatile secretion of insulin in relatives of patients with non-insulin-dependent diabetes. *N. Engl. J. Med.* 318, 1225–1230.
75. Jarrett, R.J., and Keen, H. (1969). Diurnal variation of oral glucose tolerance: a possible pointer to the evolution of diabetes mellitus. *Br. Med. J.* 2, 341–344.
76. Teo, S.Y.M., Kanaley, J.A., Guelfi, K.J., Dimmock, J.A., Jackson, B., and Fairchild, T.J. (2021). Effects of diurnal exercise timing on appetite, energy intake and body composition: a parallel randomized trial. *Appetite* 167, 105600.
77. Sato, S., Basse, A.L., Schöнке, M., Chen, S., Samad, M., Altıntaş, A., Laker, R.C., Dalbram, E., Barrès, R., Baldi, P., et al. (2019). Time of exercise specifies the impact on muscle metabolic pathways and systemic energy homeostasis. *Cell Metab.* 30, 92–110.e4.
78. Erickson, M.L., Allen, J.M., Beavers, D.P., Collins, L.M., Davidson, K.W., Erickson, K.I., Esser, K.A., Hesselink, M.K.C., Moreau, K.L., Laber, E.B., et al. (2023). Understanding heterogeneity of responses to, and optimizing clinical efficacy of, exercise training in older adults: NIH NIA Workshop summary. *GeroScience* 45, 569–589.
79. Gadie, A., Shafit, M., Leng, Y., and Kievit, R.A.; Cam-CAN (2017). How are age-related differences in sleep quality associated with health outcomes? An epidemiological investigation in a UK cohort of 2406 adults. *BMJ Open* 7, e014920.
80. Inoué, S., Honda, K., and Komoda, Y. (1995). Sleep as neuronal detoxification and restitution. *Behav. Brain Res.* 69, 91–96.
81. Xie, L., Kang, H., Xu, Q., Chen, M.J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D.J., Nicholson, C., Iliff, J.J., et al. (2013). Sleep drives metabolite clearance from the adult brain. *Science* 342, 373–377.
82. Watson, A.M. (2017). Sleep and athletic performance. *Curr. Sports Med. Rep.* 16, 413–418.
83. Chase, J.D., Roberson, P.A., Saunders, M.J., Hargens, T.A., Womack, C.J., and Luden, N.D. (2017). One night of sleep restriction following heavy exercise impairs 3-km cycling time-trial performance in the morning. *Appl. Physiol. Nutr. Metab.* 42, 909–915.
84. Cizza, G., Skarulis, M., and Mignot, E. (2005). A link between short sleep and obesity: building the evidence for causation. *Sleep* 28, 1217–1220.
85. Gangwisch, J.E., Malaspina, D., Boden-Albala, B., and Heymsfield, S.B. (2005). Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep* 28, 1289–1296.
86. Leng, Y., Wainwright, N.W., Cappuccio, F.P., Surtees, P.G., Hayat, S., Luben, R., Brayne, C., and Khaw, K.T. (2014). Daytime napping and the risk of all-cause and cause-specific mortality: a 13-year follow-up of a British population. *Am. J. Epidemiol.* 179, 1115–1124.
87. Smiley, A., King, D., and Bidulescu, A. (2019). The association between sleep duration and metabolic syndrome: the NHANES 2013/2014. *Nutrients* 11, 2582.
88. Youngstedt, S.D. (2005). Effects of exercise on sleep. *Clin. Sports Med.* 24, 355–365. xi.
89. Vaara, J.P., Oksanen, H., Kyröläinen, H., Virmavirta, M., Koski, H., and Finni, T. (2018). 60-hour sleep deprivation affects submaximal but not maximal physical performance. *Front. Physiol.* 9, 1437.
90. Symons, J.D., VanHelder, T., and Myles, W.S. (1988). Physical performance and physiological responses following 60 hours of sleep deprivation. *Med. Sci. Sports Exerc.* 20, 374–380.
91. Douglas, C.M., Hesketh, S.J., and Esser, K.A. (2021). Time of day and muscle strength: a circadian output? *Physiology (Bethesda)* 36, 44–51.
92. Reilly, T., and Piercy, M. (1994). The effect of partial sleep deprivation on weight-lifting performance. *Ergonomics* 37, 107–115.
93. Aubry, A., Hausswirth, C., Louis, J., Coutts, A.J., Buchheit, M., and Le Meur, Y. (2015). The development of functional overreaching is associated with a faster heart rate recovery in endurance athletes. *PLoS One* 10, e0139754.
94. Skein, M., Duffield, R., Edge, J., Short, M.J., and Mündel, T. (2011). Intermittent-sprint performance and muscle glycogen after 30 h of sleep deprivation. *Med. Sci. Sports Exerc.* 43, 1301–1311.
95. Ma, Y., Liang, L., Zheng, F., Shi, L., Zhong, B., and Xie, W. (2020). Association between sleep duration and cognitive decline. *JAMA Netw. Open* 3, e2013573.
96. Maloney, A., Mengesteab, S., Kallas, N., Bennett, M., and Kanaley, J.A. (2023). Sleep restriction by sleep timing late night or early wake: the impact on physical activity and dietary intake in adults. *Appetite* 189, 106996.
97. Porter, J.W., Pettit-Mee, R.J., Emerson, T.S., McCrae, C.S., Lastra, G., Vieira-Potter, V.J., Parks, E.J., and Kanaley, J.A. (2021). Modest sleep restriction does not influence steps, physical activity intensity or glucose tolerance in obese adults. *J. Sleep Res.* 30, e13381.
98. Tasali, E., Wroblewski, K., Kahn, E., Kilkus, J., and Schoeller, D.A. (2022). Effect of sleep extension on objectively assessed energy intake among adults with overweight in real-life settings: a randomized clinical trial. *JAMA Intern. Med.* 182, 365–374.
99. Aird, T.P., Davies, R.W., and Carson, B.P. (2018). Effects of fasted vs fed-state exercise on performance and post-exercise metabolism: A systematic review and meta-analysis. *Scand. J. Med. Sci. Sports* 28, 1476–1493.
100. Wallis, G.A., and Gonzalez, J.T. (2019). Is exercise best served on an empty stomach? *Proc. Nutr. Soc.* 78, 110–117.
101. Civitarese, A.E., Hesselink, M.K., Russell, A.P., Ravussin, E., and Schrauwen, P. (2005). Glucose ingestion during exercise blunts exercise-induced gene expression of skeletal muscle fat oxidative genes. *Am. J. Physiol. Endocrinol. Metab.* 289, E1023–E1029.

102. Cluberton, L.J., McGee, S.L., Murphy, R.M., and Hargreaves, M. (2005). Effect of carbohydrate ingestion on exercise-induced alterations in metabolic gene expression. *J. Appl. Physiol.* (1985) *99*, 1359–1363.
103. Chen, Y.C., Travers, R.L., Walhin, J.P., Gonzalez, J.T., Koumanov, F., Betts, J.A., and Thompson, D. (2017). Feeding influences adipose tissue responses to exercise in overweight men. *Am. J. Physiol. Endocrinol. Metab.* *313*, E84–E93.
104. Van Proeyen, K., Szulcick, K., Nielens, H., Pelgrim, K., Deldicque, L., Hesselink, M., Van Veldhoven, P.P., and Hespel, P. (2010). Training in the fasted state improves glucose tolerance during fat-rich diet. *J. Physiol.* *588*, 4289–4302.
105. Van Proeyen, K., Szulcick, K., Nielens, H., Ramaekers, M., and Hespel, P. (2011). Beneficial metabolic adaptations due to endurance exercise training in the fasted state. *J. Appl. Physiol.* (1985) *110*, 236–245.
106. Grant, C.L., Dorrian, J., Coates, A.M., Pajcin, M., Kennaway, D.J., Wittert, G.A., Heilbronn, L.K., Vedova, C.D., Gupta, C.C., and Banks, S. (2017). The impact of meal timing on performance, sleepiness, gastric upset, and hunger during simulated night shift. *Ind. Health* *55*, 423–436.
107. Vitale, K., and Getzin, A. (2019). Nutrition and supplement update for the endurance athlete: review and recommendations. *Nutrients* *11*, 1289.
108. Alghannam, A.F., Gonzalez, J.T., and Betts, J.A. (2018). Restoration of muscle glycogen and functional capacity: role of post-exercise carbohydrate and protein co-ingestion. *Nutrients* *10*, 253.
109. Mansor, L.S., and Woo, G.H. (2020). Ketones for post-exercise recovery: potential applications and mechanisms. *Front. Physiol.* *11*, 613648.
110. Ferguson-Stegall, L., McCleave, E.L., Ding, Z., Doerner, P.G., 3rd, Wang, B., Liao, Y.H., Kammer, L., Liu, Y., Hwang, J., Dessard, B.M., et al. (2011). Postexercise carbohydrate-protein supplementation improves subsequent exercise performance and intracellular signaling for protein synthesis. *J. Strength Cond. Res.* *25*, 1210–1224.
111. Howarth, K.R., Moreau, N.A., Phillips, S.M., and Gibala, M.J. (2009). Co-ingestion of protein with carbohydrate during recovery from endurance exercise stimulates skeletal muscle protein synthesis in humans. *J. Appl. Physiol.* (1985) *106*, 1394–1402.
112. Vliet, S.V., Beals, J.W., Martinez, I.G., Skinner, S.K., and Burd, N.A. (2018). Achieving optimal post-exercise muscle protein remodeling in physically active adults through whole food consumption. *Nutrients* *10*, 224.
113. Valsdottir, T.D., Øvrebø, B., Falck, T.M., Littlekare, S., Johansen, E.I., Henriksen, C., and Jensen, J. (2020). Low-carbohydrate high-fat diet and exercise: effect of a 10-week intervention on body composition and CVD risk factors in overweight and obese women—a randomized controlled trial. *Nutrients* *13*, 110.
114. Perissiou, M., Borkoles, E., Kobayashi, K., and Polman, R. (2020). The effect of an 8 week prescribed exercise and low-carbohydrate diet on cardiorespiratory fitness, body composition and cardiometabolic risk factors in obese individuals: a randomised controlled trial. *Nutrients* *12*, 482.
115. Cipryan, L., Plews, D.J., Ferretti, A., Maffetone, P.B., and Laursen, P.B. (2018). Effects of a 4-week very low-carbohydrate diet on high-intensity interval training responses. *J. Sports Sci. Med.* *17*, 259–268.
116. Wu, S.H., Chen, K.L., Hsu, C., Chen, H.C., Chen, J.Y., Yu, S.Y., and Shiu, Y.J. (2022). Creatine supplementation for muscle growth: a scoping review of randomized clinical trials from 2012 to 2021. *Nutrients* *14*, 1255.
117. Dutra, M.T., Martins, W.R., Ribeiro, A.L.A., and Bottaro, M. (2020). The effects of strength training combined with vitamin C and E supplementation on skeletal muscle mass and strength: a systematic review and meta-analysis. *J. Sports Med. (Hindawi Publ. Corp)* *2020*, 3505209.
118. Trappe, T.A., and Liu, S.Z. (2013). Effects of prostaglandins and COX-inhibiting drugs on skeletal muscle adaptations to exercise. *J. Appl. Physiol.* (1985) *115*, 909–919.
119. Trappe, T.A., Carroll, C.C., Dickinson, J.M., LeMoine, J.K., Haus, J.M., Sullivan, B.E., Lee, J.D., Jemiolo, B., Weinheimer, E.M., and Hollon, C.J. (2011). Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* *300*, R655–R662.
120. Trappe, T.A., Ratchford, S.M., Brower, B.E., Liu, S.Z., Lavin, K.M., Carroll, C.C., Jemiolo, B., and Trappe, S.W. (2016). COX inhibitor influence on skeletal muscle fiber size and metabolic adaptations to resistance exercise in older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* *71*, 1289–1294.
121. Trappe, T.A., Standley, R.A., Jemiolo, B., Carroll, C.C., and Trappe, S.W. (2013). Prostaglandin and myokine involvement in the cyclooxygenase-inhibiting drug enhancement of skeletal muscle adaptations to resistance exercise in older adults. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* *304*, R198–R205.
122. Trappe, T.A., White, F., Lambert, C.P., Cesar, D., Hellerstein, M., and Evans, W.J. (2002). Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. *Am. J. Physiol. Endocrinol. Metab.* *282*, E551–E556.
123. Merritt, E.K., Stec, M.J., Thalacker-Mercer, A., Windham, S.T., Cross, J.M., Shelley, D.P., Craig Tuggle, S., Kosek, D.J., Kim, J.S., and Barmann, M.M. (2013). Heightened muscle inflammation susceptibility may impair regenerative capacity in aging humans. *J. Appl. Physiol.* (1985) *115*, 937–948.
124. Ratchford, S.M., Lavin, K.M., Perkins, R.K., Jemiolo, B., Trappe, S.W., and Trappe, T.A. (2017). Aspirin as a COX inhibitor and anti-inflammatory drug in human skeletal muscle. *J. Appl. Physiol.* (1985) *123*, 1610–1616.
125. Miller, B.F., and Thyfault, J.P. (2020). Exercise-pharmacology interactions: metformin, statins, and healthspan. *Physiology (Bethesda)* *35*, 338–347.
126. Fontaine, E. (2018). Metformin-induced mitochondrial complex I inhibition: facts, uncertainties, and consequences. *Front. Endocrinol. (Lausanne)* *9*, 753.
127. Hawley, S.A., Gadalla, A.E., Olsen, G.S., and Hardie, D.G. (2002). The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism. *Diabetes* *51*, 2420–2425.
128. Rena, G., Hardie, D.G., and Pearson, E.R. (2017). The mechanisms of action of metformin. *Diabetologia* *60*, 1577–1585.
129. Bailey, C.J. (2017). Metformin: historical overview. *Diabetologia* *60*, 1566–1576.
130. Konopka, A.R., Laurin, J.L., Schoenberg, H.M., Reid, J.J., Castor, W.M., Wolff, C.A., Musci, R.V., Safairad, O.D., Linden, M.A., Biela, L.M., et al. (2019). Metformin inhibits mitochondrial adaptations to aerobic exercise training in older adults. *Aging Cell* *18*, e12880.
131. Malin, S.K., and Braun, B. (2013). Effect of metformin on substrate utilization after exercise training in adults with impaired glucose tolerance. *Appl. Physiol. Nutr. Metab.* *38*, 427–430.
132. Malin, S.K., Gerber, R., Chipkin, S.R., and Braun, B. (2012). Independent and combined effects of exercise training and metformin on insulin sensitivity in individuals with prediabetes. *Diabetes Care* *35*, 131–136.
133. Malin, S.K., Nightingale, J., Choi, S.E., Chipkin, S.R., and Braun, B. (2013). Metformin modifies the exercise training effects on risk factors for cardiovascular disease in impaired glucose tolerant adults. *Obesity (Silver Spring)* *21*, 93–100.
134. Sharoff, C.G., Hagobian, T.A., Malin, S.K., Chipkin, S.R., Yu, H., Hirshman, M.F., Goodyear, L.J., and Braun, B. (2010). Combining short-term metformin treatment and one bout of exercise does not increase insulin action in insulin-resistant individuals. *Am. J. Physiol. Endocrinol. Metab.* *298*, E815–E823.
135. Walton, R.G., Dungan, C.M., Long, D.E., Tuggle, S.C., Kosmac, K., Peck, B.D., Bush, H.M., Villasante Tezanos, A.G., McGwin, G., Windham, S.T., et al. (2019). Metformin blunts muscle hypertrophy in response to progressive resistance exercise training in older adults: A randomized, double-blind, placebo-controlled, multicenter trial: the MASTERS trial. *Aging Cell* *18*, e13039.
136. Braun, B., Eze, P., Stephens, B.R., Hagobian, T.A., Sharoff, C.G., Chipkin, S.R., and Goldstein, B. (2008). Impact of metformin on peak aerobic capacity. *Appl. Physiol. Nutr. Metab.* *33*, 61–67.
137. Das, S., Behera, S.K., Srinivasan, A., Xavier, A.S., Selvarajan, S., Kamilanathan, S., Sahoo, J.P., and Nair, N.S. (2018). Effect of metformin on

- exercise capacity: A meta-analysis. *Diabetes Res. Clin. Pract.* 144, 270–278.
138. Malin, S.K., and Braun, B. (2016). Impact of metformin on exercise-induced metabolic adaptations to lower type 2 diabetes risk. *Exerc. Sport Sci. Rev.* 44, 4–11.
139. Moreno-Cabañas, A., Ortega, J.F., Morales-Palomo, F., Ramirez-Jimenez, M., Alvarez-Jimenez, L., and Mora-Rodriguez, R. (2022). One bout of resistance training does not enhance metformin actions in prediabetic and diabetic individuals. *Med. Sci. Sports Exerc.* 54, 1043–1050.
140. Pilmark, N.S., Oberholzer, L., Halling, J.F., Kristensen, J.M., Bonding, C.P., Elkjaer, I., Lyngbaek, M., Elster, G., Siebenmann, C., Holm, N.F.R., et al. (2022). Skeletal muscle adaptations to exercise are not influenced by metformin treatment in humans: secondary analyses of 2 randomized, clinical trials. *Appl. Physiol. Nutr. Metab.* 47, 309–320.
141. Abdelbasset, W.K. (2021). Resistance exercise versus aerobic exercise combined with metformin therapy in the treatment of type 2 diabetes: A 12-week comparative clinical study. *Endocr. Metab. Immune Disord. Drug Targets* 21, 1531–1536.
142. Boulé, N.G., Kenny, G.P., Larose, J., Khandwala, F., Kuzik, N., and Sigal, R.J. (2013). Does metformin modify the effect on glycaemic control of aerobic exercise, resistance exercise or both? *Diabetologia* 56, 2378–2382.
143. Long, D.E., Peck, B.D., Tuggle, S.C., Villasante Tezanos, A.G., Windham, S.T., Bamman, M.M., Kern, P.A., Peterson, C.A., and Walton, R.G. (2021). Associations of muscle lipid content with physical function and resistance training outcomes in older adults: altered responses with metformin. *GeroScience* 43, 629–644.
144. Kulkarni, A.S., Peck, B.D., Walton, R.G., Kern, P.A., Mar, J.C., Windham, S.T., Bamman, M.M., Barzilai, N., and Peterson, C.A. (2020). Metformin alters skeletal muscle transcriptome adaptations to resistance training in older adults. *Aging (Albany, NY)* 12, 19852–19866.
145. Long, D.E., Kosmac, K., Dungan, C.M., Bamman, M.M., Peterson, C.A., and Kern, P.A. (2022). Potential benefits of combined statin and metformin therapy on resistance training response in older individuals. *Front. Physiol.* 13, 872745.
146. Mikus, C.R., Boyle, L.J., Borengasser, S.J., Oberlin, D.J., Naples, S.P., Fletcher, J., Meers, G.M., Ruebel, M., Laughlin, M.H., Dellsperger, K.C., et al. (2013). Simvastatin impairs exercise training adaptations. *J. Am. Coll. Cardiol.* 62, 709–714.
147. Parker, B.A., and Thompson, P.D. (2012). Effect of statins on skeletal muscle: exercise, myopathy, and muscle outcomes. *Exerc. Sport Sci. Rev.* 40, 188–194.
148. Allard, N.A.E., Janssen, L., Aussieker, T., Stoffels, A.A.F., Rodenburg, R.J., Assendelft, W.J.J., Thompson, P.D., Snijders, T., Hopman, M.T.E., and Timmers, S. (2021). Moderate intensity exercise training improves skeletal muscle performance in symptomatic and asymptomatic statin users. *J. Am. Coll. Cardiol.* 78, 2023–2037.
149. Alturki, M., Liberman, K., Delaere, A., De Dobbelaar, L., Knoop, V., Mets, T., Lieten, S., Bravenboer, B., Beyer, I., and Bautmans, I. (2021). Effect of antihypertensive and statin medication use on muscle performance in community-dwelling older adults performing strength training. *Drugs Aging* 38, 253–263.
150. Panayiotou, G., Paschalis, V., Nikolaidis, M.G., Theodorou, A.A., Deli, C.K., Fotopoulou, N., Fatouros, I.G., Koutedakis, Y., Sampanis, M., and Jamurtas, A.Z. (2013). No adverse effects of statins on muscle function and health-related parameters in the elderly: an exercise study. *Scand. J. Med. Sci. Sports* 23, 556–567.
151. Riechman, S.E., Andrews, R.D., Maclean, D.A., and Sheather, S. (2007). Statins and dietary and serum cholesterol are associated with increased lean mass following resistance training. *J. Gerontol. A Biol. Sci. Med. Sci.* 62, 1164–1171.
152. Morales-Palomo, F., Ramirez-Jimenez, M., Ortega, J.F., Moreno-Cabañas, A., and Mora-Rodriguez, R. (2020). Exercise training adaptations in metabolic syndrome individuals on chronic statin treatment. *J. Clin. Endocrinol. Metab.* 105, dgz304.
153. Selva-O'Callaghan, A., Alvarado-Cardenas, M., Pinal-Fernández, I., Trallero-Araguás, E., Milisenda, J.C., Martínez, M.Á., Marín, A., Labrador-Horrillo, M., Juárez, C., and Grau-Junyent, J.M. (2018). Statin-induced myalgia and myositis: an update on pathogenesis and clinical recommendations. *Expert Rev. Clin. Immunol.* 14, 215–224.
154. Linden, M.A., Ross, T.T., Beebe, D.A., Gorgoglione, M.F., Hamilton, K.L., Miller, B.F., Braun, B., and Esler, W.P. (2019). The combination of exercise training and sodium-glucose cotransporter-2 inhibition improves glucose tolerance and exercise capacity in a rodent model of type 2 diabetes. *Metabolism* 97, 68–80.
155. Peng, Y., Qin, D., Wang, Y., Xue, L., Qin, Y., and Xu, X. (2022). The effect of SGLT-2 inhibitors on cardiorespiratory fitness capacity: A systematic review and meta-analysis. *Front. Physiol.* 13, 1081920.
156. Newman, A.A., Grimm, N.C., Wilburn, J.R., Schoenberg, H.M., Trikha, S.R.J., Luckasen, G.J., Biela, L.M., Melby, C.L., and Bell, C. (2019). Influence of sodium glucose cotransporter 2 inhibition on physiological adaptation to endurance exercise training. *J. Clin. Endocrinol. Metab.* 104, 1953–1966.
157. Mensberg, P., Nyby, S., Jørgensen, P.G., Storgaard, H., Jensen, M.T., Silvertsen, J., Holst, J.J., Kiens, B., Richter, E.A., Knop, F.K., et al. (2017). Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes. *Diabetes Obes. Metab.* 19, 172–180.
158. Peel, C., and Mossberg, K.A. (1995). Effects of cardiovascular medications on exercise responses. *Phys. Ther.* 75, 387–396.
159. Chick, T.W., Halperin, A.K., and Gacek, E.M. (1988). The effect of antihypertensive medications on exercise performance: a review. *Med. Sci. Sports Exerc.* 20, 447–454.
160. Sagoe, D., Molde, H., Andreassen, C.S., Torsheim, T., and Pallesen, S. (2014). The global epidemiology of anabolic-androgenic steroid use: a meta-analysis and meta-regression analysis. *Ann. Epidemiol.* 24, 383–398.
161. Parkinson, A.B., and Evans, N.A. (2006). Anabolic androgenic steroids: a survey of 500 users. *Med. Sci. Sports Exerc.* 38, 644–651.
162. Ferrando, A.A., Tipton, K.D., Doyle, D., Phillips, S.M., Cortiella, J., and Wolfe, R.R. (1998). Testosterone injection stimulates net protein synthesis but not tissue amino acid transport. *Am. J. Physiol.* 275, E864–E871.
163. Sinha-Hikim, I., Artaza, J., Woodhouse, L., Gonzalez-Cadavid, N., Singh, A.B., Lee, M.I., Storer, T.W., Casaburi, R., Shen, R., and Bhasin, S. (2002). Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. *Am. J. Physiol. Endocrinol. Metab.* 283, E154–E164.
164. Bhasin, S., Storer, T.W., Berman, N., Callegari, C., Clevenger, B., Phillips, J., Bunnell, T.J., Tricker, R., Shirazi, A., and Casaburi, R. (1996). The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N. Engl. J. Med.* 335, 1–7.
165. Storer, T.W., Magliano, L., Woodhouse, L., Lee, M.L., Dzekov, C., Dzekov, J., Casaburi, R., and Bhasin, S. (2003). Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. *J. Clin. Endocrinol. Metab.* 88, 1478–1485.
166. Storer, T.W., Woodhouse, L., Magliano, L., Singh, A.B., Dzekov, C., Dzekov, J., and Bhasin, S. (2008). Changes in muscle mass, muscle strength, and power but not physical function are related to testosterone dose in healthy older men. *J. Am. Geriatr. Soc.* 56, 1991–1999.
167. Bhasin, S., Woodhouse, L., Casaburi, R., Singh, A.B., Mac, R.P., Lee, M., Yarasheski, K.E., Sinha-Hikim, I., Dzekov, C., Dzekov, J., et al. (2005). Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. *J. Clin. Endocrinol. Metab.* 90, 678–688.
168. Woodhouse, L.J., Reisz-Porszasz, S., Javanbakht, M., Storer, T.W., Lee, M., Zerounian, H., and Bhasin, S. (2003). Development of models to predict anabolic response to testosterone administration in healthy young men. *Am. J. Physiol. Endocrinol. Metab.* 284, E1009–E1017.
169. Bhasin, S., Woodhouse, L., Casaburi, R., Singh, A.B., Bhasin, D., Berman, N., Chen, X., Yarasheski, K.E., Magliano, L., Dzekov, C., et al.

- (2001). Testosterone dose-response relationships in healthy young men. *Am. J. Physiol. Endocrinol. Metab.* 281, E1172–E1181.
170. Yu, J.G., Bonnerud, P., Eriksson, A., Stål, P.S., Tegner, Y., and Malm, C. (2014). Effects of long term supplementation of anabolic androgen steroids on human skeletal muscle. *PLoS One* 9, e105330.
171. Dos Santos, M.R., Sayegh, A.L., Bacurau, A.V., Arap, M.A., Brum, P.C., Pereira, R.M., Takayama, L., Barretto, A.C., Negrão, C.E., and Alves, M.J. (2016). Effect of exercise training and testosterone replacement on skeletal muscle wasting in patients with heart failure with testosterone deficiency. *Mayo Clin. Proc.* 91, 575–586.
172. Falquetto, H., Dos Santos, M.R., and Manfredi, L.H. (2022). Anabolic-androgenic steroids and exercise training: breaking the myths and dealing with better outcome in sarcopenia. *Front. Physiol.* 13, 838526.
173. Falquetto, H., Júnior, J.L.R., Silvério, M.N.O., Farias, J.C.H., Schoenfeld, B.J., and Manfredi, L.H. (2021). Can conditions of skeletal muscle loss be improved by combining exercise with anabolic-androgenic steroids? A systematic review and meta-analysis of testosterone-based interventions. *Rev. Endocr. Metab. Disord.* 22, 161–178.
174. Abbasi, A., de Paula Vieira, R., Bischof, F., Walter, M., Movassaghi, M., Berchtold, N.C., Niess, A.M., Cotman, C.W., and Northoff, H. (2016). Sex-specific variation in signaling pathways and gene expression patterns in human leukocytes in response to endotoxin and exercise. *J. Neuroinflammation* 13, 289.
175. Hackney, A.C., Kallman, A.L., and Åggön, E. (2019). Female sex hormones and the recovery from exercise: menstrual cycle phase affects responses. *Biomed. Hum. Kinet.* 11, 87–89.
176. Roberts, B.M., Lavin, K.M., Many, G.M., Thalacker-Mercer, A., Merritt, E.K., Bickel, C.S., Mayhew, D.L., Tuggle, S.C., Cross, J.M., Kosek, D.J., et al. (2018). Human neuromuscular aging: sex differences revealed at the myocellular level. *Exp. Gerontol.* 106, 116–124.
177. Wüst, R.C., Morse, C.I., de Haan, A., Jones, D.A., and Degens, H. (2008). Sex differences in contractile properties and fatigue resistance of human skeletal muscle. *Exp. Physiol.* 93, 843–850.
178. Diaz-Canestro, C., Pentz, B., Sehgal, A., and Montero, D. (2022). Sex differences in cardiorespiratory fitness are explained by blood volume and oxygen carrying capacity. *Cardiovasc. Res.* 118, 334–343.
179. Lewis, D.A., Kamon, E., and Hodgson, J.L. (1986). Physiological differences between genders. Implications for sports conditioning. *Sports Med.* 3, 357–369.
180. Spina, R.J., Ogawa, T., Kohrt, W.M., Martin, W.H., 3rd, Holloszy, J.O., and Ehsani, A.A. (1993). Differences in cardiovascular adaptations to endurance exercise training between older men and women. *J. Appl. Physiol.* (1985) 75, 849–855.
181. Landen, S., Voisin, S., Craig, J.M., McGee, S.L., Lamon, S., and Eynon, N. (2019). Genetic and epigenetic sex-specific adaptations to endurance exercise. *Epigenetics* 14, 523–535.
182. Devries, M.C. (2016). Sex-based differences in endurance exercise muscle metabolism: impact on exercise and nutritional strategies to optimize health and performance in women. *Exp. Physiol.* 101, 243–249.
183. Devries, M.C., Hamadeh, M.J., Phillips, S.M., and Tarnopolsky, M.A. (2006). Menstrual cycle phase and sex influence muscle glycogen utilization and glucose turnover during moderate-intensity endurance exercise. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 291, R1120–R1128.
184. Westerterp, K.R. (2018). Changes in physical activity over the lifespan: impact on body composition and sarcopenic obesity. *Obes. Rev.* 19 (Suppl 1), 8–13.
185. Astrand, I. (1960). Aerobic work capacity in men and women with special reference to age. *Acta Physiol. Scand. Suppl.* 49, 1–92.
186. Lexell, J., Taylor, C.C., and Sjöström, M. (1988). What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J. Neurol. Sci.* 84, 275–294.
187. Koster, A., Ding, J., Stenholm, S., Caserotti, P., Houston, D.K., Nicklas, B.J., You, T., Lee, J.S., Visser, M., Newman, A.B., et al. (2011). Does the amount of fat mass predict age-related loss of lean mass, muscle strength, and muscle quality in older adults? *J. Gerontol. A Biol. Sci. Med. Sci.* 66, 888–895.
188. Booth, F.W., Roberts, C.K., and Laye, M.J. (2012). Lack of exercise is a major cause of chronic diseases. *Compr. Physiol.* 2, 1143–1211.
189. Grevendonk, L., Connell, N.J., McCrum, C., Fealy, C.E., Bilet, L., Bruls, Y.M.H., Mevenkamp, J., Schrauwen-Hinderling, V.B., Jörgensen, J.A., Moonen-Kornips, E., et al. (2021). Impact of aging and exercise on skeletal muscle mitochondrial capacity, energy metabolism, and physical function. *Nat. Commun.* 12, 4773.
190. Lefferts, W.K., Davis, M.M., and Valentine, R.J. (2022). Exercise as an aging mimetic: a new perspective on the mechanisms behind exercise as preventive medicine against age-related chronic disease. *Front. Physiol.* 13, 866792.
191. Lazarus, N.R., and Harridge, S.D.R. (2018). The inherent human aging process and the facilitating role of exercise. *Front. Physiol.* 9, 1135.
192. Distefano, G., Standley, R.A., Zhang, X., Carnero, E.A., Yi, F., Cornell, H.H., and Coen, P.M. (2018). Physical activity unveils the relationship between mitochondrial energetics, muscle quality, and physical function in older adults. *J. Cachexia Sarcopenia Muscle* 9, 279–294.
193. Woo, J.S., Derleth, C., Stratton, J.R., and Levy, W.C. (2006). The influence of age, gender, and training on exercise efficiency. *J. Am. Coll. Cardiol.* 47, 1049–1057.
194. Distefano, G., and Goodpaster, B.H. (2018). Effects of exercise and aging on skeletal muscle. *Cold Spring Harb. Perspect. Med.* 8, a029785.
195. Robinson, M.M., Dasari, S., Konopka, A.R., Johnson, M.L., Manjunatha, S., Esponda, R.R., Carter, R.E., Lanza, I.R., and Nair, K.S. (2017). Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. *Cell Metab.* 25, 581–592.
196. Kohrt, W.M., Malley, M.T., Coggan, A.R., Spina, R.J., Ogawa, T., Ehsani, A.A., Bourey, R.E., Martin, W.H., 3rd, and Holloszy, J.O. (1991). Effects of gender, age, and fitness level on response of VO<sub>2</sub>max to training in 60–71 yr olds. *J. Appl. Physiol.* (1985) 71, 2004–2011.
197. Kumar, V., Selby, A., Rankin, D., Patel, R., Atherton, P., Hildebrandt, W., Williams, J., Smith, K., Seynnes, O., Hiscock, N., et al. (2009). Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. *J. Physiol.* 587, 211–217.
198. Lavin, K.M., Perkins, R.K., Jemiolo, B., Raue, U., Trappe, S.W., and Trappe, T.A. (2020). Effects of aging and lifelong aerobic exercise on basal and exercise-induced inflammation. *J. Appl. Physiol.* (1985) 128, 87–99.
199. Hogan, C.L., Mata, J., and Carstensen, L.L. (2013). Exercise holds immediate benefits for affect and cognition in younger and older adults. *Psychol. Aging* 28, 587–594.
200. Fujimoto, N., Prasad, A., Hastings, J.L., Arbab-Zadeh, A., Bhella, P.S., Shibata, S., Palmer, D., and Levine, B.D. (2010). Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age. *Circulation* 122, 1797–1805.
201. Stratton, J.R., Levy, W.C., Cerqueira, M.D., Schwartz, R.S., and Abrass, I.B. (1994). Cardiovascular responses to exercise. Effects of aging and exercise training in healthy men. *Circulation* 89, 1648–1655.
202. Fiatarone, M.A., O'Neill, E.F., Ryan, N.D., Clements, K.M., Solares, G.R., Nelson, M.E., Roberts, S.B., Kehayias, J.J., Lipsitz, L.A., and Evans, W.J. (1994). Exercise training and nutritional supplementation for physical frailty in very elderly people. *N. Engl. J. Med.* 330, 1769–1775.
203. Fleg, J.L., Tzankoff, S.P., and Lakatta, E.G. (1985). Age-related augmentation of plasma catecholamines during dynamic exercise in healthy males. *J. Appl. Physiol.* (1985) 59, 1033–1039.
204. Greig, C.A., Gray, C., Rankin, D., Young, A., Mann, V., Noble, B., and Atherton, P.J. (2011). Blunting of adaptive responses to resistance exercise training in women over 75y. *Exp. Gerontol.* 46, 884–890.

205. Meredith, C.N., Frontera, W.R., Fisher, E.C., Hughes, V.A., Herland, J.C., Edwards, J., and Evans, W.J. (1989). Peripheral effects of endurance training in young and old subjects. *J. Appl. Physiol.* (1985) 66, 2844–2849.
206. Chilibeck, P.D., Paterson, D.H., Petrella, R.J., and Cunningham, D.A. (1996). The influence of age and cardiorespiratory fitness on kinetics of oxygen uptake. *Can. J. Appl. Physiol.* 21, 185–196.
207. Babcock, M.A., Paterson, D.H., and Cunningham, D.A. (1994). Effects of aerobic endurance training on gas exchange kinetics of older men. *Med. Sci. Sports Exerc.* 26, 447–452.
208. Short, K.R., Bigelow, M.L., Kahl, J., Singh, R., Coenen-Schimke, J., Raghavakaimal, S., and Nair, K.S. (2005). Decline in skeletal muscle mitochondrial function with aging in humans. *Proc. Natl. Acad. Sci. USA* 102, 5618–5623.
209. Coen, P.M., Jubrias, S.A., Distefano, G., Amati, F., Mackey, D.C., Glynn, N.W., Manini, T.M., Wohlgenuth, S.E., Leeuwenburgh, C., Cummings, S.R., et al. (2013). Skeletal muscle mitochondrial energetics are associated with maximal aerobic capacity and walking speed in older adults. *J. Gerontol. A Biol. Sci. Med. Sci.* 68, 447–455.
210. Zane, A.C., Reiter, D.A., Shardell, M., Cameron, D., Simonsick, E.M., Fishbein, K.W., Studenski, S.A., Spencer, R.G., and Ferrucci, L. (2017). Muscle strength mediates the relationship between mitochondrial energetics and walking performance. *Aging Cell* 16, 461–468.
211. Lanza, I.R., Short, D.K., Short, K.R., Raghavakaimal, S., Basu, R., Joyner, M.J., McConnell, J.P., and Nair, K.S. (2008). Endurance exercise as a countermeasure for aging. *Diabetes* 57, 2933–2942.
212. Lazarus, N.R., and Harridge, S.D. (2010). Exercise, physiological function, and the selection of participants for aging research. *J. Gerontol. A Biol. Sci. Med. Sci.* 65, 854–857.
213. Gopinath, B., Kifley, A., Flood, V.M., and Mitchell, P. (2018). Physical activity as a determinant of successful aging over ten years. *Sci. Rep.* 8, 10522.
214. Tanaka, H., and Seals, D.R. (2003). Invited Review: dynamic exercise performance in Masters athletes: insight into the effects of primary human aging on physiological functional capacity. *J. Appl. Physiol.* (1985) 95, 2152–2162.
215. Pimentel, A.E., Gentile, C.L., Tanaka, H., Seals, D.R., and Gates, P.E. (2003). Greater rate of decline in maximal aerobic capacity with age in endurance-trained than in sedentary men. *J. Appl. Physiol.* (1985) 94, 2406–2413.
216. Wilson, T.M., and Tanaka, H. (2000). Meta-analysis of the age-associated decline in maximal aerobic capacity in men: relation to training status. *Am. J. Physiol. Heart Circ. Physiol.* 278, H829–H834.
217. Haran, P.H., Rivas, D.A., and Fielding, R.A. (2012). Role and potential mechanisms of anabolic resistance in sarcopenia. *J. Cachexia Sarcopenia Muscle* 3, 157–162.
218. Raue, U., Slivka, D., Minchev, K., and Trappe, S. (2009). Improvements in whole muscle and myocellular function are limited with high-intensity resistance training in octogenarian women. *J. Appl. Physiol.* (1985) 106, 1611–1617.
219. Slivka, D., Raue, U., Hollon, C., Minchev, K., and Trappe, S. (2008). Single muscle fiber adaptations to resistance training in old (>80 yr) men: evidence for limited skeletal muscle plasticity. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 295, R273–R280.
220. Harber, M.P., Konopka, A.R., Douglass, M.D., Minchev, K., Kaminsky, L.A., Trappe, T.A., and Trappe, S. (2009). Aerobic exercise training improves whole muscle and single myofiber size and function in older women. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 297, R1452–R1459.
221. Trappe, S., Godard, M., Gallagher, P., Carroll, C., Rowden, G., and Porter, D. (2001). Resistance training improves single muscle fiber contractile function in older women. *Am. J. Physiol. Cell Physiol.* 281, C398–C406.
222. Fiatarone, M.A., Marks, E.C., Ryan, N.D., Meredith, C.N., Lipsitz, L.A., and Evans, W.J. (1990). High-intensity strength training in nonagenarians. Effects on skeletal muscle. *JAMA* 263, 3029–3034.
223. Wang, E., Nyberg, S.K., Hoff, J., Zhao, J., Leivseth, G., Tørrhaug, T., Husby, O.S., Helgerud, J., and Richardson, R.S. (2017). Impact of maximal strength training on work efficiency and muscle fiber type in the elderly: implications for physical function and fall prevention. *Exp. Gerontol.* 91, 64–71.
224. Breen, L., and Phillips, S.M. (2011). Skeletal muscle protein metabolism in the elderly: interventions to counteract the ‘anabolic resistance’ of ageing. *Nutr. Metab. (Lond.)* 8, 68.
225. Dubé, J.J., Amati, F., Stefanovic-Racic, M., Toledo, F.G., Sauers, S.E., and Goodpaster, B.H. (2008). Exercise-induced alterations in intramyocellular lipids and insulin resistance: the athlete’s paradox revisited. *Am. J. Physiol. Endocrinol. Metab.* 294, E882–E888.
226. Børsø, R.S., Olesen, J., Gliemann, L., Schmidt, J.F., Matzen, M.S., Wojtaszewski, J.F., Hellsten, Y., and Pilegaard, H. (2015). Effects of exercise training on regulation of skeletal muscle glucose metabolism in elderly men. *J. Gerontol. A Biol. Sci. Med. Sci.* 70, 866–872.
227. Peterson, M.J., Morey, M.C., Giuliani, C., Pieper, C.F., Evenson, K.R., Mercer, V., Visser, M., Brach, J.S., Kritchevsky, S.B., Goodpaster, B.H., et al. (2010). Walking in old age and development of metabolic syndrome: the health, aging, and body composition study. *Metab. Syndr. Relat. Disord.* 8, 317–322.
228. Skolasinska, P., Basak, C., and Qin, S. (2023). Influence of strenuous physical activity and cardiorespiratory fitness on age-related differences in brain activations during varieties of cognitive control. *Neuroscience* 520, 58–83.
229. Bouchard, C., and Rankinen, T. (2001). Individual differences in response to regular physical activity. discussion S452–S453. *Med. Sci. Sports Exerc.* 33 (6 Suppl), S446–S451.
230. Henriksson, H., Henriksson, P., Tynelius, P., Ekstedt, M., Berglund, D., Labayen, I., Ruiz, J.R., Lavie, C.J., and Ortega, F.B. (2020). Cardiorespiratory fitness, muscular strength, and obesity in adolescence and later chronic disability due to cardiovascular disease: a cohort study of 1 million men. *Eur. Heart J.* 41, 1503–1510.
231. Stillman, C.M., Esteban-Cornejo, I., Brown, B., Bender, C.M., and Erickson, K.I. (2020). Effects of exercise on brain and cognition across age groups and health states. *Trends Neurosci.* 43, 533–543.
232. Etner, J.L., Salazar, W., Landers, D.M., Petruzzello, S.J., Han, M., and Nowell, P. (1997). The influence of physical fitness and exercise upon cognitive functioning: a meta-analysis. *J. Sport Exerc. Psychol.* 19, 249–277.
233. O’Connor, P.J., Tomporowski, P.D., and Dishman, R.K. (2015). Age moderates the association of aerobic exercise with initial learning of an online task requiring cognitive control. *J. Int. Neuropsychol. Soc.* 21, 802–815.
234. Guthold, R., Stevens, G.A., Riley, L.M., and Bull, F.C. (2020). Global trends in insufficient physical activity among adolescents: a pooled analysis of 298 population-based surveys with 1.6 million participants. *Lancet Child Adolesc. Health* 4, 23–35.
235. van Sluijs, E.M.F., Ekelund, U., Crochemore-Silva, I., Guthold, R., Ha, A., Lubans, D., Oyeyemi, A.L., Ding, D., and Katzmarzyk, P.T. (2021). Physical activity behaviours in adolescence: current evidence and opportunities for intervention. *Lancet* 398, 429–442.
236. Fernandes, A.L., Lopes-Silva, J.P., Bertuzzi, R., Casarini, D.E., Arita, D.Y., Bishop, D.J., and Lima-Silva, A.E. (2014). Effect of time of day on performance, hormonal and metabolic response during a 1000-M cycling time trial. *PLoS One* 9, e109954.
237. Deschenes, M.R., Kraemer, W.J., Bush, J.A., Doughty, T.A., Kim, D., Mullen, K.M., and Ramsey, K. (1998). Biorhythmic influences on functional capacity of human muscle and physiological responses. *Med. Sci. Sports Exerc.* 30, 1399–1407.
238. Burd, N.A., West, D.W., Staples, A.W., Atherton, P.J., Baker, J.M., Moore, D.R., Holwerda, A.M., Parise, G., Rennie, M.J., Baker, S.K., et al. (2010). Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. *PLoS One* 5, e12033.
239. Mitchell, C.J., Churchward-Venne, T.A., West, D.W., Burd, N.A., Breen, L., Baker, S.K., and Phillips, S.M. (2012). Resistance exercise load

- does not determine training-mediated hypertrophic gains in young men. *J. Appl. Physiol.* (1985) 113, 71–77.
240. Morton, R.W., Oikawa, S.Y., Wavell, C.G., Mazara, N., McGlory, C., Quadrilatero, J., Baechler, B.L., Baker, S.K., and Phillips, S.M. (2016). Neither load nor systemic hormones determine resistance training-mediated hypertrophy or strength gains in resistance-trained young men. *J. Appl. Physiol.* (1985) 127, 129–138.
241. Schoenfeld, B.J., Peterson, M.D., Ogborn, D., Contreras, B., and Sonmez, G.T. (2015). Effects of low- vs. high-load resistance training on muscle strength and hypertrophy in well-trained men. *J. Strength Cond. Res.* 29, 2954–2963.
242. West, D.W., Burd, N.A., Tang, J.E., Moore, D.R., Staples, A.W., Holwerda, A.M., Baker, S.K., and Phillips, S.M. (2010). Elevations in ostensibly anabolic hormones with resistance exercise enhance neither training-induced muscle hypertrophy nor strength of the elbow flexors. *J. Appl. Physiol.* (1985) 108, 60–67.
243. West, D.W., Kujbida, G.W., Moore, D.R., Atherton, P., Burd, N.A., Padzik, J.P., De Lisio, M., Tang, J.E., Parise, G., Rennie, M.J., et al. (2009). Resistance exercise-induced increases in putative anabolic hormones do not enhance muscle protein synthesis or intracellular signalling in young men. *J. Physiol.* 587, 5239–5247.
244. Seals, D.R., Nagy, E.E., and Moreau, K.L. (2019). Aerobic exercise training and vascular function with ageing in healthy men and women. *J. Physiol.* 597, 4901–4914.
245. Moreau, K.L., Stauffer, B.L., Kohrt, W.M., and Seals, D.R. (2013). Essential role of estrogen for improvements in vascular endothelial function with endurance exercise in postmenopausal women. *J. Clin. Endocrinol. Metab.* 98, 4507–4515.
246. Gliemann, L., and Hellsten, Y. (2019). The exercise timing hypothesis: can exercise training compensate for the reduction in blood vessel function after menopause if timed right? *J. Physiol.* 597, 4915–4925.
247. Pierce, G.L., Eskurza, I., Walker, A.E., Fay, T.N., and Seals, D.R. (2011). Sex-specific effects of habitual aerobic exercise on brachial artery flow-mediated dilation in middle-aged and older adults. *Clin. Sci. (Lond.)* 120, 13–23.
248. Nyberg, M., Seidelin, K., Andersen, T.R., Overby, N.N., Hellsten, Y., and Bangsbo, J. (2014). Biomarkers of vascular function in premenopausal and recent postmenopausal women of similar age: effect of exercise training. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 306, R510–R517.
249. Nyberg, M., Egelund, J., Mandrup, C.M., Nielsen, M.B., Mogensen, A.S., Stallknecht, B., Bangsbo, J., and Hellsten, Y. (2016). Early postmenopausal phase is associated with reduced prostacyclin-induced vasodilation that is reversed by exercise training: the Copenhagen Women Study. *Hypertension* 68, 1011–1020.
250. Egelund, J., Jørgensen, P.G., Mandrup, C.M., Fritz-Hansen, T., Stallknecht, B., Bangsbo, J., Nyberg, M., and Hellsten, Y. (2017). Cardiac adaptations to high-intensity aerobic training in premenopausal and recent postmenopausal women: the Copenhagen Women Study. *J. Am. Heart Assoc.* 6, e005469.
251. Pierce, G.L., Donato, A.J., LaRocca, T.J., Eskurza, I., Silver, A.E., and Seals, D.R. (2011). Habitually exercising older men do not demonstrate age-associated vascular endothelial oxidative stress. *Aging Cell* 10, 1032–1037.
252. Hodis, H.N., Mack, W.J., Henderson, V.W., Shoupe, D., Budoff, M.J., Hwang-Levine, J., Li, Y., Feng, M., Dustin, L., Kono, N., et al. (2016). Vascular effects of early versus late postmenopausal treatment with estradiol. *N. Engl. J. Med.* 374, 1221–1231.
253. Gavin, K.M., Kohrt, W.M., Klemm, D.J., and Melanson, E.L. (2018). Modulation of energy expenditure by estrogens and exercise in women. *Exerc. Sport Sci. Rev.* 46, 232–239.
254. Melanson, E.L., Lyden, K., Gibbons, E., Gavin, K.M., Wolfe, P., Wierman, M.E., Schwartz, R.S., and Kohrt, W.M. (2018). Influence of estradiol status on physical activity in premenopausal women. *Med. Sci. Sports Exerc.* 50, 1704–1709.
255. Blair, S.N., Kohl, H.W., 3rd, Paffenbarger, R.S., Jr., Clark, D.G., Cooper, K.H., and Gibbons, L.W. (1989). Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* 262, 2395–2401.
256. Kokkinos, P., Myers, J., Kokkinos, J.P., Pittaras, A., Narayan, P., Manolis, A., Karasik, P., Greenberg, M., Papademetriou, V., and Singh, S. (2008). Exercise capacity and mortality in black and white men. *Circulation* 117, 614–622.
257. Sarzynski, M.A., Rice, T.K., Després, J.P., Pérusse, L., Tremblay, A., Stanforth, P.R., Tchernof, A., Barber, J.L., Falciani, F., Clish, C., et al. (2022). The HERITAGE Family Study: a review of the effects of exercise training on cardiometabolic health, with insights into molecular transducers. *Med. Sci. Sports Exerc.* 54, S1–S43.
258. Hunter, G.R., Weinsier, R.L., Darnell, B.E., Zuckerman, P.A., and Goran, M.I. (2000). Racial differences in energy expenditure and aerobic fitness in premenopausal women. *Am. J. Clin. Nutr.* 71, 500–506.
259. Hunter, G.R., Weinsier, R.L., McCarthy, J.P., Enette Larson-Meyer, D., and Newcomer, B.R. (2001). Hemoglobin, muscle oxidative capacity, and VO<sub>2</sub>max in African-American and Caucasian women. *Med. Sci. Sports Exerc.* 33, 1739–1743.
260. Skinner, J.S., Jaskólski, A., Jaskólska, A., Krasnoff, J., Gagnon, J., Leon, A.S., Rao, D.C., Wilmore, J.H., and Bouchard, C.; HERITAGE Family Study (2001). Age, sex, race, initial fitness, and response to training: the HERITAGE Family Study. *J. Appl. Physiol.* (1985) 90, 1770–1776.
261. Trowbridge, C.A., Gower, B.A., Nagy, T.R., Hunter, G.R., Treuth, M.S., and Goran, M.I. (1997). Maximal aerobic capacity in African-American and Caucasian prepubertal children. *Am. J. Physiol.* 273, E809–E814.
262. DeLany, J.P., Dubé, J.J., Standley, R.A., Distefano, G., Goodpaster, B.H., Stefanovic-Racic, M., Coen, P.M., and Toledo, F.G. (2014). Racial differences in peripheral insulin sensitivity and mitochondrial capacity in the absence of obesity. *J. Clin. Endocrinol. Metab.* 99, 4307–4314.
263. Nielsen, J., and Christensen, D.L. (2011). Glucose intolerance in the West African Diaspora: a skeletal muscle fibre type distribution hypothesis. *Acta Physiol. (Oxf.)* 202, 605–616.
264. Schutte, N.M., Nederend, I., Hudziak, J.J., Bartels, M., and de Geus, E.J.C.d. (2016). Twin-sibling study and meta-analysis on the heritability of maximal oxygen consumption. *Physiol. Genomics* 48, 210–219.
265. Swift, D.L., Johannsen, N.M., Lavie, C.J., Earnest, C.P., Johnson, W.D., Blair, S.N., Church, T.S., and Newton, R.L., Jr. (2013). Racial differences in the response of cardiorespiratory fitness to aerobic exercise training in Caucasian and African American postmenopausal women. *J. Appl. Physiol.* (1985) 114, 1375–1382.
266. Guralnik, J.M., Land, K.C., Blazer, D., Fillenbaum, G.G., and Branch, L.G. (1993). Educational status and active life expectancy among older blacks and whites. *N. Engl. J. Med.* 329, 110–116.
267. Schoenbaum, M., and Waidmann, T. (1997). Race, socioeconomic status, and health: accounting for race differences in health. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 52 Spec No, 61–73.
268. Thorpe, R.J., Jr., Brandon, D.T., and LaVeist, T.A. (2008). Social context as an explanation for race disparities in hypertension: findings from the Exploring Health Disparities in Integrated Communities (EHDIC) Study. *Soc. Sci. Med.* 67, 1604–1611.
269. LaVeist, T.A. (2005). Disentangling race and socioeconomic status: a key to understanding health inequalities. *J. Urban Health* 82 (Suppl 3), iii26–iii34.
270. Jones, S., Tillin, T., Williams, S., Eastwood, S.V., Hughes, A.D., and Chaturvedi, N. (2020). Type 2 diabetes does not account for ethnic differences in exercise capacity or skeletal muscle function in older adults. *Diabetologia* 63, 624–635.
271. Nightingale, C.M., Donin, A.S., Kerry, S.R., Owen, C.G., Rudnicka, A.R., Brage, S., Westgate, K.L., Ekelund, U., Cook, D.G., and Whincup, P.H. (2016). Cross-sectional study of ethnic differences in physical fitness among children of South Asian, black African-Caribbean and white European origin: the Child Heart and Health Study in England (CHASE). *BMJ Open* 6, e011131.

272. Foulds, H.J.A., Bredin, S.S.D., and Warburton, D.E.R. (2019). Ethnic differences in the cardiac responses to aerobic exercise. *Ethn. Health* 24, 168–181.
273. Hoppeler, H. (2018). Deciphering  $V_{O_{2,max}}$ : limits of the genetic approach. *J. Exp. Biol.* 221, jeb164327.
274. Dionne, F.T., Turcotte, L., Thibault, M.C., Boulay, M.R., Skinner, J.S., and Bouchard, C. (1993). Mitochondrial DNA sequence polymorphism,  $VO_{2max}$ , and response to endurance training. *Med. Sci. Sports Exerc.* 25, 766–774.
275. Vellers, H.L., Verheij, K.C., Burkholder, A.B., Lee, J., Kim, Y., Lightfoot, J.T., Shi, M.I.N., Weinberg, C.R., Sarzynski, M.A., Bouchard, C., et al. (2020). Association between mitochondrial DNA sequence variants and  $VO_{2max}$  trainability. *Med. Sci. Sports Exerc.* 52, 2303–2309.
276. Kiiskilä, J., Jokelainen, J., Kytövuori, L., Mikkola, I., Härkönen, P., Keinänen-Kiukaanniemi, S., and Majamaa, K. (2021). Association of mitochondrial DNA haplogroups J and K with low response in exercise training among Finnish military conscripts. *BMC Genomics* 22, 75.
277. Marcuello, A., Martínez-Redondo, D., Dahmani, Y., Casajús, J.A., Ruiz-Pesini, E., Montoya, J., López-Pérez, M.J., and Díez-Sánchez, C. (2009). Human mitochondrial variants influence on oxygen consumption. *Mitochondrion* 9, 27–30.
278. Martínez-Redondo, D., Marcuello, A., Casajús, J.A., Ara, I., Dahmani, Y., Montoya, J., Ruiz-Pesini, E., López-Pérez, M.J., and Díez-Sánchez, C. (2010). Human mitochondrial haplogroup H: the highest  $VO_{2max}$  consumer—is it a paradox? *Mitochondrion* 10, 102–107.
279. Gómez-Durán, A., Pacheu-Grau, D., Martínez-Romero, I., López-Gallardo, E., López-Pérez, M.J., Montoya, J., and Ruiz-Pesini, E. (2012). Oxidative phosphorylation differences between mitochondrial DNA haplogroups modify the risk of Leber's hereditary optic neuropathy. *Biochim. Biophys. Acta* 1822, 1216–1222.
280. Fernández-Moreno, M., Soto-Hermida, A., Vázquez-Mosquera, M.E., Cortés-Pereira, E., Relaño, S., Hermida-Gómez, T., Pértiga, S., Oreiro-Villar, N., Fernández-López, C., Garesse, R., et al. (2017). Mitochondrial DNA haplogroups influence the risk of incident knee osteoarthritis in OAI and CHECK cohorts. A meta-analysis and functional study. *Ann. Rheum. Dis.* 76, 1114–1122.
281. Bouchard, C., Antunes-Correa, L.M., Ashley, E.A., Franklin, N., Hwang, P.M., Mattsson, C.M., Negrao, C.E., Phillips, S.A., Sarzynski, M.A., Wang, P.Y., et al. (2015). Personalized preventive medicine: genetics and the response to regular exercise in preventive interventions. *Prog. Cardiovasc. Dis.* 57, 337–346.
282. Sparks, L.M. (2017). Exercise training response heterogeneity: physiological and molecular insights. *Diabetologia* 60, 2329–2336.
283. Brøns, C., Thuesen, A.C.B., Elingaard-Larsen, L.O., Justesen, L., Jensen, R.T., Henriksen, N.S., Juel, H.B., Størling, J., Ried-Larsen, M., Sparks, L.M., et al. (2022). Increased liver fat associates with severe metabolic perturbations in low birth weight men. *Eur. J. Endocrinol.* 186, 511–521.
284. Padrão, A.I., Ferreira, R., Amado, F., Vitorino, R., and Duarte, J.A. (2016). Uncovering the exercise-related proteome signature in skeletal muscle. *Proteomics* 16, 816–830.
285. Green, H.J., Helyar, R., Ball-Burnett, M., Kowalchuk, N., Symon, S., and Farrance, B. (1992). Metabolic adaptations to training precede changes in muscle mitochondrial capacity. *J. Appl. Physiol.* (1985) 72, 484–491.
286. Cotter, M., Hudlická, O., and Vrbová, G. (1973). Growth of capillaries during long-term activity in skeletal muscle. *Bibl. Anat.* 11, 395–398.
287. Waters, R.E., Rotevatn, S., Li, P., Annex, B.H., and Yan, Z. (2004). Voluntary running induces fiber type-specific angiogenesis in mouse skeletal muscle. *Am. J. Physiol. Cell Physiol.* 287, C1342–C1348.
288. Benziene, B., Burton, T.J., Scanlan, B., Galuska, D., Canny, B.J., Chibalin, A.V., Zierath, J.R., and Stepto, N.K. (2008). Divergent cell signaling after short-term intensified endurance training in human skeletal muscle. *Am. J. Physiol. Endocrinol. Metab.* 295, E1427–E1438.
289. Adams, G.R., Hather, B.M., Baldwin, K.M., and Dudley, G.A. (1993). Skeletal muscle myosin heavy chain composition and resistance training. *J. Appl. Physiol.* (1985) 74, 911–915.
290. Widrick, J.J., Stelzer, J.E., Shoepe, T.C., and Garner, D.P. (2002). Functional properties of human muscle fibers after short-term resistance exercise training. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283, R408–R416.
291. Spina, R.J., Chi, M.M., Hopkins, M.G., Nemeth, P.M., Lowry, O.H., and Holloszy, J.O. (1996). Mitochondrial enzymes increase in muscle in response to 7–10 days of cycle exercise. *J. Appl. Physiol.* (1985) 80, 2250–2254.
292. Baar, K., and Esser, K. (1999). Phosphorylation of p70(S6k) correlates with increased skeletal muscle mass following resistance exercise. *Am. J. Physiol.* 276, C120–C127.
293. Terzis, G., Georgiadis, G., Stratakos, G., Vogiatzis, I., Kavouras, S., Manta, P., Mascher, H., and Blomstrand, E. (2008). Resistance exercise-induced increase in muscle mass correlates with p70S6 kinase phosphorylation in human subjects. *Eur. J. Appl. Physiol.* 102, 145–152.
294. Zanchi, N.E., and Lancha, A.H., Jr. (2008). Mechanical stimuli of skeletal muscle: implications on mTOR/p70S6K and protein synthesis. *Eur. J. Appl. Physiol.* 102, 253–263.
295. Sandri, M., Sandri, C., Gilbert, A., Skurk, C., Calabria, E., Picard, A., Walsh, K., Schiaffino, S., Lecker, S.H., and Goldberg, A.L. (2004). Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. *Cell* 117, 399–412.
296. Coffey, V.G., Shield, A., Canny, B.J., Carey, K.A., Cameron-Smith, D., and Hawley, J.A. (2006). Interaction of contractile activity and training history on mRNA abundance in skeletal muscle from trained athletes. *Am. J. Physiol. Endocrinol. Metab.* 290, E849–E855.
297. Louis, E., Raue, U., Yang, Y., Jemiolo, B., and Trappe, S. (2007). Time course of proteolytic, cytokine, and myostatin gene expression after acute exercise in human skeletal muscle. *J. Appl. Physiol.* (1985) 103, 1744–1751.
298. Coffey, V.G., and Hawley, J.A. (2007). The molecular bases of training adaptation. *Sports Med.* 37, 737–763.
299. Hood, D.A. (2001). Invited Review: contractile activity-induced mitochondrial biogenesis in skeletal muscle. *J. Appl. Physiol.* (1985) 90, 1137–1157.
300. Popov, L.D. (2020). Mitochondrial biogenesis: an update. *J. Cell. Mol. Med.* 24, 4892–4899.
301. Memme, J.M., Erlich, A.T., Phukan, G., and Hood, D.A. (2021). Exercise and mitochondrial health. *J. Physiol.* 599, 803–817.
302. Hoffman, N.J., Parker, B.L., Chaudhuri, R., Fisher-Wellman, K.H., Kleiner, M., Humphrey, S.J., Yang, P., Holliday, M., Trefely, S., Fazakerley, D.J., et al. (2015). Global phosphoproteomic analysis of human skeletal muscle reveals a network of exercise-regulated kinases and AMPK substrates. *Cell Metab.* 22, 922–935.
303. Needham, E.J., Hingst, J.R., Parker, B.L., Morrison, K.R., Yang, G., On-slev, J., Kristensen, J.M., Højlund, K., Ling, N.X.Y., Oakhill, J.S., et al. (2022). Personalized phosphoproteomics identifies functional signaling. *Nat. Biotechnol.* 40, 576–584.
304. Hussey, S.E., Sharoff, C.G., Garnham, A., Yi, Z., Bowen, B.P., Mandarino, L.J., and Hargreaves, M. (2013). Effect of exercise on the skeletal muscle proteome in patients with type 2 diabetes. *Med. Sci. Sports Exerc.* 45, 1069–1076.
305. Vanderboom, P., Zhang, X., Hart, C.R., Kunz, H.E., Gries, K.J., Heppelmann, C.J., Liu, Y., Dasari, S., and Lanza, I.R. (2022). Impact of obesity on the molecular response to a single bout of exercise in a preliminary human cohort. *Obesity (Silver Spring)* 30, 1091–1104.
306. Contrepolis, K., Wu, S., Moneghetti, K.J., Hornburg, D., Ahadi, S., Tsai, M.S., Metvally, A.A., Wei, E., Lee-McMullen, B., Quijada, J.V., et al. (2020). Molecular choreography of acute exercise. *Cell* 181, 1112–1130.e16.
307. Huffman, K.M., Koves, T.R., Hubal, M.J., Abouassi, H., Beri, N., Bate-man, L.A., Stevens, R.D., Ilkayeva, O.R., Hoffman, E.P., Muoio, D.M., et al. (2014). Metabolite signatures of exercise training in human skeletal muscle relate to mitochondrial remodelling and cardiometabolic fitness. *Diabetologia* 57, 2282–2295.

308. Keller, P., Vollaard, N.B., Gustafsson, T., Gallagher, I.J., Sundberg, C.J., Rankinen, T., Britton, S.L., Bouchard, C., Koch, L.G., and Timmons, J.A. (2011). A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. *J. Appl. Physiol.* (1985) *110*, 46–59.
309. Raue, U., Trappe, T.A., Estrem, S.T., Qian, H.R., Helvering, L.M., Smith, R.C., and Trappe, S. (2012). Transcriptome signature of resistance exercise adaptations: mixed muscle and fiber type specific profiles in young and old adults. *J. Appl. Physiol.* (1985) *112*, 1625–1636.
310. Vissing, K., and Schjerling, P. (2014). Simplified data access on human skeletal muscle transcriptome responses to differentiated exercise. *Sci. Data* *1*, 140041.
311. Dreher, S.I., Irmeler, M., Pivovarov-Ramich, O., Kessler, K., Jürchott, K., Sticht, C., Fritsche, L., Schneeweiss, P., Machann, J., Pfeiffer, A.F.H., et al. (2023). Acute and long-term exercise adaptation of adipose tissue and skeletal muscle in humans: a matched transcriptomics approach after 8-week training-intervention. *Int. J. Obes. (Lond)* *47*, 313–324.
312. Fabre, O., Ingerslev, L.R., Garde, C., Donkin, I., Simar, D., and Barrès, R. (2018). Exercise training alters the genomic response to acute exercise in human adipose tissue. *Epigenomics* *10*, 1033–1050.
313. Amar, D., Lindholm, M.E., Norrbom, J., Wheeler, M.T., Rivas, M.A., and Ashley, E.A. (2021). Time trajectories in the transcriptomic response to exercise - a meta-analysis. *Nat. Commun.* *12*, 3471.
314. Pillon, N.J., Gabriel, B.M., Dollet, L., Smith, J.A.B., Sardón Puig, L., Bottella, J., Bishop, D.J., Krook, A., and Zierath, J.R. (2020). Transcriptomic profiling of skeletal muscle adaptations to exercise and inactivity. *Nat. Commun.* *11*, 470.
315. Group, M.S., Amar, D., Gay, N.R., Beltran, P.M.J., Adkins, J.N., Armenteros, J.J.A., Ashley, E., Avila-Pacheco, J., Bae, D., Bararpour, N., et al. (2023). Temporal dynamics of the multi-omic response to endurance exercise training across tissues. Preprint at bioRxiv. <https://doi.org/10.1101/2022.09.21.508770>.
316. Rubenstein, A.B., Smith, G.R., Zhang, Z., Chen, X., Chambers, T.L., Ruf-Zamojski, F., Mendeleev, N., Cheng, W.S., Zamojski, M., Amper, M.A.S., et al. (2023). Integrated single-cell multiome analysis reveals muscle fiber-type gene regulatory circuitry modulated by endurance exercise. Preprint at bioRxiv. <https://doi.org/10.1101/2023.09.26.558914>.
317. Muotiala, A. (1992). Anti-IFN-gamma-treated mice—a model for testing safety of live Salmonella vaccines. *Vaccine* *10*, 243–246.
318. Timmons, J.A., Knudsen, S., Rankinen, T., Koch, L.G., Sarzynski, M., Jensen, T., Keller, P., Scheele, C., Vollaard, N.B., Nielsen, S., et al. (2010). Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J. Appl. Physiol.* (1985) *108*, 1487–1496.
319. Thalacker-Mercer, A.E., Dell'Italia, L.J., Cui, X., Cross, J.M., and Barmann, M.M. (2010). Differential genomic responses in old vs. young humans despite similar levels of modest muscle damage after resistance loading. *Physiol. Genomics* *40*, 141–149.
320. Dela, F., and Stallknecht, B. (2010). Effect of physical training on insulin secretion and action in skeletal muscle and adipose tissue of first-degree relatives of type 2 diabetic patients. *Am. J. Physiol. Endocrinol. Metab.* *299*, E80–E91.
321. McLean, C.S., Mielke, C., Cordova, J.M., Langlais, P.R., Bowen, B., Miranda, D., Coletta, D.K., and Mandarino, L.J. (2015). Gene and microRNA expression responses to exercise; relationship with insulin sensitivity. *PLoS One* *10*, e0127089.
322. De Filippis, E., Alvarez, G., Berria, R., Cusi, K., Everman, S., Meyer, C., and Mandarino, L.J. (2008). Insulin-resistant muscle is exercise resistant: evidence for reduced response of nuclear-encoded mitochondrial genes to exercise. *Am. J. Physiol. Endocrinol. Metab.* *294*, E607–E614.
323. Nilsson, M.I., Greene, N.P., Dobson, J.P., Wiggs, M.P., Gasier, H.G., Macias, B.R., Shimkus, K.L., and Fluckey, J.D. (2010). Insulin resistance syndrome blunts the mitochondrial anabolic response following resistance exercise. *Am. J. Physiol. Endocrinol. Metab.* *299*, E466–E474.
324. Hernández-Alvarez, M.I., Thabit, H., Burns, N., Shah, S., Brema, I., Hattunic, M., Finucane, F., Liesa, M., Chiellini, C., Naon, D., et al. (2010). Subjects with early-onset type 2 diabetes show defective activation of the skeletal muscle PGC-1alpha/Mitofusin-2 regulatory pathway in response to physical activity. *Diabetes Care* *33*, 645–651.
325. Timmons, J.A. (2011). Variability in training-induced skeletal muscle adaptation. *J. Appl. Physiol.* (1985) *110*, 846–853.
326. Laurens, C., Bergouignan, A., and Moro, C. (2020). Exercise-released myokines in the control of energy metabolism. *Front. Physiol.* *11*, 91.
327. Pedersen, B.K. (2011). Muscles and their myokines. *J. Exp. Biol.* *214*, 337–346.
328. Pedersen, B.K., and Febbraio, M.A. (2012). Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat. Rev. Endocrinol.* *8*, 457–465.
329. Wedell-Neergaard, A.S., Lang Lehrskov, L., Christensen, R.H., Legaard, G.E., Dorph, E., Larsen, M.K., Launbo, N., Fagerlind, S.R., Seide, S.K., Nyman, S., et al. (2019). Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signaling: A randomized controlled trial. *Cell Metab.* *29*, 844–855.e3.
330. Kuramoto, K., Liang, H., Hong, J.H., and He, C. (2023). Exercise-activated hepatic autophagy via the FN1-alpha5beta1 integrin pathway drives metabolic benefits of exercise. *Cell Metab.* *35*, 620–632.e5.
331. Wei, W., Riley, N.M., Lyu, X., Shen, X., Guo, J., Raun, S.H., Zhao, M., Moya-Garzon, M.D., Basu, H., Sheng-Hwa Tung, A., et al. (2023). Organism-wide, cell-type-specific secretome mapping of exercise training in mice. *Cell Metab.* *35*, 1261–1279.e11.
332. Trefts, E., Williams, A.S., and Wasserman, D.H. (2015). Exercise and the regulation of hepatic metabolism. *Prog. Mol. Biol. Transl. Sci.* *135*, 203–225.
333. Ingerslev, B., Hansen, J.S., Hoffmann, C., Clemmesen, J.O., Secher, N.H., Scheler, M., Hrabě de Angelis, M., Häring, H.U., Pedersen, B.K., Weigert, C., et al. (2017). Angiopoietin-like protein 4 is an exercise-induced hepatokine in humans, regulated by glucagon and cAMP. *Mol. Metab.* *6*, 1286–1295.
334. Stanford, K.I., and Goodyear, L.J. (2016). Exercise regulation of adipose tissue. *Adipocyte* *5*, 153–162.
335. Li, V.L., He, Y., Contrepois, K., Liu, H., Kim, J.T., Wiggenhorn, A.L., Tanzo, J.T., Tung, A.S., Lyu, X., Zushin, P.H., et al. (2022). An exercise-inducible metabolite that suppresses feeding and obesity. *Nature* *606*, 785–790.
336. Liu, Y., Wang, Y., Ni, Y., Cheung, C.K.Y., Lam, K.S.L., Wang, Y., Xia, Z., Ye, D., Guo, J., Tse, M.A., et al. (2020). Gut microbiome fermentation determines the efficacy of exercise for diabetes prevention. *Cell Metab.* *31*, 77–91.e5.
337. Estaki, M., Pither, J., Baumeister, P., Little, J.P., Gill, S.K., Ghosh, S., Ahmadi-Vand, Z., Marsden, K.R., and Gibson, D.L. (2016). Cardiorespiratory fitness as a predictor of intestinal microbial diversity and distinct metagenomic functions. *Microbiome* *4*, 42.
338. Kelly, R.S., Kelly, M.P., and Kelly, P. (2020). Metabolomics, physical activity, exercise and health: a review of the current evidence. *Biochim. Biophys. Acta Mol. Basis Dis.* *1866*, 165936.
339. Allen, J.M., Mailing, L.J., Niemi, G.M., Moore, R., Cook, M.D., White, B.A., Holscher, H.D., and Woods, J.A. (2018). Exercise alters gut microbiota composition and function in lean and obese humans. *Med. Sci. Sports Exerc.* *50*, 747–757.
340. van Loon, L.J., Greenhaff, P.L., Constantin-Teodosiu, D., Saris, W.H., and Wagenmakers, A.J. (2001). The effects of increasing exercise intensity on muscle fuel utilisation in humans. *J. Physiol.* *536*, 295–304.
341. Han, X. (2016). Lipidomics for studying metabolism. *Nat. Rev. Endocrinol.* *12*, 668–679.
342. Bergman, B.C., Brozinick, J.T., Strauss, A., Bacon, S., Kerege, A., Bui, H.H., Sanders, P., Siddall, P., Wei, T., Thomas, M.K., et al. (2016). Muscle sphingolipids during rest and exercise: a C18:0 signature for insulin resistance in humans. *Diabetologia* *59*, 785–798.
343. Bergman, B.C., Hunerdosse, D.M., Kerege, A., Playdon, M.C., and Perreault, L. (2012). Localisation and composition of skeletal muscle

- diacylglycerol predicts insulin resistance in humans. *Diabetologia* 55, 1140–1150.
344. Bergman, B.C., Perreault, L., Hunerdosse, D.M., Koehler, M.C., Samek, A.M., and Eckel, R.H. (2009). Intramuscular lipid metabolism in the insulin resistance of smoking. *Diabetes* 58, 2220–2227.
345. Coen, P.M., Dubé, J.J., Amati, F., Stefanovic-Racic, M., Ferrell, R.E., Toledo, F.G., and Goodpaster, B.H. (2010). Insulin resistance is associated with higher intramyocellular triglycerides in type I but not type II myocytes concomitant with higher ceramide content. *Diabetes* 59, 80–88.
346. Coen, P.M., Menshikova, E.V., Distefano, G., Zheng, D., Tanner, C.J., Standley, R.A., Helbling, N.L., Dubis, G.S., Ritov, V.B., Xie, H., et al. (2015). Exercise and weight loss improve muscle mitochondrial respiration, lipid partitioning, and insulin sensitivity after gastric bypass surgery. *Diabetes* 64, 3737–3750.
347. Dubé, J.J., Amati, F., Toledo, F.G., Stefanovic-Racic, M., Rossi, A., Coen, P., and Goodpaster, B.H. (2011). Effects of weight loss and exercise on insulin resistance, and intramyocellular triacylglycerol, diacylglycerol and ceramide. *Diabetologia* 54, 1147–1156.
348. Adams, J.M., 2nd, Pratipanawatr, T., Berria, R., Wang, E., DeFronzo, R.A., Sullards, M.C., and Mandarino, L.J. (2004). Ceramide content is increased in skeletal muscle from obese insulin-resistant humans. *Diabetes* 53, 25–31.
349. Goodpaster, B.H., He, J., Watkins, S., and Kelley, D.E. (2001). Skeletal muscle lipid content and insulin resistance: evidence for a paradox in endurance-trained athletes. *J. Clin. Endocrinol. Metab.* 86, 5755–5761.
350. Amati, F., Dubé, J.J., Alvarez-Carnero, E., Edreira, M.M., Chomentowski, P., Coen, P.M., Switzer, G.E., Bickel, P.E., Stefanovic-Racic, M., Toledo, F.G., et al. (2011). Skeletal muscle triglycerides, diacylglycerols, and ceramides in insulin resistance: another paradox in endurance-trained athletes? *Diabetes* 60, 2588–2597.
351. Bruce, C.R., Thrush, A.B., Mertz, V.A., Bezaire, V., Chabowski, A., Heigenhauser, G.J., and Dyck, D.J. (2006). Endurance training in obese humans improves glucose tolerance and mitochondrial fatty acid oxidation and alters muscle lipid content. *Am. J. Physiol. Endocrinol. Metab.* 291, E99–E107.
352. Montgomery, M.K., Brown, S.H.J., Mitchell, T.W., Coster, A.C.F., Cooney, G.J., and Turner, N. (2017). Association of muscle lipidomic profile with high-fat diet-induced insulin resistance across five mouse strains. *Sci. Rep.* 7, 13914.
353. Goto-Inoue, N., Yamada, K., Inagaki, A., Furuichi, Y., Ogino, S., Manabe, Y., Setou, M., and Fujii, N.L. (2013). Lipidomics analysis revealed the phospholipid compositional changes in muscle by chronic exercise and high-fat diet. *Sci. Rep.* 3, 3267.
354. Peake, J.M., Tan, S.J., Markworth, J.F., Broadbent, J.A., Skinner, T.L., and Cameron-Smith, D. (2014). Metabolic and hormonal responses to isoenergetic high-intensity interval exercise and continuous moderate-intensity exercise. *Am. J. Physiol. Endocrinol. Metab.* 307, E539–E552.
355. Cao, H., Gerhold, K., Mayers, J.R., Wiest, M.M., Watkins, S.M., and Hotamisligil, G.S. (2008). Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. *Cell* 134, 933–944.
356. Lynes, M.D., Leiria, L.O., Lundh, M., Bartelt, A., Shamsi, F., Huang, T.L., Takahashi, H., Hirshman, M.F., Schlein, C., Lee, A., et al. (2017). The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. *Nat. Med.* 23, 631–637.
357. Burhans, M.S., Flowers, M.T., Harrington, K.R., Bond, L.M., Guo, C.A., Anderson, R.M., and Ntambi, J.M. (2015). Hepatic oleate regulates adipose tissue lipogenesis and fatty acid oxidation. *J. Lipid Res.* 56, 304–318.
358. Liu, S., Brown, J.D., Stanya, K.J., Homan, E., Leidl, M., Inouye, K., Bhargava, P., Gangl, M.R., Dai, L., Hatano, B., et al. (2013). A diurnal serum lipid integrates hepatic lipogenesis and peripheral fatty acid use. *Nature* 502, 550–554.
359. Stanford, K.I., Lynes, M.D., Takahashi, H., Baer, L.A., Arts, P.J., May, F.J., Lehnig, A.C., Middelbeek, R.J.W., Richard, J.J., So, K., et al. (2018). 12,13-diHOME: an exercise-induced lipokine that increases skeletal muscle fatty acid uptake. *Cell Metab.* 27, 1111–1120.e3.
360. Grapov, D., Fiehn, O., Campbell, C., Chandler, C.J., Burnett, D.J., Souza, E.C., Casazza, G.A., Keim, N.L., Hunter, G.R., Fernandez, J.R., et al. (2020). Impact of a weight loss and fitness intervention on exercise-associated plasma oxylipin patterns in obese, insulin-resistant, sedentary women. *Physiol. Rep.* 8, e14547.
361. American Diabetes Association (2021). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 44 (Suppl 1), S15–S33.
362. Ruiz-Canela, M., Hruby, A., Clish, C.B., Liang, L., Martínez-González, M.A., and Hu, F.B. (2017). Comprehensive metabolomic profiling and incident cardiovascular disease: a systematic review. *J. Am. Heart Assoc.* 6, e005705.
363. Sanford, J.A., Nogiec, C.D., Lindholm, M.E., Adkins, J.N., Amar, D., Dasari, S., Drugan, J.K., Fernández, F.M., Radom-Aizik, S., Schenk, S., et al. (2020). Molecular Transducers of Physical Activity Consortium (MoTrPAC): mapping the dynamic responses to exercise. *Cell* 181, 1464–1474.