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# Long-term aerobic exercise preserves muscle mass and function with age

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Research in the prevention of muscle loss and function with age has focused on resistance training as an exercise intervention. Considerably less attention has been paid to aerobic/endurance exercise and the potential benefits of lifelong aerobic exercise. We focus this review on new evidence that supports the benefits of aerobic exercise on muscle mass and function. Recent data support that aerobic exercise, especially long-term, preserves the neuromuscular junction and motor unit, mitochondrial function, and proteostasis. Although more studies are needed on exact mechanisms, it is our contention that aerobic exercise, like resistance exercise, can help prevent the decline in muscle mass and function with age.

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## Introduction

Perhaps because aerobic/endurance athletes are characterized by a lean phenotype, aerobic exercise is largely overlooked as a treatment for sarcopenia. However, a growing body of evidence supports that aerobic exercise preserves skeletal muscle mass and function with age through a variety of mechanisms. We focus on studies from the last three years that identify chronic physical activity, or aerobic exercise in particular, and their relation to maintaining skeletal muscle mass and function with age. There is a substantial literature on resistance training and nutritional interventions for the maintenance of muscle mass with age. However, we believe that long-term aerobic exercise should also be considered a viable strategy to preserve muscle mass and function with age.

## Sarcopenia, exercise, and aging

Sarcopenia is a geriatric syndrome that is characterized by a progressive loss of muscle mass and function [1]. Consistent estimates on the prevalence of sarcopenia are difficult to ascertain due to variations in the criteria used for clinical assessment. Having inflicted a loss of muscle mass alone, sarcopenia affects 5–13% of individuals between the ages of 60–70, and by age 80, 11–50% of individuals are sarcopenic [2]. Sarcopenia is associated with a number of adverse health outcomes in the elderly, including higher rates of falls and hospitalization, reduced quality of life, and increased risk of mortality [3]. The significant health-related consequences of sarcopenia have led to its formal recognition as an independent medical condition [4]. Strategies to prevent and manage sarcopenia have primarily focused on mitigating or reversing the loss of muscle mass through strength training or increasing protein intake. However, these approaches may not be sufficient to impact muscle energetics [5], which are tightly linked to physical function [6].

Evidence from master's athletes suggests that participating in long-term, performance-based exercise slows age-related decline in physical function [7•]. Given that masters level athletes often have trained at the competition-level for a majority of their lives, master's athletes are considered to be a model of skeletal muscle aging that has not been influenced by inactivity or disuse [8]. Master's athletes have significantly higher $VO_2$ values than older adults who exercise for fitness alone [7•], which translates to greater reductions in risk of mortality. In fact, in a cross-sectional analysis of master's athletes aged 40–81 years, Wroblewski *et al.* found that there were no differences in quadriceps muscle lean mass across the age groups [9] indicating that lifelong exercise preserves muscle mass.

Aerobic exercise is widely recognized for its protective effects against a variety of chronic conditions. $VO_2$max, a measure of cardiorespiratory fitness, is predictive of longevity and the benefits seem to be dose dependent [10]. Older adults who regularly engage in aerobic activities such as cycling, running, and swimming have higher $VO_2$ peak values [11••,12] and enhanced mitochondrial function [11••,13] as compared to their sedentary counterparts. Aerobic exercise also minimizes age-related accumulation of intermuscular lipids [11••,14•] that are thought to impair muscle function. Although adults who are physically active still experience some degree of muscle loss with advancing age, when physical function is normalized to muscle mass (an index of muscle quality), performance

remains comparable to that of young, active individuals [11••]. Finally, and important to our thesis, an association was shown for the first time that mitochondrial function affects muscle strength, and that mitochondrial dysfunction can impair mobility [15••]. Collectively, this evidence leads us to believe that lifelong aerobic exercise can slow the loss of muscle mass and function.

## Neuromuscular junction (NMJ) and motor units (MU)

Aging is associated with loss of motor unit (MU) number and function [16] that renders muscle fibers susceptible to atrophy and eventually degradation [17]. Some evidence suggests that MU dysfunction precedes loss of muscle size [16] and capacity [18]. For example, muscle fiber denervation increases reactive oxygen species production in both denervated and neighboring fibers before the onset of muscle atrophy [19•]. After denervation, muscle fiber reinnervation occurs in a modified manner that results in fiber-type grouping [20]. The capacity for reinnervation diminishes with age [21] and other evidence suggests that a failure to reinnervate denervated fibers distinguishes sarcopenic from non-sarcopenic older men [16]. Therefore, maintenance of MU number and function with aging is critical for preservation of skeletal muscle health.

Even a single bout of endurance activity is sufficient to increase the speed of movement execution, potentially through greater MU activation [22]. Endurance-trained collegiate athletes have increased MU firing rates, indicating that increased MU size is an adaptation to endurance exercise [23]. Improved MU function with endurance training may be maintained across the lifespan. One cross-sectional study on octogenarian, world-class track and field athletes revealed a 28% increase in number of activatable MUs in athletes compared to age-matched controls [24]. Importantly, this finding corresponded with an increase in excitable muscle mass and greater maximal lower leg force output in the octogenarian athletes.

Motor unit function is mechanistically linked with the neuromuscular junction (NMJ), the interface between alpha-motor neuron and skeletal muscle fiber. NMJ function is impaired with age [25]. Recently it was shown that endurance-like training in young, female Sprague-Dawley rats increases acetylcholinesterase content, an indicator of NMJ function [26]. Additional work suggests that NMJ remodeling following endurance training is diminished with age [27], underscoring that it may be important to engage in physical activity throughout the lifespan. In summary, recent evidence demonstrates that endurance exercise training improves MU and NMJ function, implicating endurance exercise for prevention and as treatment of age-related losses in muscle function and size.

## Mitochondria

Efficient energy production and overall mitochondrial health are crucial for maintaining skeletal muscle function. Although it is commonly reported that mitochondrial dysfunction increases with age, the determination of dysfunction is more nuanced than it appears. In a recent study using participants in the Baltimore Longitudinal Study of Aging (BLSA), it was found that there is a significant reduction in *ex vivo* mitochondrial respiration in permeabilized muscle fibers of the vastus lateralis with increasing age [28]. The authors further showed that at lower energetic demand (i.e. lower ADP concentrations) aged mitochondria function similar to young mitochondria, but were impaired compared to young at maximal ADP concentrations [28]. Other studies that compared young and old males and females showed that maximal respiration was decreased in isolated mitochondria with and without normalization to mitochondrial content [29]. Halloway *et al.* compared skeletal muscle from young and old healthy individuals and also found no differences in maximal mitochondrial respiration. However, these authors reported decreased ADP sensitivity across almost all non-saturating ADP concentrations that resulted in lower ATP production and greater ROS ($H_2O_2$) emission [30•]. Therefore, the literature on whether age per se decreases mitochondrial function is complicated and is likely dependent on many factors including chronic physical activity.

Recent studies in human subjects that account for physical activity demonstrate that aerobic exercise can maintain the mitochondria function of older subjects similar to younger subjects. First, when using both non-invasive assessment of mitochondrial function ($^{31}$P MRS) and respiration of permeabilized muscle fibers, Distefano *et al.*, showed that older subjects who were physically active (i.e. 3 d/wk of aerobic exercise consistently over the previous 6 months) have similar mitochondrial function to young physically active individuals, which were both greater compared to older sedentary individuals [11••]. These changes were associated with improved physical performance on some outcomes compared to older sedentary. In a second study, older adults who engaged in at least 150 min/wk of moderate-intensity to vigorous-intensity exercise had higher mitochondrial content, via succinate dehydrogenase staining, compared to older sedentary or pre-frailty individuals [14•]. Importantly, the higher mitochondrial content from physically activity elderly individuals was not different than young or middle-age physically active adults. Further, the higher mitochondrial content, regardless of age, was related to better physical function and protection from age-related muscle loss.

In 2018, two particularly noteworthy studies assessed the effect of lifelong, aerobic exercise on skeletal muscle mitochondrial function. Gries *et al.* examined old male

and female individuals who had a 50+ year history of aerobic exercise 4–6 day/wk for approximately 7 hour/wk [7•]. The authors found that there was a hierarchical pattern for maximal aerobic capacity ($VO_2$max) where young exercisers > lifelong exercisers > old healthy non-exercisers. In addition, when separating out lifelong exercisers that competed in endurance events, the competitors had a higher $VO_2$max than recreationally active lifelong exercisers. Finally, the lifelong exercisers had similar capillarization and mitochondrial related enzyme activity of citrate synthase, a marker of mitochondrial content, and β-hydroxyacyl-CoA dehydrogenase to young exercisers [7•]. In a second study, Pollock *et al.* used a population of 90 male and female Master's cyclists and found that the factors related to cardiorespiratory capacity correlated better with exercise training volume then with age per se [31]. These two papers illustrate that lifelong aerobic exercise can diminish the effect of age on mitochondrial function.

Aging occurs over a prolonged period of time, which begs the question if it is ever too late to start exercising. While lifelong aerobic exercise is one of the most potent interventions to prevent declines in mitochondrial dysfunction, there is evidence that aerobic exercise training started later in life has benefits in formerly sedentary, aged individuals. In fact, a study found that in elderly males and females, 16 weeks of moderate intensity aerobic exercise increased the abundance of individual mitochondrial complexes and promoted mitochondrial supercomplex formation that may increase mitochondrial coupling efficiency [32]. In another study of older adults, 12 weeks of high-intensity interval training (HIIT increased mitochondrial respiratory chain activity and mitochondrial content [33]. Robinson *et al.* compared skeletal muscle adaptations to the initiation of multiple different exercise modalities young and old subjects [29] and found that HIIT increased mitochondrial protein synthesis and respiration in older subjects to a similar extent as the younger subjects. However, these gains were not matched by increases in strength as measured by 1-repetition max (1-RM). In conclusion, aerobic exercise robustly upregulates mitochondrial adaptations that are important for slowing declines in muscle mass, strength, and overall physical function [15••], but initiation of exercise later in life could still has positive mitochondrial outcomes that slow further loss.

## Proteostasis

Protein homeostasis (proteostasis) refers to the maintenance of protein concentration, function, and localization. With aging there is a reduced capacity to maintain proteostasis through dynamic regulation of protein synthesis, degradation, and folding. Interventions which activate proteostatic mechanisms in skeletal muscle may mitigate age-related loss of muscle mass and function [34]. In regards to protein turnover, removing damaged cells/proteins through apoptosis/autophagy or abhorrent mitochondria through mitophagy and replacing them with new proteins helps maintain proteostasis. Loss of mitochondrial proteostasis is implicated in age-related reductions in skeletal muscle mass and function [35,36]. Enhancement of mitochondrial protein turnover by upregulation of mitophagy produces muscle hypertrophy in aged mice [37], emphasizing that targeting mitochondrial proteostasis may be an effective way to counteract sarcopenia. Endurance exercise is currently one of the most robust interventions for promoting proteostatic mechanisms [5], but there is a surprising lack of data related to proteostatic maintenance with lifelong aerobic exercise.

In a study of senior sportsmen versus older and younger healthy individuals, there is some evidence that the protein quality control mechanisms of older sportsmen resembled that of the young healthy individuals [38]. However, this study relied on measurements of mRNA, which can lead to confusion since it is not clear if the transcription is in response to an intervention, or if it persists because the physiological stress still exists. A more recent study clarifies this issue somewhat in that it put an older group of previously sedentary individuals on an endurance-exercise training program and compared outcomes post-training to long-term endurance trained older individuals [39]. There were distinct patterns in markers of mitochondria proteostasis that indicated remodeling of mitochondria during the four months of a new exercise training program, but somewhat opposing changes in the same markers in the long-term endurance trained individuals. In our opinion, this is representative of the positive adaptations that occur over time with exercise training that maintain mitochondria in a state that have a decreased need, compared to mitochondria of sedentary individuals, for further maintenance. Another study compared masters aged endurance athletes to younger endurance athletes to examine integrated protein synthesis under conditions mimicking recovery to strenuous, and potentially damaging, exercise [40]. There was no indication of the long-term training history of the subjects besides that they were training for the 8 weeks before study. In this study, there was lower cumulative protein synthesis in the older athletes compared to the younger athletes. However, we do not know how these rates compare to age-matched non-athletes. Using the same labeling method to study cumulative protein synthesis, a case study in a lifelong endurance-trained master's athlete during a multiday, ultra-endurance race showed cumulative mitochondrial protein synthesis during the event that was threefold greater than a control period [41]. Therefore, it appears that older endurance trained athletes are capable of maintaining proteostatic mechanisms during extreme physiological stress. Although there is a number of studies examining proteostatic responses to acute bouts of exercise in young versus old the impact of long-term endurance exercise on proteostatic mechanisms are underexplored. Our opinion is that there should be careful consideration for the methods employed for these studies. Acute snapshots could be

misleading since an acute stress my fall somewhere different on a scale of hormesis for an individual that is stress resistant/resilient versus one who is not [42].

## Other considerations for assessing muscle with age

We would like to highlight two other factors that are important considerations when assessing lifelong exercise and age-related changes in skeletal muscle with age. The first is the choice of muscle. A meta-analysis of studies using *in vivo* ($^{31}$P MRS) measurements showed that there is heterogeneity of age-related outcomes dependent on the muscle group studied [43•]. Specifically, knee extensors, which includes the vastus lateralis, were found to have reduced muscle oxidative capacity with age. In opposition, upper extremity and dorsiflexor muscles had greater muscle oxidative capacity with age, while there were no differences with age in the plantar flexor muscles. Taken together, muscles differ in their responses to aging, a finding further supported by recent studies of muscle disuse [44]. Second, the age of assessment also seems important. Stolle *et al.* provided lifelong low-fat or high-fat sucrose diet to mice, with or without access to voluntary wheel running [45]. The mice were analyzed for a variety of mitochondrial-related outcomes at 6, 12, 18, or 24 months of age. Mitochondrial respiratory flux declined with age, and lifelong wheel running access delayed this decline until 18 months, regardless of diet. After 18 months of age, the metabolic outcomes converged so that there were no differences noted between groups at 24 months of age [45]. These data indicate the importance of assessing multiple timepoints since the preservation of function would not have been noted if comparisons were only made at 6 and 24 months.

## Conclusion

It is known that life-long physical activity can delay the onset of age-related chronic diseases. The purpose of this review was to highlight how lifelong endurance/aerobic type exercise can preserve muscle mass and function with age. Although there is a heavy emphasis on resistance training to maintain muscle mass, there is evidence that lifelong aerobic exercise is also effective at maintaining skeletal muscle mass and function with age. We highlighted three potential mechanisms, but additional research is still needed on how aerobic exercise, which is typically associated with a lean muscle phenotype, preserves muscle mass, and function with age.

## Conflict of interest statement

Nothing declared.

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