HIGHLIGHTED TOPIC | Physiology and Pathophysiology of Physical Inactivity

Lifetime sedentary living accelerates some aspects of secondary aging

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Departments of 1Biomedical Sciences, 2Medical Pharmacology and Physiology, and 3Nutrition and Exercise Physiology, 4Dalton Cardiovascular Institute, University of Missouri, Columbia, Missouri; and 5The Centre of Inflammation and Metabolism at the Department of Infectious Diseases, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Denmark

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Booth FW, Laye MJ, Roberts MD. Lifetime sedentary living accelerates some aspects of secondary aging. J Appl Physiol 111: 1497–1504, 2011. First published August 11, 2011; doi:10.1152/japplphysiol.00420.2011.—Lifetime physical inactivity interacts with secondary aging (i.e., aging caused by diseases and environmental factors) in three patterns of response. First, lifetime physical inactivity confers no apparent effects on a given set of physiological functions. Second, lifetime physical inactivity accelerates secondary aging (e.g., speeding the reduction in bone mineral density, maximal oxygen consumption, and skeletal muscle strength and power), but does not alter the primary aging of these systems. Third, a lifetime of physical activity to the age of ~60–70 yr old totally prevents decrements in some age-associated risk factors for major chronic diseases, such as endothelial dysfunction and insulin resistance. The present review provides ample and compelling evidence that physical inactivity has a large impact in shortening average life expectancy. In summary, physical inactivity plays a major role in the secondary aging of many essential physiological functions, and this aging can be prevented through a lifetime of physical activity.

Primary aging has been defined by Holloszy (21) as an inevitable deterioration of cellular structure and function, independent of disease and environment. Maximum life span is a measure of the maximum amount of time one or more members of a group has been observed to survive between birth and death. Slowing of primary aging, as by caloric restriction, results in an increase in maximal life span in many species, albeit no therapy has yet been able to slow or reverse primary aging in humans (15, 18, 21, 24). It should be noted that no evidence to our knowledge exists for lifetime exercise that no evidence to our knowledge exists for lifetime exercise restriction, results in an increase in maximal life span in many species, albeit no therapy has yet been able to slow or reverse primary aging in humans (15, 18, 21, 24). It should be noted that no evidence to our knowledge exists for lifetime exercise

VARIABLE EFFECTS OF LACK OF EXERCISE ON SECONDARY AGING OF FUNCTIONS

We propose a paradigm whereby lifetime physical inactivity accelerates secondary aging for a variety of physiological func-

DEFINITIONS OF PRIMARY AND SECONDARY AGING

Primary aging has been defined by Holloszy (21) as an inevitable deterioration of cellular structure and function, independent of disease and environment. Maximum life span is a measure of the maximum amount of time one or more members of a group has been observed to survive between birth and death. Slowing of primary aging, as by caloric restriction, results in an increase in maximal life span in many species, albeit no therapy has yet been able to slow or reverse primary aging in humans (15, 18, 21, 24). It should be noted that no evidence to our knowledge exists for lifetime exercise increasing maximal life span in rats or other species (22–23, 25).

Secondary aging, as defined by Holloszy, is “caused by diseases and environmental factors, such as smoking and exposure to ultraviolet radiation” and are physiological changes that are not inevitable (21). Secondary aging alters life expectancy (average length of life in a population), but not maximum life span. The current review builds from Holloszy and Kohrt’s statement (24), “A major purpose was to distinguish between the effects of primary aging and those of exercise deficiency, with particular emphasis on those components of the deterioration in structure and function that are preventable and reversible consequences of physical inactivity.” Two themes of this review are that the physical inactivity contributes more to the secondary aging of some physiological functions than others and that the reduction in physiological function due to primary aging ultimately reduces the average life expectancy for the lifetime physically inactive population.

Physical inactivity is associated with shorter average life span

Data published by the Centers for Disease Control (CDC; Ref. 17) have determined that “no regular exercise” accounted for 23% of deaths in the US in 1986 (256,686 of 1.1. million), with these deaths being attributable to nine chronic diseases. A second CDC (32) study reported that “poor diet and physical inactivity” were the second leading cause of preventable deaths from 1980–2002. Finally, the US Department of Health and Human Services (52a) has concluded that “the data very strongly support an inverse association between lifetime physical activity and all-cause mortality” with lifetime inactive individuals having an ~30% higher risk of dying compared with lifetime active individuals. Thus multiple epidemiological reports suggest that lifetime physical inactivity decreases average life expectancy.
tions linked to mortality risk. This review is organized into three categories. The first category is physiological functions in which lifetime physical activity confers no apparent effects on primary or secondary aging (Table 1). The second category is physiological functions, such as bone mineral density, \( \dot{V}O_{2\max} \) and skeletal muscle strength, in which lifetime physical inactivity accelerates secondary aging but does not alter the primary aging of these systems. The third category contains functions, such as endothelial vasodilation and insulin sensitivity that are preventable up until the age of 60–70 yr with lifetime physical activity and protect against premature death due to atherosclerosis or Type 2 diabetes (T2D).

**PHYSIOLOGICAL FUNCTIONS IN WHICH LIFETIME PHYSICAL INACTIVITY CONFEWS NO APPARENT EFFECTS**

Examples of primary aging are the declines in maximal exercise heart rate and various senses (vision, hearing, smell, taste). No differences in rates of decline during aging exist between lifetime physically inactive populations and lifetime physically active populations on these functions. Lack of an inactivity effect on some functions during aging can be considered as advantageous to interpretations because it suggests that lifetime physical activity on other changes in secondary aging by physical inactivity may affect function through specific mechanisms, i.e., the effects of physical inactivity are not global on every bodily function.

**PHYSIOLOGICAL FUNCTIONS IN WHICH LIFETIME PHYSICAL INACTIVITY ACCELERATES SECONDARY AGING BUT DOES NOT ALTER THE PRIMARY AGING OF THESE SYSTEMS**

Inactivity effects on bone mineral density. The example of lifetime peak bone mass, or the highest value of bone mass during the life span, is influenced by both genetic and environmental factors. The National Institutes of Health (NIH; Ref. 34) has stated, “Up to 90 percent of peak bone mass is acquired by age 18 in girls and by age 20 in boys, which makes youth the best time to ‘invest’ in one’s bone health,” and at 30 years of age bones have “reached their maximum strength and density, known as peak bone mass.” Likewise, the NIH has stated that “Given the knowledge that high peak bone density reduces osteoporosis risk later in life, it makes sense to pay more attention to those factors that affect peak bone mass.” Rizzoli et al. (41) indicate that by the end of bone’s maturation process, ~40% of peak bone mass is influenced by environmental factors (e.g., adequate dietary intake of calcium and proteins and vitamin D, as well as regular weight-bearing physical activity), whereas genes determine the remaining ~60% of peak bone mass. A key concept presented herein is that inherited genes interact with environmental factors to produce lifetime peak bone mass sometime in the third decade of life. Similarly, lifetime peak \( \dot{V}O_{2\max} \) and skeletal muscle power are determined by the interaction between genetic and environmental factors, such as lifetime physical activity. Thus regular aerobic and resistance exercise during maturation contribute to higher lifetime peak \( \dot{V}O_{2\max} \) and peak skeletal muscle power, respectively. Importantly, increased lifetime peaks for \( \dot{V}O_{2\max} \) and skeletal muscle power provide a higher functional point from which declines due to primary aging are initiated.

The higher lifetime peak has clinical consequences, delaying the condition of physical frailty, the quality or state of lacking skeletal muscle strength or vigor (low \( \dot{V}O_{2\max} \)). The delay in the onset of physical frailty increases the likelihood of dying at a later age. A clinical example is in a study published by Rockwood et al. (42) in which a higher Frailty Index was associated with higher mortality and use of health care service at all ages for the analyzed 14,000 Canadians.

**INACTIVITY EFFECTS ON \( \dot{V}O_{2\max} \)**

\( \dot{V}O_{2\max} \) is also known as maximal aerobic power and is a biomarker of cardiorespiratory fitness (CRF). To establish the importance of maintaining as high as possible \( \dot{V}O_{2\max} \) throughout the life span, the relationships of \( \dot{V}O_{2\max} \), lifetime physical activity/inactivity, and average life expectancy are discussed next.

Table 1. Approximate percentage contributions of gene-physical interactions contributing to biological aging

<table>
<thead>
<tr>
<th>Function</th>
<th>References</th>
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<tr>
<td>Physiological functions in which lifetime physical inactivity confers no apparent effects</td>
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<tr>
<td>Maximal heart rate</td>
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<td>Ventricular relaxation</td>
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<td>Senses (vision, hearing, smell, taste)</td>
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<tr>
<td>Physiological functions in which regular physical inactivity accelerates secondary aging, but does not alter the primary aging of these systems</td>
<td></td>
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<tr>
<td>Bone mineral density</td>
<td>34</td>
</tr>
<tr>
<td>Maximal aerobic capacity</td>
<td>48</td>
</tr>
<tr>
<td>Maximal skeletal muscle strength/power</td>
<td>35</td>
</tr>
<tr>
<td>Arterial stiffness</td>
<td>49, 53</td>
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<tr>
<td>Selected mitochondrial proteins</td>
<td>30</td>
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<tr>
<td>Total prevention of decrements in physiological functions by regular physical activity at least to the age of ~60–70 yr of age</td>
<td></td>
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<tr>
<td>Insulin sensitivity</td>
<td>10, 45</td>
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<tr>
<td>Endothelial function</td>
<td>13</td>
</tr>
<tr>
<td>Ventricular stiffness</td>
<td>4</td>
</tr>
<tr>
<td>Left ventricular mass and stroke volume</td>
<td>4</td>
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Most studies cited use subjects no older than 65–70 ys, with a very few extending to 80 yr of age. Therefore, data are too sparse to extend conclusions to individuals >80 yr of age.
Vo2max and mortality. CRF is inversely related to mortality as shown by data which we replotted from two different studies (8, 28) in Fig. 1.

In the first study, Kokkinos and Myers (28) report a dose-response relationship for Vo2max and mortality risk that is somewhat similar to a sigmoidal drug dose-response curve (Fig. 1). Men with maximal CRF > 10 METs (~38 ml·kg⁻¹·min⁻¹ in 70 kg) or maximal METs of <4 METs had unchanging mortality risks. A MET is an index of aerobic exercise capacity whereby one MET unit is resting metabolic rate and maximal METs are multiples of resting metabolic rate. However, mortality risk was three times higher for maximal METs < 4 METs than for <10 maximal METs. A second study, a decade earlier by Blair et al. (8), similarly observed that women whose maximal MET values fell from 9 (study, a decade earlier by Blair et al. (8), similarly observed

Modulation of Vo2max and mortality risk with exercise. It is our contention that the slowing/accelerating of secondary aging by lifelong physical activity/inactivity, respectively, can alter mortality risk and thus life expectancy. In support of this hypothesis are data clearly demonstrating that improvements in maximal CRF favorably alter mortality risk in humans up to at least the age of 70 yr (Fig. 2).

Figure 2 presents data from two independent laboratories. Blair and colleagues (7, 31) determined mortality risk in 9,777 men, aged 20-82 yr old, after the second of two visits where the interval for the determination of CRF was separated by 5 yr (Fig. 2). In a second similar study, Kokkinos et al. (29) examined the association between change in CRF and the resultant change in mortality for 867 men who had their second exercise evaluation at least 6 mo (median time 8 yr) after the initial test at the age of ~70 yr old. Importantly, CRF thus is

Vo2max increases during puberty and is enhanced with regular physical training. Body growth during puberty, independent of physical activity levels, increases Vo2max with annual increases ranging from 14 and 22% in Vo2max until lifetime maximal values are reached; these being data reported in seven publications (references to these studies found in Ref. 12). A monozygotic twin study shows that aerobic training during puberty increases relative Vo2max [ml O2·kg lean body mass⁻¹ (LBM)-min⁻¹] more than in inactive cotwins (12). Briefly, one cotwin in nine previously untrained monozygotic twin pairs, aged 11-14 yr, underwent aerobic and anaerobic training for 6 mo while the other did not train. The trained cotwins had 9.0% increases in their Vo2max values compared with the untrained cotwin. Remarkably, the increased absolute Vo2max (L.O2/min) was similar in trained and untrained cotwins. Hence, the increases in relative Vo2max values in the trained vs. untrained cotwins were attributable to 1) smaller gains in total body mass in the training cotwins, 2) equivalent gains in lean body mass in the training cotwins, and 3) relative reductions in fat mass in the training cotwins (12). A conclusion made by the authors was that pubertal growth is a critical period during which higher rates of increase in values for relative Vo2max results in a significantly greater adult values (12). The findings are reminiscent of the concept for environmental enhancements of peak bone mass prior to 20 yr of age, as discussed earlier.
Regular physical activity during puberty will result in a higher lifetime peak value of relative VO₂max. Conversely, sedentary adolescents will have lower lifetime peak relative VO₂max prior to the initiation of its primary aging-induced decline in the third decade of life. Therefore, we posit that an investment in high aerobic activity during puberty contributes to higher lifetime peak relative VO₂max, which, if an adequate amount of physical activity is maintained throughout a lifetime, would delay aerobic frailty until an older age.

Primary aging causes the inevitable decline in relative VO₂max during the third decade of life, even in the lifetime of most physically active individuals. At any age between 25 and 75 yr, slopes for the percentage decline in relative VO₂max are essentially parallel between lifetime-untrained and lifetime-trained endurance athletes (designated as “Heath sedentary” and “Heath athletic” in Fig. 3A). Taken together, primary aging is inevitable for the long-term inescapable decline of relative VO₂max after the age of 20–30 yr old, but secondary aging of relative VO₂max can be slowed or accelerated by aerobically active or sedentary lifestyles, respectively, as discussed earlier.

Other important findings from Fig. 3A are that the difference of ∼25–30 ml·kg⁻¹·min⁻¹ for VO₂max·kg⁻¹·min⁻¹ between lifetime-endurance-trained and lifetime-sedentary groups is maintained between the ages of 25 and 65 yr old, as long as endurance training is continued.

Moderate exercise intensity needed to prevent the accelerated decline in CRF associated with secondary aging. Two landmark longitudinal studies were published in the mid-1990s to show the modulatory effects of aerobic activity on relative VO₂max’s (VO₂max·kg BW⁻¹·min⁻¹) decline. Trappe et al. (52) in the first publication investigated how differing aerobic training patterns over ∼20 yr affected the rate of decline in relative VO₂max values. Four groups began the study as highly trained and possessed a high resting relative VO₂max. Men (26–49 yr old), who trained for aerobic fitness (FT), had a similar rate of decline with age in relative VO₂max as those who maintained the highest level of aerobic training for competitive competition (HT in Fig. 3B). However, younger, unfit nonexercising (23–45 yr old; UT) as one group and older men (47–68 yr old; FO in Fig. 3B) that maintained a highly trained status (FO) as a second group exhibited a greater rate of decline in their relative VO₂max levels compared with the group of the younger aerobically trained men. A potential explanation for the increased rate of decline in relative VO₂max in FO is that at ages >65 yr of age, training volume and intensity declines, leading to increased rate of decline in relative VO₂max (39, 51) and a negative cycling. In the second study by Pollack et al. (39), 20-yr alterations in relative VO₂max values were determined. High- and moderate-aerobic training groups had similar rates of declines in relative VO₂max with age. In contrast, the low-intensity group had accelerated secondary aging so that relative VO₂max reached the sedentary group at the end of the 20-yr study when the low-intensity group transitioned from jogging (moderate intensity) to walking [low intensity; Fig. 3C; note walking is often now defined as moderate intensity, whereas two decades ago walking was low-intensity physical activity (1)].

CLINICAL CONSEQUENCES OF LIFETIME PHYSICAL INACTIVITY

Six clinical consequences consequently arising from the accelerated decline in VO₂max due to a lifetime of physical inactivity are 1) increased mortality so death occurs at an earlier age, as discussed above; 2) younger age for the onset of physical frailty; 3) fewer years of high quality of life; 4) lowered cardiorespiratory reserve so that stresses, such as major surgery, are insufficient to maintain homeostasis within bounds of life; 5) and increased risk of chronic diseases. Most of the consequences are discussed next.

Fig. 3. Decline in VO₂max (ml·kg⁻¹·min⁻¹) as a function of ages for two levels of habitual physical activity. Panels are drawn from three different publications. One cross-sectional data set from Heath et al. (20) is shown in all three panels. A: the top line is identified as “Health’s Athletic” and the bottom line is “Health’s Sedentary,” representing Masters athletes and untrained men, respectively. Note the slopes of VO₂max (ml·kg⁻¹·min⁻¹) vs. age for both lines have similar negative slopes. Also note the same VO₂max, of ∼41 ml·kg⁻¹·min⁻¹ for 80-yr-old Heath’s Athletic (point X) at interception of vertical line from 80 yr and Heath’s Athletic line) and at point Y for the interception of the vertical line from the Heath’s Sedentary line to the age of 37 yr. B: the original longitudinal data, collected over a mean period of 22 yr was overlaid on the Heath et al. data (20) by Trappe et al. (52), with our slight modification of the identification of the two Heath lines. The four groups overlaid on the Heath data are highly trained (HT), fitness trained (FT), untrained (UT), and fit older (FT). Note that lines for the more highly aerobically active groups (HT and FT) tend to parallel to the Heath’s Athletic line over a mean period of 22 yr, whereas the more inactive groups (UT and FO) have greater negative slopes. C: the original longitudinal data as overlaid on the Heath et al. are shown as published by Pollack et al. (39). Two-subject groups (high and moderate intensity) tend to parallel the Heath’s Athletic line over a 20-yr period, while the low-intensity group declines to the Heath Sedentary group line. Slight modifications to the original figure include identification of groups. Figures are reproduced with permission.
A lifetime of endurance training theoretically slows secondary aging of relative VO\textsubscript{2max} by three or four decades if moderate-intensity levels of physical activity were to be constantly maintained until the age of 65–70 yr [Fig. 3, A–C, and other published figures (20, 38–39, 48, 52)]. An alternative means of stating the concept is that the value of VO\textsubscript{2max} of a lifetime sedentary 30-yr-old individual has already secondarily aged to the VO\textsubscript{2max} value found in a 60- to 70-yr-old lifetime endurance-trained individual. Sedentary individuals thus reach aerobic physical frailty (≤18 ml·kg\textsuperscript{-1}·min\textsuperscript{-1}) at an earlier age relative to lifetime physically active individuals. The delay in reaching aerobic physical frailty is associated with a decreased incidence of assisted care living or nursing home residence (5). Holloszy (21) has suitably commented, “Whether an individual who lives to 95 years spends the last 10 years in bed in a nursing home or leads an active, enjoyable life is obviously of key importance.” The aforementioned quotation supports the notion that a higher relative VO\textsubscript{2max} in later life is associated with higher quality of life based on the ability to be more regularly physically active.

In addition to directly shortening average life expectancy and causing aerobic frailty earlier in life, a low VO\textsubscript{2max} means that if functional reserve falls below a threshold value needed to survive a moderate stress level, homeostasis may not be maintained and death may ensue. In direct support of this notion, Struthers et al. (47) stated “Major surgery produces a systemic inflammatory response associated with a marked increase in oxygen consumption in the immediate postoperative period. In patients with poor cardiorespiratory reserve, the inability to meet this increased demand may lead to avoidable morbidity and mortality.”

Studies show that CRF is not inevitably fixed up to 70–82 yr of age. CRF can be increased by becoming more aerobically fit with conversion from sedentary to chronic aerobic types of physical activity and that the decline of CRF with primary aging can be sped more rapidly by discontinuation of physical activities.

Low values of maximal METs (absolute VO\textsubscript{2max}) increases prevalence of one or multiple chronic diseases, which themselves shorten life expectancy (9, 52a). For example, diagnosis of T2D at the age of 30 yr is associated with 14.5/16.5 life-years lost and 23.1/26.1 quality-adjusted life-years lost above sedentary levels so that reaching the aerobic frailty threshold is delayed by decades (Fig. 3A and Fig. 4).

TWO STRATEGIES TO DELAY MORTALITY

One strategy to delay mortality is to obtain as high a lifetime peak VO\textsubscript{2max} as possible at the age of 20 yr through being aerobically active as an adolescent, and a second is to maintain a lifetime of aerobic activity as long as possible to delay the age at which maximal METs fall below 9–10 and 4, which are the thresholds for increases in mortality and aerobic frailty, respectively. The latter strategy would shift the frailty prevalence curve toward older ages and thus increase quality of life years. This proposed strategy is illustrated in Fig. 1B in Rockwood et al. (42) where frailty prevalence has an upward exponential curve that gradually begins about the age of 40 yr with an upward inflection point at ~65 yr of age and reaches ~50% of the remaining population at the age of 90 yr.

Interim Summary

Lifetime peak VO\textsubscript{2max} per kilogram per minute is set by aerobic physical activity patterns during puberty and likely throughout adolescence as well as by inherited genes (Fig. 4).

Primary and secondary aging of VO\textsubscript{2max} become evident in the third decade of life. Lifetime physical activity levels do not alter primary aging of relative VO\textsubscript{2max}, although they do delay the secondary aging of this physiological variable. Maintenance of lifetime endurance activity intensities greater than or equal to moderate intensities will retain relative VO\textsubscript{2max} values above sedentary levels so that reaching the aerobic frailty threshold is delayed by decades (Fig. 3A and Fig. 4).

INACTIVITY’S ACCELERATION OF FACTORS THAT CONTRIBUTE TO VO\textsubscript{2max}

Decreases in maximal cardiac output and maximal oxygen uptake at the skeletal muscle lead to decreased VO\textsubscript{2max} with aging (reviewed by Tanaka and Seals, Ref. 50). Hagberg et al. (16) found equal decreases in maximal stroke volume and maximal arterial-venous O\textsubscript{2} difference at skeletal muscle accounted for the 47% lower VO\textsubscript{2max} in older sedentary subjects compared with age-matched Master athletes. Potential mechanisms for physical inactivity’s lowering of VO\textsubscript{2max} include decreases in left ventricular stiffness (4), arterial stiffness (44), and losses in left ventricular mass index (40). Together, such cardiovascular changes may lead to lower maximal cardiac output with compensatory pathological cardiac right ventricle hypertrophy. On the other hand, lowering of maximal oxygen extraction by skeletal muscle may be due to the declines in skeletal muscle mitochondrial density (26) and mass (discussed in Clinical Relevance of Skeletal Muscle Strength), which are accelerated by a lifetime of inactivity.

Fig. 4. VO\textsubscript{2max}·kg\textsuperscript{-1}·min\textsuperscript{-1} is shown as a function age for hypothesized interactions between inherited genes and lifetime aerobic activity. VO\textsubscript{2max} is shown to rise from 10 to 20 yr of age, rising less rapidly in sedentary (SED) than aerobically active (ACT). Negative slopes of lines after the age of 20 yr indicate the primary aging for those maintaining an unchanged level of physical activity throughout their life span. The influence of inherited genes is schematically drawn for extreme examples for the human with the lowest inherited VO\textsubscript{2max} genetic potential (Low CRF) and from the human who inherited the highest VO\textsubscript{2max} genetic potential (High CRF). Arrows A and B show secondary aging effects, where VO\textsubscript{2max}·kg\textsuperscript{-1}·min\textsuperscript{-1} changes to a lower or higher family of declining VO\textsubscript{2max} slopes, depending on whether physical activity is chronically decreased (A) or increased (B).
CLINICAL RELEVANCE OF SKELETAL MUSCLE STRENGTH AND POWER AS WELL AS INFLUENCES OF LIFETIME ACTIVITY ON THESE VARIABLES

Skeletal muscle power is the rate at which a group of muscles can shorten against a load (27). Skeletal muscle strength is the capability for a group of muscles to generate a maximal amount of force, and whole body strength is typically represented by grip-strength measurements in epidemiological studies (46). It is important to distinguish these two variables due to the fact that runners or cyclists may possess a high power-generating potential with his/her legs but may be relatively weaker (or possess less strength) compared with a conventional weightlifter. There are clinical consequences of possessing low skeletal muscle strength. For instance strength is inversely and independently associated with death from all causes and from cancer in 20- to 80-yr-old men, even after adjusting for CRF and other potential confounders (see Ref. 43). A meta-analysis of 53,476 older individuals determined that at least one of the specified measures of skeletal muscle strength or power (grip strength, walking speed, or chair rises) predicted all-cause mortality (11). Mortality risk increased by 67% from highest to lowest quartiles of grip strengths after adjustments for age, sex, and body size in 53,000 subjects (11). Likewise, mortality risk increased by 187% from highest to lowest quartiles of walking speed after similar covariate adjustments in 14,000 subjects (11).

Previously sedentary, 55- to 79-yr-old post-menopausal women prove mean brachial artery flow-mediated dilation in previously sedentary 40-yr-old lifetime sedentary individuals, as compared with aerobic exercise training (10); however, the rate of decline in absolute peak power was greater for Master level weightlifters than for Master level weightlifters relative to sedentary individuals, this being a similar finding with relative VO₂max in endurance-trained subjects vs. sedentary counterparts (20, 38, 48). Nonetheless, the peak skeletal muscle power of 40-yr-old lifetime sedentary individuals is that of a 69-yr-old Master weightlifter. Thus the secondary aging of peak power is apparently sped in lifetime sedentary individuals. To date, however, the loss of muscle fibers past the age of 50 yr has not been shown to be reversible by resistance training (21), which suggests that the primary aging of skeletal muscle mass (and presumably strength and power) is not completely preventable. In summary, the literature seems to suggest that older individuals with greater skeletal muscle strength and/or power exhibit a dampened all-cause mortality risk.

CLINICAL SIGNIFICANCE OF VO₂max AND SKELETAL MUSCLE STRENGTH, ALONE AND TOGETHER, ON LIFE EXPECTANCY

Both low VO₂max and low handgrip strength independently predict an increased risk of impending death. Together, low values of these two variables synergistically increase mortality risk more than either alone. For instance, men that had both low CRF and muscle strength had death rates that were 60% higher than the death rate in the group of high cardiorespiratory fit men with the highest levels of muscular strength (43). Fleg and Lakatta (14) suggest that a large portion of the age-associated decline in relative VO₂max in non-endurance-trained individuals is likely due to a loss of skeletal muscle mass. Their contention suggests that primary aging of relative VO₂max is in part linked to sarcopenia.

TOTAL PREVENTION OF DECREMENTS IN PHYSIOLOGICAL FUNCTIONS, SUCH AS INSULIN RESISTANCE AND ENDOTHELIAL DYSFUNCTION, BY LIFETIME PHYSICAL ACTIVITY AT LEAST TO THE AGE OF ~60–70 YR OF AGE

Vanhoucke (54) stated, “Endothelial dysfunction is probably a fundamental initial step in the progression of atherosclerosis.” Likewise it is our contention that an initial step toward T2D is the loss of insulin sensitivity, which is extremely sensitive to changes in physical activity. Key points to be made are 1) only days of inactivity are required for normal endothelial function and insulin sensitivity to enter a dysfunctional state, 2) lifelong physical activity, at least to the ages of ~60–70 yr old, will maintain normal endothelial function and insulin sensitivity in individuals living healthy lifestyles, and 3) lifelong physical inactivity increases mortality by increasing atherosclerosis and T2D.

ENDOTHELIAL DYSFUNCTION ASSOCIATION WITH AGING AND INACTIVITY

Aerobically trained men (50–76 yrs old) do not demonstrate an age-related decline in endothelium-dependent vasodilation (EDD) as their values are similar to younger (22–35 yr old) men (13). Likewise, the addition of aerobic exercise restores the loss of EDD in 56-yr-old previously sedentary men (13). Maintenance of CRF or the adoption of a 24-wk endurance-training program prevents or reverses the decline in flow-mediated dilation in 59-yr-old women (6). However, a shorter 8-wk program of essentially daily brisk walking did not improve mean brachial artery flow-mediated dilation in previously sedentary, 75- to 79-yr-old post-menopausal women (37), suggesting that longer-term training may be necessary to reverse endothelial function in this subject group.

The clinical significance of inactivity-induced endothelial dysfunction is that when coronary risk factors are present, the endothelium may adopt a phenotype that facilitates inflammation, thrombosis, vascular constriction, and atherosclerotic lesion formation (55). Lack of exercise precedes coronary risk factors (9). Importantly, Vita and Keaney (55) conclude that a maladaptive endothelial phenotype occurs prior to the development of atherosclerosis. Thus shorter-term physical inactivity increases endothelial dysfunction, which speeds secondary aging through the initiation of the chronic disease atherosclerosis.

LOSS OF INSULIN SENSITIVITY WITH AGING AND INACTIVITY

Seals et al. (45) in 1984 observed that 1) glucose tolerance and insulin sensitivity were similar in 60-yr-old Masters athletes and 26-yr-old athletes who had virtually identical plasma glucose and insulin levels during glucose tolerance tests that were 15–18 h after their last exercise bout and 2) the Masters athletes cleared a glucose load as rapidly as the young, untrained subjects with 50% lower plasma insulin levels. The authors concluded that a deterioration of glucose tolerance and insulin sensitivity is not an inevitable process during aging and
that these systems can be preserved with regular exercise training. DeSouza and colleagues (10) in 2002 reported that 8 yr of aerobic training only prevented ~50% of age-associated loss of insulin sensitivity in 60- to 70-yr-old men and women. DeSouza and colleagues (10) explain that their differences with the Holloszy study (45) were due to DeSouza’s usage of a more sensitive assessment of whole body insulin sensitivity (the insulin-modified frequently sampled intravenous glucose tolerance test). However, Nair and colleagues (30) later found no difference between young (18–30 yr old) and older (59–76 yr old) aerobically trained individuals during the euglycemic-hyperinsulinemic clamp, both being greater than their sedentary cohorts. Thus these and other (3, 30) data clearly suggest that loss of insulin sensitivity with aging until 70 yr of age is mainly a phenomenon of lack of lifetime of physical activity.

The clinical significance of inactivity-induced decrease in insulin sensitivity is that the presence of decreased insulin sensitivity is necessary to develop prediabetes, which is necessary to develop T2D (2) and individuals with T2D have shorter average life span (discussed in variable effects of lack of exercise on secondary aging of functions). Thus, not surprisingly, lifetime physical inactivity is associated with increased T2D prevalence and mortality according to a US Government Advisory Committee Report (52a). Furthermore, glucose metabolism has been demonstrated to become dysfunctional before changes in body fat content (10, 19) and/or $V_{O2\text{max}}$ (19) occur, suggesting that this malady likely is inactivity-induced rather than whole body adiposity induced.

**SUMMARY**

Lack of lifetime physical activity plays a major role for initiators of cardiometabolic diseases, including insulin resistance and endothelial dysfunction. Although not discussed here due to length restrictions, inactivity causes numerous other specific dysfunctions, pathologies, and chronic diseases, which are discussed in more detail by us elsewhere.

**CONCLUSION**

Although death is inevitable and partially explained by inherited genes that produce primary aging, healthy aging is within the discretion of each individual. Sedentary lifestyles accelerate the secondary aging by increasing risks of chronic diseases, decreasing quality-adjusted years of life, and reducing the average life expectancy. However, studies examining the lack of exercise as a major contributor to the secondary aging of various physiological systems remain warranted. The present review provides ample and compelling evidence proving that increasing lifetime physical activity can have a large impact at lengthening the average life expectancy.

**ACKNOWLEDGMENTS**

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**DISCLOSURES**

Scivation is providing M. Roberts’ salary to study nutraceuticals on skeletal muscle mass.

**REFERENCES**

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