Exercise Physiology

Accelerated Longitudinal Decline of Aerobic Capacity in Healthy Older Adults

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Background—The ability of older persons to function independently is dependent largely on the maintenance of sufficient aerobic capacity and strength to perform daily activities. Although peak aerobic capacity is widely recognized to decline with age, its rate of decline has been estimated primarily from cross-sectional studies that may provide misleading, overly optimistic estimates of aging changes.

Methods and Results—To determine longitudinal rate of change in aerobic capacity and the influence of age, gender, and physical activity on these changes, we performed serial measurements of peak treadmill oxygen consumption (peak $\dot{V}O_2$) in 375 women and 435 men ages 21 to 87 years from the Baltimore Longitudinal Study of Aging, a community-dwelling cohort free of clinical heart disease, over a median follow-up period of 7.9 years. A linear mixed-effects regression model was used to calculate the predicted longitudinal 10-year rate of change in peak $\dot{V}O_2$, expressed in milliliters per minute, for each age decade from the 20s through the 70s after adjustment for self-reported leisure-time physical activity. A longitudinal decline in peak $\dot{V}O_2$ was observed in each of the 6 age decades in both sexes; however, the rate of decline accelerated from 3% to 6% per 10 years in the 20s and 30s to >20% per 10 years in the 70s and beyond. The rate of decline for each decade was larger in men than in women from the 40s onward. Similar longitudinal rates of decline prevailed when peak $\dot{V}O_2$ was indexed per kilogram of body weight or per kilogram of fat-free mass and in all quartiles of self-reported leisure-time physical activity. When the components of peak $\dot{V}O_2$ were examined, the rate of longitudinal decline of the oxygen pulse (ie, the O_2 utilization per heart beat) mirrored that of peak $\dot{V}O_2$, whereas the longitudinal rate of heart rate decline averaged only 4% to 6% per 10 years, and accelerated only minimally with age.

Conclusions—The longitudinal rate of decline in peak $\dot{V}O_2$ in healthy adults is not constant across the age span in healthy persons, as assumed by cross-sectional studies, but accelerates markedly with each successive age decade, especially in men, regardless of physical activity habits. The accelerated rate of decline of peak aerobic capacity has substantial implications with regard to functional independence and quality of life, not only in healthy older persons, but particularly when disease-related deficits are superimposed. (***Circulation***. 2005;112:674-682.)

Key Words: aging ■ exercise ■ follow-up studies

O f all the physiological changes that occur during the aging process, among the most important with regard to quality of life and functional independence are declines in muscle strength and in aerobic capacity, indexed as peak oxygen consumption (peak $\dot{V}O_2$). Numerous cross-sectional studies have demonstrated a decline in peak $\dot{V}O_2$ of 5% to 10% per decade in untrained individuals.[1–9] Although age per se is thought to contribute to this decline, age-associated decreases in vigorous physical activity[6,7,10,11] and muscle mass[4,7,11] exacerbate the process.

Because of their inherent selection biases, cross-sectional studies may give a falsely optimistic picture of the longitudinal rate of aging, ie, serial changes in the same individual. Healthy elderly persons who volunteer for exercise studies may have genetic and lifestyle differences from younger individuals, many of whom will not survive to old age. Nevertheless, because of the relative ease of performing cross-sectional rather than longitudinal studies, the former are often used to predict longitudinal aging changes.

Longitudinal studies examining age-associated changes in peak $\dot{V}O_2$ have generally been limited to small samples within a narrow age range not representative of the general population.[12–23] The majority of such studies have focused on elite male athletes.[12,13,16–19] Longitudinal rates of decline of peak $\dot{V}O_2$ in these studies have varied from 5% to >20% per

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decade, dependent largely on the degree to which these athletes maintained their initially intense training regimens over time. These studies provide little insight into the longitudinal changes in aerobic capacity in more typical, nonathletic populations. Furthermore, longitudinal peak V̇O₂ investigations in untrained women are essentially nonexistent. Finally, and most importantly, no studies have specifically examined whether the longitudinal rate of decline in aerobic capacity increases or remains the same with each decade of advancing age. It is likely that such changes are not linear across the age span, as assumed by both cross-sectional studies and longitudinal studies including only individuals within a narrow age range.

Peak V̇O₂ has been measured in clinically healthy volunteers from the Baltimore Longitudinal Study of Aging (BLSA) since 1978. The present study, therefore, was designed to examine longitudinal changes in peak V̇O₂ and its components, peak heart rate and oxygen pulse (the product of stroke volume and arteriovenous O₂ difference), in non–endurance-trained BLSA men and women across a broad age range. We hypothesized that longitudinal decline in peak V̇O₂ would exceed cross-sectional decline and that physical activity levels and body compositional changes would interact with age as determinants of the longitudinal rate of decline in peak V̇O₂. Additionally, we assessed the relative contributions of longitudinal changes in maximum heart rate and O₂ pulse to the decline in peak V̇O₂.

Methods

Sample
Volunteers for the present study were derived from the BLSA.[10,24] These participants are predominantly white and college educated and live or have lived in the Baltimore-Washington area. Approximately every 2 years, they spend 2 to 2.5 days at the Gerontology Research Center in Baltimore, Md, where they undergo medical, physiological, and psychological testing. Those without clinical coronary heart disease (defined by a history of angina pectoris, myocardial infarction, coronary revascularization, or significant Q waves on ECG), other significant cardiopulmonary disease, or major orthopedic/neurological disability undergo maximal treadmill exercise testing on alternate visits.

Oxygen Consumption
BLSA volunteers who performed maximal treadmill exercise tests with measurement of peak V̇O₂ between January 1978 and December 1998 were considered for this study. Exercise testing was performed in a dedicated physiology laboratory under the supervision of the same cardiologist (J.L.F.) throughout this 20-year period and the same exercise technician (J.G.W.) since August 1982. Tests were performed ≥2 hours postprandially, nearly always between 8:30 AM and noon. Tests considered submaximal, as defined by the inability to achieve ≥85% of the age-predicted maximal heart rate or the assessment of the supervising physician that the subject did not exercise to exhaustion (ie, the individual did not appear fatigued and claimed he or she could have continued at least another minute), were excluded from the current analysis. Similarly, observations during which volunteers were using β-blockers were excluded because of the known effects of these drugs to reduce peak V̇O₂.[25]

Oxygen consumption was measured continuously during a modified Balke protocol with the speed of the motor-driven treadmill usually held constant (at 3.0 mph for women and 3.5 mph for men) and the grade of the treadmill progressively increased by 3% at 2-minute intervals until voluntary exhaustion. In more fit subjects, treadmill speed was increased by 0.5 mph 1 to 3 times during the test.

Expired gas volumes were measured with either Tissot tanks or a Parkinson-Cowan gas meter. Expired O₂ and CO₂ concentrations were measured with either dedicated O₂ and CO₂ analyzers or a medical mass spectrometer (Perkin-Elmer MGA-1110), which were calibrated every morning before testing. Oxygen consumption was calculated every 30 seconds, and the highest value was termed peak V̇O₂, expressed in milliliters per minute (mL/min) or milliliters per kilogram per minute (mL/kg per minute). Oxygen pulse, expressed in milliliters per beat (mL/beat), was derived by dividing peak V̇O₂ in milliliters per minute by peak heart rate.

Blood Pressure and Anthropometric Measures
Sitting blood pressure was measured in the left arm by auscultation immediately before treadmill exercise. Body mass index was calculated by dividing the weight in kilograms measured at each visit by the square of height in meters. Weight in kilograms and height in centimeters were measured on a standard physician's balance scale and stadiometer, respectively. Total body fat mass (in kilograms) was calculated by the following formula for men: body fat (kg) = 0.39 weight (kg) − 0.13 height (cm) + 0.74 sagittal/waist diameter (cm) + 4.81 ln triceps skinfold thickness (cm) − 3.78. The formula for women was as follows: body fat (kg) = 0.64 weight (kg) − 0.19 height (cm) + 0.23 sagittal/waist diameter (cm) + 4.74 ln triceps skinfold thickness (cm) + 6.67. These estimates of fat mass correlate closely with those derived from dual energy x-ray absorptimetry ($r = 0.93$) in the 469 BLSA visits for which these data are available. Fat-free mass (FFM) was calculated as weight − total body fat.

Lifestyle Variables
A "never smoker" was defined as a person who smoked <100 cigarettes in his or her lifetime, a "current smoker" (Cursmk) as a volunteer who was currently smoking ≥10 cigarettes a day, and a "former smoker" as a participant previously defined as a smoker who no longer met the definition on his or her index BLSA visit. Leisure-time physical activity (LTPA) was self-reported on the basis of the amount of time spent performing 97 activities since the last biennial visit as previously reported[10] and converted into age decade-adjusted quartiles by gender (see online-only Data Supplement for details).

Statistical Methods
Linear mixed-effects regression models[26,27] were used to analyze parameters affecting longitudinal change in peak V̇O₂ in the BLSA volunteers. The mixed-effects regression model easily accommodates unbalanced, unequally spaced observations and consequently is an ideal tool for analyzing longitudinal changes in BLSA data. This statistical model allows for the examination of important variables that are associated with changes in peak V̇O₂ in a long-term longitudinal study. In this model, longitudinal change is represented by the follow-up time (Time) and its interactions with other variables. Significant interaction of a variable with Time indicates a significant effect on the longitudinal change in peak V̇O₂. Cross-sectional differences across age are represented by terms involving age at first examination (FAge, FAge²) and their interaction with other variables. Separate models were employed to determine the longitudinal decline in maximum heart rate and peak O₂ pulse, the components of peak V̇O₂. The Data Supplement contains additional information detailing the definition of variables that are included in the mixed-effects models.

The major variables known to determine peak V̇O₂ that were the focus of the present analysis included age, gender, body composition, and physical activity. To portray the effects of age and time on peak V̇O₂, predicted longitudinal changes and cross-sectional differences were plotted per 10 years for each age decade. Longitudinal changes were calculated as the percent difference of the predicted peak V̇O₂ at time 0 and 10 years later for each age decade. Cross-sectional differences were calculated by the percent difference of the predicted peak V̇O₂ at time 0 between successive age decades. Similar methods were employed to examine longitudinal changes in the components of peak V̇O₂, peak exercise heart rate, and oxygen

TABLE 1.   Baseline Characteristics

	Men (n=435)	Women (n=375)	P
Age, y	51.9±16	48.6±16	0.0029
Weight, kg	81.5±13.1	64.1±11.7	<0.0001
FFM, kg	59.1±6.3	40.4±4.2	<0.0001
Body mass index, kg/m^2	25.7±3.5	23.9±4.1	<0.0001
Cigarette smoker, %			
Current	20	14	0.036
Former	45	80	<0.0001
Never	35	6	<0.0001
High-intensity LTPA	155±211	129±174	0.049
No. of exercise tests	2.8±0.9	2.8±1.0	0.70
Follow-up time, y	7.9±3.6	8.3±4.7	0.22

Values are mean±SD or %. P values refer to gender comparisons. LTPA indicates leisure-time physical activity in MET-min/24 hours.

pulse. In all analyses, a 2-tailed probability value <0.05 was required for statistical significance.

To assess whether a mixed-effects model was providing an adequate model for this data, we calculated the observed per-decade change in peak $\dot{V}O_2$ for each participant as 10 × (last value − first value)/follow-up time. For each age decade and gender, we constructed 95% confidence intervals for the observed mean per-decade change. The per-decade change in peak $\dot{V}O_2$ was also predicted from the mixed-effects model for each age decade and gender and compared with the confidence intervals obtained from the raw data.

Results

From January 1978 to December 1998, 735 women and 778 men underwent a total of 3379 treadmill tests with respiratory gas analysis; 306 tests were excluded because of submaximal effort. Participants with clinical evidence of coronary heart disease either before their first visit or during the follow-up period were excluded, resulting in a loss of 204 visits and 116 participants. In addition, 102 observations involving β-blocker use were excluded. Finally, data from 205 men and 260 women with a qualifying exercise test on only one visit were excluded. The final sample consisted of 2302 observations in 375 women and 435 men who had at least 2 qualifying visits with peak $\dot{V}O_2$ measurement.

Age distribution of the sample at the time of initial peak $\dot{V}O_2$ determination is shown in Table I of the Data Supplement. All age decades from the 20s through the 70s contained >30 individuals of each gender. Because only 13 men and 11 women initially in their 80s had serial peak $\dot{V}O_2$ measurements, their data were combined with those from individuals aged 70 to 79 years in the tables and figures. Baseline characteristics of the sample appear in Table 1. On average, men were older and heavier than women, performed more high-intensity LTPA, and were more likely to be current smokers or never smokers.

Maximal exercise results are shown in Table 2. Both peak heart rate and respiratory exchange ratio were consistent with a maximal effort. Although peak $\dot{V}O_2$ per kilogram of body weight was ≈17% lower in women than in men, this gender difference was reduced to <4% when peak $\dot{V}O_2$ was indexed for FFM.

TABLE 2.   Maximal Exercise Results

	Men	Women	P
Peak heart rate, bpm	171±17	172±16	0.35
Respiratory exchange ratio	1.11±0.18	1.09±0.14	0.087
Peak $\dot{V}O_2$, mL/min	2844±664	1851±467	<0.0001
Peak $\dot{V}O_2$, mL/kg weight per minute	35.3±8.4	29.4±7.1	<0.0001
Peak $\dot{V}O_2$, mL/kg FFM per minute	48.1±9.8	46.3±9.8	0.012
O$_2$ pulse, mL/beat	16.6±3.7	10.8±2.3	<0.0001

P values refer to gender comparisons.

The variables contributing significantly to prediction of peak $\dot{V}O_2$ in milliliters per minute in the mixed-effects model are shown in the abridged Table 3 (the full set of variables is included in Table II of the Data Supplement). The mixed-effects regression equations for all variables are provided in the Data Supplement. The significant interaction terms, FAge×time and FAge^2×time, allow the longitudinal change in peak $\dot{V}O_2$ to change with first age. Similarly, the significant FAge×time×sex interaction allows the longitudinal change in peak $\dot{V}O_2$ to depend on both first age and gender. These effects can be clearly seen in Figure 1. Figure 1a shows the predicted 10-year longitudinal change in peak $\dot{V}O_2$ by gender for the 6 age decades, using the mixed-effects model, whereas the lower panel shows the 10-year predicted percent longitudinal change of peak $\dot{V}O_2$ for each age decade compared with the respective cross-sectional age declines. A striking feature of Figure 1b is the marked difference between the per-decade cross-sectional and longitudinal changes in peak $\dot{V}O_2$ in older age decades. The longitudinal rate of decline in peak $\dot{V}O_2$ with age is not linear but accelerates at higher age decades in both sexes.

TABLE 3.   Predictors of Peak $\dot{V}O_2$: Mixed-Effects Model

Effect	Slope, mL/min	P	Effect	Slope, mL/min	P
FAge (y)	−6.6235	0.2133	ACTHI-1	51.2585	0.0153
FAge^2	−0.1450	0.0007	ACTHI-2	120.95	<0.0001
Time (y)	17.9020	0.1517	ACTHI-3	129.51	<0.0001
FAge×time	−0.4674	0.0021	Cursmk	−118.55	<0.0001
FAge^2×time	0.01725	0.0082	FFM (kg)	24.8756	<0.0001
Sex	451.77	<0.0001	FAge×FFM	−0.4615	<0.0001
FAge×sex	−1.5435	0.5047	Time×FFM	−1.0690	0.0004
Time×sex	7.1463	0.2684	$\dot{V}O_2$ Method	−86.7519	<0.0001
FAge×time×sex	−0.7158	0.0004	...	...	...

Peak $\dot{V}O_2$ is expressed in mL/min. First age (FAge) is the age of the volunteer at the first examination in which a maximal treadmill test with peak $\dot{V}O_2$ determination was performed. Time in the study is the length of time in years between the first and most recent peak $\dot{V}O_2$ measurement. ACTHI indicates high-intensity leisure-time physical activity; numbers 1, 2, and 3 for ACTHI refer to increasing quartiles of ACTHI with 0 as the reference quartile. Cursmk indicates current smoker. Nonsignificant effects are retained in this final model because of the presence of significant higher-order interactions. $\dot{V}O_2$ Method is 0 for the first measurement method (before December 1990) and 1 for the second measurement method.
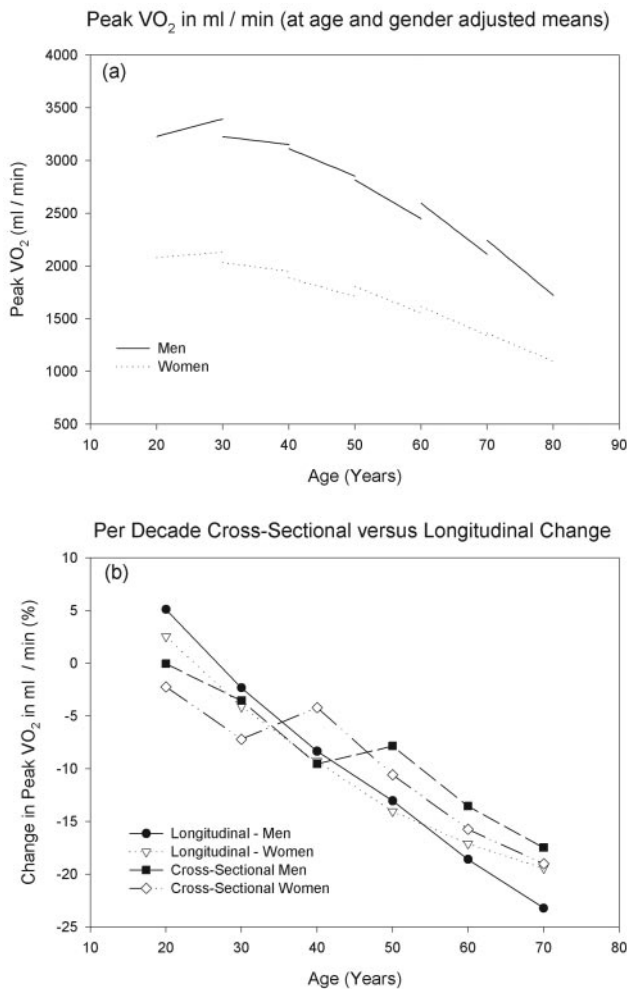
Peak VO₂ in ml / min (at age and gender adjusted means)

Per Decade Cross-Sectional versus Longitudinal Change

Figure 1. Cross-sectional and longitudinal changes in peak V̇O₂ in milliliters per minute by gender and age decade. a, The per-decade longitudinal change in peak V̇O₂ for age decades from the 20s through the 70s, predicted from a mixed-effects linear regression model. Note the progressively steeper decline in peak V̇O₂ with successive age decades, particularly in men, leading to near convergence of peak V̇O₂ in men and women at extreme old age. b, Per-decade percent cross-sectional and longitudinal changes in peak V̇O₂ by gender and age decade, derived from the mixed-effects model. Note that both longitudinal and cross-sectional declines in peak V̇O₂ steepen with age. However, from the 50s onward, longitudinal declines in peak V̇O₂ are substantially larger than cross-sectional declines.

Longitudinal Changes in Body Weight by Gender

Longitudinal Changes in Fat Free Mass by Gender

Figure 2. Longitudinal changes in body weight and FFM by gender and age decade, predicted from the mixed-effects regression model. a, Weight increases similarly in men and women from the 20s through the 60s, stabilizing in the 70s. b, FFM is relatively stable in both genders from the 20s through the 60s but declines thereafter.

Although cross-sectional and longitudinal declines in peak V̇O₂ both average ≈5% per decade at a starting age of 30 years, the longitudinal declines per decade in women and in men aged ≥70 years are substantially greater than those predicted by cross-sectional analyses. For example, in 40-year-old men, baseline peak V̇O₂ averaged 3114 mL/min and decreased by 260 mL/min (8.3%) over 10 years. In contrast, the 70-year-old men started with a peak V̇O₂ of 2244 mL/min but lost 521 mL/min (23.2%) over 10 years.

Age-associated changes in body weight and FFM are important determinants of longitudinal changes in peak V̇O₂ (Table 3). Figure 2 illustrates the linear mixed-effects regression results of longitudinal changes in body weight (Figure 2a) and FFM (Figure 2b) as a function of age and gender.
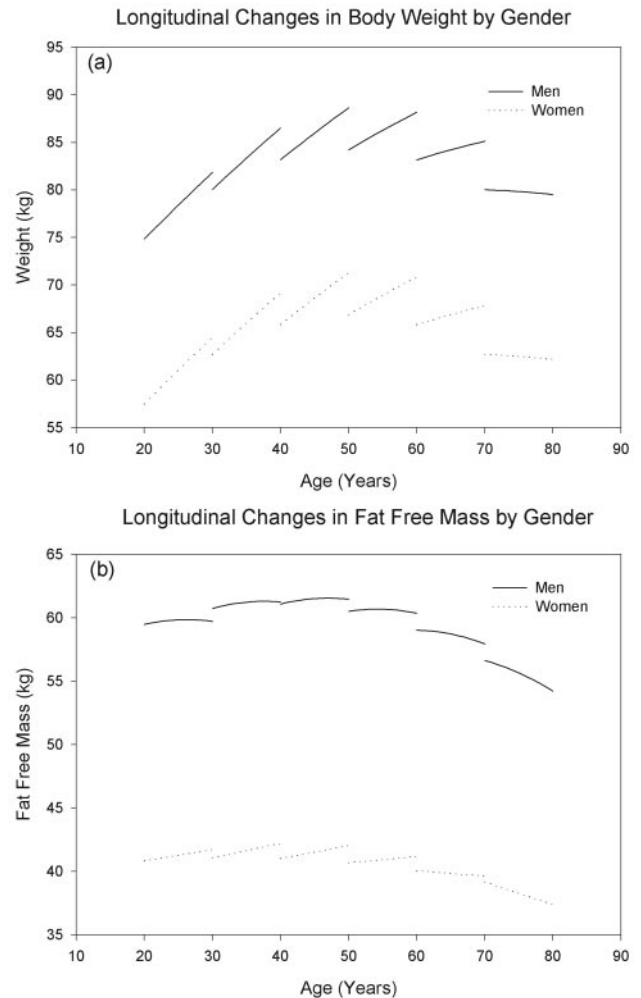
Both body weight and FFM change differently with age in men versus women. Figure 2a shows that younger volunteers of both sexes were lighter than their middle-aged counterparts at their initial visit but experienced a much greater longitudinal increase in body weight. Figure 2b shows that FFM remained stable in younger age groups of both sexes but demonstrated an accelerating decline, starting at an age of ≈50 years for men and 60 years for women. Because of a greater decline in FFM in older men than in older women, the gender difference in FFM narrowed with age after the fifth decade.

Because at least 95% of oxygen consumption during exercise occurs in exercising muscles, indexing of peak V̇O₂ for FFM is more physiological than the conventional indexing for body weight. Figure 3 shows the longitudinal changes in peak V̇O₂ adjusted for FFM. Gender curves of predicted peak V̇O₂ per kilogram FFM (Figure 3a) lie much closer to each other than the unadjusted ones (Figure 1). For example,

Peak VO$_2$ / kg ffm (at age and gender adjusted means)
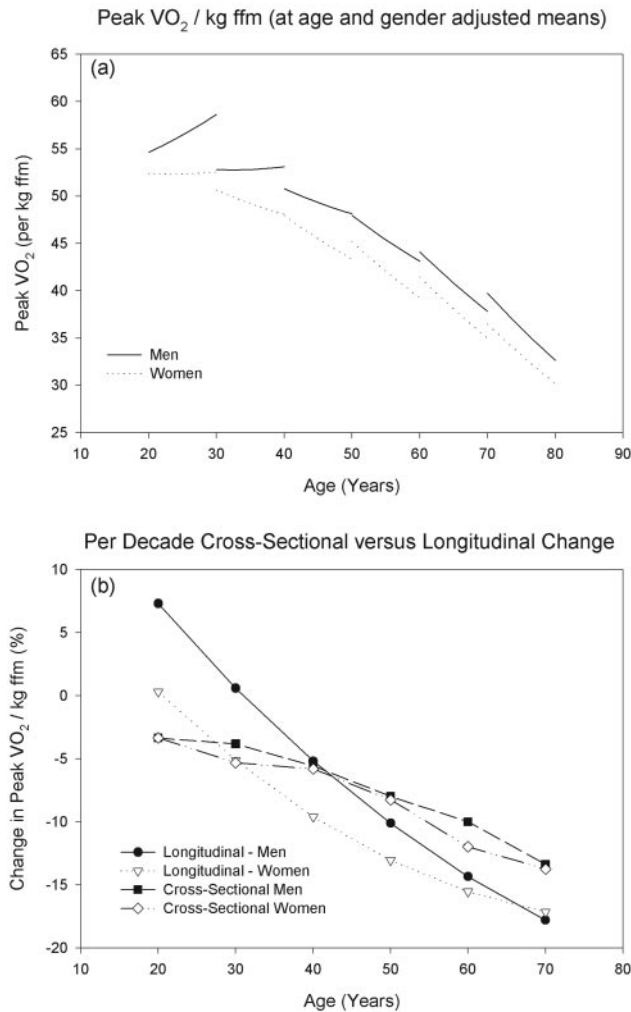

Per Decade Cross-Sectional versus Longitudinal Change

Figure 3. Longitudinal and cross-sectional changes in peak V̇o$_2$ indexed for FFM by gender and age decade, predicted from the mixed-effects model. a, peak V̇o$_2$/FFM declines progressively more steeply with advancing age, with similar declines in men and women. Note that peak V̇o$_2$ per kg FFM is only slightly higher in men than women at younger ages, converging by old age. b, Longitudinal declines in peak V̇o$_2$/FFM accelerate dramatically with age in both genders and are substantially larger then cross-sectional changes.

the baseline average peak V̇o$_2$ for 40-year-old men was 51 mL/kg FFM per minute, only 3 mL/kg FFM per minute higher than in women. Over 10 years of follow-up, 40-year-old men lost an average of only 2.6 mL/kg FFM per minute (5.1%), and 40-year-old women lost 4.6 mL/kg FFM per minute (9.6%). Among those ≥70 years of age, peak V̇o$_2$ declined 17.6% over the decade from a starting value of 39.7 mL/kg FFM per minute for men and declined 17.2% in women from an initial level of 36.5 mL/kg FFM per minute. Figure 3b compares the cross-sectional and longitudinal declines in peak V̇o$_2$, indexed for FFM. Similar to the unindexed peak V̇o$_2$ data (Figure 1a), the decline in peak V̇o$_2$ accelerates with age, the longitudinal rate of decline being substantially greater than cross-sectional changes.

Habitual levels of high-intensity physical activity are known to exert a significant influence on peak aerobic
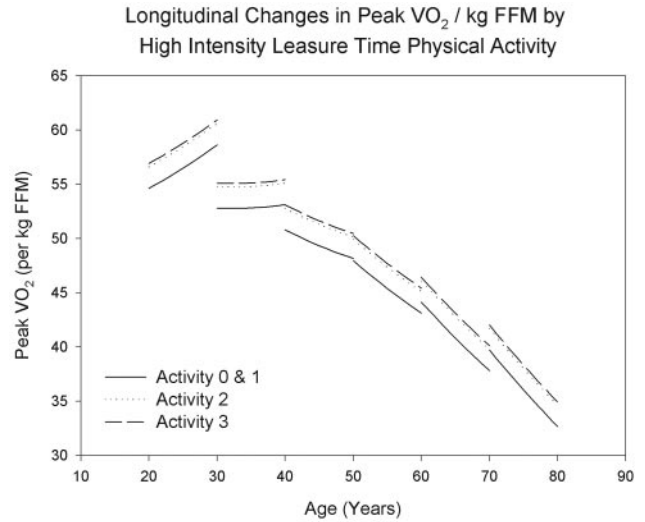
Longitudinal Changes in Peak VO$_2$ / kg FFM by High Intensity Leasure Time Physical Activity

Figure 4. Longitudinal and cross-sectional changes in peak V̇o$_2$ per kg FFM by quartile of age-adjusted high-intensity LTPA. Peak V̇o$_2$/kg FFM is higher in the more active quartiles but declines at a similar rate in all quartiles. The difference in peak V̇o$_2$ among the activity quartiles narrows progressively with age.

capacity. Higher quartiles of LTPA predict higher peak V̇o$_2$ (Table 3). Figure I in the Data Supplement shows that high-intensity LTPA declines with age, so it was necessary to determine whether the contribution of this age-associated reduction in LTPA accounted for the accelerated rate of decline in peak V̇o$_2$ with advancing decades. Figure 4 shows the predicted longitudinal change in peak V̇o$_2$ for the 4 quartiles of high-intensity LTPA reported on the baseline visit, calculated from the final mixed-effects model. Sedentary individuals (Activity 0) demonstrated consistently lower baseline peak V̇o$_2$ than more active participants in all age decade curves but appeared to lose aerobic capacity at a rate similar to that of their more active age peers. Thus, even though physical activity declines with age, this decline does not account for the accelerated rate of decline in peak V̇o$_2$ in older decades. We performed the same analysis in Figure 4 restricted to participants whose LTPA quartile remained constant across all their visits (262 participants with 745 visits). In this selected subset of individuals, the effect of high LTPA group on peak V̇o$_2$ remained the same—ie, the accelerated longitudinal rate of decline of peak V̇o$_2$ with advancing age was still present regardless of absolute level of LTPA (data not shown).

Peak V̇o$_2$ is defined by the product of maximum heart rate (MHR), stroke volume (SV), and arteriovenous oxygen difference (A−peak V̇o$_2$ diff). Although the latter 2 variables are not measured directly during routine peak V̇o$_2$ determination, the product of SV and A−peak V̇o$_2$ diff, the O$_2$ pulse (ie, peak V̇o$_2$/MHR), can be derived from the measured variables. Figure 5 shows the predicted longitudinal declines in MHR, O$_2$ pulse, and peak V̇o$_2$ from the linear mixed-effects regression analysis in men and women. Figure 5a shows that MHR decreases over time in both sexes, with a slightly steeper slope with increasing age that is more
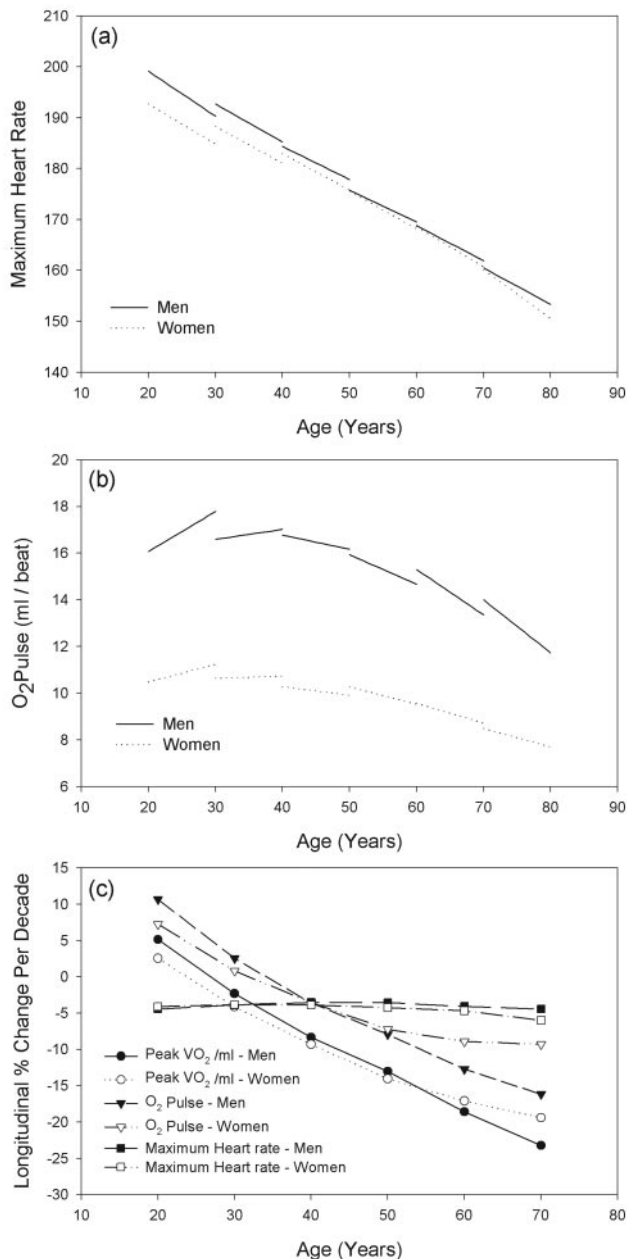
Figure 5. Longitudinal changes in maximal heart rate, O_2 pulse, and peak $\dot{V}O_2$ by gender, predicted from the mixed-effects model. a, Declines in heart rate are similar across age in men but steepen modestly with age in women. b, O_2 pulse declines progressively more steeply with age, especially in men, leading to near convergence of O_2 pulse in elderly men and women. Note the similarity of these plots to those of peak $\dot{V}O_2$ in Figure 1a. c, The longitudinal % change per decade in maximal heart rate is only 4% to 5% per decade across the age span in both genders. In contrast, longitudinal decline in O_2 pulse accelerates progressively with age, especially in men. Note the similarity in the shape and magnitude of the decline in O_2 pulse to that of peak $\dot{V}O_2$.

pronounced in women. Figure 5b shows the predicted longitudinal changes in O_2 pulse in men and women. The curves have a shape very similar to those for peak $\dot{V}O_2$, with progressively greater longitudinal declines with age and near convergence of the sexes by age 80 because of steeper declines in men. Figure 5c compares longitudinal declines in

MHR with those in O_2 pulse and peak $\dot{V}O_2$ in men and women. Note that the per-decade percent longitudinal decline in O_2 pulse is 2 to 3 times that of MHR in older adults and closely parallels the declines in peak $\dot{V}O_2$.

To determine the fidelity of the mixed-effects model estimates of the longitudinal rate of decline of peak $\dot{V}O_2$, we compared the model estimate with the calculated 10-year change from the raw data. Table 4 presents the per-decade change in peak $\dot{V}O_2$ before and after indexing for body weight and FFM in men and women. For each gender–age decade, the pair of numbers in parentheses represents the 95% confidence intervals of the raw longitudinal change per decade; the first number is the predicted change from the mixed-effects model. The predictions from the mixed-effects model are computed by using the mean FAge for the age decade and assuming a nonsmoker with body mass index between 20 and 25; the lowest quartile of high-intensity LTPA; and absence of diabetes, ischemic ST-segment response to treadmill exercise, and cardiovascular medications. Of the 36 confidence intervals and predicted values computed, the modeled estimate lay within the confidence interval for 30 gender–age decade groups (83%). Thus, the mixed-effects model appears to provide adequate estimates of the changes in peak $\dot{V}O_2$ when compared with the observed data. In both sexes, the longitudinal decline in peak $\dot{V}O_2$ accelerates with age, regardless of how peak $\dot{V}O_2$ is indexed.

Discussion

This study demonstrates that the longitudinal rate of decline in peak $\dot{V}O_2$ in healthy adults over a median follow-up period of 7.9 years is not linear but accelerates dramatically with advancing decades. A similar pattern of accelerated decline with age was observed in both sexes and in all quartiles of high-intensity physical activity, and it persisted after adjusting for changes in FFM. Of note, longitudinal rates of decline in peak $\dot{V}O_2$ in older age decades were 2- to 3-fold as great as those derived from cross-sectional analyses in these same subjects. The present sample of 435 men and 375 women ages 21 to 87 at baseline and free of clinical cardiac disease represents the largest and most heterogenous sample in which longitudinal changes in peak $\dot{V}O_2$ have been measured.

Our prior cross-sectional studies[4,10] showed lower absolute but similar percent declines in peak $\dot{V}O_2$ in women versus men, a finding borne out by both the present longitudinal and cross-sectional mixed-effects model estimates and raw data analyses. Recent meta-analyses of cross-sectional data demonstrated per-decade peak $\dot{V}O_2$ declines of 8.7% in sedentary men[9] and 10.0% in sedentary women.[8] Taken together, these data suggest similar declines with age in aerobic capacity in men and women when indexed for initial values and body composition. When expressed per kilogram of body weight, peak $\dot{V}O_2$ was substantially higher, and its longitudinal decay greater in men than in women. However, indexing peak $\dot{V}O_2$ for FFM rather than for body weight largely eliminated these gender differences, which indicates that changes in body composition do not totally explain the accelerated decline of peak $\dot{V}O_2$ with advancing age.

Cross-sectional analyses, however, provide an overly optimistic estimation of the true, ie, longitudinal, changes in

TABLE 4. Per-Decade Longitudinal Change and Per-Decade Percent Longitudinal Change in Maximal Aerobic Capacity by Age Group

	Age Decade					
	<30	30–39	40–49	50–59	60–69	≥70
Change						
Peak $\dot{V}O_2$, mL/min						
Men	28 (−80, 357)	−166 (−516, −230)	−298 (−588, −238)	−420 (−575, −270)	−486 (−656, −251)	−521 (−974, −246)
Women	−35 (−223, 134)	−129 (−204, 60)	−216 (−179, 58)	−254 (−445, −76)	−264 (−390, 30.0)	−220 (−416, −40)
Peak $\dot{V}O_2$, mL/kg per minute						
Men	−1.7 (−5.1, 0.9)	−2.9 (−9.0, −4.9)	−4.6 (−8.4, −4.6)	−5.3 (−8.3, −4.3)	−6.5 (−9.0, −4.0)	−7.8 (−11.7, −2.0)
Women	−2.2 (−5.7, 0.3)	−2.8 (−6.2, −1.9)	−3.5 (−5.0, −1.1)	−3.7 (−7.5, −2.5)	−4.3 (−6.1, 0.7)	−4.8 (−7.2, −0.2)
Peak $\dot{V}O_2$, mL/kg FFM per minute						
Men	1.3 (−2.0, 6.6)	−0.9 (−9.0, −3.8)	−4.5 (−10.0, −4.7)	−5.5 (−11.4, −5.1)	−6.6 (−10.3, −2.6)	−7.0 (−16.3, −1.7)
Women	−1.1 (−4.7, 3.5)	−3.6 (−7.8, −1.2)	−5.2 (−6.9, −0.2)	−6.1 (−13.5, −6.4)	−6.3 (−9.9, 1.9)	−5.7 (−11.0, 2.6)
% Change						
Peak $\dot{V}O_2$, mL/min						
Men	0.6 (−1.2, 13.9)	−5.4 (−13.8, −6.0)	−10.3 (−16.4, −7.1)	−15.7 (−19.8, −8.8)	−19.8 (−25.1, −5.3)	−24.3 (−38.0, 0.4)
Women	−1.8 (−6.8, 8.2)	−6.4 (−7.6, 5.7)	−11.6 (−7.3, 7.8)	−14.9 (−21.6, −2.8)	−17.1 (−23.0, 5.2)	−17.9 (−27.1, 8.8)
Peak $\dot{V}O_2$, mL/kg per minute						
Men	−4.2 (−10.5, 5.0)	−7.4 (−20.4, −10.8)	−10.8 (−21.0, −12.0)	−15.6 (−23.6, −11.0)	−20.2 (−26.5, −6.1)	−26.1 (−35.0, 4.8)
Women	−6.4 (−13.4, 0.3)	−8.4 (−16.1, −3.8)	−10.9 (−15.2, 0.1)	−13.5 (−26.0, −8.9)	−16.6 (−23.2, 5.5)	−21.1 (−25.8, 12.4)
Peak $\dot{V}O_2$, mL/kg FFM per minute						
Men	2.9 (−2.5, 15.0)	−2.9 (−14.8, −5.9)	−7.6 (−17.1, −7.6)	−12.4 (−22.5, −9.5)	−15.6 (−22.0, 0.4)	−18.2 (−35.5, 9.6)
Women	−2.0 (−5.8, 8.6)	−6.7 (−12.7, −0.3)	−10.5 (−12.7, 1.4)	−13.1 (−26.2, −13.8)	−14.8 (−23.7, 7.4)	−15.6 (−22.2, 24.5)

The first number is the predicted value from the mixed-effects model, using the mean FAge for the decade and assuming a nonsmoker with body mass index between 20 and 25; the lowest quartile of high-intensity leisure-time physical activity; and absence of diabetes, ischemic ST-segment response to treadmill exercise, and cardiovascular medications. Values in parentheses for each age decade represent the 95% CI derived from the observed data.

physiological processes. Each succeeding age decade represents a more highly selected group than its predecessor; thus, healthy 70- to 90-year-olds may have been physiologically superior to current 20- to 40-year-olds when they were of similar age. Indeed, cross-sectional analysis of peak $\dot{V}O_2$ in the present cohort illustrates this concept in Figures 1, 3, and 4 by the higher initial peak $\dot{V}O_2$ of older cohorts compared with their "age-matched" counterparts at the end of the previous decade. These apparent differences between successive age cohorts account for the relatively modest cross-sectional declines in peak $\dot{V}O_2$ in both sexes because cross-sectional age changes were estimated by connecting the initial data points for each age decade. Nevertheless, a constant rate of peak $\dot{V}O_2$ loss per year, as assumed by linear regression analysis of cross-sectional peak $\dot{V}O_2$ data, actually translates into a larger percentage yearly decline in older adults, given their lower baseline aerobic capacity than younger adults.

The role of habitual physical activity on the age-associated decline in peak $\dot{V}O_2$ remains highly controversial. Prior cross-sectional[3,6] and longitudinal studies[12,13,16,17] in small, homogenous samples of competitive athletes have suggested that middle-aged and older men who continue to exercise vigorously experience significantly attenuated reductions in peak $\dot{V}O_2$ compared with sedentary controls or athletes who stopped training. Recent cross-sectional meta-analyses, however, demonstrate no effect of training status on either absolute or relative peak $\dot{V}O_2$ declines in men[9] and show a larger absolute but similar relative decline in peak $\dot{V}O_2$ in

endurance-trained versus sedentary women.[8] The present longitudinal data further demonstrate that greater levels of habitual physical activity, though increasing the absolute peak $\dot{V}O_2$ at any age, do not appear to prevent the accelerated decline with advancing age.

We observed that the age-associated decline in MHR accelerated minimally with increasing age decades, indicating that its contribution to the accelerated decline in peak $\dot{V}O_2$ was minor. In contrast, the rate of decline in O_2 pulse accelerated steeply with increasing age, mirroring the decline in peak $\dot{V}O_2$. Because O_2 pulse is the product of stroke volume and A−peak $\dot{V}O_2$ diff, it is unclear whether cardiac or peripheral factors underlie the accelerated longitudinal decline in O_2 pulse with age. Prior data from this healthy BLSA cohort indicate that stroke volume during maximal upright cycle ergometry is preserved across age.[28] Thus, it is attractive to speculate that age-associated reduction in peripheral oxygen extraction is largely responsible for the observed accelerated rate of decline in O_2 pulse, and thus peak $\dot{V}O_2$, with advancing age. Whereas part of the absolute reduction in peak O_2 pulse in older persons is explicable by a reduced lean body mass, the accelerated rate of decline of peak $\dot{V}O_2$ with advancing age decades occurs even after accounting for body composition (Figure 3). Potential factors implicated in the accelerated decline of peak $\dot{V}O_2$ pulse with age include a reduced ability to deliver blood to exercising muscle[29] and changes intrinsic to the muscle itself that impair oxygen utilization.[30]

The accelerated loss of aerobic capacity with advancing age has important clinical ramifications. The ability of

older persons to function independently in the community depends largely on maintenance of sufficient aerobic capacity and muscle strength to perform daily activities. The perceived degree of effort and breathlessness of a given activity is determined by its oxygen cost relative to a person's peak $\dot{V}O_2$. Tasks perceived as requiring substantial effort in deconditioned individuals tend to be avoided, setting off a vicious cycle of further reduction in aerobic capacity, causing further avoidance of physical activity and further loss of muscle mass and strength. Thus, accelerated loss of aerobic capacity translates into low levels of physical activity, slow walking speeds, and early exhaustion—3 of the 5 criteria now used to define frailty.[31] Indeed, the accelerated decline in peak $\dot{V}O_2$ with advancing age in the present sample of healthy older adults able to perform a maximal treadmill exercise test is a best-case scenario. The superimposition of chronic cardiovascular and pulmonary disease, arthritis, and neuromuscular disorders on these "normative" aging decrements likely results in much larger longitudinal declines and lower levels of aerobic capacity in many older individuals than observed here.

Some limitations of the present study should be noted. Although we demonstrate an accelerated decline in peak $\dot{V}O_2$ across age decades by the present mixed-effects prediction model, our median follow-up period of 7.9 years is short relative to the adult aging process. Longitudinal data over 20 years or more in such a sample are needed to confirm these findings. Next, our lack of corresponding lower body strength data in these individuals precludes our assessing the role of muscle strength in the longitudinal decline of peak $\dot{V}O_2$. However, the strong correlation that exists between muscle strength and FFM[32] suggests that the pattern of accelerating decline in peak $\dot{V}O_2$ with age observed here would persist after indexing for strength, just as was observed after indexing for FFM. Furthermore, multiple studies have demonstrated increases in muscular endurance but no change in peak $\dot{V}O_2$ after resistance training, even among the elderly.[33–35] Finally, the predominantly white and upper-middle-class socioeconomic status of BLSA volunteers may not allow direct extrapolation to minorities and lower-income populations. In summary, the present findings demonstrate that longitudinal declines in peak $\dot{V}O_2$ are not linear across adult age, as assumed by cross-sectional studies, but accelerate with successive age decades in both sexes, even after indexing for FFM. Although this accelerated rate of decline in peak $\dot{V}O_2$ is not offset by greater physical activity, higher habitual levels of aerobic activity are accompanied by higher peak $\dot{V}O_2$ levels at any age, an advantage that is maintained over the years. Given the importance of aerobic capacity in activities of daily living, efforts to increase and maintain higher levels of peak $\dot{V}O_2$, in addition to strength training, in older adults would likely improve their ability to live independently with a high quality of life.

Acknowledgment

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