The effects of age and sex on mechanical ventilatory constraint and dyspnea during exercise in healthy humans

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Running Head: Age and sex differences in respiratory mechanics and dyspnea

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Abstract

We examined the effects of age, sex, and their interaction on mechanical ventilatory constraint and dyspnea during exercise in 22 older (age=68±1y, n=12 women) and 22 younger (age=25±1y, n=11 women) subjects. During submaximal exercise, older subjects had higher end-inspiratory (EILV) and end-expiratory (EELV) lung volumes than younger subjects (both $p<0.05$). During maximal exercise, older subjects had similar EILV ($p>0.05$), but higher EELV than younger subjects ($p<0.05$). No sex-differences in EILV or EELV were observed. We observed that women had a higher work of breathing (W_b) for a given minute ventilation ($\dot{V}_E$) ≥65 $l \cdot min^{-1}$ than men ($p<0.05$), and older subjects had a higher W_b for a given $\dot{V}_E$≥60 $l \cdot min^{-1}$ ($p<0.05$). No sex- or age-differences in W_b were present at any submaximal relative $\dot{V}_E$. At absolute exercise intensities, older women experienced expiratory flow limitation (EFL) more frequently than older men ($p<0.05$), and older subjects were more likely to experience EFL than younger subjects ($p<0.05$). At relative exercise intensities, women and older individuals experienced EFL more frequently than men and younger individuals, respectively (both $p<0.05$). There were significant effects of age, sex, and their interaction on dyspnea intensity during exercise at absolute, but not relative, intensities (all $p<0.05$). Across subjects, dyspnea at 80W was significantly correlated with indices of mechanical ventilatory constraint (all $p<0.05$). Collectively, our findings suggest age and sex have significant impacts on W_b, operating lung volumes, EFL, and dyspnea during exercise. Moreover, it appears that mechanical ventilatory constraint may partially explain sex-differences in exertional dyspnea in older individuals.

Key Words: aging, dyspnea, exercise, expiratory flow limitation, operating lung volumes, respiratory mechanics, sex-differences, work of breathing.

New & Noteworthy

We found that age and sex have a significant effect on mechanical ventilatory constraint and the perception of dyspnea during exercise. We also observed that the perception of exertional dyspnea is associated with indices of mechanical ventilatory constraint. Collectively, our results suggest that the combined influences of age and biological sex on mechanical ventilatory constraint during exercise contributes, in part, to the increased perception of dyspnea during exercise in older women.

Introduction

The normative aging of the respiratory system involves significant structural changes to the lungs, airways, chest wall, and respiratory muscles (29), leading to a progressive decline in pulmonary function (36). Consequently, when compared to individuals 20-30 years of age, those above the age of 60 have a reduced ventilatory capacity, as reflected by the size and shape of their maximum expiratory flow–volume curves (19). It follows that older individuals have a reduced reserve for accommodating increases in ventilatory demand during dynamic exercise (1). Moreover, the ventilatory response to exercise at a given absolute work rate is higher in older individuals relative to their younger counterparts (47). Thus, in older individuals it is possible that the ventilatory demand of exercise meets or even exceeds the maximum ventilatory capacity of the respiratory system, resulting in mechanical ventilatory constraint. Several indices can be used to determine the presence and magnitude of mechanical ventilatory constraint during exercise such as quantifying the work of breathing (W_b), assessing changes in operating lung volumes, and determining the presence of expiratory flow limitation (EFL) (2). Healthy aging of the respiratory system is associated with a progressive increase in mechanical ventilatory constraint to exercise hyperpnoea (12), as evidenced by a higher W_b for a given minute ventilation ($\dot{V}_E$), an increase in end-expiratory lung volume (EELV), and a higher propensity towards EFL (30, 31).

Along with age, biological sex is important when considering the mechanical ventilatory response to exercise. When matched for height, women have smaller lungs and lower maximum expiratory flows than men (11). Even when matched for lung size, women have smaller large conducting airways than men - a concept known as dysanapsis (50). Given the aforementioned sex-differences in lung size, airway size, and expiratory flow rates, healthy young women appear to be predisposed to greater mechanical ventilatory constraint during exercise compared to men. We recently demonstrated that during exercise, young women have a higher W_b for a given $\dot{V}_E$ (15, 27) and a higher oxygen-cost of breathing for a given $\dot{V}_E$ than young men (16). It has also been shown that there are sex-differences in the regulation of operating lung volumes, where young women tend to breathe at a higher end-inspiratory lung volume (EILV) for a given submaximal work rate and $\dot{V}_E$ (10), and a higher EELV at maximal exercise than young men (15). Furthermore, EFL appears to be more common in young endurance-trained women than in their male counterparts (27).

There is growing evidence suggesting that the magnitude of exertional dyspnea increases during the healthy aging process (28). For example, during cycle exercise, older men and women report a higher intensity of dyspnea for a given absolute work rate than younger men and women (39). Additionally, older women report a higher intensity of dyspnea during exercise at a standardized oxygen uptake ($\dot{V}O_2$) than older men; this is thought to be related to the interaction between the effects of age and sex on ventilatory constraint (46). Indeed, when the magnitude of ventilatory constraint is experimentally increased during exercise, the perception of dyspnea is increased concomitantly (18). Given the effects of age and sex on the mechanical ventilatory response to exercise, it can be surmised that the sex-differences in exertional dyspnea noted in older individuals may be explained, at least in part, by mechanical ventilatory constraint.

Several studies have investigated the effects of age (30, 31, 39), and sex (10, 15, 27) on the mechanical ventilatory and perceptual responses to exercise. However, few studies have assessed the combined and potentially interactive effects of age and sex on W_b, operating lung volumes, and EFL during exercise, and how they relate to dyspnea. Accordingly, the primary aim of the present study was to assess the effects of biological sex and age as well as their interaction on the mechanical ventilatory and sensory responses to exercise in a group of healthy younger and older, men and women at relative and absolute exercise intensities and ventilations. A secondary aim was to determine if indices of mechanical ventilatory constraint are related to dyspnea during exercise. Based on the above summary, we hypothesized that biological sex and healthy aging would have a significant interactive effect on indices of mechanical ventilatory constraint (W_b, operating lung volumes, and EFL) and dyspnea during exercise. We also hypothesized that, across all subjects, indices of mechanical ventilatory constraint would be significantly correlated with dyspnea intensity during exercise.

Methods

Subjects. After providing written informed consent, 22 older men and women (60-80 y, n=12 women) and 22 younger men and women (20-30 y, n=11 women) participated in the study. All subjects had normal pulmonary function based on predicted values (5, 7, 11, 44). Additional inclusion criteria were: a body mass index of 18-30 $kg \cdot m^{-2}$, peak aerobic power ≥80% predicted, and no evidence of respiratory disease. Subjects were excluded if they were current smokers or had previously smoked >5 pack-years; had a history or current symptoms of cardiovascular, metabolic or respiratory disease; were currently taking medication that would interfere with the ventilatory response to exercise; or had any contraindications to exercise testing. Eight of twenty-two older subjects (n=4 men, n=4 women) had previously smoked <5 pack/years, all of whom had quit smoking >25 y prior to participation in the current study. All healthy younger subjects had never smoked. Subjects were divided into 4 groups based on sex and age: younger women (20-30 y), younger men (20-30 y), older women (60-80 y), older men (60-80 y). All study procedures were approved by the University of British Columbia Providence Health Care Research Ethics Board, which adheres to the *Declaration of Helsinki.*

Experimental Overview. Subjects completed two days of testing separated by a minimum of 48 h. On Day 1, anthropometric measurements were taken, followed by detailed pulmonary function testing and a symptom-limited incremental cycle exercise test. The incremental exercise test performed on Day 1 was intended to familiarize subjects with the exercise protocol. On Day 2, subjects were instrumented with a balloon catheter (Guangzhou Yinghui Medical Equipment Ltd, Guangzhou, China) that was passed through the naris following the application of a topical anesthetic (Lidocan® endotracheal spray, Odan Laboratories, Montreal, QC, Canada) in order to measure esophageal pressure. Following instrumentation, lung static recoil pressure at 100% of total lung capacity ($P_{st\ 100\%TLC}$), lung static recoil pressure at 50% of vital capacity ($P_{st\ 50\%VC}$), and static lung compliance were assessed. Subjects then performed a maximal incremental cycle exercise test using the same protocol as on Day 1. During the incremental exercise test, EFL was assessed using the negative expiratory pressure (NEP) technique (see *Expiratory Flow Limitation*). On Day 2, subjects performed a series of forced vital capacity maneuvers at different efforts before and after exercise in order to construct maximum expiratory flow-volume curves by taking into account exercise-induced bronchodilation and thoracic gas compression (25). All reported resting pulmonary function data, apart from static recoil and lung compliance, were obtained on Day 1, whereas all reported exercise data were obtained on Day 2.

Pulmonary Function Testing. Spirometry, whole-body plethysmography, single breath diffusing capacity for carbon monoxide, maximum voluntary ventilation, and maximum inspiratory and expiratory pressures were assessed using a commercially available system (Vmax Encore 229, V62J Autobox; CareFusion, Yorba Linda, CA) according to standard recommendations (21, 38, 42, 53). Pulmonary function measurements were expressed as absolute values and as percentages of predicted (5, 7, 11, 44).

Exercise Protocol. Exercise testing was conducted on an electronically braked cycle ergometer (Ergoselect 200P; Ergoline, Bitz, Germany). Each test began with a 6 min rest period followed by 1 min of unloaded pedaling then 20 W step-wise increases in workload (starting at 20 W) every 2 min until volitional exhaustion. The exercise protocol was selected in order to allow for comparisons between groups at discrete work rates. Peak work rate was defined as the highest work rate sustained for at least 30 s.

Flow, Volume and Pressure. During the incremental cycle exercise test on Day 2, subjects breathed through a low resistance (0.3-0.7 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ at 0.5-8 $l \cdot s^{-1}$) circuit with minimal dead-space (130 ml). Bi-directional flow was measured using a heated, calibrated pneumotachograph (model 3813, Hans Rudolph, Kansas City, MO, USA). Volume was obtained by numerical integration of the flow signal. Mouth pressure was sampled through a port in the mouthpiece while esophageal pressure was measured using an esophageal balloon catheter. Placement of the catheter was performed as previously described (55), with 0.5 ml of air placed into the esophageal balloon. Validity of the esophageal balloon pressure was verified by performing an occlusion test, as previously described (4). Mouth pressure and esophageal pressure were measured using independent, calibrated differential pressure transducers (DP15-34, Validyne Engineering, Northridge, CA, USA). Flow, volume, and pressures were composite averaged by selecting breaths within a 30 s epoch during rest and at the end of each exercise stage.

Cardiorespiratory Responses. Standard cardiorespiratory measures were recorded on a breath-by-breath basis and averaged over 30 s periods at rest and during exercise. In the younger subjects, heart rate was measured using a heart rate monitor (Polar T34; Polar Electro, Kempele, Finland). In the older subjects, heart rate and electrocardiogram changes were monitored continuously using a 12-lead electrocardiogram (Cardiosoft Diagnostics System v6.71, GE Healthcare, Canada). Arterial oxygen saturation was measured in all subjects using a finger-pulse oximeter (Radical-7, Massimo Corporation, Irvine, CA, USA). Inspiratory capacity maneuvers were performed at rest and at the end each exercise stage. End-inspiratory lung volume (EILV) and EELV were derived from the inspiratory capacity maneuvers (24). Theoretical maximum ventilation ($\dot{V}_{ECAP}$) was calculated at rest and for each exercise stage based on the maximum expiratory airflow throughout a composite averaged tidal breath at a given lung volume as previously described (33). Fractional utilization of available ventilatory capacity ($\dot{V}_E/\dot{V}_{ECAP}$) was determined as the quotient of $\dot{V}_E$ and $\dot{V}_{ECAP}$.

Work of Breathing. W_b was determined by integrating the area within a composite averaged tidal esophageal pressure–volume loop (17). For each subject, W_b data were plotted as a function of absolute $\dot{V}_E$. To compare the effects of age, sex, and their interaction on W_b for a given absolute $\dot{V}_E$, curves were fit to each individual subject's data according to the following equation (27):

$$W_b = a\dot{V}_E^3 + b\dot{V}_E^2 \qquad \textit{(eq. 1)}$$

where, for a given absolute $\dot{V}_E$, $a\dot{V}_E^3$ represents the resistive component of W_b and $b\dot{V}_E^2$ represents the viscoelastic component of W_b. To determine the total W_b for each subject at discrete levels of absolute $\dot{V}_E$, each subject's W_b equation (*eq. 1*) was solved for successive independent variables in 5 $l \cdot min^{-1}$ increments up to each subject's maximal $\dot{V}_E$. The total W_b values for each subject were then normalized to their respective maximal $\dot{V}_E$ in 5% increments up to 100%.

Expiratory Flow Limitation. At rest and for each stage of exercise on Day 2, EFL was determined using the NEP technique (27, 37). Briefly, the NEP technique involves the generation of a negative pressure (between -5 to -10 cmH_2O) at the mouth during the expired portion of a breath. Negative pressure was achieved using an electronically controlled Venturi device (207A, Raytech Instruments, Vancouver, BC, Canada) attached to the distal portion of the pneumotachograph. A control flow-volume loop was created by composite averaging the 3 tidal breaths immediately prior to each NEP breath to represent spontaneous patterns of flow and volume at a given stage during the exercise test (37). Expiratory flow limitation was considered present when the NEP breath overlapped with the expired portion of the control breath.

Perceptual Responses. At rest and during the last 30 s of each 2 min exercise stage, subjects rated the intensity of "breathing discomfort" (dyspnea) and "leg discomfort" using the modified category-ratio 0–10 Borg scale (6). Dyspnea was defined as "the sensation of labored or difficult breathing" and leg discomfort was defined as the "sensation of leg muscle fatigue". The endpoints of the scale were anchored such that 0 represented "no breathing/leg discomfort" and 10 represented "the most severe breathing/leg discomfort ever experienced or imagined".

Data Processing. All data (see *Flow, Pressure and Volume*, and *Cardiorespiratory Responses*) were collected using a 16-channel analogue-to-digital data acquisition system (PowerLab/ 16/35, ADInstruments, Colorado Springs, CO, USA), sampled at 2000 Hz, and recorded using LabChart 7.3.7 software.

Statistical Analysis. Descriptive characteristics, pulmonary function data, and maximal exercise data were compared using a 2x2 analysis of variance for age and sex between the four groups. In the case of a significant interaction between age and sex, four pairwise comparisons were performed with Bonferroni corrections where appropriate. To determine the effect of age and sex as well as their interaction on W_b for a given absolute relative $\dot{V}_E$, W_b was compared at discrete levels of absolute $\dot{V}_E$ (in 5 $l \cdot min^{-1}$ increments) or relative $\dot{V}_E$ (in 5% increments) using a mixed model analysis of variance. In the case of a significant two-way interaction between $\dot{V}_E$ and age, $\dot{V}_E$ and sex, or a significant three-way interaction between $\dot{V}_E$, age and sex, pairwise comparisons were performed with Bonferroni corrections where appropriate. We performed a mixed-model repeated-measures analysis using generalized estimating equations to evaluate the main effects of age and sex as well as their interaction between groups and work rate (absolute and relative) on EFL at rest and during exercise. Cardiorespiratory and perceptual variables were compared at rest and at absolute submaximal work rates up to the highest equivalent work rate achieved by all subjects and at relative work rates in 20% increments from rest to peak exercise using a mixed model analysis of variance. In the case of a significant two-way interaction between work rate and age, work rate and sex, or a significant three-way interaction between work rate, age and sex, Bonferroni-adjusted post-hoc comparisons were conducted where appropriate. Pearson's product moment correlation analysis was used to determine the relationship between dyspnea and possible physiological contributors. For all analyses, the level of statistical significance was set at $p<0.05$. All data are presented as means±SE.

Results

Subjects. Subject characteristics and pulmonary function data are shown in Table 1. Resting pulmonary function was within the normal predicted range for all groups. As expected, there were significant age-related differences in maximum expiratory flows, lung volumes (with the exception of total lung capacity, $p=0.97$), diffusing capacity, and respiratory muscle strength (all $p<0.05$). Furthermore, when expressed in absolute terms, the majority of pulmonary function measures were greater in men than women (all $p<0.05$), with the exception of the ratio of forced expired volume in 1 s to forced vital capacity ($p=0.81$), forced expired flow between 25% and 75% of forced vital capacity ($FEF_{25\text{-}75\%}$) ($p=0.23$), and residual volume ($p=0.14$). There were no significant interaction effects between age and sex, indicating that the age-related decrement in pulmonary function was similar in both sexes. Regardless of sex, older subjects had lower $P_{st\ 100\%TLC}$ ($p<0.001$) and $P_{st\ 50\%VC}$ (Table 1) ($p<0.001$). Moreover, there was a significant linear correlation between $FEF_{50\%}$ and $P_{st\ 50\%VC}$ (r=0.54, $p<0.05$).

Peak exercise data are shown in Table 2. At peak exercise, there was a significant effect of age and sex on absolute $\dot{V}O_2$, work rate, $\dot{V}_E$, the ventilatory equivalent for carbon dioxide, $\dot{V}_{ECAP}$, and W_b (all $p<0.05$). When $\dot{V}O_2$ at peak exercise was expressed as a percent of predicted values, there was no significant effect of age or sex, indicating that subjects had statistically similar levels of relative fitness. Independent of sex, there was a significant effect of age on heart rate, breathing frequency, the ventilatory equivalent for oxygen, the ventilatory equivalent for carbon dioxide, and EELV (all $p<0.05$). Independent of age, there was a significant effect of sex on tidal volume ($p<0.05$). There were no significant interaction effects between age and sex at peak exercise. On average, subjects in each group achieved respiratory exchange ratios >1.10 and near maximum heart rates based on predicted normal values, indicating that maximal effort was exerted across groups. There were no significant differences in the $\dot{V}O_2$-work rate slopes between groups on the basis of age or sex (Table 2; both $p>0.05$).

Summary of Primary Results. Table 3 summarizes the primary results of the study, which are further described below and illustrated in Figures 1-8. Variables relating to the ventilatory response to exercise, indices of mechanical ventilatory constraint, and the perception of dyspnea where compared at absolute submaximal work rates and at relative work rates on the basis of sex, age, and their interaction. The main effects that reached statistical significance and, where appropriate, which interaction effects were statistically significant are highlighted.

Ventilatory Response to Exercise. Ventilatory responses to exercise are shown in Figure 1. For a given submaximal absolute work rate ≥40 W, older subjects had a higher absolute $\dot{V}_E$ than younger subjects, regardless of sex (all $p<0.05$). Men had a higher absolute $\dot{V}_E$ than women during exercise at a relative exercise intensity ≥40% of peak work rate, regardless of age (all $p<0.05$). There was no significant interaction effect between age and sex on absolute $\dot{V}_E$ at rest or during exercise at any absolute or relative work rate (both $p>0.05$).

Fractional utilization of $\dot{V}_{ECAP}$ at rest and during exercise are shown in Figure 2. Older subjects had a significantly higher $\dot{V}_E/\dot{V}_{ECAP}$ at rest and throughout submaximal exercise at an absolute work rate (all $p<0.05$). The effect of age on $\dot{V}_E/\dot{V}_{ECAP}$ was still evident when comparisons were made at relative exercise intensities (all $p<0.05$). There was no effect of sex on $\dot{V}_E/\dot{V}_{ECAP}$ at rest or during exercise ($p>0.05$), and there was no significant interaction effect between age and sex on $\dot{V}_E/\dot{V}_{ECAP}$ ($p>0.05$).

Operating lung volumes at rest and during exercise are shown in Figure 4. During exercise at a given submaximal absolute work rate, there were no significant differences in EELV or EILV on the basis of sex (both $p>0.05$), however, EELV and EILV were both higher in older than in younger subjects (all $p<0.05$). The effect of age on relative EELV and EILV were also present at rest and throughout submaximal exercise when comparisons were made at relative exercise intensities (all $p<0.05$). Moreover, at peak exercise, older subjects had a higher EELV but a similar EILV than younger subjects ($p<0.05$). There was no significant interaction effect between age and sex on EELV or EILV (both $p>0.05$).

Work of Breathing. Individual subject values for the W_b are plotted as a function of absolute $\dot{V}_E$ in Figure 4 (panels A and B), and as a function of relative $\dot{V}_E$ in Figure 5 (panels A and B). Each subject's W_b-$\dot{V}_E$ curve was fit to *eq. 1*, and without exception there was excellent fit (mean r^2:

0.99±0.01). Then, by pooling each individual's constant *a* and constant *b* from *eq. 1*, a mean curve was constructed for each group (Figure 4, panel C; Figure 5, Panel C). There were significant main effects of $\dot{V}_E$, sex, and age on W_b (all $p<0.001$). There was a significant interaction between $\dot{V}_E$ and sex, as well as $\dot{V}_E$ and age (both $p<0.001$), but no significant interaction effect between $\dot{V}_E$, sex, and age ($p>0.05$). W_b was significantly higher in women at and above a $\dot{V}_E$ of 65 l·min^{-1} ($p<0.001$), and significantly higher in older subjects at and above a $\dot{V}_E$ of 60 l·min^{-1} ($p<0.001$). When W_b was compared at relative fractions of peak exercise $\dot{V}_E$, there was no significant effect of age, sex, or their interaction at any fraction of maximal $\dot{V}_E$ below peak exercise (Figure 5, Panel C; both $p>0.05$). However, at peak exercise men had a significantly higher W_b than women, and older subjects had a significantly lower W_b than younger subjects (both $p<0.05$, Table 2).

Expiratory Flow Limitation. Examples of flow-volume loops in four subjects (one representative sample from each group) used to determine the presence of EFL using the NEP technique are shown in Figure 6. Successful NEP maneuvers were obtained at rest and at each exercise stage in all but two subjects (n=1 older woman, and n=1 younger woman) whose data were excluded from the analysis since the application of the NEP caused a sustained decrease in expiratory flow relative to the control breath. The frequency of EFL in each group at rest and throughout exercise is shown in Figure 7. No subjects had EFL at rest, but as exercise intensity increased the fraction of subjects who had EFL increased progressively. Based on our model, there was a significant main effect of age, as well as a significant interaction effect between age and sex on EFL during exercise when comparisons were made at absolute work rates (both $p<0.05$). When the analysis was repeated at relative exercise intensities, there were significant main effects of age and sex (both $p<0.05$); however, there was no significant interaction effect between age and sex ($p=0.39$).

Dyspnea. Figure 8 shows dyspnea intensity ratings in all groups at rest and during exercise. There were significant effects of age and sex, as well as their interaction on dyspnea during exercise at absolute exercise intensities (all p<0.05). Specifically, women reported higher levels of dyspnea than men at 80 W regardless of age (p<0.05), and older subjects reported higher levels of dyspnea at 60W and 80 W, regardless of age (p<0.05). At an absolute exercise intensity of 80 W, the difference in dyspnea between younger men and younger women were subtle, albeit significant (0.1±0.1 versus 0.7±0.2, p<0.001). By contrast, older women reported significantly higher dyspnea at 80 W than older men by 1.3 Borg units (0.6±0.2 versus 1.9±0.4, p<0.001). When dyspnea was compared between groups at relative exercise intensities, there was no significant effect of age, sex, or their interaction (all p>0.05).

We also found that dyspnea/$\dot{V}_E$ slopes showed a significant effect of age (0.093 vs. 0.065 Borg units·l^{-1}·min^{-1}, p<0.05) and sex (0.092±0.006 vs. 0.064±0.010 Borg units·l^{-1}·min^{-1}, p<0.05), but not their interaction (p=0.52). Finally, correlates of dyspnea intensity at a standardized absolute work rate of 80 W are shown in Table 4. The four strongest correlates of dyspnea intensity at 80 W were W_b, $\dot{V}_E/\dot{V}_{ECAP}$, breathing frequency, and $\dot{V}_E$.

Discussion

Major Findings. We assessed the effects of age and sex on the mechanical ventilatory and perceptual responses to exercise in healthy younger and older, men and women. Our major findings are five-fold. First, women have a higher W_b for a given absolute $\dot{V}_E$ ≥65 l·min^{-1} during exercise compared to men, regardless of age. However, W_b is similar between the sexes for a given relative $\dot{V}_E$ during submaximal exercise. Second, older subjects breathe at higher lung volumes during exercise at a given submaximal absolute or relative exercise intensity, but do not differ on the basis sex. Third, we observed a significant interaction effect between age and sex on the likelihood of developing EFL during exercise at an absolute work rate. We found that older subjects are more likely to develop EFL than younger subjects, and that older women have a higher propensity towards EFL than older men. During exercise at a given relative work rate, older subjects and women are more likely to experience EFL than younger subjects and men, respectively. Fourth, age and sex exert an interactive effect on the perception of dyspnea during exercise at a given absolute work rate ≥80W. Older women, and to a lesser extent younger women, report higher levels of dyspnea than older men and younger men, respectively. However, the effects of age and sex on the perception of dyspnea are absent at relative exercise intensities. Finally, dyspnea during submaximal exercise is associated with indices of mechanical ventilatory constraint. Collectively, our findings suggest that age and sex only interactively affect the propensity towards EFL and the perception of dyspnea during exercise when comparisons between groups are made at absolute exercise intensities.

Maximum Ventilatory Capacity and Ventilatory Response to Exercise. The primary age-related change to the respiratory system that contributes to decreasing pulmonary function is thought to be the progressive reduction in elastic recoil pressure of the lung (20). As the elastic recoil pressure of the lung decreases, so too does the ability to generate expired flow, thereby reducing maximum ventilatory capacity (54). As expected, older subjects had a significantly lower $P_{st\ 100\%TLC}$ and $P_{st\ 50\%VC}$ than younger subjects (Table 1). It follows that despite having similar total lung capacities, older subjects had a reduced capacity to generate expiratory flow, as evidenced by significantly lower mid-expiratory flows than younger subjects (Table 1). Accordingly, we observed a significant linear correlation between $P_{st\ 50\%TLC}$ and $FEF_{50\%}$. However, it should be noted that we did not detect statistically significant differences in $P_{st\ 50\%VC}$, $P_{st\ 100\%TLC}$, $FEF_{50\%}$ or $FEF_{25\text{-}75\%}$ on the basis of sex, indicating that the effect of age on static recoil and expiratory flows was similar between men and women. While the effect of aging on the static recoil pressure of the lung is well characterized (52), evidence of sex-differences in static recoil pressure of the lung remains equivocal (9, 20). Overall, the age-related decline in ventilatory capacity observed in our study resulted in a reduction in the available reserve for accommodating increases in ventilatory demand, as evidenced by a significantly lower absolute $\dot{V}_{ECAP}$ at rest and throughout exercise in the older relative to the younger subjects (data not shown). Moreover, due to their relatively smaller lungs, women had a lower absolute $\dot{V}_{ECAP}$ than men at rest and throughout exercise, and this relationship was unaffected by age (data not shown).

During exercise, older subjects had a higher $\dot{V}_E$ for a given absolute work rate above 20 W than younger subjects (Figure 1, Panels C and D), a finding that is in agreement with previous work (47). Given the age-related decline in $\dot{V}_{ECAP}$, the higher ventilatory response to exercise in older individuals increases the likelihood of reaching the mechanical limits of the respiratory system at a given absolute work rate. Indeed, older subjects utilized a greater fraction of their available ventilatory capacity ($\dot{V}_E/\dot{V}_{ECAP}$) at rest and during submaximal exercise at an absolute work rate than younger subjects (Figure 2). When comparisons were made at relative exercise intensities, older subjects still had a higher $\dot{V}_E/\dot{V}_{ECAP}$ than younger subjects during submaximal exercise (Figure 2, panels A & B).

Operating Lung Volumes. During incremental exercise, younger subjects reduced EELV below functional residual capacity and increased EILV up to approximately 90% of total lung capacity (Figure 4, panel D). In older subjects, the age-related reduction in vital capacity and expiratory flows results in operating lung volumes that are shifted to higher fractions of total lung capacity (46). Compared to younger subjects, we found that older subjects had a higher EELV throughout exercise by 4.9±1.5% of TLC, and a higher EILV by 4.7±1.7% of TLC during submaximal exercise (Figure 3, panel A and B). These age-related increases in EELV and EIL likely alter the length tension relationship of the respiratory muscles, and encroach on inspiratory reserve volume. Furthermore, older subjects decreased EELV during exercise remained below resting EELV. Like their younger counterparts, most older subjects reduced EELV during exercise until they approach EFL, at which point EELV may begin to increase back towards resting EELV in order to avoid excessive mechanical constraint (30). In some cases, EELV continues to increase to the extent where it exceeds resting EELV, a phenomenon known as dynamic hyperinflation (3). We observed that 7 of 22 (n=3 men, n=4 women) older subjects but none of the younger subjects showed evidence of dynamic hyperinflation at maximal exercise, which we defined as an increase in EELV >0.15 l above resting EELV. Although EILV was higher in the older subjects than the younger subjects during submaximal exercise, EILV was similar between age groups at maximal exercise. The fact that regardless of age, the highest EILV reached during exercise was approximately 90% of total lung capacity is likely due to the sigmoidal shape of the pressure-volume relationship of the respiratory system, whereby any further increase in EILV would substantially increase W_b. Overall, it appears that older individuals regulate their operating lungs volumes during exercise in a similar manner to younger individuals, but at a higher fraction of total lung capacity. However, the increase in EILV is constrained due to the age-related reduction in inspiratory reserve volume.

It can be argued that because women have smaller lungs and lower maximum expired flows than men, that they have a tendency to breathe at a higher EELV and EILV during exercise. The effect of sex on operating lung volumes has been assessed in several studies, but the results are conflicting (10, 12, 13, 15, 26, 49). In the current study, we did not observe a systematic effect of sex on operating lung volumes when EELV and EILV were expressed as a fraction of total lung capacity. While it is tempting to hypothesize that women are more likely to increase EELV and/or EILV during exercise to avoid EFL, we believe that this is an oversimplification. Although EFL has been shown to increase operating lung volumes under experimental conditions (48), the fact that an individual exhibits EFL does not guarantee that operating lung volumes will increase. For example, it is possible that in the presence of EFL, some individuals preserve relatively low lung volumes to avoid breathing on the flat portion of the pressure-volume relationship of the respiratory system.

Work of Breathing. The mechanical and metabolic cost of maintaining adequate alveolar ventilation during exercise can be substantial and increase exponentially as a function of $\dot{V}_E$ (16). Since healthy aging causes a decrease in the compliance of the chest wall (43), and a reduction in airway diameter (45), it would be expected that W_b for a given $\dot{V}_E$ would be higher in older relative to younger individuals. We demonstrated that for a given absolute $\dot{V}_E \geq 60$ $l \cdot min^{-1}$, older subjects have a significantly higher W_b than younger subjects (Figure 4). The relationship between W_b and $\dot{V}_E$ during exercise has previously been assessed in highly trained older men (31), and highly trained younger men (32). However, only one study has investigated the effect of age on W_b during exercise within the same study (8). They found that older individuals had a higher W_b than younger individuals during exercise at an absolute $\dot{V}O_2$ of 1.5 $l \cdot min^{-1}$ as well as at 40% and 60% of cardiac reserve. However, they did not normalize W_b for $\dot{V}_E$, and only included male participants. Thus, our study is the first to show that W_b is higher for a given $\dot{V}_E$ in older men and women by directly comparing them to younger men and women.

We have previously shown that for a given $\dot{V}_E$ above ~55-65 $l \cdot min^{-1}$, W_b (15, 27) and respiratory muscle $\dot{V}O_2$ (16) are higher in young women relative to young men. In the present study, we also demonstrate that for a given $\dot{V}_E \geq 65$ $l \cdot min^{-1}$, women have a significantly higher W_b than men (Figure 5). Importantly, the effect of sex on W_b appears to be independent of the effect of age. This finding is in keeping with previous work showing that older women have a higher $\dot{V}O_2$ of the respiratory muscles during exercise than older men (51).

When we compared W_b as a function of relative $\dot{V}_E$, there was no significant effect of age, sex, or their interaction on W_b at any submaximal fraction of peak $\dot{V}_E$ (Figure 5). However, it is important to contextualize this relative comparison. If one considers that activities of daily living are performed at similar rates of relative oxygen consumption (i.e. metabolic equivalents), and that age and sex both affect maximal relative VO_2 (34), it can be surmised that women and older individuals would have to dedicate a higher fraction of whole body VO_2 to their respiratory muscles in order to accomplish a given task than men and younger individuals, respectively.

Expiratory Flow Limitation. It is well known that older individuals are predisposed to EFL during exercise due to their reduced ventilatory capacity and increased ventilatory response to exercise (12, 29). In the present study, we found that healthy aging had a significant effect on EFL during exercise at absolute work rates (Figure 7, panel A). We also observed that older women have a higher propensity towards developing EFL than older men, but that this apparent sex-difference was not present in the younger subjects. We attribute our findings to the interactive influences of healthy aging and biological sex on the structure and function of the respiratory system. When ventilatory demand approaches maximum ventilatory capacity, small sex-differences in airway anatomy may play a crucial role in determining the extent of mechanical ventilatory limitation. A corollary to this finding can be drawn from previous work in young endurance-trained athletes, where the maximum capacity of the respiratory system is high, but so too is the ventilatory demand associated with the intensity of exercise they are capable of achieving (27). In the context of high ventilatory capacity and high ventilatory demand, the relatively small sex-differences in the structure of the respiratory system become important and likely predispose women to EFL. We have shown that young endurance-trained women have a higher propensity towards EFL at maximal exercise than young endurance-trained men (27). While we found a main effect of sex on EFL in the present study, the differences between men and women were only apparent in the older relative to the younger group (Figure 7), a finding that is in keeping with our previous work in younger recreationally active subjects (15). Based on previous studies (27, 40), it can be argued that young women may be more susceptible to EFL during exercise than young men. However, the factors that determine EFL are complex and multifactorial (14). While differences in lung and airway anatomy play an important contributory role, other factors may supersede these relatively small differences. By contrast, given the reduced ventilatory capacity and increased ventilatory response to exercise, sex-differences in respiratory system anatomy are likely an important determinant of EFL in older individuals.

We also observed main effects of age and sex on EFL when comparisons were made at relative exercise intensities (Figure 7, Panel B). However, there was no significant interaction effect between age and sex on EFL at relative exercise intensities. The fact that we observed a greater fraction of older subjects who were flow limited at relative exercise intensities than younger subjects likely reflects the age-associated increase in $\dot{V}_E/\dot{V}_{ECAP}$ during exercise (Figure 2, Panels C and D). By contrast, our observation of a greater fraction of women who experienced

EFL at relative exercise intensities than men is perplexing. One would expect that after normalizing for exercise intensity that the effect of sex on EFL would no longer be present. A possible explanation relates to sex-differences in airways size and the associated effects on the capacity to generate expired flow (41). However, we did not observe an effect of sex on $\dot{V}_E/\dot{V}_{ECAP}$ in women relative to men. Alternatively, since younger women and younger men have a qualitatively similar frequency of EFL during exercise at a given relative intensity, it is possible that the main effect of sex on EFL at relative exercise intensities was driven by the older women. However, given our relatively small sample size, we hesitate to draw definitive conclusions concerning this point. Future studies involving large pools of subjects are required to determine whether women are indeed more likely to experience EFL than men at a given relative exercise intensity.

Dyspnea. We found that there were significant main effects of age and sex, as well as their interaction on dyspnea at absolute work rates during exercise. Older subjects reported higher dyspnea during submaximal exercise than their younger counterparts (Figure 8), and women reported significantly higher dyspnea during submaximal exercise than men. The difference in dyspnea between men and women at 80 W was more pronounced in the older subjects. Ofir *et al.* {Ofir:2008dy} found that older women reported a higher intensity of dyspnea at a standardized $\dot{V}O_2$ of 20 $ml \cdot kg^{-1} \cdot min^{-1}$ than older men by approximately 1 Borg unit. We observed a remarkably similar finding with older women reporting dyspnea ratings that were 1.3 Borg units higher (1.9±0.4 vs. 0.6±0.2) than older men at 80 W, which corresponded to a relative $\dot{V}O_2$ of 20.5±1.0 and 21.3±0.9 $ml \cdot kg^{-1} \cdot min^{-1}$ in older men and older women, respectively. Although the perception of dyspnea in older subjects was significantly higher for any given absolute work rate above 40 W than in younger subjects, the degree of dyspnea in older subjects was relatively modest throughout exercise and only reached an average of 5.0±0.5 Borg units at maximal exercise. The relatively low dyspnea ratings observed in the healthy older subjects in our study is in close agreement with previous investigations using incremental cycle exercise (23, 46), and further supports the notion that the respiratory system is unlikely to be the primary locus of exercise limitation in healthy older individuals. In the younger subjects, women also reported a significantly higher intensity of dyspnea than men at 80 W; however, the difference was only to the order of 0.6 Borg units (0.7±0.2 vs. 0.1±0.1). At maximal exercise, dyspnea ratings were slightly but significantly lower in the older subjects than in the younger subjects, which we attribute to differences in absolute $\dot{V}_E$ (Table 2). The effects of age and sex on the perception of dyspnea during exercise were not present when comparisons were made at relative exercise intensities, a finding that is in keeping with previous work (35).

In light of the observed differences in the mechanical ventilatory response to exercise described herein, it stands to reason that respiratory mechanics may explain, at least in part, the age- and sex-differences in the perception of respiratory sensation observed at absolute exercise intensities. Across all subjects, W_b, breathing frequency, $\dot{V}_E/\dot{V}_{ECAP}$ and $\dot{V}_E$ were the strongest correlates of dyspnea at 80 W, each explaining >50% of the variance in dyspnea (Table 4). We speculate that at 80 W, those with the highest indices of mechanical constraint (W_b and $\dot{V}_E/\dot{V}_{ECAP}$) have the highest sensations of dyspnea. In addition, those who had the highest $\dot{V}_E$ response and dead-space ventilation (due to the high breathing frequency) also had higher sensations of dyspnea. We emphasize that we are cognizant of the limits of correlative evidence and of the multifactorial causes of dyspnea. In the absence of experimental manipulations, we hesitate to overstate the link between mechanical ventilatory constraint and dyspnea, nor argue the primacy of mechanical ventilatory constraint over other factors that cause dyspnea within the context of the present study. Instead, our findings present a hypothesis that awaits experimental testing.

Perspectives on Absolute and Relative Comparisons. A consistent problem when conducting studies to investigate age- or sex-differences in the pulmonary physiology of exercise concerns how to most appropriately compare groups. The principal issue revolves around whether to make comparisons in absolute or relative terms. On one hand, making comparisons in absolute terms allows for the assessment of the effects of sex and age, but ignores the potential confounding effects of body size and functional capacity. On the other hand, making comparisons in relative terms accounts for differences in body size and functional capacity, but potentially obscures important sex-differences and overlooks the physical and metabolic requirements of a given task. In the present study, we made comparisons at both absolute and relative work rates or ventilations since both are required in order to truly determine the influences of age and sex. However, our approach results in a large number of permutations and contributes to interpretive complexities. Thus, we offer the following perspectives when interpreting our findings. First, we emphasize that the results of absolute and relative comparisons each have inherent caveats, and one should not be favored at the expense the other. Second, in some instances we found some differences between groups when comparisons were made in absolute terms that were absent in relative terms. It follows that the generalizability of our findings will depend on context. For example, if one considers our findings relating to the effects of age and sex on the perception of dyspnea, the confounding influence exercise intensity is of critical importance.

Limitations. While our study reveals novel findings regarding the mechanical ventilatory and perceptual responses to exercise in older and younger men and women, two important limitations must be considered. First, our measure of W_b (integrated esophageal pressure-volume loops) does not take into account other components of ventilatory work, such as chest-wall distortion and abdominal stabilization (22). Given the age-related changes to the mechanics of the respiratory system, it is possible that age-related differences in chest wall distortion exist, and could impact total ventilatory work. However, without measures of respiratory system kinematics or estimates of respiratory muscle $\dot{V}O_2$, this limitation cannot be overcome. Second, EFL can be assessed using a variety of different methods. Second, we chose to use the NEP technique given its numerous advantages (37). However, it should be noted that the NEP technique provides an assessment of EFL at a single point in time rather than a continuous measure, or one that is averaged over a longer period of time. It follows that our measures of the frequency of EFL do not represent the entirety of each exercise stage or the dynamic nature of EFL during exercise (3). However, given that the technique was applied consistently within each subject and each group, it is unlikely that this limitation affected the overall results of our study.

Conclusions. We found that during exercise, age and sex have significant impacts on W_b, operating lung volumes, and EFL. Our results suggest that superimposing the normal age-related changes in respiratory structure and function on innate sex-differences in airway anatomy appears to have a significant effect on the mechanical ventilatory responses to exercise in older individuals. Our data also suggest that age and sex affect the perception of dyspnea for a given absolute, but not relative, exercise intensity, and that the magnitude of mechanical ventilatory constraint seems to play an important contributory role. However, experimental manipulations of respiratory mechanics are required in order to directly test this hypothesis. Overall, our study provides new insight into the complexities and interactive effects of biological sex and chronological age on the integrative response to exercise in healthy adults.

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Author contributions

YMS, PBD, GEF, LMR, JDR, JAG, and AWS designed the study. YMS, PBD, AHR, MRS, and SMS enrolled subjects and conducted data collection. YMS and PBD analyzed the data. All authors had complete access to all the study data, contributed to drafting and critically revising the manuscript. All authors approved the final version of the manuscript, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Legends

Figure 1. Ventilatory response to incremental cycle exercise at absolute and relative work rates in older men and women (Panels A, C) as well as younger men and women (Panels B, D). In panels C and D, the highest equivalent work rate achieved by all subjects was 80 W. Dashed lines within each group connect the 80 W data point to the peak exercise data point. All data are presented as mean±SE. $\dot{V}_E$, minute ventilation. * $p<0.05$, main effect of age, comparisons made between all older and all younger subjects, regardless of sex. † $p<0.05$, comparisons made between all men and all women, regardless of age. No significant interaction effect was observed.

Figure 2. Fractional utilization of ventilatory capacity during incremental cycle exercise at absolute and relative work rates in older men and women (Panels A and C) as well as younger men and women (Panels B and D). In panels C and D, the highest equivalent work rate achieved by all subjects was 80 W. Dashed lines within each group connect the 80 W data point to the peak exercise data point. All data are presented as mean±SE. $\dot{V}_E/\dot{V}_{ECAP}$, fractional utilization of ventilatory capacity. * $p<0.05$, main effect of age, comparisons made between all older and all younger subjects, regardless of sex. † $p<0.05$, comparisons made between all men and all women, regardless of age. No significant interaction effect was observed.

Figure 3. Operating lung volumes during exercise incremental cycle exercise at absolute and relative work rates in older men and women (Panels A and C) as well as younger men and women (Panels B and D). In panels C and D, the highest equivalent work rate achieved by all subjects was 80 W. Dashed lines within each group connect the 80 W data point to the peak exercise data point. All data are presented as mean±SE. EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume. * $p<0.05$, main effect of age, comparisons made between all older and all younger subjects, regardless of sex. † $p<0.05$, comparisons made between all men and all women, regardless of age. No significant interaction effect was observed.

Figure 4. The relationship between work of breathing and absolute minute ventilation during incremental cycle exercise. Individual curves of the work of breathing versus absolute minute ventilation in older men and women (panel A) and younger men and women (panel B). Mean curves relating work of breathing to minute ventilation in all groups are shown in panel C. All mean curves are based on mean values of constants *a* and *b* from *eq. 1*, and each curve has been extrapolated to the average peak minute ventilation within each group. Data for older men are displayed as thick grey lines, while data for older women are displayed as thick black lines. Data for younger men are displayed as thin grey lines, while data for older women are displayed as thin black lines. W_b, work of breathing; $\dot{V}_E$, minute ventilation. * $p<0.05$, main effect of age, comparisons made between all older and all younger subjects, regardless of sex. † $p<0.05$, comparisons made between all men and all women, regardless of age. No significant interaction effect was observed.

Figure 5. The relationship between work of breathing and relative minute ventilation during incremental cycle exercise. Individual curves of the work of breathing versus minute ventilation in older men and women (panel A) and younger men and women (panel B). Mean curves

relating work of breathing to relative minute ventilation in all groups are shown in panel C. All mean curves are based on mean values of constants *a* and *b* from *eq. 1*. Data for older men are displayed as thick grey lines, while data for older women are displayed as thick black lines. Data for younger men are displayed as thin grey lines, while data for older women are displayed as thin black lines. W_b, work of breathing; $\dot{V}_E$, minute ventilation. * $p<0.05$, main effect of age, comparisons made between all older and all younger subjects, regardless of sex. † $p<0.05$, comparisons made between all men and all women, regardless of age. No significant interaction effect was observed.

Figure 6. Tidal flow–volume loops at a fixed work rate of 100 W in 4 individual subjects closely matched for height: an older man (panel A), an older woman (panel B), a younger man (panel C), and a younger woman (panel D). Thin black lines represent the control breath and thick black lines represent the negative expiratory pressure breath. All data are raw traces.

Figure 7. Frequency of EFL at rest and during exercise at absolute (Panel A) and relative (Panel B) work rates. Older men are shown in filled grey bars, older women in filled black bars, younger men open black bars, and younger women open grey bars. On panel A, the highest equivalent work rate achieved by all subjects was 80 W.

Figure 8. Dyspnea intensity responses to incremental cycle exercise at absolute and relative work rates in older men and women (panel A and C) as well as younger men and women (panel B and D). In panels C and D, the highest equivalent work rate achieved by all subjects was 80 W. Dashed lines within each group connect the 80 W data point to the peak exercise data point. All data are presented as mean±SE. * $p<0.05$, main effect of age, comparisons made between all older and all younger subjects, regardless of sex. † $p<0.05$, comparisons made between all men and all women, regardless of age. ‡ $p<0.05$, interaction effect between age and sex, men vs. women within each age group.

Tables

Table 1. Baseline subject characteristics and pulmonary function data.

	Older (n=22)		Younger (n=22)		
	Men (n=10)	Women (n=12)	Men (n=11)	Women (n=11)	
Age, y	70±2	66±2	26±1	24±1	*
Height, cm	173±2	163±2	176±2	166±2	†
Body Mass, kg	76±4	65±3	73±3	58±2	†
BMI, kg m^{-2}	25±1	25±1	23±1	21±1	*
FVC, l	4.30±0.12	3.46±0.20	5.46±0.22	4.26±0.18	*†
FVC, % predicted	102±2	108±3	101±3	104±3	
FEV_1, l	3.06±0.13	2.49±0.16	4.27±0.19	3.55±0.13	*†
FEV_1, % predicted	102±4	104±4	99±3	106±2	
FEV_1/FVC	71±2	71±2	79±2	82±2	*
FEV_1/FVC, %predicted	99±3	96±2	94±2	95±1	
PEF, $l \cdot sec^{-1}$	8.63±0.42	6.82±0.38	10.79±0.39	7.69±0.15	*†
$FEF_{25\text{-}75}$, $l \cdot sec^{-1}$	2.10±0.29	1.90±0.12	4.18±0.18	3.67±0.22	*
$FEF_{25\text{-}75}$, %predicted	82±11	77±4	91±3	97±6	
TLC, l	6.84±0.31	5.57±0.26	6.89±0.23	5.42±0.20	†
TLC, % predicted	102±3	108±3	102±3	103±2	
VC, l	4.45±0.14	3.57±0.18	5.56±0.21	4.32±0.17	*†
VC, % predicted	101±3	109±3	103±4	102±2	
IC, l	3.03±0.26	2.39±0.21	3.48±0.17	2.77±0.15	*†
IC, % predicted	100±8	100±9	99±5	115±5	
FRC, l	3.90±0.24	3.18±0.16	3.41±0.17	2.64±0.12	*†
FRC, % predicted	97±4.25	108±4	104±6	92±4	
RV, l	2.39±0.24	1.96±0.11	1.33±0.12	1.07±0.07	*
RV, % predicted	95±8	100±5	90±11	81±5	
DL_{co}, $ml \cdot min^{-1} \cdot mmHg^{-1}$	27±2	23±1	33±2	25±1	*†
DL_{co}, % predicted	107±6	105±4	111±4	105±4	
MIP, cmH_2O	-103±8	-76±6	-138±10	-106±7	*†
MIP, % predicted	98±8	108±6	107±5	115±6	
MEP, cmH_2O	151±16	109±8	178±11	142±9	*†
MEP, % predicted	78±8	81±6	74±5	90±6	
C_l, l, $l \cdot cmH_2O^{-1}$	0.29±0.01	0.28±0.03	0.31±0.02	0.26±0.02	
$P_{st\ 100\%TLC}$, cmH_2O^{-1}	19±2	20±2	28±1	31±1	*
$P_{st\ 50\%VC}$, cmH_2O^{-1}	4.8±0.4	5.5±0.6	6.4±0.5	6.5±0.2	*

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expired volume in 1 s; PEF, peak expiratory flow; $FEF_{25\text{-}75}$, forced expired flow between 25 and 75% of FVC; TLC, total lung capacity; VC, vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; DLco, diffusion capacity of the lung for carbon monoxide; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; Cl, lung compliance; $P_{st\ 100\%TLC}$, static recoil pressure of the lungs at 100% of TLC; $P_{st\ 50\%VC}$, static recoil pressure of the lungs at 50% of vital capacity. All data are presented as mean±SE.* p<0.05, older vs. younger subjects. † p<0.05, men vs. women.

Table 2. Peak exercise data.

	Older (n=22)		Younger (n=22)		
	Men (n=10)	Women (n=12)	Men (n=11)	Women (n=11)	
$\dot{V}O_2$, $l \cdot min^{-1}$	2.63±0.20	1.89±0.12	3.91±0.29	3.01±0.15	*†
$\dot{V}O_2$, $ml \cdot kg^{-1} \cdot min^{-1}$	34.7±2.0	30.6±2.6	53.4±3.1	51.7±2.8	*†
$\dot{V}O_2$, % predicted	119±5	122±6	123±6	140±7	
$\dot{V}CO_2$, $l \cdot min^{-1}$	2.92±0.20	2.23±0.14	4.33±0.27	3.34±0.17	*†
RER	1.12±0.20	1.18±0.02	1.12±0.03	1.11±0.02	
HR, $beats \cdot min^{-1}$	150±5	153±5	186±3	185±3	*
HR, % predicted	100±2.9	98±3.2	96±1.6	95±1.8	
S_pO_2, %	98±1	98±1	97±1	98±1	
V_T, l	2.84±0.18	1.95±0.14	2.96±0.17	2.19±0.08	†
F_b, $breaths \cdot min^{-1}$	39.5±4.1	45.7±3.2	51.5±2.5	55.1±3.0	*
$\dot{V}_E$, $l \cdot min^{-1}$	108±8	85±4	151±10	119±5	*†
$\dot{V}_E/\dot{V}O_2$	42.4±3.4	46.3±2.8	39.7±2.2	39.8±1.2	*
$\dot{V}_E/\dot{V}CO_2$	37.6±2.4	39.1±2.1	35.4±1.7	35.9±1.1	*†
$P_{ET}CO_2$, mmHg	30.8±0.9	32.2±1.4	33.3±3.8	31.6±1.4	
Work rate, W	172±10	140±11	269±21	222±12	*†
$\dot{V}O_2$:Work rate slope	11.7±0.7	10.8±0.50	11.5±0.3	11.2±0.3	
EELV, % TLC	56±3	56±2	50±2	51±2	*
EILV, % TLC	91±1	92±1	91±2	91±1	
W_b, $J \cdot min^{-1}$	257±24	236±28	335±52	307±39	*†
Resistive W_b, $J \cdot min^{-1}$	76±19	101±20	61±16	140±33	†
Viscoelastic W_b, $J \cdot min^{-1}$	181±32	135±23	274±42	166±22	*
$\dot{V}_{ECAP}$, $l \cdot min^{-1}$	151.1±13.2	118.4±8.2	220.4±9.1	181.1±11.8	*†
$\dot{V}_E/\dot{V}_{ECAP}$, %	73.2±4.3	75.1±4.9	69.6±4.4	67.5±3.7	*
Dyspnea, Borg scale	4.6±0.7	5.3±0.6	6.0±0.8	6.5±0.9	*
Leg Discomfort, Borg scale	6.2±0.9	6.3±0.8	9.2±0.8	8.8±0.5	*

Abbreviations: $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$; carbon dioxide output; RER; respiratory exchange ratio; HR, heart rate; S_pO_2, oxygen saturation by pulse oximetry; V_T, tidal volume; F_b, breathing frequency; $\dot{V}_E$, minute ventilation; $\dot{V}_E/ \dot{V}O_2$, ventilatory equivalent for oxygen; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $P_{ET}CO_2$, end-tidal carbon dioxide; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; W_b, work of breathing; $\dot{V}_{ECAP}$, ventilatory capacity. All data are presented as mean±SE. * $p<0.05$, older vs. younger subjects. † $p<0.05$, men vs. women.

Table 3. Summary of main effects and interaction effects on primary outcome variables during exercise at absolute and relative work rates.

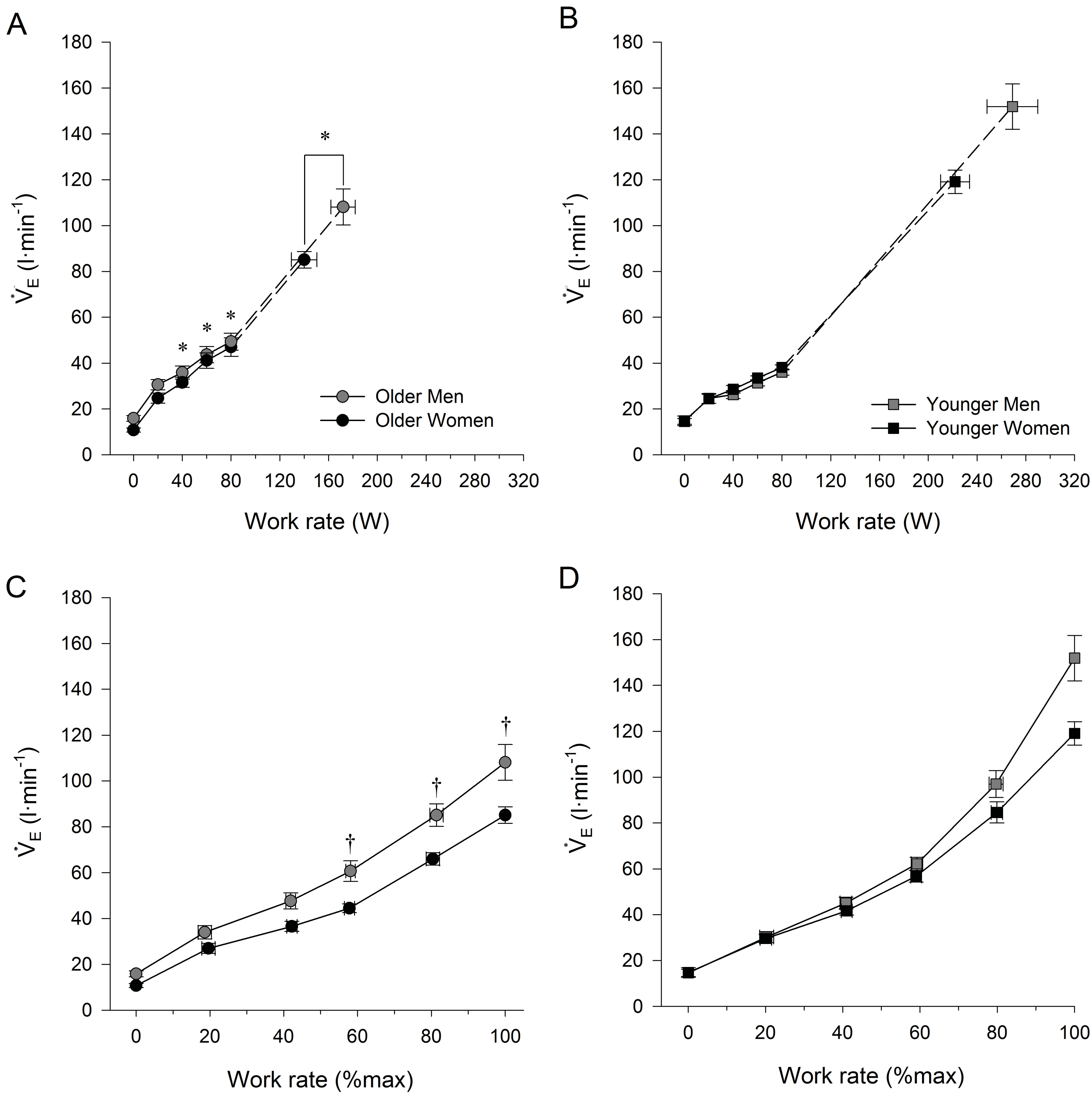
	Absolute Work Rates			Relative Work Rates		
	Age (*p*)	Sex (*p*)	Interaction (*p*)	Age (*p*)	Sex (*p*)	Interaction (*p*)
Ventilatory Response						
$\dot{V}_E$, l·min^{-1}	p<0.05	n.s.	-	n.s	p<0.05	-
$\dot{V}_E/\dot{V}_{ECAP}$, %	p<0.05	n.s.	-	p<0.05	n.s	-
Indices of Mechanical Ventilatory Constraint						
EELV, % TLC	p<0.05	n.s.	-	p<0.05	n.s.	-
EILV, % TLC	p<0.05	n.s.	-	p<0.05	n.s.	-
W_b, J·min^{-1}	p<0.05	p<0.05	n.s.	n.s.	n.s.	-
EFL	p<0.05	-	p<0.05	p<0.05	p<0.05	n.s.
Perceptual Responses						
Dyspnea, Borg Scale	p<0.05	p<0.05	p<0.05	n.s.	n.s.	-

Abbreviations: V_T, tidal volume; F_b, breathing frequency; $\dot{V}_E$, minute ventilation; $\dot{V}_E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; $\dot{V}_{ECAP}$, ventilatory capacity; $\dot{V}_E/\dot{V}_{ECAP}$, fractional utilization of ventilatory capacity; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; W_b, work of breathing; EFL, expiratory flow limitation.

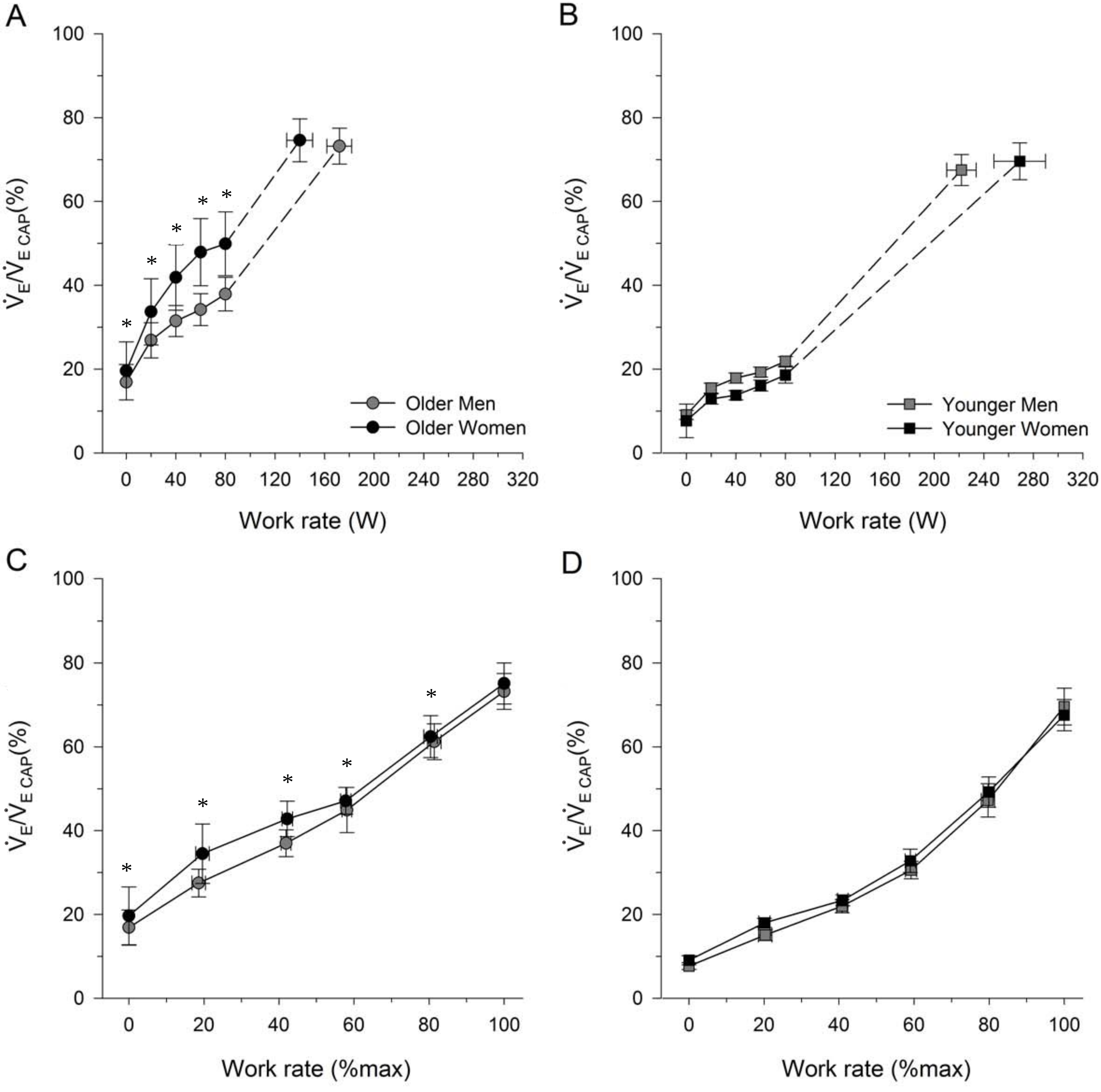
Table 4. Correlates of dyspnea at a standardized absolute work rate during exercise.

Variable	r^2	*p*-value
$\dot{V}_E$, l·min^{-1}	0.54*	<0.001
$\dot{V}_E/\dot{V}_{ECAP}$, %	0.56*	<0.001
V_T, l	-0.43	0.004
V_T, %IC	0.14	0.371
V_T, %VC	0.05	0.760
F_B, breaths·min^{-1}	0.69*	<0.001
S_pO_2, %	-0.34*	0.024
$P_{ET}CO_2$, mmHg	-0.32*	<0.001
EELV, %TLC	0.33*	0.032
IRV, %TLC	-0.23*	0.014
IC, l	-0.47*	<0.001
IC, %predicted	-0.01	0.792
ΔIC (exercise – rest), l	-0.03	0.315
Total W_b, J·min^{-1}	0.76*	<0.001

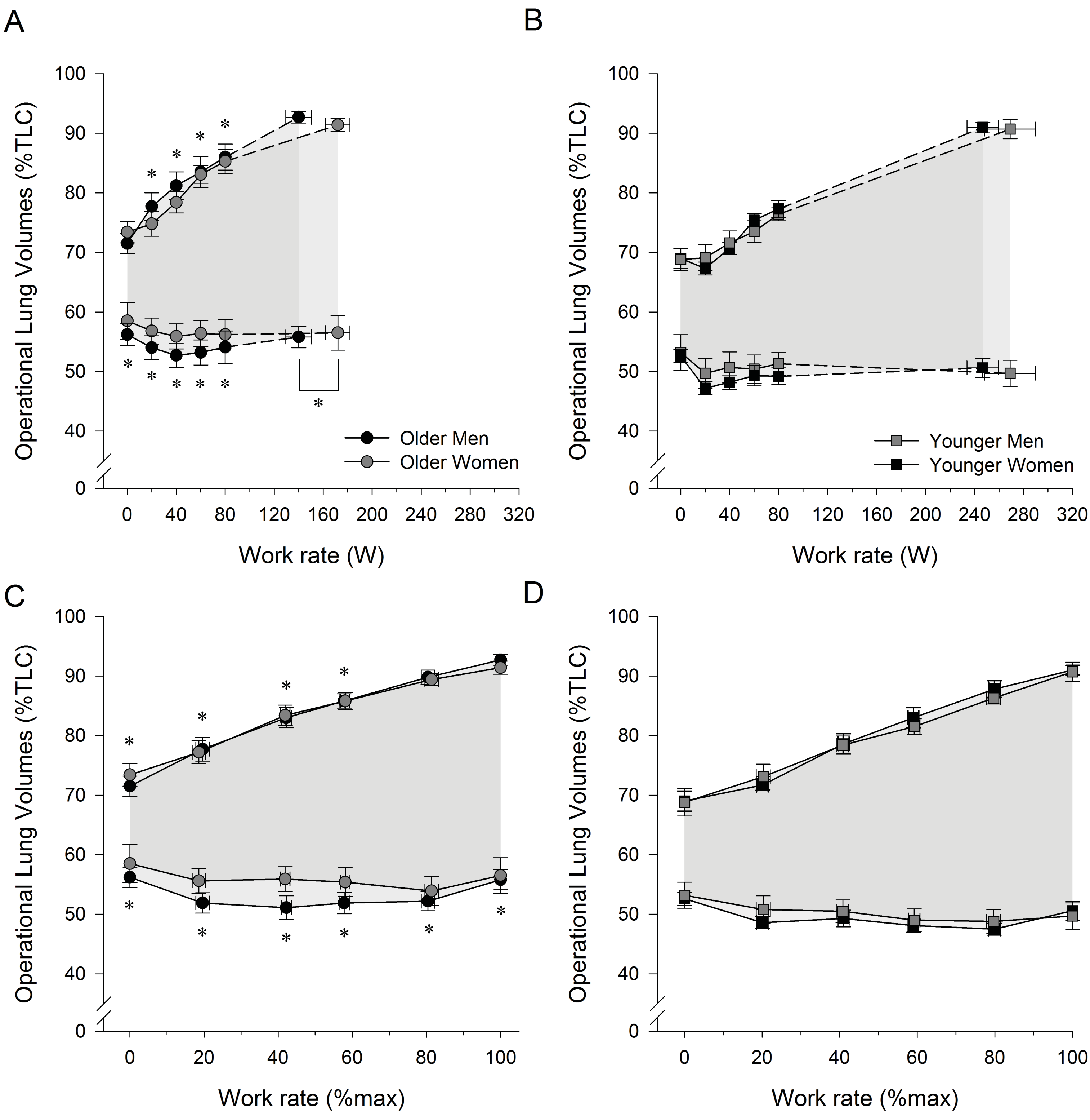
Abbreviations: $\dot{V}_E$, expired minute ventilation; $\dot{V}_E/\dot{V}_{ECAP}$, fractional utilization of ventilatory capacity; V_T, tidal volume; IC, inspiratory capacity; VC, vital capacity; F_b, breathing frequency; S_pO_2, arterial oxygen saturation by pulse oximetry; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; EELV, end-expiratory lung volume; TLC, total lung capacity; IRV, inspiratory reserve volume; W_b, work of breathing. * $p<0.05$.



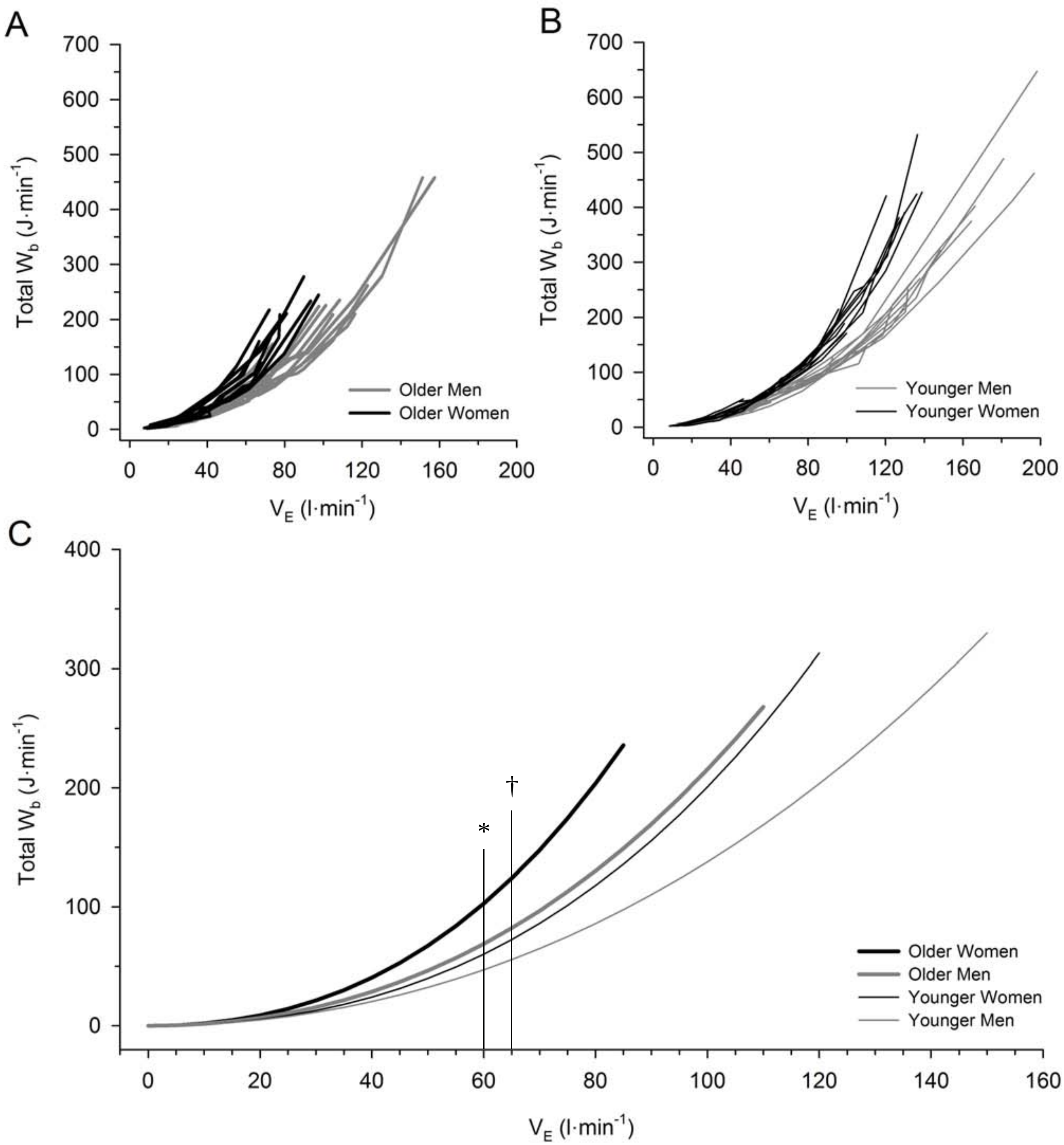
A
B
C
D
$\dot{V}_E$ (l·min^{-1})
Work rate (W)
Work rate (%max)
Older Men
Older Women
Younger Men
Younger Women
*
†

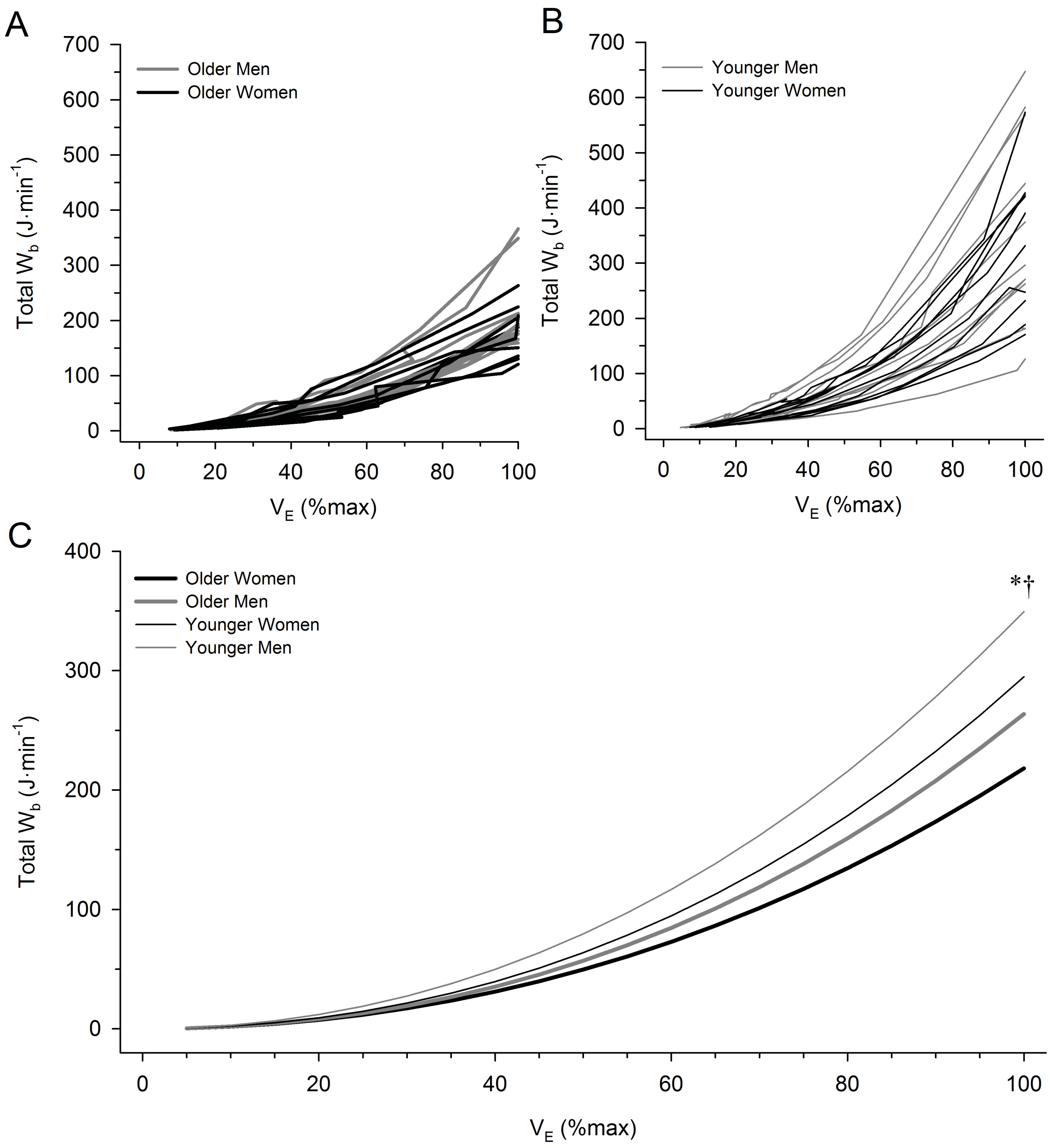


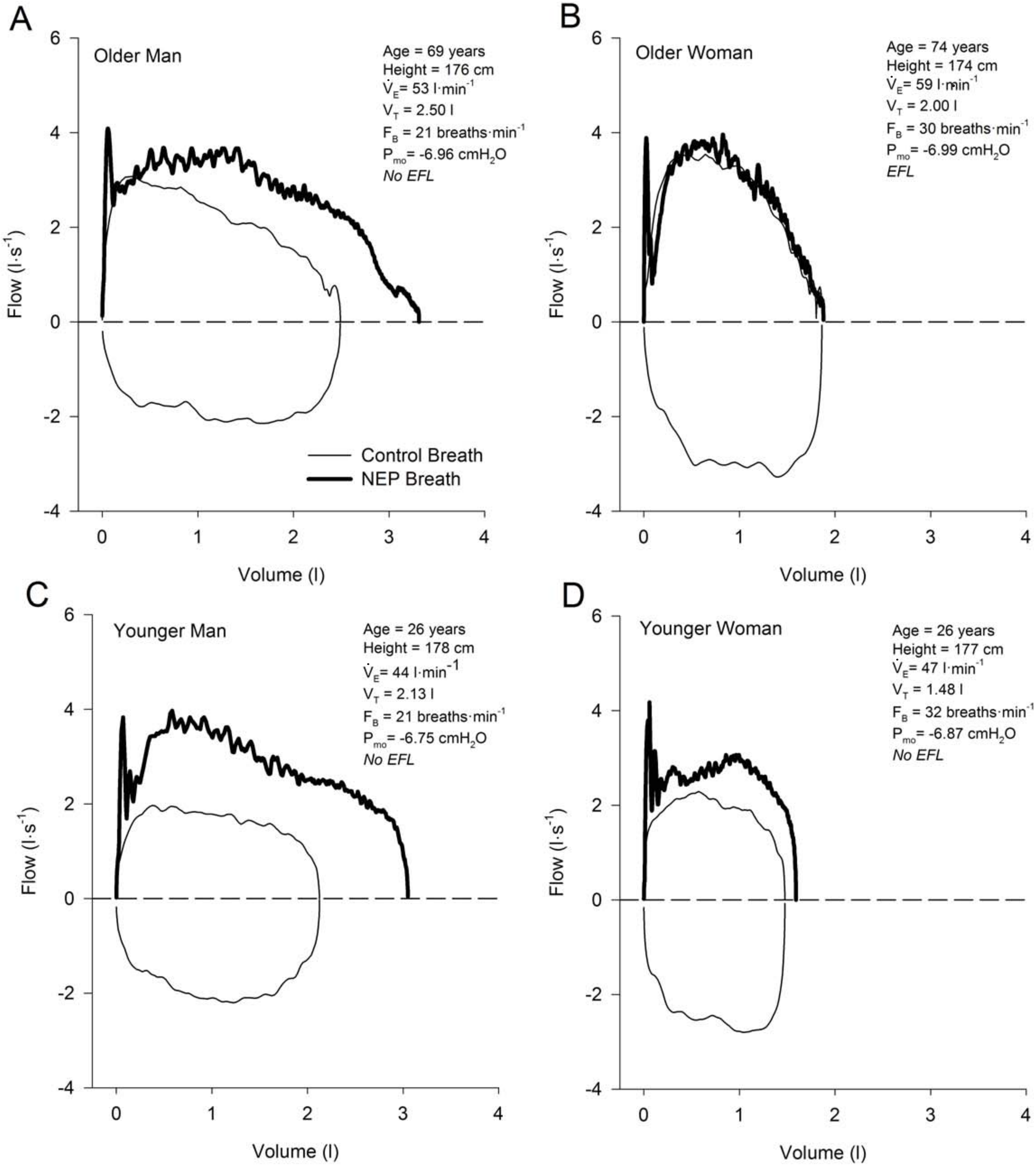
A
B
C
D
$\dot{V}_E/\dot{V}_{E\ CAP}$(%)
Work rate (W)
Work rate (%max)
Older Men
Older Women
Younger Men
Younger Women

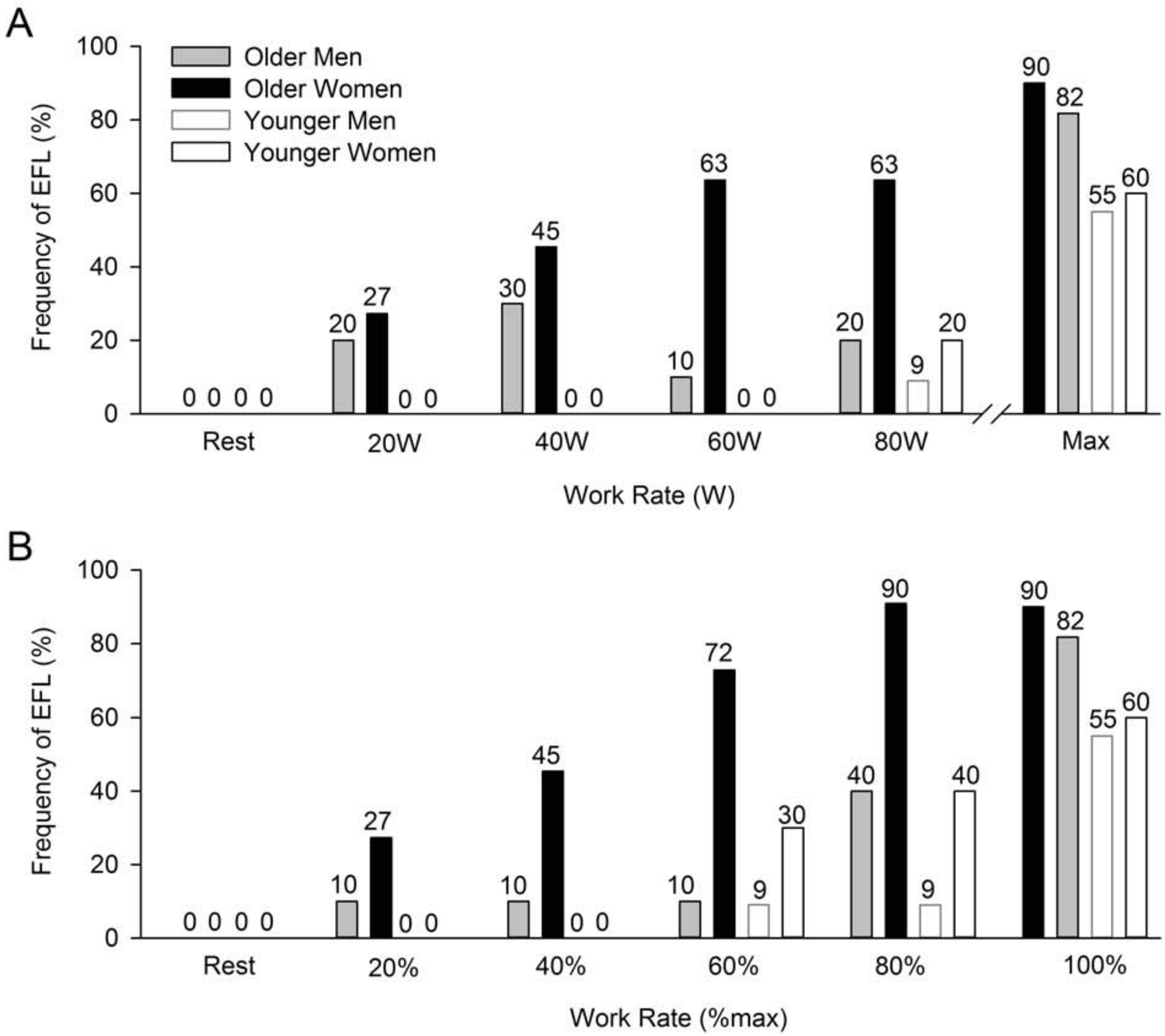


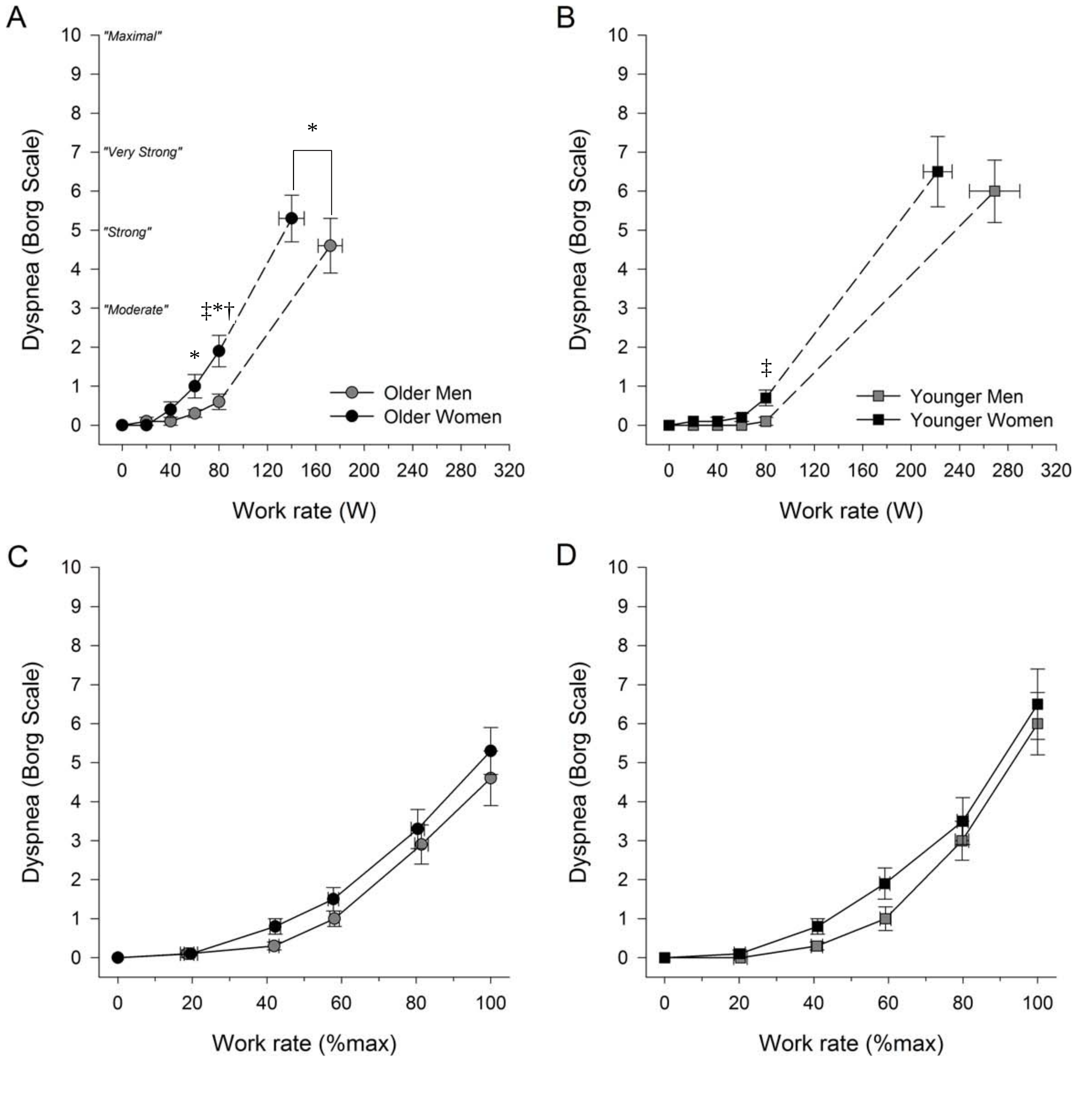
A
B
C
D
Operational Lung Volumes (%TLC)
Work rate (W)
Work rate (%max)
Older Men
Older Women
Younger Men
Younger Women


A
Total W_b (J·min^{-1})
V_E (l·min^{-1})
Older Men
Older Women
B
Total W_b (J·min^{-1})
V_E (l·min^{-1})
Younger Men
Younger Women
C
Total W_b (J·min^{-1})
V_E (l·min^{-1})
*
†
Older Women
Older Men
Younger Women
Younger Men


A
700
600
500
400
300
200
100
0
Total W_b ($J \cdot min^{-1}$)
Older Men
Older Women
0
20
40
60
80
100
V_E (%max)
B
Younger Men
Younger Women
C
400
300
Older Women
Older Men
Younger Women
Younger Men
*†


A
Older Man
Age = 69 years
Height = 176 cm
V̇E= 53 l·min-1
VT = 2.50 l
FB = 21 breaths·min-1
Pmo= -6.96 cmH2O
No EFL
Control Breath
NEP Breath
Flow (l·s-1)
Volume (l)
B
Older Woman
Age = 74 years
Height = 174 cm
V̇E= 59 l·min-1
VT = 2.00 l
FB = 30 breaths·min-1
Pmo= -6.99 cmH2O
EFL
C
Younger Man
Age = 26 years
Height = 178 cm
V̇E= 44 l·min-1
VT = 2.13 l
FB = 21 breaths·min-1
Pmo= -6.75 cmH2O
No EFL
D
Younger Woman
Age = 26 years
Height = 177 cm
V̇E= 47 l·min-1
VT = 1.48 l
FB = 32 breaths·min-1
Pmo= -6.87 cmH2O
No EFL


A
Older Men
Older Women
Younger Men
Younger Women
Frequency of EFL (%)
100
80
60
40
20
0
0 0 0 0
20 27 0 0
30 45 0 0
10 63 0 0
20 63 9 20
90 82 55 60
Rest
20W
40W
60W
80W
Max
Work Rate (W)
B
Frequency of EFL (%)
100
80
60
40
20
0
0 0 0 0
10 27 0 0
10 45 0 0
10 72 9 30
40 90 9 40
90 82 55 60
Rest
20%
40%
60%
80%
100%
Work Rate (%max)


A
B
C
D
Dyspnea (Borg Scale)
Work rate (W)
Work rate (%max)
"Maximal"
"Very Strong"
"Strong"
"Moderate"
Older Men
Older Women
Younger Men
Younger Women
‡*†
‡