

Body Composition, Obesity, and Cardiorespiratory Fitness in the Community

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ABSTRACT

Purpose: Cardiorespiratory fitness (CRF) is an integrative measure of physiologic health, but how CRF relates to different body composition components and cardiometabolic health in community-dwelling adults remains uncertain, especially in obesity. **Methods:** In Framingham Heart Study (FHS) Generation 3/Omni-2 participants, body composition measures from dual-energy X-ray absorptiometry (DXA) were related to peak oxygen uptake (VO_2) and complementary exercise phenotypes assessed via cardiopulmonary exercise testing in sex-stratified multivariable linear models. Secondary analyses examined correlates of peak VO_2 when indexed to total body weight or lean mass. **Results:** Among 2647 participants (53% women, mean age 54 years, body mass index [BMI] 27.8 kg/m^2), lean mass was the strongest correlate of CRF among body composition measures (FDR $<5\%$) and, along with age and height, accounted for 44-48% of the variance in peak VO_2 . A 1 kg-higher lean mass was associated with a 43 ml/min-higher absolute peak VO_2 . While there was broad consistency across age, sex-based differences in the relations of body composition and CRF were observed, with women demonstrating stronger positive associations between CRF and fat mass compared to men. Peak VO_2 displayed distinct cardiometabolic correlates depending on whether it was indexed to total body weight versus lean mass: “metabolically healthy” obesity displayed lower peak VO_2 compared to “metabolically healthy” non-obesity with indexing to total body weight, but peak VO_2 was similar between these two categories with indexing to lean mass. **Conclusions:** Lean mass is the strongest correlate of CRF in middle-aged, community-dwelling individuals. Indexing peak VO_2 to lean versus total mass results in different conclusions regarding the intersections of CRF with obesity and metabolic health and emphasizes the role of

cardiometabolic risk factors beyond obesity itself. **Key Words:** BODY COMPOSITION, CARDIOPULMONARY EXERCISE TESTING, FITNESS, OBESITY

ACCEPTED

INTRODUCTION

The prevalence of obesity continues to rise worldwide(1). In the United States, it is expected that approximately 1 in 2 individuals will have obesity by 2030(2). Obesity is a key contributor to several chronic diseases including cardiovascular disease (CVD), type 2 diabetes mellitus, osteoarthritis, and malignancies(3-5). Mechanisms linking obesity and CVD development are complex and involve both direct and indirect (e.g., through other risk factors) effects that contribute to subclinical organ dysfunction and culminate in overt CVD(3). While clinical assessments of obesity (e.g., body mass index [BMI] or waist circumference) are associated with increased CVD risk at the population level, there is substantial heterogeneity in individual-level risk across obesity categories(3, 4), potentially owing to cardiometabolic risk factor burden, body composition and location/type of adipose tissue(6), and degree of multiorgan impairment. With the rapid pace of development of obesity therapeutics, improving characterization of obesity and its multiorgan effects is imperative to prioritize lifestyle and pharmacologic interventions for patients most likely to benefit(7).

Assessment of cardiorespiratory fitness (CRF), an integrative measure of physiological health and longevity(8-13), has the potential to further refine multisystem risk profiles across individuals with obesity(14, 15). The gold standard assessment of CRF is peak oxygen uptake (VO_2) measured via cardiopulmonary exercise testing (CPET), which measures the volume of O_2 an individual consumes during exercise and is directly proportional to the amount of exercise performed and body size(12). Accordingly, VO_2 is typically indexed to total body weight to account for body size and expressed as milliliters of VO_2 by kilogram of body mass per minute (ml/kg/min). However, O_2 requirements during exercise vary across organ tissues; skeletal muscle, which represents 30-40% of total body mass in adults without obesity(16), is the largest

consumer of O₂ to support over a 100-fold increase in metabolic rate in skeletal muscle during aerobic exercise. Adipose tissue comprises the other large portion of total body weight that is thought to consume a minimal amount of O₂ during exercise. Based on these observations, it has been suggested that peak VO₂ indexed to lean mass (rather than total body weight) might more accurately reflect cardiorespiratory fitness and prognosis, especially in individuals with obesity or heart failure(17-20) . However, the relations of distinct components of body composition with detailed VO₂ uptake phenotypes have not been assessed in community-dwelling individuals across the obesity and fitness spectrum(17, 21-23).

Accordingly, we sought to understand the relations of body composition features assessed via dual-energy X-ray absorptiometry (DXA) with detailed CPET phenotypes in >2600 community-dwelling participants from the Framingham Heart Study (FHS). We evaluated how these measures vary by sex and age and how differences in body composition may provide insight into the relationship between CRF and the proposed phenotype of metabolically healthy obesity. As functional outcomes are increasingly emphasized in clinical trials of patients with CVD, especially when testing interventions for weight loss(24, 25), the relations of body composition and CRF are of growing importance to clinical care.

METHODS

Study sample

The FHS is a prospective epidemiological cohort of community-dwelling adults. The original FHS cohort was recruited in 1948, and the study was subsequently expanded to include their children and children's spouses (Generation 2), and their grandchildren and grandchildren's spouses (Generation 3). The Generation 3 cohort (N=4095) was enrolled in 2002-2005 and attended study visits alongside the multiethnic Omni-2 cohort (N=410), as described(26, 27). At

the third examination cycle of the Generation 3 and Omni-2 cohorts (2016-2019), whole body DXA and maximum effort CPET were performed(28). Of the 3117 participants who underwent CPET, 2866 also had valid DXA scans. From this sample, we excluded individuals with missing CPET or DXA measures (N=45), missing data to categorize metabolic health and obesity status (N=74 missing fasting blood glucose, one person missing hypertension medication use), missing covariates (N=2 missing smoking, N=2 missing diabetes status, N=1 missing physical activity index), or not meeting criteria for maximum effort during CPET (peak respiratory exchange ratio <1.05, N=94), as shown in Supplemental Figure 1 (Supplemental Digital Content, <https://links.lww.com/MSS/D454>).

All study participants provided informed consent. FHS protocols were approved by the Institutional Review Board at the Boston University Medical Campus. Anonymized data and materials from FHS are publicly available from the National Institutes of Health Database of Genotypes and Phenotypes (more information available at www.framinghamheartstudy.org).

Dual x-ray absorptiometry measurement

Participants were instructed to fast for eight hours prior to the FHS study visit during which DXA and CPET were performed. Body composition measures were obtained using a Lunar Prodigy whole body scanner (LunarCorp, Madison, WI(29)). Participants were excluded from DXA evaluation if they exceeded the weight limit of the scanner (>300 pounds), had a positive pregnancy test or the possibility of pregnancy, elected to not participate, or had metal surgical implants (excluded from hip and spine bone mineral density assessment). Quality control measures included assigning the lowest non-zero value for visceral adipose tissue (VAT) assessment for individuals with reported values of 0 and removing individuals with differences in fat or lean mass more than three standard deviations from the mean (as this likely reflects “cut

off” of a limb during scanning). DXA distinguishes between bone and soft tissue, and soft tissue is differentiated as fat and fat-free tissue based on tissue attenuation(30). As previously described, lean mass was calculated as the sum of bone-free and fat-free tissue, and the lean mass measure includes the total body skeletal muscle mass(30). Appendicular lean mass was computed by adding all four limb lean mass values. We obtained measures of visceral adipose tissue (VAT) mass at the android region using GE Healthcare, Inc. Encore v16 with CoreScan analysis software.

Cardiopulmonary exercise testing

Maximum-effort CPET was performed on a cycle ergometer (Lode, Netherlands) with breath-by-breath gas exchange measures (MedGraphics, St. Paul, MN)(28). The exercise protocol began with three minutes of unloaded (“freewheel”) exercise followed by one of two incremental ramp protocols (15 watts/min or 25 watts/min, assigned by study staff based on estimated peak watts)(31). Peak VO_2 was determined as the highest 30-second median during the final minute of exercise, and a test was considered to be a maximal effort if the peak RER was ≥ 1.05 . Predicted VO_2 was calculated using the Wasserman-Hansen equations(32). VO_2/work was calculated as the $\Delta\text{VO}_2/\Delta\text{work}$ measured from 1 minute into the incremental ramp portion of exercise up until peak exercise, and O_2 uptake efficiency slope was calculated as the slope of the regression line of VO_2 and ventilatory efficiency. Peak VO_2 pulse was computed by dividing peak oxygen consumption by peak heart rate, and VO_2 at the ventilatory threshold was determined based on the V-slope method(33).

Cardiometabolic risk factor assessment and categories of obesity and metabolic health

Height and body weight were measured at the examination cycle, and BMI was calculated as weight (kilograms, kg) divided by height (meters squared, m^2). Diabetes was

defined as fasting blood glucose ≥ 126 mg/dL, non-fasting glucose ≥ 200 mg/dL, or the use of blood sugar lowering medications. Blood pressure was measured using a manual mercury column sphygmomanometer and a cuff of appropriate size in seated participants. Smoking in the year preceding the FHS examination was assessed by self-report. The physical activity index was calculated using questionnaire-based assessment of physical activity as described(34). Consistent with prior publications, metabolic health status was defined using metabolic syndrome criteria(35), with “metabolically healthy” defined as ≤ 1 risk factors present and “metabolically unhealthy” defined as having 2 or more of the following risk factors: 1) systolic blood pressure (SBP) ≥ 130 or diastolic blood pressure (DBP) ≥ 80 , or taking antihypertensive medication, 2) fasting glucose ≥ 100 mg/dL, or on glucose-lowering medication, 3) HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women, 4) triglycerides ≥ 150 mg/dL. Next, participants were categorized by the presence or absence of obesity (BMI ≥ 30 kg/m²) and metabolic health status into 1 of 4 groups: (1) metabolically healthy non-obesity, (2) metabolically unhealthy non-obesity, (3) metabolically healthy obesity, (4) metabolically unhealthy obesity(36).

Statistical analyses

All analyses were performed using R (The R Foundation for Statistical Computing, version 4.0.3; Vienna, Austria). We evaluated the relations of DXA variables and anthropometric measures (body mass index [BMI], waist circumference, waist-to-hip ratio) with CPET exercise response measures (dependent/outcome variables) using linear models. Due to substantial sex dimorphism in the distribution of DXA and CPET measures (Supplemental Figure 2, Supplemental Digital Content, <https://links.lww.com/MSS/D454>), models were stratified by sex. Sex-stratified linear models were adjusted initially for age and height and then also for traditional cardiovascular risk factors including total cholesterol, high-density lipoprotein (HDL)

cholesterol, smoking status, systolic blood pressure, hypertension treatment, diabetes, and the physical activity index. Outcome variables were log-transformed to reduce skewness as appropriate, including absolute peak VO_2 (mL/min), relative peak VO_2 (mL/min/kg), O_2 uptake efficiency slope, peak O_2 pulse, and O_2 at the ventilatory anaerobic threshold. All variables were mean-centered and standardized to unit variance separately in men and women to facilitate comparison of beta coefficients. False discovery rate (FDR) $\leq 5\%$ by Benjamini-Hochberg was used to control type 1 error. Explained variance (R^2) of covariates for absolute peak VO_2 was assessed using ANOVA (type 1) after ensuring that substantial collinearity was not present (variance inflation factors < 5)(37). We then tested for effect modification by age and sex using multiplicative interaction terms (in the full sample without sex-stratification). A p-value threshold of 5% was used to determine statistical significance for interaction models. To assess for heterogeneity in the effect of lean mass on peak VO_2 across age, we constructed sex-specific linear models with the DXA measures as the dependent variables and age and BMI as independent (predictor) variables. The residuals from these models (representing deviation from the predicted value of the DXA measure) were then plotted against absolute peak VO_2 across five age groups.

Next, we investigated the continuous associations of BMI, waist circumference, and waist-to-hip ratio with peak VO_2 using multivariable linear regression models adjusted for age, with an interaction term for metabolic health status and the continuous metric of adiposity. To examine the associations between the four categories of metabolic health/obesity and peak VO_2 , we used multivariable logistic regression models adjusted for age, and calculated odds ratios of metabolic health and obesity status per 1-SD change in log-transformed relative peak VO_2 . The predicted probabilities of metabolic health and obesity status at the median age were calculated

from the logistic models and plotted over peak VO_2 . A p-value of <0.05 was used to denote statistical significance.

RESULTS

Characteristics of the study sample

Characteristics of the 2647 FHS participants included in the final sample are shown in Table 1. Participants were 54% women, with mean age 54 ± 9 years and BMI $27.8 \pm 5.0 \text{ kg/m}^2$. Men displayed higher total lean mass and VAT mass and lower total fat mass compared to women. Mean absolute and relative (per kg) peak VO_2 in men were $2,330 \pm 560 \text{ mL/min}$ and $26.4 \pm 6.7 \text{ mL/kg/min}$, respectively, and in women were $1,470 \pm 380 \text{ mL/min}$ and $20.9 \pm 5.9 \text{ mL/kg/min}$, respectively. Overall, peak VO_2 was $95.7 \pm 20.1\%$ of the predicted values across sex. Standard cardiovascular risk factors, such as hypertension and diabetes, were more prevalent among men than women.

Associations of body composition measures with CRF across age and sex

In sex-specific linear models adjusted for age, height, and cardiometabolic risk factors, greater lean mass and appendicular (upper and lower limb) lean mass were associated with higher fitness (absolute peak VO_2 and % predicted peak VO_2) and other CPET measures in both men and women (Figure 1A). In contrast, total fat and VAT mass were positively associated with absolute peak VO_2 in women only. Relative peak VO_2 (indexed to total body weight) displayed different associations with body composition compared to absolute peak VO_2 , with lower effect size for association with appendicular lean mass, no significant association with total lean mass, and inverse associations with measures of adiposity. Similar findings were observed in models adjusted only for age and height (Supplemental Figure 3, Supplemental Digital Content, <https://links.lww.com/MSS/D454>).

Next, we evaluated the extent to which each body composition measure explained variation in absolute peak VO_2 (Figure 1B). Age, height, and total lean body mass explained 44% and 48% of the variance in peak VO_2 in women and men, respectively, while fat mass and VAT mass each explained <3%. We tested for effect modification by age and sex on the associations of body composition measures and peak VO_2 . We observed significant interactions by sex on the association of total fat and VAT mass with absolute peak VO_2 , with more positive effect estimates for women versus men (Supplemental Table 1, Supplemental Digital Content, <https://links.lww.com/MSS/D454>). We also observed a stronger negative association of VAT mass with absolute peak VO_2 in younger versus older individuals (Supplemental Table 2, Supplemental Digital Content, <https://links.lww.com/MSS/D454>). No significant interactions by sex or age were observed for lean mass.

Given strong relations of aging with both body composition (e.g., loss of muscle mass) and reductions in CRF, we next sought to investigate heterogeneity in the effect of body composition measures on peak VO_2 across age and BMI by examining the observed versus expected relations via the regression residuals. We hypothesized that individuals with higher observed lean mass than would be expected (based on age and BMI) would have higher absolute peak VO_2 , but that this effect would be reduced at higher age ranges. However, our findings demonstrated that the lean mass residual (representing the difference between the observed lean mass and predicted lean mass based on age and BMI) was positively related to higher absolute peak VO_2 across age strata in both men and women, without apparent differences in association in older individuals (Figure 2). These relationships were not as strong for VAT or fat mass residuals, where more negative associations were observed for the youngest age group, consistent with our interaction analyses above.

Obesity, metabolic health, and CRF

Sample characteristics stratified by categories of obesity and metabolic health status are shown in Supplemental Table 3 (Supplemental Digital Content, <https://links.lww.com/MSS/D454>), demonstrating expected differences in metabolic profiles across groups. In men, 42% were categorized as metabolically healthy/non-obesity, 25% as metabolically unhealthy/non-obesity, 10% as metabolically healthy/obesity, and 23% as metabolically unhealthy/obesity. In women, 64% were categorized as metabolically healthy/non-obesity, and 12% were categorized into each of the three remaining categories. Within categories of obesity, individuals categorized with metabolically unhealthy profiles displayed less favorable values for peak VO_2 (absolute, relative, and % predicted) and other measures of O_2 uptake during exercise (Supplemental Table 4, Supplemental Digital Content, <https://links.lww.com/MSS/D454>).

The distribution of peak VO_2 across obesity/metabolic health categories is presented in Figure 3. When expressed in ml per kg of total body weight per minute (relative peak VO_2), we observed lower peak VO_2 in individuals with metabolically unhealthy profiles or obesity (Figure 3A). We did not observe significant differences between individuals with metabolically unhealthy non-obesity and metabolically healthy obesity profiles. These findings were different when peak VO_2 was expressed either in ml/min (absolute peak VO_2) or as ml/kg of lean mass/min. Using absolute peak VO_2 , women with metabolically healthy obesity profiles had significantly higher peak VO_2 than all groups; across obesity levels and sex, individuals with metabolically unhealthy profiles exhibited lower peak VO_2 (Figure 3B). When peak VO_2 was indexed to lean mass instead of total body mass, differences in peak VO_2 by obesity status were

attenuated, with significantly higher peak VO_2 among individuals with metabolically healthy compared with metabolically unhealthy profiles (Figure 3C).

In both men and women, higher clinical measures of adiposity (BMI, waist circumference, waist-to-hip ratio) were significantly associated with lower relative peak VO_2 , whereas associations with VO_2 /lean mass and absolute peak VO_2 differed across the measures (Figure 4). In addition, we observed differential impacts of metabolic health status on these relations observed by sex, with effect modification observed in women for associations of obesity metrics and relative peak VO_2 , which was not observed after lean mass adjustment (Supplemental Table 5, Supplemental Digital Content, <https://links.lww.com/MSS/D454>).

Across the range of peak VO_2 values, the predicted probabilities of having a higher peak VO_2 based on obesity/metabolic health status are shown in Figure 5, with odds ratios for each group presented in Supplemental Table 6 (Supplemental Digital Content, <https://links.lww.com/MSS/D454>). For relative peak VO_2 , an individual with a higher peak VO_2 was most likely to have metabolically healthy non-obesity, while an individual with a lower peak VO_2 was most likely to have obesity and/or a metabolically unhealthy profile. Indeed, above a relative peak VO_2 of ≈ 20 ml/kg/min in women and 30 ml/kg/min in men, the majority of participants had metabolically healthy profiles/non-obesity. Using absolute peak VO_2 , we observed contrasting findings, with flatter curves for the predicted probability of being in each obesity/metabolic health category across the range of peak VO_2 values. Using peak VO_2 indexed to lean mass, we again observed individuals with higher peak VO_2 to be much more likely to have metabolically healthy non-obesity, but there was still a 10-20% odds of having metabolically healthy obesity at the highest achieved peak VO_2 values.

DISCUSSION

We investigated how detailed measures of body composition and metabolic health influence CRF and complementary CPET measures in a large, mostly middle-aged, community-based cohort with several key findings. Consistent with prior studies mostly conducted in specific populations (e.g., patients with heart failure and other cardiopulmonary conditions), we observed that lean body mass was the strongest correlate of CRF among body composition measures in individuals across a broad spectrum of cardiometabolic risk profiles. Leveraging our large sample size, we demonstrated that total lean body mass, along with age and height, accounted for about 44-48% of the variance in peak VO_2 in men and women, and that a 1 kg-higher lean mass was associated with a 43 ml/min higher absolute peak VO_2 . Greater lean mass was consistently associated with a higher peak VO_2 across strata of age, indicating that maintenance of lean mass with aging may be important for preserving physical fitness and function. We also observed sex-based differences in the relations of body composition and CRF, with women demonstrating stronger positive associations between CRF and adiposity measures. In addition, peak VO_2 (CRF) displayed vastly different metabolic correlates in our sample depending on whether it was indexed to total body weight (as usually performed in clinical practice) versus lean body mass. These differences were especially pronounced in women and resulted in individuals with obesity being categorized as having lower peak VO_2 on the basis of body weight alone, regardless of other metrics of metabolic health. Taken together, our findings suggest that body composition measures, and the amount of lean mass in particular, are important to the understanding of CRF assessment in individuals without overt cardiopulmonary disease. Indexing peak VO_2 assessment to different assessments of body weight has important

potential implications for characterizing the relations of CRF and cardiometabolic health in the context of obesity.

Our findings build on and extend previous studies, mostly conducted in patients with established heart failure, that demonstrated that lower skeletal muscle mass is associated with lower exercise capacity(38, 39) and higher mortality(40). Indeed, studies have shown that indexing peak VO_2 to lean body mass rather than total body mass results in improved risk prediction in patients with heart failure(20, 41) and in individuals without heart failure(42). On the other hand, relations of body composition measures, including measures of subcutaneous and visceral adiposity, and CRF assessments in individuals without known cardiopulmonary disease are incompletely defined and most clinical CPET laboratories continue to index peak VO_2 to total body mass. In this context, we found that total and appendicular lean mass were the closest correlates of CRF and complementary CPET measures reflecting O_2 uptake kinetics across age, sex, and cardiometabolic risk factors. Concurrent assessment of body composition by DXA with CPET also afforded the opportunity to evaluate relations of total and visceral adiposity with CRF. We observed minimal association of these characteristics with absolute peak VO_2 in men, but positive associations in women. Moreover, our findings demonstrate that indexing peak VO_2 to total body weight results in individuals being categorized as having lower peak VO_2 based on body weight alone, and that indexing peak VO_2 to lean mass leads to different fitness assessments, especially in individuals with excess adiposity. One potential explanation for these findings is that indexing for total body weight may serve to “penalize” CRF in individuals with obesity and thereby underestimate cardiopulmonary performance. Indeed, patients with heart failure and obesity display superior cardiac performance and outcomes to patients with heart failure but without obesity at the same peak VO_2 indexed to total body weight(43, 44).

We also observed differences in the relations of body composition measures with CRF in women and men. Intriguingly, total fat and VAT mass were positively related to absolute peak VO_2 in women, but not men, in our sample. This unexpected finding, not previously reported to our knowledge, may relate to underlying differences in body composition based on sex. Sex differences in body composition are established, with skeletal muscle representing a larger component of total body mass in men versus women on average(45). It is also possible that adipose tissue in general, and VAT in particular, may have stronger deleterious effects in men, whereas women display attenuated risk due to obesity itself(46). Whether features of fat metabolism may differentially relate to fitness or exercise adaptations in women and men remains uncertain and requires further study.

We further explored whether individuals with metabolically healthy obesity profiles had reduced CRF compared to individuals with non-obesity and/or metabolically unhealthy profiles. Metabolically healthy obesity has received substantial attention based partly on conflicting data on whether it truly represents a stable clinical phenotype versus a transition stage between health and metabolic syndrome (or metabolically unhealthy obesity)(47, 48). In a prior study by Ortega *et al.* of individuals undergoing treadmill exercise testing without gas exchange assessment, individuals with metabolically healthy obesity had intermediate estimated CRF between individuals characterized as having metabolically healthy non-obesity and those with metabolically unhealthy obesity, and this may have contributed to a reduced risk of adverse events(36). Similar to the study from Ortega *et al.*, using peak VO_2 indexed to total body mass, we observed a stepwise reduction in peak VO_2 in individuals with metabolically healthy non-obesity, to metabolically healthy obesity, to metabolically unhealthy obesity. On the other hand, when peak VO_2 was indexed to total lean mass, no significant difference was observed between

individuals with metabolically healthy obesity or non-obesity, while individuals with poor metabolic health had lower CRF regardless of obesity status. Ultimately, the optimal method of scaling peak VO_2 may depend on the objective. While scaling to lean mass may provide a better indicator of the ability of cardiovascular and skeletal muscle to distribute and utilize O_2 during exercise, scaling to total body mass assesses the ability to move the body during ambulation (i.e., functional capacity)(49). Our findings suggest that if the goal is to assess cardiometabolic health status, and not obesity itself, indexing peak VO_2 to lean mass is preferable.

Several barriers remain, however, in translating these findings to clinical care. Most important, body composition quantification is rarely performed with CRF assessment. Our findings suggest that although the associations with peak VO_2 vary slightly across measures, anthropometric measures such as BMI, waist circumference, and waist to hip ratio are much less strongly associated with absolute peak VO_2 compared to lean mass. Given accumulating evidence, from our study and others, indicating the importance of body composition for understanding CRF assessment, future prospective studies are warranted to quantify the incremental value of adding body composition assessment to routine CPET in clinical care settings. In multivariable adjusted models, we observed each 1 kg of lean mass to be associated with a ≈ 43 ml/min higher peak VO_2 . For an 80 kg individual with CRF at the sample mean, we would therefore estimate that a 2 kg higher lean mass (composed mostly of skeletal muscle) would increase peak VO_2 by ≈ 1 ml/kg/min, which is considered a clinically meaningful improvement in peak VO_2 for heart failure clinical trials(50). While this finding may indicate that maintenance of skeletal muscle mass, especially with aging, is key for promoting CRF, it may not be the skeletal muscle itself that is entirely responsible for this association. Exercise training leads to far higher improvements in peak VO_2 , even without substantial increases in lean

mass(51, 52), and higher lean mass may not be beneficial in the absence of concomitant improvements in CRF(53). This consideration is especially relevant in the era of novel therapeutics for weight loss, such as glucagon-like peptide-1 receptor agonists, which may dramatically affect body composition, including reductions in lean mass alongside loss of fat mass(54).

Strengths of the present investigation include a large, community-dwelling sample with heterogeneity across age, sex, and cardiometabolic risk profile with contemporaneous assessment of CPET and body composition by DXA. However, our study also has several limitations that warrant consideration. We performed exercise using a cycle ergometer, which reduces the overall effect of body weight on exercise performance. While peak VO_2 values obtained via cycle ergometer and treadmill are correlated, values obtained via cycle ergometer tend to be lower than with treadmill testing(55). We would anticipate that our findings would also be applicable to treadmill exercise modality as adiposity leads to increased required work to move in the setting of treadmill testing, but future studies are warranted to test the consistency of our findings with other exercise modalities. Analyses were cross-sectional in nature, and residual confounding and reverse causation cannot be ruled out. As this study was conducted recently in a mostly middle-aged sample with limited subsequent cardiovascular events, we are unable to evaluate prospective associations, which should be the focus of future studies. We used DXA for assessment of body composition due to its ease of use and general applicability. While DXA is well-validated for assessment of body composition, other methods, such as MRI and deuterated creatine dilution(56), may provide more detailed assessments of skeletal muscle mass and quality(57). Furthermore, an individuals' habitual physical activity exerts multi-dimensional effects on both the exposure (body composition) and outcome (CRF) in our analyses. While we

adjusted for the physical activity index, this does not fully capture an individual's ambient exposure to activity or exercise and further studies are warranted to tease out the complex relationships between exercise, fitness, and body composition. Finally, our study sample was predominantly composed of middle-aged, White individuals largely free of chronic disease, and may not be generalizable to other patient populations and disease conditions.

In summary, lean mass is positively related to higher O₂ uptake during exercise (peak VO₂ and complementary CPET measures) across the adult range and in both men and women. Subcutaneous and visceral adipose tissue demonstrate differences in association with CRF across sex, with null associations in men and positive, but more modest, associations in women. Indexing of peak VO₂ to lean body mass, especially in individuals with obesity and in women, may be preferable to assess true cardiorespiratory adaptations to exercise, as individuals with obesity demonstrate peak VO₂ impairment when indexed to total body weight regardless of underlying metabolic risk and cardiovascular reserve capacity. Given the increasing burden of obesity in the community, heterogeneity of concomitant metabolic risk among individuals with obesity, and recent introduction of novel therapeutics with indications for obesity, our findings have important implications for assessing and targeting cardiometabolic risk in obesity.

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FIGURE LEGENDS

Figure 1: Body composition and cardiorespiratory fitness measures in men and women. (a)

Heatmap of beta coefficients from sex-stratified models between measures of body composition obtained from dual x-ray absorptiometry (DXA) and cardiopulmonary exercise testing (CPET) measures adjusted for age, height, total cholesterol, high-density lipoprotein cholesterol, smoking, systolic blood pressure, hypertension treatment, diabetes, and physical activity index. Asterisks (*) indicates associations meeting statistical significance at FDR <5%. (b) Proportion of variance in absolute peak VO_2 explained by body composition measures in men and women from type 1 sums of squares for sex-stratified models adjusted for age, height, and measures of body composition obtained from dual x-ray absorptiometry (DXA). All variance inflation factors were ≤ 5 in these models, indicating no significant collinearity between DXA measures.

Figure 2: Standardized residuals for body composition measures versus absolute peak VO_2 at selected ages in men and women.

Residuals (standard deviation [SD]) were calculated as the difference between observed and predicted values from sex-stratified linear models, with age and body mass index as independent variables and measures of body composition obtained from dual x-ray absorptiometry (DXA) as the dependent variable, and plotted against absolute peak VO_2 for five age groups (ages 30, 48, 54, 60, and 80 years).

Figure 3: Distribution of peak VO_2 by metabolic health and obesity status in men and women.

Sex-stratified boxplots of peak VO_2 (relative, absolute, or indexed by lean mass) distribution by metabolic health and obesity status. P-values represent pairwise testing.

Figure 4: Associations between body mass index, waist circumference, waist-to-hip ratio, and peak VO_2 by metabolic health status in men and women.

Beta coefficients (95% confidence intervals) from sex-stratified linear regression models between body mass index,

waist circumference, and waist-to-hip ratio and peak VO_2 (relative, absolute, or indexed by lean mass) by metabolic health status, adjusted for age.

Figure 5: Predicted probabilities of peak VO_2 by metabolic health and obesity status in men and women. Predicted probabilities from sex-stratified logistic regression models for each 1-standard deviation higher value of peak VO_2 (relative, absolute, or indexed by lean mass) and obesity/metabolic health status, adjusted for age.

SUPPLEMENTAL DIGITAL CONTENT

SDC 1: SupplementalDigitalContent-1.docx

Table 1: Sample characteristics by sex

Characteristic	Overall N = 2,647	Men N = 1,225	Women N = 1,422
Age (years)	54±9	54±9	53±9
Height (in)	66.7±3.7	69.5±2.7	64.2±2.5
Weight (kg)	80.0±17.2	89.4±14.2	71.9±15.3
Body mass index (kg/m ²)	27.8±5.0	28.7±4.2	27.0±5.5
Waist circumference (inches)	38.4±5.3	40.2±4.4	36.9±5.5
Hip circumference (inches)	41.1±3.8	40.9±2.9	41.4±4.4
Waist to hip ratio	0.93±0.08	0.98±0.06	0.89±0.07
Systolic blood pressure (mm Hg)	119±14	122±13	116±14
Diastolic blood pressure (mm Hg)	76±8	78±8	74±8
Hypertension treatment	542 (20)	296 (24)	246 (17)
Fasting blood glucose (mg/dl)	99±20	104±23	95±16
Hemoglobin A1c (%)	5.4±0.7	5.5±0.7	5.3±0.6
Diabetes*	184 (7.0)	119 (9.7)	65 (4.6)
Smoking	145 (5.5)	66 (5.4)	79 (5.6)
Physical activity index	34.0±5.5	35.1±6.5	33.1±4.2
Total cholesterol (mg/dl)	191±36	185±36	196±36
High-density lipoprotein (HDL) cholesterol (mg/dl)	60±19	51±15	68±19
Total lean mass (kg)	48.9±10.9	58.8±6.7	40.3±5.1
Total fat mass (kg)	26.7±10.3	25.6±9.1	27.7±11.1
Visceral adipose tissue (VAT) mass (kg)	1.19±0.91	1.67±0.94	0.78±0.66
Absolute peak VO ₂ (ml/min)	1,860±640	2,330±560	1,470±380
Relative peak VO ₂ (ml/kg/min)	23.5±6.9	26.4±6.7	20.9±5.9
Percent predicted peak VO ₂ (%)	95.7±20.1	93.9±18.2	97.2±21.5
Aerobic efficiency (mL/W/min)	8.9±1.0	9.3±0.8	8.6±1.0
O ₂ uptake efficiency slope	1,971±588	2,388±508	1,611±376
Peak O ₂ pulse	12.3±3.9	15.3±3.2	9.6±2.1

Characteristic	Overall N = 2,647	Men N = 1,225	Women N = 1,422
Relative VO ₂ at anaerobic threshold (mL/kg/min)	12.6±3.6	13.7±3.7	11.7±3.2
Resting heart rate (beats/min)	72±12	69±11	74±12
Peak heart rate (beats/min)	152±19	152±19	152±18
Peak work (watts)	172±60	215±53	135±35
Peak respiratory exchange ratio	1.23±0.09	1.24±0.09	1.21±0.09
Exercise duration (minutes)	9.1±2.0	9.6±1.9	8.6±2.0

Values represent mean ± standard deviation or n (%), as appropriate.

*Fasting blood glucose and HbA1c were missing in 19 and 1 individual(s), respectively, for the determination of diabetes status.

Figure 1

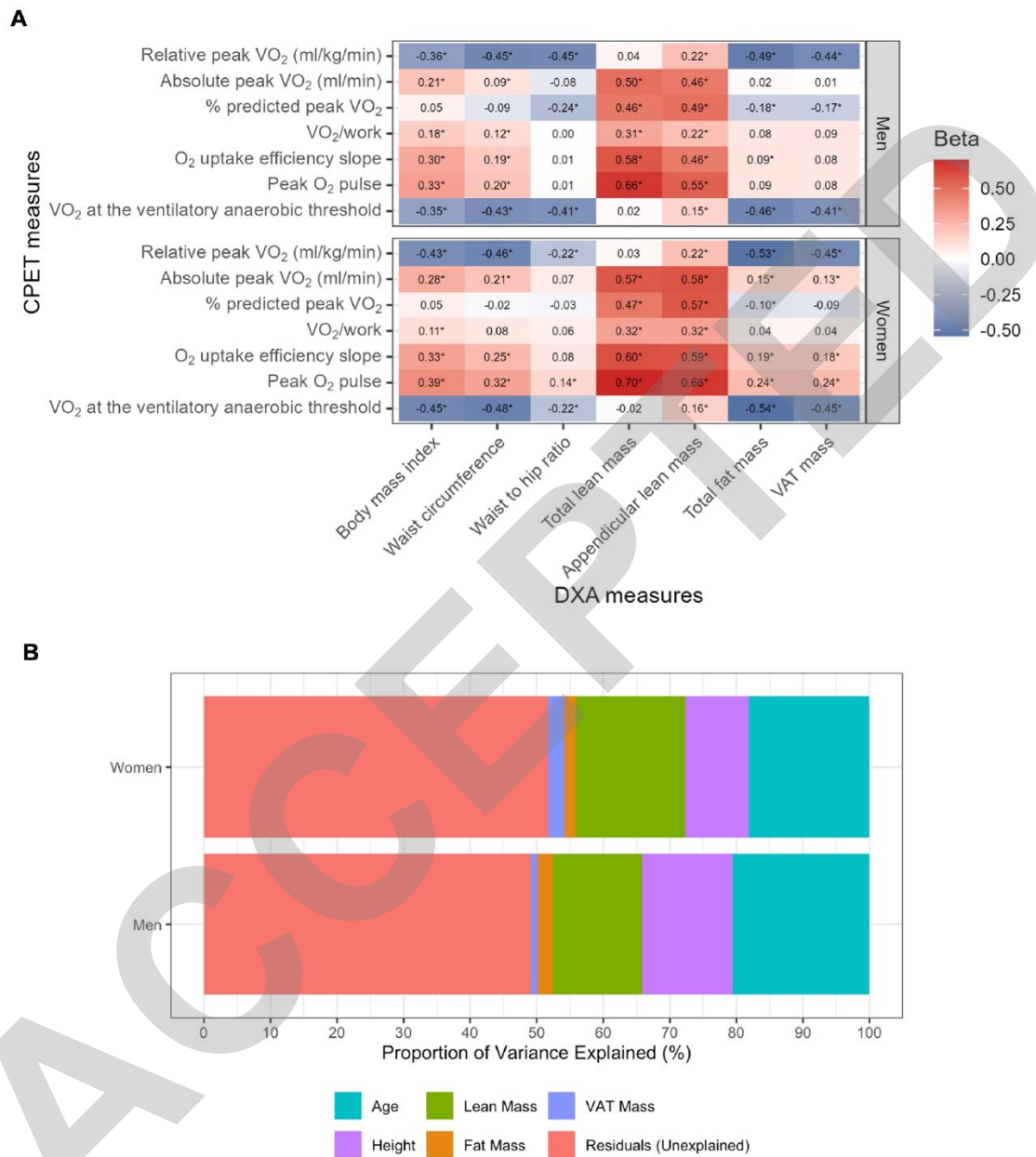


Figure 2

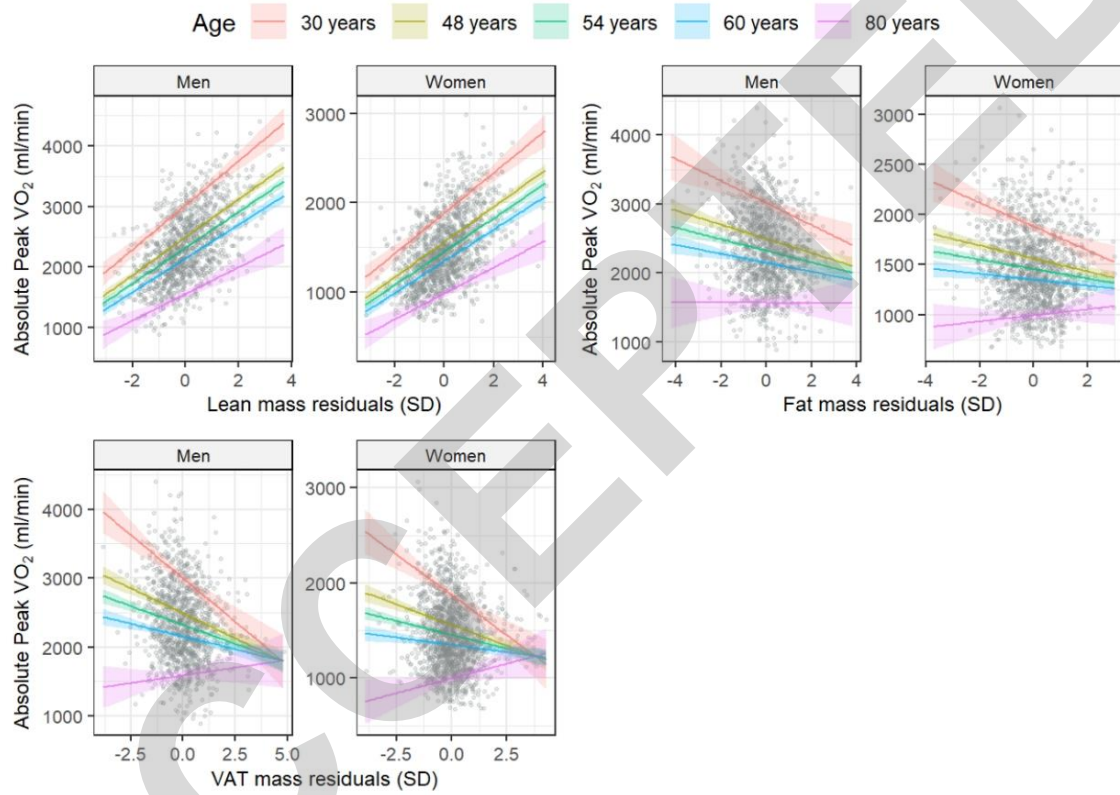


Figure 3

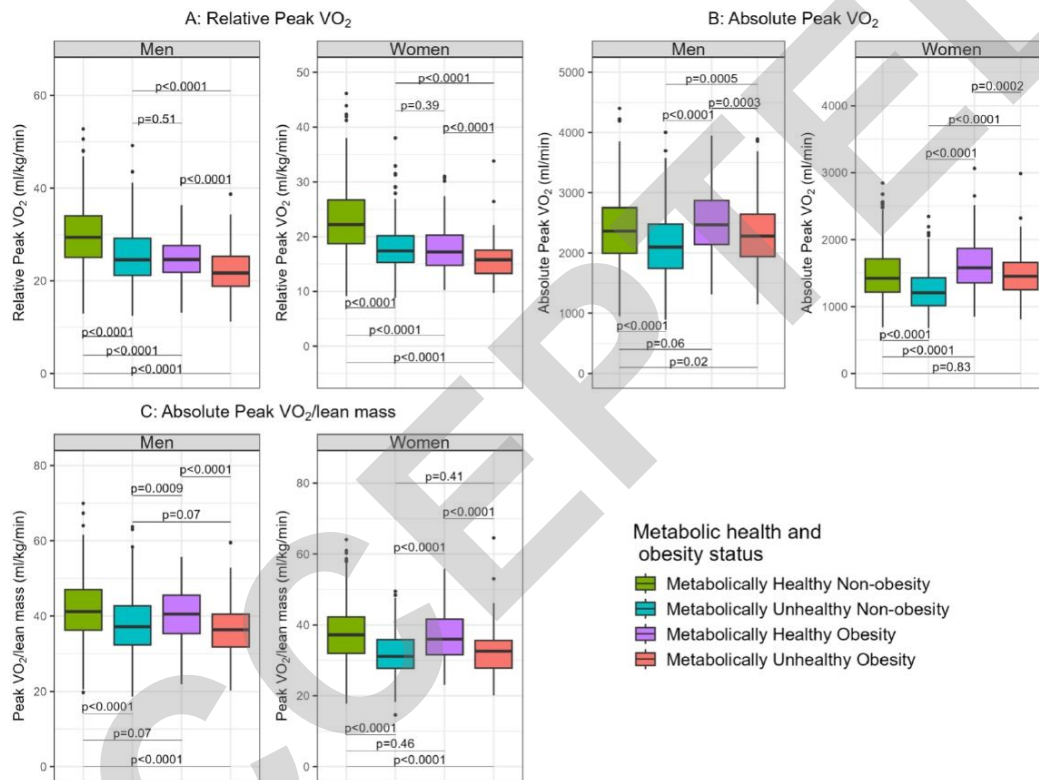


Figure 4

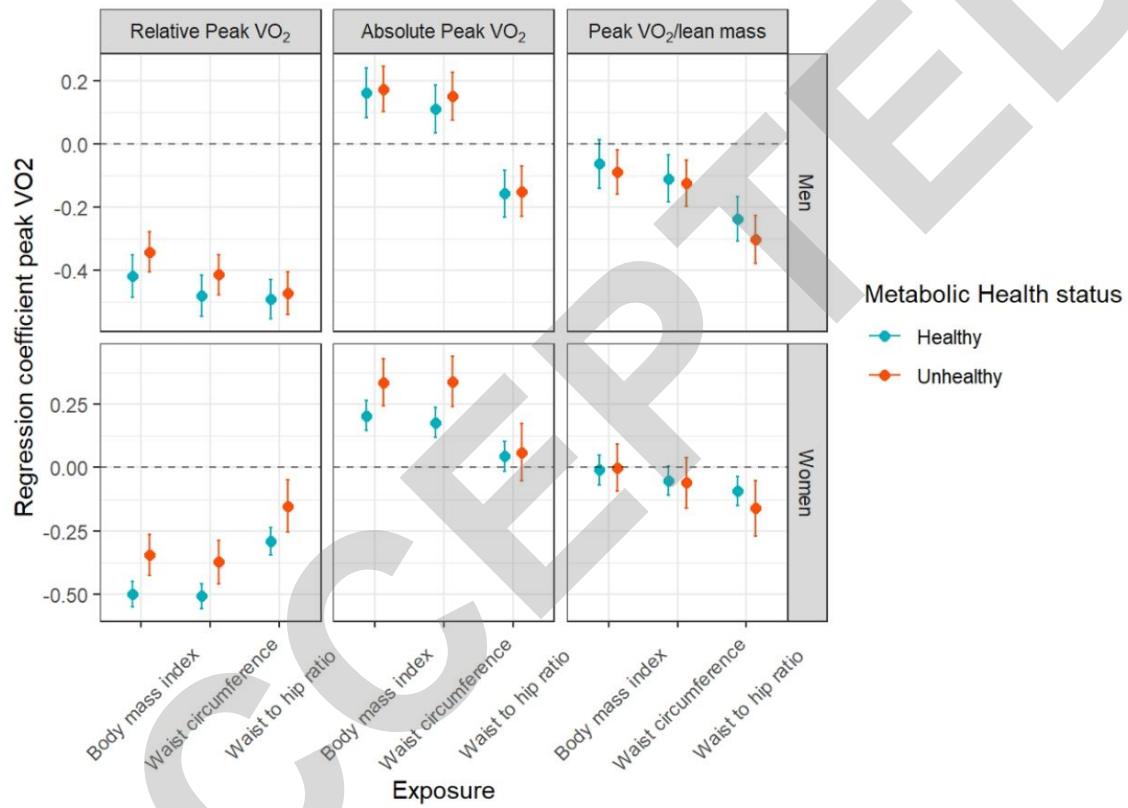


Figure 5

