Cardiorespiratory Fitness Normalized to Fat-Free Mass and Mortality Risk

MARY T. IMBODEN[1,2], LEONARD A. KAMINSKY[3], JAMES E. PETERMAN[3], HAYLEE L. HUTZLER[3], MITCHELL H. WHALEY[3], BRADLEY S. FLEENOR[3], and MATTHEW P. HARBER[3]

[1]Health and Human Performance Department, George Fox University, Newberg, OR; [2]The Health Enhancement Research Organization, Waconia, MN; and [3]Clinical Exercise Physiology, Ball State University, Muncie, IN

ABSTRACT

IMBODEN, M. T., L. A. KAMINSKY, J. E. PETERMAN, H. L. HUTZLER, M. H. WHALEY, B. S. FLEENOR, and M. P. HARBER. Cardiorespiratory Fitness Normalized to Fat-Free Mass and Mortality Risk. *Med. Sci. Sports Exerc.*, Vol. 52, No. 7, pp. 1532–1537, 2020. **Purpose:** Cardiorespiratory fitness (CRF) is known to be directly related to fat-free mass (FFM), therefore, it has been suggested that normalizing CRF to FFM ($\dot{V}O_{2peakFFM}$) may be the most accurate expression of CRF as related to exercise performance and cardiorespiratory function. However, the influence of $\dot{V}O_{2peakFFM}$ (mL·kg FFM^{-1}·min^{-1}) on predicting mortality has been largely unexplored. This study aimed to primarily assess the relationship between $\dot{V}O_{2peakFFM}$ and all-cause and disease-specific mortality risk in apparently healthy adults. Further, this study sought to compare the predictive ability of $\dot{V}O_{2peakFFM}$ to $\dot{V}O_{2peak}$ normalized to total body weight ($\dot{V}O_{2peakTBW}$) for mortality outcomes. **Methods:** Participants included 2905 adults (1555 men, 1350 women) who completed a cardiopulmonary exercise test between 1970 and 2016 to determine CRF. Body composition was assessed using the skinfold method to estimate FFM. Cardiorespiratory fitness was expressed as $\dot{V}O_{2peakTBW}$ and $\dot{V}O_{2peakFFM}$. Participants were followed for 19.0 ± 11.7 yr after their cardiopulmonary exercise test for mortality outcomes. Cox-proportional hazard models were performed to determine the relationship of $\dot{V}O_{2peakFFM}$ with mortality outcomes. Parameter estimates were assessed to compare the predictive ability of CRF expressed as $\dot{V}O_{2peakTBW}$ and $\dot{V}O_{2peakFFM}$. **Results:** Overall, $\dot{V}O_{2peakFFM}$ was inversely related to all-cause, cardiovascular disease, and cancer mortality, with a 16.2%, 8.4%, and 8.0% lower risk per 1 mL·kg FFM^{-1}·min^{-1} improvement, respectively ($P < 0.01$). Further, assessment of the parameter estimates showed $\dot{V}O_{2peakFFM}$ to be a significantly stronger predictor of all-cause mortality than $\dot{V}O_{2peakTBW}$ (parameter estimates, −0.49 vs −0.16). **Conclusions:** Body composition is an important factor when considering the relationship between CRF and mortality risk. Clinicians should consider normalizing CRF to FFM when feasible, because it will strengthen the predictive power of the measure. **Key Words:** CARDIOPULMONARY EXERCISE TESTING, BODY COMPOSITION, FITNESS, $\dot{V}O_{2PEAK}$

Cardiorespiratory fitness (CRF), measured as maximum ($\dot{V}O_{2max}$) or peak oxygen consumption ($\dot{V}O_{2peak}$), was initially described in the 1920s (1) and has been extensively examined for its relationship to functional capacity and endurance exercise performance (2). More recently, CRF has received considerable attention as a strong independent predictor of mortality and numerous clinical outcomes (3–5). Using estimated metabolic equivalents (METs) from a maximal treadmill exercise test as a surrogate of CRF, Blair and colleagues first demonstrated the inverse association between CRF and mortality in a prospective study from the Aerobics Center Longitudinal Study (6). This relationship has since been verified in numerous populations utilizing a variety of methods to estimate CRF (6–9), and more recently including directly measured CRF from cardiopulmonary exercise testing (CPX) (10,11), which is considered the gold standard method for measuring CRF (12).

To account for differences in body size, CRF is typically expressed relative to body weight with $\dot{V}O_{2peak}$ expressed as mL·kg^{-1}·min^{-1} including when expressed as METs (1 MET being equal to 3.5 mL·kg^{-1}·min^{-1}) (13,14). As $\dot{V}O_{2peak}$ is known to be directly related to fat-free mass (FFM) (15), it has been suggested that normalizing $\dot{V}O_{2peak}$ to FFM may be the most accurate expression of CRF as related to exercise performance and cardiorespiratory function (15). However, the influence of $\dot{V}O_{2peak}$ normalized to FFM (mL·kg FFM^{-1}·min^{-1}) on predicting mortality and health-related outcomes has been largely unexplored. Only one study, to date, has assessed whether normalizing CRF to FFM would yield a more accurate prediction of clinical outcomes compared with CRF reported normalized to total body weight (16). Osman et al (16) showed that in chronic heart failure patients the prognostic strength of CRF adjusted to FFM ($\dot{V}O_{2peakFFM}$) was greater than that adjusted to total body weight ($\dot{V}O_{2peakTBW}$), highlighting the importance of FFM in the prediction of clinical outcomes. However,

Address for correspondence: Matthew P. Harber, Ph.D., Clinical Exercise Physiology Program, Human Performance Laboratory, HP230 Ball State University Muncie, IN 47306; E-mail: mharber@bsu.edu.
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the generalizability of these findings is limited to cardiovascular disease (CVD) mortality in heart failure patients. Therefore, the primary purpose of this study was to assess the relationship between CPX-derived $\dot{V}O_{2peakFFM}$ and all-cause, CVD, and cancer mortality risk in apparently healthy adults. Second, this study aimed to compare the predictive ability of $\dot{V}O_{2peakFFM}$ to the more commonly reported measure, $\dot{V}O_{2peakTBW}$. It was hypothesized that $\dot{V}O_{2peakFFM}$ would be an independent predictor of mortality and would compare favorably to $\dot{V}O_{2peakTBW}$.

METHODS

A deidentified sample of 2905 participants (1555 men, 1350 women), ranging in age from 18 to 85 yr (45.3 ± 13.5 yr) was obtained from the Ball State Adult Fitness Longitudinal Lifestyle STudy (BALL ST) Cohort (10). Participants were self-referred either to a community-based exercise program or were research subjects in health-fitness related studies who provided written informed consent for their data to be used for research. All participants performed an initial comprehensive health-risk and physical fitness assessment between 1968 and 2016, including a maximal CPX. Participants were considered apparently healthy, as all were free from known CVD (history of cardiac arrest, coronary artery disease, heart failure, myocardial infarction, and stroke) and cancer at baseline. The CVD diagnosis was self-reported and verified by written physician confirmation. Further, participants were excluded if they had a mean mortality follow-up of <1.0 yr or failed to meet defined peak effort criteria of a respiratory exchange ratio ≥1.0 during the CPX.

Clinical measurements. A full explanation of the procedures for the resting clinical measurements have been described in detail elsewhere (10,17,18). In summary, participants were instructed to arrive fasted and to refrain from exercise, caffeine, and alcohol for ≥8 h before the assessment. Participants completed a health-history questionnaire, which provided self-reported information about personal and family medical history, medication use, and lifestyle behaviors.

Physical activity status was classified as inactive or active, with active designated if participants' self-reported engagement in regular physical activity was consistent with recommendations of the US physical activity guidelines for adults for aerobic activity (19). Participants' smoking status at baseline was categorized as current smoker if they used cigarettes or quit within the past year.

Study participants were assessed to determine the presence of other risk factors at baseline, including obesity, hypertension, dyslipidemia, and impaired fasting glucose, which were defined according to current accepted atherosclerotic CVD risk factor criteria (14). All measurements were performed by trained technicians using standardized laboratory procedures.

Assessment of body composition. Body composition analysis was performed using the three-site skinfold method, to estimate percent body fat (men: abdomen, chest, thigh; women: suprailium, thigh, triceps) (20,21) and estimated fat free mass was calculated using the formula ([100 − % body fat] × total body weight). This method was performed following standardized laboratory procedures (14).

Assessment of CRF. A detailed report of the procedures used to measure CRF has been reported previously (10,17,18). Briefly, a baseline CPX was performed using a standardized treadmill protocol (Bruce ([22]), Ball State University Bruce Ramp ([23]), modified Balke–Ware ([24])) or an individualized protocol to determine absolute $\dot{V}O_{2peak}$ and $\dot{V}O_{2peakTBW}$. The protocol was chosen based on the participant's self-reported physical activity level or estimated CRF obtained using a validated nonexercise prediction equation (17) to target achieving maximal effort within 8 to 12 min (14).

Gas exchange measurements were collected throughout the CPX as previously described (25). Standardized procedures were followed for metabolic cart calibration and all tests were supervised by trained clinical exercise physiologists, with additional medical supervision when appropriate (14). $\dot{V}O_{2peak}$ was defined as the mean of the highest two to three consecutive measured 20- or 30-s $\dot{V}O_2$ values within 2 $mL \cdot kg^{-1} \cdot min^{-1}$, occurring in the last 2 min of the CPX. Participants were encouraged to exercise to volitional fatigue and a respiratory exchange ratio ≥1.0 was used as an objective indicator of peak effort. $\dot{V}O_{2peak}$ was expressed in both absolute ($L \cdot min^{-1}$) and relative terms normalized to total body weight ($mL \cdot kg^{-1} \cdot min^{-1}$) or to FFM ($mL \cdot kg\ FFM^{-1} \cdot min^{-1}$).

Outcomes and follow-up. All participants were followed from the date of their CPX until the date of death or through 2018 for all-cause mortality or December 2016 for disease-specific mortality. The National Death Index was the primary source of vital status between 1979 and 2016. Deaths before 1979 were determined by the Social Security Death Index and were confirmed by obituary review. Deaths occurring after 2016, were confirmed primarily by obituary review. The underlying cause of death determined from the National Death Index report was coded according to the International Classification of Diseases (ICD), 9th revision, before 1999 and the ICD, 10th revision, from 1999 to 2016 (26,27).

Statistical analysis. SPSS V. 25 was used for all statistical analyses. Descriptive statistics were performed to summarize baseline characteristics of the participants and a univariate analysis of variance and χ^2 goodness of fit test were used when appropriate to test for significant differences between sexes and vital status (living vs deceased). Fitness percentiles were determined based on $\dot{V}O_{2peakTBW}$ using the Fitness Registry and the Importance of Exercise National Database (FRIEND). The FRIEND registry provides age and sex-specific reference values for CPX-CRF for adults in the United States. Cox proportional hazard models were used to estimate hazard ratios for all-cause and disease-specific mortality for both sexes. The Cox models were estimated with CRF expressed continuously as absolute $\dot{V}O_{2peak}$, in liters per minute, as well as $\dot{V}O_{2peakTBW}$, and expressed relative to kilograms of FFM ($\dot{V}O_{2peakFFM}$). Multiple Cox proportional hazard models were fit to the data, the first was run with CRF unadjusted, and second, adjusted for age and sex for the overall population and age only in the sex-specific models, and then further adjusted

for confounding risk factors (multivariable model; obesity, hypertension, dyslipidemia, impaired fasting glucose, physical inactivity, and smoking status), which were categorized by the presence 1, or absence, 0, of each risk factor. A Wald χ^2 test was used to compare the coefficients estimating the relationship of relative $\dot{V}O_{2peakTBW}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) and $\dot{V}O_{2peakFFM}$ ($mL \cdot kg\ FFM^{-1} \cdot min^{-1}$) with time until death for all-cause mortality. These models were analyzed with both expressions of $\dot{V}O_{2peak}$ as covariates only and then further adjusted for age and sex. To assess the assumption of proportional hazards, which underlies the Cox model, Schoenfeld residuals were examined (28). The relationships between these residuals and the model covariates were not statistically significant ($P > 0.05$), indicating that the proportional hazards assumption was met.

RESULTS

Descriptive characteristics of the overall study population, as well as for men and women separately are presented in Table 1 and a comparison of demographic characteristics between living versus deceased participants at time of follow-up is presented in Table 2. Over 46 yr of follow-up (19.5 ± 11.6), 439 participants died from all causes, approximating eights deaths per 1000 person-years.

Table 3 reports the findings from the Cox models when $\dot{V}O_{2peakFFM}$ was run as the covariate. There was an inverse relationship between $\dot{V}O_{2peakFFM}$ and all-cause, CVD, and cancer mortality when run unadjusted ($P < 0.05$) and with further adjustment for age, sex and traditional risk factors ($P < 0.05$). Importantly, this relationship between $\dot{V}O_{2peakFFM}$ and all-cause mortality remained significant when men and women were assessed independently ($P < 0.05$).

Results from the continuous Cox models predicting all-cause, CVD, and cancer mortality using absolute and $\dot{V}O_{2peakTBW}$ as covariates to provide a comparison to $\dot{V}O_{2peakFFM}$ appear in Table 4. Overall, both absolute ($L \cdot min^{-1}$) and $\dot{V}O_{2peakTBW}$ were inversely associated with risk for all-cause, CVD, and cancer mortality when run unadjusted ($P < 0.01$). The relationship with all-cause and disease-specific mortality remained significant after adjusting for age and sex ($P < 0.01$) and following multivariable adjustment ($P < 0.05$). Further, the association of absolute $\dot{V}O_{2peak}$ and $\dot{V}O_{2peakTBW}$ with all-cause mortality remained significant in all models when men were assessed independently ($P < 0.05$). However, in women, the relationship between absolute $\dot{V}O_{2peak}$ and mortality, as well

TABLE 1. Demographics of the BALL ST. cohort.

	All (N = 2905)	Men (n = 1555)	Women (n = 1350)
Age (yr)	45.3 ± 13.5	45.5 ± 13.2	45.1 ± 13.9
Abs. $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	2.55 ± 0.90	3.10 ± 0.79	1.92 ± 0.51
$\dot{V}O_{2peakTBW}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	31.4 ± 10.6	35.5 ± 10.7*	26.7 ± 8.5
$\dot{V}O_{2peakFFM}$ ($mL \cdot kg\ FFM^{-1} \cdot min^{-1}$)	42.9 ± 11.5	45.6 ± 12.2	40.6 ± 10.5
FRIEND percentile	45 ± 27	43 ± 27*	48 ± 27
BMI ($kg \cdot m^{-2}$)	27.9 ± 6.1	28.1 ± 5.2	27.6 ± 6.9
WC (cm)	91.4 ± 15.8	97.3 ± 14.0*	84.8 ± 15.1
Body fat (%)	30 ± 9	24 ± 8	34 ± 8
Obesity (%)	35	34	37
RHR (bpm)	68 ± 11	67 ± 12*	70 ± 10
SBP (mm Hg)	122 ± 16	126 ± 15*	118 ± 15
DBP (mm Hg)	78 ± 11	82 ± 10*	75 ± 10‡
Hypertensive (%)	33	38*	27
Total cholesterol ($mg \cdot dL^{-1}$)	201 ± 43	203 ± 45*	199 ± 39
Dyslipidemia (%)	59	65*	53
Glucose ($mg \cdot dL^{-1}$)	96 ± 22	99 ± 25*	93 ± 17
IFG (%)	25	28*	23
Physical inactivity (%)	71	65*	77
Smoking (%)	8	9*	6
Follow-up (yr)	19.5 ± 11.6	20.2 ± 12.1	18.7 ± 10.9

Abs, absolute; BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; IFG, impaired fasting glucose; RHR, resting heart rate; SBP, systolic blood pressure; WC, waist circumference.
*Significantly different than women; $P < 0.05$.

TABLE 2. Descriptive characteristics of the survivors and deceased participants within the BALL ST cohort at time of assessment.

	Survivors (n = 2466)	Deceased (n = 439)
Age (yr)	44.0 ± 13.4*	52.7 ± 11.6
Follow-up	19.3 ± 11.7	20.4 ± 10.5
$\dot{V}O_{2peakTBW}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	31.6 ± 10.9*	29.9 ± 8.9
Abs. $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	2.6 ± 0.9	2.4 ± 0.8
$\dot{V}O_{2peak\ FFM}$ ($mL \cdot kg\ FFM^{-1} \cdot min^{-1}$)	43.8 ± 11.5	36.8 ± 9.6
FRIEND percentile	45 ± 28	45 ± 27
BMI ($kg \cdot m^{-2}$)	28.0 ± 6.2	27.2 ± 5.2
WC (cm)	91.1 ± 15.8*	92.8 ± 15.6
Body Fat (%)	24 ± 9	31 ± 9
Obesity (%)	36*	30
SBP/DBP (mm Hg)	121* /74* ± 12/9	128/80 ± 13/8
Hypertension (%)	30*	46
RHR (bpm)	68 ± 9	67 ± 10
Total cholesterol ($mg \cdot dL^{-1}$)	197.1 ± 40.4*	221.5 ± 47.9
Dyslipidemia (%)	57*	71
Blood glucose ($mg \cdot dL^{-1}$)	96.1 ± 20.8*	97.8 ± 25.9
IFG (%)	23	26
Smoking (%)	7	13

*Significantly different between living and deceased at follow-up test; $P < 0.05$.

TABLE 3. Hazard ratios for mortality outcomes according to CRF, expressed as $\dot{V}O_{2peakFFM}$ ($mL \cdot kg\ FFM^{-1} \cdot min^{-1}$).

All-Cause Mortality	Hazard Ratio (95% CI)	% Reduction/$mL \cdot kg\ FFM^{-1} \cdot min^{-1}$ Increase
All		
Model 1	0.823* (0.801–0.846)	17.7%
Model 2	0.872* (0.846–0.898)	12.8%
Model 3	0.838* (0.807–0.870)	16.2%
Men		
Model 1	0.808* (0.782–0.836)	19.2%
Model 2	0.851* (0.820–0.883)	14.9%
Model 3	0.808* (0.770–0.847)	19.2%
Women		
Model 1	0.801* (0.765–0.838)	19.9%
Model 2	0.915* (0.866–0.967)	8.5%
Model 3	0.892* (0.832–0.956)	10.8%
CVD Mortality	**Hazard Ratio (95% CI)**	**% Reduction/$mL \cdot kg\ FFM^{-1} \cdot min^{-1}$ Increase**
All		
Model 1	0.898* (0.873–0.923)	13.1%
Model 2	0.930* (0.902–0.959)	7.6%
Model 3	0.923* (0.889–0.958)	8.4%
Cancer Mortality	**Hazard Ratio (95% CI)**	**% Reduction/$mL \cdot kg\ FFM^{-1} \cdot min^{-1}$ Increase**
All		
Model 1	0.914* (0.891–0.938)	8.6%
Model 2	0.935* (0.909–0.962)	6.7%
Model 3	0.920* (0.890–0.951)	8.0%

Model 1 was run unadjusted; model 2 was adjusted for age in the sex-specific analyses with the addition of sex in the overall sample; model 3 was the multivariable model adjusted for age, examination year, and traditional CVD risk factors (hypertension, dyslipidemia, impaired fasting blood glucose, obesity, Physical inactivity, and smoking) for the sex-specific analyses with the addition of sex in the overall sample.

TABLE 4. Hazard ratios for mortality outcomes according to CRF, expressed as absolute $\dot{V}O_{2peak}$ and $\dot{V}O_{2peakTBW}$.

All-Cause Mortality	Hazard Ratio (95% CI) $L \cdot min^{-1}$	Hazard Ratio (95% CI) $mL \cdot kg^{-1} \cdot min^{-1}$
All		
Model 1	0.695* (0.621–0.779)	0.950* (0.940–0.960)
Model 2	0.691* (0.586–0.814)	0.967* (0.954–0.979)
Model 3	0.619* (0.497–0.769)	0.959* (0.941–0.977)
Men		
Model 1	0.401* (0.341–0.472)	0.928* (0.915–0.940)
Model 2	0.646* (0.540–0.773)	0.961* (0.947–0.975)
Model 3	0.587* (0.461–0.748)	0.953* (0.933–0.974)
Women		
Model 1	0.226* (0.149–0.342)	0.913* (0.887–0.938)
Model 2	1.029 (0.635–1.667)	0.992 (0.962–1.023)
Model 3	0.978 (0.541–1.767)	0.990 (0.951–1.032)
CVD Mortality	**Hazard Ratio (95% CI) $L \cdot min^{-1}$**	**Hazard Ratio (95% CI) $mL \cdot kg^{-1} \cdot min^{-1}$**
All		
Model 1	0.794* (0.655–0.962)	0.955* (0.938–0.972)
Model 2	0.810 (0.615–1.068)	0.971* (0.949–0.991)
Model 3	0.667 (0.444–1.003)	0.965 (0.932–1.00)
Cancer Mortality	**Hazard Ratio (95% CI) $L \cdot min^{-1}$**	**Hazard Ratio (95% CI) $mL \cdot kg^{-1} \cdot min^{-1}$**
All		
Model 1	0.696* (0.558–0.870)	0.949* (0.929–0.971)
Model 2	0.574* (0.412–0.801)	0.956* (0.932–0.981)
Model 3	0.531* (0.345–0.819)	0.951* (0.917–0.987)

Model 1 was run unadjusted; model 2 was adjusted for age in the sex-specific analyses with the addition of sex in the overall sample; model 3 was the multivariable model adjusted for age, examination year, and traditional CVD risk factors (hypertension, dyslipidemia, impaired fasting blood glucose, obesity, physical inactivity, and smoking) for the sex-specific analyses with the addition of sex in the overall sample.

as $\dot{V}O_{2peakTBW}$ and mortality were only found to be significant in the unadjusted model ($P < 0.01$). The relationships were no longer significant following adjustment for age and risk factors.

Results from the Wald χ^2 test of equality comparing $\dot{V}O_{2peakTBW}$ and $\dot{V}O_{2peakFFM}$ as predictors of mortality are provided in Table 5. The analysis showed that $\dot{V}O_{2peakFFM}$ was a stronger predictor of all-cause mortality than $\dot{V}O_{2peakTBW}$ ($P < 0.05$). This relationship remained significant after further adjustment for age and sex.

DISCUSSION

Over the past century, CRF has been extensively studied for its relationship with exercise performance and more recently as a strong independent predictor of health outcomes, including all-cause and disease-specific mortality. Although it has been suggested that various components of body composition be factored in when expressing CRF (15,29), the influence of normalizing CRF to FFM on the prognostic strength of CRF for predicting mortality has been largely unexplored. Our results show that $\dot{V}O_{2peakFFM}$ holds higher prognostic value in apparently healthy adults than $\dot{V}O_{2peakTBW}$ ($mL \cdot kg^{-1} \cdot min^{-1}$). This finding suggests physiological superiority of $\dot{V}O_{2peakFFM}$ as a measure of CRF, proposing that it is not only the most accurate measure of CRF as it relates to exercise performance (15) but also the best way to present CRF as it pertains to health.

The most common expression of CRF is expressed as $\dot{V}O_{2peak}$ normalized to total body weight, which assumes that body composition is equivalent among individuals and/or does not account for the contribution of the various components of body composition on energy expenditure. Although it is known that $\dot{V}O_{2peak}$ is directly proportional to FFM mass (15), it has also been shown that FFM is inversely associated with risk of death (30). Further, there is a strong relationship between excess body fat and mortality risk (31–34) as those with excess body fat have been found to have a 45% to 60% increased mortality risk compared with those with normal body fat (32–34). Given the independent association of body composition with mortality outcomes, along with the impact body composition has on CRF (15), it is plausible that body composition influences the relationship between CRF and mortality as our results indicate.

Only one other study to date has assessed the prognostic strength of $\dot{V}O_{2peakFFM}$ on mortality risk (16). Similar to the current findings, the adjustment of CRF to FFM increased the prognostic value of CPX compared with $\dot{V}O_{2peakTBW}$ in chronic heart failure patients. Further, Osman et al. found a 9% reduction in CVD related mortality for every 1 $mL \cdot kg\ FFM^{-1} \cdot min^{-1}$ increase. Our findings show a similar reduction in risk, suggesting an approximately 8% reduction in cardiovascular mortality for each 1 $mL \cdot kg\ FFM^{-1} \cdot min^{-1}$. However, as Osman et al. (16) studied chronic heart failure patients, the current study expands on the understanding of this relationship by demonstrating that $\dot{V}O_{2peakFFM}$ has greater predictive power compared with $\dot{V}O_{2peakTBW}$ in apparently healthy adults.

Although the relationship between $\dot{V}O_{2peakFFM}$ and mortality outcomes remained significant in both men and women when assessed independently, its predictive strength in women should be highlighted. When controlling for age and traditional risk factors, the relationship between $\dot{V}O_{2peakTBW}$ and mortality risk was not significant in women. One explanation for this finding is that reference standards of body composition (30,35) show that women have higher amounts of body fat and lower amounts of FFM than men, which is consistent with our cohort (Table 1). The significantly higher body fat in women could lead to bias when normalizing CRF to total body weight, because body fat does not contribute to the consumption of oxygen during exercise (36). However, this bias can be eliminated by normalizing to FFM, strengthening the predictive ability compared with that previously found with $\dot{V}O_{2peakTBW}$. This finding in women is also consistent with results from Osman et al. demonstrating that there was a considerably better relationship between $\dot{V}O_{2peakFFM}$ and health outcomes in women with heart failure than seen with $\dot{V}O_{2peakTBW}$ (16).

TABLE 5. Comparison the relationship between $\dot{V}O_{2peakTBW}$ and $\dot{V}O_{2peak\ FFM}$ to mortality outcomes.

Wald x^2 Test of Equality	Absolute Parameter Estimate
Model 1*	
$\dot{V}O_{2peakTBW}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	0.135
$\dot{V}O_{2peakFFM}$ ($mL \cdot kg\ FFM^{-1} \cdot min^{-1}$)	0.494
Model 2*	
$\dot{V}O_{2peakTBW}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	0.162
$\dot{V}O_{2peakFFM}$ ($mL \cdot kg\ FFM^{-1} \cdot min^{-1}$)	0.494

*$\dot{V}O_{2FFM}$ significantly different than $\dot{V}O_{2peak}$; $P \le 0.05$.
Model 1 unadjusted; model 2 adjusted for age and sex.

Using $\dot{V}O_{2peakTBW}$ still provides helpful prognostic information as body composition measures are not routinely available. However, clinicians should consider performing body composition measures to allow expression of $\dot{V}O_{2peakFFM}$, especially in those of higher risk or with greater body fat. The three-site skinfold measure used in the current study is a relatively simple, efficient, and cost-effective method to estimate body fat percentage (14,37). Although a doubly indirect method, it still has a high correlation with the gold standard method of dual energy x-ray absorptiometry. Further, the results emphasize the importance of CRF and body composition to health. Given that regular physical activity and/or exercise training is known to improve CRF while increasing FFM (38), clinicians should prescribe lifestyle interventions as a way to improve overall health and longevity.

STRENGTHS AND LIMITATIONS

This study had several notable strengths. First, CRF was measured using CPX, and thus may improve classification of an individual's mortality risk. Although most studies have assessed the predictive value of CRF normalized to total body mass adjusting for obesity or body mass index category as covariates (6,10,29), this study assessed the value of CRF normalized to FFM, which is suggested to be the most accurate expression of CRF given the strong influence body composition has on $\dot{V}O_{2peak}$ (15). Further, the study sample came from Muncie, Indiana, which has been considered the average American small city (39), thus may be representative of the typical demographic characteristics that clinicians regularly see. Finally, this study had a long follow-up period of approximately 19 yr with a range of 1 to 46 yr.

Limitations included >90% non-Hispanic white cohort, thus, future work is needed to confirm these findings in populations from diverse ethnic and socioeconomic backgrounds that are known to influence body composition and health outcomes (40). Furthermore, the study cohort was all self-referred and was limited to those that were able to achieve maximal effort on a treadmill exercise test. Body composition was assessed using the skinfold method. Although this method may be more feasible in the clinical setting, it is associated with error, and the use of the gold standard method, dual-energy x-ray absorptiometry, may provide more accurate results of body composition. Finally, information on changes in lifestyle behaviors during the follow-up period were not available. Given that exercise training can improve CRF and body composition (38), future research should assess the influence of changes in $\dot{V}O_{2peakFFM}$, after exercise training, on mortality in a large, diverse cohort of apparently healthy men and women.

CONCLUSIONS

Body composition influences CRF (15) and impacts the relationship between CRF and mortality outcomes (16). Although CRF is commonly expressed normalized to total body weight as an easy way to standardize the measure across differing body sizes, these findings suggest that CRF should be standardized to FFM as it will strengthen the predictive ability. Thus, clinicians should consider normalizing CRF to FFM when feasible, especially in women, individuals with excess body fat, and those at high risk and in need of optimal predictive power.

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The authors have no conflict of interests to declare.

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