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ORIGINAL INVESTIGATIONS

Cardiorespiratory Fitness and Mortality in Healthy Men and Women

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ABSTRACT

BACKGROUND There is a well-established inverse relationship between cardiorespiratory fitness (CRF) and mortality. However, this relationship has almost exclusively been studied using estimated CRF.

OBJECTIVES This study aimed to assess the association of directly measured CRF, obtained using cardiopulmonary exercise (CPX) testing with all-cause, cardiovascular disease (CVD), and cancer mortality in apparently healthy men and women.

METHODS Participants included 4,137 self-referred apparently healthy adults (2,326 men, 1,811 women; mean age: 42.8 ± 12.2 years) who underwent CPX testing to determine baseline CRF. Participants were followed for 24.2 ± 11.7 years (1.1 to 49.3 years) for mortality. Cox-proportional hazard models were performed to determine the relationship of CRF ($ml \cdot kg^{-1} \cdot min^{-1}$) and CRF level (low, moderate, and high) with mortality outcomes.

RESULTS During follow-up, 727 participants died (524 men, 203 women). CPX-derived CRF was inversely related to all-cause, CVD, and cancer mortality. Low CRF was associated with higher risk for all-cause (hazard ratio [HR]: 1.73; 95% confidence interval [CI]: 1.20 to 3.50), CVD (HR: 2.27; 95% CI: 1.20 to 3.49), and cancer (HR: 2.07; 95% CI: 1.18 to 3.36) mortality compared with high CRF. Further, each metabolic equivalent increment increase in CRF was associated with a 11.6%, 16.1%, and 14.0% reductions in all-cause, CVD, and cancer mortality, respectively.

CONCLUSIONS Given the prognostic ability of CPX-derived CRF for all-cause and disease-specific mortality outcomes, its use should be highly considered for apparently healthy populations as it may help to improve the efficacy of the individualized patient risk assessment and guide clinical decisions. (J Am Coll Cardiol 2018;72:2283–92)

Cardiorespiratory fitness (CRF) is directly related to the integrated function of numerous physiological systems, including the respiratory, cardiovascular, and musculoskeletal systems, and is widely considered the best reflection of whole-body health and function (1). Low estimated CRF (CRF_e) has been associated with an increased risk of traditional cardiovascular risk factors (2–4) and is one of the strongest predictors of all-cause mortality and noncommunicable diseases, including cardiovascular disease (CVD) and cancer (5–14).

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ABBREVIATIONS AND ACRONYMS

CPX = cardiopulmonary exercise testing

CRF = cardiorespiratory fitness

CRF_e = estimated cardiorespiratory fitness

CVD = cardiovascular disease

FRIEND = Fitness Registry and the Importance of Exercise National Database

HR = hazard ratio

MET = metabolic equivalent

VO_{2peak} = peak oxygen uptake

Cardiopulmonary exercise (CPX) testing is the gold standard method for assessing CRF as it uses gas exchange analysis to provide an objective and accurate measurement of peak oxygen uptake (VO_{2peak}). CPX also provides a wealth of clinical information, and although its prognostic value has been firmly established in cardiovascular, pulmonary, and musculoskeletal disease patients (15–19), it is less established in apparently healthy adults (16). The importance of accurate quantification of CRF through CPX in apparently healthy men and women is becoming more recognized when assessing risk for noncommunicable diseases and mortality as it provides information on possible abnormalities that may be indicators of underlying disease, which if detected early and addressed may improve prognosis (1,20,21). Given the growing evidence supporting the prognostic value of CRF, it is important to accurately measure CRF and refine this relationship using the gold-standard method, CPX testing (21).

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To date, only 1 apparently healthy cohort has assessed the relationship of CPX-CRF with mortality (11,22,23). They found a strong, inverse relationship between CRF and mortality outcomes; the relative risk of all-cause mortality was 2.76 in the low-fit (VO_{2peak} <27.6 ml·kg^{-1}·min^{-1}) compared with high-fit (VO_{2peak} >37.1 ml·kg^{-1}·min^{-1}) men (22). However, the generalizability of these findings is limited to only Nordic men between the ages of 42 and 60 years old. Two additional considerations were that Laukkenan et al. tested with cycle ergometry, which typically results in 10% to 20% lower CRF compared with standardized treadmill protocols (24), and they tested an exclusively Nordic population, who have higher CRF than Americans (25). Recently, scientific and policy statements have called for more research that examines the clinical value of CPX measures in apparently healthy populations (16,26), as well as assessing the relationship between CRF and mortality in women (21), who typically have lower CRF than men (21,25,27). Therefore, the primary aim of this study was to assess the association of CPX-CRF on all-cause, CVD, and cancer mortality in a cohort of apparently healthy men and women across a wide age range.

METHODS

This study was reviewed by the Ball State University Institutional Review Board and determined exempt as only de-identified data were used.

A de-identified sample of 4,137 participants (2,326 men, 1,811 women), ranging in age from 18 to 85 years (43 ± 12 years) was obtained from the BALL ST (Ball State Adult fitness program Longitudinal Lifestyle STudy) cohort. Participants were self-referred either to the Ball State University Adult Physical Fitness Program, a community-based exercise program, or were research subjects in health-fitness-related studies who gave written informed consent for their data to be used for research. All participants performed an initial comprehensive health and physical fitness assessment between 1968 and 2016, including a maximal CPX test. 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 (142 participants excluded with diagnosis of CVD or cancer at the time of first examination). CVD diagnosis was self-reported and verified by written physician confirmation. Further, participants with <1.0 year of mortality follow-up (n = 51) and those not meeting defined peak effort criteria of a respiratory exchange ratio ≥1.0 during the CPX test (n = 721) were excluded.

CLINICAL MEASUREMENTS. A full explanation of the procedures for the resting clinical measurements has been described in detail elsewhere (28,29). 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 meeting the U.S. physical activity guidelines for adults for aerobic activity. Participants were classified as physically inactive if they did not participate in regular moderate-to-vigorous physical activity. Smoking status was categorized as current or nonsmoker at baseline. Participants were classified as a current smoker if they used cigarettes or quit within the past year.

Study participants were assessed to determine the presence of risk factors at baseline, including obesity, hypertension, dyslipidemia, and impaired fasting glucose, which were defined according to current accepted atherosclerotic CVD risk factor criteria (Online Table 1 [30]). All measurements were performed by trained technicians using standardized

TABLE 1 Descriptive Characteristics of the BALL ST Cohort

		Men				Women			
	All (N = 4,137)	**All (n = 2,326)**	**Low Fit (n = 992)**	**Moderate Fit (n = 787)**	**High Fit (n = 547)**	**All (n = 1,811)**	**Low Fit (n = 620)**	**Moderate Fit (n = 699)**	**High Fit (n = 492)**
Age, yrs	42.8 ± 12.2	42.8 ± 11.6	43.5 ± 11.9	44.0 ± 11.6	41.6 ± 12.0	42.9 ± 12.9	42.6 ± 12.9	43.5 ± 12.5	43.4 ± 13.7
$VO_{2peak,}$ ml·kg^{-1}·min^{-1}	33.0 ± 10.8	37.1 ± 10.6*	28.9 ± 6.2†	37.6 ± 6.1‡	49.8 ± 8.8	27.9 ± 8.5	21.3 ± 4.5†	27.6 ± 5.4‡	35.9 ± 8.9
FRIEND percentile	46 ± 27	44 ± 27*	17 ± 9†	49 ± 9	83 ± 9	48 ± 27	18 ± 9†	50 ± 10	83 ± 8
$VO_{2peak\text{-}predicted}$, ml·kg^{-1}·min^{-1} (n = 4,063)	40.2 ± 10.6	43.9 ± 9.8	37.9 ± 8.5	45.0 ± 6.9	53.3 ± 7.7	35.5 ± 9.6	29.8 ± 7.3	35.7 ± 7.9	41.9 ± 9.6
$Watts_{peak}$ (n = 3946)	169.3 ± 77.7	197.3 ± 79.8	186.9 ± 79.7	197.3 ± 77.5	215.3 ± 78.9	133.1 ± 57.5	128.2 ± 55.0	129.9 ± 55.5	140.5 ± 61.0
BMI, kg/m^2	27.1 ± 5.6	27.4 ± 5.0*	30.1 ± 5.6†	26.3 ± 3.3‡	24.2 ± 2.6	26.7 ± 6.3	31.0 ± 7.3†	25.5 ± 4.4‡	23.0 ± 3.4
Waist circumference, cm	89.8 ± 15.4	95.9 ± 13.4*	103.3 ± 14.3†	93.2 ± 9.0‡	86.3 ± 8.2	82.7 ± 14.5	92.2 ± 15.7†	80.1 ± 10.9‡	73.9 ± 9.2
Obesity	29	28	52†	17	4	31	59†	24	7
RHR, beats/min	68 ± 15	67 ± 17*	72 ± 21†	66 ± 12‡	59 ± 12	70 ± 11	73 ± 10	70 ± 10	66 ± 11
SBP, mm Hg	122 ± 15	126 ± 14*	129 ± 14	125 ± 13	124 ± 12	118 ± 15	121 ± 15	117 ± 15	115 ± 15
DBP, mm Hg	79 ± 10	82 ± 10*	83 ± 10‡	81 ± 9	79 ± 9	75 ± 10	78 ± 10	75 ± 10	73 ± 9
Hypertensive	28	33*	44†	29‡	21	22	33	21‡	13
Total cholesterol, mg/dl^{-1}	207 ± 43	211 ± 45*	215 ± 49‡	211 ± 44‡	204 ± 42	201 ± 40	203 ± 42	201 ± 40	198 ± 39
Dyslipidemia	56	67*	76†	66‡	52	43	51‡	41‡	37
Glucose, mg/dl^{-1}	96 ± 22	98 ± 23*	103 ± 29†	96 ± 19	95 ± 17	93 ± 19	93 ± 19‡	93 ± 17‡	98 ± 32
Diabetes	27	31*	39	28‡	23	21	27†	21‡	14
Physical inactivity	61	56*	73†	56‡	26	67	82†	68‡	49
Smoking	11	13*	18†	11‡	6	9	11†	9‡	5
Follow-up, yrs	24.2 ± 11.7	25.4 ± 11.9*	22.9 ± 12.1†	26.0 ± 12.0‡	27.6 ± 11.2	22.7 ± 11.4	20.7 ± 11.2†	23.2 ± 11.5	23.7 ± 11.7

Values are mean ± SD or %. Low, moderate, and high cardiorespiratory fitness corresponds to ≤33rd, 34th–66th, and ≥67th percentiles of FRIEND reference standards. *Significantly different than women; $p < 0.05$. †Significantly different than tertiles 2 and 3; $p < 0.05$. ‡Significantly different than tertile 3; $p < 0.05$.

BALL ST = Ball State Adult fitness program Longitudinal Lifestyle STudy (BALL ST) Cohort; BMI = body mass index; DBP = diastolic blood pressure; FRIEND = Fitness Registry and the Importance of Exercise National Database; RHR = resting heart rate; SBP = systolic blood pressure; VO_{2peak} = peak oxygen consumption.

laboratory procedures and included resting blood pressure, anthropometrics (height, weight, body mass index, and waist circumference), body composition, and blood chemistry.

ASSESSMENT OF CRF. A baseline CPX test was performed using standardized treadmill protocols (Bruce [31], Ball State University Bruce Ramp [32], modified Balke-Ware [33], and individualized protocols) to determine VO_{2peak}. The protocol was chosen based on the participant's self-reported physical activity level or CRF_e obtained using a validated nonexercise prediction equation (28) to target achieving maximal effort within 8 to 12 min (30). As this was participants first exercise test in our laboratory, all were provided with an explanation of the CPX test procedures/protocol before the test. Predicted VO_{2peak} was determined by using the peak speed and grade for all test files (n = 4,063) with these data available (30). Watts were calculated from body weight and peak speed and vertical displacement (grade) for all test files (n = 3,946) with these data available.

Gas exchange measurements were collected throughout the CPX test, using a Parvo metabolic testing system (Parvo Medics, Salt Lake City, Utah) since 2002 and other systems before that as previously described (28). Standardized procedures were followed for metabolic cart calibration and all tests were supervised by trained clinical exercise physiologists with additional medical supervision when appropriate (30). VO_{2peak} was determined by averaging the highest 2 to 3 consecutive measured VO_2 values within 2 ml·kg^{-1}·min^{-1}, occurring in the last 2 min of the CPX test. Participants were encouraged to exercise to volitional fatigue and a respiratory exchange ratio of ≥1.0 was used as an objective indicator of peak effort. CRF was expressed as VO_{2peak} (ml·kg^{-1}·min^{-1}), as well as in metabolic equivalents (METs).

OUTCOMES AND FOLLOW-UP. All participants were followed from the date of their CPX test until the date of death or through July 2017 for all-cause mortality or December 2015 for disease-specific mortality. The National Death Index was the primary data source for obtaining vital status between 1979 and 2015, providing date of death and cause of death. Deaths occurring before 1979 (n = 2) were confirmed using the Social Security Death Index and obituary review, and after 2015 (n = 16) were confirmed primarily by obituary review. The underlying cause of death determined from the National Death Index report was

TABLE 2 Descriptive Characteristics of the Survivors and Deceased Participants Within the BALL ST Cohort

	Men		Women	
	Survivors (n = 1,802)	Deceased (n = 524)	Survivors (n = 1,608)	Deceased (n = 203)
Age, yrs	40.9 ± 11.2*	49.2 ± 10.6	41.6 ± 12.5*	53.1 ± 11.2
VO_{2peak}, ml·kg^{-1}·min^{-1}	38.2 ± 10.8*	33.2 ± 9.1	28.2 ± 8.6*	25.1 ± 7.0
$VO_{2peak\text{-}predicted}$, ml·kg^{-1}·min^{-1}	45.3 ± 9.2*	38.8 ± 10.2	36.4 ± 9.3*	28.8 ± 8.4
$Watts_{peak}$ (n = 3,946)	211.2 ± 77.9*	134.6 ± 64.1	138.3 ± 57.1*	91.7 ± 41.2
BMI, kg/m^2	27.5 ± 5.1	27.0 ± 4.5	26.8 ± 6.4	26.0 ± 5.4
Waist circumference, cm	95.9 ± 13.6	96.2 ± 12.8	82.8 ± 14.5*	81.8 ± 13.9
Obesity	29*	25	31*	27
RHR, beats/min	67 ± 18	66 ± 14	70 ± 11*	71 ± 11
SBP, mm Hg	125 ± 13*	131 ± 16	117 ± 14*	126 ± 17
DBP, mm Hg	81 ± 9*	84 ± 10	75 ± 10*	79 ± 10
Hypertensive	30*	41	21*	36
Total cholesterol, mg/dl^{-1}	207 ± 44*	226 ± 46	198 ± 39*	221 ± 44
Dyslipidemia	64*	75	41*	58
Glucose, mg/dl^{-1}	98 ± 22	100 ± 26	93 ± 17*	98 ± 32
Diabetes	30*	33	21	23
Physical inactivity	56*	54	68*	64
Smoking	11*	20	8*	13
Follow-up, yrs	25.9 ± 12.3*	23.9 ± 10.4	22.9 ± 11.5	21.4 ± 10.4
Number of deaths		524		203
Number with CVD		162		50
Number with cancer		145		56

Values are mean ± SD or %, unless otherwise indicated. *Significantly different from deceased; $p < 0.05$.
CVD = cardiovascular disease; other abbreviations as in Table 1.

coded according to the International Classification of Diseases (ICD)-9th revision, before 1999 and the ICD-10th revision, from 1999 to 2015. CVD mortality was defined by the ICD-9th revision codes 390.0-449.9 and ICD-10th revision codes I00.0-I78.9. Cancer mortality was defined by the ICD-9th revision codes 140.0-239.0 and ICD-10th revision codes C00.0-D49.9. For all other ICD codes, cause of death was classified as other (34,35).

STATISTICAL ANALYSIS. SPSS version 24 (IBM Corp., Armonk, New York) and SAS version 9.3 (SAS Inc., Cary, North Carolina) were used for all statistical analyses. Descriptive statistics were performed to summarize baseline characteristics of the participants and a univariate analysis of variance and chi-square goodness of fit test were used when appropriate to test for significant differences between sexes, CRF level, and vital status (living vs. deceased). Cox proportional hazard models were used to estimate hazard ratios (HRs) for all-cause mortality, as well as CVD and cancer-specific mortality for both sexes. The Cox models were estimated with CRF expressed continuously as VO_{2peak} (ml·kg^{-1}·min^{-1}), and then with VO_{2peak} measures categorized into low-fitness (≤33rd percentile), moderate-fitness (34th-66th percentiles), and high-fitness groups (≥67th percentile) using percentiles from the FRIEND (Fitness Registry and the Importance of Exercise National Database) (25). The FRIEND registry provides age-specific and sex-specific reference values for CPX-CRF for adults in the United States. Multiple Cox proportional hazard models were fit to the data, first with CRF as the lone predictor, and subsequently the continuous models were adjusted for age and sex (baseline model), and then further adjusted for examination year, and 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. The categorical models were first adjusted for age (baseline model), and then run multivariably adjusted, as presented above. For these categorical CRF models, the reference group was set to be individuals in the high-fit category. Cox proportional hazard models were also used to assess the relationship between predicted CRF and mortality. The coefficient estimating this relationship was then compared to the coefficient for CPX-CRF using a Cox proportional hazard model. Additionally, analyses were performed at 5, 10, and 25 years to further assess the predictive value of CRF for long-term mortality at various landmark years. In these landmark analyses the Cox models were estimated with CRF expressed continuously. To address the issue of competing nonrelated death when assessing disease-specific mortality, and thereby provide a more direct estimate of the relationship between CRF and disease-specific mortality, we removed cancer deaths in the analysis for CVD mortality and removed CVD deaths when conducting the cancer mortality analysis (36,37). The proportional hazards assumptions were satisfied, as regression analyses relating the Schoenfeld residuals to the time variable revealed no statistically significant relationship for either low-fitness or moderate-fitness groups or the covariates ($p > 0.05$).

RESULTS

Descriptive characteristics of the study population are presented in Tables 1 and 2. Overall, there were 72 deaths per 10,000 person-years. The all-cause mortality rates declined across fitness levels from approximately 80 deaths per 10,000 person-years in the low-fit group to 50 deaths per 10,000 person-years in the high-fit group. Results from the continuous Cox models appear in Table 3. Overall, VO_{2peak} was inversely associated with risk for all-cause, CVD,

and cancer mortality after adjusting for age and sex ($p < 0.05$) and remained significant after further adjusting for examination year and risk factors ($p < 0.01$).

The inverse relationship between VO_{2peak} and all-cause mortality remained significant for both sexes when assessed independently (HR: 0.965; $p < 0.001$ and HR: 0.967; $p < 0.05$, respectively) (Table 3). However, the association of VO_{2peak} with CVD and cancer mortality differed between sexes. A significant relationship was found between VO_{2peak} and CVD mortality in men after adjusting for age ($p < 0.01$) and remained significant in the multivariable adjusted model ($p < 0.001$). However, the association between VO_{2peak} and cancer mortality was nonsignificant. In women, the opposite was found. There was a significant relationship between VO_{2peak} and cancer mortality in the multivariable adjusted model ($p < 0.05$), but the relationship between VO_{2peak} and CVD mortality was nonsignificant.

Hazard plots illustrating the cumulative hazard of each fitness level over the follow-up period for all-cause, CVD, and cancer mortality are shown in Figure 1. Results from the categorical analyses are provided in Table 4. Participants in the low-fit group were 31%, 34%, and 34% more likely to die from all-causes, CVD, and cancer during the follow-up period than those in the high-fit ($p < 0.001$) group, respectively. After adjusting for examination year and traditional risk factors, the low-fit group was associated with 73% increased risk of all-cause mortality, and a more than 2-fold increased hazard for both CVD and cancer mortality ($p < 0.01$).

There was an inverse graded relationship between CRF level and the risk of all-cause, CVD, and cancer mortality ($p < 0.01$) in men and women when assessed independently (Table 4). Men categorized as low-fit had a 54%, 49%, and 46% greater likelihood of dying from all-causes, CVD, and cancer than high-fit men ($p < 0.001$) after adjusting for age, respectively. The strength of the association of low-CRF with all-cause and CVD mortality increased after further adjustment for examination year and risk factors (HR: 1.67 and HR: 2.94, respectively; $p < 0.01$).

The low-fit women had a higher risk of dying from all-causes, CVD, and cancer during follow-up than those with moderate-fitness and high-fitness. At any point in time, low-fit women had a 28%, 34%, and 34% increased risk of dying from all-causes, CVD, and cancer compared with high-fit women ($p < 0.01$), respectively. In women, this relationship remained significant for all-cause and cancer mortality in the multivariable model (HR: 1.63; $p < 0.05$ and HR: 3.94, $p < 0.01$, respectively).

TABLE 3 Hazard Ratios for Mortality Outcomes According to CRF

	Hazard Ratio (95% CI)	% Reduction/ ml·kg^{-1}·min^{-1} Increase	% Reduction/ MET Increase
All-cause mortality			
All			
Baseline model	0.967* (0.953-0.972)	3.3	11.6
Multivariable model	0.967* (0.950-0.980)	3.3	11.6
Men			
Baseline model	0.965* (0.956-0.994)	3.5	12.3
Multivariable model	0.965* (0.958-0.989)	3.5	12.3
Women			
Baseline model	0.967* (0.929-0.999)	3.3	11.6
Multivariable model	0.967 (0.956-1.005)	3.3	11.6
CVD mortality			
All			
Baseline model	0.963* (0.945-0.981)	3.7	13.0
Multivariable model	0.954* (0.932-0.987)	4.6	16.1
Men			
Baseline model	0.957* (0.953-0.990)	4.3	15.1
Multivariable model	0.943* (0.943-0.999)	5.7	20.0
Women			
Baseline model	0.989 (0.951-1.050)	1.1	3.9
Multivariable model	0.989 (0.940-1.076)	1.1	3.9
Cancer mortality			
All			
Baseline model	0.976† (0.954-0.991)	2.4	8.4
Multivariable model	0.960* (0.944-0.999)	4.0	14.0
Men			
Baseline model	0.978 (0.964-1.001)	2.2	7.7
Multivariable model	0.971 (0.956-1.012)	2.9	10.2
Women			
Baseline model	0.959 (0.928-1.021)	4.1	14.4
Multivariable model	0.918† (0.860-0.986)	8.2	28.7

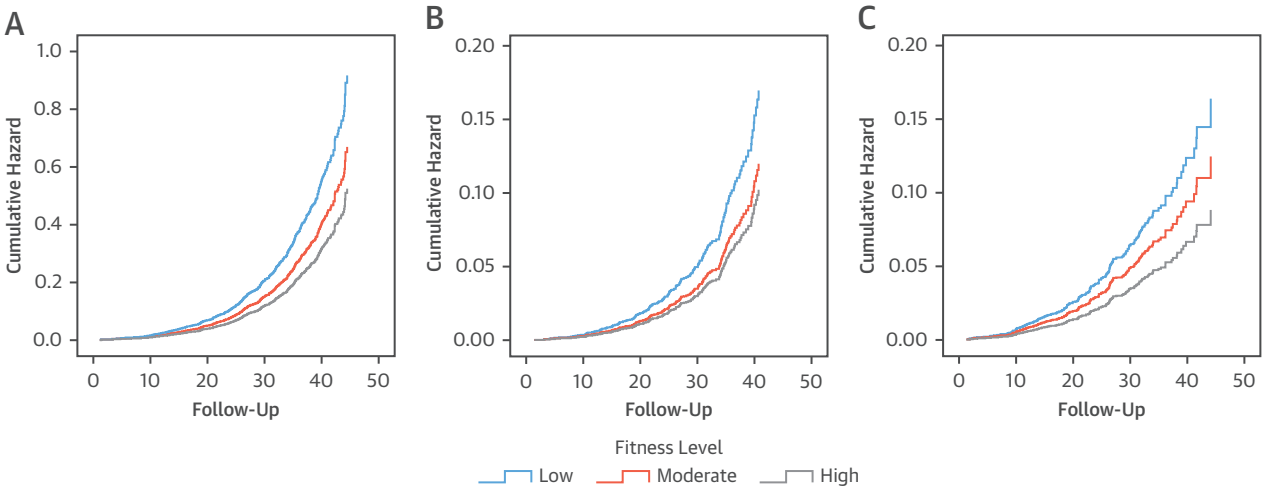
Values are VO_{2peak} (ml·kg^{-1}·min^{-1}). *Significant inverse relationship, $p < 0.01$. †Significant inverse relationship, $p < 0.05$. Baseline model adjusted for age in the sex-specific analyses with the addition of sex in the overall sample. Multivariable model adjusted for age, examination year, and traditional CVD risk factors for the sex-specific analyses with the addition of sex in the overall sample.

CI = confidence interval; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; MET = metabolic equivalent.

Results from the landmark analyses found CRF to be a significant predictor of long-term mortality at landmarks 5, 10, and 25 years (HRs: 0.981, 0.984, 0.993, $p \leq 0.01$, respectively) after adjusting for age and sex (Online Table 2). However, the relationship between CRF long-term mortality only remained statistically significant at 5-year and 10-year landmarks after multivariable adjustment (HR: 0.987; $p < 0.001$ and HR: 0.991; $p < 0.01$, respectively).

The relationship between mortality and measured CRF was of greater magnitude (both parameter estimates and HRs) than were the relationships between mortality and CRF_e and also mortality and Watts (Table 5).

FIGURE 1 Cumulative Hazard of All-Cause, Cardiovascular Disease, and Cancer Mortality by Cardiorespiratory Fitness Group



Hazard plots for **(A)** all-cause, **(B)** cardiovascular disease (CVD), and **(C)** cancer mortality according to cardiorespiratory fitness (CRF) level. Low, moderate, and high CRF corresponds to ≤33rd, 34th–66th, and ≥67th percentiles of Fitness Registry and the Importance of Exercise National Database normative values. Low-fitness was associated with increased risk of all-cause, CVD, and cancer mortality compared to both moderate-fitness and high-fitness groups over the follow-up period.

DISCUSSION

This study showed that CPX-CRF has a significant inverse association with all-cause, CVD, and cancer mortality in apparently healthy men and women (**Central Illustration**). The results of this study align with recommendations of recent scientific and policy statements (1,15,17) that regard CRF as a clinical vital sign and highlight the importance of accurately quantifying CRF in apparently healthy adults given its diagnostic and prognostic capabilities. Previous studies have established a relationship between CRF_e and mortality, using a variety of indirect methods and thresholds to define fitness levels (5,6,38–40). This has led to variability in the reported degree of risk reduction associated with improving CRF_e and the magnitude of risk associated with low-fitness. A recent scientific statement and updated review have summarized the survival benefit per MET increment ranging from approximately 10% to 30% when using CRF_e (1,21). Whereas the current results, using CPX-CRF and the FRIEND reference standards provides accurate and age-specific and sex-specific representative classifications of CRF, which may allow for a clearer understanding of the risk associated with low-CRF.

The overall results suggest that obtaining a moderate fitness level for one's age and sex is associated with lower risk of early mortality from all-causes, CVD, and cancer compared with those with low-fitness, with greater magnitude of the association observed when obtaining high fitness. We also observed that a 1-MET increment in CRF was associated with a considerably lower all-cause (12%), CVD (16%), and cancer mortality (14%) independent of traditional risk factors. This has important public health relevance as participation in regular exercise meeting current recommendations has been shown to be capable of increasing CRF by 1 to 2 METs, especially for those with low fitness (1,17,30). This emphasizes the importance of assessing CRF to identify those with low fitness as it is an important risk marker, and prescribing regular physical activity and/or exercise training as a preventative treatment for these patients.

Given the known differences in CRF between men and women, we performed sex-specific analyses, as opposed to only adjusting for sex in the overall model, which has been a more common approach in past studies. Multivariable adjusted results showed high-fitness women had 63%, 22%, and approximately 4-fold lower all-cause, CVD, and cancer mortality compared with low-fitness when women were examined independently. This strong inverse relationship between fitness and cancer mortality risk corresponded to a 29% lower risk per each 1-MET improvement in CRF. Past studies assessing the relationship between CRF_e and cancer mortality in women have shown conflicting results, with some observing an

inverse relationship and others finding no association (41,42). Although it cannot be ruled out that discrepancies in the results between these studies are due to differences in baseline characteristics of the cohorts, it is plausible that the different criteria for defining fitness thresholds and methods used in assessing CRF_e between studies played a role. The current findings using CPX-CRF, along with interpretations based on the FRIEND registry age-specific and sex-specific reference standards (25) rather than cohort-specific reference values, provides the basis for a better understanding of the relationship between CRF and cancer mortality risk in women.

In regard to CVD mortality, women with low fitness had a significantly higher risk compared with high-fitness women after adjustment for age; however, further adjustment for examination year and risk factors found the relationship to be nonsignificant. To further investigate these findings between CRF and CVD mortality in women, the women who died from CVD were separately categorized into CRF groups based on the age-specific and sex-specific FRIEND percentiles (25). The distribution of the women at baseline were similar between the three fitness groups; however, the low-fitness women were on average 6 years younger at baseline and had a significantly shorter follow-up period compared with those with moderate and high fitness (low: 16 ± 11 years; moderate: 20 ± 10 years; high: 22 ± 8 years; $p < 0.05$), suggesting that low-fitness women may be more likely to die from CVD-related causes at an earlier age compared with those with higher fitness levels.

In men, the strongest relationship was seen between CRF and CVD mortality, where low-fitness men had a 3-fold greater risk for CVD mortality compared with high-fitness men in the multivariable adjusted analysis. Further, each 1-MET increment in CRF was associated with a 20% lower CVD mortality risk. This lower risk was similar to results found by Laukkanen et al. (11) who also examined this association in apparently healthy men using the CPX test and found a 22% lower risk for CVD mortality per 1-MET increment in CRF. However, the wider age distribution of the current cohort and longer follow-up period helps to advance our understanding of CRF's influence on CVD mortality across time in men.

Finally, we assessed the relationship of CRF, CRF_e, and Watts with mortality. Although the magnitude of the relationship with mortality was greater with CRF than both CRF_e and Watts, all 3 measures of exercise capacity are important. Laukkanen et al. (11), the only other cohort with CPX-CRF, reported peak cycle test workload to have analogous findings to those from directly measured values when predicting sudden cardiac events. Recent reports (1,21) have identified multiple prediction nonexercise equations, protocol specific equations for exercise time, and other methods that can be used to derive CRF_e. Future investigations are needed to more comprehensively evaluate the comparability of CRF and CRF_e as indicators of both morbidity and mortality.

TABLE 4 Hazard Ratios for Mortality Outcomes According to Cardiorespiratory Fitness Level

	Hazard Ratio (95% CI)		
	Low Fit	Moderate Fit	High Fit (Reference Group)
All-cause mortality			
All			
Baseline model	1.31* (1.20–1.42)	1.06 (0.98–1.15)	1.00
Multivariable model	1.73* (1.20–3.50)	1.32† (1.03–1.73)	1.00
Men			
Baseline model	1.54* (1.36–1.74)	1.12† (1.00–1.26)	1.00
Multivariable model	1.67* (1.18–2.38)	1.31 (0.94–1.83)	1.00
Women			
Baseline model	1.28* (1.15–1.43)	1.03 (0.92–1.15)	1.00
Multivariable model	1.63† (1.02–2.47)	1.37 (0.89–2.03)	1.00
CVD mortality			
All			
Baseline model	1.34* (1.07–2.01)	1.11† (1.01–1.34)	1.00
Multivariable model	2.27* (1.20–3.49)	1.63† (1.00–2.65)	1.00
Men			
Baseline model	1.49* (1.31–3.01)	1.10 (0.90–2.11)	1.00
Multivariable model	2.94* (1.44–5.37)	1.84† (1.01–3.35)	1.00
Women			
Baseline model	1.34* (1.05–1.95)	1.12 (0.50–2.56)	1.00
Multivariable model	1.22 (0.46–2.96)	1.35 (0.59–2.92)	1.00
Cancer mortality			
All			
Baseline model	1.34* (1.02–1.92)	1.08 (0.85–1.28)	1.00
Multivariable model	2.07* (1.18–3.36)	1.49 (0.93–2.43)	1.00
Men			
Baseline model	1.46* (1.11–2.58)	1.07 (0.82–1.97)	1.00
Multivariable model	1.38 (0.82–1.97)	1.24 (0.70–2.22)	1.00
Women			
Baseline model	1.34* (1.29–1.93)	1.08 (0.92–1.36)	1.00
Multivariable model	3.94* (1.41–8.96)	2.13b (1.09–4.78)	1.00

Low, moderate, and high CRF corresponds to ≤33rd, 34-66th, and ≥67th percentiles of FRIEND normative values. *Significantly different than High and Moderate Fitness at a level of $p \leq 0.05$. †Significantly different than the High Fitness, $p \leq 0.05$. Baseline model adjusted for age and sex for the overall sample and adjusted for age only in the sex-specific analyses. Multivariable model was adjusted for age, examination year, and traditional CVD risk factors for the sex-specific analyses with the addition of sex in the overall sample.

Abbreviations as in Tables 1 to 3.

STUDY STRENGTHS AND LIMITATIONS. This study had several notable strengths. First, CRF was measured using CPX testing, the gold standard method, and thus may improve classification of an individual's mortality risk. The use of the FRIEND registry, which standardized our CPX-CRF interpretations by age-specific and sex-specific percentiles (25,26), provided a straightforward method to

TABLE 5 Contrasting Mortality Outcomes Between Measured and Predicted VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$) and Peak Watts

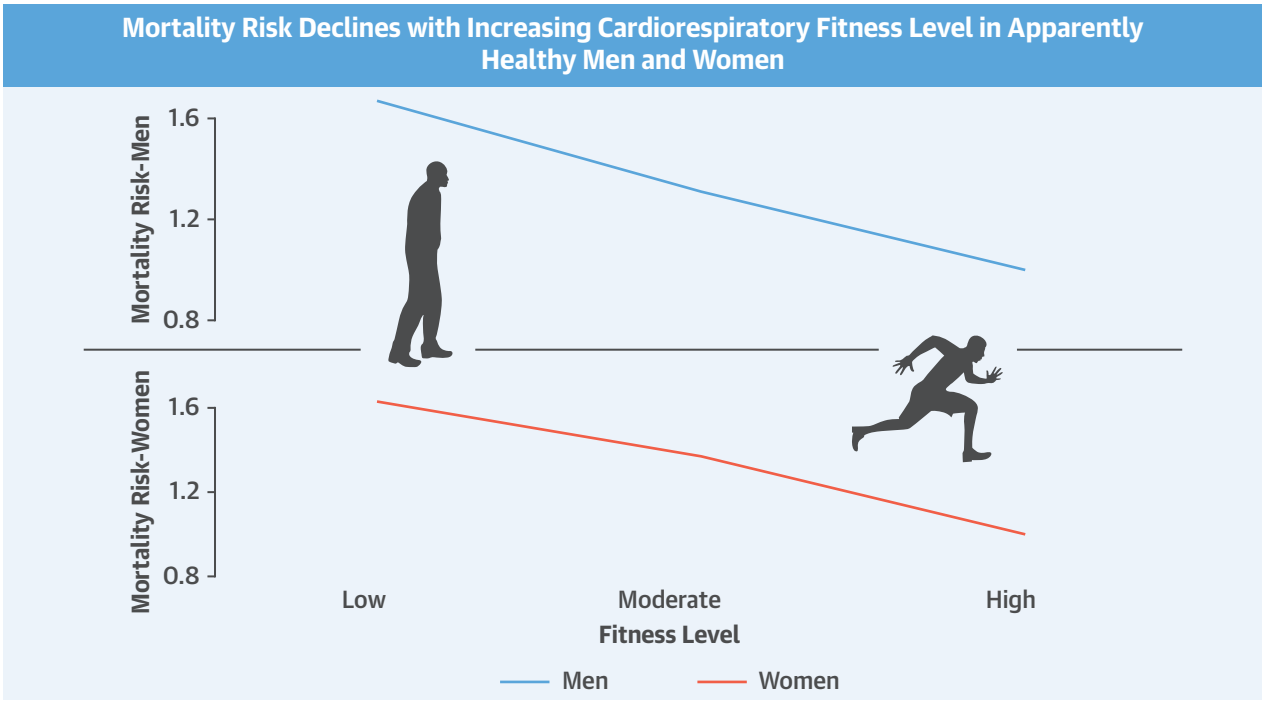
Mortality	N	Parameter Estimate	Hazard Ratio (95% CI)	p Value
Measured VO_{2peak}	4,063			
All-cause		−0.02722	0.973 (0.970-0.977)	<0.0001
CVD		−0.03091	0.971 (0.967-0.974)	<0.0001
Cancer		−0.02981	0.970 (0.966-0.973)	<0.0001
Predicted VO_{2peak}	4,063			
All-cause		−0.00309	0.997 (0.994-1.0)	0.0611
CVD		−0.00611	0.971 (0.967-0.974)	0.0002
Cancer		−0.00741	0.970 (0.966-0.973)	<0.0001
$Watts_{peak}$	3,946			
All-cause		−0.00374	0.996 (0.995-0.998)	<0.0001
CVD		−0.00594	0.994 (0.992-0.996)	<0.0001
Cancer		−0.00413	0.996 (0.994-0.998)	0.0003

Abbreviations as in Tables 1, 3, and 4.

interpret an individual's mortality risk. The importance of standardizing fitness classifications was recently emphasized in a report by Kokkinos et al. (43). In addition, our large sample size was predominantly from Muncie, Indiana, known as Middletown, U.S.A., which has been considered the average or typical American small city (44). Therefore, our sample may be representative of the population that many clinicians see on a regular basis, with a milieu of risk factors, as well as wide distribution of age and fitness levels. Future work is needed to confirm these findings in populations from diverse ethnic and socioeconomic backgrounds that are known to influence health outcomes. Further, the long follow-up period better captures the association between CRF and all-cause, and disease-specific mortality over time; this study had a mean follow-up of 24.2 years with a range of 1 to 49 years, enhancing our understanding of this relationship. Last, this study assessed the association between CPX-CRF and all-cause, CVD, and cancer-specific mortality in apparently healthy men and women. The sex-specific results provide a unique strength as few studies have assessed this relationship separately for men and women, despite known differences in CRF between sexes.

Limitations included a >90% non-Hispanic white cohort. Additionally, the lower number of deaths in women, specifically CVD-related deaths, decreased

CENTRAL ILLUSTRATION Directly Measured Cardiorespiratory Fitness for Mortality Risk Prediction



Imboden, M.T. et al. J Am Coll Cardiol. 2018;72(19):2283–92.

There is a significant reduction in mortality risk with increasing cardiorespiratory fitness level in both men and women. This graded relationship is independent of traditional cardiovascular disease risk factors.

statistical power; therefore, results related to CVD mortality in women should be interpreted with caution. Future studies should assess the relationship between CPX-CRF and all-cause and diseases-specific mortality in a cohort of women with more mortality endpoints as well as in a greater distribution of racial and ethnic backgrounds to more accurately guide clinical decisions in those populations. Furthermore, the study cohort was all self-referred and was limited to those who were able to achieve maximal effort on a treadmill exercise test. Another limitation is that there have been changes in health care over the past 4 decades, with the development of new medications, medical devices, and procedures that have helped to increase life-expectancy. How these changes may have influenced the relationship observed between CRF and mortality in this study is uncertain. Finally, information on changes in lifestyle behaviors during the follow-up period were not available. Future research should assess the influence of the acute change in CPX-CRF, due to becoming exercise trained, on mortality in a large, diverse cohort of men and women.

CONCLUSIONS

In 2016, the American Heart Association issued 2 scientific statements, 1 that recognized the importance of accurately assessing CRF and examining the clinical impact of CPX testing as a high research priority and the other advocating CRF be measured as a clinical vital sign (1,16). The results from the present study confirm that CRF has important clinical merit and would have value as a vital sign in patient assessment. The use of CPX-CRF would improve the accuracy of assessing low fitness when determining patient risk. Additionally, CPX has become increasingly accepted over recent years as associated factors, such as cost and technician training are less challenging. Further, there is added value in the unique clinical information that CPX provides, including other measures such as ventilatory threshold, exercise ventilatory power, and circulatory power, and allowing improved accuracy in the intensity component of an exercise prescription (15,45). Future research should assess the relationship of these additional clinical measures obtained by CPX testing as they may further aid in the prediction of outcomes and inform clinical decisions.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Cardiorespiratory fitness, as measured by cardiopulmonary exercise testing, is a strong predictor of all-cause, cardiovascular, and cancer mortality in apparently healthy men and women, and interpretation of the data in the context of age-specific and sex-specific reference standards provides a straightforward method for assessment of individual mortality risk.

TRANSLATIONAL OUTLOOK: Future studies should assess the predictive value of other data derived from cardiopulmonary exercise testing to improve cardiovascular risk assessment.

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KEY WORDS cancer mortality, cardiovascular disease, exercise testing, physical fitness

APPENDIX For supplemental tables, please see the online version of this paper.