Cardiorespiratory Optimal Point Is a Submaximal Exercise Test Variable and a Predictor of Mortality Risk

THE BALL STATE ADULT FITNESS LONGITUDINAL LIFESTYLE STUDY (BALL ST)

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Purpose: The cardiorespiratory optimal point (COP) is the minimum ventilatory equivalent for oxygen. The COP can be determined during a submaximal incremental exercise test. Reflecting the optimal interaction between the respiratory and cardiovascular systems, COP may have prognostic utility. The aim of this investigation was to determine the relationship between COP and all-cause mortality in a cohort of apparently healthy adults.

Methods: The sample included 3160 apparently healthy adults (46% females) with a mean age of 44.0 ± 12.5 yr who performed a cardiopulmonary exercise test. Cox proportional hazards models were performed to assess the relationship between COP and mortality risk. Prognostic peak oxygen uptake (VO2peak) and COP models were compared using the concordance index.

Results: There were 558 deaths (31% females) over a follow-up period of 23.0 ± 11.9 yr. For males, all Cox proportional hazards models, including the model adjusted for traditional risk factors and VO2peak, had a positive association with risk for mortality (P < .05). For females, only the unadjusted COP model was associated with risk for mortality (P < .05). The concordance index values indicated that unadjusted COP models had lower discrimination compared with unadjusted VO2peak models (P < .05) and VO2peak did not complement COP models (P ≥ .13).

Conclusions: Cardiorespiratory optimal point is related to all-cause mortality in males but not females. These findings suggest that a determination of COP can have prognostic utility in apparently healthy males aged 18-85 yr, which may be relevant when a maximal exercise test is not feasible or desirable.

Key Words: cardiopulmonary exercise testing • prognosis • ventilatory expired gas

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KEY PERSPECTIVE

What is novel:
• This report finds that cardiorespiratory optimal point (COP), which reflects the optimal interaction between the respiratory and cardiovascular systems, is related to all-cause mortality in apparently healthy males but not in females.
• The addition of peak oxygen uptake did not complement the fully adjusted COP models in predicting mortality in either males or females.

What are the clinical and/or research implications:
• These findings highlight that a determination of COP can have prognostic utility in apparently healthy males.
• Considering COP can be measured from a submaximal exercise test, COP could be assessed when a maximal exercise test is not feasible or desirable in males.

Cardiopulmonary exercise testing (CPX) is recommended in routine clinical practice to improve patient management and risk stratification.1 The traditional variable of interest from CPX, and the most commonly used as an indicator of health, is maximum or peak oxygen uptake (VO2peak).1,2 A plethora of research indicates that high VO2peak levels are associated with decreased risk for mortality and noncommunicable diseases such as diabetes, cardiovascular disease (CVD), and some forms of cancer.1,3 Other variables collected during CPX have received less attention but may also have prognostic utility. Of particular interest are variables that do not require a patient to perform a maximal effort since this is speculated to be a reason why CPX is not commonly performed in clinical practice.1 One such submaximal variable is cardiorespiratory optimal point (COP).

The COP is defined as the minimum ventilatory equivalent for oxygen (ventilation divided by oxygen uptake [VE/VO2]) at any given minute during an incremental exercise test.4 Since COP reflects the optimal interaction between the respiratory and cardiovascular systems, lower levels are considered better. Furthermore, the VE/VO2 follows a U-shaped curve during increasing exercise intensities meaning that COP occurs at submaximal intensities. Accordingly, COP can easily be determined from a submaximal exercise test with ventilatory gas analysis5,6 considering VE/VO2 like the ventilatory equivalent for carbon dioxide, is a standard and well-recognized measurement.7,8 Researchers have begun to examine how COP may be related to health outcomes. One study involving a cohort

Prevention
consisting predominantly of individuals with CVD demonstrated significant associations between COP and all-cause mortality. When the healthy participants from the study were analyzed separately, the Kaplan-Meier survival curves suggested that the group with the lowest COP values had greater survival rates, although a low sample size was a limitation in this subsample analysis. Other studies have reported COP to be significantly associated with mortality in patients with heart failure or have reported statistically nonsignificant trends between COP and mortality in patients with transposition of the great arteries. Finally, studies on Finnish males with and without CVD found COP to be a significant predictor of sudden cardiac death, CVD mortality, and all-cause mortality.

Previous research highlights the potential prognostic utility of COP; however, additional research with larger sample sizes of males and females is needed to substantiate this relationship in apparently healthy adults. To date, previous research has focused primarily on the relationship between COP and mortality in males and/or those with CVD. Sex differences in COP have been reported, which necessitates separate analyses along with further exploration of the relationship between COP and mortality in healthy populations. Furthermore, research is needed to determine whether COP models have similar risk discrimination compared with VO\textsubscript{peak} models and whether VO\textsubscript{peak} complements COP in predicting health outcomes in apparently healthy populations. Thus, the purpose of this study was to evaluate the relationship between COP and all-cause mortality in a cohort of apparently healthy males and females. We hypothesized that COP would be a significant predictor of mortality in males and females, and VO\textsubscript{peak} would complement COP in predicting mortality.

METHODS

Data from the Ball State Adult Fitness Longitudinal Lifestyle Study (BALL ST) cohort were used for this analysis. The sample included apparently healthy adults aged 18-85 yr who performed a comprehensive health and fitness assessment between January 1, 1973, and December 31, 2018. The BALL ST participants were either self-referred to a community-based exercise program or were research participants in studies who provided written informed consent for their data to be used for research. The participants were defined as apparently healthy if they were free from known CVD (eg, history of cardiac arrest, coronary artery disease, heart failure, myocardial infarction, stroke, and peripheral artery disease) and lung disease (eg, chronic obstructive pulmonary disease and emphysema). In addition, the participants were excluded if they were taking a β-blocker medication, did not use the treadmill as the mode of exercise during CPX, did not achieve a respiratory exchange ratio of ≥1.0 during CPX, had <1 yr of follow-up, or were missing data for the variables of interest. The protocol for this study was reviewed by the Ball State University Institutional Review Board and determined to be exempt as only de-identified data were used.

ASSESSMENT OF COP

To determine COP, the participants performed CPX on a treadmill using protocols such as the Bruce, Ball State University Bruce Ramp, modified Balke-Ware, or an individualized protocol. The treadmill protocol was selected on the basis of self-reported physical activity level with the goal of participants achieving maximal effort within 8-12 min. During each CPX, the participants were encouraged to exercise to volitional fatigue. Ventilatory expired gas measurements were collected using commercially available computerized indirect calorimetry systems as described previously. The indirect calorimetry systems were calibrated prior to exercise testing according to manufacturer instructions. Ventilatory expired gas data were averaged every 20 or 30 sec. In agreement with the original research that introduced COP as a potential prognostic variable, COP was defined as the lowest VE/VO\textsubscript{2} value calculated from data averaged every minute during CPX. The VO\textsubscript{peak} was determined by averaging the highest two to three consecutively measured VO\textsubscript{2} values occurring in the last 2 min of the test. Peak heart rate was determined as the highest sinus-node rate (average of five consecutive beats) recorded on the electrocardiogram during the final minutes of CPX.

ASSESSMENT OF RISK FACTORS

Prior to CPX, the participants reported to the laboratory in a fasted state while having refrained from exercise, caffeine, and alcohol for ≥8 hr. Resting blood pressure was measured in the seated position following a 5-min rest period. Height and weight were measured without shoes and while wearing minimal clothing (light sweats or shorts and t-shirt) and then used to calculate body mass index. Waist circumference was determined in the horizontal plane at the narrowest circumference of the abdominal region. Venous blood samples were taken by a trained phlebotomist to determine blood lipid profile and fasting blood glucose.

The participants also completed a health-history questionnaire, which provided self-reported smoking status, physical activity status, medication use, and medical history. From the questionnaire, the participants were categorized as a smoker if they used cigarettes or quit smoking within the past year. Self-reported physical activity data were collected using the BALL ST scale, which captures both lifestyle and occupational physical activity. The presence of other risk factors (obesity, hypertension, dyslipidemia, prediabetes/diabetes, and physical inactivity) was defined according to the current American College of Sports Medicine criteria while the presence of metabolic syndrome was defined according to the National Cholesterol Education Program (NCEP-ATP III).

OUTCOMES AND FOLLOW-UP

All participants were followed from the date of CPX until the date of death or through December 31, 2019. The National Death Index was the primary source of mortality status although some deaths were determined by the Social Security Death Index and were confirmed by obituary review.

STATISTICAL ANALYSIS

Analyses were performed in R version 3.6.3 (R Core Team). Descriptive statistics were performed to summarize baseline characteristics of the participants. Age- and sex-specific cardiorespiratory fitness percentiles were determined based on the basis of VO\textsubscript{peak} using the 2021 reference standards from the Fitness Registry and the Importance of Exercise National Database (FRIEND). To test for differences between sexes and mortality status (survivor vs deceased), independent samples t tests and χ\textsuperscript{2} tests were performed when appropriate. Cox proportional hazards models were used to estimate hazard ratios and evaluate the relationship between COP and all-cause mortality. Multiple Cox proportional hazards models were fit to the following data: (1) COP unadjusted;
(2) COP adjusted for age and sex for the overall cohort and age only in the sex-specific models; (3) COP further adjusted for risk factors (obesity, hypertension, dyslipidemia, diabetes, physical inactivity, and smoking status), which were categorized by the presence (1) or absence (0) of each risk factor; and (4) COP further adjusted for VO_{2peak}.

To compare the predictive capability of COP with that of VO_{2peak}, the same Cox proportional hazards models (models 1-3) were fit for VO_{2peak} (mL·kg⁻¹·min⁻¹) and then compared with the respective COP models using the concordance index. Furthermore, the fully adjusted Cox proportional hazards models for COP were compared with the COP + VO_{2peak} model to determine the complementary benefit of VO_{2peak} in predicting mortality risk with a COP model. The fully adjusted VO_{2peak} model was also compared with the COP + VO_{2peak} model to determine the complementary benefit of COP in predicting mortality risk with a VO_{2peak} model.

To assess the assumption of proportional hazards underlying the Cox models, Schoenfeld residuals were examined. The relationships between the Schoenfeld residuals and the model covariates were either not statistically significant (P > .05), indicating that the proportional hazards assumption was met, or the fit line of the plots of the residuals fell within the CI bounds for a horizontal linear trend suggesting that statistically significant violations were not problematic. Statistical significance was set at P < .05, two-tailed. Data are presented as mean ± SD.

RESULTS
Descriptive characteristics of the sample are shown in Table 1. The sample included a total of 3160 participants (46% females) with an age of 44.0 ± 12.5 yr. The mean COP was 24.6 ± 4.9 and occurred at a mean of 35 ± 20% of total CPX time. Table 2 provides a comparison of the descriptive characteristics for participants identified as either living or deceased at the time of follow-up. A total of 18% of the participants (n = 558, 31% females) died during the follow-up period of 23.0 ± 11.9 yr. Cardiorespiratory optimal tidal volume was significantly lower in participants identified as living compared with deceased at the time of follow-up (24.3 ± 4.7 and 26.0 ± 5.4, respectively).

Results from the Cox proportional hazards models assessing risk for mortality are shown in Table 3. Overall, when analyzing across the whole study sample, COP had a significant positive association with risk for mortality in the unadjusted model (model 1, P < .05), after adjusting for age, sex, and test year (model 2, P < .05), and remained significant following further adjustments for risk factors (model 3, P < .05). When adjusting for VO_{2peak} (model 4), the associations were no longer statistically significant. For males, each Cox proportional hazards model, including the model adjusted for VO_{2peak}, had a significant positive association with risk for mortality (P < .05). For females, only the unadjusted COP model (model 1) was significantly associated with risk for mortality (P < .05).

Significant inverse relationships were observed between VO_{2peak} and mortality (summarized in Table 3). The concordance values for the unadjusted VO_{2peak} models were significantly greater (P < .05) than those for the unadjusted COP models (model 1) within the whole sample as well as the sex-specific analyses. Concordance values for the other models were not statistically different. Table 4 presents the concordance values for the fully adjusted COP models (model 3), fully adjusted VO_{2peak} models (model 3), and the same fully adjusted COP + VO_{2peak} models (model 4). For each analysis, the concordance did not improve to a statistically significant level when the models included both COP and VO_{2peak} (P ≥ .13).

DISCUSSION
The COP can be measured from a submaximal exercise test, making it a potentially valuable tool for clinicians. Thus, the present study examined the prognostic utility of COP in apparently healthy males and females. Within males, as hypothesized, COP had a significant positive association with all-cause mortality, similar to findings of previous research on different cohorts.6–10 However, contrary to our hypothesis, significant relationships between COP and mortality were not observed in females following adjustments for potential confounders. In addition, the concordance index values indicated that VO_{2peak} was not a better discriminant of risk compared with COP. When examining the benefit of including both COP and VO_{2peak} in prediction models, the concordance index indicated no significant improvement over either the fully adjusted COP model or VO_{2peak} model. Overall, these findings suggest that COP may have prognostic utility within apparently healthy males, particularly when accurate assessment of VO_{2peak} is not available or feasible.

Prediction models using COP were related to mortality in males independent of traditional risk factors, including VO_{2peak}. There were sex differences in the predictive capability of COP though, as only the univariate COP model was significantly associated with mortality in females. Similar null results were also found for VO_{2peak} within females, comparable with previous research.4,22–23 These findings add to other reports of sex differences in the prognostic utility of CPX variables.4,22–24 The reason for these differences is not well established because of a dearth of research on the prognostic utility of CPX variables in healthy females. For COP, previous research has shown that females have a greater cost of ventilation,21,26 which may explain their higher COP values and therefore influence the prognostic utility of COP compared with males. Nonetheless, the results from the present study suggest that in females the prognostic contribution from the other model covariates outweighs those from COP or VO_{2peak}. Although additional research is needed to better understand the sex differences in predicting mortality risk with COP, these findings highlight the need to continue including females when examining the utility of CPX variables as sex differences can exist.

The concordance index values indicated that the fully adjusted COP models did not statistically differ compared with the fully adjusted VO_{2peak} models. Furthermore, VO_{2peak} did not complement COP models and COP did not complement VO_{2peak} models. These findings suggest that determinations of COP alone could be beneficial when a CPX determination of VO_{2peak} is not feasible or desirable as VO_{2peak} did not improve risk discrimination. However, the present findings contrast with previous research, which found that VO_{2peak} was a better risk predictor than COP and reported improved discrimination with VO_{2peak} + COP models.6,14 Of note, the cohorts in the previous research included individuals with CVD, which may have influenced the strength of the relationships. Slightly different statistical analyses and model covariates may also explain some of the differences. Further research is needed to elucidate the potential difference in risk discrimination between COP and VO_{2peak} and explore the possible benefit of COP + VO_{2peak} models with a focus on apparently healthy populations.

Of note, the mean COP values in the present study were similar to those in previous reports on Brazilian and Finnish
Table 1
Descriptive Characteristics of the Cohort

|                          | All (n = 3160) | Males (n = 1707) | Females (n = 1453) |
|--------------------------|---------------|------------------|-------------------|
| Age, yr, n               | 44.0 ± 12.5   | 43.9 ± 12.1      | 44.0 ± 12.9       |
| 18-29                    | 443           | 216              | 227               |
| 30-39                    | 729           | 413              | 316               |
| 40-49                    | 914           | 517              | 397               |
| 50-59                    | 725           | 386              | 339               |
| 60-69                    | 291           | 144              | 147               |
| 70-85                    | 58            | 31               | 27                |
| COP                      | 24.6 ± 4.9    | 23.8 ± 4.9       | 25.5 ± 4.8        |
| VO_{2peak}, mL·kg^{-1}·min^{-1} | 32.8 ± 10.5   | 37.0 ± 10.5      | 27.7 ± 8.0        |
| FRIEND VO_{2peak} percentile | 54.4 ± 25.5   | 55.3 ± 25.7      | 53.4 ± 25.2       |
| Peak HR, bpm             | 177.3 ± 15.5  | 178.0 ± 15.8     | 176.4 ± 15.1      |
| Peak RER                 | 1.19 ± 0.10   | 1.19 ± 0.10      | 1.18 ± 0.10       |
| Peak systolic BP, mm Hg  | 175.6 ± 23.8  | 184.5 ± 22.3     | 168.8 ± 21.9      |
| Peak diastolic BP, mm Hg | 80.7 ± 11.6   | 82.1 ± 12.0      | 79.3 ± 10.9       |
| BMI, kg·m^{-2}           | 27.2 ± 5.6    | 27.6 ± 4.9       | 26.8 ± 6.2        |
| Waist circumference, cm  | 89.7 ± 15.2   | 95.8 ± 13.3      | 82.9 ± 14.4       |
| Resting systolic BP, mm Hg | 121.4 ± 15.0  | 125.1 ± 14.3     | 117.0 ± 14.7      |
| Resting diastolic BP, mm Hg | 78.0 ± 10.3   | 80.9 ± 9.7       | 74.5 ± 9.9        |
| Fasting blood glucose, mg·dL^{-1} | 95.7 ± 19.5  | 98.5 ± 22.2      | 92.6 ± 15.3       |
| Triglycerides, mg·dL^{-1} | 132.5 ± 97.1  | 148.5 ± 114.9    | 114.5 ± 67.6      |
| Low-density lipoprotein cholesterol, mg·dL^{-1} | 120.5 ± 36.2  | 125.1 ± 37.4     | 116.1 ± 34.4      |
| High-density lipoprotein cholesterol, mg·dL^{-1} | 52.2 ± 15.2   | 46.1 ± 12.4      | 58.8 ± 15.2       |
| Total cholesterol, mg·dL^{-1} | 203.7 ± 42.9  | 207.4 ± 45.0     | 199.4 ± 40.0      |
| Metabolic syndrome       | 26            | 31               | 20                |
| Obesity                  | 31            | 30               | 33                |
| Hypertension             | 54            | 66               | 41                |
| Dyslipidemia             | 52            | 55               | 48                |
| Prediabetes/diabetes     | 28            | 34               | 21                |
| Smoker                   | 10            | 12               | 8                 |
| Inactive                 | 70            | 65               | 75                |
| Ethnicity                |               |                  |                  |
| Asian or Pacific Islander| 0.3           | 0.2              | 0.3               |
| Black, not of Hispanic origin | 0.4           | 0.2              | 0.6               |
| Hispanic                 | 0.0           | 0.1              | 0.0               |
| White, not of Hispanic origin | 99.3         | 99.5             | 99.0              |
| Follow-up, yr            | 23.0 ± 11.9   | 24.0 ± 12.0      | 21.8 ± 11.5       |

Abbreviations: BMI, body mass index; BP, blood pressure; COP, cardiopulmonary optimal point; FRIEND, Fitness Registry and the Importance of Exercise National Database; HR, heart rate; RER, respiratory exchange ratio; VO_{2peak}, peak oxygen uptake.

Data are presented as mean ± SD, or %.

Significantly different from males (P < .05).

In both of these previous studies though, COP was determined from CPX using cycle ergometers while the participants in the present study used a treadmill. These findings suggest that COP may not be influenced by exercise mode, as is observed when determining VO_{2peak}. In addition, COP may be consistent between countries, unlike the differences observed with VO_{2peak}. However, more research is needed on the potential consistency of COP across
Table 2
Descriptive Characteristics of the Survivors and Deceased Participants Within the Cohorta

| Age, yr, n | Survivors (n = 2602) | Deceased (n = 558) | Survivors (n = 1323) | Deceased (n = 384) | Survivors (n = 1279) | Deceased (n = 174) |
|-----------|---------------------|-------------------|---------------------|-------------------|---------------------|-------------------|
| 18-29     | 42.4 ± 12.1         | 51.3 ± 11.1b      | 42.1 ± 11.7         | 50.4 ± 11.0b      | 42.7 ± 12.6         | 53.4 ± 11.2b      |
| 30-39     | 432                 | 11                | 209                 | 7                 | 223                 | 4                 |
| 40-49     | 660                 | 69                | 359                 | 54                | 301                 | 15                |
| 50-59     | 746                 | 168               | 393                 | 124               | 353                 | 44                |
| 60-69     | 543                 | 182               | 261                 | 125               | 282                 | 57                |
| 70-85     | 194                 | 97                | 88                  | 56                | 106                 | 41                |
|          | 27                  | 31                | 13                  | 18                | 14                  | 13                |
| COP       | 24.3 ± 4.7          | 26.0 ± 5.4a       | 23.3 ± 4.6          | 25.6 ± 5.3b       | 25.3 ± 4.6          | 26.9 ± 5.5b       |
| VO2peak, mL·kg⁻¹·min⁻¹ | 33.1 ± 10.7 | 31.2 ± 9.2b       | 37.9 ± 10.7         | 34.0 ± 9.0b       | 28.1 ± 8.2          | 25.3 ± 6.4b       |
| FRIEND VO2peak percentile | 53.9 ± 25.5 | 56.7 ± 25.4b       | 55.1 ± 25.7         | 55.9 ± 25.9       | 52.7 ± 25.3         | 58.4 ± 24.4b       |
| Peak HR, bpm | 178.5 ± 15.0       | 171.3 ± 16.4b     | 179.7 ± 15.2        | 172.2 ± 16.3b     | 177.3 ± 14.6        | 169.2 ± 16.6b     |
| Peak RER  | 1.19 ± 0.10         | 1.17 ± 0.11b      | 1.20 ± 0.10         | 1.18 ± 0.10b      | 1.18 ± 0.10         | 1.15 ± 0.11b      |
| Peak systolic BP, mm Hg | 174.1 ± 23.3       | 188.7 ± 24.5b     | 182.9 ± 21.9        | 194.7 ± 22.3b     | 166.0 ± 21.6        | 177.2 ± 24.5b     |
| Peak diastolic BP, mm Hg | 80.1 ± 11.3        | 86.2 ± 12.3b      | 81.4 ± 11.7         | 86.7 ± 13.1b      | 78.9 ± 10.8         | 85.2 ± 10.6b      |
| BMI, kg·m⁻² | 27.3 ± 5.7          | 26.7 ± 4.9b       | 27.7 ± 5.0          | 27.2 ± 4.6        | 26.9 ± 6.3          | 25.8 ± 5.3b       |
| Waist circumference, cm | 89.4 ± 15.3        | 91.0 ± 14.7b      | 95.8 ± 13.5         | 95.8 ± 12.7       | 83.2 ± 14.5         | 81.2 ± 13.6       |
| Resting systolic BP, mm Hg | 120.0 ± 14.6       | 127.7 ± 15.6b     | 123.8 ± 13.6        | 129.5 ± 15.7b     | 116.1 ± 14.5        | 123.6 ± 14.8b     |
| Resting diastolic BP, mm Hg | 77.2 ± 10.1         | 81.6 ± 10.1b      | 80.3 ± 9.6          | 83.0 ± 9.8b       | 74.0 ± 9.8          | 73.8 ± 10.0b      |
| Fasting blood glucose, mg·dL⁻¹ | 95.4 ± 18.8        | 97.3 ± 22.5b      | 98.1 ± 21.4         | 100.1 ± 24.9      | 92.7 ± 15.4         | 91.4 ± 14.7       |
| Triglycerides, mg·dL⁻¹ | 130.7 ± 95.9        | 141.4 ± 102.2b    | 147.1 ± 116.1       | 153.8 ± 110.6     | 114.2 ± 66.2        | 116.5 ± 77.3      |
| Low-density lipoprotein cholesterol, mg·dL⁻¹ | 118.8 ± 35.3        | 138.2 ± 39.8b     | 122.6 ± 35.8        | 143.0 ± 43.1b     | 115.3 ± 34.6        | 128.4 ± 29.7b     |
| High-density lipoprotein cholesterol, mg·dL⁻¹ | 52.4 ± 15.3        | 51.0 ± 14.6b      | 46.1 ± 12.3         | 46.0 ± 12.5       | 58.6 ± 15.4         | 61.0 ± 13.4       |
| Total cholesterol, mg·dL⁻¹ | 199.6 ± 41.2       | 222.8 ± 45.6b     | 202.0 ± 42.7        | 225.8 ± 47.6b     | 197.0 ± 39.4        | 216.4 ± 40.4b     |
| Metabolic syndrome | 25                 | 30b               | 30                  | 35                | 20                  | 21                |
| Obesity   | 33                  | 26b               | 32                  | 27                | 34                  | 24b               |
| Hypertension | 51                 | 70b               | 63                  | 76b               | 38                  | 57b               |
| Dyslipidemia | 51                 | 55                | 53                  | 61b               | 49                  | 40b               |
| Prediabetes/diabetes | 27                 | 32b               | 33                  | 38                | 22                  | 18                |
| Smoker    | 9                   | 8b                | 10                  | 19b               | 8                   | 14b               |
|Inactive  | 69                  | 73b               | 63                  | 70b               | 75                  | 80                |
| Follow-up, yr | 23.0 ± 12.2       | 22.9 ± 10.3        | 24.2 ± 12.5        | 23.3 ± 10.4        | 21.8 ± 11.7         | 22.0 ± 10.1       |

Abbreviations: BMI, body mass index; BP, blood pressure; COP, cardiorespiratory optimal point; FRIEND, Fitness Registry and the Importance of Exercise National Database; HR, heart rate; RER, respiratory exchange ratio; VO2peak, peak oxygen uptake.

aData are presented as mean ± SD, or (%).
bSignificantly different from survivors (P < .05).

eexercise testing modes and countries, since the Finnish cohort included those with CVD and were older in age while the Brazilian cohort involved stricter inclusion criteria in defining their healthy participants.

The American Heart Association suggests that VO2peak be considered a clinical vital sign that should be regularly assessed alongside other established risk factors. Recent advancements have overcome many of the previous barriers associated with directly assessing VO2peak, yet the need for individuals to exercise to a maximal intensity remains a deterrent. Although estimations of VO2peak can be performed, they are associated with significant error. Therefore, a considerable benefit associated with measuring COP is that it can be assessed from a submaximal exercise test—in the present study, the COP occurred at a mean of 35 ± 20% of total test time. Compared with nonexercise estimations of VO2peak, exercise testing to determine COP also has other value in that metrics assessed during exercise
can have clinical utility (eg, exercising electrocardiogram and blood pressure). As a result, the determination of COP is favorable when maximal exercise is not feasible or desirable in males. The submaximal nature of exercise testing to determine COP could also increase the prevalence of exercise testing in clinical settings as part of preventative measures to reduce the risk of developing CVD.30

The strengths of the present study include the assessment of apparently healthy males and females with a diverse range of ages and fitness levels. In addition, this study had a long average follow-up period of 23.0 yr. There were, however, some limitations that should be noted. The range of the follow-up period (1.1-48.2 yr) included shorter time periods, which could have an impact on the results, particularly within the younger participants. The cohort was also limited to those who were able to achieve a respiratory exchange ratio of ≥1.0 during the exercise test. The study included only those who performed CPX on a treadmill and involved different testing protocols, which may have impacted the determination of COP. There were also some potential confounders that we were unable to precisely quantify. For instance, the analysis included smoking status (smoker vs nonsmoker) but did not incorporate more detailed smoking habits (eg, packs/day) since individual smoking habits were not always recorded in the database. Furthermore, the validity of the BALL ST scale used to determine physical activity status is not known, which could influence the assessment of this variable. In addition, menopausal status was also not recorded and considering that the menopause transition is associated with changes such as greater CVD risk,11 this may have influenced the ability to detect a significant association between COP and mortality for the female-specific analysis. Finally, the ethnicity of the cohort was predominantly White (≈99%). Future work is needed to confirm these findings in other ethnicities and populations.

In conclusion, COP is predictive of all-cause mortality in males independent of traditional risk factors, including VO_{peak}. For females, however, COP is not related to

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### Table 3

Hazard Ratios for Mortality According to Cardiorespiratory Optimal Point and Peak Oxygen Uptake

| COP | Hazard Ratio (95% CI) | Concordance Index | Hazard Ratio (95% CI) | Concordance Index |
|-----|----------------------|-------------------|----------------------|-------------------|
|     |                      |                   |                      |                   |
| All |                      |                   |                      |                   |
| Model 1 | 1.031 (1.016-1.045)^a | 0.553             | 0.958 (0.949-0.967)^a | 0.623^a           |
| Model 2 | 1.019 (1.004-1.035)^a | 0.765             | 0.971 (0.960-0.982)^a | 0.770             |
| Model 3 | 1.017 (1.001-1.033)^a | 0.773             | 0.970 (0.957-0.984)^a | 0.775             |
| Model 4 | 1.012 (0.996-1.028)  | 0.776             |                      |                   |
| Males |                      |                   |                      |                   |
| Model 1 | 1.041 (1.024-1.059)^a | 0.579             | 0.936 (0.925-0.947)^a | 0.670^a           |
| Model 2 | 1.029 (1.011-1.047)^a | 0.743             | 0.968 (0.956-0.981)^a | 0.748             |
| Model 3 | 1.027 (1.009-1.046)^a | 0.752             | 0.968 (0.953-0.983)^a | 0.754             |
| Model 4 | 1.023 (1.004-1.042)^a | 0.755             |                      |                   |
| Females |                      |                   |                      |                   |
| Model 1 | 1.029 (1.002-1.056)^a | 0.556             | 0.916 (0.893-0.940)^a | 0.675^a           |
| Model 2 | 0.997 (0.968-1.026)  | 0.800             | 0.988 (0.960-1.016)  | 0.801             |
| Model 3 | 0.990 (0.962-1.019)  | 0.810             | 0.992 (0.960-1.025)  | 0.811             |
| Model 4 | 0.989 (0.961-1.018)  | 0.811             |                      |                   |

Abbreviations: COP, cardiorespiratory optimal point; VO_{peak}, peak oxygen uptake.

^aThe models include (1) COP or VO_{peak} unadjusted; (2) adjusted for age, test year, and sex (sex was not included in the sex-specific models); (3) further adjusted for risk factors (obesity, hypertension, dyslipidemia, diabetes, physical inactivity, and smoking status), which were categorized by the presence (1) or absence (0) of each risk factor; and (4) further adjusted for VO_{peak} (only in the COP models).

^bSignificant relationship (P < .05).

^cSignificant difference from COP (P < .05).

### Table 4

Concordance and AIC Values Comparing Fully Adjusted Peak Oxygen Uptake Cox Proportional Hazards Models With Those That Also Include a Measure of Cardiorespiratory Optimal Point

| COP Concordance | VO_{peak} Concordance | COP + VO_{peak} Concordance | COP and COP + VO_{peak} Comparison P Value | VO_{peak} and COP + VO_{peak} Comparison P Value |
|----------------|-----------------------|-----------------------------|-------------------------------------------|-----------------------------------------------|
| All            | 0.773                 | 0.775                       | 0.776                                    | 0.13                                          | 0.063                                        |
| Males          | 0.752                 | 0.754                       | 0.755                                    | 0.25                                          | 0.32                                         |
| Females        | 0.810                 | 0.811                       | 0.811                                    | 0.57                                          | 0.86                                         |

Abbreviations: COP, cardiorespiratory optimal point; VO_{peak}, peak oxygen uptake.
mortality following adjustment for potential confounders. Furthermore, no statistical differences were observed between fully adjusted COP and VO_{2peak} models and VO_{2peak} did not complement COP models. These findings suggest that COP has prognostic utility in apparently healthy males but not females. Considering that COP can be determined from a submaximal exercise test, COP should be determined when measures of VO_{2peak} are not feasible and submaximal exercise testing to determine COP could increase the uptake of exercise testing in clinical settings.

REFERENCES

1. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. Circulation. 2019;139(21):2102-2119.
2. Kaminsky LA, Arena R, Ellingsen O, et al. Cardiorespiratory fitness and cardiovascular disease—the past, present, and future. Prog Cardiovasc Dis. 2019;62(2):86-93.
3. Letnes JM, Dalen H, Vesterbekkmo EK, Wisloff U, Nes BM. Peak oxygen uptake and incident coronary heart disease in a healthy population: the HUNT Fitness Study. Eur Heart J. 2019;40(20):1635-1639.
4. Imboden MT, Harber MP, Whaley MH, Finch WH, Bishop DL, Kaminsky LA. Cardiorespiratory fitness and mortality in healthy men and women. J Am Coll Cardiol. 2018;72(19):2283-2292.
5. Pedersen BK, Saltin B. Exercise as medicine—evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports. 2015;25(suppl 3):1-72.
6. Ramos PS, Ricardo DR, Araujo CG. Cardiorespiratory optimal point: a submaximal variable of the cardiopulmonary exercise testing. Arq Bras Cardiol. 2012;99(5):988-996.
7. Silva CGS, Castro CLB, Franca JF, Bottino A, Myers J, Araujo CGS. Cardiorespiratory optimal point in professional soccer players: a novel submaximal variable during exercise. Int J Cardiovasc Sci. 2018;31(4):323-332.
8. Arena R, Myers J, Harber M, et al. The V̇E/V̇CO₂ slope during maximal treadmill cardiopulmonary exercise testing: references standards from FRIEND (Fitness Registry and the Importance of Exercise: A National Database). J Cardiopulm Rehab Prev. 2021;41(3):194-198.
9. Balady GJ, Arena R, Sieksema K, et al. Clinician’s guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010;122(2):191-225.
10. Ramos PS, Araujo CG. Cardiorespiratory optimal point during exercise testing as a predictor of all-cause mortality. Rev Port Cardiol. 2017;36(4):261-269.
11. Dias Ferreira Reis JP, Goncalves A, Bras P, et al. Prognostic value of the cardiopulmonary optimal point during submaximal exercise testing. Eur Heart J. 2020;41(suppl 2):2957.
12. Goncalves AV, Mano T, Agapito A, et al. Prognostic power of anaerobic threshold parameters in patients with transposition of the great arteries and systemic right ventricle. Cardiol Young. 2019;29(12):1445-1451.
13. Laukkanaen JA, Savonen K, Hupin D, Araujo CGS, Kunutsor SK. Cardiorespiratory optimal point during exercise testing and sudden cardiac death: a prospective cohort study. Prog Cardiovasc Dis. 2021;68:12-18.
14. Laukkanaen JA, Kunutsor SK, Araujo CG, Savonen K. Cardiorespiratory optimal point during exercise testing is related to cardiovascular and all-cause mortality. Scand J Med Sci Sports. 2021;31(10):1949-1961.
15. Liguori G, Feito Y, Fontaine C, Roy BA. ACSM’s Guidelines for Exercise Testing and Prescription. 11th ed. Philadelphia, PA: Wolters Kluwer; 2021.
16. Kaminsky LA, Whaley MH. Evaluation of a new standardized ramp protocol: the BSU/Bruce Ramp Protocol. J Cardiopulm Rehabil. 1998;18(6):438-444.
17. Batek B, Waele RW. An experimental study of physical fitness of air force personnel. US Armed Forces Med J. 1959;10(6):675-688.
18. Whaley HM, Kaminsky LA, Dwyer GB, Getchell LH. Failure of predicted VO2peak to discriminate physical fitness in epidemiological studies. Med Sci Sports Exerc. 1995;27(1):85-91.
19. Harber MP, Metz M, Peterman JE, Whaley MH, Fleenor BS, Kaminsky LA. Trends in cardiorespiratory fitness among apparently healthy adults from the Ball State Adult Fitness Longitudinal Lifestyle Study (BALL ST) cohort from 1970-2019. PLoS One. 2020;15(12):e0242995.
20. Grundy SM, Cleeman JJ, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. Circulation. 2005;112:2735-2752.
21. Kaminsky LA, Arena R, Myers J, et al. Updated reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the Fitness Registry and the Importance of Exercise National Database (FRIEND). Mayo Clin Proc. 2022;97(2):285-293.
22. Imboden MT, Kaminsky LA, Peterman JE, et al. Cardiorespiratory fitness normalized to fat-free mass and mortality risk. Med Sci Sports Exerc. 2020;52:1532-1537.
23. Salter Erikkson J, Ekblom B, Andersson G, Wallin P, Ekblom-Bak E. Scaling VO2max to body size differences to evaluate associations with CVD incidence and all-cause mortality risk. BMJ Open Sport Exerc Med. 2021;5(1):e000858.
24. Peterman JE, Harber MP, Chaudhry S, Arena R, Kaminsky LA. Peak oxygen pulse and mortality risk in healthy women and men: the Ball State Adult Fitness Longitudinal Lifestyle Study (BALL ST). Prog Cardiovasc Dis. 2021;68:19-24.
25. Dominelli PB, Molgart-Soon Y, Bingham D, et al. Dysanapsis and the resistive work of breathing during exercise in healthy men and women. J Appl Physiol. 2015;119(10):1105-1113.
26. Guenette JA, Witt JD, McKenzie DC, Road JD, Sheel AW. Respiratory mechanics during exercise in endurance-trained men and women. J Physiol. 2007;581(pt 3):1309-1322.
27. Peterman JE, Arena R, Myers J, et al. Development of global reference standards for directly measured cardiorespiratory fitness: a report from the Fitness Registry and Importance of Exercise National Database (FRIEND). Mayo Clin Proc. 2020;95(2):255-264.
28. Peterman JE, Harber MP, Imboden MT, et al. Accuracy of exercise-based equations for estimating cardiorespiratory fitness. Med Sci Sports Exerc. 2021;53(1):74-82.
29. Peterman JE, Whaley MH, Harber MP, et al. Comparison of non-exercise cardiorespiratory fitness prediction equations in apparently healthy adults. Eur J Prev Cardiol. 2021;28(2):142-148.
30. Franklin BA, Brubaker PH, Harber MP, Lavie CJ, Myers J, Kaminsky LA. The Journal of cardiorespiratory rehabilitation and prevention at 40 years and its role in promoting lifestyle medicine for prevention of cardiovascular diseases: PART 1. J Cardiopulm Rehabil Prev. 2020;40(3):131-137.
31. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. Circulation. 2020;142(25):e306-e332.