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Cardiorespiratory optimal point during exercise testing is related to cardiovascular and all-cause mortality

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Abstract

Cardiorespiratory optimal point (COP) during exercise may be a potentially clinically useful cardiopulmonary exercise testing (CPET) variable, but its prognostic relevance for adverse cardiovascular disease (CVD) outcomes is unknown. We aimed to assess the association of COP during exercise with fatal mortality outcomes and the extent to which COP could improve the prediction of CVD mortality. Cardiorespiratory optimal point, the minimum value of the ventilatory equivalent for oxygen (VE/VO2) in a given minute of a CPET, was defined in 2,205 men who underwent CPET. Hazard ratios (HRs) (95% confidence intervals [CIs]) for outcomes and measures of risk discrimination for CVD mortality were calculated. During a median follow-up of 28.8 years, 402 fatal CHDs, 607 fatal CVDs, and 1,348 all-cause mortality events occurred. COP was continually associated with each outcome in a dose-response manner. On adjustment for established and emerging risk factors, the HRs (95% CIs) for fatal CHD, fatal CVD, and all-cause mortality were 3.05 (1.94–4.81), 2.82 (1.91–4.18) and 2.46 (1.85–3.27), respectively, per standard deviation increase in COP. After further adjustment for high sensitivity C-reactive protein, the HRs were 2.82 (1.78–4.46), 2.57 (1.73–3.81), and 2.27 (1.70–3.02), respectively. Addition of COP to a CVD mortality risk prediction model containing established risk factors was associated with a C-index change of 0.0139 (0.0040 to 0.0238; $p = 0.006$) at 25 years. COP during exercise is directly associated with fatal cardiovascular and all-cause mortality events in dose-response fashions. COP during exercise may improve the prediction of the long-term risk for CVD mortality.

KEYWORDS

cardiopulmonary exercise testing, cardiorespiratory optimal point, cardiovascular disease, cohort study, prognosis

1 | INTRODUCTION

Peak oxygen uptake (VO_{2peak}), commonly used as a measure of cardiorespiratory fitness (CRF), is one of the best measures for assessing aerobic fitness during the cardiopulmonary exercise testing (CPET).[12] Cardiorespiratory fitness is well comparable with established cardiovascular risk factors such as smoking, hypertension, type 2 diabetes, and high cholesterol as related to survival[3]; a wealth of accumulating data suggests that aerobic fitness, either measured directly or estimated indirectly, is inversely and independently associated with fatal cardiovascular vascular disease (CVD) outcomes and mortality[3-10] Unfortunately, despite the accumulating evidence on its potential clinical utility as an established risk factor for cardiovascular outcomes, CRF is not routinely measured in clinical settings.[2]

During a maximum incremental CPET, expired gas analysis data could be obtained with diagnostic and/or prognostic implications, such as $VO2_{peak}$, the maximum oxygen pulse, both absolute and relative to body weight, the ventilatory anaerobic threshold (VAT), the ventilatory equivalent for carbon dioxide (VE/VCO2) slope and the oxygen uptake efficiency slope (OUES) curve.[1-3] However, there are also limitations with the measurement of these variables, partially due to complex and different manners of calculation and/or identification, and the fact that most of these requires that a truly maximum or near maximal exercise test have been completed, which eventually is not feasible and/ or desirable and depends on the strong motivations of both evaluator and the subject being evaluated.

In this sense, it will be potentially useful to have an expired gas analysis-related variable that could be obtained at relatively low exercise intensity, by simple calculation and practically observer-free error. In an incremental intensity exercise protocol, as occurs in a CPET, the oxygen ventilatory equivalent behaves in a U-shape curve pattern for all subjects. Some years ago, the bottom value of this curve was characterized and named the cardiorespiratory optimal point (COP).[11] COP is reflecting the best circulatory-respiratory interaction and sex- and age-reference values have been presented for healthy adults.[11] Though there is limited data on age- and sex-specific reference values, there is a trend for COP to increase with aging and to be higher in women compared to men. In the original study by Ramos and colleagues, median values for men and women 35–44 years old were, respectively, 21.9 and 23.3 and for men and women aged 55–64 years, the corresponding values were 24.9 and 26.6, respectively.[11] In a recent cohort study,[12] COP has been shown to be a strong predictor of all-cause mortality both in healthy and unhealthy middle-aged and elderly subjects. Our objective was to assess the nature and magnitude of the association between COP and coronary heart disease (CHD), overall CVD and all-cause mortality in a population-based cohort of middle-aged men from eastern Finland. A second objective was to investigate the extent to which COP measurements could improve the risk prediction of CVD mortality when added to conventional risk factors.

2 | METHODS

2.1 | Study design and participants

Participants of the Kuopio Ischaemic Heart Disease (KIHD) risk factor study were used for the current analysis. The KIHD study is a population-based observational prospective cohort study of the incidence of atherosclerotic CVD outcomes and their risk factors among Finnish adults. Participants were selected to be a representative sample of men aged 42–61 years living in the city of Kuopio and its surrounding rural communities in eastern Finland. A complete description of the study design, objectives, and recruitment methods have been described previously.[13] Briefly, of the 3,433 men randomly selected to be potentially eligible, 3235 were actually eligible for inclusion. A total of 2,682 men were eventually included into the study following exclusion of those who declined to give informed consent or did not respond to the invitation. Their baseline examinations were performed between March 1984 and December 1989. The final cohort for this analysis comprised of 2,205 men with complete information on COP, relevant covariates and all outcomes. The study design and protocol were approved by the Research Ethics Committee of the University of Eastern Kuopio in accordance with the Declaration of Helsinki. All participants provided written informed consent. This study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (Table S1).

2.2 | Identification of cardiorespiratory optimal point

Peak oxygen uptake was used as a measure of CRF, which was directly assessed between 8:00 am and 10:00 am with a respiratory gas analyzer (Medical Graphics, MCG, St. Paul, Minnesota) during a symptom-limited cycle ergometer exercise tolerance test.[14] The standardized testing protocol comprised a graded increase in the workload of 20 W/min until exhaustion. During CPET, electrocardiogram, blood pressure, and heart rate were also recorded. To ensure safety, all CPET were conducted under the supervision of an experienced physician and a nurse. CPET's expired gas data were reviewed for each subject and results of relevant variables averaged for each minute of exercise.[15,16] Cardiorespiratory optimal point, the main CPET exposure in this study, was

obtained by identifying the lowest value of the ratio between the ventilation (VE) (L.min-1) and oxygen uptake (VO2) (L.min-1) results at a given minute during the maximum CPET, resulting in a dimensionless ratio value.[11,12]

2.3 | Assessment of risk markers

Detailed description of blood sample collection, physical measurements, assessment of lifestyle characteristics, and assays for lipids, lipoproteins and other blood-based biomarkers have been provided in previous reports.[17,18] Self-administered questionnaires were used to assess sociodemographic and lifestyle characteristics such as smoking and alcohol consumption, baseline diseases and use of medication.[17] For blood sample collection, participants were instructed to fast overnight, refrain completely from drinking alcohol for at least 3 days and from smoking for at least 12 hours prior to assessment. Blood samples were collected between 08:00 and 10:00 hours. The serum samples were frozen at −80°C and stored for 0.2 – 2.5 years. The cholesterol content of lipoprotein fractions and serum triglycerides were assayed enzymatically (Boehringer Mannheim, Mannheim, Germany).[19] An immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC) was used to measure high-sensitivity C-reactive protein (hsCRP). Fasting plasma glucose (FPG) was measured using the glucose dehydrogenase method (Merck, Darmstadt) following protein precipitation by trichloroacetic acid. Adulthood socioeconomic status (SES) was assessed using self-reported questionnaires as a combined measure of the following: income, education, occupation, occupational prestige, material standard of living and housing conditions.[20] The composite SES index is a continuous variable ranging from 0 to 25, with higher values indicating lower SES. Physical activity status was assessed from a 12-month physical activity history modified from the Minnesota Leisure-Time Physical Activity Questionnaire[21] and has been described in detail previously.[14]

2.4 | Ascertainment of outcomes

We included all cardiovascular deaths that occurred from study enrollment through to 2018. Follow-up time was calculated from date of baseline assessment till end of follow-up or outcome event. All deaths were ascertained from a comprehensive review of hospital records, death certificates, informant interviews, health practitioner questionnaires, medico-legal reports, and vital statistics offices. Cardiovascular causes of deaths were coded according to the International Classification of Diseases (ICD 9th revision codes 390 – 459 and 10th revision codes I00-I99). Each CHD deaths were coded (ICD-9 codes 410–414 and ICD-10 codes I20–I25). Two independent physicians checked all documents. The classification of outcomes was confirmed by members of an Independent Events Committee, who were masked to clinical data. In the KIHD study, participants (using personal identification codes) are under continuous annual surveillance for all outcomes including mortality events. There are no losses to follow-up.

2.5 | Statistical analysis

Baseline data were summarized using descriptive statistics: means (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and (N) percentages for categorical variables. Age, SES, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP), CRF, total and high-density lipoprotein cholesterol (HDL-C), FBG and COP were summarized as mean (SD); whereas alcohol consumption, physical activity, triglycerides, and hsCRP were summarized as median (IQR). Age-adjusted partial correlation coefficients were estimated to assess the cross-sectional associations of COP with several risk markers. Cox proportional hazard models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) fatal CHD and CVD events and all-cause mortality. To explore potential nonlinear dose-response relationships between COP and outcomes, we constructed restricted cubic splines with knots at the 5th, 35th, 65th, and 95th percentiles of the distribution of COP in multivariable models adjusted for age, smoking status, history of type 2 diabetes, systolic blood pressure, total cholesterol, HDL-C, BMI, FPG, alcohol consumption, history of hypertension, prevalent CHD, use of cholesterol medication, physical activity status and SES. We modelled COP as both continuous [per SD increase] and categorical (quintiles) variables. Three progressive models were used for our adjustments: (Model 1) age; (Model 2) model 1 plus smoking status, history of type 2 diabetes, SBP, total cholesterol and HDL-C, BMI, FPG, alcohol consumption, history of hypertension, prevalent CHD, use of cholesterol medication, physical activity status and SES and (Model 3) model 2 plus hsCRP. To assess statistical evidence of effect modification by pre-specified individual level characteristics, we performed subgroup analyses using tests of interaction. To minimize any bias due to reverse causation, sensitivity analysis involved excluding the first five years of follow-up and those with prevalent CVD.

To assess whether adding information on COP to established cardiovascular risk factors is associated with improvement in prediction of CVD mortality risk, we calculated measures of discrimination for censored time-to-event data (Harrell's C-index [22]) and reclassification.[23,24] To investigate the change in C-index on the addition of COP, two CVD mortality risk prediction models were fitted: one model based on

traditional risk factors (ie, age, SBP, history of diabetes, total cholesterol, HDL-C, and smoking) and the second model with these risk factors plus COP. In addition to Harrel's C-index, we tested differences in the −2 log likelihood of prediction models with and without inclusion of COP. The −2 log likelihood test has been recommended as a more sensitive risk discrimination method.[25,26] Reclassification analyses were restricted to the first 25 years of follow-up and were assessed using the net-reclassification-improvement (NRI)[23,24] and integrated-discrimination-improvement (IDI)[23] by comparing the model containing conventional risk factors to the predicted risk from the model containing conventional risk factors plus COP. Given the long follow-up of the cohort, reclassification analyses weref based on predicted 25-year CVD mortality risk categories of low (<8%), intermediate (8 to <30%), and high (≥30%) risk as previously reported.[27-29] We compared COP with absolute and relative CRF in risk prediction analyses. All statistical analyses were conducted using Stata MP version 16 (Stata Corp, College Station). An .05 level of probability was chosen for statistical significance.

3 | RESULTS

3.1 | Baseline characteristics and correlates of cardiorespiratory optimal point during exercise

The overall mean (SD) age and COP at baseline were 53 (5) years and 23.3 (4.5), respectively (**Table 1**). Significant negative correlations were observed between COP and age, SES, BMI, alcohol consumption, blood pressure, total cholesterol, triglycerides, and hsCRP; whereas, significant positive correlations were observed with physical activity, absolute CRF, and HDL-C. Values of COP were significantly lower in men with pre-existing disease such as type 2 diabetes and CHD compared to those without.

3.2 | Cardiorespiratory optimal point and CHD mortality

During a median (IQR) follow-up of 28.8 (19.3–31.3) years (54,267 person-years at risk), 402 CHD deaths occurred. Based on a restricted cubic spline curve analysis adjusted for conventional cardiovascular risk factors as described above, the risk of CHD mortality augmented continuously with increasing COP from 26 and beyond with no threshold effect (p-value for non-linearity = 0.08) (Figure 1A). In age-adjusted analysis, the HR (95% CI) per 1 SD increase in COP for CHD mortality was 5.86 (3.82–8.98), which was attenuated to 3.05 (1.94–4.81) after further adjustment for risk factors as previously described (**Table 2**). According to model 3, on additional adjustment for hsCRP, HR (95% CI) was minimally attenuated to 2.82 (1.78–4.46). Alternatively, comparing the extreme quintiles of COP, the corresponding adjusted HRs (95% CIs) for CHD mortality were 2.51 (1.81–3.47), 1.87 (1.34–2.63) and 1.81 (1.29–2.54), respectively. Though the associations were consistent in several subgroups, there was some evidence of effect modification by age and history of type 2 diabetes (p for interaction <0.05 for all) (Figure 2). In analyses that excluded the first five years of follow-up in the whole population and those with prevalent CVD, the significant associations between COP and CHD mortality remained (Table S1).

3.3 | Cardiorespiratory optimal point and CVD mortality

During the follow-up period, there were 607 CVD deaths. In a multivariable restricted cubic spline curve analysis, the risk of CVD mortality increased continuously with increasing COP from 25 and beyond (p-value for non-linearity = 0.02) (Figure 1B). When adjusting for age, the HR (95% CI) per 1 SD increase in COP for CVD mortality was 4.66 (3.22–6.74), which was attenuated to 2.82 (1.91–4.18) after further adjustment for established and other potential risk factors (**Table 2**). Adding hsCRP to the analysis had a minimal effect on the HR (95% CI): 2.57 (1.73–3.81). Comparing the extreme quintiles of COP, the corresponding adjusted HRs (95% CIs) were 2.29 (1.76–2.98), 1.83 (1.39–2.41) and 1.75 (1.33–2.31), respectively. There was evidence of interaction by age and physical activity status on the association between COP and CVD mortality (p for interaction < 0.05 for all) (Figure 3). When excluding the first five years of follow-up in the whole population and those with prevalent CVD, the association between COP and CVD mortality remained (Table S1).

3.4 | Cardiorespiratory optimal point and all-cause mortality

A total of 1,348 all-cause deaths occurred during the follow-up period. The multivariable restricted cubic spline curve showed the risk of all-cause mortality increased continuously with increasing COP from 25 and beyond (p-value for non-linearity=0.004) (Figure 1C). In analysis adjusted for age, the HR (95% CI) per 1 SD increase in COP for all-cause mortality was 3.46 (2.66–4.51), which was attenuated to 2.46 (1.85–3.27) after further adjustment for established and other potential risk factors (**Table 2**). The HR (95% CI) was minimally attenuated to 2.27 (1.70–3.02) on additional adjustment for hsCRP. In comparing the extreme quintiles

TABLE 1 Baseline participant characteristics and correlates of cardiorespiratory optimal point

	Mean (SD), median (IQR), or %	Pearson correlation r (95% CI)[a]	Percentage difference (95% CI) in values of percentage of COP per 1 SD higher or compared to reference category of correlate[b]
Cardiorespiratory optimal point	23.3 (4.5)	-	-
Questionnaire/Prevalent conditions			
Age at survey (years)	52.8 (5.2)	−0.09 (−0.13, −0.05)***	−1.88% (−2.76, −0.99)***
Alcohol consumption (g/week)	31.5 (6.4 – 90.5)	−0.10 (−0.15, −0.06)***	−2.17% (−3.12, −1.22)***
Socioeconomic status	8.33 (4.20)	−0.12 (−0.16, −0.08)***	−2.55% (−3.46, −1.64)***
History of type 2 diabetes			
No	2,097 (95.1)	-	Ref
Yes	108 (4.9)	-	−14.12% (−18.19, −10.05)***
History of hypertension			
No	1,548 (70.2)	-	Ref
Yes	657 (29.8)	-	−9.89% (−11.79, −7.99)***-
Smoking status			
Other	1,525 (69.2)	-	Ref
Current	680 (30.8)	-	−7.29% (−9.18, −5.40)***
History of CHD			
No	1,694 (76.8)	-	Ref
Yes	511 (23.2)	-	−15.79% (−17.83, −13.76)***
History of CVD			
No	1,398 (63.4)	-	Ref
Yes	807 (36.6)	-	−11.91% (−13.73, −10.09)***
History of stroke			
No	2,160 (98.1)	-	Ref
Yes	43 (1.9)	-	−17.15% (−23.48, −10.82)***
Medication for dyslipidemia			
No	2,193 (99.5)	-	Ref
Yes	12 (0.5)	-	−24.89% (−36.79, −12.99)***
Physical measurements			
BMI ($kg.m_{-2}$)	26.9 (3.5)	−0.38 (−0.41, −0.34)***	−7.91% (−8.73, −7.08)***
SBP (mmHg)	134 (17)	−0.13 (−0.18, −0.09)***	−2.85% (−3.73, −1.96)***
DBP (mmHg)	89 (10)	−0.13 (−0.17, −0.09)***	−2.81% (−3.69, −1.93)***
Physical activity (kj/day)	1204 (631 – 1964)	0.14 (0.10, 0.18)***	2.94% (2.06, 3.82)***
CRF* ($ml.min^{-1}$)	2426 (623)	0.78 (0.77, 0.80)***	18.14% (17.53, 18.74)***
CRF ($ml.kg^{-1}.min^{-1}$)	30.5 (7.9)	0.97 (0.97, 0.97)***	21.91% (21.68, 22.14)***
Blood-based markers			
Total cholesterol (mmol/l)	5.89 (1.06)	−0.08 (−0.12, −0.03)**	−1.60% (−2.49, −0.72)**
HDL-C (mmol/l)	1.29 (0.30)	0.26 (0.22, 0.30)***	5.55% (4.70, 6.41)***
Triglycerides (mmol/l)	1.10 (0.80–1.55)	−0.32 (−0.36, −0.28)***	−6.71% (−7.56, −5.86)***
Fasting plasma glucose (mmol/l)	5.33 (1.19)	−0.20 (−0.24, −0.15)***	−4.12% (−4.99, −3.25)***
High-sensitivity CRP (mg/l)	1.24 (0.68 – 2.36)	−0.34 (−0.38, 0.30)***	−7.22% (−8.05, −6.38)***

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; COP, cardiorespiratory optimal point; CRF, cardiorespiratory fitness; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure; [a], Pearson correlation coefficients between percentage of age-predicted exercise capacity and the row variables; [b], Percentage change in values of COP per 1-SD increase in the row variable (or for categorical variables, the percentage difference in mean values of COP for the category versus the reference); asterisks indicate the level of statistical significance: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

CRF was assessed directly using a respiratory gas analyzer during a symptom-limited cycle ergometer exercise tolerance test.

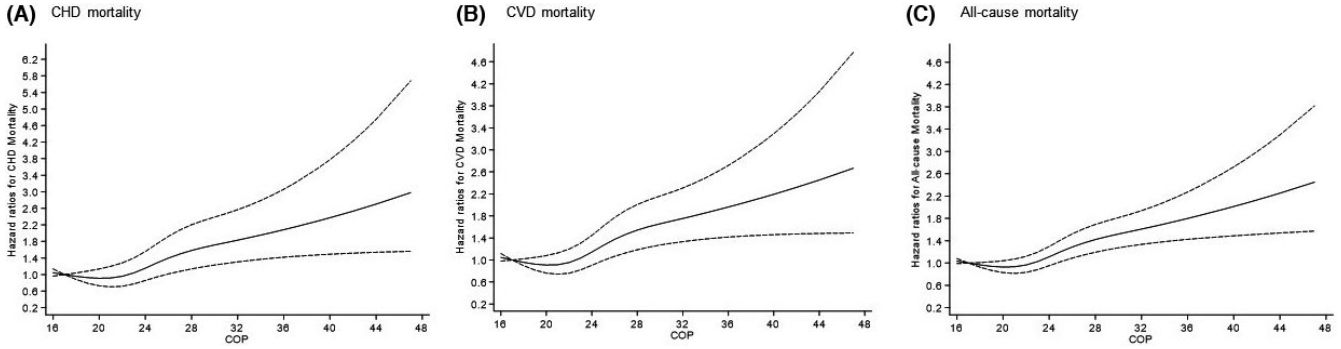

FIGURE 1 Restricted cubic splines of the hazard ratios of fatal CHD and CVD and all-cause mortality with cardiorespiratory optimal point. CHD, coronary heart disease; CVD, cardiovascular disease. Models were adjusted for age, smoking status, history of type 2 diabetes, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol, body mass index, fasting plasma glucose, alcohol consumption, history of hypertension, prevalent coronary heart disease, use of cholesterol medication, physical activity and socioeconomic status

of COP, the corresponding adjusted HRs (95% CIs) for all-cause mortality were 1.99 (1.67–2.37), 1.63 (1.36–1.96) and 1.57 (1.30–1.88) respectively. There was evidence of interaction by age, physical activity and smoking status on the association between COP and all-cause mortality (p for interaction < 0.05 for all) (Figure 4). In analyses that excluded the first five years of follow-up in the whole population and those with prevalent CVD, the association between COP and all-cause mortality persisted (Table S1).

3.5 | Cardiorespiratory optimal point and CVD mortality risk prediction

A CVD mortality risk prediction model containing established risk factors yielded a C-index of 0.7082 (95% CI: 0.6832–0.7331). After addition of information on COP, the C-index was 0.7221 (0.6972–0.7469), representing a significant increase of 0.0139 (0.0040 to 0.0238; $p = 0.006$). The −2 log likelihood was significantly improved on addition of COP to the risk model (p for comparison < 0.001). There was no significant improvement in the classification of participants into predicted 25-year CVD mortality risk categories (NRI: 2.80%, −1.18, 6.78%; $p = 0.17$). The IDI was 0.0166 (0.0092–0.0240; $p < 0.001$) (Table S1).

To compare the predictive ability of COP with absolute and relative CRF in the same participants, information on these exposures was each added to the model containing conventional risk factors. There was a C-index change of 0.0222 (95% CI: 0.0071–0.0373; $p = 0.004$), after adding absolute CRF to the model. The −2 log likelihood was significantly improved on addition of absolute CRF to the model (p for comparison < 0.001). There was a significant improvement in the classification of participants into CVD mortality risk categories (NRI: 5.72%, 1.12–10.32%; $p = 0.02$). The IDI was 0.0293 (0.0215–0.0372; $p < 0.001$) (Table S1). For relative CRF, the corresponding values were C-index change: 0.0330 (95% CI: 0.0164–0.0497; $p < 0.001$); −2 log likelihood: (p for comparison < 0.001); NRI: (9.77%, 4.49–15.05%; $p < 0.001$) and IDI: 0.0443 (0.0341–0.0545; $p < 0.001$) Table S1).

4 | DISCUSSION

We have evaluated the association of COP with cardiovascular and all-cause mortality and the extent to which COP assessments could improve the prediction of CVD mortality when added to information provided by conventional risk factors in a population-based prospective cohort study of men. Our results showed a strong and independent association of COP with CHD, CVD and all-cause mortality, which was consistent with a continuous dose-response relationship. Though there appeared to be evidence of effect modification by age across all outcomes, the direction of the associations was generally similar in most of the clinically relevant subgroups. On addition of information on COP to a CVD mortality model containing conventional risk factors, there was a significant improvement in risk discrimination, but this was a modest change. Additional comparison analyses in the same set of participants showed that the improvements in risk discrimination and reclassification across clinical risk categories provided by absolute and relative CRF were superior to that of COP. Relative CRF provided the most improvements, which was not unexpected given that it is by far the most established CRF indicator and predictor of cardiovascular and mortality outcomes in the existing literature.[3,30]

Cardiorespiratory optimal point has been proposed as an alternative approach to report aerobic fitness level, in a simple way and using a single dimensionless exposure, indicating the best interaction between circulatory and respiratory responses during CPET.[11] For obtaining COP, ventilation and oxygen uptake data are required,

TABLE 2 Associations of cardiorespiratory optimal point with fatal coronary heart disease, fatal cardiovascular disease, and all-cause mortality

Models/ COP (unit)	Fatal coronary heart disease			Fatal cardiovascular disease			All-cause mortality		
	Events / Participants	Hazard ratio (95% CI)	*p*-value	Events / Participants	Hazard ratio (95% CI)	*p*-value	Events / Participants	Hazard ratio (95% CI)	*p*-value
Model 1									
Per 1 SD increase	402 / 2205	5.86 (3.82–8.98)	<0.001	607 / 2205	4.66 (3.22–6.74)	<.001	1348 / 2205	3.46 (2.66–4.51)	<0.001
Quintile 1 (7.73–20.26)	54 / 441	1 [Reference]		85 / 441	1 [Reference]		202 / 441	1 [Reference]	
Quintile 2 (20.27–22.23)	63 / 441	1.04 (0.72–1.50)	0.82	96 / 441	1.02 (0.76–1.36)	0.91	234 / 441	1.05 (0.87–1.26)	0.65
Quintile 3 (22.24–23.96)	74 / 441	1.18 (0.83–1.68)	0.35	115 / 441	1.18 (0.89–1.57)	0.24	270 / 441	1.18 (0.98–1.42)	0.07
Quintile 4 (23.97–26.30)	87 / 441	1.45 (1.03–2.04)	0.04	138 / 441	1.48 (1.13–1.95)	0.005	94 / 441	1.35 (1.12–1.61)	0.001
Quintile 5 (>26.30)	124 / 441	2.51 (1.81–3.47)	<0.001	173 / 441	2.29 (1.76–2.98)	<0.001	348 / 441	1.99 (1.67–2.37)	<0.001
p-value for trend			<0.001			<0.001			<0.001
Model 2									
Per 1 SD increase	402 / 2205	3.05 (1.94–4.81)	<0.001	607 / 2205	2.82 (1.91–4.18)	<0.001	1348 / 2205	2.46 (1.85–3.27)	<0.001
Quintile 1 (7.73–20.26)	54 / 441	1 [Reference]		85 / 441	1 [Reference]		202 / 441	1 [Reference]	
Quintile 2 (20.27–22.23)	63 / 441	1.06 (0.73–1.53)	0.76	96 / 441	1.04 (0.77–1.40)	0.80	234 / 441	1.04 (0.86–1.25)	0.72
Quintile 3 (22.24–23.96)	74 / 441	1.11 (0.78–1.60)	0.55	115 / 441	1.14 (0.86–1.52)	0.37	270 / 441	1.13 (0.94–1.36)	0.21
Quintile 4 (23.97–26.30)	87 / 441	1.25 (0.88–1.77)	0.21	138 / 441	1.31 (0.99–1.73)	0.06	94 / 441	1.22 (1.01–1.46)	0.04
Quintile 5 (>26.30)	124 / 441	1.87 (1.34–2.63)	<.001	173 / 441	1.83 (1.39–2.41)	<0.001	348 / 441	1.63 (1.36–1.96)	<0.001
p-value for trend			<0.001			<0.001			<0.001
Model 3									
Per 1 SD increase	402 / 2205	2.82 (1.78–4.46)	<.001	607 / 2205	2.57 (1.73–3.81)	<0.001	1348 / 2205	2.27 (1.70–3.02)	<0.001
Quintile 1 (7.73–20.26)	54 / 441	1 [Reference]		85 / 441	1 [Reference]		202 / 441	1 [Reference]	
Quintile 2 (20.27–22.23)	63 / 441	1.07 (0.74–1.54)	0.73	96 / 441	1.05 (0.78–1.41)	0.76	234 / 441	1.04 (0.86–1.26)	0.69
Quintile 3 (22.24–23.96)	74 / 441	1.11 (0.78–1.59)	0.56	115 / 441	1.14 (0.85–1.51)	.38	270 / 441	1.12 (0.93–1.35)	0.23
Quintile 4 (23.97–26.30)	87 / 441	1.25 (0.88–1.77)	0.21	138 / 441	1.30 (0.99–1.72)	0.06	94 / 441	1.21 (1.01–1.45)	0.04
Quintile 5 (>26.30)	124 / 441	1.81 (1.29–2.54)	0.001	173 / 441	1.75 (1.33–2.31)	<0.001	348 / 441	1.57 (1.30–1.88)	<0.001
p-value for trend			<0.001			<0.001			<0.001

Abbreviations: CI, confidence interval; COP, cardiorespiratory optimal point; SD, standard deviation.

Model 1: Adjusted for age.

Model 2: Model 1 plus smoking status, history of type 2 diabetes, systolic blood pressure, total cholesterol, high-density lipoprotein-cholesterol, body mass index, fasting plasma glucose, alcohol consumption, history of hypertension, prevalent coronary heart disease, use of cholesterol medication, total physical activity and socioeconomic status.

Model 3: Model 2 plus high-sensitivity C-reactive protein.

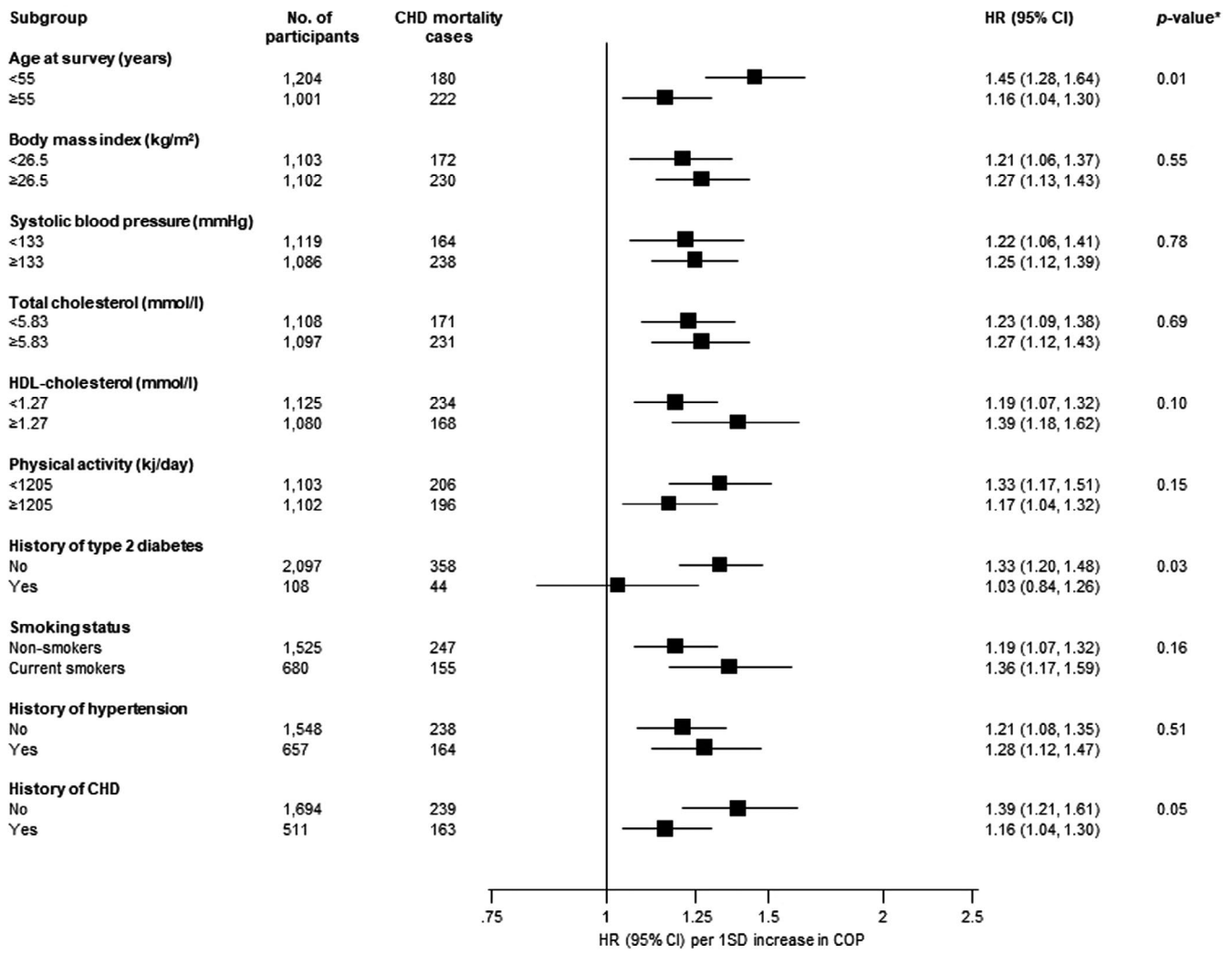

FIGURE 2 Association of cardiorespiratory optimal point with CHD mortality in clinically relevant subgroups. Hazard ratios were adjusted for age, smoking status, history of type 2 diabetes, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol, body mass index, fasting plasma glucose, alcohol consumption, history of hypertension, prevalent coronary heart disease, use of cholesterol medication, physical activity and socioeconomic status; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; *, *P*-value for interaction; cut-offs used for age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol; and physical activity are median values

making it less amenable to dietary influences as it has been shown with the use of carbon dioxide production data.[31] It is worthwhile to emphasize that due its mathematical simplicity, COP can be calculated from CPET with VE and VO2 data in most exercise testing laboratories. Therefore, the COP is not only much less dependent on the evaluator—virtually no intra-observer differences in its detection—but it is also simple to measure with great accuracy using various exercise testing protocols. Additionally, there are published reference data for COP values in a large age range of subjects, facilitating the clinical interpretation.[11] Median COP values for men at similar age were identical between the current Finnish study and earlier published Brazilian cohorts, that is 23.4, reinforcing the external validity of COP.[11]

The use of COP has been recently proposed in some other clinical studies.[32-36] Frazão et al.[36] studied 61 elderly subjects with ventilatory inefficiency using CEPT and found that COP was moderately related to maximal oxygen uptake ($r = -0.59$). In a study of 44 patients with surgical correction of congenital transposition of the great arteries, COP was not a significant marker of one-year heart failure risk.[34] In a completely distinct but homogeneous sample of 198 professional football players, De Souza e Silva et al[32] found no association between COP and maximal oxygen uptake. A recent preliminary report from Portugal [35] identified that a COP above 31 was associated with mortality in 487 patients with heart failure that were followed for a mean time of 11 months, presenting the highest AUC value (0.915) among several other CPET variables with a stronger

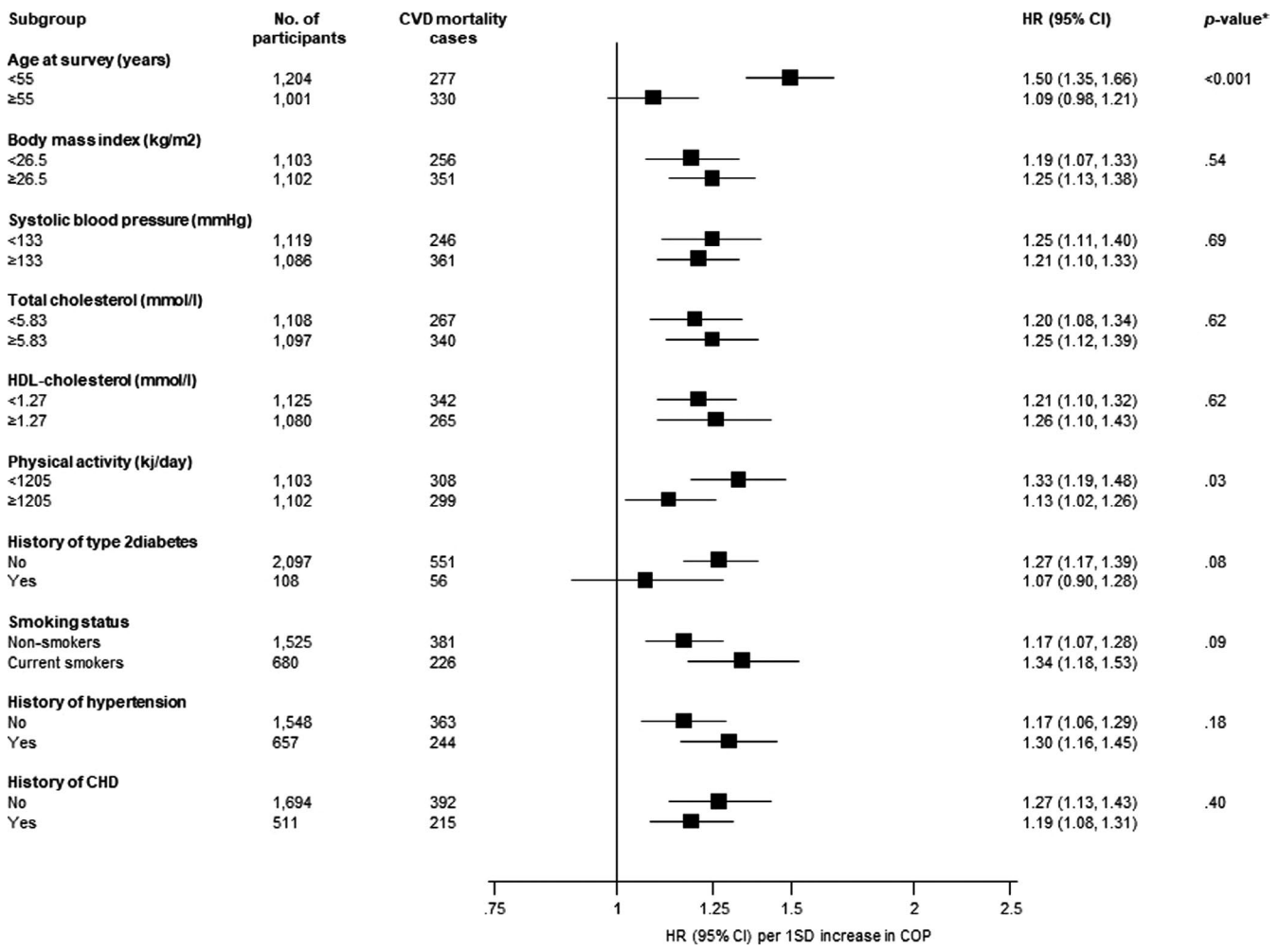

FIGURE 3 Association of cardiorespiratory optimal point with CVD mortality in clinically relevant subgroups. Hazard ratios were adjusted for age, smoking status, history of type 2 diabetes, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol, body mass index, fasting plasma glucose, alcohol consumption, history of hypertension, prevalent coronary heart disease, use of cholesterol medication, physical activity and socioeconomic status; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; *, *P*-value for interaction; cut-offs used for age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol; and physical activity are median values

prognostic power than VO_{2peak}. Overall, a useful physiological and clinical information can be obtained from COP which may offer complementary information, with a definitive association between these two CEPT variables being only evident in unhealthy older subjects.[37]

An important characteristic of COP is that—unlike most of other ventilatory indices or variables derived from a CPET—in order to obtain COP data, it is not necessary to perform a truly maximal exercise. The relevance of this fact was exemplified in a study with patients suffering from panic disorders submitted to CPET.[38] COP is possible to define while truly VO2peak is not feasible to be achieved during CPET in all the unhealthy and aging subjects. It is worthy to note that COP value is easily readable from submaximal VE/VO2 values at each minute of a CPET, with no complex calculations or decisions to include and/or exclude part of data (mainly, first and last minutes of CPET as it occurs with VE/VCO2 slope). Indeed, with an incremental exercise when detecting that VE/VO2 starts to increase in a given minute, this indicates that the COP was already reached in the previous minute, most often at a relatively modest submaximal exercise intensity corresponding to only 30 to 50% of VO_{2peak}, and well below VAT threshold, even for elderly subjects with poor aerobic fitness.

This is one of the first large population-based studies showing that CVD mortality risk prediction can be improved by additional information on COP, a dimensionless ventilatory variable obtained at a low submaximal exercise intensity in a CPET. Cardiorespiratory fitness is already recognized as an important marker of both functional ability, cardiovascular health and mortality, although the information needed to obtaining COP is readily available when expired gas analysis is performed, it has not been used earlier in clinical practice. Our findings show that like CRF,

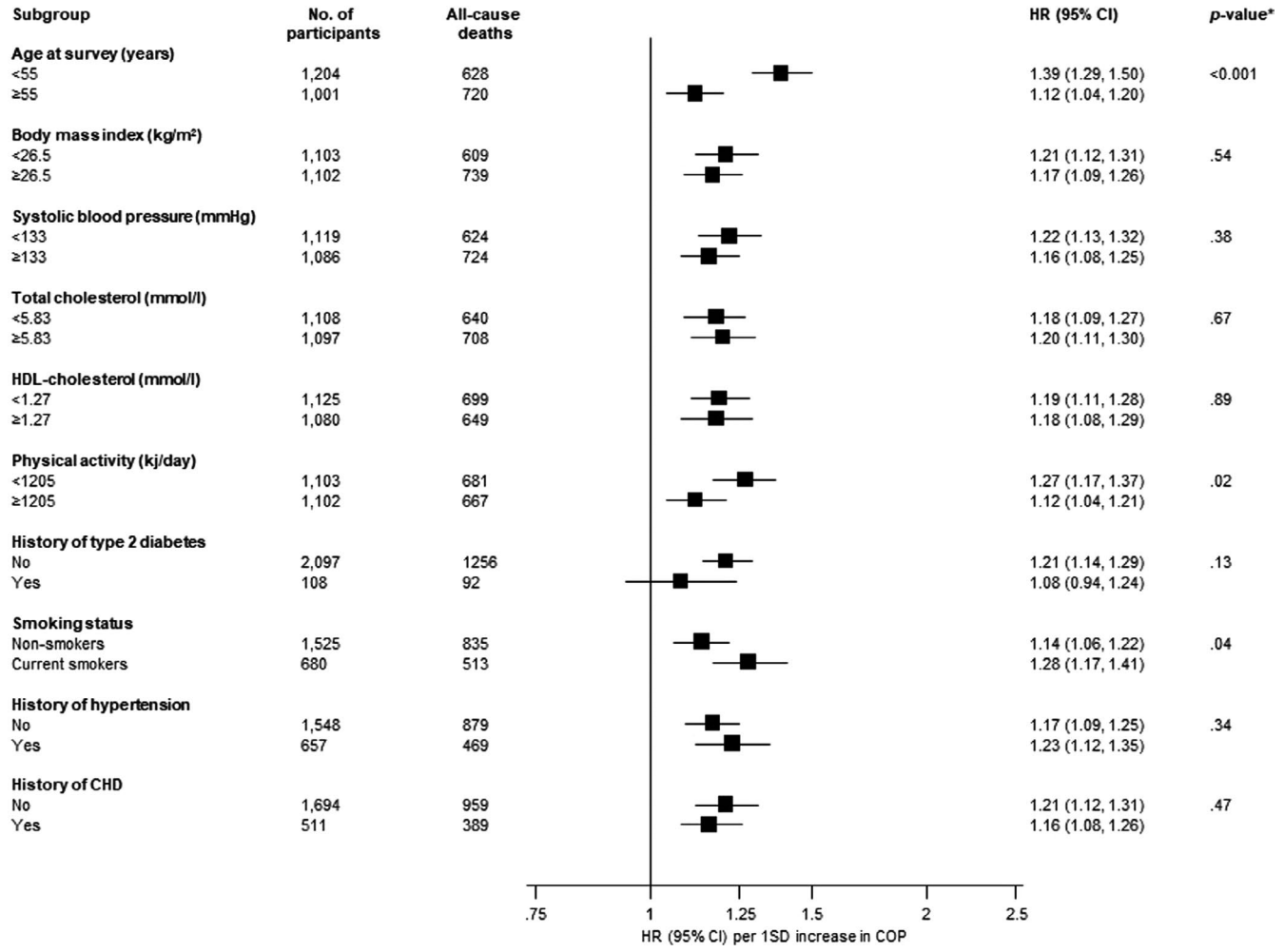

FIGURE 4 Association of cardiorespiratory optimal point with all-cause mortality in clinically relevant subgroups. Hazard ratios were adjusted for age, smoking status, history of type 2 diabetes, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol, body mass index, fasting plasma glucose, alcohol consumption, history of hypertension, prevalent coronary heart disease, use of cholesterol medication, physical activity and socioeconomic status; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; *, *P*-value for interaction; cut-offs used for age, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol; and physical activity are median values

COP provides additional prognostic value to CVD mortality when added on top on conventional risk factors, though the improvements provided by relative CRF were better. Thus, COP constitutes a novel submaximal exercise test index which provides an additional approach to CVD risk assessing. Previous studies have shown that VO2 at anaerobic threshold (AT) is inversely and independently associated with the risk of fatal cardiovascular and all-cause mortality events.[27,28] However, when comparing VO2 at AT and COP assessments, COP presents methodological advantages. Though the clinical utility of COP may seem limited compared to CRF, there are very limited studies on its role as a risk factor and predictor of cardiovascular outcomes. Hence, the current findings add to the body of knowledge in showing that the COP obtained at submaximal exercise intensity in a CPET is strongly associated with cardiovascular deaths and overall mortality and predicts CVD mortality. Furthermore, these findings should stimulate further research on the potential clinical utility of COP.

4.1 | Strengths and limitations

This unique data indicates that a safe submaximal exercise intensity testing protocol provides an opportunity to clarify the relationship between COP and cardiovascular and all-cause mortality within the general population in exercise testing. The current is the first prospective assessment of the multivariable-adjusted associations of COP with the risk of CVD mortality, corroborating the clinical and prognostic relevance of COP obtained in submaximal CPET. We

also compared the potential utility of COP for CVD mortality risk prediction. Other strengths included the relatively large sample size which was also representative of the general population of middle-aged men, the long follow-up period and measurements on a comprehensive panel of many cardiovascular risk markers and biochemical factors which enabled adequate statistical adjustment for potential confounding. We also conducted detailed analyses which included assessment of the dose-response relationship, subgroup analyses in clinically relevant groups and sensitivity analyses.

There were also limitations which deserve mention. First, our analyses were based on a single baseline measurement of COP, introducing the possibility of regression dilution bias and underestimation of the degree of association. Second, there was a potential for residual confounding due to other unmeasured covariates and errors in measurements of risk markers. However, the associations remained robust and consistent in most of investigated subgroups and in a sensitivity analysis which involved exclusion of the first 5 years of follow-up. Third, our study findings were based on a male population, which is noteworthy, given that the value of exercise-test including COP level determination results may differ between men and women; however, the value of CRF as a risk marker is well documented in both sexes. Fourth, the measurement of oxygen uptake during exercise testing requires a well-equipped laboratory with skilled and experienced laboratory personnel but the non-invasive assessment of COP does not require more time or skills than more expensive cardiac imaging techniques. In both the current KIHD study and the Brazilian cohort in which COP has been implemented, CPET was undertaken in cycling exercise and studies on treadmill exercise testing will be needed. As a proof concept in exercise physiology, it is easier to perform a ramp rate of increment in exercise intensity in a cycling, especially when speed (mixing walking and running) and slope are simultaneously being modified along a single CPET. Nevertheless, so far, it is uncertain how COP will behave in prognostic terms on maximal treadmill CPET-derived data.

5 | CONCLUSIONS

Cardiorespiratory optimal point, a respiratory gas ratio easily obtained in a submaximal CPET, is strongly associated with fatal cardiovascular and all-cause mortality events in dose-response fashions in a general population of men. In addition to conventional cardiovascular risk factors, the assessment of COP may be a valuable variable in fatal CVD risk prediction. Future longitudinal studies should explore if COP changes with time (aging) and/or after pharmacological and non-pharmacological interventions (ie, coronary revascularization, drug treatments or exercise training) and how this might influence its prognostic relationship with major unfavorable health outcomes.

6 | PERSPECTIVES

During an incremental CPET, expired gas analysis data could be obtained with diagnostic and/or prognostic implications, using VO_{2peak}, the ventilatory anaerobic threshold (VAT), the ventilatory equivalent for carbon dioxide (VE/VCO2) slope and the oxygen uptake efficiency slope (OUES) curve. These measurements usually require a truly maximum or near maximal exercise test, which is not always viable to perform in aging populations. In an incremental intensity exercise, the oxygen ventilatory equivalent behaves in a U-shape curve pattern for all subjects. Cardiorespiratory optimal point is a dimensionless ventilatory variable obtained at a low submaximal exercise intensity in a CPET that is related to mortality. The current findings show the associations of COP with the risk of CHD, CVD, and all-cause mortality, corroborating the clinical and prognostic relevance of COP obtained in submaximal CPET. In addition to common risk factors, the assessment of COP may be a valuable variable in fatal CVD risk prediction.

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CONFLICTS OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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