Joint Associations Between Cardiorespiratory Fitness, Adiposity, and Mortality in Cardiac Outpatients Within a Secondary Prevention Program

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Purpose: Both cardiorespiratory fitness (CRF) and obesity have been well-established as predictors of cardiometabolic risk and mortality. This study sought to investigate the joint association of CRF and adiposity measures with all-cause and cardiovascular (CVD) mortality in a cohort of patients with stable CVD.

Methods: Data were extracted from the ITER registry. The sample was composed of 2860 cardiac patients involved in an exercise-based secondary prevention program between 1997 and 2023. Patient CRF was estimated using the 1-km treadmill walking test, and measures of body mass index (BMI) and predicted body fat percentage (pBF%) were determined. Cox proportional hazard models were used to determine associations with mortality. All results were adjusted for demographic and clinical confounders.

Results: A total of 1034 deaths (463 of CVD) occurred over a median of 11 years. Each of the fitness-fatness combinations was associated with an increased risk of mortality as compared with normal weight-fit or low pBF%-fit groups. As regards BMI, compared to the reference group, higher mortality risks were observed for overweight-unfit (HR = 1.93: 95% CI, 1.55-2.41; $P < .0001$), and obese-unfit patients (HR = 1.63: 95% CI, 1.28-2.08; $P < .0001$). Similar magnitudes were detected in the moderate pBF%-unfit (HR = 2.47: 95% CI, 1.99-3.06) and high pBF%-unfit (HR = 2.07: 95% CI, 1.69-2.54; $P < .0001$) groups. A similar pattern was observed for CVD mortality.

Conclusion: While overweight and obesity have been associated with an increased risk of death, maintaining CRF can mitigate this risk. These findings support the fundamental role of CRF in exercise assessment and prescription in secondary prevention programs.

Key Words: body composition • cardiorespiratory fitness • cardiovascular disease • epidemiology • mortality • secondary prevention

KEY PERSPECTIVES

What is novel?

- The study reinforces the effectiveness of cardiorespiratory fitness in mitigating all-cause and cardiovascular disease mortality in a cohort of cardiac outpatients involved in an exercise-based secondary prevention program.

What are the clinical and/or research implications?

- The impact of these findings is particularly significant for cardiac outpatients. It underscores the essential role of cardiorespiratory fitness in evaluating and prescribing exercise within secondary prevention programs and provides further evidence about the utilization of the 1-km treadmill walking test for exercise testing and risk stratification.

The prevalence of overweight and obesity has progressively increased in recent decades.[1,2] Currently, approximately one-third of adults in Western societies are

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G.G. and A.R. had access to all of the data and took full responsibility for the integrity of the data and the accuracy of the data analysis. A.R., S.M., and T. P. performed statistical analyses. J.M. and V.Z. drafted the manuscript. A.R., S.M., V.Z., E.M., and T.P. contributed to acquisition of the data. S.M., G.M., G.G., and J.M. contributed to conceptual design. S.M. and J.M. contributed to analyses and interpretation of the results. All authors contributed to drafting the article or reviewing it for significant intellectual content. All authors gave final approval for the version to be submitted.

The study was an investigator-driven clinical trial conducted by the University of Ferrara, Italy.

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.

The study protocol was approved by the institutional ethics committee (cod. 105/2023/Oss/UniFe) and was conducted in accordance with the principles of the Declaration of Helsinki. Patients were informed that their participation was voluntary, and all of them gave written informed consent.

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either overweight or obese.[3,4] These conditions are related to multiple comorbidities and have been widely recognized as major risk factors for all-cause and cardiovascular disease (CVD) mortality.[5-8]

In this context, since the late 1990s, a growing body of evidence focused on the hypothesis that higher cardiorespiratory fitness (CRF) levels could counteract the negative effects of increased levels of body weight on cardiometabolic health, the so-called "fat-but-fit" paradox.[9-16] A recent meta-analysis aimed to summarize the findings regarding the relationship between CRF, body max index (BMI), and CVD mortality.[17] It concluded that even though an elevated BMI was associated with higher mortality risk, being fit nearly reduced this risk in overweight and obese individuals.[17] Other studies investigated this association in populations with existing metabolic or cardiovascular conditions.[11-13,18] These findings could have relevant implications in public health, suggesting that policies should primarily consider physical activity interventions for CRF improvement aiming at reducing the clinical and economic burden of CVD.[17]

In this context, physical activity and CRF are considered well-established markers of health and core components of cardiac rehabilitation and secondary prevention programs.[19-24] However, they are not routinely assessed and remain overlooked when compared with other major risk factors.[25] In addition, few studies investigated the relationship between CRF and body composition in patients with CVD involved in cardiac rehabilitation and secondary prevention interventions. In particular, one paper focused on the combined effects of CRF and adiposity in patients with coronary artery disease attending a traditional cardiac rehabilitation program. The study reported that adiposity and lower levels of CRF were significantly associated with increased mortality.[13] The analysis was well-conducted and provided important evidence on this issue, but it focused only on all-cause mortality and the sample was relatively small, which may have influenced the results.

Therefore, considering the significance of the topic, this prospective analysis aimed to investigate the association of CRF and body fatness indicators with all-cause and CVD mortality in a cohort of patients with stable CVD enrolled in a secondary prevention program.

METHODS

STUDY POPULATION

Data were extracted from the ITER (InTegrating exERcise into lifestyle of cardiac outpatients) study which is a patient registry observational study coordinated by the Center of Sport and Exercise Science, University of Ferrara, Italy (ClinicalTrials.gov. NCT05817305). The purpose of this registry is to assess the efficacy of an exercise-based secondary prevention program among outpatients with stable CVD. The starting sample was comprised of 3327 patients referred by cardiologists or general practitioners to the Center between 1997 and 2023. CVD history was defined as follows: acute myocardial infarction (AMI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft, or heart valve repair or replacement. Coronary heart bypass graft superseded other reasons for hospitalization. If the admitting diagnosis was AMI and a subsequent PTCA was or was not performed, it was coded as an AMI. If a PTCA was performed in the absence of AMI, it was coded as PTCA without AMI. If valvular replacement was performed in the absence of AMI, it was coded as valvular replacement. Admitting diagnosis of heart transplantation, cardiac tumors, or coronary artery anomalies were coded as other. Specific diagnoses were identified according to the International Classification of Diseases coding system, version 10. The study was approved by the Ethics Committee of the University of Ferrara, cod. 105/2023/Oss/UniFe. Written informed consent was obtained from all participants at the time of enrolment.

MEASURES

During each center-based session, patients received a clinical evaluation including medical history, fasting blood chemical analysis, and major cardiovascular risk factor control. Blood pressure was measured at each visit. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.[26] Body mass index was calculated as weight (kg)/height (m^2) and categorized as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2), according to the World Health Organization criteria.[27] Body fat percentage was indirectly predicted (pBF%) through the Deurenberg equation.[28]

All patients performed a submaximal, moderate, and perceptually regulated 1-km treadmill walking test for the estimation of CRF.[29] The test began at a walking speed of 2.0 km/h, increasing by 0.3 km/h every 30 seconds until reaching a speed corresponding to a perceived exertion of 11 to 13 on the Borg 6 to 20 rating of perceived exertion scale. During the test, participants were invited to maintain this intensity for up to 1000 m if walking speed was ≥3.0 km/h. The Borg scale was administered approximately every 2 minutes, modifying walking speed to maintain the selected moderate perceived intensity. Heart rate was continuously monitored using a Polar RS100 heart rate monitor (Polar Electro). CRF reported as peak oxygen uptake was estimated using a specific equation considering distance, age, height, weight, heart rate, and β-blocker use,[29] and was specifically adapted for women.[30] Patients unable to complete the test at a walking speed ≥3.0 km/h performed the test over distances of 500 or 200 m.[31-33] Based on the results of the test, a home-based exercise program was designed. The training program was continuously individualized, aiming for 30 to 60 minutes of moderate-intensity aerobic activity (10-14 on the 6-20 Borg Scale), such as brisk walking, at least 5 days, and preferably 7 days per week. Less fit or less motivated patients were encouraged to accumulate the daily recommended volume in bouts of at least 10 minutes. The program was regularly adjusted during subsequent visits, while individualized goals (eg, achievement of recommended physical activity levels) were discussed and used as a basis for exercise prescription.

Participants were followed for all-cause and CVD mortality. Information on deaths was provided by the regional Health Service Registry of the Emilia-Romagna region or by contacting the patient's general practitioner or relatives to determine vital status. Time from baseline to death was calculated in months.

STATISTICAL ANALYSES

Participants were categorized as fit or unfit based on their estimated peak oxygen uptake, adjusting for age and sex to create homogeneous groups. According to the methodology described above, participants were subsequently categorized as normal weight, overweight, or obese based on BMI. Additionally, participants were divided into tertiles based on pBF%, resulting in three groups: low, moderate, and high body fat percentage. A detailed description of CRF cut-offs is reported in Table S1, Supplemental Digital Content, https://www.R-project.org/, http://links.lww.com/JCRP/A594. Descriptive statistics are presented as mean and SD for continuous variables and frequency and percentage for categorical variables. Normal distribution was verified through a Kolmogorov-Smirnov test. All-cause and CVD mortality were the endpoints for survival analyses. For each patient, the follow-up ended on the date of death or the end of follow-up (December 31, 2023). Association between fitness-fatness combination and all-cause and CVD mortality were investigated performing Cox proportional hazard models, and all results are reported as HR and 95% CI. The normal weight-fit and low pBF%-fit groups were considered reference categories. Associations were adjusted for confounders with three models that included an increasing number of covariates. Model 0 was unadjusted. Model 1 (minimally adjusted model) was adjusted for age, sex, marital status, and education. Model 2 (clinical variables model) was adjusted for all variables in model 1 plus AMI, coronary artery bypass graft, family history, hypertension, diabetes, β-blockers, calcium antagonists, statins, diuretics, antiplatelets, hemoglobin, creatinine, serum glucose, and triglycerides. Schoenfeld residual analysis was performed to assess the assumption of proportionality. The proportional hazard assumption was met for all models. To reduce the potential influence of reverse causality, a sensitivity analysis was performed, excluding all participants who died in the first three years or reported more than three major risk factors at baseline. The level of statistical significance was set at $P < .05$. Statistical analyses were performed using R Statistical Software (R Core Team. A language and environment for statistical computing. Published online 2021; https://www.R-project.org/).

RESULTS

Of the 3327 patients, 2860 people were included in this study. 467 patients (14%) were excluded for the following reasons: (1) inability to complete the test; (2) heart failure classified as class III or higher according to the New York Heart Association[34]; (3) other physical or psychological conditions that interfered with walking ability; or (4) missing data for measures or covariates considered in the analysis. The 1-km treadmill walking test was performed by all the patients without any major complication. The average peak oxygen uptake estimated by the test was 22.2 ± 3.9 ml/kg/min. The median follow-up period was 11 years (IQR: 5.8-17.8, or 16,436 person-years) during which a total of 1034 people died from any cause (463 due to CVD), with an average annual mortality of 6.1%. Demographic and clinical characteristics of the patients stratified by median of estimated CRF are given in Table 1. Compared to the low-fit group, individuals in the high-fit group were relatively younger. In terms of medical history, they presented a higher percentage of AMI diagnoses as well as a higher percentage of PTCA. Finally, they had a higher overall percentage of medication use, except for calcium antagonists and diuretics.

Table 1

Baseline Characteristics of 2860 Italian Patients With Cardiovascular Disease Stratified by Median Value of Estimated Cardiorespiratory Fitness, 1997-2023[a]

Variable	All Patients N = 2860	Low Fit N = 1363	High Fit N = 1497	*P* Value
Estimated VO_{2peak}, mL/kg/min				
Mean ± SD	22.2 ± 3.9	16.8 ± 4.1	27.4 ± 3.8	<.0001
Range, min–max	5.1-43.4	5.1-22.2	22.3-43.4	
Demographics				
Age, yr	65 ± 11	68 ± 10	62 ± 11	<.0001
Female sex	501 (18)	303 (22)	198 (13)	<.0001
LV ejection fraction, %	58 ± 9	57 ± 8	58 ± 9	<.05
Married	2287 (80)	1069 (78)	1218 (81)	NS
High school education	1308 (46)	562 (41)	746 (50)	<.0001
BMI category				
Normal	789 (28)	353 (26)	436 (30)	<.01
Overweight	1341 (48)	617 (46)	724 (49)	<.01
Obese	672 (24)	368 (28)	304 (21)	NS
pBF% category				
Low	951 (33)	357 (26)	594 (40)	<.0001
Moderate	959 (34)	444 (33)	515 (34)	NS
High	949 (33)	562 (41)	387 (26)	<.0001
Risk factors				
Family history	1200 (42)	517 (38)	683 (46)	<.0001
Hypertension	1738 (61)	903 (66)	835 (56)	<.0001
Diabetes	498 (17)	276 (20)	222 (15)	<.001
Current smoking	635 (22)	293 (21)	342 (23)	NS
Hemoglobin, mg/dL	13.5 ± 1.9	13.4 ± 1.9	13.6 ± 1.8	<.01
Total cholesterol, mg/dL	183 ± 48	183 ± 50	183 ± 46	NS
HDL cholesterol, mg/dL	49 ± 15	49 ± 15	49 ± 15	NS
Serum triglycerides, mg/dL	132 ± 69	130 ± 70	134 ± 68	NS
Serum creatinine, mg/dL	1.07 ± 0.32	1.08 ± 0.32	1.06 ± 0.33	<.0001
Medical history				
Myocardial infarction	931 (33)	411 (30)	520 (35)	<.01
PTCA	801 (28)	333 (24)	468 (31)	<.01
CABG	1110 (39)	567 (42)	543 (36)	<.01
Valve replacement	481 (17)	281 (21)	200 (13)	<.0001
Other	534 (19)	248 (18)	286 (19)	<.05
Medications				
ACE inhibitor or ARB	1669 (58)	824 (60)	845 (56)	<.05
Aspirin	2097 (73)	956 (70)	1141 (76)	<.001
β -blocker	1933 (68)	894 (66)	1039 (69)	<.05
Calcium antagonist	527 (18)	308 (23)	219 (15)	<.0001
Statin	1780 (62)	819 (60)	961 (64)	<.05
Diuretic	668 (23)	471 (35)	197 (13)	<.0001

(*continues*)

Table 1

Baseline Characteristics of 2860 Italian Patients With Cardiovascular Disease Stratified by Median Value of Estimated Cardiorespiratory Fitness, 1997-2023a (*Continued*)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; HDL, high-density lipoprotein; LV, left ventricular; NS, nonsignificant; pBF%, predicted body fat percentage; PTCA, percutaneous transluminal coronary angioplasty, stenting, or both; VO_{2peak}, peak oxygen uptake.
[a]Data are presented as mean ± SD or n (%) unless otherwise stated.

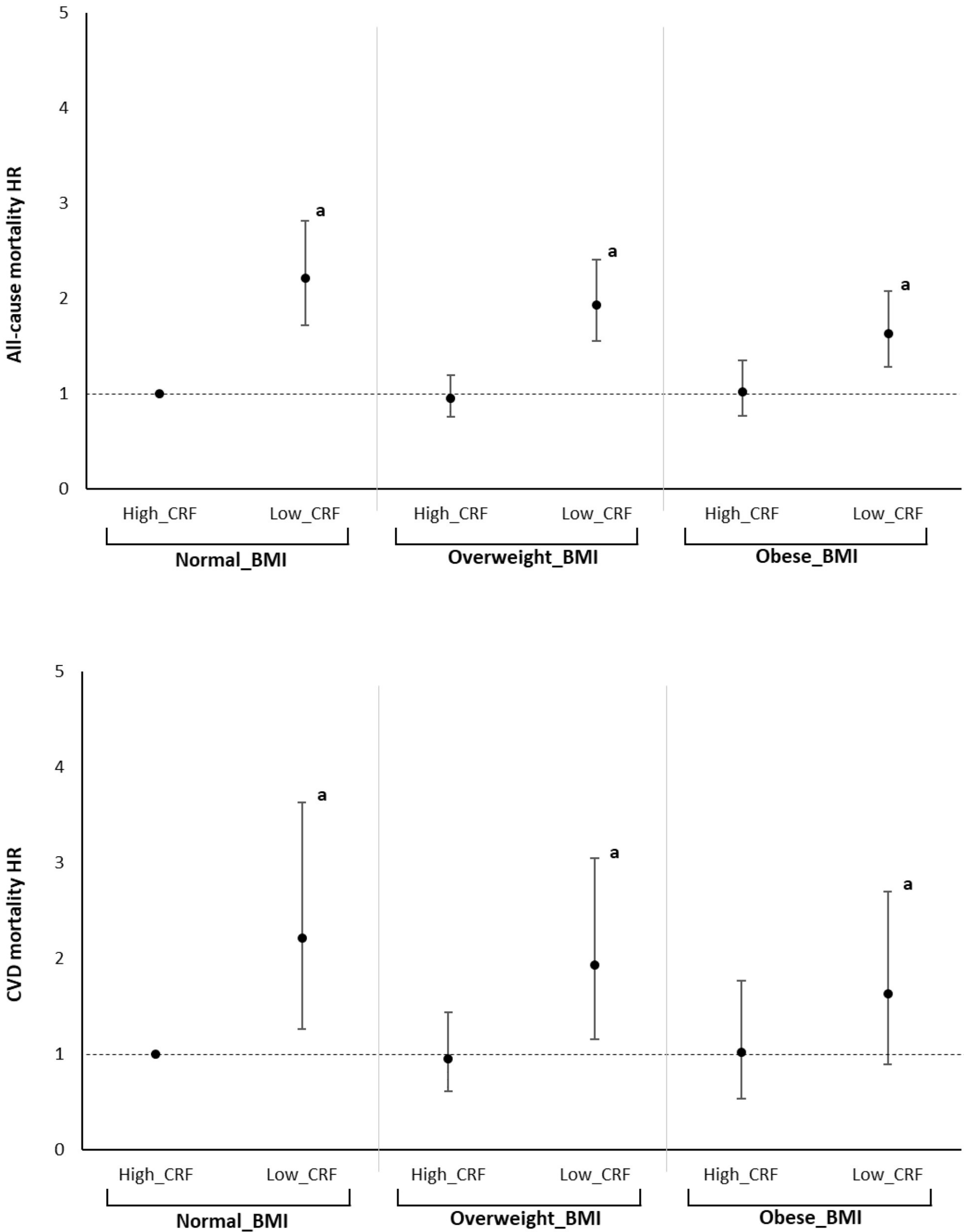

Figure 1. Associations between cardiorespiratory fitness and body mass index with all-cause and CVD mortality in Italian patients with cardiovascular disease, 1997-2023. Data are presented as HR and 95% CI. The reference group were patients with a higher level of cardiorespiratory fitness and normal BMI. Analyses were adjusted for age, sex, marital status, education, myocardial infarction, coronary artery bypass graft, family history, hypertension, diabetes, β-blockers, calcium antagonists, statins, diuretics, antiplatelets, hemoglobin, creatinine, serum glucose, and triglycerides. BMI, body mass index; CRF, cardiorespiratory fitness; CVD, cardiovascular disease.

[a]$P < .0001$.

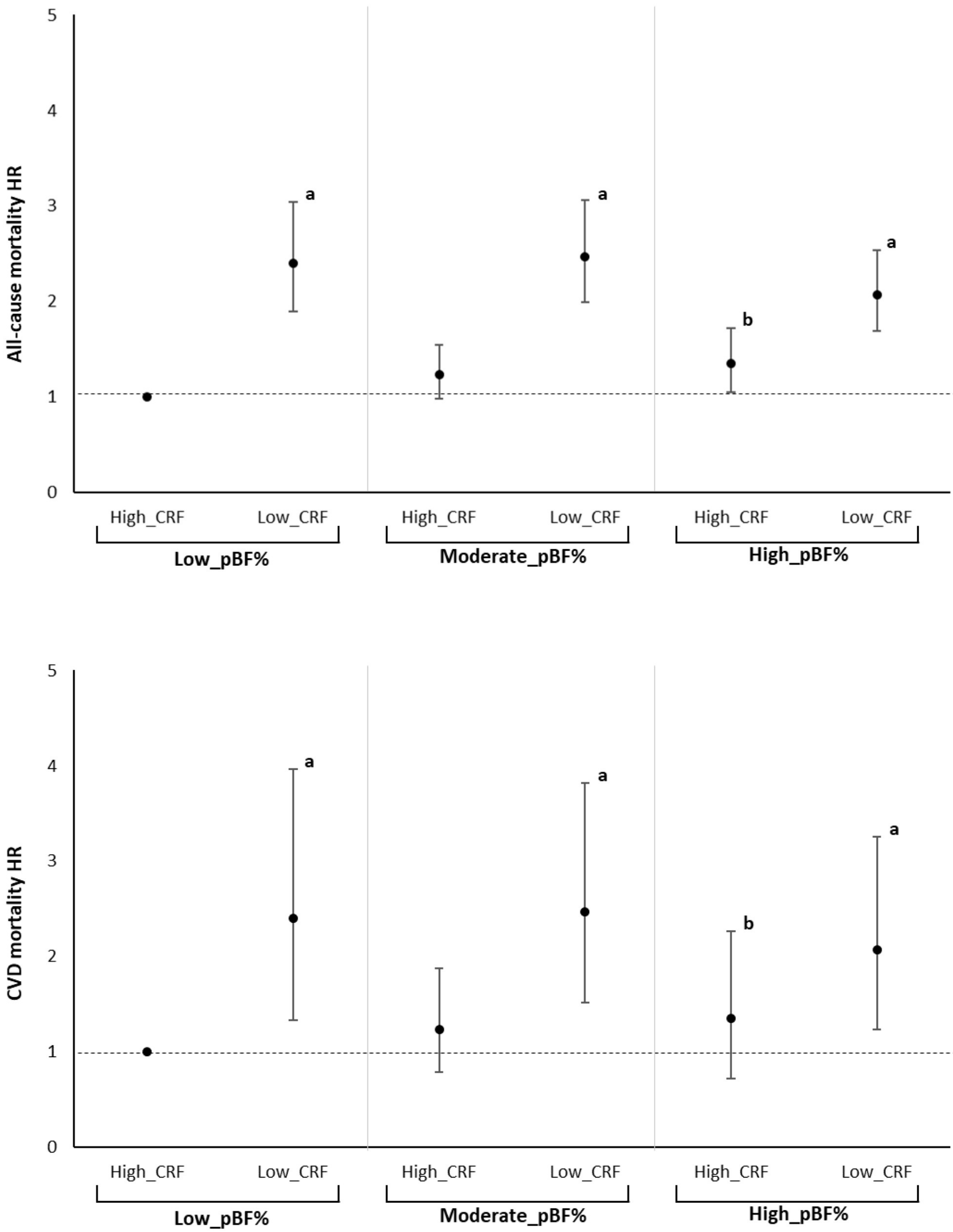

Figure 2. Associations between cardiorespiratory fitness and predicted body percentage with all-cause and CVD mortality in Italian patients with cardiovascular disease, 1997-2023. Data are presented as HR and 95% CI. The reference group were patients with a higher level of cardiorespiratory fitness and lower level of pBF%. Analyses were adjusted for age, sex, marital status, education, myocardial infarction, coronary artery bypass graft, family history, hypertension, diabetes, β-blockers, calcium antagonists, statins, diuretics, antiplatelets, hemoglobin, creatinine, serum glucose, and triglycerides. Abbreviations: CRF, cardiorespiratory fitness; CVD, cardiovascular disease; pBF%, predicted body fat percentage.
[a]$P < .0001$,
[b]$P < .05$.

After adjusting for confounding factors, all fitness-fatness combinations were associated with an increased risk of mortality as compared with reference groups. For all-cause mortality, individuals who were overweight and unfit (HR = 1.93: 95% CI, 1.55-2.41; $P < .0001$) or obese and unfit (HR = 1.63: 95% CI, 1.28-2.08; $P < .0001$) were at higher risk compared to the normal weight-fit group. Notably, a clear difference was evident between high and low CRF levels for all weight categories (Figure 1). This trend was similar when stratifying by pBF%, where both patients who were moderate pBF%-unfit (HR = 2.47: 95% CI, 1.99-3.06; $P < .0001$) and high pBF%-unfit (HR = 2.07: 95% CI, 1.69-2.54; $P < .0001$) were at higher risk of all-cause mortality when compared to the reference group (Figure 2). Similar patterns resulted from associations with CVD mortality (Figures 1 and 2). Detailed descriptions of fitness-fatness combinations and mortality, calculated for each model, are reported in Table S2, Supplemental Digital Content, https://www.R-project.org/, http://links.lww.com/JCRP/A594. Sensitivity analysis, conducted by excluding 569 patients who died during the first three years of follow-up or with the presence of more than three major risk factors, showed similar results to the main analysis (Table S3, Supplemental Digital Content, https://www.R-project.org/, http://links.lww.com/JCRP/A594).

DISCUSSION

The main outcome of the current study was the inverse relationship between CRF levels, associated with adiposity measures, and all-cause or CVD mortality in patients with known CVD. This aspect is particularly significant, as they already present a higher risk than the general population. The association between CRF and BMI revealed that overweight and obese patients in the highest quantiles of CRF had lower risks of all-cause and CVD mortality when compared to unfit peers. Similar results were obtained by combining CRF with percentage of body fat, allowing us to hypothesize a significant relationship, based on the assumption that the excess adiposity predicts mortality, and therefore body fat percentage would be a stronger predictor of death than BMI.[8] This is relevant considering that although several studies demonstrated that CRF modifies association of BMI with mortality, only few of them included measures of body fat.[18]

The current findings are consistent with previous literature and extend the evidence regarding the protective effects of CRF in overweight and obese individuals. Among 77,169 participants from the UK Biobank followed over a median of 7.7 years, all fitness-fatness combinations were associated with an increased risk of mortality, as compared to the normal weight-fit reference group. Compared with the reference, HRs were 1.66 (95% CI, 1.30-2.10), 1.55 (95% CI, 1.19-1.92), and 1.76 (95% CI, 1.41-2.20) for normal weight-unfit, overweight-unfit, and obese-unfit categories, respectively, with HRs ranging from 1.23 to 1.27 for overweight-fit and obese-fit groups.[35]

In terms of body fat percentage, our results are consistent with other studies. In the analysis reported by Lee et al., conducted on 21,925 men during eight years, the relationship between CRF and body fat revealed that lean-unfit men had a higher risk of all-cause and CVD mortality compared to participants who were fit and obese.[9] A similar pattern was observed among 9563 men from the Aerobics Center Longitudinal Study with documented or suspected coronary heart disease, with higher risk of all-cause and CVD mortality in unfit people across body fat categories.[18]

Finally, among patients with CVD enrolled in a cardiac rehabilitation program, Goel et al. described a similar analysis on 855 patients enrolled in CR at the Mayo Clinic over eight years of follow-up. Significant differences in all-cause mortality risk were detected between normal weight-unfit (HR = 9.6: 95% CI, 2.9-31.8), and overweight-fit (HR = 2.2: 95% CI, 0.63-7.40), compared to the normal weight-fit group.[13]

Regarding our indirect CRF assessment, the predictive utility of the 1-km treadmill walking test has been previously investigated.[36-38] The current study aimed to extend the body of evidence supporting the efficacy of this test in stratifying risk, even when used in conjunction with other measurements. In terms of practical applications, the findings suggest that CRF estimated by the 1-km treadmill walking test may complement other clinical tools in the context of cardiac rehabilitation and secondary prevention when direct CRF determination is not possible. Additionally, the 1-km treadmill walking test is feasible and simple to use, providing health professionals with an effective tool for exercise prescription and assessing interventions related to lifestyles of patients with CVD.[39,40]

LIMITATIONS OF THE STUDY

This study has several limitations. First, the results were obtained from volunteers with an interest in participating in an exercise-based secondary prevention program. Hence, the magnitude of these associations could differ among nonparticipants. Second, direct measurement of body fat was not available, and it, therefore, was assessed through a validated equation, generating a potential error of estimation. Third, other variables such as sleep habits, alcohol consumption, and previous smoking levels were not available, nor were socioeconomic data. Therefore, a comparison between "metabolically healthy" and "metabolically unhealthy" obesity was not possible.[41] Fourth, patients with severe clinical, physical, or cognitive conditions were excluded given the impossibility to perform functional evaluations or manage the long-term follow-up. Fifth, given the progressive loss of statistical power, further investigations considering mortality for specific causes or gender-specific analysis were not possible. Lastly, the prognostic value of CRF may have been modified by behavioral or clinical intervention strategies occurring during the follow-up period, and we were not able to account for these factors.

CONCLUSIONS

The current results confirm that CRF is a powerful predictor of mortality. While overweight and obesity have been associated with an increased risk of death, maintaining higher levels of exercise capacity helps to mitigate this risk. The magnitude of this impact is significant for the general population, and even more so for patients with stable CVD. Thus, these findings support the fundamental role of CRF in exercise assessment and prescription as part of secondary prevention programs.

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