Cardiorespiratory Fitness, Body Mass Index, and Heart Failure Mortality in Men: Cooper Center Longitudinal Study

Farrell et al: Fitness, BMI, Heart Failure Mortality

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Abstract

Background—We evaluated the individual and joint associations among cardiorespiratory fitness (CRF), body mass index (BMI), and heart failure (HF) mortality as well as the additive effect of increasing number of cardiovascular risk factors on HF mortality in fit versus unfit men.

Methods and Results—44,674 men without a history of cardiovascular disease underwent a baseline examination between 1971-2010. Measures included BMI and CRF quantified as duration of maximal treadmill exercise testing. Participants were divided into age-specific low, moderate, and high CRF categories. Hazard ratios (HRs) were computed with Cox regression analysis. During a mean follow-up of 19.8±10.4 years, 153 HF deaths occurred. Adjusted HRs across high, moderate, and low CRF categories were 1.0, 1.63, and 3.97 respectively, while those of normal, overweight, and obese BMI categories were 1.0, 1.56, and 3.71 respectively (P for trend <0.0001 for each). When grouped into categories of fit and unfit (upper 80% and lower 20% of CRF distribution respectively), HRs were significantly lower in fit compared with unfit men in normal and overweight BMI strata (P<0.002), but not in obese men. Within men matched for number of HF risk factors, fit men had significantly lower HF mortality than unfit men (P<0.02).

Conclusions—Higher baseline CRF is associated with lower HF mortality risk in men, regardless of the number of HF risk factors present. Men should be counseled on physical activity with the goal of achieving at least a moderate level of CRF, thereby presumably decreasing their risk of HF mortality.

Key Words: body mass index; cardiorespiratory fitness; heart failure, mortality
Heart failure (HF) is a common cause of mortality in older U.S. adults; accounting for 292,214 deaths where HF is listed as a primary or secondary cause, and 58,933 where it is listed as the underlying cause of death. For individuals ≥65 years of age, HF is the most frequent cause of hospitalization and it is estimated that 6 million Americans are living with HF. In addition to its physical and psychological toll, HF also places a significant economic burden on society. The estimated direct and indirect cost of HF in the U.S. was $37.2 billion in 2009.

Well-established risk factors for HF include age, hypertension, tobacco use, diabetes, obesity, high alcohol intake, previous myocardial infarction, sleep apnea and valve disease. While many studies have examined the association between physical activity and cardiovascular disease mortality, much less is known regarding the association between physical activity and HF mortality. Studies which have examined this association relied exclusively on self-reported physical activity patterns, which are only moderately correlated with objective measures of cardiorespiratory fitness (CRF). To our knowledge, there is no reported data relating an objective measure of CRF with HF mortality. While there has been an important recent report on the joint exposures of multiple adiposity measures, physical activity, and incidence of HF, there is no reported data on the joint exposures of CRF and BMI with subsequent HF mortality. Because overweight and obesity, as well as physical inactivity, are highly prevalent in the U.S. population, we believe it is important to examine these issues. Thus, the primary purpose of our investigation is to examine the individual and joint associations among CRF, BMI, and HF mortality in a large cohort of men in the Cooper Center Longitudinal Study (CCLS). A secondary purpose is to examine the additive effect of an increasing number of risk factors on HF mortality in fit versus unfit men.
Methods

Study Participants and Measurements

The CCLS is an updated continuation of the Aerobics Center Longitudinal Study (ACLS)\textsuperscript{19} and includes additional clinical variables, an expanded biobank, and mortality data collected through 2010. Participants in the present study included 44,674 men without a personal history of cardiovascular disease who completed a baseline comprehensive medical examination at the Cooper Clinic in Dallas, TX during 1971-2010. All participants were U.S. residents, and the majority (~90%) were white and from middle-to-upper socioeconomic strata. After receiving written informed consent from each participant, a clinical evaluation was performed and included an examination by a physician, fasting blood chemistry assessment, personal and family health history, anthropometry, resting blood pressure and electrocardiogram, and a maximal graded treadmill exercise test. A standard physician’s scale and stadiometer were used to measure weight and height. BMI was calculated as weight in kilograms divided by height in meters squared. We categorized men as normal weight (BMI 18.5-24.9 kg/m\textsuperscript{2}), overweight (BMI 25.0-29.9 kg/m\textsuperscript{2}), or obese (BMI $\geq$30 kg/m\textsuperscript{2}).

CRF was quantified as the duration of a maximal treadmill exercise test using a modified-Balke protocol\textsuperscript{20} as described elsewhere. Exercise duration from this protocol correlates highly ($r=0.92$) with directly measured maximal oxygen uptake in men.\textsuperscript{21} All participants were encouraged to provide a maximal effort, and those that did not achieve at least 85% of age-predicted maximal heart rate (n=1697) were excluded from the analyses. We felt it was important to exclude these men to avoid CRF misclassification and because some men in this group may have had subclinical disease, which may have prevented them from achieving a maximal test. To standardize exercise test performance, we computed maximal metabolic
equivalent (1 metabolic equivalent = 3.5 ml O₂ uptake/kg body weight/minute) levels of CRF based on the final treadmill speed and grade.²²

Trained Cooper Clinic technicians analyzed blood chemistry using automated techniques following standardized procedures. This laboratory participates in and meets quality control standards of the Centers for Disease Control and Prevention Lipid Standardization Program. The CCLS undergoes annual review and approval by the Institutional Review Board of The Cooper Institute.

Men with previously-diagnosed HF, myocardial infarction, stroke, or cancer (n=5945) were excluded from analyses, as well as men with a BMI <18.5 kg/m² (n=82) and men with <1 year (n=670) of follow-up. Following these exclusions, the resultant sample size of the cohort was 44 674.

Mortality Surveillance

The National Death Index (NDI) was used to ascertain vital status. The NDI has a sensitivity of 96% and a specificity of 100% for determining deaths in the general population.²³ Once we identified possible decedents, Departments of Vital Statistics in the appropriate states were contacted and official copies of death certificates were requested. We compared information on the death certificates with clinical records to confirm that the death certificate matched the individual. A nosologist coded the underlying and contributing cause(s) of death according to the International Classification of Diseases, Ninth and Tenth Editions, Revised.

Statistical Analyses

We followed study participants for mortality from the date of their baseline examination to the date of death for decedents, or to December 31, 2010 for survivors. We computed man-years of exposure as the sum of follow-up time among decedents and survivors. There were 153 HF
19.8±10.4 years of follow-up and 883,870 man-years of exposure. Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of HF mortality according to exposure categories. HR’s were used instead of odds ratios (OR’s) because HR’s are used in cohort studies to express the relative effect of a variable on the risk of an event over time. In our primary analysis, BMI was grouped as described previously. CRF was grouped as fit and unfit based on the upper 80% and the lower 20% of the age-standardized CRF distribution, as previously reported in the CCLS.24 Next, comparisons of HF mortality between fit and unfit men were performed within groups of men with 0, 1, or ≥2 risk factors. Finally, we examined the HRs for each of the individual HF risk factors, with the low risk group (normal resting blood pressure and no personal history of hypertension, current nonsmoker, no personal history of diabetes mellitus, BMI < 30 kg/m², fit, and no family history of CVD) as the referent, and using dichotomies for all comparisons. We assessed interaction among exposure groups using likelihood ratio tests of nested models. All P values are 2-sided, and P<0.05 was regarded as statistically significant.
Results

Of the 1486 total CVD deaths in the cohort, 153 (10.2%) were from HF. Baseline characteristics of the overall cohort and according to vital status are presented in Table 1. On average, decedents were significantly older (49.8 vs. 43.4 yrs), had a higher BMI (27.8 vs. 26.7 kg/m²), lower CRF (9.6 vs. 11.7 METs), higher resting systolic (131.0 vs. 121.6 mmHg) and diastolic (86.5 vs. 81.5 mmHg) blood pressure; and higher total cholesterol (223.2 vs. 206.9 mg/dl), triglyceride (179.5 vs. 137.5 mg/dl), and blood glucose (111.1 vs. 99.8 mg/dl) values than survivors. In addition, decedents had a higher prevalence of smoking than survivors (24.8% vs. 17.4%), as well as a higher prevalence of diabetes (6.5% vs. 1.8%) and hypertension (32.0% vs. 14.4%), P<0.01 for all comparisons).

Baseline characteristics of the cohort across CRF categories are presented in Table 2. Other than alcohol intake and family history of CVD, which were similar across categories of CRF, each of the baseline characteristics was significantly associated with categories of CRF. More specifically, higher levels of CRF were strongly associated with more favorable risk status (P for trend <0.0001 for each characteristic).

Adjusted HRs for HF mortality according to exposures group are presented in Table 3. There was a significant inverse trend in HF mortality across CRF categories (HRs=1.0, 1.63, and 3.97 for high, moderate, and low fit men respectively, P for trend <0.0001. The trend was only slightly attenuated (P<0.0001) following adjustment for BMI (results not shown). As also shown in Table 3, there was a significant positive trend in HF mortality across incremental BMI categories (HRs=1.0, 1.56, and 3.71 for normal weight, overweight, and obese men respectively, P for trend <0.0001. The trend was only slightly attenuated (P<0.003) following adjustment for CRF (results not shown).
To place our findings into a more clinically relevant perspective, we jointly regressed HF mortality rates on BMI and CRF exposures grouped according to standardized definitions (Figure 1). HRs across incremental BMI categories of normal weight, overweight, and obese men were higher in unfit (3.96, 3.64, and 6.11 respectively) than fit (1.0, 1.72, and 4.47 respectively) men. However, these differences reached statistical significance in the normal weight and overweight BMI categories only ($P<0.002$).

We next examined HF mortality in fit vs. unfit men within groups having none (referent) or any 1, or ≥2 risk factors (Figure 2). Within each of these three groups, fit men had significantly lower HF mortality than unfit men ($P<0.02$). In Figure 3, we show the age- and exam-year-adjusted HRs for HF mortality using each individual HF risk factor. HRs for obese (3.29, 2.3-4.7) and unfit (3.37, 2.4-4.7) men were very similar, and were the highest of all risk factors examined.

**Discussion**

To our knowledge, this is the first study using objective measures of both CRF and BMI examining the individual and joint associations among CRF, BMI, and HF mortality in men, as well as examining HF mortality in fit versus unfit men with a varying number of risk factors. CRF was strongly and inversely associated with HF mortality. Compared to men with high CRF, moderate fit and low fit men were 1.63 and 3.97 times more likely to die from HF respectively after adjusting for potential confounding variables over an average follow-up of 19.8 years. BMI was also independently and significantly associated with HF mortality. Importantly, mortality rates were lower in fit than unfit men within each BMI strata, particularly within the normal weight and overweight groups. These findings suggest that among men with
no personal history of cardiovascular disease at baseline, measurement of both CRF and BMI may be preferable to measurement of BMI only for assessing risk of future HF mortality.

As mentioned, a moderate-to-high level of CRF did not provide as much protection from HF mortality in obese men as compared to normal weight and overweight men. Upon exploring this finding further, we determined that the average MET level for fit-obese men (11.0±1.2) was lower than that of fit-overweight (12.0±1.7) and fit-normal weight men (13.2±2.2, \( P \) for trend <0.0001). Thus in the obese group, the level of CRF in moderate-to-high fit men may not be sufficiently greater than that of the unfit men to provide cardioprotective benefit in HF mortality.

An additional novel finding was the marked difference in HF mortality between fit and unfit men with the same number of HF risk factors. HRs for fit men with 0, any 1, or \( \geq \)2 risk factors were substantially lower than in unfit men with the same number of risk factors. For example, among men with \( \geq \)2 risk factors, HRs for fit vs. unfit were 3.01 and 7.27 respectively (\( P=0.0002 \)). Thus, a moderate-to-high level of CRF appears to offer substantial protection against HF mortality irrespective of the number of traditional HF risk factors present. Our findings are consistent with other CCLS papers which have shown that relative to low fit individuals, attaining a moderate to high level of CRF attenuates mortality risk in obese individuals 25, hypertensives 26, type 2 diabetics 27, and smokers 28.

We were also able to compare the relative strength of each risk factor on HF mortality. Low CRF (unfit) and obesity emerged as the two strongest risk factors with HRs of 3.37 and 3.29 respectively (\( p<0.0001 \) for each). As previously mentioned, there are few studies in the literature which have examined the relationships between physical activity, adiposity, and HF incidence. In a recent study of 28,842 Finnish men with a mean follow-up of 18.4 years, Hu reported an inverse association between physical activity and the incidence of HF, as well as a
direct association between various adiposity measures and incidence of HF.\textsuperscript{14} Joint associations revealed a protective effect of physical activity across all levels of BMI. For 21 094 male participants in the Physicians Health Study, a strong positive association was reported between BMI and HF incidence, and a strong inverse association was found between vigorous physical activity and HF incidence.\textsuperscript{13} More specifically, each 1-kg/m\textsuperscript{2} increase in BMI was associated with an 11\% increase in HF incidence, and men who reported vigorous physical activity 5-7 days per week were 27\% less likely to develop HF compared to men who reported that they rarely or never performed vigorous activity. Within each category of BMI, risk of HF incidence was reduced in men who reported vigorous physical activity. In this same study, the effects of BMI and vigorous activity on HF mortality were shown to be similar to their effects on HF incidence.

There are many possible mechanisms by which moderate-to-high CRF may be protective against HF mortality. As early as 1972, cross-sectional analyses by Bjorntorp showed that fit middle-aged men had significantly lower insulin responses to a glucose challenge than their unfit peers.\textsuperscript{29} Numerous training and prospective studies performed since that time have shown that moderate-to-high levels of physical activity are associated with improved insulin sensitivity,\textsuperscript{30} which in turn reduces the incidence of type 2 diabetes\textsuperscript{31} and metabolic syndrome.\textsuperscript{32} Furthermore, mortality among individuals with type 2 diabetes\textsuperscript{33} and metabolic syndrome\textsuperscript{34} is significantly lower across increasing levels of CRF. In both cross-sectional\textsuperscript{35} and prospective studies, moderate-to-high levels of CRF are shown to be associated with more favorable blood lipid profiles,\textsuperscript{36} decreased resting blood pressure,\textsuperscript{37} and decreased mortality among those with hypertension,\textsuperscript{26} as well as a decreased likelihood of developing hypertension.\textsuperscript{38}

In addition to exerting favorable effects on HF risk factors, there is cross-sectional and prospective evidence that exercise training is associated with beneficial structural and functional
changes in the myocardium. Levy found that a progressive 6-month aerobic training program significantly increased end-diastolic volume, absolute peak filling rate, and peak early or single peak diastolic filling rate at rest and during exercise at all matched heart rates in younger (n=17) and older (n=14) males. In cross-sectional analyses, Seals found that endurance-trained older men had significantly better left ventricular systolic function than sedentary controls. More specifically, the trained men had greater left ventricular end-diastolic volume at rest and during peak exercise, as well as greater left ventricular exercise reserve (defined as the change in ejection fraction between rest and exercise). Additionally, a greater decrease in end-systolic volume was shown in the trained men during exercise than the controls, despite similar increases in systolic blood pressure in the two groups. Left ventricular fractional shortening was also higher during peak exercise in the trained group. Because the left ventricular wall thickness-to-radius ratio did not differ between the two groups, these findings indicated a pattern of volume-overload left ventricular hypertrophy in the trained men. In a cross-sectional study comparing long distance runners to sedentary controls, Haskell found a >2-fold greater vasodilatory capacity of the coronary arteries in the running group than in controls during nitroglycerin administration. More recently, greater coronary vasodilation in response to nitroglycerin was shown in a more representative population (physically active older individuals versus less active older individuals). Both daily volume and intensity of activity were significantly correlated to vasodilation. These findings remained significant following adjustment for a number of potential confounders. Fujimoto examined the effects of a 1-year progressive jogging program on myocardial function in 9 sedentary men and women with a mean age of 70 years. Following training, volume-overload left ventricular hypertrophy was shown. Although aerobic power, total aortic compliance, and arterial elastance were significantly improved by training, there was
no change in left ventricular stiffness. The authors speculated that lack of improvement in LV stiffness may have been due to either the age at which the exercise program was initiated, or an insufficient duration of training.

An important point to consider when interpreting the joint associations of CRF and BMI with HF mortality is the method in which CRF was grouped for this analysis. Currently there is not a widely accepted method of defining CRF levels for use in clinical or public health research. In the CCLS, we standardized the definition of low fitness (unfit) according to the bottom 20% of the age-standardized distribution of maximal exercise duration within the overall CCLS population with individuals in the remaining 80% of the distribution considered to be fit. By our definition, it would thus appear that even modest levels of CRF are associated with lower risk of HF mortality. For example, a 50-59-year-old man would need to achieve a maximal MET level of 8.9 or higher to qualify for the fit category. This is equivalent to covering approximately 1.2 miles in the Cooper 12-Minute Run-Walk Test or achieving a treadmill time of approximately 8.5 minutes on a standard Bruce Treadmill Test. This level of CRF can be achieved by many, perhaps even most, apparently healthy adults through moderate amounts and intensities of aerobic physical activity such as brisk walking.

Among the strengths of the current study are a large and well-characterized cohort of men, the use of objective measures for CRF and BMI, and an extensive follow-up. While BMI is a proxy measure of body fatness, it was significantly correlated with percent body fat in the subset of the cohort for whom percent body fat was measured (n=39 971, r=0.68; data not shown). To decrease the possibility that pre-existing disease was present at baseline, men with a BMI <18.5 kg/m², those who were not able to achieve at least 85% of predicted maximal heart rate, and men with <1 year of follow-up were excluded from analyses. Restricting our analyses
to men with ≥3 years follow-up (n=42,764) did not materially change the strength or patterns of these associations (data not shown), making us more confident that subclinical HF was not a cause of low CRF and subsequent greater HF mortality in the low-fit group. We were also able to adjust for a large number of potentially confounding variables in the multivariate analyses.

This study has limitations. The cohort consists of men only who are primarily white and from middle-to-upper socioeconomic strata; therefore, our findings must be cautiously interpreted when generalizing to other populations. This same limitation strengthens the internal validity of our findings by reducing potential confounding by these variables. Furthermore, median levels of CRF in CCLS men are very similar to median values obtained on a representative sample of U.S. men.46 We also point out that the overall prevalence of metabolic syndrome among men in the CCLS cohort between 1979-2010 is ~25%, which is similar to the prevalence that has been reported among NHANES men in recent years.47 These findings suggest that Cooper Clinic men have similar risk profiles compared to other U.S. men.

Using CRF and BMI exposures as categorical rather than continuous variables could also be viewed as a potential limitation. We chose the latter approach because we feel that the use of clinically established cut points is more understandable and useful for healthcare professionals. Because a relatively large number of decedents in the cohort did not have a waist circumference measurement (n=78), we were unable to evaluate the effects of central adiposity on mortality risk. We are reporting only baseline data on adiposity exposures and CRF. It is possible that changes in these exposures may have occurred during the follow-up period, which in turn may have influenced our results. An additional limitation includes the absence of more extensive information on smoking habits, such as number of pack-years. The relatively low number of obese men (n=7244, 16%) in the cohort may have limited our ability to detect a significant
difference in mortality between fit and unfit obese men. Because the Cooper Clinic did not begin to measure HDL and LDL cholesterol until 1978, we have missing data for these variables in Table 1. We do not have information regarding the presence or absence of sleep apnea in the cohort. Because high alcohol intake (>21 drinks/week) was not significantly associated with CHF mortality in our cohort, and because a substantial number of men (n= 7952) had missing data for the alcohol intake question, we did not include this variable in our multivariate analyses. However, by including men in the analyses who were missing the alcohol intake variable, we were able to increase our number of HF deaths. Finally, we were unable to evaluate medication use or dietary factors in this cohort.

In summary, the inverse relationship between baseline CRF and HF mortality in men is quite strong and is materially unaffected by adjustment for BMI and other potential confounders. Within each category of BMI, HF mortality was lower in fit compared to unfit men. Irrespective of the number of risk factors present, fit men had substantially lower HF mortality than unfit men. When examining the individual strength of each risk factor on HF mortality, low CRF (unfit) and obesity functioned as the strongest risk factors. Regardless of the number of HF risk factors present, clinicians are encouraged to counsel their male patients to increase their levels of physical activity with the goal of achieving at least a moderate level of CRF, thereby presumably decreasing their risk of HF mortality.

Acknowledgements

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Disclosures

None.

References


44. Cooper KH. A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. JAMA. 1968;203:201-204.
Table 1. Baseline Characteristics of 44,674 Men, Cooper Center Longitudinal Study; 1971-2010

<table>
<thead>
<tr>
<th></th>
<th>All (n=44,674)</th>
<th>Survivors (n=44,521)</th>
<th>HF decedents (n=153)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>43.4±9.2</td>
<td>43.4±9.2</td>
<td>49.8±9.0</td>
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<tr>
<td>BMI, kg/m²</td>
<td>26.7±3.9</td>
<td>26.7±3.9</td>
<td>27.8±4.0</td>
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<td>Cardiorespiratory fitness level, METs</td>
<td>11.6±2.4</td>
<td>11.7±2.4</td>
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<tr>
<td>Resting heart rate</td>
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<td>61.2±10.7</td>
<td>64.0±12.0</td>
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<td>Systolic blood pressure, mmHg</td>
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<td>121.6±13.0</td>
<td>131.0±18.2</td>
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<td>81.5±9.5</td>
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<td>Cholesterol, mg/dL</td>
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<td>206.9±40.0</td>
<td>223.2±39.4</td>
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<td>HDL, mg/dL</td>
<td>46.2±12.0</td>
<td>46.2±12.0</td>
<td>41.7±11.3</td>
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<td>(n missing=9137)</td>
<td>(n missing=9060)</td>
<td>(n missing=77)</td>
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<td>LDL, mg/dL</td>
<td>132.4±35.3</td>
<td>132.3±35.3</td>
<td>147.5±35.5</td>
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<td>(n missing=9978)</td>
<td>(n missing=9895)</td>
<td>(n missing=84)</td>
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<td>Triglycerides, mg/dL</td>
<td>137.6±113.1</td>
<td>137.5±112.8</td>
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<td>Glucose, mg/dL</td>
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<td>Alcohol, drinks/week</td>
<td>8.4±10.6</td>
<td>8.4±10.6</td>
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<tr>
<td>(n missing=3976)</td>
<td>(n missing=3961)</td>
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<tr>
<td>Smoking, %</td>
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<tr>
<td>Nonsmoker</td>
<td>25,495 (57.1)</td>
<td>25,436 (57.1)</td>
<td>59 (38.6)</td>
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<td>Former smoker</td>
<td>11,380 (25.5)</td>
<td>11,324 (25.4)</td>
<td>56 (36.6)</td>
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<td>Current smoker</td>
<td>7,799 (17.5)</td>
<td>7,761 (17.4)</td>
<td>38 (24.8)</td>
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<td>Personal history of diabetes, %</td>
<td>802 (1.8)</td>
<td>792 (1.8)</td>
<td>10 (6.5)</td>
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<tr>
<td>Personal history of hypertension, %</td>
<td>6,457 (14.5)</td>
<td>6,408 (14.4)</td>
<td>49 (32.0)</td>
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<tr>
<td></td>
<td>19 792 (44.3)</td>
<td>19 719 (44.3)</td>
<td>73 (47.7)</td>
</tr>
<tr>
<td>--------------------------------</td>
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<tr>
<td>Family history of CVD, %</td>
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<tr>
<td>Follow-up, y</td>
<td>19.8±10.4</td>
<td>19.8±10.3</td>
<td>23.0±9.0</td>
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Unless otherwise specified, data are means±SD.

HF, heart failure; BMI, body mass index; METs, 1 metabolic equivalent = 3.5 ml O$_2$ uptake/kg body weight/minute; HDL, high density lipoprotein; LDL, low density lipoprotein; CVD, cardiovascular disease.
Table 2. Baseline Characteristics of 44 674 Men Across Different Categories of Cardiorespiratory Fitness, Cooper Center Longitudinal Study; 1971-2010

<table>
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<tr>
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<th>Low Fitness (n=9120)</th>
<th>Moderate Fitness (n=17 775)</th>
<th>High Fitness (n=17 779)</th>
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<td>43.6±9.2</td>
<td>42.9±9.1</td>
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<td>BMI, kg/m²</td>
<td>29.7±5.1</td>
<td>26.9±3.2</td>
<td>25.0±2.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cardiorespiratory fitness level, METs</td>
<td>8.7±1.1</td>
<td>10.9±0.9</td>
<td>13.8±1.8</td>
<td>&lt;0.0001</td>
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<tr>
<td>Resting heart rate</td>
<td>67.7±10.6</td>
<td>62.6±9.6</td>
<td>56.4±9.5</td>
<td>&lt;0.0001</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>124.7±13.8</td>
<td>121.5±12.8</td>
<td>120.1±12.6</td>
<td>&lt;0.0001</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84.2±9.9</td>
<td>81.9±9.5</td>
<td>79.7±9.0</td>
<td>&lt;0.0001</td>
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<td>Cholesterol, mg/dL</td>
<td>215.9±42.1</td>
<td>210.0±40.1</td>
<td>199.1±37.3</td>
<td>&lt;0.0001</td>
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<td>HDL, mg/dL (n missing=2486)</td>
<td>41.1±10.5</td>
<td>44.5±11.0 (n missing=2879)</td>
<td>49.9±12.3 (n missing=1956)</td>
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<tr>
<td>LDL, mg/dL (n missing=2790)</td>
<td>136.9±37.5</td>
<td>135.6±35.5 (n missing=3199)</td>
<td>127.6±33.6 (n missing=2057)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>184.7±157.2</td>
<td>144.9±109.4</td>
<td>105.5±71.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>104.6±24.6</td>
<td>99.8±16.4</td>
<td>97.3±11.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol, drinks/week</td>
<td>8.3±11.0</td>
<td>8.4±10.7</td>
<td>8.3±10.4</td>
<td>0.50</td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>4215 (46.2)</td>
<td>9971 (56.1)</td>
<td>11 309 (63.6)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>2272 (24.9)</td>
<td>4449 (25.0)</td>
<td>4659 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>2633 (28.9)</td>
<td>3355 (18.9)</td>
<td>1811 (10.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Personal history of diabetes, %</td>
<td>371 (4.1)</td>
<td>300 (1.7)</td>
<td>131 (0.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Personal history of hypertension, %</td>
<td>2133 (23.4)</td>
<td>2623 (14.8)</td>
<td>1701 (9.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>3918 (43.0)</td>
<td>7882 (44.3)</td>
<td>7992 (45.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>21.2±11.1</td>
<td>19.9±10.6</td>
<td>19.0±9.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Unless otherwise specified, data are means±SD.

BMI, body mass index; METs, 1 metabolic equivalent = 3.5 ml O₂ uptake/kg body weight/minute; HDL, high density lipoprotein; LDL, low density lipoprotein; CVD, cardiovascular disease.
Table 3. Adjusted* Hazard Ratios (95% Confidence Intervals) for Heart Failure Mortality Across Cardiorespiratory Fitness and Body Mass Index Categories in 44,674 Men who were Followed for an Average of 19.8±10.4 Years, Cooper Center Longitudinal Study, 1971-2010

<table>
<thead>
<tr>
<th>CRF Category</th>
<th>High (Quintile 4-5)</th>
<th>Moderate (Quintile 2-3)</th>
<th>Low (Quintile 1)</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n</td>
<td>17,775</td>
<td>9120</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HF deaths, n</td>
<td>21</td>
<td>1.63</td>
<td>3.97</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>1.0-2.7</td>
<td>2.4-6.5</td>
<td></td>
</tr>
<tr>
<td>BMI category</td>
<td>Normal Weight</td>
<td>Overweight</td>
<td>Obese</td>
<td></td>
</tr>
<tr>
<td>kg/m²</td>
<td>18.5-24.9</td>
<td>25.0-29.9</td>
<td>≥30</td>
<td></td>
</tr>
<tr>
<td>Total n</td>
<td>16,043</td>
<td>21,387</td>
<td>7,244</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HF deaths, n</td>
<td>38</td>
<td>74</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>1.56</td>
<td>3.71</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>1.1-2.3</td>
<td>2.4-5.8</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, exam year, systolic blood pressure, smoking status, family history of cardiovascular disease, and diabetes.

CRF, cardiorespiratory fitness; HF, heart failure; HR, hazard ratio; CI, confidence intervals; BMI, body mass index.
Figure Legends

Figure 1. Joint association of cardiorespiratory fitness and body mass index in men with adjusted* rates of heart failure (HF) mortality, Cooper Center Longitudinal Study, 1971-2010.

Figure 2. Adjusted* hazard ratios for heart failure (HF) mortality in fit and unfit men based on number of risk factors, Cooper Center Longitudinal Study, 1971-2010.

Figure 3. Adjusted* hazard ratios for heart failure (HF) mortality in men based on presence of individual risk factors, Cooper Center Longitudinal Study, 1971-2010.
Figure 1. Joint Association of CRF and BMI with Adjusted* Rates of Heart Failure (HF) Mortality, CCLS Men, 1971-2010.

*Adjusted for age, exam year, resting systolic BP, smoking status, family history of CVD, and diabetes.

Numbers on top of boxes represent HRs (95% CI).

*P<0.002 compared to fit

1.0

Fit (n=14,580)

Normal Weight (18.5-24.9)

3.96* (2.1-7.6)

Unfit (n=1463)

3.64* (2.1-6.2)

Unfit (n=3539)

1.72 (1.0-2.9)

Fit (n=17,435)

4.47 (2.1-9.4)

Unfit (n=3952)

6.11 (3.5-10.7)

Obese (≥30)

HR for HF Mortality

BY GUEST ON JULY 9, 2017 http://CIRCHARTFAILURE.AHAJOURNALS.ORG/Downloaded FROM http://CIRCHARTFAILURE.AHAJOURNALS.ORG/
Figure 2. Adjusted* Hazard Ratios for Heart Failure (HF) Mortality in Men Based on Number of Risk Factors and Cardiorespiratory Fitness Level, CCLS, 1971-2010.

*adjusted for age and exam year.

Numbers on top of boxes represent HRs (95% CI).

- *P=0.02 compared to fit
- **P<0.0001 compared to fit
- ***P=0.0002 compared to fit

*Risk factors include elevated resting blood pressure (≥140/90 mmHg) or personal history of hypertension, current smoking, personal history of diabetes, obesity (BMI ≥30 kg/m²), and family history of CVD.
Figure 3. Adjusted* Hazard Ratios for Heart Failure (HF) Mortality in Men Based on Presence of Individual Risk Factors, CCLS, 1971-2010.

*Adjusted for age and exam year. All comparisons are dichotomies with the referent category being the group who does not have the risk factor.

Numbers on top of boxes represent HRs (95% CI).
Numbers in boxes represent HF deaths.

*P<0.0001
**P<0.005

Hypertension (n=14,028)  
Current Smoking (n=7799)  
Diabetes (n=802)  
BMI ≥ 30 kg/m² (n=7244)  
Unfit (n=9120)  
Family History of CVD (n=19,792)

Heart Failure Risk Factor
Cardiorespiratory Fitness, Body Mass Index, and Heart Failure Mortality in Men: Cooper Center Longitudinal Study
Stephen W. Farrell, Carrie E. Finley, Nina B. Radford and William L. Haskell

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