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

Stephen W. Farrell, PhD; Carrie E. Finley, MS; Nina B. Radford, MD; William L. Haskell, PhD

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

Methods and Results—A total of 44,674 men without a history of cardiovascular disease underwent a baseline examination between 1971 and 2010. Measures included body mass index and CRF quantified as duration of maximal treadmill exercise testing. Participants were divided into age-specific low, moderate, and high CRF categories. Hazard ratios were computed with Cox regression analysis. During a mean follow-up of 19.8±10.4 years, 153 HF deaths occurred. Adjusted hazard ratios across high, moderate, and low CRF categories were 1.0, 1.63, and 3.97, respectively, whereas those of normal, overweight, and obese body mass index 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), hazard ratios were significantly lower in fit compared with unfit men in normal and overweight body mass index strata (P<0.002) but not in obese men. Within men matched for the same 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. (Circ Heart Fail. 2013;6:898-905.)

Key Words: body mass index ■ heart failure ■ physical fitness

Heart failure (HF) is a common cause of mortality in older US adults, accounting for 292,214 deaths where HF is listed as a primary or secondary cause and for 58,933 deaths where it is listed as the underlying cause of death.1 For individuals aged ≥65 years, 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 the society. The estimated direct and indirect cost of HF in the United States is $37.2 billion in 2009.1

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Well-established risk factors for HF include age, hypertension, tobacco use, diabetes mellitus, obesity, high alcohol intake, previous myocardial infarction, sleep apnea,2 and valve disease.3-6 Although many studies have examined the association between physical activity and cardiovascular disease (CVD) mortality,7-12 much less is known about the association between physical activity and HF mortality. Studies that have examined this association relied exclusively on self-reported physical activity patterns,13-15 which are only moderately correlated with objective measures of cardiorespiratory fitness (CRF).16 To our knowledge, there are no reported data relating an objective measure of CRF with HF mortality. Although there has been an important recent report on the joint exposures of multiple adiposity measures, physical activity, and incidence of HF,14 there are no reported data on the joint exposures of CRF and body mass index (BMI) with subsequent HF mortality. Because overweight and obesity, as well as physical inactivity, are highly prevalent in the US population,17,18 we think 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)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 CVD who completed a baseline comprehensive medical examination at the Cooper Clinic in Dallas, TX, during
Mortality Surveillance
The National Death Index was used to ascertain vital status. The National Death Index 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 causes 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 from the date of their baseline examination to the date of death for decedents or to December 31, 2010, for survivors. 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), as well as men with a BMI <18.5 kg/m² (n=82) and men with <1 year (n=670) of follow-up, were excluded from analyses. Following these exclusions, the resultant sample size of the cohort was 44,674.

Results
Of the 1486 total CVD deaths in the cohort, 153 (10.2%) were from HF. Baseline characteristics of the overall cohort according to vital status are presented in Table 1. On average, decedents were significantly older (49.8 versus 43.4 years), had higher BMI (27.8 versus 26.7 kg/m²), lower CRF (9.6 versus 11.7 METs), higher resting systolic (131.0 versus 121.6 mmHg) and diastolic (86.5 versus 81.5 mmHg) blood pressure, and higher total cholesterol (223.2 versus 206.9 mg/dL), triglyceride (179.5 versus 137.5 mg/dL), and blood glucose (111.1 versus 99.8 mg/dL) values than survivors. In addition, decedents had a higher prevalence of smoking than survivors (24.8% versus 17.4%), as well as a higher prevalence of diabetes mellitus (6.5% versus 1.8%) and hypertension (32.0% versus 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) after 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) after 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 versus unfit men within groups having none (referent) or any 1 or ≥2 risk factors.
As mentioned, a moderate-to-high level of CRF did not significantly lower HF mortality than unfit men ($P<0.02$). In Figure 2, we show the age-adjusted and examination-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 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 with men with high CRF, moderate-fit and low-fit men were 1.63 and 3.97× more likely to die from HF, respectively, after adjusting for potential confounding variables during 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 CVD 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 compared with normal weight and overweight men. On exploring this finding further, we determined that the average MET level for fit–obese men (11.0±1.2) was lower than that in 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 in 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 ≥2 risk factors were substantially lower than those in unfit men with the same number of risk factors. For example, among men with ≥2 risk factors, HRs for fit versus unfit were 3.01 and 7.27, respectively ($P=0.0002$). Thus, a moderate-to-high level of CRF seems to offer substantial protection against HF mortality, irrespective of the number of traditional HF risk factors present. Our findings are consistent with other CCLS articles that have shown that relative to low-fit individuals, attaining a moderate-to-high level of CRF attenuates mortality risk in obese individuals, hypertensives, type 2 diabetes mellitus individuals, and smokers.

We were also able to compare the relative strength of each risk factor on HF mortality. Low CRF (unfit) and obesity emerged as the 2 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 that have examined the relationships among 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 et al 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. Joint associations revealed a
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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. More specifically, each 1 kg/m² increase in BMI was associated with an 11% increase in HF incidence, and men who reported vigorous physical activity 5 to 7 days per week were 27% less likely to develop HF compared with 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. 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, which in turn

Table 3. Adjusted† HRs (95% CIs) for Heart Failure Mortality Across Cardiorespiratory Fitness and BMI Categories in 44,674 Men Who Were Followed for an Average of 19.8±10.4 Years in the Cooper Center Longitudinal Study During 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>17 779</td>
<td>17 775</td>
<td>9120</td>
<td></td>
</tr>
<tr>
<td>HF deaths, n</td>
<td>21</td>
<td>47</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>1.63</td>
<td>3.97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.0–2.7</td>
<td>2.4–6.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI category, kg/m²</td>
<td>Normal Weight</td>
<td>18.5–24.9</td>
<td>25.0–29.9</td>
<td>≥30</td>
</tr>
<tr>
<td>Total, n</td>
<td>16 043</td>
<td>21 387</td>
<td>7244</td>
<td></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>&lt;0.0001</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.1–2.3</td>
<td>2.4–5.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

†Adjusted for age, examination year, systolic blood pressure, smoking status, family history of cardiovascular disease, and diabetes mellitus.
reduces the incidence of type 2 diabetes mellitus and metabolic syndrome. Furthermore, mortality among individuals with type 2 diabetes mellitus and metabolic syndrome is significantly lower across increasing levels of CRF. In both cross-sectional and prospective studies, moderate-to-high levels of CRF are shown to be associated with more favorable blood lipid profiles, decreased resting blood pressure, and decreased mortality among those with hypertension, as well as a decreased likelihood of developing hypertension.

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 et al 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) men. In cross-sectional analyses, Seals et al found that endurance-trained older men had significantly better left ventricular (LV) systolic function than sedentary controls. More specifically, the trained men had greater LV end-diastolic volume at rest and during peak exercise, as well as greater LV exercise reserve (defined as the change in ejection fraction between rest and exercise). In addition, 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 2 groups. LV fractional shortening was also higher during peak exercise in the trained group. Because the LV wall thickness-to-radius ratio did not differ between the 2 groups, these findings indicated a pattern of volume-overload LV hypertrophy in the trained men. In a cross-sectional study comparing long-distance runners with sedentary controls, Haskell et al found a >2-fold greater vasodilatory capacity of the coronary arteries in the running group than in

**Figure 1.** Joint association of cardiopulmonary fitness and body mass index (BMI) in men with adjusted* rates of heart failure (HF) mortality in the Cooper Center Longitudinal Study during 1971–2010. *Adjusted for age, exam year, resting systolic blood pressure, smoking status, family history of cardiovascular disease, and diabetes mellitus. Numbers on top of boxes represent hazard ratios (HRs; 95% confidence interval [CI]). NS indicates nonsignificant.

**Figure 2.** Adjusted hazard ratios (HRs) for heart failure (HF) mortality in fit and unfit men based on the number of risk factors in the Cooper Center Longitudinal Study during 1971–2010. *Adjusted for age and exam year. Numbers on top of boxes represent HRs (95% confidence interval [CI]). Risk factors include elevated resting blood pressure (≥140/90 mm Hg) or personal history of hypertension, current smoking, personal history of diabetes mellitus, obesity (body mass index ≥30 kg/m²), and family history of cardiovascular disease.*P=0.02 compared with fit. **P<0.0001 compared with fit. ***P=0.0002 compared with fit.
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 after adjustment for several potential confounders. Fujimoto et al. 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. After training, volume-overload LV hypertrophy was shown. Although aerobic power, total aortic compliance, and arterial elastance were significantly improved by training, there was no change in LV stiffness. The authors speculated that the lack of improvement in LV stiffness may have been because of 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 no 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 seem that even modest levels of CRF are associated with lower risk of HF mortality. For example, a 50- to 59-year-old man would need to achieve a maximal MET level of ≥8.9 to qualify for the fit category. This is equivalent to covering 1.2 miles in the Cooper 12-minute run-walk test or achieving a treadmill time of 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. Although 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=39971; 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 ≥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 of follow-up (n=42764) did not materially change the pattern 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 only men 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 similar to median values obtained on a representative sample of US men. We also point out that the overall prevalence of metabolic syndrome among men in the CCLS cohort between 1979 and 2010 is 25%, which is similar to the prevalence that has been reported among NHANES (National Health and Nutrition Examination Survey) men in recent years. These findings suggest that Cooper Clinic men have similar risk profiles compared with other US 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

![Figure 3. Adjusted hazard ratios (HRs) for heart failure (HF) mortality in men based on the presence of individual risk factors in the Cooper Center Longitudinal Study during 1971–2010. *Adjusted for age and exam year. All comparisons are dichotomous with the referent group being the group who does not have the risk factor. NS, nonsignificant.](http://circheartfailure.ahajournals.org/Downloaded from)
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 high-density lipoprotein and low-density lipoprotein 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 HF 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 with 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.

Acknowledgments

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Disclosures

None.

References


Cardiorespiratory fitness was measured via a maximal treadmill stress test. Partici-
pants were followed for 20 years, during which there were 153 deaths from HF. Adjusted hazard ratios across high, moderate,
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cardiorespiratory fitness is an important determinant of subsequent HF mortality. In addition, HF mortality rates were lower
in fit than in unfit men within each body mass index strata, particularly within the normal weight and overweight groups. An
additional novel finding in our data was the marked difference in HF mortality between fit and unfit men with the same number
of traditional HF risk factors. Importantly, the level of fitness at which the risk of HF mortality is lower seems to be modest.
Thus, patients who can meet current public health guidelines for physical activity (2×150 minutes per week of moderate intensity
aerobic exercise) are likely to be at substantially lower risk with regard to future HF mortality. This is especially true if they are also able to control other HF risk factors such as obesity, hypertension, smoking, and diabetes mellitus.

CLINICAL PERSPECTIVE
To our knowledge, there are no reported data relating an objective measure of cardiorespiratory fitness with subsequent heart
failure (HF) mortality. In this article, we report on 44,674 apparently healthy men who underwent a baseline examination at
the Cooper Clinic between 1971 and 2010. Cardiorespiratory fitness was measured via a maximal treadmill stress test. Partici-
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